ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 7522–7524

www.rsc.org/chemcomm

COMMUNICATION

Structure-based tuning of T_m in lipid-like ionic liquids. Insights from Tf_2N^- salts of gene transfection agents†

Arsalan Mirjafari,[a] Samuel M. Murray,[b] Richard A. O'Brien,[a] Alexandra C. Stenson,[a] Kevin N. West*[b] and James H. Davis Jr.*[a]

Received 18th May 2012, Accepted 11th June 2012
DOI: 10.1039/c2cc33609j

Ionic liquids of cations bearing two lipid-like aliphatic tails are shown to have values of T_m that can be very low, and that can be tuned up or down by the addition, deletion, or combination of dipolar modules and side-chain double bonds.

An old English maxim asserts that 'two heads are better than one'.[1] But what about two tails? The question is important to the design of new room-temperature ionic liquids, especially ones capable of dissolving highly lipophilic substrates. To that end, we recently demonstrated that low values of T_m can be maintained in ionic liquids containing imidazolium ions bearing a very long (lipophilic) *N*-bound alkyl tail, provided it is unsaturated in character.[2] By doing so we exploited a key structure-property principle foundational to the natural phenomenon of homeoviscous adaptation.[3] In that process, organisms modulate the fluidity of their cell membranes on a temperature-dependent basis by varying the proportions of saturated and unsaturated phospholipid components. However, unlike naturally occurring zwitterionic phospholipids, our new IL cations bear a single long aliphatic substituent, not two. And, since we are interested in creating ILs with high degrees of lipophilic (but not amphiphilic) character, the synthesis of ILs with two long, unsaturated aliphatic substituents appended to their cationic head groups seems logical to pursue. But, in natural systems the two long aliphatic chains of phospholipids 'point the same direction,' a structural attribute that allows them to self-assemble into their distinctly biphasic construct with water. In the imidazolium cations characteristically used in ILs, alkylation of the two ring nitrogens with long aliphatic substituents is known to result in cations in which the latter effectively 'point in opposite directions.' This impacts the nature of their nanoscale assemblies relative to those which are observed when imidazolium cations with a single long (unidirectional) substituent assemble.[4]

Conceptually, this conundrum can be solved by creating imidazolium cations bearing two long aliphatic substituents (prospectively unsaturated) in neighbouring positions, *e.g.* at N-1 and C-2. In principle, such ions are 'make-able', but their synthesis and purification is likely to be rather involved. So, it seemed sensible to seek a quick and easy approach that would allow us to *first* establish whether the idea of maintaining low T_m values in salts with double (and arguably parallel) tails – regardless of their cation head group structure – was even plausible. This proved to be quite straightforward, and by doing so we gained insights into lipidic IL structure-property (T_m) relationships that add to and deepen those uncovered by our earlier work.

By exchanging the chloride anions of off-the-shelf, commercially available gene transfection agents ('cationic lipids')[5] for the bis(trifluoromethanesulfonyl)amide anion, Tf_2N^-, fully hydrophobic ILs – two with T_m values below normal room temperature – are readily prepared. Furthermore, each of these salts contains a cationic head group to which two long, parallel aliphatic chains are covalently tethered. Ionic liquids **1** and **2** are a case in point.

As shown in Fig. 1, ILs **1** and **2** each contain a trimethylammonio- moiety tethered to a glyceryl-derived module. The latter component, in turn, connects to two C_{18} aliphatic appendages. In **1**, these appendages are fully saturated, while in **2**, each appendage is *cis*-unsaturated between chain carbon atoms 9 and 10. In turn, mono-tailed reference compounds **3** and **4** are first-generation lipidic ILs featuring *N*-methylimidazolium cations

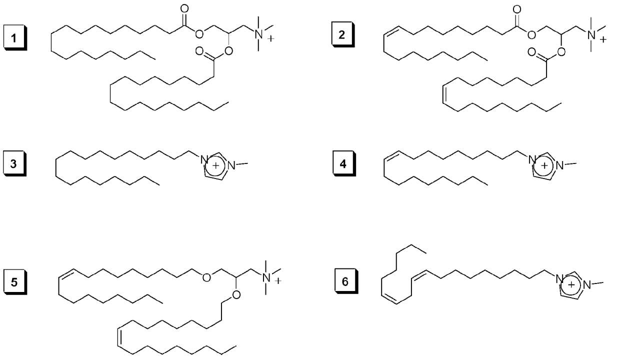

Fig. 1 Structures of new lipidic ILs (**1**, **2** and **5**) and reference lipidic ILs (**3**, **4** and **6**).

