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Lipidlike Ionic Liquids

The Fluid-Mosaic Model, Homeoviscous Adaptation, and Ionic Liquids: Dramatic Lowering of the Melting Point by Side-Chain Unsaturation**

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Dedicated to Professor Thomas P. Murray

Proposed by Singer and Nicolson in 1972,[1] the fluid-mosaic model holds that the phospholipid bilayer is a dynamic two-dimensional solvent milieu. Its proper function is closely tied to its "fluidity", and that is often quantified by reference to the melting point, T_m (increased fluidity corresponds to a lower T_m value). The fluid-mosaic model is highly evocative of the emerging picture of nanoscale structuring in ionic liquids (ILs),[2,3] and just as the function of phospholipid bilayers is tied to the T_m value, so too is the utility of ILs. Whereas the former often have low T_m values despite being composed of charged species with long aliphatic appendages, the fluidity of ILs generally decreases when progressively longer aliphatic appendages are used.[4]

It is a challenge to design imidazolium ILs (the most common IL class) that incorporate progressively more lipophilic structural elements while keeping their melting points below room temperature (Figure 1).[4–9] Indeed, the T_m values of these ILs begin to rise dramatically once an appended *N*-alkyl group exceeds seven carbon atoms in length. Herein we report that by using an approach modeled on homeoviscous adaptation (HVA),[10] ILs with very long alkyl appendages and very low T_m values can be prepared. This discovery may have significant implications for IL use in enzymatic catalysis, lubricants, heat-transfer fluids, and gas storage and separation, among other applications.

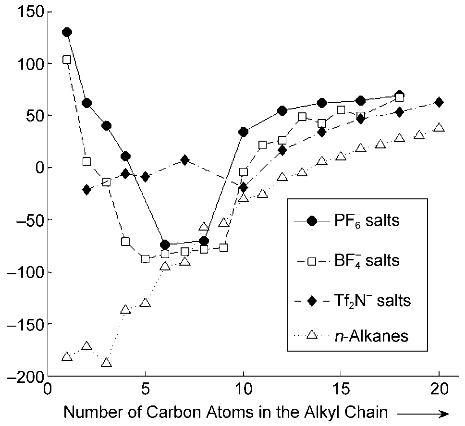

Figure 1. Influence of alkyl-chain length on T_m in *N*-alkyl *N*-methylimidazolium salts and the corresponding *n*-alkanes. The graph includes data from the literature[4–9] and newly synthesized ionic liquids.

Widely accepted as a mechanism by which the melting temperature of cell membranes is modulated, HVA is the incorporation into cell membranes of phospholipids with "kinked" tail structures.[10] It is argued that the packing efficiency of the collective membrane hydrophobic components is diminished by the presence of these phospholipids and that increased fluidity results. A comparison of the T_m value of distearoylphosphatidylcholine with that of dioleylphosphatidylcholine provides a dramatic example of how much impact this seemingly trivial difference can have. The former, with its linear, saturated C_{18} tails has a T_m value of 58 °C; the latter, with its "kinked" C_{18} tails (each of which incorporates a *cis*-alkenyl group), has a T_m value of −22 °C. This effect is also at the heart of the T_m difference between the solid triacyl glycerols called fats, and those that are liquid at room temperature known as oils. In both instances, the effect is probably entropic in nature, as in the case of anthracene ("linear", $T_m = 217\,°C$) and phenanthrene ("kinked", $T_m = 99\,°C$).[11] Accordingly, we hypothesized that ILs with long, unsaturated, aliphatic tail structures would, like the corresponding phospholipids, have significantly lower T_m values than their counterparts with saturated appendages.

To test the validity of our hypothesis by measuring their T_m values, we prepared a series of lipid-inspired ILs in a three-step process from high-purity (99+ %) fatty-alcohol mesylates, 1-methylimidazole, NaI, and $NaTf_2N$.[12] Each of the ILs (Scheme 1) had a long alkyl appendage identical to that in a natural fatty acid. Compounds **1**, **3**, and **8** feature fully saturated C_{16}, C_{18}, and C_{20} side chains, respectively, and their

