A thesis submitted to the Faculty of Science, Monash University, in fulfilment of requirements for the degree of Doctor of Philosophy
July 2011

PHARMACEUTICALLY ACTIVE IONIC LIQUIDS

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Acknowledgments

I would like to express my sincere gratitude to everyone that has helped and supported me throughout my PhD. To my main supervisor, Professor Douglas MacFarlane – thank you for all the guidance and the life lessons you taught me throughout the years. I would also like to acknowledge my co-supervisor, Professor Glen Deacon. I appreciate the discussions and advice I received from you. To the two people that have been there for me whenever I needed help and have taught me so much, Dr Jenny Pringle and Dr Bronya Clare – I honestly don't know how I would have done this without you – thank you so much for your patience and for sharing your wisdom. I would like to give special thanks to Dr Ekaterina Pas (neé Izgorodina) and Dr Peter Newman – I really appreciate all of the help and advice you gave me. To Finlay Shanks, Peter Nichols and Sally Duck - thank you for you help with IR, NMR and MS.

A special thank you to Kevin "Grumpy" Fraser, Pamela Dean and Gary Annat – right from the start you made me feel welcome and have been great office buddies and friends. To the other people I have gotten to know throughout the years – Maria Forsyth, Nathalie Rocher, Tim Khoo, Brianna Thompson, Vijay Ranganathan, Huy Ha, Ted Abraham, Rob Kerr, Radha Maganti and all the others who have been a part of the MacFarlane/Forsyth groups – thank you for your friendship and the fun times we shared together. And to the three special women that have made the last couple of years so much fun, who have been there for me and have made me laugh (sometimes hysterically) – Kylie "Jacob" Vongsanga, Mega "Feet" Kar and Vanessa Armel – thank you girls. I hope to always have you in my life.

To my two best friends – Jovana and Dragana – thank you for all your support and friendship. To my family-in-law and Sandra, my beautiful sister-in-law, thanks for all the encouragement and support you gave me.

A big thank you to my amazing aunty Goga and my beautiful cousin Sara – the two of you have been through so much yet have given me so much support in my time of need. To my grandma Zdenka and my aunty Ljilja – I know you have been watching over me and giving me strength. I MISS YOU BOTH SO MUCH!

To my wonderful parents, Mirjana and Milan, and my brother, Mladen – I honestly could never have asked for a more supportive family. You have been there for me from the beginning, through the sad and the happy times, and have done so much for me throughout the years – I cannot thank you enough! I love you all so much and I need you to always know that!

And finally, to the love of my life and my rock – my amazing husband, Mario – I really do not have many words that can describe how thankful I am to you for being there for me every minute of every day, encouraging me to keep going and putting up with my grumpiness. You have opened my eyes in so many ways and taught me so many life lessons. I have become a better person because of you. I could not have even dreamed of a better life partner. Volim te najviše! SAMO TI!!!

Mariu

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PART A: General Declaration

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Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17/Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 5 original papers published in peer reviewed journals and 1 unpublished publication. The core theme of the thesis is pharmaceutically active ionic liquids. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Chemistry under the supervision of Professor Douglas MacFarlane.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapter One, Two and Three my contribution to the work involved the following:

[If this is a laboratory-based discipline, a paragraph outlining the assistance given during the experiments, the nature of the experiments and an attribution to the contributors could follow.]

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
1	Crystalline vs. Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper	Published: Pharmaceutical research 2010	Author, initiation, key ideas, experimental data, manuscript development and write up 85%
2	Exploring an Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids	Published: Crystal Growth and Design 2009	Joint-author, initiation, key ideas, experimental design, experimentation, data generation, partial manuscript write up. 25%

2	Methyl 9*H*-Xanthene-9-carboxylate	Published: Acta Crystallographica 2008	Initiation, experimental design, experimentation 5%
3	Ionicity and Proton Transfer in Protic Ionic Liquids	Published: Physical Chemistry Chemical Physics 2010	Author, initiation, key ideas, experimental design, experimentation, data generation, manuscript development and write up 90%
3	Protic Pharmaceutical Ionic Liquid and Solids: Aspects of Protonics	Accepted: Faraday Discussions 2011	Author, initiation, key ideas, experimental design, experimentation, data generation, manuscript development and write up 85%
3	Enhanced Membrane Transport of Pharmaceutically Active Protic Ionic Liquids	Submitted: Chemical Communications 2011	Author, initiation, key ideas, experimental design, experimentation, data generation, manuscript development and write up 95%

[* For example, ‘published’/ ‘in press’/ ‘accepted’/ ‘returned for revision’/ 'submitted']

I have / have not (circle that which applies) renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ……

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Abstract

Many pharmaceutical solids can exist in different physical forms including polymorphs, solvates, hydrates and co-crystals. Polymorphism is observed in more than half of all crystalline pharmaceutical drugs. A drug substance can have multiple polymorphs, each exhibiting different properties including solubility, bioavailability, stability, efficacy *etc.* Inter-conversion of different polymorphs of a drug during its isolation, manufacture, transport and storage can have profound effects on the quality and performance of the drug product. Therefore, in order to ensure reproducible bioavailability of the drug during its shelf life under a variety of storage conditions, it is desirable to develop the most thermodynamically stable polymorph of that compound, although this is not an easy task. Hence, developing drugs that do not have an inherent tendency to crystallise is a potentially promising avenue of investigation for the pharmaceutical industry. For this reason, liquid drug forms of established active pharmaceutical ingredients (APIs) have been proposed as a new approach towards alleviating the problems associated with polymorphism of solid drugs.

Ionic liquids, compounds comprised entirely of ions and that melt below 100 ^{o}C, exhibit a lack of crystallisation at ambient temperature and pressure as a result of decreased lattice energies in the crystalline state. These compounds are known for their ability to be tailored, where ions can be chosen to obtain ionic liquids with particular characteristics (*e.g.* water soluble *vs.* water insoluble ionic liquids *etc*.) It is therefore possible to combine pharmaceutically active ions with Generally Recognised as Safe (GRAS) counter ions to obtain liquid salt forms of known APIs. This is the basis of the research discussed within. The concept of dual pharmaceutically active ionic liquids, whereby two APIs with synergistic activities are combined in order to obtain ionic liquids with dual pharmaceutical activity, is also explored.

Predicting whether a particular ion pair will generate a liquid at room temperature is difficult due to the number of possible combinations of anions and cations and the intricacies of their interactions. In this project, a concept known as “anti-crystal engineering” was employed in order to aid in the selection of ions most likely to produce

liquids, and this approach was successful in generating a wide range of pharmaceutically active ionic liquids. These new compounds have been fully characterised and their physical properties are reported. As most organic acid/base drugs are only sparingly soluble in water, while many of the corresponding salts of these drugs are water soluble, pharmaceutically active *protic* ionic liquids have also been developed in order to extend this research strategy to a wider number of drugs, rendering them water soluble in most cases. In order to gain more information about their potential behaviour in delivery systems, these compounds were subjected to a number of experimental techniques, such as infrared analysis and transport property studies, where their chemical and physical properties were determined. As protic ionic liquids do not necessarily consist entirely of ions, but may also contain small amounts of the acid/base species they are derived from, it is also imperative to determine the degree of proton transfer in these compounds. For the protic ionic liquid to be considered a "pure" salt, and not a mixture of the starting materials and the salt, the proton transfer should be at least 99 %. We have established a relationship between the presence of certain functional groups, the extent of proton transfer and the level of association between ions, which will be a useful tool for the future design of the most efficient liquid protic drugs.

Finally, model membrane transport studies were performed using the pharmaceutically active protic ionic liquids. These have shown very promising initial results, indicating that these compounds can be designed to have enhanced membrane transport when compared to the original solid form of the drug. These results are an important step towards the application of liquid APIs.

Abbreviations and symbols

AIL	Aprotic Ionic Liquid
API	Active Pharmaceutical Ingredient
Bro^+ Ibu^-	Bromohexinium Ibuprofenate
BzH	Benzoic acid
COSMO-RS	Conductor like Screening Model for Realistic Solvents
D	Diffusion Coefficient
DFT	Density Functional Theory
DSC	Differential Scanning Calorimetry
(EtOH)pyr	2-pyrrolidinoethanol
$(EtOH)pyrH^+$ Bz^-	2-pyrrolidiniumethanol Benzoate
$(EtOH)pyrH^+$ $(Bz\text{-}Bz)^-$	2-pyrrolidiniumethanol bis(Benzoate)
$(EtOH)pyrH^+$ $(Bz\text{-}Sal)^-$	2-pyrrolidiniumethanol Benzoate-Salicylate
$(EtOH)pyrH^+$ Gen^-	2-pyrrolidiniumethanol Gentisate
$(EtOH)pyrH^+$ Sal^-	2-pyrrolidiniumethanol Salicylate
FDA	Food and Drug Administration
FTIR-ATR	Fourier Transform InfraRed – Attenuated Total Reflectance
GenH	Gentisic acid
GRAS	Generally Recognised as Safe
HOPL	Highest Occupied Proton Level
IL	Ionic Liquid
K	Partition Coefficient
LUPL	Lowest Unoccupied Proton Level
M	Madelung constant

MBC	Minimum Biocidal Concentration
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
MIC	Minimum Inhibitory Concentration
MS-ESI	Electrospray Ionization Mass Spectrometry
NMR	Nuclear Magnetic Resonance
N_AH_2	Amantadine
$N_AH_3^+$ Bz^-	Amantadinium Benzoate
$N_AH_3^+$ Gen^-	Amantadinium Gentisate
$N_AH_3^+$ Sal^-	Amantadinium Salicylate
$N_BH_3^+$ Ace^-	Butylammonium Acetate
$N_HH_3^+$ Ace^-	Heptylammonium Acetate
$[NTf_2]^-$	Bis(trifluoromethanesulfonyl)amide
N_TH_2	Tuaminoheptane
$N_TH_3^+$ Bz^-	Tuammoniumheptane Benzoate
$N_TH_3^+$ $(Bz\text{-}Bz)^-$	Tuammoniumheptane bis(Benzoate)
$N_TH_3^+$ $(Bz\text{-}Sal)^-$	Tuammoniumheptane Benzoate-Salicylate
$N_TH_3^+$ Gen^-	Tuammoniumheptane Gentisate
$N_TH_3^+$ Sal^-	Tuammoniumheptane Salicylate
PG	Propylene Glycol
PIL	Protic Ionic Liquid
PSP	Phenolsulfonphthalein
RTIL	Room Temperature Ionic Liquid
SalH	Salicylic acid
t_{50}	Time to permeate to 50% saturation
TGA	Therapeutic Goods Administration

CHAPTER ONE

INTRODUCTION

CHAPTER ONE - INTRODUCTION

Section 1.1 Specific Declaration

Monash University

Declaration for Thesis Chapter One

Declaration by candidate

In the case of Chapter One, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Initiation, key ideas, experimental data, manuscript development and writing up	85%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Douglas R. MacFarlane	Key ideas, proof reading, final drafting	-
Katharina Bica	Key ideas, experimental data, final drafting	-
Robin D. Rogers	Key ideas, proof reading, final drafting	-

Candidate's Signature	Jelena Stoimenovski (neé Turanjanin)	Date

Declaration by co-authors

The undersigned hereby certify that:
(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic

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(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Chemistry, Monash University, Clayton, Victoria, 3800, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted] Douglas R. MacFarlane	25/07/2011
Signature 2		
Signature 3	[redacted] Robin D. Rogers	16/7/11

Chapter One: Introduction

Section 1.2 Salts

Salts are generally considered to be solid at room temperature. Sodium chloride, or more commonly table salt, is an inorganic salt with a melting point of 801 ^{o}C.[1] From the crystal structure of sodium chloride, one can observe that each sodium ion (Na^{+}) is surrounded by six chloride ions (Cl^{-}) and vice versa. This compound is held together by ionic bonds, strong bonds that require large amounts of energy to be broken. Under ambient conditions, sodium chloride is a highly stable compound. However, as the temperature increases, the ions begin to vibrate and obtain enough energy to escape the attraction of neighbouring ions, leading to disruption of the crystal lattice and thus melting of the salt. In the molten state, each ion is able to move individually.

Looking at this from a thermodynamic point of view, while the change in Gibbs free energy of fusion (ΔG_f) at the melting point is zero, the enthalpy (H) and the entropy (S) of fusion of the compound are increasing (Equation 1(a)).

$$\Delta G_f = 0 = \Delta H_f - T_m \Delta S_f \qquad \text{Eq. 1a}$$

$$\therefore T_m = \Delta H / \Delta S \qquad \text{Eq. 1b}$$

Equation 1. (a) Gibbs free energy of fusion is zero **(b)** the melting point of a compound is dependent on its enthalpy and entropy

Therefore, the melting point of any substance relates to the balance of its entropy and its enthalpy of fusion. Sodium chloride, like many other traditional salts, is a substance that has a high enthalpy of fusion.

Section 1.3 Ionic Liquids

1.3.1 Definition

An ionic liquid (IL), in simple terms, is a liquid comprised entirely of ions, with a melting point below the boiling point of water. In a further classification, room temperature ionic liquids (RTILs) are defined as having melting points below room temperature. ILs are also known by other synonyms including ionic melts, liquid electrolytes, liquid salts, ionic fluids and so on. Salts with melting points above 100 ^{o}C are usually referred to as molten salts. The low melting points of ILs are usually due to the structural features of the cations/anions of which they are comprised, resulting in low lattice energies of these salts. Large organic asymmetric cations and bulky anions with delocalised charges frustrate the coordination (packing ability) of these ions in space and also minimise the interaction between the ions. Thermodynamically, the large asymmetric ions, usually of flexible and rotatable nature, have more degrees of freedom and hence larger ΔS_f values, which usually lead to compounds with lower melting points (Equation 1(b)). The melting point of an IL can often be further depressed by the addition of another salt to give a eutectic mixture. Utilising only the currently known cations and anions, it has been suggested that over 10^{18} different ILs can be synthesised;[2] however, this number is expected to rise further with the continued discovery of new cations and anions.

1.3.2 A Brief History of Ionic Liquids

One of the first examples of an organic salt with a melting point of <100 ^{o}C, ethanolammonium nitrate, was a protic IL (for definition see section 1.3.4) with a melting point of 52-55 ^{o}C, reported by Gabriel in 1888. [3,4]

The first designed room temperature IL, ethylammonium nitrate, was a protic IL with a melting point of 12.5 ^{o}C, synthesised by Paul Walden in 1914.[5] This compound is formed by the simple reaction of ethylamine and concentrated nitric acid. At the time, the discovery of this IL did not prompt any great amount of interest, particularly as the material had potentially explosive properties. Over the ensuing decades, a number of novel ILs were reported, primarily as solvents for organic reactions and as high

temperature media for electrochemical studies, most notably the chloroaluminate series, but most were found to be extremely prone to hydrolysis. The big surge of novel and more stable ILs came in the 1990s with the breakthrough made by Wilkes and Zawarotko who reported air and water stable ILs, based on weakly coordinating anions such as tetrafluoroborate, $[BF_4]^-$, and hexafluorophosphate, $[PF_6]^-$.[6] However, ILs based on these anions were later also found to be hydrolytically unstable under certain experimental conditions, producing hydrofluoric acid, with those based on $[BF_4]^-$ anion being the more unstable of the two, over a broad range of conditions.[7] Nonetheless, in the last decade, a number of more stable ions, such as bis(trifluoromethanesulfonyl)-amide (NTf_2)[8] and dicyanamide (DCA)[9] anions and phosphonium[10] and imidazolium[11] based cations, to name a few, have been utilised to synthesise novel ILs which have been exploited in a number of applications.

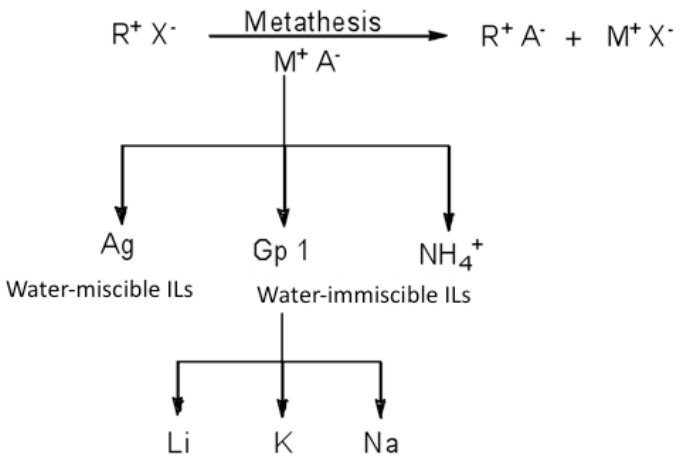
1.3.3 Applications of Ionic Liquids

Due to their unique properties, ILs have been widely studied for a range of applications. According to SciFinder, pre-2000 there was ~1330 research publications on ILs. This number has drastically increased over the years, with 2010 alone producing ~5407 research articles and patents.

The use of ILs for various applications has been well reviewed in recent years; they have been investigated for use as electrolytes for batteries,[12, 13] fuel cells,[14-16] dye sensitised solar cells,[17, 18] electrodeposition,[19, 20] electrosynthesis,[21, 22] supercapacitors and actuators.[23, 24] ILs have also been implemented as solvents in both organic and inorganic synthesis,[4, 25] in chromatography[26] and in amphiphile self-assembly media.[27] They have also been used as catalysis media,[28, 29] including enzyme catalysis.[30] A number of groups have investigated the use of ILs for the extraction and conversion of naturally occurring compounds such as cellulose, carbohydrates and biomass.[31-33] ILs have also been utilized as lubricants[34, 35] and biological solvents.[36]

1.3.4 Aprotic *vs.* Protic Ionic Liquids

ILs can be divided into two subclasses – aprotic and protic. The term ionic liquid most commonly refers to aprotic ILs (AILs) and these have been the focus of the majority of IL research. This type of IL is usually synthesised via a metathesis reaction between a halide salt or a similar salt of the desired cation and a silver, group 1 metal or ammonium salt of the desired anion (Scheme 1):[37, 38]



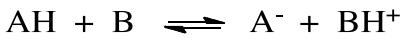
Scheme 1. General metathesis routes to ILs[37]

AILs exhibit a wide range of properties depending on the nature of the cations/anions of which they are comprised. They can be water miscible or water immiscible. Some are acidic, some basic and others neutral. Hence, ILs have been dubbed "designer solvents", as they can each be made with pre-selected characteristics and for a specific application by simply varying either ion.[39, 40]

One of the most useful properties exhibited by AILs is their negligible vapour pressure at temperatures up to their thermal decomposition temperature. This characteristic is due to the strong coulombic interactions among the ions in the liquid. As a result, AILs can be utilized in a range of applications requiring high temperatures, where the traditional molecular solvents fail due to their volatility. The negligible vapour pressure typically exhibited by AILs at moderate temperatures contributes to their reputation as "green solvents" as they do not produce toxic vapours during use, as volatile organic compounds can. Additionally, they can often be recycled, which is another reason that they are

commonly described as "green". Other typical properties seen in AILs, which are not seen in conventional molecular solvents, can include non-flammability, inherent ionic conductivity, wide liquid range, thermal and chemical stability and a wide electrochemical window.

Protic ionic liquids (PILs), on the other hand, are formed upon a proton transfer from a Brønsted acid to a Brønsted base, in an acid-base neutralisation reaction (Scheme 2).



Scheme 2. Acid-base neutralisation reaction

PILs, therefore, do not only contain ions but also small quantities of molecular species (*i.e.* the acid and base), which exist in equilibrium with the salt. PILs manifest notably different chemical and physical properties compared to AILs due to the presence of the exchangeable proton, which also allows for hydrogen bonding. These properties are highly dependent on the degree of proton transfer; this process will be discussed in more detail in Chapter 3.

1.3.5 Impact of impurities

Although the synthesis of ILs is often synthetically straightforward, purification of these compounds is non-trivial. Being liquid, they cannot simply be recrystallised to remove the impurities, as is possible with solid compounds, and their low volatility prohibits purification by distillation like conventional liquids. Quantifying impurities in ILs is an extremely important process for the successful characterisation and reproduction of experiments involving these compounds.

One of the most abundant and most difficult impurities to remove is water. Although many applications in which ILs are used are not affected by the presence of water, for those that are, the fundamental characterisation of new ILs should be carried out on very dry samples (preferably less than 100 ppm). Given that AILs have very low vapour pressures, this type of IL can be heated and dried under vacuum for several hours to remove the water. This procedure, however, is not appropriate for PILs, as the conjugate acid or base species

present in the PIL may also be volatile, in which case a loss of one of the species may occur.

Other impurities, including traces of acids, halide ions, residual solvents and any unreacted volatile organic compounds used in the synthesis of the ILs can also have profound effects on the chemical, physical and spectroscopic characteristics of the ILs.[41] Impurities can depress the melting points of compounds significantly, to the extent that they may be wrongfully defined as an IL if their crystallisation is never observed, and can significantly alter fundamental physical properties such as conductivity and viscosity.[41, 42] Hence, it is crucial to accurately establish the purity of any new IL. The level of acceptable impurities in ILs is, to a certain extent, dependent on the specific application of these compounds and must therefore be defined by the researchers within that specific area of application.

In this project, the synthesised compounds were thoroughly purified and analysed by techniques including Nuclear Magnetic Resonance (NMR), Infrared spectroscopy (IR), Electrospray Ionization Mass Spectrometry (MS-ESI) *etc.,* as detailed in the experimental sections of the enclosed manuscripts and the supplementary information.

Section 1.4 Pharmaceutically Active Ionic Liquids

The potential use of ILs with antimicrobial activity as antiseptics, disinfectants and anti-fouling agents has prompted several investigations over the years. In 2003, Pernak and co-workers reported a range of 3-alkoxymethyl-1-methylimidazolium antimicrobial ILs with chloride, $[BF_4]^-$ and $[PF_6]^-$ anions, which were tested against a range of strains of bacteria and fungi including *Staphylococcus aureus*, *Escherichia coli* and the fungus *Candida albicans*. They reported the minimum inhibitory concentrations (MICs) and minimum biocidal concentrations (MBCs) for the ILs, indicative of the minimum concentrations of antimicrobial agents that inhibit the growth of or kill a microorganism; low values indicate high potencies of antimicrobial agents. A closer look at the results of this study unveiled a relationship between the structure of the IL cation and the resultant antimicrobial activity; ILs containing alkoxyl groups with 10, 11, 12 or 14 carbon atoms displayed the highest activity, while those with shorter cation substituents were not active against bacteria and fungi.[43] The relationship between antimicrobial activity and the structure of the cation was observed again with alkylimidazolium and alkylpyridinium ILs, as reported by Docherty *et al.*[44] and also in ILs based on chiral alkylammonium cations with more than five carbon atoms, as studied by Pernak *et al*.. Exchanging the anions in these studies did not affect the antimicrobial activities of the synthesised ILs.

However, in 2005, Cieniecka-Roslonkiewicz *et al.*[45] reported a number of phosphonium ILs with a range of different anions that displayed anti-microbial activity as well as anti-electrostatic activity, in which the structure of both the cation and the anion had an effect on the biological activities of the ILs. Further, the halide based anions displayed anti-microbial activities comparable to those of a standard commercial biocide, benzalkonium chloride. However, substituting the halide anion for other anions resulted in a loss of antimicrobial activity.

The work on antimicrobial ILs has led to the birth of a new type of IL; in 2007, pharmaceutically active ILs emerged. These are based strictly on ions that are active pharmaceutical ingredients (APIs) or generally recognised as safe (GRAS) compounds – all substances that have been approved by the Food and Drug Administration (FDA) in the

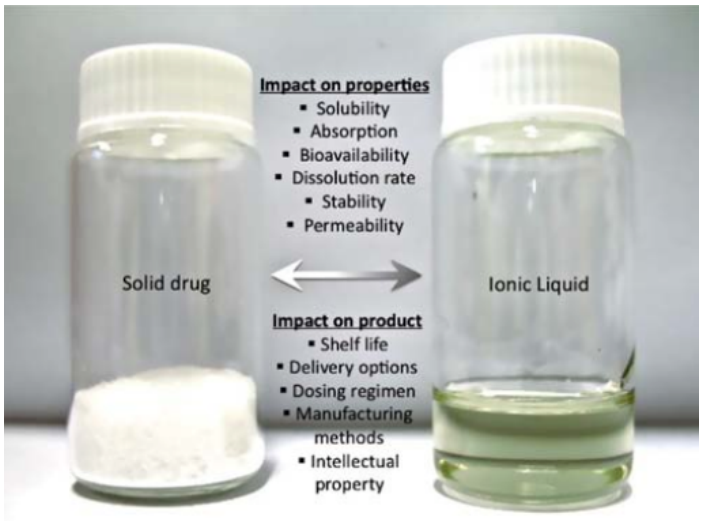
U.S. or the Therapeutic Goods Administration (TGA) in Australia to be safe and reliable for use as food additives and in drug formulations.

Publication 1.1 "Crystalline *vs.* Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper" is a review article that discusses pharmaceutically active ILs, describing in more detail the beginnings and future directions of this new and exciting area of IL research.

Publication 1.1

Crystalline *vs.* Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper

Jelena Stoimenovski, Douglas R. MacFarlane, Katharina Bica, Robin D. Rogers



Pharmaceutical Research, Vol. 27, No. 4, April 2010 (© 2009)
DOI: 10.1007/s11095-009-0030-0

Commentary

Crystalline *vs.* Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper

Jelena Stoimenovski,[1] Douglas R. MacFarlane,[1,4] Katharina Bica,[2,3] and Robin D. Rogers[2,3]

Received September 30, 2009; accepted December 4, 2009; published online February 9, 2010

Abstract. Why not consider liquid salt forms of active pharmaceutical ingredients (APIs) as an alternative versatile tool in the pharmaceutical industry? Recent developments have shown that known APIs can be readily converted into ionic liquids and that these novel phases often possess different properties (e.g., improved solubilities and dissolution rates), which may have a direct impact on the pharmacokinetics and pharmacodynamics of the drug. They may also offer the potential of novel and more efficient delivery modes, as well as patent protection for each of the new forms of the drug. Since these pharmaceutically active ionic liquids represent a thermodynamically stable phase, they avoid the troublesome issues surrounding polymorphism and "polymorphic transformation." In some cases, an active cation and an active anion can be combined to produce a liquid possessing dual functionality. Here we examine and challenge the current industry reliance on crystalline APIs by discussing the breadth and potential impact of liquid salts as a possible approach to phase control.

KEY WORDS: active pharmaceutical ingredient; delivery modes; ionic liquid; polymorphism; salt.

INTRODUCTION

More than 50% of drugs on the market today are sold as organic salts (1). Salification (i.e., salt formation) of a drug substance, a crucial step in drug development, can have a huge impact on its properties, including solubility, dissolution rate, hygroscopicity, stability, impurity profile and particle characteristics. The cation that is most commonly used in the salification process in FDA-approved pharmaceutical salts is the sodium ion, while the most encountered anion is chloride (2). The pharmaceutical industry relies predominantly on *solid, primarily crystalline* forms for the delivery of APIs, mainly for reasons of purity, thermal stability, manufacturability, and ease of handling. In contrast, liquid drug formulations are only rarely found and are usually based on eutectic mixtures (3). However, problems associated with the solid form of many drugs exist, including polymorphic conversion, low solubility, and low bioavailability for crystalline solids, and the tendency of amorphous forms to spontaneously crystallize (4). For these reasons, but also for considerable financial interests caused by legal ramifications, a constant screening for new drug forms, including salts, solvates, and co-crystals, is ongoing (5).

Most screening protocols for salt, solvate, co-crystal, or indeed even neutral APIs, discard any results for which an 'oil' is obtained. That is, if the result of the test conditions is not a solid, the material and the result are discarded and typically unreported in the open literature. The protocols are typically designed to produce crystalline forms, despite the fact that if the counterion is carefully chosen, an API can be *designed* to possess a low, or even non-existent, melting point and hence be present as a liquid at room temperature or below (6–9). These liquid salts represent a new phase of any given pharmaceutical active ingredient (API) and therefore offer a potentially new suite of properties for that active, not to mention intellectual property. Equally, these liquid salts offer a versatile solution to phase change issues with known APIs.

The reliance of pharma on the solid state remains, despite the fact that many drugs exhibit multiple crystalline forms (polymorphs, solvates, etc.), which can have a profound effect on the solubility, physical and chemical stability, dissolution rate and, in some cases, bioavailability of the compound (10–12). An interconversion between crystal forms occasionally occurs, which can create differences in the bioavailability of the drug, leading to inconsistencies in its efficacy. The pharmaceutical industry's concern with this phenomenon has intensified as a result of "polymorphic transformations," where one crystal form transforms into another during storage or manufacturing processes, and the legal ramifications of this effect. A number of court cases regarding the polymorphism of salts have proven to be extremely significant and remarkably costly (e.g., GlaxoSmith-Kline *vs.* Apotex–Paxil) (13), leading to the establishment of a legal precedent concerning polymorphism. Thus, different

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phases of a given drug can, in principle, be separately patented (1). It is also now accepted by regulatory bodies in the US that different solid forms of a drug are effectively different drugs, i.e., have different pharmacokinetics and pharmacodynamics; however, European regulators currently view them to be the same.

A *liquid phase* of the given active is therefore considered to be a usefully different form of the active compound as it certainly avoids the issues arising from polymorphism. Other developments have been approaching similar territory where liquid drug formulations were prepared as eutectic mixtures (14); however, this tends to introduce a substantial quantity of inactive ballast in the formulation, diluting the API. In addition, pure liquid phases of APIs would lend themselves to many alternative delivery or treatment options.

Ionic liquids (ILs) are commonly accepted as being salts or mixtures of salts that have melting points below 100°C (15), an extremely broad classification. In the present context of pharmaceutical applications, the liquid phase is preferably present below room temperature. These low melting points are largely induced by packing frustration of the usually asymmetric cations. In addition, a more diffuse charge on one or both of the ions typically yields a lowering of the melting point. For example, 3-ethyl-1-methylimidazolium chloride is a simple organic salt with a melting point of 77–79°C; replacment of the chloride with a dicyanamide anion lowers the melting point below room temperature, and, thus, the salt at room temperature appears as a stable, fluid liquid with a glass transition of −104°C and a melting point of −21°C (16).

The huge interest in ILs has led to an extensive and diverse range of ions known to support IL formation. An equally diverse range of applications has emerged, from electrochemical devices (17–19) to chemical solvents (17,20), biopolymer solvents (21), and protein formulations (22–25) to name a few. While the popularity of ILs in biosciences might have been delayed by the (sometimes heated) debate on the toxicity of some ILs, this very property can be desirable and lead to a variety of pharmaceutical applications (26). For instance, the antimicrobial activity of ILs is subject to an increasing number of publications and can be beneficial for the development of new bioactive materials, for example as antiseptics or as antifouling reagents, or even as potential anticancer therapeutic agents (9,27–32). Carson *et al.* have investigated the antibiofilm activity of 1-alkyl-3-methylimidazolium chloride ILs and reported potent, broad spectrum activity against a variety of clinically significant microbial pathogens, including MRSA (33).

There is certainly no doubt that many pharmaceuticals and other bioactive moieties can be made into an ionic liquid phase. A number of examples have been published recently where APIs have been combined with counterions capable of lowering their melting point below room temperature. One approach taken is to pair an active ion with a counterion which is a known excipient. For example, the IL *propantheline acesulfamate* contains the active cation from the API propantheline bromide (an antimuscurinic used to treat a number of conditions such as excessive sweating, cramps, spasms of the stomach, etc.) with *acesulfamate*, a known artificial sweetener and a pharmaceutical additive (6). The IL formed from these two ions has no observable melting point and passes into a glassy state at −20°C; bulk samples of this material have been stable in the liquid state for more than one year.

One of the most appealing features of ILs for pharmaceutical application is that they are *customisable materials* that can be specially made with pre-selected characteristics by varying the cations and anions of which they are comprised. Combinations of different cations and anions result in various ILs which can provide wide ranges of hydrophobicity/hydrophilicity, acidity/basicity, viscosities, etc. (34). Perhaps most importantly in the context discussed here, combining cations and anions with little opportunity for strong attractive intermolecular (or interionic) hydrogen bonded interactions in an "anti-crystal engineering" approach decreases the likelihood of crystallization and provides an elegant access to pharmaceutically active ILs (6). This approach will inherently lead to different salts (ion combinations) that would otherwise not be explored where crystallization is the prime objective. Indeed, the frequently used term "designer solvents" for ILs might as easily be adapted for IL "designer drugs," since physical, chemical and biological properties of a drug can be tuned by choice of the counterion rather than by covalent modification (Fig. 1).

What new treatment options are we missing when drug discovery or development approaches are exclusively focused on the crystalline state? Let us explore some aspects of ILs that we should start to consider when looking to refill our product portfolio.

ELIMINATION OF POLYMORPHISM

If polymorphism is an issue, one can design an IL form of the API without changing or compromising the molecular integrity or solubility of the API. Ranitidine hydrochloride (Zantac™), an anti-ulcer drug that gained dubious fame for extensive litigations over polymorphic forms and purity (35) was easily reacted with sodium docusate, a common emollient (36), to form the room temperature ionic liquid *ranitidine docusate* with a glass transition temperature of −12°C. Similarly, propantheline bromide is an API that can be present in different polymorphs (37); the *propantheline*



Fig. 1. Designer drugs: tunable properties by design and choice of ions.

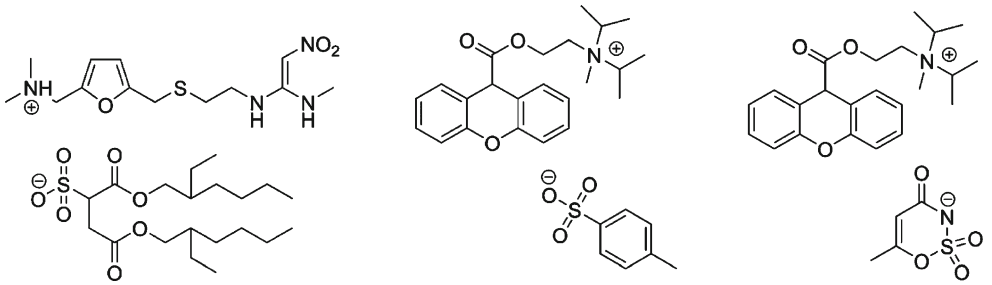


Fig. 2. Ranitidine docusate (*left*), Propantheline toluenesulfonate (*middle*), and Propantheline acesulfamate (*right*).

acesulfamate, and the other *propantheline* ILs described in reference 6, are new compounds of this API that avoid the polymorphism problem (Fig. 2).

CONTROLLED SOLUBILITY

While the elimination of polymorphism in an IL formulation of drug is a logical consequence, it is by far not the only potential advantage arising from use of the liquid state. Many Phase II trials of new active compounds end in failure due to their poor efficacy, often related to limited solubility (38). The design of the IL via the choice of the counterion can dramatically improve or decrease the solubility of the API (39,40). While most current salt approaches aim to increase solubility, ILs also offer the possibility of rendering an active *less* soluble, giving rise to hydrophobic liquid salts and new concentrated liquid delivery modes.

Strongly hydrophilic ionic actives often possess insufficient ability to penetrate biological membranes (1). Combining such an active ion with another of a more lipophilic character may offer a solution to this problem. For example, *lidocaine docusate*, an IL form of the local surface anaesthetic lidocaine, combines the relatively hydrophobic lidocaine cation with a hydrophobic anion, docusate (an emollient), to produce a hydrophobic IL salt, which exhibits *reduced or controlled* water solubility (Fig. 3) and thus should exhibit extended residence time on the skin (41).

A number of delivery modes can be employed to deliver such hydrophobic liquid salts to the site of action more efficiently than dissolved crystalline APIs in a more concentrated and effective manner, including iontophoresis, passive patches, aerosols, etc. Hydrophobic IL phases of an active make it possible to deliver a concentrated drug in a more localised manner, potentially avoiding the toxic impact of the drug and its metabolites on the rest of the body. While such hydrophobic properties can be achieved in crystalline APIs which are then used in a concentrated solution form, one of the advantages of the IL phase in this respect is that the ion combination used to prepare the salt is not required to produce a high melting point to be a useful drug; much wider combinations of ions are applicable.

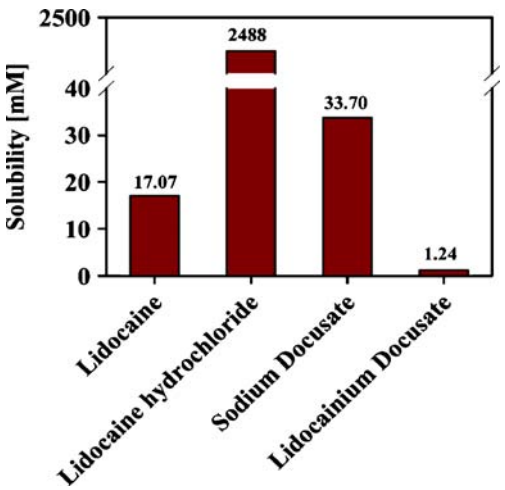


Fig. 3. Improved hydrophobicity and decreased solubility of lidocaine docusate.

ION-PAIR BASED TRANSPORT

Whether the IL ions will stay together in aqueous solution as ion pairs or clusters rather than independent solvated ions remains to be investigated. ILs are designed to be chaotropic, and, thus, the aqueous and solution chemistries are only sparingly explored (42). Recent molecular dynamics simulation studies (43–45), as well as spectroscopic investigation via NMR techniques (46,47), suggest that ILs do not dissolve as independent ions but keep a nanostructured organization in aqueous media. After all, the inherent properties of ILs are not like traditional crystalline salts, and the very properties that make ILs low melting also make them behave differently both in the melt and in solution.

Some pharmaceutically active ILs are highly ion-associated systems displaying high viscosities and low conductivities. This phenomenon has already been encountered and described in the IL field where tetradecyltrihexyl- and tetrabutyl-phosphonium cations are paired with chloride and sulfonylamide anions to yield highly viscous and low conducting compounds (48,49). These liquids are thought of as being an intermediate state between true ionic and true molecular liquids.

In the pharmaceutical world, drugs that are highly ionic have difficulty crossing the membrane in order to reach their site of action. Ion-pair formation enhances the transport of various ionic drugs through the skin and across the absorbing membrane (1). Therefore, highly ion-associated pharmaceuti-

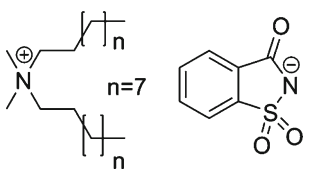


Fig. 4. Dual biological function: Didecyldimethylammonium saccharinate.

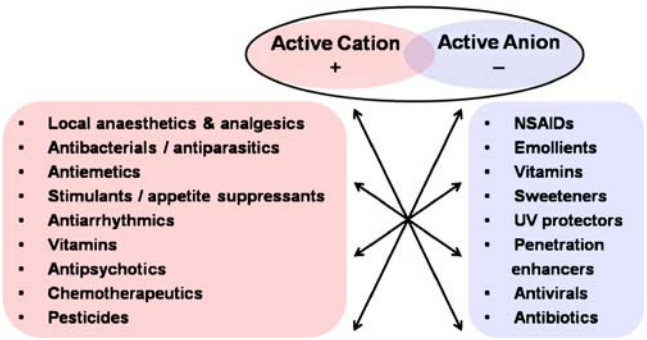


Fig. 5. A number of different combinations possible for dual functional liquids.

cally active ILs would be highly beneficial forms of the original pharmaceutical active salts, as they could cross the membrane more rapidly (50). In fact, measurements show that one of the propantheline salts, *propantheline* p-*toluenesulfonate* (Fig. 2) is one of these highly paired ionic liquids.

EXPLOITING THE FULL POTENTIAL OF SALTS—DUAL FUNCTIONALITY

With (solid) salts frequently used to provide the desired physico-chemical properties of a neutral drug, the chosen counterions are usually of inactive nature. There have been a few examples of 'combination salts' utilizing two actives in a single compound (1) but the overall promise of such an approach seems to be moderated by a) the need to have a crystalline material, and b) the fixed stoichiometry of actives found in such a crystalline salt. So called 'dual functionality' has been a highly explored aspect of the IL field in general, for example in dual acidic or double chiral ILs (51). In the context of APIs it adds new avenues for exploration in pharmaceutical action.

Only recently have examples in the IL literature appeared which report the designed incorporation of two biologically active ions where both the cation and anion were chosen based on the desired physical, chemical, and biological properties (9). Sweet and antimicrobial salts can be prepared from antibacterial quaternary ammonium cations and non-nutritive sweetener anions such as acesulfamate or saccharinate. *Didecyldimethylammonium saccharinate* (Fig. 4) and *didecyldimethylammonium acesulfamate* not only retain their initial antimicrobial properties, but exhibited decreased water solubility, high thermal stability, and good deterrent activity against insects. While these quaternary ammonium cations

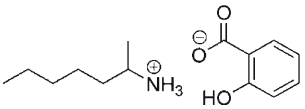


Fig. 7. Partially ionised 1-methylhexylammonium salicylate.

are frequently found as antimicrobials and disinfectants (52), the introduction of sweetness as a second functionality in one formulation can certainly be an additional factor for oral applications, e.g. mouthwashes.

In the context of APIs, a variety of approaches can be contemplated where the two actives can be chosen (Fig. 5), for example on the basis of:

- one counteracting the side effects of the other active ingredient;
- both ions being pharmacologically independent, but either aiding the therapeutic properties of the other or providing treatment for a different symptom; or
- the ions acting in a synergistic manner supplementing the desired effects (1).

It is important to also note that a co-formation of two separate solid actives in a solid dosage form does significantly differ from a dual functional IL formulation (Fig. 6). The ions in an IL will dissolve in the body fluids in exactly the same way—since one ion cannot dissolve without the other; this is not true of separate solid forms administered at the same time since each may dissolve at quite different rates.

PROTIC IONIC LIQUIDS FROM API ACIDS AND BASES: A QUESTION OF IONIZATION AND CONFUSION

A subclass of ILs, protic ILs (PILs), is based on an acid/base exchangeable proton system. As a result of the exchangeable proton, these ILs have been used as solvents in various acid catalysed reactions (53,54) and are suitable as proton conductors (55). Pharmaceutically active acids and bases can be utilised to produce pharmaceutically active protic ILs, and, in fact, an overwhelming majority of all pharmaceutically active salts in use are protonated species. It is thought that $\Delta pKa^{aq} > 10$ is needed for full ionisation to occur (56); $\Delta pKa^{aq} < 10$ implies low degree of ionisation, hence a dynamic mixture of ions and parent acid and base. There may be a significant advantage of drugs with low degree of ionisation over the fully ionised ones due to their ability to

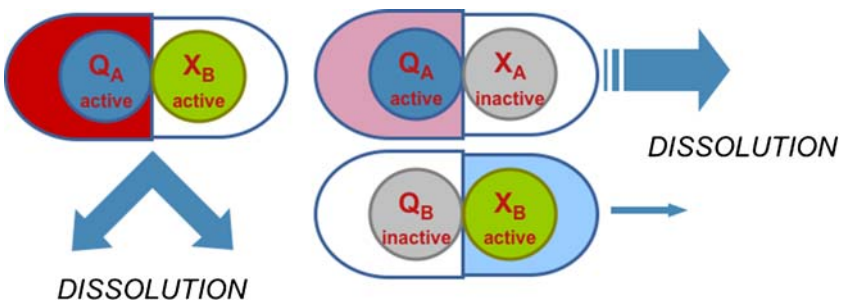


Fig. 6. Schematic illustration demonstrating a potentially different dissolution of dual functional liquid (*left*) *vs*. solid co-formulation of 2 active salts (*right*).

$$[B'_yHB]^+A^- \xleftarrow{y\ B'} HB^+A^- \xrightarrow{x\ HA'} HB^+[A(HA')_x]^-$$

Scheme 1. Altering stoichiometry to produce oligomeric anions or cations.

cross membranes more efficiently. An example of a partially ionized pharmaceutically active IL is *1-methylhexylammonium salicylate* (Fig. 7) (57). Salicylic acid, an analgesic with a p*K*a value of 2.98, was reacted with 1-methylhexylamine, a nasal decongestant with a p*K*a value of 10.5, to produce a liquid at room temperature with a T_g at −40°C and a ΔpK_a^{aq} of 7.52. Walden plot (48) analysis of this compound shows a low degree of ionisation implying incomplete proton transfer from salicylic acid to 1-methylhexylamine. In fact, it is most probable that this compound is a mixture of the parent acid and base and salicylate and 1-methylhexylammonium ions.

Most current research on ILs, and indeed virtually all modeling efforts, deals with salts of definite chemical composition. However, in light of growing understanding of IL behavior, we have begun to question whether modification to the stoichiometry, especially non-integral stoichiometry, is not, in fact, an unrecognized tool to improve IL physical properties. Angell and others studied "proton transfer RTIL systems" using reactions between neat Brønsted acids and bases and found that when one of the components is used in excess, the resulting proton transfer is incomplete, and cations and anions exist in equilibrium with molecular species, resulting in formation of either associated ions or weak proton transfer systems (58–60). With proper knowledge of the chemistry, the properties of the ILs can be modified by addition of excess solid or liquid acid or base in order to form oligomeric anions or cations (Scheme 1) (61).

CONCLUSIONS AND FUTURE DIRECTIONS

We propose here that IL phases offer much promise, incredible flexibility, and an ability to finely tune physical, chemical, and biological properties without covalent manipulation of the active. Certainly there are issues which must be addressed, including manufacturing, scale-up, purification, stability, and delivery, to name a few. Nonetheless, the headlong rush to find new pharmacophores via molecular manipulation and discovery may have obscured the fact that many known actives can be manipulated into more effective treatments by simple salt chemistry—albeit a salt chemistry unlike any other yet attempted by the industry.

While better strategies for prediction and proper design for pharmaceutically active ILs are needed and many unknown aspects of synergies, antagonists, ion pairing, and aggregation are involved, the risk in conducting such research would seem to be outweighed by the potential for dramatically increasing our product portfolios. We therefore suggest that the liquid state *per se* should not be ignored—or worse, discarded—but more considered as an alternative to common solid-state techniques. A plethora of new possibilities, challenges, and thrilling opportunities might be the reward.

ACKNOWLEDGEMENTS

DRM is grateful to the Australian Research Council for his Federation Fellowship.

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Section 1.5 Thesis Overview and Aim of Study

This thesis is presented in a "thesis by publication" format. It is made up of five published journal articles, one patent (see Appendix) and one submitted manuscript. Each chapter contains an introduction in which the articles and their supplementary information are placed within the context of the thesis as a whole. The introduction chapter contains a review article, primarily focussing on our work and the work of our collaborators, which introduces the topic of this thesis. The two main chapters are then focused on:

(i) Pharmaceutically active **aprotic** ionic liquids

This part of the work is concerned with the synthesis and characterisation of a number of novel pharmaceutically active ILs based on aprotic active pharmaceutical ingredients; these were prepared as examples of the concept and to probe some of the complications of achieving low melting point compounds. The use of "anti-crystal engineering" to select ions to yield liquid salts is also discussed. The work of this section is presented in Chapter 2 in the following publications:

- Publication 2.1 - Exploring an Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids
- Publication 2.2 – Methyl 9*H*-xanthene-9-carboxylate

(ii) Pharmaceutically active **protic** ionic liquids – ionicity and proton transfer

Chapter 3 focuses not only on the preparation and characterisation of pharmaceutically active protic ionic liquids but also on the very important question of ionicity and the degree of proton transfer in protic ILs in general. The chapter also presents our initial investigations into the membrane transport of these materials, which is a fundamental step towards the development of real-life applications.

These topics are presented in the following publications:

- Publication 3.1 – Ionicity and Proton Transfer in Protic Ionic Liquids

- Publication 3.2 – Protic Pharmaceutical Ionic Liquids and Solids: Aspects of Protonics
- Publication 3.3 – Enhanced Membrane Transport of Pharmaceutically Active Protic Ionic Liquids

Finally, our research into the different aprotic and protic pharmaceutically active ionic liquids is summarised in the conclusion section (Chapter 4), where some future avenues of investigation are also discussed.

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- Crystalline *vs.* Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper
  http://www.springerlink.com/content/4g14306n81x7t8n0/

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- Exploring an Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids
  http://pubs.acs.org/doi/abs/10.1021/cg8009496

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- Methyl 9*H*-xanthene-9-carboxylate
  http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2961166/

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CHAPTER TWO

PHARMACEUTICALLY ACTIVE APROTIC IONIC LIQUIDS

CHAPTER TWO – PHARMACEUTICALLY ACTIVE *APROTIC* IONIC LIQUIDS

Section 2.1 Specific Declaration

Monash University

Declaration for Thesis Chapter Two

Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Initiation, key ideas, synthesis and characterisation of compounds, analysis of data, manuscript write up (supplementary information)	25% + 5%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Masahiro Yoshizawa-Fujita	*Publication 2.1* Preliminary synthesis and characterisation of compounds	-
Pamela M. Dean	*Publication 2.1, 2.2* Initiation, key ideas, crystallographic data, manuscript write up	70% + 95%
Douglas R. MacFarlane	*Publication 2.1, 2.2* Initiation, key ideas, final drafting	-
Janet L. Scott	*Publication 2.1* Initiation, key ideas, manuscript write up	-

Candidate's Signature	Jelena Stoimenovski (neé Turanjanin)	**Date**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Chemistry, Monash University, Clayton, Victoria, 3800, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted] Masahiro Yoshizawa-Fujita	**Date** 06/07/2011
Signature 2	[redacted] Pamela M. Dean	08/07/2011
Signature 3	[redacted] Douglas R. MacFarlane	25/07/2011
Signature 4	[redacted] Janet L. Scott	06/07/2011

Chapter Two: Pharmaceutically Active *Aprotic* Ionic Liquids

Section 2.2 General Overview

The physical form of a drug substance can have a huge impact on its chemical and physical properties.[1] Most active pharmaceutical ingredients (APIs) are formulated and marketed as crystalline forms, predominantly because crystalline compounds are easier to isolate and purify and also possess better physico-chemical stability. The difficulties that can occur with crystalline forms, however, are related to their poor solubility as well as the potential existence of more than one crystalline form of an API.[2] Drugs with poor solubility exhibit slow dissolution rates and hence the onset of the pharmacological activity of these drugs is also slow, while different polymorphs of a drug can display different pharmacokinetic profiles, influencing the overall performance of the drug candidate.[3] Other crystalline states of APIs include co-crystals, solvates, hydrates and salts.[4] All of these forms are multi-component crystalline phases rather than covalent modifications of the active molecules. However, depending on the chemical nature and three-dimensional structure of the molecule, an API can also exist in the amorphous form.[4] When compared to crystalline forms, amorphous forms usually display higher solubilities and higher dissolution rates, due to the lack of lattice energy - a thermodynamic barrier to dissolution.[5] Since 50 % of APIs on the market are administered as simple salts,[1] and the amorphous forms of the drug offer better solubility and dissolution rates, a liquid salt form of an API may provide advantages over the currently available phases of APIs due to an improvement of the overall pharmacokinetics of the drug.

Publication 2.1 outlines a number of aprotic compounds synthesised during this project as an example of this concept. The cations used were the active components of these compounds, all APIs, while the anions were selected from the GRAS category of compounds. The synthetic procedures and characterisation data are reported in the experimental section of the article and the supporting information. Three compounds were found to satisfy the definition of pharmaceutically active *aprotic* ionic liquids, while the others were crystalline samples, used to test the validity of the concept known as “anti-

crystal engineering". This concept, which was developed in collaboration with another PhD student at the time (Pamela Dean), was used to identify cation/anion pairs that have the lowest likelihood of crystallising and hence lead to the formation of liquid salt forms of the active species.

In addition to the improved solubility and dissolution rate of the API, the synthesised pharmaceutically active AILs could potentially offer other advantages in their liquid form. One advantage is the potential to tailor these compounds to obtain different physical properties (*e.g.* hydrophobicity/hydrophilicity) by simply varying the counterion of the active. Another advantage is the possibility of delivering these new forms of known drugs in a different way; one which may be preferred by the patient. Being ionised liquids, there is an opportunity to deliver the drugs using Iontophoresis, which is a non-invasive technique used to deliver drugs through the skin using a small electric current.[6] A third potential advantage is the capacity to synthesise dual active pharmaceutical AILs by combining ions of synergistic behaviour (either to enhance the desired effects or to counteract the unwanted side-effects).

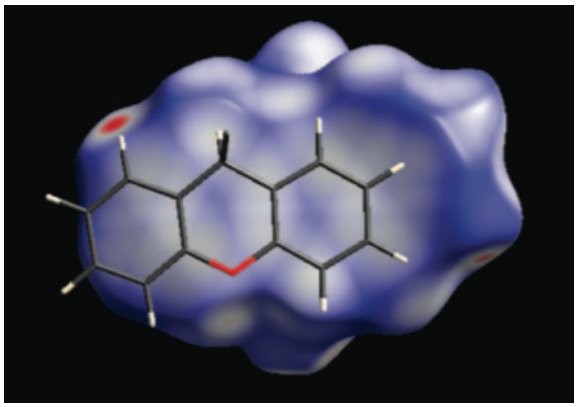
A patent application (Patent A1) was developed on the basis of this work in collaboration with the Rogers group at University of Alabama. The patent is entitled "Dual Functioning Ionic Liquids and Salts Thereof", and is included in the Appendix.

Finally, in order to prepare the purest compounds for this study, all of the starting materials were recrystallised prior to the synthesis of the active ILs. During the recrystallisation of propantheline bromide, methyl 9*H*-xanthene-9-carboxylate, a by-product obtained from the transesterification of this API by methanol,[7] was obtained. A single crystal of this sample was successfully acquired and subjected to crystallographic examination, and this data is summarised in Publication 2.2.

Publication 2.1

Exploring an Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids

Pamela M. Dean, Jelena Turanjanin, Masahiro Yoshizawa-Fujita, Douglas R. MacFarlane, Janet L. Scott



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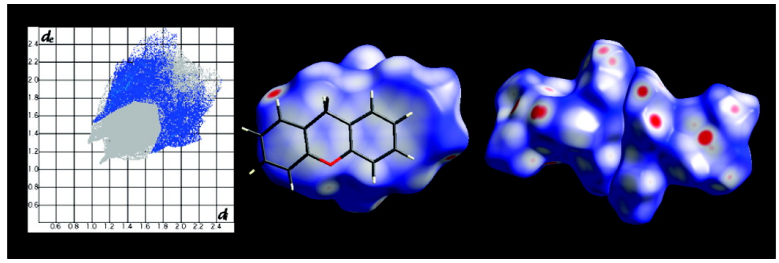
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Cryst. Growth Des., **2009**, 9 (2), 1137-1145• DOI: 10.1021/cg8009496 • Publication Date (Web): 23 December 2008

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CRYSTAL GROWTH & DESIGN
2009
VOL. 9, NO. 2
1137–1145

Exploring an Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids

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Received August 27, 2008; Revised Manuscript Received November 23, 2008

ABSTRACT: A series of salts, some of which are ionic liquids, are prepared from cations and anions drawn from Active Pharmaceutical Ingredients (APIs) and Generally Recognized As Safe (GRAS) materials. Using the solid-state structures of the crystalline salts as a basis, an anti-crystal engineering approach to the preparation of "Active Ionic Liquids" (AILs) is explored.

Introduction

The physical form of a drug substance is of great importance as it directly affects the manner in which the material is formulated and presented to the consumer, as well as influencing more fundamental characteristics such as solubility and dissolution rate, which, in turn, impact on bioavailability. These factors, as well as the considerable financial gains to be realized by effective patent protection of new physical forms, have resulted in a flurry of activity in screening for novel solid forms, including salts, polymorphs, pseudopolymorphs (or solvates), and co-crystals.[1] There are myriad examples in the scientific literature, with doubtless many more in the closed research files of large pharmaceutical companies. More than 50% of drug compounds are marketed are salts,[2] and the exploitation of differences in the number of crystal forms, interconversion of these, and the attendant changes in physical properties are not insignificant. In addition, the counterion is sometimes little more than ionic "ballast" as the identity of this often follows from synthesis or purification routes, rather than rational choice or screening.

Recently Rogers and co-workers have reported ionic liquids formed from active pharmaceutical ingredients (APIs) and have commented on the potential scope of this, to date poorly exploited, drug phase.[3] (The term "ionic liquid" is now widely accepted to describe salts with melting points <100 °C, although some authors distinguish a subset of these salts as Room Temperature Ionic Liquids or RTILS, that is, those salts that are in the liquid phase at ambient temperature.) Clearly a salt that does not exhibit a crystalline phase will not be bedevilled by polymorphism, but there are further advantages to be realized and exploited in the delivery of the API. In particular, a non-crystalline salt in a liquid or glassy phase will almost certainly exhibit the enhanced solubility exhibited by amorphous phases. This concept bears further discussion as it is potentially one of the most important advantages of the formulation of APIs as ionic liquid phases. A schematic comparison of the accessible phases and the relative free energy of each is presented in Figure 1.[4]

A significant number of drugs currently on the market are formulated as amorphous materials, and the most common means of preparing the amorphous phase is by quenching: rapid cooling from the melt; rapid precipitation from solution (for example on addition of an antisolvent); spray drying; flash evaporation; lyophilisation; or, indeed, any method that allows the disordered glassy phase to be "frozen in" before nucleation and growth lead to the appearance of crystals of the API.[5] Unfortunately, in cases where a stable crystalline form exists at ambient temperature, ΔG_f° for the crystalline phase is *lower* than that for the amorphous material formed by quenching, and thus quenching results in trapping in a form that is not the thermodynamically most stable phase at that temperature, Figure 1a. Thus, any event that initiates nucleation may lead to growth of a crystalline phase at the expense of the amorphous glass. Such nucleation initiators may include heating (yielding a plastic phase that then crystallizes) or localized shock, such as that applied during size reduction (grinding) or formulation. In some cases, even the desired increased solubility leads immediately to crystallization of a stable crystalline phase. Thus, upon addition of amorphous Indomethecin to water, dissolution of the amorphous material yields a localized concentration of the drug that is higher than its saturation limit, leading to immediate crystallization.[4]

Here, we consider the concept of ionic liquids formed from API ions in the light of the extensive literature on crystalline drug forms, "crystal engineering"[6,7] and the exploitation of "supramolecular synthons";[8] concepts which have been applied in developing strategies for increasing solubility of drug compounds[9] and in the choice of co-crystal formers[10] for poorly soluble drugs,[11] such as carbamazepine.[12] Emphasis must be placed on the preparation of a salt that has an amorphous phase as its thermodynamically most stable form (in the temperature range of interest), that is, a salt that is a liquid or glass, but NOT a supercooled liquid, such as that depicted in Figure 1b. A less preferred, but nonetheless effective form, would be one with T_{fusion} for the stable form below the T of interest, as in Figure 1c.

Combining an understanding of the effect of robust supramolecular synthons on the process of crystallization, with the concepts familiar to chemists working with ionic liquids, we propose the development of an "anti-crystal engineering" approach to the synthesis of Active Ionic Liquids (AILs). This would comprise identifying and intentionally *avoiding* the pairing of cations and anions that might yield common supramolecular synthons, with the goal of decreasing the likelihood of crystallization of salt. This "anti-crystal engineering" approach is postulated as a means of narrowing the search for AILs to cation and anion pairs that have a higher likelihood of NOT crystallizing. Thus, herein, we begin to illustrate this approach by preparing and analyzing a series of API salts some of which crystallize readily, while others are AILs and remain in an

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Published on Web 12/23/2008

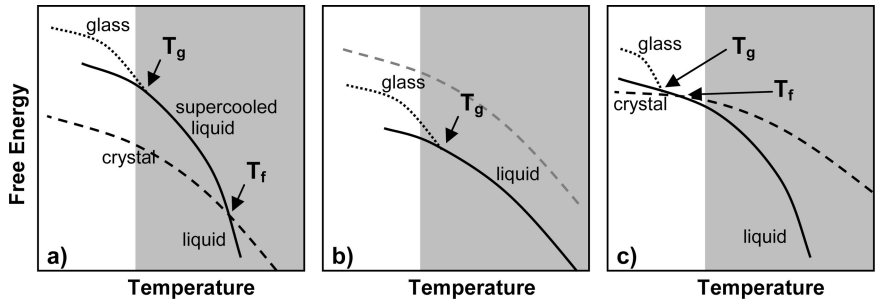
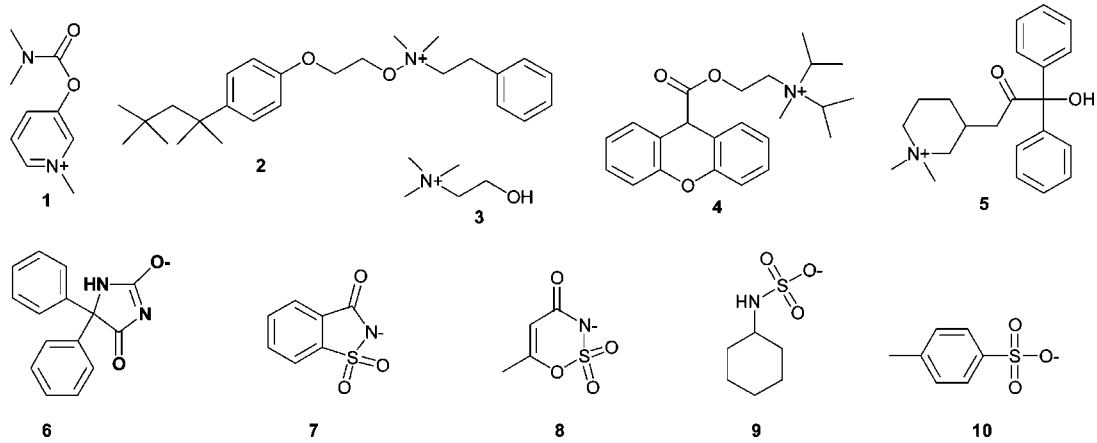


Figure 1. Simplified schematic of free energy vs temperature for (a) a compound with a stable crystalline phase, which may be supercooled to form an unstable supercooled liquid or glass and thus exhibits a tendency to crystallize when the system is perturbed; (b) a compound without a stable crystalline phase [or (gray dashed line) with a crystalline phase that is at a higher energy than the liquid phase over the entire region shown], such as an ionic liquid; (c) a compound with T_{fusion} below ambient temperature, which has a stable crystalline phase, but only at sub-ambient temperatures.

Chart 1. Pharmaceutically Active Cations[a]



[a] 3-(Dimethylaminocarbonyloxy)-1-methylpyridinium cation (pyridostigmine) **1**; benzyl-dimethyl[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl] ammonium cation (benzethonium) **2**; methyl-bis(1-methylethyl)-[-(9H-xanthen-9-carbonyloxy)ethyl ammonium cation (propantheline) **4**; (1,1-dimethyl-3,4,5,6-tetrahydro-2H-pyridin-3-yl) 2-hydroxy-2,2-diphenyl-acetate cation (mepenzolate)**5**; and anion: 5-oxo-4,4-diphenyl-1H-imidazol-2-olate cation (phenytoin) **6** are combined with sweetener anions: saccharinate **7**, acesulfamate **8**, and cyclamate **9** or with the GRAS ions: choline **3**, or *p*-toluenesulfonate **10**.

amorphous glass or liquid form in spite of vigorous attempts to bring about crystallization.

Results and Discussion

A small group of cations and anions selected from API salts and the Generally Recognized As Safe (GRAS) list were chosen for combination to yield salts containing active ions (Chart 1). Pyridostigmine **1** is an acetylcholinesterase inhibitor and is marketed as the slightly soluble crystalline Br^- salt, branded as Mestinon; benzethonium **2** is used in the form of the Cl^- salt as an anti-infective agent in many topical antiseptic gels and is marketed under many trade names, such as Salanine; propantheline **4**, a muscarinic acetylcholine receptor antagonist, is marketed in its Br^- salt form as Pro-Banthine; mepenzolate **5** is used as a skeletal muscle relaxant and is currently administered in the crystalline Br^- salt form generally known as Cantil; and phenytoin **6**, as its sodium salt, is an antiepileptic marketed variously as Phenytek, Dilantin, Eptoin, or Epanutin. The choline cation **3**, *p*-toluenesulfonate anion **10**, and sweetener anions saccharinate **7**, acesulfamate **8**, and cyclamate **9** are all to be found in the GRAS list and are potential counterions that are known to form ionic liquids in other cases. All cations contain tetra-alkylated ammonium or alkylpyridinium moieties commonly found in ionic liquids, and all anions, bar phenytoin, have been previously used in the preparation of ionic liquids.[13−18]

The salts were prepared via ion metathesis reactions commonly used in ionic liquid synthesis and were analyzed, with respect to purity, with particular attention to residual ions such as Br^-. Combinations of these ions yielded a number of isolable salts (Table 1), including three that exhibit no detectable phase changes ascribable to the existence of crystalline phases, on Differential Scanning Calorimetric (DSC) analysis. Melting, crystallization, and glass transition events were inferred from endotherms, exotherms, or changes in heat capacity detected by DSC analysis in multiple quenching, heating, and cooling experiments. In all cases at least three repeated heating and cooling cycles in the range −100 to 200 °C were effected. Positive identification of AILs (as with all ionic liquids) is not as simple as isolation of a salt that is oily or glassy at room temperature, as such materials may simply be solids in which crystallization is frustrated by the presence of impurities, or quenched amorphous phases, that is, supercooled melts. Thus, in addition to the low temperature DSC experiments described above, various attempts were made to induce crystallization: bulk (2 g) samples of the pure liquids were stored and examined over extended periods (4 months or more) for signs of crystallization, and standard crystal growth techniques, such as dissolution in suitable solvents (including wet solvents) followed by slow cooling or slow evaporation, were employed to test the integrity of the liquid state.

Table 1. Glass Transition Temperatures or Melting Points of Salts Prepared and As Reported for the Marketed Salts and Starting Materials

salt		T_{glass} / °C	T_{fusion} / °C
pyridostigmine bromide[a]	**1**·Br	*b*	154−157[c]
benzethonium chloride[a]	**2**·Cl	*b*	164−166[c]
choline chloride[a]	**3**·Cl	*b*	302−305 (dec.)[c]
propantheline bromide[a]	**4**·Br	*b*	159−161[c]; 165−169[d]
mepenzolate bromide[a]	**5**·Br	*b*	228−229[c]; 232−235[d]
phenytoin sodium[a]	Na·**6**	*b*	>350 (dec.)[c]
sodium saccharinate[a]	Na·**7**	*b*	>250 (dec.)[c]
potassium acesulfamate[a]	K·**8**	*b*	225−229[c]
sodium cyclamate[a]	Na·**9**	*b*	262−265[c]
silver *p*-toluenesulfonate[a]	Ag·**10**	*b*	192−194[c]
pyridostigmine saccharinate	**1**·**7**	4[e]	94−96[d]
benzethonium saccharinate	**2**·**7**	−4	
choline phenytoin	**3**·**6**	*f*	215−217[d]
propantheline saccharinate	**4**·**7**	18[e]	133−135[d]
propantheline acesulfamate	**4**·**8**	−20	
propantheline cyclamate	**4**·**9**	20[e]	133−137[d]
propantheline *p*-toluenesulfonate	**4**·**10**	7	
mepenzolate saccharinate	**5**·**7**	53[e]	187−189[d]
mepenzolate acesulfamate	**5**·**8**	34[e]	135−137[d]

[a] Starting material. [b] Not measured. [c] Literature. [d] DSC measurement. [e] Tg values measured on DSC heating cycles subsequent to melt, indicative of supercooling; in all cases samples were analyzed over 3 heating/cooling cycles in the range −100 to 200 °C (or 220 and 240°C for **3**·**6** and **5**·Br, respectively). [f] No T_g detected on DSC cool/heat cycles, compound recrystallizes on cooling.

It is important to distinguish between quenched amorphous phases, obtained by rapidly freezing a salt (for example by rapid cooling or solvent quenching of a melt) and salts that do not exhibit a crystalline phase, such as propantheline *p*-toluenesulfonate (**4**·**10**), which DSC trace is presented in Figure 2a. The former is trapped in a metastable state with a higher free energy than that of the crystalline form, so that events promoting nucleation, such as shock or abrasion common during formulation, may cause such salts to crystallize. By contrast, a salt without a crystalline phase (or with a sub-ambient melting point) is in the thermodynamically most stable phase as a liquid or glass at ambient temperature. Thus, **2**·**7**, **4**·**8**, and **4**·**10** are AILs while **1**·**7**, **4**·**7**, **4**·**9**, **5**·**7**, and **5**·**8** are merely crystalline salts with a tendency to supercool (which may lend themselves to formulation as amorphous materials as per many other pharmaceutical salts) but are *not* AILs.

The tendency of many of these salts to form supercooled amorphous glassy phases is reflected in the presence of glass transitions and lack of clear endothermic melting events on the second DSC heating cycle, as illustrated for propantheline saccharinate (**4**·**7**) in Figure 2b. This is reflected in the very slow crystallization of some of these salts: **1**·**7**, **4**·**9**, and **5**·**8** slowly crystallized from bulk samples over a time scale of weeks to months. Indeed, such supercooling led us initially to erroneously assign propantheline saccharinate (**4**·**7**) as an ionic liquid as, in early experiments, no crystalline product was obtained and no melting point detected in multiple DSC quench/heat/cool/heat experiments; however, crystals slowly formed in a stored bulk sample after many months. We will return to this discussion when we consider the crystal structures of the salts. The salts prepared all exhibit lower melting points than the chloride or bromide salts (of the cations) or sodium, potassium, or silver salts (of the anions) used as starting materials, Table 1, which lends some credence to the choice of counterions as bulky, unsymmetrical, and/or charge diffuse ions.

To begin exploration of the anti-crystal engineering approach to choosing cation/anion combinations, which would entail identifying robust supramolecular synthons, such as strong hydrogen bonds (usually considered to impart a tendency toward crystallization[19,20]) that should be avoided in the quest for AILs, we chose to prepare a range of salts, including some expected to crystallize. If one were to adopt a highly reductionist approach, one might formulate the following hypothesis: complementary hydrogen bond donor and acceptor groups are likely to lead to hydrogen bonded supramolecular synthons, which promote order and thus crystallization, that is, will not form AILs. This hypothesis may then be tested. Functional groups with the potential for formation of such synthons may be counted, and a crude prediction made of which pairs are more or less likely to crystallize because of the influence of strong hydrogen bonds, as is illustrated in Table 2.

Examining Table 2, it appears that our hypothesis, that is, "the existence of functional groups leading to hydrogen bonded synthons is likely to yield crystalline materials", holds (albeit as part of a very small sample), and all cation/anion combinations bearing both hydrogen bond donor and acceptor groups yield crystalline salts (**3**·**6**, **4**·**9**, **5**·**7**, and **5**·**8**). Such a result would have been predicted in the light of the extensive literature on the topic of hydrogen bonded supramolecular synthons. Gratifyingly, the pair which might be predicted to form the greatest number of strong, directional hydrogen bonds between different ions yields the salt with the highest melting point: choline phenytoin (**3**·**6**). Of greater interest, however, are those salts that are crystalline solids and yet do not (at first examination of individual ions) exhibit the capability to form hydrogen bonded synthons (**1**·**7** and **4**·**7**), and we turn to an examination

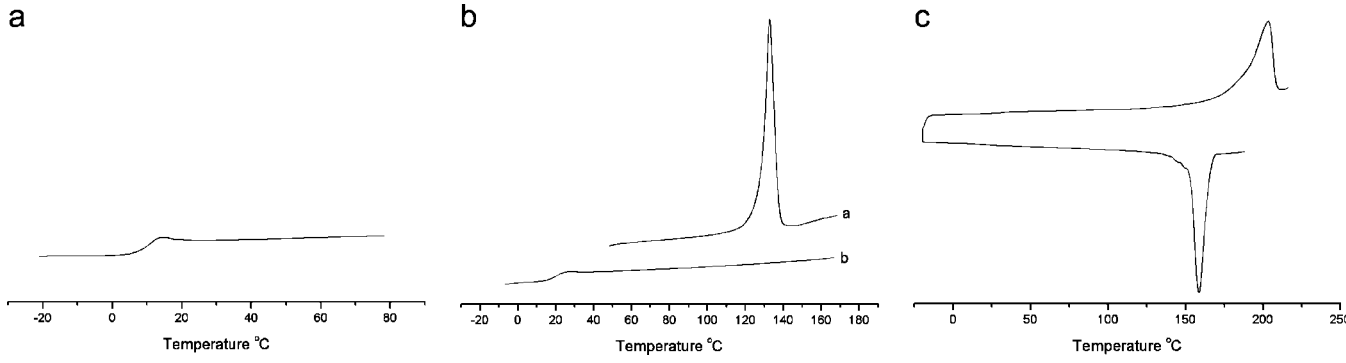


Figure 2. DSC traces of pure samples of (a) propantheline *p*-toluenesulfonate (**4**·**10**), an AIL, which exhibits a T_g only; (b) propantheline saccharinate (**4**·**7**), a crystalline salt that is prone to supercooling post melting (i.e., forms a typical amorphous salt phase), which is not an AIL; and (c) choline phenytoin (**3**·**6**), a highly crystalline salt, which does not supercool but instead recrystallizes during the cooling cycle. Note that while all samples were analyzed in multiple heating cooling cycles over the range −100 to 200 °C, selected data is presented here for the purposes of illustration. In addition, the DSC trace of **3**·**6** over the range −10 to −220 °C is presented.

Table 2. Hydrogen Bond Donor and Acceptor Groups Likely to Form Strong Hydrogen Bonds

	cation		anion		
salt	donors	acceptors	donors	acceptors	comments
1·7		R_3N C=O −O−		O=S=O −O− C=O N^-	low melting solid (mp 94−96 °C)
2·7		−O− −O−		O=S=O −O− C=O N^-	AIL
3·6	OH	OH	R_2NH	C=O =N− R_2NH $C-O^-$	−NH−C=O tend to form dimers; high mp solid (mp 215−217 °C); no tendency to supercool
4·7		−O− C=O −O−		O=S=O −O− C=O N^-	solid (mp 133−135 °C)
4·8		−O− C=O −O−		−O− O=S=O N^- C=O	AIL
4·9		−O− C=O −O−	R_2NH	R_2NH O=S=O $S-O^-$	solid (mp 133−137 °C)
4·10		−O− C=O −O−		O=S=O $S-O^-$	AIL
5·7	OH	OH C=O		O=S=O −O− C=O N^-	solid (mp 187−189 °C)
5·8	OH	OH C=O		−O− O=S=O N^- C=O	solid (mp 135−137 °C)

of representative crystal structures in an attempt to understand other more subtle interactions that may serve to promote crystallization and/or result in lattice energy stabilization. A number of crystal structures were obtained, and crystal and refinement data are summarized in Table 3. Specific details of crystal structure analysis and Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagrams showing molecular numbering are contained in the Supporting Information.

Choline Phenytoin (3·6): Both Cation and Anion Bear Hydrogen-Bond Donor and Acceptor Functionality; High Probability of Crystallization. The amide moiety, NH−C=O, has been identified by Aakeröy and Zaworotko as likely to form a robust supramolecular synthon: the amide dimer,[21] and thus it is probably not surprising that this synthon manifests in these crystals as a dimer of the phenytoin ion, Figure 3a. A cation to anion hydrogen bond of the choline hydroxyl group to the phenytoin deprotonated nitrogen atom is also easily discerned by examination of intermolecular contacts, Figure 3b.

Examination of Hirshfeld fingerprint plots prepared using CrystalExplorer[22] reveal both strong and weak intermolecular interactions by providing a fingerprint plot of close contacts derived from Hirshfeld surface analysis, Figure 4. (The Hirshfeld surface is a 3D isosurface, which effectively defines the molecular volume in the crystal, as the surface is defined so that for each point on the surface "1/2 of the electron density is due to the spherically averaged noninteracting atoms comprising the molecule, and the other half is due to those comprising the

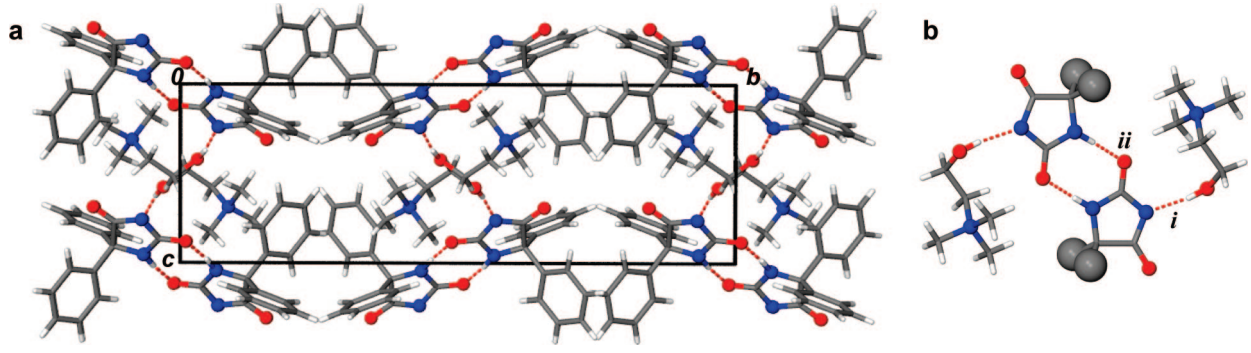


Figure 3. (a) Packing diagram of **3·6** viewed down 100. (b) Closeup of hydrogen bonded cation···anion/anion···cation dimers. Hydrogen bonds are indicated by dotted lines and N and O atoms depicted as spheres. Hydrogen bond geometry: (i) O1−H1···N1A *d* DH 0.89(3) Å; *d* D···A 2.804(2) Å; *d* H···A 1.92(3) Å; ∠ DHA 171.4(3)°; (ii) N2A-H2A···O1A(−*x*, −*y*, 2 − *z*) *d* DH 0.95(3) Å; *d* D···A 2.858(2) Å; *d* H···A 1.92(3) Å; ∠ DHA 173(2)°.

Table 3. Crystal and Refinement Data

	choline phenytoin **3·6**	propantheline cyclamate **4·9**	mepenzolate saccharinate **5·7**	propantheline saccharinate **4·7**
CCDC No.	658086	658085	658084	689108
empirical formula	$C_{20}H_{25}N_3O_3$	$C_{29}H_{42}N_2O_6S_1$	$C_{28}H_{30}N_2O_6S_1$	$C_{30}H_{34}N_2O_6S_1$
M_r	355.43	546.73	522.60	550.67
crystal system	monoclinic	triclinic	orthorhombic	monoclinic
space group	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$	$P2_1/n$
a/Å	8.8575(2)	8.9636(3)	8.6732(1)	7.8305(16)
b/Å	25.5711(7)	12.5667(5)	11.5678(2)	13.694(3)
c/Å	8.6333(2)	12.7652(4)	24.6021(4)	25.404(5)
α/deg	90.0	88.606(2)	90.0	90.0
β/deg	111.604(1)	83.860(2)	90.0	96.20(3)
γ/deg	90.0	75.653 (2)	90.0	90.0
V/Å^3	1818.0(1)	1385.1(1)	2468.33(7)	2708.1(9)
Z'; Z	4	2	4	4
D_c/g.cm^{-3}	1.299	1.3107	1.4061	1.351
μ/mm^{-1}	0.090	0.163	0.179	0.167
refl. unique	4967	6809	7155	6037
refl. $I > 2\sigma(I)$	3084	6194	6716	1260
R_1/wR_2 [$I > 2\sigma(I)$]	0.0637/0.1566	0.0449/0.0901	0.0356/0.0900	0.1147/0.1537
R_1/wR_2 [all data]	0.1108/0.1876	0.0488/0.0939	0.0392/0.0929	0.4870/0.2587
GOF on F^2	0.980	1.020	1.115	0.911
parameters/restraints	335/0	511/0	340/0	357/0

rest of the crystal".[23]) The choline to phenytoin hydrogen bond results in a donor "spike" in the cation fingerprint plot (Figure 4a), which is complemented by a matching feature in the anion plot (Figure 4d) indicating the acceptor interaction. While the anion/anion hydrogen bonded pair results in symmetrical sharp features in Figure 4e, it is in detection of subtler interactions that 2D Hirshfeld fingerprint plots are particularly useful. Thus, CH···O short contacts between protons on carbon atoms α to the positively charged N atom result in smaller donor and acceptor "spikes", highlighted in panels b and e of Figure 4. CH···π interactions cation to anion produce "wings" visible in panels c and f of Figure 4, and the geometry of these interactions may be summarized: C3B−H3B(1 − x, −y, 2 − z)···centroid (C4A−C9A); d C−H 1.037 Å; d H···centroid 2.47 Å; ∠ CHcentroid 144.7 °; C3−H3A(−x, −y, 1 − z)···centroid (C10A−C15A); d C−H 0.947 Å; d H···centroid 2.58 Å; 164.8°.

Thus, in this highly crystalline salt, with no tendency to glass formation, all hydrogen bond interactions are maximized with the carbonyl O-atom of the anion acting as an acceptor for a number of weak (but concerted) C−H donors.

Propantheline cyclamate (4·9): Cation Contains Hydrogen-Bond Acceptor Functionality while Anion Bears Potential Hydrogen Bond Donors and Acceptors;

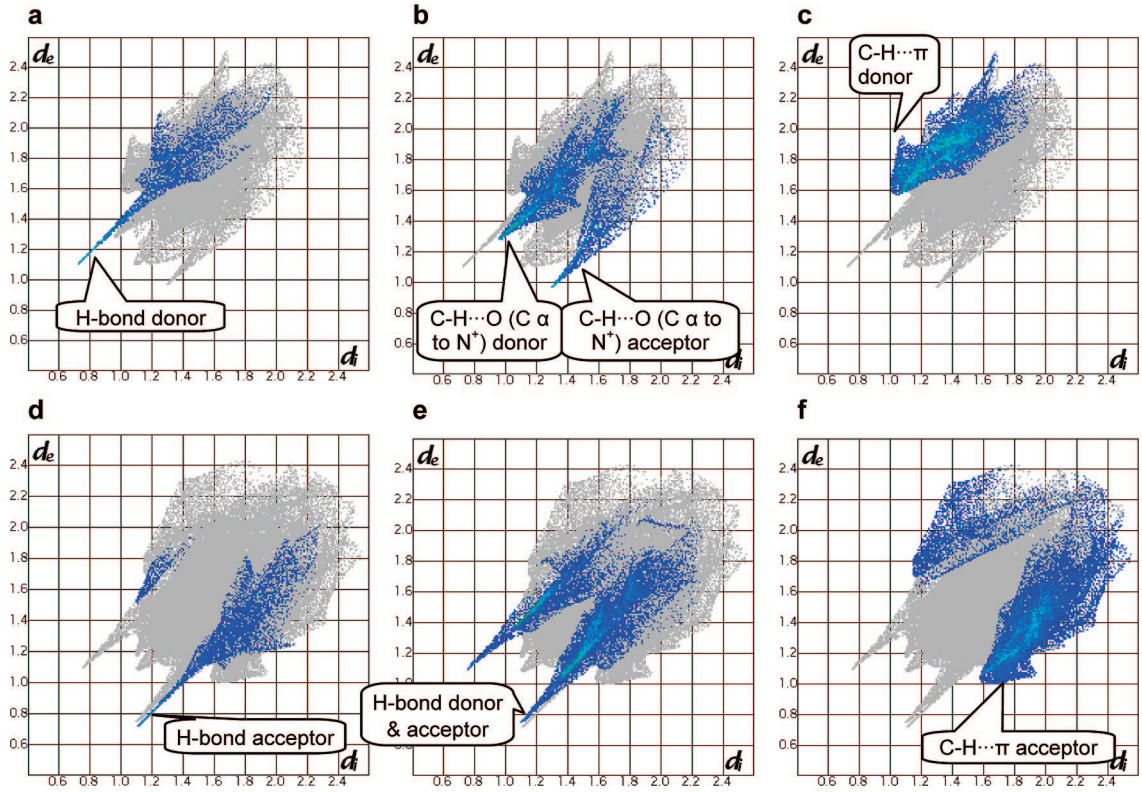


Figure 4. Decomposed Hirshfeld fingerprint plots[24] for **3·6**. Specific contacts are highlighted, while the entire 2D fingerprint is shown in gray. Top: Choline cation: (a) H···N contacts (and reciprocal i.e none); (b) H···O contacts (and reciprocal); (c) H···C contacts (and reciprocal, i.e., none). Bottom: Phenytoin anion. (d) N···H contacts (and reciprocal); (e) O···H contacts (and reciprocal); (f) H···C contacts (and reciprocal).

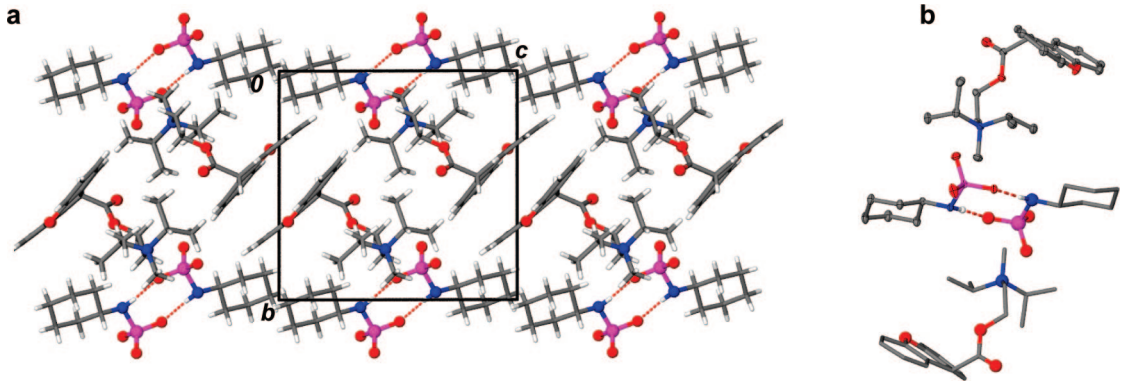


Figure 5. (a) Packing diagram of **4·9** viewed down [−100]. Anion/anion hydrogen bonds NH···O are indicated by dotted lines, and N, O, and S atoms depicted as spheres. (b) Closeup of hydrogen bonded anion dimer with attendant cations, asymmetric unit atoms are displayed as ellipsoids at the 50% probability level. H-bond geometry: N1A−H1A···O3A *d* DH 0.88(2) Å; *d* D···A 2.921(1) Å; *d* H···A 2.04(2) Å; ∠DHA 176(2)° (*d* O−S 1.460 Å).

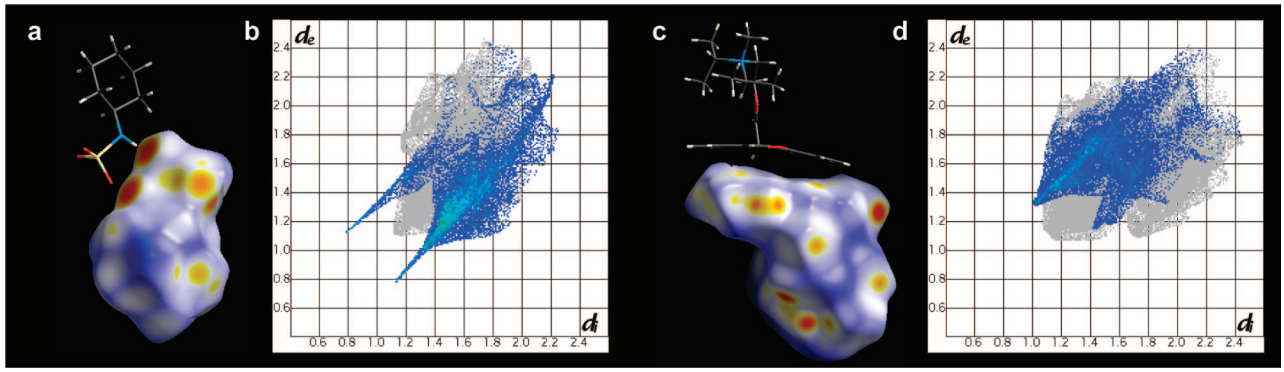


Figure 6. Propantheline cyclamate (**4·9**): (a) anion/anion dimers with one of the pair shown with its Hirshfeld surface (colors represent normalized d_e vs d_i plotted on the surface; "hot" colors reflect close contacts) and the other in stick mode with the accompanying 2D fingerprint plot in which the sharp symmetrical features associated with complementary hydrogen-bond donors are clearly visible; (b) decomposed 2D fingerprint plot with O−H···N contacts highlighted; (c) a cation/cation pair with one of the pair shown with its Hirshfeld surface (normalized d_e vs d_i plotted on the surface) and the other in stick mode, exhibiting complementary CH···π interactions with a small π···π component; (d) in the accompanying Hirshfeld fingerprint plot it is clear that the cation participates in no close contacts while the CH···π interactions are visible as characteristic "wings" in the donor region.

Predicted Cation/Anion and Anion/Anion Interactions. The propantheline cation (**4**) bears a number of hydrogen bond acceptors, while the cyclamate anion (**9**) contains one classical hydrogen-bond donor, leading one to expect anion/cation hydrogen bonds. While **4·9** crystallizes very slowly and has a distinct tendency to supercool, the melting point of 133−137 °C is only 30 °C (measured by DSC) below that of the marketed Br^- salt, and examination of the crystal structure reveals no anion/cation hydrogen bonding but instead the presence of anion/anion dimers, Figure 5. Examination of the Hirshfeld fingerprint plot for the anion in this structure reveals the supramolecular interactions in these dimers as typical symmetrical "horns" in the plot of d_e versus d_i, Figure 6. This suggests that the cyclamate anion is *not* a useful anti-crystal engineering building block since this tendency toward formation of anion dimers is likely to occur in many of its salts.

Mepenzolate saccharinate (5·7): Cation Bears Hydrogen-Bond Donor and Acceptor Functionality while Anion Bears Acceptors Only; Predicted Cation/Cation and Cation/Anion Interactions. Predictably, ion pairs in crystals of this salt exhibit cation to anion O−H···O⊂C hydrogen bonds as depicted in Figure 7.

Again, analysis of features observed in Hirshfeld surface fingerprint plots (Figure 8) provide information about both strong (and predictable) and weaker interactions. The cation/anion hydrogen-bond, O−H···O⊂C, is clearly indicated by the long horns in the donor region of Figure 8a, depicting cation H···O contacts, and the acceptor region of Figure 8c, depicting anion cation H···O contacts, while cation/cation C−H···π interactions result in the characteristic symmetrical "wings" noted in Figure 8b.

It is interesting to analyze more closely the dense set of points indicating O···H contacts in Figure 8c as these do not appear to be perfectly matched by H···O contacts in Figure 8a, instead there is a significant component because of N−C(α)−H···O interaction. The somewhat acidic protons of the carbon atoms α to N^+ are all disposed in close contact with oxygen atoms of the saccharinate anion as illustrated in Figure 8e. While CH···O hydrogen bonds are notoriously weak, there are *ten* such close contacts in each cation/anion pair, which would be expected to contribute significantly to attractive interactions between crystal components.

Thus, while the predicted cation/cation interactions are not exhibited in the crystal structure, cation/anion interactions are not limited to the hydroxyl to carbonyl hydrogen bond but include a large number of weaker C−H···O interactions.

Propantheline saccharinate (4·7): Both Cation and Anion Contain Hydrogen-Bond Acceptor Functionality Only; No Predicted Strong Cation/Anion Hydrogen

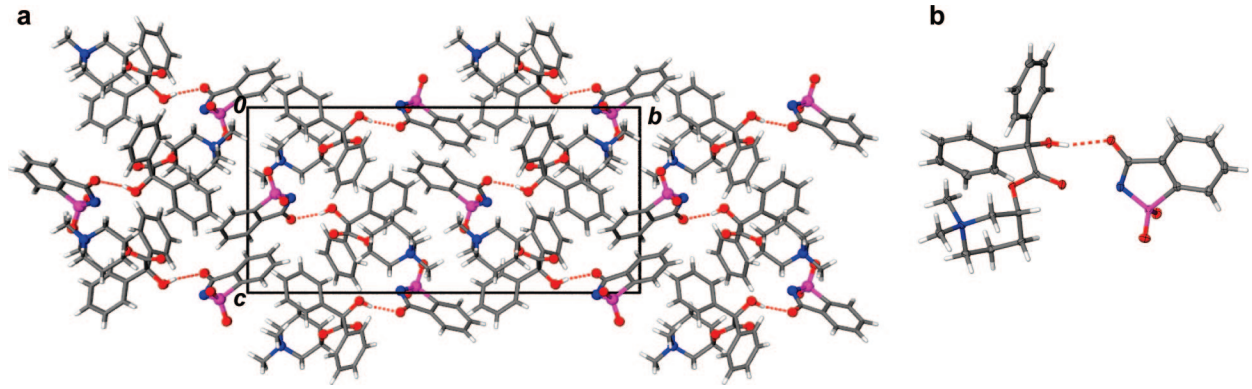


Figure 7. (a) Packing diagram of **5·7** viewed down [−100]. (b) Closeup view of hydrogen bonded cation/anion pair. N, O, and S atoms are depicted as spheres, and cation/anion hydrogen bonds OH···O are indicated by dotted lines. Hydrogen bond geometry: O1−H1···O3A: *d* D−H 0.85(3) Å; *d* D···A 2.752(2) Å; *d* H···A 1.94(3) Å; ∠ DHA 160(3)°.

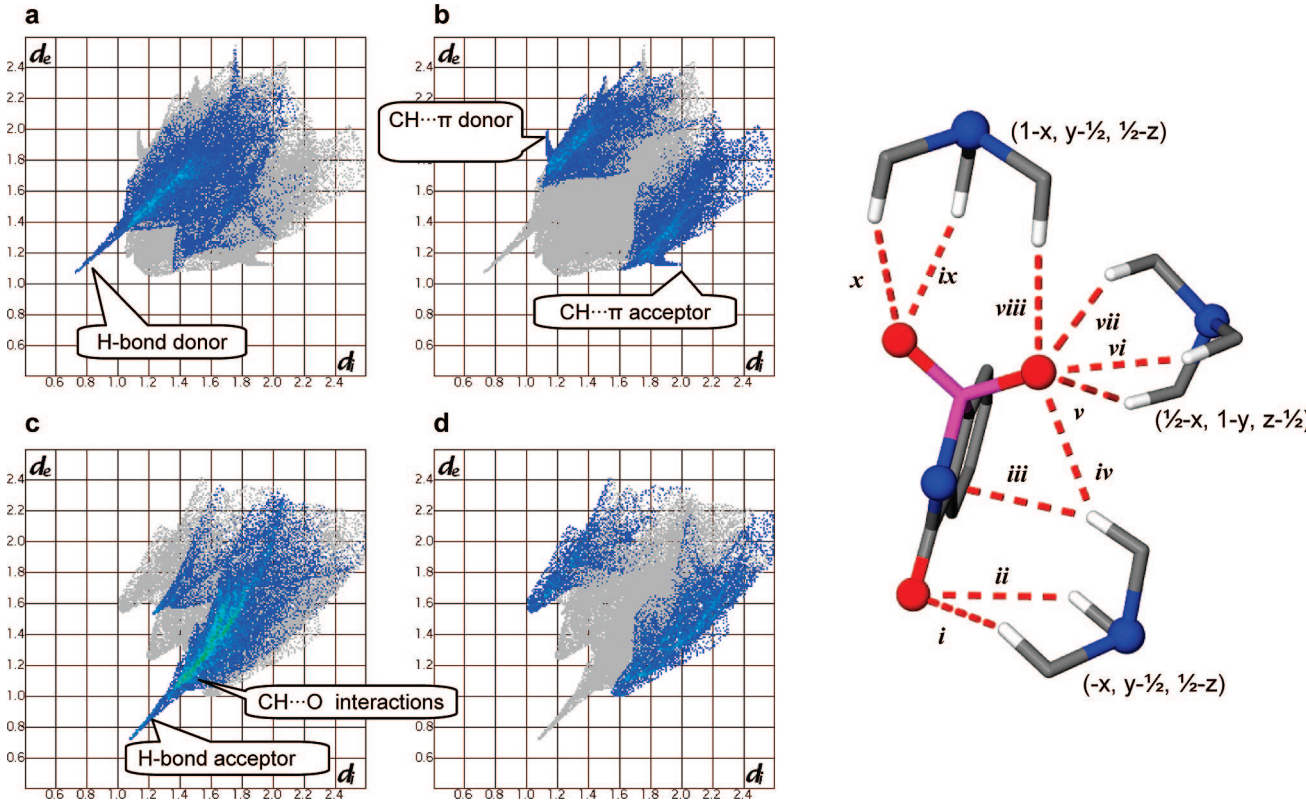


Figure 8. Hirshfeld fingerprint plots. Top: mepenzolate cation (**5**): (a) H···O contacts (including reciprocal contacts); (b) (**5**) H···C contacts (including reciprocal contacts). Bottom: saccharin anion (**7**): (c) H···O contacts (including reciprocal contacts); and (d) (**7**) H···C contacts (including reciprocal contacts). (e) Close contacts between protons borne on carbon atoms α to N^+ and anion O-atoms. Geometry of unique contacts: (i) H19A···O3A 2.52 Å; (ii) H20A···O3A 2.88 Å; (iii) N1A···H21C 2.71 Å; (iv) O1A···H21C 2.66 Å; (v) O1A···H18B 2.79 Å; (vi) O1A···H20C 2.53 Å; (vii) O1A···H21A 2.55 Å; (viii) O1A···H18A 2.61 Å; (ix) O2A···H20B 2.42 Å; (x) O2A···H19B 2.62 Å.

Bonds, Hence Possible AIL Former? Were hydrogen bonds the only driving force for crystallization in these salts, one would predict the combination of propantheline cation (**4**) and saccharinate anion (**7**), a cation/anion pair containing no classical hydrogen bond donor groups, to be a likely AIL former, but crystals of this salt *do* form in the supercooled melt (albeit extremely slowly). Single crystals examined were generally of poor quality, but the refined structure obtained is nonetheless suitable for analysis of packing and intermolecular distances. Analysis of the single crystal structure reveals no hydrogen bonds, as is illustrated in the packing diagram (Figure 9), and analysis of the 2D Hirshfeld fingerprint plots, Figure 10, reveals no short intermolecular contacts.

It is clear, from the packing diagram (Figure 9), that the "flat" face of the propantheline cation forms an offset $\pi\cdots\pi$ interaction with a symmetry related neighbor, and this is highlighted in panels e and f of Figures 10. Such $\pi\cdots\pi$ interactions are not readily discerned from examination of the features of the 2D Hirshfeld fingerprint plot as the atom···atom distances are typically of the order of 3.5 Å and thus obscured in the main body of points representing van der Waals interactions.

This salt may be described, somewhat anthropomorphically, as a "reluctant crystallizer", which nonetheless, once crystalline, exhibits a melting point well above ambient temperature. As with all salts, the most important contributor to lattice energy is, of course, Coulombic interactions between cation and anion,

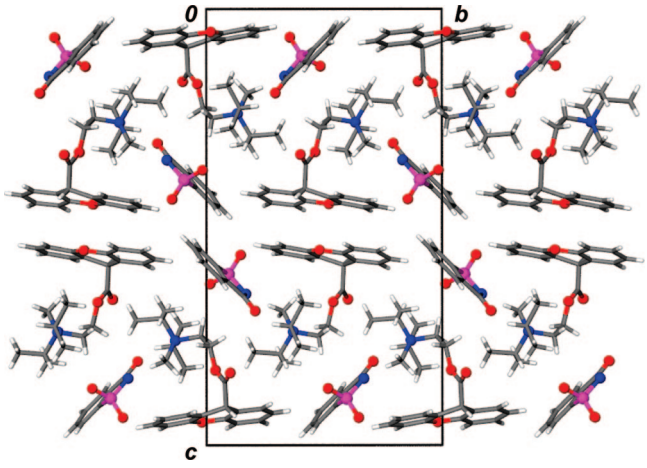


Figure 9. Packing diagram of **4·7** viewed down [1 0 0].

but the poor quality of the crystals formed, which contain a large number of crystal defects (reflected in high mosaicity values in crystal structure analysis) and the reluctance to crystallize, would seem to indicate that highly directional intermolecular (or interionic) interactions may be important in the process of crystallization.

Conclusion

AILs versus Crystalline Solids. Of this small library of salts prepared, all cation/anion combinations, with the potential to form classical hydrogen bonds (i.e., with ions bearing both hydrogen bond donor and acceptor groups), yielded salts that were crystalline solids (albeit with melting points lower than that of the marketed halide salts). In the single instance where both cation and anion bore both donor and acceptor groups, a high melting crystalline solid, with no tendency to supercool, resulted. Of the four cation/anion combinations with no opportunity for the formation of classical hydrogen bonds (because of a dearth of donor groups) one crystallized, while three formed AILs, which could not be induced to crystallize in spite of vigorous attempts. Propantheline saccharinate (**4·7**) appears to be the only salt, in this group, to counter our null hypothesis.

As postulated, complementary functional groups leading to supramolecular synthons associated with strong attractive intermolecular (or interionic) hydrogen bonded interactions must clearly be avoided in the preparation of AILs. However, as has been demonstrated, time and again, in crystal engineering, a wide range of other possible supramolecular synthons must be considered. Clearly, considerations of charge (in this study only monoanions and monocations were considered), charge separation, and shape are significant in determining whether or not a salt exists as a crystalline solid, and, indeed, lattice energy is the ultimate determinant of melting point (and crystallinity). Nonetheless we suggest that an "anti-crystal engineering" approach to the rational choice of ions for the preparation of non-crystallizing salts, including AILs, may provide another application for the knowledge gained in the study of crystal engineering by guiding the choice of complementary ions from the large number of candidates.

Experimental Section

Synthesis. Materials. Benzethonium chloride ($C_{27}H_{42}ClNO_2$, ≥99%, Sigma), choline chloride ($C_{15}H_{11}N_2O_2Cl_1$), mepenzolate bromide ($C_{21}H_{26}BrNO_3$, >99%, Sigma), propantheline bromide ($C_{23}H_{30}NO_3Br$, ≥97%, Sigma), pyridostigmine bromide ($C_9H_{13}BrN_2O_2$, >99%, Sigma), potassium acesulfame ($C_4H_4KNO_4S$, ≥99%, Fluka), silver p-toluenesulfonate ($AgCH_3C_6H_4SO_3$, ≥99%, Aldrich), sodium cyclamate ($C_6H_{12}NNaO_3S$, ≥99%, Merck), sodium 5,5-diphenylhydantoin ($NaC_5H_{14}NO$, >99%, Sigma), and sodium saccharinate

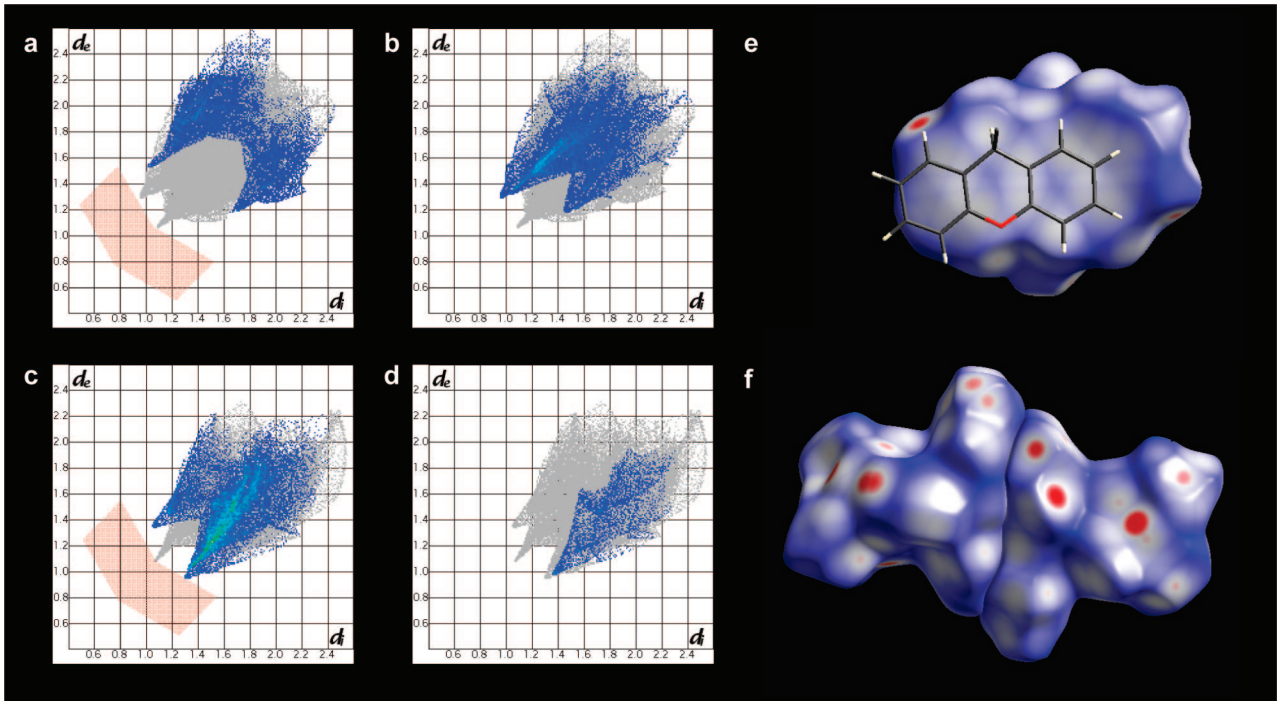


Figure 10. 2D Hirshfeld fingerprint plots for **4·7**. Top, propantheline cation (**4**): (a) C···H contacts (and reciprocal), (b) H···O contacts (and reciprocal). Bottom, saccharinate anion (**7**): (c) O···H contacts (and reciprocal); (d) N···H contacts (and reciprocal, i.e., none). No short-range contacts corresponding to hydrogen bonds, indicated by close approaches of atoms, are noted (these would fall in the pink shaded regions). (e) Hirshfeld surface for **4** with symmetry generated cation (aromatic moiety) overlaid; offset $\pi\cdots\pi$ interaction yields the multicenterd spoked pattern. (f) A pair of cations depicted as their Hirshfeld surfaces.

