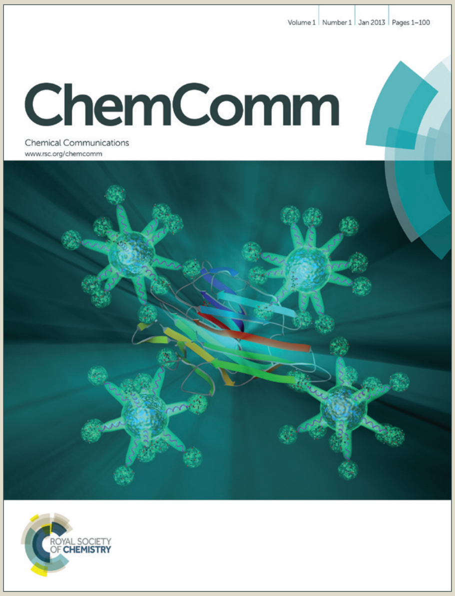
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Multi-ion ionic liquids and a direct, reproducible, diversity-oriented way to make them

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Alexandra C. Stenson,[a] Kevin N. West,[b] W. Matthew Reichert,[a] Phiwat Klomkaew,[a] Cody G. Cassity,[a] Breanna M. Dobyns,[b] Benjamin Siu,[a] and James H. Davis, Jr.[a*]

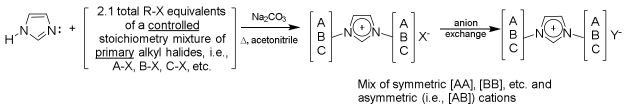
Multi-ion ionic liquids featuring large numbers of distinct imidazolium cations can be easily and reproducibly prepared in a simple one-pot procedure. The method provides a dramatic improvement in efficiency over the almost universally used approach of mixing pre-existing ILs to make multi-ion systems.

Although ionic liquids containing multiple anion and/or cation types have been known for some time, little attention has been paid to them relative to single-anion single-cation formulations.[1] Multi-ion systems account for a large portion of the 10^{18} ILs postulated by Seddon (1997)[2] to be possible, and considerable utility is foreseen for them.[1,2] Accordingly, the authors of recent reviews have persuasively advocated for more research on these materials.[1]

Most work reported thus far with multi-ion ILs has involved examples in which two or occasionally three cation types were paired with one anion type, or vice-versa.[1,2] And, while the authors of the aforementioned reviews differ with respect to how to think of and name such ILs – 'mixed ionic liquids' or 'double salt ionic liquids,' for example – there is little doubt about the almost universal route taken to prepare them: mixing two or more existing salts.[1-3] Yet, when considering the creation of multi-ion systems, the notional ease of 'mixing' ILs makes it easy to overlook the total effort required to make the pre-mix salts, effort that grows rapidly with system complexity.

Given our longstanding involvement in the design and synthesis of new ILs, and having previously worked with multi-ion ILs (i.e., "MILIEUS")[4] created using the make-then-mix approach, we decided to explore an alternate[3] means for their preparation. Here we describe an extremely simple new strategy that provides a clear improvement in efficiency over making the same system in a linear fashion. Better still, gains in efficiency become ever greater the more complex the system one wishes to create.

To set the stage for describing our methodology, let us consider a hypothetical system the ion diversity of which is of the same order of magnitude as the more complex multi-ion ILs studied to date. It is to feature three different imidazolium cations and a single anion type. The cations are to differ from one another in terms of the appendages attached to the cation at the N(1) and N(3) positions. These appendages will be referred to as A and B. When placed in all possible combinations in the N(1) and N(3) positions on the imidazolium rings, three unique cations are possible: [AA], [AB], and [BB]. Using common approaches to the synthesis of the individual salts, and disregarding any anion exchange step, the symmetrical [AA] and [BB] cations can be prepared in one- or two-step procedures for a total of two to four (collective) steps. However, the synthesis of the unsymmetrical [AB] cation will be considerably more involved because of the need for protection and de-protection at various stages. Indeed, if making the [AB] cation from imidazole (a logical point of departure), five or more steps may be required for its preparation. Consequently, seven to nine total steps would be needed to access the three targeted imidazolium salts that are to be 'simply' mixed to create the targeted multi-ion IL. Our concept, shown in Scheme 1, leads to the synthesis of a three-cation (or far more, *vide infra*) [AA], [BB], [AB] milieu in a *single* step (again omitting anion exchange). While a key concern likely to be voiced is that the strategy would surely be poorly reproducible, in our hands it has repeatedly yielded clean, composition-predictable, composition-controllable multi-ion ILs. As evidence, we now discuss five multi-ion systems made using it, **1a**, **1b**, **1c**, **2**, and **3**; full characterization data for each is provided as supporting information.