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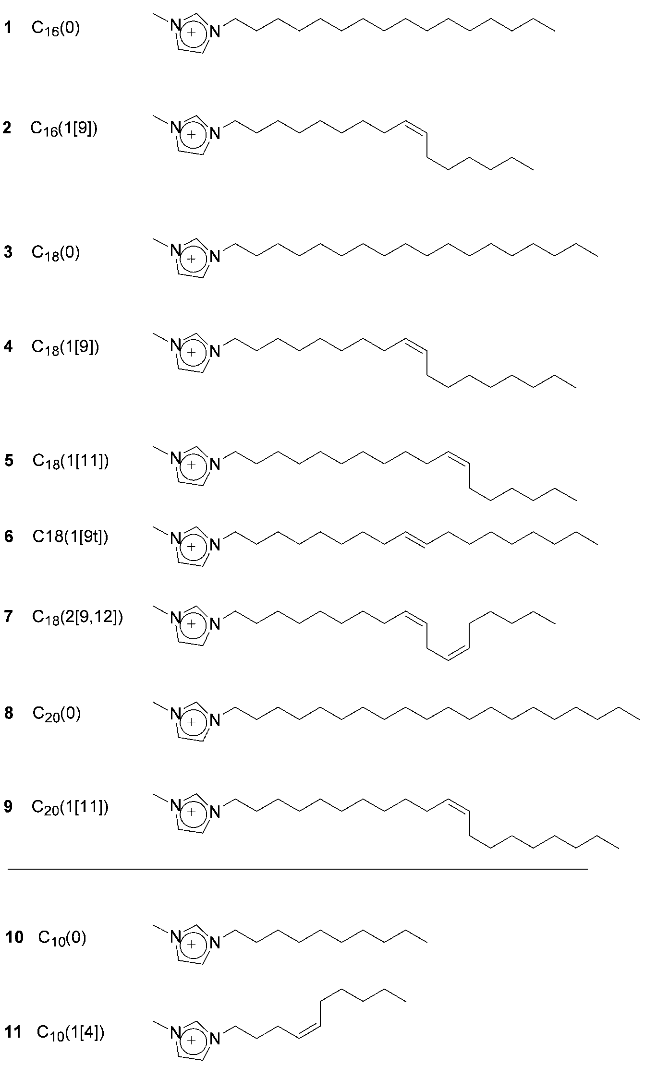

Scheme 1. Cations of the lipidic ILs **1**–**11**. Except for **11a** (see text), each IL is a Tf_2N^- salt (Tf = trifluoromethanesulfonyl).

T_m values provided a baseline against which the T_m values of unsaturated variants of the same chain length could be compared. Compound **2**, the unsaturated counterpart of **1**, is *cis*-unsaturated between C9 and C10. Likewise, **4**–**7** are analogues of **3** with C_{18} side chains containing one or two double bonds. These compounds differ further on the basis of the configuration (*cis* in **4**, **5**, and **7**, *trans* in **6**) and location along the C_{18} backbone of the double bond(s). With *cis* unsaturation between C11 and C12, **9** is the "kinked" analogue of the C_{20} IL **8**.

As is often the case for ionic liquids[4] and lipids alike,[13,14] the reproducible acquisition by differential scanning calorimetry (DSC) of the T_m values of the lipid-inspired ILs was challenging, but possible under appropriate conditions (see the Experimental Section). Notably, scans from ILs **1**, **3**–**6**, and **8**–**10** exhibited the type of multifeatured traces common to lipidic biomaterials and many ILs. However, **2**, **7**, and **11** consistently produced scans that were featureless down to about −170 °C. For that reason, the T_m values of those ILs were assigned after observation of their behavior during very slow, repeated heating/cooling cycles in a thermostatically controlled bath (±1.0 °C). To confirm that the latter procedure produced reliable results, we also applied it to samples of **1**, **3**–**6**, and **8**–**10** to determine if their DSC T_m values corresponded to the temperatures at which the visual onset of liquefaction had been apparent with the former approach. Additionally, the T_m values of **1**, **3**, and **8**, all of which were above normal room temperature, were measured by using a standard melting-point apparatus. Significantly, consistent melting points were observed in all cases when more than one technique was used.

The T_m values of all ILs studied are listed in Table 1, along with published T_m values for the corresponding native fatty acids and fatty-acid methyl esters. The implications of the data are quite clear. The introduction of *cis* double bonds ("kinks") into the long aliphatic tails of these salts leads to an increase in fluidity that closely parallels that observed for their molecular relatives (Table 1, Figure 2). Indeed, unsaturation leads to a radical decrease in the T_m value with respect to that of the relevant saturated IL standard **1**, **3**, or **8**. Specifically, ΔT_m for the saturated/unsaturated pairs **1**/**2**, **3**/**4**, and **8**/**9** was 68.9, 74.4, and 58.3 °C, respectively. Interestingly, the lowest T_m values were observed for ILs **11b**, **2**, and **7**. Compound **11b** has an unsaturated C_{10} side chain, **2** has an unsaturated C_{16} side chain, and **7** has a C_{18} side chain containing two *cis* olefin groups.