($C_7H_4NNaO_3S \cdot xH_2O$, ≥99%, Sigma) were used as received without further purification.

^{1}H NMR Spectroscopy. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 200 or 300 MHz on a Bruker DPX-300 and Bruker DPX-200 spectrometers in the deuterated solvents indicated, which were supplied by Cambridge Isotope Laboratories.

MS-ESI. Electrospray Mass Spectrometry (ESI) was carried out on the Micromass Platform II API QMS Electrospray Mass Spectrometer with a cone voltage of 25 or 35 V, using methanol or acetonitrile as the mobile phases. Analyses were conducted in both positive (ES^+) and negative (ES^-) modes.

Halide Analysis. An Ionode S14 bromide selective electrode was used to measure the bromide content for **1·7**, **4·7**, **4·8**, **4·9**, **4·10**, **5·7**, and **5·8**. Calibration curves were constructed in the range 1 ppm to 1000 ppm for aqueous bromide solutions. The limit of detection corresponded to a Br^- ion concentration, in the sample, of 100 ppm and all salts prepared from Br^- salts exhibited residual bromide ion concentrations below this value, except **4·8** in which $Br^- = 210 \pm 10$ ppm. The absence of chloride ions in **2·7** and **3·6** was inferred from the absence of turbidity in a silver nitrate test.

General Synthetic Method. Details of the preparation of each salt and characterization data are provided in the Supporting Information. Salts were prepared by methathesis reactions of equimolar quantities of bromide or chloride salts of the cations with silver or sodium salts of the anions in suitable solvents. Silver salts of saccharinate, acesulfamate, and cyclamate were prepared prior to use and protected from light. Equimolar quantities of silver nitrate and sodium saccharinate, potassium acesulfamate or sodium cyclamate in distilled water were stirred overnight at room temperature. The resultant white precipitates were filtered, washed with cold distilled water, and dried in vacuo overnight at 50−55 °C to provide silver saccharinate, silver acesulfamate, or silver cyclamate.

Dry acetonitrile or dichloromethane were used as the reaction solvents allowing by-product salts to be removed by filtration post-reaction and, in the latter case, to facilitate washing to remove any trace impurities. In all cases, great care was taken to remove by-product salts and to test for halide impurities.

Differential Scanning Calorimetry. DSC experiments were performed on a T.A. Instruments Perkin-Elmer Q100. Samples of mass 5−20 mg were sealed in vented aluminum pans and placed in the furnace with a 50 mL/min dry nitrogen and analyzed in the range −100 to 200 °C (220 °C for **3·6**) at a scan rate of 10 °C min^{-1}. Heating/cooling cycles were repeated three times for each sample. The reference pan was an empty aluminum pan.

Crystallography. Crystallization of **3·6**, **4·9**, **5·7**, and **4·7** was observed in the metathesis product as detailed in the Experimental Section. The reflection intensity data were measured on a Bruker X8 APEX KAPPA CCD single crystal X-ray diffractometer (**4·9**, **5·7**) and a Nonius KAPPA CCD single crystal X-ray diffractometer (**3·6**, **4·7**), using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Crystals were coated with Paratone N oil (Exxon Chemical Co., TX, U.S.A.) immediately after isolation and cooled in a stream of nitrogen vapor on the diffractometer. Structures were solved by direct methods using the program SHELXS-97 and refined by full matrix least-squares refinement on F^2 using SHELXL-97.[25] All non-hydrogen atoms were revealed in the E-map and subsequent difference electron density maps and thus placed and refined anisotropically. All hydrogen atoms were observed in difference syntheses and were either refined isotropically or placed in geometrically idealized positions and constrained to ride on their parent atoms with C−H distances in the range 0.95−1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where $x = 1.5$ for methyl and 1.2 for all other C atoms. Specific details of refinement are contained in the relevant CIF files.

Hirshfeld Analysis. The program CrystalExplorer (version 2.0 and 2.1)[22] was used to render all surfaces and fingerprint plots.

Acknowledgment. P.M.D. is grateful to Monash University for a Monash Graduate Scholarship and Monash International Postgraduate Research Scholarship, D.R.M. is grateful to the Australian Research Council for a Federation Fellowship. We also acknowledge the perspicacious referees' comments received, which enabled us to improve this manuscript in revision.

Supporting Information Available: Full details of synthesis and characterization for each salt; Ortep diagrams with molecular numbering and packing diagrams for **3·6**, **4·7**, **4·9**, and **5·7**, and X-ray crystallographic information files (CIF) for **3·6**, **4·7**, **4·9**, and **5·7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CG8009496

An Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids (AILs)

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Supporting Information

Synthesis and characterisation

Pyridostigmine saccharinate, 1·7

A mixture of pyridostigmine bromide (1.67 g, 6.4 mmol) and silver saccharinate (1.86 g, 6.4 mmol) in distilled water (150 cm^3) was stirred for 2 h, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove precipitated AgBr (dichloromethane was added to aid precipitation of the impurity). After treatment with activated carbon, the mixture was filtered through basic alumina to provide a colourless solution. The solvent was removed *in vacuo* at 80 °C to give the product **1·7** as a yellow oil, which crystallised on standing (1.16 g, 51 %). M.p. 94-96 °C

^{1}H NMR (300 MHz; D_2O) δ 2.86 (s, 3H), 2.97 (s, 3H), 4.31 (s, 3H), 7.60 – 7.70 (m, 4H), 7.91 (t, 1H), 8.17 (d, 1H), 8.54 (d, 1H), 8.66 (s, 1H). MS (ESI): ES+ *m/z* 181.8 (pyridostigmine$^+$, 100 %), ES- *m/z* 180.8 (saccharinate$^-$, 100 %).

Benzethonium saccharinate, 2·7

A solution of benzethonium chloride (2.96 g, 6.61 mmol) and sodium saccharinate (1.63 g, 7.93 mmol) in dichloromethane (80 cm^3) was stirred at 25 °C for 24 h. The precipitated NaCl was removed by filtration, followed by repeated washing of the organic phase with small volumes of water until no Cl^- was detected ($AgNO_3$ test). The organic phase was dried ($MgSO_4$) and concentrated under reduced

pressure before drying *in vacuo,* at 70 °C, for 48 h, giving the product **2·7** as a colourless oil (3.18 g, 86 %).

^{1}H NMR (300 MHz; DMSO-d_6) δ 0.62 (s, 9H), 1.24 (s, 6H), 1.63 (s, 2H), 2.97 (s, 6H), 3.51 (s, 2H), 3.79 (s, 2H), 3.96 (s, 2H), 4.07 (s, 2H), 4.55 (s, 2H), 6.80 (s, 2H), 7.21 (s, 2H), 7.53 (s(b)*, 9H). MS (ESI): ES+ *m/z* 412.4 (Benzethonium$^+$, 100 %), ES- *m/z* 181.9 (Saccharinate$^-$, 100 %).

Choline phenytoin, 3.6

Choline chloride (2.54 g, 18.00 mol) and sodium 5,5-diphenylhydantoin (5 g, 18.00 mmol) were mixed in 100 ml dry acetone and NaCl filtered off. The clear solution was stored at *ca* 4 °C for 3 d, whereupon large colourless crystals of the **3.6** formed and were isolated (4.67 g, 73 %). M.p. 215-217 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 3.12 (s, 9H), 3.44 (m, 2H), 3.86-3.83 (m, 2H), 7.44-7.21 (m, 10H) ppm. MS (ESI): ES+ m/z: 104.0 (Choline$^+$, 100 %), ES- m/z: 251.3 (5,5-diphenylhydantoin $^-$, 100 %).

Propantheline saccharinate, 4·7

A mixture of propantheline bromide (9.72 g, 21.70 mmol) and silver saccharinate (6.29 g, 21.70 mmol) in acetonitrile (150 cm^3) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr. After treatment with activated carbon, the mixture was filtered through basic alumina to provide a colourless solution which was concentrated under reduced pressure giving a yellow oil of **4·7,** which crystallised slowly on standing (10.62 g, 89 %). M.p. 133-135 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.01-1.17 (t, J_1 = 6.0, 12H), 2.66 (s, 3H), 3.43-4.46 (t, J_1 = 4.7, 2H), 3.70-3.79 (m, 2H), 4.35-4.38 (t, J_1 = 4.7, 2H), 5.31 (s, 1H), 7.14-7.22 (m, 4H), 7.35-7.42 (m, 4H), 7.57-7.59 (m, 4H). MS (ESI): ES+ *m/z*: 368.2 (Propantheline$^+$, 100 %), ES- *m/z:* 181.8 (Saccharinate$^-$, 100 %).

Propantheline acesulfamate, 4·8

A mixture of propantheline bromide (3.05 g, 6.80 mmol) and silver acesulfamate (1.84 g, 6.80 mmol) in acetonitrile (150 cm^3) was stirred overnight, protected from light, at room temperature. The reaction

mixture was filtered through Celite to remove AgBr and the solution concentrated under reduced pressure before drying *in vacuo,* at 55 ^{o}C, for 72 h to give the product **4·8** as a colourless oil (3.12 g, 86 %).

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.05-1.18 (t, J_1 = 6.0, 12H), 1.87-1.90 (d, J_1 = 1.0, 3H), 2.66 (s, 3H), 3.43-3.46 (t(b), J_1 = 4.7, 2H), 3.73-3.77 (m, 2H), 4.36-4.39 (t(b), J_1 = 4.7, 2H), 5.24-5.26 (q, J_1 = 1.0, 1H), 5.30 (s, 1H), 7.16-7.22 (m, 4H), 7.40-7.42 (m, 4H). MS (ESI): ES+ *m/z*: 368.1 (Propantheline^{+}, 100 %), ES- *m/z:* 161.7 (Acesulfamate^{-}, 100 %).

Propantheline cyclamate, 4·9

A mixture of propantheline bromide (2.46 g, 5.49 mmol) and silver cyclamate (1.57 g, 5.49 mmol) in acetonitrile (150 cm^{3}) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr and the solution concentrated to leave a clear viscous residue, which was dried *in vacuo* at 55 ^{o}C for 72 h to yield **4·9** as a colourless oil, , which crystallised on standing (2.76 g, 92 %). M.p. 133-137 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 0.95-1.21 (m, 5H) 1.14-1.19 (t, *J* 6.0), 1.47-1.52 (m, 1H), 1.57-1.64 (m, 2H), 1.85-1.91 (m, 2H), 2.66 (s, 3H), 2.81-2.91 (m, 1H), 3.43-3.47 (t(b), J_1 = 4.7, 2H), 3.73-3.78 (m, 2H), 4.36-4.39 (t(b), J_1 = 4.7, 2H), 5.31 (s, 1H), 7.17-7.22 (m, 4H), 7.35-7.42 (m, 4H). MS (ESI): ES+ *m/z*: 368.1 (Propantheline^{+}, 100 %), ES- *m/z:* 177.8 (Cyclamate^{-}, 100 %).

Propantheline *p*-toluenesulfonate, 4·10

A mixture of propantheline bromide (1.55 g, 5.56 mmol) and silver *p*-toluenesulfonate (2.49 g, 5.56 mmol) in acetonitrile (100 cm^{3}) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr and the solution concentrated to leave a clear viscous residue, which was dried *in vacuo* at 55 ^{o}C for 72 h yielding **4·10** as a colourless oil (2.42 g, 81 %).

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.14-1.18 (t, J_1 = 6.0, 12H), 2.29 (s, 3H), 2.66 (s, 3H), 3.42-3.45 (t(b), J_1 = 4.7, 2H), 3.70-3.79 (m, 2H), 4.36-4.39 (t(b), J_1 = 4.7, 2H), 5.31 (s, 1H), 7.09-7.12 (m, 2H),

7.12-7.22 (m, 4H), 7.39-7.40 (m, 4H), 7.46-7.49 (m, 2H). MS (ESI): ES+ *m/z*: 368.1 (Propantheline$^+$, 100 %), ES- *m/z:* 170.8 (*p*-Toluenesulfonate$^-$, 100 %).

Mepenzolate saccharinate, 5·7

A mixture of mepenzolate bromide (5.80 g, 14.00 mmol) and silver saccharinate (4.0 g, 14.00 mmol) in dry acetonitrile (120 cm^3) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr and the solution concentrated to give a colourless oil, which was dried *in vacuo* at 55 °C for 72 h at which point the product crystallized. The product was successfully recrystallized using acetonitrile (excess and heating), resulting in colourless crystals (4.83 g, 66 %). M.p. 187-189 °C.

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.85-1.69 (m, 4H), 2.81 (s, 3H), 3.08 (s, 3H), 3.32-3.44 (m, 2H), 3.53 (d, J_1 = 13.5 Hz, 1H), 3.42 (d, J_1 = 13.5 Hz, 1H), 5.30 (m, 1H), 6.80 (s, 1H), 7.31-7.40 (m, 10H), 7.58-7.61 (m, 4H) ppm. MS (EI): ES+ m/z: 340.2 (Mepenzolate$^+$, 100%), ES$^-$ m/z 181.8 (Saccharinate$^-$, 100%).

Mepenzolate acesulfamate, 5·8

A mixture of mepenzolate bromide (1.56 g, 3.70 mmol) and silver acesulfamate (1.0 g, 3.70 mmol) in acetonitrile (150 cm^3) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite and 0.45 and 0.20 μm membrane filters to remove AgBr. The solvent was evaporated to give a colourless oil, which crystallized within 1 h giving **5·8** as colourless crystals (1.63 g, 88 %). M.p. 135-137 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.68-1.85 (m, 4H), 1.89-1.90 (d, J_1 = 1.0, 3H), 2.82 (s, 3H), 3.08 (s, 3H), 3.33-3.35 (m, 2H), 3.48-3.56 (d.d, J_1 = 13.45, J_2 = 5.02 Hz, 1H), 3.57-3.62 (d.d, J_1 = 13.45, J_2 = 5.02 Hz, 1H), 5.27-5.30 (m, 1H), 5.26-5.27 (q, J_1 = 1.0, 1H), 6.81 (s, 1H), 7.32-7.38 (m, 10H). MS (ESI): ES+ *m/z*: 340.2 (Mepenzolate$^+$, 100 %), ES- *m/z:* 161.9 (Acesulfamate$^-$, 100 %).

Crystallographic ORTEP and packing diagrams

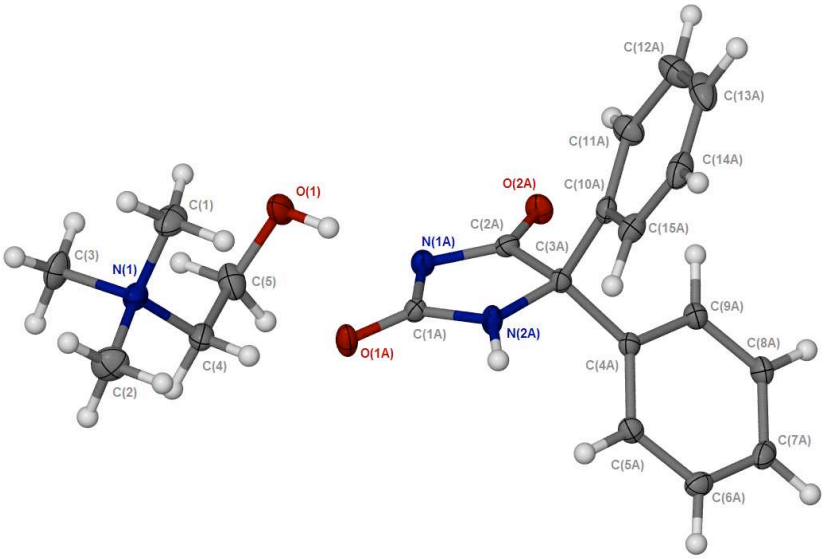


Figure 1a. The asymmetric unit of *choline phenytoin* shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

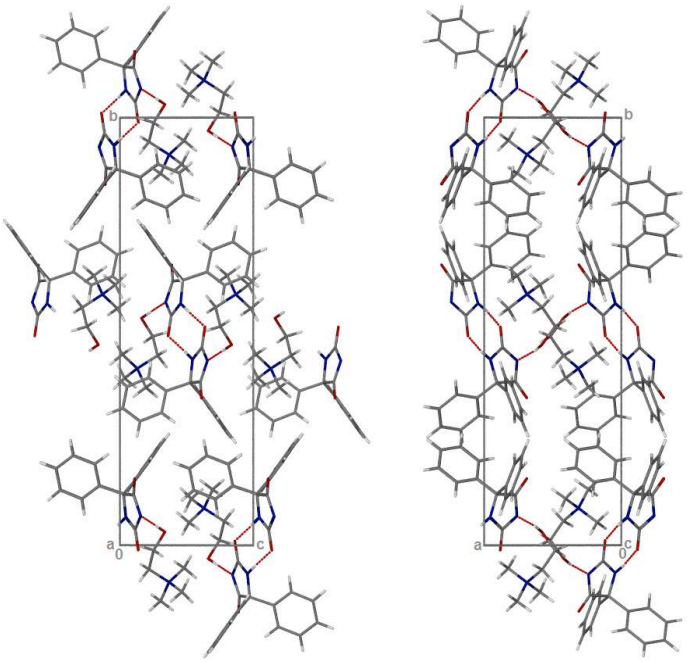


Figure 1b. Stick representation of the unit cell contents of *choline phenytoin* viewed down *b**, hydrogen bonding is indicated by red dashed lines.

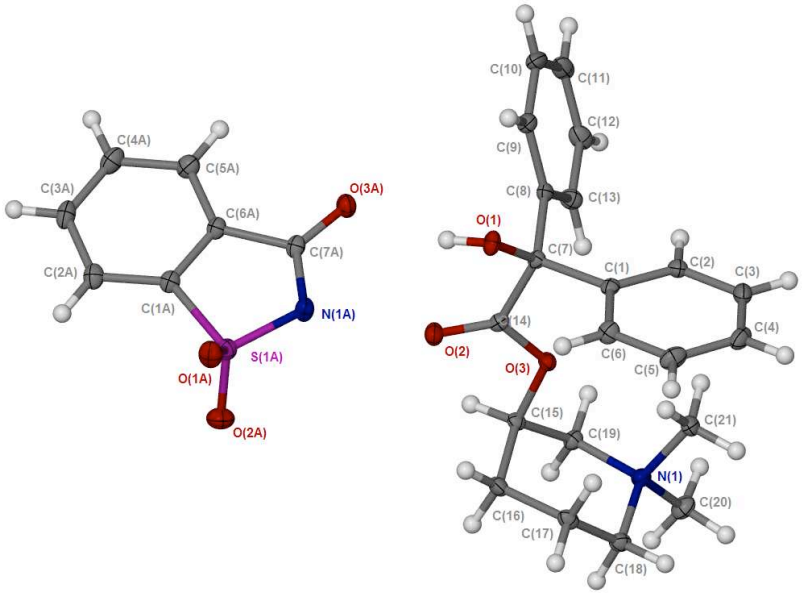


Figure 2a. The asymmetric unit of *mepenzolate saccharinate* shown with 50% thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

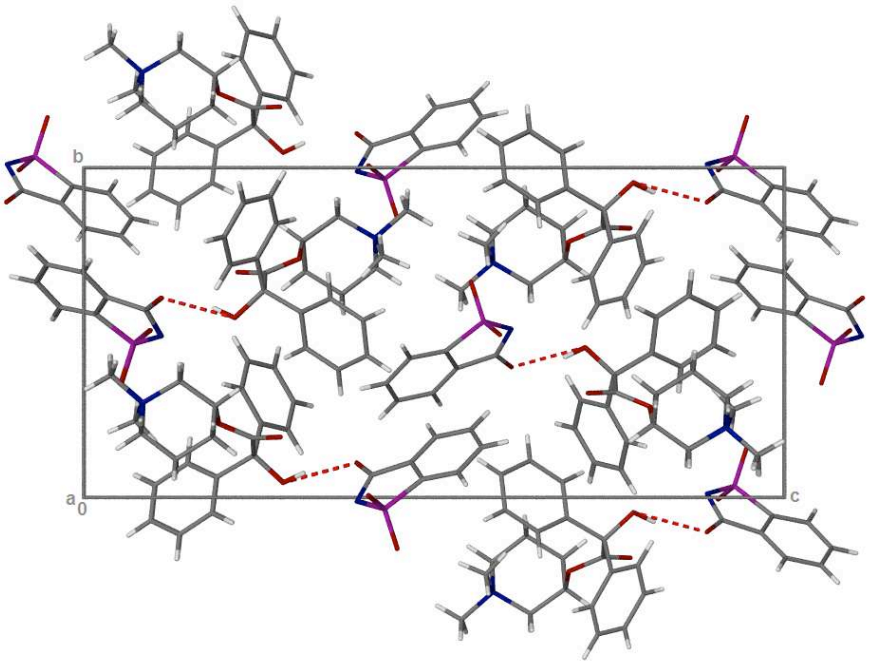


Figure 2b. Packing diagram of *mepenzolate saccharinate* with hydrogen bonding indicated by dashed red lines.

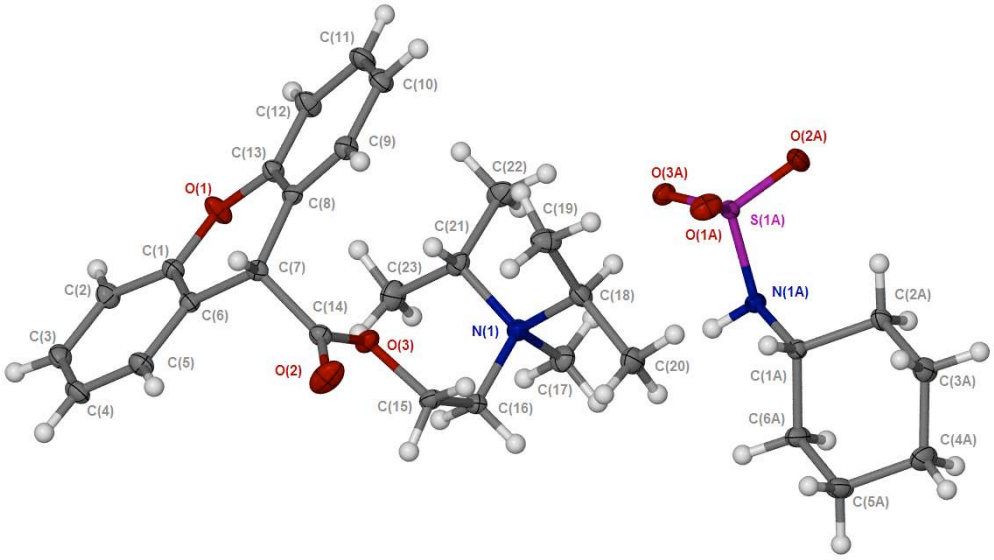


Figure 3a. The asymmetric unit of *propantheline cyclamate* shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

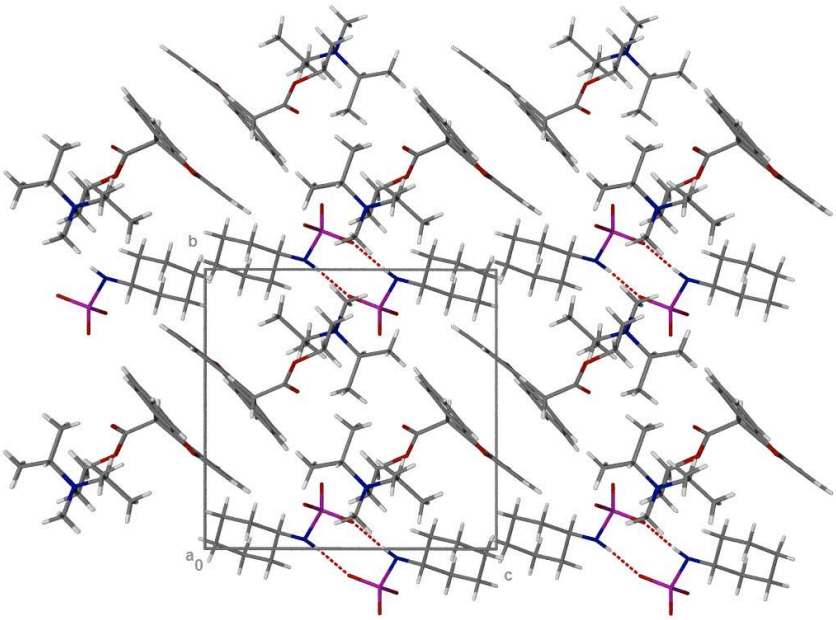


Figure 3b. Packing diagram of *propantheline cyclamate* viewed down the *a*-axis with hydrogen bonding indicated by dashed red lines.

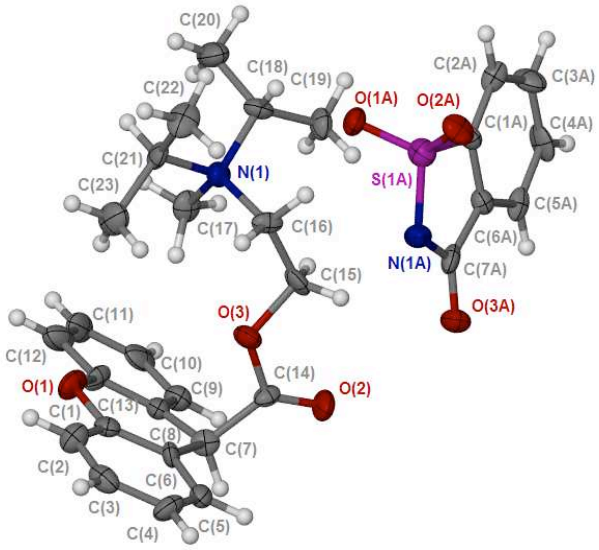


Figure 4a. The asymmetric unit of *propantheline saccharinate* shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

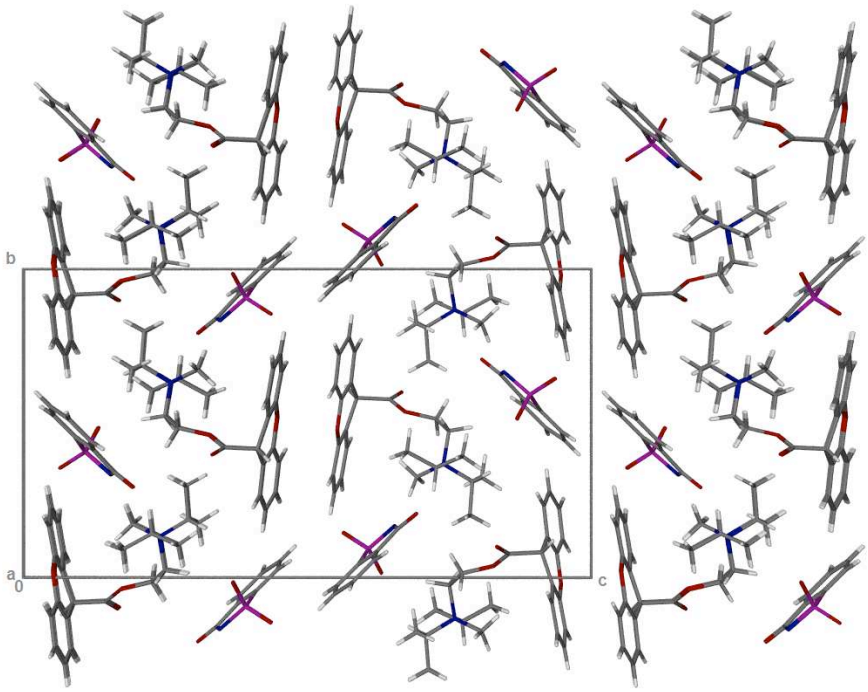
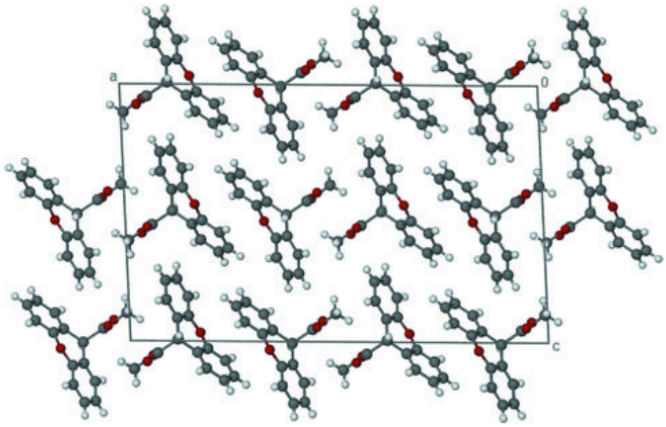


Figure 4b. Packing diagram of *propantheline saccharinate* viewed down the *a*-axis with hydrogen bonding indicated with dashed red lines.

Publication 2.2

Methyl 9*H*-xanthene-9-carboxylate

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Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Methyl 9*H*-xanthene-9-carboxylate

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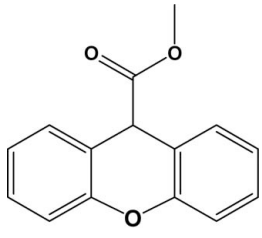
Received 20 February 2008; accepted 4 March 2008

Key indicators: single-crystal X-ray study; T = 123 K; mean σ(C–C) = 0.003 Å; R factor = 0.051; wR factor = 0.106; data-to-parameter ratio = 16.1.

The title compound, $C_{15}H_{12}O_3$, was obtained unintentionally as the by-product of an attempted recrystallization from methanol of propantheline bromide, an antimuscarinic drug. The xanthone unit is folded, with a dihedral angle of 24.81 (9)° between the benzene rings. The ester substituent adopts a *trans* staggered conformation, with a C—C—O—C torsion angle of 178.4 (1)°. The molecules pack in distinct layers, facilitated by C—H···π and weak π–π ring interactions. A weak C—H···O interaction also occurs; however, no classical hydrogen bonding is observed.

Related literature

For details of the first spectroscopic evidence of the transesterification of propantheline bromide by methanol to 9*H*-xanthene-9-carboxylic acid methyl ester, see: Avdovich *et al.* (1986). For a description of the comparative effectiveness of propantheline bromide for the treatment of neurogenic detrusor overactivity, see: George *et al.* (2007).



Experimental

Crystal data

$C_{15}H_{12}O_3$
M_r = 240.25
Monoclinic, $C2/c$
a = 25.6601 (16) Å
b = 5.7624 (3) Å
c = 15.7578 (9) Å
β = 92.933 (4)°
V = 2327.0 (2) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 123 (2) K
0.50 × 0.50 × 0.50 mm

Data collection

Bruker Kappa APEXII diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2005)
T_{min} = 0.932, T_{max} = 0.954
11906 measured reflections
2672 independent reflections
1985 reflections with $I > 2\sigma(I)$
R_{int} = 0.050

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.106
S = 1.05
2672 reflections
166 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C15—H15C···O2^{i}	0.98	2.53	3.407 (3)	149
C3—H3···$Cg2^{ii}$	0.95	2.95	3.668 (2)	133
C11—H11···$Cg1^{iii}$	0.95	3.18	3.825 (2)	127
C15—H15B···$Cg1^{iv}$	0.98	3.06	3.432 (2)	104
C15—H15C···$Cg1^{iv}$	0.98	3.11	3.432 (2)	101

Symmetry codes: (i) $x, y-1, z$; (ii) $x, -y, z-\frac{1}{2}$; (iii) $-x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iv) $-x+1, -y, -z+1$. $Cg1$ is the centroid of ring C1–C6; $Cg2$ is the centroid of ring C8–C13.

Table 2
Geometrical parameters (Å, °) of the inter-ring π—π interactions.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
$Cg1$	$Cg2$	5.590 (1)	59.44	$x, 1-y, -\frac{1}{2}+z$
$Cg1$	$Cg2$	4.944 (1)	24.81	$\frac{1}{2}-x, \frac{1}{2}-y, 1-z$
$Cg2$	$Cg1$	4.863 (1)	59.44	$x, -y, \frac{1}{2}+z$
$Cg2$	$Cg2$	3.684 (1)	0.03	$\frac{1}{2}-x, \frac{1}{2}-y, 1-z$

α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J. $Cg1$ is the centroid of ring C1–C6; $Cg2$ is the centroid of ring C8–C13.

Data collection: *APEX2* (Bruker, 2005); cell refinement: *APEX2*; data reduction: *APEX2*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *POV-RAY for Windows* (Persistence of Vision, 1999); software used to prepare material for publication: *PLATON* (Spek, 2003).

PMD is grateful to Monash University for the Monash Graduate Scholarship and Monash International Postgraduate Research Scholarship, and to Monash University, School of Chemistry for funding for JT.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: WN2242).

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supplementary materials

Acta Cryst. (2008). E**64**, o854 [**doi:10.1107/S1600536808005990**]

Methyl 9*H*-xanthene-9-carboxylate

P. M. Dean, J. Turanjanin and D. R. MacFarlane

Comment

It was found that propantheline bromide (George *et al.*, 2007) undergoes facile transesterification by methanol to produce the by-product 9*H*-xanthene-9-carboxylic acid methyl ester (Avdovich *et al.*, 1986). Surprisingly, the structural elucidation of this analogue (Fig. 1) has not been reported in the literature until now. Now the structural determination and analysis is briefly described.

The xanthone unit is bent, with the aromatic planes oriented to each other by an interplanar angle of 24.81 (9)°. The ester substituent adopts a *trans* staggered conformation with a C7—C14—O3—C15 torsion angle of 178.4 (1)°. Additionally, as is typical of an ester, the O3—C14 distance is 1.326 (2) Å and the O3—C15 distance is 1.448 (2) Å, indicating the sp^2 hybridization of C14.

The overall packing is shown in Fig. 2. Molecules are related by centres of symmetry, resulting in a head-to-head arrangement, that packs in aromatic and non-aromatic layers lying parallel to the (100) plane. Fig. 2 displays the orientation of the molecules, facilitating the weak C—H···O hydrogen bonding between the methyl and carbonyl groups (distance: C15—H15C···O2^{i} (i = *x*,*y* - 1,*z*) 3.407 (2) Å - see Table 1) and the C—H···π and weak π···π ring interactions (Table 2). A short range contact, 2.683 (2) Å, also occurs between the aromatic C4—H4 and the carbonyl oxygen O2 (distance: C4—H4···O2^{ii} (ii = *x*,1 - *y*,-1/2 + *z*).

Experimental

The title compound was obtained unintentionally as the product of an attempted recrystallization of propantheline bromide (50 mg) in methanol (2 ml) at room temperature. Crystals resulted after 6 days; these were coated with Paratone N oil (Exxon Chemical Co., TX, USA) immediately after isolation and cooled in a stream of nitrogen vapour on the diffractometer. Melting point: 360.7 K.

Refinement

All H atoms were observed in difference syntheses and were then placed in geometrically idealized positions and constrained to ride on their parent atoms with C—H distances in the range 0.95–1.00 Å. U_{iso}(H) = xU_{eq}(C), where x = 1.5 for methyl and 1.2 for all other C atoms.

Figures

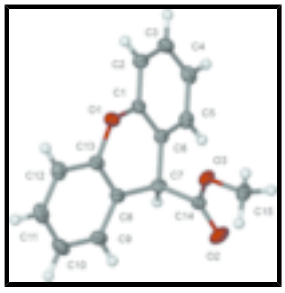


Fig. 1. The molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level and hydrogen atoms as spheres of arbitrary radius.

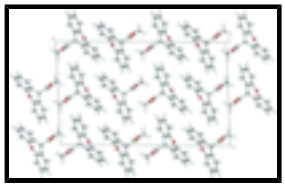


Fig. 2. A ball-and-stick representation of the unit-cell contents, viewed down the *b* axis.

Methyl 9*H*-xanthene-9-carboxylate

Crystal data

$C_{15}H_{12}O_3$	F_{000} = 1008
M_r = 240.25	D_x = 1.372 Mg m^{-3}
Monoclinic, *C*2/*c*	Melting point: 360.7 K
Hall symbol: -C 2yc	Mo *K*α radiation λ = 0.71073 Å
a = 25.6601 (16) Å	Cell parameters from 1829 reflections
b = 5.7624 (3) Å	θ = 2.6–25.8º
c = 15.7578 (9) Å	μ = 0.10 mm^{-1}
β = 92.933 (4)º	*T* = 123 (2) K
V = 2327.0 (2) Å^3	Prismatic, colourless
Z = 8	0.50 × 0.50 × 0.50 mm

Data collection

Bruker KappaAPEXII diffractometer	2672 independent reflections
Radiation source: fine-focus sealed tube	1985 reflections with $I > 2\sigma(I)$
Monochromator: graphite	R_{int} = 0.050
T = 123(2) K	θ_{max} = 27.5º
0.5° frames in φ and ω scans	θ_{min} = 1.6º
Absorption correction: multi-scan (SADABS; Bruker, 2005)	*h* = −33→33
T_{min} = 0.932, T_{max} = 0.954	*k* = −7→7
11906 measured reflections	*l* = −20→20

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.050$	H-atom parameters constrained
$wR(F^2) = 0.106$	$w = 1/[\sigma^2(F_o^2) + (0.0212P)^2 + 2.7981P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.06$	$(\Delta/\sigma)_{max} < 0.001$
2672 reflections	$\Delta\rho_{max} = 0.20$ e Å^{-3}
166 parameters	$\Delta\rho_{min} = -0.21$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	Extinction correction: none

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.33199 (5)	−0.0433 (2)	0.46758 (8)	0.0291 (4)
O3	0.44741 (5)	0.1331 (2)	0.55663 (8)	0.0317 (4)
C1	0.35919 (6)	0.0509 (3)	0.40209 (11)	0.0246 (4)
O2	0.46182 (5)	0.5104 (2)	0.57999 (10)	0.0460 (5)
C5	0.41061 (7)	0.3418 (3)	0.33969 (11)	0.0296 (5)
H5	0.4285	0.4860	0.3432	0.036*
C8	0.34065 (6)	0.3209 (3)	0.54356 (11)	0.0270 (5)
C14	0.43644 (7)	0.3568 (3)	0.54706 (11)	0.0269 (4)
C9	0.32151 (7)	0.4651 (4)	0.60572 (11)	0.0340 (5)
H9	0.3374	0.6117	0.6166	0.041*
C4	0.40994 (7)	0.2167 (4)	0.26464 (12)	0.0344 (5)
H4	0.4275	0.2744	0.2174	0.041*
C2	0.35812 (7)	−0.0765 (3)	0.32741 (11)	0.0296 (5)
H2	0.3400	−0.2202	0.3236	0.036*
C12	0.27490 (7)	0.0372 (4)	0.57561 (11)	0.0320 (5)
H12	0.2591	−0.1099	0.5653	0.038*
C10	0.27969 (7)	0.3977 (4)	0.65182 (12)	0.0404 (6)
H10	0.2668	0.4983	0.6936	0.048*

C11	0.25674 (7)	0.1837 (4)	0.63695 (12)	0.0383 (6)
H11	0.2282	0.1369	0.6691	0.046*
C3	0.38359 (7)	0.0071 (4)	0.25876 (12)	0.0336 (5)
H3	0.3831	−0.0792	0.2074	0.040*
C6	0.38552 (6)	0.2600 (3)	0.41010 (11)	0.0255 (4)
C7	0.38629 (7)	0.3930 (3)	0.49288 (11)	0.0265 (5)
H7	0.3828	0.5622	0.4796	0.032*
C13	0.31655 (6)	0.1086 (3)	0.52950 (11)	0.0266 (4)
C15	0.49380 (7)	0.0797 (4)	0.60921 (12)	0.0349 (5)
H15A	0.4911	0.1505	0.6654	0.052*
H15B	0.5245	0.1415	0.5825	0.052*
H15C	0.4972	−0.0889	0.6154	0.052*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0329 (7)	0.0252 (7)	0.0294 (7)	0.0015 (5)	0.0027 (5)	−0.0008 (5)
O3	0.0293 (7)	0.0257 (7)	0.0385 (8)	0.0029 (6)	−0.0121 (5)	−0.0011 (6)
C1	0.0234 (8)	0.0252 (10)	0.0251 (9)	0.0051 (7)	−0.0011 (7)	−0.0002 (7)
O2	0.0419 (8)	0.0328 (8)	0.0611 (10)	−0.0017 (7)	−0.0166 (7)	−0.0116 (7)
C5	0.0264 (9)	0.0298 (10)	0.0324 (10)	0.0028 (8)	−0.0027 (7)	0.0057 (8)
C8	0.0260 (9)	0.0296 (10)	0.0248 (9)	0.0088 (7)	−0.0044 (7)	−0.0016 (7)
C14	0.0281 (9)	0.0249 (10)	0.0276 (9)	0.0000 (8)	0.0010 (7)	−0.0043 (8)
C9	0.0329 (10)	0.0396 (12)	0.0284 (10)	0.0133 (9)	−0.0089 (8)	−0.0074 (8)
C4	0.0309 (10)	0.0457 (13)	0.0267 (10)	0.0086 (9)	0.0019 (7)	0.0050 (9)
C2	0.0288 (9)	0.0280 (10)	0.0314 (10)	0.0060 (8)	−0.0048 (7)	−0.0042 (8)
C12	0.0286 (9)	0.0384 (11)	0.0285 (10)	0.0052 (8)	−0.0038 (7)	0.0087 (8)
C10	0.0360 (10)	0.0603 (15)	0.0245 (10)	0.0203 (10)	−0.0028 (8)	−0.0072 (9)
C11	0.0298 (10)	0.0604 (15)	0.0246 (10)	0.0124 (10)	0.0005 (7)	0.0091 (9)
C3	0.0321 (10)	0.0426 (12)	0.0254 (10)	0.0111 (9)	−0.0044 (7)	−0.0061 (8)
C6	0.0248 (8)	0.0244 (10)	0.0267 (9)	0.0050 (7)	−0.0040 (7)	0.0002 (7)
C7	0.0310 (9)	0.0204 (9)	0.0277 (9)	0.0051 (7)	−0.0037 (7)	−0.0015 (7)
C13	0.0279 (9)	0.0303 (10)	0.0210 (9)	0.0082 (8)	−0.0030 (7)	0.0017 (7)
C15	0.0261 (9)	0.0417 (12)	0.0361 (11)	0.0036 (8)	−0.0071 (8)	0.0010 (9)

Geometric parameters (Å, °)

O1—C13	1.384 (2)	C4—C3	1.385 (3)
O1—C1	1.386 (2)	C4—H4	0.9500
O3—C14	1.326 (2)	C2—C3	1.379 (3)
O3—C15	1.448 (2)	C2—H2	0.9500
C1—C6	1.384 (2)	C12—C11	1.382 (3)
C1—C2	1.386 (2)	C12—C13	1.385 (2)
O2—C14	1.201 (2)	C12—H12	0.9500
C5—C4	1.384 (3)	C10—C11	1.381 (3)
C5—C6	1.393 (2)	C10—H10	0.9500
C5—H5	0.9500	C11—H11	0.9500
C8—C13	1.384 (3)	C3—H3	0.9500
C8—C9	1.393 (2)	C6—C7	1.512 (2)

C8—C7	1.509 (2)	C7—H7	1.0000
C14—C7	1.522 (2)	C15—H15A	0.9800
C9—C10	1.382 (3)	C15—H15B	0.9800
C9—H9	0.9500	C15—H15C	0.9800
C13—O1—C1	116.79 (14)	C11—C10—H10	120.1
C14—O3—C15	115.78 (14)	C9—C10—H10	120.1
C6—C1—O1	122.37 (15)	C10—C11—C12	120.52 (18)
C6—C1—C2	121.80 (16)	C10—C11—H11	119.7
O1—C1—C2	115.83 (16)	C12—C11—H11	119.7
C4—C5—C6	121.21 (18)	C2—C3—C4	120.11 (17)
C4—C5—H5	119.4	C2—C3—H3	119.9
C6—C5—H5	119.4	C4—C3—H3	119.9
C13—C8—C9	117.98 (17)	C1—C6—C5	117.73 (16)
C13—C8—C7	120.76 (15)	C1—C6—C7	120.31 (16)
C9—C8—C7	121.26 (17)	C5—C6—C7	121.95 (16)
O2—C14—O3	124.06 (17)	C8—C7—C6	109.91 (15)
O2—C14—C7	124.42 (16)	C8—C7—C14	108.79 (14)
O3—C14—C7	111.45 (15)	C6—C7—C14	112.80 (14)
C10—C9—C8	120.9 (2)	C8—C7—H7	108.4
C10—C9—H9	119.6	C6—C7—H7	108.4
C8—C9—H9	119.6	C14—C7—H7	108.4
C5—C4—C3	119.72 (18)	C8—C13—O1	122.03 (15)
C5—C4—H4	120.1	C8—C13—C12	121.96 (17)
C3—C4—H4	120.1	O1—C13—C12	116.00 (17)
C3—C2—C1	119.42 (18)	O3—C15—H15A	109.5
C3—C2—H2	120.3	O3—C15—H15B	109.5
C1—C2—H2	120.3	H15A—C15—H15B	109.5
C11—C12—C13	118.81 (19)	O3—C15—H15C	109.5
C11—C12—H12	120.6	H15A—C15—H15C	109.5
C13—C12—H12	120.6	H15B—C15—H15C	109.5
C11—C10—C9	119.83 (18)		
C13—O1—C1—C6	21.8 (2)	C13—C8—C7—C6	22.5 (2)
C13—O1—C1—C2	−157.71 (15)	C9—C8—C7—C6	−157.52 (16)
C15—O3—C14—O2	−1.3 (3)	C13—C8—C7—C14	−101.48 (18)
C15—O3—C14—C7	−178.43 (14)	C9—C8—C7—C14	78.5 (2)
C13—C8—C9—C10	0.0 (3)	C1—C6—C7—C8	−22.1 (2)
C7—C8—C9—C10	179.99 (16)	C5—C6—C7—C8	157.52 (16)
C6—C5—C4—C3	0.5 (3)	C1—C6—C7—C14	99.48 (19)
C6—C1—C2—C3	−0.5 (3)	C5—C6—C7—C14	−80.9 (2)
O1—C1—C2—C3	179.03 (15)	O2—C14—C7—C8	−105.6 (2)
C8—C9—C10—C11	0.6 (3)	O3—C14—C7—C8	71.48 (18)
C9—C10—C11—C12	−0.7 (3)	O2—C14—C7—C6	132.14 (19)
C13—C12—C11—C10	0.1 (3)	O3—C14—C7—C6	−50.7 (2)
C1—C2—C3—C4	0.0 (3)	C9—C8—C13—O1	178.26 (15)
C5—C4—C3—C2	0.0 (3)	C7—C8—C13—O1	−1.7 (2)
O1—C1—C6—C5	−178.53 (15)	C9—C8—C13—C12	−0.6 (3)
C2—C1—C6—C5	1.0 (2)	C7—C8—C13—C12	179.41 (16)
O1—C1—C6—C7	1.1 (2)	C1—O1—C13—C8	−21.5 (2)

C2—C1—C6—C7	−179.37 (15)	C1—O1—C13—C12	157.43 (15)
C4—C5—C6—C1	−1.0 (2)	C11—C12—C13—C8	0.5 (3)
C4—C5—C6—C7	179.39 (16)	C11—C12—C13—O1	−178.37 (15)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C15—H15C···O2^{i}	0.98	2.53	3.407 (3)	149
C3—H3···Cg2^{ii}	0.95	2.95	3.668 (2)	133
C11—H11···Cg1^{iii}	0.95	3.18	3.825 (2)	127
C15—H15B···Cg1^{iv}	0.98	3.06	3.432 (2)	104
C15—H15C···Cg1^{iv}	0.98	3.11	3.432 (2)	101

Symmetry codes: (i) *x*, *y*−1, *z*; (ii) *x*, −*y*, *z*−1/2; (iii) −*x*+1/2, −*y*+1/2, −*z*+1; (iv) −*x*+1, −*y*, −*z*+1.

Table 2

Geometrical parameters (Å, °) of the inter-ring π—π interactions. α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
Cg1	Cg2	5.590 (1)	59.44	x,1-y,-1/2+z
Cg1	Cg2	4.944 (1)	24.81	1/2-x,1/2-y,1-z
Cg2	Cg1	4.863 (1)	59.44	x,-y,1/2+z
Cg2	Cg2	3.684 (1)	0.03	1/2-x,1/2-y,1-z

Notes: Cg1 is the centroid of ring C1/C6; Cg2 is the centroid of ring C8/C13.

Fig. 1

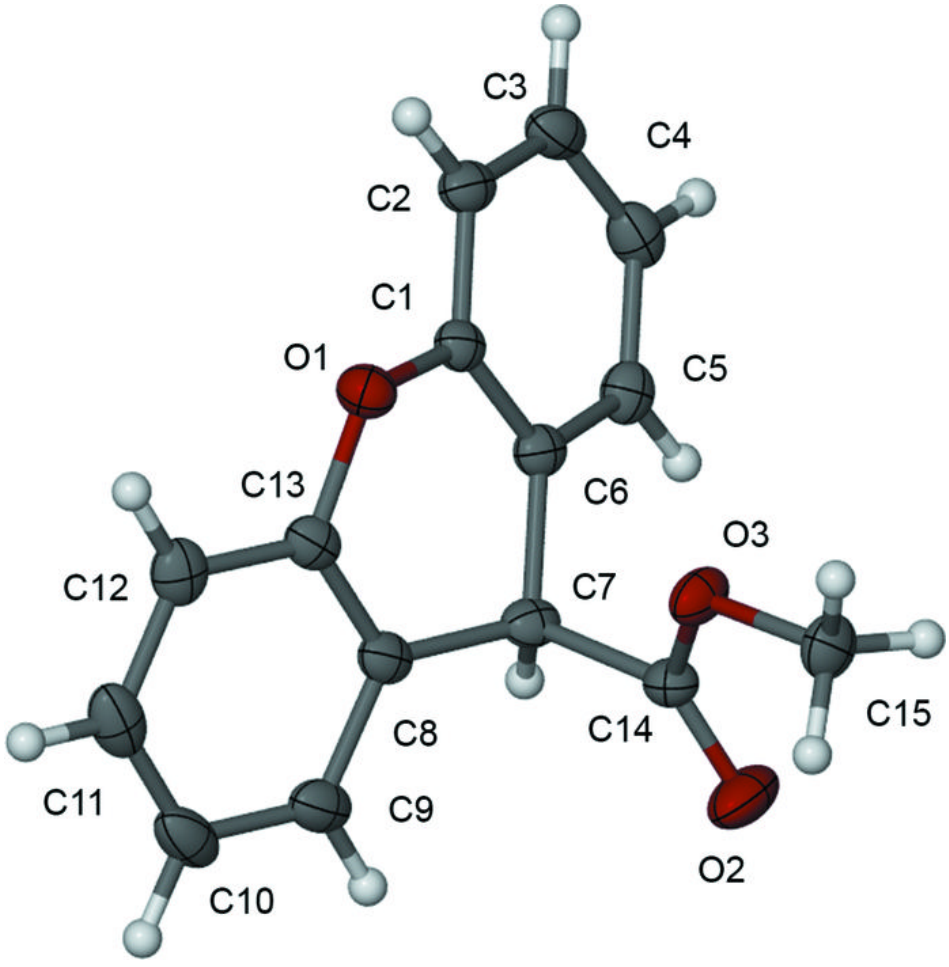
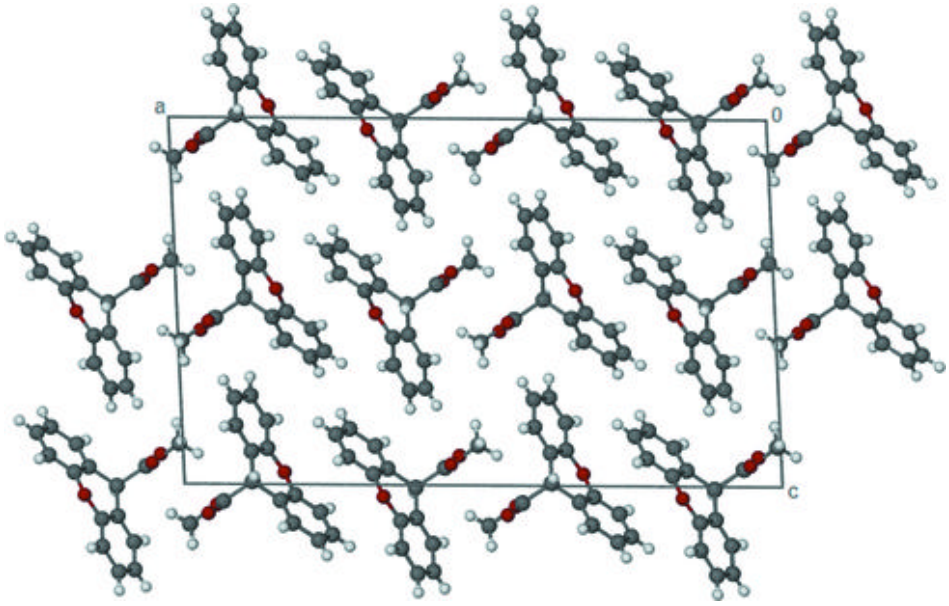


Fig. 2



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CHAPTER THREE

PHARMACEUTICALLY ACTIVE PROTIC IONIC LIQUIDS

CHAPTER THREE – PHARMACEUTICALLY ACTIVE *PROTIC* IONIC LIQUIDS

Section 3.1 Specific Declaration

Monash University

Declaration for Thesis Chapter Three

Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Initiation, key ideas, synthesis and characterisation of compounds, experimentation, crystallographic analysis, development and write up of manuscript including supplementary information	90% + 85 % + 95 %

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Pamela M. Dean	*Publication 3.2* Crystallographic data acquisition and analysis	-
Ekaterina I. Izgorodina	*Publication 3.1, 3.2* Key ideas, computational data and part write-up, final drafting	-
Douglas R. MacFarlane	*Publication 3.1, 3.2, 3.3* Key ideas, final drafting	-

Candidate's Signature	Jelena Stoimenovski (neé Turanjanin)	**Date**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	School of Chemistry, Monash University, Clayton, Victoria, 3800, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted] Pamela M. Dean	**Date** 08/07/2011
Signature 2	[redacted] Ekaterina I. Izgorodina	08/07/2011
Signature 3	[redacted] Douglas R. MacFarlane	25/07/2011

Section 3.2 General Overview

The physical, chemical and biological characteristics of a drug can be modified by salt formation without modifying its structure.[2] A number of active pharmaceutical ingredients (APIs) are acids and bases capable of forming salts. Since most organic acids and bases are water insoluble, converting them into a salt form may render them more water-soluble and hence more bioavailable. Therefore, as salt formation is a means of modifying important properties of a protic drug substance, a basic understanding of the ionization equilibria and the degree of proton transfer is necessary in order to successfully apply this tool. This is the main theme of this chapter.

Publication 3.1 and Publication 3.2 explore the proton transfer concept in AILs both via experimental data and computational studies. Publication 3.1 is based on model amines that are not pharmaceutically active but allow a number of important comparisons to be made. A clear relationship between the use of primary and tertiary amines (of comparable pK_a^{aq} values), with a common acid, and the degree of proton transfer is established.

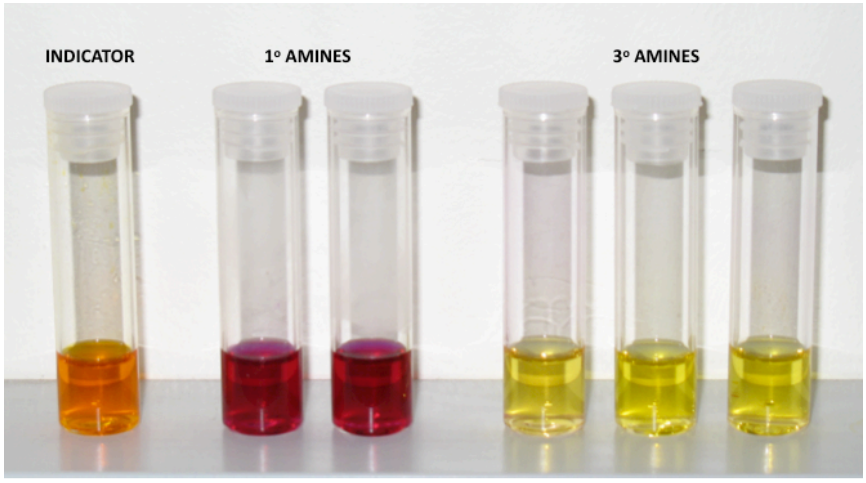
Publication 3.2 is focused on those that are active ILs. The paper shows that there is substantial proton transfer in all of the cases studied. However, Walden plot analysis suggests strong association in some cases. Computational studies suggest that this is the result of strong inter-ionic H-bonding. Analysis of crystal structures of related compounds supports this conclusion. The original hypothesis of modified solubility characteristics was confirmed in most cases.

The transport of pharmaceutically active protic ionic liquids through a model membrane is described in Publication 3.3. This is the first time such studies have been reported. We show that formation of hydrogen bonded clusters of ions within the liquid enhances the transport of the ILs through the model membrane compared to the administered solid salt forms of the drugs. Hence, the major advantage of this protic IL strategy is that the existing APIs can be formulated in such a way as to diffuse more rapidly through the membranes, reach the target of action more quickly and hence exert their pharmacological activity more rapidly.

Publication 3.1

Ionicity and Proton Transfer in Protic Ionic Liquids

Jelena Stoimenovski, Ekaterina I. Izgorodina, Douglas R. MacFarlane



Ionicity and proton transfer in protic ionic liquids

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Received 16th April 2010, Accepted 8th June 2010
DOI: 10.1039/c0cp00239a

Proton transfer in protic ionic liquids is poorly understood. Some acid/base proton transfer reactions do not proceed to the extent that is expected from ΔpK_a^{aq} data from aqueous solutions, yet some do. In this work we have investigated protic ionic liquids obtained by proton transfer from a common acid, acetic acid, to a range of amine bases of similar pK_a^{aq} values. Probe indicator observations, transport property data allowing the construction of Walden plots and computational studies all suggest that there is a clear distinction between the behaviour of simple primary *vs*. tertiary amines, the proton transfer being more complete in the former case than the latter. The origins of this seem to be related to the hydrogen bonding ability of the ammonium ions in providing a good solvating environment for the ions produced by the proton transfer.

Introduction

Over the past decade much attention has been given to ionic liquids (ILs), a class of compounds comprised only of ions, with melting points below 100 °C.[1] ILs have become of interest in many fields (chemistry, biochemistry and materials engineering to name a few) as their unique properties offer a basis for new and improved technologies. Typical characteristics, such as non-flammability, non-volatility, increased thermal stability and high ionic conductivity, are just some of the many distinctive properties that can be found amongst the huge IL family, which can all be customized through careful choice of cation and anion.[2,3] They can be utilized as solvents in a variety of organic and inorganic reactions, as electrolytes in batteries, fuel cells and solar cells, as protein solubilising and stabilising media, as pharmaceutical delivery aids and as pharmaceuticals in some cases.[4–9]

ILs are divided into two major subclasses: aprotic and protic. In aprotic systems the parent base molecule is ionised (thus becoming a cation) by accepting any group *other than a proton* to its basic site.[10] Protic ionic liquids (PILs), on the other hand, are compounds which are formed upon proton transfer from a Brönsted acid (HA) to a Brönsted base (B) (eqn (1)).[10]

$$HA + B \rightleftharpoons BH^+ + A^- \quad (1)$$

PILs possess notably different chemical properties to conventional aprotic ILs, including in some cases an ability to distil due to high volatility, although distillation takes place *via* the neutral acid and base. Possessing an exchangeable proton, PILs exhibit Brönsted acidity, which allows these compounds to be used as solvents for a number of acid catalysed reactions including Diels–Alder, Mannich and esterification reactions.[11–13] PILs have also been found to be suitable electrolytes in fuel cells due to the presence of the mobile proton.[14]

However, the properties exhibited by PILs depend largely on their degree of ionization, *i.e*. the degree of proton transfer from acid to base. In principle, since ILs are composed entirely of ions, the equilibrium of eqn (1) should lie predominantly to the right, for a "pure" salt to be formed. Some of the literature suggests that the extent of proton transfer should be at least 99% for the PIL to be considered a "pure" salt.[15,16] Yoshizawa *et al*. demonstrated the use of a Walden plot to qualitatively assess ionicity and the degree of proton transfer in ILs.[10] However, it has become clear that the Walden plot is unable to distinguish between low ionicity in an IL, that can arise for example from ion pairing, and a low degree of proton transfer.[17]

Yoshizawa and co-workers have also used aqueous pK_a values as the basis for estimates of the degree of proton transfer in PILs.[10] By finding a simple relationship between the observed boiling points and the difference in pK_a^{aq} values for the acid and the base, ΔpK_a^{aq}, Yoshizawa *et al*. observed that $\Delta pK_a^{aq} > 10$ seemed to be required for the full proton transfer to occur in the PILs studied. This result is somewhat surprising given that simple equilibrium calculations[18] indicate that, in aqueous solution, $\Delta pK_a^{aq} = 4$ is sufficient to produce 99% proton transfer. This suggests that the IL solvation environment can have a very strong effect on the energy of proton transfer, *i.e*. that ΔpK_a^{aq} is a relatively poor estimate of the effective ΔpK_a in the ionic liquid environment. The work of Johansson *et al*. appears to support these observations.[19] However, the situation becomes more perplexing when one considers the work of Banerjee and co-workers[20] who present crystal structures for a number of compounds formed by combination of acids and bases of varying ΔpK_a^{aq} and show that proton transfer has substantially taken place in the crystalline salt when ΔpK_a^{aq} is greater than 3. Below this value the crystal structure is that of a co-crystal of the acid and base.[20] Thus this work seems to indicate that proton transfer in the *solid state* of an ionic compound can be substantial for

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$\Delta pK_a^{aq} > 3$ and this is considered a rule of thumb in the co-crystal field. Since the "solvent" environments can be expected to have many similarities in the liquid and solid states of salts, these observations seem to be in conflict with those of Yoshizawa *et al.* This paper explores the proton transfer in these liquids in more depth in an attempt to probe these issues.

It is difficult to assess proton transfer using standard methods such as pH measurements. Burrell *et al.*[21] have recently illustrated the use of ^{15}N NMR to distinguish between neutral and ionised amine bases. However, NMR literature has shown that the effect of proton transfer on the chemical shifts of nitrogens cannot be distinguished from that of hydrogen bonding[22,23] and hence this technique is not applicable to the present work. An alternative approach involves the use of an indicator acid existing in various protonated forms depending on the pH of the medium. In this study, phenol red (also known as phenolsulfonphthalein or PSP) was chosen as a typical probe indicator acid due to the strong degree of colouration in both its acid and base forms. In the crystalline form and in solution under very acidic conditions, PSP exists in its zwitterionic form, appearing as an orange-red coloured solution (Fig. 1). As the pH increases ($pK_a = 1.03$) the proton from the ketone group is lost and the solution becomes yellow. At an even higher pH ($pK_a = 8.00$) a second proton is lost from the phenolic group, resulting in the bright pink (fuchsia) colour.[24]

Owing to sufficient difference in the pK_{a1}^{aq} and pK_{a2}^{aq} values of the PSP indicator, it is possible to visually assess the ionic state of PSP in a variety of different media. In this work, PSP was used to determine its degree of protonation in a group of amines (Fig. 2) of relatively similar values of pK_a^{aq} and hence of similar ΔpK_a^{aq} values ($\sim$6) when paired with acetic acid. These were chosen to exemplify different structural features, in particular the hydrogen bonding ability that is present in the primary amines but not in the tertiary. The amines were subsequently used to prepare acetate-containing PILs for which transport properties were determined and were compared to each other on a Walden plot.

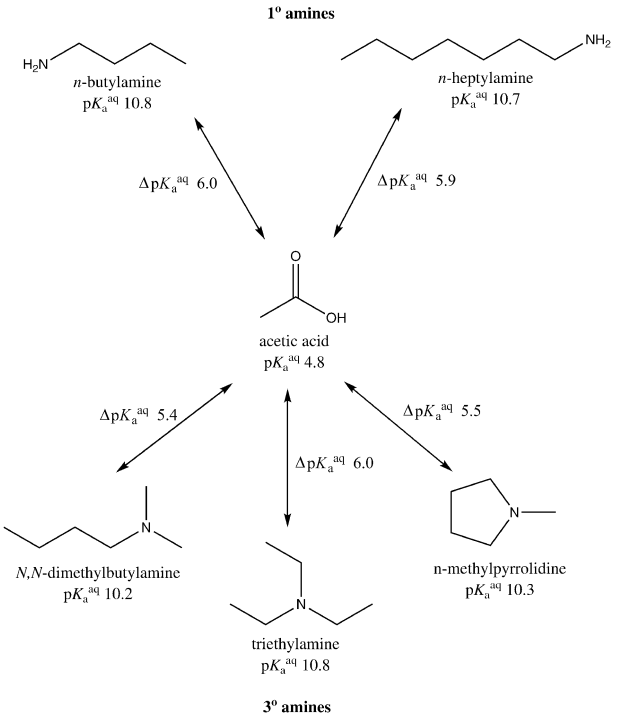


Fig. 2 pK_a^{aq} and ΔpK_a^{aq} values of acetic acid and amines used in the study.

Experimental

General

All amines were purchased from Aldrich Chemical Company and were further purified by distillation over KOH. Glacial acetic acid (99.9+%) was purchased from Sigma-Aldrich (USA) and was used without further purification.

NMR data were recorded on a Bruker Avance400 (9.4 Tesla magnet) with a 5 mm broadband autotunable probe with Z-gradients and BACS 60 tube autosampler.

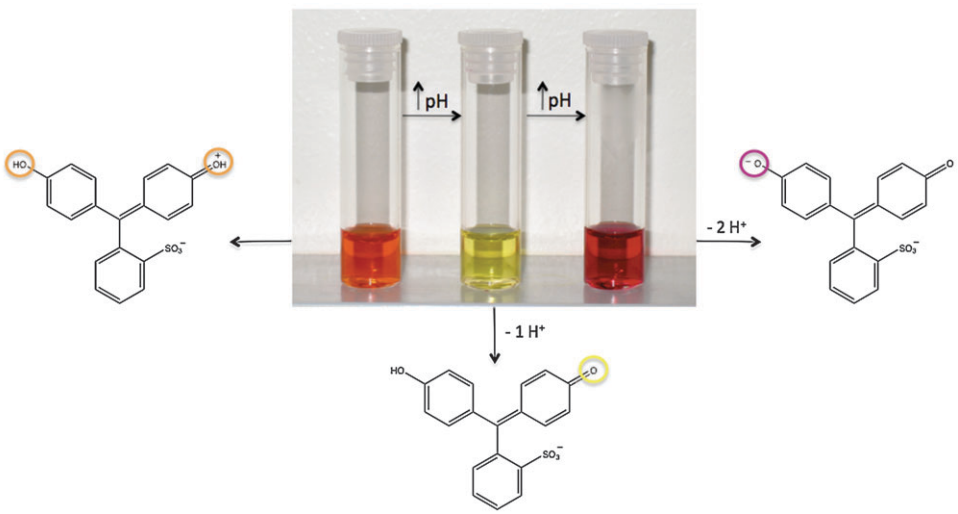


Fig. 1 Different forms of PSP, and the corresponding colours, as pH is increased.

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Density data were collected using an Anton Paar DMA 5000 density meter. The density of the compounds was determined using the ''oscillating U-tube principle''.

The viscosity measurements were performed using a falling ball technique on an Anton Paar AMVn viscosity meter.

Conductivity measurements were carried out on a locally designed dip cell probe containing two platinum wires covered in glass. 0.01 M KCl solution at 25 °C was used to determine the cell constant. The conductivities were obtained by measuring the complex impedance spectra between 1 MHz and 0.01 Hz on a Solatron SI 1296 dielectric interface.

Synthesis

***N*-Butylammonium acetate.** *N*-Butylamine (7.14 g, 97.60 mmol) was added dropwise to glacial acetic acid (5.86 g, 97.60 mmol). The mixture was stirred together in an ice bath for three hours, after which a clear viscous liquid remained.

^{1}H NMR (400 MHz, D_2O) δ (ppm) 0.92–0.96 (t, *J* 7.6, 3H), 1.36–1.45 (sextet, *J* 7.2 2H), 1.61–1.68 (p, *J* 7.6, 2H), 1.92 (s, 3H), 2.98–3.02 (t, *J* 7.6, 2H).

***N*-Heptylammonium acetate.** *N*-Heptylamine (7.56 g, 65.61 mmol) was added dropwise to glacial acetic acid (3.94 g, 65.61 mmol). The mixture was stirred together in an ice bath for three hours, after which a clear viscous liquid remained. The product crystallized after approximately 2 h standing at room temperature.

^{1}H NMR (400 MHz, D_2O) δ (ppm) 0.88–0.92 (t, *J* 6.9, 3H), 1.32–1.44 (m, 8H), 1.65–1.72 (p, *J* 7.5, 2H), 1.94 (s, 1H), 3.00–3.04 (t, *J* 7.5, 2H).

Triethylammonium acetate. Triethylamine acetate (6.90 g, 68.22 mmol) was added dropwise to glacial acetic acid (4.10 g, 68.22 mmol). The mixture was stirred together in an ice bath forming an emulsion.

***N*-Methylpyrrolidinium acetate[19].** *N*-Methylpyrrolidine (7.92 g, 92.98 mmol) was added dropwise to glacial acetic acid (5.58 g, 92.98 mmol). The mixture was stirred together in an ice bath for three hours, after which a slightly yellow clear liquid remained.

^{1}H NMR (400 MHz, D_2O) δ (ppm) 1.94 (s, 3H), 2.00–2.10 (m, 2H), 2.14–2.21 (m, 2H), 2.94 (s, 3H), 3.05–3.12 (m, 2H), 3.64–3.68 (m, 2H).

***N*,*N*-Dimethylbutylammonium acetate[25].** *N*,*N*-Dimethylbutylamine (7.22 g, 71.32 mmol) was added dropwise to glacial acetic acid (4.28 g, 71.32 mmol). The mixture was stirred together in an ice bath for three hours, after which a clear liquid remained.

^{1}H NMR (400 MHz, D_2O) δ (ppm) 0.87–0.90 (t, *J* 7.4, 3H), 1.28–1.37 (sextet, *J* 7.4, 2H), 1.60–1.68 (m, 2H), 1.86 (s, 3H), 2.81 (s, 6H), 3.06–3.10 (m, 2H).

Theoretical procedures

Standard *ab initio* molecular orbital theory and density functional theory (DFT) calculations were carried out using the GAUSSIAN 09[26] and ADF 2009[27] sets of programs. All geometry optimizations were performed at the B3LYP/6-31+G(d) level of theory. Individual amines, except for *N*-heptylamine, were fully conformationally screened at this level of theory to ensure the global (rather than merely local) minima were obtained. The screening was achieved by exploring all conformations arising from the rotations around single chemical bonds. The conformation of the lowest energy was selected as the global minimum for each species. In the case of *N*-heptylamine the ethyl fragment was added to the lowest energy conformation of *N*-butylamine and the conformational search was restricted to the rotation around the single C_4–C_5 bond. Quantum chemical free energies of solvation in aqueous solution were calculated using the COSMO-RS approach[28,29] as implemented in the ADF 2009 set of programs.

Molecular volumes were computed using the HF/aug-cc-pVTZ electron density with tight criteria (an increased density of points for more accurate integration). The effective ionic radii were calculated assuming that the ions studied have a spherical shape:

$$V_{\mathrm{calc}} = \tfrac{4}{3}\pi R_{\mathrm{ion}}^3 \qquad (2)$$

Results

Initial studies of the extent of protonation using the PSP indicator are presented in Fig. 3. Simple addition of a small quantity of the indicator acid to the *pure liquid* amine resulted in the various changes in colour of the otherwise colourless compounds shown in Fig. 3. There was a clear distinction observed between the primary amines, in which the PSP was a pink (fuchsia) colour, and the tertiary amines in which the indicator became bright yellow in colour.

It appears that the indicator acid is entirely deprotonated to its dibasic form in the primary amines, while in the tertiary amines the PSP has only been deprotonated to its monobasic form. It is not surprising that all of the amines were able to deprotonate the PSP acid to at least the monobasic form since pK_a^{aq} for this proton is $\sim$1.0 and hence $\Delta pK_a^{aq} > 9$ for all of the amines involved. However, only the primary amines were able to deprotonate the second proton ($\Delta pK_a^{aq} \approx 2.5$) of the indicator. Several secondary amines (dipropylamine and pyrrolidine) were also studied (not shown) and found either to deprotonate the second proton of the indicator, and hence behave as primary amines do, or to deprotonate only the first proton of PSP and therefore act more like tertiary amines. Thus the secondary amines as a class seem to be transitional depending on the details of their chemical structure.

The density data for the synthesised PILs, displayed in Fig. 4, show that the densities of the primary amine based PIL, butylammonium acetate, and a tertiary amine based PIL, methylpyrrolidinium acetate, are very similar. Dimethylbutylammonium acetate exhibits the lowest density of all of the synthesised PILs. It was very clear in handling these compounds during these measurements that the tertiary amine based salts were quite volatile (strong amine smell), whereas the primary amine salts were not.

Typical viscosity and conductivity data are presented in Fig. 5 and 6 as a function of temperature.

The viscosity data presented illustrate the immense difference between the viscosities of the primary and tertiary amine based

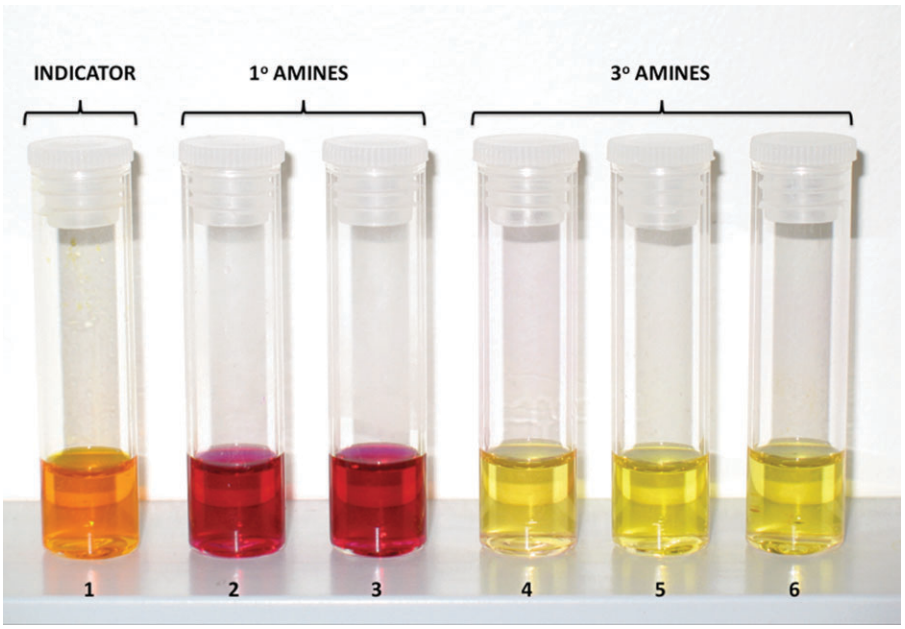


Fig. 3 PSP in acidic aqueous solution (1), in neat *N*-butylamine + PSP (2), *N*-heptylamine + PSP (3), triethylamine + PSP (4), *N*-methylpyrrolidine + PSP (5), *N*,*N*-dimethylbutylamine + PSP (6).

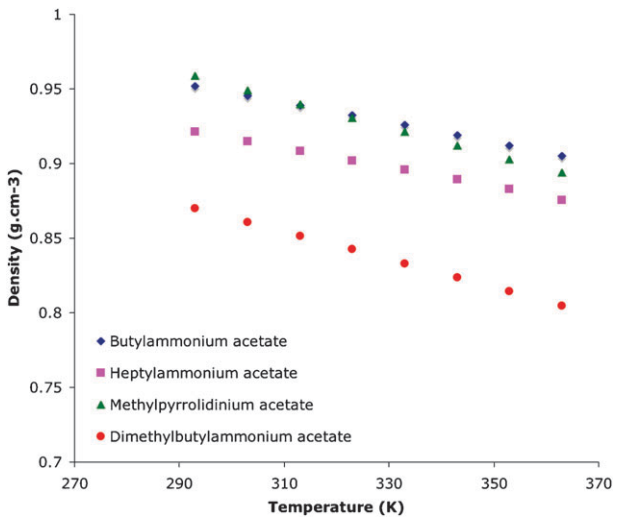


Fig. 4 Density data for the synthesised PILs.

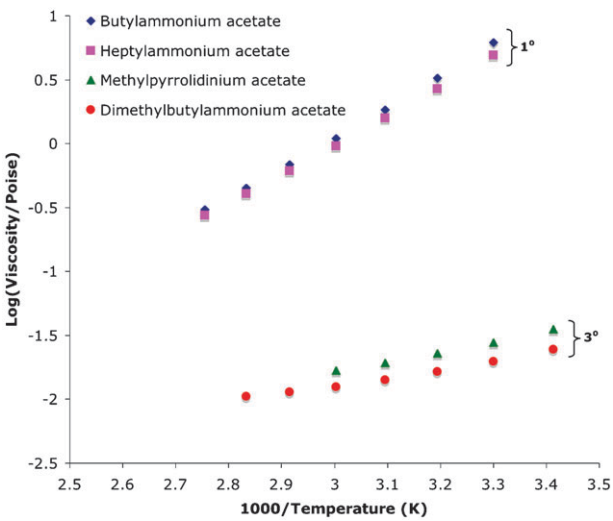


Fig. 5 Viscosity data for the synthesised PILs as a function of temperature.

PILs; this difference is immediately obvious in the handling of these PILs. The primary amine based PILs possess viscosities more than an order of magnitude higher than the tertiary amine-based PILs. In addition, the viscosities of the latter change only slightly over the temperature range studied, while the former show a significant increase. As discussed below, this may be the result of disruption of the hydrogen bonding between the ions as the temperature increases. Note that in the case of methylpyrrolidinium acetate, the viscosity data could not be obtained for the whole range of temperatures chosen for this study (*i.e.* 70–90 °C) due to volatility of the sample at elevated temperatures.

The conductivities of the synthesised PILs (Fig. 6) differ substantially from one another at room temperature. In the case of heptylammonium acetate, a distinct step in conductivity can be observed due to the melting of the sample at approximately 30 °C. The primary amine based PILs have significantly *lower* conductivities than the tertiary amine based PILs. However, with the temperature increase, the difference in the conductivity between the primary and tertiary amine based PILs becomes smaller, whereby at 70 °C the conductivities of butylammonium acetate and dimethylpyrrolidinium acetate are comparable. At even higher temperatures, butylammonium acetate has higher conductivity than that of dimethylbutylammonium acetate. Methylpyrrolidinium acetate exhibits the highest conductivity, while the primary amine based PIL, heptylammonium acetate, possesses lowest conductivity of all the synthesised PILs. It might seem that the tertiary amine based PILs are appearing more "ionic" on the basis of these data, however as we show below, this is an incorrect conclusion.

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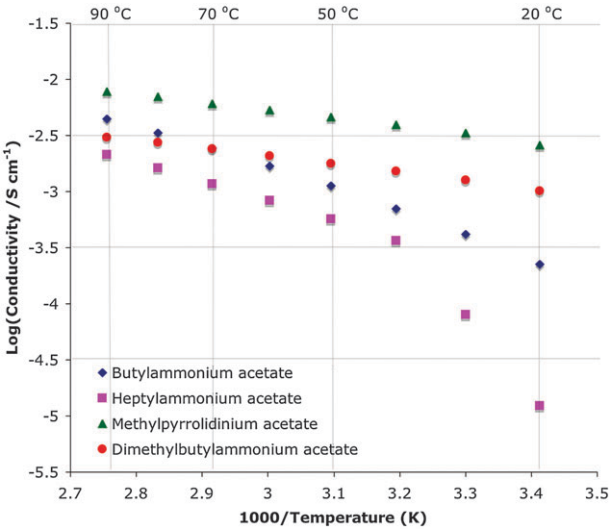


Fig. 6 Conductivity data for the synthesised PILs as a function of temperature.

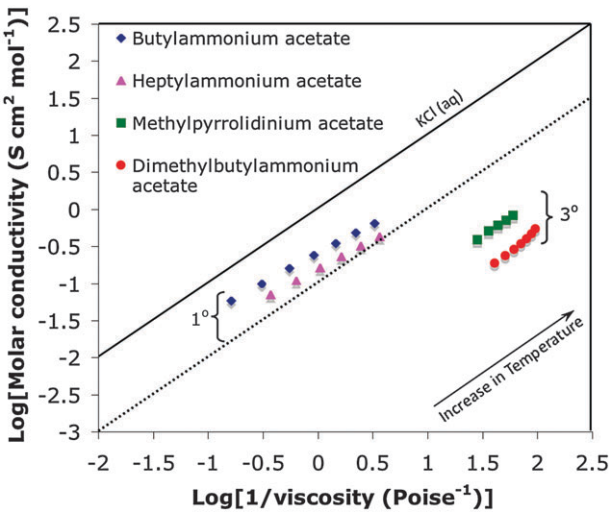


Fig. 7 Walden plot for the synthesised PILs.

A Walden plot encompassing all of the density, viscosity and conductivity data is presented in Fig. 7. The Walden rule:

$$\Lambda\eta = \text{constant} \quad (3)$$

where, Λ is the molar conductivity and η the viscosity, predicts a simple inverse relationship between these two key transport properties, which can be tested using a plot of log Λ *versus* log η, as described by Yoshizawa *et al.*, in which data for a 0.1 M aqueous KCl solution are used as a point of reference.[10] Hence, an "ideal" line representing the behaviour of an ideal electrolyte (in which ions act in an independent fashion) runs directly through the KCl point with unity slope.[10,17,30] Any negative deviation from this reference line is thought to indicate a lack of complete proton transfer, or formation of neutral clusters that cannot conduct. The vertical deviation, ΔW, from the "ideal line" can be taken as a measure of this phenomenon. For example, $\Delta W = 1$ represents the situation where the IL is exhibiting only 10% of the conductivity that might be expected on the basis of its viscosity, according to the Walden rule. In the case of PILs, a large ΔW may also indicate incomplete proton transfer, *i.e.* the presence of the parent acid and base molecules.

Table 1 Deviations from the Walden plot, ΔW, with and without an adjustment for ion size

Synthesised PILs	ΔW (±0.1) @ 313 K	Adjusted ΔW (±0.1) @ 313 K
Butylammonium acetate	0.49	0.32
Heptylammonium acetate	0.72	0.57
Methylpyrrolidinium acetate	1.78	1.62
Dimethylbutylammonium acetate	2.33	2.15

Fig. 7 shows two distinct groups of PILs. One observes a large deviation (Table 1) from the "ideal line" for tertiary amine based PILs, while the primary amine based PILs lie close to the ideal line. As discussed recently[17] the Walden plot axis should be adjusted to allow for the effect of ion size. Doing so in this case produces small adjustments to ΔW, which are also listed in Table 1. If anything, this accentuates the difference between the two families of compounds. The data suggest that the primary amine based PILs are predominantly proton transferred, *i.e.* the equilibrium in eqn (1) lies predominantly towards the ionic species, while the tertiary amine based PILs, with ΔW values of well over 1, demonstrate the presence of neutral non-conducting species, possibly the parent acid and base (though we reiterate that large values of ΔW can also arise from neutral ion pairs and aggregates).

Discussion

The reactions of the primary amines with acetic acid resulted in highly viscous liquids, much more viscous and much less volatile than the parent acid and base. Both acid and base have readily accessible hydrogen bond donor and acceptor sites and therefore there is no obvious reason why mixing them would produce such a significant increase in viscosity *via* additional hydrogen bonding alone. These observations indicate that some reaction has occurred between the acid and the base. These PILs exhibit molar conductivities close to that expected on the basis of the Walden rule (small ΔW). As shown in Fig. 3, the indicator tests tended to show that the indicator acid rapidly displayed a colouration typical of the fully deprotonated form. These pieces of evidence taken together indicate that the extent of proton transfer in these PILs is relatively close to complete.

On the other hand, upon the addition of the tertiary amines to acetic acid, very fluid liquids were produced, the fluidity being similar to that of the original starting materials. The mixtures remained quite volatile. It seemed that only partial reaction occurred. Reaction of triethylamine and acetic acid resulted in an emulsion, indicating an inability of the two liquids to mix at all; presumably, therefore, no reaction has occurred. The "PILs" resulting from these amines tended to show large deviations from the Walden rule and the indicator acid appeared to remain in the mono-protonated state in the pure base. This evidence taken as a whole seems to indicate

that relatively little proton transfer has taken place in these cases.

However, the amines selected for this study all have comparable pK_a^{aq} values, such that the difference, ΔpK_a^{aq}, for the various combinations is very similar ($\sim$6). These compounds were chosen in order to allow an examination of the hypothesis that $\Delta pK_a^{aq} > 10$ is required for strong proton transfer. Thus it appears, from the various observations described above, that proton transfer equilibria in PILs based on simple primary amines behave, in fact, much as expected on the basis of aqueous pK_a values, *i.e.* that $\Delta pK_a^{aq} > 2$ is sufficient to produce predominant proton transfer ($\sim$90%) and $\Delta pK_a^{aq} > 4$ will produce >99% ionisation. On the other hand, in this work values substantially greater than those around $\Delta pK_a^{aq} = 6$ are required to produce strong proton transfer with the simple tertiary amines and hence it is these cases that are behaving unusually. Secondary amines seem to lie between these extremes. The work of Yoshizawa *et al.*[10] mostly focussed on tertiary amines and hence the conclusions reached here are quite consistent with their observations.

The molecular origins of these differences almost certainly relate to differences in the hydrogen bonding environments offered by the amine/ammonium ions. In the primary amine case (and the corresponding alkyl ammonium ions) the cation has multiple hydrogen bond donors available to interact with and solvate the carboxylate anion that is formed by the proton transfer reaction. One might expect its solvation in this respect to be relatively similar to that of water. On the other hand, the hydrogen bonding frustrated environment offered by the tertiary amine/ammonium ion is distinctly different to that of water. The hydrogen bonding acceptor sites on the acetate anion (two sites on each of two oxygens) have only the single proton on any given neighbouring cation with which to hydrogen bond. This could be expected to provide a less stabilising solvent environment for the anion (and also the cation) and hence proton transfer to form these ions is energetically less favoured. The case of ''triethylammonium acetate'' presents an interesting extreme in which the acid and base do not even mix.

This distinction between primary and tertiary amine based PILs assists in understanding the various effects that can be observed in the Walden plot. The case of butylammonium acetate, with an adjusted ΔW of 0.32, probably represents an example of a close-to-ideal PIL (''ideal'' indicating fully proton transferred and all ions independently mobile). The two tertiary amine based ''PILs'', which are in fact very poorly proton transferred, sit low on the Walden plot for this reason. Heptylammonium acetate illustrates the further phenomenon that influences the Walden plot in that it is likely to be fully proton transferred but sits lower in the Walden plot because of association between the ions. In this case hydrogen bonding is clearly the origin of the association. Any other functional groups on either ion that can add further basis for hydrogen bonding or ion association will exacerbate this effect. This is true of many of the pharmacologically active ILs under investigation in our laboratories.[9]

A further factor in the proton transfer process in these neat liquids is the possibility of more complex species forming, of the type A–H–A$^-$, as described by Johansson *et al.*[19] In the case of the tertiary amine system studied in that work, the formation of these ions in compositions which are acid rich, thus providing a further hydrogen bond donor to assist in stabilising A$^-$, was observed to support much stronger proton transfer than at the stoichiometric composition.

Computational studies

The free energy of the proton transfer process, ΔG_{PT}, can be expressed as follows:

$$\Delta G_{PT} = G_{tot}(BH^+) - G_{tot}(B) + G_{tot}(A^-) - G_{tot}(AH) \quad (4)$$

where $G_{tot} = G_{gas} + \Delta G_{solv}$ for each solvated species and is obtained from the sum of the free energy of the gas phase species plus its free energy of solvation in the solvent. Eqn (5) can then be re-written in the following form:

$$\Delta G_{PT} = \Delta G_{gas} + \Delta G_{solv}(BH^+) - \Delta G_{solv}(B) + \Delta G_{solv}(A^-) - \Delta G_{solv}(AH) \quad (5)$$

where ΔG_{gas} is the free energy of proton transfer in the gas phase. This equation makes explicit the role of solvation energies in the observed proton transfer processes in any given solvent.

Quantum chemical calculations of ΔG_{solv} in aqueous solutions were performed for the protonated amines. The COSMO-RS approach was employed to extract the free energies of solvation, as it explicitly treats contributions from hydrogen bonding sites in the molecule to the total free energy of solvation. The results are given in Table 2. Analysis of the results reveals, as expected, that primary ammonium ions have substantially larger solvation energies in water compared to those of the tertiary ammonium ions, indicating that the protonated primary amines are strongly stabilised by the hydrogen bonding environment that water represents. While this type of calculation cannot directly probe the IL environment it is our hypothesis here that similar hydrogen bond stabilisation is available for both cation and anion by the protonated primary amine in the IL. On the other hand the hydrogen bonding ''starved'' environment represented by the protonated tertiary ammonium cation ionic liquid presents far less stabilisation of the ions and therefore the proton transfer reaction is relatively discouraged in that medium. These observations are all also consistent with the crystal structure observations of Banerjee *et al.*; however, recognising that hydrogen bonding is a key element in the phenomena here suggests that crystal structures in which hydrogen bonding is strongly enabled, by the fixed arrangement of the ions, might exhibit stronger proton transfer than the liquid state of the

Table 2 Free energies of solvation (ΔG_{solv}, in kJ mol^{-1}) of the primary and tertiary ammonium cations. $\Delta\Delta G_{solv}$ expresses the differences relative to the dimethylbutylammonium ion

	ΔG_{solv}/kJ mol^{-1}	$\Delta\Delta G_{solv}$/kJ mol^{-1}
N,*N*-Dimethylbutylammonium	−228.4	0.0
N-Methylpyrrolidinium	−234.7	−6.3
N-Heptylammonium	−304.1	−75.7
N-Butylammonium	−307.5	−79.1
Acetate	−357.2	−129.0

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same material. This would suggest that crystallisation might encourage proton transfer in some cases.

Conclusions

In this work we have shown that primary and tertiary amines of similar pK_a^{aq} values lead to a different extent of proton transfer when paired with a common acid, acetic acid. The Walden plot for four synthesised PILs reveals that PILs obtained from primary amines exhibit a ''close-to-ideal'' behaviour, whereas those from tertiary amines sit far below the ideal line ($\Delta W > 1$). Based on this and a range of physical property observations we conclude that simple primary amines produce highly ionised ILs, whereas tertiary amines tend to form mixtures with a low degree of proton transfer. COSMO-RS free energies of solvation of protonated amines indicate that the solvation of primary ammonium ions is substantially stronger due to the increased hydrogen bonding ability of the former. It is important to note that these trends can be easily disturbed by other solvation effects, for example longer chain alkyl groups bring hydrophobic interactions into play and other functional groups elsewhere in either molecule, especially –OH or other hydrogen bonding sites, will have a major effect on the outcome.

Acknowledgements

We gratefully acknowledge generous allocations of computing time from the National Facility of the National Computational Infrastructure and the Monash Sun Grid Cluster at the e-research centre of Monash University. EII gratefully acknowledges the support of the Australian Research Council for her postdoctoral fellowship, as does DRM for his Federation Fellowship.

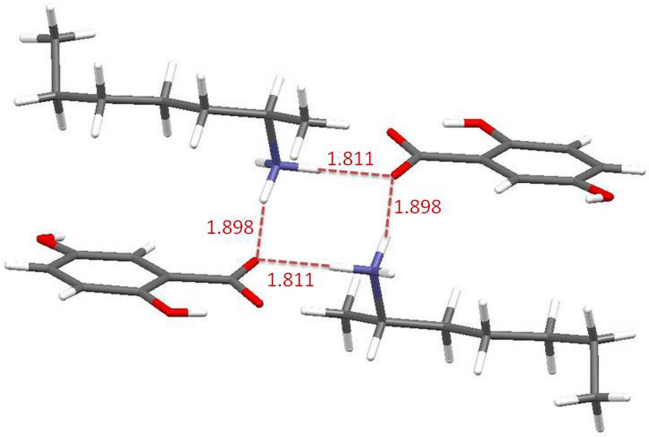
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Publication 3.2

Protic Pharmaceutical Ionic Liquids and Solids: Aspects of Protonics

Jelena Stoimenovski, Pamela M. Dean, Ekaterina I. Izgorodina, Douglas R. MacFarlane



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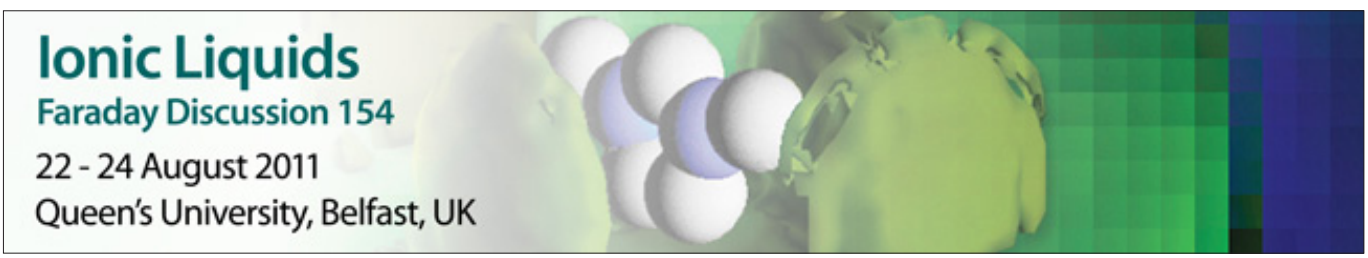
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Protic pharmaceutical ionic liquids and solids: Aspects of Protonics

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A series of new protic compounds based on active pharmaceutical ingredients have been synthesised and characterised. Some of the salts synthesised produced ionic liquids, while others that were associated with rigid molecular structures tended to produce high melting points. The "protonic" behaviour of these compounds was found to be a major determinant of their properties. Indicator studies, FTIR-ATR and transport properties (Walden plot) were used to probe the extent of proton transfer and ion association in these ionic liquids. While proton transfer was shown to have taken place in all cases, the Walden plot indicated strong ion association in the primary amine based examples due to hydrogen bonding. This was further explored via crystal structures of related compounds, which showed that extended hydrogen bonded clusters tend to form in these salts. These clusters may dictate membrane transport properties of these compounds *in vivo.*

1. Introduction

Many drug substances on the market are organic acids or bases that have an ability to form salts.[1] Converting a drug from its acid or base form to a salt form can often allow a useful manipulation or optimisation of the drug's properties, such as its absorption, pharmacodynamics or pharmacokinetics.[2, 3] In addition, by keeping an active ion constant and changing the counterion of the drug salt, either by combining with another active, or other biocompatible ion, one can further alter its chemical and biological properties without changing the structure of the active ingredient. Different salt forms of an active are now accepted to be different drugs, with individual chemical and biological profiles, resulting in varying clinical efficacies and safety.[1] Turning the pharmaceutical salt into an ionic liquid (IL) is a further conceptual step that has been discussed recently in this regard.[4] ILs are salts with melting points below 100 ^{o}C and are typically comprised of cations and anions that have either relatively low symmetry or delocalised charge; these structural properties tend to provide a low, or sometimes nonexistent melting point.[5, 6] A wide range of different physical and chemical properties can be designed into the liquid by simply varying the cations and anions of which it is comprised.[6] From solvents for chemical reactions,[7] to electrolytes for electrochemical cells,[8] ILs are now of intense interest in a range of applications in different areas. Recently, recognising that more than half of pharmaceuticals currently on the market are organic salts, ILs have also been proposed as a novel approach to drug design and optimisation in the pharmaceutical world.[4, 9-11] In 2007, Rogers and co-workers, in conjunction with our group, filed a

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series of patents in which the preparation of ILs from known active pharmaceutical ingredients (APIs) was described.[12] The concept involved the replacement of what was usually a "ballast" counterion, for example sodium or bromide, with an alternative counterion that lowered the melting point of the salt such that it was liquid at ambient temperature, thus offering a range of different delivery modalities. If the "counterion" itself has active pharmaceutical properties then the compound can be considered a dual active, potentially presenting a synergistic combination of effects in a single compound. Other groups have been investigating ILs for related applications including anti-microbial[13] and anti-bacterial activity.[14-16]

However, unlike the broader ILs field where the design or choice of cation and anion is, to an extent, flexible such that the desired low melting point can be achieved, this is not a case with pharmaceutical ILs. In this field the identity of at least one of the ions is specified, hence lowering the melting point of its salts becomes a challenging goal. This challenge has been explored over the last few years using an "anti-crystal engineering" approach,[17] aided by a greater understanding of the lattice energy of crystalline organic salts as revealed by the Madelung constant.[18] It was found, not surprisingly, that the extent of specific intermolecular interactions, such as hydrogen bonding, directly influences the phase behaviour of the product. Hence the advantageous combinations of active ion and counterion that can produce the low melting point required to form an IL will typically be those that avoid or disrupt all of these identifiable interactions.

Protic Ionic Liquids – the proton transfer conundrum

Protic Ionic Liquids, PILs, are a subclass of ILs formed by reacting a Brønsted acid with a Brønsted base. Unlike *aprotic* ILs, PILs exhibit Brønsted acidity due to the exchangeable proton, and can hence be used as solvents for acid catalysed reactions;[19-21] for the same reason, they are also found to be suitable proton conducting electrolytes for fuel cells.[22] Given their ease of preparation, being simply the product of an acid (HA) - base (B) neutralisation reaction (Scheme 1),

$$HA + B \rightleftharpoons BH^+ + A^-$$

Scheme 1. Neutralisation reaction between an acid and a base

this IL family is of significant potential in the broad, multifaceted pharmaceutical application. Many pharmaceuticals are in fact delivered as simple salts of organic bases, or metal ion salts of organic acids. However, the properties manifested by PILs depend predominantly on the degree of proton transfer from the acid to the base as well as the hydrogen bonding in which the proton is involved; the possible outcomes are summarised in Figure 1 and all of these outcomes have been observed in recent examples. For the PIL to be considered a "pure" salt and not a complex mixture of acid, base and salt, the extent of proton transfer should be at least 99 %.[23, 24] Despite the fact that in aqueous solution the proton transfer between the acids and bases usually involved would be strongly complete, the situation is more complex in the "neat" salt for complex reasons. Yoshizawa *et. al.*[25] originally revealed the problem by correlating observed boiling points with differences in pK_a^{aq} values (ΔpK_a^{aq}) between the acid and the amine base. On the basis of a comparison of Walden

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products (explained further below) it appeared that $\Delta pK_a^{aq} \rangle 10$ was needed for the full proton transfer to be observed (*i.e.* to achieve the situation in Figure 1c rather than the acid-base mixture of Figure 1a).[25]

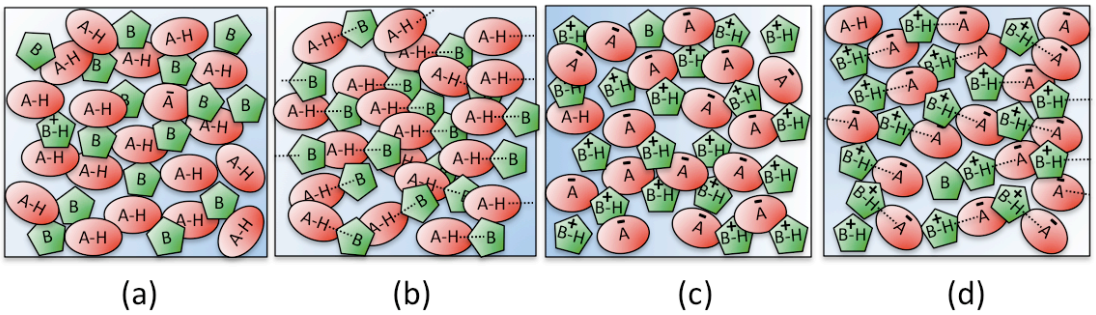


Figure 1. The four possible outcomes in PILs **(a)** mostly un-ionised acid and base **(b)** hydrogen bonded acid-base pairs (no proton transfer) **(c)** mostly ionised PIL (proton transfer occurred, independent ions), **(d)** associated PIL (proton transfer occurred but ions associated through hydrogen bonding).

To further investigate this phenomenon we explored a series of carefully chosen primary and tertiary amines of very similar pK_a^{aq} values.[26] We found that restricted proton transfer was clearly exhibited by the tertiary amine base systems, and $\Delta pK_a^{aq} \rangle$ 10 was indeed required to produce substantial proton transfer. On the other hand, the primary amine systems tended to be fully ionised even at $\Delta pK_a^{aq} > 5$. In other words, the primary amine based ILs tend to behave much more like aqueous systems. The strong difference in behaviour appears to be related to the hydrogen bond donor ability of the protonated base cation. In the tertiary amine case, only the single, transferred proton is available to hydrogen bond with the anion, whereas the primary base cation can offer multiple hydrogen bond sites. Free energy of solvation calculations from COSMO-RS confirmed this difference in the solvation environment in the two cases.[26] However, clearly, additional intermolecular interactions stemming from long alkyl chains, π---π interactions and other hydrogen bonding sites in either ion, for example –OH functionality, can easily disturb these trends. Hence, introduction of such characteristics into tertiary amine based ILs could induce a stronger degree of proton transfer. These phenomena are crucial to attempts to form PILs based on APIs, since the lack of complete proton transfer may render the formulation nothing more than an acid/base/salt mixture. On the other hand, as we will show, the H-bonding introduced, involving both the transferred proton and also the residual conjugate base anion, can also produce strong ion-association in the PIL, potentially producing a further dimension of property variation in the product. We attempt to describe this complex set of interconnected phenomena surrounding the labile proton, its energetics and dynamics, in terms of a single unified concept – protonics. Exploring these phenomena in the context of APIs is the main theme of this paper.

