Ephedrinium-Based Protic Chiral Ionic Liquids for Enantiomeric Recognition

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Contribution to the Proceedings of the 21st International Symposium on Chirality [ISCD 21]

ABSTRACT We report the synthesis of a series of novel structurally related protic chiral ionic liquids (PCILs) derived from ephedrines. Enantiopure norephedrine, ephedrine, and methylephedrine were neutralized by use of fluorinated acids, bis(trifluoromethanesulfonyl)imide, and bis(pentafluoroethanesulfonyl)imide to afford six PCILs with protonated primary, secondary, and tertiary amines. The goal of this study is to investigate the influence of structure on both chiral recognition abilities and physicochemical properties of these closely related PCILs. The newly synthesized PCILs were characterized by use of nuclear magnetic resonance (NMR), thermal gravimetric analysis, differential scanning calorimetry, circular dichroism (CD), mass spectrometry, and elemental analysis. The PCILs were thermally stable up to 220°C and had glass transition temperatures between −60 and −30°C. Both enantiomers of the PCILs retained chirality throughout the synthesis as demonstrated by use of CD measurements. More interestingly, these ephedrinium PCILs displayed strong chiral recognition capabilities as evidenced by peak splitting of the chemical shift of the trifluoro group of potassium Mosher's salt by use of ^{19}F-NMR. In addition, these PCILs demonstrated enantiomeric recognition capabilities toward a range of structurally diverse analytes using steady-state fluorescence spectroscopy. *Chirality 23:54–62, 2011.*

KEY WORDS: chiral recognition; fluorescence; circular dichroism; fluorine NMR; Mosher's salt

INTRODUCTION

Over the last decade, an increased interest in the study of ionic liquids (ILs) has been observed from data in the literature.[1,2] ILs are essentially low-melting organic salts consisting of bulky organic cations and typically inorganic anions. Room-temperature ILs are liquid at room temperature and were first reported by Walden in 1914.[3] ILs have unique physicochemical properties including high ionic conductivity, low vapor pressure, stability in air, and a wide range of solvation properties.[4,5] Such properties have allowed for the application of ILs in a variety of different areas, which include separations,[6] catalysis,[7] electrochemistry,[8] and spectroscopy.[9]

Chiral ionic liquids (CILs) are ILs containing a chiral cation,[10] anion,[11] or both.[12] Since their inception, various types of CILs have been prepared.[11–19] A number of CILs such as (3-chloro-2-hydroxypropyl)trimethylammonium bis((trifluoromethyl)sulfonyl)imide have been prepared through facile methods derived from commercially available chiral precursors.[20] However, other CILs such as the isomannide-derived CIL reported elsewhere required a series of more elaborate synthesis steps.[21] CILs have been used in gas chromatography as stationary phases,[22,23] as catalysts in organic synthesis,[24] and also as chiral selectors and solvents in fluorescence spectroscopy.[20,22–25] Leitner and coworkers have reported the first use of a CIL in combination with a racemic catalyst where the CIL blocked one of the catalyst ligands, thus resulting in enantioselective hydrogenation.[26] Another CIL was synthesized through alkylation of phenethylamine, followed by ion exchange for potential use as a chiral electrochemical sensor.[27]

Protic ionic liquids (PILs) are ILs formed through the transfer of protons from a Bronsted acid to a Bronsted base.[28] In general, the use of stronger acids and/or bases leads to increased proton transfer and subsequently higher ionicity, i.e., the presence of a higher number of ionic species and fewer neutral species. PILs have recently proven successful for heterogeneous catalysis and for the synthesis of polymeric materials that are good proton conductors in fuel cells.[29–32] However, relatively few studies have been performed where physicochemical properties of structurally related PILs were investigated. In one study, the ionic conductivity and thermal properties of 21 ILs, prepared through the reaction of various amines with tetrafluoroboric acid, were investigated. The measured properties appeared to be dependent on both cation and anion structure.[33] In another study, the physicochemical properties of a series of alkylammonium-based PILs with different organic and inorganic anions were studied.[34] In the same study, the authors suggested that PILs could possibly be synthesized through rational design aimed at specific applications.

Ephedrine is an alkaloid that functions as a decongestant, stimulant, and appetite suppressant.[35–37] It belongs to a group of precursors that have been used for synthesizing CILs from the chiral pool. Wasserscheid et al. reported an aprotic *N*,*N*-dimethylephedrinium IL using a three-step synthesis, which included a Leuckart–Wallach reaction with (−)-(1*R*, 2*S*)-

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: National Science Foundation (NSF); Contract grant number: CHE-0911118; Contract grant sponsor: Phillip West Endowment.

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Received for publication 10 November 2009; Accepted 14 July 2010
DOI: 10.1002/chir.20920
Published online 2 November 2010 in Wiley Online Library (wileyonlinelibrary.com).

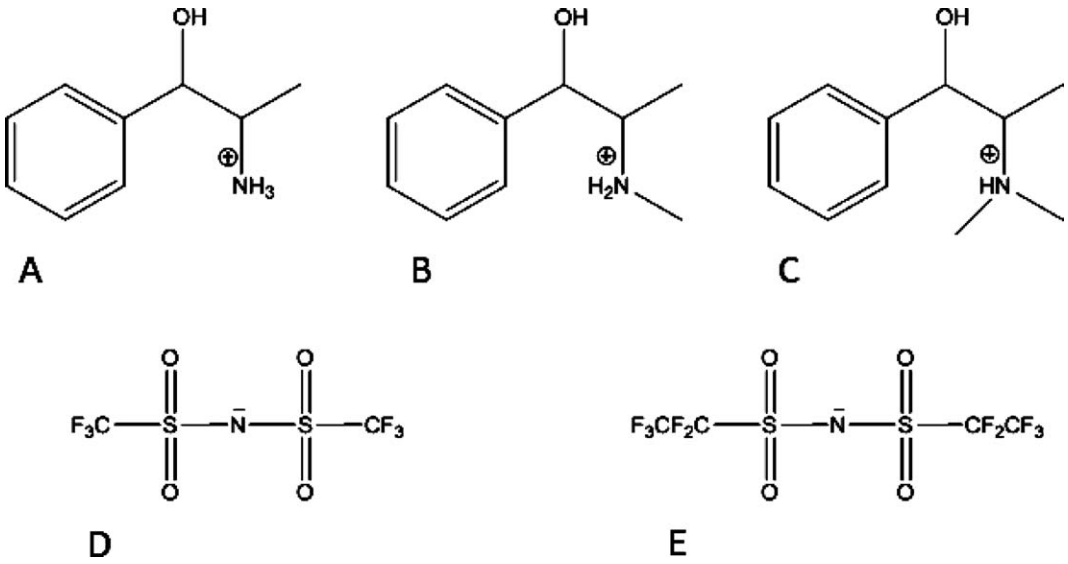


Fig. 1. Structures of PCIL cations (**A**) [NorHeph$^+$], (**B**) [HEph$^+$], (**C**) [MeHEph$^+$] and anions (**D**) [Tf_2N^-] and (**E**) [BETI$^-$].

