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Design and synthesis of a novel imidazolium-based ionic liquid with planar chirality

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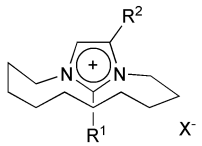
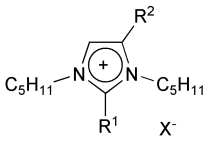
As the first example of a planar chiral ionic liquid, a cyclophane-type imidazolium salt was synthesized; its potential use in chiral recognition was demonstrated by ^{1}H NMR studies.

Ionic liquids are promising candidates as recyclable reaction media for organic synthesis, because of their unique properties, such as involatility, incombustibility, and dissolvability of many kinds of polar molecules.[1,2] Among them, chiral ionic liquids are quite attractive for their potential application to chiral discrimination, including asymmetric synthesis and optical resolution of racemates. However, very few chiral ionic liquids have been reported so far,[3–5] only one of which has achieved a successful result in chiral discrimination.[5] In addition, some of these chiral ionic liquids possess highly reactive functional group(s), which limit their application. Herein, we propose a novel class of chiral ionic liquids, *imidazolium salts with cyclophane-type planar chirality*,[6] which realize both chemical stability and well-defined three-dimensionally dissymmetric structure.



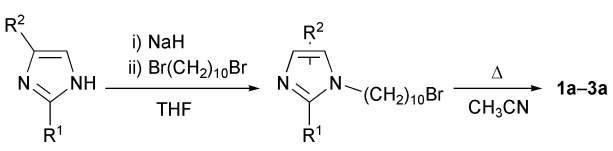
1: $R^1 = R^2 = H$
2: R^1 = Me, $R^2 = H$
3: $R^1 = R^2$ = Me



4: $R^1 = R^2 = H$
5: $R^1 = R^2$ = Me

a: $X^- = Br^-$
b: $X^- = (CF_3SO_2)_2N^-$
c: $X^- = (C_2F_5SO_2)_2N^-$
d: X^- = (1*S*)-(+)-10-camphorsulfonate

As a preliminary study of cyclophane-type imidazolium salts,[7] we synthesized achiral **1** and **2** (Scheme 1).† Imidazole and 2-methylimidazole were converted into the corresponding 1-(10-bromodecyl)imidazoles upon treating them with sodium hydride and 1,10-dibromodecane. Highly diluted solutions of the 1-(10-bromodecyl)imidazoles in acetonitrile were refluxed for 8–10 d to give mixtures of the corresponding monomeric salts and undesired oligomeric salts, respectively; the monomeric salts **1a** and **2a** were isolated by column chromatography (~40% yield, 2 steps). The efficiency and selectivity of the cyclization reaction depended considerably on the length of the alkyl chain. For example, the cyclization of analogous compounds, derived from 1,9-dibromononane or 1,8-dibromooctane, required a longer reaction time and proceeded with a lower selectivity (20–27 d, < 19% yield for 2 steps). The phenomenon is very similar to those observed for the synthesis of the usual cyclophanes. Thus obtained bromide salts **1a** and **2a** were converted into the bis(trifluoromethanesulfonyl)imide salts **1b** and **2b** in almost quantitative yields upon ion-exchanging with the use of lithium bis(trifluoromethanesulfonyl)imide.[8]



Scheme 1 Synthesis of cyclophane-type imidazolium salts.

The effect of such a cyclic structure on the melting point was examined by DSC. The cyclophane-type imidazolium salts **1b** and **2b** having bis(trifluoromethanesulfonyl)imide as the counteranion were shown to have melting points at 86 and 98 °C respectively, whereas an acyclic analogue of **1b**, 1,3-dipentylimidazolium bis(trifluoromethanesulfonyl)imide (**4b**), was shown to have a melting point at a temperature lower than room temperature (around −30 °C), as was observed for common dialkylimidazolium bis(trifluoromethanesulfonyl)imides.[8] These results indicate that cyclic imidazoliums are less favorable from the viewpoint of the melting point, although these examples might provide a clue to elucidation of the relationship between the structure of imidazolium and melting point.

The structural profiles of the cyclophane-type imidazolium salts **1a** and **2a** were investigated by ^{1}H NMR in $CDCl_3$. Noteworthy is that the signals of two sets of methylene protons were significantly upfield-shifted ($\Delta\delta \sim 1$ ppm). This phenomenon indicates that the alkyl chain overlays the imidazolium ring to be affected by a shielding effect. The fact that the shift of these aliphatic protons was independent of the concentration suggests that this ring current effect is likely operated in an intramolecular manner.