Scheme 1. Procedure for the one-pot synthesis of ILs with multiple imidazolium cation variants.

System **1a**, a Tf_2N^- salt (as are all of the new systems herein reported), contains three imidazolium ions of types [AA], [BB], and [AB]. The two side chain types, A and B, in the three cations of **1a** are allyl and propyl groups that were introduced during the one-pot

---

[a] *Department of Chemistry, University of South Alabama, Mobile, Alabama 36688 USA. jdavis@southalabama.edu*
[b] *Department of Chemical and Biomolecular Engineering, University of South Alabama, Mobile, Alabama 36688 USA*

Electronic Supplementary Information (ESI) available: [Synthetic procedures, NMR spectra, ESI-MS, elemental analyses, DSC, water content]. See DOI: 10.1039/x0xx00000x cation formation process. The ESI-MS, ^{1}H-, and ^{13}C-NMR spectra of **1a** fully comport with the expected mix of [allyl/allyl], [allyl/propyl], and [propyl/propyl] cations. In the MS, the only peaks present are those consistent with the expected cations and their isotopomers. The NMR data are equally supportive of the IL containing all of (and only) the expected cations. Moreover, the ^{1}H-spectrum in particular is consistent with the proposed cations being present in a statistically expected ratio of ca. 1:2:1. While supported by various characteristics of the spectrum, this relative population distribution is most clearly apparent in the imidazolium ring C(2)-H resonances in the ^{1}H spectrum (Figure 1).

Of course, for the new approach to be of general utility it must *reproducibly* generate the *same* multi-ion system from preparation to preparation. Accordingly, we prepared **1a** twice more, using different batches of alkyl halide mix in a deliberate effort to impede reproducibility. In each case, a pale ivory, water-immiscible final product was obtained, as had been the case with the first preparation. Most significantly, the ESI-MS, ^{1}H-, and ^{13}C-NMR spectra of the second and third batches were indistinguishable from the original and from each other. Even so, we sought further verification of batch-to-batch compositional uniformity, and turned to an analytical technique not often used in conjunction with ionic liquids – combustion (elemental) analysis.

Anecdote has it that ionic liquids, routinely subjected neither to crystallization nor distillation for purification, do not give satisfactory results when evaluated by combustion analysis. Regardless, we studied each using this technique. We reasoned that even if anecdote was true, the *origin* of any deviation from theory might be systematic, at least from batch-to-batch with a given IL. If that proved to be the case, we should find the same C, H, and N values from preparation-to-preparation if the method reproducibly yields the same system, even if these values differed from theory by a margin greater than the accepted analytical benchmark of 0.4% per element. Consequently, it was especially gratifying when the C, H, and N values from each batch not only fell within 0.4% (respectively), they all likewise fell within 0.4% of theory.

An obvious strength of the IL-mixing approach to multi-ion IL formulation is the ease with which the relative quantities of component ions can be adjusted, i.e., by combining different proportions of the independently prepared initial ILs.[1,2] To establish that our approach also allows compositional tuning, we prepared systems **1b** and **1c**. These contained the same cations as **1a**, but in different proportions. Doing so required only one change in the preparative approach; to make **1b**, the alkylating agent composition consisted of a 2:1 (mol/mol) ratio of allyl bromide to n-propyl bromide, while an alkylating agent composition having a 1:2 (mol/mol) ratio of those reagents was used to prepare **1c**.