---

[a] *Department of Chemistry, The University of South Alabama, Mobile, Alabama, 36688, USA. E-mail: jdavis@jaguar1.usouthal.edu; Fax: +1 251 460 7359; Tel: +1 251 460 7427*
[b] *Department of Chemical & Biomolecular Engineering, The University of South Alabama, Mobile, Alabama 36688, USA. E-mail: kevinwest@southalabama.edu*

† Electronic supplementary information (ESI) available: Synthetic details, NMR and MS data. See DOI: 10.1039/c2cc33609j

bearing a single C_{18} appendage, saturated in the former and unsaturated in the latter.

Significantly, the T_m difference (Table 1) between **1** and its imidazolium counterpart **3** is a scant 1.3 °C, despite the doubled cation side-chain organic content of the former. While acknowledging the comparison of **1** and **3** to be something of an 'apples and oranges' matter because of their different head group types, the fact remains that the T_m of **1** is still low in absolute terms (well below the 100 °C benchmark used as the upper T_m cut off for defining ionic liquids). This, then, lends credence to the hypothesis that a putative imidazolium analogue incorporating two saturated C_{18} chains arranged in parallel might be reasonably anticipated to likewise manifest a sub-100 °C value of T_m.

A comparison of the T_m values of new ILs **1** and **2** with each other is also informative. As noted, these differ only in the nature of their lipidic side chains as either saturated (**1**) or unsaturated (**2**). Here again, as with the lipidic imidazolium ILs, the incorporation of a double bond in the side chain results in a substantial decrease in T_m – that of **1** is 54.8 °C, while that of **2** is 14.6 °C, a ΔT_m of 40.2 °C. This demonstrates that the T_m-lowering effect of side chain unsaturation is relevant not just when an IL head group is an imidazolium ring. Rather, it is clearly operative across *both* classes of ionic liquids, with their dramatically different head group types and total organic content. This buttresses our expectation that the 'double bond effect' is likely to prove very general, and broadly applicable when designing ILs of various classes whenever low melting points must be retained while still imbuing the material with a high degree of hydrocarbon side-chain content.

Although the salutary effect upon T_m of unsaturated *versus* saturated side chains is again evident in these results, the absolute 14.6 °C T_m value of double-tailed lipid IL **2** is still considerably higher than that observed for benchmark imidazolium IL **4**. Of course, as would be the case for any IL, its T_m value is the outworking of a number of factors, among which are the number and strengths of all possible cohesive forces. In typical (*e.g.*, non-functionalized) imidazolium-type ILs, two inter-particulate force types – Coulombic and London – are thought to predominate.[6] However, the inter-particulate cohesive forces acting in **1** and **2** would clearly include strong dipolar contributions from the two ester linkages present in the cation head group area of each.[7] Note that the imidazolium IL benchmarks **3** and **4** are devoid of such components. So, to probe the impact these ester groups have upon T_m, we prepared IL **5** by anion exchange from a third commercially available cationic lipid chloride salt.

Table 1 T_m values of lipidic ionic liquids. The values for compounds **3**, **4**, and **6** are taken from ref. 2

Ionic liquid	T_m (°C)	±
1	54.8	0.5
2	14.6	0.5
3	53.5	1.0
4	−20.9	1.0
5	−42.2	0.5
6	−46.8	1.0

Net excision of the carbonyl moieties from the structure of **2** formally results in cation structure **5**. The effect of doing so is remarkable. While the T_m value of **2** is 14.6 °C, that of **5** is −42.2 °C, a ΔT_m of 56.8 °C. This is clearly the direct result of suppressing the strong, carbonyl-induced dipolar contribution to the inter-particulate cohesive forces acting in **2**. Not only is the T_m value of **5** very low in absolute terms, it is quite similar to that of imidazolium IL **6**, lowest-melting (−46.8 °C) member of the first generation of lipidic ILs. A 'map' illustrating the effect of these changes upon T_m is shown in Fig. 2.