ephedrine, followed by alkylation with dimethylsulfate and ion exchange with lithium bis(trifluoromethylsulfonyl)imide ([Li][Tf_2N]).[38] A green, solvent-less method was subsequently developed for the synthesis of similar CILs. For example, (1*R*, 2*S*)-*N*-methylephedrine was alkylated with bromoalkanes under microwave irradiation followed by ion exchange.[39] This method yielded aprotic ephedrinium CILs with different alkyl chain lengths and anions. Several *N*,*N*-dimethylephedrinium-based ILs were also used for the enantiomeric gas chromatographic separation of a series of chiral compounds such as chiral alcohols (including diols), chiral sulfoxides, chiral epoxides, and acetylated amines.[23] In addition, the aprotic ephedrinium CIL reported earlier was also used for asymmetric glycine alkylation in the presence of optically active orthopalladated phenanthrylamine as a phase transfer catalyst.[38,40]

The objective of this study is to synthesize protic chiral ionic liquids (PCILs) derived from structurally related alkaloids such as norephedrine (NorEph), ephedrine (Eph), and methylephedrine (MeEph) through facile acid–base neutralization with fluorinated imide acids (Fig. 1). This leads to the formation of a series of primary, secondary, and tertiary amine-based PCILs, respectively. Thus, the PCILs described here are all protic in contrast to the aprotic ephedrinium CILs reported elsewhere.[38] Herein, we report the effects of the degree of alkylation (varying hydrogen-bonding capability, van der Waals bonding, and steric hindrance) on the physicochemical properties and chiral recognition abilities of these ephedrinium-based PCILs.

EXPERIMENTAL

Chemicals and Materials

L-(−)-Norephedrine, D-(+)-norephedrine, (−)-ephedrine, (+)-ephedrine, (−)-*N*-methylephedrine, (+)-*N*-methylephedrine, racemic Mosher's acid, and bis(trifluoromethanesulfonyl)imide were purchased from Sigma-Aldrich (Milwaukee, WI). Enantiomerically pure chiral analytes of propranolol (PROP), 1-(9-anthryl)-2,2,2-trifluoroethanol (TFAE), 1,1′-binaphthyl-2,2′-diamine (BNA), 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNP), glucose, and serine were also purchased from Sigma-Aldrich (Milwaukee, WI). Bis(pentafluoroethane)sulfonimide was purchased from SynQuest Laboratories (Alachua, FL). All solvents used including acetonitrile and dichloromethane were of HPLC grade (J.T. Baker, Philipsburg, NJ). Deuterated solvents such as chloroform-d_1, D_2O, and dimethyl sulfoxide-d_6 were obtained from Sigma-Aldrich (Milwaukee, WI). All reagents were used without further purification. Triply deionized ultrapure water (18.2 MΩ) obtained using an Elga model PURELAB Ultra^{TM} water filtration system was used in the study.

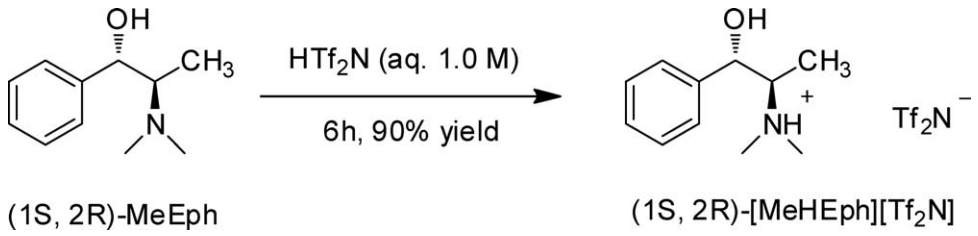
General Instrumental Methods

^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were acquired by use of a Bruker AV-400 spectrometer. The ^{1}H-NMR and ^{13}C-NMR chemical shifts are given in parts per million (δ) with respect to TMS as an internal standard. ^{19}F-NMR (236 MHz) spectra were acquired on a Bruker DPX 250 NMR spectrometer. Solvents used for preparing the samples were DMSO-d_6 for ^{1}H-NMR and ^{13}C-NMR and $CDCl_3$ for ^{19}F-NMR. Elemental analyses were conducted by Atlantic Microlab (Atlanta, GA). Samples were also analyzed with mass spectrometry on a Hitachi MS-8000 3DQ LC-ion trap mass spectrometer with electrospray and APCI ionization methods in both the positive and negative ion mode. The moisture contents of synthesized PCILs were measured using a Mettler Toledo DL32 Karl-Fischer Coulometric titrator. CD measurements were obtained by analyzing 1 mM methanolic solutions at room temperature in 4-mm quartz cuvettes on a Jasco-710 spectropolarimeter. Thermal stability was measured with a TGA Q50 thermogravimetric analyzer (TA Instruments) by heating 10 mg of sample under nitrogen at a rate of 15°C min^{-1} from 25 to 550°C. Similarly, glass transition and melting point were investigated with a DSC Q 100 differential calorimeter (TA Instruments, USA) by cooling a 5–10 mg sample of PCIL to −80°C and subsequently heating it at a rate of 5°C min^{-1} to 150°C.

Fluorescence analyses were performed in the steady-state mode on a Spex Fluorolog-3 spectrofluorimeter (model FL3-22TAU3; Jobin Yvon Edison, NJ) equipped with a 450-W Xe lamp and R928 PMT emission detector. Excitation and emission wavelengths with 3-nm bandpasses were selected as well as an integration time of 0.1 s per point. Fluorescence data were corrected by taking the quotient of the analyte signal and the reference signal. Excitation emission matrix (EEM) scans were performed with excitation from 250 to 400 nm and emission spectra collected between 250 and 500 nm. The step sizes used for the excitation and emission scans were 2.5 and 5 nm, respectively.

