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Synthesis and properties of a diastereopure ionic liquid with planar chirality

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Abstract—An imidazolium-based ionic liquid with cyclophane-type planar chirality was synthesized in an optically pure form for the first time. The resultant ionic liquid existed as a liquid at room temperature ($T_g = -35$ °C), and was found to be applicable as an NMR chiral shift reagent for racemic anions. Excellent robustness of the ionic liquid to a highly elevated temperature (270 °C) was proved from the viewpoints of isomerization and thermal decomposition.
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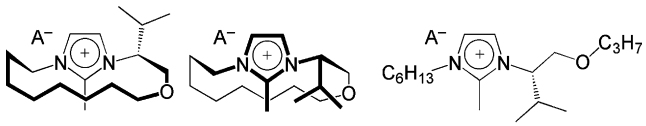
Owing to their unique chemical and physical properties, ionic liquids have recently attracted considerable attentions as replacements of traditional volatile organic solvents.[1] Among them, optically active ionic liquids are of special interest, because they would provide a simple entry to explore the potential application of optically active solvents.[2] In fact, several optically active ionic liquids have been reported in these four years.[3] At the present time, however, only a few types of optically active ionic liquids have been known to exhibit a chiral recognition ability; (i) ammonium salts derived from (−)-ephedrine[3a,e,g,h] and α-pinene,[3c] (ii) azolinium salts derived from (*R*)-2-amino-1-butanol[3b] and (*S*)-valinol,[3d] (iii) imidazolium salts with a chiral N-substituent derived from (+)-tartarate,[3f] (−)-camphorsulfonate,[3i] and (*S*)-proline,[3j] and (iv) a salt of borate anions derived from (−)-malic acid.[3k] In most of these reported examples, an interactive moiety such as a hydroxy group and/or a conformationally restricted, optically active nonaromatic azolinium ring seems to play an important role for the chiral recognition processes. However, the chemical stability of these key units is uncertain, due to the possibilities of the β-elimination of the hydroxy group,[3g] the Hoffmann elimination at the quaternary ammonium moiety, and the hydrolysis of the nonaromatic azolinium ring. In addition, their physical properties as ionic liquids, such as the melting point, hydrophobicity, viscosity, and miscibility with organic solvents, are unpredictable, because peculiar species are used as the cationic unit of these ionic liquids. Therefore, for the development of ideal optically active ionic liquids possessing a chiral recognition ability and a chemical stability at the same, a conceptually novel approach is required.[4]



(S_p,*S*)-**1**-A (R_p,*S*)-**1**-A (*S*)-**5**-TSAC

1-Cl: $A^- = Cl^-$
1-PF_6: $A^- = PF_6^-$
1-TFSI: $A^- = (CF_3SO_2)_2N^-$
1-TSAC: $A^- = (CF_3SO_2)(CF_3CO)N^-$

$A^- = (CF_3SO_2)(CF_3CO)N^-$

Recently, we have reported a simple and reliable method for the synthesis of chiral ionic liquids based on cyclophane-type imidazolium salts with planar chirality.[4a,d,f] The planar-chiral imidazolium salts could be easily prepared by connecting the two nitrogens of 2,4-dimethylimidazole with an oligomethylene or oligo(oxyethylene) chain. Their chemical stability was quite promising, because the cationic parts of these ionic liquids were regarded as imidazoliums with simple alkyl and/or alkoxyalkyl substituents.[1] Furthermore, a well-defined three-dimensionally dissymmetric structure was constructed without resorting to a polar/rigid

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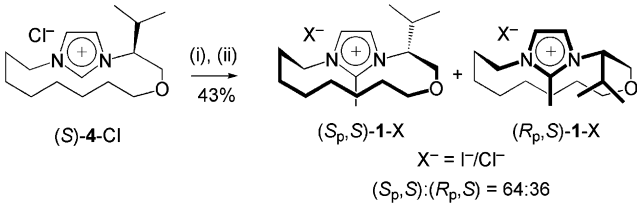
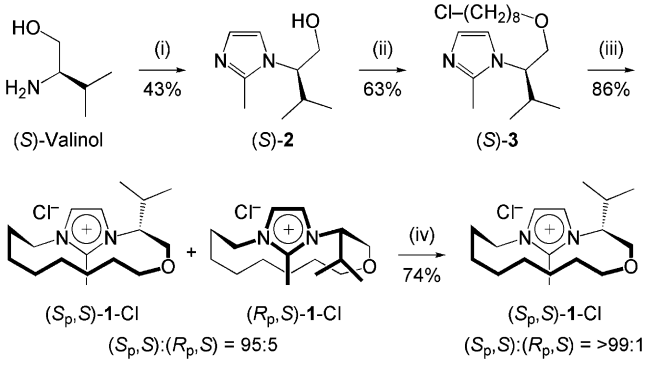
substituent nor nonaromatic azolium skeleton. As a result, the ionic liquids based on this concept realized low melting point, chemical stability, and chiral recognition ability at the same time. Despite such attractive characteristics, this approach has a serious problem in the availability of optically active materials, because the enantioseparation of such racemic quaternized salts is not easy in general. In addition, any general method for the stereocontrolled synthesis of planar-chiral compounds has not been established to date. In order to evolve our ongoing program in this field to the next stage, the preparation of non-racemic salt is indispensable; we decided to attempt the stereocontrolled synthesis of planar-chiral imidazolium cyclophanes by the aid of a stereogenic carbon center placed on the bridge unit (Scheme 1). Here we report the first synthesis of a planar-chiral ionic liquid in *a stereopure form* and its successful application to the chiral recognition of racemic anions.

