

Vol. 80 Commemorative Accounts

Ionic Liquids Then and Now: From Solvents to Materials to Active Pharmaceutical Ingredients

Whitney L. Hough[1] **and Robin D. Rogers***[1,2]

[1]Center for Green Manufacturing and Department of Chemistry, The University of Alabama, Tuscaloosa, AL 35487, USA

[2]QUILL and School of Chemistry & Chemical Engineering, The Queen's University of Belfast, Belfast BT9 5AG, Northern Ireland, U.K.

Received August 7, 2007; E-mail: RDRogers@bama.ua.edu

Ionic liquids (ILs) have evolved from salts studied primarily for their physical properties (low melting salts which could be used as solvents) to tunable materials based upon the physical, chemical, and now even biological properties that can be introduced through either ion. In this perspective, we follow this interesting evolution with respect to our work in this growing field, and discuss possible future directions, such as the use of ILs as active pharmaceutical ingredients (APIs).

Ionic Liquids as Novelties

Ionic liquids (ILs) are now being defined (perhaps loosely) as salts composed solely of ions, with a melting point below 100 °C.[1–7] Although compounds fitting this definition have been known for over a century,[8] it has been only relatively recently, first with the utilization of ILs as electrochemical solvents[9] and later with the suggestion that ILs could be "green solvents,"[1,10] that a phenomenal growth in industrial and academic interest has occurred. As of the writing of this article, more than 8000 publications (including 900 patents) have appeared discussing ILs; 97% of which have been published since 1998 when Michael Freemantle wrote an article for *Chem. Eng. News* entitled "Designer Solvents—Ionic Liquids May Boost Clean Technology Development."[11] It would be constructive to first discuss the origins of this growth, then how misconceptions may actually be hindering the advancement of this field, and finally what the future may hold.

One of the twelve principles of green chemistry, as developed by Anastas and Warner, states that the use of auxiliary substances such as solvents, separation agents, etc., should be made unnecessary and if used should be innocuous.[12] One primary target for "greening" the chemical industry would be the replacement of an industrial workhorse, volatile organic compounds (VOCs) with safer alternatives. ILs can exhibit certain desirable physical properties, such as high solvency, wide liquidus range, and negligible vapor pressure, which merit the consideration of ILs as solvent replacements.

The potential of ILs as "green" replacement solvents was the focus of a NATO Advanced Research Workshop: *Green Industrial Applications of Ionic Liquids* held in April 2000, in Crete, Greece.[3,13,14] The purpose of this workshop was to increase awareness of the IL field, bring new research expertise into the IL field, and set a research agenda for the future of this field. The workshop, which had ample representation from both industry and academia, concentrated on the potential greening of industrial processes by using ILs as "designer solvents," and major IL-related knowledge gaps which needed to be filled. The outcomes of this meeting were significant:[3]

(i) "ILs are intrinsically interesting and worthy of study for advancing science (ionic vs. molecular solvents) with the expectation that something useful may be derived from their study."

(ii) "Combined with green chemistry, a new paradigm of thinking about synthesis in general, ILs provide an opportunity for science/engineering/business to work together from the beginning of the field's development."

(iii) "Readily available, well-characterized ILs, free of intellectual property, are needed to encourage development of applications."

(iv) "Toxicity, biodegradation, bio-accumulation, safety, health, and environment (SHE) impact data are needed immediately."

(v) "IL research should consider cost/benefit, economic, and life-cycle analysis."

(vi) "Regulatory road blocks to IL implementation should be tackled now."

(vii) "A public (free), verified, web-based database of physical, thermodynamic, and related data (i.e. not process specific) is needed, and work should start immediately on identifying the best methods to accomplish this."