Representative Procedure: Synthesis of [MeHEph][Tf_2N]

MeEph (0.50 g, 3.31 mmol) was dissolved in water and reacted with equimolar bis(trifluoromethanesulfonyl)imide by slow addition and stirring to obtain [MeHEph][Tf_2N] (Scheme 1). The neutralization reaction



Scheme 1. Synthesis of [MeHEph][Tf_2N].

was performed in an ice bath for 6 h. The mixture was subsequently stirred at room temperature for 12 h. After water was removed in vacuo by freeze-drying, a viscous colorless liquid was obtained. The viscous PCIL was further purified by washing with small amounts of triple distilled water and freeze-dried by lyophilization. [MeHEph][Tf_2N], colorless liquid, 90.3%, ^{1}H-NMR (250 MHz, DMSO-d_6) δ (ppm): 7.40 (s, 3H), 7.30 (s, 2H), 76.2 (s, 3H), 5.22 (d, 1H), 3.47 (m, 1H), 2.81 (s, 1H), 1.0 (d, J = 6.8 Hz, 3H). ^{13}C-NMR δ (ppm): 142.0, 128.7 127.9, 126.2, 121.6, 118.4, 115.2, 114.2, 69.0, 66.0, 41.2, 7.4. Anal Calcd for $C_{13}H_{18}F_6N_2O_5S_2$: C, 33.88; H, 3.90; N, 6.08. Found: C, 34.09; H, 3.81; N, 6.09.

RESULTS AND DISCUSSION

Synthesis and Characterization of Ephedrine-Based PCILs

The synthesized PCILs (Scheme 1) were characterized using ^{1}H- and ^{13}C-NMR, elemental analysis, and electrospray ionization mass spectrometry (ESI-MS). The results from ^{1}H- and ^{13}C-NMR were in agreement with the chemical structures of the PCILs and were further confirmed with elemental analysis. The respective ^{1}H- and ^{13}C-NMR spectra were also compared with those of the precursors from which the PCILs were derived. As expected, the spectra were similar, because the chemical structures of the product PCILs were comparable to those of the corresponding chiral precursors. Fluorine (^{19}F)-NMR was used to confirm the success of neutralization (introduction of fluorinated anions). Mass spectrometry was conducted in the positive and negative ion mode. In the Supporting Information (Fig. S1), the respective mass spectra are illustrated for [NorHEph][Tf_2N], [HEph][Tf_2N], and [MeHEph][Tf_2N] PCILs. In the positive ion mode a strong peak is observed for each of the respective parent ions with m/z = 152.10, 166.12, and 180.13 confirming their presence. In the negative ion mode, the presence of [Tf_2N^-] and [$BETI^-$] for [NorHEph][Tf_2N] and [NorHEph][BETI] was confirmed by strong peaks observed at m/z = 279.18 and 379.19 (Supporting Information Fig. S1).

To determine whether configurational integrity was maintained throughout the synthesis, circular dichroism (CD) was used to compare the bands of the starting materials and the IL products. The CD spectra of both enantiomers of MeEph and IL derived therefrom, [MeHEph][Tf_2N], are shown in Figure 2. The relative peak intensities of both enantiomers of MeEph and [MeHEph][Tf_2N] remain constant throughout the synthesis, suggesting that chirality was maintained.

After purification, followed by freeze-drying overnight and subsequent purging with argon gas, the water content of the PCILs was determined using coulometric Karl-Fischer titration. The water content of the PCILs varied between 50 and 150 ppm (Table 1). All other PCILs were characterized in the same manner as [MeHEph][Tf_2N]. The PCILs were viscous liquids with [NorHEph][Tf_2N] and [HEph][Tf_2N] having higher viscosities at room temperature.

Thermal Properties of PCILs

The thermal stabilities of the PCILs were studied by use of thermal gravimetric analysis (TGA). Samples were heated under nitrogen atmosphere at a rate of 15°C min^{-1} from room temperature up to 600°C. Thermal decomposition of the PCILs ranged between 230 and 250°C with onset temperatures around 400°C (Table 2). PILs with ammonium, imidazolium, and other heterocyclic cations generally exhibit good thermal stabilities and low melting points with [Tf_2N^-] anions.[41,42] The ephedrinium-based PCILs with [Tf_2N^-] anions had higher thermal stability than those with [$BETI^-$]

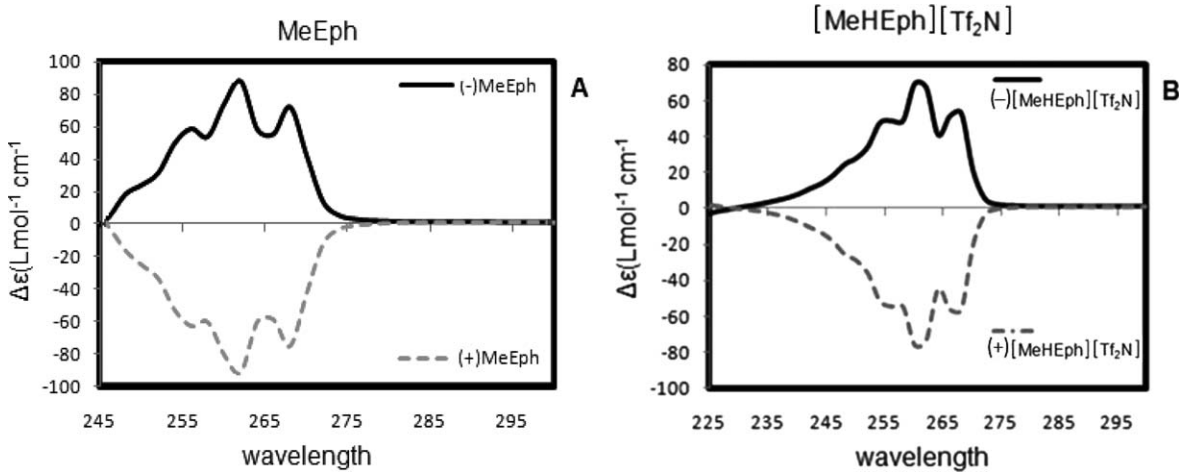


Fig. 2. Circular dichroism of enantiomers (+ and −) of (**A**) 10 mM MeEph and (**B**) 10 mM MeEphTf_2N in methanol.