Table 1: T_m values of lipid-inspired ILs and related compounds.

IL	Alkyl group[a]	T_m [°C]	T_m (fatty acid) [°C][b]	T_m (methyl ester) [°C]
1	$C_{16}(0)$	46.9	63.5	33.5
2	$C_{16}(1[9])$	−22.0	0.5	−33.9
3	$C_{18}(0)$	53.5	69.6	38.9
4	$C_{18}(1[9])$	−20.9	16.2	−19.6
5[c]	$C_{18}(1[11])$	−9.8	12.0	–
6	$C_{18}(1[9t])$	16.0	43.7	10.3
7	$C_{18}(2[9,12])$	−46.8	−6.5	−35.0
8	$C_{20}(0)$	62.5	75.5	54.0
9[d]	$C_{20}(1[11])$	4.2	23.5	−34.0
10	$C_{10}(0)$	−18.9	31.0	−12.5
11b	$C_{10}(1[4])$	−37.0	–	–

[a] (*x*[*y*]): *x* = number of double bonds in the alkyl group; *y* = first carbon atom of the double bond; t = *trans* olefin. [b] Common names of the corresponding fatty acids (top to bottom): palmitic, palmitoleic, stearic, oleic, *cis*-vaccenic, elaidic, linoleic, arachidic, gondoic, capric, obtusilic. [c] Glass-transition temperature: $T_g = -13.5$. [d] $T_g = -3.42$ °C.

Data from the C_{18} IL family also reveals that a *cis* double bond at C11–C12 rather than at C9–C10 is less effective at lowering the T_m value, but only moderately so. In particular, the 11.1 °C difference in ΔT_m for **3**/**4** versus **3**/**5**—the putative "position effect"—is small in comparison to the "unsaturation effect" evident from the ΔT_m values for each of these pairs. The observation that the ΔT_m value of 58.3 °C for **8**/**9** is much closer to that of the **3**/**5** pair (63.3 °C) than that of the **3**/**4** pair (74.4 °C) also provides tentative support for this inference, although the two-carbon-atom chain-length difference in the systems complicates the comparison.

Although the double-bond position in the side chain of the C_{18} ILs studied accounts for a relatively small difference in ΔT_m (as compared to the effect of introducing unsaturation at either position in the side chain), the effect of its geometry (*cis*

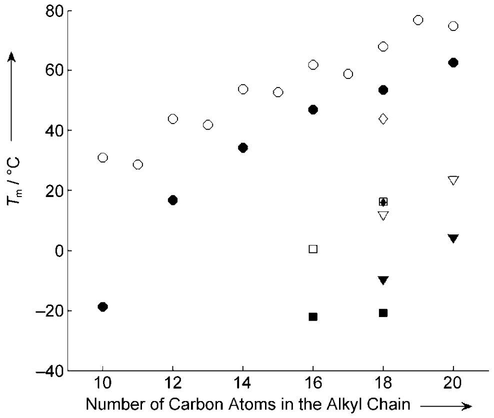

Figure 2. T_m value versus alkyl-chain length for saturated C_{10}–C_{20} alkyl $MIM^+Tf_2N^-$ ILs, the new lipid-inspired unsaturated ILs, and the corresponding saturated fatty acids:[9] ○ saturated fatty acids, ● saturated alkyl $MIM^+Tf_2N^-$ ILs, □ 9-*cis* fatty acids, ■ 9-*cis* alkyl $MIM^+Tf_2N^-$ ILs, ◇ 9-*trans* fatty acid, ◆ 9-*trans* alkyl $MIM^+Tf_2N^-$ IL, ▽ 11-*cis* fatty acids, ▼ 11-*cis* alkyl $MIM^+Tf_2N^-$ ILs (MIM = methylimidazolium).

or *trans*) is more substantial. Whereas the presence of the *cis* double bond in **4** leads to a T_m decrease of 74.4 °C relative to that of IL **3** with a saturated side chain, the T_m decrease induced by the *trans* double bond at the same position in **6** is only 37.5 °C. This effect closely resembles that observed for the analogous C_{18} fatty acids and their methyl esters. For example, the difference in the T_m values of stearic acid and oleic acid is 53.4 °C, whereas the difference in the T_m values of stearic acid and elaidic acid is 25.9 °C. In the case of the corresponding methyl esters, these values are 58.5 and 28.6 °C, respectively. The consistently smaller T_m differences due to *trans* versus *cis* unsaturation across this series of related compounds probably results from a smaller packing-disruption effect imposed by *trans* double bonds. When the alkyl chains of these molecules are depicted in their low (rotational) energy *trans* conformations (as in Scheme 1), saturated and *trans*-unsaturated chains can clearly be "linear", whereas *cis*-unsaturated chains are plainly constrained to kink.