Published on the web December 13, 2007; doi:10.1246/bcsj.80.2262

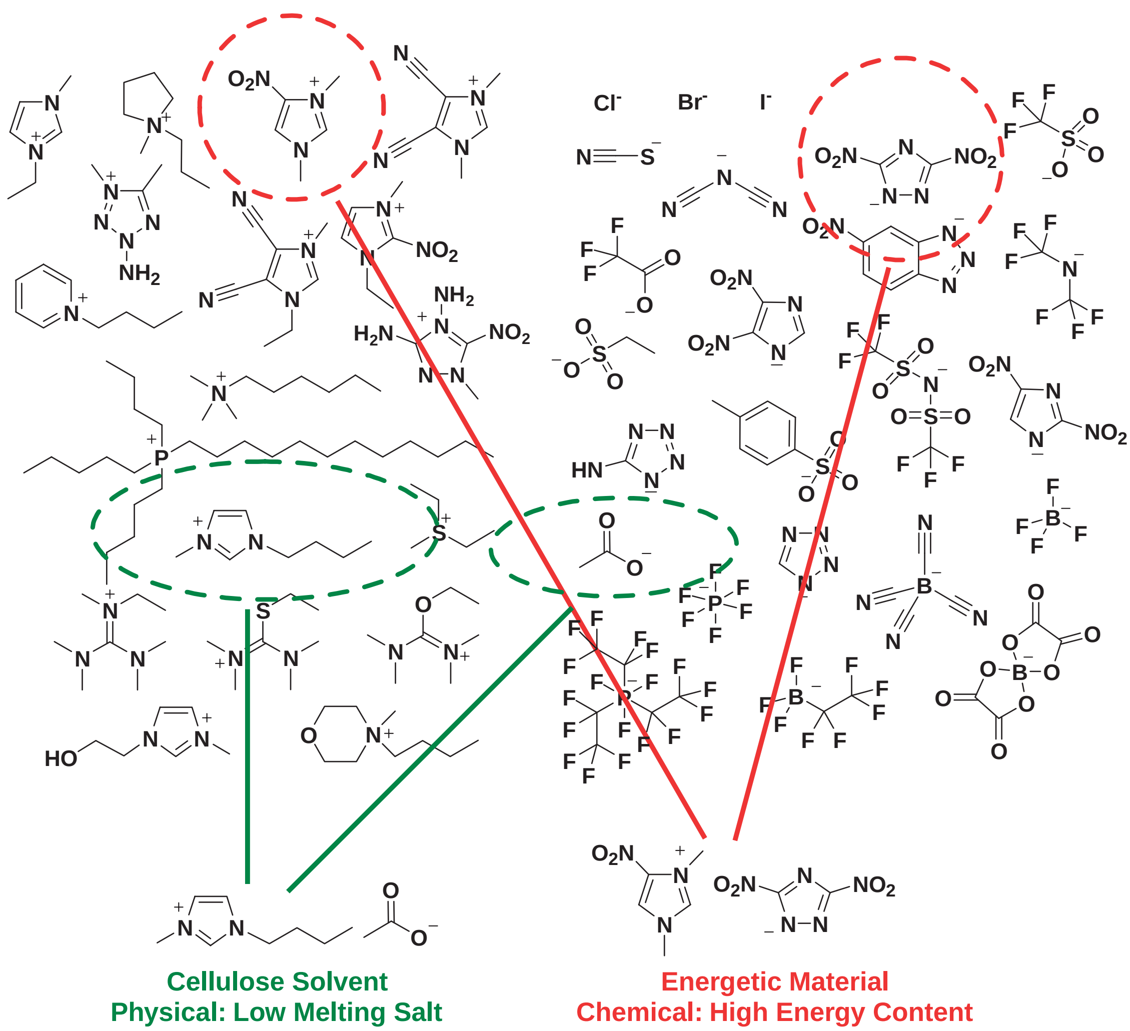


Fig. 1. Emphasis on physical and chemical properties.

(viii) "There is an urgent need to increase the number, but especially the areas of expertise, of IL researchers. A model of open collaboration needs to be encouraged."

(ix) "International collaboration, communication, and education regarding the results are needed."

(x) "A brochure should be developed to advance the understanding of ILs and their applications."

At this first international IL meeting, a solid link was made between green chemistry, academia, industry, and ILs. The goal of the workshop, to educate and intrigue scientists and engineers about ILs, was accomplished and the remarkable worldwide growth in IL-based papers and patents mentioned above accelerated. However, it is important to point out that ILs were neither restricted in their scope of use to solvents, nor anointed as "green," a concept that has become a battlefield for IL research.

ILs, as defined by melting point, cover an extremely wide range of composition, and thus offer a convenient way to study the effects of slight (or substantial) modifications in the structures or combinations of their ions on the resulting physical and chemical properties. However, many researchers have wanted to study a "typical" IL and apply it to a specialized problem (often solvent replacement), rather than find a specialized IL to solve a specific problem. This originally led to study of a limited number of "typical" ILs, with salts of dialkylimidazolium cations and hexafluorophosphate anions leading the list (Fig. 1).[1,10] It also led to broad overgeneralizations of ILs as everything from nontoxic, nonflammable, and nonvolatile to toxic, flammable, and volatile; each of these statements clearly can be true for a single IL salt, but cannot be true for the entire range of possible compounds which meet the definition of an IL!

Ionic Liquids as Technology Enablers and Novel Materials

Recently, many scientists and engineers (many well outside chemistry-related fields[15]) have realized that ILs are actually customizable materials for a variety of specialized applications, and through their research broadened the number of cations and anions that are used to form ILs (Fig. 2).[16] The true power of this field will ultimately come from how we exploit our understanding of these modularly tunable liquid salts, and industrial technologies are already appearing.

ILs are evolving from electrochemical and general solvents,[17,18] to novel materials in diverse applications such as specialized solvents,[19] lubricants,[20–22] thermal fluids,[23] magnetic fluids,[24–26] optical fluids,[27] propellants,[28,29] etc. Interdis-

