Building a bridge between aprotic and protic ionic liquids

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Supporting Information

Representative Synthesis – Compounds **1a** and **1b**

The synthetic approach used to prepare the cations (as their presumably mixed chloride-iodide salts) of the APILs reported in this paper derives from that of Katz, *et al.* (I. Yudovin-Farber, I. Gurt, R. Hope, A.J. Domb, and E. Katz, *Antiviral Chemistry and Chemotherapy*, **2009**, *20*, 87-98).

3-(N,N-dimethylamino)propyl amine (47.30g, 0.4637 mol) was weighed into a 500 mL round bottomed flask, to which was then added 250 mL of reagent-grade methanol. The flask was charged with a magnetic stir bar, and immersed in an ice-water bath. Separately, di-*tert*-butoxycarbonic anhydride (101.28g, 0.4640 mol) was weighed out into a beaker. It was then added, in portions, to the stirred amine solution. Upon addition, brisk CO_2 evolution occurred; Care was taken to add the anhydride to the amine solution at a rate sufficiently slow to prevent the effervescing liquid from overflowing the flask. Once addition was complete, tissues were loosely placed into the flask neck, the ice bath was removed, and stirring continued overnight (Caution! Do NOT stopper the flask – CO_2 continues to be given off for some time even after the apparent gas evolution has ceased).

After stirring overnight, the volatiles (methanol and *tert*-butyl alcohol) were removed *in vacuo* on a rotary evaporator, while heating with a water bath at *ca.* 95 ^{o}C. After several hours, the flask was removed, allowed to cool, and an NMR taken of the yellow glass to verify completion of the *tert*-butoxycarbonylation of the primary amine group (we have had no instances with this compound or others where the protection step has failed to proceed to completion). A portion of the product (42.39g, 0.2010 mol) was then dissolved in 200 mL of reagent grade acetonitrile, to which was then added one molar equivalent (38.6g) of *n*-butyl iodide. The flask was stoppered, and the reaction mixture stirred for 24 h. Afterwards, the volatiles were removed, again using a rotary evaporator in conjunction with a hot water bath. At this juncture, a viscous yellow liquid remained, which cooled to a glassy solid. Proton NMR of this material was consistent with the structure anticipated from addition of the butyl iodide to the tertiary amine group of the BOC-protected diamine intermediate. It is vital to make sure (NMR) that no un-alkylated amine remains, as its removal at a later stage is quite difficult. If any remains, additional n-butyl iodide is added (along with acetonitrile) and the alkylation process repeated until full conversion has been achieved.

Having confirmed the completeness of the alkylation reaction, the residue was then dissolved in ~ 400 mL of 2.0M aqueous HCl and stirred. Moderate but steady gas evolution ensued, and continued for several hours. After stirring overnight, volatiles were removed by rotary evaporation (with heating to 100 ^{o}C), producing an orange glass. Here again, NMR is used to check for completeness of de-protection, as any remaining protected material will be essentially impossible to remove from the final product, and attempts to continue the de-protection process after the anion exchange step may be fruitless! In the event de-protection is not complete, the de-protection step is repeated until the NMR spectrum of the reaction residue shows it to be complete!

The glassy solid remaining after the de-protection step was re-dissolved in 200 mL of water, then treated (while being stirred) with a solution of KTf_2N (14.00g, 0.4400 mol) dissolved in ~150 mL of hot water. Upon mixing a second liquid phase immediately separated from solution. After 3 h, stirring was stopped and the liquids allowed to fully separate. The upper, moderately yellow aqueous layer was discarded, while the lower, dark yellow IL layer was washed with 2 x 100 mL of water, the faintly colored washings also being discarded.

Once washing was complete, the IL layer was rotary evaporated overnight while being heated (95 °C). It was then removed from the rotary evaporator and allowed to cool, at which point IL **1b** was a viscous but pourable straw-colored liquid.

The preparation of **1a** was identical to that of **1b** until the last step. To prepare **1a**, the de-protected mixed chloride-iodide salt was dissolved in water per the above procedure, and treated with an aqueous solution of $NaBPh_4$ instead of KTf_2N. On mixing, a thick, white mass precipitated. This was isolated by gravity filtration, washed with water, then dried, giving a coarse white solid. Crystals of the latter suitable for X-ray diffraction were grown by slow evaporation of a methanol-acetonitrile solution.

