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Synthesis and thermophysical properties of ionic liquids: cyclopropyl moieties versus olefins as T_m-reducing elements in lipid-inspired ionic liquids

Man-Lung Kwan [a], Arsalan Mirjafari [b,†], John R. McCabe [c], Richard A. O'Brien [b], David F. Essi IV [a], Leah Baum [a,b,c,‡], Kevin N. West [c], James H. Davis Jr. [b,*]

[a] Department of Chemistry, John Carroll University, University Heights, OH 44118, USA
[b] Department of Chemistry, University of South Alabama, Mobile, AL 36688, USA
[c] Department of Chemical and Biomolecular Engineering, University of South Alabama, Mobile, AL 36688, USA

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ABSTRACT

Cyclopropyl moieties embedded in the long aliphatic side chains of imidazolium-type ionic liquids are shown to be highly effective in lowering the T_m of such materials relative to counterparts bearing linear, saturated side chains. While not as efficient as olefins in bringing about this effect, ILs incorporating side-chain cyclopropanated modules are likely to be more resistant to aerobic degradation than those employing the former.

In certain respects, the nanoscale structure of lipid bilayers is evocative of the emerging picture of nanoscale structuring in ionic liquids (ILs).[1] And, just as the function of phospholipid bilayers is tied to their fluidity—as reflected in their T_m—so too is the utility of ILs. However, while lipid bilayers usually have low values of T_m despite being composed of charged species with long aliphatic appendages, it is generally observed that the fluidity of ILs—typified by those containing *N,N′*-dialkylimidazolium ions—decreases when progressively longer aliphatic appendages are tethered to their cation charge centers.[2]

Indeed, it can be a challenge to design imidazolium ILs that incorporate progressively more lipophilic structural elements while retaining melting points that are below room temperature. However, using an approach modeled on the natural phenomenon of homeoviscous adaptation (HVA),[3] we have recently been able to systematically prepare ILs that exhibit very low T_m values while still incorporating very long alkyl appendages.[4] At the heart of our success in this endeavor was the use of geometrically *cis* olefin modules integrated into the long aliphatic side chains of our IL cations, a change which disrupts side-chain packing and leads to lower values of T_m compared to otherwise identical counterparts with linear, saturated side chains.

Unfortunately, for certain applications (especially those in which an IL might be employed at somewhat higher temperatures in the presence of air) a double bond could prove to be an Achilles' Heel, rendering the salt susceptible to slow oxidative degradation (akin to the process of fat rancidification). Consequently, we embarked on a program of preparing other types of lipid-inspired ILs, ones in which the packing-disruptive module in the long alkyl appendage is something other than an olefinic moiety.

Among the lipid structural features found in nature that, like olefins, tend to depress T_m values (relative to saturated, linear counterparts) are *cisoid* cyclopropyl moieties.[5] Such moieties occur most commonly in lipids of non-mammalian sources that range from microorganisms to fruiting plants, the seed oils of which may—like those of *Litchi chinensis*, for example—contain relatively large amounts of cyclopropanated components.[5]

The biosynthesis of cyclopropanated fatty acids involves the net addition of a methylene (CH_2) fragment to the double bond of a pre-existing unsaturated fatty acid by way of *S*-adenosylmethionine.[5] Such addition to the double bond of the most prevalent natural unsaturated fatty acid—oleic acid—gives rise to dihydrosterculic acid, a derivative in which the oleyl *cis* double bond between chain carbon atoms 9 and 10 has been (stereospecifically) *cis* cyclopropanated.[5]

* Corresponding author. Tel.: +1 251 460 7427; fax: +1 251 460 7359.
E-mail addresses: jdavis@southalabama.edu, jdavis@jaguar1.usouthal.edu (J.H. Davis).
† Current address: Department of Chemistry and Mathematics, Florida Gulf Coast University, Fort Myers, FL 33965, USA.
‡ NSF-REU summer student from SUNY Buffalo.