As with **1a**, the analytical data for **1b** and **1c** (ESI-MS, ^{1}H-NMR, ^{13}C-NMR and C, H, N analysis) fully comport with their expected three-cation compositions. Most significantly, the imidazolium C(2)-H region of the ^{1}H-NMR spectra of **1b** and **1c** (when compared to that from **1a**) allows us to substantiate a key point about the preparative approach. Specifically, the synthetic rubric is (logically) predisposed to generate multi-ion systems in which the different cation populations are (insofar as can be gauged by spectroscopic means) those one would statistically expect based upon the relative quantities of the alkylating agents employed. Note that the individual C(2)-H resonances for each of the three component cations are clearly visible in all three spectra, but a difference in their relative intensities is likewise apparent (Figure 1).

Since these intensities can be correlated with the relative cation populations, we concluded that assignments could be made from the spectra of the three salts as to which C(2)-H peak arises from which cation. Nevertheless, we separately prepared [N,N-di(allyl)imidazolium]Tf_2N[5] and [N,N-di(n-propyl)imidazolium]Tf_2N[6] – the symmetrical cation ILs formed in the preparations of **1a**, **1b**, and **1c**. We then doped each of these into $CDCl_3$ solutions of **1a** to observe which of the three C(2)-H peaks grew with their addition. Doing so validated our assignments, and provided further support for concluding that the relative quantities of each of the cations formed by our approach can be statistically anticipated (Figure 1).

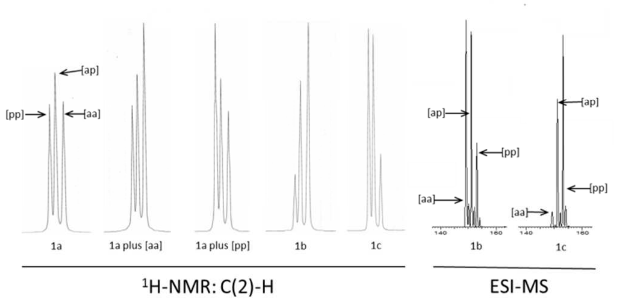


Figure 1. Selected ^{1}H-NMR and ESI-MS features of **1a**, **1b**, and **1c**, as well as **1a** doped with separately prepared [N,N-di(allyl)imidazolium]Tf_2N ([aa]) and [N,N-di(propyl)imidazolium]Tf_2N ([pp]). Signals from the mixed allyl/propyl imidazolium cation are denoted as [ap]. The peak intensities in the ESI-MS also (albeit qualitatively) follow the expected pattern, although potential differences in ion sensitivity make quantitation less straightforward than with NMR. Although not shown here, in the ESI-MS of **1a**, the centre ([ap]) peak is (significantly) of the greatest intensity, as should be the case.

We next determined that the new rubric works to prepare a multi-ion embodiment of an important class of ILs known as functionalized or “task-specific” ionic liquids (TSILs).[7] To do so, we duplicated the approach used to prepare **1a**, but replaced n-propyl bromide with 5-bromovaleronitrile. Once again, the ESI-MS, ^{1}H-, and ^{13}C-NMR spectra of the new IL, **2**, fully comport with the expected mix of [allyl/allyl], [allyl/nitrile], and [nitrile/nitrile] cations. The NMR data are supportive of the IL containing only the expected cations, and are again consistent with them being present in a statistically expected ratio of ca. 1:2:1. In turn, the ESI-MS exhibits only peaks consistent with the same species. Finally, combustion analysis of **2** returned results that were within 0.4% of theory for C, H, and N.