TABLE 1. Moisture content of PCILs measured by Karl-Fischer titration

PCIL	H_2O content (ppm)	Mass (mg)
[NorHEph][Tf_2N]	93.0	7.2
[HEph][Tf_2N]	99.8	10.0
[MeHEph][Tf_2N]	150.1	14.1
[NorHEph][BETI	53.2	5.3
[HEph][BETI]	55.9	8.6
[MeHEph][BETI]	47.5	11.8

anions (Table 2). These results were consistent with earlier reports for ammonium-based ILs in which the PILs with [Tf_2N^-] anions had higher thermal stability than those that contained [$BETI^-$] anions.[43]

Differential scanning calorimetry was used to determine the thermal transitions of the PCILs occurring throughout the heating and cooling steps of the samples. The PCILs were cooled from room temperature to −80°C, followed by heating to 150°C at a rate of 5°C min^{-1} under nitrogen. Crystallization and melting transitions were not observed for the PCILs under these conditions. A glass transition (T_g) between −60 and −20°C was found for the PCILs increasing in the order [NorHEph][Tf_2N], [HEph][Tf_2N], and [MeHEph][Tf_2N]. The [$BETI^-$]-containing PCILs had higher T_g values than the [Tf_2N^-]-containing PCILs because of the higher polarizability of these anions.[44] The [$BETI^-$]-containing PCILs showed an opposite trend in T_g values.

Enantiomeric Recognition Studies of PCILs Toward Racemic Mosher's Salt Using ^{19}F-NMR

Enantiomeric recognition capabilities of the PCILs were investigated by using a previously described method in which CILs derived from aminobutanol, valine, and methylephedrine were dissolved in a deuterated solvent with racemic Mosher's salt.[38] The chemical shift differences or peak splittings of the two diastereomeric associates were measured by use of ^{19}F-NMR, where the extent of peak splitting of CF_3 in Mosher's salt was related to the strength of diastereomeric interactions. Mosher's salt was obtained by neutralization of Mosher's acid solution with an equimolar solution of potassium hydroxide and subsequent freeze-drying and lyophilization. The feedstock solution for the ^{19}F-NMR tests was prepared by dissolving 121.3 mg of racemic Mosher's salt (0.45 mmol) and 119.5 mg of crown ether (18C6, 0.45 mmol) in 15 ml $CDCl_3$ as previously reported.[45] The 18C6 was added to increase the solubility of potassium Mosher's salt in chloroform-d_1 by forming a complex between potassium and crown ether.[46] For ^{19}F-NMR analysis, a fivefold molar excess of respective PCIL with regard to potassium Mosher's salt was dissolved in 0.5 ml of the feedstock solution.

The chiral recognition ability of the precursor NorEph was compared with that of the PCIL [NorHEph][Tf_2N]. In the absence of either NorEph or [NorHEph][Tf_2N], a single peak of −70.50 Hz chemical shift was observed for the potassium Mosher's salt racemate. In the presence of NorEph or the [NorHEph][Tf_2N], peak splittings were observed, which are related to the strength of the diastereomeric interactions between potassium Mosher's salt racemate and the chiral compounds. The significantly greater peak splitting of potassium Mosher's salt with PCIL [NorHEph][Tf_2N] versus noncharged precursor NorEph as chiral selector suggests that a higher chiral recognition ability was obtained by forming PCILs from the neutral NorEph (Fig. 3). These results suggest the presence of a positive charge as an important factor for chiral discrimination by an ion-pair interaction. Rizvi and Shamsi have reported that electrostatic interactions between the acidic analyte and cationic IL micelle played a profound role in enantioseparation.[47] In another study, Wasserscheid and coworkers have reported an asymmetric synthesis that solely relied on the strength of ion pairing in a CIL to induce high chirality in an asymmetric hydrogenation reaction.[48] This work demonstrates the importance of ion-pair interactions in chiral induction or chirality transfer. The chiral recognition abilities of the [Tf_2N^-]-containing PCILs including NorHEph, HEph, and MeHEph were also compared, i.e., the effect of the degree of amine alkylation on Mosher's salt peak splitting was investigated (Fig. 4). The recorded values for these PCILs in the presence of Mosher's salt were 12.7, 5.7, and 4.3 Hz, respectively (Fig. 4). In addition to a larger peak splitting, the ^{19}F-NMR change in chemical shift for [NorHEph][Tf_2N] was also highest. Thus, it appears that as the extent of hydrogen bonding decreases and steric hindrance increases (i.e., going from the primary to the tertiary ephedrinium-based PCIL), chiral recognition ability of PCILs toward Mosher's salt decreased. Analysis of peak splitting for the [$BETI^-$]-containing PCILs showed almost identical results. A control experiment was performed to determine the role of the [Tf_2N^-] anion in chiral recognition. The chiral recognition abilities of [NorHEph][Cl], [HEph][Cl], and [MeHEph][Cl] were determined, and it was found that chiral recognition ability of PCILs with Tf_2N^- as anions was much higher than that of ionic compounds with Cl^- as anions (Supporting Information Fig. S23). Chiral recognition studies performed by Wilhelm and coworkers indicate that the counteranions used in CILs play an important role in chiral discrimination. A 10-fold increase in peak splitting was observed when ^{19}F-NMR was carried out on Mosher's salt in the presence of enantiopure CIL with [Tf_2N^-] as counterion compared with [BF_4^-] as the counterion.

Enantiomeric Recognition of Chiral Analytes by PCILs Through the Use of Steady-State Fluorescence Spectroscopy

After confirming enantioselectivity of the PCILs for Mosher's salt with ^{19}F-NMR, further investigations were performed using fluorescence spectroscopy. Recently, a fluorescence spectroscopic method was reported for investigating chiral recognition between a CIL and each enantiomeric form of various fluorescent drug analytes.[49] The two enantiomeric forms of chiral drug analytes exhibited different fluorescence

TABLE 2. Thermal properties of ephedrinium PCILs

PCIL	T_g (°C)[a]	T_{start} (°C)[b]	T_{onset} (°C)[c]
[NorHEph][Tf_2N]	−53.9	216.4	414.8
[NorHEph][BETI]	−27.1	222.0	382.5
[HEph][Tf_2N]	−48.6	248.0	417.5
[HEph][BETI]	−31.2	249.2	383.5
[MeHEph][Tf_2N]	−41.3	242.6	436.3
[MeHEph][BETI]	−33.1	231.3	391.3

[a]Glass transition temperature.
[b]The beginning decomposition temperature.
[c]The temperature at which the sample loses weight at the fastest speed.