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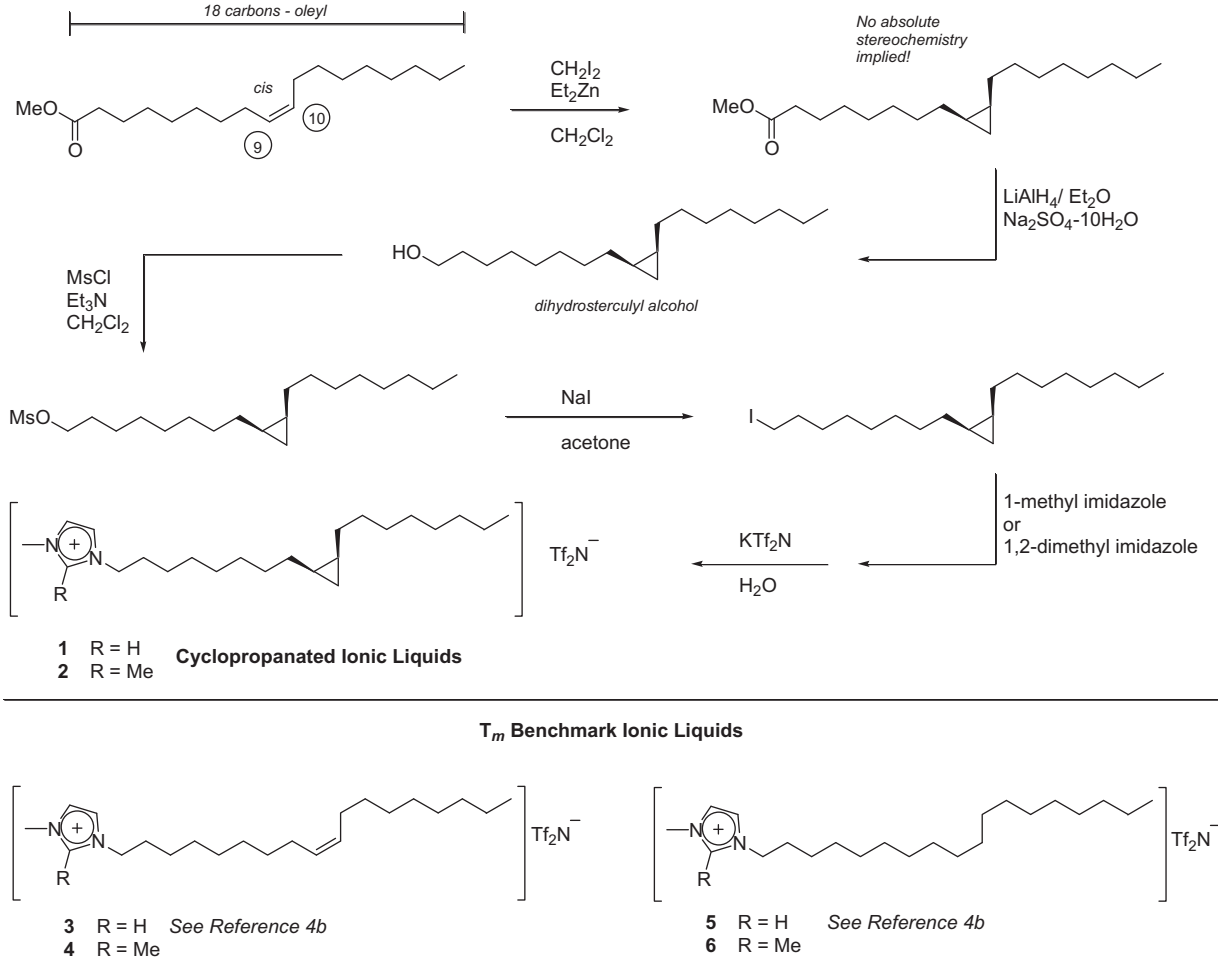
Since our overarching interests center on the development of ionic liquids for use in practical applications, it seemed fitting that we should focus the present investigation of the T_m depressing effect of cyclopropanation on lipid-inspired ionic liquids on species most likely to be readily accessible in the event further development was warranted. So, we decided to explore the synthesis and properties of lipidic ILs bearing aliphatic appendages akin to the dihydrosterculyl fragment. However, since isolated cyclopropanated fatty acids and their derivatives are not currently available commercially (despite their relative abundance in some natural sources), it was necessary to make the cyclopropanated appendage for the present ILs.

