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Chiral Ionic Liquids as Stationary Phases in Gas Chromatography

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Recently, it has been found that room-temperature ionic liquids can be used as stable, unusual selectivity stationary phases. They show "dual nature" properties, in that they separate nonpolar compounds as if they are nonpolar stationary phases and separate polar compounds as if they are polar stationary phases. Extending ionic liquids to the realm of chiral separations can be done in two ways: (1) a chiral selector can be dissolved in an achiral ionic liquid, or (2) the ionic liquid itself can be chiral. There is a single precedent for the first approach, but nothing has been reported for the second approach. In this work, we present the first enantiomeric separations using chiral ionic liquid stationary phases in gas chromatography. Compounds that have been separated using these ionic liquid chiral selectors include alcohols, diols, sulfoxides, epoxides, and acetylated amines. Because of the synthetic nature of these chiral selectors, the configuration of the stereogenic center can be controlled and altered for mechanistic studies and reversing enantiomeric retention.

Room-temperature ionic liquids (RTILs) are low-melting (<100 °C) salts which represent a new class of nonmolecular, ionic solvents. These solvents possess a number of interesting properties, such as negligible vapor pressure, ease of preparation and reuse, and high thermal stability. In recent years, considerable attention has been focused on the use of RTILs as alternatives to classical organic solvents. There are many reports concerning the applications of ionic liquids (ILs) as excellent solvents for a number of organic reactions, such as Diels−Alder reactions,[1−4] Friedel−Crafts reaction,[5,6] isomerizations,[7] and hydrogenation.[8] Ionic liquids are among the most versatile and complex solvents in terms of their interaction/solvation parameters and abilities.[9] There also has been a great deal of interest in the application of the ionic liquids as novel biphasic catalysts,[10] extraction solvents,[11] highly selective transport membranes,[12] and stationary phases for gas chromatography.[13,14]

The first application of molten salts as gas chromatographic stationary phase was reported by Barber et al.[15] Since the early 1980s, Poole and co-workers have published a series of papers on using organic molten salts as GC stationary phases.[16−20] Although the initial alkylammonium- and alkylphosphonium-based molten salts had been used as GC stationary phases, they had limitations, such as relatively narrow liquid ranges, thermal instability, and poor wetability toward the surface of fused silica. Later-emerging ionic liquids containing alkylimidazolium or alkylpyridinium cations possessed improved properties (wider liquid range and better thermal stability) and were more suitable for GC stationary phases. Recently, we demonstrated that alkylimidazolium-based ILs can be used as stable, unusual selectivity stationary phases.[13,14] They show "dual nature" properties. They separate nonpolar compounds as if they are nonpolar stationary phases and separate polar compounds as if they are polar stationary phases. We also introduced the achiral ILs to the realm of chiral separations by dissolving the chiral selector (methylated cyclodextrins) in 1-butyl-3-methylimidazolium chloride and 1-butyl-3-methylimidazolium hexafluorophosphate ILs.[21]

Although there have been many publications on ionic liquids, only a few examples of chiral ILs have been reported so far. Howarth and co-workers described the use of chiral imidazolium cation in Diels−Alder reactions;[22] however, the synthesis of these

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systems required an expensive chiral alkylating agent. The use of ILs with chiral anions is somehow more obvious, since some of these are readily available as sodium salts. For example, Seddon et al. investigated Diels−Alder reactions in lactate-based ILs.[4] More recently, Wasserscheid and co-workers synthesized three different groups of chiral ionic liquids.[23] They observed the positive diasteriomeric interactions between racemic substrates and chiral ILs by NMR spectroscopy. Bao et al. reported the first synthesis of chiral imidazolium ILs derived from natural amino acids.[24] Recently, Thanh et al. designed an efficient method for the preparation of ephedrinium-based chiral ILs under microwave (MV) activation.[25] They also reported the use of these ILs as reaction media in the asymmetric Baylis−Hillman reaction between benzaldehyde and methyl acrylate.[26] The experimental results indicated that significant enantiomeric excesses were obtained for the first time. The application of chiral ILs as stationary phases in chromatography has not been reported to our knowledge.