The cyclophane-type imidazolium salt **1**-Cl was synthesized as follows (Scheme 1): According to the synthetic procedure, which we have recently reported,[5] with some modifications, the enantiopure imidazole (*S*)-**2** with a chiral N-substituent was prepared in one step from (*S*)-valinol. The imidazole (*S*)-**2** was then coupled with 1,8-dichlorooctane by applying the general procedure for an aliphatic ether formation to afford ether (*S*)-**3**. Finally, the intramolecular quaternization of (*S*)-**3** was carried out upon heating a solution of (*S*)-**3** in *N*,*N*-dimethylacetamide. When the reaction was conducted at 150 °C, the quaternization proceeded smoothly to afford two kinds of imidazolium salts in 82% and 4% yields. The yields of the two imidazolium salts were not influenced by the initial concentration of (*S*)-**3** from 1 to 100 mM, which strongly suggests that the intramolecular quaternization reaction is overwhelmingly faster than the intermolecular quaternization reaction. The two cyclic imidazolium salts were most likely to be the diastereoisomers (S_p,*S*)-**1**-Cl and (R_p,*S*)-**1**-Cl, because the products are expected to possess planar chirality which arose from the prochiral imidazolium plane and the point chirality of the stereogenic center at their C(1′) position. In order to confirm this assumption, an authentic mixture of (S_p,*S*)- and (R_p,*S*)-**1**-X (the counter anion $X^- = Cl^-/I^-$) was prepared by the methylation of the C(2) position of the N,N′-bridged (*S*)-**4** with CH_3I, as shown in Scheme 2.[6,7] A small amount of the authentic sample prepared by the methylation of (*S*)-**4** was added to **1**-Cl obtained by the intramolecular quaternization of (*S*)-**3**, and the ^1H NMR spectrum of the resultant mixture was measured. Because the ^1H NMR spectrum suggested that only two kinds of imidazolium cation were incorporated in the mixture, it was unequivocally concluded that they were the diastereoisomers (S_p,*S*)- and (R_p,*S*)-**1**. Worth noting is the unexpectedly high diastereoselectivity (d.r. = 95:5), which enabled the isolation of the target material in a diastereopure form in satisfactory yield;[8,9] the major isomer was easily purified by recrystallization from CH_2Cl_2/AcOEt.[10]

In order to determine the stereochemistry of the major isomer, an X-ray crystallographic analysis was carried out. Because the major isomer of **1**-Cl was too hygroscopic, the anionic part of this salt was exchanged from chloride to hexafluorophosphate to give a single crystal suitable for an X-ray analysis. With respect to the absolute configuration of the stereogenic center at the C(1′) position, the absolute configuration of the planar chirality in the major product was deduced to be *S* (Fig. 1). Upon comparing the molecular structure of (S_p,*S*)-**1** thus obtained with that of (R_p,*S*)-**1** estimated on the basis of molecular modeling, the highly diastereoselective formation of the (S_p,*S*) isomer through the intramolecular quaternization of (*S*)-**3** could be clearly elucidated as follows: In the case of the minor product (R_p,*S*)-**1**, the



Scheme 2. Preparation of an authentic mixture of (S_p,*S*)- and (R_p,S)-**1**-X ($X^- = Cl^-/I^-$). Reagents and conditions: (i) *n*-BuLi (1.2 equiv), CH_3I (1.6 equiv), CH_2Cl_2, −78 °C then rt; (ii) silica gel column chromatography.