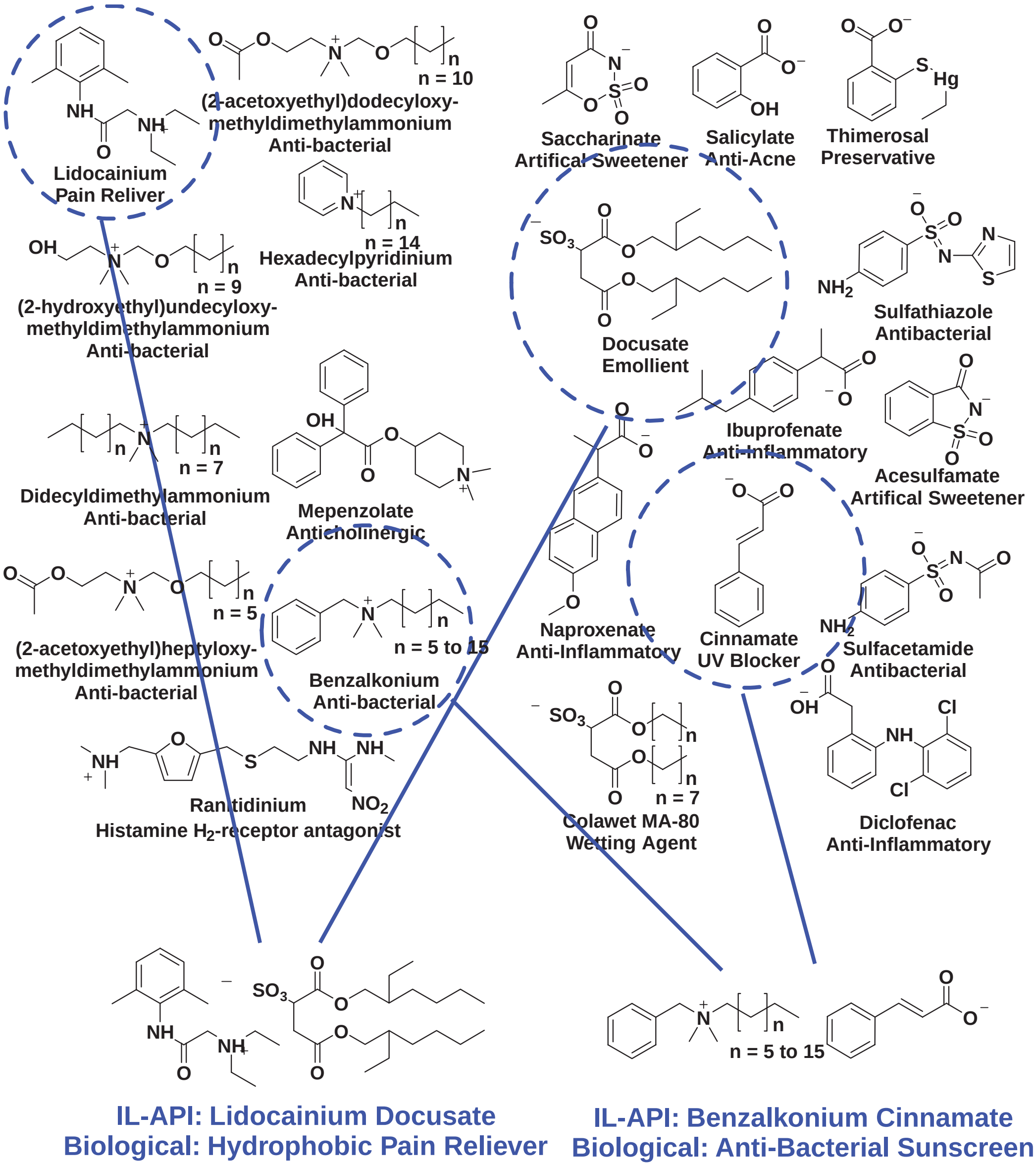


Fig. 2. Emphasis on biological activity.

ciplinary exploration of both properties and potential uses of ILs have led to such technologies as BASIL®,[30] the first industrial application of ILs,[31] where the IL acts as a biphasic acid scavenger. BASF has also launched new product lines like BASIONIC™ (a range of ILs) and CELLIONIC®, 5 wt % cellulose solutions in 1-ethyl-3-methylimidazolium acetate ([C_2mim][OAc]).[32] Large companies such as Merck KGaA have developed hundreds of specialty IL products[33] and several companies have been founded to synthesize ILs in small to bulk quantities and find novel applications (e.g., Solvent Innovation,[34] Iolitec,[35] Solvionic,[36] Bioniqs,[37] etc.).

Many among the plethora of new applications appearing for ILs, take advantage of the unique combinations of chemical and physical properties addressable by their dual-functional (two component) nature and their inherent compartmentalized design flexibility which allow targeted synthesis of "tuned" materials. ILs make a unique architectural platform on which, at least potentially, the properties of both cation and anion components can be independently modified, while retaining the core desirable features of the IL state of matter.[38]

Ionic Liquids as Toxic Chemicals

It is ironic then, that although ILs have been extensively studied for their tunability, and there could be the oft-quoted 10^{18} possible IL combinations,[39] many researchers insist in using overgeneralizations when praising and criticizing the field. Nowhere has this been more evident than in the debate over whether ILs are "toxic" or not.[40,41] Given the broad definition of an "IL" and the aforementioned tunability of ion combinations, it should be clear that ILs can be designed that are toxic, flammable, or corrosive, just as easily as they can be designed to be non-toxic, non-flammable, and non-corrosive.

The truth is, "toxicity" can be a desirable property of ILs! Many useful and necessary chemicals are toxic, including, of course, many pharmaceuticals. "The poison is in the dose," as pointed out by Theophrastus Paracelsus (1493–1541),[42] and more recently (2007) by Circa Survive in their song "The Difference Between Medicine and Poison is in the Dose."[43] Might not delivery of biological activity in a liquid salt form be another example of where IL technology could make an impact?

The pharmaceutical industry has cautiously studied ILs for the replacement of VOCs in the synthesis of active pharmaceutical ingredients (APIs) and crystallization.[44] Although favorable results were obtained, the industry does not yet appear to take ILs seriously as solvents due to questions regarding purity, toxicity, and regulatory approval.[45] And yet, one wonders why an industry that is quite focused on salt forms of their major products (APIs),[46] has not intensely studied how the fundamental knowledge generated about ILs could help improve their product performance.