Pharmaceutically Active PROTIC Ionic Liquids

A number of groups including us have investigated the use of PILs of various compositions as an approach to pharmaceutically active ILs.[27, 28] For example, Bica *et. al.*[27] described a series of salts of aspirin, *e.g.* lidocainium acetylsalicylate, T_g=-14°C, where lidocaine is a topical anaesthetic and aspirin is a broad analgesic. In the

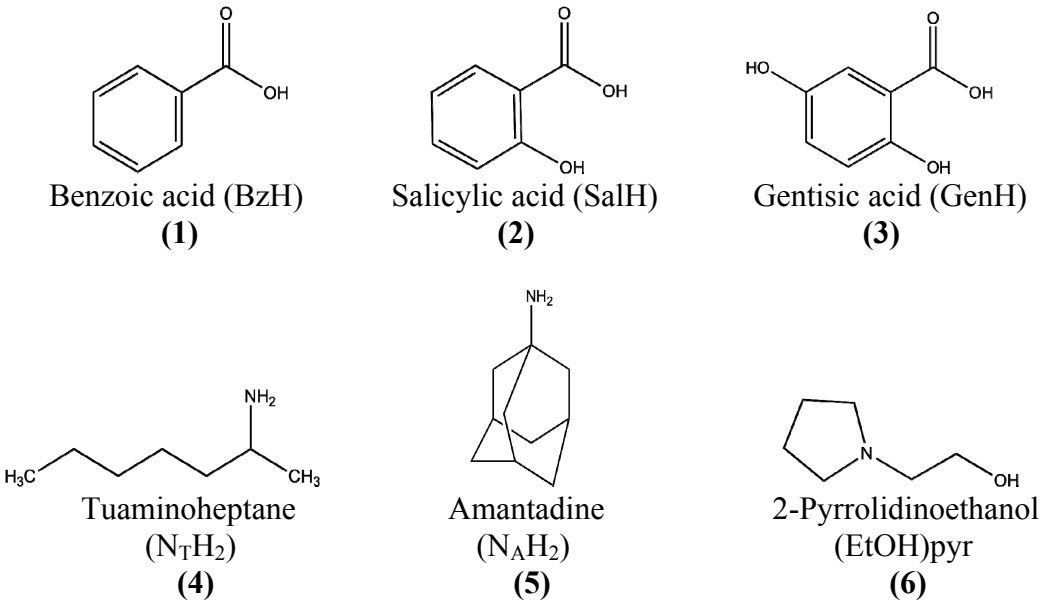
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present work we have focussed on salt formation and the issue of proton transfer in a number of families of pharmaceutically active acids and bases. For the purposes of a systematic study, a series of acids and bases (Figure 2) were selected with slight structural variations and physico-chemical properties, with the objective of understanding the factors controlling melting point, H-bonding and proton transfer. A library of nine compounds and four oligomeric PILs was synthesised and characterised. Benzoic, salicylic and gentisic acids were chosen for this study, as these are frequently encountered in pharmaceutical compounds/formulations. Benzoic acid, BzH, a common preservative and pharmaceutical aid (antifungal), is used in a range of products on the market including ointments, mouthwashes and cosmetics. A derivative of benzoic acid, salicylic acid (SalH), is a widely recognized and used keratolytic, also possessing anti-inflammatory, analgesic and antipyretic properties as a sodium salt. Gentisic acid, GenH, another benzoic acid derivative, is used in the pharmaceutical industry as an analgesic and anti-inflammatory.[29]

The three pharmaceutical bases were chosen on the basis of their pK_a^{aq} values and their structure (Figure 2). Tuaminoheptane, N_TH_2, a primary amine base with a pK_a^{aq} value of 10.50, is used as a nasal decongestant. Amantadine, N_AH_2, also a primary amine base with a pK_a^{aq} value of 10.10, is an antiviral/anti-Parkinsonian drug. 2-Pyrrolidinoethanol, (EtOH)pyr, a "generally recognised as safe compound", is a tertiary amine with a pK_a^{aq} value of 9.44.[29]



Benzoic acid (BzH) **(1)**

Salicylic acid (SalH) **(2)**

Gentisic acid (GenH) **(3)**

Tuaminoheptane (N_TH_2) **(4)**

Amantadine (N_AH_2) **(5)**

2-Pyrrolidinoethanol (EtOH)pyr **(6)**

Figure 2. Acids and bases used in this study

2. Experimental

2.1 General

Tuaminoheptane (N_TH_2), amantadine (N_AH_2), 2-pyrrolidinoethanol ((EtOH)pyr) and gentisic acid (GenH) were purchased from Aldrich Chemical Company. Benzoic acid

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(BzH) was purchased from Sigma-Aldrich, while salicylic acid (SalH) was supplied by Chem Supply.

The synthesis procedure and the characterisation of the resulting compounds can be found in the Electronic Supplementary Information.

2.2 Instrumental

Nuclear Magnetic Resonance (NMR) data were recorded on either a Bruker Avance 400 (9.4 Tesla magnet) with a 5mm broadband autotunable probe with Z-gradients and BACS 60 tube autosampler or on a Bruker DPX-200 spectrometer. All samples were measured as solutions in deuterated dimethylsulfoxide supplied by Cambridge Isotope Laboratories. Multiplicities are reported according to their relative splittings, as a singlet (s), doublet (d), doublet of doublets (d(d)), triplet (t), pentet (p), sextet, multiplet (m) or a broad signal (b).

Electrospray Mass Spectrometry (ESI) was carried out on the Micromass Platform II API QMS Electrospray Mass Spectrometer with a cone voltage of 25 V or 35 V, using methanol as the mobile phase. Analyses were conducted in both positive (ESI^+) and negative (ESI^-) modes.

Density data was collected using an Anton Paar DMA 5000 density meter. The density of the compounds was determined using the "oscillating U-tube principle". The viscosity measurements were performed using a falling ball technique on an Anton Paar AMVn viscosity meter. Conductivity measurements were carried out on a locally designed dip cell probe containing two platinum wires covered in glass. 0.01M KCl solution at 25 ^oC was used to determine the cell constant. The conductivities were obtained by measuring the complex impedance spectra between 1 MHz and 0.01 Hz on a Solatron SI 1296 dielectric interface.

Where crystals were obtained, the reflection intensity data were measured on a Bruker X8 APEX KAPPA CCD single crystal X-ray diffractometer ($(EtOH)pyr^+$ Gen^-; $N_AH_3^+$ Gen^-; $N_AH_3^+$ Sal^-; $N_TH_3^+$ Gen^-; $(EtOH)pyr^+$ Bz^-; $(EtOH)pyr^+$ Sal^-) and a Nonius KAPPA CCD single crystal X-ray diffractometer ($N_AH_3^+$ Bz^-), using graphite-monochromated Mo KR radiation (λ) 0.71073 Å. Crystals were coated with Paratone N oil (Exxon Chemical Co.,TX, U.S.A.) immediately after isolation and cooled in a stream of nitrogen vapor on the diffractometer. Structures were solved by direct methods using the program SHELXS-97 and refined by full matrix least-squares refinement on F2 using SHELXL-97.25 All non-hydrogen atoms were revealed in the E-map and subsequent difference electron density maps and thus placed and refined anisotropically. All hydrogen atoms were observed in difference syntheses and were either refined isotropically or placed in geometrically idealized positions and constrained to ride on their parent atoms with C-H distances in the range 0.95-1.00 Å and Uiso(H)) xUeq(C), where x) 1.5 for methyl and 1.2 for all other C atoms.[30] Specific details of refinement are contained in the relevant CIF files. The crystal structures of most of the synthesised salts are described here for the first time (CCDC Refcodes: 802629 for $N_TH_3^+$ Gen^-, 802627 for $N_AH_3^+$ Gen^-, 802625 for $N_AH_3^+$ Sal^-, 802628 for $(EtOH)pyrH^+$ Bz^-, 802630 for $(EtOH)pyrH^+$ Sal^- and 802624 for $(EtOH)pyrH^+$ Gen^-. The crystal structures for $N_AH_3^+$ Bz^- has been reported before and can be found in reference [31]. However, we have solved the structure of this compound and submitted the report as part of the supplementary information.

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Differential scanning calorimetry (DSC) scans were carried out at a heating/cooling rate of 10 ^{o}C/min in the range of -150 ^{o}C to 200 ^{o}C using a T.A Instruments Q100 differential scanning calorimeter. Thermal scans below room temperature were calibrated with the cyclohexane solid-solid transition and melting point at -87.0 °C and 6.5 °C respectively. Thermal scans above room temperature were calibrated with the indium, tin, lead and zinc. Transition temperatures are reported using the peak maximum of the thermal transition.

The FTIR-ATR spectra for all the samples were obtained using Bruker IFS Equinox FTIR system, fitted with a Golden GateTM single bounce diamond. The FTIR spectrometer was connected to a computer equipped with OPUS 6.0 software, which was used for the analysis of spectra.

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3. Results and Discussion

3.1 Protic Pharmaceutical Salts

Table 1 summarises the protic salts made in this work. Of the thirteen compounds synthesised, nine satisfy the definition of an IL by having melting points below 100 ^{o}C. Five of these are room temperature ILs. Salts containing the N_AH_2 base all possess high melting points. ILs containing the (EtOH)pyrH^+ ion all have melting points below 100 ^{o}C, while those based on the $N_TH_3^+$ cation have no obvious trend amongst their melting points.

When reacted with the same acid, the two *primary* amines, N_TH_2 and N_AH_2, give rise to compounds with significantly different melting points. The compounds based on the $N_TH_3^+$ cation, a seven carbon molecule, have melting points of 121±2^{o}C and below, while those based on the $N_AH_3^+$ cation, a nine carbon molecule, possess melting points of 216±2^{o}C and above. These differences can be understood from a thermodynamic point of view. Given that the change in Gibbs free energy of fusion (ΔG_f) at the melting point is zero by definition, the enthalpy (ΔH_f) and the entropy (ΔS_f) of fusion of the compound determine T_m (equation 1).

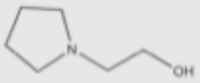
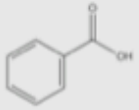
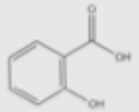
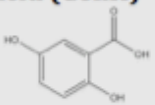
$$\Delta G_f = 0 = \Delta H_f - T_m \Delta S_f \quad \Rightarrow T_m = \Delta H_f / \Delta S_f \qquad \text{Eqn 1}$$

Being a long-chain molecule, the $N_TH_3^+$ cation has more degrees of rotational freedom that can become active on melting and hence exhibits a larger ΔS_f; this in turn leads to compounds with a lower melting point. On the other hand, $N_AH_3^+$, a rigid multi-ringed structure, has fewer rotational degrees of freedom that can become active on melting, resulting in a smaller ΔS_f and hence higher melting point of the resulting compounds. Thus, in order to synthesise low melting PILs, the more flexible anion/cation structures are desirable.

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	Tuaminoheptane (N_TH_2) - *Nasal decongestant*  (liquid, b.p. 143 °C, pK_a 10.50, *water insoluble*)		**Amantadine (N_AH_2)** - *Antiviral/antiparkinson*  (solid, m.p. 206-208 °C, pK_a 10.10, *water insoluble*)	**2-Pyrrolidinoethanol ((EtOH)pyr)** – *GRAS*  (liquid, b.p. 80 °C, pK_a 9.44, *water soluble*)	
Benzoic acid (BzH) - *Preservative*  (solid, m.p. 122 °C, pK_a 4.19, *soluble in hot water*)	**$N_TH_3^+$ Bz^- 1:1** ΔpK_a 6.31 solid DSC: T_m 91±2°C *Water soluble*	**$N_TH_3^+$ (Bz-Bz)$^-$ 1:2*** liquid DSC: T_g -43±2°C *Water insoluble*	**$N_AH_3^+$ Bz^- 1:1** ΔpK_a 5.91 solid DSC: T_m 256±2°C *Poorly water soluble*	**(EtOH)pyrH$^+$ Bz^- 1:1** ΔpK_a 5.25 solid, DSC: T_g -40±2°C, T_r -24±2°C, T_m 28±2°C *Water soluble*	**(EtOH)pyrH$^+$ (Bz-Bz)$^-$ 1:2*** liquid DSC: T_g -49±2°C *Water insoluble*
Salicylic acid (SalH) - *Keratolytic*  (solid, m.p. 159 °C, pK_a 2.98, *poorly soluble in water*)	**$N_TH_3^+$ Sal^- 1:1** ΔpK_a 7.52 liquid DSC: T_g -40±2°C *Water soluble*	**$N_TH_3^+$ (Bz-Sal)$^-$ 1:2*** liquid DSC: T_g -40±2°C *Water insoluble*	**$N_AH_3^+$ Sal^- 1:1** ΔpK_a 7.12 solid DSC: T_m 216±2°C *Water insoluble*	**(EtOH)pyrH$^+$ Sal^- 1:1** ΔpK_a 6.46 solid DSC: T_g -44±2°C, T_r 6±2°C, T_m 49±2°C *Water soluble*	**(EtOH)pyrH$^+$ (Bz-Sal)$^-$ 1:2*** liquid DSC: T_g -46±2°C *Water insoluble*
Gentisic acid (GenH) - *Analgesic*  (solid, m.p. 200 °C, pK_a 2.93, *soluble in hot water*)	**$N_TH_3^+$ Gen^- 1:1** ΔpK_a 7.57 solid DSC: T_m 121±2°C *Water soluble*		**$N_AH_3^+$ Gen^- 1:1** ΔpK_a 7.17 solid DSC: T_m 250±2°C *Water insoluble*	**(EtOH)pyrH$^+$ Gen^- 1:1** ΔpK_a 6.51 solid DSC: T_m 97±2°C *Water soluble*	

* Represents compounds with two moles of acid, in some cases two different acids, to one mole of base

Table 1. The protic pharmaceutical compounds prepared in this study including a number that are ILs

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3.2 Oligomeric Compositions

Another domain of PILs that has been explored recently are the protic oligomers, whereby several equivalents of acid were reacted with one equivalent of base to form H-bonded acid-oligomer based ILs (Scheme 2).[32] For example, in the case of 2HA + B, the anionic species present appears to be $[A\text{-}H\text{-}A]^-$. Proton transfer at this stoichiometry can be stronger than at the 1:1 stoichiometry.

$$(A\text{-}H)_x + B \rightleftharpoons H_{x-1}(A^-)_x + B^+H$$

Scheme 2. Anion oligomer based PIL formation[32]

Bica *et. al.* have reported pharmaceutical ILs based on such oligomeric ions; these compositions allow one to alter the dose of one active ingredient over the other active ingredient in the case of dual protic pharmaceutical ILs.[33] Recognising that such 2:1 mixtures may also represent "buffer" type properties,[34] they may also have a useful property in controlling pH. A similar approach was investigated in Table 1 in which a second mole of acid, in some cases a different acid, was incorporated into the formulation, in principle forming the "dimer" acid/anion species. In the case of the formulations involving two different acids HA_1 and HA_2, there is no intrinsic reason why the dimeric species should be uniquely $A_1\text{-}H\text{-}A_2$; the real situation will be a dynamic equilibrium between all of the possible species, with this overall composition.

3.3 Physical Properties, Proton Transfer and Ion Association

As discussed above, certain important physicochemical properties of pharmaceutical acids/bases can be altered by converting them into salts of an appropriate counter ion. For example, in this study the salts of the originally water insoluble/slightly soluble acids and bases have been rendered water soluble in most cases. In the case of the dimer-acid based ILs, an additional acid molecule decreases the water solubility of the compounds. This in turn demonstrates the ease of water solubility manipulation, an important factor in drug delivery.

The effects of proton transfer and ion association on physical properties are illustrated by the two salicylate compounds, one based on a *primary* amine, $N_TH_3^+$ Sal^-, and the other on a *tertiary* amine, $(EtOH)pyrH^+$ Sal^-. Both compounds have low melting points. Indicator studies, the basis of which was described in detail in our previous paper,[26] were used to show that both the primary amine, N_TH_2, as well as the tertiary amine, (EtOH)pyr, have the capability to completely deprotonate the polyprotic indicator-acid, phenol red. This is shown in Figure 3 where the amines have both turned a fuchsia colour in the presence of the indicator acid, which originally exists as an orange coloured solution. One would observe a yellow colour if only a partial deprotonation occurred. The proton transfer behaviour of the (EtOH)pyr, a tertiary amine, is therefore different to the behaviour of the simple tertiary amine cases studied previously,[26] presumably as a result of the presence of the hydroxyl group.

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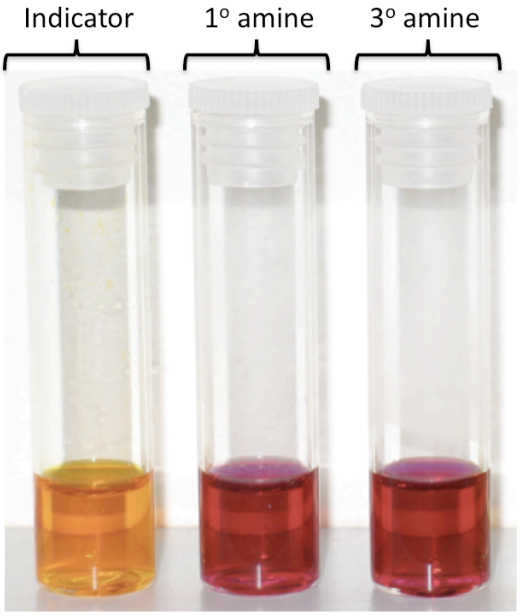


Figure 3. The primary amine, N_TH_2, and tertiary amine, (EtOH)pyr, with indicator phenol red

Further evidence of proton transfer in this case is seen in the FTIR-ATR spectra of (EtOH)pyrH^+ Sal^-, $N_TH_3^+$ Sal^- and the starting materials (EtOH)pyr, N_TH_2 and SalH displayed in Figure 4. The spectra of the PILs (shown in red) are notably different to those of the starting materials. A peak at 1655 cm^{-1} in the SalH spectrum (shown in blue), corresponding to the C=O stretch of the acid, is absent in both PIL spectra, which is indicative of complete proton transfer in the ILs. Also, the disappearance of, or shift in, other peaks when compared to the original starting materials are all consistent with strong proton transfer in these PILs.

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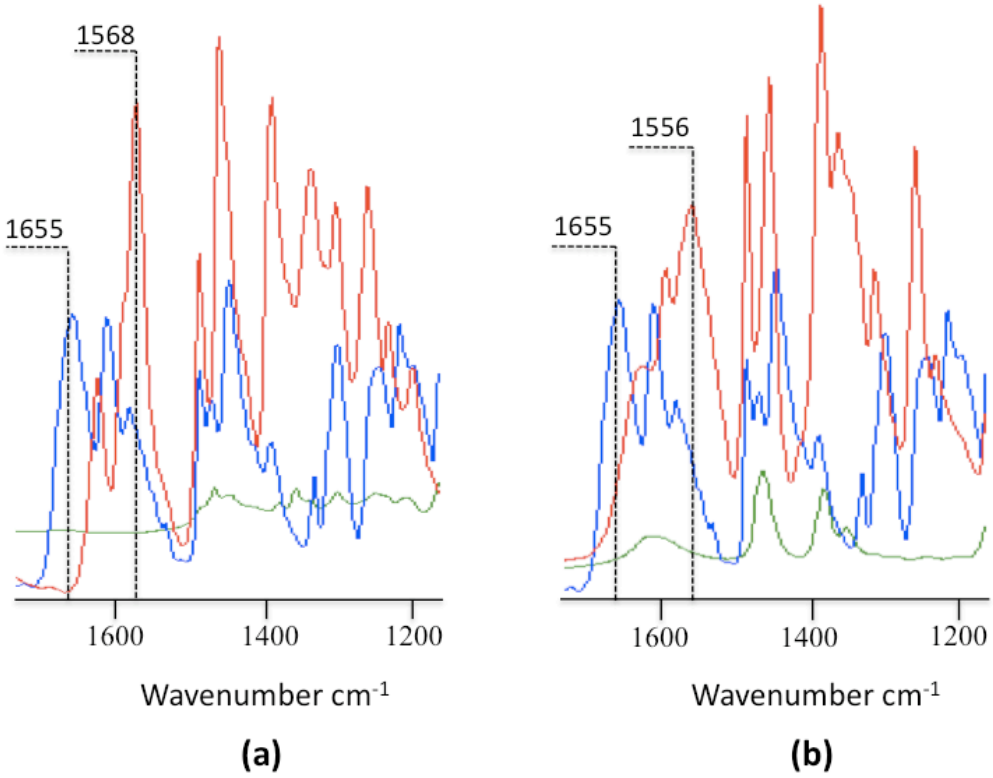


Figure 4. FTIR-ATR spectra of **(a)** (EtOH)pyrH^+ Sal^- (red), (EtOH)pyr (green) and SalH (blue) and **(b)** $N_TH_3^+$ Sal^- (red), N_TH_2 (green) and SalH (blue)

The effect of ion association is subtly revealed by the bulk properties in these systems. The density data (Figure 5) reveals two distinctly different groups of liquids, where the tertiary amine based PILs (including the 2:1 mixtures) appear to be denser than the primary amine based examples. This in turn implies that ions in the tertiary amine based PILs pack more tightly than in the primary amine based PILs. As will be shown below, the latter have a tendency to form open hydrogen bonded structures that produce lower densities.

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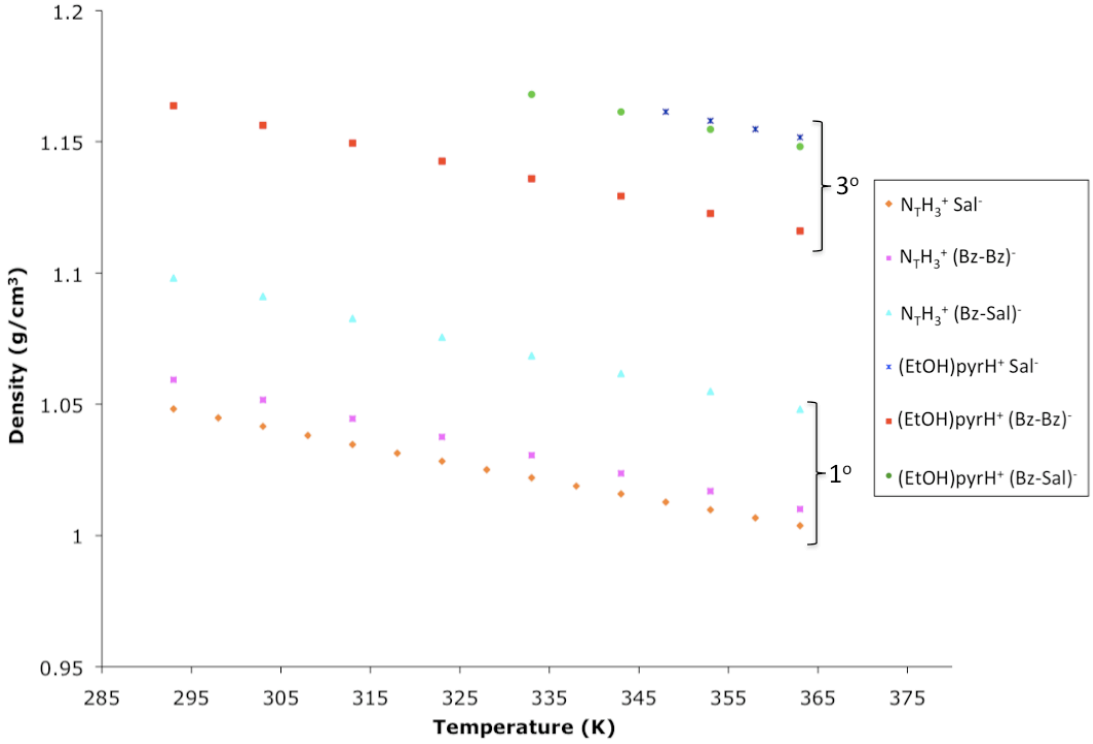


Figure 5. Density data of the synthesised PILs

The ionic conductivity (Figure 6) also shows two distinctly different groups of compounds; the tertiary amine based PILs have a conductivity approximately one order of magnitude greater than the primary amine based ILs, despite the fact that both families appear to be substantially proton transferred. On the other hand, their viscosities (Figure 6) show no distinct differences. Of all the compounds analysed in this study, the primary amine based PIL, $N_TH_3^+$ Sal^-, displayed the highest viscosity followed by the tertiary amine based PIL, (EtOH)pyrH^+ Sal^-.

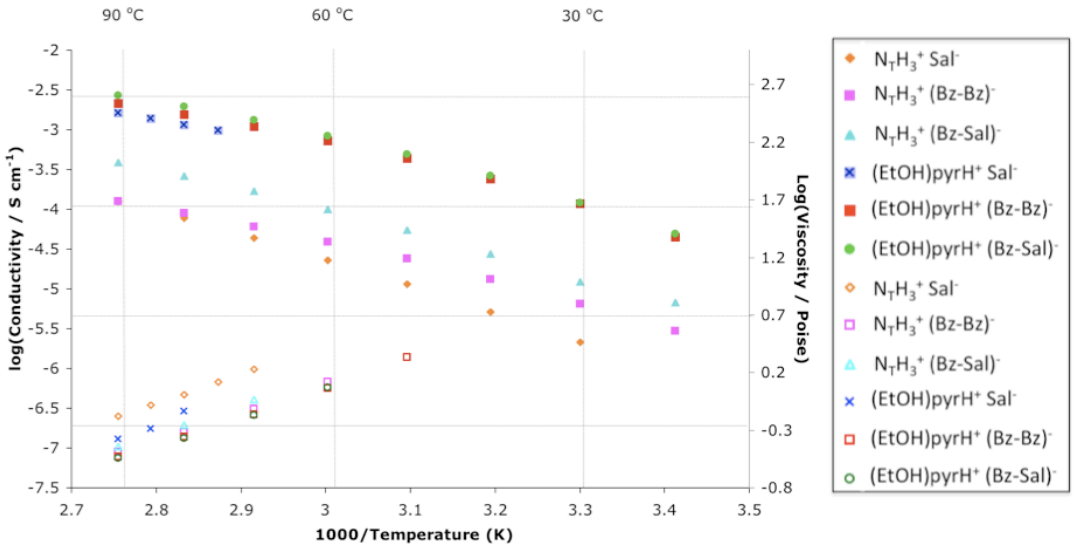


Figure 6. Conductivity (full symbols) and viscosity data (hollow symbols) of the synthesised PILs

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The transport property and density data can be combined into the Walden plot, to provide a revealing perspective on proton transfer and ion association. The Walden plot[25, 35, 36] is a method of comparing transport property data using the well-known Walden rule that states:

$$\Lambda\eta = k \qquad \text{Eqn 2}$$

where Λ is the molar conductivity and η is the viscosity. An estimate of the constant (k) can be obtained from data for a 0.1M aqueous solution of KCl, which is thought to be a good example of a fully dissociated salt. The Walden rule then appears as a straight line on a plot of log(molar conductivity) versus log(1/viscosity). Previous discussion of this in the literature[35] has shown that many ILs fall quite close to the Walden rule line, as do many molten salts. ILs that fall well below the line are thought of as exhibiting signs of ion association in a way that inhibits conduction, but not viscosity. Additionally, in the protic systems incomplete proton transfer can also produce transport properties that fall well below the line. As a reminder of the impact of the logarithmic scale of Figure 7, the dashed line indicates the situation where the molar conductivity is only 10% of that expected from the Walden rule. Such systems are clearly showing a low degree of proton transfer and/or strong signs of ion-association.

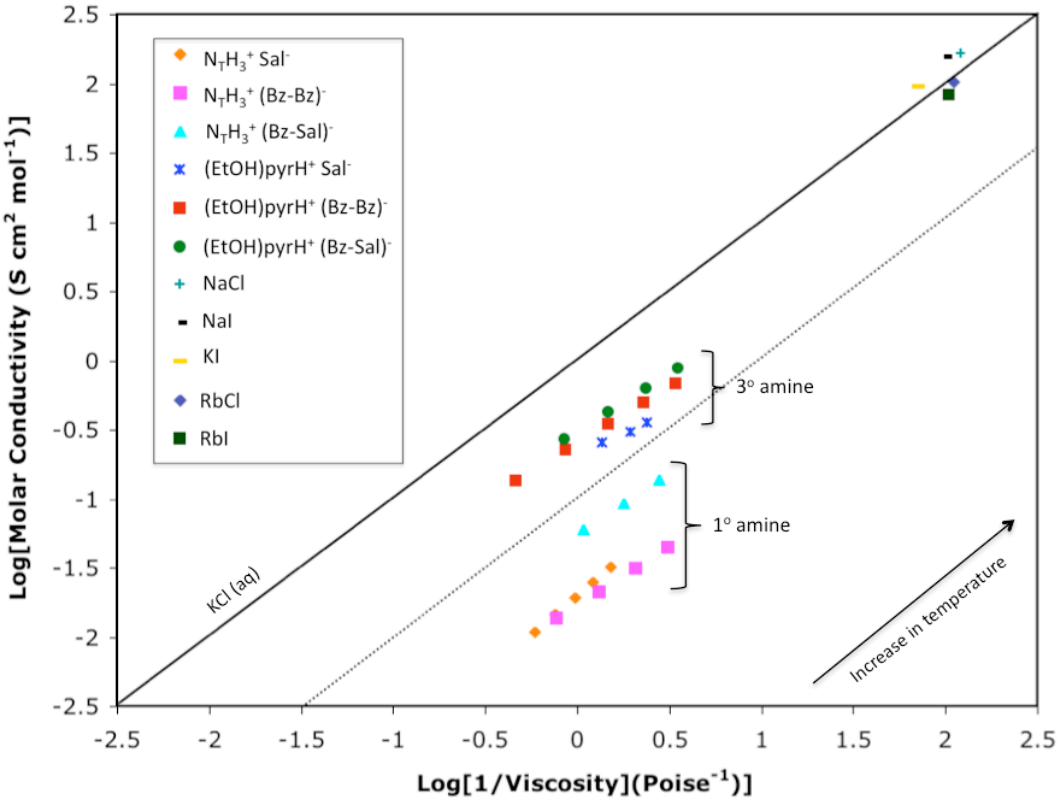


Figure 7. Walden plot of transport property data for the synthesised PILs. Each data set represents a temperature series for the compound above its melting point. Also included are some data points for a number of simple inorganic salts at temperatures just above their respective melting points.[37]

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In the Walden plot in Figure 7 the PILs based on the $N_TH_3^+$ cation display a significant deviation from the ideal line, whereas those containing the (EtOH)pyrH$^+$ cation show better concordance with the Walden rule. The latter is consistent with the infra-red evidence, which indicates strong proton transfer and might be considered a normal example of a PIL. However, the $N_TH_3^+$ salts appear surprisingly low on the Walden plot, given that the infra-red spectra indicated strong proton transfer. This perhaps indicates that these salts, although proton transferred, are highly associated in the liquid state. Ion pairs and larger clusters that have zero net charge are unable to conduct and therefore cannot contribute to the molar conductivity of the material. The N_TH_3 Sal case in Figure 7 is exhibiting only 1% of the conductivity that would be expected on the basis of the Walden rule; this indicates that the overwhelming majority of the ions in this case are "tied up" in ion pairs and clusters. We will return to the nature of association in these salts later, however, we will now present some data showing how association is of some importance in the membrane transport properties of these pharmaceutically active PILs.

3.4 Membrane Transport Properties

One of the benefits of synthesising IL forms of known actives is the potential to modulate the membrane permeation properties of an active. Tuning and controlling membrane transport is the key to a variety of novel delivery methods including slow, continuous-release transdermal approaches. Recent work by us[38] and others[39] provides some insight into the membrane transport properties of these pharmaceutically active IL compounds. It is a well established fact that salts *do not* readily cross the lipid bilayer unless there are active transport mechanisms available. Hence, it is not immediately obvious that IL forms of an active will be readily membrane permeable. On the other hand, if the IL has a propensity to form neutral species, ion-pairs or clusters then membrane transport may be enhanced as compared to an inorganic salt of the active. To further investigate this hypothesis in respect of these protic examples, we have carried out model membrane transport studies following the method of Tantishaiyakul *et. al.*.[39] A full publication describing these results will be presented elsewhere[38]; we present here an overview of the trends observed. Typical data, for example for $N_TH_3^+$ Sal$^-$ and its parent acid and base, as well as its simple salt forms that are used commercially, show that while the component acid is rapidly transported through the membrane, the sodium salt is not, nor is the sulfate salt (the form normally used pharmaceutically). On the other hand, the neat IL form, despite being a salt, is found to rapidly transport through the membrane over a period of one or two hours. Therefore the IL form is clearly more membrane permeable than the active ingredients that were the starting materials. Interestingly, the IL is *not* readily transported when dissolved in propylene glycol; this indicates that the situation is not simply one of providing an alternate, but independent, counter-ion. Indeed, Tantishaiyakul *et. al.* have speculated that ion-pairing can play a significant role in the transport of these types of compounds.[39] It is interesting to note that $N_TH_3^+$ Sal$^-$ shows signs of strong ion pairing/aggregation by sitting low in the Walden plot and hence this aspect of the behaviour of these PILs may be of importance in their membrane transport properties. The nature of this ion pairing/aggregation is further explored in the next sections. It is also possible that reverse proton transfer to form the neutral acid and base at the point of dissolution into the membrane is the basis of transport – partially the result of a relatively smaller pK_a gap than the inorganic salts. At this stage it is not possible to discriminate between these hypotheses, however doing so will allow us to understand how

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modulating the counter acid/base in these systems can be used to control their interaction with membranes.

3.5 Ion association - what can we learn from crystal structures?

Crystal structures can also provide some insight into the existence of proton transfer and ion association, and thereby serve as a guide to the existence of these phenomena in related liquid phases. Crystal structures for several of the compounds synthesised here have been solved and can be found in the supplementary information. The two ion-pairs shown in Figure 8 are the asymmetric units of the crystal structures of the tertiary amine based PIL, (EtOH)pyrH^+ Sal^-, and of the primary amine based PIL, $N_TH_3^+$ Gen^-. As can be seen from the displayed structures, the proton transfer has occurred in both cases. However, we should note that proton transfer in the solid state is likely to be stronger since it incurs a smaller entropic penalty than in the liquid and therefore produces a larger free energy change. This occurs because proton transfer in the neat liquid case causes a sharp loss of the configurational degrees of freedom that are characteristic of the liquid state and have a substantially negative ΔS.

Figure 8a also shows that the hydroxyl group of the (EtOH)pyrH^+ cation stabilises a resonating carbonyl group in the Sal^- anion, through hydrogen bonding, thus supporting the proton transfer. The O···H distances observed in this pair are 1.805 and 1.937 Å, comparable to the hydrogen bond distances in water.

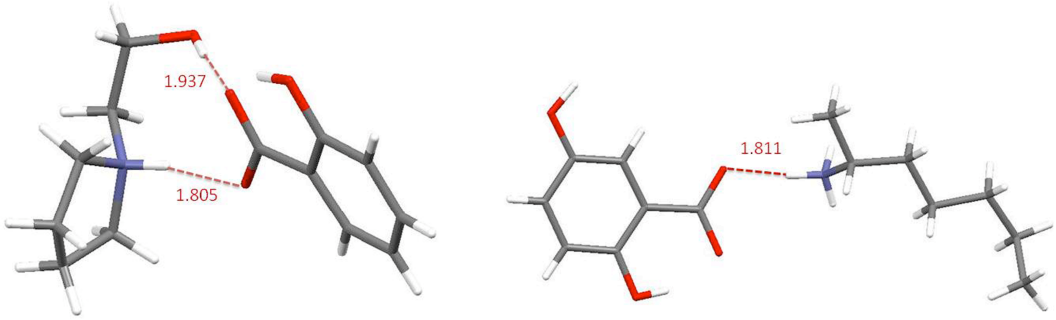


Figure 8. Crystal structures **(a)** of the tertiary amine based IL, (EtOH)pyrH^+ Sal^- (m.p. 49±2 °C); N-H···O and O-H···O distances are shown in red; **(b)** of the primary amine based salt, $N_TH_3^+$ Gen^- (m.p. 121±2 °C) (N-H···O distance is shown in red)

The asymmetric unit of $N_TH_3^+$ Gen^-, shown in Figure 8b, displays relatively short interionic N-H···O contacts of 1.811 Å, indicating strong hydrogen bonding between the ions. Additional O-H···O and C-H···O hydrogen bonding is also observed between the cations.

Although the proton transfer is clearly complete in both cases, in accord with the FTIR-ATR data, a large difference between their positions in the Walden plot (> 1 orders of magnitude) demands explanation - an explanation that cannot be based on lack of proton transfer. Figure 9 provides a possible answer; $N_TH_3^+$ Gen^- organises itself in the crystal in a cyclic cluster-like complex consisting of two cations and two anions.

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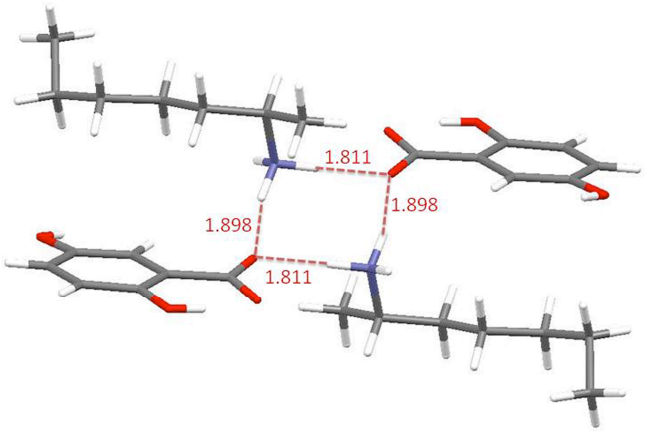


Figure 9. Cluster-like complex conformation of the primary amine based IL, $N_TH_3^+$ Gen^-

If a cyclic arrangement such as this, with its overall zero charge, is reasonably long lived in the liquid state then the molar conductivity will be lower than expected, despite the strong degree of proton transfer. Part of the origin of this cluster-like complex may lie in the inter-ring interactions as seen in Figure S2. $\pi \cdots \pi$ stacking between phenyl rings in the anions imposes a certain arrangement of ions in the crystal structure that results in a strong hydrogen-bonded lattice.

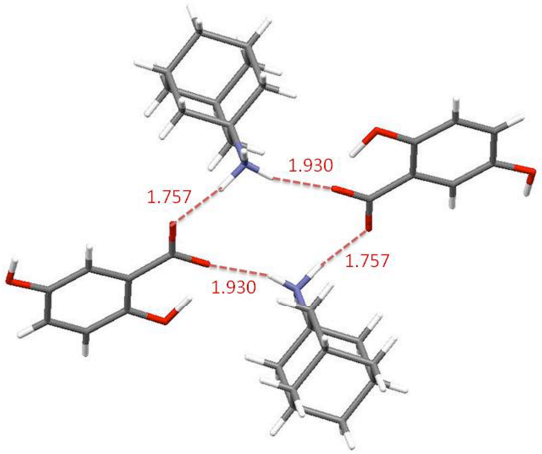


Figure 10. Cluster-like complex confirmation of the primary amine based IL, $N_AH_3^+$ Gen^-

Another example of this phenomenon was found in the analysis of the $N_AH_3^+$ Gen^- crystal structure (m.p. = 250±2 ^oC) containing the $N_AH_3^+$ ion (Figure 10). In this case, a cyclic cluster-like complex is formed with both oxygens of the carboxylic group partaking in hydrogen bonding. Due to spatial constraints, one of the $H \cdots O$ bonds is longer than the other by 0.173 Å. A closer inspection of the packing diagram reveals that the cyclic arrangement extends beyond the cluster-like complex, with oxygens of the COO^- group and the hydrogens of the NH_3^+ group forming distinct channels of hydrogen-bonded interactions (Figure S3). Extended associated structures would also have the effect of placing these compounds low on the Walden plot,

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despite there being a high degree of proton transfer. Associations such as these would appear to also be crucial to the rapid membrane transport of these salts.

Recently we have developed a generalised approach for the calculation of Madelung constants based on crystal structures.[18] The Madelung constant, M, represents a measure of the net electrostatic energy in ionic solids and thus determines the stability of the ionic lattice with respect to an isolated ion pair. For stable lattices M is expected to be more than 1, with larger values indicating greater stability of the lattice. The Madelung constant can also be viewed as a geometric parameter; it provides us with a static perspective on cation-anion arrangements that might persist to an extent in the liquid state. Values of the Madelung constant closer to 1 represent ionic solids dominated by ion-pair interactions, whereas larger values indicate an extended lattice of inter-ionic interactions. In this study Madelung constants and electrostatic lattice energies (Table 2) were calculated for the PILs whose crystal structures were resolved in this work. Inspection of Table 2 reveals values that are relatively low; by comparison, a simple symmetrical organic salt such as $[NMe_4][BF_4]$ has a Madelung constant close to that of NaCl (1.75). Ion association in the solid state is therefore lowering M considerably in all cases. Values for the $(EtOH)pyrH^+$ based salts are closer to 1, indicating that the ion pairs are somewhat more isolated in this case.

The electrostatic lattice energies also seem to generally follow the trend in measured melting points, with $N_AH_3^+$ based salts having the largest lattice energies and highest melting points. As discussed elsewhere,[40] this indicates that the electrostatic part of the lattice energy plays a dominant role in the overall energetics of melting of these compounds, despite the obvious influence of H-bonding and ion association in other properties.

Table 2. Madelung constants, electrostatic lattice energies and melting points of protic pharmaceutical salts prepared in this work.

	M	**Electrostatic Lattice energy, kJ mol^{-1}**	**T_m, °C**
$N_TH_3^+$ Gen$^-$	1.2307	-551	121
$N_AH_3^+$ Bz$^-$	1.2320	-624	256
$N_AH_3^+$ Sal$^-$	1.2566	-625	216
$N_AH_3^+$ Gen$^-$	1.2358	-616	250
(EtOH)pyrH Bz$^-$	1.1731	-546	28
(EtOH)pyrH Sal$^-$	1.0748	-493	49
(EtOH)pyrH Gen$^-$	1.0831	-487	97

3.6 Perspectives on Protonics

In a number of fields of application, including ionic liquids and solids for fuel cell electrolytes,[41] protein stabilising ionic liquids[34] and water electrolysis[42] the focus is on understanding the energetics and dynamics of protons and how they impact on the properties of the substance. Just as an understanding of the electronic structure of a molecule is vital to understanding its bonding and reactivity, we have found it useful

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to adopt a holistic view of protonic behaviour in these contexts in order to fully understand its subtleties. Much of the discussion above has concerned the location of the proton in these protic pharmaceutical systems, the consequences of its transfer from acid to base and the impact of its H-bonding, or lack of, in determining properties. The neat IL provides a rather unique environment in which to observe proton transfer, since there is an almost complete lack of a dielectric solvent to shield the charges from one another and the liquid is so concentrated that the charges are never more than one ion-pair diameter apart. Unlike water and other solvents, in which the protonic properties are heavily dominated by the properties of the *solvent*, in PILs the IL species themselves are the only acid and base present. The proton energy levels involved are therefore more directly revealed and manipulated, but they are also strongly impacted by the molecular structure of the species involved.

The distinction between the H-bonded acid-base complex and the H-bonded, proton-transferred ion-pair becomes very slight in a PIL. In fact, it amounts to simply the matter of where the proton sits on a potential energy surface between the two heavy atoms involved (usually N and O). This is illustrated in Figure 11 for the case of acetic acid and methylpyrrolidine in the gas phase, where the proton transfer amounts to only a ~0.4A° shift in an otherwise H-bonded complex. Charge is usually a significant distinction between these two states in a solvent based system, but becomes less so in the PIL, because H-bonding in the neutral complex involves some generation of a partial charge on each atom, while, on the other hand, H-bonding in the ion-pair acts to diminish the unit charge that notionally exists on the heavy atoms. In the case of acetic acid and methylpyrrolidine these minor changes in position and charge do not produce a sufficiently significant free energy change to create a substantial population of the proton transferred species, in either the gas phase or the ionic liquid.[26] As we will discuss in more detail below, further solvation interactions are required to push this proton transfer along.

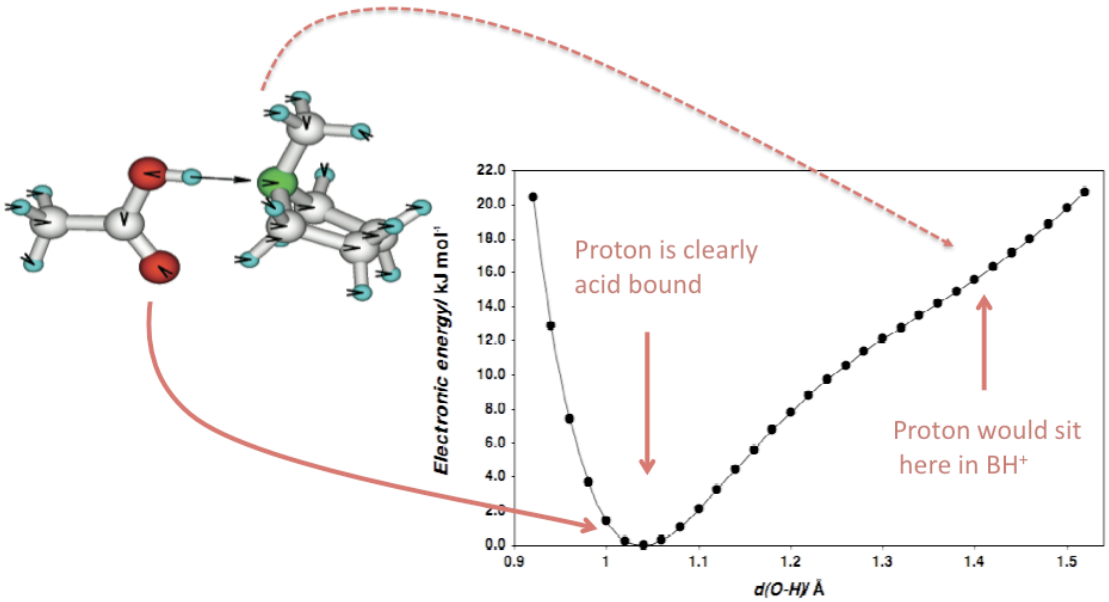


Figure 11. *Ab initio* calculations for acetic acid and methylpyrrolidine $\Delta pK_a^{aq} = 5$. The potential energy surface was generated as a relaxed scan of the O-H bond stretch at the MP2/6-31G+(d,p) level of theory. The optimised points on the PES were then

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improved at the MP2/aug-cc-pVTZ level of theory. All calculations were performed using GAUSSIAN 03[43]

Angell and coworkers[44, 45] have discussed the use of a proton free-energy scale, first introduced by Gurney[46], to assist in understanding the energetics in these materials. In this perspective, the proton site in an acid moiety is considered as one of high proton chemical potential, and the available site on the base moiety as being one of low proton chemical potential. The energy scale involved bears many features in common with electrochemical potential scales; in particular the chemical potential of the proton is the difference in free energies between that of the acid HA and its conjugate base A^-. The highest occupied proton level (HOPL) in the system thus corresponds to the species having the highest free energy change available from a proton donation process $HA \rightleftharpoons A^- + H^+$. The lowest unoccupied proton level (LUPL) similarly corresponds to the site offering the largest free energy change from a proton addition process. A number of scenarios are illustrated in Figure 12. Note that the LUPL of the base, B, is also the HOPL of the corresponding protonated species BH^+.

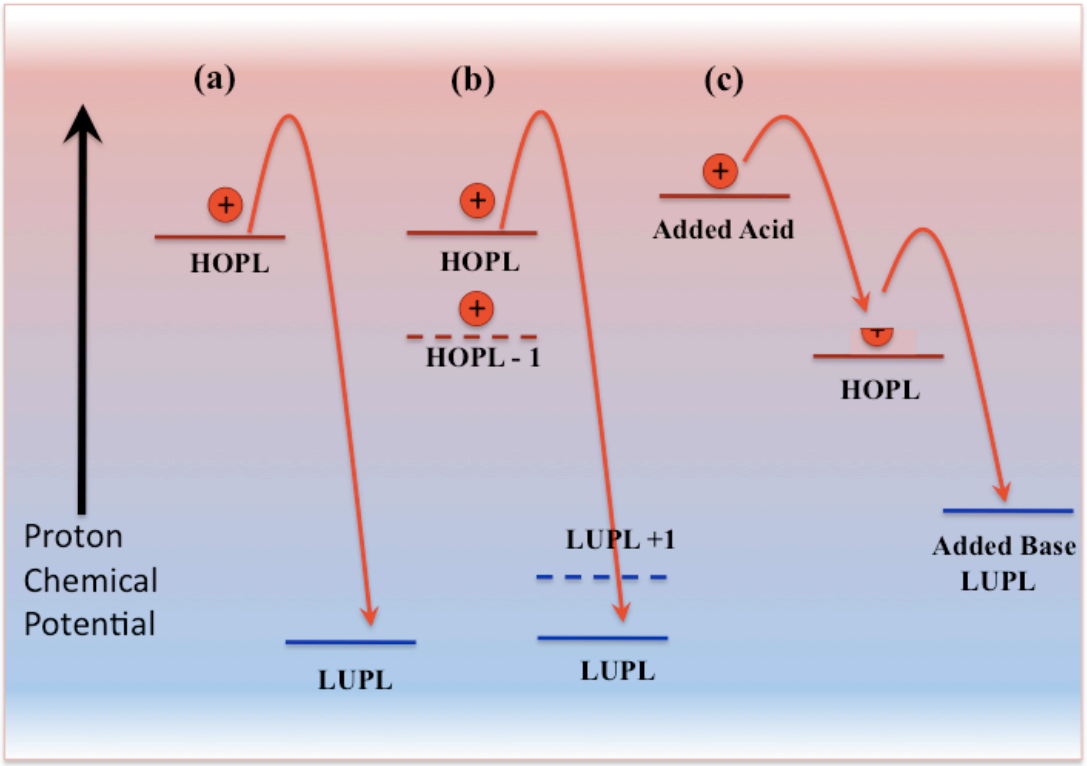


Figure 12. Proton Energy levels in (a) a simple, solvent-free acid-base mixture (b) a more complex case in which either the acid or base is multi-protic and (c) a buffer case where the HOPL is ~50% occupied and hence can accept or donate protons to an added strong acid or base to create a buffer action.[34]

The impact of hydrogen bonding and other solvation interactions on these proton energy levels is the key aspect we focus upon here, being dominated by the absence of, or limited presence of, H-bond donating species in the acid or base. Recognizing that the proton energy levels in Figure 12 actually represent a free energy change in a process that involves both the protonated and the unprotonated species, it is necessary

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to further deconstruct this diagram to explicitly identify the free energy of each species and then separately consider the effect of solvation on each. Figure 13 shows such an energy level diagram. The diagram begins by considering the isolated gas phase species and, as discussed above, in some cases there may be no proton transfer at all, as illustrated. Then, as shown in Figure 13, providing a source of solvation or additional hydrogen bonding, for example by a primary ammonium cation, impacts on the energy levels and hence ultimately on the proton transfer.[26] In the case of the protic systems described here, other H-bonding sites in the molecules have additional solvating effects and hence further alter the respective positions of the proton energy levels available.

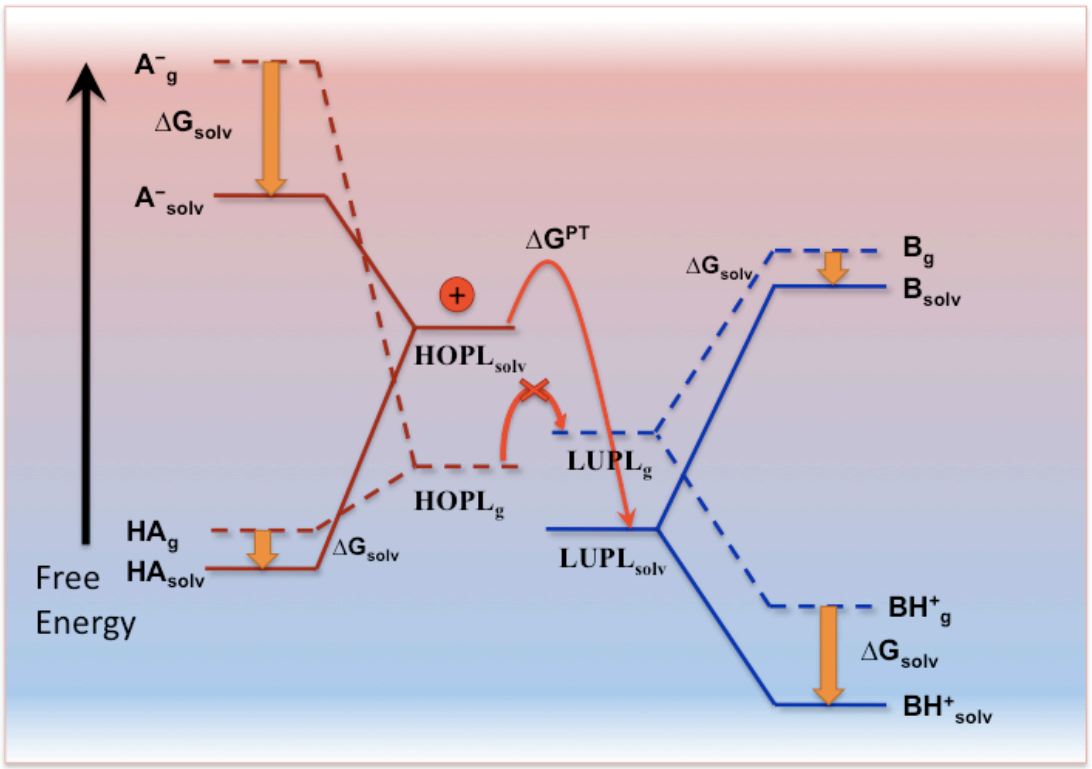


Figure 13. Free energy diagram showing the component molecular free energies that make up the proton energy levels in the gas phase and the effect of solvation on these.

Where proton transfer does not take place in the liquid state, despite the expectation from aqueous pK_a data that it should, another phenomenon related to H-bonding can occur: un-ionised acid-base complex formation, as shown in Figure 1b. A number of examples from the lidocaine:fatty acid family of liquids have been described recently in the context of pharmaceutically active compounds where the ΔpK_a^{aq} values were ~3 and it was shown that proton transfer did not take place.[47] In this situation the lack of H-bonding or solvation interactions strongly alters the positions of the individual ionised species in Figure 13 and thereby the HOPL and LUPL levels, to the point that proton transfer is not energetically favoured. However, a complete suppression of the melting point indicated formation, instead, of a hydrogen bonded acid-base complex. Such un-ionised complexes can be thought of as a liquid analogue of the "co-crystals" that are much studied in the pharmaceutical field. In the liquid co-crystal case the association of the two components produces a stabilising interaction in the liquid state that results in a sharp lowering of the melting point.

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4. Conclusions

A number of protic ionic liquids and salts based on pharmaceutical acids and bases have been synthesised and characterised. FTIR-ATR and Walden plot studies were used to assess the proton transfer and determine the degree of ionicity in the synthesised compounds. It was found that additional hydrogen bonding functional groups in the tertiary amine case can promote proton transfer. In the case of primary amines, formation of cluster-like species containing protonated base/deprotonated acid pairs can result in salts possessing higher melting points and decreased ionicity. These findings are supported by crystal structures and Madelung constant calculations. Nonetheless, for application purposes, PILs with lower ionicity are more desirable for drug delivery as they may cross the membrane barrier more easily than the more ionised species. Membrane studies are currently being carried out in order to further investigate this phenomenon and are showing promising results.

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Supplementary Information

Protic pharmaceutical ionic liquids and solids: Aspects of Protonics

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SYNTHESIS

$N_TH_3^+$ Bz^-

N_TH_2 (0.763 g, 6.622 mmol), dissolved in methanol, was slowly added to BzH (0.809 g, 6.622 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white solid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 0.82-0.88 (t, *J* 6.7, 3H), 1.13-1.16 (d, *J* 6.5, 3H), 1.25-1.55 (m, 8H), 3.01-3.08 (sextet, *J* 6.5, 1H), 7.26-7.35 (m, 3H), 7.85-7.90 (m, 2H). **MS** (**ESI**): ES+ *m/z*: 115.7 ($N_TH_3^+$), ES- *m/z:* 120.8 (Bz^-). **DSC:** T_m 91±2 °C.

Note: This compound has been reported previously by Rohrmann *et. al.*.[1] The melting point presented here agrees with the reported value.

$N_TH_3^+$ Sal^-

N_TH_2 (1.251 g, 10.860 mmol), dissolved in methanol, was slowly added to SalH (1.500 g, 10.860 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting viscous liquid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 0.83-0.89 (t, *J* 6.8, 3H), 1.16-1.20 (d, *J* 6.5, 3H), 1.26-1.57 (m, 8H), 3.11-3.21 (sextet, *J* 6.5, 1H), 6.57-6.65 (m, 2H), 7.10-7.15 (m, 1H), 7.64-7.69 (m, 1H), 7.87-8.08 (s(b), 1H). **MS** (**ESI**): ES+ *m/z*: 116.14 ($N_TH_3^+$), ES- *m/z:* 137.0 (Sal^-), 93.0 (Sal^- - OC=O). **DSC:** T_g -40±2 °C.

$N_TH_3^+$ Gen^-

N_TH_2 (0.748 g, 6.488 mmol), dissolved in methanol, was slowly added to GenH (1.000 g, 6.488 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting opaque solid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 0.83-0.87 (t, *J* 6.8, 3H), 1.18-1.19 (d, *J* 6.4, 3H), 1.21-1.33 (m, 6H), 1.41-1.45 (sextet, *J* 7.6, 1H), 1.58-1.61 (sextet, *J* 7.6, 1H), 3.13-3.18 (m, 1H), 6.48-6.50 (d, *J* 8.8, 1H), 6.63-6.66 (m, 1H), 7.15 (d, *J* 3.1, 1H), 7.98-8.45 (s(b), 1H). **MS** (**ESI**): ES+ *m/z*: 116.0 ($N_TH_3^+$), ES- *m/z:* 152.9 (Gen^-). **DSC:** T_m 121±2 °C.

$N_AH_3^+$ Bz^-

N_AH_2 (1.500 g, 9.917 mmol), dissolved in methanol, was slowly added to BzH (1.211 g, 9.917 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white powder was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 1.52-1.73 (m, 12H), 2.04 (s(b), 3H), 3.17-4.89 (s(b), 1H), 7.32-7.36 (m,

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3H), 7.85-7.90 (m, 2H). **MS** (**ESI**): ES+ *m/z*: 151.9 ($N_AH_3^+$), ES- *m/z:* 120.9 (Bz^-). **DSC:** T_m 256±2 °C.
Note: The above compound has been previously reported by Zheng *et. al.*[2] in a crystal structure report. The synthetic details are very comparable to those above but the characterisation data has not been reported. We have also solved the crystal structure of our synthesised compound.

$N_AH_3^+$ Sal^-
N_AH_2 (1.500 g, 9.917 mmol), dissolved in methanol, was slowly added to SalH (1.370 g, 9.917 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white solid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 1.54-1.81 (m, 12H), 2.09 (s(b), 3H), 3.08-4.53 (s(b), 1H), 6.56-6.65 (m, 2H), 7.10-7.18 (m, 1H), 7.64-7.70 (m, 1H), 7.79-8.24 (s(b), 1H). **MS** (**ESI**): ES+ *m/z*: 151.8 ($N_AH_3^+$), ES- *m/z:* 136.8 (Sal^-), 92.8 (Sal^- - OC=O). **DSC:** T_m 216±2 °C.
Note: The above compound has been previously reported before in a patent.[3]

$N_AH_3^+$ Gen^-
N_AH_2 (1.472 g, 9.733 mmol), dissolved in methanol, was slowly added to GenH (1.500 g, 9.733 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white powder was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 1.48-1.80 (m, 12H), 2.02-2.09 (s(b), 3H), 3.11-3.48 (s(b), 1H), 6.42-6.46 (m, 1H), 6.56-6.62 (m, 1H), 7.12-7.13 (d, *J* 2.8, 1H), 7.92-8.13 (s(b), 1H). **MS** (**ESI**): ES+ *m/z*: 152.0 ($N_AH_3^+$), ES- *m/z:* 153.0 (Gen^-), 307.0 (2 x Gen^- + H^+), 329.0 (2 x Gen^- + Na^+), 505.0 (3 x Gen^- + 2 x Na^+). **DSC:** T_m 250±2 °C.

(EtOH)pyrH^+ Bz^-
(EtOH)pyr (0.979 g, 8.501 mmol), dissolved in methanol, was slowly added to BzH (1.038 g, 8.501 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting yellow solid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 1.79-1.83 (p, *J* 3.6, 4H), 2.89-2.97 (m, 6H), 3.63-3.66 (t, *J* 6.0, 2H), 6.42-7.12 (s(b), 1H), 7.36-7.40 (m, 2H), 7.43-7.47 (m, 1H), 7.91-7.93 (m, 2H). **MS** (**ESI**): ES+ *m/z*: 116.1 ((EtOH)pyrH^+), ES- *m/z:* 120.8 (Bz^-), 265.0 (2 x Bz^- + Na^+). **DSC:** T_g -40±2 °C, T_r -24±2 °C, T_m 28±2 °C.

(EtOH)pyrH^+ Sal^-
(EtOH)pyr (1.251 g, 10.860 mmol), dissolved in methanol, was slowly added to SalH (1.500 g, 10.860 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting yellow solid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 1.91-1.99 (p, *J* 3.5, 4H), 3.17-3.31 (m, 6H), 3.69-3.75 (t, *J* 5.5, 2H), 6.60-6.69 (m, 2H), 7.14-7.22 (m, 1H), 7.67-7.72 (m, 1H). **MS** (**ESI**): ES+ *m/z*: 116.0 ((EtOH)pyrH^+), ES- *m/z:* 136.8 (Sal^-), 92.7 (Sal^- - OC=O). **DSC:** T_g -44±2 °C, T_r 6±2 °C, T_m 49±2 °C.

(EtOH)pyrH^+ Gen^-
(EtOH)pyr (0.747 g, 6.488 mmol), dissolved in methanol, was slowly added to GenH (1.000 g, 6.488 mmol) in methanol solution. The reaction was stirred for 4 hours in an

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ice bath. Methanol was subsequently removed under vacuum and the resulting yellow solid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (200 MHz, DMSO-d_6) δ (ppm) 1.91-1.99 (p, *J* 3.5, 4H), 3.15-3.30 (m, 6H), 3.69-3.75 (t, *J* 5.5, 2H), 6.49-6.53 (d, *J* 8.6, 1H), 6.64-6.70 (d(d), *J* 8.6, 3.1, 1H), 7.15-7.16 (d, *J* 3.1, 1H). **MS (ESI)**: ES+ *m/z*: 115.9 ((EtOH)pyrH$^+$), ES- *m/z:* 152.9 (Gen$^-$), 307.1 (2 x Gen$^-$ + H$^+$), 328.9 (2 x Gen$^-$ + Na$^+$). **DSC:** T_m 97±2 °C.

***$N_TH_3^+$ (Bz-Bz)$^-$**

N_TH_2 (2.278 g, 19.771 mmol), dissolved in methanol, was slowly added to BzH (4.829 g, 39.543 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting colourless viscous liquid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 0.81-0.84 (t, *J* 6.4, 3H), 1.18-1.20 (d, *J* 6.4, 3H), 1.23-1.32 (m, 6H), 1.37-1.44 (m, 1H), 1.58-1.65 (m, 1H), 3.12-3.17 (sextet, *J* 6.4 1H), 7.26-7.35 (m, 6H), 7.85-7.90 (m, 4H). **DSC:** T_g -43±2 °C.

***$N_TH_3^+$ (Bz-Sal)$^-$**

N_TH_2 (2.043 g, 17.731 mmol), dissolved in methanol, was slowly added to a mixture of SalH (2.449g, 17.731 mmol) and BzH (2.165 g, 17.731 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting colourless viscous liquid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 0.83-0.86 (t, *J* 6.8, 3H), 1.18-1.19 (d, *J* 6.4, 3H), 1.21-1.34 (m, 6H), 1.38-1.45 (m, 1H), 1.55-1.62 (m, 1H), 3.14-3.18 (sextet, *J* 6.4 1H), 6.63-6.69 (m, 2H), 7.16-1.21 (m, 1H), 7.47-7.51 (m, 2H), 7.58-7.63 (m, 1H), 7.70-7.72 (m, 1H), 7.94-7.97(m, 2H), 7.98-8.34 (s(b), 1H). **DSC:** T_g -40±2 °C.

***(EtOH)pyrH$^+$ (Bz-Bz)$^-$**

(EtOH)pyr (2.243 g, 19.476 mmol), dissolved in methanol, was slowly added to BzH (4.757 g, 38.953 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting yellow viscous liquid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 1.84-1.88 (p, *J* 3.6, 4H), 3.02-3.04 (t, *J* 5.6, 2H), 3.07-3.11 (m, 4H), 3.67-3.70 (t, *J* 5.6, 2H), 7.41-7.45 (m, 4H), 7.49-7.54 (m, 2H), 7.55-7.90 (s(b), 1H), 7.92-7.95 (m, 4H). **DSC:** T_g -49±2 °C.

***(EtOH)pyrH$^+$ (Bz-Sal)$^-$**

(EtOH)pyr (2.147 g, 16.642 mmol), dissolved in methanol, was slowly added to a mixture of SalH(2.575 g, 16.642 mmol) and BzH (2.277 g, 16.642 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting yellow viscous liquid was dried at 40 °C on a Schlenk line (~0.3 torr). **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm) 1.91-1.94 (p, *J* 3.6, 4H), 3.02-3.04 (t, *J* 5.6, 2H), 3.07-3.11 (m, 4H), 3.67-3.70 (t, *J* 5.6, 2H), 6.64-6.70 (m, 2H), 7.18-7.22 (m, 1H), 7.47-7.51 (m, 2H), 7.59-7.63 (m, 1H), 7.70-7.73 (m, 1H), 7.94-7.94 (m, 2H). **DSC:** T_g -46±2 °C.

***All of the dimer compounds showed evidence of partial crystallinity at room temperature. All characterisation measurements were carried out above the apparent melting point.**

FTIR-ATR

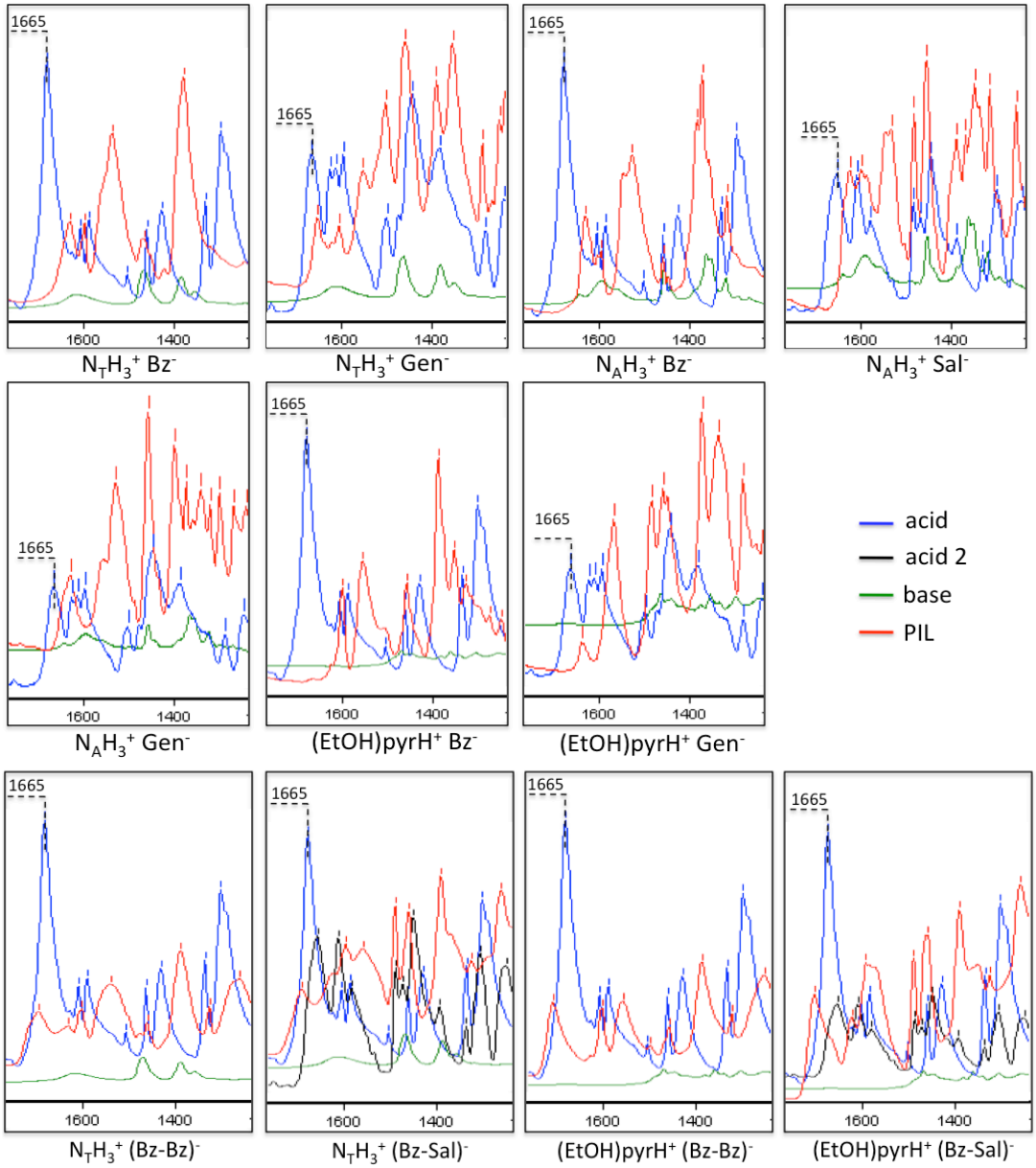


Figure S1. FTIR-ATR data for the synthesised compounds

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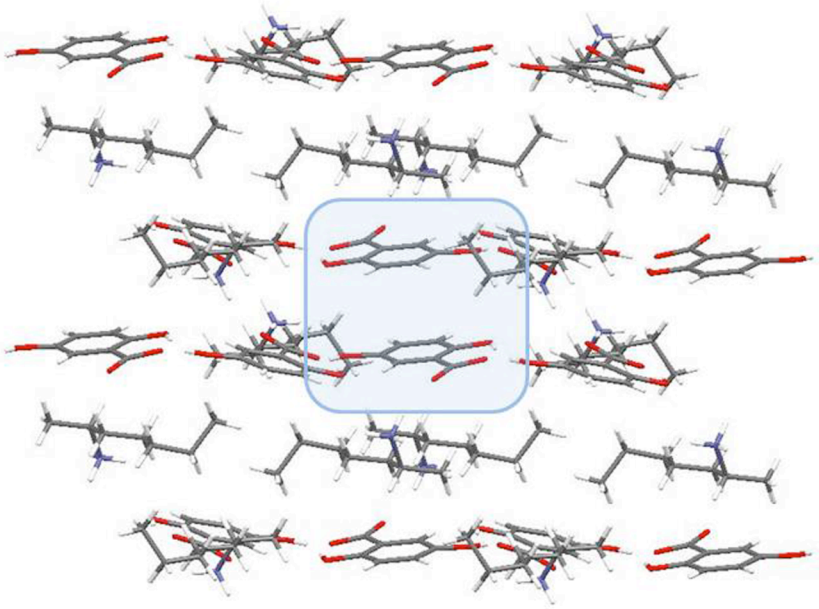


Figure S2. π···π stacking observed in the primary amine based ionic liquid, $N_TH_3^+$ Gen^-

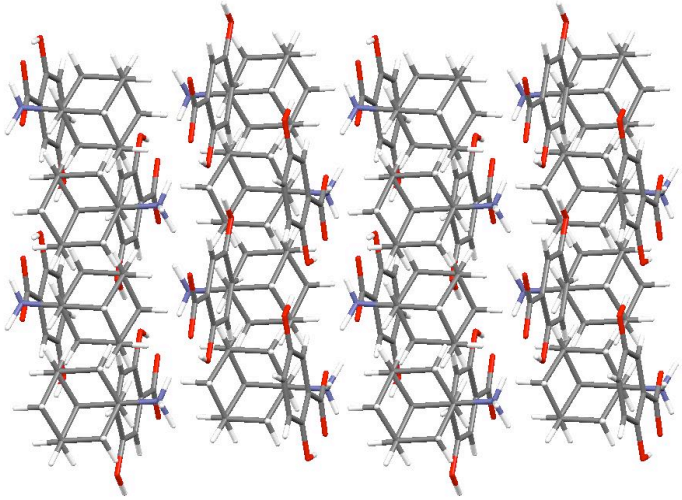


Figure S3. Distinct channels observed in the crystal structure of the ionic liquid forming salt, $N_AH_3^+$ Gen^-.

The crystal structure reports are attached as separate documents while the CCDC Refcodes can be found in the experimental section of the main article.

References

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2. W. N. Zheng and B. Wang, *Acta Crystallogr., Sect. E Struct. Rep. Online*, 2009, **E65**, o2769.
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1-(2-hydroxyethyl)pyrrolidin-1-ium benzoate

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1-(2-hydroxyethyl)pyrrolidin-1-ium benzoate, $C_6H_{14}N_1O_1$. $C_7H_5O_2$, displays interionic N—H···O, C—H···O and O—H···O hydrogen bonding and interanionic C—H···O hydrogen bonding. A π···π ring interaction is also seen.

Experimental

Crystal data

$C_6H_{14}NO·C_7H_5O_2$
$M_r = 237.29$
Monoclinic, $C2/c$
$a = 19.760$ (4) Å
$b = 11.178$ (2) Å
$c = 11.485$ (2) Å
$\beta = 95.28$ (1)°
$V = 2525.9$ (7) Å^3
$Z = 8$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$\mu = 0.09$ mm^{-1}
$T = 123$ K
0.20 × 0.20 × 0.20 mm

Data collection

Bruker X8 APEX KAPPA CCD diffractometer
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)
$T_{min} = 0.983$, $T_{max} = 0.983$
16525 measured reflections
3152 independent reflections
1676 reflections with $I > 2\sigma(I)$
$R_{int} = 0.066$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.049$
$wR(F^2) = 0.131$
$S = 1.00$
3152 reflections
158 parameters
0 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.20$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O2*A*^{i}	1.06	1.61	2.6483 (18)	165
O1—H1*O*···O1*A*^{i}	0.98	1.72	2.7078 (18)	179
C3*A*—H3*AA*···O1*A*^{ii}	0.95	2.49	3.371 (2)	154
C1—H1*A*···O1^{iii}	0.99	2.53	3.382 (2)	145
C4—H4*B*···O1*A*	0.99	2.53	3.436 (2)	152

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Symmetry codes: (i) *x*, −*y*−1, *z*+1/2; (ii) −*x*+1/2, −*y*+1/2, −*z*+1; (iii) −*x*+1/2, −*y*−1/2, −*z*+1.

Table 2

Geometrical parameters (Å, °) of selected inter-ring π—π interactions. α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
Cg1	Cg1	4.9166 (15)	0	-X,-Y,1-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Data collection: Bruker Apex II V 1.0 (Bruker ASX, 2005); cell refinement: Bruker Apex II V 1.0 (Bruker ASX, 2005); data reduction: Bruker Apex II V 1.0 (Bruker ASX, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *POV-RAY* for windows, version 3.1; software used to prepare material for publication: Microsoft Office.

References

NOT FOUND

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supplementary materials

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1-(2-hydroxyethyl)pyrrolidin-1-ium benzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single 1-(2-hydroxy-ethyl)-pyrrolidinium cation and a single benzoate anion (Figure 1). The 1-(2-hydroxy-ethyl)-pyrrolidinium cation adopts the preferred chair conformation with the hydroxyl substituent adopting a gauche conformation with a torsional angle of -66.3 (2) ° [N1—C5—C6—O1], which is not the energetically favoured conformation. The hydrogen (H1N) was located in the fourier difference map at a 1.06 (4) Å distance away from N1. The benzoate anion displays a planar aromatic ring with one carboxylic acid group displaying standard bond distances and angles (C1A—O1A 1.257 (2) and C1A—O2A 1.261 (2) Å respectively). Three main types of hydrogen bonding occurs, strong O—H···O and N—H···O hydrogen bonding and weak interionic C—H···O hydrogen bonding (Table 1, Figure 2). A π···π interaction is also seen (Table 2). The extended structure (Figure 3) consists of distinct layers of cations and anions, which are connected by the above mentioned hydrogen bonds. The aromatic moeities are grouped together via the π···π interaction and the charged centres are clearly grouped and linked via hydrogen bonding (Figure 4).

Experimental

1-(2-hydroxyethyl)-pyrrolidine (0.979 g, 8.501 mmol), dissolved in methanol, was slowly added to benzoic acid (1.038 g, 8.501 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting yellow solid was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the N—H and O—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

1-(2-hydroxyethyl)pyrrolidin-1-ium benzoate

Crystal data

$C_6H_{14}NO{\cdot}C_7H_5O_2$	$F(000) = 1024$
$M_r = 237.29$	$D_x = 1.248$ Mg m^{-3}
Monoclinic, $C2/c$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Hall symbol: -C 2yc	Cell parameters from 1724 reflections
$a = 19.760$ (4) Å	$\theta = 2.7–20.1°$
$b = 11.178$ (2) Å	$\mu = 0.09$ mm^{-1}
$c = 11.485$ (2) Å	$T = 123$ K
$\beta = 95.28$ (1)°	Anhedral, Yellow
$V = 2525.9$ (7) Å^3	0.20 × 0.20 × 0.20 mm

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$Z = 8$

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	3152 independent reflections
Radiation source: fine-focus sealed tube	1676 reflections with $I > 2\sigma(I)$
graphite	$R_{int} = 0.066$
0.5 deg frames in phi and ω scans	$\theta_{max} = 28.5°$, $\theta_{min} = 2.7°$
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	$h = -24 \rightarrow 26$
$T_{min} = 0.983$, $T_{max} = 0.983$	$k = -14 \rightarrow 14$
16525 measured reflections	$l = -13 \rightarrow 15$

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.049$	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2) = 0.131$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.00$	$w = 1/[\sigma^2(F_o^2) + (0.057P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
3152 reflections	$(\Delta/\sigma)_{max} < 0.001$
158 parameters	$\Delta\rho_{max} = 0.20$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.19$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O2A	0.15506 (6)	0.23557 (10)	0.79772 (10)	0.0411 (3)
O1A	0.22717 (6)	0.28472 (10)	0.66732 (10)	0.0436 (3)
O1	0.18219 (6)	−0.20488 (10)	0.64121 (11)	0.0491 (4)
N1	0.30678 (6)	−0.06656 (11)	0.58757 (11)	0.0335 (3)
C2A	0.11844 (8)	0.21267 (13)	0.59740 (14)	0.0336 (4)
C3A	0.13424 (9)	0.20345 (13)	0.48291 (14)	0.0369 (4)
H3AA	0.1794	0.2181	0.4643	0.044*

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C1A	0.17097 (8)	0.24600 (13)	0.69441 (15)	0.0339 (4)
C4	0.31957 (8)	0.02385 (15)	0.68317 (13)	0.0381 (4)
H4A	0.2964	0.0011	0.7527	0.046*
H4B	0.3037	0.1042	0.6565	0.046*
C3	0.39607 (9)	0.02180 (16)	0.71020 (15)	0.0441 (5)
H3A	0.4095	−0.0376	0.7719	0.053*
H3B	0.4131	0.1015	0.7366	0.053*
C1	0.36295 (8)	−0.04432 (15)	0.51128 (14)	0.0425 (5)
H1B	0.3512	0.0226	0.4566	0.051*
H1A	0.3719	−0.1167	0.4655	0.051*
C5	0.23817 (8)	−0.06143 (16)	0.52255 (15)	0.0444 (5)
H5A	0.2359	−0.1208	0.4583	0.053*
H5B	0.2314	0.0189	0.4870	0.053*
C6	0.18158 (9)	−0.08598 (15)	0.59860 (17)	0.0491 (5)
H6B	0.1856	−0.0301	0.6657	0.059*
H6A	0.1375	−0.0705	0.5530	0.059*
C7A	0.05275 (10)	0.19311 (19)	0.62217 (18)	0.0602 (6)
H7AA	0.0417	0.1983	0.7008	0.072*
C2	0.42412 (9)	−0.01300 (17)	0.59498 (16)	0.0503 (5)
H2B	0.4495	0.0546	0.5642	0.060*
H2A	0.4550	−0.0825	0.6066	0.060*
C4A	0.08440 (10)	0.17298 (17)	0.39560 (16)	0.0551 (5)
H4AA	0.0955	0.1646	0.3173	0.066*
C5A	0.01867 (12)	0.1548 (2)	0.42230 (19)	0.0827 (8)
H5AA	−0.0157	0.1343	0.3622	0.099*
C6A	0.00273 (11)	0.1662 (2)	0.5349 (2)	0.0890 (9)
H6AA	−0.0428	0.1555	0.5530	0.107*
H1N	0.3157	−0.1522	0.6248	0.063 (5)*
H1O	0.2152	−0.2079	0.7106	0.085 (8)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O2A	0.0480 (8)	0.0454 (7)	0.0309 (7)	−0.0095 (5)	0.0080 (6)	−0.0030 (5)
O1A	0.0327 (7)	0.0558 (8)	0.0433 (7)	−0.0059 (5)	0.0087 (6)	−0.0049 (6)
O1	0.0459 (8)	0.0452 (7)	0.0548 (9)	−0.0076 (6)	−0.0022 (7)	0.0049 (6)
N1	0.0362 (8)	0.0359 (8)	0.0284 (7)	0.0016 (6)	0.0026 (6)	0.0008 (6)
C2A	0.0321 (10)	0.0362 (9)	0.0330 (10)	−0.0005 (7)	0.0062 (8)	−0.0036 (7)
C3A	0.0407 (10)	0.0343 (9)	0.0364 (10)	−0.0007 (7)	0.0070 (8)	0.0006 (7)
C1A	0.0347 (10)	0.0297 (8)	0.0381 (10)	0.0014 (7)	0.0079 (8)	−0.0026 (7)
C4	0.0439 (11)	0.0393 (9)	0.0320 (9)	−0.0014 (8)	0.0079 (8)	−0.0031 (7)
C3	0.0423 (11)	0.0507 (10)	0.0395 (10)	−0.0091 (8)	0.0051 (8)	−0.0010 (8)
C1	0.0503 (11)	0.0466 (10)	0.0328 (10)	−0.0010 (8)	0.0155 (9)	0.0002 (8)
C5	0.0419 (11)	0.0454 (10)	0.0437 (10)	0.0008 (8)	−0.0088 (9)	0.0055 (8)
C6	0.0371 (10)	0.0484 (11)	0.0599 (12)	−0.0010 (8)	−0.0057 (9)	0.0072 (9)
C7A	0.0405 (12)	0.0999 (17)	0.0417 (12)	−0.0159 (11)	0.0128 (10)	−0.0145 (11)
C2	0.0441 (11)	0.0605 (12)	0.0481 (11)	−0.0024 (9)	0.0141 (9)	0.0010 (9)
C4A	0.0642 (14)	0.0672 (13)	0.0341 (11)	−0.0101 (11)	0.0060 (10)	−0.0032 (9)
C5A	0.0608 (16)	0.138 (2)	0.0480 (14)	−0.0356 (15)	−0.0046 (12)	−0.0109 (14)
C6A	0.0443 (13)	0.165 (3)	0.0579 (15)	−0.0396 (15)	0.0055 (12)	−0.0200 (16)

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Geometric parameters (Å, º)

O2A—C1A	1.2605 (19)	C3—H3B	0.9900
O1A—C1A	1.2573 (19)	C1—C2	1.515 (2)
O1—C6	1.4159 (19)	C1—H1B	0.9900
O1—H1O	0.9834	C1—H1A	0.9900
N1—C5	1.4876 (19)	C5—C6	1.506 (2)
N1—C4	1.4965 (19)	C5—H5A	0.9900
N1—C1	1.497 (2)	C5—H5B	0.9900
N1—H1N	1.0568	C6—H6B	0.9900
C2A—C7A	1.372 (2)	C6—H6A	0.9900
C2A—C3A	1.383 (2)	C7A—C6A	1.375 (3)
C2A—C1A	1.498 (2)	C7A—H7AA	0.9500
C3A—C4A	1.382 (2)	C2—H2B	0.9900
C3A—H3AA	0.9500	C2—H2A	0.9900
C4—C3	1.515 (2)	C4A—C5A	1.377 (3)
C4—H4A	0.9900	C4A—H4AA	0.9500
C4—H4B	0.9900	C5A—C6A	1.365 (3)
C3—C2	1.531 (2)	C5A—H5AA	0.9500
C3—H3A	0.9900	C6A—H6AA	0.9500

C6—O1—H1O	107.2	C2—C1—H1A	110.8
C5—N1—C4	115.27 (12)	H1B—C1—H1A	108.8
C5—N1—C1	112.98 (12)	N1—C5—C6	113.13 (13)
C4—N1—C1	103.48 (12)	N1—C5—H5A	109.0
C5—N1—H1N	110.4	C6—C5—H5A	109.0
C4—N1—H1N	107.7	N1—C5—H5B	109.0
C1—N1—H1N	106.4	C6—C5—H5B	109.0
C7A—C2A—C3A	119.08 (16)	H5A—C5—H5B	107.8
C7A—C2A—C1A	119.31 (16)	O1—C6—C5	112.85 (14)
C3A—C2A—C1A	121.60 (15)	O1—C6—H6B	109.0
C4A—C3A—C2A	120.01 (16)	C5—C6—H6B	109.0
C4A—C3A—H3AA	120.0	O1—C6—H6A	109.0
C2A—C3A—H3AA	120.0	C5—C6—H6A	109.0
O1A—C1A—O2A	124.56 (16)	H6B—C6—H6A	107.8
O1A—C1A—C2A	117.96 (15)	C2A—C7A—C6A	120.95 (18)
O2A—C1A—C2A	117.47 (14)	C2A—C7A—H7AA	119.5
N1—C4—C3	103.77 (13)	C6A—C7A—H7AA	119.5
N1—C4—H4A	111.0	C1—C2—C3	106.02 (14)
C3—C4—H4A	111.0	C1—C2—H2B	110.5
N1—C4—H4B	111.0	C3—C2—H2B	110.5
C3—C4—H4B	111.0	C1—C2—H2A	110.5
H4A—C4—H4B	109.0	C3—C2—H2A	110.5
C4—C3—C2	105.10 (13)	H2B—C2—H2A	108.7
C4—C3—H3A	110.7	C5A—C4A—C3A	119.91 (18)
C2—C3—H3A	110.7	C5A—C4A—H4AA	120.0
C4—C3—H3B	110.7	C3A—C4A—H4AA	120.0
C2—C3—H3B	110.7	C6A—C5A—C4A	120.1 (2)
H3A—C3—H3B	108.8	C6A—C5A—H5AA	119.9
N1—C1—C2	104.97 (12)	C4A—C5A—H5AA	119.9

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N1—C1—H1B	110.8	C5A—C6A—C7A	119.9 (2)
C2—C1—H1B	110.8	C5A—C6A—H6AA	120.1
N1—C1—H1A	110.8	C7A—C6A—H6AA	120.1

C7A—C2A—C3A—C4A	−1.1 (2)	C4—N1—C5—C6	−62.36 (18)
C1A—C2A—C3A—C4A	−179.73 (15)	C1—N1—C5—C6	178.95 (13)
C7A—C2A—C1A—O1A	−167.12 (16)	N1—C5—C6—O1	−66.29 (19)
C3A—C2A—C1A—O1A	11.5 (2)	C3A—C2A—C7A—C6A	−0.8 (3)
C7A—C2A—C1A—O2A	11.4 (2)	C1A—C2A—C7A—C6A	177.88 (19)
C3A—C2A—C1A—O2A	−169.93 (14)	N1—C1—C2—C3	−18.24 (18)
C5—N1—C4—C3	−164.87 (13)	C4—C3—C2—C1	−6.84 (19)
C1—N1—C4—C3	−41.02 (15)	C2A—C3A—C4A—C5A	1.7 (3)
N1—C4—C3—C2	29.34 (17)	C3A—C4A—C5A—C6A	−0.4 (4)
C5—N1—C1—C2	162.06 (14)	C4A—C5A—C6A—C7A	−1.5 (4)
C4—N1—C1—C2	36.73 (16)	C2A—C7A—C6A—C5A	2.1 (4)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O2*A*^{i}	1.06	1.61	2.6483 (18)	165
O1—H1*O*···O1*A*^{i}	0.98	1.72	2.7078 (18)	179
C3*A*—H3*AA*···O1*A*^{ii}	0.95	2.49	3.371 (2)	154
C1—H1*A*···O1^{iii}	0.99	2.53	3.382 (2)	145
C4—H4*B*···O1*A*	0.99	2.53	3.436 (2)	152

Symmetry codes: (i) *x*, −*y*−1, *z*+1/2; (ii) −*x*+1/2, −*y*+1/2, −*z*+1; (iii) −*x*+1/2, −*y*−1/2, −*z*+1.

Figure 1

Figure 1. The asymmetric unit of 1-(2-hydroxy-ethyl)-pyrrolidinium benzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Schematic displaying selected interactions within 1-(2-hydroxy-ethyl)-pyrrolidinium benzoate. Figure 3. Extended packing diagram as viewed down the c-axis highlighting hydrogen bonding in red dashed lines. Figure 4. Extended packing diagram as viewed down the a-axis highlighting hydrogen bonding in red dashed lines.

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1-(2-hydroxy-ethyl)-pyrrolidinium 2,5-dihydroxy-benzoate

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1-2-HEP 2,5 DHB, systematic name 1-(2-hydroxy-ethyl)-pyrrolidinium 2,5-dihydroxy-benzoate, $C_6H_{14}N_1O_1.C_7H_5O_4$, displays interionic N—H···O and O—H···O hydrogen bonding and interanionic O—H···O hydrogen bonding. A C—H···π ring interaction is also seen.

Experimental

Crystal data

$C_6H_{14}NO1;C_7H_5O_4$
$M_r = 269.29$
Monoclinic, $P2_1/c$
$a = 12.0463$ (8) Å
$b = 9.4802$ (5) Å
$c = 11.8853$ (6) Å
$\beta = 110.191$ (3)°
$V = 1273.91$ (13) Å^3
$Z = 4$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$\mu = 0.11$ mm^{-1}
$T = 123$ K
0.60 × 0.50 × 0.50 mm

Data collection

Bruker X8 APEX KAPPA CCD diffractometer
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)
$T_{min} = 0.938$, $T_{max} = 0.948$
14184 measured reflections
2735 independent reflections
2316 reflections with $I > 2\sigma(I)$
$R_{int} = 0.025$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.124$
$S = 1.10$
2735 reflections
188 parameters
0 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.93$ e Å^{-3}
$\Delta\rho_{min} = -0.34$ e Å^{-3}

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*	0.90 (2)	1.91 (2)	2.778 (2)	162 (2)
O1—H1*O*···O2*A*	0.85 (3)	1.93 (3)	2.766 (2)	168 (2)
O4*A*—H4*AO*···O1*A*^{i}	0.82 (2)	1.90 (2)	2.695 (2)	162 (2)
O3*A*—H3*AO*···O2*A**	0.85 (2)	1.76 (3)	2.560 (2)	154 (2)
C3—H3*A*···O4*A*^{ii}	0.99	2.59	3.378 (2)	136
C5—H5*A*···O4*A*^{iii}	0.99	2.50	3.418 (2)	153

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C6—H6*A*···O3*A*^{iv}	0.99	2.48	3.358 (2)	148

Symmetry codes: (i) −*x*+1, *y*+1/2, −*z*+1/2; (ii) −*x*+1, *y*−1/2, −*z*+1/2; (iii) −*x*+1, −*y*+1, −*z*; (iv) −*x*, −*y*+1, −*z*.

Data collection: Bruker Apex II V 1.0 (Bruker ASX, 2005); cell refinement: Bruker Apex II V 1.0 (Bruker ASX, 2005); data reduction: Bruker Apex II V 1.0 (Bruker ASX, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *POV-RAY* for windows, version 3.1; software used to prepare material for publication: Microsoft Office.

References

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supplementary materials

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1-(2-hydroxy-ethyl)-pyrrolidinium 2,5-dihydroxy-benzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single 1-(2-hydroxy-ethyl)-pyrrolidinium cation and a single 2,5-dihydroxy-benzoate anion (Figure 1). The 1-(2-hydroxy-ethyl)-pyrrolidinium cation adopts the preferred chair conformation with the hydroxyl substituent adopting a gauche conformation with a torsional angle of 62.4 (2) [N1—C5—C6—O1]. The hydrogen (H1N) was located in the fourier difference map at a 0.90 (2) Å distance away from N1. The 2,5-dihydroxy-benzoate anion displays a planar aromatic ring with two hydroxyl groups and a carboxylic acid group displaying standard bond distances and angles (C3A—O3A 1.362 (2), C6A O4A 1.371 (2), C1A—O1A 1.263 (2) and C2A—O1A 1.268 (2) Å respectively). The hydroxy hydrogen atoms was also located and placed in the difference fourier map (O3A—H3AO 0.86 (3) and O4A H4AO 0.82 (2)).

Two main types of hydrogen bonding occurs, strong O···H—O and N···H—O hydrogen bonding and weak interionic C—H···O hydrogen bonding (Table 1, Figure 2 [one intramoleculat bond occurs as indicated by a * in Table 1]). An additional interaction which occurs is an inter-ring C—H···π interaction (C4—H4B···Cg1, 2.85 Å, 151 °, symmetry of the benzoate ring: X,1/2-Y,-1/2+Z).

The extended structure (Figure 3) consists of a 'diamandoid' trellis-like structure constructed from the 2,5-dihydroxy-benzoate anions and their hydrogen bonding network. The cations are located within the centres of the 'diamonds' connected by the N—H···O hydrogen bond and inter-ring C—H···π interaction, thus resulting in two dimensional sheets of anions and cations.

Experimental

Heptane-2-amine (0.748 g, 6.488 mmol), dissolved in methanol, was slowly added to 2,5-dihydroxybenzoic acid (1.000 g, 6.488 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting opaque solid was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the N—H and O—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

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1-(2-hydroxy-ethyl)-pyrrolidinium; 2,5-dihydroxy-benzoate

Crystal data

$C_6H_{14}NO1;C_7H_5O_4$	$F(000) = 576$
$M_r = 269.29$	$D_x = 1.404$ Mg m^{-3}
Monoclinic, $P2_1/c$	Melting point: 370 K
Hall symbol: -P 2ybc	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 12.0463$ (8) Å	Cell parameters from 2431 reflections
$b = 9.4802$ (5) Å	$\theta = 2.8$–$24.7°$
$c = 11.8853$ (6) Å	$\mu = 0.11$ mm^{-1}
$\beta = 110.191$ (3)°	$T = 123$ K
$V = 1273.91$ (13) Å^3	Anhedral, Colourless
$Z = 4$	0.60 × 0.50 × 0.50 mm

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	2735 independent reflections
Radiation source: fine-focus sealed tube	2316 reflections with $I > 2\sigma(I)$
graphite	$R_{int} = 0.025$
0.5 deg frames in phi and ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 1.8°$
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	$h = -15 \rightarrow 11$
$T_{min} = 0.938$, $T_{max} = 0.948$	$k = -11 \rightarrow 12$
14184 measured reflections	$l = -15 \rightarrow 14$

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.043$	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2) = 0.124$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.10$	$w = 1/[\sigma^2(F_o^2) + (0.0632P)^2 + 0.5925P]$ where $P = (F_o^2 + 2F_c^2)/3$
2735 reflections	$(\Delta/\sigma)_{max} < 0.001$
188 parameters	$\Delta\rho_{max} = 0.93$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.34$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-

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factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.22679 (11)	0.18123 (14)	−0.12185 (11)	0.0165 (3)
C2A	0.29771 (13)	0.61401 (15)	0.11834 (12)	0.0156 (3)
C5A	0.38228 (13)	0.80657 (16)	0.30662 (13)	0.0190 (3)
H5AA	0.4111	0.8710	0.3714	0.023*
C7A	0.41911 (13)	0.64195 (15)	0.16971 (12)	0.0165 (3)
H7AA	0.4732	0.5941	0.1408	0.020*
C4A	0.26227 (14)	0.78037 (16)	0.25661 (14)	0.0205 (3)
H4AA	0.2090	0.8270	0.2873	0.025*
C3A	0.21889 (13)	0.68606 (16)	0.16144 (13)	0.0176 (3)
C6A	0.46094 (13)	0.73868 (16)	0.26226 (13)	0.0170 (3)
C4	0.33890 (14)	0.09157 (17)	−0.08545 (14)	0.0243 (4)
H4B	0.3457	0.0419	−0.1560	0.029*
H4A	0.4097	0.1516	−0.0503	0.029*
C3	0.32831 (18)	−0.0134 (2)	0.00605 (16)	0.0347 (4)
H3B	0.3612	−0.1062	−0.0044	0.042*
H3A	0.3702	0.0206	0.0886	0.042*
C1	0.15449 (16)	0.12717 (18)	−0.04948 (15)	0.0263 (4)
H1B	0.0690	0.1292	−0.0971	0.032*
H1A	0.1689	0.1840	0.0241	0.032*
C2	0.19773 (18)	−0.0232 (2)	−0.01892 (18)	0.0390 (5)
H2A	0.1812	−0.0574	0.0524	0.047*
H2B	0.1597	−0.0875	−0.0870	0.047*
O3A	0.09954 (9)	0.66736 (13)	0.11433 (11)	0.0241 (3)
O1A	0.32653 (9)	0.42712 (11)	−0.00237 (9)	0.0200 (3)
O2A	0.14244 (10)	0.50129 (12)	−0.03547 (10)	0.0264 (3)
O4A	0.58025 (9)	0.76416 (13)	0.30647 (10)	0.0228 (3)
C5	0.16178 (14)	0.17721 (17)	−0.25418 (13)	0.0209 (3)
H5B	0.1324	0.0802	−0.2775	0.025*
H5A	0.2174	0.2006	−0.2962	0.025*
C1A	0.25307 (13)	0.50751 (15)	0.01984 (12)	0.0174 (3)
O1	0.09317 (12)	0.42082 (13)	−0.27146 (12)	0.0324 (3)
C6	0.05843 (14)	0.27854 (17)	−0.29441 (13)	0.0211 (3)
H6B	0.0162	0.2663	−0.3815	0.025*
H6A	0.0026	0.2550	−0.2526	0.025*
H4AO	0.594 (2)	0.821 (2)	0.362 (2)	0.039 (6)*
H1O	0.099 (2)	0.439 (3)	−0.200 (3)	0.059 (8)*
H3AO	0.091 (2)	0.611 (3)	0.056 (2)	0.048 (7)*
H1N	0.2503 (16)	0.270 (2)	−0.0984 (16)	0.021 (4)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0188 (6)	0.0149 (6)	0.0150 (6)	0.0010 (5)	0.0049 (5)	−0.0015 (5)
C2A	0.0181 (7)	0.0119 (7)	0.0141 (7)	−0.0002 (5)	0.0024 (5)	0.0032 (5)
C5A	0.0231 (8)	0.0155 (7)	0.0174 (7)	−0.0033 (6)	0.0060 (6)	−0.0014 (5)

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C7A	0.0178 (7)	0.0138 (7)	0.0172 (7)	0.0015 (6)	0.0052 (6)	0.0022 (5)
C4A	0.0223 (8)	0.0182 (8)	0.0224 (8)	0.0018 (6)	0.0094 (6)	−0.0011 (6)
C3A	0.0154 (7)	0.0160 (7)	0.0194 (7)	−0.0003 (6)	0.0035 (6)	0.0041 (5)
C6A	0.0161 (7)	0.0161 (7)	0.0162 (7)	−0.0028 (6)	0.0021 (5)	0.0024 (5)
C4	0.0240 (8)	0.0241 (8)	0.0222 (8)	0.0086 (7)	0.0048 (6)	−0.0012 (6)
C3	0.0458 (11)	0.0251 (9)	0.0297 (9)	0.0084 (8)	0.0085 (8)	0.0055 (7)
C1	0.0353 (9)	0.0257 (9)	0.0230 (8)	−0.0008 (7)	0.0167 (7)	0.0026 (6)
C2	0.0436 (11)	0.0328 (10)	0.0371 (10)	−0.0046 (9)	0.0094 (9)	0.0108 (8)
O3A	0.0151 (5)	0.0259 (6)	0.0283 (6)	−0.0005 (4)	0.0039 (5)	−0.0041 (5)
O1A	0.0225 (6)	0.0163 (5)	0.0179 (5)	0.0023 (4)	0.0026 (4)	−0.0018 (4)
O2A	0.0191 (6)	0.0260 (6)	0.0263 (6)	0.0004 (5)	−0.0023 (5)	−0.0076 (5)
O4A	0.0171 (5)	0.0244 (6)	0.0241 (6)	−0.0046 (5)	0.0036 (4)	−0.0068 (5)
C5	0.0212 (8)	0.0271 (8)	0.0137 (7)	0.0018 (6)	0.0050 (6)	−0.0027 (6)
C1A	0.0216 (7)	0.0121 (7)	0.0154 (7)	0.0001 (6)	0.0027 (6)	0.0024 (5)
O1	0.0396 (8)	0.0227 (6)	0.0250 (6)	−0.0019 (5)	−0.0015 (6)	0.0025 (5)
C6	0.0214 (7)	0.0235 (8)	0.0164 (7)	0.0000 (6)	0.0039 (6)	−0.0029 (6)

Geometric parameters (Å, º)

N1—C5	1.4960 (18)	C3—C2	1.500 (3)
N1—C1	1.509 (2)	C3—H3B	0.9900
N1—C4	1.526 (2)	C3—H3A	0.9900
N1—H1N	0.90 (2)	C1—C2	1.518 (3)
C2A—C7A	1.402 (2)	C1—H1B	0.9900
C2A—C3A	1.402 (2)	C1—H1A	0.9900
C2A—C1A	1.498 (2)	C2—H2A	0.9900
C5A—C4A	1.383 (2)	C2—H2B	0.9900
C5A—C6A	1.391 (2)	O3A—H3AO	0.86 (3)
C5A—H5AA	0.9500	O1A—C1A	1.2629 (18)
C7A—C6A	1.386 (2)	O2A—C1A	1.2676 (18)
C7A—H7AA	0.9500	O4A—H4AO	0.82 (2)
C4A—C3A	1.394 (2)	C5—C6	1.514 (2)
C4A—H4AA	0.9500	C5—H5B	0.9900
C3A—O3A	1.3624 (18)	C5—H5A	0.9900
C6A—O4A	1.3707 (18)	O1—C6	1.411 (2)
C4—C3	1.512 (2)	O1—H1O	0.84 (3)
C4—H4B	0.9900	C6—H6B	0.9900
C4—H4A	0.9900	C6—H6A	0.9900

C5—N1—C1	113.26 (12)	C2—C3—H3A	111.0
C5—N1—C4	112.00 (11)	C4—C3—H3A	111.0
C1—N1—C4	106.11 (12)	H3B—C3—H3A	109.0
C5—N1—H1N	110.1 (12)	N1—C1—C2	103.73 (14)
C1—N1—H1N	108.8 (12)	N1—C1—H1B	111.0
C4—N1—H1N	106.2 (12)	C2—C1—H1B	111.0
C7A—C2A—C3A	119.01 (13)	N1—C1—H1A	111.0
C7A—C2A—C1A	120.45 (13)	C2—C1—H1A	111.0
C3A—C2A—C1A	120.53 (13)	H1B—C1—H1A	109.0
C4A—C5A—C6A	120.13 (14)	C3—C2—C1	103.83 (15)
C4A—C5A—H5AA	119.9	C3—C2—H2A	111.0
C6A—C5A—H5AA	119.9	C1—C2—H2A	111.0

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C6A—C7A—C2A	120.62 (13)	C3—C2—H2B	111.0
C6A—C7A—H7AA	119.7	C1—C2—H2B	111.0
C2A—C7A—H7AA	119.7	H2A—C2—H2B	109.0
C5A—C4A—C3A	120.49 (14)	C3A—O3A—H3AO	102.9 (16)
C5A—C4A—H4AA	119.8	C6A—O4A—H4AO	108.8 (16)
C3A—C4A—H4AA	119.8	N1—C5—C6	113.02 (12)
O3A—C3A—C4A	117.63 (13)	N1—C5—H5B	109.0
O3A—C3A—C2A	122.55 (13)	C6—C5—H5B	109.0
C4A—C3A—C2A	119.82 (13)	N1—C5—H5A	109.0
O4A—C6A—C7A	117.82 (13)	C6—C5—H5A	109.0
O4A—C6A—C5A	122.30 (13)	H5B—C5—H5A	107.8
C7A—C6A—C5A	119.88 (13)	O1A—C1A—O2A	123.41 (13)
C3—C4—N1	106.53 (13)	O1A—C1A—C2A	118.79 (13)
C3—C4—H4B	110.4	O2A—C1A—C2A	117.79 (13)
N1—C4—H4B	110.4	C6—O1—H1O	107.7 (19)
C3—C4—H4A	110.4	O1—C6—C5	112.89 (13)
N1—C4—H4A	110.4	O1—C6—H6B	109.0
H4B—C4—H4A	108.6	C5—C6—H6B	109.0
C2—C3—C4	103.98 (14)	O1—C6—H6A	109.0
C2—C3—H3B	111.0	C5—C6—H6A	109.0
C4—C3—H3B	111.0	H6B—C6—H6A	107.8

C3A—C2A—C7A—C6A	0.4 (2)	C1—N1—C4—C3	0.65 (16)
C1A—C2A—C7A—C6A	−178.90 (13)	N1—C4—C3—C2	23.16 (17)
C6A—C5A—C4A—C3A	−0.1 (2)	C5—N1—C1—C2	99.39 (15)
C5A—C4A—C3A—O3A	−178.50 (13)	C4—N1—C1—C2	−23.88 (16)
C5A—C4A—C3A—C2A	1.9 (2)	C4—C3—C2—C1	−38.16 (18)
C7A—C2A—C3A—O3A	178.37 (13)	N1—C1—C2—C3	38.61 (17)
C1A—C2A—C3A—O3A	−2.3 (2)	C1—N1—C5—C6	66.85 (17)
C7A—C2A—C3A—C4A	−2.1 (2)	C4—N1—C5—C6	−173.18 (13)
C1A—C2A—C3A—C4A	177.24 (13)	C7A—C2A—C1A—O1A	11.7 (2)
C2A—C7A—C6A—O4A	−178.26 (12)	C3A—C2A—C1A—O1A	−167.63 (13)
C2A—C7A—C6A—C5A	1.4 (2)	C7A—C2A—C1A—O2A	−169.69 (13)
C4A—C5A—C6A—O4A	178.07 (13)	C3A—C2A—C1A—O2A	11.0 (2)
C4A—C5A—C6A—C7A	−1.6 (2)	N1—C5—C6—O1	62.43 (17)
C5—N1—C4—C3	−123.41 (14)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*	0.90 (2)	1.91 (2)	2.778 (2)	162 (2)
O1—H1*O*···O2*A*	0.85 (3)	1.93 (3)	2.766 (2)	168 (2)
O4*A*—H4*AO*···O1*A*^{i}	0.82 (2)	1.90 (2)	2.695 (2)	162 (2)
O3*A*—H3*AO*···O2*A**	0.85 (2)	1.76 (3)	2.560 (2)	154 (2)
C3—H3*A*···O4*A*^{ii}	0.99	2.59	3.378 (2)	136
C5—H5*A*···O4*A*^{iii}	0.99	2.50	3.418 (2)	153
C6—H6*A*···O3*A*^{iv}	0.99	2.48	3.358 (2)	148

Symmetry codes: (i) −*x*+1, *y*+1/2, −*z*+1/2; (ii) −*x*+1, *y*−1/2, −*z*+1/2; (iii) −*x*+1, −*y*+1, −*z*; (iv) −*x*, −*y*+1, −*z*.