In order to investigate the dynamic profiles of the bridging alkyl chain, variable-temperature ^{1}H NMR measurements were carried out. In the case of **1a** having no substituent at the C(2) of the imidazolium ring, the methylene protons adjacent to the imidazolium nitrogens gave a triplet signal at 20 °C. Thus, the rope-skipping of the alkyl chain of **1a** seems to be so fast that the geminal protons were not discriminated from each other in an NMR time scale at this temperature. In contrast, the signal of the corresponding methylene protons of **2a**, in which a methyl group was introduced at the C(2) of the imidazolium ring, split into a multiplet, probably due to the unequivalence of the geminal protons. These observations clearly demonstrate that the rope-skipping of the bridging alkyl chain is significantly suppressed by the steric effect of the C(2) substituent. As a stopper at the C(2), a methyl group is so efficient that similar split signals were observed even at temperatures up to 180 °C in DMSO-d_6.

On the basis of the results described above, we designed a chiral cyclophane-type imidazolium salt **3**, which possesses two methyl groups; the C(4) methyl group for the induction of planar chirality, and the C(2) methyl group for the suppression of a rope-skipping process, which would result in the racemization of planar-chiral cyclophanes. The dissymmetric imidazolium salt **3a** was synthesized in a similar manner to the synthesis of **1a** and **2a** (36% yield, 2 steps). The ^{1}H NMR profiles of **3a**, which were quite similar to those of **2a**, indicated that the

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oligomethylene bridge of **3a** covered one of the prochiral faces and hardly flipped up to 180 °C. The suppression of the rope-skipping of **3a**, which corresponds to the suppression of racemization, is largely advantageous for the practical use of the salts of **3** as chiral ionic liquids.

The introduction of a substituent at the C(4) of the imidazolium ring not only induced planar chirality of **3**, but also dramatically lowered the melting point; the imidazolium bis(trifluoromethanesulfonyl)imide **3b** showed an obviously low melting point at 42–45 °C, compared with those of the analogues **1b** and **2b** with high symmetry.‡ Such lowering in melting point is presumably due to the dissymmetric structure of **3**; the phenomenon is in good agreement with the empirical understanding that high symmetry of a cation is undesirable for achieving low melting point.[9] Our quest for a room temperature cyclophane-type ionic liquid was realized upon changing the counteranion of **3**. Among several salts having a different counteranion synthesized in the present study, the imidazolium bis(pentafluoroethanesulfonyl)imide **3c**[10] had a melting point lower than room temperature (−20 °C).‡ Thus, an imidazolium-based room temperature ionic liquid with planar chirality was synthesized for the first time.

As an initial study on the chiral recognition ability of the cyclophane-type ionic liquids **3**, we attempted to detect diastereomeric interaction between the cation part of **3** and chiral anions.[5] The ^{1}H NMR spectrum of a $CDCl_3$ solution of the diastereomeric mixture **3d**, which was generated *in situ* from silver(I) (1*S*)-(+)-10-camphorsulfonate[11] and racemic **3a**, presented a pair of doublet signals for the C(5)-H (Fig. 1a).§ Since the salts with achiral anions, such as **3a**, gave a doublet for the C(5)-H, the resultant split signals were likely to be assigned to the C(5)-H signals of both diastereomers. This assignment was confirmed by a control experiment using an acyclic analogue, 2,4-dimethyl-1,3-dipentylimidazolium (1*S*)-(+)-10-camphorsulfonate (**5d**), for which no splitting of the corresponding signal was observed (Fig. 1b).