N-butyldimethylammoniumpropylammonium bis Tf_2N PIL. ^{13}C-NMR (75.57 mHz, d^6-DMSO), δ: 13.47, 19.14, 20.42, 23.58, 39.49, 50.18, 59.76, 63.24, 119.58 (q, anion CF_3). ^{1}H-NMR (300 mHz, d^6-DMSO), δ: 0.94 (t, 3H, CH_3); 1.30 (m, 2H, CH_2); 1.65 (m, 2H, CH_2); 1.91 (m, 2H, CH_2); 2.85 (t, 2H, CH_2); 3.00 (s, 6H, CH_3); 3.28 (complex m, 4H, CH_2); 7.72 (broad singlet, 3H, $-NH_3^+$). Note: The peak at 7.72 disappears upon addition of D_2O, confirming its assignment as the –NH3+ group. Furthermore, in the ^{1}H-NMR of the same cation, as the (presumably mixed) Cl-/I- salt that is the synthetic precursor to **1a**, the chemical shifts and peak multiplicities are: δ: 0.96 (t, 3H, CH_3); 1.40 (m, 2H, CH_2); 1.76 (m, 2H, CH_2); 2.20 (m, 2H, CH_2); ~3.08 (somewhat obscured by overlap; m, 2H, CH_2); 3.12 (s, 6H, CH_3); 3.36 (m, 2H, CH_2); 3.42 (m, 2H, CH_2); 8.21 (br, 3H, $-NH_3^+$). Note that there are multiple chemical shift differences of 0.10 ppm and greater between the CH_2, CH_3, and $-NH_3^+$ groups of the same cation in these two different anion environments, and that these are consistent with strong H-bonding between the protons of these groups and the halide counterion(s). This comports nicely with the strong C-H to Cl^- and $-NH_3^+$ to Cl^- interactions computationally predicted for the (hypothetical) dichloride salt of cation **1**.

N-methylpyrrolidinium bis Tf_2N PIL. ^{13}C-NMR (75.57 mHz, d^6-DMSO), δ: 21.14, 21.72, 36.28, 47.65, 60.26, 63.93, 119.62 (q, anion CF_3). ^{1}H-NMR (300 mHz, d^6-DMSO), δ: 1.95-2.18 (complex multiplet, CH_2, 6H); 2.82-3.11 (complex multiplet, CH_2, 2H), 3.01 (singlet, N-CH_3, 3H); 3.25-3.62 (complex multiplet, CH_2, 6H); 7.75 (broad singlet, NH_3, 3H).

Butylimidazoliumpropylammonium bis Tf_2N PIL. ^{13}C-NMR (75.57 mHz, d^6-DMSO), δ: 13.19, 18.84, 27.61, 31.33, 36.00, 46.13, 48.78, 119.57 (q, anion CF_3), 122.45, 122.70, 136.22. ^{1}H-NMR (300 mHz, d^6-DMSO), δ: 0.91 (t, 3H, CH_3); 1.26 (m, 2H, CH_2); 1.79 (m, 2H, CH_2); 2.06 (m, 2H, CH_2); 2.80 (br, 2H, CH_2); 4.17 (t, 2H, CH_2); 4.24 (t, 2H, CH_2); 7.71 (br, 3H, $-NH_3^+$); 7.78 (s, 1H, CH); 7.82 (s, 1H, CH); 9.15 (s, 1H, CH). Note: The peak at 7.71 in the ^{1}H-NMR disappears upon addition of D_2O; simultaneously, the previously broad, unresolved CH_2 resonance at 2.80 ppm sharpens into a distinct triplet. Furthermore, in the ^{1}H-NMR of the same cation, as the (presumably mixed) Cl-/I- salt that is the synthetic precursor to **1**, the chemical shifts and peak multiplicities are: δ: 0.91 (t, 3H, CH_3); 1.26 (m, 2H, CH_2); 1.79 (m, 2H, CH_2); 2.13 (m, 2H, CH_2); 2.78 (m, 2H, CH_2); 4.16 (t, 2H, CH_2); 4.33 (t, 2H, CH_2); 7.84 (s, 1H, CH); 7.85 (s, 1H, CH); 8.19 (br, 3H, $-NH_3^+$); 9.35 (s, 1H, CH). In particular, the differences between the halide and Tf_2N^- salts, especially the 0.48 ppm difference in $-NH_3^+$ location as well as the 0.20 ppm difference in the C(2)-H, are consistent with strong H-bonding between these protons and the halide counterion(s). This comports nicely with the strong $-NH_3^+$-Cl^- interactions computationally predicted for the (hypothetical) dichloride salt of cation **1**.