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Figure 1

Figure 1. The asymmetric unit of 1-(2-hydroxy-ethyl)-pyrrolidinium 2,5-dihydroxy-benzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Schematic displaying selected interactions within 1-(2-hydroxy-ethyl)-pyrrolidinium 2,5-dihydroxy-benzoate. Figure 3. Extended packing diagram as viewed down the a-axis highlighting hydrogen bonding in red dashed lines.

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1-(2-hydroxyethyl)pyrrolidin-1-ium 2-hydroxybenzoate

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1-(2-hydroxyethyl)pyrrolidin-1-ium 2-hydroxybenzoate, $C_6H_{14}N_1O_1$. $C_7H_5O_3$, displays interionic N—H···O, C—H···O and O—H···O hydrogen bonding and interanionic C—H···O hydrogen bonding. C—H···π and π···π ring interactions are also seen.

Experimental

Crystal data

$C_6H_{14}NO·C_7H_5O_3$	V = 1268.9 (3) Å^3
M_r = 253.29	Z = 4
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 11.668 (2) Å	μ = 0.10 mm^{-1}
b = 9.365 (1) Å	T = 123 K
c = 12.161 (2) Å	0.20 × 0.20 × 0.20 mm
β = 107.290 (4)°	

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	3126 independent reflections
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	1558 reflections with $I > 2\sigma(I)$
T_{min} = 0.981, T_{max} = 0.981	R_{int} = 0.053
9186 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.070	0 restraints
$wR(F^2)$ = 0.221	H atoms treated by a mixture of independent and constrained refinement
S = 1.07	$\Delta\rho_{max}$ = 0.46 e Å^{-3}
3126 reflections	$\Delta\rho_{min}$ = −0.49 e Å^{-3}
175 parameters	

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*^{i}	0.90 (4)	1.81 (4)	2.697 (3)	169 (4)
O1—H1*O*···O2*A*^{i}	0.80 (4)	1.94 (4)	2.739 (3)	176 (3)
O3*A**—H3*AO*···O2*A*	0.96 (4)	1.60 (4)	2.520 (3)	159 (3)
C1—H1*B*···O1^{ii}	0.99	2.46	3.431 (3)	167
C6—H6*A*···O3*A*^{iii}	0.99	2.51	3.391 (4)	148

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Symmetry codes: (i) −*x*+1, *y*+1/2, −*z*+1/2; (ii) −*x*+2, *y*−1/2, −*z*+1/2; (iii) *x*+1, −*y*−1/2, *z*−3/2.

Table 2

Geometrical parameters (Å, °) of selected inter-ring C-H···π interactions. The CgJ refer to the Ring Centre-of-Gravity

X–H	CgJ	H..Cg	X-H..Cg	X..Cg	Symmetry position of CgJ
C4–H4B	Cg1	2.69	162	3.640 (3)	1-X,-Y,1-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Table 3

Geometrical parameters (Å, °) of selected inter-ring π—π interactions. α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
Cg1	Cg1	5.686 (2)	82	1-X,-1/2+Y,3/2-Z
Cg1	Cg1	5.686 (2)	82	1-X,1/2+Y,3/2-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Data collection: Bruker Apex II V 1.0 (Bruker ASX, 2005); cell refinement: Bruker Apex II V 1.0 (Bruker ASX, 2005); data reduction: Bruker Apex II V 1.0 (Bruker ASX, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *POV-RAY* for windows, version 3.1; software used to prepare material for publication: Microsoft Office.

References

NOT FOUND

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supplementary materials

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1-(2-hydroxyethyl)pyrrolidin-1-ium 2-hydroxybenzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single 1-(2-hydroxy-ethyl)-pyrrolidinium cation and a single 2-hydroxy-benzoate anion (Figure 1). The 1-(2-hydroxy-ethyl)-pyrrolidinium cation adopts a slightly twisted ring conformation with the hydroxyl substituent adopting a gauche conformation with a torsional angle of 62.9 (3) ° [N1—C5—C6—O1], both of which are not the energetically favoured conformation. The hydrogen (H1N) was located in the fourier difference map at a 0.91 (4) Å distance away from N1. The 2-hydroxybenzoate anion displays a planar aromatic ring with one hydroxyl group and a carboxylic acid group displaying standard bond distances and angles (C3A—O3A 1.355 (3), C1A—O1A 1.249 (3) and C1A—O2A 1.279 (3) Å respectively). The hydroxy hydrogen atoms was also located and placed in the difference fourier map (O3A—H3AO 0.96 (3). Three main types of hydrogen bonding occurs, strong O···H—O and N···H—O hydrogen bonding and weak interionic C—H···O hydrogen bonding (Table 1, Figure 2 [one intramoleculat bond occurs as indicated by a * in Table 1]). Additional interactions which occur are inter-ring C—H···π and weak π···π interactions (Tables 2 and 3). The extended structure (Figure 3) consists of a 'zig-zag' arrangement, constructed from alternating groups of cations and anions, which are connected by the above mentioned hydrogen bonds. The aromatic moeities are grouped together with the charged centres grouped and linked via hydrogen bonding (Figure 4).

Experimental

1-(2-hydroxyethyl)-pyrrolidine (1.251 g, 10.860 mmol), dissolved in methanol, was slowly added to 2-hydroxy-benzoic acid (1.500 g, 10.860 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting yellow solid was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the N—H and O—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

1-(2-hydroxyethyl)pyrrolidin-1-ium 2-hydroxybenzoate

Crystal data

$C_6H_{14}NO·C_7H_5O_3$	$F(000) = 544$
$M_r = 253.29$	$D_x = 1.326$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Hall symbol: -P 2ybc	Cell parameters from 1042 reflections

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a = 11.668 (2) Å	θ = 2.8–20.9°
b = 9.365 (1) Å	μ = 0.10 mm^{-1}
c = 12.161 (2) Å	T = 123 K
β = 107.290 (4)°	Triangular, Translucent
V = 1268.9 (3) Å^3	0.20 × 0.20 × 0.20 mm
Z = 4	

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	3126 independent reflections
Radiation source: fine-focus sealed tube	1558 reflections with $I > 2\sigma(I)$
graphite	R_{int} = 0.053
0.5 deg frames in phi and ω scans	θ_{max} = 28.3°, θ_{min} = 2.8°
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	h = −11→15
T_{min} = 0.981, T_{max} = 0.981	k = −11→12
9186 measured reflections	l = −16→16

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.070	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2)$ = 0.221	H atoms treated by a mixture of independent and constrained refinement
S = 1.07	$w = 1/[\sigma^2(F_o^2) + (0.1005P)^2 + 0.0349P]$ where $P = (F_o^2 + 2F_c^2)/3$
3126 reflections	$(\Delta/\sigma)_{max} < 0.001$
175 parameters	$\Delta\rho_{max}$ = 0.46 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.49 e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
O3A	0.11258 (16)	0.1736 (2)	0.60312 (17)	0.0439 (5)
O2A	0.14050 (15)	−0.0056 (2)	0.45867 (15)	0.0440 (5)

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O1A	0.32267 (17)	−0.0856 (2)	0.46823 (18)	0.0513 (6)
C3A	0.2338 (2)	0.1795 (3)	0.6446 (2)	0.0342 (6)
C1A	0.2548 (2)	−0.0040 (3)	0.5011 (2)	0.0364 (6)
C2A	0.3073 (2)	0.0981 (3)	0.5970 (2)	0.0339 (6)
C4A	0.2839 (3)	0.2683 (3)	0.7382 (2)	0.0491 (8)
H4AA	0.2330	0.3228	0.7703	0.059*
C7A	0.4316 (2)	0.1122 (3)	0.6431 (3)	0.0489 (8)
H7AA	0.4834	0.0605	0.6103	0.059*
C6A	0.4796 (3)	0.2011 (4)	0.7365 (3)	0.0667 (12)
H6AA	0.5642	0.2098	0.7680	0.080*
C5A	0.4040 (4)	0.2776 (4)	0.7839 (3)	0.0616 (10)
H5AA	0.4372	0.3369	0.8489	0.074*
N1	0.7830 (2)	0.1729 (3)	0.13429 (19)	0.0357 (6)
O1	0.9166 (2)	0.4176 (2)	0.26853 (19)	0.0577 (7)
C6	0.9517 (3)	0.2747 (3)	0.2906 (2)	0.0455 (8)
H6B	0.9954	0.2641	0.3735	0.055*
H6A	1.0078	0.2498	0.2465	0.055*
C5	0.8483 (2)	0.1719 (3)	0.2596 (2)	0.0415 (7)
H5B	0.8787	0.0743	0.2826	0.050*
H5A	0.7918	0.1969	0.3032	0.050*
C4	0.6728 (3)	0.0773 (3)	0.1019 (3)	0.0464 (7)
H4B	0.6657	0.0244	0.1701	0.056*
H4A	0.5990	0.1345	0.0698	0.056*
C1	0.8596 (2)	0.1271 (3)	0.0602 (2)	0.0411 (7)
H1A	0.8828	0.2108	0.0219	0.049*
H1B	0.9334	0.0791	0.1075	0.049*
C2	0.7864 (3)	0.0286 (6)	−0.0250 (4)	0.1023 (18)
H2A	0.7536	0.0783	−0.0996	0.123*
H2B	0.8363	−0.0522	−0.0365	0.123*
C3	0.6910 (4)	−0.0230 (5)	0.0140 (3)	0.0822 (14)
H3B	0.7108	−0.1193	0.0479	0.099*
H3A	0.6167	−0.0300	−0.0515	0.099*
H3AO	0.103 (3)	0.105 (4)	0.542 (3)	0.056 (9)*
H1N	0.754 (3)	0.260 (4)	0.108 (3)	0.059 (10)*
H1O	0.898 (3)	0.436 (4)	0.201 (3)	0.056 (10)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O3A	0.0392 (11)	0.0425 (14)	0.0539 (12)	0.0003 (9)	0.0200 (9)	−0.0097 (9)
O2A	0.0362 (11)	0.0420 (14)	0.0515 (11)	0.0008 (9)	0.0096 (8)	−0.0135 (9)
O1A	0.0469 (12)	0.0346 (13)	0.0812 (14)	0.0039 (9)	0.0327 (11)	−0.0079 (10)
C3A	0.0389 (15)	0.0257 (15)	0.0374 (13)	−0.0058 (12)	0.0103 (11)	0.0033 (11)
C1A	0.0377 (15)	0.0256 (16)	0.0503 (15)	0.0003 (12)	0.0198 (12)	0.0009 (12)
C2A	0.0334 (14)	0.0247 (16)	0.0430 (14)	−0.0011 (11)	0.0106 (11)	0.0082 (11)
C4A	0.073 (2)	0.0290 (18)	0.0452 (16)	−0.0090 (15)	0.0167 (15)	−0.0004 (12)
C7A	0.0387 (16)	0.0343 (19)	0.071 (2)	−0.0025 (13)	0.0127 (14)	0.0168 (14)
C6A	0.0430 (19)	0.056 (2)	0.079 (2)	−0.0238 (17)	−0.0156 (17)	0.0297 (19)
C5A	0.076 (2)	0.043 (2)	0.0538 (18)	−0.0227 (18)	0.0000 (18)	0.0062 (15)
N1	0.0424 (13)	0.0237 (14)	0.0488 (13)	−0.0020 (10)	0.0256 (11)	0.0018 (10)
O1	0.0884 (17)	0.0378 (15)	0.0449 (12)	−0.0102 (11)	0.0169 (12)	−0.0050 (10)

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C6	0.0635 (19)	0.0379 (19)	0.0379 (14)	−0.0040 (14)	0.0192 (13)	0.0003 (12)
C5	0.0537 (17)	0.0338 (18)	0.0448 (15)	0.0008 (13)	0.0264 (13)	0.0036 (12)
C4	0.0413 (16)	0.0333 (18)	0.0731 (19)	−0.0079 (13)	0.0298 (14)	0.0034 (15)
C1	0.0461 (17)	0.0387 (18)	0.0468 (15)	−0.0027 (13)	0.0266 (13)	−0.0046 (12)
C2	0.073 (3)	0.138 (5)	0.112 (3)	−0.053 (3)	0.052 (2)	−0.082 (3)
C3	0.101 (3)	0.090 (3)	0.071 (2)	−0.058 (3)	0.048 (2)	−0.035 (2)

Geometric parameters (Å, º)

O3A—C3A	1.355 (3)	O1—C6	1.402 (4)
O3A—H3AO	0.96 (3)	O1—H1O	0.80 (3)
O2A—C1A	1.279 (3)	C6—C5	1.502 (4)
O1A—C1A	1.249 (3)	C6—H6B	0.9900
C3A—C4A	1.391 (4)	C6—H6A	0.9900
C3A—C2A	1.395 (4)	C5—H5B	0.9900
C1A—C2A	1.491 (4)	C5—H5A	0.9900
C2A—C7A	1.397 (4)	C4—C3	1.485 (5)
C4A—C5A	1.349 (4)	C4—H4B	0.9900
C4A—H4AA	0.9500	C4—H4A	0.9900
C7A—C6A	1.385 (5)	C1—C2	1.458 (4)
C7A—H7AA	0.9500	C1—H1A	0.9900
C6A—C5A	1.387 (6)	C1—H1B	0.9900
C6A—H6AA	0.9500	C2—C3	1.417 (5)
C5A—H5AA	0.9500	C2—H2A	0.9900
N1—C5	1.487 (3)	C2—H2B	0.9900
N1—C1	1.508 (3)	C3—H3B	0.9900
N1—C4	1.520 (3)	C3—H3A	0.9900
N1—H1N	0.91 (4)		

C3A—O3A—H3AO	100.9 (18)	C5—C6—H6A	108.9
O3A—C3A—C4A	117.9 (3)	H6B—C6—H6A	107.7
O3A—C3A—C2A	121.7 (2)	N1—C5—C6	112.5 (2)
C4A—C3A—C2A	120.4 (3)	N1—C5—H5B	109.1
O1A—C1A—O2A	123.2 (3)	C6—C5—H5B	109.1
O1A—C1A—C2A	119.4 (2)	N1—C5—H5A	109.1
O2A—C1A—C2A	117.4 (2)	C6—C5—H5A	109.1
C3A—C2A—C7A	118.3 (3)	H5B—C5—H5A	107.8
C3A—C2A—C1A	121.0 (2)	C3—C4—N1	105.5 (2)
C7A—C2A—C1A	120.7 (3)	C3—C4—H4B	110.6
C5A—C4A—C3A	120.5 (3)	N1—C4—H4B	110.6
C5A—C4A—H4AA	119.7	C3—C4—H4A	110.6
C3A—C4A—H4AA	119.7	N1—C4—H4A	110.6
C6A—C7A—C2A	120.3 (3)	H4B—C4—H4A	108.8
C6A—C7A—H7AA	119.8	C2—C1—N1	106.2 (2)
C2A—C7A—H7AA	119.8	C2—C1—H1A	110.5
C7A—C6A—C5A	119.9 (3)	N1—C1—H1A	110.5
C7A—C6A—H6AA	120.0	C2—C1—H1B	110.5
C5A—C6A—H6AA	120.0	N1—C1—H1B	110.5
C4A—C5A—C6A	120.4 (3)	H1A—C1—H1B	108.7
C4A—C5A—H5AA	119.8	C3—C2—C1	109.3 (3)
C6A—C5A—H5AA	119.8	C3—C2—H2A	109.8

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C5—N1—C1	113.3 (2)	C1—C2—H2A	109.8
C5—N1—C4	113.5 (2)	C3—C2—H2B	109.8
C1—N1—C4	106.5 (2)	C1—C2—H2B	109.8
C5—N1—H1N	113 (2)	H2A—C2—H2B	108.3
C1—N1—H1N	106 (2)	C2—C3—C4	108.6 (3)
C4—N1—H1N	104 (2)	C2—C3—H3B	110.0
C6—O1—H1O	112 (3)	C4—C3—H3B	110.0
O1—C6—C5	113.4 (2)	C2—C3—H3A	110.0
O1—C6—H6B	108.9	C4—C3—H3A	110.0
C5—C6—H6B	108.9	H3B—C3—H3A	108.3
O1—C6—H6A	108.9		

O3A—C3A—C2A—C7A	178.8 (2)	C3A—C4A—C5A—C6A	1.4 (5)
C4A—C3A—C2A—C7A	−2.3 (4)	C7A—C6A—C5A—C4A	−1.4 (5)
O3A—C3A—C2A—C1A	−2.6 (4)	C1—N1—C5—C6	62.4 (3)
C4A—C3A—C2A—C1A	176.3 (2)	C4—N1—C5—C6	−176.0 (2)
O1A—C1A—C2A—C3A	−172.9 (2)	O1—C6—C5—N1	62.9 (3)
O2A—C1A—C2A—C3A	5.2 (4)	C5—N1—C4—C3	−123.4 (3)
O1A—C1A—C2A—C7A	5.8 (4)	C1—N1—C4—C3	1.9 (3)
O2A—C1A—C2A—C7A	−176.1 (2)	C5—N1—C1—C2	135.3 (3)
O3A—C3A—C4A—C5A	179.4 (3)	C4—N1—C1—C2	9.9 (4)
C2A—C3A—C4A—C5A	0.5 (4)	N1—C1—C2—C3	−18.8 (5)
C3A—C2A—C7A—C6A	2.4 (4)	C1—C2—C3—C4	20.5 (5)
C1A—C2A—C7A—C6A	−176.3 (3)	N1—C4—C3—C2	−13.5 (4)
C2A—C7A—C6A—C5A	−0.5 (5)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*^{i}	0.90 (4)	1.81 (4)	2.697 (3)	169 (4)
O1—H1*O*···O2*A*^{i}	0.80 (4)	1.94 (4)	2.739 (3)	176 (3)
O3*A**—H3*AO*···O2*A*	0.96 (4)	1.60 (4)	2.520 (3)	159 (3)
C1—H1*B*···O1^{ii}	0.99	2.46	3.431 (3)	167
C6—H6*A*···O3*A*^{iii}	0.99	2.51	3.391 (4)	148

Symmetry codes: (i) −*x*+1, *y*+1/2, −*z*+1/2; (ii) −*x*+2, *y*−1/2, −*z*+1/2; (iii) *x*+1, −*y*−1/2, *z*−3/2.

Figure 1

Figure 1. The asymmetric unit of 1-(2-hydroxy-ethyl)-pyrrolidinium 2-hydroxybenzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Schematic displaying selected interactions within 1-(2-hydroxy-ethyl)-pyrrolidinium 2-hydroxybenzoate. Figure 3. Extended packing diagram as viewed down the a-axis highlighting hydrogen bonding in red dashed lines. Figure 4. Extended packing diagram as viewed down the b-axis highlighting hydrogen bonding in red dashed lines.

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(3s,5s,7s)-adamantan-1-ammonium benzoate

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Adamantylammonium benzoate,systematic name (3s,5s,7s)-adamantan-1-aminium benzoate $C_{10}H_{18}N_1$. $C_7H_5O_2$, displays interionic N—H···O hydrogen bonding and interanionic π···π ring interactions. In addition a weak intramolecular C—H···O hydrogen bond and an interionic C—H···π interaction is also seen.

Experimental

Crystal data

$C_{10}H_{18}N·C_7H_5O_2$	V = 1474.0 (5) Å^3
M_r = 273.36	Z = 4
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 10.808 (2) Å	μ = 0.08 mm^{-1}
b = 6.5508 (13) Å	T = 173 K
c = 21.104 (4) Å	0.20 × 0.10 × 0.10 mm
β = 99.42 (3)°	

Data collection

Enraf Nonius KAPPA CCD diffractometer	4440 independent reflections
Absorption correction: Empirical (using intensity measurements) *SORTAV* (R.H. Blessing 1997)	1673 reflections with $I > 2\sigma(I)$
T_{min} = 0.984, T_{max} = 0.992	R_{int} = 0.242
20392 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.099	0 restraints
$wR(F^2)$ = 0.299	H atoms treated by a mixture of independent and constrained refinement
S = 0.98	$\Delta\rho_{max}$ = 0.34 e Å^{-3}
4440 reflections	$\Delta\rho_{min}$ = −0.41 e Å^{-3}
184 parameters	

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*^{i}	1.19	1.60	2.780 (3)	169
N1—H2*N*···O2*A*	0.87	1.86	2.720 (4)	165
N1—H3*N*···O1*A*^{ii}	0.99	1.80	2.777 (4)	170
C7*A*—H7*AA*···O2*A**	0.95	2.42	2.749 (4)	100

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Symmetry codes: (i) −*x*+1/2, *y*+1/2, −*z*+1/2; (ii) *x*, *y*+1, *z*.

Table 2

Geometrical parameters (Å, °) of selected inter-ring C-H···π interactions. The CgJ refer to the Ring Centre-of-Gravity

X–H	CgJ	H..Cg	X-H..Cg	X..Cg	Symmetry position of CgJ
C10–H10B	Cg1	2.61	173	3.594 (4)	-1/2-X,1/2+Y,1/2-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Table 3

Geometrical parameters (Å, °) of selected inter-ring π—π interactions. α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
Cg1	Cg1	3.992 (2)	0	-X,-Y,-Z
Cg1	Cg1	5.443 (2)	0	-X,1-Y,-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Data collection: Nonius Collect (Bruker ASX 2005); cell refinement: *HKL-2000* (Bruker ASX 2004); data reduction: *HKL-2000* (Bruker ASX 2004); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *X-SEED* / *POV-RAY*; software used to prepare material for publication: Microsoft Office 2000.

References

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supplementary materials

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(3s,5s,7s)-adamantan-1-ammonium benzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single adamantan-1-ammonium cation and a single benzoate anion (Figure 1). The adamantan-1-ammonium cation adopts the standard tetrahedral symmetry with all four cyclohexane rings adopting the preferred chair conformation with with angles ranging from 108.57 to 109.91 °. The charged ammonium substituent occurs 1.500 (4) Å from C1. All the ammonium hydrogens were located and placed in the difference map. H1N is the longest (N1—H1N 1.1911 Å) with H2N and H3N being shorter (N1—H2N 0.8757, N1—H3N 0.9907 Å). The benzoate anion displays a planar aromatic ring with a carboxylic acid group displaying standard bond distances and angles (O1A—C1A 1.262 (4) and O2A—C1A 1.244 (4) Å respectively). Two main types of hydrogen bonding occurs, strong N···H—O hydrogen bonding and weak intra-molecular C—H···O (indicated by a * in Table 1) hydrogen bonding (Table 1). Additional interactions which occur are inter-ring π···π and C—H···π interactions (Figure 2 and Tables 2 & 3). The extended structure (Figure 3) consists of layers of hydrogen bonded ionic clusters lying perpendicular to the ac-plane. Each cluster is associated with the other via the inter-ring π···π and C—H···π interactions.

Experimental

Adamantan-1-amine (1.500 g, 9.917 mmol), dissolved in methanol, was slowly added to benzoic acid (1.211 g, 9.917 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white powder was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the N—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

(3s,5s,7s)-adamantan-1-ammonium benzoate

Crystal data

$C_{10}H_{18}N·C_7H_5O_2$	$F(000)$ = 592
M_r = 273.36	D_x = 1.232 Mg m^{-3}
Monoclinic, $P2_1/n$	Melting point: 529 K
Hall symbol: -P 2yn	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 10.808 (2) Å	Cell parameters from 4440 reflections
b = 6.5508 (13) Å	μ = 0.08 mm^{-1}
c = 21.104 (4) Å	T = 173 K
β = 99.42 (3)°	Needle, Colourless
V = 1474.0 (5) Å^3	0.20 × 0.10 × 0.10 mm

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$Z = 4$

Data collection

Enraf Nonius KAPPA CCD diffractometer	4440 independent reflections
Radiation source: fine-focus sealed tube	1673 reflections with $I > 2\sigma(I)$
graphite	$R_{int} = 0.242$
1 deg frames in phi and ω scans	$\theta_{max} = 30.5°$, $\theta_{min} = 2.0°$
Absorption correction: Empirical (using intensity measurements) *SORTAV* (R.H. Blessing 1997)	$h = -15 \rightarrow 15$
$T_{min} = 0.984$, $T_{max} = 0.992$	$k = -9 \rightarrow 9$
20392 measured reflections	$l = -30 \rightarrow 29$

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.099$	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2) = 0.299$	H atoms treated by a mixture of independent and constrained refinement
$S = 0.98$	$w = 1/[\sigma^2(F_o^2) + (0.1345P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
4440 reflections	$(\Delta/\sigma)_{max} < 0.001$
184 parameters	$\Delta\rho_{max} = 0.34$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.41$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1A	0.1275 (2)	0.1800 (4)	0.18623 (11)	0.0381 (7)
N1	0.1418 (2)	0.8009 (4)	0.24585 (12)	0.0266 (7)
C2	0.0629 (3)	0.6174 (5)	0.33276 (15)	0.0298 (8)
H2A	0.1504	0.5947	0.3542	0.036*
H2B	0.0375	0.5006	0.3038	0.036*
C1	0.0548 (3)	0.8141 (5)	0.29427 (14)	0.0246 (7)
C8	−0.0795 (3)	0.8477 (5)	0.25971 (15)	0.0300 (8)

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H8B	−0.1056	0.7326	0.2301	0.036*
H8A	−0.0842	0.9751	0.2342	0.036*
C2A	−0.0300 (3)	0.2318 (5)	0.09449 (14)	0.0259 (7)
O2A	0.0693 (2)	0.4974 (4)	0.15982 (11)	0.0468 (7)
C3	−0.0240 (3)	0.6324 (5)	0.38334 (16)	0.0328 (8)
H3	−0.0186	0.5035	0.4090	0.039*
C4	0.0155 (3)	0.8126 (6)	0.42783 (16)	0.0391 (9)
H4A	0.1024	0.7919	0.4503	0.047*
H4B	−0.0402	0.8221	0.4606	0.047*
C9	0.0957 (3)	0.9956 (5)	0.33872 (15)	0.0315 (8)
H9B	0.0915	1.1233	0.3134	0.038*
H9A	0.1833	0.9761	0.3604	0.038*
C7	−0.1664 (3)	0.8624 (5)	0.31029 (16)	0.0354 (9)
H7	−0.2547	0.8832	0.2882	0.042*
C3A	−0.0576 (3)	0.0271 (5)	0.08431 (16)	0.0318 (8)
H3AA	−0.0167	−0.0723	0.1132	0.038*
C6A	−0.1758 (3)	0.3129 (6)	−0.00124 (17)	0.0417 (9)
H6AA	−0.2153	0.4113	−0.0309	0.050*
C7A	−0.0902 (3)	0.3744 (5)	0.05153 (16)	0.0337 (8)
H7AA	−0.0725	0.5155	0.0583	0.040*
C10	−0.1590 (3)	0.6646 (5)	0.34975 (16)	0.0369 (9)
H10B	−0.2156	0.6738	0.3821	0.044*
H10A	−0.1860	0.5475	0.3212	0.044*
C5A	−0.2036 (3)	0.1085 (6)	−0.01060 (17)	0.0419 (10)
H5AA	−0.2630	0.0659	−0.0464	0.050*
C5	0.0080 (3)	1.0101 (5)	0.38894 (16)	0.0367 (9)
H5	0.0340	1.1276	0.4184	0.044*
C1A	0.0617 (3)	0.3096 (5)	0.15149 (15)	0.0269 (8)
C6	−0.1271 (3)	1.0430 (6)	0.35462 (17)	0.0401 (9)
H6B	−0.1841	1.0552	0.3867	0.048*
H6A	−0.1323	1.1708	0.3293	0.048*
C4A	−0.1448 (3)	−0.0331 (6)	0.03207 (16)	0.0384 (9)
H4AA	−0.1642	−0.1738	0.0257	0.046*
H2N	0.1308	0.6933	0.2210	0.039 (11)*
H3N	0.1381	0.9282	0.2203	0.039 (10)*
H1N	0.2435	0.7690	0.2756	0.098 (16)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1A	0.0323 (13)	0.0430 (16)	0.0356 (14)	−0.0043 (11)	−0.0044 (11)	0.0113 (12)
N1	0.0282 (14)	0.0288 (16)	0.0232 (14)	−0.0017 (12)	0.0052 (11)	−0.0034 (13)
C2	0.0320 (18)	0.029 (2)	0.0290 (18)	0.0032 (15)	0.0050 (14)	−0.0005 (15)
C1	0.0239 (15)	0.0265 (18)	0.0232 (16)	−0.0001 (13)	0.0033 (13)	0.0012 (14)
C8	0.0272 (17)	0.036 (2)	0.0260 (17)	0.0001 (14)	0.0024 (13)	0.0024 (15)
C2A	0.0228 (15)	0.035 (2)	0.0200 (15)	−0.0001 (14)	0.0054 (12)	−0.0010 (14)
O2A	0.0572 (17)	0.0375 (17)	0.0401 (16)	0.0004 (13)	−0.0084 (12)	−0.0116 (13)
C3	0.0368 (19)	0.032 (2)	0.0307 (18)	0.0008 (15)	0.0084 (15)	0.0056 (15)
C4	0.038 (2)	0.051 (3)	0.0286 (18)	−0.0016 (18)	0.0085 (15)	−0.0035 (18)
C9	0.0325 (18)	0.032 (2)	0.0302 (18)	−0.0028 (15)	0.0051 (14)	−0.0045 (15)
C7	0.0236 (17)	0.046 (2)	0.036 (2)	0.0036 (15)	0.0042 (14)	0.0019 (17)

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C3A	0.0291 (18)	0.036 (2)	0.0300 (18)	0.0033 (15)	0.0049 (14)	−0.0012 (16)
C6A	0.040 (2)	0.047 (3)	0.035 (2)	0.0056 (18)	−0.0014 (16)	0.0066 (19)
C7A	0.0340 (19)	0.034 (2)	0.0314 (19)	0.0022 (15)	−0.0003 (15)	0.0007 (15)
C10	0.0355 (19)	0.044 (2)	0.0330 (19)	−0.0062 (17)	0.0119 (15)	−0.0005 (17)
C5A	0.040 (2)	0.053 (3)	0.0305 (19)	0.0019 (19)	−0.0015 (16)	−0.0104 (18)
C5	0.047 (2)	0.034 (2)	0.0309 (19)	−0.0031 (17)	0.0108 (16)	−0.0079 (16)
C1A	0.0259 (16)	0.032 (2)	0.0251 (17)	0.0009 (15)	0.0115 (13)	0.0003 (15)
C6	0.041 (2)	0.041 (2)	0.042 (2)	0.0102 (17)	0.0187 (17)	0.0014 (18)
C4A	0.037 (2)	0.036 (2)	0.041 (2)	−0.0005 (16)	0.0029 (17)	−0.0116 (18)

Geometric parameters (Å, º)

O1A—C1A	1.262 (4)	C4—H4B	0.9900
N1—C1	1.500 (4)	C9—C5	1.536 (5)
N1—H2N	0.8757	C9—H9B	0.9900
N1—H3N	0.9907	C9—H9A	0.9900
N1—H1N	1.1911	C7—C6	1.525 (5)
C2—C1	1.518 (4)	C7—C10	1.535 (5)
C2—C3	1.536 (4)	C7—H7	1.0000
C2—H2A	0.9900	C3A—C4A	1.385 (4)
C2—H2B	0.9900	C3A—H3AA	0.9500
C1—C8	1.529 (4)	C6A—C5A	1.379 (5)
C1—C9	1.534 (4)	C6A—C7A	1.386 (5)
C8—C7	1.536 (4)	C6A—H6AA	0.9500
C8—H8B	0.9900	C7A—H7AA	0.9500
C8—H8A	0.9900	C10—H10B	0.9900
C2A—C3A	1.383 (4)	C10—H10A	0.9900
C2A—C7A	1.387 (4)	C5A—C4A	1.374 (5)
C2A—C1A	1.516 (4)	C5A—H5AA	0.9500
O2A—C1A	1.244 (4)	C5—C6	1.535 (5)
C3—C4	1.525 (5)	C5—H5	1.0000
C3—C10	1.529 (5)	C6—H6B	0.9900
C3—H3	1.0000	C6—H6A	0.9900
C4—C5	1.527 (5)	C4A—H4AA	0.9500
C4—H4A	0.9900		

C1—N1—H2N	114.6	H9B—C9—H9A	108.3
C1—N1—H3N	110.4	C6—C7—C10	109.7 (3)
H2N—N1—H3N	111.2	C6—C7—C8	109.5 (3)
C1—N1—H1N	106.2	C10—C7—C8	109.9 (3)
H2N—N1—H1N	101.4	C6—C7—H7	109.2
H3N—N1—H1N	112.7	C10—C7—H7	109.2
C1—C2—C3	109.2 (3)	C8—C7—H7	109.2
C1—C2—H2A	109.8	C2A—C3A—C4A	120.1 (3)
C3—C2—H2A	109.8	C2A—C3A—H3AA	120.0
C1—C2—H2B	109.8	C4A—C3A—H3AA	120.0
C3—C2—H2B	109.8	C5A—C6A—C7A	119.9 (3)
H2A—C2—H2B	108.3	C5A—C6A—H6AA	120.1
N1—C1—C2	109.1 (2)	C7A—C6A—H6AA	120.1
N1—C1—C8	109.6 (2)	C6A—C7A—C2A	120.6 (3)
C2—C1—C8	110.2 (2)	C6A—C7A—H7AA	119.7

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N1—C1—C9	108.1 (2)	C2A—C7A—H7AA	119.7
C2—C1—C9	110.2 (3)	C3—C10—C7	109.2 (3)
C8—C1—C9	109.6 (2)	C3—C10—H10B	109.8
C1—C8—C7	108.6 (3)	C7—C10—H10B	109.8
C1—C8—H8B	110.0	C3—C10—H10A	109.8
C7—C8—H8B	110.0	C7—C10—H10A	109.8
C1—C8—H8A	110.0	H10B—C10—H10A	108.3
C7—C8—H8A	110.0	C4A—C5A—C6A	119.7 (3)
H8B—C8—H8A	108.4	C4A—C5A—H5AA	120.2
C3A—C2A—C7A	119.0 (3)	C6A—C5A—H5AA	120.2
C3A—C2A—C1A	123.0 (3)	C4—C5—C6	109.6 (3)
C7A—C2A—C1A	117.9 (3)	C4—C5—C9	109.5 (3)
C4—C3—C10	109.2 (3)	C6—C5—C9	109.3 (3)
C4—C3—C2	109.6 (3)	C4—C5—H5	109.5
C10—C3—C2	109.4 (3)	C6—C5—H5	109.5
C4—C3—H3	109.5	C9—C5—H5	109.5
C10—C3—H3	109.5	O2A—C1A—O1A	124.4 (3)
C2—C3—H3	109.5	O2A—C1A—C2A	117.6 (3)
C3—C4—C5	109.9 (3)	O1A—C1A—C2A	117.9 (3)
C3—C4—H4A	109.7	C7—C6—C5	109.2 (3)
C5—C4—H4A	109.7	C7—C6—H6B	109.8
C3—C4—H4B	109.7	C5—C6—H6B	109.8
C5—C4—H4B	109.7	C7—C6—H6A	109.8
H4A—C4—H4B	108.2	C5—C6—H6A	109.8
C1—C9—C5	108.7 (3)	H6B—C6—H6A	108.3
C1—C9—H9B	109.9	C5A—C4A—C3A	120.7 (3)
C5—C9—H9B	109.9	C5A—C4A—H4AA	119.6
C1—C9—H9A	109.9	C3A—C4A—H4AA	119.6
C5—C9—H9A	109.9		

C3—C2—C1—N1	178.8 (2)	C4—C3—C10—C7	60.2 (4)
C3—C2—C1—C8	−60.8 (3)	C2—C3—C10—C7	−59.7 (3)
C3—C2—C1—C9	60.2 (3)	C6—C7—C10—C3	−60.5 (3)
N1—C1—C8—C7	−179.5 (3)	C8—C7—C10—C3	60.0 (4)
C2—C1—C8—C7	60.4 (3)	C7A—C6A—C5A—C4A	−0.8 (5)
C9—C1—C8—C7	−61.0 (3)	C3—C4—C5—C6	59.9 (3)
C1—C2—C3—C4	−59.5 (3)	C3—C4—C5—C9	−60.0 (4)
C1—C2—C3—C10	60.2 (3)	C1—C9—C5—C4	59.7 (3)
C10—C3—C4—C5	−60.2 (3)	C1—C9—C5—C6	−60.3 (3)
C2—C3—C4—C5	59.6 (4)	C3A—C2A—C1A—O2A	−172.3 (3)
N1—C1—C9—C5	−179.6 (3)	C7A—C2A—C1A—O2A	6.5 (4)
C2—C1—C9—C5	−60.4 (3)	C3A—C2A—C1A—O1A	9.6 (4)
C8—C1—C9—C5	61.0 (3)	C7A—C2A—C1A—O1A	−171.7 (3)
C1—C8—C7—C6	60.9 (3)	C10—C7—C6—C5	59.8 (3)
C1—C8—C7—C10	−59.7 (3)	C8—C7—C6—C5	−60.9 (4)
C7A—C2A—C3A—C4A	−0.4 (5)	C4—C5—C6—C7	−59.4 (4)
C1A—C2A—C3A—C4A	178.3 (3)	C9—C5—C6—C7	60.6 (4)
C5A—C6A—C7A—C2A	1.3 (5)	C6A—C5A—C4A—C3A	−0.2 (5)
C3A—C2A—C7A—C6A	−0.6 (5)	C2A—C3A—C4A—C5A	0.9 (5)
C1A—C2A—C7A—C6A	−179.5 (3)		

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Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*^{i}	1.19	1.60	2.780 (3)	169
N1—H2*N*···O2*A*	0.87	1.86	2.720 (4)	165
N1—H3*N*···O1*A*^{ii}	0.99	1.80	2.777 (4)	170
C7*A*—H7*AA*···O2*A**	0.95	2.42	2.749 (4)	100

Symmetry codes: (i) −*x*+1/2, *y*+1/2, −*z*+1/2; (ii) *x*, *y*+1, *z*.

Figure 1

Figure 1. The asymmetric unit of adamantylammonium benzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Schematic displaying selected interactions within adamantylammonium benzoate. Figure 3. Extended packing diagram as viewed down the b-axis highlighting hydrogen bonding in red dashed lines.

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(3s,5s,7s)-adamantan-1-ammonium 2,5-dihydroxybenzoate

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Adamantylammonium dihydroxybenzoate, systematic name; (3s,5s,7s)-adamantan-1-aminium 2,5-dihydroxybenzoate, $C_{10}H_{18}N_1$. $C_7H_5O_4$; displays interionic N—H···O hydrogen bonding and interanionic O—H···O and π···π ring interactions. In addition a interionic C—H···π interaction is also seen.

Experimental

Crystal data

$C_{10}H_{18}N·C_7H_5O_4$
$M_r = 305.36$
Monoclinic, $P2_1/n$
$a = 12.157$ (3) Å
$b = 6.9992$ (17) Å
$c = 17.778$ (4) Å
β = 92.728 (14)°
$V = 1511.0$ (6) Å^3
$Z = 4$
Mo $K\alpha$ radiation, λ = 0.71073 Å
μ = 0.10 mm^{-1}
$T = 296$ K
0.02 × 0.02 × 0.01 mm

Data collection

Bruker X8 APEX KAPPA CCD diffractometer
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)
$T_{min} = 0.998$, $T_{max} = 0.999$
25942 measured reflections
2647 independent reflections
1266 reflections with $I > 2\sigma(I)$
$R_{int} = 0.233$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.071$
$wR(F^2) = 0.186$
$S = 0.91$
2647 reflections
219 parameters
0 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.49$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*^{i}	1.03 (5)	1.76 (5)	2.781 (4)	170 (3)
N1—H2*N*···O1*A*^{ii}	1.09 (4)	1.75 (4)	2.818 (4)	166 (3)
N1—H3*N*···O2*A*^{iii}	0.91 (4)	1.93 (4)	2.809 (4)	162 (3)
O4*A*—H4*AO*···O3*A*^{iv}	0.98 (3)	1.73 (4)	2.709 (4)	175 (4)
O3*A**—H3*AO*···O2*A*	1.08 (4)	1.47 (4)	2.504 (4)	157 (3)

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Symmetry codes: (i) −*x*+3/2, *y*+1/2, −*z*+1/2; (ii) *x*−1/2, −*y*−1/2, *z*−1/2; (iii) *x*−1/2, −*y*+1/2, *z*−1/2; (iv) *x*, *y*−1, *z*.

Table 2

Geometrical parameters (Å, °) of selected inter-ring π—π interactions. α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
Cg1	Cg1	4.805 (2)	5	3/2-X,-1/2+Y,1/2-Z
Cg1	Cg1	4.806 (2)	5	3/2-X,1/2+Y,1/2-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Data collection: Bruker Apex II V 1.0 (Bruker ASX, 2005); cell refinement: Bruker Apex II V 1.0 (Bruker ASX, 2005); data reduction: Bruker Apex II V 1.0 (Bruker ASX, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *POV-RAY* for windows, version 3.1; software used to prepare material for publication: Microsoft Office.

References

NOT FOUND

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supplementary materials

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(3s,5s,7s)-adamantan-1-ammonium 2,5-dihydroxybenzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single adamantan-1-ammonium cation and a single dihydroxybenzoate anion (Figure 1). The adamantan-1-ammonium cation adopts the standard tetrahedral symmetry with all four cyclo-hexane rings adopting the preferred chair conformation with angles ranging from 108.36 to 110.35 °. The charged ammonium substituent occurs 1.503 (4) Å from C1. All the ammonium hydrogens were located and placed in the difference map. H2N is the longest (N1—H2N 1.09 (4) Å) with H1N and H3N being shorter (N1—H1N 1.03 (4), N1—H3N 0.91 (4) Å). The 2,5-dihydroxy-benzoate anion displays a planar aromatic ring with two hydroxyl groups and a carboxylic acid group displaying standard bond distances and angles (C3A—O3A 1.360 (4), C6A O4A 1.366 (4), C1A—O1A 1.248 (4) and C1A—O2A 1.270 (4) Å respectively). The hydroxy hydrogen atoms were also located and placed in the difference fourier map (O3A—H3AO 1.08 (4) and O4A H4AO 0.98 (4)). Two main types of hydrogen bonding occurs, strong O—H···O and N—H···O hydrogen bonding (Table 1, Figure 2 [one intramoleculat bond occurs as indicated by a * in Table 1]). Additional interactions which occur is a inter-ring C—H···π interaction (C6—H6B···Cg, 2.72 Å, 172 °, symmetry of the benzoate ring: 1-X,1-Y,1-Z) and π···π interactions (Table 2). The extended structure (Figure 3) consists of sheets of groups of cations and anions constructed from the layered dihydroxybenzoate anions and their hydrogen bonding network to the ammonium substituent of the cation.

Experimental

Adamantan-1-amine (1.472 g, 9.733 mmol), dissolved in methanol, was slowly added to 2,5-dihydroxybenzoic acid (1.500 g, 9.733 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white powder was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the O—H and N—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

(3s,5s,7s)-adamantan-1-ammonium 2,5-dihydroxybenzoate

Crystal data

$C_{10}H_{18}N{\cdot}C_7H_5O_4$	$F(000) = 656$
$M_r = 305.36$	$D_x = 1.342$ Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Hall symbol: -P 2yn	Cell parameters from 2095 reflections

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a = 12.157 (3) Å	θ = 3.1–21.5°
b = 6.9992 (17) Å	μ = 0.10 mm^{-1}
c = 17.778 (4) Å	T = 296 K
β = 92.728 (14)°	Anhedral, Translucent
V = 1511.0 (6) Å^3	0.02 × 0.02 × 0.01 mm
Z = 4	

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	2647 independent reflections
Radiation source: fine-focus sealed tube	1266 reflections with $I > 2\sigma(I)$
graphite	R_{int} = 0.233
0.5 deg frames in phi and ω scans	θ_{max} = 25.0°, θ_{min} = 3.1°
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	h = −14→14
T_{min} = 0.998, T_{max} = 0.999	k = −8→8
25942 measured reflections	l = −21→21

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.071	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2)$ = 0.186	H atoms treated by a mixture of independent and constrained refinement
S = 0.91	$w = 1/[\sigma^2(F_o^2) + (0.0905P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
2647 reflections	$(\Delta/\sigma)_{max} < 0.001$
219 parameters	$\Delta\rho_{max}$ = 0.49 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.32 e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
N1	0.9550 (2)	0.7191 (5)	0.55584 (19)	0.0264 (8)
C1	0.8368 (3)	0.7076 (5)	0.5766 (2)	0.0248 (9)

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C10	0.7756 (3)	0.8810 (5)	0.5443 (2)	0.0327 (10)
H10A	0.7800	0.8833	0.4899	0.039*
H10B	0.8089	0.9971	0.5645	0.039*
C2	0.7857 (3)	0.5273 (5)	0.5432 (2)	0.0326 (10)
H2A	0.8255	0.4163	0.5626	0.039*
H2B	0.7901	0.5289	0.4889	0.039*
C8	0.6028 (3)	0.6891 (6)	0.5321 (2)	0.0411 (11)
H8A	0.6056	0.6908	0.4776	0.049*
H8B	0.5263	0.6818	0.5449	0.049*
C5	0.6599 (3)	0.5116 (6)	0.6487 (2)	0.0418 (11)
H5A	0.6990	0.4006	0.6688	0.050*
H5B	0.5837	0.5023	0.6623	0.050*
C7	0.6550 (3)	0.8702 (5)	0.5650 (2)	0.0368 (10)
H7	0.6151	0.9821	0.5449	0.044*
C3	0.8332 (3)	0.7055 (5)	0.6614 (2)	0.0340 (10)
H3A	0.8668	0.8208	0.6823	0.041*
H3B	0.8737	0.5963	0.6818	0.041*
C9	0.6656 (3)	0.5164 (6)	0.5639 (2)	0.0364 (10)
H9	0.6325	0.3995	0.5426	0.044*
C4	0.7117 (3)	0.6939 (6)	0.6824 (2)	0.0396 (11)
H4	0.7075	0.6919	0.7373	0.048*
C6	0.6500 (3)	0.8667 (6)	0.6503 (2)	0.0439 (11)
H6A	0.6826	0.9826	0.6713	0.053*
H6B	0.5738	0.8615	0.6640	0.053*
O3A	0.6008 (2)	0.5759 (3)	0.24842 (15)	0.0336 (7)
O2A	0.5493 (2)	0.4488 (3)	0.11990 (14)	0.0351 (7)
O1A	0.54677 (19)	0.1376 (3)	0.09731 (14)	0.0308 (7)
O4A	0.6707 (2)	−0.1566 (4)	0.34995 (15)	0.0360 (7)
C2A	0.5984 (3)	0.2404 (5)	0.22140 (19)	0.0244 (9)
C7A	0.6163 (3)	0.0556 (5)	0.24841 (19)	0.0246 (9)
H7AA	0.6035	−0.0475	0.2162	0.030*
C4A	0.6558 (3)	0.3582 (5)	0.3450 (2)	0.0294 (9)
H4AA	0.6689	0.4602	0.3778	0.035*
C5A	0.6733 (3)	0.1750 (5)	0.3699 (2)	0.0285 (9)
H5AA	0.6992	0.1528	0.4192	0.034*
C1A	0.5623 (3)	0.2764 (5)	0.1406 (2)	0.0278 (9)
C3A	0.6185 (3)	0.3924 (5)	0.2710 (2)	0.0261 (9)
C6A	0.6523 (3)	0.0225 (5)	0.3215 (2)	0.0274 (9)
H1N	0.963 (3)	0.695 (5)	0.499 (3)	0.064 (14)*
H2N	0.998 (3)	0.593 (6)	0.578 (2)	0.064 (13)*
H3N	0.985 (4)	0.836 (6)	0.566 (2)	0.066 (15)*
H4AO	0.648 (3)	−0.250 (5)	0.311 (2)	0.057 (13)*
H3AO	0.581 (3)	0.555 (5)	0.189 (2)	0.046 (11)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0177 (19)	0.035 (2)	0.027 (2)	−0.0026 (16)	0.0059 (14)	−0.0040 (16)
C1	0.013 (2)	0.035 (2)	0.027 (2)	−0.0019 (16)	0.0048 (16)	−0.0011 (18)
C10	0.028 (2)	0.038 (2)	0.033 (2)	0.0035 (18)	0.0058 (18)	0.0038 (19)
C2	0.027 (3)	0.035 (2)	0.036 (2)	−0.0042 (17)	0.0029 (18)	−0.0058 (18)

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C8	0.020 (2)	0.066 (3)	0.037 (3)	−0.002 (2)	0.0026 (18)	−0.003 (2)
C5	0.028 (3)	0.054 (3)	0.044 (3)	−0.003 (2)	0.002 (2)	0.010 (2)
C7	0.027 (2)	0.042 (2)	0.042 (3)	0.0097 (19)	0.0033 (19)	0.004 (2)
C3	0.023 (2)	0.049 (2)	0.030 (2)	0.0012 (18)	0.0027 (17)	0.0032 (19)
C9	0.020 (2)	0.045 (3)	0.045 (3)	−0.0084 (19)	0.0035 (19)	−0.003 (2)
C4	0.029 (3)	0.068 (3)	0.023 (2)	0.002 (2)	0.0072 (18)	0.002 (2)
C6	0.025 (2)	0.061 (3)	0.046 (3)	0.001 (2)	0.009 (2)	−0.008 (2)
O3A	0.0378 (17)	0.0287 (15)	0.0339 (17)	0.0001 (12)	−0.0031 (13)	−0.0009 (13)
O2A	0.0348 (17)	0.0330 (17)	0.0369 (17)	0.0038 (12)	−0.0041 (13)	0.0059 (14)
O1A	0.0291 (16)	0.0323 (15)	0.0309 (16)	−0.0057 (12)	0.0004 (12)	−0.0051 (13)
O4A	0.0447 (18)	0.0301 (16)	0.0326 (16)	0.0024 (13)	−0.0044 (13)	0.0016 (14)
C2A	0.017 (2)	0.030 (2)	0.026 (2)	−0.0023 (15)	0.0048 (16)	−0.0023 (18)
C7A	0.019 (2)	0.033 (2)	0.022 (2)	−0.0007 (16)	0.0028 (16)	0.0007 (18)
C4A	0.023 (2)	0.035 (2)	0.029 (2)	0.0013 (18)	−0.0004 (17)	−0.0018 (19)
C5A	0.024 (2)	0.035 (2)	0.026 (2)	0.0039 (17)	−0.0016 (17)	0.0031 (19)
C1A	0.012 (2)	0.038 (2)	0.034 (3)	−0.0029 (17)	0.0071 (17)	0.003 (2)
C3A	0.018 (2)	0.028 (2)	0.033 (2)	0.0054 (16)	0.0052 (17)	0.0043 (19)
C6A	0.023 (2)	0.026 (2)	0.034 (3)	0.0040 (16)	0.0048 (18)	0.0026 (19)

Geometric parameters (Å, º)

N1—C1	1.503 (4)	C3—H3A	0.9700
N1—H1N	1.03 (4)	C3—H3B	0.9700
N1—H2N	1.09 (4)	C9—H9	0.9800
N1—H3N	0.91 (4)	C4—C6	1.519 (5)
C1—C3	1.510 (5)	C4—H4	0.9800
C1—C2	1.515 (5)	C6—H6A	0.9700
C1—C10	1.522 (5)	C6—H6B	0.9700
C10—C7	1.530 (5)	O3A—C3A	1.360 (4)
C10—H10A	0.9700	O3A—H3AO	1.08 (4)
C10—H10B	0.9700	O2A—C1A	1.270 (4)
C2—C9	1.525 (5)	O2A—H3AO	1.47 (4)
C2—H2A	0.9700	O1A—C1A	1.248 (4)
C2—H2B	0.9700	O4A—C6A	1.366 (4)
C8—C7	1.523 (5)	O4A—H4AO	0.98 (4)
C8—C9	1.524 (5)	C2A—C7A	1.393 (5)
C8—H8A	0.9700	C2A—C3A	1.396 (5)
C8—H8B	0.9700	C2A—C1A	1.504 (5)
C5—C9	1.512 (5)	C7A—C6A	1.371 (5)
C5—C4	1.532 (5)	C7A—H7AA	0.9300
C5—H5A	0.9700	C4A—C5A	1.370 (5)
C5—H5B	0.9700	C4A—C3A	1.392 (5)
C7—C6	1.520 (5)	C4A—H4AA	0.9300
C7—H7	0.9800	C5A—C6A	1.387 (5)
C3—C4	1.543 (5)	C5A—H5AA	0.9300

C1—N1—H1N	111 (2)	C1—C3—H3B	110.0
C1—N1—H2N	108 (2)	C4—C3—H3B	110.0
H1N—N1—H2N	99 (3)	H3A—C3—H3B	108.4
C1—N1—H3N	112 (3)	C5—C9—C8	110.0 (3)
H1N—N1—H3N	107 (4)	C5—C9—C2	109.4 (3)

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H2N—N1—H3N	118 (3)	C8—C9—C2	109.8 (3)
N1—C1—C3	108.6 (3)	C5—C9—H9	109.2
N1—C1—C2	109.1 (3)	C8—C9—H9	109.2
C3—C1—C2	110.6 (3)	C2—C9—H9	109.2
N1—C1—C10	108.7 (3)	C6—C4—C5	109.3 (3)
C3—C1—C10	110.3 (3)	C6—C4—C3	109.2 (3)
C2—C1—C10	109.4 (3)	C5—C4—C3	109.3 (3)
C1—C10—C7	109.0 (3)	C6—C4—H4	109.7
C1—C10—H10A	109.9	C5—C4—H4	109.7
C7—C10—H10A	109.9	C3—C4—H4	109.7
C1—C10—H10B	109.9	C4—C6—C7	110.2 (3)
C7—C10—H10B	109.9	C4—C6—H6A	109.6
H10A—C10—H10B	108.3	C7—C6—H6A	109.6
C1—C2—C9	109.0 (3)	C4—C6—H6B	109.6
C1—C2—H2A	109.9	C7—C6—H6B	109.6
C9—C2—H2A	109.9	H6A—C6—H6B	108.1
C1—C2—H2B	109.9	C3A—O3A—H3AO	100.7 (19)
C9—C2—H2B	109.9	C1A—O2A—H3AO	102.3 (14)
H2A—C2—H2B	108.3	C6A—O4A—H4AO	108 (2)
C7—C8—C9	109.0 (3)	C7A—C2A—C3A	118.0 (3)
C7—C8—H8A	109.9	C7A—C2A—C1A	121.2 (3)
C9—C8—H8A	109.9	C3A—C2A—C1A	120.7 (3)
C7—C8—H8B	109.9	C6A—C7A—C2A	121.4 (3)
C9—C8—H8B	109.9	C6A—C7A—H7AA	119.3
H8A—C8—H8B	108.3	C2A—C7A—H7AA	119.3
C9—C5—C4	109.4 (3)	C5A—C4A—C3A	120.3 (3)
C9—C5—H5A	109.8	C5A—C4A—H4AA	119.9
C4—C5—H5A	109.8	C3A—C4A—H4AA	119.9
C9—C5—H5B	109.8	C4A—C5A—C6A	120.0 (3)
C4—C5—H5B	109.8	C4A—C5A—H5AA	120.0
H5A—C5—H5B	108.2	C6A—C5A—H5AA	120.0
C6—C7—C8	109.6 (3)	O1A—C1A—O2A	123.3 (3)
C6—C7—C10	109.0 (3)	O1A—C1A—C2A	119.2 (3)
C8—C7—C10	109.5 (3)	O2A—C1A—C2A	117.6 (3)
C6—C7—H7	109.6	O3A—C3A—C4A	118.8 (3)
C8—C7—H7	109.6	O3A—C3A—C2A	120.8 (3)
C10—C7—H7	109.6	C4A—C3A—C2A	120.4 (3)
C1—C3—C4	108.4 (3)	O4A—C6A—C7A	123.0 (3)
C1—C3—H3A	110.0	O4A—C6A—C5A	117.0 (3)
C4—C3—H3A	110.0	C7A—C6A—C5A	119.9 (3)

N1—C1—C10—C7	179.9 (3)	C1—C3—C4—C5	59.5 (4)
C3—C1—C10—C7	−61.1 (4)	C5—C4—C6—C7	−59.1 (4)
C2—C1—C10—C7	60.8 (4)	C3—C4—C6—C7	60.3 (4)
N1—C1—C2—C9	−179.7 (3)	C8—C7—C6—C4	59.8 (4)
C3—C1—C2—C9	60.9 (4)	C10—C7—C6—C4	−60.0 (4)
C10—C1—C2—C9	−60.9 (4)	C3A—C2A—C7A—C6A	0.1 (5)
C9—C8—C7—C6	−59.7 (4)	C1A—C2A—C7A—C6A	178.1 (3)
C9—C8—C7—C10	59.8 (4)	C3A—C4A—C5A—C6A	−0.9 (5)
C1—C10—C7—C6	59.5 (4)	C7A—C2A—C1A—O1A	1.0 (5)
C1—C10—C7—C8	−60.3 (4)	C3A—C2A—C1A—O1A	178.9 (3)
N1—C1—C3—C4	179.9 (3)	C7A—C2A—C1A—O2A	−179.0 (3)

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C2—C1—C3—C4	−60.4 (4)	C3A—C2A—C1A—O2A	−1.1 (5)
C10—C1—C3—C4	60.9 (4)	C5A—C4A—C3A—O3A	179.3 (3)
C4—C5—C9—C8	−60.2 (4)	C5A—C4A—C3A—C2A	0.1 (5)
C4—C5—C9—C2	60.5 (4)	C7A—C2A—C3A—O3A	−178.9 (3)
C7—C8—C9—C5	60.4 (4)	C1A—C2A—C3A—O3A	3.2 (5)
C7—C8—C9—C2	−60.0 (4)	C7A—C2A—C3A—C4A	0.3 (5)
C1—C2—C9—C5	−60.2 (4)	C1A—C2A—C3A—C4A	−177.6 (3)
C1—C2—C9—C8	60.6 (4)	C2A—C7A—C6A—O4A	180.0 (3)
C9—C5—C4—C6	59.1 (4)	C2A—C7A—C6A—C5A	−1.0 (5)
C9—C5—C4—C3	−60.2 (4)	C4A—C5A—C6A—O4A	−179.5 (3)
C1—C3—C4—C6	−60.0 (4)	C4A—C5A—C6A—C7A	1.3 (5)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O1*A*^{i}	1.03 (5)	1.76 (5)	2.781 (4)	170 (3)
N1—H2*N*···O1*A*^{ii}	1.09 (4)	1.75 (4)	2.818 (4)	166 (3)
N1—H3*N*···O2*A*^{iii}	0.91 (4)	1.93 (4)	2.809 (4)	162 (3)
O4*A*—H4*AO*···O3*A*^{iv}	0.98 (3)	1.73 (4)	2.709 (4)	175 (4)
O3*A**—H3*AO*···O2*A*	1.08 (4)	1.47 (4)	2.504 (4)	157 (3)

Symmetry codes: (i) −*x*+3/2, *y*+1/2, −*z*+1/2; (ii) *x*−1/2, −*y*−1/2, *z*−1/2; (iii) *x*−1/2, −*y*+1/2, *z*−1/2; (iv) *x*, *y*−1, *z*.

Figure 1

Figure 1. The asymmetric unit of adamantylammonium dihydroxybenzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Schematic displaying selected interactions within adamantylammonium dihydroxybenzoate. Figure 3. Extended packing diagram as viewed down the b-axis highlighting hydrogen bonding in red dashed lines.

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(3s,5s,7s)-adamantan-1-ammonium 2-hydroxybenzoate

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Adamantylammonium hydroxybenzoate, systematic name; (3s,5s,7s)-adamantan-1-ammonium 2-hydroxybenzoate, $C_{10}H_{18}N_1$. $C_7H_5O_3$; displays interionic N—H···O hydrogen bonding and interanionic π···π ring interactions. In addition a interionic C—H···π and C—H···O interaction is also seen.

Experimental

Crystal data

$C_{10}H_{18}N·C_7H_5O_3$	γ = 82.988 (4)°
M_r = 289.36	V = 761.99 (10) Å^3
Triclinic, $P\overline{1}$	Z = 2
a = 6.7080 (5) Å	Mo $K\alpha$ radiation, λ = 0.71073 Å
b = 9.3067 (7) Å	μ = 0.09 mm^{-1}
c = 12.7864 (9) Å	T = 296 K
α = 80.421 (5)°	0.50 × 0.50 × 0.01 mm
β = 76.338 (4)°	

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	3717 independent reflections
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	2109 reflections with $I > 2\sigma(I)$
T_{min} = 0.958, T_{max} = 0.999	R_{int} = 0.039
10562 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.050	0 restraints
$wR(F^2)$ = 0.137	H atoms treated by a mixture of independent and constrained refinement
S = 1.00	$\Delta\rho_{max}$ = 0.18 e Å^{-3}
3717 reflections	$\Delta\rho_{min}$ = −0.23 e Å^{-3}
206 parameters	

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O2*A*^{i}	0.93 (2)	1.90 (2)	2.814 (2)	168 (2)
N1—H2*N*···O1*A*^{ii}	0.95 (2)	1.85 (2)	2.784 (2)	167 (2)
N1—H3*N*···O1*A*	1.01 (2)	1.85 (2)	2.825 (2)	162 (2)
N1—H3*N*···O2*A*	1.01 (2)	2.49 (2)	3.301 (2)	138 (2)
O3*A**—H3*AO*···O2*A*	0.93 (2)	1.68 (3)	2.524 (2)	150 (3)

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C10—H10*B*···O3*A*^{iii}	0.97	2.58	3.440 (2)	148

Symmetry codes: (i) −*x*+1, −*y*, −*z*+1; (ii) −*x*, −*y*, −*z*+1; (iii) −*x*+1, −*y*+1, −*z*+1.

Table 2

Geometrical parameters (Å, °) of selected inter-ring π—π interactions. α is the dihedral angle between planes I and J, CgI is the centroid of plane I and CgJ the centroid of plane J.

CgI	CgJ	Cg···Cg	α	Symmetry position of CgJ
Cg1	Cg1	3.6528 (10)	0	-X,-Y,2-Z

Notes: Cg1 is the centroid of ring C2A/C3A/C4A/C5A/C6A/C7A.

Data collection: Bruker Apex II V 1.0 (Bruker ASX, 2005); cell refinement: Bruker Apex II V 1.0 (Bruker ASX, 2005); data reduction: Bruker Apex II V 1.0 (Bruker ASX, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *POV-RAY* for windows, version 3.1; software used to prepare material for publication: Microsoft Office.

References

NOT FOUND

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supplementary materials

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(3s,5s,7s)-adamantan-1-ammonium 2-hydroxybenzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single adamantan-1-ammonium cation and a single hydroxybenzoate anion (Figure 1). The adamantan-1-ammonium cation adopts the standard tetrahedral symmetry with all four cyclohexane rings adopting the preferred chair conformation with angles ranging from 108.63 to 109.97 °. The charged ammonium substituent occurs 1.503 (2) Å from C1. All the ammonium hydrogens were located and placed in the difference map. H3N is the longest (N1—H3N 1.01 (2) Å) with H1N and H2N being shorter (N1—H1N 0.92 (2), N1—H2N 0.95 (2) Å). The 2-hydroxybenzoate anion displays a planar aromatic ring with one hydroxyl group and a carboxylic acid group displaying standard bond distances and angles (C3A—O3A 1.351 (2), C1A—O1A 1.255 (2) and C1A—O2A 1.273 (2) Å respectively). The hydroxy hydrogen atom was also located and placed in the difference fourier map (O3A—H3AO 0.93 (2)). Three main types of hydrogen bonding occurs; strong N—H···O bonds, a intramolecular O—H···O bond and a weak C—H···O hydrogen bond (Table 1, Figure 2 [the intramolecular bond is indicated by a * in Table 1]). Additional interactions which occur is a inter-ring C—H···π interaction (C4—H4A···Cg, 2.67 Å, 157 °, symmetry of the benzoate ring: -X,1-Y,1-Z) and a π···π interaction (Table 2). The extended structure (Figure 3 and 4) consists of layers of cations and anions constructed from the layered dihydroxybenzoate anions and their hydrogen bonding network to the ammonium substituent of the cation. The cycloalkane moeity of the cation group together, effectively 'sandwiched' between the above mentioned interactions.

Experimental

Adamantan-1-amine (1.500 g, 9.917 mmol), dissolved in methanol, was slowly added to 2-hydroxybenzoic acid (1.370 g, 9.917 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting white solid was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the O—H and N—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

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(3s,5s,7s)-adamantan-1-ammonium 2-hydroxybenzoate

Crystal data

$C_{10}H_{18}N·C_7H_5O_3$	$Z = 2$
$M_r = 289.36$	$F(000) = 312$
Triclinic, $P\overline{1}$	$D_x = 1.261$ Mg m^{-3}
Hall symbol: -P 1	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 6.7080$ (5) Å	Cell parameters from 1725 reflections
$b = 9.3067$ (7) Å	$\theta = 2.2$–$28.6°$
$c = 12.7864$ (9) Å	$\mu = 0.09$ mm^{-1}
$\alpha = 80.421$ (5)°	$T = 296$ K
$\beta = 76.338$ (4)°	Thin, Translucent
$\gamma = 82.988$ (4)°	0.50 × 0.50 × 0.01 mm
$V = 761.99$ (10) Å^3	

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	3717 independent reflections
Radiation source: fine-focus sealed tube	2109 reflections with $I > 2\sigma(I)$
graphite	$R_{int} = 0.039$
0.5 deg frames in phi and ω scans	$\theta_{max} = 28.6°$, $\theta_{min} = 3.0°$
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	$h = -8 \rightarrow 8$
$T_{min} = 0.958$, $T_{max} = 0.999$	$k = -12 \rightarrow 12$
10562 measured reflections	$l = -17 \rightarrow 16$

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.050$	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2) = 0.137$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.00$	$w = 1/[\sigma^2(F_o^2) + (0.0642P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
3717 reflections	$(\Delta/\sigma)_{max} < 0.001$
206 parameters	$\Delta\rho_{max} = 0.18$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.23$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-

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factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C2A	0.0585 (2)	0.12982 (16)	0.79566 (12)	0.0255 (3)
O2A	0.35085 (15)	0.10614 (12)	0.65153 (9)	0.0391 (3)
O1A	0.05659 (16)	0.04709 (12)	0.62945 (9)	0.0401 (3)
N1	0.2785 (2)	0.06658 (14)	0.41103 (12)	0.0296 (3)
O3A	0.37562 (17)	0.19407 (14)	0.82406 (13)	0.0516 (4)
C1	0.2978 (2)	0.22107 (16)	0.35469 (12)	0.0280 (4)
C7A	−0.1505 (2)	0.11628 (16)	0.83888 (13)	0.0318 (4)
H7AA	−0.2294	0.0865	0.7969	0.038*
C3A	0.1725 (2)	0.17745 (17)	0.86047 (14)	0.0332 (4)
C7	0.4694 (2)	0.28475 (18)	0.38690 (14)	0.0372 (4)
H7A	0.5986	0.2264	0.3663	0.045*
H7B	0.4389	0.2837	0.4650	0.045*
C1A	0.1591 (2)	0.09194 (16)	0.68597 (13)	0.0290 (4)
C4A	0.0780 (3)	0.20778 (19)	0.96404 (14)	0.0434 (5)
H4AA	0.1538	0.2403	1.0064	0.052*
C5A	−0.1256 (3)	0.19005 (19)	1.00386 (14)	0.0449 (5)
H5AA	−0.1868	0.2081	1.0742	0.054*
C6	0.0945 (2)	0.31083 (18)	0.38995 (14)	0.0379 (4)
H6B	0.0632	0.3099	0.4681	0.046*
H6A	−0.0160	0.2693	0.3712	0.046*
C2	0.3467 (3)	0.22040 (18)	0.23240 (13)	0.0364 (4)
H2B	0.2381	0.1785	0.2123	0.044*
H2A	0.4748	0.1613	0.2107	0.044*
C6A	−0.2430 (3)	0.14580 (18)	0.94194 (14)	0.0407 (4)
H6AA	−0.3827	0.1361	0.9695	0.049*
C9	0.2839 (3)	0.53351 (19)	0.36373 (16)	0.0457 (5)
H9A	0.2527	0.5336	0.4418	0.055*
H9B	0.2949	0.6337	0.3283	0.055*
C8	0.4870 (2)	0.44195 (19)	0.32909 (15)	0.0422 (5)
H8	0.5977	0.4836	0.3491	0.051*
C10	0.5355 (3)	0.44342 (19)	0.20670 (15)	0.0495 (5)
H10A	0.6662	0.3876	0.1842	0.059*
H10B	0.5467	0.5432	0.1702	0.059*
C3	0.3655 (3)	0.37730 (19)	0.17490 (15)	0.0461 (5)
H3	0.3971	0.3780	0.0960	0.055*
C5	0.1133 (3)	0.46831 (19)	0.33181 (15)	0.0455 (5)
H5	−0.0173	0.5269	0.3535	0.055*
C4	0.1616 (3)	0.4685 (2)	0.20962 (16)	0.0529 (5)
H4A	0.1713	0.5681	0.1726	0.063*
H4B	0.0518	0.4280	0.1895	0.063*
H1N	0.406 (3)	0.014 (2)	0.3982 (14)	0.047 (5)*
H2N	0.177 (3)	0.0241 (19)	0.3878 (14)	0.049 (5)*
H3N	0.227 (3)	0.060 (2)	0.4924 (17)	0.061 (6)*
H3AO	0.407 (4)	0.178 (3)	0.752 (2)	0.091 (8)*

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Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C2A	0.0282 (8)	0.0232 (8)	0.0253 (8)	−0.0002 (6)	−0.0060 (6)	−0.0048 (7)
O2A	0.0261 (6)	0.0441 (7)	0.0452 (8)	−0.0014 (5)	−0.0009 (5)	−0.0124 (6)
O1A	0.0389 (7)	0.0524 (8)	0.0332 (7)	−0.0105 (5)	−0.0059 (5)	−0.0163 (6)
N1	0.0262 (7)	0.0326 (8)	0.0301 (9)	−0.0009 (6)	−0.0048 (6)	−0.0080 (6)
O3A	0.0329 (7)	0.0652 (10)	0.0663 (10)	−0.0058 (6)	−0.0166 (6)	−0.0274 (8)
C1	0.0249 (8)	0.0284 (9)	0.0303 (9)	−0.0023 (6)	−0.0026 (6)	−0.0075 (7)
C7A	0.0322 (8)	0.0300 (9)	0.0332 (10)	−0.0022 (6)	−0.0059 (7)	−0.0069 (7)
C3A	0.0331 (9)	0.0308 (9)	0.0390 (10)	0.0015 (7)	−0.0136 (7)	−0.0087 (8)
C7	0.0308 (9)	0.0411 (11)	0.0448 (11)	−0.0021 (7)	−0.0107 (7)	−0.0180 (8)
C1A	0.0321 (8)	0.0233 (8)	0.0312 (9)	0.0005 (6)	−0.0075 (7)	−0.0044 (7)
C4A	0.0536 (11)	0.0459 (12)	0.0383 (11)	0.0024 (8)	−0.0208 (8)	−0.0175 (9)
C5A	0.0581 (12)	0.0455 (12)	0.0283 (10)	0.0049 (9)	−0.0043 (8)	−0.0114 (9)
C6	0.0260 (8)	0.0385 (10)	0.0466 (11)	0.0010 (7)	−0.0016 (7)	−0.0107 (8)
C2	0.0402 (9)	0.0363 (10)	0.0329 (10)	−0.0079 (7)	−0.0033 (7)	−0.0093 (8)
C6A	0.0388 (10)	0.0424 (11)	0.0359 (11)	−0.0016 (8)	0.0012 (7)	−0.0068 (8)
C9	0.0492 (11)	0.0351 (11)	0.0511 (12)	−0.0018 (8)	−0.0015 (8)	−0.0169 (9)
C8	0.0358 (9)	0.0403 (11)	0.0534 (12)	−0.0114 (7)	−0.0047 (8)	−0.0163 (9)
C10	0.0505 (11)	0.0376 (11)	0.0544 (13)	−0.0135 (8)	0.0104 (9)	−0.0137 (9)
C3	0.0656 (12)	0.0385 (11)	0.0330 (11)	−0.0130 (9)	−0.0042 (8)	−0.0047 (9)
C5	0.0356 (9)	0.0366 (11)	0.0591 (13)	0.0056 (7)	−0.0030 (8)	−0.0094 (9)
C4	0.0633 (13)	0.0383 (11)	0.0612 (14)	−0.0081 (9)	−0.0269 (10)	0.0027 (10)

Geometric parameters (Å, º)

C2A—C7A	1.3929 (19)	C5A—H5AA	0.9300
C2A—C3A	1.404 (2)	C6—C5	1.535 (2)
C2A—C1A	1.485 (2)	C6—H6B	0.9700
O2A—C1A	1.2727 (17)	C6—H6A	0.9700
O1A—C1A	1.2550 (17)	C2—C3	1.527 (2)
N1—C1	1.5031 (19)	C2—H2B	0.9700
N1—H1N	0.923 (18)	C2—H2A	0.9700
N1—H2N	0.952 (18)	C6A—H6AA	0.9300
N1—H3N	1.01 (2)	C9—C5	1.523 (2)
O3A—C3A	1.3508 (18)	C9—C8	1.528 (2)
O3A—H3AO	0.93 (2)	C9—H9A	0.9700
C1—C2	1.521 (2)	C9—H9B	0.9700
C1—C6	1.522 (2)	C8—C10	1.519 (2)
C1—C7	1.522 (2)	C8—H8	0.9800
C7A—C6A	1.375 (2)	C10—C3	1.522 (2)
C7A—H7AA	0.9300	C10—H10A	0.9700
C3A—C4A	1.385 (2)	C10—H10B	0.9700
C7—C8	1.530 (2)	C3—C4	1.531 (3)
C7—H7A	0.9700	C3—H3	0.9800
C7—H7B	0.9700	C5—C4	1.519 (3)
C4A—C5A	1.361 (2)	C5—H5	0.9800
C4A—H4AA	0.9300	C4—H4A	0.9700
C5A—C6A	1.378 (2)	C4—H4B	0.9700

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C7A—C2A—C3A	117.67 (14)	C1—C2—H2B	109.9
C7A—C2A—C1A	121.39 (13)	C3—C2—H2B	109.9
C3A—C2A—C1A	120.93 (13)	C1—C2—H2A	109.9
C1—N1—H1N	109.5 (10)	C3—C2—H2A	109.9
C1—N1—H2N	109.8 (10)	H2B—C2—H2A	108.3
H1N—N1—H2N	112.5 (15)	C7A—C6A—C5A	119.01 (16)
C1—N1—H3N	113.2 (11)	C7A—C6A—H6AA	120.5
H1N—N1—H3N	107.4 (15)	C5A—C6A—H6AA	120.5
H2N—N1—H3N	104.4 (15)	C5—C9—C8	108.86 (14)
C3A—O3A—H3AO	105.6 (15)	C5—C9—H9A	109.9
N1—C1—C2	108.90 (12)	C8—C9—H9A	109.9
N1—C1—C6	108.54 (12)	C5—C9—H9B	109.9
C2—C1—C6	110.29 (13)	C8—C9—H9B	109.9
N1—C1—C7	109.39 (12)	H9A—C9—H9B	108.3
C2—C1—C7	110.08 (12)	C10—C8—C9	109.55 (15)
C6—C1—C7	109.62 (13)	C10—C8—C7	109.88 (14)
C6A—C7A—C2A	121.72 (15)	C9—C8—C7	109.51 (13)
C6A—C7A—H7AA	119.1	C10—C8—H8	109.3
C2A—C7A—H7AA	119.1	C9—C8—H8	109.3
O3A—C3A—C4A	118.51 (15)	C7—C8—H8	109.3
O3A—C3A—C2A	121.18 (15)	C8—C10—C3	109.69 (13)
C4A—C3A—C2A	120.30 (14)	C8—C10—H10A	109.7
C1—C7—C8	108.79 (13)	C3—C10—H10A	109.7
C1—C7—H7A	109.9	C8—C10—H10B	109.7
C8—C7—H7A	109.9	C3—C10—H10B	109.7
C1—C7—H7B	109.9	H10A—C10—H10B	108.2
C8—C7—H7B	109.9	C10—C3—C2	109.96 (15)
H7A—C7—H7B	108.3	C10—C3—C4	108.77 (15)
O1A—C1A—O2A	121.37 (14)	C2—C3—C4	109.10 (14)
O1A—C1A—C2A	120.43 (13)	C10—C3—H3	109.7
O2A—C1A—C2A	118.20 (13)	C2—C3—H3	109.7
C5A—C4A—C3A	120.02 (16)	C4—C3—H3	109.7
C5A—C4A—H4AA	120.0	C4—C5—C9	109.97 (14)
C3A—C4A—H4AA	120.0	C4—C5—C6	109.52 (15)
C4A—C5A—C6A	121.25 (16)	C9—C5—C6	109.49 (14)
C4A—C5A—H5AA	119.4	C4—C5—H5	109.3
C6A—C5A—H5AA	119.4	C9—C5—H5	109.3
C1—C6—C5	108.63 (12)	C6—C5—H5	109.3
C1—C6—H6B	110.0	C5—C4—C3	109.71 (14)
C5—C6—H6B	110.0	C5—C4—H4A	109.7
C1—C6—H6A	110.0	C3—C4—H4A	109.7
C5—C6—H6A	110.0	C5—C4—H4B	109.7
H6B—C6—H6A	108.3	C3—C4—H4B	109.7
C1—C2—C3	109.03 (13)	H4A—C4—H4B	108.2

C3A—C2A—C7A—C6A	−1.1 (2)	C7—C1—C2—C3	−60.32 (17)
C1A—C2A—C7A—C6A	177.49 (14)	C2A—C7A—C6A—C5A	0.1 (2)
C7A—C2A—C3A—O3A	−179.63 (14)	C4A—C5A—C6A—C7A	1.4 (3)
C1A—C2A—C3A—O3A	1.8 (2)	C5—C9—C8—C10	60.03 (18)
C7A—C2A—C3A—C4A	0.7 (2)	C5—C9—C8—C7	−60.55 (18)
C1A—C2A—C3A—C4A	−177.86 (14)	C1—C7—C8—C10	−59.78 (17)
N1—C1—C7—C8	−179.93 (12)	C1—C7—C8—C9	60.60 (17)

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C2—C1—C7—C8	60.45 (17)	C9—C8—C10—C3	−60.92 (19)
C6—C1—C7—C8	−61.03 (17)	C7—C8—C10—C3	59.43 (18)
C7A—C2A—C1A—O1A	0.3 (2)	C8—C10—C3—C2	−59.19 (19)
C3A—C2A—C1A—O1A	178.77 (13)	C8—C10—C3—C4	60.22 (19)
C7A—C2A—C1A—O2A	−179.67 (14)	C1—C2—C3—C10	59.33 (17)
C3A—C2A—C1A—O2A	−1.2 (2)	C1—C2—C3—C4	−59.88 (17)
O3A—C3A—C4A—C5A	−179.00 (16)	C8—C9—C5—C4	−59.75 (19)
C2A—C3A—C4A—C5A	0.7 (3)	C8—C9—C5—C6	60.64 (18)
C3A—C4A—C5A—C6A	−1.7 (3)	C1—C6—C5—C4	59.80 (17)
N1—C1—C6—C5	−179.55 (13)	C1—C6—C5—C9	−60.85 (18)
C2—C1—C6—C5	−60.33 (17)	C9—C5—C4—C3	60.04 (19)
C7—C1—C6—C5	61.03 (17)	C6—C5—C4—C3	−60.32 (18)
N1—C1—C2—C3	179.77 (12)	C10—C3—C4—C5	−59.70 (19)
C6—C1—C2—C3	60.77 (16)	C2—C3—C4—C5	60.25 (18)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*···O2*A*^{i}	0.93 (2)	1.90 (2)	2.814 (2)	168 (2)
N1—H2*N*···O1*A*^{ii}	0.95 (2)	1.85 (2)	2.784 (2)	167 (2)
N1—H3*N*···O1*A*	1.01 (2)	1.85 (2)	2.825 (2)	162 (2)
N1—H3*N*···O2*A*	1.01 (2)	2.49 (2)	3.301 (2)	138 (2)
O3*A**—H3*AO*···O2*A*	0.93 (2)	1.68 (3)	2.524 (2)	150 (3)
C10—H10*B*···O3*A*^{iii}	0.97	2.58	3.440 (2)	148

Symmetry codes: (i) −*x*+1, −*y*, −*z*+1; (ii) −*x*, −*y*, −*z*+1; (iii) −*x*+1, −*y*+1, −*z*+1.

Figure 1

Figure 1. The asymmetric unit of adamantylammonium hydroxybenzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Schematic displaying selected interactions within adamantylammonium hydroxybenzoate. Figure 3. Extended packing diagram as viewed down the a-axis highlighting hydrogen bonding in red dashed lines. Figure 3. Extended packing diagram as viewed down the c-axis highlighting hydrogen bonding in red dashed lines.

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Heptan-2-ammonium 2,5-dihydroxybenzoate

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Heptan-2-ammonium 2,5-dihydroxybenzoate , $C_7H_{18}N_1$. $C_7H_5O_4$, displays interionic N—H···O and interanionic O—H···O and C—H···O hydrogen bonding. Interring interactions are also seen.

Experimental

Crystal data

$C_7H_{18}N{\cdot}C_7H_5O_4$
$M_r = 269.33$
Monoclinic, $P2_1/n$
$a = 10.165$ (1) Å
$b = 12.302$ (1) Å
$c = 11.254$ (1) Å
$\beta = 97.111$ (7)°
$V = 1396.4$ (2) Å^3
$Z = 4$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$\mu = 0.09$ mm^{-1}
$T = 123$ K
0.02 × 0.01 × 0.01 mm

Data collection

Bruker X8 APEX KAPPA CCD diffractometer
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)
$T_{min} = 0.998$, $T_{max} = 0.999$
18233 measured reflections
3512 independent reflections
1745 reflections with $I > 2\sigma(I)$
$R_{int} = 0.159$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.105$
$wR(F^2) = 0.202$
$S = 1.07$
3512 reflections
194 parameters
0 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

Table 1

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4*A*—H4*AO*···O2*A*^{i}	0.98 (4)	1.70 (4)	2.662 (4)	167 (4)
N1—H1*N*···O1*A*^{ii}	0.97 (4)	1.81 (4)	2.777 (4)	173 (3)
O3*A**—H3*AO*···O2*A*	0.82 (5)	1.77 (5)	2.544 (4)	157 (5)
N1—H2*N*···O1*A*^{iii}	0.98 (4)	1.90 (4)	2.848 (4)	163 (4)
N1—H3*N*···O3*A*^{iv}	0.87 (5)	2.42 (4)	2.979 (5)	122 (3)
N1—H3*N*···O4*A*^{v}	0.87 (5)	2.27 (4)	2.905 (4)	130 (3)
C7*A*—H7*A*···O2*A*^{i}	0.95	2.57	3.225 (4)	126

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Symmetry codes: (i) −*x*+1/2, *y*−1/2, −*z*+3/2; (ii) −*x*, −*y*+1, −*z*+1; (iii) *x*, *y*+1, *z*; (iv) −*x*+1/2, *y*+1/2, −*z*+3/2; (v) *x*−3/2, −*y*−1/2, *z*−3/2.

Data collection: Bruker Apex II V 1.0 (Bruker ASX, 2005); cell refinement: Bruker Apex II V 1.0 (Bruker ASX, 2005); data reduction: Bruker Apex II V 1.0 (Bruker ASX, 2005); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *POV-RAY* for windows, version 3.1; software used to prepare material for publication: Microsoft Office.

References

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supplementary materials

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Heptan-2-ammonium 2,5-dihydroxybenzoate

Pamela M. Dean* and Jelena Stoimenovski

Comment

The asymmetric unit consists of a single heptan-2-ammonium cation and a single 2,5-dihydroxy-benzoate anion (Figure 1). The alkyl end of the heptan-2-ammonium cation adopts a gauche conformation with a torsional angle of 69.5 (5) [C4—C5—C6—C7], the ammonium end displays a trans conformation [C4—C3—C2—C1, -178.9 (4)]. The hydrogen atoms of the ammonium substituent, with a standard terahedral arrangment, were located in the fourier difference map [N1 H1N 0.97 (4); N1 H2N 0.97 (4); N1 H3N 0.88 (4) Å]. The 2,5-dihydroxy-benzoate anion displays a planar aromatic ring with two hydroxyl groups and a carboxylic acid group displaying standard bond distances and angles (C3A—O3A 1.359 (4), C6A—O4A 1.377 (4), C1A—O1A 1.255 (4) and C1A—O2A 1.276 (4) Å respectively). The hydroxy hydrogen atoms was also located and placed in the difference fourier map (O3A—H3AO 0.82 (5) and O4A—H4AO 0.99 (4)). Three main types of hydrogen bonding occurs, strong O···H—O and N···H—O hydrogen bonding and weak interanionic C—H···O hydrogen bonding (Table 1, Figure 2 [one intramoleculat bond occurs as indicated by a * in Table 1]). Additional interactions which also occurs is an inter-ring C—H···π and π···π interactions (C3—H3B···Cg1, 2.78 Å, 156 °, symmetry of the benzoate ring: 1-X,1-Y,1-Z; Cg1···Cg1, 3.819 (2) Å, 0 °, symmetry of the benzoate ring: 1-X,-Y,2-Z). The extended structure (Figure 3) consists of tightly interlayered cationic and anionic chains constructed from the hydrogen bonding and interring interaction network.

Experimental

Heptane-2-amine (0.748 g, 6.488 mmol), dissolved in methanol, was slowly added to 2,5-dihydroxybenzoic acid (1.000 g, 6.488 mmol) in methanol solution. The reaction was stirred for 4 hours in an ice bath. Methanol was subsequently removed under vacuum and the resulting opaque solid was dried on a Shlenk line for 5 hours.

Refinement

All H atoms were initially located in a difference Fourier map. Thereafter, all H atoms, except the N—H and O—H atoms, were placed in geometrically fixed idealised positions and constrained to ride on their parent atoms with C—H distances in the range 0.95-1.00 Å and $U_{iso}(H) = xU_{eq}(C)$, where x = 1.5 for methyl and 1.2 for all other atoms.

(heptan-2-ammonium 2,5-dihydroxybenzoate)

Crystal data

$C_7H_{18}N·C_7H_5O_4$	$F(000) = 584$
$M_r = 269.33$	$D_x = 1.281$ Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Hall symbol: -P 2yn	Cell parameters from 2321 reflections

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a = 10.165 (1) Å	θ = 2.6–22.2°
b = 12.302 (1) Å	μ = 0.09 mm^{-1}
c = 11.254 (1) Å	T = 123 K
β = 97.111 (7)°	Small, Translucent
V = 1396.4 (2) Å^3	0.02 × 0.01 × 0.01 mm
Z = 4	

Data collection

Bruker X8 APEX KAPPA CCD diffractometer	3512 independent reflections
Radiation source: fine-focus sealed tube	1745 reflections with $I > 2\sigma(I)$
graphite	R_{int} = 0.159
0.5 deg frames in phi and ω scans	θ_{max} = 28.5°, θ_{min} = 2.9°
Absorption correction: Multi-scan *SADABS* (Bruker AXS, 2005)	h = −13→13
T_{min} = 0.998, T_{max} = 0.999	k = −16→14
18233 measured reflections	l = −15→14

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Secondary atom site location: Difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.105	Hydrogen site location: Inferred from neighbouring sites
$wR(F^2)$ = 0.202	H atoms treated by a mixture of independent and constrained refinement
S = 1.07	$w = 1/[\sigma^2(F_o^2) + (0.054P)^2 + 1.074P]$ where $P = (F_o^2 + 2F_c^2)/3$
3512 reflections	$(\Delta/\sigma)_{max} < 0.001$
194 parameters	$\Delta\rho_{max}$ = 0.26 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.32 e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2$sigma(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
O2A	0.1822 (2)	0.1955 (2)	0.7382 (2)	0.0325 (7)
O1A	0.1416 (2)	0.0330 (2)	0.6545 (2)	0.0246 (7)

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O4A	0.5393 (3)	−0.1927 (2)	0.8268 (2)	0.0287 (7)
O3A	0.4074 (3)	0.2404 (2)	0.8526 (3)	0.0313 (7)
C3A	0.4372 (4)	0.1339 (3)	0.8388 (3)	0.0248 (9)
C2A	0.3471 (3)	0.0606 (3)	0.7773 (3)	0.0195 (9)
C5A	0.5941 (4)	−0.0110 (3)	0.8839 (3)	0.0249 (9)
H5A	0.6786	−0.0354	0.9192	0.030*
C7A	0.3845 (4)	−0.0481 (3)	0.7715 (3)	0.0241 (9)
H7A	0.3253	−0.0981	0.7286	0.029*
C6A	0.5042 (4)	−0.0845 (3)	0.8258 (3)	0.0249 (9)
C4A	0.5608 (4)	0.0964 (3)	0.8902 (3)	0.0241 (9)
H4A	0.6227	0.1461	0.9301	0.029*
C1A	0.2150 (4)	0.0976 (3)	0.7185 (3)	0.0234 (9)
N1	0.1067 (3)	0.8974 (3)	0.4479 (3)	0.0243 (8)
C4	0.3823 (4)	0.8008 (3)	0.4464 (4)	0.0295 (10)
H4B	0.3215	0.7659	0.4971	0.035*
H4C	0.3743	0.7619	0.3688	0.035*
C3	0.3433 (4)	0.9200 (3)	0.4254 (4)	0.0298 (10)
H3A	0.3575	0.9581	0.5035	0.036*
H3B	0.4045	0.9527	0.3736	0.036*
C2	0.2038 (4)	0.9419 (3)	0.3698 (4)	0.0280 (10)
H2	0.1891	0.9046	0.2903	0.034*
C5	0.5239 (4)	0.7927 (3)	0.5072 (4)	0.0309 (10)
H5B	0.5322	0.8379	0.5805	0.037*
H5C	0.5838	0.8237	0.4530	0.037*
C1	0.1764 (4)	1.0625 (3)	0.3509 (4)	0.0318 (10)
H1A	0.1911	1.1002	0.4281	0.048*
H1B	0.0842	1.0728	0.3154	0.048*
H1C	0.2361	1.0922	0.2970	0.048*
C6	0.5705 (4)	0.6780 (3)	0.5416 (4)	0.0307 (10)
H6A	0.6561	0.6824	0.5940	0.037*
H6B	0.5053	0.6435	0.5882	0.037*
C7	0.5877 (5)	0.6072 (4)	0.4352 (4)	0.0441 (12)
H1	0.5019	0.5979	0.3861	0.066*
H7B	0.6221	0.5361	0.4631	0.066*
H7C	0.6502	0.6418	0.3873	0.066*
H1N	0.017 (4)	0.916 (3)	0.414 (3)	0.026 (11)*
H2N	0.124 (4)	0.931 (3)	0.527 (4)	0.035 (12)*
H3N	0.112 (4)	0.827 (4)	0.457 (3)	0.030 (12)*
H4AO	0.466 (4)	−0.242 (4)	0.798 (4)	0.048 (13)*
H3AO	0.332 (5)	0.244 (4)	0.817 (4)	0.061 (18)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O2A	0.0324 (17)	0.0166 (16)	0.0456 (18)	0.0034 (12)	−0.0068 (14)	−0.0045 (13)
O1A	0.0238 (15)	0.0218 (15)	0.0262 (14)	0.0014 (11)	−0.0052 (12)	−0.0043 (12)
O4A	0.0280 (17)	0.0185 (16)	0.0370 (17)	0.0027 (13)	−0.0068 (13)	0.0027 (13)
O3A	0.0321 (19)	0.0193 (17)	0.0395 (18)	0.0011 (13)	−0.0072 (14)	−0.0050 (13)
C3A	0.032 (3)	0.020 (2)	0.022 (2)	−0.0017 (18)	0.0030 (18)	−0.0004 (17)
C2A	0.021 (2)	0.021 (2)	0.0176 (19)	−0.0001 (16)	0.0043 (16)	0.0019 (16)
C5A	0.019 (2)	0.033 (3)	0.022 (2)	−0.0037 (18)	−0.0020 (17)	0.0041 (18)

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C7A	0.026 (2)	0.021 (2)	0.024 (2)	−0.0040 (17)	−0.0012 (17)	−0.0022 (17)
C6A	0.023 (2)	0.024 (2)	0.027 (2)	0.0053 (18)	−0.0004 (17)	0.0047 (18)
C4A	0.021 (2)	0.026 (2)	0.025 (2)	−0.0067 (18)	−0.0013 (16)	−0.0036 (17)
C1A	0.026 (2)	0.021 (2)	0.023 (2)	−0.0026 (18)	0.0008 (17)	0.0058 (17)
N1	0.022 (2)	0.021 (2)	0.029 (2)	−0.0004 (15)	−0.0019 (15)	0.0007 (16)
C4	0.030 (2)	0.028 (2)	0.030 (2)	0.0038 (19)	0.0012 (18)	−0.0008 (19)
C3	0.030 (2)	0.028 (2)	0.030 (2)	0.0004 (18)	0.0002 (18)	0.0040 (18)
C2	0.027 (2)	0.029 (2)	0.028 (2)	−0.0030 (18)	0.0013 (18)	0.0034 (18)
C5	0.029 (2)	0.036 (3)	0.028 (2)	0.0000 (19)	0.0049 (18)	0.0018 (19)
C1	0.033 (3)	0.026 (2)	0.035 (2)	0.0004 (18)	−0.0021 (19)	0.0085 (19)
C6	0.029 (2)	0.032 (3)	0.031 (2)	0.0072 (19)	0.0036 (18)	0.0031 (19)
C7	0.054 (3)	0.040 (3)	0.038 (3)	0.020 (2)	0.004 (2)	0.002 (2)

Geometric parameters (Å, º)

O2A—C1A	1.276 (4)	C4—C3	1.529 (5)
O1A—C1A	1.255 (4)	C4—H4B	0.9900
O4A—C6A	1.377 (4)	C4—H4C	0.9900
O4A—H4AO	0.99 (4)	C3—C2	1.502 (5)
O3A—C3A	1.359 (4)	C3—H3A	0.9900
O3A—H3AO	0.82 (5)	C3—H3B	0.9900
C3A—C4A	1.395 (5)	C2—C1	1.519 (5)
C3A—C2A	1.405 (5)	C2—H2	1.0000
C2A—C7A	1.393 (5)	C5—C6	1.523 (5)
C2A—C1A	1.493 (5)	C5—H5B	0.9900
C5A—C4A	1.368 (5)	C5—H5C	0.9900
C5A—C6A	1.389 (5)	C1—H1A	0.9800
C5A—H5A	0.9500	C1—H1B	0.9800
C7A—C6A	1.368 (5)	C1—H1C	0.9800
C7A—H7A	0.9500	C6—C7	1.508 (5)
C4A—H4A	0.9500	C6—H6A	0.9900
N1—C2	1.504 (5)	C6—H6B	0.9900
N1—H1N	0.97 (4)	C7—H1	0.9800
N1—H2N	0.97 (4)	C7—H7B	0.9800
N1—H3N	0.88 (4)	C7—H7C	0.9800
C4—C5	1.519 (5)		

C6A—O4A—H4AO	114 (2)	C2—C3—H3A	108.1
C3A—O3A—H3AO	101 (3)	C4—C3—H3A	108.1
O3A—C3A—C4A	118.3 (3)	C2—C3—H3B	108.1
O3A—C3A—C2A	122.3 (3)	C4—C3—H3B	108.1
C4A—C3A—C2A	119.4 (4)	H3A—C3—H3B	107.3
C7A—C2A—C3A	118.3 (3)	C3—C2—N1	110.2 (3)
C7A—C2A—C1A	120.5 (3)	C3—C2—C1	112.4 (3)
C3A—C2A—C1A	121.2 (3)	N1—C2—C1	108.3 (3)
C4A—C5A—C6A	120.0 (3)	C3—C2—H2	108.6
C4A—C5A—H5A	120.0	N1—C2—H2	108.6
C6A—C5A—H5A	120.0	C1—C2—H2	108.6
C6A—C7A—C2A	121.7 (4)	C4—C5—C6	115.0 (3)
C6A—C7A—H7A	119.1	C4—C5—H5B	108.5
C2A—C7A—H7A	119.1	C6—C5—H5B	108.5

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C7A—C6A—O4A	122.4 (3)	C4—C5—H5C	108.5
C7A—C6A—C5A	119.6 (4)	C6—C5—H5C	108.5
O4A—C6A—C5A	118.0 (3)	H5B—C5—H5C	107.5
C5A—C4A—C3A	120.9 (3)	C2—C1—H1A	109.5
C5A—C4A—H4A	119.5	C2—C1—H1B	109.5
C3A—C4A—H4A	119.5	H1A—C1—H1B	109.5
O1A—C1A—O2A	123.2 (3)	C2—C1—H1C	109.5
O1A—C1A—C2A	120.0 (3)	H1A—C1—H1C	109.5
O2A—C1A—C2A	116.8 (3)	H1B—C1—H1C	109.5
C2—N1—H1N	110 (2)	C7—C6—C5	113.3 (3)
C2—N1—H2N	109 (2)	C7—C6—H6A	108.9
H1N—N1—H2N	108 (3)	C5—C6—H6A	108.9
C2—N1—H3N	113 (3)	C7—C6—H6B	108.9
H1N—N1—H3N	109 (3)	C5—C6—H6B	108.9
H2N—N1—H3N	108 (3)	H6A—C6—H6B	107.7
C5—C4—C3	110.2 (3)	C6—C7—H1	109.5
C5—C4—H4B	109.6	C6—C7—H7B	109.5
C3—C4—H4B	109.6	H1—C7—H7B	109.5
C5—C4—H4C	109.6	C6—C7—H7C	109.5
C3—C4—H4C	109.6	H1—C7—H7C	109.5
H4B—C4—H4C	108.1	H7B—C7—H7C	109.5
C2—C3—C4	116.7 (3)		

O3A—C3A—C2A—C7A	−177.7 (4)	O3A—C3A—C4A—C5A	177.0 (3)
C4A—C3A—C2A—C7A	0.9 (5)	C2A—C3A—C4A—C5A	−1.6 (6)
O3A—C3A—C2A—C1A	2.9 (5)	C7A—C2A—C1A—O1A	−6.3 (5)
C4A—C3A—C2A—C1A	−178.5 (3)	C3A—C2A—C1A—O1A	173.1 (3)
C3A—C2A—C7A—C6A	1.4 (5)	C7A—C2A—C1A—O2A	172.9 (3)
C1A—C2A—C7A—C6A	−179.1 (4)	C3A—C2A—C1A—O2A	−7.7 (5)
C2A—C7A—C6A—O4A	176.1 (4)	C5—C4—C3—C2	−177.8 (3)
C2A—C7A—C6A—C5A	−3.1 (6)	C4—C3—C2—N1	60.1 (5)
C4A—C5A—C6A—C7A	2.3 (6)	C4—C3—C2—C1	−178.9 (4)
C4A—C5A—C6A—O4A	−176.8 (3)	C3—C4—C5—C6	175.4 (3)
C6A—C5A—C4A—C3A	0.0 (6)	C4—C5—C6—C7	69.5 (5)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4*A*—H4*AO*···O2*A*^{i}	0.98 (4)	1.70 (4)	2.662 (4)	167 (4)
N1—H1*N*···O1*A*^{ii}	0.97 (4)	1.81 (4)	2.777 (4)	173 (3)
O3*A**—H3*AO*···O2*A*	0.82 (5)	1.77 (5)	2.544 (4)	157 (5)
N1—H2*N*···O1*A*^{iii}	0.98 (4)	1.90 (4)	2.848 (4)	163 (4)
N1—H3*N*···O3*A*^{iv}	0.87 (5)	2.42 (4)	2.979 (5)	122 (3)
N1—H3*N*···O4*A*^{v}	0.87 (5)	2.27 (4)	2.905 (4)	130 (3)
C7*A*—H7*A*···O2*A*^{i}	0.95	2.57	3.225 (4)	126

Symmetry codes: (i) −*x*+1/2, *y*−1/2, −*z*+3/2; (ii) −*x*, −*y*+1, −*z*+1; (iii) *x*, *y*+1, *z*; (iv) −*x*+1/2, *y*+1/2, −*z*+3/2; (v) *x*−3/2, −*y*−1/2, *z*−3/2.