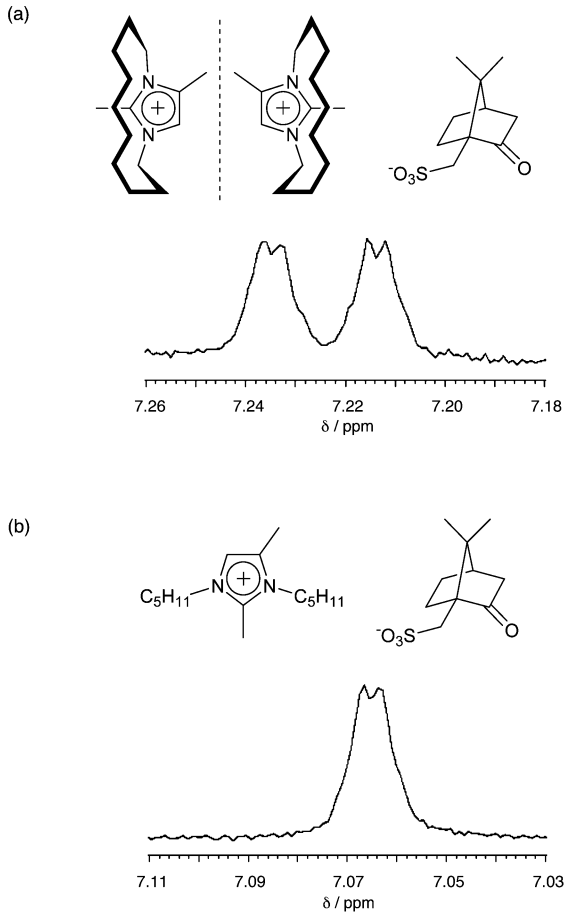

Fig. 1 The resonances for the imidazolium C(5)-H of (a) **3d** and (b) **5d** in $CDCl_3$ recorded on a Varian Mercury 300 (300 MHz) at 20 °C.

In conclusion, we have designed and synthesized a novel imidazolium-based ionic liquid with cyclophane-type planar chirality. The planar-chiral imidazolium cation formed diastereomeric salts with camphorsulfonate anion, which showed a potential of the ionic liquid as a chiral solvent for asymmetric synthesis and/or optical resolution. The preparation and application of optically active ionic liquids with planar chirality will be discussed in the near future.

We acknowledge Prof. Yutaka Ueda and Dr. Hiroshi Kageyama (Institute of Solid State Physics, The University of Tokyo) for the use of DSC equipment.

Notes and references

† A representative procedure for the preparation of cyclophane-type imidazolium salts. Synthesis of **3a**: To a solution of 2,4-dimethylimidazole (743 mg, 7.7 mmol) in dry THF (25 ml) under nitrogen atmosphere was added 360 mg (9.0 mmol) of 60% sodium hydride with a mineral oil. The mixture was stirred for 2 h, and then 1,10-dibromodecane (6.75 g, 22.5 mmol) was added to the mixture. The reaction mixture was stirred overnight at room temperature. The solid that appeared was filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, chloroform–methanol) to afford a mixture of 1-(10-bromodecyl)-2,4-dimethylimidazole and 1-(10-bromodecyl)-2,5-dimethylimidazole (1.32 g, 4.2 mmol, 54%) as a colourless oil. The oil was dissolved in acetonitrile (3 L) and refluxed for 10 d. After being cooled to room temperature, the reaction mixture was concentrated and successively subjected to column chromatography (silica gel deactivated with 10% of water, chloroform–methanol) and reversed-phase column chromatography (Waters, Sep-Pak® Vac tC18) to give **3a** as a white solid (866 mg, 2.8 mmol, 66%). ^{1}H NMR ($CDCl_3$, 20 °C): δ = 0.34–0.70 (m, 2H), 1.02–1.28 (m, 8H), 1.42–1.62 (m, 2H), 1.62–1.84 (m, 2H), 1.98–2.15 (m, 2H), 2.40 (d, 3H, J = 1 Hz), 2.98 (s, 3H), 4.12–4.51 (m, 4H), 7.44 (d, 1H, J = 1 Hz); FAB-MS: Calcd. for $C_{15}H_{27}N_2$ $[M]^+$ = 235, Found 235.

‡ Elemental analyses. **3b**: Calcd. for $C_{17}H_{27}F_6N_3O_4S_2$: C, 39.61; H, 5.28; N, 8.15%. Found: C, 39.55; H, 5.14; N, 8.17%. **3c**: Calcd. for $C_{19}H_{27}F_{10}N_3O_4S_2$: C, 37.07; H, 4.42; N, 6.83%. Found: C, 37.03; H, 4.49; N, 6.71%.

§ A representative procedure for the preparation of ^{1}H NMR samples of imidazolium (1*S*)-(+)-10-camphorsulfonates. To a $CDCl_3$ solution (500 μL) of **3a** (3.2 mg, 0.01 mmol) in a NMR sample tube was added silver(I) (1*S*)-(+)-10-camphorsulfonate[11] (3.4 mg, 0.01 mmol). The sample tube was shaken continually for 1 h, and the spectrum was recorded.

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