Scheme 1. Synthesis of the planar-chiral imidazolium salt **1**-Cl. Reagents and conditions: (i) CH_3CHO (5.0 equiv), glyoxal (1.0 equiv), NH_4OAc (1.0 equiv), MeOH, rt; (ii) NaH (1.2 equiv), 1,8-dichlorooctane (3.0 equiv), DMF, 0 °C then 50 °C; (iii) DMAc, 150 °C; (iv) recrystallization from CH_2Cl_2/AcOEt.

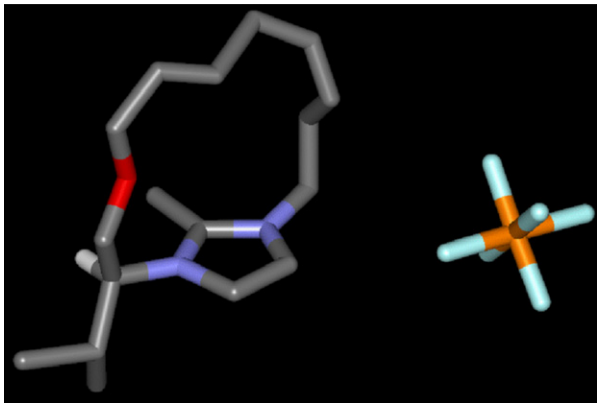


Figure 1. Crystal structure of (S_p,*S*)-**1**-PF_6. Hydrogen atoms except for C(1′)H were omitted for clarity.

methyl group at the C(2) position in the imidazolium ring and the isopropyl group at the C(1′) position in the bridge should be arranged quite near to each other to cause extremely large steric hindrance. As a result, the formation of (R_p,S)-**1** was likely to be disadvantageous, compared with that of (S_p,S)-**1** in kinetic and thermodynamic viewpoints.[9]

In the next stage, we attempted to lower the melting point by exchanging the counter anion of the salt of (S_p,S)-**1** from chloride to imide anions, bis(trifluoromethylsulfonyl)imide (TFSI) and 2,2,2-trifluoro-*N*-(trifluoromethylsulfonyl)acetamide (TSAC), which are widely used for the studies on ionic liquids.[11] For the anion exchange, the standard anion metathesis method was applied to give the corresponding imide salts in high yields (86% and 95%, respectively) with sufficient purity.[10] Although the melting point of (S_p,S)-**1**-TFSI was not satisfactorily low (melting point: 53 °C), (S_p,S)-**1**-TSAC existed as a liquid at room temperature (glass-transition point: −35 °C). The exceptionally low melting point of (S_p,S)-**1**-TSAC was most likely owing to the dissymmetric structure of the anionic part. Thus, a planar-chiral room temperature ionic liquid, (S_p,S)-**1**-TSAC, was synthesized in an optically pure form for the first time.

As can be seen from the crystal structure of (S_p,S)-**1**-PF_6, the cationic part of the planar-chiral ionic liquid (S_p,S)-**1**-TSAC takes a well-defined dissymmetric structure, which prompted us to evaluate its chiral recognition ability. We attempted to detect the diastereomeric interaction between the imidazoium cation with racemic anions by using NMR spectroscopy. As we expected, the imidazolium cation (S_p,S)-**1** could recognize the chirality of the anion of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA): The ^{19}F NMR spectrum of a mixture of the potassium salt of racemic MTPA, (S_p,S)-**1**-TSAC (3.0 equiv), and 18-crown-6 (1.0 equiv) in $CDCl_3$ was measured. Interestingly, the signal attributable to the CF_3 group in MTPA was observed as two partially resolved peaks (Fig. 2a). In addition, the two peaks observed at higher and lower fields were assigned to be the CF_3 signals of (*S*)- and (*R*)-MTPA, respectively, by using the salt of (*S*)-enriched MTPA (Fig. 2b). Therefore, it is concluded that such a split undoubtedly arose from the difference in diastereomeric interaction between the imidazolium cation (S_p,S)-**1** and the enantiomers of MTPA anion. Furthermore, the imidazolium cation (S_p,S)-**1** could also recognize the P-chirality of *O*-ethyl phenylphosphonothioate (OEPT) anion,[12] which was clearly demonstrated by ^{31}P NMR spectroscopy (Fig. 2d and e). Worth noting is the fact that such a diastereomeric interaction was not observed at all, when the acyclic analog (*S*)-**5** was used in the place of (S_p,S)-**1** (Fig. 2c and f). It means that the diastereomeric interaction between (S_p,S)-**1** and the chiral anions most likely arose from the conformationally restricted cyclic structure rather than the asymmetric carbon in the imidazolium cation (S_p,S)-**1**.