An IL approach seems more than appropriate in the design of APIs, where a delicate balance exists between the exact chemical functionality needed for the desired effect in the absence of adverse side effects and the physical properties required for manufacturing, stability, solubility, transport, and bioavailability.[47,48] Currently, the pharmaceutical industry and regulatory agencies rely mostly on crystalline APIs. Unfortunately, many pharmaceuticals fail during testing because of issues with, for example, delivery mechanisms such as dissolution, transport, and bioavailability or poor control over polymorphism which can dramatically change properties such as solubility.[49]

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 the crystalline lattice.[50] Many pharmaceuticals exhibit polymorphism, for example, 70% of barbiturates, 60% of sulfonamides, and 23% of steroids are believed to exist in multiple polymorphic forms.[51] In addition, many APIs crystallize as solvates which may be stoichiometric or non-stoichiometric[52] and which may also exhibit polymorphism. The existence of polymorphs or solvates can negatively affect an API's performance, since the solid-state structure determines its physical properties such as dissolution rate, solubility, bioavailability, mechanical strength, etc.[53] Moreover, many manufacturing processes are often hampered by the lack of control of variable solvate formation, polymorphism, and polymorphic conversion that can render the API dosages ineffective or even deadly.[54]

The possibility of polymorphism and solvate formation can exist for any particular API, but the conditions required to prepare polymorphs or solvates are not easily determined.[50,55] Even the knowledge that one type of polymorph or solvate of a crystalline form of a compound exists, or that a given set of crystallization conditions leads to the production of one type of polymorph or solvate, does not allow the prediction of other types of polymorphs or solvates that might exist, or what type of polymorph or solvates would be produced by other crystallization conditions.[50,56] Thus, the existence and control of polymorphism and solvates can be the biggest challenge to obtaining a drug product of constant quality (or indeed, a pesticide, herbicide, nutriceutical, cosmetic, food additive, explosive, etc.).

Amorphous solid forms of compounds have attracted some interest for overcoming problems associated with polymorphs. Amorphous forms are of higher energy than crystalline compounds,[57] which allows them to have higher dissolution rates and solubilities, as there is no lattice structure to overcome or the need to inhibit solvation. However, amorphous solids have a tendency to crystallize spontaneously to a lower energy crystalline form at possibly inopportune times.[58] Thus, the strategy has been to search for salts or polymorphs or solvates that have the desired "obtainable" properties.

Ionic Liquids as Active Pharmaceutical Ingredients (APIs)

Biologically active cations such as quaternary ammonium compounds and anions such as acesulfamate and saccharinate have previously been used to form ILs.[59–62] These were paired with traditional IL-forming counter ions to control physical properties, especially melting point, but with a focus on preparing ILs, not on preparing biologically active salts. In fact only recently, have specific ILs with biologically active ions been prepared and shown to retain their biological activity; specifically, IL salts of anti-bacterial quaternary ammonium cations were shown to be active against various types of bacteria and in some cases, an increased anti-bacterial effect was observed.[63–66]

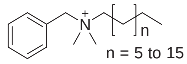
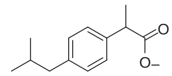
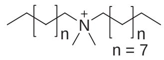
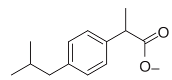
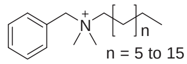
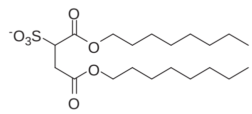
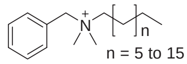
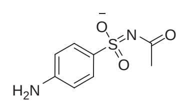
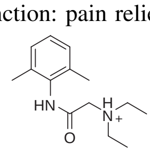
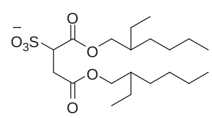
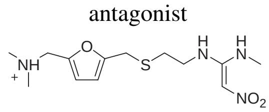
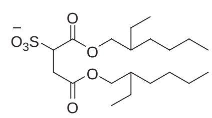
But ILs are composed of a minimum of two ions (a cation and an anion) and both may impart biological activity to the resulting salt. This dual functionality inherent in ILs is rarely exploited,[67,68] and we have only recently published our first paper with the designed incorporation of two biologically active ions into an IL.[69]

Given that polymorphism and solvate formation cannot be predicted; that the exact crystalline state affects chemical (e.g., dissolution rate, solubility), biological (e.g., bioavailability, pharmacokinetics), mechanical, and physical properties, as well as, manufacturing processes; and that polymorphs and solvates may inconveniently interconvert—what are needed are chemical compositions that a) are effective for their intended purpose; b) have controlled and tunable chemical, biological, and physical properties, c) are in a form that is not subject to polymorphism, and d) for which controlled tunable dissolution and solubility are possible. In other words, ionic liquids.

A Few Ionic Liquid-API Examples

In our first attempts to specifically prepare biologically active ILs,[69] we chose to utilize relatively straightforward metathesis routes utilized within the IL community[1,10] (and elsewhere), although more complicated routes can certainly be envisaged.[70–72] The general syntheses consisted of separately dissolving the salt of the cation and the anion in a solvent (e.g., water or methanol) and then combining these solutions and allowing them to stir with heating (to ca. 90 °C if necessary) or at room temperature. The products were then extracted from the aqueous phase with chloroform and the chloroform phase washed with water to remove any inorganic salt (typically NaCl which was monitored by a silver nitrate test). A rotary evaporator was used to remove the solvent and the resulting IL was placed on a high vacuum line to remove any residual solvent. The structure and purity of each IL was confirmed by ^{1}H and ^{13}C NMR and silver nitrate test, and were further characterized with thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Table 1 illustrates