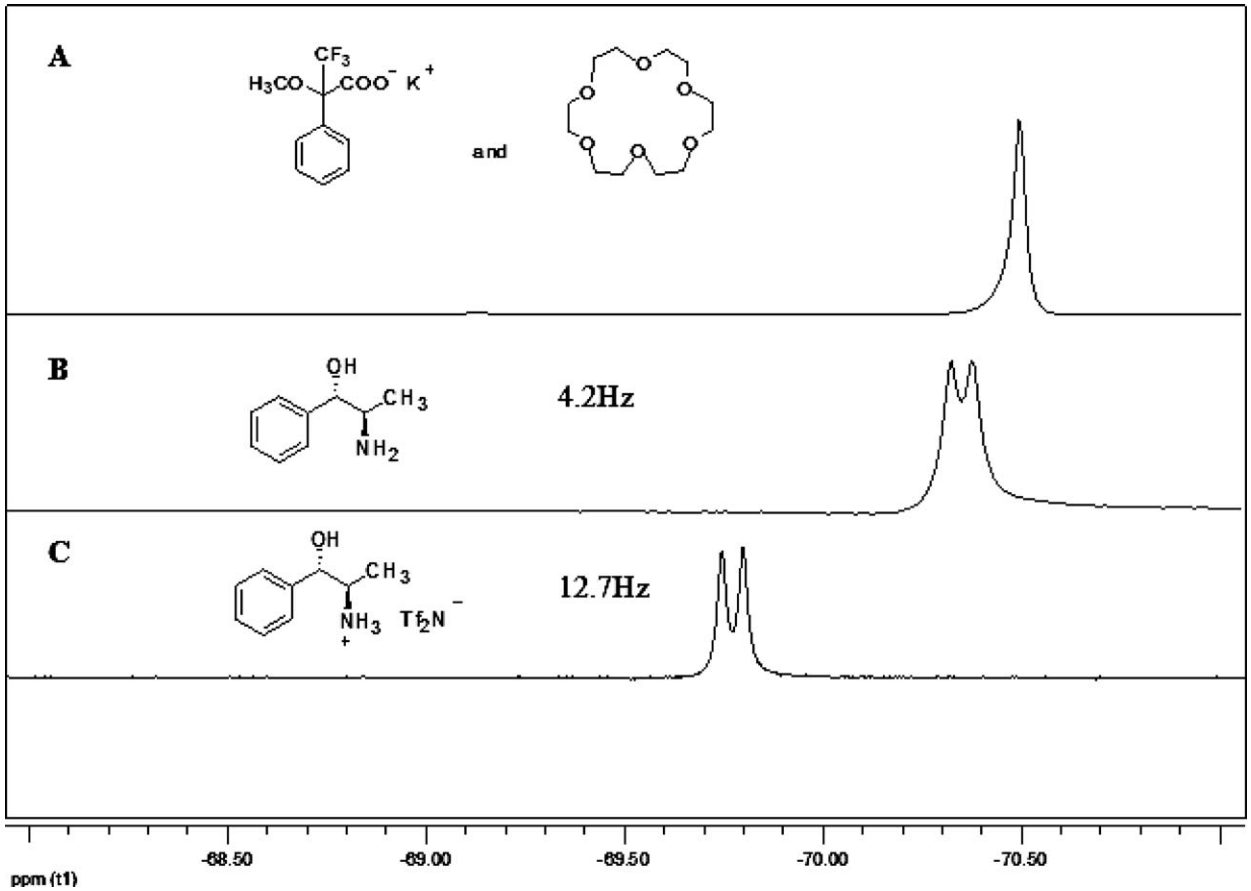


Fig. 3. ^{19}F-NMR ($CDCl_3$) spectra of potassium Mosher's salt (**A**) without chiral selector and with (**B**) (1*S*,2*R*)-NorEph and (**C**) (1*S*,2*R*)-NorHEphTf_2N chiral selector.

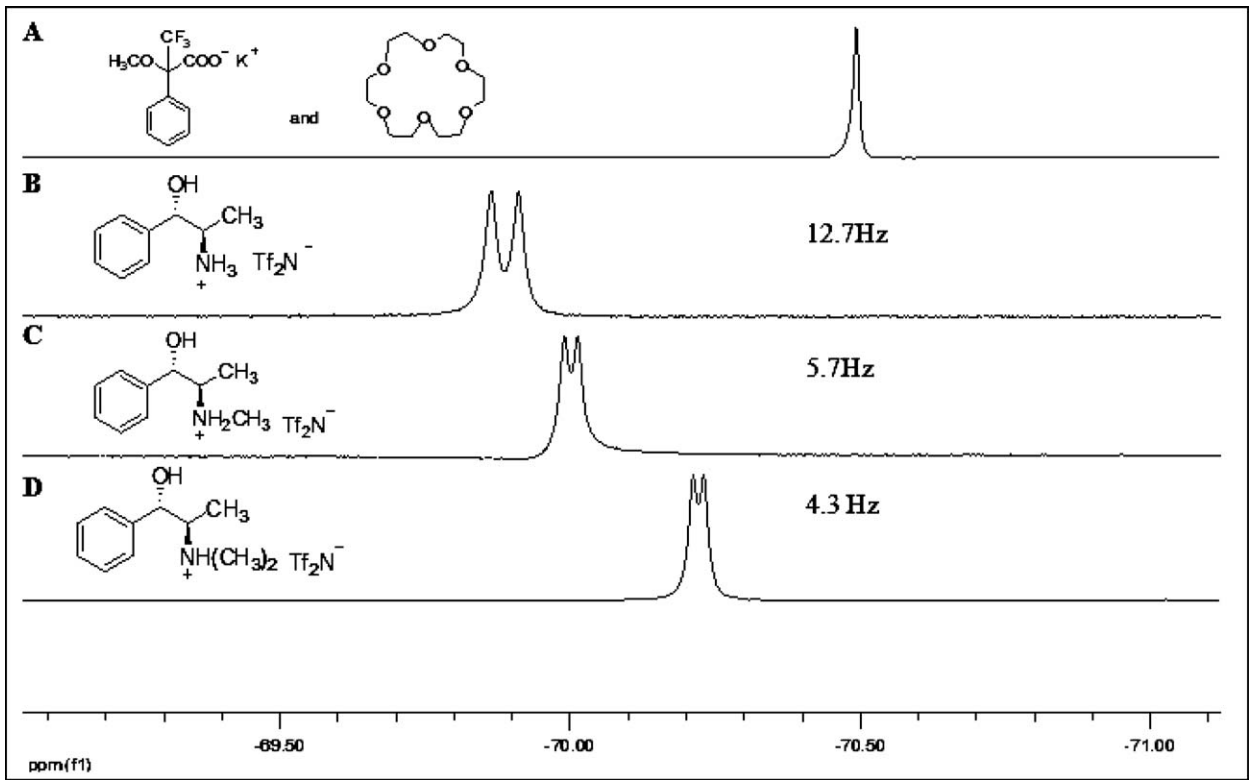


Fig. 4. ^{19}F-NMR ($CDCl_3$) spectra of potassium Mosher's salt (**A**), potassium Mosher's salt with (1*S*,2*R*)-NorHEphTf_2N as chiral selector (**B**), potassium Mosher's salt with (1*S*,2*R*)-HEphTf_2N as chiral selector (**C**), and potassium Mosher's salt with (1*S*,2*R*)-MeHEphTf_2N as chiral selector (**D**).