In this work, we present the first direct enantiomeric separations of several different compounds using chiral IL stationary phases in gas chromatography. Some of the mechanistic studies involving enantioselective retention are also discussed.

EXPERIMENTAL SECTION

Materials. (1*S*,2*R*)-(+)-*N*-Methylephedrine, (1*R*,2*S*)-(−)-*N*-methylephedrine, (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine, dimethyl sulfate, dichloromethane, *N*-lithiotrifluoromethanesulfonimide, and all test solutes were purchased from Aldrich (Milwaukee, WI). Dimethyl sulfate is a toxic solution and must be handled with care. Untreated fused-silica capillary tubing (250-μm i.d.) coated with a brown polyimide layer was purchased from Supelco (Bellafonte, PA).

Methods. The synthesis of (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium-bis(trifluoromethanesulfon)imidate, (1*R*,2*S*)-(−)-dimethylephedrinium-bis(trifluoromethanesulfon)imidate, and (1*S*,2*S*)-(+)-*N*,*N*-dimethylpseudoephedrinium-bis(trifluoromethanesulfon)imidate are described elsewhere.[23] Briefly, *N*-methylephedrine was dissolved in dichloromethane, and an equimolar amount of dimethyl sulfate was added slowly. The solvent was removed under reduced pressure, and the residue was dissolved in water. Addition of an aqueous solution of equimolar *N*-lithiotrifluoromethanesulfonimide led to the separation of an ionic liquid phase, which then was washed three times with water. The final product was heated under reduced pressure at 100 °C to eliminate the remaining water. The purity of the product was verified by NMR and ESI-MS. ^{1}H NMR (300 MHz), DMSO-TMS: d = 1.16 (3H, d, J = 6.4 Hz), 3.22 (9H, s), 3.65 (1H, dq, J = 6.4 Hz, J = 6.8 Hz), 5.41 (1H, d, J = 6.8 Hz), 6.06 (1H, s), 7.19−7.31 (5H, m). The observed m/z peaks for the ILs in positive and negative ion modes were 194 and 280 Da, respectively.

All capillary columns were coated via the static method at 40 °C using a 0.25% (w/v) of the IL stationary phase dissolved in dichloromethane. Following the coating process, the columns were flushed with dry helium gas overnight and then conditioned from 40 to 120 °C at 1 °C /min. Column efficiency was tested by naphthalene at 100 °C. All columns had efficiencies over 2100 plates/m.

The racemic test compounds were dissolved in dichloromethane. A Hewlett-Packed model 6890 gas chromatograph and a Hewlett-Packard 6890 series integrator were used for all separations. Split injection and flame ionization detection were utilized with injection and detection temperatures of 250 °C. Helium was used as the carrier gas with a flow rate of 1.0 mL/min.

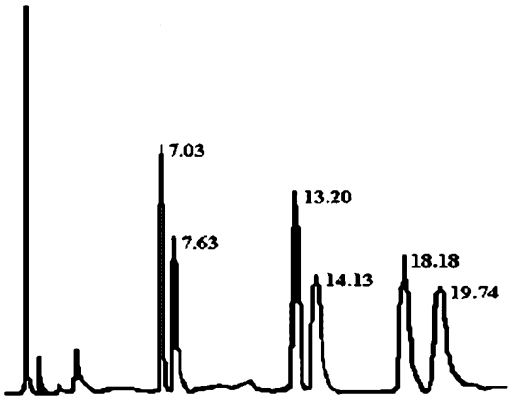

Figure 1. GC chromatogram showing the enantiomeric separation of (from left to right) *sec*-phenethyl alcohol, 1-phenyl-1-butanol, and *trans*-1,2-cyclohexanediol. Chromatographic conditions: column = 8m long × 250 μm (i.d.) fused-silica capillary coated with (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium-bis(trifluoromethanesulfon)imidate. Temp = 120 °C, He flow rate = 1.0 mL/min, split ratio = 100:1, FID.