Table 1. Examples of IL-APIs

API properties	Cation	Anion	IL
Anti-bacterial, anti-inflammatory	Benzalkonium chloride function: anti-bacterial 	Sodium ibuprofenate function: anti-inflammatory 	[Benzalkonium][Ibuprofenate][a)] Form: Yellow gel Melting point: −41 °C *T* (glass transition): −77 °C
Anti-bacterial, anti-inflammatory	Didecyldimethylammonium bromide function: anti-bacterial 	Sodium ibuprofenate function: anti-inflammatory 	[Didecyldimethylammonium]-[Ibuprofenate][b)] Form: Yellow liquid Melting point: Liquid at RT *T* (glass transition): −73 °C *T* (liquid–liquid transition): 69 °C
Anti-bacterial, wetting agent	Benzalkonium chloride function: anti-bacterial 	Colawet MA-80 function: wetting agent 	[Benzalkonium][Colawet MA-80][a)] Form: Clear liquid Melting point: Liquid at RT *T* (glass transition): −28 °C *T* (liquid–liquid transition): 77 °C
Anti-bacterial, anti-acne	Benzalkonium chloride function: anti-bacterial 	Sodium sulfacetamide function: anti-acne 	[Benzalkonium][Sulfacetamide][a)] Form: Yellow gel Melting point: Liquid at RT *T* (glass transition): 46 °C
Pain reliever, emollient	Lidocaine hydrochloride function: pain reliever 	Sodium docusate function: emollient 	[Lidocainium][Docusate][b)] Form: Colorless gel Melting point: Liquid at RT *T* (glass transition): −29 °C *T* (liquid–liquid transition): 78 °C
Histamine H_2-receptor antagonist, emollient	Ranitidine hydrochloride function: histamine H_2-receptor antagonist 	Sodium docusate function: emollient 	[Ranitidinium][Docusate][b)] Form: Dark red liquid Melting point: Liquid at RT *T* (glass transition): −12 °C *T* (liquid–liquid transition): 29 °C

a) The synthesis and characterization can be found in the Supporting Information. b) The synthesis and characterization can be found in Ref. 69.

examples of this approach exhibiting melting points below or near room temperature.

But it is not the synthesis of these compounds which is the key to the IL-API approach; it is making the proper choices of ions. Our first goal was to choose a specific function for each ion and then combine them to form an IL. This approach requires not only knowledge of specific biological function possessed by each ion, but also what ion combinations will produce ILs. The knowledge base for the latter is still incomplete and predicting ion combinations that will lead to ILs is, unfortunately, a hit-or-miss proposition. Nonetheless, it did not escape our notice that: 1) many IL-forming cations bear similarity with many APIs or API-precursors, and 2) that many biologically active ions are large, charge diffuse, and asymmetric—all characteristics which should lead to low melting salts. Thus, our choices to test our approach were based on our experience with ion types likely to lead to IL formation. Let us briefly review how those choices led to IL-APIs.

Figure 2 represents several different biologically active cations and anions, which on the surface would appear to be likely candidates for IL formation. Indeed ILs of large quaternary ammonium cations such as benzalkonium ($[BA]^+$) and didecyldimethylammonium ($[DDA]^+$) are known to form ILs and to retain their anti-microbial properties.[63] The cations of lidocaine and ranitidine also appear to have characteristics favorable for IL formation. The anions of docusate, ibuprofen, colawet MA-80, and sulfacetamide, are all FDA-approved compounds for use in pharmaceutical or agricultural applications. Docusate has been observed to form ILs in combinations with appropriate cations.[73,74]

From the limited set of ions likely to form ILs in Fig. 2, one can choose the appropriate candidates based upon the desired outcome. For example, ranitidine hydrochloride, an anti-ulcer drug commonly known as Zantac™, has been the subject of extensive litigation over polymorphic forms and purity.[75] By combining ranitidine hydrochloride with docusate, it is possible to prepare an IL which will not crystallize and thus will not suffer from polymorphism (Table 1).[69]

An anion could just as easily be chosen as the primary active agent. Ibuprofen is a common nonsteroidal anti-inflammatory drug used to treat arthritis symptoms, fever, and can also have use as an analgesic.[76] The sodium salt is readily available and is primarily used to increase the water solubility of ibuprofen, which is less than $1\,mg\,mL^{-1}$ in neutral form.[77] One can envision using an anti-bacterial ion to combat inflammation caused by bacterial infections, combined with the ibuprofenate anion to prepare a dual action IL, as shown in Table 1 for the ILs [BA][Ibuprofenate][78] and [DDA][Ibuprofenate].[69]

An agricultural wetting agent, colawet MA-80, is structurally similar to docusate, which has been previously shown to lower melting points and increase viscosity and hydrophobicity in ILs.[74] Wetting agents are most commonly used in agriculture and increase the spreading and penetrating properties of a liquid by lowering its surface tension. It is known that bacteria and fungi can cause severe damage to crops and, if left untreated, can render a crop unusable. Therefore, the combination, in theory, of an anti-bacterial and a wetting agent would allow for better penetration of the anti-bacterial to the roots of the plant, which might be a better treatment option than absorption via the leaves. The IL, [BA][Colawet MA-80],[78] was obtained as a clear liquid (Table 1).

Sulfacetamide is a sulfonamide antibiotic that is used in both skin[79] and ophthalmic[80] applications and is prescribed exclusively as the sodium salt. By pairing this anion with a quaternary ammonium cation it should be possible to increase the antibiotic activity, which in turn, could increase the spectrum of bacteria for which it could be used. This combination of antibiotic and anti-bacterial could also potentially reduce bacterial resistance, which is commonly seen in anti-acne treatments. Utilizing the IL-API approach, [BA][Sulfacetamide] was prepared and obtained as a yellow gel (Table 1).[78]

Of course, much research remains to be done. While the IL community can bring considerable skills in pairing ions likely to form ILs, the effect of ion pairing on the biological efficacy remains to be seen. It is not clear, for example, whether two ions paired to form a hydrophobic IL will dissolve into "free" solvated ions, ion pairs, or even clusters that might have measurable lifetimes in solution. Such questions are vital to the ultimate use of ILs as APIs, since synergistic effects could enhance or decrease the effectiveness of a particular pharmaceutical.