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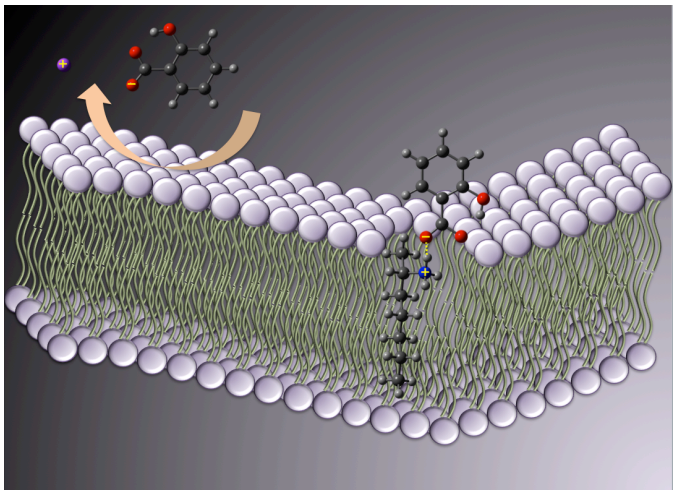
Figure 1

Figure 1. The asymmetric unit of heptan-2-ammonium 2,5-dihydroxybenzoate shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme. Figure 2, Packing diagram as viewed down the b-axis, displaying selected interactions within heptan-2-ammonium 2,5-dihydroxybenzoate. Figure 3. Extended packing diagram as viewed down the a-axis.

Publication 3.3

Enhanced Membrane Transport of Pharmaceutically Active Ionic Liquids

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Cite this: *Chem. Commun.*, 2011, **47**, 11429–11431

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COMMUNICATION

Enhanced membrane transport of pharmaceutically active protic ionic liquids†

Jelena Stoimenovski* and Douglas R. MacFarlane

Received 18th July 2011, Accepted 17th August 2011
DOI: 10.1039/c1cc14314j

We show that pharmaceutically active protic ionic liquids can be designed to rapidly transport through model membranes as neutral hydrogen bonded clusters.

Ionic liquids (ILs) are currently being investigated for use in a number of areas of science.[1] Some years ago, Rogers and co-workers proposed ILs based on active pharmaceutical ingredients (APIs), whereby the synthesised ILs not only retain pharmaceutical activity but also have the added benefits of existing in a liquid form.[2] Some of the benefits of the liquid state include improved solubility, stability, bioavailability and alternative delivery modes of the drug. Being amorphous, pharmaceutical ILs could be a possible solution to one of the more significant problems in the pharmaceutical industry – polymorphic inter-conversion, whereby one polymorph of a drug converts into another over time.[3] Given that the counter-ion chosen for the formation of the IL can have a significant influence on the pharmacokinetics of the drug candidate, the new salt form of the registered drug would need to be treated as a new chemical entity, meaning that it can be separately patented.[4] Hence, the formation of ILs of existing APIs could assist in the development of new forms of the API.

Since their emergence, pharmaceutically active ILs have been studied by a number of groups. Hough *et al.* and our group have reported on pharmaceutically active ILs containing cations/anions of various actives.[5] One of the compounds, lidocaine docusate, was shown to have enhanced analgesic effect compared to the parent lidocaine chloride salt.[5a] This is just one of the examples where combining two pharmaceutical/biocompatible ions results in compounds with characteristics superior to the parent drugs. Bica and co-workers have reported ILs based on analgesic, anti-pyretic and anti-inflammatory compounds, acetylsalicylic and salicylic acids,[6] while Cybulski *et al.* have synthesised and characterised ILs based on antiseptic/disinfectant cations and enzyme/amino acid anions and the resulting ILs were found to be very effective against bacteria and fungi.[7,8] A large number of drugs on the market are based on actives that are acids and bases (or simple salts thereof) and hence we have also recently reported on pharmaceutically active *protic* ILs (PILs), where we reacted pharmaceutically active acids with pharmaceutical/biocompatible bases to produce salts with dual activity, *e.g.* an analgesic/nasal decongestant dual activity PIL.[9]

However, it is a well-established fact that ionic drugs do not readily cross biological membranes and skin due to their lack of sufficient lipophilicity.[4] *Stratum corneum* is the main barrier for permeation of most drugs through the skin and only a small number of drug molecules have the optimal physicochemical characteristics to penetrate it sufficiently to exert their therapeutic effect. A number of strategies have been proposed to overcome skin impermeability. Wotton *et al.* suggest that an increase in the diffusion coefficient (D) or the partition coefficient (K) of the drug, or both, can result in a multiplicative effect on the flux of the permeant.[10] Penetration enhancement is most commonly achieved by incorporating solvents that promote transfer through the *stratum corneum*.[11]

Here we describe a series of attenuated total reflectance–Fourier transform infrared (ATR-FTIR) experiments designed to investigate the permeation of different types of PILs through a model membrane. We show that some of the PILs exhibit strongly enhanced permeation properties, probably due to the formation of hydrogen bonded complexes in the membrane. The results of this study will assist in the design of the most effective pharmaceutically active ILs.

The use of the ATR-FTIR spectroscopic technique to study the diffusion of permeants is well established in the pharmaceutical field.[12] The model membrane used for this study is a silicone membrane. Although the *stratum corneum* is a more complex molecular structure, the trends observed are thought to be similar to those seen in the silicone membrane and it is thus accepted as a useful model in this context.[12a] The synthetic procedures and characterisation data for the compounds investigated and the detailed experimental procedures are given in the supporting information. Following the work of Tantishaiyakul *et al.*,[12a] propylene glycol (PG) was used as the solvent for the control experiments. PG was found not to change the properties or diffusion barrier of the membrane.

The two types of PILs that were chosen for study were (i) those that have been shown to be proton transferred and fully dissociated[13] due a sufficiently large difference in pK_a between acid and base and (ii) those that are thought to be proton

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† Electronic supplementary information (ESI) available: synthetic procedures, diffusion profiles of the studied compounds and an example FTIR membrane experiment. See DOI: 10.1039/c1cc14314j

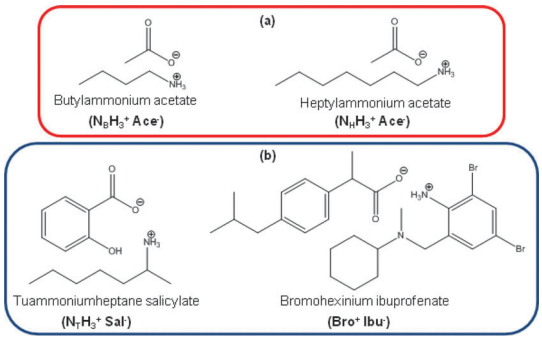


Fig. 1 The types of protic ILs investigated: (a) proton transferred and fully dissociated;[13] (b) proton transferred but form hydrogen bonded clusters.[9]

transferred, but form hydrogen bonded clusters[9] (Fig. 1). The PILs in (ii) are dual active PILs, with both the cation and anion pharmaceutically active. This is the first report of the pharmaceutical IL bromohexinium ibuprofenate; we have previously described the preparation and properties of the other compounds.[9,13] In that previous work, the IR spectroscopy and Walden plot analysis of the transport properties were used to assess the extent of proton transfer; proton transfer was found to be high in all cases. However, as discussed in more detail below, the existence of ion pairs and clusters was identified, supported by a crystal structure analysis of analogous compounds.[9]

Fig. 2 shows the relative absorbances of the species crossing the membrane over time for $N_TH_3^+$ Sal^- (as a pure liquid and as a PG solution) and its starting materials (in PG). ATR-FTIR spectroscopy allows the concurrent measurement of the diffusional parameters of both the primary permeant and its formulation solvent, if both species diffuse into the membrane under study (and their absorbance bands are distinct from each other).[12b] In the case of the salicylate compounds we monitored the carboxylate asymmetrical stretching band at 1570 cm^{-1}, whereas in salicylic acid the C=O stretching at 1665 cm^{-1} was analysed. Internal hydrogen bonding present in salicylic acid reduces the frequency of the carbonyl stretching absorption, which is normally observed at 1760 cm^{-1}.[20] Fig. 2 clearly illustrates that $N_TH_3^+$ Sal^- permeates the model membrane very rapidly, achieving saturation (100% relative absorbance) in ~20 h. However, when this compound is

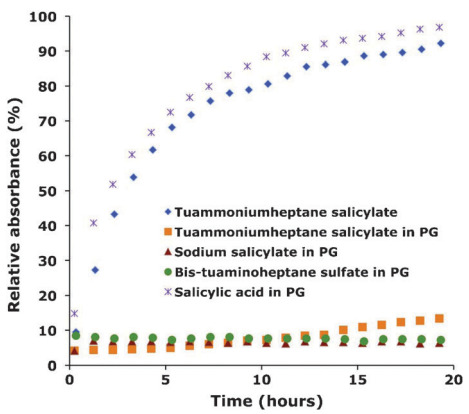


Fig. 2 Membrane transport of $N_TH_3^+$ Sal^- (pure and as a saturated PG solution) and its starting materials as saturated PG solutions.

present as a PG solution a very different behaviour is observed; it permeates slowly through the membrane, achieving only 15% of saturation in 20 h. The two pure salt starting materials for this PIL, sodium salicylate and $N_TH_3^+$ sulphate, when dissolved in PG, permeate < 10% in a 20 h period. Thus the IL form is significantly more permeable than either of the inorganic salt forms of the actives.

Salicylic acid (SalH) in PG was also examined in order to determine how the permeation of a neutral compound would compare to the ionic species. The salicylic acid was found to permeate about as rapidly as the salicylate-containing IL. Since the two starting materials, which are simple salts, do not cross the membrane, whereas the pure acid form does, it appears that neutral species are the most rapidly permeable in this type of membrane. This is in accord with the general observation that ionic compounds do not cross the membrane as readily as neutral compounds. The behaviour of the IL may therefore appear paradoxical. However, our previous studies[9] have suggested, on the basis of crystallographic analysis of analogous compounds and gas phase *ab initio* structure calculations, that $N_TH_3^+$ Sal^- may exist as a cyclic, two ion-pair complex.[9] Thus, as this neutral complex, the PIL can cross the membrane as rapidly as unionised neutral species. Furthermore, it is likely that the cyclic complex ceases to exist in the PG solution, dissociating into individual ions and hence limiting the permeability. The fact that some level of permeation is observed, as shown in Fig. 2, may relate to the presence of a small equilibrium fraction of neutral species being present, or formed at the membrane interface. As these are removed by permeation from the membrane's outer surface, their concentration is maintained by the equilibrium process in the liquid.

Thus, it appears that the permeation of salt forms of actives can be enhanced by formation of a PIL in which there is significant association present in the form of neutral species. In the case of $N_TH_3^+$ Sal^-, the permeation of both ions is strongly enhanced. Fig. 3 summarises the extent of permeation over time for two types of PILs. Like $N_TH_3^+$ Sal^-, Bro^+ Ibu^- shows evidence of ion pairing; the IR data suggests full proton transfer, but it sits well below the ideal line on the Walden plot. It shows the same permeation trends as $N_TH_3^+$ Sal^-, achieving saturation in ~20 h.

$N_BH_3^+$ Ace^- and $N_HH_3^+$ Ace^- are both highly ionised PILs but, in contrast to those discussed above, they sit closer to the ideal line on the Walden plot,[13] indicating a lesser tendency to form associated species. These PILs also permeate through the model membrane, but significantly slower than the associated PILs. As before, our hypothesis is that this arises from the transport of neutral species through the membrane, but in these less associated PILs this process is slower because the concentration of the neutral species is considerably lower. To put this on a more quantitative basis, Table 1 summarises the time for these compounds to permeate to 50% saturation (t_{50}). There is a clear distinction between the associated and less associated PILs.

A molecule will permeate the membrane well if it is highly soluble in the membrane and if it diffuses rapidly within it. Further analysis of these factors for the two types of PILs studied assists in understanding their different permeation behaviour. Experimental values of relative absorbance intensities

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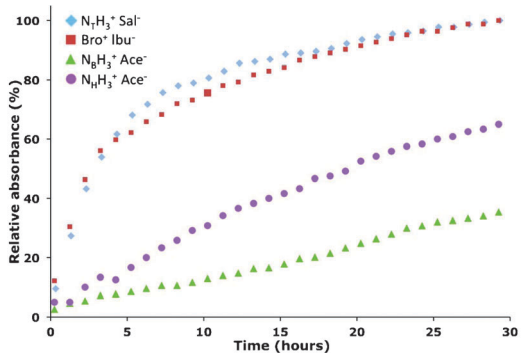


Fig. 3 Membrane diffusion of the various types of Protic ILs.

against time were fitted using a previously reported membrane diffusive flux equation:[12a,b]

$$\frac{A}{A_\infty} = 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{2n+1} \times \exp\left(\frac{-D(2n+1)^2\pi^2 t}{4h^2}\right) \qquad (1)$$

where A is the absorbance intensity at time t, D the permeant diffusion coefficient, h the film thickness and A_∞ the intensity of the permeant peak corresponding to the saturation of the membrane. Table 1 summarises the diffusion values obtained from a fit of eqn (1) for the compounds studied. A single diffusion coefficient did not provide an adequate fit to the data (including up to an $n = 3$ fit), except for the $N_BH_3^+$ Ace^- case. However, introducing a second component, involving a second diffusion coefficient, provided a very good fit to the data (see ESI), as also observed by Dias *et al.*[14] It appears therefore that there are two processes contributing to the diffusion of these compounds (D_1 and D_2, Table 1), one approximately an order of magnitude slower than the other. In the work of Dias *et al.*, it was suggested that the second process arose from diffusion through a membrane already swollen by the permeant. It is interesting to note that the diffusion processes being observed here are relatively rapid, in some cases only two orders of magnitude slower than typical diffusion coefficients of ions in water.

From Fick's equation the overall flux, F, of molecules through the membrane is determined by $F = P.C_{IL}$ where P is the permeation coefficient given by $P = DK/h$ and C_{IL} is the concentration of the IL, K the partition coefficient of the species between the liquid phase and the membrane and h is the thickness of the membrane. The appearance of the partition coefficient in these relationships indicates the role of the intrinsic solubility of the permeant in the membrane. It is likely that the very low permeability of some species in Fig. 2 and 3 relate primarily to a very low solubility, rather than a low diffusion coefficient. An IL form of the actives does not necessarily address the solubility factor *per se*, other than the fact that the active ions are presented at very high concentrations. However, in cases where neutral species are present in the IL, the solubility in a membrane such as that used here would be enhanced. Solubility measurements in model membranes such as these would allow determination of the relationship between permeability and structure to be understood more fully and thus enable IL design. However, such measurements are difficult to achieve accurately.

Table 1 Membrane diffusion coefficients and t_{50} values for PILs

	R[a]	D_1 Fraction	$D_1 \times 10^{-8}$ ($cm^2\ s^{-1}$)	$D_2 \times 10^{-8}$ ($cm^2\ s^{-1}$)	t_{50} (hours)
$N_TH_3^+$ Sal^-	0.9982	0.69 ± 0.03	1.3 ± 0.1	10.1 ± 1.7	~2
Bro^+ Ibu^-	0.9933	0.50 ± 0.02	0.5 ± 0.1	6.1 ± 0.9	~2
$N_HH_3^+$ Ace^-	0.9977	0.74 ± 0.03	0.17 ± 0.01	1.5 ± 0.2	~20
$N_BH_3^+$ Ace^-	0.9981	—	0.097 ± 0.003	—	~50
SalH in PG	0.9993	0.58 ± 0.01	1.11 ± 0.02	15.6 ± 0.8	~2

In summary, we have shown that protic pharmaceutically active ILs are, in some cases, rapidly transported through a model membrane, most likely as hydrogen bonded complexes. We hypothesize that these paired compounds behave more like "neutral" species and hence cross the membrane faster than the more "ionic" drugs. It is interesting to note that hydrogen bonded complexes of un-ionised acid–base mixtures have also been found to display unusual properties recently.[15] One of the advantages of this protic IL approach is that active formulations can be designed that will be more membrane diffusive in a way that is not otherwise possible.

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Electronic Supplementary Material (ESI) for Chemical Communications
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Electronic Supplementary Information (ESI)

Enhanced membrane transport of pharmaceutically active protic ionic liquids

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General

The silicone membranes (thickness 0.005 inch) produced by Sterilin Ltd., UK, were used as supplied. Bromohexine hydrochloride (≥ 98) was purchased from Fluka, sodium ibuprofen (≥ 99.5 %) was supplied by Sigma and propylene glycol (≥ 99%) was purchased from Biotech Pharmaceuticals. All chemicals were used without further purification.

The synthesis and characterisation data of butylammonium acetate, heptylammonium acetate and tuammoniumheptane salicylate were reported in our previous work.[1, 2]

NMR spectra were recorded in d_6-DMSO (Cambridge Isotope Laboratories) on a Bruker Avance 400 (9.4 Tesla magnet) with a 5 mm broadband autotunable probe with Z-gradients and BACS 60 tube autosampler. Each resonance is reported according to the following convention: chemical shift (δ) measured in parts per million (ppm) from the reference signal tetramethylsilane, multiplicity, observed coupling constants (*J* Hz), number of hydrogen atoms and assignment. Multiplicities are reported as a singlet (s), doublet (d), quartet (q), or a multiplet (m).

Electrospray Mass Spectrometry (ESI) was carried out on the Micromass Platform II API QMS Electrospray Mass Spectrometer with a cone voltage of 25 V or 35 V, using methanol as the mobile phase. Analyses were conducted in both positive (ESI^+) and negative (ESI^-) modes.

Karl Fischer analysis was performed on a 831 KF Coulometer which uses the coulometric titrator system. Hydranal Coulomat AG was used as the titration solution.

An Anton Paar DMA 5000 density meter was used to measure the density of the liquids. The density meter is based on the "oscillating U-tube principle". The viscosity measurements were collected using an Anton Paar AMVn viscosity meter.

Conductivity measurements were performed on a locally designed dip cell probe containing two platinum wires sheathed in glass. The cell constant was ascertained with a solution of 0.01 M KCl at 25 ^oC. The conductivities were obtained by measuring the complex impedance spectra between 1 MHz and 0.01 Hz on a Solatron SI 1296 Dielectric interface at 5 ^oC (±1 ^oC) intervals. A Eurotherm 2204e temperature controller, interfaced to the Solatron and a cartridge heater set in a brass

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block with a cavity for the cell, was used to control the temperature. A K-type thermocouple was set in the block adjacent to the cell.

Membrane studies were performed on a Digilab FTS 3000MX Excalibur series spectrometer with ATR crystal ZnSe. Good contact between the membrane and the crystal was ensured as this can influence the degree of penetration of the IR beam. An initial delay of 15 minutes was allowed for the purging of the sample chamber. Sixteen scans were taken every hour (2 cm^{-1} resolution) and an average spectrum was produced at each time point. The FTIR spectrometer was connected to a computer equipped with OPUS 6 software, which was used to analyse the spectra. In Figure 2 of the communication, all of the data, apart from salicylic acid in PG, was normalised by setting the maximum absorption of $N_TNH_3^+$ Sal^- to 100%. In the salicylic acid solution the carbonyl stretching band was monitored, which is not present in the other samples.

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Synthesis and characterisation of bromohexinium ibuprofenate

A mixture of sodium ibuprofenate (3.92 g, 17.20 mmol) and bromohexinium hydrochloride (7.08 g, 17.20 mmol) in 50 ml of dry methanol was stirred overnight at room temperature. The reaction mixture was filtered through filter aid and the solution re-filtered using syringe microfilters (0.20 µm). The solvent was removed under vacuum and the yellow viscous residue was redissolved in dichloromethane. This organic phase was washed with distilled water to remove any residual sodium chloride (monitored by the silver nitrate test). The solvent was removed under vacuum leaving a clear yellow viscous liquid. The IL was further dried *in vacuo* at 55 ^{o}C for 72 hours. Yield: 84%. Glass transition temperature, Tg(DSC), 10°C/min) = -15°C (midpoint). After several months storage the sample crystallised, Tm (onset) = 28°C.

^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 0.84-0.86 (d, *J* 6.6, 6H, CH_3), 1.01-1.29 (m, 5H, CH), 1.33-1.34 (d, *J* 7.1, 3H, CH_3), 1.56-1.59 (m, 1H, CH), 1.74-1.85 (m, 5H, CH), 2.06 (s, 3H, CH_3), 2.34-2.40 (m, 1H, CH), 2.39-2.41 (d, *J* 7.1, 2H, CH_2), 3.55 (s, 2H, CH_2), 3.59-3.64 (q, *J* 7.1, 1H, CH), 7.08-7.10 (d, *J* 8.1, 2H, CH), 7.17-7.20 (d, *J* 8.1, 2H, CH), 7.19 (s, 1H, CH), 7.48 (s, 1H, CH).

MS (ESI): ES^{+} *m/z* 377.1 (Bromohexinium^{+}, 100 %), ES- *m/z* 205.2 (Ibuprofenate^{-}, 35%), 161.2 (Ibuprofenate^{-} – CO_2, 100%)*

* Ion is unstable in the mass spectrometer (evidenced by the identical behaviour of the sodium ibuprofenate starting material)

Water content (Karl Fischer): 407 ppm.

Cl^{-} content: <100 ppm

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Preparation of PG solutions

The propylene glycol solutions were prepared by dissolving the compounds with stirring and heating in 1 ml of PG until saturation solution was achieved.

Table S1. Transport properties of bromohexinium ibuprofenate

Temperature (^{o}C)	**Conductivity x 10^{-7} (S cm^{-1})**	**Density (g cm^{-3})**	**Viscosity (Poise)**
25	0.034	-	-
30	0.082	-	-
35	0.176	-	-
40	0.344	-	-
45	0.641	-	-
50	1.082	-	-
55	1.721	-	-
60	2.569	-	-
65	3.681	1.264	-
70	4.956	1.260	-
75	6.445	1.255	-
80	7.986	1.250	-
85	9.544	1.246	-
90	11.112	1.242	0.533

* Density could only be measured in the range of 65-90 ^{o}C, while the viscosity could only be measured at 90 ^{o}C.

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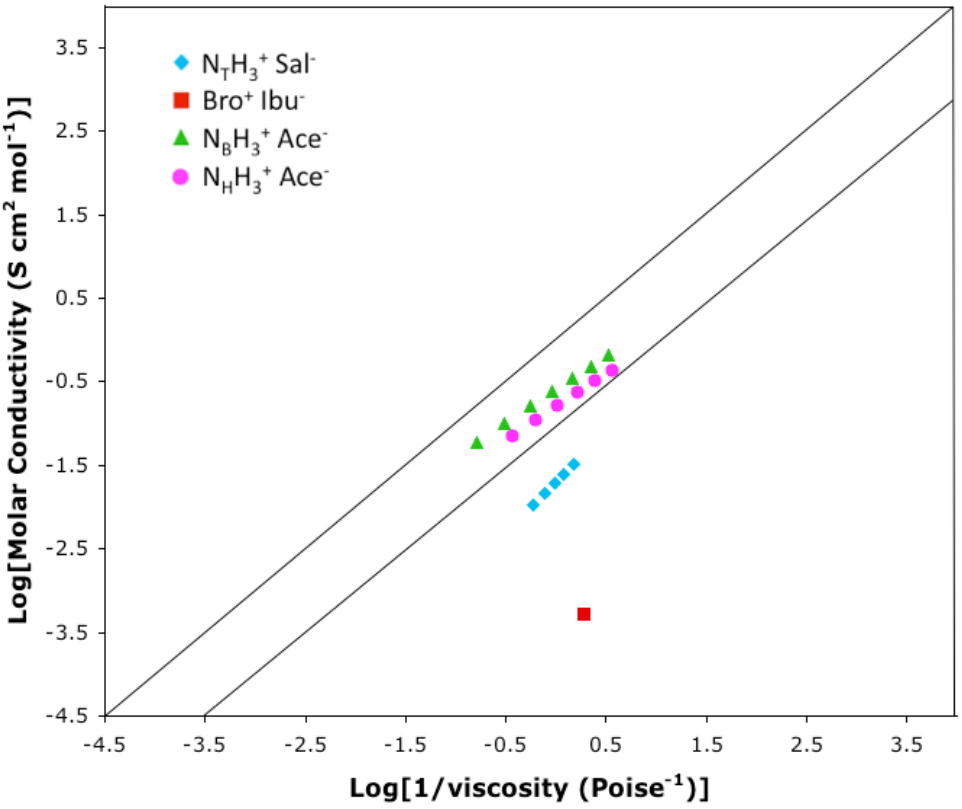


Figure S1. The Walden plot of the studied PILs ($N_TH_3^+$ Sal^-, $N_BH_3^+$ Ace^-, $N_HH_3^+$ Ace^- have been reproduced from our previous work[1, 2])

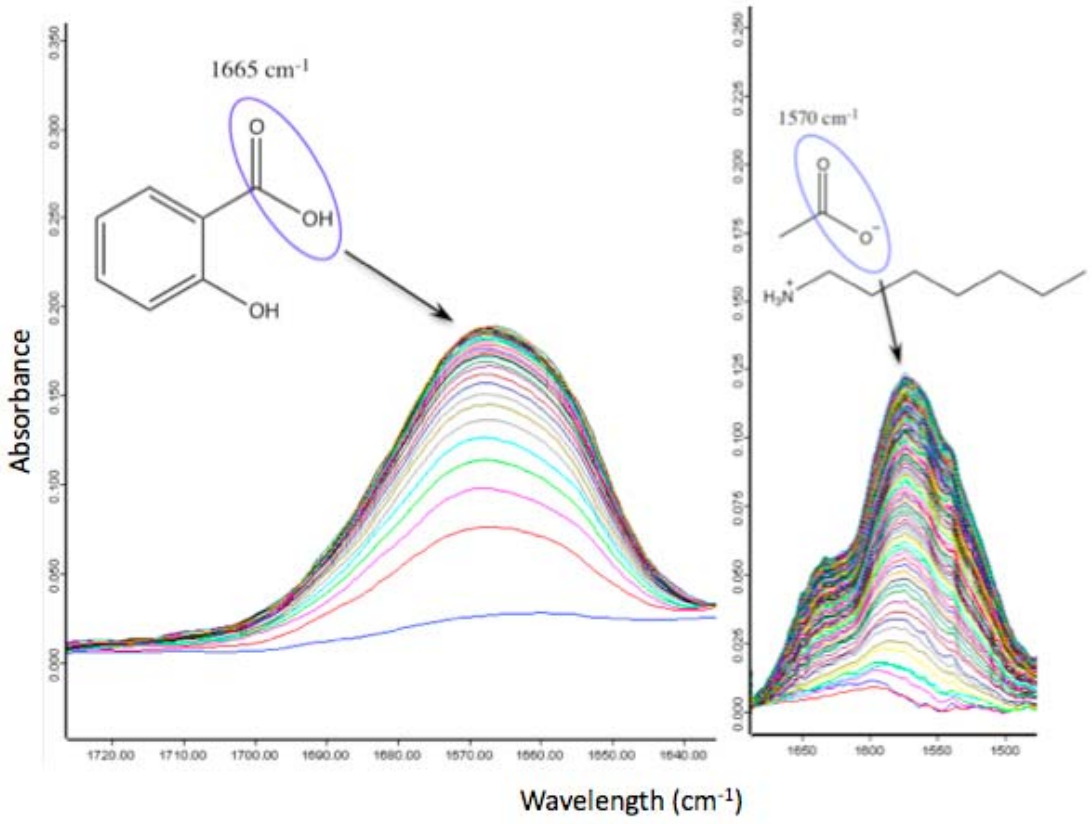


Figure S2. Examples of the FTIR experiments; membrane permeation data over time for (left) salicylic acid in PG and (right) heptylammonium acetate

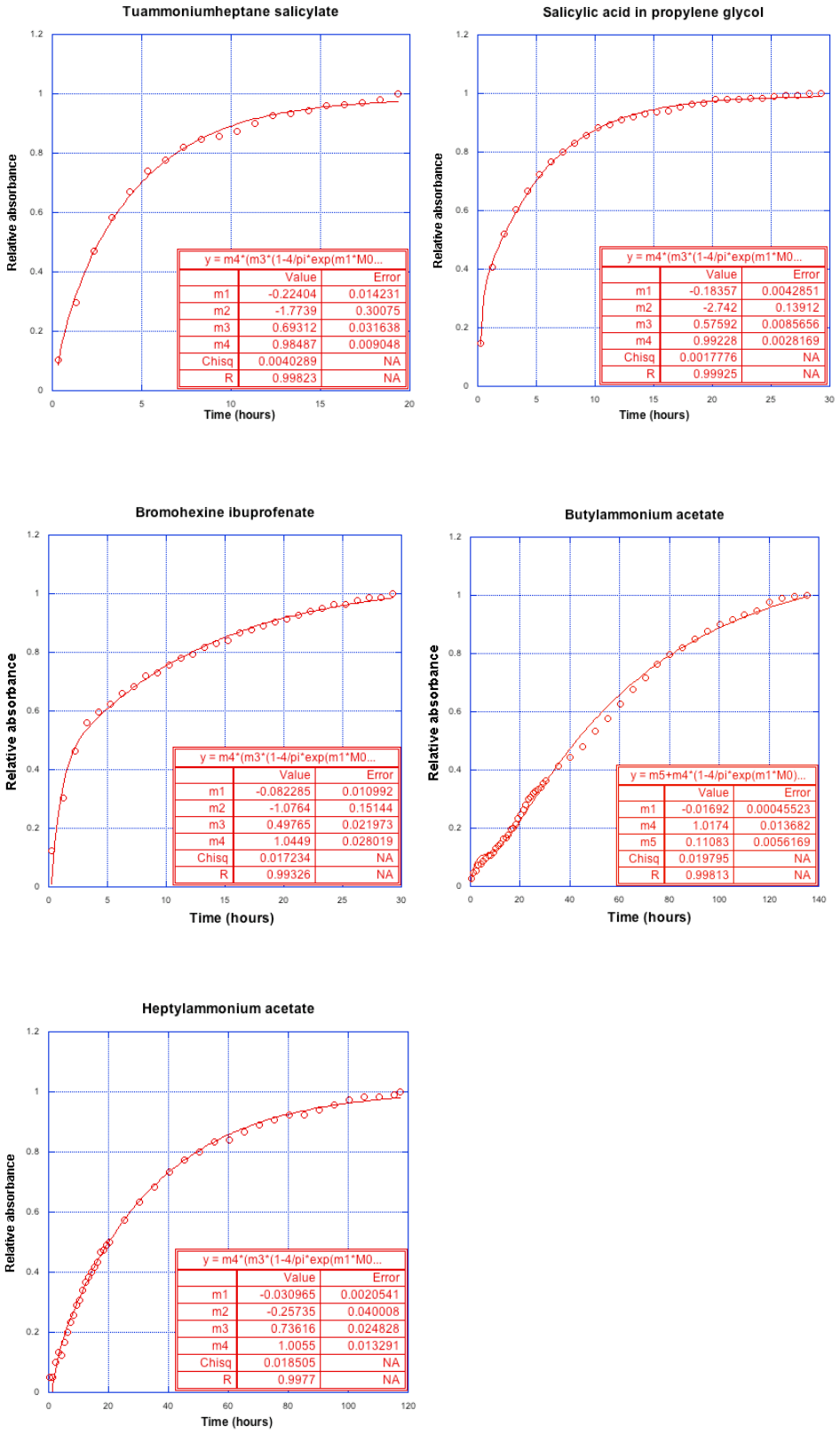


Figure S3. Diffusion profiles of the studied compounds

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Section 3.3 References

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CHAPTER FOUR

CONCLUSIONS AND FUTURE WORK

Section 4.1 Conclusions

The work in this thesis focused on a novel class of ILs, pharmaceutically active ILs, based on existing active pharmaceutical ingredients and generally recognised as safe compounds. The project involved the synthesis and characterisation of both aprotic and protic pharmaceutically active ILs.

Chapter 2 described the successful preparation, purification and characterisation of a number of active crystalline and liquid samples from simple salts of existing APIs and generally recognised as safe compounds (publication 2.1). It was demonstrated that the combination of ions that bear both hydrogen bond donor and acceptor groups have the ability to form classical hydrogen bonds, resulting in crystalline salts. On the other hand, our research into the combination of ions that cannot form classical hydrogen bonds (*i.e.* both the anion and the cation lack either hydrogen bond donor or hydrogen bond acceptor functionality) produced three liquid AILs. These compounds therefore successfully demonstrate our concept of "anti-crystal engineering", whereby ions are carefully chosen in order to *avoid* any complementary functional groups that lead to the supramolecular synthons that encourage crystallisation. Other supramolecular synthons, charge, charge separation and shape, are all factors that can have considerable influence on the physical form of a compound, while lattice energy is the ultimate determinant of melting point and, in turn, crystallinity. Hence, the results demonstrate that the "anti-crystal engineering" concept can be successfully used to guide the rational choice of ions that lead to non-crystallising salts and therefore, in this case, liquid forms of APIs. The "anti-crystal engineering" approach was also effectively employed for a number of other synthesised compounds, including dually active ILs.

The choice of experimental conditions for the synthesis of AILs was also found to be of importance. Propantheline bromide, an active used to synthesise a number of salts, was found to undergo facile transesterification by methanol during the preliminary purification stage, generating a by-product, methyl 9*H*-xanthene-9-carboxylate. The structure of this compound was successfully analysed by single crystal x-ray crystallography (Publication 2.2).

Chapter 3 focused on the preparation and characterisation of model protic ILs, PILs, and an investigation into the extent of proton transfer in these compounds. Using chemicals that are not used in the pharmaceutical industry, but are readily available, a number of PILs based on primary and tertiary amines and acetic acid were synthesized and studied in depth (Publication 3.1). All of the amines used in that work had comparable pK_a^{aq} values. Using indicator studies, transport properties and computational chemistry data, a relationship between the degree of proton transfer and the level of amine substitution (primary *vs.* tertiary amine) was established. It was demonstrated that the extent of proton transfer in primary amine based PILs (*e.g.* butylammonium acetate) was more complete than in the tertiary amine based PILs (*e.g.* methylpyrrolidinium acetate). Hence the physical properties of the two types of PILs were found to be significantly different; the primary amine based PILs lie closer to the ideal line on a Walden plot than the tertiary amine based species. Using COSMO-RS, a computational approach, the free energies of solvation of the primary and tertiary ammonium cations were also calculated. These indicated that the large difference between the solvation environments of the two types of amines is due to the increased hydrogen bonding ability of the primary ammonium cations, leading to the substantially stronger solvation compared to the tertiary ones. However, it was postulated that other solvation effects, such as the presence of functional groups that offer hydrogen bonding sites (*e.g.* OH groups) can easily disrupt these trends.

This concept was further investigated by synthesising a library of pharmaceutically active PILs, including those utilising primary amines and also a tertiary amine with an OH group (Publication 3.2). Formulations that conceptually involved oligomeric anions were also studied. These investigations produced a range of protic ionic liquids and crystalline compounds. The crystalline materials were analysed using x-ray crystallography, while the liquid salts were subjected to physical property studies, such as conductivity and diffusion measurements. Infrared spectroscopy indicated that, unlike previous examples where the tertiary amine based ILs were not fully proton transferred, all of these PILs were fully proton transferred. However, a reverse trend was observed in the transport property data, where the tertiary amine based PIL (2-pyrrolidiniumethanol salicylate) appeared closer to the ideal line on the Walden plot than the primary amine based PIL (tuammoniumheptane salicylate). To further investigate this unexpected trend, x-ray crystallography was used to analyse analogous compounds utilising the two different types of amines. This revealed that, in the tertiary amine based PIL, the hydroxyl functional group improved the hydrogen

bonding ability of the cation, thereby promoting the proton transfer. However, in the primary amine based PIL the crystal structure revealed the presence of hydrogen bonded cluster-like species, indicating decreased ionicity of the primary amine based PIL. These findings, together with the computational data, explain the observations of the Walden plot analysis.

In consideration of the final application of these pharmaceutical ILs, it was hypothesised that active ILs with lower ionicity would be more desirable for drug delivery as these neutral complexes should be able to cross biological membranes more rapidly than the more ionised species. This postulation was explored using ATR-FTIR experiments and a model skin membrane (Publication 3.3). The salt forms of the active acids and bases were also found to have the added advantage of improved water solubility, which is an important property of pharmaceutical compounds. A range of PILs with different degrees of ionisation were selected for this study. Tuammoniumheptane salicylate, which was shown to be fully proton transferred but formed hydrogen bonded complexes, was investigated in depth by comparing its membrane transport properties with those of simple salts of its starting materials. This PIL was demonstrated to be significantly more efficient in crossing the membrane than the starting materials, which are more ionised. The measured membrane transport diffusion rates of this salt are comparable to those of salicylic acid, a neutral compound. When compared to tuammoniumheptane salicylate and bromohexinium ibuprofenate (the two less ionised PILs), butylammonium acetate and heptylammonium acetate were found to cross the membrane at a significantly slower rate because the concentration of the associated species in these highly ionised PILs is considerably lower. Hence, it was found that pharmaceutically active PILs based on existing APIs can be synthesised in such a way as to enhance the membrane transport of these drugs through membranes and therefore speed up the onset of their pharmacological effect.

In summary, this work has successfully demonstrated our initial hypothesis, that liquid forms of existing drugs can improve key physico-chemical properties of these therapeutics, making them more efficient, and that this approach can overcome certain complications, such as polymorphism and solubility problems, observed in solid forms of APIs. The ability to produce dually active compounds and substances with tailored properties to suit each specific application has also been demonstrated. Enhanced membrane transport of

these liquid forms was one of the main advantages of these new API phases. Hence, this project provides the pharmaceutical industry with a tool that can be used to improve and customise the physical, chemical and biological properties of existing drugs therefore resulting in improved pharmaceuticals, novel treatments and delivery options.

Section 4.2 Future Work

Although this project has illustrated the advantages of liquid forms of known APIs, much more research and development is required in order to utilise these compounds as pharmaceuticals and prove that they are safe for human use. Experiments including further membrane studies, toxicity assays and pharmacological activity studies are needed in order to obtain a more complete picture of the behaviour of these compounds *in vivo*. In addition, from the fundamental perspective, solution studies of associated ILs would help to determine the potential behaviour of these salts in the body.

APPENDIX

Patent A1

Dual Functioning Ionic Liquids and Salts Thereof

Robin D. Rogers, Daniel T. Daly, Gabriela Gurau, Douglas R. MacFarlane, Jelena Turanjanin, Pamela M. Dean, Janet L. Scott, Katharina Bica, Kenneth R. Seddon

The Appendix contains the cover page, priority, field, background, summary and the claims sections of the patent application.

For the full patent application including the detail description section and examples, please see:
Rogers, R. D.; Daly, D. T.; MacFarlane, D.; Scott, J. L.; Seddon, K. R.; Gurau, G.; Bica, K.; Turanjanin, J.; Dean, P. M., "Dual Functioning Ionic Liquids and Salts Thereof," U.S. Provisional Patent 61/141,168 filed 29/12/2008. PCT Int. Appl. (2010) WO 2010/078300, July 8, 2010.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 July 2010 (08.07.2010)

PCT

(10) International Publication Number
WO 2010/078300 A1

(51) International Patent Classification:
A01N 55/02 (2006.01) *A61K 31/555* (2006.01)

(21) International Application Number:
PCT/US2009/069652

(22) International Filing Date:
29 December 2009 (29.12.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/141,168 29 December 2008 (29.12.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,

[Continued on next page]

(54) Title: DUAL FUNCTIONING IONIC LIQUIDS AND SALTS THEREOF

(57) Abstract: Disclosed herein are ionic liquid compositions comprising active pharmaceutical, biological, and nutritional compounds, and methods of use. Further disclosed are compositions of matter including liquid ion pairs alone or in solution and their use; compositions of ionic liquids that are 'solvated,' for example, 'hydrated' and their uses.

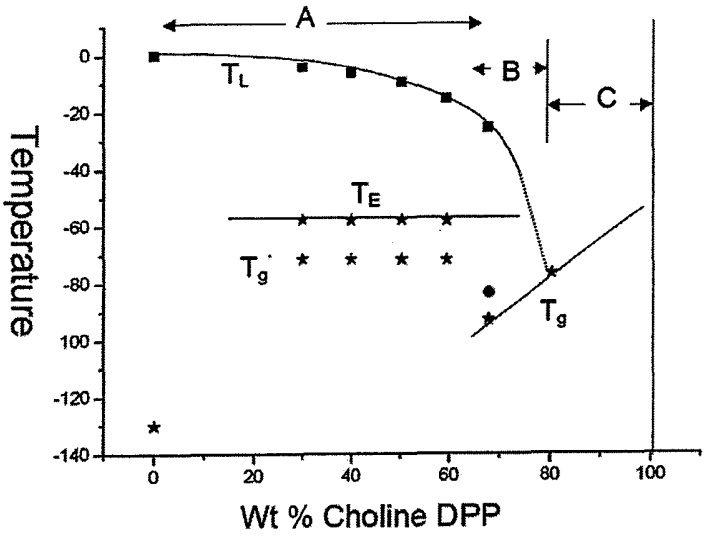


Fig. 1

WO 2010/078300 A1

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

DUAL FUNCTIONING IONIC LIQUIDS AND SALTS THEREOF

PRIORITY

This application claims the benefit of Provisional Application Serial Number 61/141,168 filed on December 29, 2008, the entire disclosure of which is incorporated herein by reference.

FIELD

Disclosed herein are ionic liquid compositions comprising active pharmaceutical, biological, and nutritional compounds, and methods of use. Further disclosed are compositions of matter including liquid ion pairs alone or in solution and their use; compositions of ionic liquids that are 'solvated,' for example, 'hydrated' and their uses.

BACKGROUND

Polymorphism is the ability of a substance to exist in two or more crystalline forms that have a different arrangement and/or conformation of molecules in a crystalline lattice (*see e.g.*, Chawla and Bansal, *CRIPS* 2004, 5(1):9-12; Bernstein, "Polymorphism in Molecular Crystals," *IUCR Monographs on Crystallography 14*, Oxford Science Publications, 2002, pp. 1-28, 240-256). It has been estimated that a large number of pharmaceuticals exhibit polymorphism. For example, 70% of barbiturates, 60% of sulfonamides, and 23% of steroids are believed to exist in different polymorphic forms or "polymorphs" (Haleblian *et al.*, *J Pharm Sci* 1975, 64:1269-1288).

In some cases, when crystals of a compound are forming (*e.g.*, crystallizing from a solution), solvent molecules may become entrapped or bound within the crystal lattice. The presence of the entrapped solvent molecules may affect the three-dimensional crystal lattice that eventually crystallizes. The occurrence of a compound (target molecule) crystallizing in different three-dimensional lattices based upon the presence of solvent molecules has been termed "pseudo-polymorphism." Akin to polymorphs, such "pseudo-polymorphs," also known as "solvates" (or "hydrates" when the solvent is water), are crystalline solids containing either stoichiometric (*i.e.*, whole number ratios of target molecules to solvent molecules) or non-stoichiometric (*i.e.*, non-whole number ratios of target molecules to solvent molecules) amounts of a solvent incorporated within the crystal structure. In general, different crystalline forms of molecules (*e.g.*, pharmaceutical compounds) can exist in the same or different hydrated or solvated states.

The existence of various polymorphs or pseudo-polymorphs can greatly affect a pharmaceutical's performance since each form can have different physical and chemical

properties. For example, one particular polymorph pseudo-polymorph may be more bioavailable, more stable (*e.g.*, longer shelf life), or more easily formulated or tableted than another polymorph. Similarly, one polymorph pseudo-polymorph may be more active or less toxic than another. Some specific examples of the dramatic difference that can exist between various pharmaceutical polymorphs are described in, *e.g.*, Brittain *et al.*, *J Pharm Sci* 2002, 91:1573-1580 and Morissette *et al.*, *Proc Natl Acad Sci USA* 2003, 100:2180-2184.

The effects of polymorphism and pseudo-polymorphism on quality and performance of a drug is widely recognized. The exact solid state polymorph (or pseudo-polymorph) of a compound determines its physical properties such as dissolution rate, solubility, bioavailability, crystal habit, mechanical strength, etc. (Datta *et al.*, *Nature Reviews–Drug Discovery,* 2004, 3:42-57). The delivery of an exact dosage in manufacture and the manufacturing process itself often depend on which of several possible polymorphs or pseudo-polymorphs are present.

The variation in properties among different polymorphs (or pseudo-polymorphs) usually means that one crystalline form is desired or preferred over other forms. Obtaining a particular form can be difficult, however. Typically, researchers have to experiment with a multitude of variables in crystallization conditions, such as aqueous solvent mixtures, amount of water, amount of target compound, relative humidity, temperature of incubation, incubation time, etc., in a process characterized by trial and error. Further, the search for salts of crystalline forms (usually sought after to control dissolution rate and solubility) can require extensive experimentation. Each salt of a drug or each different solvent used to crystallize the drug or a salt of the drug may lead to polymorphs or pseudo-polymorphs that have to be fully investigated and that have different properties (*see e.g.*, Reutzel-Edens *et al.*, "Anhydrates and hydrates of olanzapine: Crystallization, solid-state characterization, and structural relationships," *Crystal Growth & Design*, 2003, 3:897-907).

Another common problem that exists with many pharmaceuticals, agrochemicals, nutraceuticals etc. is low solubility. Low solubility can make formulating a particular compound difficult, and generally low solubility translates into low bioavailability. Much research is conducted on finding ways to improve a compound's solubility and availability. Typically methods include complex delivery devices and chemical modifications of the drug.

Polymorphism and pseudo-polymorphism is difficult to predict, i.e., there is a relationship between the crystalline state of a compound and its chemical properties (*e.g.*, dissolution rate, solubility), biological properties (*e.g.*, bioavailability, pharmacokinetics), mechanical and physical properties, and manufacturing processes. In some instances

polymorphs and pseudo-polymorphs can interconvert. Moreover, there is a need for compositions that can manifest their base property, for example, their pharmacological properties, while having controllable and/or adjustable chemical, biological, and physical properties, that the formulator can "tune" to the desired properties while at the same time avoiding any undesirable polymorphism. In addition, there is a need for compounds having these properties which have modifiable dissolution and solubility properties. As such, there is further needed methods of preparing and using compositions having these controllable properties. Further, there is a need for methods of converting compounds that are difficult to solubilize into a form that allows for increased solubility. Disclosed herein are compositions and methods that provide for the above compounds, compositions, and methods.

SUMMARY

In accordance with the purposes of the disclosed materials, compounds, compositions, devices, and methods, as embodied and broadly described herein, the disclosed subject matter, in one aspect, relates to compounds and compositions and methods for preparing and using such compounds and compositions. In a further aspect, the disclosed subject matter relates to ionic liquid compositions that can be used for or in biological, pharmaceutical, nutritional, cosmetic, industrial, and commercial compositions. Methods for making the disclosed ionic liquid compositions are also disclosed. Also disclosed are methods of preparing ionic liquid compositions of active pharmaceutical, biological, nutritional, and energetic ingredients. Also the disclosed are methods of using the compositions described herein to overcome polymorphism, overcome solubility and delivery problems, to control release rates, add functionality, enhance efficacy, and improve ease of use and manufacture. Also disclosed is the use of multiple functional co-ionic liquids with excess of any free base or any free acid in equilibrium with cation or anion that are composed of active pharmaceutical, biological, nutritional, or energetic ingredients. The present disclosure is based upon the discovery that the physico-chemical properties of common pharmaceutical salts can be modified by by addition of the corresponding protic acid or base to form new ionic liquid species of the type $[B^1HB^2]A$ or $B[A^1HA^2]$.

Also disclosed is a process for preparation via solvent-free methods, e.g. grinding or reaction in molten state. The process can include addition of a acid or base to a common pharmaceutical active salt or by direct solvent-free reaction of acid with base in a ratio other than 1:1 to form co-ionic liquids of the type $[B^1HB^2]A$ or $B[A^1HA^2]$.

Additional advantages will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the aspects described below. The advantages described below will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive.

Further disclosed is the use of ionic liquids for immobilization, delivery, and controlled release of pharmaceutically active neutral compounds. This use is based upon the discovery that neutral active compounds, especially pharmaceuticals, can be covalently linked with ionic structural moiety and turned into an ionic liquid by appropriate choice of the counter ion. The ionic liquid acts not only as support for the active compounds, being able to store pharmaceuticals in inactive form but also allow a simple tuning of physical properties like solubility, bioavailability, lipophilicity or control over polymorphism as well as the control over release kinetics of the active compound.

Yet further discloses is a synthetic methodology to transfer neutral compounds into salts, wherein the active compound can be of either positive or negative charge, with the possibility to form dual functioning salts by introduction of a second, pharmaceutically or biologically active counterion.

Further described herein is a method for the immobilization of volatile fragrance and flavor compounds in the form of ionic liquids of neglible volatility for storage as well for controlled and prolonged release of the fragrance- or flavor compounds under defined conditions such as temperature, or pH value.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the binary phase diagram for choline DPP as example for ionic liquid diluates.

Figure 2 depicts the depression and elimination of the melting point of $P(Bu)_4[Sal_xH_{x-1}]$ in a series of co-ionic liquids comprising oligomeric anions.

Figure 3 despicts the conductivity and viscosity of various $P(Bu)_4[Sal_xH_{x-1}]$ compositions in a series of co-ionic liquids comprising oligomeric anions.

Figure 4 depicts the depression of glass transition and saturation of double functional co-ionic liquids based on lidocainium salicylate.

Figure 5 depicts the decomposition of the prodrug ionic liquids 1-[2-(4-acetamidophenoxy)-2-oxoethyl]-3-methyl-1H-imidazol-3-ium chloride (●) and [2-(4-

acetamidophenoxy)-2-oxoethyl]tributylphosphonium chloride (■) versus time in phosphate buffer pH 7.4 at 37 °C.

Figure 6 depicts the decomposition of (*E*)-4-(3,7-dimethylocta-2,6-dienyloxy)-4-oxobutanoic acid versus on temperature. The first decomposition step represents the release of the volatile fragrance geraniol.

Figure 7 depicts the Walden plot for various propantheline *p*-toluenesulfonates.

DETAILED DESCRIPTION

The materials, compounds, compositions, articles, and methods described herein may be understood more readily by reference to the following detailed description of specific aspects of the disclosed subject matter and the Examples included therein.

Before the present materials, compounds, compositions, articles, devices, and methods are disclosed and described, it is to be understood that the aspects described below are not limited to specific synthetic methods or specific reagents, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting.

Also, throughout this specification, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which the disclosed matter pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

Throughout the description and claims of this specification the word "comprise" and other forms of the word, such as "comprising" and "comprises," means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

As used in the description and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a composition" includes mixtures of two or more such compositions, reference to "an ionic liquid" includes mixtures of two or more such ionic liquids, reference to "the compound" includes mixtures of two or more such compounds, and the like.

"Optional" or "optionally" means that the subsequently described event or

circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that when a value is disclosed, then "less than or equal to" the value, "greater than or equal to the value," and possible ranges between values are also disclosed, as appropriately understood by the skilled artisan. For example, if the value "10" is disclosed, then "less than or equal to 10" as well as "greater than or equal to 10" is also disclosed. It is also understood that throughout the application data are provided in a number of different formats and that this data represent endpoints and starting points and ranges for any combination of the data points. For example, if a particular data point "10" and a particular data point "15" are disclosed, it is understood that greater than, greater than or equal to, less than, less than or equal to, and equal to 10 and 15 are considered disclosed as well as between 10 and 15. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

As used herein, by a "subject" is meant an individual. Thus, the "subject" can include domesticated animals (*e.g.*, cats, dogs, etc.), livestock (*e.g.*, cattle, horses, pigs, sheep, goats, etc.), laboratory animals (*e.g.*, mouse, rabbit, rat, guinea pig, etc.), and birds. "Subject" can also include a mammal, such as a primate or a human.

By "reduce" or other forms of the word, such as "reducing" or "reduction," is meant lowering of an event or characteristic (*e.g.*, microorganism growth or survival). It is understood that this is typically in relation to some standard or expected value, in other words it is relative, but that it is not always necessary for the standard or relative value to be referred to. For example, "reduces bacteria growth" means lowering the amount of bacteria relative to a standard or a control.

By "prevent" or other forms of the word, such as "preventing" or "prevention," is meant to stop a particular event or characteristic, to stabilize or delay the development or

progression of a particular event or characteristic, or to minimize the chances that a particular event or characteristic will occur. Prevent does not require comparison to a control as it is typically more absolute than, for example, reduce. As used herein, something could be reduced but not prevented, but something that is reduced could also be prevented. Likewise, something could be prevented but not reduced, but something that is prevented could also be reduced. It is understood that where reduce or prevent are used, unless specifically indicated otherwise, the use of the other word is also expressly disclosed.

By "treat" or other forms of the word, such as "treated" or "treatment," is meant to administer a composition or to perform a method in order to reduce, prevent, inhibit, break-down, or eliminate a particular characteristic or event (*e.g.*, microorganism growth or survival). The term "control" is used synonymously with the term "treat."

By "antimicrobial" is meant the ability to treat or control (*e.g.*, reduce, prevent, inhibit, break-down, or eliminate) microorganism growth or survival at any concentration. Similarly, the terms "antibacterial," "antiviral," and "antifungal" respectively mean the ability to treat or control (*e.g.*, reduce, prevent, inhibit, break-down, or eliminate) bacterial, viral, and fungal growth or survival at any concentration.

It is understood that throughout this specification the identifiers "first" and "second" are used solely to aid in distinguishing the various components and steps of the disclosed subject matter. The identifiers "first" and "second" are not intended to imply any particular order, amount, preference, or importance to the components or steps modified by these terms.

References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

The term "ion," as used herein, refers to any molecule, portion of a molecule, cluster of molecules, molecular complex, moiety, or atom that contains a charge (positive, negative, or both (*e.g.*, zwitterions) or that can be made to contain a charge. Methods for producing a charge in a molecule, portion of a molecule, cluster of molecules, molecular complex,

moiety, or atom are disclosed herein and can be accomplished by methods known in the art, *e.g.*, protonation, deprotonation, oxidation, reduction, alkylation, etc.

The term "anion" is a type of ion and is included within the meaning of the term "ion". An "anion" is any molecule, portion of a molecule (*e.g.*, zwitterion), cluster of molecules, molecular complex, moiety, or atom that contains a net negative charge or that can be made to contain a net negative charge. The term "anion precursor" is used herein to specifically refer to a molecule that can be converted to an anion via a chemical reaction (*e.g.*, deprotonation).

The term "cation" is a type of ion and is included within the meaning of the term "ion". A "cation" is any molecule, portion of a molecule (*e.g.*, zwitterion), cluster of molecules, molecular complex, moiety, or atom, that contains a net positive charge or that can be made to contain a net positive charge. The term "cation precursor" is used herein to specifically refer to a molecule that can be converted to a cation via a chemical reaction (*e.g.*, protonation or alkylation).

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

"D^1," "D^2," "D^3," and "D^4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

The term "aliphatic" as used herein refers to a non-aromatic hydrocarbon group and includes branched and unbranched, alkyl, alkenyl, or alkynyl groups.

The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can also be substituted or unsubstituted. The alkyl group can be substituted with one or more groups including, but not limited to, alkyl, halogenated alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, or thiol, as described below.

Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "alkylamino" specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When "alkyl" is used in one instance and a specific term such as "alkylalcohol" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "alkylalcohol" and the like.

This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a "halogenated alkoxy," a particular substituted alkenyl can be, *e.g.*, an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

The term "alkoxy" as used herein is an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group can be defined as —OD^1 where D^1 is alkyl as defined above.

The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(D^1D^2)C=C(D^3D^4)$ are intended to include both the *E* and *Z* isomers. This may be presumed in structural formulae herein wherein an asymmetric alkene

is present, or it may be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, halogenated alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, or thiol, as described below.

The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be substituted with one or more groups including, but not limited to, alkyl, halogenated alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, or thiol, as described below.

The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term "aryl" also includes "heteroaryl," which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term "non-heteroaryl," which is also included in the term "aryl," defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, halogenated alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of aryl. Biaryl refers to two aryl groups that are bound together *via* a fused ring structure, as in naphthalene, or are attached *via* one or more carbon-carbon bonds, as in biphenyl.

The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. The term "heterocycloalkyl" is a cycloalkyl group as defined above where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl,

aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, or thiol as described herein.

The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one double bound, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, and the like. The term "heterocycloalkenyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, nitro, silyl, sulfo-oxo, sulfonyl, sulfone, sulfoxide, or thiol as described herein.

The term "cyclic group" is used herein to refer to either aryl groups, non-aryl groups (*i.e.*, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl groups), or both. Cyclic groups have one or more ring systems that can be substituted or unsubstituted. A cyclic group can contain one or more aryl groups, one or more non-aryl groups, or one or more aryl groups and one or more non-aryl groups.

The term "aldehyde" as used herein is represented by the formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for C=O.

The terms "amine" or "amino" as used herein are represented by the formula $ND^1D^2D^3$, where D^1, D^2, and D^3 can be, independently, hydrogen, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "carboxylic acid" as used herein is represented by the formula —C(O)OH. A "carboxylate" as used herein is represented by the formula $—C(O)O^-$.

The term "ester" as used herein is represented by the formula $—OC(O)D^1$ or $—C(O)OD^1$, where D^1 can be an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "ether" as used herein is represented by the formula D^1OD^2, where D^1 and D^2 can be, independently, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "ketone" as used herein is represented by the formula $D^1C(O)D^2$, where D^1 and D^2 can be, independently, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "halide" as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

The term "hydroxyl" as used herein is represented by the formula —OH.

The term "nitro" as used herein is represented by the formula $—NO_2$.

The term "silyl" as used herein is represented by the formula $—SiD^1D^2D^3$, where D^1, D^2, and D^3 can be, independently, hydrogen, alkyl, halogenated alkyl, alkoxy, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "sulfo-oxo" as used herein is represented by the formulas $—S(O)D^1$, $—S(O)_2D^1$, $—OS(O)_2D^1$, or $—OS(O)_2OD^1$, where D^1 can be hydrogen, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above. Throughout this specification "S(O)" is a short hand notation for S=O.

The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula $—S(O)_2D^1$, where D^1 can be hydrogen, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "sulfonylamino" or "sulfonamide" as used herein is represented by the formula $—S(O)_2NH—$.

The term "sulfone" as used herein is represented by the formula $D^1S(O)_2D^2$, where D^1 and D^2 can be, independently, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "sulfoxide" as used herein is represented by the formula $D^1S(O)D^2$, where D^1 and D^2 can be, independently, an alkyl, halogenated alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl group described above.

The term "thiol" as used herein is represented by the formula —SH.

"R^1," "R^2," "R^3," "R^n," etc., where n is some integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an amine group, an alkyl group, a halide,

and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

The term "bioactive property" is any local or systemic biological, physiological, or therapeutic effect in a biological system. For example, the bioactive property can be the control of infection or inflammation, enhancement or suppression of growth, action as an analgesic, anti-viral, pesticidal, herbicidal, or nutrientional action, etc. Many examples of bioactive properties are disclosed herein.

Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer, diastereomer, and meso compound, and a mixture of isomers, such as a racemic or scalemic mixture.

Reference will now be made in detail to specific aspects of the disclosed materials, compounds, compositions, articles, and methods, examples of which are illustrated in the accompanying Examples.

Materials and Compositions

Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, WI), Acros Organics (Morris Plains, NJ), Fisher Scientific (Pittsburgh, PA), Sigma (St. Louis, MO), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). Other materials, such as the active pharmaceutical ingredients, pesticides, herbicides, and other biological agents disclosed herein can be obtained from commercial sources.

In one aspect, disclosed herein are ionic liquid compositions. The term "ionic liquid" has many definitions in the art, but is used herein to refer to salts (*i.e.*, compositions comprising cations and anions) that are liquid at a temperature of at or below about 150°C. That is, at one or more temperature ranges or points at or below about 150°C the disclosed ionic liquid compositions are liquid; although, it is understood that they can be solids at other temperature ranges or points. Since the disclosed ionic liquid compositions are liquid, and thus not crystalline solids, at a given temperature, the disclosed compositions do not suffer from the problems of polymorphism associated with crystalline solids.

The use of the term "liquid" to describe the disclosed ionic liquid compositions is meant to describe a generally amorphous, non-crystalline, or semi-crystalline state. For example, while some structured association and packing of cations and anions can occur at the atomic level, the disclosed ionic liquid compositions have minor amounts of such ordered structures and are therefore not crystalline solids. The compositions disclosed herein can be fluid and free-flowing liquids or amorphous solids such as glasses or waxes at a temperature at or below about 150°C. In particular examples disclosed herein, the disclosed ionic liquid compositions are liquid at the body temperature of a subject.

Further, the disclosed ionic liquid compositions are materials composed of at least two different ions; each of which can independently and simultaneously introduce a specific characteristic to the composition not easily obtainable with traditional dissolution and formulation techniques. Thus, by providing different ions and ion combinations, one can change the characteristics or properties of the disclosed ionic liquid compositions in a way not seen by simply preparing various crystalline salt forms. Examples of characteristics that can be controlled in the disclosed compositions include, but are not limited to, melting, solubility control, and rate of dissolution. It is this multi-nature/functionality of the disclosed ionic liquid compositions which allows one to fine-tune or design in very specific desired material properties.

It is further understood that the disclosed ionic liquid compositions can include solvent molecules (*e.g.*, water); however, these solvent molecules should not be present in excess in the sense that the disclosed ionic liquid compositions are dissolved in the solvent, forming a solution. That is, the disclosed ionic liquid compositions contain no or minimal amounts of solvent molecules that are free and not bound or associated with the ions present in the ionic liquid composition. Thus, the disclosed ionic liquid compositions can be liquid hydrates or solvates, but not solutions.

Ionic liquids have been of general interest because they are environmentally-friendly

alternatives to organic solvents for various chemical processes, *e.g.*, liquid/liquid extractions, catalysis, separations, and electrochemistry. Ionic liquids have also become popular alternative media for chemical synthesis because of their low volatility and low toxicity. *See e.g.*, Wasserscheid and Keim, *Angew Chem Int Ed Engl*, 2000, 39:3772; and Wasserscheid, "Ionic Liquids in Synthesis," 1st Ed., Wiley-VCH, 2002. Further, ionic liquids can reduce costs, disposal requirements, and hazards associated with volatile organic compounds. Other exemplary properties of ionic liquids are high ionic conductivity, non-volatility, non-flammability, high thermal stability, wide temperature for liquid phase, highly solvability, and non-coordinating. For a review of ionic liquids see, for example, Welton, *Chem Rev.* 1999, 99:2071-2083; and Carlin *et al.*, Advances in Nonaqueous Chemistry, Mamantov *et al.* Eds., VCH Publishing, New York, 1994.

The specific physical properties (*e.g.*, melting point, viscosity, density, water solubility, etc.) of ionic liquids are determined by the choice of cation and anion, as is disclosed more fully herein. As an example, the melting point for an ionic liquid can be changed by making structural modifications to the ions or by combining different ions. Similarly, the particular chemical properties (*e.g.*, bioactivity, toxicity, pharmacokinetics, etc.), can be selected by changing the constituent ions of the ionic liquid.

The ionic liquid compositions disclosed herein are comprised of at least one kind of anion and at least one kind of cation. The at least one kind of cation, the at least one kind of anion, or both can be a pharmaceutical active, a pesticidal active, a herbicidal active, a food additive, a nutraceutical, or the like, including any combination thereof, as is disclosed herein. It is contemplated that the disclosed ionic liquid compositions can comprise one kind of cation with more than one kind of anion (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more different kinds of anions). Likewise, it is contemplated that the disclosed ionic liquid compositions can comprise one kind of anion with more than one kind of cation (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more different kinds of cations). Further, the disclosed ionic liquids can comprise more than one kind of anion (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more different kinds of anions) with more than one kind of cation (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different kinds of cations). Specific examples include, but are not limited to, one kind of cation with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 2 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 3 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 4 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 5 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 6 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 7 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9,

10, or more kinds of anions, 8 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 9 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, 10 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions, or more than 10 kinds of cations with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of anions.

Other specific examples include, but are not limited to, one kind of anion with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 2 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 3 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 4 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 5 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 6 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 7 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 8 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 9 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, 10 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations, or more than 10 kinds of anions with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more kinds of cations.

In addition to the cations and anions, the ionic liquid compositions disclosed herein can also contain nonionic species, such as solvents, preservatives, dyes, colorants, thickeners, surfactants, viscosity modifiers, mixtures and combinations thereof and the like. However, the amount of such nonionic species is typically low (*e.g.*, less than about 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 wt.% based on the total weight of the composition). In some examples described herein, the disclosed ionic liquid compositions are neat; that is, the only materials present in the disclosed ionic liquids are the cations and anions that make up the ionic liquid compositions. It is understood, however, that with neat compositions, some additional materials or impurities can sometimes be present, albeit at low to trace amounts (*e.g.*, less than about 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 wt.% based on the total weight of the composition).

The disclosed ionic liquid compositions are liquid at some temperature range or point at or below about 150°C. For example, the disclosed ionic liquids can be a liquid at or below about 150, 149, 148, 147, 146, 145, 144, 143, 142, 141, 140, 139, 138, 137, 136, 135, 134, 133, 132, 131, 130, 129, 128, 127, 126, 125, 124, 123, 122, 121, 120, 119, 118, 117, 116, 115, 114, 113, 112, 111, 110, 109, 108, 107, 106, 105, 104, 103, 102, 101, 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0, -1, -2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -19, -20, -21, -22, -23, -24, -25, -26, -27, -28,

-29, or -30°C, where any of the stated values can form an upper or lower endpoint when appropriate. In further examples, the disclosed ionic liquids can be liquid at any point from about -30°C to about 150°C, from about -20°C to about 140°C, -10°C to about 130°C, from about 0°C to about 120°C, from about 10°C to about 110°C, from about 20°C to about 100°C, from about 30°C to about 90°C, from about 40°C to about 80°C, from about 50°C to about 70°C, from about -30°C to about 50°C, from about -30°C to about 90°C, from about -30°C to about 110°C, from about -30°C to about 130°C, from about -30°C to about 150°C, from about 30°C to about 90°C, from about 30°C to about 110°C, from about 30°C to about 130°C, from about 30°C to about 150°C, from about 0°C to about 100°C, from about 0°C to about 70°C, from about 0° to about 50°C, and the like.

Further, in some examples the disclosed ionic liquid compositions can be liquid over a wide range of temperatures, not just a narrow range of, say, 1-2 degrees. For example, the disclosed ionic liquid compositions can be liquids over a range of at least about 4, 5, 6, 7, 8, 9, 10, or more degrees. In other example, the disclosed ionic liquid compositions can be liquid over at least about a 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more degree temperature range. Such temperature ranges can begin and/or end at any of the temperature points disclosed in the preceding paragraph.

In many examples disclosed herein the disclosed ionic liquid compositions are liquid at the temperature at which they will be used or processed. For example, many of the disclosed ionic liquid compositions can be used for therapeutic or nutritional purposes in a subject. In this case, the disclosed ionic liquid compositions can be liquid at the subject's body temperature (*e.g.*, about 37°C for a human). Other examples include compositions that can be used as herbicides or pesticides, which are liquid at the temperature of their use (*e.g.*, ambient temperature). In still other examples, the disclosed compositions can be liquid at the temperature at which they are formulated or processed.

It is understood, however, that the disclosed ionic liquid compositions can, though need not, be solubilized, and solutions of the disclosed ionic liquids are contemplated herein. Further, the disclosed ionic liquid compositions can be formulated in an extended or controlled release vehicle, for example, by encapsulating the ionic liquids in microspheres or microcapsules using methods known in the art. Still further, the disclosed ionic liquid compositions can themselves be solvents for other solutes. For example, the disclosed ionic liquids can be used to dissolve a particular nonionic or ionic pharmaceutical active. These and other formulations of the disclosed ionic liquids are disclosed elsewhere herein.

In some examples, the disclosed ionic liquids are not solutions where ions are

dissolved in a solute. In other examples, the disclosed ionic liquid compositions do not contain ionic exchange resins. In still other examples, the disclosed ionic liquids are substantially free of water. By substantially free is meant that water is present at less than about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.5, 0.25, or 0.1 wt.%, based on the total weight of the composition.

The disclosed ionic liquid compositions can be prepared by methods described herein. Generally, the particular cation(s) and anion(s) used to prepare the disclosed ionic liquids are selected as described herein. Then, with the particular cation(s) and anion(s) in hand, they can be combined, resulting in ionic liquid compositions as disclosed herein. Additionally, the method for the preparation of the disclosed ionic liquid compositions can include the reaction in which two neutral species: an anion precursor (*e.g.*, in the form of an inorganic acid, carboxylic organic acid, non-carboxylic acid, or zwitterion species) and a cation precursor (*e.g.*, inorganic base, organic base, zwitterion species) are combined resulting in ionic liquid compositions as disclosed herein.

Providing ions used to prepare the disclosed ionic liquids depends, in one aspect, on the desired properties of the resulting ionic liquid composition. As described herein, the disclosed ionic liquid compositions can have multiple desired properties, which, at least in part, come from the properties of the cation(s) and/or anion(s) used to prepare the ionic liquid. Thus, to prepare the disclosed ionic liquids, one or more kinds of cations with a desired property(ies) are provided. One or more kinds of anions with a desired property(ies) that is similar or different to that of the cation(s) can likewise be provided. Of course, providing a desired anion(s) and cation(s) can be done in any order, depending on the preference and aims of the practitioner. For example, a particular cation(s) can be provided and then a particular anion(s) can be provided. Alternatively, a particular anion(s) can be provided and then a particular cation(s) can be provided. Further, the cation(s) and anion(s) can be provided simultaneously.

As noted, providing a suitable ion can be based on selecting an ion that possesses a property that is desired (*e.g.*, the ion has a property that is desired to be possessed by the resulting ionic liquid). Examples of properties that could be desired in a suitable cation and/or anion (and thus the ionic liquid made therefrom) include, but are not limited to, biological, therapeutic, prophylactic, nutritional, pesticidal, and/or herbicidal activity. Inertness, taste, viscosity modulation, solubility modulation, stability, and toxicity are other properties of a given ion that could be desired and considered. While more specific properties are disclosed elsewhere herein, the disclosed methods and compositions are not

limited to any particular combination of properties, as such will depend on the preferences and goals of the practitioner.

Typically, the desired properties of the cation(s) and anion(s) will be different or complimentary to one another. In this way, the resulting ionic liquid can possess multiple desired properties: those properties imparted by the cation(s) and those imparted by the anion(s). In other words, some or all of the ions present in the disclosed ionic liquids can independently and simultaneously introduce a specific functionality or property to the disclosed ionic liquid compositions. It is this multiple functionality characteristic that can allow one to fine-tune or design very specific physical, chemical, and bioactive properties in the disclosed ionic liquid compositions. Additional functionality can be obtained by using the disclosed ionic liquid compositions as solvents to dissolve a solute(s) with another desired property, thus resulting in a solution where the ions of the ionic liquid as well as the solute contribute desired properties to the composition. General and specific examples of various combinations of ions and their associated properties are disclosed herein.

In some particular examples, one or more ions in the disclosed ionic liquid composition (*e.g.*, the anions, cations, or both) can be a pharmaceutical active, *e.g.*, an existing drug that is ionic or that can be made ionic. Many drugs exist naturally or at physiological conditions as an ion, or they can be converted to ions *via* simple chemical transformations (*e.g.*, alkylation, protonation, deprotonation, etc.). As such, these drugs can be used to prepare an ionic liquid composition as disclosed herein. Such drugs can possess any therapeutic or prophylactic activity, many of which are described herein. Combining such drugs with other ions to prepare an ionic liquid, as is disclosed herein, can result in the modification and/or enhancement of the drug's properties. For example, a first drug ion with a given property can be combined with an oppositely charged second ion with another property to effect the controlled release, controlled delivery, biological impact, taste, physical properties (stability, solubility, toxicity, melting point, etc.), or to overcome polymorphism in the first drug ion. In this way, new drug compositions can be created by forming ionic liquids with functionality crafted into the combination of the ions, as disclosed herein.

As another example, the first drug ion may be combined with a second drug ion that has properties complimentary to the first. Examples of this can include, but are not limited to, an ion having anesthetic properties being combined with an ion having antibacterial properties, an ion having anesthetic properties being combined with an ion having coagulation properties, or an ion having coagulation properties being combined with an ion having antibacterial properties. Ionic liquids resulting from such combinations could find

uses in wound repair, for example. Still other examples of desirable combination include ions having therapeutic or prophylactic efficacy being combined with ions having taste enhancement properties (*i.e.*, taste modifiers). Ionic liquids resulting from this combination can be useful in enhancing the taste and palatability of medicines. Still further examples can include two differently charged ions each with similar uses but with different mechanisms of action. Specific examples of such combinations can include, but are not limited to, combinations of ions with antineoplastic properties or antiviral properties. Ionic liquids prepared from such ion combinations can be useful as drug "cocktails," where two or more bioactive agents are present in a single ionic liquid combination.

According to the methods and compositions disclosed herein, ion identification and combination, as disclosed herein, can involve any ion, not just ionic drugs, as long as the combination results in an ionic liquid. For example, ions that have pesticidal properties can be combined with oppositely charged ions having pesticidal, herbicidal, antimicrobial properties, and the like. In other examples, ions with antibacterial properties can be combined with oppositely charges ions that have preservative properties, taste modifiers, etc. In still other examples, an ion with one therapeutic or prophylactic property can be combined with another therapeutic or prophylactic ion. As should be appreciated, the various combinations of ions according to the disclosed methods are numerous, and depend only on the desired combination of properties and whether the resulting ion combination is an ionic liquid as defined herein.

Specific examples of properties that can be exhibited by the disclosed compositions include antibacterial, FDA approved dyes, anti-acne, antibiotic, UV blocker, wetting agents, preservative, emollient, anti-inflammatory, and vitamin.

IONIC LIQUID IMMOBILIZED FRAGRANCES

Fragrance and flavor formulations suffer from limited lifetime because their constituents evaporate, are degrading or lost during storage. Perfumes in consumer products tend to fade by evaporation, oxidation, chemical degradation or interaction with other ingredients. The flavor industry has addresses the issue of performance loss of flavors by developing specific delivery systems. At the present time, sustained release techniques for flavor and fragrance delivery present in literature are usually based on encapsulation either in hydrophilic matrices, via spray drying, granulation and spray-coating, encapsulation by coacervation and interfacial polymerization and the use of colloidal carriers for the application in aqueous products (Quellet *et al. Chimia* 2001, 55:421-428).

The use of ionic liquid in fragrance and flavor industry is mainly dealing with solvent applications for the synthesis of fragrance and flavor materials in ionic liquids or with the extraction of naturals (Sullivan, N. *Innovations in Pharmaceutical Technology* 2006, 20:75-77).

For example, Forsyth et al. investigated the utilization of ionic liquid solvents for the synthesis of lily-of-the-valley fragrance and fragrance intermediate Lilial (Forsyth *et al., J. Mol. Cat. A.* 2005, 231:61-66). The role of ionic liquids in consumer products and fragrances is comparingly less explored (Davey, *Perf. Flav.* 2008, 33:34-35; Liu, *Flav. Frag. Cosm. (Xiangliao Xiangjing Huazhuangpin)* 2004, 29:30-36). Creavis noted that the rate of evaporation of a perfume could be slowed using an ionic liquid as fixative (Petrat *et al.* US 2006/0166856; Creavis AG DE 10337579A1). Examples include a chypre accord, a musk base and a rose composition with increased fiber substantivity compared to the same composition without the ionic liquid. The modification of textile surfaces, optionally adding a benefit agent which includes a perfume followed by removal of the ionic liquid was described by Procter and Gamble. (US 20060090271, US 20060090777, EP 1807497). Benefit agent delivery systems comprising ionic liquids and their uses in detergent compositions have also been reported. (Price *et al.* US2006094617)

Delivery devices or storage media for fragrances and flavors based on ionic liquids that include a covalent attachment of the active compound and immobilization as a salt and there application for storage as well as for prolonged and controlled triggered relase not mentioned in any form in prior literature.

Ions

The disclosed ionic liquids contain at least one kind of cation and at least one kind of anion. Examples of suitable cations and anions are disclosed herein. It should be understood that when a particular compound is disclosed as being a cation, for example, it can also, in other circumstances, be an anion and *vice versa*. Many compounds are known to exist as cations in some environments and anions in other environments. Further, many compounds are known to be convertible to cations and anions through various chemical transformations. Examples of such compounds are disclosed herein.

The materials, compounds, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions are disclosed herein. It is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference

of each various individual and collective combinations and permutation of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if an ionic liquid composition is disclosed and a number of modifications that can be made to a number of components of the ionic liquid composition are discussed, each and every combination and permutation that are possible are specifically contemplated unless specifically indicated to the contrary. Thus, if a class of cations A, B, and C are disclosed as well as a class of anions D, E, and F and an example of a ionic liquid A-D is disclosed, then even if each is not individually recited, each is individually and collectively contemplated. Thus, in this example, each of the ionic liquids A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are specifically contemplated and should be considered disclosed from disclosure of A, B, and C; D, E, and F; and the example ionic liquid A-D. Likewise, any subset or combination of these is also specifically contemplated and disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E are specifically contemplated and should be considered disclosed from disclosure of A, B, and C; D, E, and F; and the example combination A-D. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods of making and using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific aspect or combination of aspects of the disclosed methods, and that each such combination is specifically contemplated and should be considered disclosed.

Cations

Particular examples of cationic compounds that can be present in the disclosed ionic liquid compositions are compounds that contain nitrogen atoms. Nitrogen atoms can exist or can be converted to positively-charged quaternary ammonium species, for example, through alkylation or protonation of the nitrogen atom. Thus compounds that possess a quaternary nitrogen atom (known as quaternary ammonium compounds (QACs)) are typically cations. According to the methods and compositions disclosed herein, any compound that contains a quaternary nitrogen atom or a nitrogen atom that can be converted into a quaternary nitrogen atom can be a suitable cation for the disclosed ionic liquid compositions.

QACs can have numerous biological properties that one may desire to be present in the disclosed ionic liquid compositions. For example, many QACs are known to have antibacterial properties. The antibacterial properties of QACs were first observed toward the end of the 19th century among the carbonium dyestuffs, such as auramin, methyl violet, and malachite green. These types of compounds are effective chiefly against the Gram-positive organisms. Jacobs and Heidelberger first discovered QACs antibacterial effect in 1915

studying the antibacterial activity of substituted hexamethylene-tetrammonium salts (Jacobs and Heidelberger, *Proc Nat Acad Sci USA*, 1915, 1:226; Jacobs and Heidelberger, *J Biol Chem*, 1915, 20:659; Jacobs and Heidelberger, *J Exptl Med*, 1916, 23:569).

Browning *et al.* found great and somewhat less selective bactericidal powers among quaternary derivatives of pyridine, quinoline, and phenazine (Browning *et al.*, *Proc Roy Soc London*, 1922, 93B:329; Browning *et al.*, *Proc Roy Soc London*, 1926, 100B:293). Hartman and Kagi observed antibacterial activity in QACs of acylated alkylene diamines (Hartman and Kagi, *Z Angew Chem*, 1928, 4:127).

In 1935, Domagk synthesized long-chain QACs, including benzalkonium chloride, and characterized their antibacterial activities (Domagk, *Deut Med Wochenschr*, 1935, 61:829). He showed that these salts are effective against a wide variety of bacterial strains. This study of the use of QACs as germicides was greatly stimulated.

Many scientists have focused their attention on water soluble QACs because they exhibit a range of properties: they are surfactants, they destroy bacteria and fungi, they serve as a catalyst in phase-transfer catalysis, and they show anti-electrostatic and anticorrosive properties. They exert antibacterial action against both Gram-positive and Gram-negative bacterial as well as against some pathogen species of fungi and protozoa. These multifunctional salts have also been used in wood preservation, their application promoted in the papers of Oertel and Butcher *et al.* (Oertel, *Holztechnologie*, 1965, 6:243; Butcher *et al.*, *For Prod J*, 1977, 27:19; Butcher *et al.*, *J For Sci*, 1978, 8:403).

QACs are also widely used as skin antiseptics, disinfectants, fabric softeners, antistatic agents, cleaning agents, and preservatives. Detergent properties and antimicrobial activities of QACs have made them useful for general environmental sanitations, for examples, in hospitals and food production facilities. In pharmacological preparations they are used such as mouth rinses, lozenges, sprays and gels.

In humans and animals QACs have been considered too toxic for systematic applications, but are accepted to be safe for topical applications. Furthermore, QACs have recently been used as penetration enhancers for transnasal and transbuccal drug delivery, as well as in nasal vaccination (Klinguer *et al.*, *Vaccine*, 2001, 19:4236). This ability to penetrate and open cell membrane has been widely used in drug delivery *via* liposomes (mainly QACs with two long alkyl chains) and non-viral gene delivery (Liu and Huang, *J Contr Rel*, 2002, 78:259). Many examples of compounds having nitrogen atoms, which exist as quaternary ammonium species or can be converted into quaternary ammonium species, are disclosed herein.

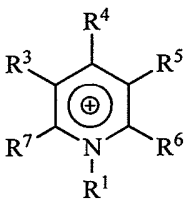
In some examples, when the cation is a quaternary ammonium compound, the anion is not an inorganic anion, examples of which are disclosed herein. In other examples, where the cation is a quaternary ammonium compound, the anion is not a halide.

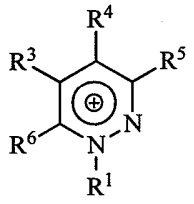
Aliphatic Heteroaryls

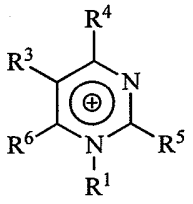
Some specific QACs suitable for use herein are aliphatic heteroaryls. An aliphatic heteroaryl cation is a compound that comprises an aliphatic moiety bonded to a heteroaryl moiety. In the aliphatic heteroaryl cation, the aliphatic moiety can be any alkyl, alkenyl, alkynyl, cycloalkyl, or cycloalkenyl group, as described herein. Generally, the aliphatic moiety can comprise at least 10, at least 12, at least 14, at least 16, at least 18, or at least 20 carbon atoms. In other examples, the aliphatic moiety can comprise a mixture of aliphatic groups having a range of carbon atoms. For example, the aliphatic moiety can comprise from 10 to 40, from 12 to 38, from 14 to 36, from 16 to 34, from 18 to 32, from 14 to 18, or from 20 to 30 carbon atoms. In some specific examples, the aliphatic moiety can contain 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 carbon atoms, where any of the stated values can form an upper or lower endpoint when appropriate. Examples of specific aliphatic moieties that can be used include, but are not limited to, decyl, dodecyl (lauryl), tetradecyl (myristyl), hexadecyl (palmityl or cetyl), octadecyl (stearyl), eicosyl (arachidyl), and linolenyl groups, including branched derivatives thereof and any mixtures thereof. In the aliphatic heteroaryl cations, the aliphatic moiety is bonded to a heteroatom in the heteroaryl moiety.

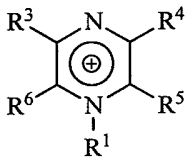
In the aliphatic heteroaryl cation, the heteroaryl moiety can be any heteroaryl moiety as described herein. For example, the heteroaryl moiety can be an aryl group having one or more heteroatoms (*e.g.*, nitrogen, oxygen, sulfur, phosphorous, or halonium). Examples of specific heteroaryl moieties that can be used in the aliphatic heteroaryl cations include, but are not limited to, pyrazole, pyridine, pyrazine, pyrimidine, pryidazine, indolizine, isoindole, indole, indazole, imidazole, oxazole, triazole, thiazole, purine, isoquinoline, quinoline, phthalazine, quinooxaline, phenazine, and the like, including substituted derivatives and mixtures thereof. In the aliphatic heteroaryl cations, a heteroatom in the heteroaryl moiety is bonded to the aliphatic moiety. When the heteroatom of the heteroaryl is nitrogen, this forms a quaternary ammonium cation, as described herein.

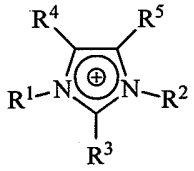
Further examples of aliphatic heteroaryl cations are those having the following structures:

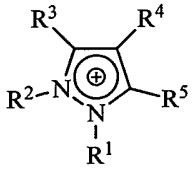

PYRIDINIUM

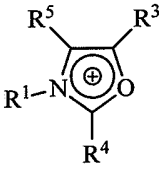

PYRIDAZINIUM

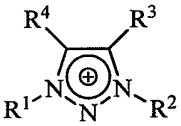
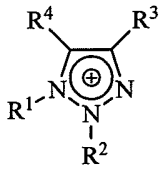

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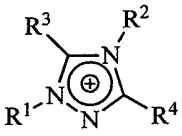

PYRAZINIUM

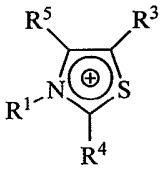

IMIDAZOLIUM

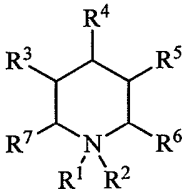

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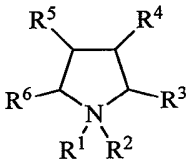

OXAZOLIUM

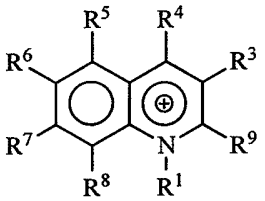


1,2,3-TRIAZOLIUM

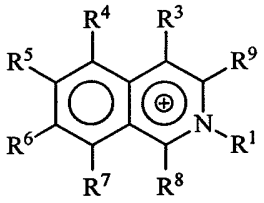

1,2,4-TRIAZOLIUM


THIAZOLIUM


PIPERIDINIUM


PYRROLIDINIUM


QUINOLIUM


ISOQUINOLIUM

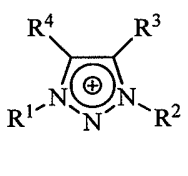
wherein R^1 and R^2 are, independently, a C_1-C_6 alkyl group or a C_1-C_6 alkoxyalkyl group, and R^3, R^4, R^5, R^6, R^7, R^8, and R^9 (R^3-R^9), when present, are independently H, a C_1-C_6 alkyl, a C_1-C_6 alkoxyalkyl group, a C_1-C_6 alkoxy group, or an energetic substituents such as nitro, amino, cyano, azido, alkyl nitro, alkyl amino, alkyl cyano, alkyl azido, alkoxy nitro, alkoxy amino, alkoxy cyano, and alkoxy azido. In other examples, both R^1 and R^2 groups are C_1-C_4 alkyl, with one being methyl, and R^3-R^9, when present, are H. Exemplary C_1-C_6 alkyl groups and C_1-C_4 alkyl groups include methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl, *iso*-butyl, pentyl, *iso*-pentyl, hexyl, 2-ethylbutyl, 2-methylpentyl, and the like. Corresponding C_1-C_6 alkoxy groups contain the above C_1-C_6 alkyl group bonded to an oxygen atom that is also bonded to the cation ring. An alkoxyalkyl group contains an ether group bonded to an alkyl

group, and here contains a total of up to six carbon atoms. It is to be noted that there are two isomeric 1,2,3-triazoles. In some examples, all R groups not required for cation formation can be H.

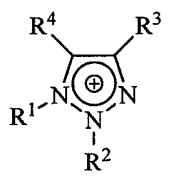
The phrase "when present" is often used herein in regard to substituent R group because not all cations have all of the numbered R groups. All of the contemplated cations contain at least four R groups, which can be H, although R^2 need not be present in all cations.

In one example, all R groups that are not required for cation formation; *i.e.*, those other than R^1 and R^2 for compounds other than the imidazolium, pyrazolium, and triazolium cations shown above, are H.

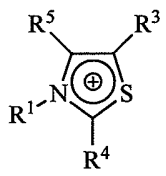
A cation that contains a single five-membered ring that is free of fusion to other ring structures is suitable for use herein. Exemplary cations are illustrated below wherein R^1, R^2, and R^3-R^5, when present, are as defined before.



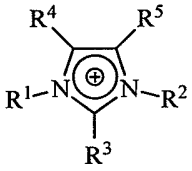
1,2,3-TRIAZOLIUM



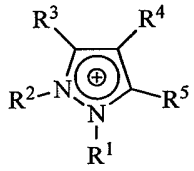
1,2,4-TRIAZOLIUM



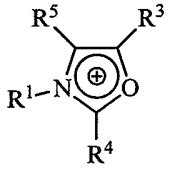
THIAZOLIUM



IMIDAZOLIUM

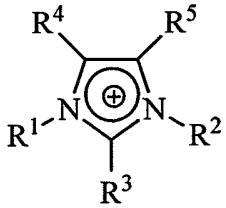


PYRAZOLIUM



OXAZOLIUM

Of the cations that contain a single five-membered ring free of fusion to other ring structures, an imidazolium cation that corresponds in structure to Formula A is also suitable, wherein R^1, R^2, and R^3-R^5, are as defined before.



(A)

In a further example, an *N,N*-1,3-di-(C_1-C_6 alkyl)-substituted-imidazolium ion can be used; *i.e.*, an imidazolium cation wherein R^3-R^5 of Formula A are each H, and R^1 and R^2 are independently each a C_1-C_6 alkyl group or a C_1-C_6 alkoxyalkyl group. In yet another example, the cation illustrated by a compound that corresponds in structure to Formula B, below, wherein R^3 -R^5 of Formula A are each hydrogen and R^1 is a C_1-C_6 -alkyl group or a

C_1-C_6 alkoxyalkyl group.

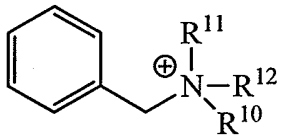


(B)

Aliphatic Benzylalkyl Ammonium

The disclosed ionic liquid compositions can also comprise an aliphatic benzylalkyl ammonium cation. An aliphatic benzylalkyl ammonium cation is a cation that comprises an aliphatic moiety bonded to the nitrogen atom of a benzylalkyl amine moiety. The aliphatic moiety can be as described herein. The benzylalkyl amine moiety can be a benzyl amine where the amine is bonded to an alkyl or cyclic alkyl group, as described herein. One or more types of aliphatic benzylalkyl ammonium cation can be used in the ionic liquid compositions disclosed herein. The aliphatic benzylalkyl ammonium cation suitable for use herein can be prepared by methods known in the art or can be obtained from commercial sources.

In one aspect, the aliphatic benzylalkyl ammonium cation can be represented by the following formula:



wherein R^{10} is an aliphatic group, as described above, R^{11} and R^{12} are, independent of one another, alkyl groups or cyclic alkyl groups as described herein. In some examples, one or more of the "R" substituents can be a long chain alkyl group (*e.g.*, the number of carbon atoms is 10 or greater). In other examples, one or more of the "R" substituents can be a short chain alkyl group (*e.g.*, the number of carbon atoms is less than 10). In still other examples, one of the "R" substituents is a long chain alkyl group and the other two "R" substituents are short chain alkyl groups.

In one aspect, the aliphatic benzylalkyl ammonium cation can have any of the aliphatic moieties disclosed herein bonded to any benzylalkyl amine moieties disclosed herein. In some specific examples, R^{10} in the formula of aliphatic benzylalkyl ammonium cation can be an aliphatic group of from 10 to 40 carbon atoms, *e.g.*, a decyl, dodecyl (lauryl), tetradecyl (myristyl), hexadecyl (palmityl or cetyl), octadecyl (stearyl), or eicosyl (arachidyl) group, and R^{11} and R^{12} can each be, independent of one another, a methyl, ethyl, propyl, butyl, pentyl, or hexyl group.

In another aspect, the aliphatic benzylalkyl ammonium cation can include, but are not limited to, alkyl dimethyl benzyl ammonium cations. Specific examples of alkyl dimethyl benzyl ammonium cations include, but are not limited to, cetyl dimethyl benzyl ammonium, lauryl dimethyl benzyl ammonium, myristyl dimethyl benzyl ammonium, stearyl dimethyl benzyl ammonium, and arachidyl dimethyl benzyl ammonium.

In yet another aspect, the aliphatic benzylalkyl ammonium cation can include, but are not limited to, alkyl methylethyl benzyl ammonium cations. Specific examples of alkyl methylethyl benzyl ammonium cations include, but are not limited to, cetyl methylethyl benzyl ammonium, lauryl methylethyl benzyl ammonium, myristyl methylethyl benzyl ammonium, stearyl methylethyl benzyl ammonium, and arachidyl methylethyl benzyl ammonium.

Dialiphatic Dialkyl Ammonium

Still further examples of QACs that can be used in the disclosed ionic liquid compositions are dialiphatic dialkyl ammonium cations. A dialiphatic dialkyl ammonium cation is a compound that comprises two aliphatic moieties and two alkyl moieties bonded to a nitrogen atom. The aliphatic moieties can be the same or different and can be any aliphatic group as described above. The alkyl moieties can be the same or different can be any alkyl group as described above. In the disclosed dialiphatic dialkyl ammoniums cations, the two aliphatic moieties can have 10 or more carbon atoms and the two alkyl moieties can have less than 10 carbon atoms. In another alternative, the two aliphatic moieties can have less than 10 carbon atoms and the two alkyl moieties can have 10 or more carbon atoms. One or more types of dialiphatic dialkyl ammonium cations can be used in the ionic liquid compositions disclosed herein.

In some particular examples, the dialiphatic dialkyl ammonium cation can be di-dodecyl dimethyl ammonium, di-tetradecyl dimethyl ammonium, dihexadecyl dimethyl ammonium, and the like, including combinations thereof.

Tetraalkyl Ammonium

The disclosed ionic liquid compositions can also comprise a tetraalkyl ammonium cation. Suitable tetraalkyl ammonium cations comprise four alkyl moieties, as disclosed herein. In one example, a tetraalkyl ammonium cation can comprise one long chain alkyl moiety (*e.g.*, 10 or more carbon atoms in length) and three short chain alkyl moieties (*e.g.*, less than 10 carbon atoms in length).

Some specific examples of tetraalkyl ammonium cations that can be included in the

disclosed ionic liquid compositions include, but are not limited to, cetyl trimethyl ammonium, lauryl trimethyl ammonium, myristyl trimethyl ammonium, stearyl trimethyl ammonium, arachidyl trimethyl ammonium, or mixtures thereof. Other examples include, but are not limited to, cetyl dimethylethyl ammonium, lauryl dimethylethyl ammonium, myristyl dimethylethyl ammonium, stearyl dimethylethyl ammonium, arachidyl dimethylethyl ammonium, or mixtures thereof.

Other Cations

Other cations that are suitable for use in the disclosed methods and compositions are compounds that contain metals. According to the methods and compositions disclosed herein, any compound that contains a metal atom can be a suitable cation. Organometallic compounds or metal complexes commonly have one or more metal atom in a positive oxidation state. Examples of metals that can be present in a suitable cation include, but are not limited to, lithium, sodium, potassium beryllium, magnesium, calcium, strontium, chromium, manganese, iron, cobalt, nickel, copper, and zinc. Silver nanoparticles can also be used. Examples of suitable organometallic cations include, but are not limited to, metallocenium, alkylgermanyl, alkyltin, or alkylsilyl (*e.g.*, trimethylsilylium, triethylsilylium, tris(trimethylsilyl)silylium, tribenzylsilylium, triphenylsilylium, tricyclohexylsilylium, and dimethyloctadecylsilylium).

Another suitable group of quaternary ammonium cations are those that have been prepared by esterifying a compound containing a carboxylic acid moiety or transesterifying a compound with an ester moiety with a choline moiety. Such choline esters can be biofriendly, permanent ions that are amenable to being added to various compounds while still being easily cleavable under physiological conditions. The choline esters can be used to increase the solubility and bioavailability of many neutral compounds.

Futher examples of cations include (2-hydroxyethyl)-dimethylundecyloxymethyl-ammonium, (2-acetoxyethyl)-heptyloxymethyldimethylammonium, and (2-acetoxyethyl)-dodecyloxymethyldimethylammonium, mepenzolate, sulfathiazole, thimerosal, and valproic acid.

In other examples, the cation can be an energetic cation as disclosed in Katritzky *et al.*, "ILs Based on Energetic Imidazolium Cations: Nitro- and Nitrile-substituted N,N' Dialkylimidazolium Salts" *New J Chem* 30:349, 2006, which is incorporated by reference herein at least for its teachings of energetic ions.

Anions

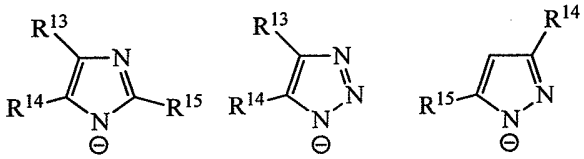
Particular examples of anionic compounds that can be present in the disclosed ionic liquids are compounds that contain oxygen atoms. Oxygen atoms can exist or can be converted to negatively charged, anionic species, for example, through deprotonation of alcohols or acids, through saponification of esters, or through alkylation of ketones. Likewise, compounds that contain sulfur atoms can also exist or be converted to anionic species through similar reactions. Still further, compounds that contain nitrogen atoms, especially nitrogen atoms adjacent to electron withdrawing groups or resonance stabilizing structures, can be converted to anions through deprotonation. According to the methods and compositions disclosed herein, any compound that contains an oxygen, sulfur, or nitrogen atom can be a suitable anion for the disclosed ionic liquid compositions.

Other suitable anions include, but are not limited to, halides (*e.g.*, fluoride, chloride, bromide, and iodide), sulfates (SO_4^-), carbonates, bicarbonates, phosphates, phosphates, nitrates (NO_3^-), nitrites (NO_2^-), acetates ($CH_3CO_2^-$), and the like. Other examples of anions include, but are not limited to PF_6^- that is immiscible in water and BF_4^- that is miscible in water depending on the ratio of ionic liquid to water, system temperature, and alkyl chain length of cation. Other anions include triflate (TfO; $CF_3SO_2^-$), nonaflate (NfO; $CF_3(CF_2)_3SO_2^-$), bis(triflyl)amide (Tf_2N; $(CF_3SO_2)_2N^-$), trifluoroacetate (TFA; $CF_3CO_2^-$), and heptaflurorobutanoate (HB; $CF_3(CF_2)_3SO_2^-$). Other types of ionic liquids include haloaluminates, such as chloroaluminate.

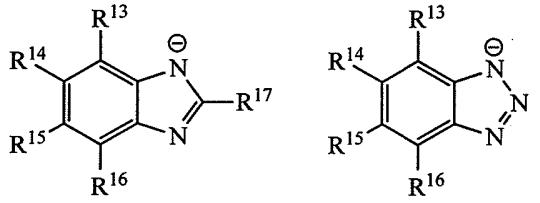
Other suitable anions contemplated herein are saccharin and acesulfame. Saccharin, as an alkali metal salt, and acesulfame (6-methyl-3,4-dihydro-1,2,3-oxathiazin-4-one 2,2-dioxide), which has previously only been offered as potassium salt, are in widespread use in foodstuffs as non-nutritive sweeteners. Such anions can be used when one desires to prepare an ionic liquid composition that has sweetness as one of its desired properties. For example, saccharin and acesulfame can be combined with pharmaceutically active cations to prepare sweet tasting ionic liquids that have pharmaceutical activity.

Specific examples of other anions include piperacillin, folic acid, ibuprofen, fast green FCF, docusate, acesulfamate, penicillin G, Colawet MA-80, salicylic acid, saccharinate, sulfacetamide, naproxen, benzoate, diclofenac, and *trans*-cinnamic acid.

Other suitable anions include, but are not limited to, substituted and un-substituted imidazolates, 1,2,3-triazolates, and 1,2,4-triazolates, benzimidazolates, benz-1,2,3-triazolates, as shown bellow:



imidazolate 1,2,3-triazolate 1,2,4-triazolate



benzimidazolate benz-1,2,3-triazolate

wherein R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, (R^{13-17}), when present, are independently H, a C_1-C_6 alkyl, a C_1-C_6 alkoxyalkyl group, a C_1-C_6 alkoxy group, or energetic substituents like nitro, amino, cyano, azido, alkyl nitro, alkyl amino, alkyl cyano, alkyl azido, alkoxy nitro, alkoxy amino, alkoxy cyano, and alkoxy azido. Exemplary C_1-C_6 alkyl groups and C_1-C_4 alkyl groups include methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, iso-butyl, pentyl, iso-pentyl, hexyl, 2-ethylbutyl, 2-methylpentyl, and the like. Corresponding C_1-C_6 alkoxy groups contain the above C_1-C_6 alkyl group bonded to an oxygen atom that is also bonded to the cation ring. An alkoxyalkyl group contains an ether 10 group bonded to an alkyl group, and here contains a total of up to six carbon atoms. It is to be noted that there are two isomeric 1,2,3-triazoles. In some examples, all R groups not required for anion formation can be H.

Further examples of suitable energetic anions are disclosed in Katritzky *et al.*, "ILs Based on Energetic Azolate Anions," *Chem Eur J* 12:4630, 2006, which is incorporated by reference herein at least for its teachings of energetic anions.

Compound that can exist that as both: Anion or Cation

Examples of compounds that exist as cations in some environments and anions in other environments include, but are not limited to, 1,3-dimethylimidazolium, 1-butyl-3-methylimidazolium, 1,2,3-triazolium, tetrazolium, 1,2,4-triazolium, 1,3-dimethyl-1,2,3-triazolium, and 1,3-dimethyl-4-nitroimidazolium, which exist as a cations, and 4-nitroimidazolate, 4,5-dinitroimidazolate, 3,5-dinitro-1,2,4-triazolate, tetrazolate, 5-aminotetrazolate, 2-nitroimidazolate, which exist as an anion. Those separate ions can still form single product ionic liquids.

Examples of compounds that can change from an anion in one environment to a cation in another environment due to chemical modifications are the sulfur ylides through the reaction of a sulfide with methyliodide to form the sulfonium ion.

Specific Examples of Pharmaceutical Actives

When pharmaceutical activity is a desired property of the disclosed ionic liquids, one or more of the ions in the disclosed ionic liquid compositions can be a pharmaceutical active. Pharmaceutical actives that exist as ions or can be converted to ions, and which are suitable for use in preparing the disclosed ionic liquid compositions, include the following categories and specific examples. It is not intended that the category be limited by the specific examples. Those of ordinary skill in the art will be able to readily identify those pharmaceutical actives that can be used in the disclosed methods and compositions. For example, one can identify a compound with a given property or activity by consulting various sources, such as the Merck Index (13th Edition, Wiley, 2001), The United States Pharmacopeia–National Formulary (USP–NF), and the FDA's Orange book, which are each incorporated by reference herein at least for their teachings of pharmaceutical actives. Once a compound with a desired property is identified, the skilled artisan can determine whether the compound is ionic or can be made ionic. Such determinations can be performed based on the compound's structure, which can readily be determined by consulting the sources mentioned herein or experimentally. Knowing a compound's structure can readily reveal if the compound is ionic. In fact, many pharmaceutical actives exist as salts and are thus suitable for use in preparing the disclosed ionic liquid compositions. Further, if a compound is not ionic, but contains an ion forming moiety (*e.g.*, nitrogen, oxygen, sulfur, or metal atoms, as described herein), the compound can be converted to an ion and then combined with a suitable counterion to prepare the disclosed ionic liquid compositions. Those of ordinary skill in the art will recognize numerous other compounds that fall within the categories and that are useful according to the disclosed compositions and methods.

