Confused ionic liquid ions—a "liquification" and dosage strategy for pharmaceutically active salts†

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We present a strategy to expand the liquid and compositional ranges of ionic liquids, specifically pharmaceutically active ionic liquids, by simple mixing with a solid acid or base to form oligomeric ions.

The pharmaceutical industry relies predominantly on the solid crystalline or amorphous state for the manufacture and delivery of active pharmaceutical ingredients (APIs), despite the increasing instances of problems associated with the solid form of many drugs including polymorphic conversion, low solubility, and low bioavailability, and the tendency of amorphous forms to spontaneously crystallize.[1,2]

We have recently questioned the reliance of the pharma industry on solid APIs and suggested that in some instances a liquid salt form (*i.e.*, an ionic liquid, IL, loosely defined as salts with melting points below 100 °C) might prove beneficial.[3,4] An IL form of an API not only eliminates problems associated with polymorphism by virtue of being a liquid, but can also dramatically influence a drug's solubility. Dual-functional ILs composed of two active ions may even lead to synergistic effects and we note recent commercialization efforts along these lines.[5] In our own ongoing search for new ILs and new IL APIs, we have found that by carefully generating oligomeric ions with 'confused' protons (compared with simple eutectics such as mixtures of quaternary ammonium halides and hydrogen bond donors),[6] we can dramatically increase the liquid range of a classic salt.

Hydrogen-bonded homoconjugated oxoanions (A^- hydrogen-bonded to their corresponding acid to form HA_2^-) are frequently found in transition metal complexes and can be classified as weakly coordinating anions.[7] The O–H–O bond in carboxylic acid–carboxylate systems is considered to be a low-barrier hydrogen bond with considerable covalent character, an overall bond length of 2.5 Å or below, and to have an unusually strong interaction energy (≥10 kcal mol^{-1}).[8]

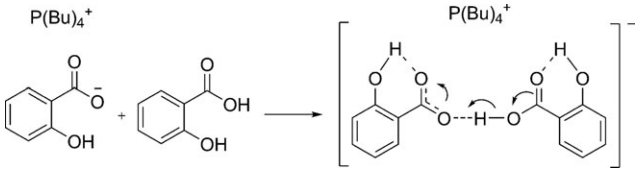
Given the importance of weakly coordinating anions for ILs, surprisingly few explicit studies of oligomeric ILs can be found in the literature, although evidence for their presence is found in the context of protic ILs.[9] Only recently McFarlane *et al.* presented dimeric and oligomeric anions in the protic *N*-methylpyrrolidine–acetic acid system, with the highest degree of ionicity being present for the oligomeric species $[(AcO)_3H_2]^-$.[10] However, oligomeric anions can also be seen in Lewis acidic ILs that are composed of monomeric, dimeric, and mixed-valent anions such as $AlCl_4^-$, $Al_2Cl_7^-$, and $AlCl_3Cl_9^-$ or for halides, *e.g.*, iodides complexed to I_2, with oligomeric species based on $[I_3]^-$, $[I_5]^-$, $[I_7]^-$, and $[I_9]^-$.[11,12]

Here, we present results which suggest the formation of oligomeric hydrogen bonded cations or anions in pharmaceutically active ILs. Such a strategy can have profound effects for improving the properties of salts of APIs, for example, in modification of stoichiometry for dosage options, in liquefaction for drug delivery, *etc*. However, we also recognize that such a strategy might be generally used by the IL community to provide relatively easy modification of melting points and other physical properties as part of an overall 'tuning' strategy for a particular solvent/material need.

We chose to first test our hypothesis by attempting the formation of an oligomeric anion based on salicylate (Sal^-) with the permanent cation tetrabutylphosphonium ($P(Bu)_4^+$); thus allowing us to ignore hydrogen bonding between cation and anion (Scheme 1). Salicylic acid, a key ingredient of skin-care products, has antiseptic, preservative, analgesic, and anti-inflammatory properties, covering a broad spectrum of applications,[13] and $P(Bu)_4^+$ has known antimicrobial effects.[14]

Tetrabutylphosphonium salicylate [**1**] was easily prepared by reaction of salicylic acid with a solution of tetrabutylphosphonium hydroxide in H_2O and obtained as a colorless, rather hygroscopic solid with a moderate melting point of 57 °C.[15] However, when tetrabutylphosphonium hydroxide was reacted with two equivalents of salicylic acid, a clear liquid with only a glass transition at −46 °C was obtained. These results prompted us to look for new synthetic methods that would allow us to eliminate any influence of trace solvent and to explore the dependence of thermal properties on composition.