The synthesis of the requisite dihydrosterculyl appendage for the target cyclopropanated ILs was a multi-step endeavor. Beginning from high-purity methyl oleate (Nu-Chek Prep, >98%), dihydrosterculyl alcohol was prepared in high yield using known reactions combined into a two-step protocol.[6] Next, the alcohol was quickly, easily, and quantitatively (^{1}H NMR) converted into the corresponding mesylate. It, in turn, was quantitatively (^{1}H NMR) converted into iodide using the Finkelstein reaction. It is important to note here that since the next step in the preparation of the targeted ILs is the quaternization of the requisite *N*-alkyl imidazoles with the dihydrosterculyl precursor, one would anticipate that this should be easily (perhaps better) done with the mesylate rather than the iodide. However, our past experience has been that the mesylates of fatty alcohols are actually rather poor alkylators of nitrogen compared to their iodide counterparts.[4b]

Once the dihydrosterculyl iodide was in hand, quaternization of 1-Me imidazole and 1,2-dimethylimidazole was accomplished over a period of 48 h at 50 °C in acetonitrile. Having verified for each imidazole the completion of its coupling to the lipidic appendage, the crude iodide salts were dissolved in two-phase water–CH_2Cl_2 systems, to which were then added 20% molar excesses of $KNTf_2N$ [potassium bis(trifluoromethanesulfonyl)imide]. After stirring for 24 h, the lower (CH_2Cl_2) phase of each reaction was removed, dried over anhydrous $MgSO_4$, and the final products (**1** and **2**) were isolated by filtration followed by the removal of the solvent in vacuo. Using the same overall synthetic scheme, new ILs **4** and **6** were also prepared in order to provide baseline standards against which the T_m-lowering efficacy of the cyclopropyl group in **2** might be gauged. The overall synthetic approach (as exemplified for **1** and **2**) is depicted in Scheme 1, as are the structures of all four (**1**, **2**, **4**, and **6**) new ILs.

As is apparent from the data in Table 1, inclusion of cyclopropyl moieties in the C_{18} side chain of imidazolium-type lipidic ionic liquids—for example, **1** and **2**—results in sharp decreases in their melting points relative to benchmark ILs **5** and **6**, with their linear saturated side-chains. Here again, as in our earlier studies,[4] a strategy employed by nature to modulate T_m in lipidic materials proves to have a parallel effect when applied within an ionic liquid context.

The T_m values reported in Table 1 were determined by differential scanning calorimetry, DSC. Like most lipid-like materials, the new ILs exhibited rich phase behavior below their T_m (the reported T_m values being those of the highest temperature phase changes



Scheme 1. Synthesis of cyclopropanated ILs **1** and **2**, and structures of T_m benchmark ILs **3**–**6**.

Table 1
Relationships between structure and T_m in ILs **1**–**6** (see Scheme 1 for IL structures)

IL	Substituent at imidazolium ring C(2) position	Specialized lipid side-chain feature	IL Melting point (°C)
1	H	Cyclopropyl	−8.6(±0.5)
2	Me	Cyclopropyl	18.0(±1.0)
3	H	*cis*-Alkenyl	−20.9(±1.0)[4b]
4	Me	*cis*-Alkenyl	16.0(±1.0)
5	H	None	53.5(±1.0)[4b]
6	Me	None	70.0(±1.0)