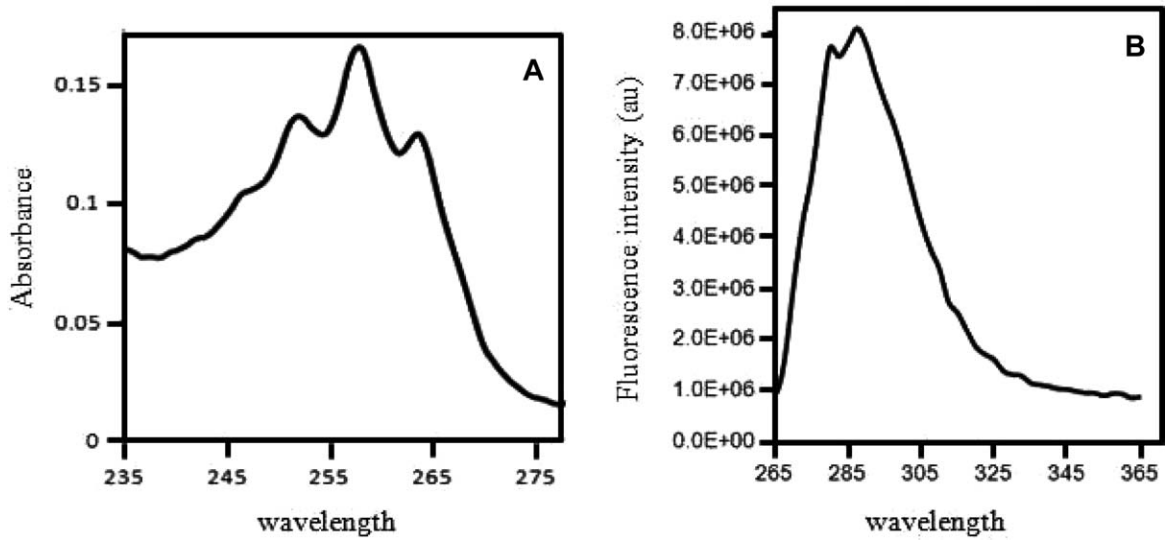


Fig. 5. (**A**) UV–vis spectrum of 10 mM MeHEphTf_2N in methanol. (**B**) Fluorescence of neat MeHEphTf_2N excited at 260 nm with front-face illumination.

intensities with the CIL as a result of specific diastereomeric complexes being formed. This method could therefore be used to determine the presence of a particular enantiomer in a given sample. Alanine-based and more recently a phenylalanine-based CIL were also synthesized in our laboratory and investigated for enantiomeric recognition.[25,50,51]

The PCILs reported in this study are intrinsically fluorescent and could therefore also be used for probing nonfluorescent enantiomers by monitoring their intrinsic fluorescence intensities.

Intrinsic Fluorescence of PCILs

The absorption maxima for the ephedrinium PCILs were found to occur at 257 nm, as illustrated for [MeHEph][Tf_2N] (Fig. 5). To determine the optimum intrinsic fluorescence, an EEM scan was run for neat [MeHEph][Tf_2N]. As seen in Figure 5, a sharp fluorescence peak was recorded at around 292 nm for this PCIL. Measurements were performed in a reduced-volume cuvette (0.4 ml) with front-face illumination to minimize inner-filter effects. Because of the relatively high viscosity of [NorHEph][Tf_2N] and [HEph][Tf_2N], fluorescence measurements of the neat PCILs were limited to that of [MeHEph][Tf_2N]. To compare the PCILs as chiral selectors, they were dissolved in water at concentrations of 30 mM. Solubility in water decreased in the order of [NorHEph][Tf_2N], [HEph][Tf_2N], and [MeHEph][Tf_2N], suggesting a decrease in hydrogen-bonding ability for the PCILs.

Enantiomeric Recognition of Fluorescent and Nonfluorescent Analytes by Use of Fluorescence Spectroscopy

Fluorescence spectroscopy was used to determine the chiral recognition capability of the PCILs for fluorescent and nonfluorescent analytes in aqueous solution. A series of analytes of pharmaceutical and biological significance were investigated. The fluorescent analytes included PROP, BNA, TFAE and BNP. The nonfluorescent analytes investigated included serine and glucose (Fig. 6).

Enantiomers for each analyte were prepared at 10 μM concentrations in 30 mM of aqueous PCILs solutions containing [Tf_2N^-] anions. To determine the wavelength-dependent fluorescence for the PCILs and the fluorescent chiral analytes, an EEM scan was run with excitation wavelengths ranging from 250 to 400 nm. The enantioselectivities of the PCILs were judged based on differences in the fluorescence bands with respect to shape and intensity, upon binding to different enantiomeric forms of the analyte. Based on the results obtained, it could be determined which PCIL exhibited the highest enantioselectivity for a particular analyte. Because the PCILs and the chiral analytes were both fluorescent, the fluorescence signal intensity was monitored for the PCIL between 270 and 320 nm and for the analyte peaks between 320 and 520 nm (Supporting Information Fig. S22). To amplify the differences in signal intensities, i.e., to clearly distinguish between fluorescence signals of both enantiomers, mean centered plots (MCPs) were used. The difference was calculated between the average and individual fluorescence spectra for each enantiomer. As a result, a negative MCP spectrum was obtained for the lower intensity peak and a positive MCP spectrum for the higher intensity peak. Thus, MCP plots aid to easily differentiate between individual enantiomers in the presence of PCILs (Fig. 7).