Solid **1** and solid salicylic acid (mp = 158.1 °C) were ground or melted under an atmosphere of dry nitrogen to form several new liquid compositions. Each liquid form was studied by differential scanning calorimetry (DSC; Table S1 in ESI†).



Scheme 1 Proposed formation of oligomeric ions based on salicylate/salicylic acid.

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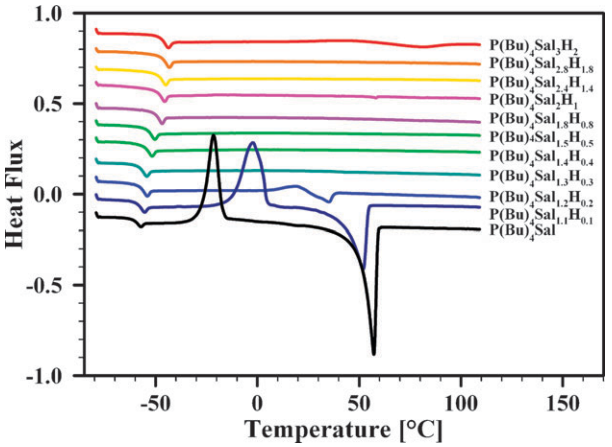


Fig. 1 DSC traces of $P(Bu)_4Sal$–SalH salts.

The addition of excess salicylic acid resulted in dramatic reductions in the melting point; an excess of only 0.1 equiv. salicylic acid reduced the observed melting point from 57 °C ($P(Bu)_4Sal$, mole fraction salicylic acid $\chi_{SalH} = 0$) to 48 °C ($P(Bu)_4Sal_{1.1}H_{0.1}$, $\chi_{SalH} = 0.09$). The addition of 0.4 equiv. salicylic acid ($P(Bu)_4Sal_{1.4}H_{0.4}$ ($\chi_{SalH} = 0.29$)) resulted in the complete elimination of the melting point to yield a free flowing liquid (Fig. 1), despite the fact that both **1** and the free acid are solid at room temperature.

A point of saturation was observed with 2 equiv. of salicylic acid at a composition of $P(Bu)_4Sal_3H_2$ ($\chi_{SalH} = 0.67$) and slow precipitation of crystalline salicylic acid was observed after some time. Between the first liquid composition and saturation, a glass transition temperature at ~ -50 °C that is slightly shifted to higher temperature with increasing salicylic acid, is the only observed transition.

Thermogravimetric analysis (TGA) of PBu_4Sal [**1**] showed a single decomposition with high thermal stability ($T_{onset5\%}$ = 308 °C), however, a two-step decomposition is obtained for the corresponding salts with oligomeric anions. The thermal stability decreases with increasing excess salicylic acid, gradually approaching the decomposition temperature of pure salicylic acid (Fig. S2, Table S1 in ESI†).

The striking behavior observed above can be explained by a fast proton exchange between anion and corresponding acid and the formation of hydrogen-bonded oligomeric anions as previously described for salicylic acid–salicylate systems.[16] The permanent delocalization of a "confused" proton in the homoconjugated HA_2^- anion apparently prevents the salt from crystallizing. In addition, the homoconjugated HA_2^- anion should be more weakly coordinating (*i.e.*, a weaker base) than A^-, thereby affecting the various physicochemical properties of the IL. However, whereas McFarlane *et al.* reported a characteristic maxima in conductivity and viscosity for the oligomeric anions $[(AcO)_3H_2]^-$ in the protic *N*-methylpyrrolidine–acetic acid system,[10] we observed a constant decrease of conductivity and increase of viscosity (Table S1 in ESI†) with addition of salicylic acid, thus indicating that liquefaction of the solid IL $P(Bu)_4Sal$ [**1**] is achieved at the cost of ionicity.