Significantly, both **5** and **6** have two side-chain double bonds, although they are in the same chain in **6** but two separate side chains in **5**. With this in mind, and noting that there is a substantial difference in T_m resulting from having one (IL **4**) *versus* two (IL **6**) double bonds in a given cation, it seems likely that the double bond effect is cumulative. At the same time, it appears that the specific locations of the side-chain double bonds may be of secondary importance; this comports with observations we made in our earlier study vis-à-vis the T_m differences between ILs as a function of the position of double bonds in the lipidic side chain.[2]

It also bears noting that the T_m decrease (40.2 °C) brought about by the formal introduction of two double bonds into the cation structure of **1** to generate cation **2** is a substantial proportion – about 70% – of the magnitude of the T_m increase (56.8 °C) that is induced by the formal introduction into **5** of two dipolar carbonyl groups, a change which likewise generates **2** (Fig. 2). This indicates that it is possible to take a basic cation framework and temper the impact that one modification to it has – pertaining here to its conceptual 'baseline' T_m – by making a simultaneous modification of opposing effect to the same ion.

The overall features of the DSC curves (Fig. 3) from which the T_m values of **1**, **2** and **5** are extracted are highly evocative of those observed with many natural lipids and polymers.[8,9] Among these is the magnitude of the enthalpy change associated with the melting events. In this regard it is notable that the transitions of ILs **2** and **5** are very weak compared to that of **1**. This is indicative of solid states on the parts of **2** and **5** in which side-chain interactions are not optimal due to the disorder brought about by the double-bond induced side-chain kinking, a phenomenon clearly observed with saturated *versus* unsaturated natural

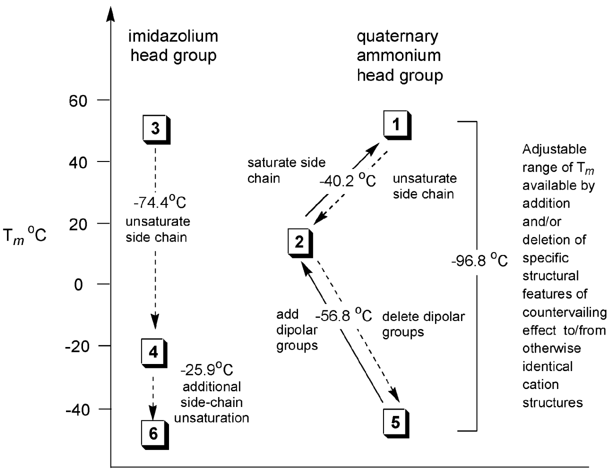

Fig. 2 Structural changes and their T_m impacts.

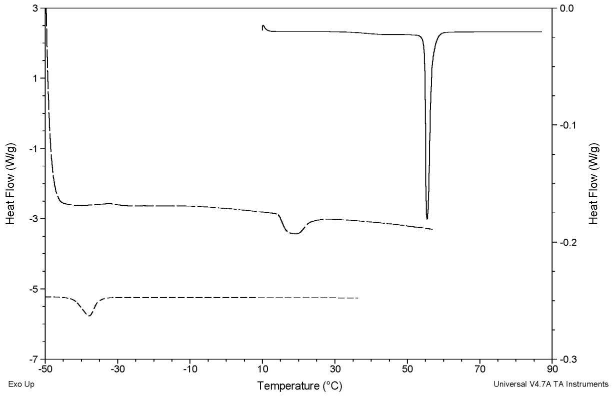

Fig. 3 DSC traces obtained for (top to bottom) **1**, **2** and **5**. Those of **1** and **5** are referenced to the left y axis while that for **2** is referenced to the right y axis. The traces are offset to distinguish them, but are not rescaled.

lipids.[9] This further implies that in these ILs, the unsaturated side chains pack less densely than those which are saturated, a phenomenon likely to affect properties of practical importance such as the solubility of various gases in the ILs.