RESULTS AND DISCUSSION

When used as a chiral stationary phase for gas chromatography, *N*,*N*-dimethylephedrinium-based ionic liquids show enantioselective retention for at least four general classes of compounds: (1) chiral alcohols (including diols), (2) chiral sulfoxides, (3) some chiral epoxides, and (4) acetylated amines. The separation data for several of these compounds is given in Table 1. A chromatogram showing the separation of chiral alcohols (and one diol) is shown in Figure 1.

Since the chiral ionic liquids in this study are synthetic in nature, it is possible to produce either enantiomer. This means that it should be possible to reverse the enantioselectivity and elution order of all enantiomeric compounds that separate on these chiral stationary phases. Furthermore, these chiral selectors have two stereogenic centers. Consequently, it is also possible to make diasteromeric versions of this ionic liquid. As will be shown (*vide infra*), this could have important consequences for mechanistic and chiral recognition studies. Three versions of a basic chiral ionic liquid in which only the stereochemistry differed were synthesized. They are (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium-bis-(trifluoromethanesulfon)imidate, (1*R*,2*S*)-(−)-*N*,*N*-dimethylephedrinium-bis(trifluoromethanesulfon)imidate, and (1*S*,2*S*)-(+)-*N*,*N*-dimethylpesudoephedrinium-bis(trifluoromethanesulfon)imidate. The structure of the first of these cations is shown in Figure 2. Typical analyte retention orders for these different isomeric ionic liquids are given in Table 2. As expected, the enantiomeric elution order is reversed for all analytes when they are chromatographed on the (1*S*,2*R*)- versus the (1*R*,2*S*)-*N*,*N*-dimethylephe-

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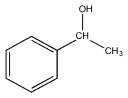
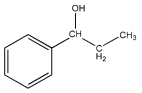
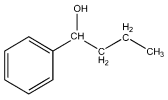
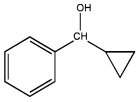
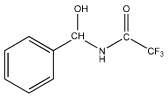
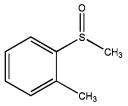
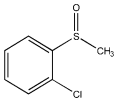
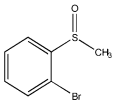
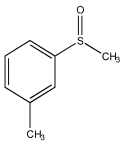
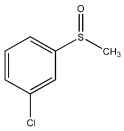
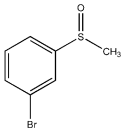
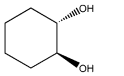
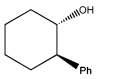
Table 1. Separation of 14 Compounds on (1*S*,2*R*)-(+)-*N*,*N*-Dimethylephedrinium-bis(trifluoromethanesulfon)imidate Column[a]

#	Compound	Structure	T(°C)	k_1	α
1	*sec*-Phenethyl alcohol		120	7.64	1.11
2	1-Phenyl-1-propanol		120	10.1	1.11
3	1-Phenyl-1-butanol		120	15.3	1.07
4	α-Cyclopropylbenzyl alcohol		100	37.4	1.03
5	α-Phenylethylamine (TFA derivative)		100	84.1	1.02
6	β-Pinene Oxide		100	12.3	1.03
7	*m*-Methylphenylmethyl sulfoxide		140	73.3	1.03
8	*m*-Chlorophenylmethyl sulfoxide		140	35.4	1.02
9	*m*-Bromophenylmethyl sulfoxide		140	59.2	1.02
10	*p*-Methylphenylmethyl sulfoxide		120	241	1.01
11	*p*-Chlorophenylmethyl sulfoxide		120	196	1.01
12	*p*-Bromophenylmethyl sulfoxide		120	374	1.01
13	*trans*-1,2- Cyclohexandiol		120	21.4	1.10
14	*trans*-2-Phenyl-1-cyclohexanol		100	100	1.02

[a] Column length, 8 m; flow rate, 1 mL/min.