Additional Notes

I. It bears mentioning that, while there are known to be ILs with cations comprised of two or more linked cationic centres, insofar as we can ascertain these have been (within a given dication) uniformly protic *or* aprotic in character.

II. In part, the present study has its roots in our earlier experiences making “task-specific” (functionalized) ILs containing aprotic cations (e.g. imidazolium) that are covalently linked to primary amine groups. These compounds were developed for and found to be effective agents in the reversible covalent capture of CO_2, a discovery on which we and many others have since built. Conceptually, the addition of a Brønsted acid to such cations should culminate in a proton transfer, generating a ‘protic’ primary ammonium group that is covalently tethered to an ‘aprotic’ heterocyclic or quaternary ammonium center.

III. The structures of the putative acetate and chloride salts of the cation of APIL **1** (See Figure S1, below) were optimized using the Gaussian 09 [1] implementation of the B3LYP density functional method[2] and the valence triple-zeta 6-311+G** basis set[3] augmented by diffuse functions.[4] DMSO was represented as solvent using the integral equation formalism variant of the Polarizable Continuum Model (PCM)[5]. All species were fully optimized under the default parameters of Gaussian 09, and analytic vibrational frequencies were computed to verify the structures as local minima. NMR properties were computed using the default GIAO method.[6]

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[3] (a) McLean, A.D.; Chandler, G.S. J. Chem. Phys. 1980, 72, 5639; (b) Raghavachari, K.; Binkley, J.S.; Seeger, R.; Pople, J.A. J. Chem. Phys. 1980, 72, 650.

[4] Clark, T.; Chandrasekhar, J.; Spitznagel, G.W.; Schleyer, P.v.R. J. Comp. Chem. 1983, 4, 294.

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[6] Cheeseman, J.R.; Trucks, G.W.; Keith, T.A.; Frisch, M.J. J. Chem. Phys.1996, 104, 5497.