Collectively, the foregoing results provide useful insights into features and relationships that are consistent with achieving low T_m values in salts with lipid-like cation appendages, features that are not apparent from our earlier study. Specifically, *cis* double bonds in the adjacent/parallel side chains of the new salts are observed to be powerful downward drivers of T_m even though the alkyl content in these cations is effectively doubled relative to first generation salts. Further, the more highly charge-localized nature of the quaternary ammonium head groups of the present salts appears to have little intrinsic impact on T_m in lipidic ILs. Note that the T_m of **5**, with its quaternary ammonium head group, is a scant 5 °C higher that that of **6**, the lowest melting of the first-generation lipidic ILs. In the final analysis, we believe the present findings not only provide ample justification for pursuing the synthesis of new imidazolium ILs with long but adjacent aliphatic appendages, but those with a myriad of other cationic heads as well as functional groups[10] which can be used in conjunction with these appendages to create 'designer' melting points.

The corresponding authors would like to thank the National Science Foundation (Grant No. CBET-1133101) for their support of our research.

Notes and references

1 Informative remarks on the origin of the phrase may be found at: http://www.phrases.org.uk/meanings/two-heads-are-better-than-one.html. Accessed 05/05/2012.

2 (*a*) S. M. Murray, R. A. O'Brien, K. M. Mattson, C. Ceccarelli, R. E. Sykora, K. N. West and J. H. Davis, Jr., *Angew. Chem., Int. Ed.*, 2010, **49**, 2755–2758; (*b*) J. H. Davis, Jr, *International Symposium on Ionic Liquids and Life Science*, Keio University, Yokohama, Japan, 2007, Session VI.A.

3 M. Sinensky, *Proc. Natl. Acad. Sci. U. S. A.*, 1974, **71**, 522–525.

4 X. Wang, F. W. Heinemann, M. Yang, B. U. Melcher, M. Fekete, A.-V. Mudring, P. Wasserscheid and K. Meyer, *Chem. Commun.*, 2009, 7405–7407.

5 P. L. Felgner, T. R. Gadek, M. Holm, R. Roman, H. W. Chan, M. Wenz, J. P. Northrop, G. M. Ringold and M. Danielsen, *Proc. Natl. Acad. Sci. U. S. A.*, 1987, **84**, 7413–7417.

6 See, for example: I. López-Martin, E. Burello, P. N. Davey, K. R. Seddon and G. Rotherberg, *ChemPhysChem*, 2007, **14**, 690–695.

7 The capacity of functional groups to impart dipolar character to IL cations has been previously documented and quantified. See: (*a*) N. K. Sharma, M. D. Tickell, J. L. Anderson, J. Kaar, V. Pino, B. F. Wicker, D. W. Armstrong, J. H. Davis, Jr. and A. J. Russell, *Chem. Commun.*, 2006, 646–648; (*b*) P. Twu, Q. Zhao, W. R. Pitner, W. E. Acree Jr., G. A. Baker and J. L. Anderson, *J. Chromatogr., A*, 2011, **1218**, 5311–5318.

8 E. M. Antipov, V. G. Kulichikhin and N. A. Platé, *Polym. Eng. Sci.*, 1992, **32**, 1188–1203.

9 R. N. A. H. Lewis, D. A. Mannock and R. N. McElhaney, in *Methods in Molecular Biology*, ed. A. M. Dopico, Humana Press, Totowa, NJ, 2007, vol. 400, pp. 171–195.

10 (*a*) J. H. Davis, Jr., *Chem. Lett.*, 2004, **33**, 1072–1077; (*b*) S. Tang, G. A. Baker and H. Zhao, *Chem. Soc. Rev.*, 2012, **41**, 4030–4066.