We felt that X-ray crystallographic studies of one of our materials might provide more insight into these issues. Despite considerable effort, we were unable to isolate the unsaturated materials in single-crystalline form. Consequently, we prepared unsaturated but progressively shorter-chained analogues with various anions until we isolated a material, the salt **11a**, which formed suitable crystals at room temperature. We then studied **11a** by X-ray diffraction (Figure 3). Significantly, the unit cell contains four symmetry-independent cations, each of which has its long (C_{10}) appendage contorted substantially away from the conformationally *all-trans* linear norm seen in the crystal structures of imidazolium ions with long saturated side chains.[15] In each C_{10} chain, the kinking induced by the double bond is clear, and the overall irregular orientation of the side chains in these cations is probably representative of the orientation of the longer-chain unsaturated counterparts.

Having synthesized the imidazolium iodide salt for use in the preparation of **11a**, we decided prepare **11b** (its Tf_2N^- counterpart) as well, and for sake of comparion compound **10**, the Tf_2N^- salt of the saturated analog of the cation in **11a/b**. We thought this worth doing because the site of unsaturation in **11**, unlike those in **2**, **4–7** and **9**, is in the so-called "symmetry breaking region" of the imidazolium cation.[4] As described by Rothenberg and co-workers in regard to *N*-alkyl *N*-methylimidazolium salts, the *N*-alkyl groups cause the symmetry reduction responsible for poor ion packing of the cations and low melting points.[4] However, the T_m values of such salts are commonly observed to rise again (Figure 1) once the alkyl group exceeds seven carbon atoms in length, as a result of the increasing cohesion due to van der Waals forces in the "hydrophobic region" (that portion of the alkyl group beyond C_7).[4,16] Significantly, a comparison of the T_m values of **10** and **11b** indicates that the effects of side-chain unsaturation are operative whether the double bond is in the symmetry-breaking or hydrophobic region. However, the impact of unsaturation within the symmetry-breaking region (18 °C in this case) is substantially less than when it occurs in the hydrophobic region in **2**, **4**, **5**, **7**, and **9**. Overall, we take this data to indicate that: a) the effect of the symmetry-breaking region on the T_m value can be amplified through structural modifications within it; and b) the incorporation of structural irregularities (kinks) in the hydrophobic region can act to counter the T_m increase that normally occurs as van der Waals forces accumulate in this part of the ion.

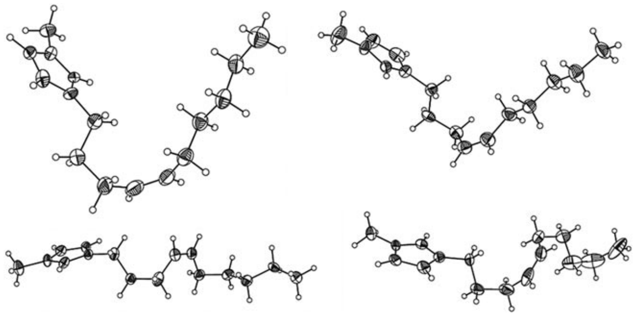

Figure 3. ORTEP diagrams of the four symmetry-independent cations in crystals of **11a** (a BPh_4^- salt). Each ORTEP diagram has been independently oriented to make clear the side-chain nonlinearity. The double bond is between the fourth and fifth carbon atoms of the C_{10} group.

The melting point is not the only fluid characteristic of these ILs that is affected by unsaturation; viscosity is also influenced. Although the data accumulated thus far on the viscosity of lipid-inspired ILs are less extensive than the T_m data, they also support a connection between side-chain unsaturation and IL liquidity. Specifically, although the viscosity of **3** was measured only at 60 °C (because of its melting point of 53.5 °C), it is considerably higher than that of the other C_{18} ILs at the same temperature. At 60 °C, **3** has a viscosity of 54.3 cSt, whereas its oleyl counterpart **4** has a viscosity of 36.9 cSt. Likewise, the vaccenyl IL **5** has a viscosity of 34.4 cSt at 60 °C. This value is close to that of **4**, but again significantly lower than that of **3**. As expected, the viscosities of the unsaturated ILs are higher at lower temperatures. For example, **4** and **5** have viscosities of 165.3 and 149.6 cSt, respectively, at 25 °C.