In recently published preliminary studies,[69] we have seen evidence for synergistic effects in [Lidocainium][Docusate], an IL prepared from combining an analgesic (lidocaine hydrochloride) and an emollient (sodium docusate). Mouse antinociception assays were utilized to determine the onset and duration of the analgesic effect and the data indicated that [Lidocainium][Docusate] possesses not only a higher onset analgesic ability, but also a longer duration when compared to lidocaine hydrochloride. This may be in part due to not only the hydrophobicity of [Lidocainium][Docusate], but also potential differences in the mechanism of the analgesic activity.[81]

The Future of ILs as APIs?

Although only a few examples of IL-APIs are presented here, the possible combinations are only limited to one's imagination. A modular IL strategy could potentially revolutionize the pharmaceutical and medical industries in ways never thought to be possible and provide a platform for improved activity, new treatment options, or even personalized medication; or it could lead to such complexity that these materials would never be accepted as pharmaceuticals. The possibility to overcome problems such as polymorphism, solubility, and bioavailability, that have stopped the use of many proposed pharmaceuticals, might give abandoned APIs a second life; or speed the adoption of new candidate drugs. While we can certainly not predict the future of ILs as potential APIs, we do suggest that the pharmaceutical industry should join the growing number of other industries that are considering the use of ILs as materials for many different process options, and not just as solvents.

The Future of ILs?

Ionic liquids are continually evolving and these unique tunable materials appear to have potentially limitless applications in a growing variety of disciplines. The knowledge based generated by worldwide efforts in IL research and the willingness of the research community to try new things will continue to provide new and exciting applications. We look forward with anticipation to a bright future for these fascinating salts.

Our research into the nature and application of ionic liquids has been supported by the US Air Force Office of Scientific Research, BASF North America, the US Department of Energy, and the US Environmental Protection Agency. The work with IL-APIs has been a team effort with collaborators (Prof. Juliusz Pernak (Poznań University of Technology), Prof. James E. Davis, Jr., Prof. Richard D. Carliss, Morgan D. Soutullo (University of South Alabama), Prof. Judith E. Grisel (Furman University), Dr. Daniel T. Daly (The University of Alabama)) and students and staff of The University of Alabama (Marcin Smiglak, Dr. Héctor Rodríguez, Dr. Richard P. Swatloski, and Dr. Scott K. Spear).

Supporting Information

All synthesis and characterization data for [Benzalkonium]-[Ibuprofenate], [Benzalkonium][Sulfacetamide], and [Benzalkonium][Colawet MA-80] is reported here. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

References

1 *Ionic Liquids; Industrial Applications to Green Chemistry, ACS Symposium Series 818*, ed. by R. D. Rogers, K. R. Seddon, American Chemical Society, Washington D.C., **2002**.

2 *Ionic Liquids as Green Solvents: Progress and Prospects, ACS Symposium Series 856*, ed. by R. D. Rogers, K. R. Seddon, American Chemical Society, Washington D.C., **2003**.

3 *Green Industrial Applications of Ionic Liquids, NATO Science Series II. Mathematics, Physics, and Chemistry*, ed. by R. D. Rogers, K. R. Seddon, S. Volkov, Kluwer, Dordrecht, **2003**, Vol. 92.

4 *Ionic Liquids IIIA: Fundamentals, Progress, Challenges, and Opportunities—Properties and Structure, ACS Symposium Series 901*, ed. by R. D. Rogers, K. R. Seddon, American Chemical Society, Washington D.C., **2005**.

5 *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities—Transformations and Processes, ACS Symposium Series 902*, ed. by R. D. Rogers, K. R. Seddon, American Chemical Society, Washington D.C., **2005**.

6 *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications, ACS Symposium Series 913*, ed. by C. S. Brazel, R. D. Rogers, American Chemical Society, Washington D.C., **2005**.

7 *Ionic Liquids Not Just Solvents Anymore, ACS Symposium Series 975*, ed. by J. F. Brennecke, R. D. Rogers, K. R. Seddon, American Chemical Society, Washington D.C., **2007**.

8 P. Walden, *Bull. Acad. Sci. Imp. St. Petersbourg* **1914**, 405.

9 C. G. Swain, A. Ohno, D. K. Roe, R. Brown, T. Maugh, II, *J. Am. Chem. Soc.* **1967**, *89*, 2648.

10 *Ionic Liquids in Synthesis*, ed. by P. Wasserscheid, T. Welton, Wiley-VCH, Weinheim, **2003**, p. 380.

11 M. Freemantle, *Chem. Eng. News* **1998**, *76*, 32.

12 P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**.

13 http://bama.ua.edu/˜rdrogers/NATO, last accessed on March 31, **2007**.

14 M. Freemantle, *Chem. Eng. News* **2000**, *78*, 37.

15 E. F. Borra, O. Seddiki, R. Angel, D. Eisenstein, P. Hickson, K. R. Seddon, S. P. Worden, *Nature* **2007**, *447*, 979.

16 These ions represent only a sampling from the dramatically increasing number of ions which have been confirmed to form ionic liquids.

17 J. S. Wilkes, J. A. Levisky, R. A. Wilson, C. L. Hussey, *Inorg. Chem.* **1982**, *21*, 1263.

18 P. G. Jessop, D. J. Heldebrant, *Environ. Catal.* **2005**, 627.

19 N. Winterton, *J. Mater. Chem.* **2006**, *16*, 4281.

20 L. Weng, X. Liu, Y. Liang, Q. Xue, *Tribol. Lett.* **2007**, *26*, 11.

21 A.-E. Jiménez, M.-D. Bermúdez, *Tribol. Lett.* **2007**, *26*, 53.

22 J. Qu, J. J. Truhan, S. Dai, H. Luo, P. J. Blau, *Tribol. Lett.* **2006**, *22*, 207.

23 D. M. Blake, L. Moens, D. Rudnicki, H. Pilath, *J. Sol. Energy Eng.* **2006**, *128*, 54.

24 Y. Yoshida, G. Saito, *J. Mater. Chem.* **2006**, *16*, 1254.

25 M. Okuno, H. O. Hamaguchi, S. Hayashi, *Appl. Phys. Lett.* **2006**, *89*, 132506.

26 S. Hayashi, S. Saha, H. Hamaguchi, *IEEE Trans. Magn.* **2006**, *42*, 12.

27 K. Lunstroot, K. Driesen, P. Nockemann, C. Göerller-Walrand, K. Binnemans, S. Bellayer, J. Le Bideau, A. Vioux, *Chem. Mater.* **2006**, *18*, 5711.