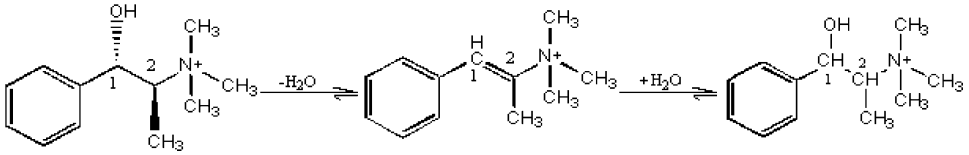


Figure 2. Structure of (1*S*,2*R*)−(+)-*N*,*N*-dimethylephedrinium ion, its achiral dehydration product, and racemic nature upon addition of water.

drinium-bis(trifluoromethanesulfon)imidate. Also interesting is the fact that the (1*S*,2*S*) ionic liquid chiral stationary phase (CSP) cannot separate the chiral alcohols, but does separate the chiral sulfoxides in the same manner as the (1*S*,2*R*) ionic liquid CSP. It appears that the separation of some chiral analytes is sensitive to the configuration of both stereogenic centers of the chiral selector, but the separation of other analytes is predominantly controlled by the configuration of one of the CSP's stereogenic centers.

It was observed that after several weeks of use, only at temperatures ≥140 °C, that the dimethylephedrinium-based chiral stationary phase lost enantioselectivity for certain compounds (e.g., the alcohols), but not for others (e.g., the chiral sulfoxides). As previously stated, the *N*,*N*-dimethylephedrinium cation contains two stereogenic centers (Figure 2). The dehydration reaction of Figure 2 produces the achiral conjugated alkene, which upon addition of water would produce the fully racemic product. To explore the thermal stability of the chiral ILs, (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium-bis(trifluoromethanesulfon)imidate was placed in a sealed vial at 140 °C for 4 days. Figure 3 shows the mass spectrum of the final product. The dehydration product was observed (m/z = 176 Da). The optical rotation of the chiral IL also changed from +21.2° to +6.6° upon heating under the aforementioned conditions. However, neither the alkene nor the racemic ionic liquid of Figure 2 would be expected to separate any enantiomeric analytes. Thus, it can be concluded either that complete racemization of the IL stationary phases does not occur under the GC conditions studied in these experiments or that a thermally induced epimerization of the chiral ionic liquids also can take place at temperatures ≥140 °C. These results and the data in Table 2 indicate that chiral recognition and enantiomeric separation of the sulfoxide analytes require a fixed configuration of the ionic liquid's first stereogenic center, but not the second. However, the enantioselective separation of chiral alcohols on this CSP requires not only that the stereochemistry of both stereogenic centers be fixed, but also that they have the opposite (*R*,*S* or *S*,*R*) absolute configuration. Thus, it appears that the stereochemically fixed hydroxyl group on these ionic liquid CSPs is necessary for the enantioseparation of all chiral compounds in Table 1, but is