Having succeeded in preparing **1a**, **1b**, **1c**, and **2**, we set our sights on a considerably more complex system – one containing fifteen unique cations. It was our view that success with a system of such complexity would provide particularly strong evidence for the reliability of the new method in controllably and predictably making specific multi-ion systems. Furthermore, it would emphasize the efficiency of the rubric over a linear make-then-mix approach, since we would be reducing to one step a synthesis which could otherwise require ca. fifty-five steps. Accordingly, system **3** was prepared as outlined in Scheme 1, but employing 2.1 equivalents (rel. to imidazole) of an equimolar mixture (1:1:1:1:1) of five primary halides – ethyl bromide, 1-bromopropane, 1-iodobutane, allyl bromide, and 4-bromobutene. After workup and anion exchange, IL **3** was isolated as a mobile, pale yellow liquid; we think it likely to be the most ion-diverse IL yet reported.

The presence in the IL matrix of the expected cations was provided by ESI-MS, and no residual starting materials were observed. The NMR spectra of **3** are complex but fully comport with the proposed collective of cation structures. For example, despite heavy signal overlap, resonances for at least eleven of the expected fifteen imidazolium C(2)-H groups can be picked out in the ^{1}H-NMR, and the number of signals in the imidazolium region of the ^{13}C-NMR spectrum correlates with that expected for the fifteen imidazolium cations proposed to constitute the system.

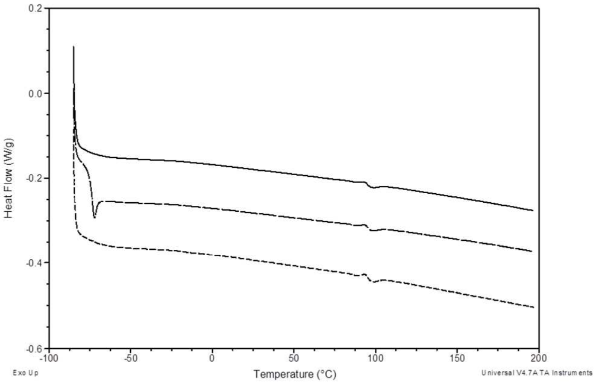


Figure 2. DSC traces compounds **1a** (solid), **2** (long dash) and **3** (short dash). The DSC indicates no discernible phase transitions for **1a** and **3**, but a low temperature glass transition observed for **2**. The thermal event at ca. 100°C with each compound is likely the loss of trace water; however, the event is minor (note the y axis scale). The y axis values have been offset, but not rescaled.

In keeping with our desire to establish the reproducibility of the present approach, we prepared **3** twice more. Each time, a clear, pale yellow, water-immiscible liquid was obtained; all three batches were visually indistinguishable. More importantly, the ESI-MS of the three were also indistinguishable, as were their ^{1}H- and ^{13}C-NMR spectra. But, to further verify their compositional uniformity, elemental analyses (C,H,N) were obtained on each sample. Once again, these yielded values falling within 0.4% of the theoretical values for C, H, and N.

Since the key phase transition for 'pure' ionic liquids and their 'mixtures' is the solid/liquid transition, we analysed several of the compounds using differential scanning calorimetry to identify these phase boundaries. With **1a** and **3**, no discernible first order phase transitions are observed between -85°C and 200°C, conceivably due to melting point depression. In turn, **2** has a T_g near -75°C. Each of the compounds likely forms an amorphous gel at low T that transitions into the isotropic liquid. A weak thermal event around 100°C in each scan is ascribed to the outgassing of trace water in the samples.

In closing, it should be noted that while IL-mixing can be used to prepare multi-imidazolium ion systems in which all of the cations are symmetrically substituted, the present approach instead guarantees the presence of unsymmetrically substituted imidazolium ions in any system it is used to create. However, the latter are generally preferred over symmetrical counterparts due to their salutary effect in lowering T_m values. Consequently, our new approach may be useful in the easy generation of very low melting multi-ion salts with unique thermophysical and chemical properties. We also suggest that the applicability of the present approach, like that of IL-mixing, has the potential to be quite wide-ranging. There are few organo-cation syntheses which do not involve alkylation of a Lewis base, and that reaction is at the heart of the work described here; indeed, we can already confirm that multi-ion systems of quaternary ammonium ions have been successfully prepared by our new rubric via multi-alkylation of primary and secondary amines. Moreover, the creation of multi-ion systems via one-pot 'non-mixing' processes need not be limited to ion generation by alkylation, and we have already begun developing ways to bring it to bear on additional multi-cation systems as well as multi-anion systems. All of these additional developments will be fully described in due course.