Some specific examples of pharmaceutical actives that can be used in the disclosed ionic liquids include, but are not limited to, aspirin, LIBRIUM™, isoniazid, penicillin, PRONTOSIL™, cisplatin, 6-mercaptopurine, RITUXAN™, TAXOL™, phenobarbital, PROZAC™, ALLEGRA™, VIOXX™, quinine, ivermectin, L-dopa, THORAZINE™, salvarsan, TAGAMET™, AZT, crixivan, salbutamol, digoxin, fluride, LOVASTATIN™, erythropoietin, hydrocortisone, insulin, oral contraceptives, oxytocin, PREMARIN™, RU-486, thyroxine, thalidomide, cyclosporine, fentanyl, methadone, morphine, botox, vitamins, FOSAMAX™, RITALIN™, and VIAGRA™, including ionic derivatives thereof.
Other examples of pharmaceutical active ions or pharmaceutical actives that can be made ionic include, but are not limited to, pantoprazole, sold under the trade names PROTONIX™ and PANTOZOL™, and rabeprazole, sold under the trade names ACIPHEX™ and

PARIET™, which are used to treat gastrointestinal disorders. Risedronate, sold under the trade name ACTONEL™, and alendronate, sold under the trade name FOSAMAX™, are used to treat osteoporosis and are further examples of suitable compounds that can be used to prepare the disclosed ionic liquid compositions. Further examples include losartan, sold under the trade names NU-LOTAN™, COZAAR™, and HYZAAR™, and fosinopril, sold under the trade name MONOPRIL™, which are used to treat hypertension and are other examples of suitable compounds that can be used to prepare the disclosed ionic liquid compositions. Atorvastatin, sold under the trade name LIPITOR™, and pravastatin, sold under the trade name PRAVACHOL™, are used to treat cholesterol and are further examples of suitable compounds that can be used to prepare the disclosed ionic liquid compositions. A further example is montelukast, which is used to treat asthma and is sold under the trade name SINGULAIR™. Further examples of pharmaceutical actives that are ionic or can be made ionic and combined with other ions to form the disclosed ionic liquid compositions are: prostaglandin E_2, prostaglandin $F2_A$, sulprostone, cetapril, benzaepril, captopril, methyl hexaneamine, synephrine, isoetharine, methoxyphenamine, tamsulosin, tolazoline, bufuralol, nadoxolol, acetylsalicylsalicylic acid, ammonium salicylate, buthalital sodium, thiopental sodium, isobutyl p-aminobenzoate, phenol, clortermine, fenproporex, dermatol, niclosamide, pelletierine, dithiazanine iodide, thiabendazole, antimony sodium thioglycolate, niridazole, isotretinoin, lodoxamide, ramatroban, finasteride, minoxidil, carbarsone, diphetarsone, flutamide, nilutamide, nicorandil, ozagrel, bunitrolol, ipratropium bromide, pyridinol carbamate, bucillamine, diacerein, amlexanox, cromolyn, azidamfenicol, thiamphenicol, brodimoprim, tetroxoprim, acetosulfone sodium, dapsone, benzoylpas, cyamelide, picotamide, acetylpheneturide, albutoin, caroxazone, indalpine, calcium mesoxalate, buformin, alkofanone, metformin, edrophomium chloride, neostigmine, p-aminopropiophenon, methylene blue, folinic acid, tiopronin, fomepizole, asoxime chloride, obidoxime chloride, chlonidine, tiapride, alizapride, bromopride, potassium p-aminobenzoate, chlordantoin, bromosalicylchloranilide, acetazolamide, benfunolol, allopurinol, carprofen, acrivastine, Metron S, Acifran, Benfluorex, Chlorisoncl-amine chloride, Pentamethon-ium bromide, 2-Aminothiazole, Methylthio-uracil, Amexinium Methyl Sulfate, Dopamine Hydrochloride, Balsalazide, Mesalamine, Enfenamic Acid, Menfenamic Acid, Flufenamic Acid Aluminum Salt, Berberine, Chloguanide, Valproic Acid, Lisuride, Naratriptan, Ambutonium Bromide, Benzilonium Bromide, 9-Amino-camptothecin, Tenuazonic Acid, Clometocillin, Fluoxetine Hydrochloride, Pamidronic Acid, Risedronate Sodium, Benserazide Hydrochloride, Carbidopa, Metyrosine, Phentolamine, Elfornithine

Hydrochloride monohydrate, Sulfamethox-azole, Tamsulosin Hydrochloride, Terazosin, Nitazoxanide, Acranil [r], Hydroxystil-bamidine, Pentamidine, Pyrimethamine, Acetarsone, Aminitrozole, Benznidazole, Eflornithine Hydrochlo-ride, Acitretin, 6-Azauridine, Amisulpride, Remoxipride Hydrochloride Monohydrate, Bufe-xamac, Bumadizon, Chloramphenicol, Benzoxonium, Chloride, Cetalkonium Chloride, Aliben-dol,Ambutonium Bromide, Arshpenamine, Sodium Arsanilate, Anagrelide, Beraprost, Cilostazol, Bibenzonium Bromide, Sodium Dibunate, Aldioxa, Cimetidine, Allopurinol, Succinimide, Foscarnet Sodium, Efavirenz, Etifoxine, Valnoctamide, Cannabinol, Oxitropium Bromide, Tiotropium Bromide, Fendiline Hydrochloride, Prenylamine, Acetazolamide, Flumethiazide, Acadesine, Cariporide, Levosimendan, Pimobendan Hydrochloride, Ursodiol, Chenodiol, Cholic Acid Monohydrate, Clanobutin, Echothiophate Iodide, Edrophonium Chloride, Ambenonium , hloride, Distigmine Bromide, Asoxime Chloride, Obidoxime Chloride, Pemoline, Phenmetrazine, Celecoxib, Cetraxate, Irsogladine, Naphazoline Hydrochloride, Nordefrin Hydrochloride, Dapsone, Sulfapyridine Sodium Salt, Mercapto-merin Sodium, Mercumatilin Sodium, Pergolid, Pramipexole , Dihydro-chloride, Amisulpride, Sulpiride, Cephaeline, Bromhexine, Ambroxol Hydrochloride, Carnitine, Cinitapride, Cisapride, Cortivazol, Enoxolone, Clomiphene, Pentoxifylline , Adrenalone, Carbazo-chrome , odium Sulfonate, Thioctic Acid, Timonacid, Pidotimod, Bucillamine, 6-Mercapto-purine, Brequinar, Retinoic Acid, Salicylic Acid, Docusate Calcium (Sodium), Picosolfate Sodium, Ibudilast, Zafirlukast, Choline Chloride, Methionine, Bismuth Sodium Triglycollam-ate, Chloroquine, Prinomastat, Carbachol, Neostigmine, Acetylcysteine, Bromhexine, Tetrazepam, Tizanidine, Tropicamide, Phenylephrine , Hydrochloride, Cyclazocine, Amiphenazole, Zanamivir, Succinyl-choline Bromide/ Chloride/, Iodide, Fazadinium Bromide, Omapatrilat, Riluzole, Repinotan, Indeloxazine Hydrochloride, Donepezil, Carboprost, Pinacidil, Nicorandil, Fampridine, Tedisamil, Cabergoline, Beraprost, Dimefline, Fominoben, 2-Hexyl-decanoic Acid, Sodium Tetradecyl Sulfate, Flurazepam, Etodroxizine, Hexafluor-enium , romide, Ritodrine, Terbutaline, p-Amino-benzoic Acid, Solisobenzone, Ticrynafen, Orotic Acid, Nafronyl, Nicametate, Perhexiline, Cloricromen, Ciclonicate, Cinepazide, Chromocarb, Dobesilate Calcium, Thiamine (Vit. B), Pyridoxine Hydrochloride (Vit. B_5), Oxaceprol, Acetylcysteine, Penicillamine, Allopurinol,

Further examples of pharmaceutical actives that are ionic or can be made ionic and combined with other ions to form the disclosed ionic liquid compositions are detailed below, along with their typically pharmaceutical use.

Adrenergic: adrenalone, amidephrine mesylate, apraclonidine hydrochloride,

brimonidine tartrate, dapiprazole hydrochloride, deterenol hydrochloride, dipivefrin, dopamine hydrochloride, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephryl borate, esproquin hydrochloride, etafedrine hydrochloride, hydroxyamphetamine hydrobromide, levonordefrin, mephentermine sulfate, metaraminol bitartrate, metizoline hydrochloride, naphazoline hydrochloride, norepinephrine bitartrate, oxidopamine, oxymetazoline hydrochloride, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, phenylpropanolamine polistirex, prenalterol hydrochloride, propylhexedrine, pseudoephedrine hydrochloride, tetrahydrozoline hydrochloride, tramazoline hydrochloride, xylometazoline hydrochloride.

Adrenocortical steroid: ciprocinonide, desoxycorticosterone acetate, desoxycorticosterone pivalate, dexamethasone acetate, fludrocortisone acetate, flumoxonide, hydrocortisone hemisuccinate, methylprednisolone hemisuccinate, naflocort, procinonide, timobesone acetate, tipredane.

Adrenocortical suppressant: aminoglutethimide, trilostane.

Alcohol deterrent: disulfiram.

Aldosterone antagonist: canrenoate potassium, canrenone, dicirenone, mexrenoate potassium, prorenoate potassium, spironolactone.

Amino acid: alanine, aspartic acid, cysteine hydrochloride, cystine, histidine, isoleucine, leucine, lysine, lysine acetate, lysine hydrochloride, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine.

Ammonia detoxicant: arginine: arginine glutamate, arginine hydrochloride.

Anabolic: bolandiol dipropionate, bolasterone, boldenone undecylenate, bolenol, bolnantalate, ethylestrenol, methenolone acetate, methenolone enanthate, mibolerone, nandrolone cyclotate, norbolethone, pizotyline, quinbolone, stenbolone acetate, tibolone, zeranol.

Analeptic: modafinil.

Analgesic: acetaminophen, alfentanil hydrochloride, aminobenzoate potassium, aminobenzoate sodium, anidoxime, anileridine, anileridine hydrochloride, anilopam hydrochloride, anirolac, antipyrine, aspirin, benoxaprofen, benzydamine hydrochloride, bicifadine hydrochloride, brifentanil hydrochloride, bromadoline maleate, bromfenac sodium, buprenorphine hydrochloride, butacetin, butixirate, butorphanol, butorphanol tartrate, carbamazepine, carbaspirin calcium, carbiphene hydrochloride, carfentanil citrate, ciprefadol succinate, ciramadol, ciramadol hydrochloride, clonixeril, clonixin, codeine, codeine phosphate, codeine sulfate, conorphone hydrochloride, cyclazocine, dexoxadrol

hydrochloride, dexpemedolac, dezocine, diflunisal, dihydrocodeine bitartrate, dimefadane, dipyrone, doxpicomine hydrochloride, drinidene, enadoline hydrochloride, epirizole, ergotamine tartrate, ethoxazene hydrochloride, etofenamate, eugenol, fenoprofen, fenoprofen calcium, fentanyl citrate, floctafenine, flufenisal, flunixin, flunixin meglumine, flupirtine maleate, fluproquazone, fluradoline hydrochloride, flurbiprofen, hydromorphone hydrochloride, ibufenac, indoprofen, ketazocine, ketorfanol, ketorolac tromethamine, letimide hydrochloride, levomethadyl acetate, levomethadyl acetate hydrochloride, levonantradol hydrochloride, levorphanol tartrate, lofemizole hydrochloride, lofentanil oxalate, lorcinadol, lomoxicam, magnesium salicylate, mefenamic acid, menabitan hydrochloride, meperidine hydrochloride, meptazinol hydrochloride, methadone hydrochloride, methadyl acetate, methopholine, methotrimeprazine, metkephamid acetate, mimbane hydrochloride, mirfentanil hydrochloride, molinazone, morphine sulfate, moxazocine, nabitan hydrochloride, nalbuphine hydrochloride, nalmexone hydrochloride, namoxyrate, nantradol hydrochloride, naproxen, naproxen sodium, naproxol, nefopam hydrochloride, nexeridine hydrochloride, noracymethadol hydrochloride, ocfentanil hydrochloride, octazamide, olvanil, oxetorone fumarate, oxycodone, oxycodone hydrochloride, oxycodone terephthalate, oxymorphone hydrochloride, pemedolac, pentamorphone, pentazocine, pentazocine hydrochloride, pentazocine lactate, phenazopyridine hydrochloride, phenyramidol hydrochloride, picenadol hydrochloride, pinadoline, pirfenidone, piroxicam olamine, pravadoline maleate, prodilidine hydrochloride, profadol hydrochloride, propiram fumarate, propoxyphene hydrochloride, propoxyphene napsylate, proxazole, proxazole citrate, proxorphan tartrate, pyrroliphene hydrochloride, remifentanil hydrochloride, salcolex, salethamide maleate, salicylamide, salicylate meglumine, salsalate, sodium salicylate, spiradoline mesylate, sufentanil, sufentanil citrate, talmetacin, talniflumate, talosalate, tazadolene succinate, tebufelone, tetrydamine, tifurac sodium, tilidine hydrochloride, tiopinac, tonazocine mesylate, tramadol hydrochloride, trefentanil hydrochloride, trolamine, veradoline hydrochloride, verilopam hydrochloride, volazocine, xorphanol mesylate, xylazine hydrochloride, zenazocine mesylate, zomepirac sodium, zucapsaicin.

Androgen: fluoxymesterone, mesterolone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, nisterime acetate, oxandrolone, oxymetholone, silandrone, stanozolol, testosterone, testosterone cypionate, testosterone enanthate, testosterone ketolaurate, testosterone phenylacetate, testosterone propionate, trestolone acetate.

Anesthesia, adjunct to: sodium oxybate.

Anesthetic: aliflurane, benoxinate hydrochloride, benzocaine, biphenamine hydrochloride, bupivacaine hydrochloride, butamben, butamben picrate, chloroprocaine hydrochloride, cocaine, cocaine hydrochloride, cyclopropane, desflurane, dexivacaine, diamocaine cyclamate, dibucaine, dibucaine hydrochloride, dyclonine hydrochloride, enflurane, ether, ethyl chloride, etidocaine, etoxadrol hydrochloride, euprocin hydrochloride, fluroxene, halothane, isobutamben, isoflurane, ketamine hydrochloride, levoxadrol hydrochloride, lidocaine, lidocaine hydrochloride, mepivacaine hydrochloride, methohexital sodium, methoxyflurane, midazolam hydrochloride, midazolam maleate, minaxolone, nitrous oxide, norflurane, octodrine, oxethazaine, phencyclidine hydrochloride, pramoxine hydrochloride, prilocaine hydrochloride, procaine hydrochloride, propanidid, proparacaine hydrochloride, propofol, propoxycaine hydrochloride, pyrrocaine, risocaine, rodocaine, roflurane, salicyl alcohol, sevoflurane, teflurane, tetracaine, tetracaine hydrochloride, thiamylal, thiamylal sodium, thiopental sodium, tiletamine hydrochloride, zolamine hydrochloride.

Anorectic compounds including dexfenfluramine.

Anorexic: aminorex, amphecloral, chlorphentermine hydrochloride, clominorex, clortermine hydrochloride, diethylpropion hydrochloride, fenfluramine hydrochloride, fenisorex, fludorex, fluminorex, levamfetamine succinate, mazindol, mefenorex hydrochloride, phenmetrazine hydrochloride, phentermine, sibutramine hydrochloride.

Antagonist: atipamezole, atosiban, bosentan, cimetidine, cimetidine hydrochloride, clentiazem maleate, detirelix acetate, devazepide, donetidine, etintidine hydrochloride, famotidine, fenmetozole hydrochloride, flumazenil, icatibant acetate, icotidine, isradipine, metiamide, nadide, nalmefene, nalmexone hydrochloride, naloxone hydrochloride, naltrexone, nilvadipine, oxilorphan, oxmetidine hydrochloride, oxmetidine mesylate, quadazocine mesylate, ranitidine, ranitidine bismuth citrate, ranitidine hydrochloride, sufotidine, teludipine hydrochloride, tiapamil hydrochloride, tiotidine, vapiprost hydrochloride, zaltidine hydrochloride.

Anterior pituitary activator: epimestrol.

Anterior pituitary suppressant: danazol.

Anthelmintic: albendazole, anthelmycin, bromoxanide, bunamidine hydrochloride, butonate, cambendazole, carbantel lauryl sulfate, clioxanide, closantel, cyclobendazole, dichlorvos, diethylcarbamazine citrate, dribendazole, dymanthine hydrochloride, etibendazole, fenbendazole, furodazole, hexylresorcinol, mebendazole, morantel tartrate, niclosamide, nitramisole hydrochloride, nitrodan, oxantel pamoate, oxfendazole,

oxibendazole, parbendazole, piperamide maleate, piperazine, piperazine citrate, piperazine edetate calcium, proclonol, pyrantel pamoate, pyrantel tartrate, pyrvinium pamoate, rafoxanide, stilbazium iodide, tetramisole hydrochloride, thiabendazole, ticarbodine, tioxidazole, triclofenol piperazine, vincofos, zilantel.

Anti-acne: adapalene, erythromycin salnacedin, inocoterone acetate, accutane.

Anti-adrenergic: acebutolol, alprenolol hydrochloride, atenolol, bretylium tosylate, bunolol hydrochloride, carteolol hydrochloride, celiprolol hydrochloride, cetamolol hydrochloride, cicloprolol hydrochloride, dexpropranolol hydrochloride, diacetolol hydrochloride, dihydroergotamine mesylate, dilevalol hydrochloride, esmolol hydrochloride, exaprolol hydrochloride, fenspiride hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxolol hydrochloride, levobunolol hydrochloride, metalol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pamatolol sulfate, penbutolol sulfate, phentolamine mesylate, practolol, propranolol hydrochloride, proroxan hydrochloride, solypertine taitrate, sotalol hydrochloride, timolol, timolol maleate, tiprenolol hydrochloride, tolamolol, zolertine hydrochloride.

Anti-allergic: amlexanox, astemizole, azelastine hydrochloride, eclazolast, minocromil, nedocromil, nedocromil calcium, nedocromil sodium, nivimedone sodium, pemirolast potassium, pentigetide, pirquinozol, poisonoak extract, probicromil calcium, proxicromil, repirinast, tetrazolast meglumine, thiazinamium chloride, tiacrilast, tiacrilast sodium, tiprinast meglumine, tixanox.

Anti-amebic: berythromycin, bialamicol hydrochloride, chloroquine, chloroquine hydrochloride, chloroquine phosphate, clamoxyquin hydrochloride, clioquinol, emetine hydrochloride, iodoquinol, paromomycin sulfate, quinfamide, symetine hydrochloride, teclozan, tetracycline, tetracycline hydrochloride.

anti-androgen: benorterone, cioteronel, cyproterone acetate, delmadinone acetate, oxendolone, topterone, zanoterone.

Anti-anemic: epoetin alfa, epoetin beta, ferrous sulfate, dried, leucovorin calcium.

Anti-anginal: amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochloride, tosifen, verapamil hydrochloride.

Anti-anxiety agent: adatanserin hydrochloride, alpidem, binospirone mesylate, bretazenil, glemanserin, ipsapirone hydrochloride, mirisetron maleate, ocinaplon, ondansetron hydrochloride, panadiplon, pancopride, pazinaclone, serazapine hydrochloride,

tandospirone citrate, zalospirone hydrochloride.

Anti-arthritic: lodelaben.

Anti-asthmatic: ablukast, ablukast sodium, azelastine hydrochloride, bunaprolast, cinalukast, crornitrile sodium, cromolyn sodium, enofelast, isamoxole, ketotifen fumarate, levcromakalim, lodoxamide ethyl, lodoxamide tromethamine, montelukast sodium, ontazolast, oxarbazole, oxatomide, piriprost, piriprost potassium, pirolate, pobilukast edamine, quazolast, repirinast, ritolukast, sulukast, tetrazolast meglumine, tiaramide hydrochloride, tibenelast sodium, tomelukast, tranilast, verlukast, verofylline, zarirlukast.

Anti-atherosclerotic: mifobate, timefuronc.

Anticholelithic: monoctanoin.

Anticholelithogenic: chenodiol, ursodiol.

Anticholinergic: alverinc citrate, anisotropine methylbromide, atropine, atropine oxide hydrochloride, atropine sulfate, belladonna, benapryzine hydrochloride, benzetimide hydrochloride, benzilonium bromide, biperiden, biperiden hydrochloride, biperiden lactate, clidinium bromide, cyclopentolate hydrochloride, dexetimide, dicyclomine hydrochloride, dihexyverine hydrochloride, domazoline fumarate, elantrine, elucaine, ethybenztropine, eucatropine hydrochloride, glycopyrrolate, heteronium bromide, homatropine hydrobromide, homatropine methylbromide, hyoscyamine, hyoscyamine hydrobromide, hyoscyamine sulfate, isopropamide iodide, mepenzolate bromide, methylatropine nitrate, metoquizine, oxybutynin chloride, parapenzolate bromide, pentapiperium methylsulfate, phencarbamide, poldine methylsulfate, proglumide, propantheline bromide, propenzolate hydrochloride, scopolamine hydrobromide, tematropium methylsulfate, tiquinamide hydrochloride, tofenacin hydrochloride, toquizine, triampyzine sulfate, trihexyphenidyl hydrochloride, tropicamide.

Anticoagulant: ancrod, anticoagulant citrate dextrose solution, anticoagulant citrate phosphate dextrose adenine solution, anticoagulant citrate phosphate dextrose solution, anticoagulant heparin solution, anticoagulant sodium citrate solution, ardeparin sodium, bivalirudin, bromindione, dalteparin sodium, desirudin, dicumnarol, heparin calcium, heparin sodium, lyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium, warfarin sodium.

Anticoccidal: maduramicin.

Anticonvulsant: albutoin, ameltolide, atolide, buramate, carbamazepine, cinromide, citenamide, clonazepam, cyheptamide, dezinamide, dimethadione, divalproex sodium, eterobarb, ethosuximide, ethotoin, flurazepam hydrochloride, fluzinamide, fosphenytoin

sodium, gabapentin, ilepcimide, lamotrigine, magnesium sulfate, mephenytoin, mephobarbital, methetoin, methsuximide, milacemide hydrochloride, nabazenil, nafimidone hydrochloride, nitrazepam, phenacemide, phenobarbital, phenobarbital sodium, phensuximide, phenytoin, phenytoin sodium, primidone, progabide, ralitoline, remacemide hydrochloride, ropizine, sabeluzole, stiripentol, sulthiame, thiopental sodium, tiletamine hydrochloride, topiramate, trimethadione, valproate sodium, valproic acid, vigabatrin, zoniclezole hydrochloride, zonisamide.

Antidepressant: adatanserin hydrochloride, adinazolam, adinazolam mesylate, alaproclate, aletamine hydrochloride, amedalin hydrochloride, amitriptyline hydrochloride, amoxapine, aptazapine maleate, azaloxan fumarate, azepindole, azipramine hydrochloride, bipenamol hydrochloride, bupropion hydrochloride, butacetin, butriptyline hydrochloride, caroxazone, cartazolate, ciclazindol, cidoxepin hydrochloride, cilobamine mesylate, clodazon hydrochloride, clomipramine hydrochloride, cotinine fumarate, cyclindole, cypenamine hydrochloride, cyprolidol hydrochloride, cyproximide, daledalin tosylate, dapoxetine hydrochloride, dazadrol maleate, dazepinil hydrochloride, desipramine hydrochloride, dexamisole, deximafen, dibenzepin hydrochloride, dioxadrol hydrochloride, dothiepin hydrochloride, doxepin hydrochloride, duloxetine hydrochloride, eclanamine maleate, encyprate, etoperidone hydrochloride, fantridone hydrochloride, fehmetozole hydrochloride, fenmetramide, fezolamine fumarate, fluotracen hydrochloride, fluoxetine, fluoxetine hydrochloride, fluparoxan hydrochloride, gamfexine, guanoxyfen sulfate, imafen hydrochloride, imiloxan hydrochloride, imipramine hydrochloride, indeloxazine hydrochloride, intriptyline hydrochloride, iprindole, isocarboxazid, ketipramine fumarate, lofepramine hydrochloride, lortalamine, maprotiline, maprotiline hydrochloride, melitracen hydrochloride, milacemide hydrochloride, minaprine hydrochloride, mirtazapine, moclobemide, modaline sulfate, napactadine hydrochloride, napamezole hydrochloride, nefazodone hydrochloride, nisoxetine, nitrafudam hydrochloride, nomifensine maleate, nortriptyline hydrochloride, octriptyline phosphate, opipramol hydrochloride, oxaprotiline hydrochloride, oxypertine, paroxetine, phenelzine sulfate, pirandamine hydrochloride, pizotyline, pridefine hydrochloride, prolintane hydrochloride, protriptyline hydrochloride, quipazine maleate, rolicyprine, seproxetine hydrochloride, sertraline hydrochloride, sibutramine hydrochloride, sulpiride, suritozole, tametraline hydrochloride, tampramine fumarate, tandamine hydrochloride, thiazesim hydrochloride, thozalinone, tomoxetine hydrochloride, trazodone hydrochloride, trebenzomine hydrochloride, trimipramine, trimipramine maleate, venlafaxine hydrochloride, viloxazine hydrochloride, zimeldine

hydrochloride, zometapine.

Antidiabetic: acetohexamide, buformin, butoxamine hydrochloride, camiglibose, chlorpropamide, ciglitazone, englitazone sodium, etoformin hydrochloride, gliamilide, glibornuride, glicetanile sodium, gliflumide, glipizide, glucagon, glyburide, glyhexamide, glymidine sodium, glyoctamide, glyparamide, insulin, insulin, dalanated, insulin human, insulin human, isophane, insulin human zinc, insulin human zinc, extended, insulin, isophane, insulin lispro, insulin, neutral, insulin zinc, insulin zinc, extended, insulin zinc, prompt, linogliride, linogliride fumarate, metformin, methyl palmoxirate, palmoxirate sodium, pioglitazone hydrochloride, pirogliride tartrate, proinsulin human, seglitide acetate, tolazamide, tolbutamide, tolpyrramide, troglitazone, zopolrestat, and sitagliptin.

Antidiarrheal: rolgamidine, diphenoxylate hydrochloride (lomotil), metronidazole (flagyl), methylprednisolone (medrol), sulfasalazine (azulfidine).

Antidiuretic: argipressin tannate, desmopressin acetate, lypressin.

Antidote: dimercaprol, edrophonium chloride, fomepizole, leucovorin calcium, levoleucovorin calcium, methylene blue, protamine sulfate.

Antidyskinetic: selegiline hydrochloride.

Anti-emetic: alosetron hydrochloride, batanopride hydrochloride, bemesetron, benzquinamide, chlorpromazine, chlorpromazine hydrochloride, clebopride, cyclizine hydrochloride, dimenhydrinate, diphenidol, diphenidol hydrochloride, diphenidol pamoate, dolasetron mesylate, domperidone, dronabinol, fludorex, flumeridone, galdansetron hydrochloride, granisetron, granisetron hydrochloride, lurosetron mesylate, meclizine hydrochloride, metoclopramide hydrochloride, metopimazine, ondansetron hydrochloride, pancopride, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, thiethylperazine, thiethylperazine malate, thiethylperazine maleate, trimethobenzamide hydrochloride, zacopride hydrochloride.

Anti-epileptic: felbamate, loreclezole, tolgabide.

Anti-estrogen: clometherone, delmadinone acetate, nafoxidine hydrochloride, nitromifene citrate, raloxifene hydrochloride, tamoxifen citrate, toremifene citrate, trioxifene mesylate.

Antifibrinolytic: nafamostat mesylate.

Antifungal: acrisorcin, ambruticin, amphotericin b, azaconazole, azaserine, basifungin, bifonazole, biphenamine hydrochloride, bispyrithione magsulfex, butoconazole nitrate, calcium undecylenate, candicidin, carbol-fuchsin, chlordantoin, ciclopirox, ciclopirox olamine, cilofungin, cisconazole, clotrimazole, cuprimyxin, denofungin, dipyrithione,

doconazole, econazole, econazole nitrate, enilconazole, ethonam nitrate, fenticonazole nitrate, filipin, fluconazole, flucytosine, fungimycin, griseofulvin, hamycin, isoconazole, itraconazole, kalafungin, ketoconazole, lomofimgin, lydimycin, mepartricin, miconazole, miconazole nitrate, monensin, monensin sodium, naftifine hydrochloride, neomycin undecylenate, nifuratel, nifurmerone, nitralamine hydrochloride, nystatin, octanoic acid, orconazole nitrate, oxiconazole nitrate, oxifungin hydrochloride, parconazole hydrochloride, partricin, potassium iodide, proclonol, pyrithione zinc, pyrrolnitrin, rutamycin, sanguinarium chloride, saperconazole, scopafungin, selenium sulfide, sinefungin, sulconazole nitrate, terbinafine, terconazole, thiram, ticlatone, tioconazole, tolciclate, tolindate, tolnaftate, triacetin, triafungin, undecylenic acid, viridofulvin, zinc undecylenate, zinoconazole hydrochloride. One specific antifungal that is suitable is itraconazole.

Antiglaucoma agent: alprenoxime hydrochloride, colforsin, dapiprazole hydrochloride, dipivefrin hydrochloride, naboctate hydrochloride, pilocarpine, pimabine.

Antihemophilic: antihemophilic factor.

Antihemorrhagic: poliglusam.

Antihistaminic: acrivastine, antazoline phosphate, astemizole, azatadine maleate, barmastine, bromodiphenhydramine hydrochloride, brompheniramnine maleate, carbinoxamine maleate, cetirizine hydrochloride, chlorpheniramine maleate, chlorpheniramine polistirex, cinnarizine, clemastine, clemastine fumarate, closiramine aceturate, cycliramine maleate, cyclizine, cyproheptadine hydrochloride, dexbrompheniramnine maleate, dexchlorpheniramine maleate, dimethindene maleate, diphenhydramine citrate, diphenhydramnine hydrochloride, dorastine hydrochloride, doxylamine succinate, ebastine, levocabastine hydrochloride, loratadine, mianserin hydrochloride, noberastine, orphenadrine citrate, pyrabrom, pyrilamine maleate, pyroxamnine maleate, rocastine hydrochloride, rotoxamine, tazifylline hydrochloride, temelastine, terfenadine, tripelennamine citrate, tripelennamine hydrochloride, triprolidine hydrochloride, zolamine hydrochloride.

Antihyperlipidemic: cholestyramine resin, clofibrate, colestipol hydrochloride, crilvastatin, dalvastatin, dextrothyroxine sodium, fluvastatin sodium, gemfibrozil, lecimibide, lovastatin, niacin, pravastatin sodium, probucol, simvastatin, tiqueside, xenbucin.

Antihyperlipoproteinemic: acifran, beloxamide, bezafibrate, boxidine, butoxamine hydrochloride, cetaben sodium, ciprofibrate, gemcadiol, halofenate, lifibrate, meglutol, nafenopin, pimetine hydrochloride, theofibrate, tibric acid, treloxinate.

Antihypertensive: alfuzosin hydrochloride, alipamide, althiazide, amiquinsin

hydrochloride, amlodipine besylate, amlodipine maleate, anaritide acetate, atiprosin maleate, belfosdil, bemitradine, bendacalol mesylate, bendroflumethiazide, benzthiazide, betaxolol hydrochloride, bethanidine sulfate, bevantolol hydrochloride, biclodil hydrochloride, bisoprolol, bisoprolol fumarate, bucindolol hydrochloride, bupicomide, buthiazide: candoxatril, candoxatrilat, captopril, carvedilol, ceronapril, chlorothiazide sodium, cicletanine, cilazapril, clonidine, clonidine hydrochloride, clopamide, cyclopenthiazide, cyclothiazide, darodipine, debrisoquin sulfate, delapril hydrochloride, diapamide, diazoxide, dilevalol hydrochloride, diltiazem malate, ditekiren, doxazosin mesylate, ecadotril, enalapril maleate, enalaprilat, enalkiren, endralazine mesylate, epithiazide, eprosartan, eprosartan mesylate, fenoldopam mesylate, flavodilol maleate, flordipine, flosequinan, fosinopril sodium, fosinoprilat, guanabenz, guanabenz acetate, guanacline sulfate, guanadrel sulfate, guancydine, guanethidine monosulfate, guanethidine sulfate, guanfacine hydrochloride, guanisoquin sulfate, guanoclor sulfate, guanoctine hydrochloride, guanoxabenz, guanoxan sulfate, guanoxyfen sulfate, hydralazine hydrochloride, hydralazine polistirex, hydroflumethiazide, indacrinone, indapamide, indolaprif hydrochloride, indoramin, indoramin hydrochloride, indorenate hydrochloride, lacidipine, leniquinsin, levcromakalim, lisinopril, lofexidine hydrochloride, losartan potassium, losulazine hydrochloride, mebutamate, mecamylamine hydrochloride, medroxalol, medroxalol hydrochloride, methalthiazide, methyclothiazide, methyldopa, methyldopate hydrochloride, metipranolol, metolazone, metoprolol fumarate, metoprolol succinate, metyrosine, minoxidil , monatepil maleate, muzolimine, nebivolol, nitrendipine, ofornine, pargyline hydrochloride, pazoxide, pelanserin hydrochloride, perindopril erbumine, phenoxybenzamine hydrochloride, pinacidil, pivopril, polythiazide, prazosin hydrochloride, primidolol, prizidilol hydrochloride, quinapril hydrochloride, quinaprilat, quinazosin hydrochloride, quinelorane hydrochloride, quinpirole hydrochloride, quinuclium bromide, ramipril, rauwolfia serpentina, reserpine, saprisartan potassium, saralasin acetate, sodium nitroprusside, sulfinalol hydrochloride, tasosartan, teludipine hydrochloride, temocapril hydrochloride, terazosin hydrochloride, terlakiren, tiamenidine, tiamenidine hydrochloride, ticrynafen, tinabinol, tiodazosin, tipentosin hydrochloride, trichlormethiazide, trimazosin hydrochloride, trimethaphan camsylate, trimoxamine hydrochloride, tripamide, xipamide, zankiren hydrochloride, zofenoprilat arginine.

Antihypotensive: ciclafrine hydrochloride, midodrine hydrochloride.

Anti-infective: difloxacin hydrochloride, lauryl isoquinolinium bromide, moxalactam disodium, ornidazole, pentisomicin, sarafloxacin hydrochloride, protease inhibitors of hiv and

other retroviruses, integrase inhibitors of hiv and other retroviruses, cefaclor (CECLOR™), acyclovir (ZOVIRAX™), norfloxacin (NOROXIN™), cefoxitin (MEFOXIN™), cefuroxime axetil (CEFTIN™), ciprofloxacin (CIPRO™).

Anti-infective, topical: alcohol, aminacrine hydrochloride, benzethonium chloride: bithionolate sodium, bromchlorenone, carbamide peroxide, cetalkonium chloride, cetylpyridinium chloride: chlorhexidine hydrochloride, clioquinol,. domiphen bromide, fenticlor, fludazonium chloride, fuchsin, basic, furazolidone, gentian violet, halquinols, hexachlorophene: hydrogen peroxide, ichthammol, imidecyl iodine, iodine, isopropyl alcohol, mafenide acetate, meralein sodium, mercufenol chloride, mercury, ammoniated, methylbenzethonium chloride, nitrofurazone, nitromersol, octenidine hydrochloride, oxychlorosene, oxychlorosene sodium, parachlorophenol, camphorated, potassium permanganate, povidone-iodine, sepazonium chloride, silver nitrate, sulfadiazine, silver, symclosene, thimerfonate sodium, thimerosal: troclosene potassium.

Anti-inflammatory: acetominophen, alclofenac, alclometasone dipropionate, algestone acetonide, alpha amylase, amcinafal, amcinafide, amfenac sodium, amiprilose hydrochloride, anakinra, anirolac, anitrazafen, apazone, balsalazide disodium, bendazac, benoxaprofen, benzydamine hydrochloride, bromelains, broperamole, budesonide, carprofen, cicloprofen, cintazone, cliprofen, clobetasol propionate, clobetasone butyrate, clopirac, cloticasone propionate, cormethasone acetate, cortodoxone, deflazacort, desonide, desoximetasone, dexamethasone dipropionate, diclofenac potassium, diclofenac sodium, diflorasone diacetate, diflumidone sodium, diflunisal, difluprednate, diftalone, dimethyl sulfoxide, drocinonide, endrysone, enlimomab, enolicam sodium, epirizole, etodolac, etofenamate, felbinac, fenamole, fenbufen, fenclofenac, fenclorac, fendosal, fenpipalone, fentiazac, flazalone, fluazacort, flufenamic acid, flumizole, flunisolide acetate, flunixin, flunixin meglumine, fluocortin butyl, fluorometholone acetate, fluquazone, flurbiprofen, fluretofen, fluticasone propionate, furaprofen, furobufen, halcinonide, halobetasol propionate, halopredone acetate, ibufenac, ibuprofen, ibuprofen aluminum, ibuprofen piconol, ilonidap, indomethacin, indomethacin sodium, indoprofen, indoxole, intrazole, isoflupredone acetate, isoxepac, isoxicam, ketoprofen, lofemizole hydrochloride, lornoxicam, loteprednol etabonate, meclofenamate sodium, meclofenamic acid, meclorisone dibutyrate, mefenamic acid, mesalamine, meseclazone, methylprednisolone suleptanate, momiflumate, nabumetone, naproxen, naproxen sodium, naproxol, nimazone, olsalazine sodium, orgotein, orpanoxin, oxaprozin, oxyphenbutazone, paranyline hydrochloride, pentosan polysulfate sodium, phenbutazone sodium glycerate, pirfenidone, piroxicam, piroxicam cinnamate, piroxicam

olamine, pirprofen, prednazate, prifelone, prodolic acid, proquazone, proxazole, proxazole citrate, rimexolone, romazarit, salcolex, salnacedin, salsalate, sanguinarium chloride, seclazone, sermetacin, sudoxicam, sulindac, suprofen, talmetacin, talniflumate, talosalate, tebufelone, tenidap, tenidap sodium, tenoxicam, tesicam, tesimide, tetrydamine, tiopinac, tixocortol pivalate, tolmetin, tolmetin sodium, triclonide, triflumidate, zidometacin, zomepirac sodium.

Antikeratinizing agent: doretinel, linarotene, pelretin.

Antimalarial: acedapsone, amodiaquine hydrochloride, amquinate, arteflene, chloroquine, chloroquine hydrochloride, chloroquine phosphate, cycloguanil pamoate, enpiroline phosphate, halofantrine hydrochloride, hydroxychloroquine sulfate, mefloquine hydrochloride, menoctone, mirincamycin hydrochloride, primaquine phosphate, pyrimethamine, quinine sulfate, tebuquine.

Antimicrobial: aztreonam, chlorhexidine gluconate, imidurea, lycetamine, nibroxane, pirazmonam sodium, propionic acid, pyrithione sodium, sanguinarium chloride, tigemonam dicholine.

Antimigraine: dolasetron mesylate, naratriptan hydrochloride, sergolexole maleate, sumatriptan succinate, zatosetron maleate.

Antimitotic: podofilox.

Antimycotic: amorolfine.

Antinauseant: buclizine hydrochloride, cyclizine lactate, naboctate hydrochloride.

Antineoplastic: acivicin, aclarubicin, acodazole hydrochloride, acrqnine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, edatrexate, eflomithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, ethiodized oil I 131, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine,

fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine hydrochloride, gold au 198, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofosine, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-N3, interferon beta-Ia, interferon gamma- Ib, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedepa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprine, rogletimide, safmgol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, strontium chloride sr 89, sulofenur, talisomycin, taxane, taxoid, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, topotecan hydrochloride, toremifene citrate, trestolone acetate, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3, 5-ethynyluracil, abiraterone, aclarubicin, acylfulvene, adecypenol, adozelesin, aldesleukin, ALL-TK antagonists, altretamine, ambamustine, amidox, amifostine, aminolevulinic acid, amrubicin, atrsacrine, anagrelide, anastrozole, andrographolide, angiogenesis inhibitors, antagonist D, antagonist G, antarelix, anti-dorsalizing morphogenetic protein-1, antiandrogen, prostatic carcinoma, antiestrogen, antineoplaston, antisense oligonucleotides, aphidicolin glycinate, apoptosis gene modulators, apoptosis regulators, apurinic acid, ara-CDP-DL-PTBA, arginine deaminase, asulacrine, atamestane, atrimustine, axinastatin 1, axinastatin 2, axinastatin 3, azasetron, azatoxin, azatyrosine, baccatin III derivatives, balanol, batimastat, BCR/ABL antagonists, benzochlorins, benzoylstaurosporine, beta lactam derivatives, beta-

alethine, betaclamycin B, betulinic acid, bFGF inhibitor, bicalutamide, bisantrene, bisaziridinylspermine, bisnafide, bistratene A, bizelesin, breflate, bropirimine, budotitane, buthionine sulfoximine, calcipotriol, calphostin C, camptothecin derivatives, canarypox IL-2, capecitabine, carboxamide-amino-triazole, carboxyamidotriazole, CaRest M3, CARN 700, cartilage derived inhibitor, carzelesin, casein kinase inhibitors (ICOS), castanospermine, cecropin B, cetrorelix, chlorins, chloroquinoxaline sulfonamide, cicaprost, cis-porphyrin, cladribine, clomifene analogues, clotrimazole, collismycin A, collismycin B, combretastatin A4, combretastatin analogue, conagenin, crambescidin 816, crisnatol, cryptophycin 8, cryptophycin A derivatives, curacin A, cyclopentanthraquinones, cycloplatam, cypemycin, cytarabine ocfosfate, cytolytic factor, cytostatin, dacliximab, decitabine, dehydrodidemnin B, deslorelin, dexifosfamide, dexrazoxane, dexverapamil, diaziquone, didemnin B, didox, diethylnorspermine, dihydro-5-azacytidine, dihydrotaxol, 9-dioxamycin, diphenyl spiromustine, docosanol, dolasetron, doxifluridine, droloxifene, dronabinol, duocannycin SA, ebselen, ecomustine, edelfosine, edrecolomab, eflornithine, elemene, emitefur, epirubicin, epristeride, estramustine analogue, estrogen agonists, estrogen antagonists, etanidazole, etoposide phosphate, exemestane, fadrozole, fazarabine, fenretinide, filgrastim, fmasteride, flavopiridol, flezelastine, fluasterone, fludarabine, fluorodaunorunicin hydrochloride, forfenimex, formestane, fostriecin, fotemustine, gadolinium texaphyrin, gallium nitrate, galocitabine, ganirelix, gelatinase inhibitors, gemcitabine, glutathione inhibitors, hepsulfam, heregulin, hexamethylene bisacetamide, hypericin, ibandronic acid, idarubicin, idoxifene, idramantone, ilmofosine, ilomastat, imidazoacridones, imiquimod, immunostimulant peptides, insulin-like growth factor-1 receptor inhibitor, interferon agonists, interferons, interleukins, iobenguane, iododoxorubicin, ipomeanol, 4-irinotecan, iroplact, irsogladine, isobengazole, isohomohalicondrin B, itasetron, jasplakinolide, kahalalide F, lamellarin-N triacetate, lanreotide, leinamycin, lenograstim, lentinan sulfate, leptolstatin, letrozole, leukemia inhibiting factor, leukocyte alpha interferon, leuprolide+estrogen+progesterone, leuprorelin, levamisole, liarozole, linear polyamine analogue, lipophilic disaccharide peptide, lipophilic platinum compounds, lissoclinamide 7, lobaplatin, lombricine, lometrexol, lonidamine, losoxantrone, lovastatin, loxoribine, lurtotecan, lutetium texaphyrin, lysofylline, lytic peptides, maitansine, mannostatin A, marimastat, masoprocol, maspin, matrilysin inhibitors, matrix metalloproteinase inhibitors, menogaril, merbarone, meterelin, methioninase, metoclopramide, MIF inhibitor, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitomycin analogues, mitonafide, mitotoxin fibroblast growth factor-saporin, mitoxantrone, mofarotene,

molgramostim, monoclonal antibody, human chorionic gonadotrophin, monophosphoryl lipid A +myobacterium cell wall sk, mopidamol, multiple drug resistance genie inhibitor, multiple tumor suppressor 1-based therapy, mustard anticancer agent, mycaperoxide B, mycobacterial cell wall extract, myriaporone, N-acetyldinaline, N-substituted benzamides, nafarelin, nagrestip, naloxone +pentazocine, napavin, naphterpin, nartograstim, nedaplatin, nemorubicin, neridronic acid, neutral endopeptidase, nilutamide, nisamycin, nitric oxide modulators, nitroxide antioxidant, nitrullyn, O6-benzylguanine, octreotide, okicenone, oligonucleotides, onapristone, ondansetron, ondansetron, oracin, oral cytokine inducer, ormaplatin, osaterone, oxaliplatin, oxaunomycin, paclitaxel analogues, paclitaxel derivatives, palauamine, palmitoylrhizoxin, pamidronic acid, panaxytriol, panomifene, parabactin, pazelliptine, pegaspargase, peldesine, pentosan polysulfate sodium, pentostatin, pentrozole, perflubron, perfosfamide, perillyl alcohol, phenazinomycin, phenylacetate, phosphatase inhibitors, picibanil, pilocarpine hydrochloride, pirarubicin, piritrexim, placetin A, placetin B, plasminogen activator inhibitor, platinum complex, platinum compounds, platinum-triamine complex, porfimer sodium, porfiromycin, propyl bis-acridone, prostaglandin J2, proteasome inhibitors, protein A-based immune modulator, protein kinase C inhibitor, protein kinase C inhibitors, microalgal, protein tyrosine phosphatase inhibitors, purine nucleoside phosphorylase inhibitors, purpurins, pyrazoloacridine, pyridoxylated hemoglobin polyoxyethylene conjugate, raf antagonists, raltitrexed, ramosetron, ras farnesyl protein transferase inhibitors, ras inhibitors, ras-GAP inhibitor, retelliptine demethylated, rhenium Re 186 etidronate, rhizoxin, ribozymes, RII retinamide, rogletimide, rohitukine, romurtide, roquinimex, rubiginone B1, ruboxyl, safingol, saintopin, SarCNU, sarcophytol A, sargramostim, Sdi 1 mimetics, semustine, senescence derived inhibitor 1, sense oligonucleotides, signal transduction inhibitors, signal transduction modulators, single chain antigen binding protein, sizofiran, sobuzoxane, sodium borocaptate, sodium phenylacetate, solverol, somatomedin binding protein, sonermin, sparfosic acid, spicamycin D, spiromustine, splenopentin, spongistatin 1, squalamine, stem cell inhibitor, stem-cell division inhibitors, stipiamide, stromelysin inhibitors, sulfmosine, superactive vasoactive intestinal peptide antagonist, suradista, suramin, swainsonine, synthetic glycosaminoglycans, tallimustine, tamoxifen methiodide, tauromustine, tazarotene, tecogalan sodium, tegafur, tellurapyrylium, telomerase inhibitors, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, tetrazomine, thaliblastine, thalidomide, thiocoraline, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrinan, thyroid stimulating hormone, tin ethyl etiopurpurin, tirapazamine, titanocene dichloride, topotecan,

topsentin, toremifene, totipotent stem cell factor, translation inhibitors, tretinoin, triacetyluridine, triciribine, trimetrexate, triptorelin, tropisetron, turosteride, tyrosine kinase inhibitors, tyrphostins, UBC inhibitors, ubenimex, urogenital sinus-derived growth inhibitory factor, urokinase receptor antagonists, vapreotide, variolin B, vector system, erythrocyte gene therapy, velaresol, veramine, verdins, verteporfin, vinorelbine, vinxaltine, vitaxin, vorozole, zanoterone, zeniplatin, zilascorb, zinostatin stimalamer.

Anti-cancer supplementary potentiating agents: tricyclic anti-depressant drugs (*e.g.*, imipramine, desipramine, amitryptyline, clomiprainine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline), non-tricyclic anti-depressant drugs (*e.g.*, sertraline, trazodone and citalopram), Ca^{++} antagonists (*e.g.*, verapamil, nifedipine, nitrendipine and caroverine), calmodulin inhibitors (*e.g.*, prenylamine, trifluoroperazine and clomipramine), amphotericin B, triparanol analogues (*e.g.*, tamoxifen), antiarrhythmic drugs (*e.g.*, quinidine), antihypertensive drugs (*e.g.*, reserpine), thiol depleters (*e.g.*, buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL.

Antineutropenic: filgrastim, lenograstim, molgramostim, regramostim, sargramostim.

Antiobsessional agent: fluvoxamine maleate.

Antiparasitic: abamectin, clorsulon, ivermectin.

Antiparkinsonian: benztropine mesylate, biperiden, biperiden hydrochloride, biperiden lactate, carmantadine, ciladopa hydrochloride, dopamantine, ethopropazine hydrochloride, lazabemide, levodopa, lometraline hydrochloride, mofegiline hydrochloride, naxagolide hydrochloride, pareptide sulfate, procyclidine hydrochloride, quinetorane hydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. antiperistaltic: difenoximide hydrochloride, difenoxin, diphenoxylate hydrochloride, fluperamide, lidamidine hydrochloride, loperamide hydrochloride, malethamer, nufenoxole, paregoric.

Antipneumocystic: atovaquone.

Antiproliferative agent: piritrexim isethionate.

Antiprostatic hypertrophy: sitogluside.

Antiprotozoal: amodiaquine, azanidazole, bamnidazole, carnidazole, chlortetracycline bisulfate, chlortetracycline hydrochloride, flubendazole, flunidazole, halofuginone hydrobromide, imidocarb hydrochloride, ipronidazole, metronidazole, misonidazole, moxnidazole, nitarsone, partricin, puromycin, puromycin hydrochloride, ronidazole, sulnidazole, tinidazole.

Antipruritic: cyproheptadine hydrochloride, methdilazine, methdilazine

hydrochloride, trimeprazine tartrate.

Antipsoriatic: acitretin, anthralin, azaribine, calcipotriene, cycloheximide, enazadrem phosphate, etretinate, liarozole fumarate, lonapalene, tepoxalin.

Antipsychotic: acetophenazine maleate, alentemol hydrobromide, alpertine, azaperone, batelapine maleate, benperidol, benzindopyrine hydrochloride, brofbxine, bromperidol, bromperidol decanoate, butaclamol hydrochloride, butaperazine, butaperazine maleate, carphenazine maleate, carvotroline hydrochloride, chlorpromazine, chlorpromazine hydrochloride, chlorprothixene, cinperene, cintriamide, clomacran phosphate, clopenthixol, clopimozide, clopipazan mesylate, cloroperone hydrochloride, clothiapine, clothixamide maleate, clozapine, cyclophenazine hydrochloride, droperidol, etazolate hydrochloride, fenimide, flucindole, flumezapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, fluspiperone, fluspirilene, flutroline, gevotroline hydrochloride, halopemide, haloperidol, haloperidol decanoate, iloperidone, imidoline hydrochloride, lenperone, mazapertine succinate, mesoridazine, mesoridazine besylate, metiapine, milenperone, milipertine, molindone hydrochloride, naranol hydrochloride, neflumozide hydrochloride, ocaperidone, olanzapine, oxiperomide, penfluridol, pentiapine maleate, perphenazine, pimozide, pinoxepin hydrochloride, pipamperone, piperacetazine, pipotiazine palniitate, piquindone hydrochloride, prochlorperazine edisylate, prochlorperazine maleate, promazine hydrochloride, remoxipride, remoxipride hydrochloride, rimcazole hydrochloride, seperidol hydrochloride, sertindole, setoperone, spiperone, thioridazine, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, tioperidone hydrochloride, tiospirone hydrochloride, trifluoperazine hydrochloride, trifluperidol, triflupromazine, triflupromazine hydrochloride, ziprasidone hydrochloride.

Antirheumatic: auranofin, aurothioglucose, bindarit, lobenzarit sodium, phenylbutazone, pirazolac, prinomide tromethamine, seprilose.

Antischistosomal: becanthone hydrochloride, hycanthone, lucanthone hydrochloride, niridazole, oxamniquine, pararosaniline pamoate, teroxalene hydrochloride.

Antiseborrheic: chloroxine, piroctone, piroctone olamine, resorcinol monoacetate.

antisecretory: arbaprostil, deprostil, fenoctimine sulfate, octreotide,, octreotide acetate, omeprazole sodium, rioprostil, trimoprostil.

Antispasmodic: stilonium iodide, tizanidine hydrochloride.

Antithrombotic: anagrelide hydrochloride, bivalirudin, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, ifetroban, ifetroban sodium, tinzaparin sodium, trifenagrel.

Antitussive: benzonatate, butamirate citrate, chlophedianol hydrochloride, codeine polistirex, codoxime, dextromethorphan, dextromethorphan hydrobromide, dextromethorphan polistirex, ethyl dibunate, guaiapate, hydrocodone bitartrate, hydrocodone polistirex, levopropoxyphene napsylate, noscapine, pemerid nitrate, pipazethate, suxemerid sulfate.

Anti-ulcerative: aceglutamide aluminum, cadexomer iodine, cetraxate hydrochloride, enisoprost, isotiquimide, lansoprazole, lavoltidine succinate, misoprostol, nizatidine, nolinium bromide, pantoprazole, pifarnine, pirenzepine hydrochloride, rabeprazole sodium, remiprostol, roxatidine acetate hydrochloride, sucralfate, sucrosofate potassium, tolimidone.

Anti-urolithic: cysteamine, cysteamine hydrochloride, tricitrates.

Appetite suppressant: dexfenfluramine hydrochloride, phendimetrazine tartrate, phentermine hydrochloride.

Benign prostatic hyperplasia therapy agent: tamsulosin hydrochloride.

Blood glucose regulators: human insulin, glucagon, tolazamide, tolbutamide, chloropropamide, acetohexamide and glipizide.

Bone resorption inhibitor: alendronate sodium, etidronate disodium, pamidronate disodium.

Bronchodilator: albuterol, albuterol sulfate, azanator maleate, bamifylline hydrochloride, bitolterol mesylate, butaprost, carbuterol hydrochloride, clorprenaline hydrochloride, colterol mesylate, doxaprost, doxofylline, dyphylline, enprofylline, ephedrine, ephedrine hydrochloride, fenoterol, fenprinast hydrochloride, guaithylline, hexoprenaline sulfate, hoquizil hydrochloride, ipratropium bromide, isoetharine, isoetharine hydrochloride, isoetharine mesylate, isoproterenol hydrochloride, isoproterenol sulfate, metaproterenol polistirex, metaproterenol sulfate, nisbuterol mesylate, oxtriphylline, picumeterol fumarate, piquizil hydrochloride, pirbuterol acetate, pirbuterol hydrochloride, procaterol hydrochloride, pseudoephedrine sulfate, quazodine, quinterenol sulfate, racepinephrine, racepinephrine hydrochloride, reproterol hydrochloride, rimiterol hydrobromide, salmeterol, salmeterol xinafoate, soterenol hydrochloride, sulfonterol hydrochloride, suloxifen oxalate, terbutaline sulfate, theophylline, xanoxate sodium, zindotrine, zinterol hydrochloride.

Carbonic anhydrase inhibitor: acetazolamide, acetazolamide sodium, dichlorphenamide, dorzolamide hydrochloride, methazolamide, sezolamide hydrochloride.

Cardiac depressant: acecainide hydrochloride, acetylcholine chloride, actisomide, adenosine, amiodarone, aprindine, aprindine hydrochloride, artilide fumarate, azimilide Dihydrochloride, bidisomide, bucainide maleate, bucromarone, butoprozine

hydrochloride, capobenate sodium, capobenic acid, cifenline, cifenline succinate, clofilium phosphate, disobutamide, disopyramide, disopyramide phosphate, dofetilide, drobuline, edifolone acetate, emilium tosylate, encainide hydrochloride, flecainide acetate, ibutilide fumarate, indecainide hydrochloride, ipazilide fumarate, lorajmine hydrochloride, lorcainide hydrochloride, meobentine sulfate, mexiletine hydrochloride, modecainide, moricizine, oxiramide, pirmenol hydrochloride, pirolazamide, pranolium chloride, procainamide hydrochloride, propafenone hydrochloride, pyrinoline, quindonium bromide, quinidine gluconate, quinidine sulfate, recainam hydrochloride, recainam tosylate, risotilide hydrochloride, ropitoin hydrochloride, sematilide hydrochloride, suricainide maleate, tocainide, tocainide hydrochloride, transcainide.

Cardioprotectant: dexrazoxane, draflazine.

Cardiotonic: actodigin, amrinone, bemoradan, butopamine, carbazeran, carsatrin succinate, deslanoside, digitalis, digitoxin, digoxin, dobutamine, dobutamine hydrochloride, dobutamine lactobionate, dobutamine tartrate, enoximone, imazodan hydrochloride, indolidan, isomazole hydrochloride, levdobutamine lactobionate, lixazinone sulfate, medorinone, milrinone, pelrinone hydrochloride, pimobendan, piroximone, prinoxodan, proscillaridin, quazinone, tazolol hydrochloride, vesnarinone.

Cardiovascular agent: dopexamine, dopexamine hydrochloride.

Choleretic: dehydrocholic acid, fencibutirol, hymecromone, piprozolin, sincalide, tocamphyl.

Cholinergic: aceclidine, bethanechol chloride, carbachol, demecarium bromide, dexpanthenol, echothiophate iodide, isoflurophate, methacholine chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine, physostigmine salicylate, physostigmine sulfate, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate, pyridostigmine bromide.

Cholinergic agonist: xanomeline, xanomeline tartrate.

Cholinesterase deactivator: obidoxime chloride, pralidoxime chloride, pralidoxime iodide, pralidoxime mesylate.

Coccidiostat: arprinocid, narasin, semduramicin, semduramicin sodium.

Dognition adjuvant: ergoloid mesylates, piracetam, pramiracetam hydrochloride, pramiracetam sulfate, tacrine hydrochloride.

Cognition enhancer: besipirdine hydrochloride, linopirdine, sibopirdine .

Depressant: omeprazole.

Diagnostic aid: aminohippurate sodium, anazolene sodium, arclofenin, arginine, bentiromide, benzylpenicilloyl polylysine, butedronate tetrasodium, butilfenin, coccidioidin,

corticorelin ovine triflutate, corticotropin, repository, corticotropin zinc hydroxide, diatrizoate meglumine, diatrizoate sodium, diatrizoic acid, diphtheria toxin for schick test, disofenin, edrophonium chloride, ethiodized oil, etifenin, exametazime, ferristenc, ferumoxides, ferumoxsil, fluorescein, fluorescein sodium, gadobenate dimeglumine, gadoteridol, gadodiamide, gadopentetate dimegiumine, gadoversetamide, histoplasmin, impromidine hydrochloride, indigotindisulfonate sodium, indocyanine green, lobenguane sulfate I^{123}, iobenzamic acid, iocarmate meglumine, locarmic acid, iocetamic acid, iodamide, lodamide megiumine, iodipamide meglumine, iodixanol, iodoxamate meglumine, iodoxamic acid, ioglicic acid, ioglucol, ioglucomide, ioglycamic acid, iogulamide, lohexol, iomeprol, iopamidol, iopanoic acid, iopentol, iophendylate, iprofenin, iopronic acid, ioprocemic acid, iopydol, iopydone, iosefamic acid, ioseric acid, iosulamide meglumine, iosumetic acid, iotasul, iotetric acid, iothalamate meglumine, iothalamate sodium, iothalamic acid, iotrolan, iotroxic acid, ioversol, ioxaglate meglumine, ioxagiate sodium, ioxaglic acid, ioxilan, ioxotrizoic acid, ipodate calcium, ipodate sodium, isosulfan blue, leukocyte typing serum, lidofenin, mebrofenin, meglumine, metrizamide, metrizoate sodium, metyrapone, metyrapone tartrate, mumps skin test antigen, pentetic acid, propyliodone, quinaldine blue, sermorelin acetate, sodium iodide I^{123}, sprodiamide, stannous pyrophosphate, stannous sulfur colloid, succimer, teriparatide acetate, tetrofosmin, tolbutamide sodium, tuberculin, tyropanoate sodium, xylose.

Diuretic: ambuphylline, ambuside, amiloride hydrochloride, azolimine, azosemide, brocrinat, bumetanide, chlorothiazide, chlorthalidone, clazolimine, clorexolone, ethacrynate sodium, ethacrynic acid, etozolin, fenquizone, furosemide, hydrochlorothiazide, isosorbide, mannitol, mefruside, ozolinone, piretanide, spiroxasone, torsemide, triamterene, triflocin, urea.

Dopaminergic agent: ibopamine.

Ectoparasiticide: nifluridide, permethrin.

Emetic: apomorphine hydrochloride.

Enzyme inhibitor: acetohydroxamic acid, alrestatin sodium, aprotinin, benazepril hydrochloride, benazeprilat, benurestat, bromocriptine, bromocriptine mesylate, cilastatin sodium, flurofamide, lergotrile, lergotrile mesylate, levcycloserine, libenzapril, pentopril, pepstatin, perindopril, polignate sodium, sodium amylosulfate, sorbinil, spirapril hydrochloride, spiraprilat, taleranol, teprotide, tolfamide, zofenopril calcium.

Estrogen: chlorotrianisene, dienestrol, diethylstilbestrol, diethylstilbestrol diphosphate, equilin, estradiol, estradiol cypionate, estradiol enanthate, estradiol undecylate,

estradiol valerate, estrazinol hydrobromide, estriol, estrofurate, estrogens, conjugated, estrogens, esterified, estrone, estropipate, ethinyl estradiol, fenestrel, mestranol, nylestriol, quinestrol.

Fibrinolytic: anistreplase, bisobrin lactate, brinolase.

Free oxygen radical scavenger: pegorgotein.

Gastrointestinal motility agents: cisapride (PROPULSID™), metoclopramide (REGLAN™), hyoscyamine (LEVSIN™).

Glucocorticoid: amcinonide, beclomethasone dipropionate, betamethasone, betamethasone acetate, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, carbenoxolone sodium, clocortolone acetate, clocortolone pivalate, cloprednol, corticotropin, corticotropin, repository, corticotropin zinc hydroxide, cortisone acetate, cortivazol, descinolone acetonide, dexamethasone, dexamethasone sodium phosphate, diflucortolone, diflucortolone pivalate, flucloronide, flumethasone, flumethasone pivalate, flunisolide, fluocinolone acetonide, fluocinonide, fluocortolone, fluocortolone caproate, fluorometholone, fluperolone acetate, fluprednisolone, fluprednisolone valerate, flurandrenolide, formocortal, hydrocortisone, hydrocortisone acetate, hydrocortisone buteprate, hydrocortisone butyrate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydrocortisone valerate, medrysone, methylprednisolone, methylprednisolone acetate, methylprednisoloime sodium phosphate, methylprednisolone sodium succinate, nivazol, paramethasone acetate, prednicarbate, prednisolone, prednisolone acetate, prednisolone hemisuccinate, prednisolone sodium phosphate, prednisolone sodium succinate, prednisolone tebutate, prednisone, prednival, ticabesone propionate, tralonide, triamcinolone, triamcinolone acetonide, triamcinolone acetonide sodium, triamcinolone diacetate, triamcinolone hexacetonide.

Gonad-stimulating principle: buserelin acetate, clomiphene citrate, ganirelix acetate, gonadorelin acetate, gonadorelin hydrochloride, gonadotropin, chorionic, menotropins.

Hair growth stimulant: minoxidil.

Hemostatic: aminocaproic acid, oxamarin hydrochloride, sulmarin, thrombin, tranexamic acid.

Histamine H2 receptor antagonists: ranitidine (ZANTAC™), famotidine (PEPCID™), cimetidine (TAGAMET™), nizatidine (AXID™).

Hormone: diethylstilbestrol, progesterone, 17 hydroxy progesterone, medroxyprogesterone, norgestrel, norethynodrel, estradiol, megestrol (megace), norethindrone, levonorgestrel, ethyndiol, ethinyl estradiol, mestranol, estrone, equilin, 17

alpha dihydroequilin, equilenin, 17 alpha dihydroequilenin, 17 alpha estradiol, 17 beta estradiol, leuprolide (LUPRON^{TM}), glucagon, testolactone, clomiphene, human menopausal gonadotropins, human chorionic gonadotropin, urofollitropin, bromocriptine, gonadorelin, luteinizing hormone releasing hormone and analogs, gonadotropins, danazol, testosterone, dehydroepiandrosterone, androstenedione, dihydroestosterone, relaxin, oxytocin, vasopressin, folliculostatin, follicle regulatory protein, gonadoctrinins, oocyte maturation inhibitor, insulin growth factor, follicle stimulating hormone, luteinizing hormone, tamoxifen., corticorelin ovine triftutate, cosyntropin, metogest, pituitary, posterior, seractide acetate, somalapor, somatrem, somatropin, somenopor, somidobove.

Hypocholesterolemic: lifibrol.

Hypoglycemic: darglitazone sodium: glimepiride.

Hypolipidemic: azalanstat dihydrochloride, colestolone, surfomer, xenalipin.

Hypotensive: viprostol.

Hmgcoa reductase inhibitors: lovastatin (MEVACOR^{TM}), simvastatin (ZOCOR^{TM}), pravastatin (PRAVACHOL^{TM}), fluvasatin (LESCOL^{TM}).

Immunizing agent: antirabies serum, antivenin (*latrodectus mactans*), antivenin (*micrurus fulvius*), antivenin (*crotalidae*) polyvalent, BCG vaccine, botulism antitoxin, cholera vaccine, diphtheria antitoxin, diphtheria toxoid, diphtheria toxoid adsorbed, globulin, immune, hepatitis b immune globulin, hepatitis B virus vaccine inactivated, influenza virus vaccine, measles virus vaccine live, meningococcal polysaccharide vaccine group A, meningococcal polysaccharide vaccine group C, mumps virus vaccine live, pertussis immune globulin, pertussis vaccine, pertussis vaccine adsorbed, plague vaccine, poliovirus vaccine inactivated, poliovirus vaccine live oral, rabies immune globulin, rabies vaccine, Rh_o (D) immune globulin, rubella virus vaccine live, smallpox vaccine, tetanus antitoxin, tetanus immune globulin, tetanus toxoid, tetanus toxoid adsorbed, typhoid vaccine, yellow fever vaccine, vaccinia immune globulin, varicella-zoster immune globulin.

Immunomodulator: dimepranol acedoben, imiquimod, interferon beta-Ib, lisofylline, mycophenolate mofetil, prczatide copper acetate.

Immunoregulator: azarole, fanetizole mesylate, frentizole, oxamisole hydrochloride, ristianol phosphate, thymopentin, tilomisole.

Immunostimulant: loxoribine, teceleukin.

Immunosuppressant: azathioprine, azathioprine sodium, cyclosporine, daltroban, gusperimus trihydrochloride, sirolimus, tacrolimus.

Impotence therapy adjunct: delequamine hydrochloride.

Inhibitor: acarbose, atorvastatin calcium, benserazide, brocresine, carbidopa, clavulanate potassium, dazmegrel, docebenone, epoprostenol, epoprostenol sodium, epristeride, finasteride, flurbiprofen sodium, furegrelate sodium, lufironil, miglitol, orlistat, pimagedine hydrochloride, pirmagrel, ponalrestat, ridogrel, sulbactam benzathine, sulbactampivoxil, sulbactam sodium, suronacrine maleate, tazobactam, tazobactam sodium, ticlopidine hydrochloride, tirilazad mesylate, tolrestat, velnacrine maleate, zifrosilone, zileuton.

Keratolytic: alcloxa, aldioxa, benzoyl peroxide, dibenzothiophene, etarotene, isotretinoin, motretinide, picotrin diolamine, resorcinol, resorcinol monoacetate, salicylic acid, sumarotene, tazarotene, tetroquinone, tretinoin.

LHRL agonist: deslorelin, goserelin, histrelin, lutrelin acetate, nafarelin acetate.

Liver disorder treatment: malotilate.

Luteolysin: fenprostalene.

Memory adjuvant: dimoxamine hydrochloride, ribaminol.

Mental performance enhancer: aniracetam.

Mood regulator: fengabine.

Mucolytic: acetylcysteine, carbocysteine, domiodol.

Mucosal protective agents: misoprostol (CYTOTEC™).

Mydriatic: berefrine.

Nasal decongestant: nemazoline hydrochloride, pseudoephedrine polistirex.

Neuroleptic: duoperone fumarate, risperidone.

Neuromuscular blocking agent: atracurium besylate, cisatracurium besylate, doxacurium chloride, gallamine triethiodide, metocurine iodide, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, vecuronium bromide.

Neuroprotective: dizocilpine maleate.

NMDA antagonist: selfotel.

Non-hormonal sterol derivative: pregnenolone succinate.

Oxytocic: carboprost, carboprost methyl, carboprost tromethamine, dinoprost, dinoprost tromethamine, dinoprostone, ergonovine maleate, meteneprost, methylergonovine maleate, oxytocin, sparteine sulfate.

Plasminogen activator: alteplase, urokinase.

Platelet activating factor antagonist: lexipafant.

Platelet aggregation inhibitor: acadesine, beraprost, beraprost sodium, ciprostene

calcium, itazigrel, lifarizine, oxagrelate.

Post-stroke and post-head trauma treatment: citicoline sodium.

Potentiator: pentostatin, talopram hydrochloride.

Progestin: algestone acetophenide, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogesterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, tigestol.

Prostaglandin: cloprostenol sodium, fluprostenol sodium, gemeprost, prostalene, sulprostone.

Prostate growth inhibitor: pentomone.

Prothyrotropin: protirelin.

Psychotropic: minaprine.

Pulmonary surface: beractant, colfosceril palmitate.

Radioactive agent: fibrinogen I^{125}, fludeoxyglucose F^{18}, fluorodopa F^{18}, insulin I^{125}, insulin I^{131}, iobenguane I^{123}, iodipamide sodium I^{131}, iodoantipyrine I^{131}, iodocholesterol I^{131}, iodohippurate sodium I^{123}, iodohippurate sodium I^{125}, iodohippurate sodium I^{131}, iodopyracet I^{125}, iodopyracet I^{131}, iofetamine hydrochloride I^{123}, iomethin I^{125}, iomethin I^{131}, iothalamate sodium I^{125}, iothalamate sodium I^{131}, iotyrosine I^{131}, liothyronine I^{125}, liothyronine I^{131}, merisoprol acetate Hg^{197}, merisoprol acetate Hg^{203}, merisoprol Hg^{197}, selenomethionine Se^{75}, technetium Tc^{99m} antimony trisulfide colloid, technetium Tc^{99m} bicisate, technetium Tc^{99m} disofenin, technetium Tc^{99m} etidronate, technetium Tc^{99m} exametazime, technetium Tc^{99m} furifosmin, technetium Tc^{99m} gluceptate, technetium Tc^{99m} lidofenin, technetium Tc^{99m} mebrofenin, technetium Tc^{99m} medronate, technetium Tc ^{99m} medronate disodium, technetium Tc^{99m} mertiatide, technetium Tc^{99m} oxidronate, technetium Tc^{99m} pentetate, technetium Tc^{99m} pentetate calcium trisodium, technetium Tc^{99m} sestamibi, technetium Tc^{99m} siboroxime, technetium Tc^{99m} succimer, technetium Tc^{99m} sulfur colloid, technetium Tc^{99m} teboroxime, technetium Tc^{99m} tetrofosmin, technetium Tc^{99m} tiatide, thyroxine I^{125}, thyroxine I^{131}, tolpovidone I^{131}, triolein I^{125}, triolein I^{131}.

Regulator: calcifediol, calcitonin, calcitriol, clodronic acid, dihydrotachysterol, etidronic acid, oxidronic acid, piridronate sodium, risedronate sodium, secalciferol.

Relaxant: adiphenine hydrochloride, alcuronium chloride, aminophylline, azumolene sodium, baclofen, benzoctamine hydrochloride, carisoprodol, chlorphenesin carbamate, chlorzoxazone, cinflumide, cinnamedrine, clodanolene, cyclobenzaprine hydrochloride, dantrolene, dantrolene sodium, fenalamide, fenyripol hydrochloride, fetoxylate hydrochloride, flavoxate hydrochloride, fletazepam, flumetramide,-flurazepam hydrochloride, hexafluorenium bromide, isomylamine hydrochloride, lorbamate, mebeverine hydrochloride, mesuprine hydrochloride, metaxalone, methocarbamol, methixene hydrochloride, nafomine malate, nelezaprine maleate, papaverine hydrochloride, pipoxolan.

Hydrochloride, quinctolate, ritodrine, ritodrine hydrochloride, rolodine, theophylline sodium glycinate, thiphenamil hydrochloride, xilobam.

Repartitioning agent: cimaterol.

Scabicide: amitraz, crotamiton.

Sclerosing agent: ethanolamine oleate, morrhuate sodium, tribenoside.

Sedative: propiomazine.

Sedative-hypnotic: allobarbital, alonimid, alprazolam, amobarbital sodium, bentazepam, brotizolam, butabarbital, butabarbital sodium, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide hydrochloride, cloperidone hydrochloride, clorethate, cyprazepam, dexclamol hydrochloride, diazepam, dichloralphenazone, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, fosazepam, glutethimide, halazepam, lormetazepam, mecloqualone, meprobamate, methaqualone, midaflur, paraldehyde, pentobarbital, pentobarbital sodium, perlapine, prazepam, quazepam, reclazepam, roletamide, secobarbital, secobarbital sodium, suproclone, thalidomide, tracazolate, trepipam maleate, triazolam, tricetamide, triclofos sodium, trimetozine, uldazepam, zaleplon, zolazepam hydrochloride, zolpidem tartrate.

Selective adenosine a1 antagonist: apaxifylline.

Serotonin antagonist: altanserin tartrate, amesergide, ketanserin, ritanserin.

Serotonin inhibitor: cinanserin hydrochloride, fenclonine, fonazine mesylate, xylamidine tosylate.

Serotonin receptor antagonist: tropanserin hydrochloride.

Steroid: dexamethasone aceflrate, mometasone furoate.

Stimulant: amfonelic acid, amphetamine sulfate, ampyzine sulfate, arbutamine hydrochloride, azabon, caffeine, ceruletide, ceruletide diethylamine, cisapride, dazopride fumarate, dextroamphetamine, dextroamphetamine sulfate, difluanine hydrochloride, dimefline hydrochloride, doxapram hydrochloride, etryptamine acetate, ethamivan,

fenethylline hydrochloride, flubanilate hydrochloride, flurothyl, histamine phosphate, indriline hydrochloride, mefexamide, methamphetamine hydrochlo ride, methylphenidate hydrochloride, pemoline, pyrovalerone hydrochloride, xamoterol, xamoterol fumarate.

Suppressant: amfhutizole, coxchicine, tazofelone.

Symptomatic multiple sclerosis: fampridine.

Synergist: proadifen hydrochloride.

Thyroid hor mone: levothyroxine sodium, liothyronine sodium, liotrix.

Thyroid inhibitor: methimazole, propyithiouracil.

Thyromimetic: thyromedan hydrochloride.

Tranquilizer: bromazepam, buspirone hydrochloride, chlordiazepoxide, clazolam, clobazam, clorazepate dipotassium, clorazepate monopotassium, demoxepam, dexmedetomidine, enciprazine hydrochloride, gepirone hydrochloride, hydroxyphenamate, hydroxyzine

Hydrochloride, hydroxyzine pamoate, ketazolam, lorazepam, lorzafone, loxapine, loxapine succinate, medazepam hydrochloride, nabilone, nisobamate, oxazepam, pentabamate, pirenperone, ripazepam, roliprarn, sulazepam, taciamine hydrochloride, temazepam, triflubazam, tybamate, valnoctamide.

Amyotrophic lateral sclerosis agents: riluzole.

Cerebral ischemia agents: dextrorphan hydrochloride.

Paget's disease agents: tiludronate disodium.

Unstable angina agents: tirofiban hydrochloride.

Uricosuric: benzbromarone, irtemazole, probenecid, sulfinpyrazone.

Vasoconstrictor: angiotensin amide, felypressin, methysergide, methysergide maleate.

Vasodilator: alprostadil, azaclorzine hydrochloride, bamethan sulfate, bepridil hydrochloride, buterizine, cetiedil citrate, chromonar hydrochloride, clonitrate, diltiazem hydrochloride, dipyridamole, droprenilamine, erythrityl tetranitrate, felodipine, flunarizine hydrochloride, fostedil, hexobendine, inositol niacinate, iproxamine hydrochloride, isosorbide dinitrate, isosorbide mononitrate, isoxsuprine hydrochloride, lidoflazine, mefenidil, mefenidil fumarate, mibefradil dihydrochloride, mioflazine hydrochloride, mixidine, nafronyl oxalate, nicardipine hydrochloride, nicergoline, nicorandil, nicotinyl alcohol, nifedipine, nimodipine, nisoldipine, oxfenicine, oxprenolol hydrochloride, pentaerythritol tetranitrate, pentoxifylline, pentrinitrol, perhexiline maleate, pindolol, pirsidomine, prenylamine, propatyl nitrate, suloctidil, terodiline hydrochloride, tipropidil hydrochloride, tolazoline hydrochloride, xanthinol niacinate.

Vulnerary: allantoin.

Wound healing agent: ersofermin.

Xanthine oxidase inhibitor: allopurinol, oxypurinol.

Other pharmaceutical agents include: 1-decpyrrolidinone, 1-dodecpyrrolidinone, 16α-fluoroestradiol, 16-epiestriol, 16α-gitoxin, 17α estradiol, 17β estradiol, 1alpha-hydroxyvitamin D2,2'-nor-cGMP, 20-epi-1,25 dihydroxyvitamin D3, 22-oxacalcitriol, 2CVV, 3-isobutyl GABA, 6-FUDCA, 7-methoxytacrine, abamectin, abanoquil, abecarnil, abiraterone, acadesine, acamprosate, acarbose, aceclofenac, acemannan, acetomepregenol, acetyl-L-carnitine, acetylcysteine, N-acetylmethadol, acifran, acipimox, acitemate, acitretin, aclarubicin, aclatonium, napadisilate, aconiazide, acrivastinet, adafenoxate, adapalene, adatanserin, adecypenol, adefovir dipivoxil, adelmidrol, ademetionine, adinazolam, adiposin, adozelesin, adrafinil, alacepril, aladapcin, alaptide, albendazole, albolabrin, aldecalmycin, aldesleukin, alendronic acid, alentemol, alfacalcidol, alfuizosin, alglucerase, alinastine, alosetron, alpha idosone, alprostadil, altretamine, altromycin B, ambamustine, amelometasone, amesergide, amezinium metilsulfate, amfebutamone, amidox, amifloxacin, amifostine, amiodarone, amisulpride, amlexanox, amlodipine, amlodipine, ampiroxicam, arninone, amrubicin, amsacrine, amylin, amythiamicin, anagrelide, anakinra, ananain, anaritide, anastrozole, andrographolide, anordrin, apadoline, apafant, apaxifylline, aphidicolin glycinate, apraclonidine, aprosulate sodium, aptiganel, apurinic acid, aranidipine, arbekacin, arbidol, arbutamine, ardeparin sodium, arecatannin B1, argatroban, aripiprazol, arotinolol, asimadoline, aspalatone, asperfuran, aspoxicillin, astemizole, asulacrine, atamestanie, atenolol, S-atevirdine, atosiban, atovaquone, atpenin B, atrimustine, atrinositol, aureobasidin A, azadirachtine, azasetron, azatyrosine, azelaic acid, azelastine, azelnidipine, azimilide, azithromycin, azosemide, aztreonam, baccatin III, bacoside A, bacoside B, bactobolamine, balazipone, balhimycin, balofloxacin, balsalazide, bambuterol, baohuoside 1, bamidipine, basifungin, batebulast, batimastat, beauvericin, becaplermin, becliconazole, befloxatone, belfosdil, bellenamine, benflumetol, benidipine, benzisoxazole, benzochlorins, benzoidazoxan, benzoylstaurosporine, benztropine, bepridil, beractant, beraprost, berlafenone, bertosamil, besipirdine, beta-alethine, betaclamycin B, betamipron, betaxolol, betulinic acid, bevantolol, bicalutamide, bifemelane, birnakalim, bimithil, binospirone, bioxalomycin alpha2, biriperone, bis-benzimidazole A, bis-benzimidazole B, bisantrene, bisaramil, bisaziridinylspermine, bisnafide, bisoprolol, bistramide D, bistramide K, bistratene A, boldine, bopindolol, brefeldin, breflate, brimonidine, bromfenac, bromperidol, bropirimine, bucindolol, budesonide, budipine, budotitane, bunaprolast, bunazosin,

butenafine, buthionine sulfoximine, butixocort propionate, cadexomer iodine, calanolide A, calcipotriol, calphostin C, camonagrel, candesartan, candesartan cilexetil, candoxatril, candoxatrilat, capecitabine, capromab, capsaicin, captopril, carbazomycin C, carbetocin, carbovir, carboxamide-amino-triazole, carboxyamidotriazole, carboxymethylated β-1,3-glucan, carperitide, carteolol, carumonam, carvedilol, carvotroline, carzelesin, castanospermine, cebaracetam, cecropin B, cefcapene pivoxil, cefdaloxime pentexil tosilate, cefdinir, cefditoren pivoxil, cefepime, cefetamet, cefetamet pivoxil, cefixime, cefluprenam, cefmnetazole, cefmninox, cefodizime, cefoselis, cefotetan, cefotiam, cefotiam hexetil, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefsulodin, cefteram, ceftibuten, cefiriaxone, cefuroxime axetil, celastrol, celikalim, celiprolol, cepacidine A, cericlamine, cerivastatin, ceronapril, certoparin sodium, cetiedil, cetirizine, chloroorienticin A, chloroorienticin B, chloroquinoxaline sulfonamide, cibenzoline, cicaprost, ciclesonide, cicletanine, cicloprolol, cidofovir, cilansetron, cilazapril, cilnidipine, cilobradine, cilostazol, cimetropium bromide, cinitapride, cinolazepam, cioteronel, ciprofibrate, ciprofloxacin, ciprostene, cis-porphyrin, cisapride, cisatracurium besilate, cistinexine, citalopram, citicoline, citreamicin alpha, cladribine, clarithromycin, clausenamide, clebopride, clinafloxacin, clobazam, clobetasone butyrate, clodronic acid, clomethiazole, clopidogrel, clotrimazole, colestimide, colfosceril palmitate, collismycin A, collismycin B, combretastatin A4, complestatin, conagenin, contignasterol, contortrostatin, cosalane, costatolide, cotinine, coumermycin A1, cucumariosid, curacin A, curdlan sulfate, curiosin, cyclazosin, cyclic HPMPC, cyclobenzaprine, cyclobut A, cyclobut G, cyclocapron, cycloplatam, cyclosin, cyclothialidine, cyclothiazomycin, cypemycin, cyproterone, cytarabine ocfosfate, cytochalasin B, dacliximab, dactimicin, daidzein, daidzin, dalfopristin, dalteparin sodium, danaparoid, daphnodorin A, dapiprazole, dapitant, darifenacin, darlucin A, darsidomine, ddUTP, decitabine, deferiprone, deflazacort, dehydrodidemnin B, dehydroepiandrosterone, delapril, delequamine, delfaprazine, delmopinol, delphinidin, deoxypyridinoline, deprodone, depsidomycin, deramciclane, dermatan sulfate, desflurane, desirudin, deslorelin, desmopressin, desogestrel, desoxoarniodarone, detajmium bitartrate, dexifosfamide, dexketoprofen, dexloxiglumide, dexmedetomidine, dexpemedolac, dexrazoxane, dexsotalol, dextrin 2-sulphate, dexverapamil, dezinamide, dezocine, diaziquone, diclofenac digolil, diclofenac potassium, dicranin, didemnin B, didox, dienogest, diethylhomospermine, diethylnorspermine, dihydrexidine, dihydro-5-azacytidine, dimethyl prostaglandin A1, dimethylhomospermine, dimiracetam, dioxamycin, diphencyprone, diphenyl spiromustine, diprafenone, dipropylnorspermine, dirithromycin, discodermolide,

disulfiram, ditekiren, docarpamine, docosanol, 1-dofetilide, dolasetron, domitroban, dopexamine, dorzolamide, dosmalfate, dotarizine, doxacurium chloride, doxazosin, doxifluridine, doxofylline, draculin, draflazine, droloxifene, dronabinol, drosperidone, drotaverine acephyllinate, droxicam, ebiratide, ebrotidine, ebselen, ecabapide, ecabet, ecadotril, ecdisteron, echicetin, echistatin, ecomustine, ecteinascidin 722, ecteinascidin 729, ecteinascidin 743, edaravone, edelfosine, edobacomab, edrecolomab, efegatran, eflornithine, efonidipine, egualen, elcatonin, eletriptan, elgodipine, eliprodil, eltenac, emakalim, emedastine, emiglitate, emitefur, emoctakin, enadoline hydrochloride, enalapril, enazadrem, englitazone, enlimomab, enoxacin, enoxaparin sodium, enoximone, entacapone, enterostatin, epoprostenol, epoxymexrenone, epristeride, eprosartan, eptastigmine, erdosteine, ersentilide, ersofermin, erytlritol, esuprone, etanidazole, etanterol, ethacizin, ethinylestradiol, etizolam, etodolac, etoposide phosphate, etrabamine, everninomicin, examorelin, exemestane, fadrozole, faeriefungin, famciclovir, fampridine, fantofarone, faropenem, fasidotril, fasudil, fazarabine, fedotozine, felbamate, fenofibrate, fenoldopam, fenretinide, fenspiride, fenticonazole, fepradinol, ferpifosate sodium, ferristene, ferrixan, ferumoxsil, fexofenadine, flavopiridol, flecainide, flerobuterol, fleroxacin, flesinoxan, flezelastine, flobufen, flomoxef, florfenicol, florifenine, flosatidil, fluasterone, fluconazole, fludarabine, flumazenil, flumecinol, flumequine, flunarizine, fluocalcitriol, fluorodaunorunicin hydrochloride, fluoxetine, R-fluoxetine, S-fluparoxan, flupirtine, flurbiprofen axetil, flurithromycin, fluticasone propionate, flutrimazole, fluvastatin, fluvoxamine, forasartan, forfenimex, formestane, formoterol, formoterol, R,R-fosfomycin, trometamol, fosinopril, fosphenytoin, fostriecin, fotemustine, gabapentin, gadobenic acid, gadobutrol, gadodiamide, gadodiamide-EOB-DTPA, gadolinium texaphyrin, gadoteric acid, gadoteridol, gadoversetamide, galantamine, galdansetron, gallopamil, galocitabine, gamolenic acid, ganirelix, gepirone, gestrinone, girisopam, glaspimod, glaucocalyxin A, glutapyrone, glycopine, glycopril, granisetron, grepafloxacin, halichondrin B, halofantrine, halomon, halopredone, hatomamicin, hatomarubigin A, hatomarubigin B, hatomarubigin C, hatomarubigin D, ibogaine, ibopamine, ibudilast, illimaquinone, ilmofosine, ilomastat, iloperidone, iloprost, imidapril, imidazenil, indinavir, indolidan, indometacin farnesil, indometacin, tropine ester, indoramin, inocoterone, inogatran, inolimomab, interferon alfa, interferon alfa-2a, interferon alfa-2B, interferon alfa-N 1, interferon alfa-N3, interferon β, interferon β-1 Al, interferon β-1B, interferon gamma-1A, interferon gamma-1B, interferon omega, interferon, consensus, interleukin-1, interleukin-1 alpha, interleukin-1 β, interleukin-10, interleukin-11, interleukin-12, interleukin-12, interleukin-15, interleukin-2, interleukin-3, interleukin-4, interleukin-5,

interleukin-7, interleukin-8, iobenguane, iobitridol, iodoamiloride, iododoxorubicin, iofratol, iomeprol, iopentol, iopromide, iopyrol, iotriside, ioversol, ioxilan, ipazilide, IpdR, ipenoxazone, ipidacrine, ipomeanol, 4-ipriflavone, ipsapirone, irbesartan, irinotecan, irloxacin, irsogladine, irtemazole, isalsteine, isbogrel, isepamicin, isobengazole, isofloxythepin, isohomohalicondrin B, isopropyl unoprostone, isradipine, itameline, itasetron, itopride, itraconazole, ketoprofen, R-ketoprofen, S-ketorolac, lacidipine, lactitol, lactivicin, laennec, lafutidine, lamelrarin-N triacetate, lamifiban, lamivudine, lamotrigine, lanoconazole, lanperisone, lanreotide, lansoprazole, latanoprost, lateritin, laurocapram, lazabemide, lemefloxacin, lemildipine, leminoprazole, lenercept, lenograstim, lentinan sulfate, leptin, leptolstatin, lercanidipine, lerisetron, lesopitron, letrazuril, letrozole, leucomyzin, leuprorelin, levcromakalim, levetiracetam, levobetaxolol, levobunolol, levobupivacaine, levocabastine, levocamitine, levodropropizine, levofloxacin, levomoprolol, levonorgestrel, levormeloxifene, levosimendan, levosulpiride, linotroban, linsidomine, lintitript, lintopride, liothyronine sodium, lirexapride, lisinopril, lobaplatin, lobucavir, lodoxamide, lombricine, lomefloxacin, lomerizine, lometrexol, lonazolac, lonidamine, loracarbef, loratadine, lorglumide, lornoxicam, losartan, losigamone, losoxantrone, loteprednol, loviride, loxoribine, lubeluzole, lurtotecan, luteinizing hormone, lutetium, luzindole, lydicamycin, lysofylline, lysostaphin, magainin 2 amide, magnolol, mallotochromene, mallotojaponin, malotilate, mangafodipir, manidipine, maniwamycin A, mannostatin A, manumycin E, manumycin F, mapinastine, marimastat, masoprocol, maspin, massetolide, meterelin, methoxatone, methylhistamine, R-alpha, methylinosine monophosphate, methylprednisolone aceponate, methylprednisolone suleptanate, metipamide, metoclopramide, metoprolol, S-metrifonate, mibefradil, michellarnine B, microcolin A, midodrine, mifepristone, miglitol, milacemide, milameline, mildronate, milnacipran, milrinone, miltefosine, minaprine, miokamycin, mipragoside, mirfentanil, mirimostim, mirtazapine, misoprostol, mitoguazone, mitolactol, mitonafide, mitoxantrone, mivacurium chloride, mivazerol, mixanpril, mizolastine, mizoribine, moclobemide, modafinil, moexipril, mofarotene, mofezolac, molgramostim, mometasone, montirelin, mopidamol, moracizine, mosapramine, mosapride, motilide, moxiraprine, moxonidine, nadifloxacin, nadroparin calcium, nafadotride, nafamostat, nafarelin, naftopidil, naglivan, nagrestip, nalmefene, naphterpin, napsagatran, naratriptan, nartograstim, nasaruplase, nateplase, niperotidine, niravoline, nisamycin, nisin, nisoldipine, nitazoxanide, nitecapone, nitrendipine, nitrendipine, S-nitrofurantoin monohydrate, nitrullyn, nizatidine, ofloxacin, okicenone, olanzapine, olopatadine, olprinone, olsalazine, omeprazole, onapristone, ondansetron, ondansetron, R-ontazolast, oracin, otenzepad, oxaliplatin,

oxamisole, oxandrolone, oxaprozin, oxaunomycin, oxcarbazepine, oxiconazole, oxiracetam, oxodipine, ozagrel, palauamine, palinavir, palmitoylrhizoxin, pamaqueside, pamicogrel, pamidronic acid, panamesine, panaxytriol, panipenem, panipenum, pannorin, panomifene, pantethine, pantoprazole, parabactin, pamaparin sodium, paroxetine, parthenolide, pazelliptine, pazufloxacin, pefloxacin, pegaspargase, peldesine, pemedolac, pemirolast, penciclovir, pentafuside, pentamidine, pentamorphone, pentigetide, pentosan, pentostatin, pentrozole, perflubron, perfosfamide, pergolide, perindoprilat, perospirone, phenaridine, phenazinomycin, phenserine, phensuccinal, phentolamine mesilate, phenylacetate, phenylalanyl ketoconazole, picenadol, picibanil, picroliv, picumeterol, pidotimod, pilocarpine hydrochloride, pilsicainide, pimagedine, pimilprost, pimobendan, pinacidil, pinocebrin, pioglitazone, pipecuronium bromide, pirarubicin, piretanide, pirfenidone, piritrexim, pirlindole, pirmagrel, pirmenol, pirodavir, pirodomast, piroxicam cinnamate, propagermanium, propentofylline, propionylcamitine, L-propiram, propiram +paracetamol, propiverine, propyl bis-acridone, prostaglandin J2, prostratin, protegrin, protosufloxacin, prulifloxacin, pyrazoloacridine, quazepam, quetiapine, quiflapon, quinagolide, quinapril, quinfamide, quinupristin, raloxifene, raltitrexed, ramatroban, ramipril, ramosetron, ranelic acid, ranitidine bismuth citrate, ranolazine, recainam, regavirumab, relaxin, repirinast, resinferatoxin, reticulon, reviparin sodium, revizinone, ricasetron, ridogrel, rifabutin, rifapentine, rifaximin, rilopirox, riluzole, rimantadine, rimexolone, rimoprogin, riodipine, ripisartan, risedronic acid, rispenzepine, risperidone, ritanserin, ritipenem, ritipenem acoxil, ritolukast, ritonavir, rizatriptan benzoate, rohitukine, rokitamycin, ropinirole, ropivacaine, roquinimex, roxatidine, roxindole, roxithromycin, rubiginone B1, ruboxyl, rufloxacin, rupatidine, ruzadolane, safingol, safironil, saintopin, salbutamol, R-salmeterol, salmeterol, R-sainacedin, sameridine, sampatrilat, sanfetrinem, saprisartan, sapropterin, saquinavir, sarcophytol A sargramostim, sarpogrelate, saruplase, saterinone, satigrel, satumomab pendetide, selegiline, selenium thiosemicarbazone, sematilide, semduramicin, semotiadil, semustine, sermorelin, sertaconazole, sertindole, sertraline, setiptiline, sevirumab, sevoflurane, sezolamide, silipide, silteplase, simendan, simvastatin, sinitrodil, sinnabidol, sipatrigine, sirolimus, sizofiran, somatomedin B, somatomedin C, somatrem, somatropin, sonermin, stalol, staurosporine, stavudine, stepronin, stipiamide, stiripentol, stobadine, succibun, sucralfate, sulfasalazine, sulfmosine, sulfoxamine, sulopenem, sultamicillin, sultopride, sulukast, sumatriptan, symakalim, tandospirone, tapgen, taprostene, tasosartan, tazanolast, tazarotene, teicoplanin, telenzepine, tellurapyrylium, telmesteine, telmisartan, temocapril, temoporfin, temozolomide, tenidap, teniposide, tenosal, tenoxicam, tepirindole,

tepoxalin, terazosin, terbinafine, terfenadine, terflavoxate, terguride, terlakiren, terlipressin, terodiline, tertatolol, testosterone buciclate, tetrachlorodecaoxide, tetrazomine, thaliblastine, thalidomide, thiocoraline, thiofedrine, thiomarinol, thioperamide, thyroid stimulating hormone, tiagabine, tianeptine, tiapafant, tibolone, ticlopidine, tienoxolol, tilisolol, tilnoprofen arbamel, tiludronic acid, tinzaparin sodium, tiotropium bromide, tipredane, tiqueside, tirandalydigin, tirapazamine, tirilazad, tirofiban, tiropramide, topsentin, torasemide, toremifene, tosufloxacin, trafermin, trandolapril, traxanox, tretinoin, tretinoin tocoferil, triacetyluridine, tricaprilin, trichohyalin, trichosanthin, alpha, triciribine, trientine, triflavin, trimegestone, triptorelin, troglitazone, trombodipine, tropisetron, trospectomycin, trovafloxacin, trovirdine, tucaresol, tulobuterol, tylogenin, urapidil, uridine triphosphate, valaciclovir, valproate magnesium, valproate semisodium, valsartan, vamicamide, vanadeine, vaninolol, vapreotide, variolin B, velaresol, venlafaxine, veramine, verapamil, S-verdins, veroxan, verteporfin, vesnarinone, vexibinol, vigabatrin, vinbumine citrate, vinburnine resinate, vinconate, vinorelbine, vinpocetine, vinpocetine citrate, vintoperol, vinxaltine, voriconazole, vorozole, voxergolide, xemilofiban, ximoprofen, yangambin, zabicipril, zacopride, zacopride, R-zafirlukast, zalcitabine, zaleplon, zalospirone, zaltoprofen, zanamivir, zankiren, zanoterone, zatebradine, zatosetron, zenarestat, zeniplatin, zifrosilone, zilascorb, zileuton, zinostatin stimalamer, ziprasidone, zoledronic acid, zolmitriptan, zolpidem, zonisamide, zopiclone, zopiclone, S-zopolrestat, zotepine.

Specific Examples of Antibacterials

When antibacterial activity is a desired property of the disclosed ionic liquids, one or more of the ions in the disclosed ionic liquids can be an antibacterial. That is the one or more kinds of cations, one or more kinds of anions, or both cations and anions can be an antibacterial. Many of suitable antibacterial have already been disclosed herein (*e.g.*, many QACs have antibacterial properties). Further examples of suitable antibacterial agents include, but are not limited to, acedapsone, acetosulfone sodium, alamecin, alexidine, amdinocillin, amdinocillin pivoxil, amicycline, amifloxacin, amifloxacin mesylate, amikacin, amikacin sulfate, aminosalicylic acid, aminosalicylate sodium, amoxicillin, amphomycin, ampicillin, ampicillin sodium, apalcillin sodium, apramycin, aspartocin, astromicin sulfate, avilamycin, avoparcin, azithromycin, azlocillin, azlocillin sodium, bacampicillin hydrochloride, bacitracin, bacitracin methylene disalicylate, bacitracin zinc, bambermycins, benzoylpas calcium, berythromycin, betamicin sulfate, biapenem, biniramycin, biphenamine hydrochloride, bispyrithione magsulfex, butikacin, butirosin sulfate, capreomycin sulfate, carbadox, carbenicillin disodium, carbenicillin indanyl sodium, carbenicillin phenyl sodium,

carbenicillin potassium, carumonam sodium, cefaclor, cefadroxil, cefamandole, cefamandole nafate, cefamandole sodium, cefaparole, cefatrizine, cefazaflur sodium, cefazolin, cefazolin sodium, cefbuperazone, cefdinir, cefepime, cefepime hydrochloride, cefetecol, cefixime, cefmenoxime hydrochloride, cefmetazole, cefmetazole sodium, cefonicid monosodium, cefonicid sodium, cefoperazone sodium, ceforanide, cefotaxime sodium, cefotetan, cefotetan disodium, cefotiam hydrochloride, cefoxitin, cefoxitin sodium, cefpimizole, cefpimizole sodium, cefpiramide, cefpiramide sodium, cefpirome sulfate, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin sodium, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime, cefuroxime axetil, cefuroxime pivoxetil, cefuroxime sodium, cephacetrile sodium, cephalexin, cephalexin hydrochloride, cephaloglycin, cephaloridine, cephalothin sodium, cephapirin sodium, cephradine, cetocycline hydrochloride, cetophenicol, chloramphenicol, chloramphenicol palmitate, chloramphenicol pantothenate complex, chloramphenicol sodium succinate, chlorhexidine phosphanilate, chloroxylenol, chlortetracycline bisulfate, chlortetracycline hydrochloride, cinoxacin, ciprofloxacin, ciprofloxacin hydrochloride, cirolemycin, clarithromycin, clinafloxacin hydrochloride, clindamycin, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, clofazimine, cloxacillin benzathine, cloxacillin sodium, cloxyquin, colistimethate sodium, colistin sulfate, coumermycin, coumermycin sodium, cyclacillin, cycloserine, dalfopristin, dapsone, daptomycin, demeclocycline, demeclocycline hydrochloride, demecycline, denofungin, diaveridine, dicloxacillin, dicloxacillin sodium, dihydrostreptomycin sulfate, dipyrithione, dirithromycin, doxycycline, doxycycline calcium, doxycycline fosfatex, doxycycline hyclate, droxacin sodium, enoxacin, epicillin, epitetracycline hydrochloride, erythromycin, erythromycin acistrate, erythromycin estolate, erythromycin ethylsuccinate, erythromycin gluceptate, erythromycin lactobionate, erythromycin propionate, erythromycin stearate, ethambutol hydrochloride, ethionamide, fleroxacin, floxacillin, fludalanine, flumequine, fosfomycin, fosfomycin tromethamine, fumoxicillin, furazolium chloride, furazolium tartrate, fusidate sodium, fusidic acid, gentamicin sulfate, gloximonam, gramicidin, haloprogin, hetacillin, hetacillin potassium, hexedine, ibafloxacin, imipenem, isoconazole, isepamicin, isoniazid, josamycin, kanamycin sulfate, kitasamycin, levofuraltadone, levopropylcillin potassium, lexithromycin, lincomycin, lincomycin hydrochloride, lomefloxacin, lomefloxacin hydrochloride, lomefloxacin mesylate, loracarbef, mafenide, meclocycline, meclocycline sulfosalicylate, megalomicin potassium phosphate, mequidox, meropenem, methacycline, methacycline hydrochloride, methenamine, methenamine hippurate, methenamine mandelate, methicillin sodium, metioprim,

metronidazole hydrochloride, metronidazole phosphate, mezlocillin, mezlocillin sodium, minocycline, minocycline hydrochloride, mirincamycin hydrochloride, monensin, monensin sodiumr, nafcillin sodium, nalidixate sodium, nalidixic acid, natainycin, nebramycin, neomycin palmitate, neomycin sulfate, neomycin undecylenate, netilmicin sulfate, neutramycin, nifuiradene, nifuraldezone, nifuratel, nifuratrone, nifurdazil, nifurimide, nifiupirinol, nifurquinazol, nifurthiazole, nitrocycline, nitrofurantoin, nitromide, norfloxacin, novobiocin sodium, ofloxacin, onnetoprim, oxacillin sodium, oximonam, oximonam sodium, oxolinic acid, oxytetracycline, oxytetracycline calcium, oxytetracycline hydrochloride, paldimycin, parachlorophenol, paulomycin, pefloxacin, pefloxacin mesylate, penamecillin, penicillin G benzathine, penicillin G potassium, penicillin g procaine, penicillin g sodium, penicillin V, penicillin V benzathine, penicillin V hydrabamine, penicillin V potassium, pentizidone sodium, phenyl aminosalicylate, piperacillin sodium, pirbenicillin sodium, piridicillin sodium, pirlimycin hydrochloride, pivampicillin hydrochloride, pivampicillin pamoate, pivampicillin probenate, polymyxin B sulfate, porfiromycin, propikacin, pyrazinamide, pyrithione zinc, quindecamine acetate, quinupristin, racephenicol, ramoplanin, ranimycin, relomycin, repromicin, rifabutin, rifametane, rifamexil, rifamide, rifampin, rifapentine, rifaximin, rolitetracycline, rolitetracycline nitrate, rosaramicin, rosaramicin butyrate, rosaramicin propionate, rosaramicin sodium phosphate, rosaramicin stearate, rosoxacin, roxarsone, roxithromycin, sancycline, sanfetrinem sodium, sarmoxicillin, sarpicillin, scopafungin, sisomicin, sisomicin sulfate, sparfloxacin, spectinomycin hydrochloride, spiramycin, stallimycin hydrochloride, steffimycin, streptomycin sulfate, streptonicozid, sulfabenz, sulfabenzamide, sulfacetamide, sulfacetamide sodium, sulfacytine, sulfadiazine, sulfadiazine sodium, sulfadoxine, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethoxazole, sulfamonomethoxine, sulfamoxole, sulfanilate zinc, sulfanitran, sulfasalazine, sulfasomizole, sulfathiazole, sulfazamet, sulfisoxazole, sulfisoxazole acetyl, sulfisboxazole diolamine, sulfomyxin, sulopenem, sultamricillin, suncillin sodium, talampicillin hydrochloride, teicoplanin, temafloxacin hydrochloride, temocillin, tetracycline, tetracycline hydrochloride , tetracycline phosphate complex, tetroxoprim, thiamphenicol, thiphencillin potassium, ticarcillin cresyl sodium, ticarcillin disodium, ticarcillin monosodium, ticlatone, tiodonium chloride, tobramycin, tobramycin sulfate, tosufloxacin, trimethoprim, trimethoprim sulfate, trisulfapyrimidines, troleandomycin, trospectomycin sulfate, tyrothricin, vancomycin, vancomycin hydrochloride, virginiamycin, and zorbamycin. Penicillin G, which is used as an antibacterial agent for infections including pneumonia, meningitis, and skin, bone, joint, stomach, blood, and heart

valve infections, is a particular example suitable for use herein. tazobactum, sold under the trade names ZOSYN™ and TAZOCIN™, ceftrioxone, sold under the trade name ROCEPHIN™, and metronidazol, sold under the trade name FLAGYL™, are also used to treat bacterial infections and are further examples of suitable compounds that can be used to prepare the disclosed ionic liquids.