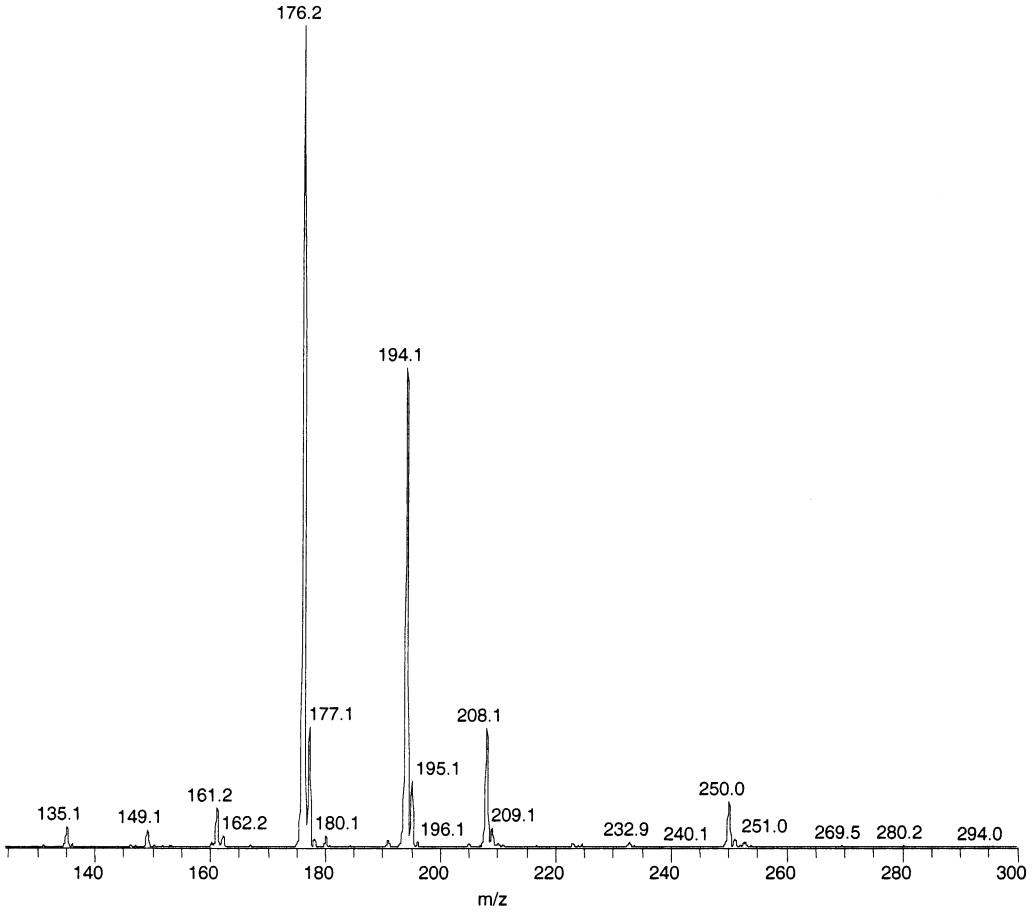
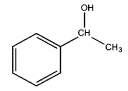
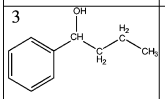
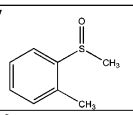
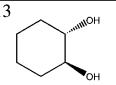


Figure 3. Mass spectrum of (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium bis(trifluoromethanesulfon)imidate IL after heating at 140 °C for 4 days. The *m*/*z* = 194 Da is the (1*S*,2*R*)-(+)-*N*,*N*-dimethylephedrinium ion, and the *m*/*z* = 176 Da is the dehydration product ion as shown in Figure 2.

Table 2. Elution Order for Selected Compounds on Different Chiral Ionic Liquid Stationary Phases

	(1*S*,2*R*)–(+)–*N*,*N*–dimethylephedrinium-bis(trifluoromethanesulfon)imidate	(1*R*,2*S*)–(-)–*N*,*N*–dimethylephedrinium-bis(trifluoromethanesulfon)imidate	(1*S*,2*S*)–(+)–*N*,*N*–dimethylephedrinium-bis(trifluoromethanesulfon)imidate
1 	(S), (R)	(R), (S)	Not separated
3 	(S), (R)	(R), (S)	Not separated
7 	(R), (S)	(S), (R)	(R), (S)
13 	(1R, 2S), (1S,2R)	(1S, 2R), (1R, 2S)	Not separated

not sufficient for the enantiomeric separation of the chiral alcohols, epoxide, and acetylated amine.

CONCLUSIONS

Chiral ionic liquids were shown for the first time to be effective chiral stationary phases in gas chromatography. The fact that they are synthetic allows one to produce CSPs of the opposite stereochemistry, which can reverse the enantiomeric elution order of all analytes that are separable. This cannot be done on a routine basis with the popular cyclodextrin-based GC−CSPs, since cyclodextrins are natural products, and their enantiomers do not exist. The *N*,*N*-dimethylephedrinium-based CSPs have two stereogenic centers, and their absolute configuration can be altered. In addition, racemic and diastereomeric versions of this CSP can be produced. By varying the stereochemistry of the chiral selector in a controlled fashion and examining its effect on enantioselectivity, the factors or functional groups that affect chiral recognition can be pinpointed and evaluated. This type of direct evaluation of the effect of the configuration of each stereogenic center cannot be done easily with other chiral selectors commonly used in GC, LC, or CE. *N*,*N*-dimethylephedrinium-based CSPs are particularly effective in separating enantiomers of alcohols, diols, sulfoxides, and some N-blocked amines and epoxides.

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