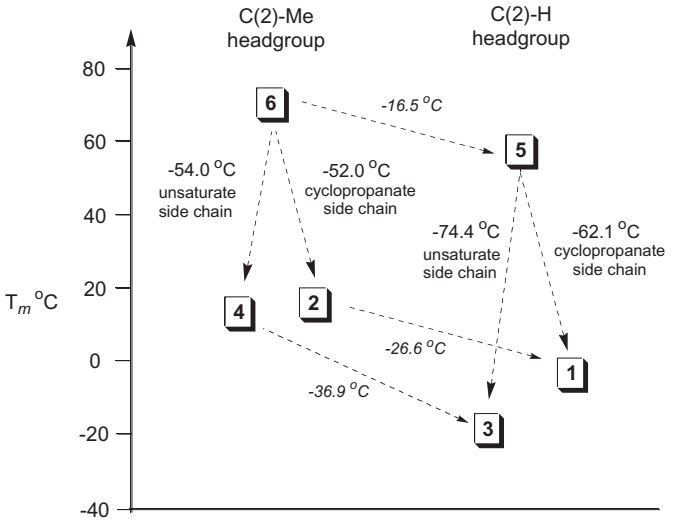


Figure 1. Relationships between IL head group and side chain structures and T_m. Italicized values indicate ΔT_m relationships between ILs with like side chains but having C(2)–H versus C(2)–Me head groups.

exhibited by the materials, the products of which are in a liquid state).

Significantly, the overall depressions in T_m brought about by the inclusion of a cyclopropyl moiety in the IL cation side chain (62.1 °C in **1** vs. **5**, and 52.0 °C in **2** vs. **6**) are substantial regardless of whether the latter is H- or CH_3-bearing at the imidazolium C(2) position (see Fig. 1). However, in the ILs with C(2)–H imidazolium head groups, the *absolute* decrease in T_m (62.1 °C) is about 83% of that brought about by unsaturation. In contrast, in the IL series with C(2)-Me imidazolium head groups, the absolute magnitude of the ΔT_m induced by cyclopropanation (52.0 °C) is only about 66% of that which it delivers in the C(2)–H case. Even so, the comparative *efficiency* of cyclopropanation versus unsaturation within the C(2)–Me IL series is 96% [(T_m depression by cyclopropanation vs saturated benchmark IL/T_m depression by olefination vs saturated benchmark IL) × 100] of that brought about by unsaturation.

Interestingly, the data in Table 1 point up another important relationship as well—the *synergistic* impact upon T_m of the cation side-chain and head-group structures. Note that the ΔT_m of the saturated benchmark ILs **5** and **6** is 16.5 °C—the C(2)–Me species having the higher T_m of the two. However, when the T_m values of the two cyclopropanated ILs (**1** and **2**) are compared, the head-group effect jumps to 26.6 °C. Then, when the arguably 'best' T_m-depressing structural element—unsaturation—is introduced into the side chains, the head group effect increases yet again, to 36.9 °C, more than double its magnitude in the case of saturated side-chain ILs **5** and **6**. Taken together with similar observations we recently made with an entirely different category of lipidic ILs, a strong case is emerging for an argument that it may become possible in the relatively near term to design lipidic ILs to manifest T_m values in relatively narrow ranges.[4a]

In sum, the present data show a clear capacity on the part of side-chain included cyclopropyl groups to bring about depressions in the T_m values of lipidic ILs. Furthermore, the magnitude of these changes is substantial even when compared to those wrought by chain-included olefins, and they are achieved with (presumably) less sensitivity toward oxidative degradation.[7] However, the overall utility of side-chain cyclopropanation as a strategy for T_m depression in lipidic ILs must take into account the need (at present) for the multi-step synthesis of these side chains, a sequence that employs some relatively expensive and hazardous reagents (Et_2Zn, $LiAlH_4$). Accordingly, until naturally-derived cyclopropanated lipid starting materials become commercially available, it seems prudent to seek more readily accessed compliments to olefin groups as IL T_m depressors, an endeavor in which we are already engaged.

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7. It should be borne in mind that cyclopropyl groups bring with them their own chemical sensitivities, such as ring-opening by Lewis acids.