The presence of the oligomeric anion could be demonstrated by NMR spectroscopy. Low-barrier hydrogen bonds in

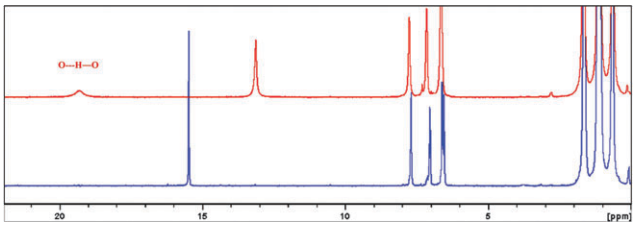


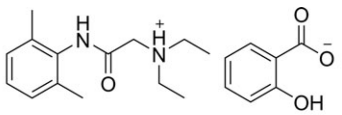
Fig. 2 ^{1}H-NMR spectra of $P(Bu)_4Sal$ [**1**] (bottom) and $P(Bu)_4Sal_2H_1$ (top).

proton-bound isomeric tautomers are typically characterized by an unusual downfield shift of the delocalized proton of >15 ppm in aprotic, low-polarity solvents.[8c,17,18] When we performed low temperature NMR spectroscopy of $P(Bu)_4Sal$ [**1**] and $P(Bu)_4Sal_2H_1$ in a mixture of $CDClF_2/CDF_3$[19] at 173 K, we observed a broad peak at 19.2 ppm for $P(Bu)_4Sal_2H_1$ as is typical for short, strong hydrogen bonds of the type O–H–O, thus indicating the presence of a hydrogen-bonded oligomeric anion with strong interaction energy (Fig. 2).

The formation of oligomeric ions as discussed above, need not be carried out using the parent acid (corresponding to homoconjugated oxoanions $[HA_2]^-$), but can also be observed for heteroconjugated oxoanions of the type $[HAA']^-$. We have demonstrated this with the non-steroidal anti-inflammatory drug (NSAID) ibuprofen and the UV-protector cinnamic acid as examples of solid biologically active acids with a reasonable pK_a difference ($\Delta pK_a < 2$) to allow a permanent hydrogen exchange in the mixed dimeric anion $[HAA']^-$. When these solid acids were reacted with one equiv. of $P(Bu)_4Sal$ [**1**], we obtained liquid products with only a glass transition: −45.01 °C ibuprofen; −43.81 °C cinnamic acid.

Since the majority of all APIs can be considered as protic acids or bases,[1] we were curious whether the addition of excess acid to a salt comprised of the conjugate base of a protic acid or addition of excess base to a salt comprised of the conjugate acid of a protic base (Scheme 2) would (a) result in oligomeric ions and (b) if the presence of such oligomers would significantly alter the physical properties of the salt. We investigated this possibility with the addition of excess acid *or base* to lidocainium salicylate [**2**] (Scheme 2). Here, we hoped to not only expand the scope of the oligomeric anions to the corresponding oligomeric cations, but to also provide a method which would allow the individual dosing of two or more active compounds in one liquid salt form, that is, obviating the need for stoichiometric component ions.

Lidocainium salicylate [**2**] was prepared by anion metathesis from lidocainium hydrochloride monohydrate and sodium salicylate and was obtained as a very viscous liquid with only



[HLid]$^+$Sal$^-$ [2]

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

Scheme 2 Proposed oligomeric ion approach.

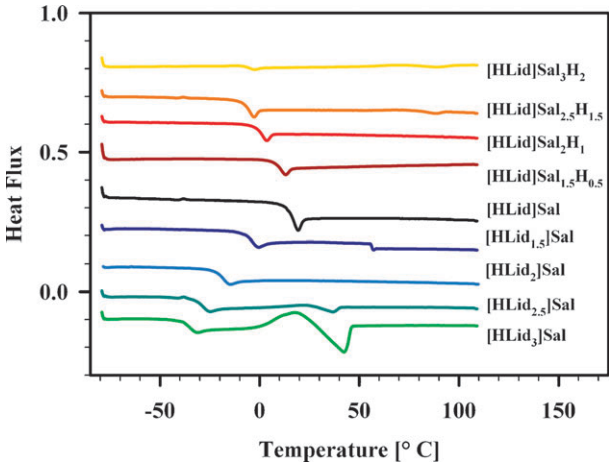


Fig. 3 DSC traces of lidocainium salicylate [**2**] and oligomers.

a glass transition at 19.8 °C observable in the DSC.[12] When excess salicylic acid *or* excess lidocaine (free base) was ground with **2** in a manner analogous to that above, a less dramatic but similar reduction of the glass transition temperatures in both directions, until saturation and solid samples are obtained, was observed (Fig. 3).