JHD, and JHD, WMR, and ACS, thank the National Science Foundation for grants CHE-1464740 and CHE-1039944, respectively, for support of this work. WMR thanks the Air Force Office of Scientific Research for funding through the Young Investigators Program, grant number FA9550-11-1-0053.

Notes and references

1 H. Niedermeyer, J. P. Hallett, I. J. Villar-Garcia, P. A. Hunt, T. Welton, *Chem. Soc. Rev.*, **2012**, *41*, 7780; G. Chatel, J. F. B. Pereira, V. Debetti, H. Wang, R. D. Rogers, *Green Chem.*, **2014**, *16*, 2051; M. Kick, P. Keil, A. König, *Fluid Phase Equilib.* **2013**, *338*, 172; M. Smiglak, O. Stolarska, A. Soto, H. Rodríguez, *RSC Adv.*, **2015**, *5*, 22178; G. J. Maximo, R. J. B. N. Santos, P. Brandão, J. M. S. S. Esperança, M. C. Costa, A. J. A. Meirelles, M. G. Freire, J. A. P. Coutinho, *Cryst. Growth Des.*, **2014**, *14*, 4270.

2 K. R. Seddon, *J. Chem. Technol. Biotechnol.*, **1997**, *68*, 351.

3 A very small number of other 'non-mixing' approaches to multi-ion ILs have been described. See: R. D. Rogers, D. T. Daly, G. Gurau, US 2012/0216705 A1, 2012; M. Smiglak, N. J. Bridges, M. Dilip, R. D. Rogers, *Chem. Eur. J.*, **2008**, *14*, 11314; M. J. Earle, J. M.S.S. Esperança, M. A. Gilea, J. N. Canongia Lopes, L. P.N. Rebelo, J. W. Magee, K. R. Seddon, J. A. Widegren, *Nature*, **2006**, *439*, 831.

4 M. Freemantle, *Chem. Eng. News*, **2000**, *78* (20), 37; J. H. Davis, Jr. In *Green Industrial Applications of Ionic Liquids*. R. D. Rogers, K. R. Seddon, S. Volkov, Eds; Kluwer, Dordrecht, 2002; p 385; T. L. Merrigan, E. D. Bates, S. C. Dorman, J. H. Davis Jr., *Chem. Commun.*, **2000**, 2051; A. E. Visser, R. P. Swatloski, W. M. Reichert, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis, Jr., R. D. Rogers, *Chem. Commun.*, **2001**, 135; A. E. Visser, R. P. Swatloski, W. M. Reichert, R. Mayton, S. Sheff, A. Wierzbicki, J. H. Davis, Jr., R. D. Rogers, *Environ. Sci. Technol.*, **2002**, *36*, 2523.

5 T. Mizumo, E. Marwanta, N. Matsumi, H. Ohno, *Chem. Lett.*, **2004**, *33*, 1360.

6 D. Xiao , L. G. Hines , Jr., S. Li , R. A. Bartsch, E. L. Quitevis, O. Russina, A. Triolo, *J. Phys. Chem. B*, **2009**, *113*, pp 6426.

7 C. Chiappe, C. S. Pomelli, *Eur. J. Org. Chem.*, **2014**, 6120; Z. Fei, P. J. Dyson, *Chem. Commun.*, **2013**, *49*, 2594; S. Tang, G. A. Baker, H. Zhao, *Chem. Soc. Rev.*, **2012**, *41*, 4030; M. Pucheault, M. Vaultier, *Top. Curr. Chem.*, **2009**, *290*, 83; H. Ohno, *Bull. Chem. Soc. Jap.*, **2006**, *79*, 1665; S.-G. Lee, *Chem. Commun.*, **2006**, 1049; J. H. Davis, Jr. *ACS Symp. Ser.*, **2005**, *902*, 49; J. H. Davis, Jr. *Chem. Lett.*, **2004**, *33*, 1072.