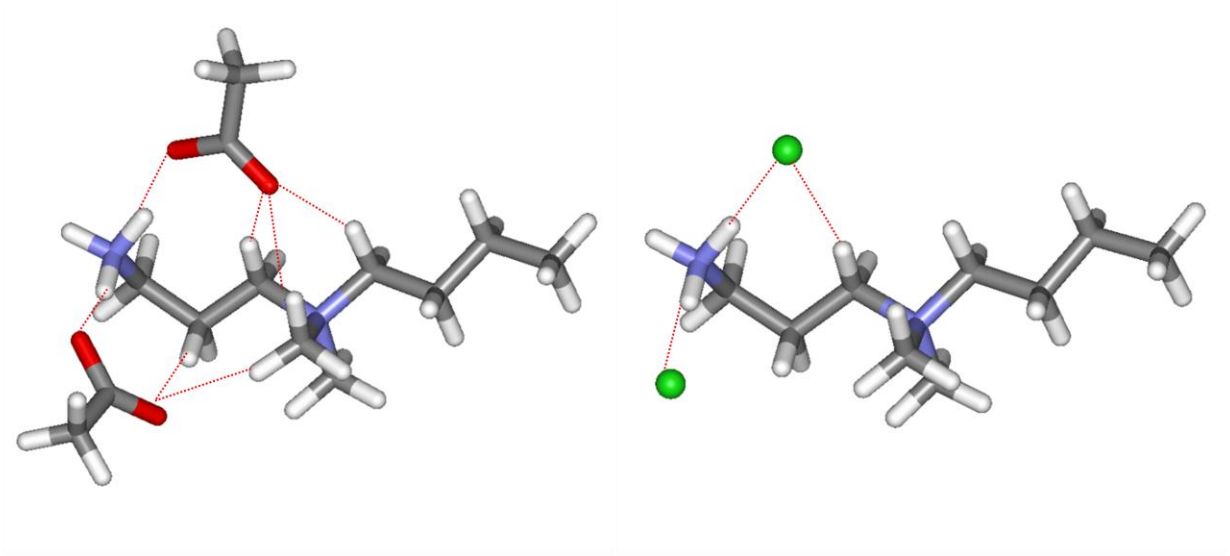

Figure S1. Computed interactions between acetate (left) and chloride (right) anions with the cation of APIL **1**. Note that the strongest interactions (indicated by dotted red lines) between the respective anions and the cation very much mirror those observed experimentally in the crystal structures of **1** and **2**. Collectively, these findings strongly suggest that the high degree of ammonium N-H to anion H-bonding believed to exist in heretofore known, classical 'protic' ILs is very much preserved even when the 'protic' cationic centre is covalently tethered to a permanent, 'aprotic' cation.

IV. Protic ILs, usually to a degree dependent upon the acid-base donor-acceptor gap, cause pH indicator dyes to respond in fashions very much akin to their normal aqueous phase behaviors, and this has been used in the past to demonstrate the 'protic' character of PILs. Accordingly, we dissolved phenol red in three systems: IL **4**, which is the free-amine, conjugate base of APIL **1**; IL**4** to which has been added 0.5 mol equivalents of HOAc, presumably setting up a system in which there is present both **4** and its APIL counterpart which has both an acetate and a Tf_2N^- anion, and finally a system in which **4** has been allowed to react with 1.0 mol equivalents of HOAc. As can be seen from Figure S2 (below), there is a decided color change in the system as the IL moves from being ‘un-protonated’ through to being ‘fully protonated.’ Furthermore, the change in (apparent) pH of the system is accompanied by a distinct changes in the ^{1}H-NMR of the system, which include changes in the chemical shift of the ammonium protons, as well as changes in the chemical shifts of the CH_2 groups in the proximity of the $–NH_2$/$-NH_3$ group.

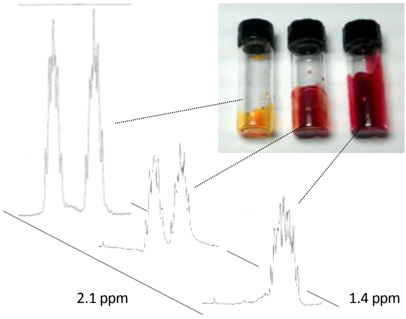

Figure S2. Photo (left to right) – APIL, 50% protonation, basic PIL. Note the behavior of the mid-linker CH_2 chemical shifts as a function of the degree of cation protonation.

As expected, the peak for the NH_3^+ protons in **1** appear as a slightly broad singlet at 7.72 ppm. In contrast, the NH_3^+ protons in the mixed sample gave a very broad signal only slightly above the baseline, centred around 3.7 ppm. A further change was apparent in pure **4**, the NH_2 protons of which were *tentatively* assigned to a baseline rise around 2.8 ppm. Again, this behaviour is consistent with that described by others for normal protic ILs. [(a) J. Stoimenovski, E. I. Izgorodina, and D. R. MacFarlane, *Phys. Chem. Chem. Phys.*, 2010, **12**, 10341; (b) J. Stoimenovski, P. M. Dean, E. I. Izgorodina, and D. R. MacFarlane, *Faraday Discuss.*, 2012, 335].

V. Interestingly, the chemical shift of the NH_3^+ protons in *neat* **1** (coaxial tube, d^6-DMSO lock and reference) is 7.13 ppm, ~0.6 ppm more shielded than in DMSO, indicating a significant δ sensitivity on the part of the NH_3^+ protons to their immediate environment. In contrast was the temperature *insensitivity* of this resonance; for example, the δ of the NH_3^+ signal in **3** only changes from 7.13 ppm at 25 ^{o}C to 7.10 ppm at 65 ^{o}C. This lack of temperature sensitivity appears to differ with that observed by Watanabe, *et al.*, with the R_3NH^+ resonance of a neat superbase Tf_2N^- PIL with only a protic cationic centre. [M. S. Miran, H. Kinoshita, T. Yasuda, A. B. H. Susan and M. Watanabe, *Chem. Commun.*, 2011, **47**, 12676]

VI. ORTEP (below) of **1** showing specific H-bond distances.