In conclusion, oligomeric ion formation has a tremendous influence on physical properties that allows expansion of the liquid ranges of some solid salts. We are aware that the term "ionic liquids" for this type of liquid salt formulation might be controversial and has to be verified by further investigation concerning ionicity and simple eutectic behavior (these studies are currently ongoing in our lab). However, it is important to note that the concept of oligomeric ions enables liquefaction of solid ILs (or other salts) by simply changing the stoichiometry or complexity of the ions and the strategy need not employ the parent of the anion or cation in use. This can be particularly useful for pharmaceutically active salts or ILs, since, although some efforts towards the prediction of the state of ILs have been made,[4] the design of IL pharmaceuticals will benefit from this strategy to modify the physical properties of a given salt form once obtained.

Notes and references

1 *Handbook of Pharmaceutical Salts*, ed. P. H. Stahl and C. G. Wermuth, Wiley-VCH, Weinheim, 2002; S. M. Berge, L. D. Bighley and D. C. Monkhouse, *J. Pharm. Sci.*, 1977, **66**, 1.

2 H. G. Brittain, *J. Pharm. Sci.*, 2002, **91**, 1573.

3 (*a*) W. L. Hough and R. D. Rogers, *Bull. Chem. Soc. Jpn.*, 2007, **80**, 2262; (*b*) W. L. Hough, M. Smiglak, H. Rodriguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis Jr. and R. D. Rogers, *New J. Chem.*, 2007, **31**, 1429; (*c*) R. D. Rogers, D. T. Daly, R. P. Swatloski, W. L. Hough, J. H. Davis, M. Smiglak, J. Pernak and S. K. Spear, *PCT Int. Appl.*, 2007044693, 2007.

4 P. M. Dean, J. Turanjanin, M. Yoshizawa-Fujita, D. R. MacFarlane and J. L. Scott, *Cryst. Growth Des.*, 2009, **9**, 1137.

5 (*a*) *Chem. Eng. News*, October 5 2009, **87**(40), p. 26; (*b*) Etodolac Patch (MRX-7EAT) in Phase I clinical trials in the US. http://www.medrx.co.jp/english/newsrelease.html (last accessed 15/12/09).

6 (*a*) A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142; (*b*) A. P. Abbott, J. C. Barron, K. S. Ryder and D. Wilson, *Chem.–Eur. J.*, 2007, **13**, 6495; (*c*) A. P. Abbott, G. Capper, D. L. Davies, K. J. McKenzie and S. U. Obi, *J. Chem. Eng. Data*, 2006, **51**, 1280; (*d*) A. P. Abbott, G. Capper and S. Gray, *ChemPhysChem*, 2006, **7**, 803; A. P. Abbott, G. Capper, D. L. Davies, R. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70.

7 O. G. Polyakov, B. G. Nolan, B. P. Fauber, S. M. Miller, O. P. Anderson and S. H. Strauss, *Inorg. Chem.*, 2000, **39**, 1735.

8 (*a*) P. Gilli, V. Bertolasi, V. Ferretti and G. Gilli, *J. Am. Chem. Soc.*, 1994, **116**, 909; (*b*) G. A. Kumar, Y. Pan, C. J. Smallwood and M. A. McAllister, *J. Comput. Chem.*, 1998, **19**, 1345; (*c*) A. Brück, L. J. McCoy and K. V. Kilway, *Org. Lett.*, 2000, **2**, 2007; (*d*) K. M. Harmon, K. E. Shaw and S. M. Sadeki, *J. Mol. Struct.*, 2000, **526**, 191; (*e*) P. Barczynski, I. Kowalczyk, M. Grundwald-Wyspianska and M. Szafran, *J. Mol. Struct.*, 1999, **484**, 117; (*f*) C. L. Perrin and J. B. Nielson, *J. Am. Chem. Soc.*, 1997, **119**, 12734; (*g*) C. L. Perrin and J. B. Nielson, *Annu. Rev. Phys. Chem.*, 1997, **48**, 511.