28 C. B. Jones, R. Haiges, T. Schroer, K. O. Christe, *Angew. Chem., Int. Ed.* **2006**, *45*, 4981.

29 M. Smiglak, A. Metlen, R. D. Rogers, *Acc. Chem. Res.* **2007**. doi:10.1021/ar7001304.

30 R. D. Rogers, K. R. Seddon, *Science* **2003**, *302*, 792.

31 J. D. Holbrey, *Chim. Oggi* **2004**, *22*, 35.

32 M. Maase, in *Multiphase Homogeneous Catalysis*, ed. by B. Cornils, Wiley-VCH, Weinheim, Germany, **2005**, pp. 560–566.

33 http://www.ionicliquids-merck.de, last accessed August 5, **2007**.

34 http://www.solvent-innovation.de/pr_20061211.php, last accessed July 31, **2007**.

35 http://www.iolitec.de/ionic_e.htm, last accessed July 31, **2007**.

36 http://www.solvionic.com, last accessed July 31, **2007**.

37 http://www.bioniqs.com, last accessed July 31, **2007**.

38 M. Smiglak, W. M. Reichert, J. D. Holbrey, J. S. Wilkes, L. Sun, J. S. Thrasher, K. Kirichenko, S. Singh, A. R. Katritzky, R. D. Rogers, *Chem. Commun.* **2006**, 2554.

39 J. D. Holbrey, K. R. Seddon, *Clean Prod. Processes* **1999**, *1*, 223.

40 M. Peplow, news@nature.com, Published online 3 Nov. **2005**. doi:10.1038/news051031-8.

41 D. Zhao, Y. Liao, Z. Zhang, *Clean Soil, Air, Water* **2007**, *35*, 42.

42 “All things are poison and nothing is without poison, only the dose permits something not to be poisonous.” from http://en.wikipedia.org/wiki/Paracelsus, last accessed July 29, **2007**.

43 http://www.circasurvive.com, last accessed July 31, **2007**.

44 R. Freer, A. Curzons, in *Green Industrial Applications of Ionic Liquids, NATO Science Series II. Mathematics, Physics, and Chemistry*, ed. by R. D. Rogers, K. R. Seddon, S. Volkov, Kluwer, Dordrecht, **2003**, Vol. 92, pp. 129–136.

45 D. J. C. Constable, C. Jimenez-Gonzalez, R. K. Henderson, *Org. Process Res. Dev.* **2007**, *11*, 133.

46 *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, ed. by P. H. Stahl, C. G. Wermuth, Wiley-VCH, Weinheim, Germany, **2002**.

47 *Pharmaceutical Production—An Engineering Guide, Institution of Chemical Engineers*, ed. by B. Bennett, G. Cole, Inst. of Chemical Engineers, UK, **2003**.

48 S. R. Byrn, R. R. Pfeiffer, G. Stephenson, W. J. D. Grant, W. B. Gleason, *Solid-State Chemistry of Drugs*, SSCI, West Lafayette, IN, **1999**.

49 D. Schuster, C. Laggner, T. Langer, *Curr. Pharm. Des.* **2005**, *11*, 3545.

50 J. Bernstein, *Polymorphism in Molecular Crystals, IUCR Monographs on Crystallography 14*, Oxford Science Publications, Oxford, UK, **2002**.

51 J. K. Haleblian, *J. Pharm. Sci.* **1975**, *64*, 1269.

52 K. R. Morris, in *Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences*, ed. by H. G. Brittain, Marcel Dekker, Inc., New York, NY, **1999**, Vol. 95, pp. 125–181.

53 S. Datta, D. J. Grant, *Nat. Rev. Drug Discovery* **2004**, *3*, 42.

54 *Polymorphism in the Pharmaceutical Industry*, ed. by R. Hilfiker, Wiley-VCH, New York, NY, **2006**.

55 J. Bernstein, *ACA Trans.* **2004**, *39*, 14.

56 J. K. Guillory, in *Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences*, ed. by H. G. Brittain, Marcel Dekker, Inc., New York, NY, **1999**, Vol. 95, pp. 183–226.

57 B. Shah, V. K. Kakumanu, A. K. Bansal, *J. Pharm. Sci.* **2006**, *95*, 1641.

58 B. C. Hancock, C. R. Dalton, *Pharm. Dev. Technol.* **1999**, *4*, 125.

59 E. B. Carter, S. L. Culver, P. A. Fox, R. D. Goode, I. Ntai, M. D. Tickell, R. K. Traylor, N. W. Hoffman, J. H. Davis, Jr., *Chem. Commun.* **2004**, 630.

60 P. Nockemann, B. Thijs, K. Driesen, C. R. Janssen, K. Van Hecke, L. Van Meervelt, S. Kossmann, B. Kirchner, K. Binnemans, *J. Phys. Chem. B* **2007**, *111*, 5254.