Like unsaturated fats, ILs **2**, **4–7**, **9**, and **11** discolor over time if left in contact with air. This observation indirectly suggests a high solubility of gases (e.g., O_2) in these new species, as in unsaturated fats such as olive oil.[17] Although the degree of oxidation is sufficiently low as to be undetectable by NMR spectroscopy after a month, discoloration is apparent sooner, and these ILs gradually acquire a faint odor of decomposition products associated with side-chain oxidation. Although likely to render the cations biodegradable,[18] this reactivity will be deleterious for many other applications. Oxidation can be suppressed by storing the ILs under N_2 or by adding to them small quantities (ca. 1 mol%) of butylated hydroxytoluene (BHT), an antioxidant used to prevent rancidification in processed foods.

Not surprisingly, the new ILs are good solvents for cholesterol, a major membrane component in many organisms. Whereas little cholesterol dissolves in "typical" ILs, such as [BMIM]Tf_2N (BMIM = 1-butyl-3-methylimidazolium), we have observed the dissolution of up to 30 mass percent in **4** at room temperature. This result prompts us to suggest that these new unsaturated ILs and similar ILs may be useful as solvents for biomolecules that are membrane-localized or drug molecules that act on membrane components or passively diffuse through the phospholipid bilayer to enter the cell. One category of species that are expressly interesting in this context is the lipases, which have been investigated for their catalytic behavior in more typical ILs.[19] Although the factors governing enzyme activity and stability in ILs are complex,[19] it seems reasonable to propose that IL solvents more akin to those environments in which such enzymes naturally function may offer advantages over other IL solvents.

In conclusion, the present data show that ILs with long alkyl appendages respond to side-chain modification—specifically unsaturation—in a fashion reminiscent of homeoviscous adaptation by living organisms. It is a phenomenon that is eminently exploitable from a utilitarian standpoint and that we believe creates new opportunities for manipulating the properties of ILs and other synthetic soft materials. Studies aimed at assessing an array of such possibilities are in progress.

Experimental Section

High-purity (> 99 %) fatty-alcohol mesylates were obtained from Nu-Chek Prep, Inc. and used as received for the preparation (under Finkelstein conditions)[20] of the corresponding iodides. The ILs were prepared and characterized by using standard techniques,[7] with the exception that all reactions were performed under N_2. Melting points were determined by using a Seiko Instruments differential scanning calorimeter, model SSC/5200-DSC 220U, with a heating rate of $5° min^{-1}$. The reported data are the average of at least three trials, and were reproducible to within 1 °C. The phase transition identified as the melting point is the one for which a liquid is the product; the former state may have been either crystalline or amorphous. Several of the new ILs were difficult to crystallize even by cooling to −170 °C. However, we found that preheating of the samples at 75 °C for 10 min followed by slow cooling to −170 °C resulted in an exothermic event on subsequent heating that was consistent with a glass transition or crystallization from a gel. Subsequent warming then reproducibly yielded a reliable T_m value. Viscosities were measured by using the traditional flow technique in Cannon Ubbelohde Viscotesters 200L119 and 300L33. The viscometers were immersed in a water bath with an HCTB-3030 immersion cooler from Omega Instruments that was capable of maintaining temperatures within 0.05 °C. The measured viscosities were reproducible to within 0.1 cSt.

Crystal data for **11a**: $C_{38}H_{45}BN_2$, $M_r = 540.57$, $0.17 \times 0.02 \times 0.02\ mm^3$, monoclinic, $P2_1/c$, $a = 18.1597(8)$, $b = 35.5151(11)$, $c = 21.3555(7)$ Å, $\beta = 111.634(5)°$, $V = 12802.9(8)$ Å^3, $Z = 16$, $\rho_{calcd} = 1.122\ g\,cm^{-3}$, $\mu = 0.479\ mm^{-1}$, $Cu_{K\alpha}$ radiation ($\lambda = 1.54178$ Å), $T = 100(2)$ K, $2\tau_{max} = 59.06°$, 38370 measured and 17595 independent reflections, $R_{int} = 0.1026$, $R = 0.0579$, $wR = 0.1084$, Oxford Diffraction Ltd., Xcalibur CCD system, solution with direct methods and refinement with 1490 parameters, difference map between +0.193 and −0.209 e Å^{-3}. CCDC 752914 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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