These and other suitable antibacterials can be identified based on the desired properties of the antibacterial and whether the antibacterial active is or can be converted into an ion. As noted, identification of whether an antibacterial active is an ion or can be converted into an ion can be done by a skilled artisan inspecting the chemical structure of the antibacterial.

Specific Examples of Antiviral

When antiviral activity is a desired property of the disclosed ionic liquids, one or more of the ions in the disclosed ionic liquids can be an antiviral. Examples of suitable antiviral actives include, but are not limited to, acemannan, acyclovir, acyclovir sodium, adefovir, alovudine, alvircept sudotox, amantadine hydrochloride, aranotin, arildone, atevirdine mesylate, avridine, cidofovir, cipamfylline, cytarabine hydrochloride, delavirdine mesylate, desciclovir, didanosine, disoxaril, edoxudine, enviradene, enviroxime, famciclovir, famotine hydrochloride, fiacitabine, fialuridine, fosarilate, foscarnet sodium, fosfonet sodium, ganciclovir, ganciclovir sodium, idoxuridine, kethoxal, lamivudine, lobucavir, memotine hydrochloride, methisazone, nevirapine, penciclovir, pirodavir, ribavirin, rimantadine hydrochloride, saquinavir mesylate, somantadine hydrochloride, sorivudine, statolon, stavudine, tilorone hydrochloride, trifluridine, valacyclovir hydrochloride, vidarabine, vidarabine phosphate, vidarabine sodium phosphate, viroxime, zalcitabine, zidovudine, zinviroxime, and Tamiflu.

These and other suitable antivirals can be identified based on the desired properties of the antiviral and whether the antiviral is or can be converted into an ion. As noted, identification of whether an antiviral is an ion or can be converted into an ion can be done by a skilled artisan inspecting the chemical structure of the antiviral.

Specific Examples of Pesticidal Actives

When pesticidal activity is a desired property of the disclosed ionic liquids, one or more of the ions in the disclosed ionic liquids can be a pesticide. Included within the meaning of "pesticide" are insecticides and fungicides. Examples of suitable pesticides include, but are not limted to, carfentrazone-ethyl, sulfentrazone, clomazone, diclofop-methyl, oxamyl propargite, prosulfuron, pyridate, pyriftalid, S-metolachlor, simazine, terbuthylazine,

terbutryn, triasulfuron, trifloxysulfuron, trinexapac-ethyl, ametryn, atrazine, benoxacor, bifenthrin, butafenacil, choline azide, chlortoluron, cinosulfuron, clodinafop, cloquintocet, DEET, desmetryn, dicamba, dimethachlor, dimethametryn, DTPA NaFe, EDDHA NaFe, fenclorim, flumetralin, fluometuron, fluthiacetmethyl, halosulfuron, isoproturon, metobromuron, metolachlor, norflurazon, oxasulfuron, piperophos, pretilachlor, primisulfuron, prometryn, propaquizafop, acibenzolar-s-methyl, chlorothalonil, cyproconazole, cyprodinil, difenoconazole, fenpropidin, fenpropimorph, furalaxyl, metalaxyl, metalaxyl-m, oxadixyl, penconazole, propiconazole, pyrifenox, thiabendazol, abamectin, bromopropylate, cypermethrin, cypermethrin high- cis, cyromazine, diafenthiuron, diazinon, dichlorvos, disulfoton, emamectinbenzoate, fenoxycarb, formothion, furathiocarb, lufenuron, methidathion, permethrine, codlemone, phosphamidon, profenofos, pymetrozine, quinalphos, terrazole, thiamethoxam, thiocyclam, thiometon, triallate, trifloxystrobin, vinclozolin, zetacypermethrin, and the like. Prohexadione is a FDA approved reduced risk fungicide and is also useful for the disclosed ionic liquids. Further examples of suitable pesticides can be found in The Pesticide Manual, 11th Edition, British Crop Protection Council, 1997, which is incorporated by reference herein at least for its teaching of pesticides.

These and other suitable pesticides can be identified based on the desired properties of the pesticide and whether the pesticide is or can be converted into an ion. As noted, identification of whether a pesticide is an ion or can be converted into an ion can be done by a skilled artisan inspecting the chemical structure of the pesticide.

Specific Examples of Herbicidal Actives

When herbicidal activity is a desired property of the disclosed ionic liquids, one or more of the ions in the disclosed ionic liquids can be a herbicide. Examples of suitable herbicides include, but are not limited to, carfentrazone, imazapyr, benefin, acifluorfen, and 2-[2-chloro-3-(2,2,2-trifluoroethoxymethyl)-4-methylsulfonylbenzoyl]cyclohexane-1.

Other suitable herbicides include inhibitors of the biosynthesis of branched amino acids such as ethoxysulfuron, flumetsulam, halosulfuron, imazamox, imazapyr, imazaquin, imazethapyr, metosulam, nicosulfuron, primisulfuron, prosulfuron, rimsulfuron, thifensulfuron-methyl, triflusulfuron, N-[(4,6-dimethoxypyrimidin-2-yl)aminocarbonyl]-2-dimethylaminocar-bonyl-5-formylaminobenzenesulfonamide (Foramsulfuron), and the like. Still further, suitable herbicides include inhibitors of the photosynthesis electron transport such as ametryne, atrazine, bromoxynil, cyanazine, diuron, hexazinone, metribuzin, pyridate, terbuthylazine, and the like. In yet further examples, suitable herbicides for the disclosed ionic liquids include synthetic auxins such as copyralid, dicamba, diflufenzopyr, fluroxypyr,

and the like. Inhibitors of fatty acid biosynthesis, such as butylate, EPTC, fenoxaprop-P-ethyl, and the like, can also be used in the disclosed ionic liquid compositions. In other examples, suitable herbicides can include inhibitors of cell division such as acetochlor, alachlor, dimethenamid, flufenacet, mefenacet, metolachlor, S-metolachlor, thenylchlor, and the like. In still other examples, the herbicide can be an inhibitor of protoporphyrinogen oxidase, such as fluthiacet-methyl, carfentrazone-ethyl, and the like. Inhibitors of hydroxyphenylpyruvate dioxygenase, such as isoxaflutole, mesotrione, sulcotrione, 4-(4-trifluoromethyl-2-methylsulfonylbenzoyl)-5-hydroxy-1-methyl-3-methylpyrazole, and the like, can also be used. Further examples of suitable herbicides include, but are not limited to, glyphosate, pendimethalin, trifluralin, asulam, triaziflam, diflufenican, glufosinate-ammonium, and the like. Clofencet, fluroxpyr, mesosulfuron, diflufenzopyr are further examples of suitable herbicides and they are FDA approved.

Specific Examples of Other Ions

In addition to the pharmaceutical, antibacterial, antiviral, pesticidal, and herbicidal actives disclosed herein, other compounds that are ions or can be converted to ions can be used in the disclosed ionic liquid compositions. Specific examples of these include, but are not limited to, the food additives Allura Red AC (FD&C Red No.40), Tartrazine (FD&C Yellow No. 5), Indigotine (FD&C Blue No.2), Erythrosine (FD&C Red No.3), and Sunset Yellow (FD&C Yellow No. 6), which are FDA-approved color additives for food use. Further, nutraceuticals such as fatty acids, cholesterols, vitamins, minerals, and trace elements can be suitable ions for the disclosed ionic liquid compositions. SEA-NIN-211 is an antifoulant that can be used as an ion id the disclosed compositions.

LIQUID ION PAIRS

Dual functioning organic salts that do not behave as free ions either neat or in a solvent (including water) will retain the functionality of each ion in close enough proximity to lead to synergistic effects. The degree of association (or conversely dissociation) will affect the physical, chemical, and importantly, the biological properties.

- Ion pairing/clustering which imparts some extra (other than merely additive) effect in operation, e.g., enhances the therapeutic effect or increases the activity of the individual ions OR decreases the activity! While this latter may often seem to be unimportant there are cases where it would be desirable, e.g., in slow release formulations (activity here may refer to solubility or rate of diffusion from the reservoir).

- The ability to "design" a liquid salt that is the thermodynamically most stable state AT a specific temperature, i.e., NOT a quenched amorphous phase that may crystallize, is important as this offers opportunities in formulation of, e.g., emulsions and will almost always provide a more soluble or dispersible form than a crystalline form.
- The concept of specific stoichiometric salts – note that this sort of clustering may also be of import.
- The activity of drugs in the body is not the only consideration, but also the formulation advantages that may accrue from having an ion-pairing or ion-clustering salt.
- In applications other than drugs (though also applies here, particularly to pro-drugs that hydrolyze or easily degraded drugs – analogous to protection against UV degradation by formulation as inclusion complexes), some of the advantages will be in the ability to create a liquid formulation that DOES NOT require water – advantages are a) stabilization; b) ease of dispersion/dissolution upon introduction into an aqueous system and c) possibilities to dissolve other substances in these salts – for example "edible IL to dissolve drugs" – the liquid salts could be used to dissolve other solid actives.

Many examples of liquid organic salts are far from fully ionized. Instead, they form ion pairs and aggregates of ions in the liquid state and are better described as Liquid Ion Pairs than "Ionic Liquids". The distinction between these states can be made on the basis of the behavior of the transport property data when plotted in a Walden plot. The Walden plot is a graph of log equivalent conductivity (corrected for molar volume) *vs.* log fluidity and thus may be used to estimate the degree of association cations and anions (as correlated motion of cation and anion clusters). Ionic Liquids typically lie within one order of magnitude of the "Ideal Ionic Liquid" line (that line on which salts which exhibit no correlated motion of cation and anion lie) meaning that they are between 10 and 100% ionic. Liquid Ion Pairs lie beyond this region, i.e., more than one order of magnitude away from the Ideal line. Such liquid salts are less than 10% ionized. Examples of such liquid salts of therapeutic ions include propanthaline tosylate which is about 1% ionized, as estimated from the Walden plot (Fig. 7).

This degree of association of cations and anions (as ion pairs or larger clusters) will affect various physico-chemical properties of the salts; for example, greater "ion-pairing"

(which should be understood to mean clustering of any number of cations and anions) will yield a more fluid and more volatile salt as ion pairs (or clusters) move as single entities and may be vaporized as uncharged clusters which thus more readily escape the liquid due to decreased coloumbic interactions with the bulk.

If such ion-pairing, or clustering, persists in solution cation or anion interactions with the environment, e.g., the body, will not simply be additive and the salt will not behave in the same way as a 1:1 molar mixture of salts containing the same cation and anion. In addition, such ion-pairing, or ion-clustering, salts may form a separate phase in certain solvent systems and may thus be utilized as emulsions or other dispersed phases. The non-additive effect of cation and anion in ion-paired, or clustered, salts may be either synergistic (enhanced efficacy) or antagonistic (decreased efficacy) and this allows modulation of properties by judicious choice of cation/anion pairs in salt formation.

Opportunities exist for the preparation of:

- Enhanced therapeutic salt substances which combine:
  - 2 API ions chosen for specific activity
  - an API ion and second active which alters physicochemical properties such as lipophilicity, thus changing, for example, membrane or transdermal transport
  - an API ion and second ion which serves to mask unpleasant taste and/or smell
  - animal therapeutic substances
- Enhanced agrochemical substances which may have similar effects to those above and
  - yields a material easily dispersible in a second carrier, for example, as an emulsion, which nonetheless retains its lipophilicity and thus is not easily removed from surfaces, e.g. leaves

SOLVATES/HYDRATES

Liquid salts can exist in a defined intermediate stage where they are solvated, but not 'in solution. This stage is characterized by all solvent present in the liquid salt being bound rather than free as demonstrated by DSC and other data.

A convenient method of determining the point where an ionic liquid containing dissolved water becomes an aqueous solution, in which water is the solvent rather than the solute, is low temperature thermal analysis. By this means we can determine the point, with increasing water content, at which the crystallization and melting of bulk ice first appears in the mixtures. The low temperature phase behaviour of aqueous salt solutions has been extensively studied in the context of cryobiology (Angell, C.A., D.R. MacFarlane *et al.*,

Journal of Physical Chemistry, 1981. 85 p.1461-1464; MacFarlane, D.R., R.K. Kadiyala, and C.A. Angell, *Journal of Chemical Physics, 1983.* 79 p. 3921-3927; *Journal of Physical Chemistry,1983.* 87 p. 1094-1095; MacFarlane, D., *Cryobiology, 1985.* 22 p. 601-602; MacFarlane, D.R., *Cryobiology, 1986.* 23 p. 559-560; MacFarlane, D.R., *Cryobiology, 1986.* 23 p. 230-244;MacFarlane, D.R., *Cryobiology, 1987.* 24 p. 181-195). Typical binary phase diagrams have been established and show the characteristics illustrated in Fig 1.

At high water contents (Region A of the diagram) the sample will crystallize ice during cooling in the DSC and exhibit a subsequent melting peak during warming. This peak is more precisely described as the ice liquidus peak, corresponding to the process of ice dissolution into the solution. The liquidus line of ice in these solutions is denoted TL.

At lower water contents, corresponding to the middle of this diagram, Region B, the ice crystalisation during cooling, or at low temperatures during subsequent warming, becomes less extensive and more sluggish, since less bulk water is available to freeze into ice. Annealing experiments can be used to allow the ice to form and one observes the liquidus line falling rapidly in Region B. In the absence of a fully formed eutectic, which is common in many aqueous – salt binaries, part of the solution remains unfrozen during the cooling or annealing treatment. This part contains all of the salt and some water. The composition of the unfrozen part can be estimated from the phase diagram and the lever rule. Evidence for this can also be seen via the appearance of a glass transition at temperature denoted Tg' in the partially frozen solution. Since the composition of the unfrozen fraction is independent of starting concentration, Tg' is almost composition independent through regions A and B as seen in the diagram.

At some point in region B, depending on the cooling rate applied, it will be possible to quench the sample into the glassy state without the crystallisation of any ice. The warming DSC trace then will show the true Tg for that composition (marked as Tg in Fig 1). Typically Tg is a strong function of composition through regions B and C. Despite the ability to quench into a fully glassy state, the sample can still crystallize ice during warming in region B, indicating that solvent water still exists in the solution.

However, in region B TL is rapidly approaching Tg and, at the composition where it falls below Tg, formation of ice becomes an insignificant event on any measurable timescale. At that point it can be said that the solution shows no evidence, on any measurable timescale, of "solvent" water and that the remaining water is involved in direct solvation interactions with the ions. This marks the beginning of region C, which we refer to as the 'hydrate ionic liquid' region. In this region the ionic liquid should be considered to be the solvent.

Note that it is possible that the melting point of the pure salt may be higher than room temperature, or even higher than 100°C. If the addition of the solute amount of water to the salt to form a mixture of composition in region C is sufficient to lower the melting point of the salt to below room temperature (or other temperature of interest) then the mixture can still be considered to be a hydrate ionic liquid. The important properties of such mixtures is that they are still (in common with single component ionic liquids) liquids comprised solely of ions, in this case hydrated ions.

The use of the term "hydrate" here is justified by its use in solid state chemistry to describe salts which contain water molecules in their crystal structures. In many cases eg $Ca(NO_3)_2.4H_2O$, there is a well understood metal solvation involved such that one could consider this salt to be $Ca(H_2O)_4(NO_3)_2$. Indeed it melts *congruently* at 65°C to a fluid, conductive liquid state. Such hydrate salt ionic liquids have been studied in detail (MacFarlane, D.R. and D.K.Y. Wong, *Journal of Physical Chemistry, 1985.* 89 p. 5849-5855; MacFarlane, D.R. and C.A. Angell, *Journal of Physical Chemistry, 1984.* 88 p. 4779-4781). The solid hydrate salts often contain a variable number of water molecules suggesting a solid solution situation exists in some cases. Nonetheless these salts are still referred to as hydrates. We therefore propose that the parallel situation in which a liquid salt-water mixture containing a variable amount of solute water be referred to as a hydrate ionic liquid as long as it exists in Region C of the binary phase diagram.

INTERMEDIATE PARTIALLY IONIZED LIQUID PHASES:

Without wishing to be bound by theory, for the purposes of the present disclosure, when a disclosed acid (HA) is combined with a disclosed base (B), an equilibrium can exist as follows:

$$\mathbf{HA + B \leftrightarrow [BH]A}$$

As such, the combination of a functional acid, HA, and a functional base, B, can produce liquid compositions having a dual function or capacity, i.e., the properties of each individual component. Disclosed herein are examples of an acid that is a solid at room temperature which when combined with a base that is a solid at room temperature, leads to a liquid that is a partially ionized composition. Therefore, the formulator, by contoling the equilibrium, can also adjust or modifiy the physical, chemical, and biological properties of the final compound.

MULTIPLE FUNTIONAL CO-IONIC LIQUIDS

Disclosed herein are pharmaceutically active, multiply functional co-ionic liquids comprising oligomeric cations or anions and wherein the co-ionic liquids provide a method for the modification of physico-chemical properties of pharmaceutically active salts. Used here, the term "co-ionic liquids" includes ionic liquids with excess of any free base in equilibrium with the cation or excess of any free acid anion in equilibrium with the anion; thus it is possible to prepare pharmaceutically active ionic liquids with dimeric or oligomeric ions of the type:

$$[B'_yHB]^+A^- \xleftarrow{y\ B'} HB^+A^- \xrightarrow{x\ HA'} B^+[A(HA')_x]^-$$

These compositions differ from conventional mixture of ionic liquids with neutral compounds by the fact that a proton is shared between anion and any acid or between cation andany base and all components are therefore present as ions.

These compositions also differ from conventional mixtures of ionic liquids by the fact that the total amount of cationic compounds is not balanced by the total amount of anionic compounds anymore, although an overall cation:anion ratio of 1:1 is obtained.

For example, whereas a conventional ionic liquid would have been 1 part cation, 0.5 part first anion, and 0.5 part second anion, the co-ionic liquids disclosed in this invention can be 1 part cation, 1 part first anionic unit and 1 part of a second anionic unit that are in proton exchanged to form one mixed anion with a total charge of -1.. When the disclosed ionic liquid compositions have two or more ions with a bioactive property (*e.g.*, pharmaceutical active ingredients, pesticidal actives, herbicidal actives, and the like), these compositions can be particularly desired because each of the active ingredients in the composition would have the same solubility and would dissolve together when formulated or administered.

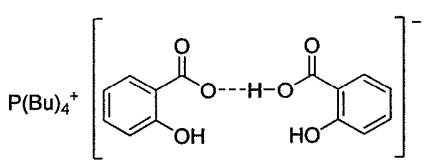
The present invention provides in a first aspect a method to transform solid salts into liquid mixtures by simply changing the stoichiometry of the active pharmaceutical salts without addition of a new compound that might completely alter the biological properties. This can be particularly useful when overcoming formulation, solubility, bioavailability, size, and polymorphism issues.

In the current invention, it is not even necessary to add an additional equivalent of acid or base to form dimeric anions or cations. For example, an co-ionic liquid composition disclosed herein can eliminate the melting point of a solid salt by addition of sub-stoichiometric amounts of acid, as it is demonstrated in the example with tetrabutylphosphonium salicylate: an excess of 0.1 equivalent of salicylic acid does already reduce the melting point of the conventional salt from 57 to 39 °C, and a 0.3 molar excess

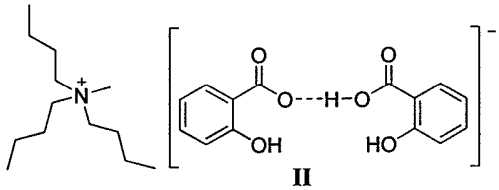
completely eliminates the melting point to yield a free flowing liquid (Fig. 2), despite the fact that both ionic liquid and free acid are solid at room temperature. A permanent proton exchange between anion and corresponding acid is present in these coionic liquids making both species undistinguishable on a NMR time scale. The degree of additional acid or base does therefore affect various physico-chemical properties of the salts; for example, the formation of a "super-anion" or "super-cation" (which is a result of a proton exchange between the ion and the corresponding acid or base) will lead to a permanent delocalization of charge and depress the melting point or completely eliminate crystallization. The presence of distinct oligomeric species, e.g. dimeric or trimeric anions can be demonstrated via conductivity measurements: The presence of local maxima for conductivity of $P(Bu)_4[(Sal)_xH]$ for the species $P(Bu)_4Sal_2H$ and $P(Bu)_4Sal_3H$ strongly indicates the presence of hydrogen-bonded oligomeric anions (Fig. 3).

Current strategies for reduction of melting point of pharmaceutical active salts mainly rely on the formation of conventional eutectics, however, this includes the addition of a third and different compound that could completely alter the chemical properties of the salt. Our invention differs by the absence of an eutectic point: Addition of acid or base eliminates the melting point or drives it below the glass transition temperature and will eventually lead to a point of saturation at a certain stoichiometry. Higher concentrations result in the precipitation of excess acid andin a suspension of solid acid in a co-ionic liquid with a dimeric anion. The identity of the cation or of the anion is not critical to the scope of this invention: Independently of the cation, a depression of elimination of the melting point or - in case of salts that appear as glasses - a decrease of the glass transition temperature was observed was observed with different pharmaceutically active acids with 2- or 3-fold excess. Some specific examples of co-ionic liquids include, but are not limited to the pharmaceutically active anions salicylate and ibuprofenate as well as to the biological active cations cetylpyridinium, lidocainium, ephedrinium, choline or caffeine.

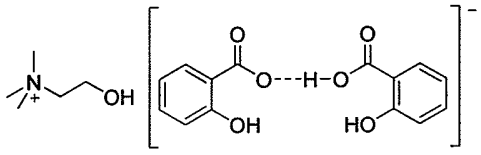
Salicylate is chiefly used in anti-acne formulation, but also in various skin-care products. Ibuprofen is used as an anti-inflammatory and available as over-the-counter analgesic. Lidocaine is a common local anesthetic. Cetylpyridinium is used as an antiseptic agent alone or in combination with other drugs for oral and throat care. It is essentially nontoxic and can be applied to the skin or mucous membranes. Besides their pharmaceutical activity, caffeine and ephedrine are also common in dietary supplement.



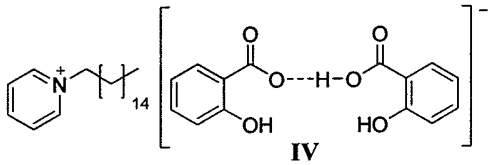
I



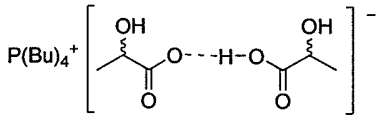
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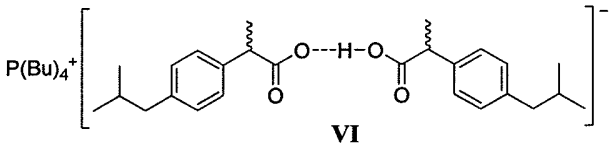
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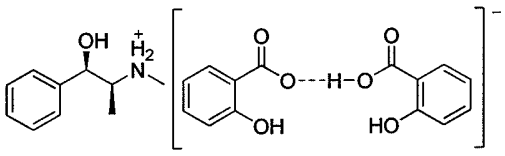
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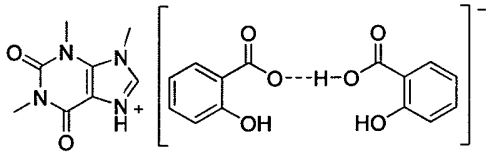
V



VI



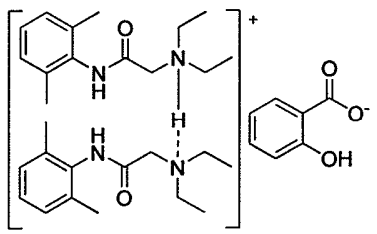
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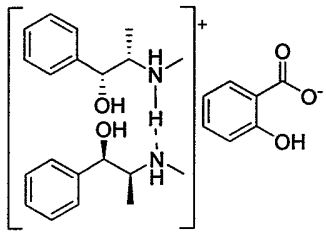
VIII

By example, an elimination of melting point or a reduction of melting point or glass transition with excess acid was obtained for tetrabutylphosphonium salicylate **I**, tributylmethylammonium salicylate **II** choline salicylate **III**, cetylpyridinium salicylate **IV**, tetrabutylphoshonium lactate **V**, tetrabutylphoshonium ibuprofenate **VI**, lidocaine salicylate **VII** and caffeine salicylate **VIII** for tetrabutylphosphonium lactate.

In further examples, the disclosed co-ionic liquid compositions are not limited to higher anionic species, but can be observed almost in the same manner when excess base is added: An excess of lidocaine to the parent salt lidocaine salicylate results not only in a decreased glass transition temperature, but also in a notable reduction of viscosity until at a certain excess of lidocaine a point of saturation is obtained and a solid sample results (Fig. 4). Specific examples of such protic compositions include, but are not limited to, compositions where the cation is a local anesthetic like lidocaine **IX** or a decongestant like ephedrine **X** or one of its diastereomers and are shown below.



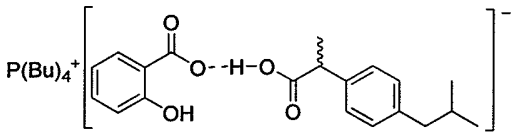
IX



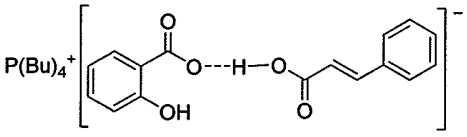
X

In the present invention, the concept double functional co-ionic liquids is not limited to mixtures of a neutral salt with the corresponding acid or base, but can be also applied to the addition of different solid acids or bases other than the parent compounds to obtain liquids type $B[A^1HA^2]$ or $[B^1HB^2]A$. It is therefore possible to expand the scope of ionic liquids to more than two compounds that are none the less all involved in proton-exchange process and therefore differ from a simple solution of a third compound in a conventional ionic liquid.

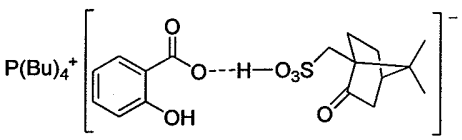
Some specific examples of co-ionic liquids include, but are not limited to the pharmaceutically active anions salicylate and ibuprofenate, or the vitamin niacine. Examples also include chiral species, as it was demonstrated with camphorsulfonic acid.



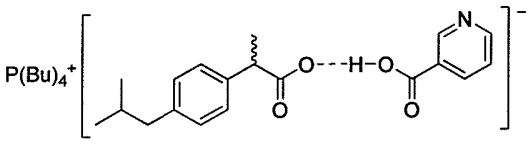
XI



XII

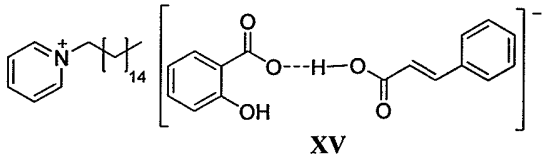


XIII

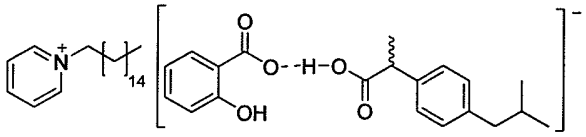


XIV

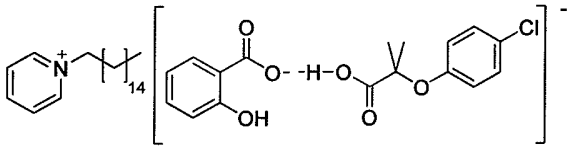
It is notable in all cases a liquid product is obtained with a glass transition temperature at around -50 °C only, although both starting materials tetrabutyl phosphonium salicylate and the shown acids are solid at room temperature. This elimination of melting point is most likely related to a formation of a mixed "super-anion" that is derived from proton delocatization as it was observed in the tetrabutylphosphonium salicylate-salicylic acid dimer. A reasonable difference in pKa of about 2 units is therefore necessary to allow a permanent hydrogen exchange between the acids A^1 and A^2 and the inhibition of crystallization.



XV

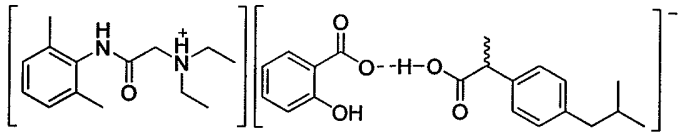


XVI

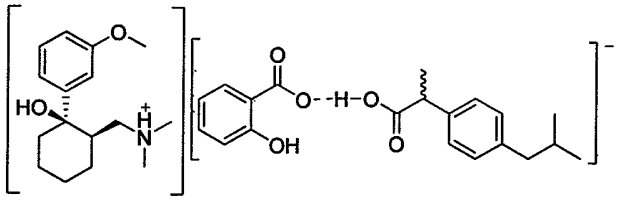


XVII

Other therapeutic useful combinations of 3 or more active compounds include the antibacterial cation cetylpyridinium in combination with various pharmaceutically active anions: Salicylate is chiefly used in anti-acne formulation, but also in various skin-care products. Ibuprofen is used as an anti-inflammatory and available as over-the-counter analgesic, and clofibric acid is used as lipid-lowering agent. Some specific examples of triple functional ionic liquids that show a melting depression compared to the common dual functional co-ionic liquids include, but are not limited to the combinations cetylpyridinium salicylate-cinammate **XV**, cetylpyridinium salicylate-ibuprofenate **XVI** and cetylpyridinium salicylate-clofibrate **XVII**.



XVIII

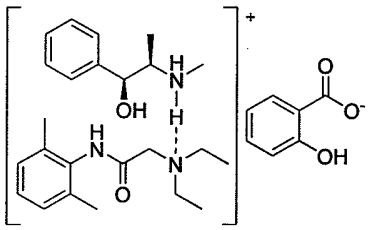


XIX

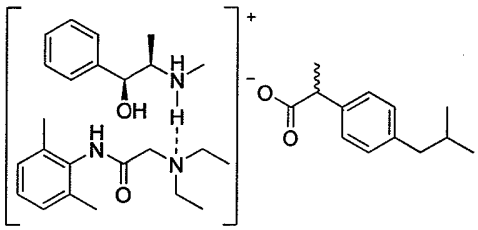
Other examples include co-ionic liquids comprising three analgesics compounds, as demonstrated in the compounds lidocaine salicylate-ibuprofenate **XVIII** and tramadolium salicylate-ibuprofenate **XIX**.

In another embodiment of the disclosed co-ionic liquids relates to ionic liquids comprising two or more biologically functional compoun sharing one proton with the total charge of +1 and one biological functional anion. Non-limiting examples of this embodiment include combinations of the decongestant ephedrine with two analgesic or anaesthetic

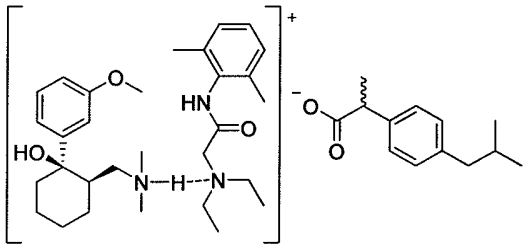
compounds, as present in ephedrinium-lidocainium salicylate **XX** or ephedrinium-lidocainium ibuprofenate **XXI**. Similarly to dimeric anions, triple functional painkillers can be prepared from 3 analgesic compounds like tramadolium-lidocainium ibuprofenate **XXII** or tramadolium-lidocainium salicylate **XXIII**.



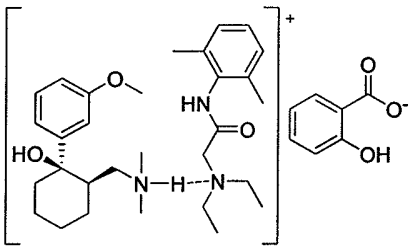
XX



XXI



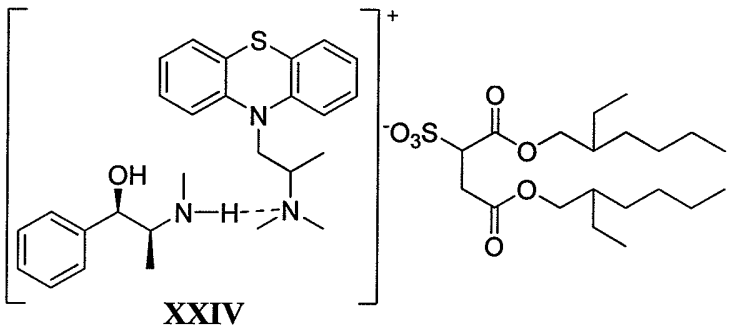
XXII



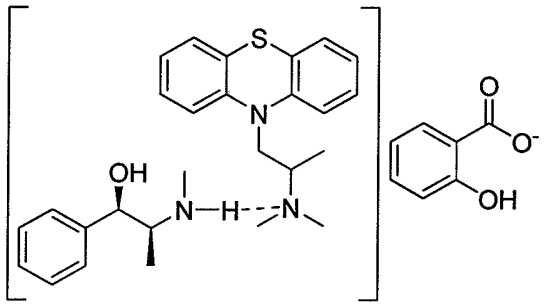
XXIII

Despite the fact that lidocaine, tramadole hydrate, ibuprofene and even the conventional salt tramadolium ibuprofenate are solid at room temperature the co-ionic liquid of the type $[B^1HB^2]A$ was obtained as clear liquid with a glass transition temperature at –37 °C. Synergistic (enhanced efficiency) as previously described for API ionic liquids, e.g. in lidocainium docusate are very likely in these multiple-compound ionic liquids and allow modulation of properties by judicious choice of cation/anions with the desired activities.

Other therapeutically useful combinations include ionic liquids comprised of the decongestant ephedrine and the common antiemetic and antihistaminic promethazine, a combination of promethazine and ephedrine that is established against e.g. seasickness. Triple functional ionic liquids can be obtained in combination with an emollient anion like docusate **XXIV** or with salicylicylate **XXV**. It notable that these triple-functional ionic liquids are not limited to stoichiometric mixtures of the three active compounds in the ratio 1:1:1, but allow individual dosing of a selected compounds, as would be present in the co-ionic liquid promethazine-ephedrinium docusate in the ratio 0.5:1:1.



XXIV



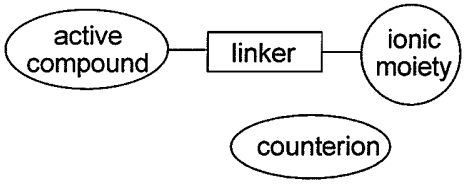
XXV

In a further aspect, this invention relates to solvent-free methods of preparation for co-ionic liquids. The synthesis of double- or multiple functional co-ionic liquids can be easily achieved by stirring additional acid or base with the conventional API IL in an appropriate solvent that dissolves both starting materials, e.g. reaction of cetylpyridinium salicylate and salicylic acid in acetone. Alternatively, if the cation is available as hydroxide salt, direct reaction with the appropriate excess of one ore more acids in a co-solvent will directly give rise to co-ionic liquids of the type $B[A^1HA^2]$, as demonstrated with tetrabutylphosphonium salicylate-salicylic acid.

However, methods of preparation also include solvent-free techniques, e.g. grinding or reaction in molten state. Solid tetrabutylphoshonium salicylate and salicylic acid can be easily liquefied by simple grinding in a mortar or by melting the solid tetrabutylphoshonium salicylate and salicylic acid to obtain the liquid tetrabutylphosphonium salicylate-salicylic acid. This solvent-free preparation technique can be even expanded to the preparation of triple-functional co-ionic liquids directly from the acid/base precursors: Grinding of solid lidocaine, ibuprofenic acid and salicylic acid for 15 minutes at room temperature gave the liquid lidocainium-ibuprofenate-salicylate salt of the type $B[A^1HA^2]$. Similarly, if the melting points of at least one of the starting materials or the product are below the decomposition temperature of the API-IL, the pharmaceutically active co-ionic liquids can be prepared in molten state from the acid-base precursors, as it was demonstrated with the system ephedrinium-salicylate 3:1.

IONIC LIQUID PRODRUGS

This invention relates to the use of ionic liquids for immobilization, delivery, and controlled release of pharmaceutically active liquid or low melting salt compositions. The present invention is based upon the discovery that active compounds, especially pharmaceuticals, can be covalently linked with ionic structural moiety and turned into an ionic liquid by appropriate choice of the counter ion.



Current methods for the modification of the physical properties of solid drugs rely mainly on its transformation into a salt; however, this is limited to acidic or basic pharmaceutically active compounds. The term "active compound" is used to include any pharmaceutically or biologically active compound, but also nutritional, fragrance or flavour compound, as long as a functional group, typically a hydroxy or amine group, is present to covalently attach this compound on the ionic structure. Thus the neutral compound can be transferred into salts, wherein the active compound is immobilized as part of the ionic liquid in either positive or negative charge.

The term "linking unit" comprises a spacer to attach the neutral active compound to the charged moiety, thus it must possess two reactive positions. In the present invention, linking is achieved by esterification of the neutral active compound with a halogenated acid chloride, e.g. chloroacetyl chloride that can be further alkylated with any cation precursor to transfer the neutral compound into a charged species. The labile ester bond allows cleaving the prodrug and liberating the active compound under defined conditions that include, but are not limited to hydrolysis, pH-dependent cleavage, enzymatic hydrolysis, thermical cleavage or photo cleavage.

However, the linking unit is not limited to ester functionalities; basically, any functional group that can be cleaved under defined conditions can be used as linking unit. Examples include, but are not limited to esters, amides, acetals, diorthoesters, vinylethers, dithiols or azo conjugates.

The term "ionic moiety" can include both cationic or anionic groups covalently attached to the active compound. In case of cations, conventional ionic liquids structural motives include, but are not limited to, quaternary ammonium or phosphonium compounds like imidazolium, pyridinium, pyrrolidinium. Special emphasis has to be put

pharmaceutically acceptable cationsthat will leave approved materials after cleavage, e.g. alkylation with trimethylamine will leave betaine after hydrolysis and release of the active compound. The role of this cationic group is, however not limited to conventional ionic liquid cations, it is also possible to attach the neutral active compound to a second, charged active compound.

Alternatively, in case of immobilization of the neutral compound on the anion, any functional group bearing a negative charge can be chosen. Examples include, but are not limited to carboxylates, sulphates, sulphonates or phosphonates.

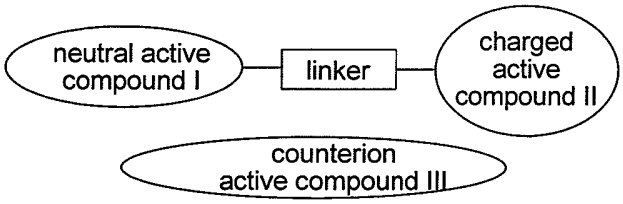
The term "counter ion" can include both cations and anions, including pharmaceutical or biological active compounds. The role of the counterion is to control the physilogical properties of the ionic liquid composition, such as liquid range, hydrophobicity and lipophilicity, melting point, etc. In the current invention, the ionic liquid acts not only as support for the active compounds, being able to store pharmaceuticals in inactive form but also allow a simple tuning of physical properties of compounds that cannot be directly transferred into salts.

This invention provides in a first aspect a synthetic methodology to transfer neutral compounds into liquid salts to overcome polymorphism, overcome solubility and delivery problems, to control release rates, add functionality, enhance efficacy (synergy), and improve ease of use and manufacture. It has been discovered that the physical properties of the active compound are depending both on the type of ionic liquid ion used for immobilization but also on the counter ion. An appropriate choice of the counter ion can therefore be used to dramatically change solubility of the parent compound or turn hydrophilic salts into hydrophobic salts.

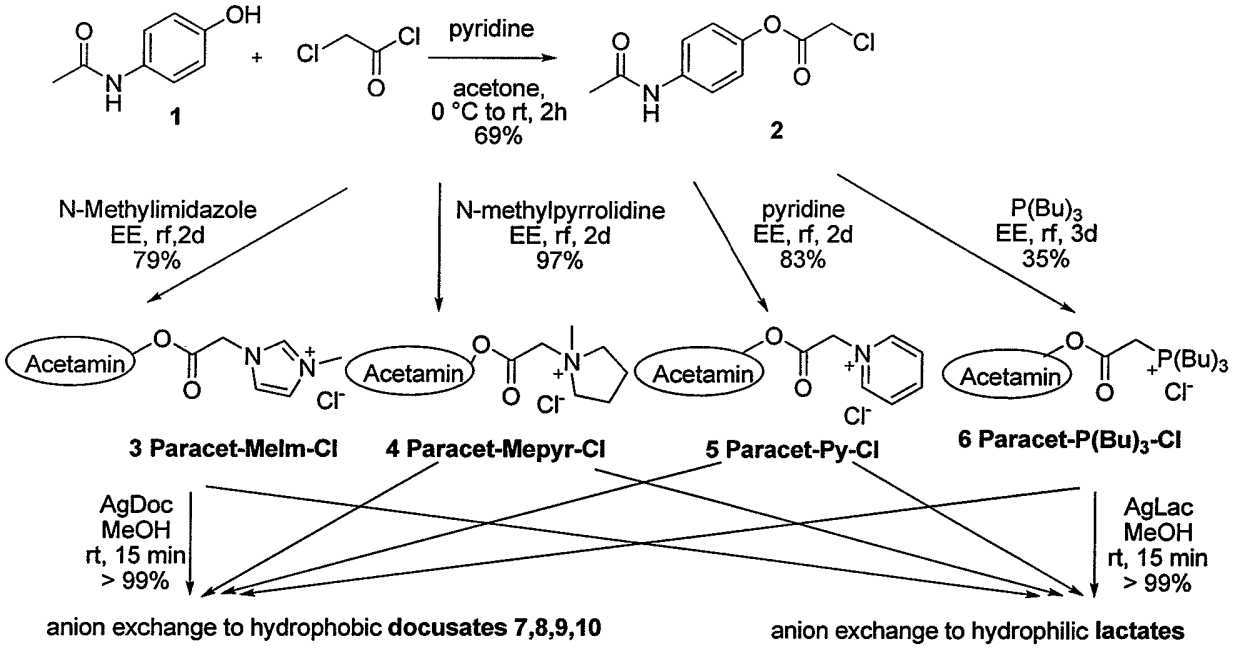
This ionic liquid prodrug approach provides an opportunity to model release kinetics of the active compound on the structure. The choice of linking unit, the covalently attached ionic moiety and the counter ion can all be used to design a prodrug that is labile under defined conditions only. For example, in the present invention it has been demonstrated that a change of ionic liquid unit covalently attached to the active compound can dramatically influence drug release. Specifically, the ionic liquid prodrugs can be considered as versatile liquid delivery systems with a wide range of tuneable properties for neutral compounds.

The invention also provides the possibility to form dual functioning salts by introduction of a second, pharmaceutically or biologically active counter ion or a second, charged active compound. Prodrug decomposition will than provide a neutral and a charged active compound in exactly the same dosage.

This invention also includes triple-functional salts, wherein a neutral active compound is covalently attached to a second, charged active compounds, replace to the typical structural elements that are present in ionic liquids, e.g. imidazolium cations. The constitution of which, can then be paired with a third charged active compounds, which will result in the delivery of 3 active compounds in the same dosage.



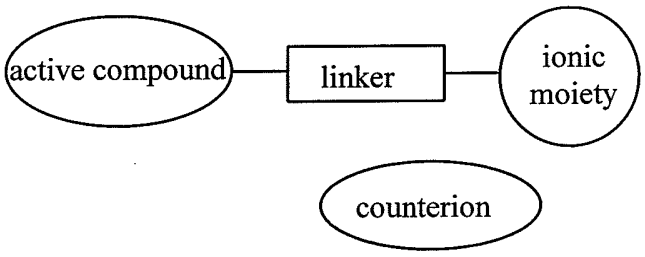
Specific examples in the current invention include ionic liquids prodrugs based on acetaminophen, a widely used analgesic and antipyretic drug used for the relief of fever, headaches, and other minor aches and pains. The phenol proton is not acidic enough to form a stable anion and pair it with appropriate cations; however, we demonstrated that our ionic liquid prodrug strategy can be used to transfer acetaminophen in a stable liquid salt.



IONIC LIQUID SUPPORTED FRAGRANCES

This invention relates to the use of ionic liquids for storage and controlled release of volatile compounds, especially fragrances and flavors as liquid salt compositions. The present invention is based upon the discovery that volatile compounds can be covalently

linked with ionic structural moiety and turned into an ionic liquid by appropriate choice of the counter ion.



Current methods to issue the loss of volatile frangance or flavour compounds address specific delivery systems like microcapsules and carriers for long-lasting scents.

In the current invention, the ionic liquid acts not only as support for the active compounds, being able to store fragrances and flavors or, in general volatile compounds in non-volatile form but also allows a simple tuning of release conditions.

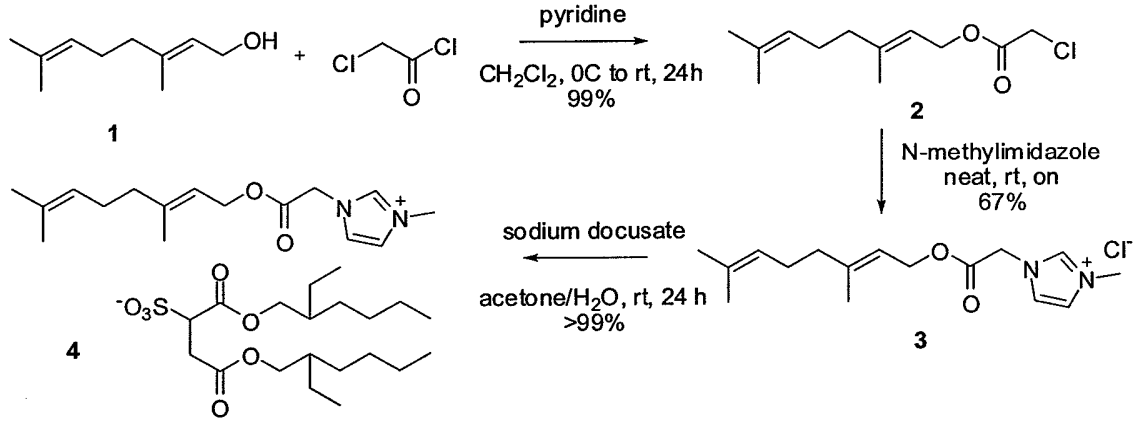
This invention provides in a first aspect a synthetic methodology to transfer neutral volatile compounds into liquid salts to modify physical properties, avoid evaporation, overcome solubility and delivery problems, to control release rates, add functionality, and improve ease of use, storage and manufacture. It has been discovered that the physical properties of the active compound are depending both on the type of ionic liquid ion used for immobilization, the linking unit but also on the counter ion. The term "active compound" is used to include any active compound, but especially nutritional, fragrance or flavor compound, as long as a functional group, typically a hydroxy or amine group, is present to covalently attach this compound on the ionic structure. Thus the neutral compound can be transferred into a low-volatile salt, wherein the active compound is immobilized as part of the ionic liquid in either positive or negative charge. Examples include, but are not limited to fragrance alcohols like geraniol, menthol, prenol, citronellol or farnesol. The term "linker" comprises a spacing unit to attach the neutral active compound to the charged moiety, thus it must possess two reactive positions. For specific examples in the present invention, linking is achieved by esterification of a fragrance alcohol with a halogenated acid chloride, e.g. chloroacetyl chloride that can be further alkylated with any cation precursor to transfer the neutral compound into a charged species. The labile ester bond allows cleaving the prodrug and liberating the neutral active compound under defined conditions that include, but are not limited to hydrolysis, pH-dependent cleavage, enzymatic hydrolysis, thermical cleavage, photo cleavage or electrodecomposition.

However, the linking unit is not limited to ester functionalities; basically, any functional group that can be cleaved under defined conditions can be used as linking unit.

Examples include, but are not limited to esters, amides, acetals, diorthoesters, vinylethers, dithiols or azo conjugates.

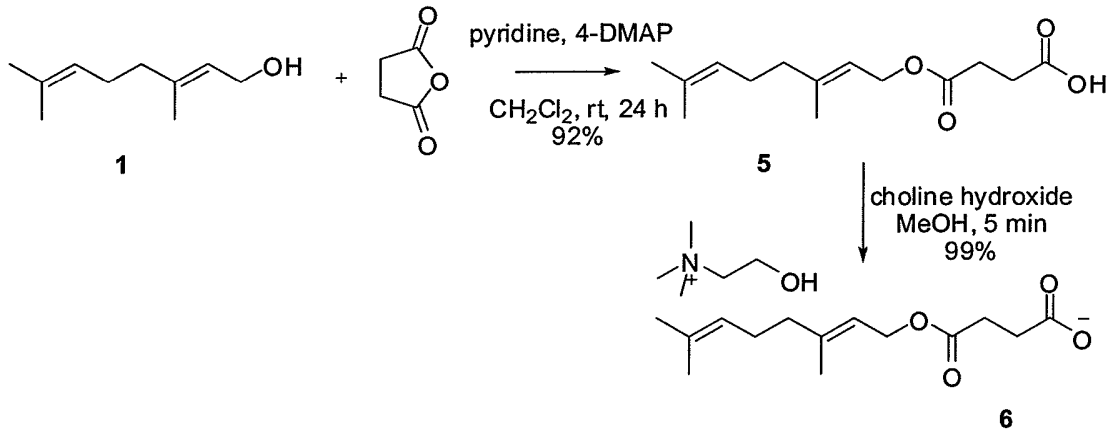
The selection of a particular linker, ionic group and counterion depends on the nature of the product in which the delivery system is to be used as well as on the kind of release mechanism required. For example, in the present invention it has been demonstrated that a change of linking unit can lead to different release systems. Specifically, the ionic liquid compositions can be considered as smart retention and delivery devices for triggered release of fragrance, flavour or any other volatile compound.

By example, the typical fragrance alcohol geraniol can be reacted with chloroacetyl chloride as linking unit and further alkylated with N-methylimidazol to the quaternary imidazolium salt **3**, which provides, as any ionic liquid neglible volatility. Further ion exchange to docusate **4** can dramatically change physical properties, e.g. solubility and turn a hydrophilic chloride salt **3** into a hydrophobic liquid.



Ionic liquid-supported hydrophobic fragrance **4** shows, as typically for any ionic liquid, neglible volatility but can be decomposed by means of heat only to liberate geraniol (Fig. 6).

Food and pharmaceutical regulations restrict the palette of material used for sustained release. The invention also includes example for immobilization of the active compound on the anion of the ionic liquid delivery system, which can be completely composed of GRAS (Generally Recognized As Safe) compounds. A typical example of this type of ionic liquid delivery system includes the immobilization of fragrance alcohols as hemisuccinates that can be further deprotonated with any basic component, e.g. hydroxides of quaternary amines to give an ionic liquid.



1 5 6

Cleavage of ionic liquid immobilized fragrance **6** by the process of acidic, basic or enzymatic ester hydrolysis will release the fragrance and leave only choline (a vitamine) and succinic acid, a compound that is generally recognized as safe (GRAS).

The invention also provides the possibility to form dual functioning salts by introduction of a second active counter ion or a second, charged active compound. Ionic liquid decomposition will than provide a neutral and a charged active fragrance or flavour in exactly the same dosage.

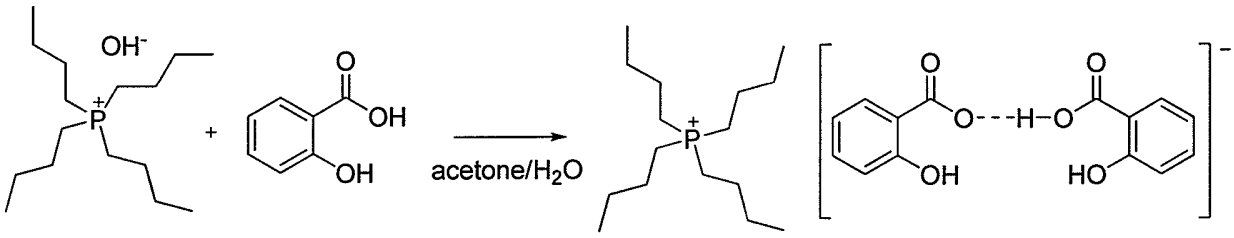
This invention also includes triple-functional salts, wherein a neutral active compound is covalently attached to a second, charged active compounds, replace to the typical structural elements that are present in ionic liquids, e.g. imidazolium cations. The constitution of which, can then be paired with a third charged active compounds, which will result in the delivery of 3 active compounds in the same rate and dosage.

EXAMPLES

The following examples are set forth below to illustrate the methods and results according to the disclosed subject matter. These examples are not intended to be inclusive of all aspects of the subject matter disclosed herein, but rather to illustrate representative methods and results. All chemicals used were of analytical grade, purchased from Sigma-Aldrich (UK), and used without further purification unless otherwise noted. Commercially available solutions of hydroxides were titrated prior to use to determine the exact concentration.

MULTIPLE FUNCTIONAL CO-IONIC LIQUIDS

Example 1: Tetrabutylphosphonium salicylate – salicylic acid



Salicylic acid (5-20 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried under reduced pressure (0.01 mbar, 50 °C) with stirring for 24 hrs. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.74 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.32 (dt, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 6.8 (m, 2H), 2.20 (m, 4 H), 1.41 (m, 8 H), 0.9 (t, J = 7.1 Hz, 6 H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.1. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9(s), 163.1(s), 131.1 (d), 129.8(d), 120.6 (s), 115.7 (d), 115.6 (d), 23.3 (d, J = 16.4 Hz), 22.6 (d, J = 4.8 Hz), 17.3 (d, J = 47.3 Hz), 13.2 (s).

TABLE I

Composition $P(Bu)_4$:Sal	Appearance	mp [°C] [a]	$T_{5\%onset}$ [°C] [c]	water content[% m/m]
1:1	Solid	57	312	0.0766
1:1.1	Solid	52	297	0.1359
1:1.2	Solid	-54 [b]	211	0.1283
1:1.3	Liquid	-54 [b]	207	0.2280
1:1.4	Liquid	-51 [b]	209	0.1308
1:1.5	Liquid	-52 [b]	206	0.1587
1:1.6	Liquid	-50 [b]	200	0.3210
1:1.7	Liquid	-48 [b]	194	0.1807
1:1.8	Liquid	-47 [b]	198	0.1529
1:1.9	Liquid	-46 [b]	198	0.2462
1:2	Liquid	-46 [b]	192	0.1924
1:2.4	Liquid	-45 [b]	184	0.1517
1:2.7	Liquid	-43 [b]	173	0.1412
1:2.8	Liquid	-43 [b]	169	0.1127

1:3.0	Liquid	-43 [b]	164	
1:3.1	Suspension	-43 [b]		
1:3.5	Suspension	-45 [b]		
1:3.7	Suspension	-43 [b]	150	0.1033
Salicylic acid	Solid	158 (lit)	136	

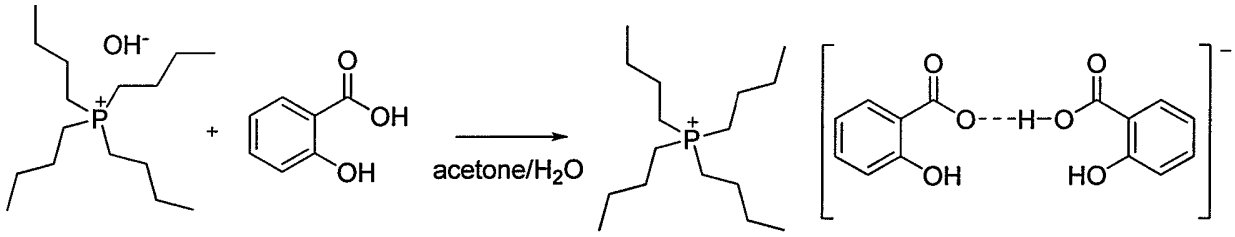
[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature. [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min under nitrogen.

Table I shows thermal data and water content of different tetrabutylphosphonium salicylate-salicylic acid co-ionic liquids.

Figure 2 is a plot of the melting point depression and melting point elimination curves for the data depicted in Table I.

Figure 3 despicts the conductivity of different $P(Bu)_4[Sal_xH]$ compositions in a series of co-ionic liquids comprising oligomeric anions.

Example 2: Tetrabutylphosphonium salicylate - salicylic acid - Solvent-free synthesis via grinding

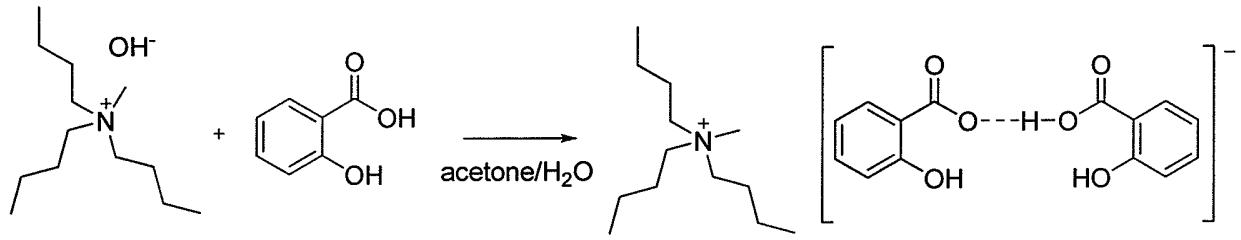


Solid tetrabutylphosphonium salicylate (3.963 g, 10 mmol) and Salicylic acid (1.601 g, 10 mmol) were grinded for 2 minutes in a mortar until a colorless, free-flowing liquid was obtained. Physical data were similar to those obtained with conventional synthesis (example 1).

^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.74 (dd, J_1 = 7.7 Hz, J_2 = 1.87 Hz), 7.32 (dt, J_1 = 7.6 Hz, J_2 = 1.80 Hz, 1H), 6.77 (m, 2H), 2.20 (m, 4 H), 1.41 (m, 8 H), 0.9 (t, J = 7.1 Hz, 6 H).

^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.0 (s), 162.3 (s), 133.8 (d), 130.5 (d), 117.9 (d), 117.1 (s), 116.8 (d), 23.30 (d, J = 15.94 Hz), 22.61 (d, J = 5.31 Hz), 17.31 (d, J = 47.82 Hz), 13.73 (s).

Example 3: Methyltributylammonium salicylate – salicylic acid



Salicylic acid (5-20 mmol) and tributylmethylammonium hydroxide (5 mmol, 40% solution in H_2O) were dissolved in 20 ml of acetone stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs.

^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.63 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.10 (m, 1H), 6.57 (m, 2H), 3.19 (m, 6H), 2.94 (s, 3H), 1.59 (m, 6H), 1.29 (sext, J = 7.4 Hz, 6H), 0.9 (t, J = 7.4 Hz, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9, 162.0, 133.4, 130.1, 117.5, 116.9, 60.4, 47.5, 23.4, 19.2, 13.5.

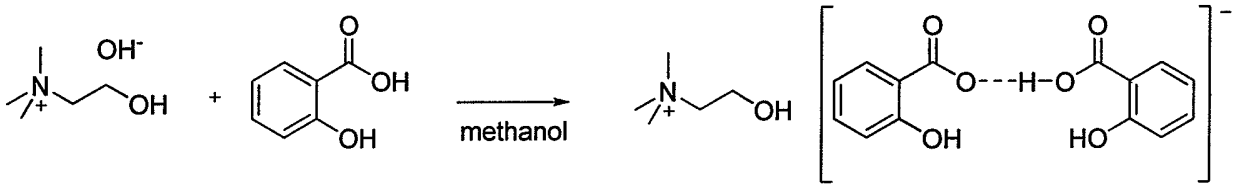
TABLE II

Ratio $N(Bu)_3Me$:Sal	Appearance	mp [°C] [a]	$T_{5\%onset}$ [°C] [c]
1:1	solid	83	193
1:2	liquid	-37[b]	196
1:3	liquid	-41 [b] (T_g)	177

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature. [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min under nitrogen.

Table II shows thermal data of different tributylmethylammonium salicylate-salicylic acid co-ionic liquids.

Example 4: Choline salicylate – salicylic acid



Salicylic acid (5 or 10 mmol) and choline hydroxide (5 mmol, 40% solution in MeOH) were dissolved in 20 ml of methanol and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.64 (dd, J_1 = 7.4 Hz, J_2 = 1.9 Hz, 1H), 7.3 (m, 1H), 6.6 (m, 2H), 3.8 (m, 2H), 3.4 (m, 2H), 3.1 (s, 9H).

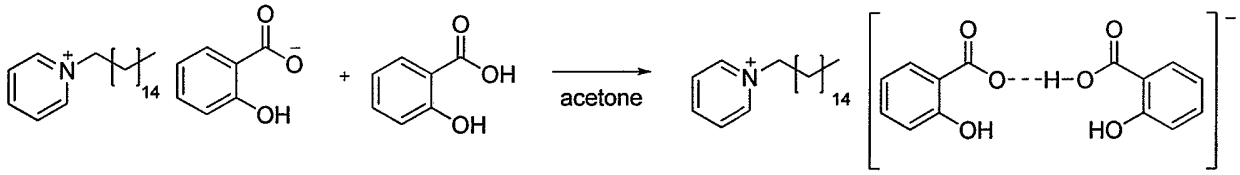
TABLE III

Ratio Cho:Sal	Appearance	mp [°C][a]	$T_{5\%onset}$ [°C][c]
1:1	solid	48 (lit)	203
1:2	liquid	-41 [b]	173

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature. [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min under nitrogen.

Table III shows thermal data of different choline salicylate-salicylic acid co-ionic liquids.

Example 5: Cetylpyridinium salicylate –salicylic acid



Salicylic acid (5-15 mmol) and cetylpyridinium salicylate (5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs.
^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.12 (d, J = 6.1 Hz, 2H), 8.59 (t, J = 8.3 Hz, 1H), 8.16 (t, J = 7.3 Hz, 2H), 7.64 (d, 7.5 Hz, 1H), 7.12 (t, J = 7.5, 1H), 6.57 (m, 2H), 4.59 (t, J = 7.4 Hz, 2H), 1.88 (m, 2H), 1.22 (s, 27H), 0.84 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.8, 163.4, 145.8, 145.2, 131.4, 130.2, 128.4, 121.1, 116.1, 160.0, 61.2, 31.7, 31.2, 29.4, 29.3, 29.2, 29.1, 28.8, 25.8, 22.5, 14.2.

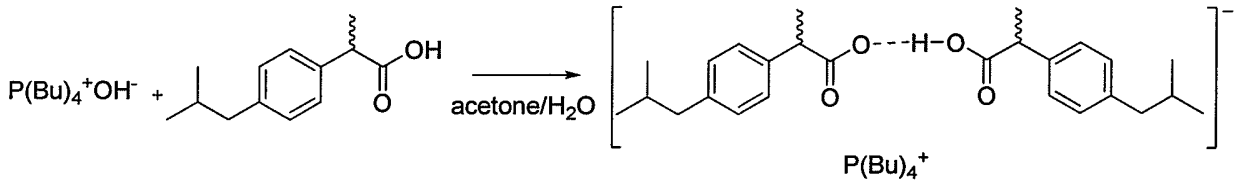
TABLE IV

Ratio CetPy:Sal	Appearance	mp [°C] [a]	$T_{5\%onset}$ [°C] [c]
1:1	solid	71	206
1:2	solid	54	184
1:3	solid	-21 [b]	162

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature. [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min under nitrogen.

Table IV shows thermal data of different cetylpyridinium salicylate-salicylic acid co-ionic liquids.

Example 6: Tetrabutylphosphonium ibuprofenate –ibuprofenic acid



Ibuprofenic acid (5-15 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414g, 5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.13 (d, J = 8.1 Hz, 2H), 6.94 (d, 8.1 Hz, 2H), 3.21 (q, 7.7 Hz, 1H), 2.48 (m, 2H), 2.36 (d, 7.3 Hz, 2H), 2.14 (m, 8H), 1.77 (sept, 6.2 Hz, 1H), 1.40 (m, 16 H), 1.18 (d, J = 7.0 Hz, 3H), 0.91 (t, 7.0 Hz, 12H), 0.84 (d, J = 7.0 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 174.8, 144.2, 136.9, 127.8, 127.2, 49.3, 44.4, 29.7, 23.4 (d, J = 15.8 Hz), 22.7 (d, J = 4.7 Hz), 22.2, 20.5, 17.3 (d, J = 48.1 Hz), 13.3.

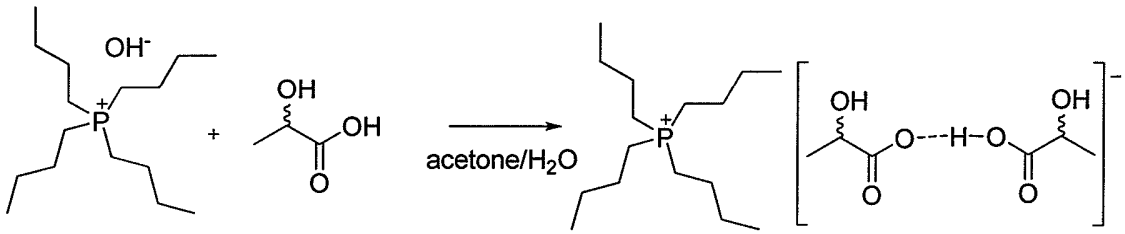
TABLE V

Ratio P(Bu)$_4$Ibu	Appearance	T_g [°C] [a]	$T_{5\%onset}$ [°C] [b]
1:1	liquid	-43	234
1:2	liquid	-40	264
1:3	liquid	-39	189

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min under nitrogen.

Table V shows thermal data of different tetrabutylphosphonium ibuprofenate-ibuprofenic co-ionic liquids.

Example 7: Tetrabutylphosphonium lactate –lactic acid



Lactic acid (5-15 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 3.84 (br s, 1H), 3.44 (q, J = 6.7 Hz, 1H), 2.18 (m, 8H), 1.41 (m, 16H), 1.05 (d, J = 7.2 Hz, 3H), 0.91 (t, J = 6.7 Hz, 12H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.0. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 176.8, 67.3, 23.72 (d, J = 15.5 Hz), 23.01 (d, J = 4.7 Hz), 21.91, 17.70 (d, J = 47.9 Hz), 13.62 (s).

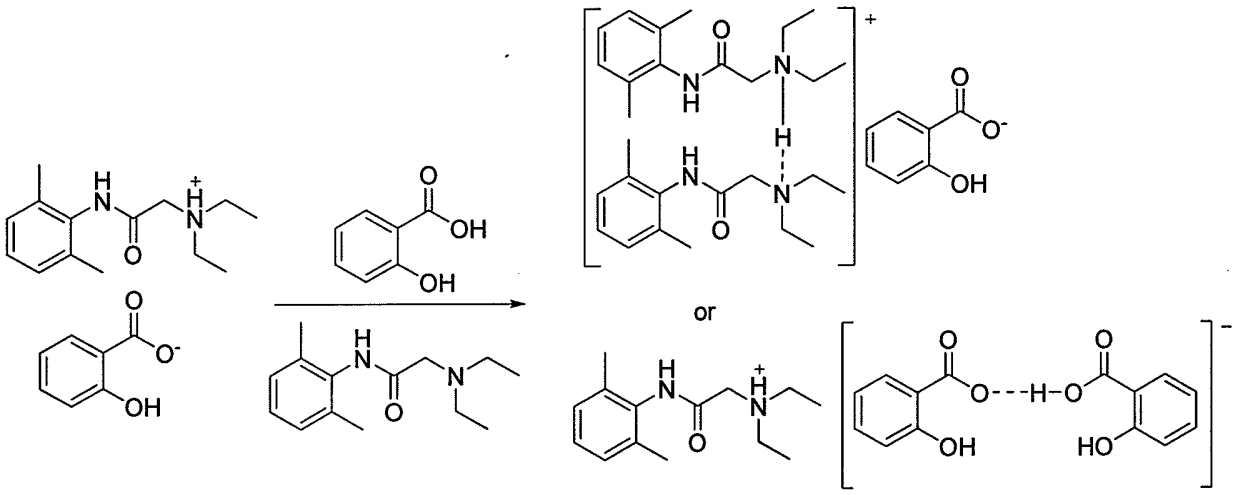
TABLE VI

Ratio $P(Bu)_4Lac$	Appearance	T_g [°C] [a]	$T_{5\%onset}$ [b]
1:1	liquid	1.78 (mp)	262
1:2	liquid	-56	215
1:3	liquid	-55	176

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min. under nitrogen.

Table VI shows thermal data of different tetrabutylphosphonium lactate-lactic acid co-ionic liquids.

Example 8: Lidocaine salicylates



Salicylic acid or lidocaine free base (0.5, 1, 1.5 or 2 eq.) and lidocaine salicylate were suspended in acetone (20 ml) and stirred at room temperature until a clear solution was obtained. The solvent was evaporated and remaining volatile material removed under vacuum (0.01 mbar, 40 °C). ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.05 (br s, 1H), 7.72 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.24 (m, 1H), 7.09 (s, 3H), 6.70 (m, 2H), 3.98 (s, 2H), 3.10 (q, J = 7.3 Hz, 4 H), 2.16 (s, 6H), 1.22 (t, J = 7.3 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9, 164.6, 161.9, 135.0, 134.0, 133.4, 130.1, 127.8, 126.9, 117.6, 116.9, 116.4, 53.3, 48.3, 18.1, 9.5.

TABLE VII

Lid	Sal	Appearance	T_g [°C] [a]	$T_{onset5\%}$ [°C] [b]
3	1	solid	-32	161
2.5	1	solid	-25	137
2	1	glass	-15	154
1.5	1	glass	-1	169
1	1	glass	19	161
1	1.5	viscous liquid	13	142
1	2	viscous liquid	3	138
1	2.5	solid	-4	132
1	3	solid	-3	128
1		solid	69 (mp)	152
	1	solid	160 (mp)	134

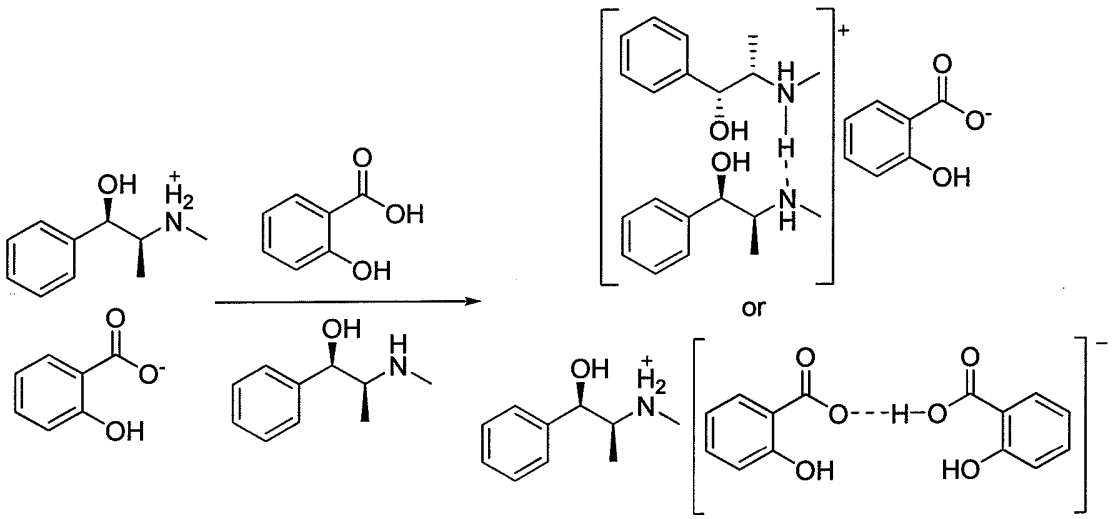
[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with -2.5 °C /min to -80 °C for 3 cycles. [b] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min. under nitrogen.

Table VII shows thermal data of different lidocaine salicylateco-ionic liquids.

Figure 4 depicts the depression of glass transition and saturation of double functional co-

ionic liquids based on lidocainium salicylate.

Example 9: Ephedrine salicylate



Salicylic acid or ephedrine free base (0.5, 1, 1.5 or 2 eq.) and ephedrinium salicylate were suspended in acetone (20 ml) and stirred at room temperature until a clear solution was obtained. The solvent was evaporated and remaining volatile material removed under vacuum (0.01 mbar, 40 °C). ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.30 (br s, 2H), 7.76 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.38 (m, 4H), 7.24 (m, 2H), 6.70 (m, 2H), 6.48 (br s, 1H), 5.21 (s, 1H), 3.41 (m, 1H), 2.69 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.9, 162.1, 141.4, 132.0, 130.3, 128.2, 127.2, 125.8, 119.6, 116.8, 116.0, 69.6, 59.3, 30.6, 9.1.

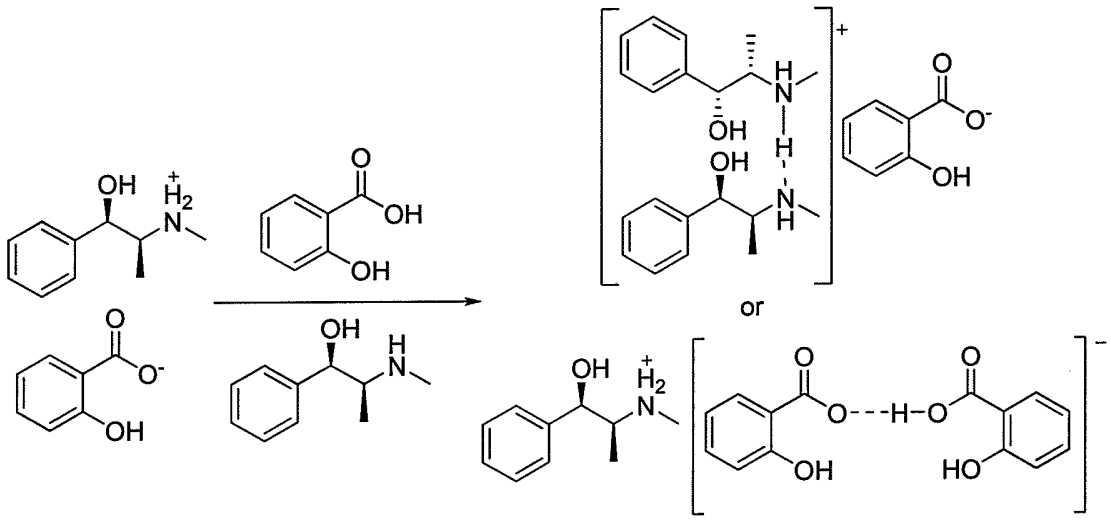
TABLE VIII

Ratio Eph:Sal	Appearance	mp [°C] [a]	$T_{onset5\%}$ [°C] [c]
1:3	solid	61	-
1:2	solid	61	130
1:1	solid	97	161
2:1	glass	2 [b]	127
3:1	liquid	-5[b]	123

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with 5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min. under nitrogen.

Table VIII shows thermal data of different ephedrinium salicylate co-ionic liquids.

Example 10: Ephedrine salicylate – solvent-free synthesis via grinding



Salicylic acid or ephedrine free base (0.5, 1, 1.5 or 2 eq.) and ephedrinium salicylate were grinded for 15 minutes in a mortar. Analytical data were similar to those obtained in conventional synthesis. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.30 (br s, 2H), 7.76 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.38 (m, 4H), 7.24 (m, 2H), 6.70 (m, 2H), 6.48 (br s, 1H), 5.21 (s, 1H), 3.41 (m, 1H), 2.69 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.9, 162.1, 141.4, 132.0, 130.3, 128.2, 127.2, 125.8, 119.6, 116.8, 116.0, 69.6, 59.3, 30.6, 9.1.

TABLE IX

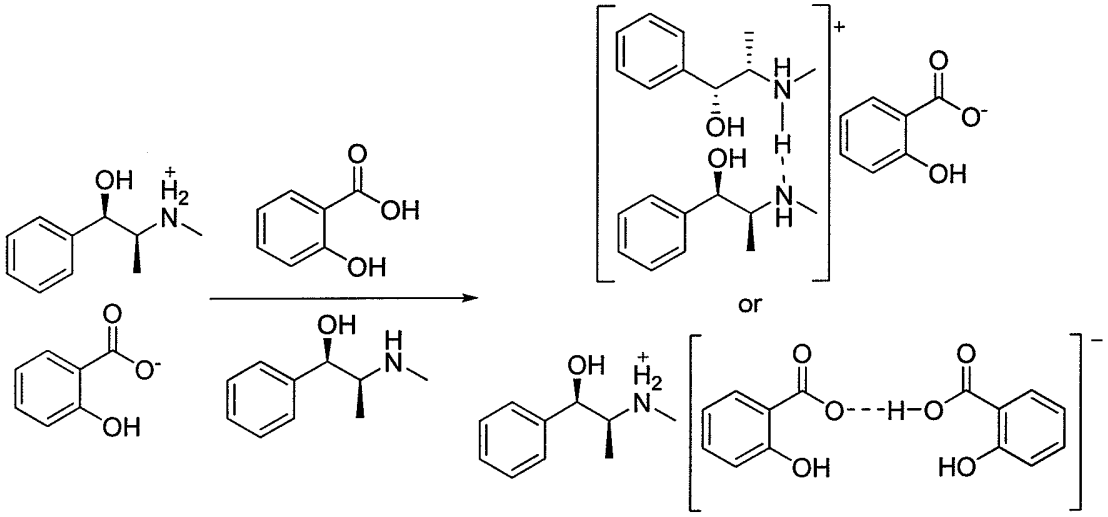
Ratio Eph:Sal	Appearance	mp [°C][a]	$T_{onset5\%}$ [°C] [c]
1:4	solid	61	124
1:3	solid	61	122
1:2	solid	61	131
1:1.4	solid	61	153
1:1.3	solid	60	147
1:1.2	solid	60	154
1:1.1	solid	91	163

1:1	solid	97	161
2:1	glass	5 [b]	118
3:1	liquid	-4 [b]	115

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with 5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min. under nitrogen.

Table IX shows thermal data of different ephedrinium salicylate co-ionic liquids prepared by grinding.

Example 11: Ephedrine salicylate – solvent-free synthesis in molten state



Salicylic acid and ephedrine free base (1, 2 or 3 eq.) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture was cooled to room temperature and, in case of solid products grinded to obtain colourless powders. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.30 (br s, 2H), 7.76 (dd, J_1 = 7.66 Hz, J_2 = 1.80 Hz, 1H), 7.38 (m, 4H), 7.24 (m, 2H), 6.70 (m, 2H), 6.48 (br s, 1H), 5.21 (s, 1H), 3.41 (m, 1H), 2.69 (s, 3H), 0.95 (d, J = 6.76 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.9, 162.1, 141.4, 132.0, 130.3, 128.2, 127.2, 125.8, 119.6, 116.8, 116.0, 69.6, 59.3, 30.6, 9.1.

TABLE X

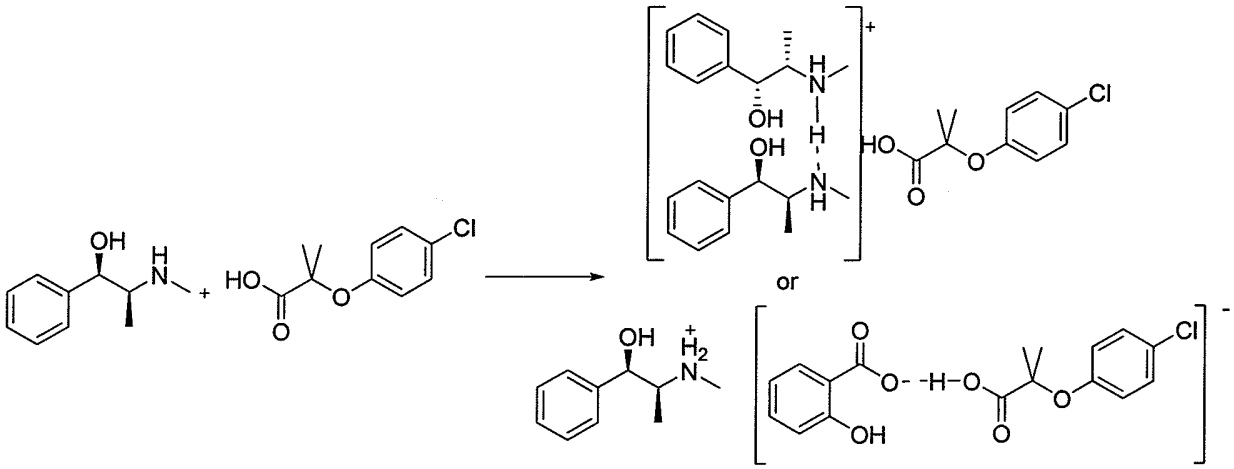
Ratio Eph:Sal	Appearance	mp [°C][a]	$T_{onset5\%}$ [°C] [c]
1:3	solid	61	135
1:2	solid	61	133
1:1	solid	97	161

2:1 .	glass	7[b]	144
3:1	liquid	-2 [b]	128

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with 5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min under nitrogen.

Table X shows thermal data of different ephedrinium salicylate co-ionic liquids prepared by melting.

Example 12: Ephedrinium clofibrate – solvent-free synthesis via melting



Clofibric acid (1 or 2 eq.) and ephedrine free base (1 or 2 eq.) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture was cooled to room temperature and, in case of solid products, grinded to obtain yellow powders. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.36 (br s, 2H), 7.30 (m, 5H), 7.19 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.10 (s, 1H), 3.12 (m, 1H), 2.52 (s, 3H), 1.41 (s, 6H), 0.85 (d, J = 6.6 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 176.8, 155.5, 141.8, 128.5, 128.0, 126.9, 125.8, 123.4, 119.2, 80.2, 69.8, 59.5, 30.7, 25.8, 9.6.

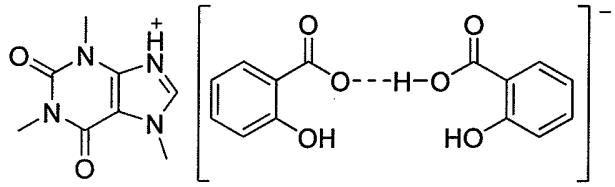
TABLE XI

Ratio Eph:Clofib	Appearance	mp [°C] [a]	$T_{onset5\%}$ [°C] [c]
1:2	glass	12 [b]	182
1:1	solid	131	169
2:1	glass	7 [b]	135

[a] determined on a Mettler Toledo Star^e DSC unit by heating to 110 °C with 5 °C/min and cooling with 5 °C /min to -80 °C for 3 cycles. [b] glass transition temperature [c] determined on a Mettler Toledo Star^e TGA/DSC unit by heating from 25 °C to 600 °C with 5 °C/min. under nitrogen.

Table XI shows thermal data of different ephedrinium clofibrate co-ionic liquids prepared by melting.

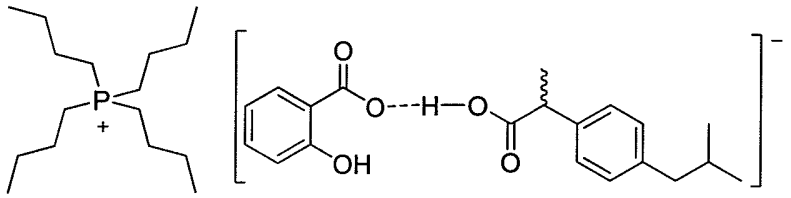
Example 13: Caffeine salicylate – solvent-free synthesis via grinding



Caffeine salicylate (19.40 mg, 0.058 mmol) and salicylic acid (8.06 mg, 0.058 mmol) were grinded for 15 minutes in a mortar at room temperature. A colorless powder was obtained.

^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 11.29 (br s, 1H), 8.01 (s, 1H), 7.90 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 2H), 7.51 (t, J = 7.83 Hz, 2H), 6.94 (m, 4H), 3.07 (s, 3H), 3.41 (s, 3H), 3.21 (s, 3H). mp 122 °C, $T_{5\%onset}$ 111 °C

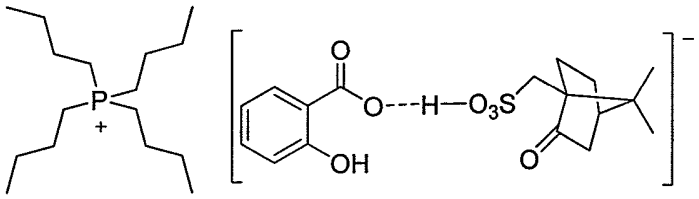
Example 14: Tetrabutylphosphonium salicylate-ibuprofenic acid P(Bu)$_4$[SalIbu]H



Ibuprofenic acid (1.032 g, 5 mmol), salicylic acid (0.6909 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs. The desired compound is isolated as a colourless liquid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.65 (dd, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 7.18 (d, 8.0 Hz, 2H), 7.11 (m, 3H), 6.59 (m, 2H), 3.63 (q, J = 7.2 Hz, 2H), 2.41 (d, 7.2 Hz, 2H), 2.17 (m, 8H), 1.80 (sept, J = 6.70, 1H), 1.42 (m, 16 H), 1.34 (s, J = 7.1 Hz, 3H), 0.9 (t, J = 6.9 Hz, 12 H), 0.85 (d, 6.7 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 175.4, 171.2, 162.9, 139.5,138.5, 131.3, 129.9, 128.9, 127.1, 115.9, 115.8, 44.3, 44.2, 29.6, 23.3 (d, J = 15.8 Hz), 22.6 (d, 4.8 Hz), 22.2, 18.5, 17.3 (47.6 Hz), 13.7.

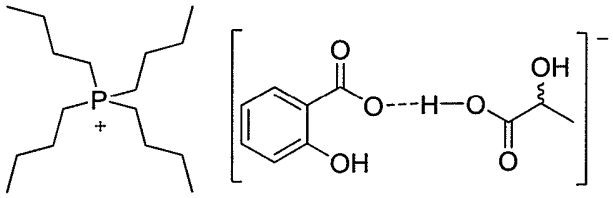
T_g -45°C, $T_{5\%onset}$ 181°C

Example 15: Tetrabutylphosphonium salicylate-camphorsulfonic acid P(Bu)$_4$[SalCSA]H



Camphorsulphonic acid (5 mmol), salicylic acid (0.6909 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs. The desired compound is isolated as a colourless liquid; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.79 (dd, J_1 = 7.9 Hz, J_2 = 1.8 Hz), 7.52 (m, 1H), 6.94 (m, 3H), 2.97 (d, J = 14.8 Hz, 1H), 2.71 (quin, J = 10.8 Hz, 1H), 2.36 (d, J = 14.8 Hz, 1H), 2.19 (m, 9H), 1.93 (t, J = 4.5 Hz, 1H), 1.84 (m, 2H), 1.42 (m, 16 H), 1.26 (m, 2H), 1.05 (s, 3H), 0.91 (t, J = 6.9 Hz, 12H), 0.74 (s, 3H). T_g -33°C, $T_{5\%onset}$ 203°C.

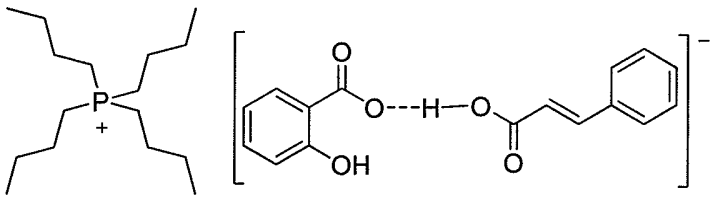
Example 16: Tetrabutylphosphonium salicylate-lactic acid P(Bu)$_4$[SalLac]H



Lactic acid (0.4504 g, 5 mmol), salicylic acid (0.6909 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs. The desired compound is isolated as a colourless liquid; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.63 (dd, J_1 = 7.6 Hz, J_2 = 1.9 Hz), 7.11 (m, 1H), 6.58 (m, 3H), 4.03 (q, J = 6.9 Hz, 1H), 2.17 (m, 8H), 1.42 (m, 16 H), 1.23 (d, 7.0 Hz, 3H), 0.90 (t, J = 7.3 Hz, 12 H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.0. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 176.3, 171.1, 163.0, 131.2, 129.9, 120.5, 117.8, 115.767.3, 23.4 (d, J = 15.8 Hz), 22.6 (d, J = 4.3 Hz), 20.5, 17.3 (d, J = 47.7 Hz), 13.3 (s).

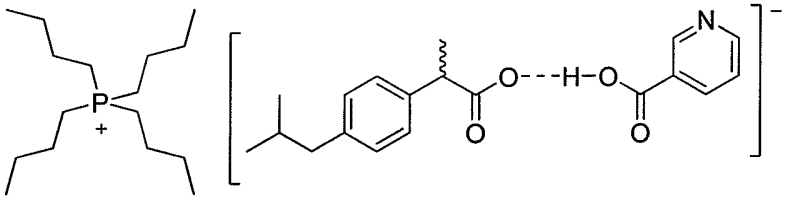
T_g -53°C, $T_{5\%onset}$ 178°C

Example 17: Tetrabutylphosphonium salicylate-cinnamic acid P(Bu)$_4$[SalCinn]H



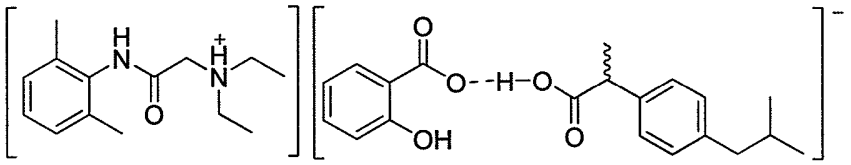
Cinnamic acid (0.7408 g, 5 mmol), salicylic acid (0.6909 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol.in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone stirred and for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs. Identity and purity was confirmed via ^{1}H NMR. The desired compound is isolated as a colourless liquid; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.67 (m, 3H), 7.57 (d, J = 19.1 Hz, 1H), 7.41 (m, 3H), 7.12 (m, 1H), 6.56 (m, 3H),2.17 (m, 8H), 14.1 (m, 16.H), 0.91 (t, J = 6.9 Hz, 12 H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.1. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.2, 167.6, 163.0, 143.3, 134.4, 131.1, 130.0, 129.9, 128.9, 128.1, 120.7, 120.0, 115.7, 115.6, 23.3 (d, J = 15.9 Hz), 22.6 (d, 4.2 Hz), 17.3 (47.8 Hz), 13.2 (s). T_g -43°C, $T_{5\%onset}$ 191 °C

Example 18: Tetrabutylphosphonium ibuprofenate-niacin P(Bu)$_4$[IbuNia]H



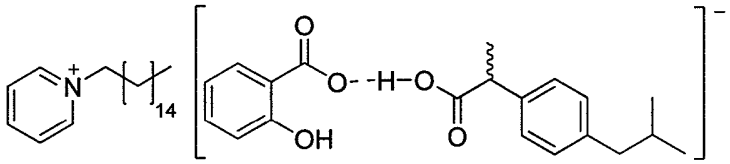
Ibuprofenic acid (1.0315 g, 5 mmol), niacine (0.6155 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs. Identity and purity was confirmed via ^{1}H NMR. The desired compound is isolated as a colourless liquid; ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 8.97 (s, 1H), 8.50 (dd, J_1 = 4.9 Hz, J_2 = 1.7 Hz, 1H), 8.12 (m, 1H), 7.31 (m, 1H), 7.19 (d, 7.9 Hz, 2H), 7.06 (d, 7.9 Hz, 2H), 3.62 (q, J = 7.3 Hz, 2H), 2.40 (d, 7.1 Hz, 2H), 2.18 (m, 8H), 1.80 (sept, J = 6.9, 1H), 1.41 (m, 16 H), 1.31 (s, J = 7.2 Hz, 3H), 0.9 (t, J = 7.2 Hz, 12 H), 0.85 (d, 6.6 Hz, 6H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.1. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 175.7, 166.9, 150.5, 149.7, 139.5, 139.0, 136.2, 134.2, 128.7, 127.1, 122.6, 45.0, 44.2, 29.6, 23.3 (d, J = 15.8 Hz), 22.6 (d, 4.8 Hz), 22.1, 18.9 17.3 (47.6 Hz), 13.2. T_g -44°C, $T_{5\%onset}$ 201°C

Example 19: Lidocaine ibuprofenate-salicylic acid Lid[IbuSal]H – Solvent-free synthesis



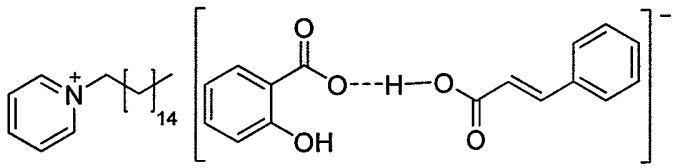
Ibuprofenic acid (206.28 mg, 1 mmol), salicylic acid (160.11 mg, 1 mmol) and lidocaine (234.34 mg, 1 mmol) were grinded in a mortar for 15 minutes until a clear viscose liquid was obtained. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.91 (br s, 1H), 7.72 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.25 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.10 (m, 5H), 6.71 (m, 2H), 3.63 (q, J = 7.1 Hz, 1H), 3.06 (q, J = 7.4 Hz, 4H), 2.41 (d, J = 7.1 Hz, 2H), 2.17 (s, 6H), 1.80 (sept, J = 6.8 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 6H), 0.86 (d, J = 7.2 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 175.5, 171.9, 165.5, 162.2, 139.5, 138.5, 135.0, 134.2, 132.8, 130.1, 129.0, 127.8, 127.1, 126.8, 117.9, 117.1, 116.2, 53.9, 48.2, 44.3, 44.2, 29.6, 22.2, 18.5, 18.1, 10.0. T_g -2 °C, $T_{5\%onset}$ 153 °C

Example 18: Cetylpyridinium salicylate – ibuprofenate CetPySalIbuH



Cetylpyridinium salicylate (2 mmol) and ibuprofenic acid (2 mmol) were grinded for 15 minutes in a mortar until a colourless cream was obtained. Identity and purity of the obtained product was confirmed via ^{1}H NMR. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.12 (d, J = 6.2 Hz, 2H), 8.60 (t, J = 7.8 Hz, 1H), 8.12 (t, J = 6.8 Hz, 2H), 7.66 (d, 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 2H), 7.09 (m, 3H), 6.60 (m, 2H), 4.59 (t, J = 7.6 Hz, 2H), 3.6 (q, J = 6.9 Hz, 2H), 2.40 (d, J = 7.6 Hz, 2H), 1.84 (m, 3H), 1.32 (d, J = 7.6 Hz, 3H), 1.23 (s, 27H), 0.84 (m, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.8, 163.4, 145.8, 145.2, 131.4, 130.2, 128.4, 121.1, 116.1, 160.0, 61.2, 31.7, 31.2, 29.4, 29.3, 29.2, 29.1, 28.8, 25.8, 22.5, 14.2. mp 16 °C, $T_{5\%onset}$ 173 °C

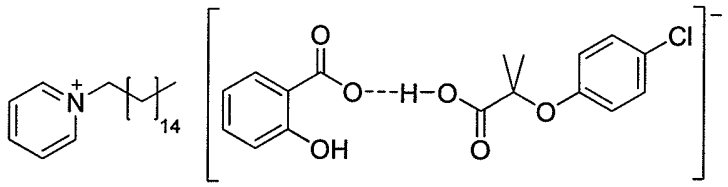
Example 19: Cetylpyridinium salicylate – cinnamate CetPySalCinnH



Cetylpyridinium salicylate (2 mmol) and ibuprofenic acid (2 mmol) were grinded for 15 minutes in a mortar until a colourless cream was obtained. Identity and purity of the obtained product was confirmed via ^{1}H NMR. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) =

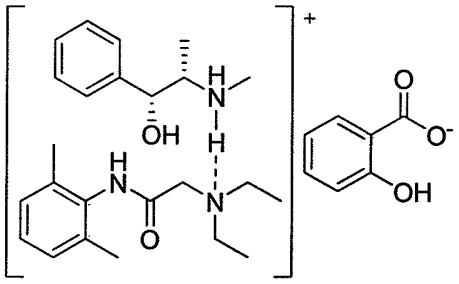
9.14 (d, J = 5.8 Hz, 2H), 8.60 (t, J = 7.7 Hz, 1H), 8.16 (t, J = 6.6 Hz, 2H), 7.64 (m, 3H), 7.56 (d, J = 16.3 Hz, 1H), 7.39 (m, 3H), 7.13 (m, 1H), 6.60 (m, 2H), 6.56 (d, J = 16.3 Hz, 1H), 4.60 (t, J = 7.5 Hz, 2H), 1.88 (m, 2H), 1.20 (m, 27H), 0.84 (t, J = 7.0 Hz, 3H). mp 15 °C, $T_{5\%onset}$ 162 °C

Example 22: Cetylpyridinium salicylate – clofibrate CetPySalClofib



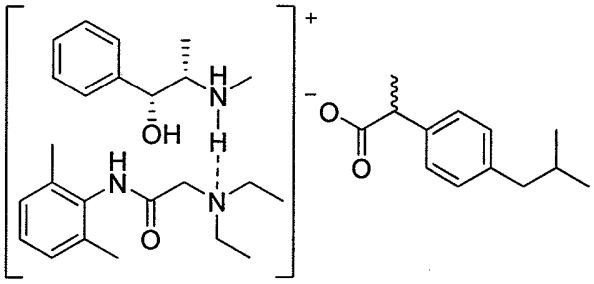
Cetylpyridinium salicylate (2 mmol) andclofibric acid (2 mmol) were grinded for 15 minutes in a mortar until a colourless cream was obtained. Identity and purity of the obtained product was confirmed via ^{1}H NMR. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.13 (d, J = 6.3 Hz, 2H), 8.60 (t, J = 7.7 Hz, 1H), 8.16 (t, J = 7.0 Hz, 2H), 7.67 (d, 8.0 Hz, 1H), 7.28 (d, J = 9,1 Hz, 2H), 7.14 (t, J = 6.7, 1H), 6.84 ((d, J = 9.1 Hz, 2H), 6.61 (m, 2H), 4.59 (t, J = 7.5 Hz, 2H), 1.89 (m, 2H), 1.47 (s, 6H), 1.22 (s, 27H), 0.84 (t, J = 7.0 Hz, 3H). mp 8 °C, $T_{5\%onset}$ 197 °C

Example 23: Ephedrinium-lidocaine salicylate H[EphLid]Sal



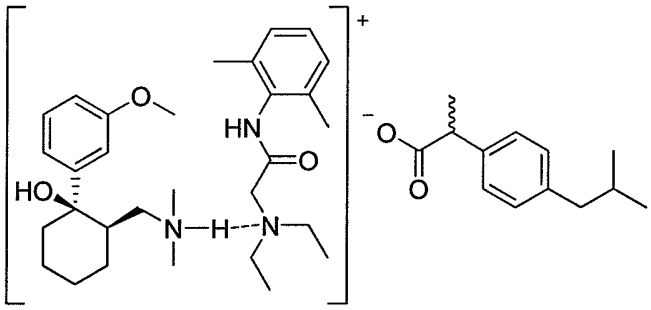
Lidocaine (468.67 mg, 2 mmol) and ephedrinium salicylate (606.72 mg, 2 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs. The desired compound is isolated as a colourless viscous liquid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.23 (br s, 1H), 7.72 (dd, J1 = 7.6 Hz, J2 = 1.8 Hz, 1H), 7.38 (m, 4H), 7.28 (m, 1H), 7.07 (s, 3H), 6.66 (m, 2H), 5.16 (d, J = 2.4 Hz, 1H), 3.40 (m, 1H), 3.18 (s, 2H), 2.67 (s, 3H), 2.64 (q, J = 7.3 Hz, 4H), 2.14 (s, 6H), 1.08 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.8 Hz, 3H). T_g -4 °C; $T_{5\%onset}$ 149. °C

Example 24: Ephedrinium-lidocaine Ibuprofenate H[EphLid]Ibu



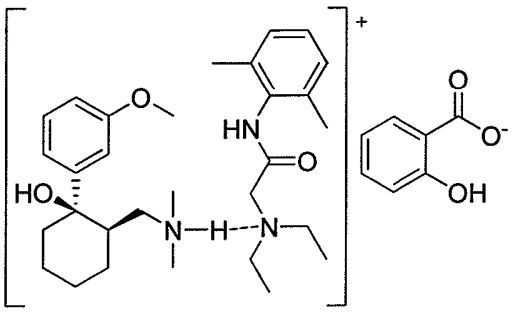
Lidocaine (468.67 mg, 2 mmol) and ephedrinium ibuprofenate (743.02 mg, 2 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs and solidified after 1 week. The desired compound is isolated as a colourless solid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.19 (br s, 1H), 7.32 (m, 5H), 7.20 (d, J = 8.1 Hz, 2H), 7.09 (s, 3H), 7.05 (d, J = 8.2 Hz, 2H), 5.03 (m, 1H), 3.50 (q, J = 7.1 Hz, 1H), 3.13 (m, 3H), 2.62 (q, J = 6.7 Hz, 4H), 2.45 (s, 3H), 2.40 (d, J = 7.1 Hz, 2H), 2.15 (s, 6H), 1.79 (sept, J = 6.7 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 6H), 0.86 (m, 9H). mp 87 °C, $T_{5\%onset}$ 134 °C

Example 25: Tramadolium-lidocaine Ibuprofenate H[TramLid]Ibu



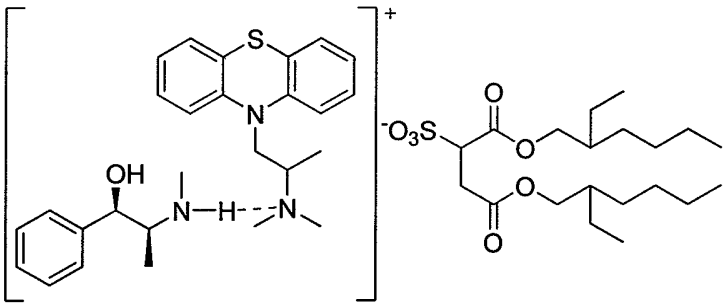
Lidocaine (270. 13 mg, 1.15 mmol) and tramadolium ibuprofenate (541.4 mg, 1.153 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs. The desired compound is isolated as a colourless liquid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.17 (br s, 1H), 7.19 (m, 3H), 7.06 (m, 7H), 6.73 (dd, J1 = 8.1 Hz, J2 = 2.3 Hz, 1H), 4.42 (br s, 2H), 3.74 (s, 3H), 3.61 (q, J = 7.0 Hz, 1H), 3.13 (s, 2H), 2.61 (q, J = 7.2 Hz, 4H), 2.50 (s, 2H), 2.41 (d, J = 7.4 Hz, 2H), 2.13 (s, 7H), 1.94 (s, 6H), 1.89-1.41 (m, 8H), 1.33 (d, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 6H), 0.86 (d, J = 6.6 Hz, 6H). T_g -20°C, $T_{5\%onset}$ 154 °C

Example 26: Tramadolium-lidocaine Salicylate H[TramLid]Sal



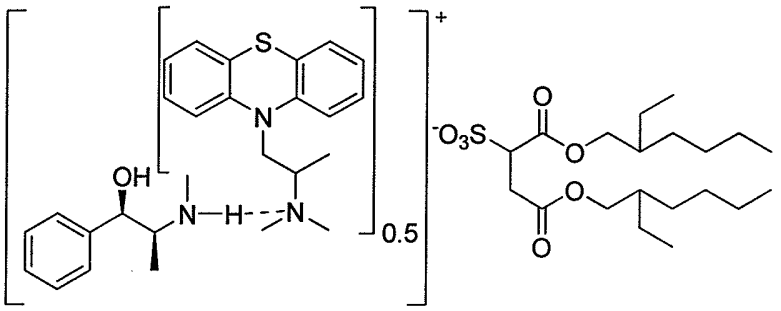
Lidocaine (5 mmol) and tramadolium salicylate (5 mmol) were dissolved in 20 ml of acetone and stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.01 mbar with stirring for 24 hrs and solidified after into a colourless solid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.32 (br s, 1H), 7.672 (dd, J = 7.8 Hz, 1H), 7.26 (t, J = 8.2 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.06 (m, 5H), 6.79 (d, J = 8.7 Hz, 1H), 6.62 (m, 2H), 3.76 (s, 3H), 3.39 (br s, OH), 2.69 (m, 4H), 2.51 (m, 6H), 2.14 (m, 9H), 1.61 (m, 7H), 1.09 (t, J = 7.0 Hz, 6 H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.7, 162.2, 159.1, 150.2, 135.1, 135.0, 131.6, 130.0, 129.0, 127.6, 126.4, 119.9, 117.2, 116.2, 115.8, 111.4, 111.1, 73.9, 59.6, 56.2, 54.9, 48.1, 40.8, 40.2, 25.7, 24.6, 21.2, 18.1, 11.7. mp 64 °C, $T_{5\%onset}$ 181 °C

Example 27: Promethazine-ephedrinium docusate 1:1:1



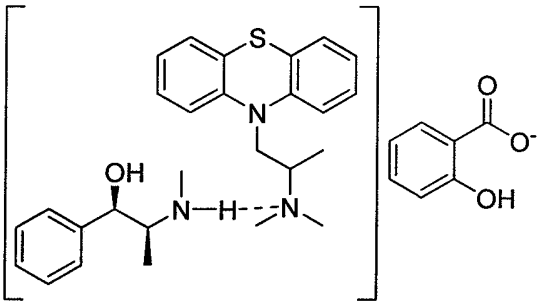
Promethazine (2 mmol) was added to ephedrinium docusate (2 mmol) and stirred for 15 minutes at 50 °C to obtain a light yellow viscous oil. Identity and purity were confirmed via ^{1}H and ^{13}C NMR. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.39 (d, J = 4.5 Hz, 3H), 7.29 (m, 1H), 7.19 (m, 4H), 7.08 (d, J = 8.1 Hz, 2H), 6.95 (t, 7.4 Hz, 2H), 5.04 (d, J = 2.7 Hz, 1H), 4.05 (dd, J1 = 13.81 Hz, J2 = 5.0 Hz, 1H), 3.89 (m, 4H), 3.68 (m, 2H), 3.35 (m, 1H), 2.87 (m, 3H), 12.63 (s, 3H), 2.24 (s, 6H), 1.49 (m, 2H), 1.23 (m, 16H), 0.84 (m, 18H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0, 168.3, 145.1, 141.0, 128.1, 127.6, 1227.3, 127.2, 125.8, 124.4, 122.6, 116.2, 69.9, 66.2, 66.1, 61.5, 59.0, 55.6, 49.7, 40.6, 38.2, 38.2, 34.1, 30.8, 29.7, 29.6, 29.5, 28.3, 23.2, 23.0, 22.4, 13.9, 12.2, 10.8, 9.5. T_g -19 °C, $T_{5\%onset}$ 164 °C

Example 28: Promethazine-ephedrinium docusate 0.5:1:1



Promethazine (1 mmol) was added to ephedrinium docusate (2 mmol) and stirred for 15 minutes in acetone. The solvent was evaporated and remaining volatile material was removed under reduced pressure (0.01 mbar, 50 °C). ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.39 (d, J = 4.5 Hz), 7.29 (m), 7.19 (m), 7.08 (d, J = 8.1 Hz), 6.95 (t, 7.4 Hz), 5.04 (d, J = 2.7 Hz), 4.05 (dd, J_1 = 13.81 Hz, J_2 = 5.0 Hz), 3.89 (m, 4H), 3.68 (m), 3.35 (m), 2.87 (m), 12.63 (s,), 2.24 (s), 1.49 (m, 2H), 1.23 (m, 16H), 0.84 (m, 18H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0, 168.3, 145.1, 141.0, 128.1, 127.6, 1227.3, 127.2, 125.8, 124.4, 122.6, 116.2, 69.9, 66.2, 66.1, 61.5, 59.0, 55.6, 49.7, 40.6, 38.2, 38.2, 34.1, 30.8, 29.7, 29.6, 29.5, 28.3, 23.2, 23.0, 22.4, 13.9, 12.2, 10.8, 9.5.