61 J. Pernak, F. Stefaniak, J. Weglewski, *Eur. J. Org. Chem.* **2005**, 650.

62 W. L. Hough, T. Wilson, M. Smiglak, J. Pernak, S. K. Spear, J. H. Davis, Jr., R. D. Rogers, Abstract of Papers, 231st ACS National Meeting, Atlanta, GA, **2006**, Abstr., No. I&EC 106.

63 J. Pernak, A. Skrzypezak, G. Lota, E. Frackowiak, *Chem. Eur. J.* **2007**, *13*, 3106.

64 J. Pernak, J. Feder-Kubis, *Chem. Eur. J.* **2005**, *11*, 4441.

65 J. Pernak, M. Smiglak, S. T. Griffin, W. L. Hough, T. B. Wilson, A. Pernak, J. Zabielska-Matejuk, A. Fojutowski, K. Kita, R. D. Rogers, *Green Chem.* **2006**, *8*, 798.

66 A. Cieniecka-Rosłonkiewicz, J. Pernak, J. Kubis-Feder, A. Ramani, A. J. Robertson, K. R. Seddon, *Green Chem.* **2005**, *7*, 855.

67 L. P. N. Rebelo, J. N. C. Lopes, J. M. S. S. Esperanca, H. J. R. Guedes, J. Lachwa, V. Najdanovic-Visak, Z. P. Visak, *Acc. Chem. Res.* **2007**. doi: 10.1021/ar7000556.

68 Z. Fei, T. J. Geldbach, D. Zhao, P. J. Dyson, *Chem. Eur. J.* **2006**, *12*, 2122.

69 W. L. Hough, M. Smiglak, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., R. D. Rogers, *New J. Chem.* **2007**, *31*, 1429.

70 J. D. Holbrey, W. M. Reichert, I. Tkatchenko, E. Bouajila, O. Walter, I. Tommasi, R. D. Rogers, *Chem. Commun.* **2003**, 28.

71 M. Smiglak, J. D. Holbrey, S. T. Griffin, W. M. Reichert, R. P. Swatloski, A. R. Katritzky, H. Yang, D. Zhang, K. Kirichenko, R. D. Rogers, *Green Chem.* **2007**, *9*, 90.

72 N. J. Bridges, C. C. Hines, M. Smiglak, R. D. Rogers, *Chem. Eur. J.* **2007**, *13*, 5207.

73 J. H. Davis, Jr., P. A. Fox, *Chem. Commun.* **2003**, 1209.

74 N. Nishi, T. Kawakami, F. Shigematsu, M. Yamamoto, T. Kakiuchi, *Green Chem.* **2006**, *8*, 349.

75 A. Goho, *Sci. News* **2004**, *166*, 122, from http://www.sciencenews.org/articles/20040821/bob9.asp, last accessed July 31, **2007**.

76 *The Merck Index*, 13th ed., ed. by M. J. O'Neil, A. Smith, P. E. Heckelman, S. Budavari, Merck & Co., Inc., Whitehouse Station, NJ, **2001**.

77 M. Geppi, S. Guccione, G. Mollica, R. Pignatello, C. A. Veracini, *Pharm. Res.* **2005**, *22*, 1544.

78 The syntheses and characterization of all new compounds reported here are provided in the Supporting Information.

79 D. J. Magolis, *Cutis* **2005**, *75*, 8.

80 M. S. Sridhar, U. Gopinathan, P. Garg, S. Sharma, G. N. Rao, *Surv. Ophthalmol.* **2001**, *45*, 361.

81 We are very much indebted to our collaborators for the biological studies, Prof. R. D. Carliss (University of South Alabama) and Prof. J. E. Grisel (Furman University).

Robin D. Rogers was born in Ft. Lauderdale, FL (USA) in 1957 and moved to Alabama in 1960. He obtained both his B.S. in Chemistry (1978, Summa Cum Laude) and his Ph.D. in Chemistry (1982) at The University of Alabama, where he is currently Distinguished Research Professor, Robert Ramsay Chair of Chemistry, and Director of the Center for Green Manufacturing. Recently, he accepted the position Chair of Green Chemistry and Co-Director of QUILL at The Queen's University of Belfast in Northern Ireland (UK). Dr. Rogers is Editor-in-Chief of the ACS journal *Crystal Growth and Design* and on the Editorial Advisory Boards of *Separation Science & Technology, Solvent Extraction and Ion Exchange, Green Chemistry*, and *Chemical Communications*. He has had an influential role in the expansion of interest and research in ionic liquids, his initial paper on ionic liquid/aqueous partitioning (*Chem. Commun.* **1998**, 1765) effectively sparked interest in ionic liquids for clean separations. In 2005, he won the Presidential Green Chemistry Challenge Award (Academic) for dissolution of cellulose by ionic liquids, a technology that was licensed to BASF that same year. Dr. Rogers continues to work at the interface of fundamental knowledge and innovative technology.

Whitney L. Hough was born in Hartford, CT (USA) in 1984 and moved to Alabama in 1989. She graduated from The University of Alabama in 2006 with her B.S. in Chemistry (Cum Laude, ACS Certified). During her undergraduate career, she was a member of Zeta Tau Alpha sorority, and worked as an undergraduate researcher with Prof. Rogers. In 2006, she received the Outstanding Undergraduate Research Award for her research on sweetener ionic liquids, and she is currently pursuing her doctorate degree in Chemistry at Alabama with an emphasis on medical applications of ionic liquids. Recently, she attended the Pan-American Advanced Studies Institute for Sustainability and Green Chemistry summer school in Mexico City, Mexico, where she gave a presentation regarding ionic liquids as replacement solvents. Her work on ionic liquid pharmaceuticals has already led to one patent application.