Thus, the planar-chiral ionic liquid (S_p,S)-**1**-TSAC meets the criteria required for the chiral solvents; synthetic availability, low melting point, and chiral recognition ability. Despite the cationic part of (S_p,S)-**1**-TSAC consisting of only a robust imidazolium ring, alkyl ether, and alkyl units, this ionic liquid showed a chiral recognition ability comparable to the precedent successful examples. An anxiety about the structural instability of (S_p,S)-**1**-TSAC is the isomerization by the rope skipping of the bridge through the imidazolium ring to transform it into the (R_p,S) form.[13] Therefore, we examined the thermal stability of (S_p,S)-**1**-TSAC by monitoring the degree of isomerization and decomposition at elevated temperatures. For example, the heating of (S_p,S)-**1**-TSAC at 160 °C for 6 h caused neither isomerization nor decomposition at a level detectable by ^1H and ^{19}F NMR spectroscopies. Moreover, even when the temperature was elevated to 270 °C, the good thermal stability was again retained because the formation of any other species was not observed, while the isomerization partially proceeded to give a mixture of (S_p,S)- and (R_p,S)-**1**-TSAC. Although the undesired isomerization took place at such an elevated temperature, worth noting is the fact that the diastereomeric ratio was still satisfactorily maintained at a high level; the diastereomeric ratio only decreased from >99:1 to 93:7 after 1 h, and the same ratio was kept during the additional heating for 5 h. Under such conditions, the isomerization reaction undoubtedly reached to an equilibrium state of a diastereomeric ratio of 93:7, because the ratio was not changed even when the starting material with a lower diastereomeric ratio ((S_p,S):(R_p,S) = 82:18) was used. From these observations, (S_p,S)-**1**-TSAC is

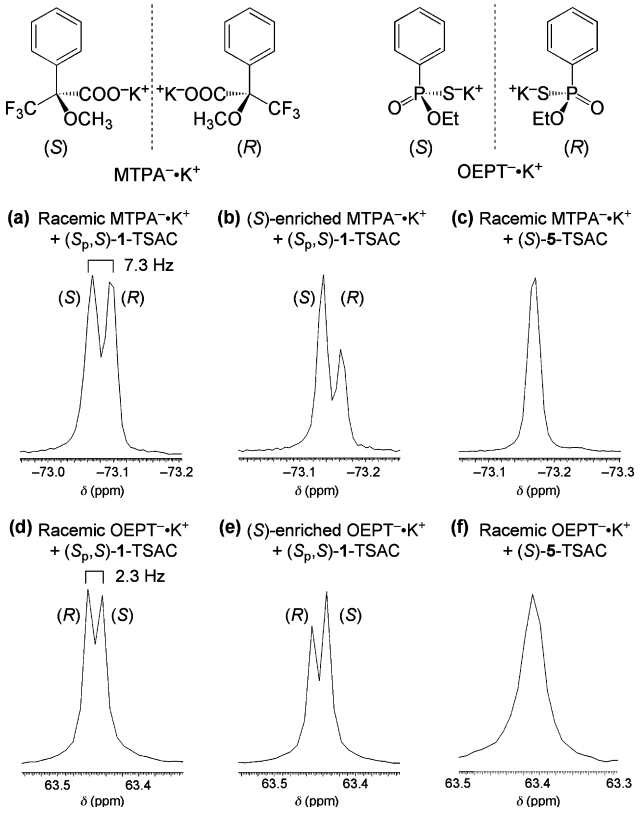


Figure 2. Enantio-differenciating solvation of the potassium salts of racemic acids with (S_p,S)-**1**-TSAC.

concluded to be stable at 160 °C, whereas the planar chirality of **1**-TSAC is kinetically unstable at 270 °C. However, even at an equilibrium state, **1**-TSAC preferentially took an *S* configuration in terms of its planar chirality; the net directional rope skipping occurred owing to the large differences in thermodynamic stability between the (S_p,*S*)- and (R_p,*S*)-isomers, which was calculated to be 2.8 kcal mol^{-1}. In other words, the ionic liquid **1**-TSAC can be used as an optically active medium possessing planar chirality up to an extremely high temperature.[14]

In conclusion, we succeeded in the first synthesis of a planar-chiral room-temperature ionic liquid in an optically pure form by using the diastereoselective intramoleculer quaternization of the precursor imidazole (*S*)-**3** as a key reaction. The planar chirality of this ionic liquid was preserved even at 270 °C, which would allow us to apply it to a wide range of practical uses. Application of this ionic liquid as a chiral stationary phase of gas chromatographies currently being conducted in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.101.

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