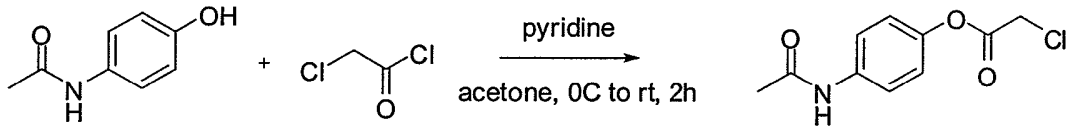
Example 29: Promethazine-ephedrinium salicylate



Promethazine (2 mmol) and ephedrinium salicylate (2 mmol) were dissolved in 25 ml of acetone and stirred for 15 min at room temperature, the solvent was evaporated and remaining volatile material was removed under vacuum (0.01 mbar, 50 °C) to yield the product as colourless viscous glass. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.72 (dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.42-7.15 (m, 10H), 7.0 (m, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.96 (t, J = 7.2 Hz, 2H), 6.65 (m, 2H), 5.13 (d, J = 2.5 Hz, 1H), 4.10 (dd, J_1 = 14.0 Hz, J_2 = 5.0 Hz, 1H), 3.72 (dd, J_1 = 14.2 Hz, J_2 = 8.6 Hz), 3.37 (m, 1H), 3.01 (m, 1H), 2.65 (s, 3H), 2.2.9 (s, 6H), 0.99 (d, J = 6.6 Hz, 3H), 0.92 (d, 6.8 Hz, 3H). T_g 14 °C, $T_{5\%onset}$ 151 °C.

IONIC LIQUID PRODRUGS

Example 30: Synthesis of 4-Acetamidophenyl 2-chloroacetate [2]



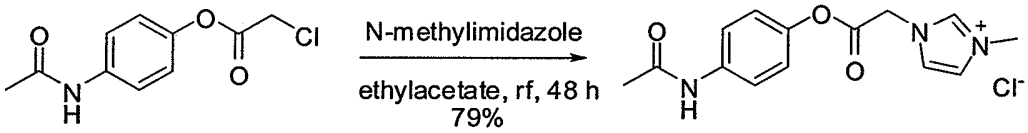
[1]
$C_8H_9NO_2$
151.16

[2]
$C_{10}H_{10}ClNO_3$
227.64

Paracetamol **[1]** (15.117 g, 50 mmol) and pyridine (7.910 g, 50 mmol) were suspended in anhydrous acetone (200 ml) and chilled to 0 °C under an atmosphere of dry nitrogen. Chloroacetylchloride (11.29 g, 50 mmol) was added dropwise (violent reaction) and the resulting solution was stirred for additional 2 hours at room temperature. Water (300 ml) was added and the mixture was heated until a clear solution was obtained. The product [2] precipitated upon cooling and was collected via filtration, washed with water and dried under reduced pressure (0.01 mbar, 50 °C) to yield **[2]** as colourless needles in 72% yield. The product was pure according to ^{1}H NMR and directly subjected to the next step without further purification.

^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.05 (s, 1H), 7.62 (d, J = 9.01 Hz, 2H), 7.10 (d, J = 9.01 Hz, 2H), 4.67 (s, 2H), 3.38 (s, 3H), 2.05 (s, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 168.7, 166.9, 145.6, 137.2, 122.0, 120.3, 41.6, 24.3. mp 186 °C

Example 31: Synthesis of 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride [3]



[2]
$C_{10}H_{10}ClNO_3$
227.64

[3]
$C_{14}H_{16}ClN_3O_3$
309.75

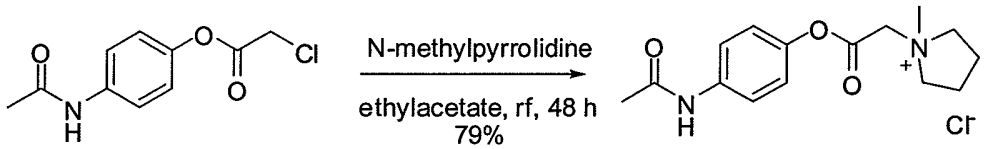
4-Acetamidophenyl 2-chloroacetate **[2]** (1.138 g, 5 mmol) and N-methylimidazol (0.492 g, 6 mmol) were suspended in 50 ml of anhydrous ethyl acetate and refluxed for 48 hrs. After cooling to room temperature the white precipitate was filtered, washed with ethylacetate and diethylether and dried under reduced pressure to give [3] in 79% yield. The product was pure according to ^{1}H NMR and was directly subjected to the next step without further purification.

The desired compound is isolated as a colourless powder. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.08 (s, 1H), 9.28 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.68 (d, J = 9.01 Hz, 2H), 7.13 (d, J = 9.01 Hz, 2H), 5.57 (s, 2H), 3.93 (s, 3H), 2.05 (s, 3H). ^{13}C-NMR (75 MHz, d_6-

DMSO) δ(ppm) = 168.4, 166.1, 144.9, 137.9, 137.7, 123.8, 123.5, 121.4, 119.9, 49.7, 36.0, 23.9.

mp 206 °C (dec), $T_{5\%onset}$ 200 °C.

Example 32: 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium chloride [4]

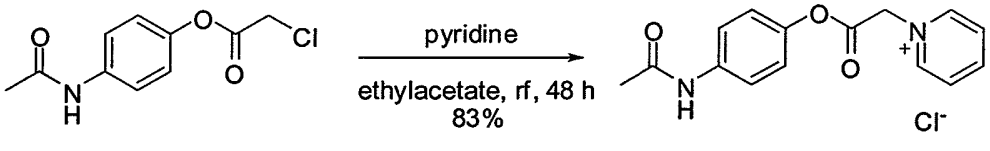


[2]
$C_{10}H_{10}ClNO_3$
227.64

[4]
$C_{15}H_{21}ClN_2O_3$
312.79

4-Acetamidophenyl 2-chloroacetate [2] (1.138 g, 5 mmol) and N-methylpyrrolidine (0.511 g, 6 mmol) were suspended in 50 ml of anhydrous ethyl acetate and refluxed for 48 hrs. After cooling to room temperature the white precipitate was filtered, washed with ethylacetate and diethylether and dried under reduced pressure to give [4] in 97% yield. The product was pure according to ^{1}H NMR and was directly subjected to the next step without further purification. The desired compound is isolated as a colourless powder. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.48 (s, 1H), 7.72 (d, J = 8.90 Hz, 2H), 7.17 (d, J = 8.90 Hz, 2H), 4.91 (s, 2H), 3.75 (m, 4H), 3.26 (s, 3H), 2.13 (m, 4H), 2.06 (s, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 168.8, 164.8, 144.4, 138.2, 121.9, 120.2, 65.5, 62.0, 49.7, 24.3, 21.7. mp 186 °C (dec), $T_{5\%onset}$ 197 °C

Example 33: 1-(2-(4-acetamidophenoxy)-2-oxoethyl)pyridinium chloride [5]



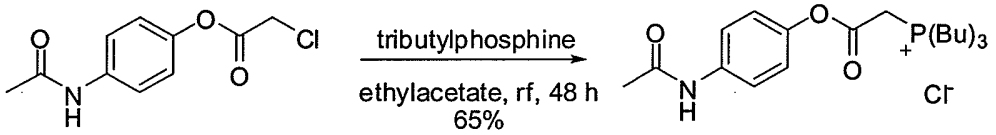
[2]
$C_{10}H_{10}ClNO_3$
227.64

[5]
$C_{15}H_{15}ClN_2O_3$
306.74

4-Acetamidophenyl 2-chloroacetate [2] (1.138 g, 5 mmol) and pyridine (0.475 g, 6 mmol) were suspended in 50 ml of anhydrous ethyl acetate and refluxed for 48 hrs. After cooling to room temperature the white precipitate was filtered, washed with ethylacetate and diethylether and dried under reduced pressure to give [5] in 97% yield. The product was pure according to ^{1}H NMR and was directly subjected to the next step without further purification. The desired compound is isolated as a colourless powder. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.31 (s, 1H), 9.27 (d, J = 6.5 Hz, 2H), 8.76 (t, 7.9 Hz, 1H), 8.29 (t, 7.2 Hz, 2H),

7.71 (d, J = 9.7 Hz, 2H), 7.11 (d, J = 9.7 Hz, 2H), 4.69 (s, 2H), 2.08 (s, 3H). mp 199 °C (dec), $T_{5\%onset}$ 198 °C

Example 34: (2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium chloride [6]

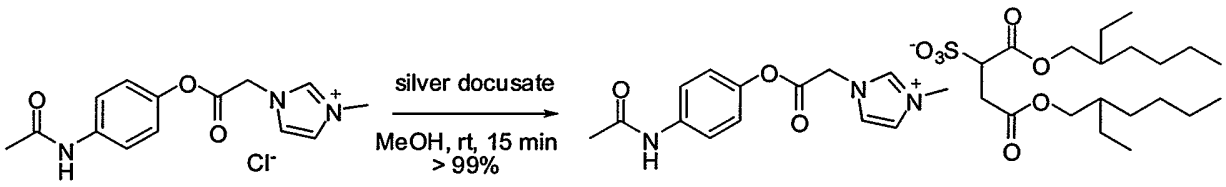


[2]
$C_{10}H_{10}ClNO_3$
227.64

[6]
$C_{22}H_{37}ClNO_3P$
429.96

4-Acetamidophenyl 2-chloroacetate [**2**] (1.138 g, 5 mmol) and tributylphosphine (0.475 g, 6 mmol) were suspended in 50 ml of anhydrous ethyl acetate and refluxed for 48 hrs. After cooling to room temperature the white precipitate was filtered, washed with ethylacetate and diethylether and dried under reduced pressure to give [**6**]. The crude product was crystallized twice from acetonitrile to give pure [**6**] in 65% yield. Identity and purity was confirmed via ^1H and ^{13}C NMR. The desired compound is isolated as colourless needles. ^1H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.49 (s, 1H), 7.71 (d, J = 8.95 Hz, 2H), 7.12 (d, J = 8.95 Hz, 2H), 4.18 (d, J = 14.33, 2H), 2.41 (m, 3H), 2.06 (s, 3H), 1.55 (m, 6H), 1.41 (m, 6H), 0.91 (t, J = 7.17). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 34.8. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 168.4, 164.7, 144.8, 137.8, 121.4, 119.9, 25.8 (d, J = 47.9 Hz), 23.9, 23.3 (d, J = 16.77 Hz), 22.6 (d, J = 4.43 Hz), 18.2 (d, J = 47.7 Hz), 13.2. mp 199 °C (dec), $T_{5\%onset}$ 197 °C

Example 35: Synthesis of 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium docusate [7]

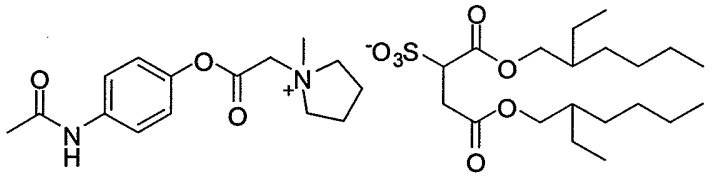


[3] [7]

Chloride [**3**] (309.1 mg, 1 mmol) and silver docusate (529.4 mg, 1 mmol) were suspended in 50 ml of anhydrous methanol and stirred in the dark at room temperature for 15 min. The suspension was filtered over celite and the filtrate was evaporated <40 °C. Remaining volatile material was removed under reduced pressure (0.01 mbar, 40 °C) to yield product [**7**] in quantitative yield. The desired compound is isolated as a yellow oil. ^1H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.07 (s, 1H), 9.16 (s, 1H), 7.82 (s, 1H), 7.77(s, 1H), 7.64 (d, J = 9.2 Hz, 2H), 7.14 (d, J = 9.2 Hz, 2H), 5.51 (s, 2H), 3.93 (s, 3H), 3.88 (m, 4H), 3.65 (dd, J_1 = 11.5 Hz, J_2 = 3.8 Hz, 1H), 2.85 (m, 2H), 2.04 (s, 3H), 1.49 (m, 2H), 1.23 (m, 16 H), 0.86 (m, 12H).

^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0,168.4, 166.0, 144.9, 137.8, 137.5, 123.8, 123.5, 121.5, 119.9, 66.1, 61.5, 49.7, 38.1, 36.0, 34.1, 29.7, 29.6, 28.3, 23.9, 23.2, 22.4, 13.9, 10.8, 10.7. $T_{5\%onset}$ 217 °C

Example 36: 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium docusate [8]

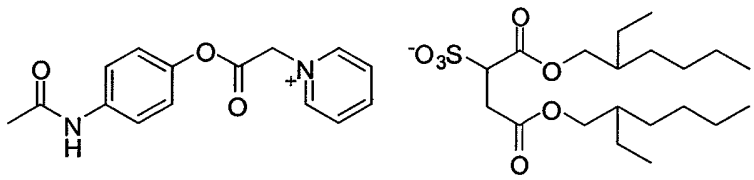


[8]

Prepared according to example **35** in quantitative yield. The desired compound is isolated as a yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.011 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 4.82 (s, 2H), 3.88 (m, 2H), 3.72 (m, 5H), 3.25 (s, 3H), 2.88 (m, 2H), 2.14 (m, 4H), 2.05 (s, 3H), 1.47 (m, 2H), 1.23 (m, 16H), 0.82 (m, 12H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 168.4, 166.1, 144.9, 137.9, 137.7, 123.8, 123.5, 121.4, 119.9, 49.7, 36.0, 23.9. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0, 168.4, 164.4, 144.5, 137.7, 121.6, 119.8, 66.1, 65.1, 61.6, 49.4, 38.1, 34.1, 29.7, 29.6, 28.3, 23.9, 23.2, 23.0, 22.4, 21.4, 13.8, 10.7.

$T_{5\%onset}$ 233 °C

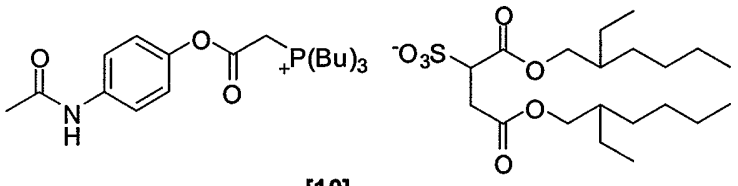
Example 37: 1-(2-(4-acetamidophenoxy)-2-oxoethyl)pyridinium docusate [9]



[9]

Prepared according to example **35** in quantitative yield. The desired compound is isolated as a yellow glass. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.13 (s, 1H), 9.21 (d, J = 6.2 Hz, 2H), 8.82 (t, 7.8 Hz, 1H), 8.36 (t, 7.2 Hz, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 6.00 (s, 2H), 3.96 (m, 4H), 3.71 (dd, J_1 = 11.3 Hz, J_2 = 3.7 Hz, 1H), 2.94 (m, 2H), 2.12 (s, 3H), 1.56 (m, 2H), 1.00 (m, 16 H), 0.93 (m, 12H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 71.0, 168.4, 165.6, 147.0, 146.5, 144.9, 137.6, 127.9, 121.5, 119.9, 66.2, 66.1, 61.5, 60.4, 38.1, 34.1, 29.7, 29.6, 28.3, 23.2, 23.1, 23.0, 22.4, 13.9, 10.8, 10.7. T_g 25 °C,$T_{5\%onset}$ 238 °C

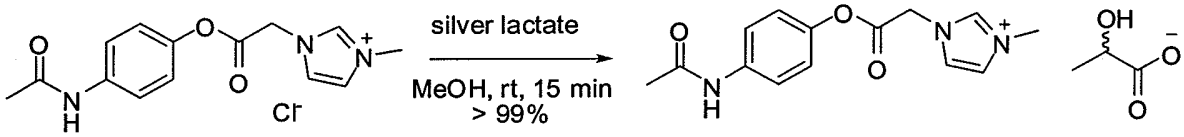
Example 38: (2-(4-acetamidophenoxy)-2-oxoethyl)tributylphosphonium docusate [10]



[10]

Prepared according to example **35** in quantitative yield. The desired compound is isolated as a yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.07 (s, 1H), 7.64 (s, 2H), 7.14 (s, 2H), 4.07 (d, J = 14.6 Hz, 2H), 3.88 (s, 4H), 3.62 (s, 1H), 2.84 (m, 2H), 2.36 (s, 6H), 2.04 (s, 3H), 1.49 (m, 14 H), 1.23 (m, 16H), 0.89 (m, 21 H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 168.4, 166.1, 144.9, 137.9, 137.7, 123.8, 123.5, 121.4, 119.9, 49.7, 36.0, 23.9. T_g -17 °C, $T_{5\%onset}$ 227 °C

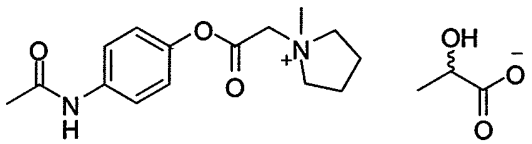
Example 39: Synthesis of 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium lactate [11]



[3] [11]

Chloride **[3]** (309.1 mg, 1 mmol) and racemic silver lactate (196.4 mg, 1 mmol) were suspended in 25 ml of anhydrous methanol and stirred in the dark at room temperature for 15 min. The suspension was filtered over celite and the filtrate was evaporated at <40 °C. Remaining volatile material was removed under reduced pressure (0.01 mbar, 40 °C) to yield product **[11]** as yellow oil in quantitative yield. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.85 (s, 1H), 9.18 (s, 1H), 7.75 (s, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.68 (d, J = 8.1 Hz, 2H), 5.29 (s, 2H), 3.90 (s, 3H), 3.57 (q, J = 6.8 Hz, 1H), 1.98 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H).

Example 40: 1-(2-(4-acetamidophenoxy)-2-oxoethyl)-1-methylpyrrolidinium lactate [12]



[12]

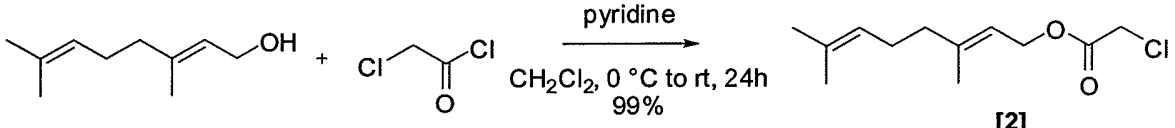
Prepared according to example **39** in quantitative yield. Identity and purity were confirmed via ^{1}H and ^{13}C NMR. The desired compound is isolated as a yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.82 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 88 Hz, 2H), 4.55 (s, 2H), 3.76 (s, 3H), 3.66 (m, 4H), 3.54 (q, J = 6.7 Hz, 1H), 2.09 (m, 4H), 1.97 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H). $T_{5\%onset}$ 166 °C

Example 41: Prodrug hydrolysis – General procedure

Acetaminophen prodrug (0.5 mmol) was dissolved in 5 ml phosphate buffer pH 7.4. The resulting 0.1 M solutions were stirred in a preheated oil bath at 37 °C. Sample of 0.05 ml were withdrawn at intervals, diluted with D_2O to 0.5 ml and ^1H NMR spectra was immediately measured. Decomposition could be monitored via integration of representing aromatic signals of prodrug and of free acetaminophen.

IONIC LIQUID IMMOBILIZED FRAGRANCES

Example 42: Synthesis of (E)-3,7-dimethylocta-2,6-dienyl 2-chloroacetate [2]

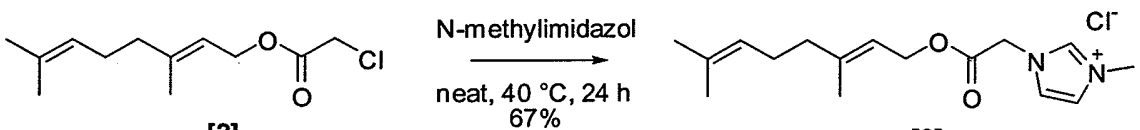


[1] [2]

Geraniol **[1]** (7.711 g, 50 mmol) and pyridine (3.955 g, 50 mmol) were suspended in anhydrous dichloromethane (200 ml) and chilled to 0 °C under an atmosphere of dry nitrogen. Chloroacetylchloride (5.647 g, 50 mmol) was added dropwise (violent reaction) and the resulting solution was stirred for 24 hrs at room temperature. Water (100 ml) was added, the organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic layers were successively washed with 2N HCl, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to yield product **[2]** as yellow liquid. The product was pure according to ^1H NMR and directly subjected to the next step without further purification.

^1H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 5.31 (t, J = 7.4 Hz, 1H), 5.06 (m, 1H), 4.64 (d, J = 7.4 Hz, 2H), 4.38 (s, 2H), 2.03 (m, 4H), 1.68 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 167.3, 142.4, 131.1, 123.7, 117.8, 62.2, 41.1, 38.9, 25.7, 25.4, 17.5, 16.2.

Example 43: Synthesis of (E)-1-(2-(3,7-dimethylocta-2,6-dienyloxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium chloride [3]

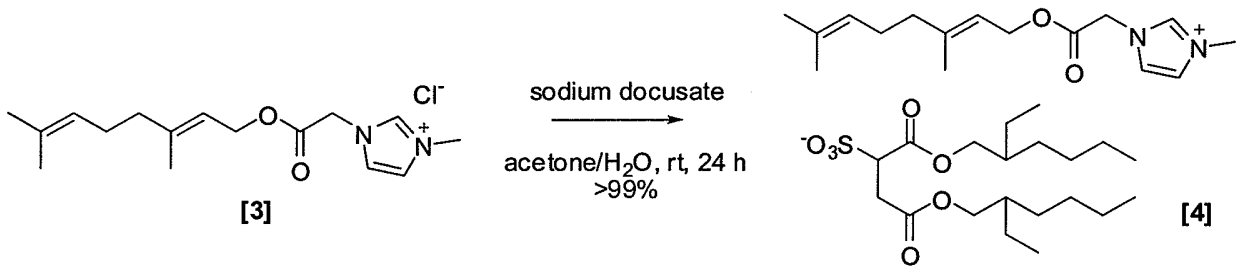


[2] [3]

Geraniol ester **[2]** (2.307 g, 10 mmol) and N-methylimidazole (0.821 g, 10 mmol) were mixed in and stirred in a sealed vessel at 40 °C for 24 hrs. A light-brown solid was formed and suspended in anhydrous diethylether. The solid precipitate was filtered, washed with diethylether and dried under reduced pressure (0.01 mbar) to give imidazolium chloride

[3] in 67% yield as light-yellow hygroscopic solid. The product was pure according to ^{1}H NMR and directly subjected to the next step without further purification. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.36 (s, 1H), 7.82 (s, 2H), 5.37 (s, 2H), 5.33 (t, J = 7.0 Hz, 1H), 5.07 (s, 1H), 4.68 (d, J = 7.1 Hz, 2H), 3.93 (s, 3H), 2.03 (m, 4H), 1.66 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 166.9, 142.6, 137.8, 131.1, 123.7, 123.6, 123.3, 117.8, 62.4, 49.4, 35.9, 25.8, 25.5, 17.6, 16.1. mp 160 °C (dec), $T_{5\%onset}$ 125 °C

Example 44: Synthesis of (E)-1-(2-(3,7-dimethylocta-2,6-dienyloxy)-2-oxoethyl)-3-methyl-1H-imidazol-3-ium docusate [4]

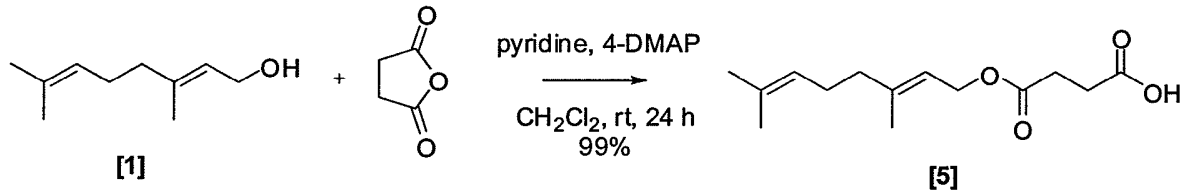


[3] [4]

Imidazolium chloride **[3]** (312.8 mg, 1 mmol) and sodium docusate (444.6 mg, 1 mmol) were dissolved in 20 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give imidazolium docusate **[4]** in quantitative yield as yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.07 (s, 1H), 7.71 (s, 2H), 5.33 (t, J = 7.3 Hz, 1H), 5.24 (s, 2H), 5.07 (m, 1H), 4.69 (d, J = 7.3 Hz, 2H), 3.91 (s, 3H), 3.90 (m, 4H), 3.62 (dd, J_1 = 11.39 Hz, J_2 = 3.88 Hz, 1H), 2.86 (m, 2H), 2.04 (m, 4H),1.68 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.49 (m, 2H), 1.24 (m, 16 H), 0.84 (m, 12H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.1, 168.1, 166.9, 142.7, 137.7, 131.2, 123.7, 123.6, 123.4, 117.6, 66.2, 66.1, 62.4, 61.4, 49.5, 38.1, 356.0, 34.1, 29.8, 29.6, 28.3, 25.8, 25.5, 23.2, 23.0, 22.4, 17.6, 16.2, 13.9, 10.8. $T_{5\%onset}$ 170 °C

Thermocleavage of the immobilized fragrance Geraniol **[4]** was demonstrated with TGA (Figure 6). Mass loss of the first decomposition step obtained corresponds to mass percentage of Geraniol **[1]** in the prodrug **[4]**.

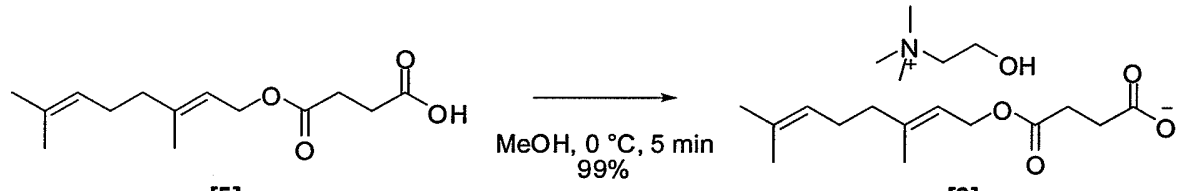
Example 45: Synthesis of (E)-4-(3,7-dimethylocta-2,6-dienyloxy)-4-oxobutanoic acid [5]



[1] [5]

Geraniol **[1]** (1.542 g, 10 mmol), succinic anhydride (1.201 g, 12 mmol) and 4-DMAP (10 mg, cat) were suspended in anhydrous dichloromethane (50 ml) under an atmosphere of dry nitrogen. Pyridine (0.791 g, 10 mmol) was added and the reaction mixture was stirred for 24 hrs at room temperature. The reaction mixture was successively washed with 2N HCl and H_2O, dried over Na_2SO_4 and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to yield product **[2]** as yellow liquid in 99% yield. The product was pure according to ^{1}H NMR and directly subjected to the next step without further purification. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 12.24 (br s, 1H), 5.29 (t, J = 7.0 Hz, 1H), 5.08 (t, 6.7, 1H), 4.55 (d, J = 7.1 Hz, 2H), 2.49 (m, 2H), 2.03 (m, 4H), 1.67 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 173.3, 172.2, 141.2, 131.1, 123.7, 118.5, 60.7, 38.9, 28.7, 28.6, 25.8, 25.5, 17.5, 16.1.

Example 46: Synthesis of 2-Hydroxy-N,N,N-trimethylethanaminium (E)-4-(3,7-dimethylocta-2,6-dienyloxy)-4-oxobutanoate [6]

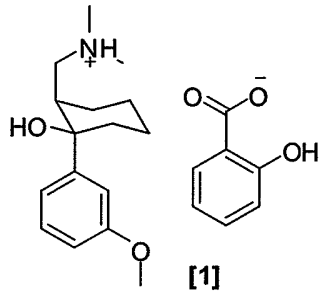


[5] [6]

Hemisuccinate **[5]** (1.0173 g, 4 mmol) was dissolved in 10 ml of methanol and chilled to 0 °C. Choline hydroxide in (1.13 ml, 40% sol. in methanol, 4 mmol) was added dropwise and the reaction mixture was stirred for 5 min at 0 °C. The solvent was evaporated and remaining volatile material was removed under reduced pressure (0.01 mbar) to yield product **[6]** as yellow liquid in quantitative yield. The product was pure according to ^{1}H NMR without further purification. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 5.28 (t, J = 7.0 Hz, 1H), 5.07 (t, J = 6.8 Hz, 1H), 4.49 (d, J = 7.0 Hz, 2H), 3.85 (m, 2H), 3.44 (m, 2H), 3.13 (s, 9H), 2.36 (t, J = 7.2 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 2.03 (m, 4H, 1.65 (s, 6H), 1.57 (s, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 174.0, 173.6, 140.7, 131.1, 123.8, 119.0, 67.3, 60.2, 55.0, 53.1, 39.3, 32.8, 31.2, 25.8, 25.5, 17.6, 16.2. T_g -65 °C, $T_{5\%onset}$ 170 °C.

NEW API ILs

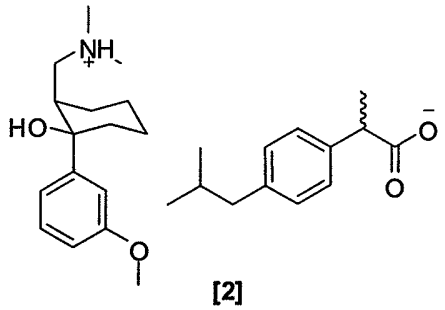
Example 47: Tramadolium salicylate [1]



[1]

Tramadolium hydrochloride (1.499 g, 5 mmol) and sodium salicylate (0.801 g, 5 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The obtained suspension was chilled to 0 °C, the precipitate was collected via filtration, washed with H_2O and dried under reduced pressure (0.01 mbar) to isolate tramadolium salicylate as colourless solid in 79 % yield. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.69 (dd, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.19 (m, 1H), 7.08 (m, 2H), 6.79 (m, 1H), 6.66 (m, 2H), 3.76 (s, 3H), 3.56 (br s, 1H), 2.83 (t, J = 11.9 Hz, 1H), 2.52 (s, 6H), 2.33 (d, 13.0 Hz, 1H), 2.24 (m, 1H), 1.89 (m, 1H), 1.64 (m, 7H).^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.0, 262.3, 159.2, 150.0, 131.9, 120.1, 129.1, 119.5, 117.2, 116.5, 117.2, 116.5, 115.9, 111.5, 111.1, 73.9, 59.4, 55.0, 43.0, 40.5, 40.4, 25.7, 24.6, 21.2. mp 183 °C, $T_{5\%onset}$ 220 °C.

Example 48: Tramadolium *rac*-ibuprofenate [2]

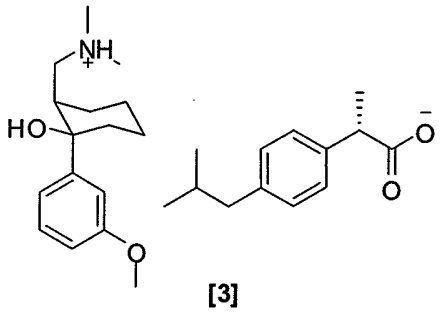


[2]

Tramdolium hydrochloride (1.499 g, 5 mmol) and racemic sodium ibuprofenate (1.1441 g, 5 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give tramadolium *rac*-ibuprofenate [**2**] in 89% yield as viscous glass that solidified after 2 weeks. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.19 (m, 3H), 7.08 (m, 2H), 7.00 (m, 2H), 6.72 (dd, J_1 = 8.1, J_2 = 2.3 Hz, 1H)), 3.73 (s, 3H), 3.58

(q, J = 7.0 Hz, 1H), 2.40 (d, J = 7.0 Hz, 2H), 2.11 (m, 1H), 1.91 (s, 6H), 1.85-1.35 (m, 9H), 1.31 (d, J = 7.1 Hz, 3H,), 0.85 (d, J = 7.7 Hz, 6H,) ppm. mp 75 °C, $T_{5\%onset}$ 175 °C.

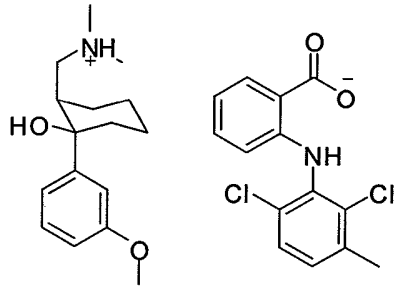
Example 49: Tramadolium (*S*)-ibuprofenate [3]



[3]

Prepared according to example **48** in 76% yield. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.19 (m, 3H), 7.08 (m, 2H), 7.00 (m, 2H), 6.72 (dd, J_1 = 8.1, J_2 = 2.3 Hz, 1H)), 3.73 (s, 3H), 3.58 (q, J = 7.0 Hz, 1H), 2.40 (d, J = 7.0 Hz, 2H), 2.11 (m, 1H), 1.91 (s, 6H), 1.85-1.35 (m, 9H), 1.31 (d, J = 7.1 Hz, 3H,), 0.85 (d, J = 7.7 Hz, 6H,) ppm.

Example 50: Tramadolium meclofenamate [4]

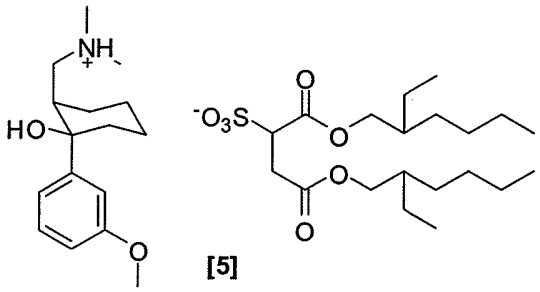


[4]

Tramadolium hydrochloride (0.492 g, 1.64 mmol) and sodium meclofenamate (0.522 g, 1.64 mmol) were dissolved in 20 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give tramadolium meclofenamate [3] in 95% yield as colourless solid foam. Identity and purity of the obtained product were confirmed via ^{1}H NMR. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.62 (br s, 1H), 7.95 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 7.50 (d, J = 8.3, 1H), 7.3 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.10 (m, 2H), 6.80 (dd, J_1 = 8.1 Hz, J_2 = 2.2 Hz, 1H), 6.71 (t, J = 7.5 Hz, 1H), 5.82 (br s, 1H), 3.78 (s, 3H), 2.60 (m, 1H, 2.40 (s, 3H), 2.32 (s, 6H), 2.11 (m, 2H), 1.99 (d, 11.9 Hz, 1H), 1.61 (m, 7H).^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.3, 159.1, 150.7,

146.3, 136.3, 135.8, 133.2, 131.7, 131.6, 130.1, 128.9, 128.4, 128.0, 117.3, 116.7, 112.3, 74.2, 59.7, 54.9, 43.9, 41.6, 40.7, 26.2, 25.0, 21.4, 20.2. T_g 38 °C, $T_{5\%onset}$ 172 °C

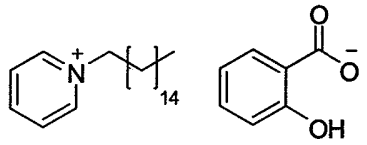
Example 51: Tramadolium docusate [5]



[5]

Tramadolium hydrochloride (0.5997 g, 2 mmol) and sodium docusate (0.8892 g, 2 mmol) were dissolved in 20 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give tramadolium docusate [**3**] in quantitative yield as yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.26 (t, 1H, J = 8.0 Hz), 7.06 (m, 2H,), 6.79 (dd, 1H, J_1 = 8.1, J_2 = 2.3 Hz), 5.17 (b s, 1H, OH), 3.88 (m, 2H), 3.74 (s, 3H), 3.64 (dd, 1H, J_1 = 3.7 Hz, J_2 = 11.1 Hz), 2.86 (m, 3H), 2.38 (d, 2H), 2.22 (m, 2H), 1.9-1.5 (m, 4H), 1.5 (m, 2H), 1.3-1.1 (m, 16H),0.8 (m, 12H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.36, 168.62, 159.54, 150.11, 129.52, 117.48, 111.88, 111.43, 74.15, 66.60, 66.53, 66.49, 66.44, 61.80, 59.89, 55.29, 40.68, 38.49, 34.40, 30.08, 29.97, 29.91, 28.69, 25.79, 24.68, 23.52, 23.36, 22.76, 22.73, 21.45, 14.24, 14.21, 11.14, 11.11, 11.07. T_g -6 °C, $T_{5\%onset}$ 226 °C

Example 52: Cetylpyridinium salicylate [6]

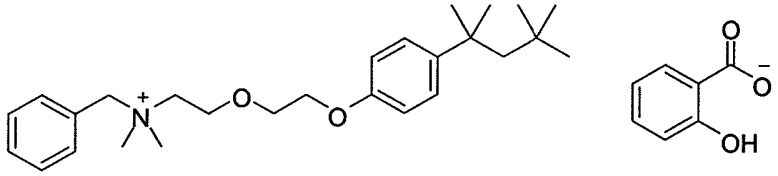


[6]

Cetylpyridinium chloride monohydrate (20.64 g, 56 mmol) and sodium salicylate (8.96 g, 56 mmol) were dissolved in 100 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 100 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed

under reduced pressure (0.01 mbar) to give cetylpyridinium salicylate [6] in 56% yield as colourless waxy solid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.12 (d, J = 6.08 Hz, 2H), 8.59 (t, J = 8.29 Hz, 1H), 8.16 (t, J = 7.27 Hz, 2H), 7.64 (d, 7.54 Hz, 1H), 7.12 (t, J = 7.54, 1H), 6.57 (m, 2H), 4.59 (t, J = 7.44 Hz, 2H), 1.88 (m, 2H), 1.22 (s, 27H), 0.84 (t, J = 7.14 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.8, 163.4, 145.8, 145.2, 131.4, 130.2, 128.4, 121.1, 116.1, 160.0, 61.2, 31.7, 31.2, 29.4, 29.3, 29.2, 29.1, 28.8, 25.8, 22.5, 14.2. mp 57 °C, $T_{5\%onset}$ 206 °C.

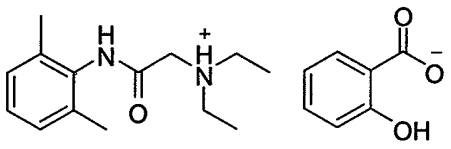
Example 53: Benzethonium salicylate [7]



[7]

Benzethonium chloride (4.481 g, 10 mmol) and sodium salicylate (1.601 g, 10 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give benzethonium salicylate [6] as yellow glass. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.65 (m, 1H), 7.53 (m, 5H), 7.26 (d, J = 8.9 Hz, 2H), 7.10 (s, 1H), 6.82 (d, J = 8.9 Hz, 2H), 6.57 (m, 2H), 4.61 (s, 2H), 4.11 (s, 2H), 4.00 (m, 2H), 3.82 (s, 2H), 3.39 (m, 2H), 3.02 (s, 6H), 1.67 (s, 2H), 1.28 (s, 6 H), 0.66 (s, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0, 168.3, 141.0, 128.2, 127.4, 125.8, 69.7, 66.2, 61.5, 59.1, 38.2, 34.1, 30.7, 29.8, 29.6, 28.4, 23.2, 23.0, 22.5, 13.9, 10.8, 9.2. T_g -14 °C, $T_{5\%onset}$ 180 °C

Example 54: Lidocainium salicylate [8]



[8]

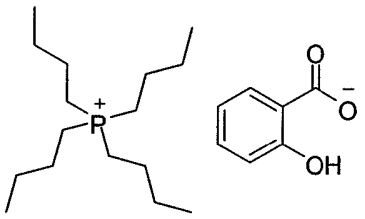
Lidocaine hydrochloride monohydrate (23.105 g, 80 mmol) and sodium salicylate (8.962 g, 80 mmol) were dissolved in 10 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 100 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more

chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give lidocainium salicylate [**8**] in 54% yield as pale yellow viscous oil.

Solvent-free procedure:

Salicylic acid (5 mmol) and lidocaine free base (5 mmol) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture was cooled to room temperature and formed a viscous glass. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 10.05 (br s, 1H), 7.72 (dd, J_1 = 7.75 Hz, J_2 = 1.80 Hz, 1H), 7.24 (m, 1H), 7.09 (s, 3H), 6.70 (m, 2H), 3.98 (s, 2H), 3.10 (q, J = 7.28 Hz, 4 H), 2.16 (s, 6H), 1.22 (t, J = 7.34 Hz, 6 H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9, 164.6, 161.9, 135.0, 134.0, 133.4, 130.1, 127.8, 126.9, 117.6, 116.9, 116.4, 53.3, 48.3, 18.1, 9.5. T_g 19 °C, $T_{5\%onset}$ 161 °C.

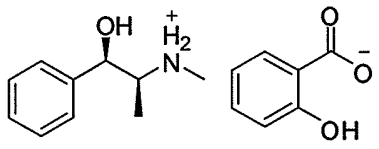
Example 55: Tetrabutylphosphonium salicylate [9]



[9]

Salicylic acid (0.691 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs to obtain tetrabutylphosphonium salicylate [**9**] in quantitative yield as colourless crystals. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.74 (dd, J_1 = 7.73 Hz, J_2 = 1.87 Hz, 1H), 7.32 (dt, J_1 = 7.59 Hz, J_2 = 1.80 Hz, 1H), 6.77 (m, 2H), 2.20 (m, 8 H), 1.41 (m, 16 H), 0.9 (t,J = 7.06 Hz, 12 H). ^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 35.1. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.9(s), 163.1(s), 131.1 (d), 129.8(d), 120.6 (s), 115.7 (d), 115.6 (d), 23.31 (d, J = 16.36 Hz), 22.62 (d, 4.84 Hz), 17.30 (47.27 Hz), 13.19 (s). mp 57 °C; $T_{5\%onset}$ 312 °C; water content(KF) 0.076% (m/m).

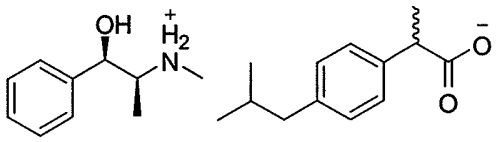
Example 56: Ephedrinium salicylate [10]



[10]

Salicylic acid (0.691 g, 5 mmol) and ephedrine (0.826 g, 5 mmol) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture was cooled to room temperature solidified and was grinded to obtain a colourless powder in quantitative yield. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.30 (br s, 2H), 7.76 (dd, J_1 = 7.66 Hz, J_2 = 1.80 Hz, 1H), 7.38 (m, 4H), 7.24 (m, 2H), 6.70 (m, 2H), 6.48 (br s, 1H), 5.21 (s, 1H), 3.41 (m, 1H), 2.69 (s, 3H), 0.95 (d, J=6.76 Hz, 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.9, 162.1, 141.4, 132.0, 130.3, 128.2, 127.2, 125.8, 119.6, 116.8, 116.0, 69.6, 59.3, 30.6, 9.1. mp 97 °C, $T_{5\%onset}$ 161 °C.

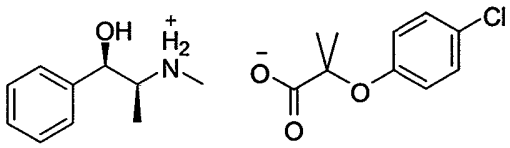
Example 57: Ephedrinium ibuprofenate [11]



[11]

Ibuprofenic acid (0.691 g, 5 mmol) and ephedrine (0.826 g, 5 mmol) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture was cooled to room temperature, solidified and was grinded to obtain a colourless powder in quantitative yield. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.34 (m, 4H), 7.19 (m, 3H), 7.03 (d, J = 7.89 Hz, 2H), 5.80 (br s, 1H), 4.97 (d, J = 2.8 Hz, 1H), 3.45 (q, J = 7.1 Hz, 1H), 3.04 (m, 1H), 2.45 (s, 3H), 2.38 (d, J = 7.15 Hz, 2H), 1.78 (sept, J = 6.8 Hz, 1H), 1.30 (d, J = 7.17, 3 H), 0.83 (m, 9H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 177.9, 142.4, 140.9, 138.5, 128.5, 127.9, 127.1, 126.7, 125.9, 70.6, 59.8, 46.6, 44.3, 31.5, 29.7, 22.2, 19.5, 10.7. mp 110 °C, $T_{5\%onset}$ 238 °C

Example 58: Ephedrinium clofibrate [12]

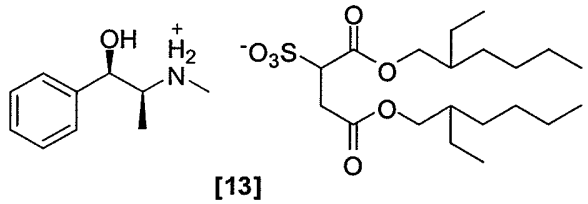


[12]

Clofibric acid (1.073 g, 5 mmol) and ephedrine (0.826 g, 5 mmol) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture solidified at room temperature and was grinded to obtain a yellow powder in quantitative yield. ^{1}H-NMR (300

MHz, d_6-DMSO) δ(ppm) = 9.36 (br s, 2H), 7.30 (m, 5H), 7.19 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.75 Hz, 2H), 5.10 (s, 1H), 3.12 (m, 1H), 2.52 (s, 3H), 1.41 (s, 6H), 0.85 (d, J = 6.58 Hz), 3H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 176.8, 155.5, 141.8, 128.5, 128.0, 126.9, 125.8, 123.4, 119.2, 80.2, 69.8, 59.5, 30.7, 25.8, 9.6. mp 131 °C, $T_{5\%onset}$ 166 °C

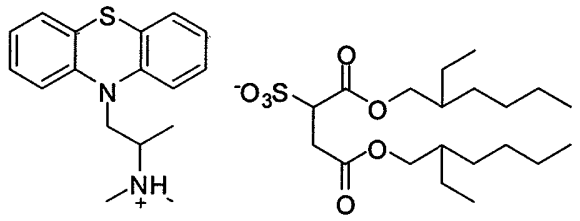
Example 59: Ephedrinium docusate [13]



[13]

Ephedrinium hydrochloride (2.017 g, 10 mmol) and sodium docusate (4.446 g, 10 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give ephedrinium docusate [13] in 98% yield as colourless viscous oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 8.45 (br s, 2H), 7.34 (m, 5H), 6.13 (d, J = 4.24 Hz, 1H), 5.06 (t, J = 3.22 Hz, 1H), 3.89 (m, 4H), 3.65 (dd, J_1 = 11.47 Hz, J_2 = 3.91 Hz, 1H), 2.86 (m, 2H), 2.64 (s, 3H), 1.49 (m, 2H), 1.23 (m, 16 H), 0.86 (m, 15 H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0, 168.3, 141.0, 128.2, 127.4, 125.8, 69.6, 66.2, 61.5, 59.0, 38.2, 34.1, 30.7, 29.8, 29.6, 28.4, 23.2, 23.0, 22.5, 13.9, 10.8, 9.2. T_g -25 °C, $T_{5\%onset}$ 238 °C

Example 60: Promethazine docusate [14]

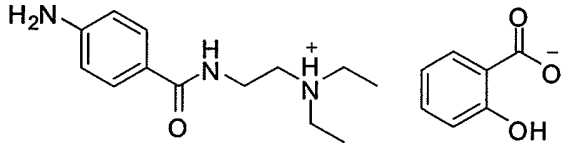


[14]

Promethazine hydrochloride (3.209 g, 10 mmol) and sodium docusate (4.446 g, 10 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution),

dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give promethazine docusate **[14]** in 99% yield as light yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.59 (br s, 1H), 7.26 (m, 6H), 7.04 (t, J = 7.3 Hz, 2H), 4.37 (dd, J_1 = 14.3 Hz, J_2 = 4.8 Hz, 1H), 4.05 (dd, J_1 = 14.6 Hz, J_2 = 8.1 Hz, 1H), 3.89 (m, 4H), 3.66 (m, 2H), 2.91 (m, 2H), 2.82 (s, 6H), 1.49 (m, 2H), 1.28 (d, J = 6.5 Hz, 3H), 1.22 (m, 16 H), 0.83 (m, 12 H). $T_{5\%onset}$ 246 °C.

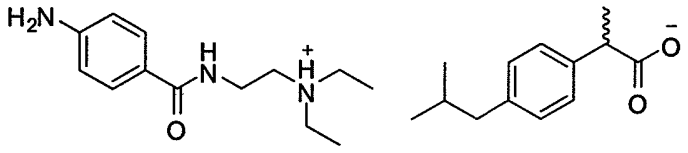
Example 61: Procainamide salicylate [15]



[15]

Procainamide hydrochloride (2.718 g, 10 mmol) and sodium salicylate (1.601 g, 10 mmol) were dissolved in 10 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The clear solution was evaporated and the residue dissolved in anhydrous acetone. The suspension was filtered over celite and the filtrate was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give procainamide salicylate [**15**] as pale yellow viscous oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 8.47 (t, J= 5.6 Hz, 1H), 7.72 (dd, J_1 = 7.7 Hz, J_2 = 1.9 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.23 (m, 1H), 6.71 (m, 2H), 6.54 (d, J = 8.6 Hz, 2H), 3.60 (s, 2H), 3.19 (m, 6H), 1.23 (t, J = 7.1 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 172.5, 166.9, 162.2, 152.0, 132.2, 130.2, 128.8, 120.4, 119.1, 116.8, 1160.0, 112.5, 50.0, 46.7, 34.3, 8.6. $T_{5\%onset}$ 199 °C

Example 62: Procainamide ibuprofenate [16]



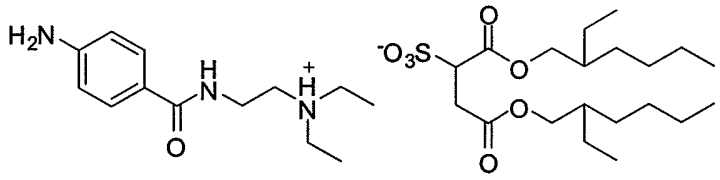
[16]

Procainamide hydrochloride (2.718 g, 10 mmol) and racemic sodium ibuprofenate (2.283 g, 10 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed

under reduced pressure (0.01 mbar) to give procainamide ibuprofenate [**16**] in as viscous yellow liquid.

^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.96 (t, J=5.7 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.69 (d, 8.8 Hz, 2H), 6.54 (d, J = 8.6 Hz, 2H), 5.60 (br s, 2H), 3.61 (q, 7.2 Hz, 1H), 3.29 (m, 2H), 2.56 (m, 6H), 2.42 (d, J = 7.2 Hz, 2H), 1.82 (sept, 6.9 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H), 0.99 (t, 7.1 Hz, 6H), 0.86 (d, J = 6.8 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 175.7, 166.1, 151.5, 139.4, 138.9, 128.9, 128.6, 127.1, 121.3,112.5, 51.6, 46.7, 44.6, 44.2, 37.0, 29.6, 22.2, 18.7, 11.6. $T_{5\%onset}$ 182 °C

Example 63: Procainamide docusate [17]

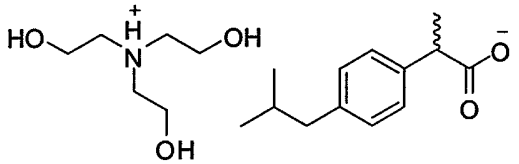


[17]

Procainamide hydrochloride (2.718 g, 10 mmol) and sodium docusate (4.4456 g, 10 mmol) were dissolved in 20 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give procainamide docusate [**17**] in quantitative yield as yellow oil. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 9.08 (br s, 1H), 8.27 (t, J = 5.6 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.6 Hz, 2H), 5.71 (br s, 2H), 3.89 (m, 4H), 3.65 (dd, J_1 = 11.5 Hz, J_2 = 38 Hz, 1H), 3.53 (q, 6.1 Hz, 2H), 3.2 (m, 6H), 2.87 (m, 4H), 1.49 (m, 2H), 1.22 (m, 22H), 0.84 (m, 12H).

$T_{5\%onset}$ 231 °C

Example 64: Triethanolammonium ibuprofenate [18]

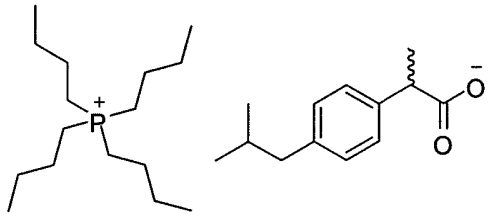


[18]

Ibuprofenic acid (1.032 g, 5 mmol) and triethanolamine (0.746 g, 5 mmol) were molten in a hot mortar until a free-flowing clear liquid was obtained. The mixture solidified at room temperature and was grinded to obtain colourless powder in quantitative yield. ^{1}H-

NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.20 (d, J = 8.1 Hz, 2H), 7.1 (d, 8.1 Hz, 2H), 5.77 (br s, 3H), 3.61 (q, 7.2 Hz, 1H), 3.45 (t, J = 6.1, 6H), 2.61 (t, J = 6.1 Hz, 6H), 2.42 (d, J = 7.2 Hz, 2H), 2.42 (d, 7.2 Hz, 2H), 1.82 (sept, 6.8 Hz, 1H), 1.35(d, J = 7.1 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 175.7, 139.4, 138.8, 128.9, 127.1, 59.0, 57.1, 44.6, 44.3, 29.6, 22.2, 18.7. mp 90 °C, $T_{5\%onset}$ 163 °C

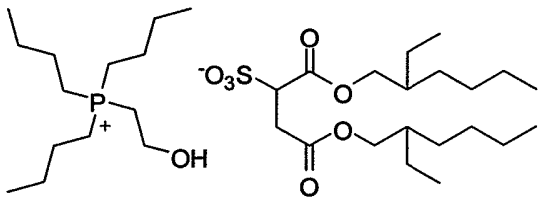
Example 65: Tetrabutylphosphonium ibuprofenate [19]



[19]

Ibuprofenic acid (1.032 g, 5 mmol) and tetrabutylphosphonium hydroxide (~40% sol. in H_2O) (3.414 g, 5 mmol) were dissolved in 20 ml of acetone stirred for 15 min at room temperature. The solvent was evaporated and the remaining viscous liquid was dried at 0.1 mbar with stirring for 24 hrs to obtain tetrabutylphosphonium ibuprofenate [**19**] in qunatitative yield as colourless viscous liquid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 7.13 (d, J = 8.08 Hz, 2H), 6.94 (d, 8.08 Hz, 2H), 3.21 (q, 7.74 Hz, 1H), 2.48 (m, 2H), 2.36 (d, 7.28 Hz, 2H), 2.14 (m, 8H), 1.77 (sept, 6.15 Hz, 1H), 1.40 (m, 16 H), 1.18 (d, J = 7.03 Hz, 3H), 0.91 (t, 7.02 Hz, 12H), 0.84 (d, J = 7.02 Hz, 6H). ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 174.8, 144.2, 136.9, 127.8, 127.2, 49.3, 44.4, 29.7, 23.4 (d, J = 15.8 Hz), 22.7 (d, J = 4.7 Hz), 22.2, 20.5, 17.3 (d, J = 48.1 Hz), 13.3. mp -43 °C, $T_{5\%onset}$ 234 °C.

Example 66: Tributylhydroxyethylphosphonium docusate [20]

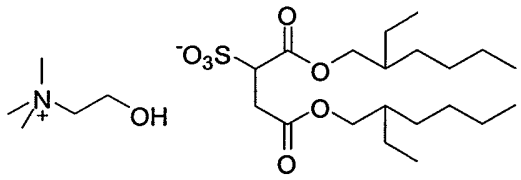


[20]

Tributylhydroxyethylphosphonium chloride (10.019 g, 35.5 mmol) and sodium docusate (15.770 g, 35.5 mmol) were dissolved in 100 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 100 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material

was removed under reduced pressure (0.01 mbar) to give tributylhydroxyethylphosphonium docusate [**20**] in 92% yield as colourless liquid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 5.77 br s, 1H), 3.82 (m, 6H), 3.63 (dd, J_1 = 11.3 Hz, J_2 = 3.8 Hz, 1H), 2.85 (m, 2H), 2.42 (m, 2H), 2.20 (m, 6H), 1.43 (m, 14H), 0.92 (t, J = 7.1 Hz, 9H), 0.84 (m, 12H).^{31}P-NMR (121.5 MHz, d_6-DMSO) δ(ppm) = 34.5. ^{13}C-NMR (75 MHz, d_6-DMSO) δ(ppm) = 171.0, 163.3, 66.1, 66.0, 61.4, 54.4, 54.3, 38.1, 34.1, 29.7, 28.6, 29.5, 28.3, 23.6 (d, J = 15.9 Hz), 23.2, 23.0, 22.7 (d, 4.9 Hz), 22.4, 22.3, 18.1 (d, 48.5), 13.9, 13.8, 13.2, 10.7. T_g -45 °C, $T_{5\%onset}$ 280 °C

Example 67: Choline docusate [21]



[21]

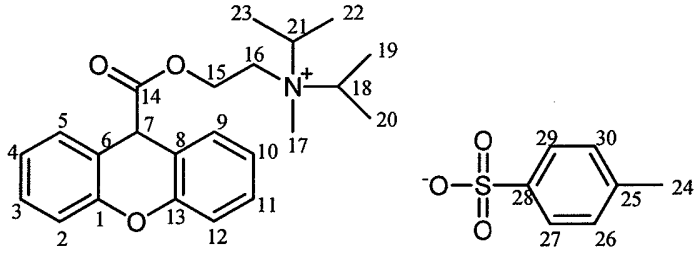
Choline chloride (1.396 g, 10 mmol) and sodium docusate (4.4456 g, 10 mmol) were dissolved in 50 ml of acetone/H_2O 1:1 and stirred overnight at room temperature. The remaining suspension was diluted with 50 ml of H_2O and extracted with dichloromethane. The organic layer was washed successively with water until no more chloride ions could be detected in the washings (checked by addition of $AgNO_3$ solution), dried over $MgSO_4$ and the solvent was evaporated. Remaining volatile material was removed under reduced pressure (0.01 mbar) to give choline docusate [**21**] in quantitative yield as yellow very viscous liquid. ^{1}H-NMR (300 MHz, d_6-DMSO) δ(ppm) = 4.88 (t, J = 5.4 Hz, 1H), 4.21 (dd, J_1 = 10.6 Hz, J_2 = 4.32 Hz, 1H), 4.02 (m, 6H), 3.63 (m, 2H), 3.8 (s, 9H), 3.2 (m, 4H), 1.57 (m, 2H), 1.27 (m, 16H), 0.87 (m, 12H). $T_{5\%onset}$ 189 °C

IONIC LIQUID SOLVATES

Example 68: Propantheline *p*-Toluenesulfonate

A mixture of propantheline bromide (3.32 g, 7.41 mmol) and silver *p*-toluenesulfonate (2.07 g, 7.41 mmol) in acetonitrile (100 mL) was protected from light and stirred overnight at room temperature. A yellow precipitate formed instantaneously. The reaction mixture was filtered through Celite to remove AgBr. The filtrate was then re-filtered through microfilters (0.20 μm). The solvent was evaporated to leave a clear yellow viscous residue. To remove any colour from the sample, propantheline *p*-toluenesulfonate was re-dissolved in acetonitrile and two spatulas of activated charcoal (6-12 Mesh) were added to the solution. The mixture was

left stirring overnight and then filtered through activated aluminum oxide (basic, Brockmann I). The solvent was removed leaving a clear viscous oily residue. The product was dried under vacuum on a Shlenk line at 55 °C for 3 hours. (crude yield: 91 %)



Propantheline *p*-Toluenesulfonate ^{1}H NMR (300 MHz, d_6-DMSO): δ 1.13-1.18 (q, *J* 3.9, 12H; H19, H20, H22, H23), 2.28 (s, 3H; H24), 2.66 (s, 3H; H17), 3.41-3.46 (t(b), *J* 4.7, 2H; H16), 3.71-3.77 (m, 2H; H18, H21), 4.34-4.39 (t(b), *J* 4.7, 2H; H15), 5.31 (s, 1H; H7), 7.09-7.12 (m, 2H; H26, H30), 7.12-7.22 (m, 4H; H2, H4, H10, H12), 7.39-7.40 (m, 4H; H3, H5, H9, H11), 7.46-7.49 (m, 2H; H27, H29). ^{13}C NMR (75 MHz, d_6-DMSO): δ 16.13-16.20 (C19, C20, C22, C23); 20.70 (C24); 40.81 (C17); 44.07 (C7); 54.18 (C16); 59.72 (C15); 63.84 (C18, C21); 116.54 (C2, C12); 118.22 (C6, C8); 123.62 (C4, C10); 125.44 (C27, C29); 127.95 (C26, C30); 129.35 (C3, C11); 129.53 (C5, C9); 137.46 (C28); 145.85 (C25); 150.86 (C1, C13); 170.32 (C14). MS (ESI): ES+ *m/z*: 368.0 (propantheline$^+$), ES- *m/z:* 171.0 (*p*-toluenesulfonate$^-$). ISE: The bromide concentration was determined by dissolving 0.2056 g of propantheline *p*-toluenesulfonate in 10 mL of methanol, indicating <100 ppm bromide. DSC: A reproducible Tg at 7 ± °C.

COMPOSITIONS

Viscosity, conductivity and ΔW values for various propantheline *p*-toluenesulfonate (PtTos) / water composites.

TABLE X

Compositions	Viscosity (mPa.s) ± 1%	Conductivity (S cm^{-1})**	ΔW
PtTos pure*	>2000*	5.41 x 10^{-7}	2.0
Water : PTTos (25 wt%)	3	30.1 x 10^{-4}	0.69
Water : PTTos (20 wt%)	3	26.1 x 10^{-4}	0.77
Water : PTTos (4.8 wt%)	1	15.2 x 10^{-4}	0.63

* instrument limit

** conductivity error does not exceed the data point in all cases

*** ΔW – distance form the ideal line

The low ionicity nature of the ionic liquid is demonstrated via the Walden plot according to the discussion of Fraser *et al* (Chem Commun 2007). Data for this compound are plotted in **Figure 7** which shows that it lies 2 log units below the reference line, suggesting the degree of ionicity is only approximately 1 %. With addition of 25 weight % water, ΔW value decreased. This is true for all of the propantheline *p*-toluenesulfonate / water systems studied. With the increasing water content the ΔW seems to become approximately constant perhaps indicating that full dissociation had been reached.

WHAT IS CLAIMED IS:

1. A method for preparing a bioactive ionic liquid composition, comprising:

a) providing one or more of the following:

i) one or more cations and one or more anions, wherein either the cations, anions, or both can have a bioactive property; or

ii) one or more cation precursors and one or more anion precursors, wherein either the cation precursors, anion precursors, or both have a bioactive property when the precursor has a net charge; and

b) combining the cations and anions or the cation precursors and anion precursors, thereby producing a co-ionic liquid $[B^1HB^2]A$ or $B[A^1HA^2]$ that is liquid at a temperature at or below about 150 °C, wherein B, B^1, and B^2 represent cations, and A, A^1, and A^2 represent anions.

2. A method for preparing a bioactive ionic liquid composition, comprising:

a) providing one or more of the following:

i) one or more cations and one or more anions, wherein either the cations, anions, or both can have a bioactive property; or

ii) one or more cation precursors and one or more anion precursors, wherein either the cation precursors, anion precursors, or both have a bioactive property when charged; and

b) combining the cations and anions or the cation precursors and anion precursors, thereby producing liquid ion pairs;

wherein from about 75% to about 100% of the composition comprises an ion pair having the formula $[B^1HB^2]A$ or $B[A^1HA^2]$.

3. The method according to either Claim 1 or 2, wherein from about 50% to about 100% of the composition comprises an ion pair.

4. The method according to either Claim 1 or 2, wherein from about 5% to about 100% of the composition comprises an ion pair.

5. The method according to either Claim 1 or 2, wherein from about 75% to about 100% of the composition comprises an ion pair when the ion pair is in solution.

6. The method according to either Claim 1 or 2, wherein from about 50% to about 100% of the composition comprises an ion pair when the ion pair is in solution.

7. The method according to to either Claim 1 or 2, wherein from about 5% to about 100% of the composition comprises an ion pair when the ion pair is in solution.

8. A method for preparing a bioactive ionic liquid composition, comprising:
   a) providing one or more of the following:
      i) one or more cations and one or more anions, wherein either the cations, anions, or both can have a bioactive property; or
      ii) one or more cation precursors and one or more anion precursors, wherein either the cation precursors, anion precursors, or both have a bioactive property when charged; and
   b) combining in the presence of one or more solvents the cations and anions or the cation precursors and anion precursors, thereby producing a solvate ionic liquid;

   wherein at least a portion of the solvent provides direct solvation and wherein the composition is composed entirely of ions.

9. The method according to Claim 8, wherein water is used as the solvent.

10. The method according to Claim 1, wherein co-ionic liquids are formed by the addition of an acid or a base.

11. The method according to Claim 1, wherein co-ionic liquids are formed by adding either a corresponding acid HA or corresponding base B to an ionic liquid having the formula [BH]A, wherein further HA is the free acid form of the anions or anion precursors, and B is the free base form of the cations or cation precursors.

12. The method according to Claim 1, wherein co-ionic liquids are formed by adding a corresponding acid HA to an non-protic ionic liquid having the formula B^+A^-, wherein further HA is the free acid form of the anions or anion precursors.

13. The method according to Claim 1, wherein co-ionic liquids are formed by adding either an acid HA_1 or a base B_2 to an ionic liquid having the formula [BH]A, wherein

further HA_1 is a different acid that the acid which forms ionic liquid [BH]A, and B_2 is a different base than the base which forms ionic liquid [BH]A.

14. The method according to Claim 1, wherein co-ionic liquids are formed by adding either an acid HA_1 to an non-protic ionic liquid having the formula B^+A^-, wherein further HA_1 is a different acid that the acid which forms ionic liquid B^+A^-.

15. The method according to Claim 1, wherein the co-ionic liquid is formed by addition of an acid or a base to an ionic liquid [BH]A in a solvent-free synthesis in the molten state or by grinding.

16. The method according to Claim 1, wherein combining the cation precursor and anion precursor in step (b) is accomplished by an acid-base neutralization reaction wherein the ratio of acid to base used for the neutralization reaction is not 1:1.

17. The method according to Claim 1, wherein more than one cation precursors and one anion precursor are reacted to provide a co-ionic liquid having the formula $[B^1HB^2]A$.

18. The method according to Claim 1, wherein more than one cation precursors and one anion precursor are reacted in a solvent-free way via grinding in a ratio that is not 1:1.

19. The method according to Claim 1, wherein more than one cation precursors and one anion precursor are reacted in a solvent-free way via melting in a ratio that is not 1:1.

20. The method according to Claim 1, wherein more than one anion precursors and one cation precursor are reacted to provide a salt of the type $B[A^1HA^2]$.

21. The method according to Claim 1, wherein more than one anion precursors and one cation precursor are reacted in a solvent-free way via grinding in a ratio that is not 1:1.

22. The method according to Claim 1, wherein more than one anion precursors and one cation precursor are reacted in a solvent-free way via melting in a ratio that is not 1:1.

23. The method according to Claim 1, wherein combining the cation precursor and anion precursor is accomplished by addition of acid to hydroxide precursor of the cation in a ratio that is not 1:1.

24. The method according to Claim 1, wherein the composition further comprises a solvent, preservative, dye, colorant, thickener, surfactant, a viscosity modifier, or a mixture thereof at less than about 10 wt.% of the total ionic liquid composition.

25. The method according to Claim 1, wherein the at least one cation or at least one anion is the pharmaceutical active.

26. The method according to Claim 1, wherein the cation and the anion are both pharmaceutical actives.

27. The method according to Claim 1, wherein at least one cation is a pharmaceutical active and at least one anion is a taste modifier, or wherein at least one cation is a taste modifier and at least of anion is a pharmaceutical active.

28. The method according to Claim 1, wherein at least one cation is an antibacterial and at least one anion is a taste modifier, or wherein at least one cation is a taste modifier and at least one anion is an antibacterial.

29. The method according to Claim 1, wherein at least one cation is an antibacterial and at least one anion is a pain reliever or anti-inflammatory, or wherein at least one cation is a pain reliever or anti-inflammatory and at least one anion is an antibacterial.

30. The method according to Claim 1, wherein at least one cation is an antibacterial and at least one anion is a UV-blocker, or wherein at least one cation is a UV-blocker and at least one anion is an antibacterial.

31. The method according to Claim 1, wherein at least one cation is an anesthetic and at least one anion is an antibacterial, or wherein at least one cation is an antibacterial and at least one anion is an anesthetic.

32. The method according to Claim 1, wherein at least one cation is an anesthetic and at least one anion is a coagulator, or wherein at least one cation is a coagulator and at least one anion is an anesthetic.

33. The method according to Claim 1, wherein at least one cation is an antibacterial and at least one anion is a coagulator, or wherein at least one cation is a coagulator and at least one anion is an antibacterial.

34. The method according to Claim 1, wherein either the cation or anion or either the cation precursor or the anion precursor are chiral.

35. The method according to Claim 1, wherein both the cation and anion or both the cation precursor and anion precursor are chiral.

36. The method according to Claim 1, wherein the chiral cation comprises ephedrine or a diastereomer thereof.

37. The method according to Claim 1, wherein the chiral anion comprises camphorsulfonic acid.

38. The method according to Claim 1, wherein the cation or cation precursor is a pesticidal active or the anion or anion precursor is a pesticidal active.

39. The method according to Claim 1, wherein the cation and anion or the cation precursor and anion precursor are both pesticidal actives.

40. The method according to Claim 1, wherein the cation or cation precursor is a herbicidal active or the anion or anion precursor is a herbicidal active.

41. The method according to Claim 1, wherein the cation and anion or the cation precursor and anion precursor are both herbicidal actives.

42. The method according to Claim 1, wherein the cation or cation precursor is a nutraceutical or the anion or anion precursor is a nutraceutical.

43. The method according to Claim 1, wherein the cation and anion or the cation precursor and anion precursor are both nutraceuticals.

44. The method according to Claim 1, wherein the cation or cation precursor is a food additive or the anion or anion precursor is a food additive.

45. The method according to Claim 1, wherein the cation and anion or the cation precursor and anion precursor are both food additives.

46. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about 125 °C.

47. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about 75 °C.

48. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about 50 °C.

49. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about 25 °C.

50. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about 0 °C.

51. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about -25 °C.

52. The method according to Claim 1, wherein the composition is liquid at a temperature at or below about -50 °C.

53. The method according to Claim 1, wherein the composition is liquid at a temperature from about -30 °C to about 150 °C.

54. The method according to Claim 1, wherein the composition is liquid at a temperature from about 0 °C to about 120 °C.

55. The method according to Claim 1, wherein the composition is liquid at about 37 °C.

56. The method according to Claim 1, wherein the composition is liquid over a temperature range of at least 4 °C.

57. The method according to Claim 1, wherein the cation compromises a quaternary nitrogen or phosphor ion as cation.

58. The method according to Claim 1, wherein the at least one kind of cation comprises an aliphatic heteroaryl cation, an aliphatic benzylalkyl ammonium cation, a dialiphatic dialkyl ammonium cation, or a tetraalkyl ammonium cation.

59. The method according to Claim 1, wherein the cation compromises a protonated cation.

60. The method according to Claim 1, wherein the cation comprises choline, lidocaine, tramadolium, caffeine, cetylpyridinium, ephedrinium or promethazine.

61. The method according to Claim 1, wherein the anion comprises salicylate, ibuprofenate, lactate, camphorsulfonate, *trans*-cinnamate, docusate, niacinate or clofibrate.

62. The method according to Claim 1, wherein the cation comprises tetrabutylphosphonium and the anion comprises salicylate and ibuprofenate, cinnamate, camphorsulfonate, lactate or thiosalicylate.

63. The method according to Claim 1, wherein the cation comprises tetrabutylphosphonium and the anion comprises ibuprofenate and niacinate.

64. The method according to Claim 1, wherein the cation comprises cetylpyridinium and the anion comprise salicylate and ibuprofenate, cinnamate or clofibrate.

65. The method according to Claim 1, wherein the cation comprises lidocaine and the oligomeric anions comprises salicylate and ibuprofenate.

66. The method according to Claim 1, wherein the cation comprises tramadolium and the anion comprises salicylate and ibuprofenate.

67. The method according to Claim 1, wherein the cation comprises ephedrinium and lidocaine and the anion comprises ibuprofenate.

68. The method according to Claim 1, wherein the cation comprises tramadolium and lidocaine and the anions comprise salicylate or ibuprofenate.

69. The method according to Claim 1, wherein the oligomeric cation comprises promethazine and ephedrine and the anions comprise docusate or salicylate.

70. A method for the preparation of ionic liquid-immobilized active compounds:

a) providing one or more cations and one or more anions, wherein a biologically active neutral compound is covalently attached to either the cation or the anion, or both cation and anion; and

b) combining the cations and anions or the cation precursor and anion precursor, thereby producing an ionic liquid that is liquid at a temperature at or below 150 °C.

71. The method according to Claim 70, wherein combining the cations and anions is accomplished by a metathesis reaction.

72. The method according to Claim 70, wherein combining the cation precursor and anion precursor is accomplished by an acid-base neutralization reaction.

73. The method according to Claim 70, wherein the cation precursor is a pharmaceutical active or the anion precursor is a pharmaceutical active.

74. The method according to Claim 70, wherein the cation precursor and the anion precursor are both pharmaceutical actives.

75. The method according to Claim 70, wherein either the cation precursor or the anion precursor, or the cation precursor and the anion precursor have bioactive properties and the bioactive property comprises sensory, therapeutic, prophylactic, nutritional, pesticidal or herbicidal activity.

76. The method according to Claim 70, wherein either the cation precursor or the anion precursor, or the cation precursor and the anion precursor are food additives, flavors or fragrances.

77. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 150 °C.

78. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 125 °C.

79. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 100 °C.

80. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 75 °C.

81. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 50 °C.

82. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 37 °C.

83. The method according to Claim 70, wherein the composition is liquid at a temperature at or below about 0 °C.

84. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

85. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to an anion selected from the group of carboxylate, alkylphosphate, alkylsulfate, alkylsulfonate, alkylborate.

86. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to a cation that is pharmaceutical or biological active.

87. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to a cation that is used as nutraceutical, food additive.

88. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to a cation that is used as fragrance or flavor.

89. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to an anion that is pharmaceutical or biological active.

90. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to an anion that is used as nutraceutical or food additive.

91. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to an anion that is used as fragrance or flavor.

92. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with an anion selected from the group of halide, phosphate, alkylphosphate, nitrate, sulfate, alkylsulfate, arylsulfate, sulfonate, alkylsulfonate, arylsulfonate, alkylborate, tosylate, saccharinate, alkylcarboxylate and alkoxycarboxylate.

93. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

94. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with a biological or pharmaceutical active counterion.

95. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with nutraceutical or food additive counterion.

96. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with a flavor or fragrance counterion.

97. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released under hydrolytic conditions.

98. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released depending on the pH value.

99. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at a pH<7.

100. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at a pH<5.

101. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at a pH<3.

102. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at a pH>7.

103. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at a pH>9.

104. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at a pH>11.

105. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released under thermic conditions.

106. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released >37 °C.

107. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released >50 °C.

108. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released >75 °C.

109. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released >100 °C.

110. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released under light. Irradiation.

111. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released under UV light irradiation.

112. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released via electrodecomposition.

113. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound can be selectively released at physiological conditions.

114. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is attached to the ionic compound with an ester bond.

115. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is an alcohol or phenol.

116. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound comprises analgesics.

117. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound comprises acetaminophen.

118. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound comprises antitumor, antioxidant, antiarthritic, anti-amyloid, anti-ischemic or anti-inflammatory properties.

119. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with an emmolient.

120. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is paired with docusate.

121. A compound prepared according to Claim 70, wherein the compound is in the form of a salt and the biological active neutral compound is transferred into a hemisuccinate anion.

122. A compound prepared according to Claim 121, wherein the compound is in the form of a salt and the hemisuccinate is paired with a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

123. A compound prepared according to Claim 121, wherein the compound is in the form of a salt and the hemisuccinate is paired with choline.

124. The composition prepared according to Claim 70, wherein the composition further comprises a solvent, preservative, dye, colorant, thickener, surfactant, a viscosity modifier, or a mixture thereof at less than about 10 wt.% of the total ionic liquid composition.

125. The composition prepared according to Claim 70, wherein the composition further comprises a nonionic pharmaceutical active, nutraceutical, food additive, or mixture thereof.

126. A method for the preparation of ionic liquid-immobilized fragrances or flavors comprising:

a) providing one or more kinds of cation and one or more kinds of anion, wherein a fragrance or flavor is covalently attached to either the cation or the anion, or both cation and anion;

b) combining the cations and anions or the cation precursor and anion precursor, thereby producing an ionic liquid that is liquid at a temperature at or below 100 °C.

127. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

128. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to an anion selected from the group of carboxylate, alkylphosphate, alkylsulfate, alkylsulfonate, alkylborate.

129. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to a cation that is pharmaceutical or biological active.

130. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to a cation that is used as nutraceutical, food additive.

131. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to a cation that is used as second fragrance or flavor.

132. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to an anion that is pharmaceutical or biological active.

133. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to an anion that is used as nutraceutical or food additive.

134. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor is attached to an anion that is used as second fragrance or flavor.

135. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the cationic fragrance is paired with an anion selected from the group of halide, phosphate, alkylphosphate, nitrate, sulfate, alkylsulfate, arylsulfate, sulfonate, alkylsulfonate, arylsulfonate, alkylborate, tosylate, saccharinate, alkylcarboxylate and alkoxycarboxylate.

136. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the anionic fragrance is paired with a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

137. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the ionic fragrance is paired with a biological or pharmaceutical active counterion.

138. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the ionic fragrance is paired with nutraceutical or food additive counterion.

139. A compound prepared according to Claim 126, wherein the ionic fragrance is paired with a second flavor or fragrance counterion.

140. A compound prepared according to Claim 126, wherein the fragrance can be selectively released under hydrolytic conditions.

141. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released depending on the pH value.

142. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released at a pH<7.

143. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released at a pH<5.

144. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released at a pH<3.

145. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released at a pH>7.

146. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released at a pH>9.

147. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released at a pH>11.

148. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released under thermic conditions.

149. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released >37 °C.

150. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released >50 °C.

151. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released >75 °C.

152. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released >100 °C.

153. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released under light irradiation.

154. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released under UV light irradiation.

155. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavor can be selectively released via electrodecomposition.

156. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance can be selectively released at physiological conditions.

157. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance or flavour is an alcohol.

158. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance is a terpene.

159. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance comprises geraniol, prenol, menthol, citronellol or arnesol.

160. A compound prepared according to Claim 126, wherein the compound is in the form of a salt and the fragrance is attached to the ionic compound with an ester bond.

161. A compound prepared according to Claim 160, wherein the compound is in the form of a salt and the hemisuccinate is paired with a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

162. A compound prepared according to Claim 160, wherein the compound is in the form of a salt and the hemisuccinate is paired with a cation selected from the group of ammonium, imidazolium, pyrrolidinium, pyridinium, phosphonium or sulfonium ion.

163. A compound prepared according to Claim 160, wherein the compound is in the form of a salt and the hemisuccinate is paired with quaternary phosphonium or ammonium compounds present in detergents, phase transfer catalyst or any other laundry compounds.

164. A product comprising one or more compounds prepared according to Claim 126, wherein the product is a fine perfume, bodycare composition, toiletry, detergent perfume, fabric softener perfume, laundry detergent or a scent to mask industrial odors.

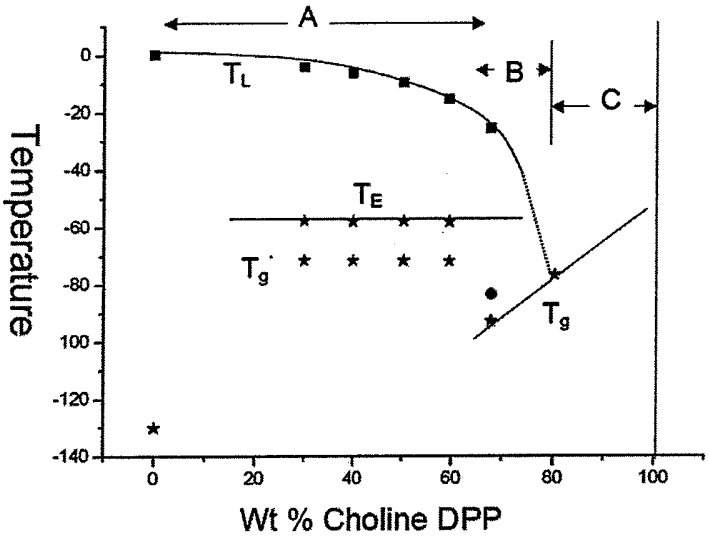

A
B
C
T_L
T_E
T_g'
T_g
Temperature
0
-20
-40
-60
-80
100
-120
-140
0
20
40
60
80
100
Wt % Choline DPP

Fig. 1

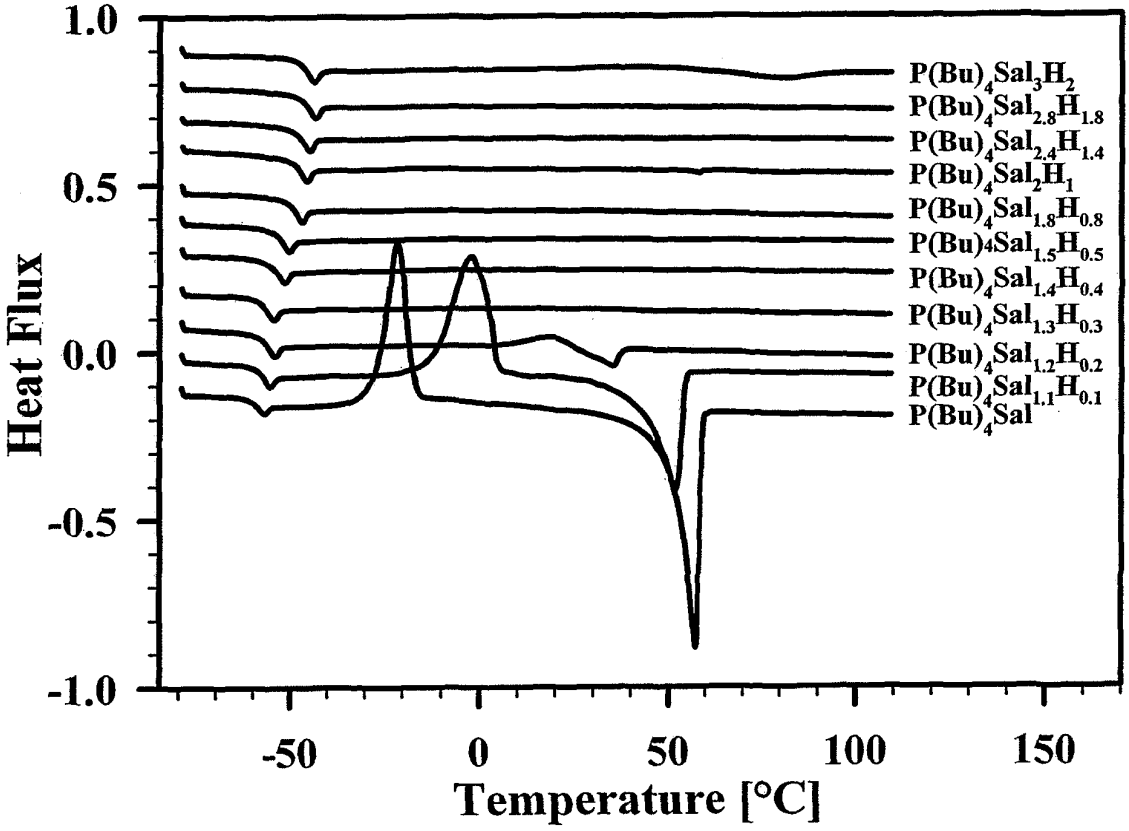

1.0
0.5
0.0
-0.5
-1.0
Heat Flux
-50
0
50
100
150
Temperature [°C]
P(Bu)4Sal3H2
P(Bu)4Sal2.8H1.8
P(Bu)4Sal2.4H1.4
P(Bu)4Sal2H1
P(Bu)4Sal1.8H0.8
P(Bu)4Sal1.5H0.5
P(Bu)4Sal1.4H0.4
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P(Bu)4Sal1.1H0.1
P(Bu)4Sal

Fig. 2

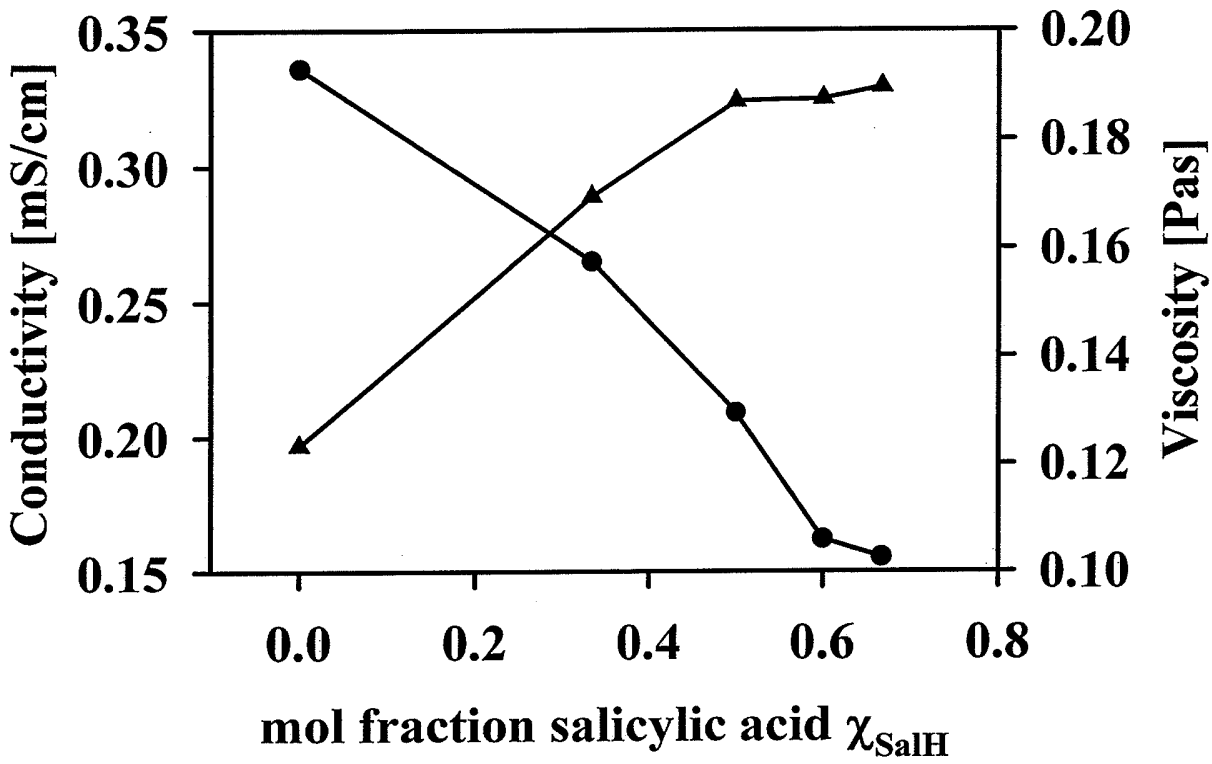

0.35
0.30
0.25
0.20
0.15
Conductivity [mS/cm]
0.20
0.18
0.16
0.14
0.12
0.10
Viscosity [Pas]
0.0
0.2
0.4
0.6
0.8
mol fraction salicylic acid χ_{SalH}

Fig. 3

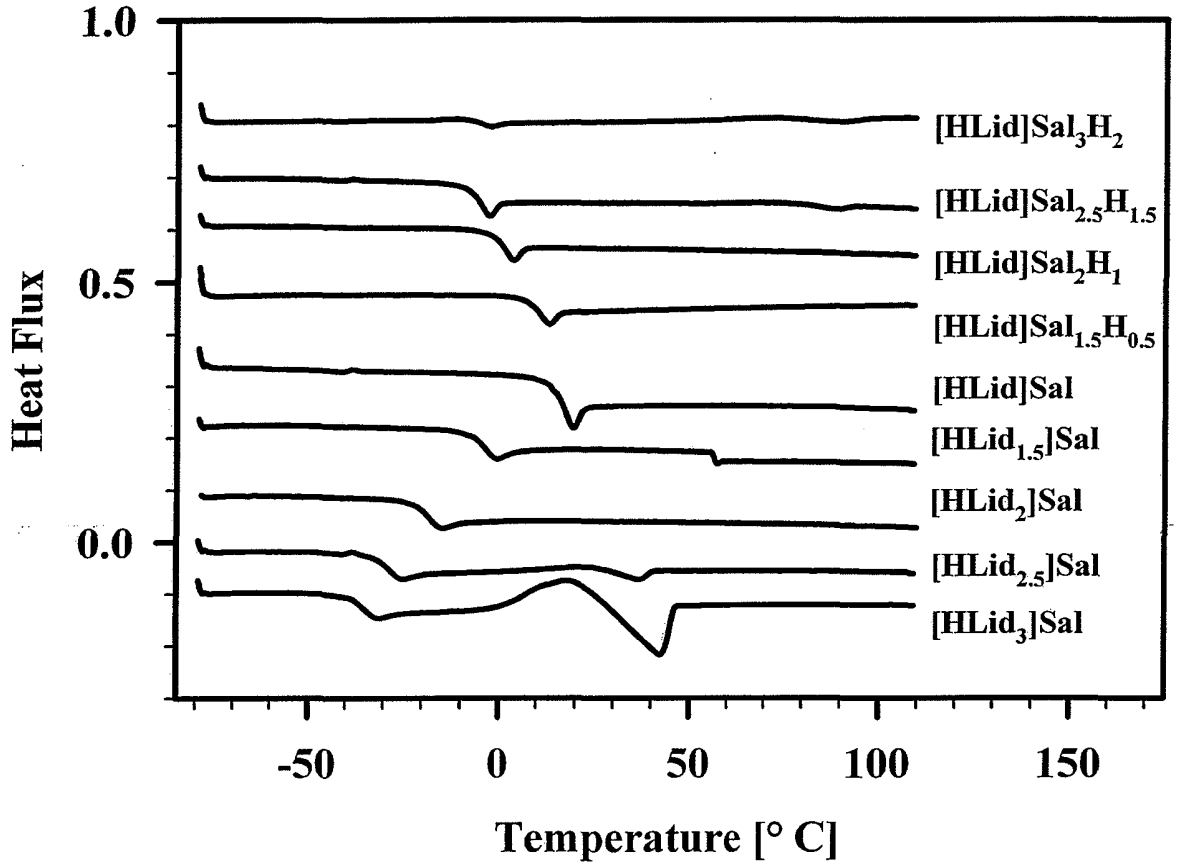

1.0
0.5
0.0
Heat Flux
[HLid]Sal3H2
[HLid]Sal2.5H1.5
[HLid]Sal2H1
[HLid]Sal1.5H0.5
[HLid]Sal
[HLid1.5]Sal
[HLid2]Sal
[HLid2.5]Sal
[HLid3]Sal
-50
0
50
100
150
Temperature [° C]

Fig. 4

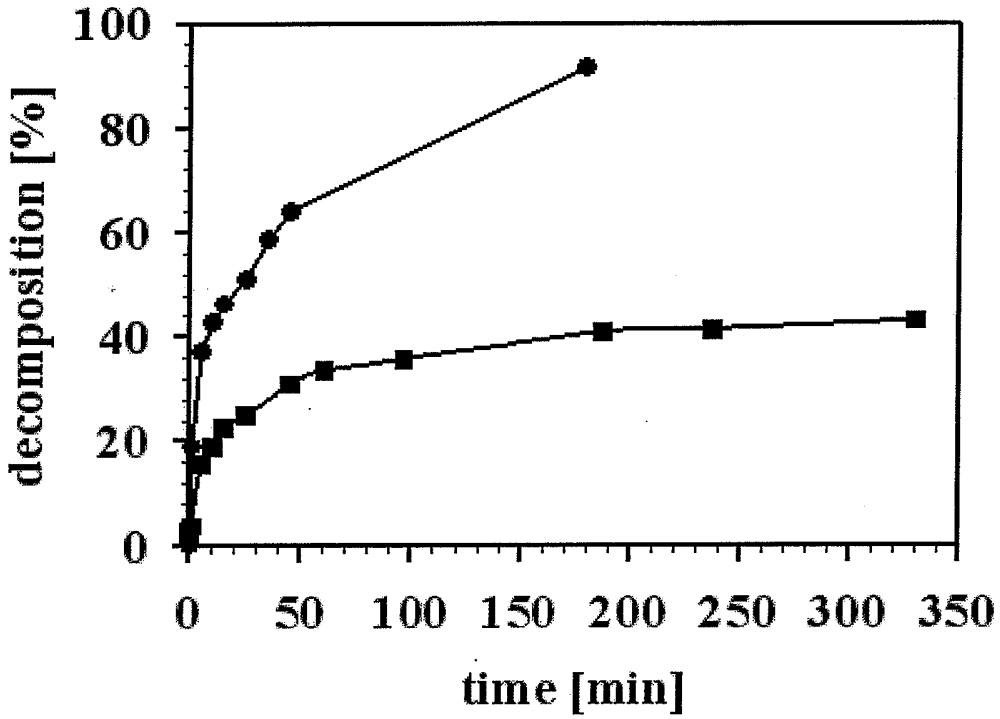

100
80
60
40
20
0
decomposition [%]
0
50
100
150
200
250
300
350
time [min]

Fig. 5

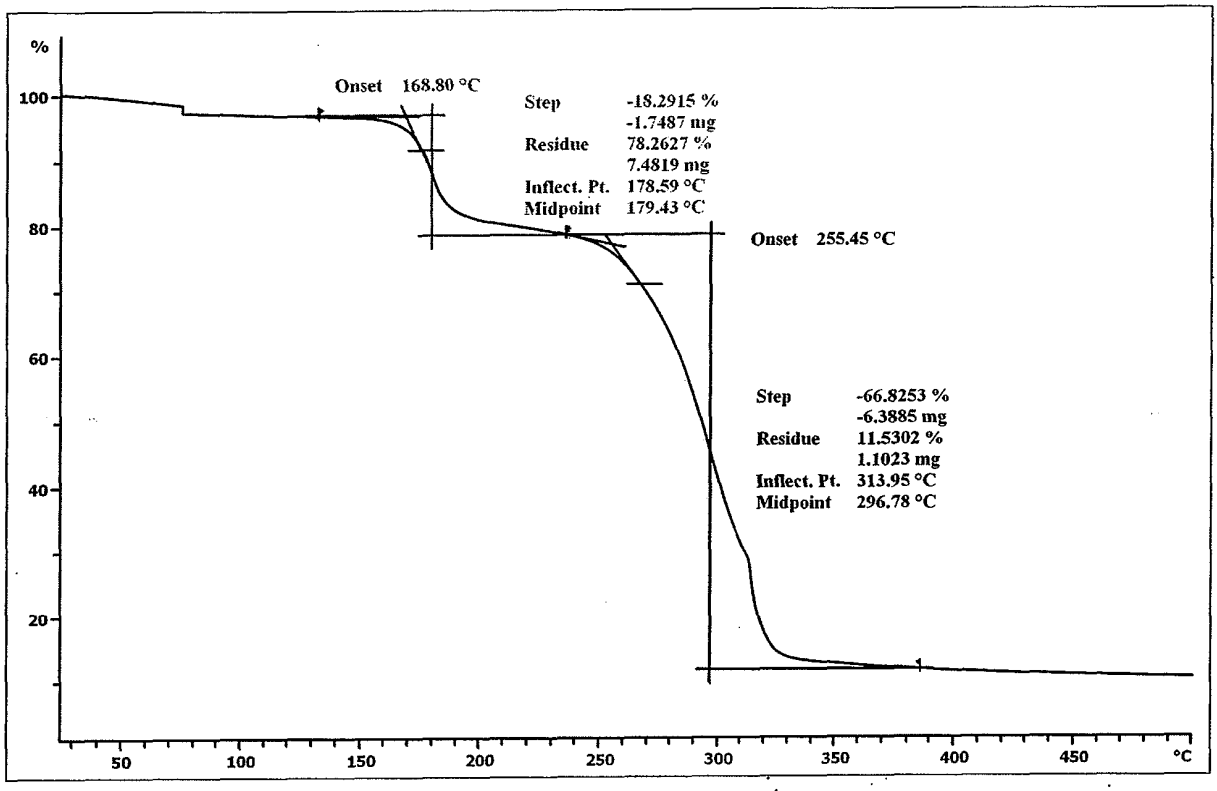

%
100
80
60
40
20
Onset 168.80 °C
Step -18.2915 %
-1.7487 mg
Residue 78.2627 %
7.4819 mg
Inflect. Pt. 178.59 °C
Midpoint 179.43 °C
Onset 255.45 °C
Step -66.8253 %
-6.3885 mg
Residue 11.5302 %
1.1023 mg
Inflect. Pt. 313.95 °C
Midpoint 296.78 °C
50
100
150
200
250
300
350
400
450
°C

Fig. 6

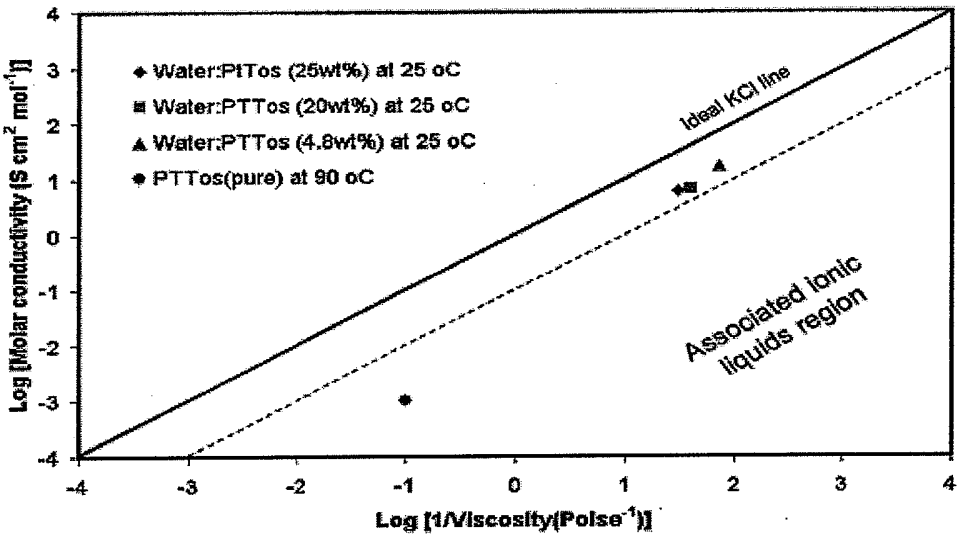

Water:PtTos (25wt%) at 25 oC
Water:PTTos (20wt%) at 25 oC
Water:PTTos (4.8wt%) at 25 oC
PTTos(pure) at 90 oC
Ideal KCl line
Associated ionic liquids region
Log [Molar conductivity (S cm2 mol-1)]
Log [1/Viscosity(Poise-1)]
4
3
2
1
0
-1
-2
-3
-4
-4
-3
-2
-1
0
1
2
3
4

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/69652

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 55/02; A61K 31/555 (2010.01)
USPC - 514/184-185
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/184-185

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 252/182.3, 182.12; 508/244, 283, 388; 514/492; 585/862 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT0, Google. Search Terms Used: bioactive, ionic liquid composition, triazolates, triazolate, benzimidazolate, triazolate, triazolium, imidazolium, pyrazolium, oxazolium, acid, base

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2007/0093462 A1 (Rogers et al.) 26 April 2007 (26.04.2007) abstract; para [0017], [0077], [0083], [0086], [0094], [0096]-[0097], [0100], [0105], [0109]-[0110], [0121], [0147]-[0149], [0157], [0360], [0367], [0382], [0338], [0399]-[0400], [0436]	1-24, 25a-33a, 25b-33b and 34-60 --- 61-155
Y	US 6,967,074 B2 (Duffy et al.) 22 November 2005 (22.11.2005) col 42, ln 41-64	61-155
A	US 2007/0006774 A1 (Rogers et al.) 11 January 2007 (11.01.2007) entire document	1-24, 25a-33a, 25b-33b and 34-155

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search	Date of mailing of the international search report
23 February 2010 (23.02.2010)	05 MAR 2010
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