In the absence of PCILs, the difference in fluorescence intensity between both enantiomers of the chiral analyte was negligible (below 1%) in the control tests (Supporting Information Fig. S24). The fluorescence of TFAE enantiomers was measured in the presence of [Nor][HephTf_2N], [HEph][Tf_2N], and [MeHEph][Tf_2N] in aqueous solution. The difference in fluorescence intensity was more pronounced for [NorHeph][Tf_2N] (Fig. 7). A similar trend was observed for PROP (Supporting Information Fig. S22). In the case of BNA and BNP, the difference in fluorescence intensity was however more pronounced for [MeHEph][Tf_2N]. Thus, [NorHeph] [Tf_2N] appeared to be a better chiral selector for TFAE and PROP, whereas [MeHeph][Tf_2N] exhibited better chiral recognition for BNA and BNP. The fluorescence and MCP spectra for TFAE in [NorHeph][Tf_2N] and BNA in [MeHeph][Tf_2N] are shown in Figure 7. In addition to fluorescent analytes, nonfluorescent analytes were also investigated. Although the PCILs were intrinsically fluorescent, their chiral recognition abilities as seen by their fluorescence

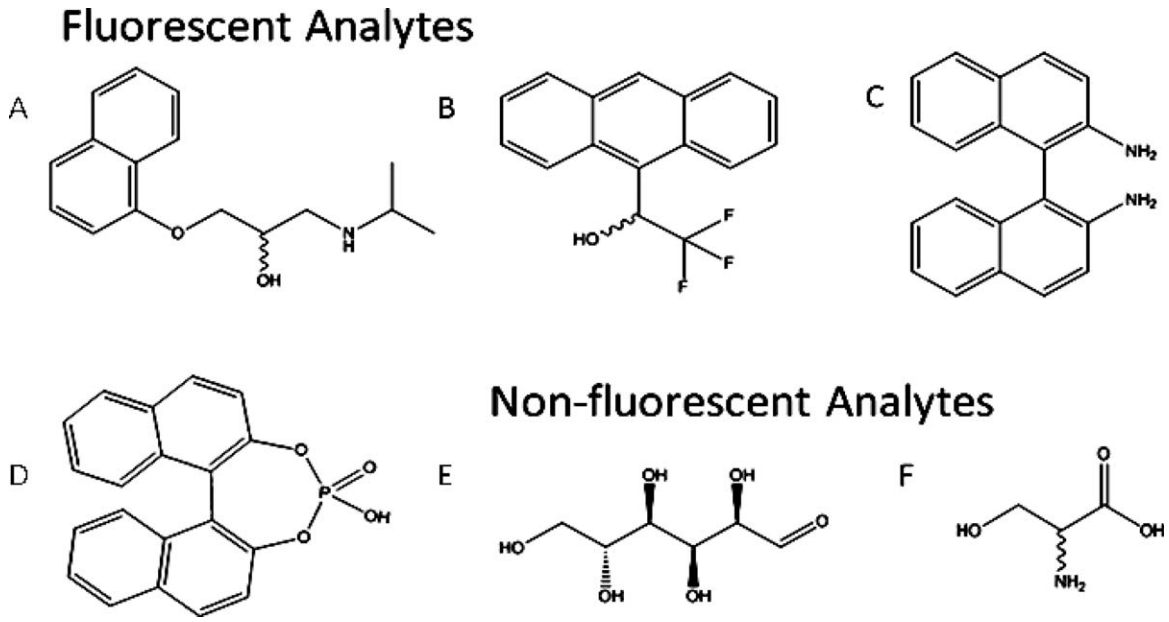


Fig. 6. Fluorescent analytes (**A**) propranolol, (**B**) 1-(9-anthryl)-2,2,2-trifluoroethanol, (**C**) 1,1′-binaphthyl-2,2′-diamine, (**D**) 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate, and nonfluorescent analytes (**E**) glucose, (**F**) serine.

intensities were not significantly different from one another. The fluorescence and MCP spectra for serine in [MeHEph][Tf_2N] are shown in Figure 8. In contrast to the fluorescent analytes, there was no pronounced signal observed above 350 nm for the nonfluorescent analytes.

The results obtained suggest that the chiral interactions between the PCILs and chiral analytes in solution are strongly affected by hydrogen bonding and hydrophobic interactions between PCILs and chiral analytes similar to chiral molecular micelles. The more polar analytes such as