9 For examples: (*a*) $H(TFA)_2^-$: M. Yoshizawa, W. Xu and C. A. Angell, *J. Am. Chem. Soc.*, 2003, **125**, 15411; (*b*) $H(TFSI)_2^-$: A. Noda, M. A. B. H. Susan, K. Kudo, S. Mitsushima, K. Hayamizu and M. Watanabe, *J. Phys. Chem. B*, 2003, **107**, 4024; M. A. B. H. Susan, A. Noda, S. Mitsushima and M. Watanabe, *Chem. Commun.*, 2003, 938; H. Nakamoto, A. Noda, K. Hayamizu, S. Hayashi, H. Hamaguchi and M. Watanabe, *J. Phys. Chem. C*, 2007, **111**, 1541; (*c*) HF_2^-: R. Hagiwara, K. Matsumoto, Y. Nakamori, T. Tsuda, Y. Ito, H. Matsumoto and K. Momota, *J. Electrochem. Soc.*, 2003, **150**, D195; R. Hagiwara and Y. Ito, *J. Fluorine Chem.*, 2000, **105**, 221; R. Hagiwara, Y. Nakamori, K. Matsumoto and Y. Ito, *J. Phys. Chem. B*, 2005, **109**, 5445; K. Matsumoto and R. Hagiwara, *J. Fluorine Chem.*, 2007, **128**, 317; Y. Saito, K. Hirai, K. Matsumoto, R. Hagiwara and Y. Minamizaki, *J. Phys. Chem. B*, 2005, **109**, 2942; C. Rijksen and R. D. Rogers, *J. Org. Chem.*, 2008, **73**, 5582; (*d*) HCl_2^-: J. W. Shuppert and C. A. Angell, *J. Chem. Phys.*, 1977, **67**, 3050; (*e*) HNO_3^{2-}: A. C. Angell, W. Xu, J.-P. Belieres and M. Yoshizawa, *PCT Int. Appl.* 2004/114445 A1, 2004; (*f*) $H(HCO)_2^-$, $H(CH_3CH_2COO)_2^-$ and $H((CH_3)_3CCOO)_2^-$: F. Kohler, H. Atrops, H. Kalali, E. Liebermann, E. Wilhelm, F. Ratkovics and T. Salamon, *J. Phys. Chem.*, 1981, **85**, 2520.

10 K. M. Johansson, E. I. Izgorodina, M. Forsyth, D. R. MacFarlane and K. R. Seddon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 2972.

11 (*a*) S. P. Wicelinski and R. J. Gale, *Anal. Chem.*, 1988, **60**, 2228; (*b*) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772.

12 (*a*) O. Bortolini, M. Bottai, C. Chiappe, V. Contec and D. Pieraccini, *Green Chem.*, 2002, **4**, 621; (*b*) M. Deetlefs, K. R. Seddon and M. Shara, *Phys. Chem. Chem. Phys.*, 2006, **8**, 642.

13 K. Wu, *Anti-Inflammatory Anti-Allergy Agents Med. Chem.*, 2007, **6**, 278.

14 (*a*) A. Cieniecka-Rosłonkiewicz, J. Pernak, J. Kubis-Feder, A. Ramani, A. J. Robertson and K. R. Seddon, *Green Chem.*, 2005, **7**, 855; (*b*) R. Grade and B. M. Thomas, *PCT Int. Appl.*, 4874526, 1989.

15 K. Bica, C. Rijksen, M. Nieuwenheuzen and R. D. Rogers, *Phys. Chem. Chem. Phys.*, 2010, accepted (manuscript number B923855G).

16 N. S. Golubev, S. N. Smirnov, P. Schah-Mohammedi, I. G. Shenderovich, G. S. Denisov, V. A. Gindin and H. H. Limbach, *Russ. J. Gen. Chem.*, 1997, **67**, 1082 (*Zh. Obshch. Khim.*, 1997, **67**, 1150).

17 N. S. Golubev, S. N. Smirnov, V. A. Gindin, G. S. Denisov, H. Benedict and H. Limbach, *J. Am. Chem. Soc.*, 1994, **116**, 12055.

18 P. M. Tolstoy, P. Schah-Mohammedi, S. N. Smirnov, N. S. Golubev, G. S. Denisov and H. Limbach, *J. Am. Chem. Soc.*, 2004, **126**, 5621.

19 J. S. Siegel and F. L. A. Annet, *J. Org. Chem.*, 1988, **53**, 2629.