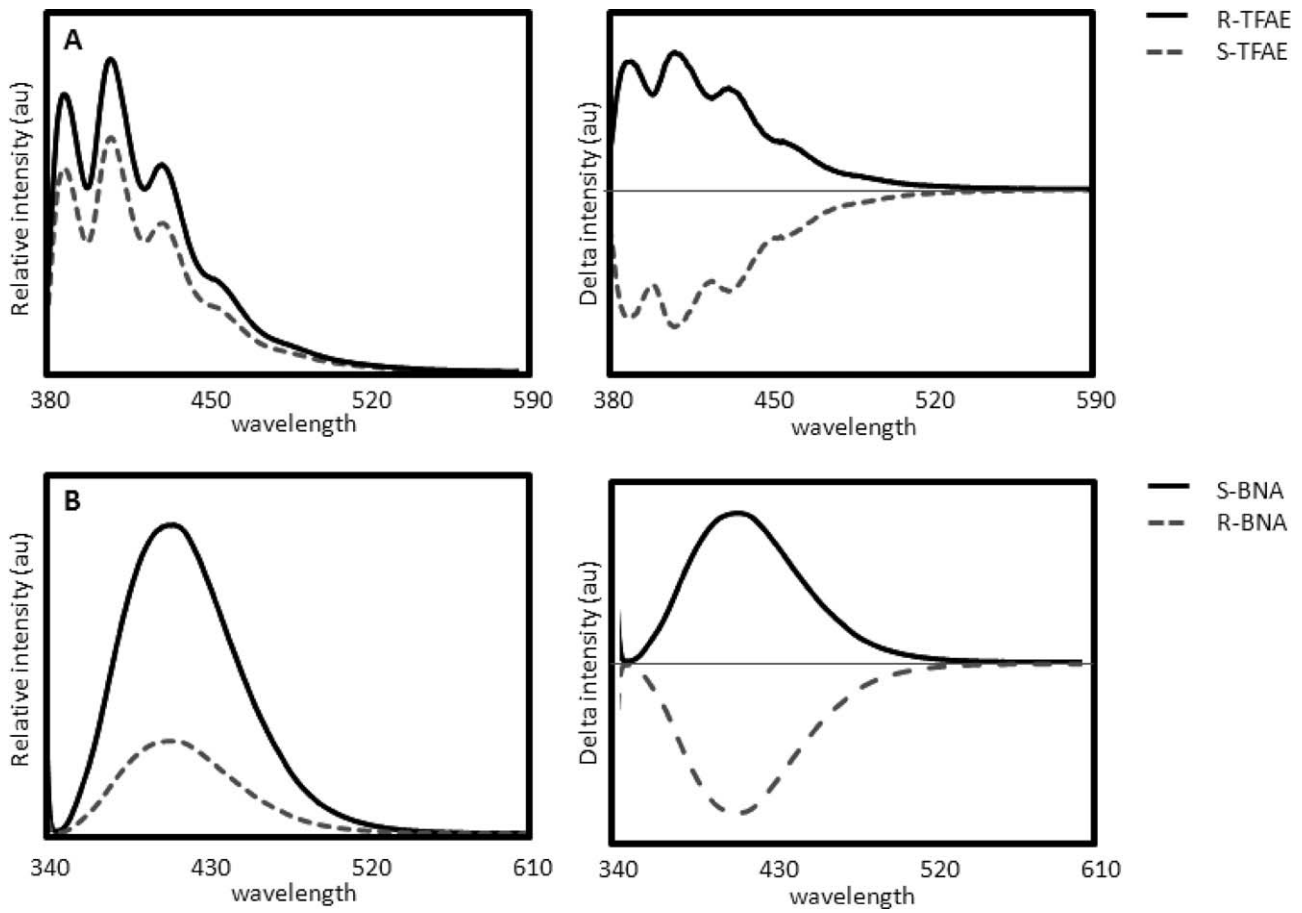


Fig. 7. A. Fluorescence spectrum of 10 μM TFAE in aqueous solution with 30 mM [NorHEph][Tf_2N] as chiral selector. B. Fluorescence spectrum of 10 μM BNA in aqueous solution with 30 mM [MeHEph][Tf_2N] as chiral selector.

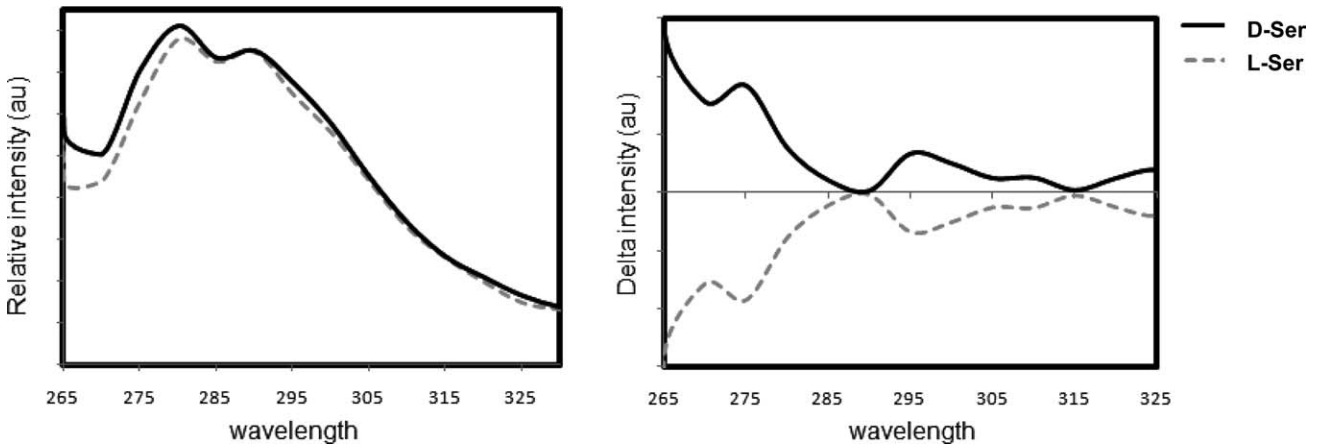


Fig. 8. Fluorescence spectrum of 10 μM serine in 30 mM aqueous solution with [NorHEph][Tf_2N] as chiral selector.

TFAE and PROP may interact more favorably with [NorHEph][Tf_2N] as a result of hydrogen bond-donating groups in the PCIL and hydrogen-bond acceptors in the analytes (Supporting Information Fig. S25). The less polar BNP interact more favorably with [MeHEph][Tf_2N], because both compounds have lower hydrogen-bonding capabilities (Supporting Information Fig. S26).

The results indicate that the degree of amine alkylation of the PCIL could have a significant effect on the enantioselective recognition ability for different chiral compounds as seen by the observed change in fluorescence intensity.[52,53] The exact mechanism of chiral recognition is still unclear. Further studies are currently underway to determine the mechanism of chiral recognition by PCILs for analytes of varying chirality. In general, the results indicated that the PCILs reported here are suitable chiral fluorescent solvents, capable of discerning between different enantiomers of fluorescent analytes.

CONCLUSIONS

Ephedrinium-based PCILs were synthesized using norephedrine, ephedrine, and methylephedrine through a single-step acid–base neutralization reaction. Configurational integrity was maintained throughout the synthesis, and the PCILs exhibited good thermal stability and chiral selectivity. Using ^{19}F-NMR, splitting of the Mosher's salt fluorine peak was highest for [NorHEph][Tf_2N], implying that this particular PCIL was the best chiral selector for Mosher's salt. From fluorescence studies, it was found that [NorHEph][Tf_2N] exhibited higher chiral recognition ability to TFAE and PROP compared with the other [Tf_2N^-] anion-containing PCILs. For BNA and BNP, higher chiral recognition was exhibited for [MeHEph][Tf_2N]. The ephedrinium-based PCILs reported here offer a range of potential applications as chiral selectors and solvents in fluorescence spectroscopy and potentially as stationary phases in chromatography, mobile phase modifiers in capillary electrophoresis, for studying protein interaction, and as catalysts in organic synthesis.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Qinglin Wu and Dr. Haiyun Liu for their assistance with TGA and DSC measurements.

LITERATURE CITED

1. Koel M. Ionic liquids in chemical analysis. Crit Rev Anal Chem 2005; 35:177–192.
2. Endres F, El Abedin SZ. Air and water stable ionic liquids in physical chemistry. Phys Chem Chem Phys 2006;8:2101–2116.
3. Walden P. Ueber die Molekulargrösse unde elektrische Leitfähigheit einiger geschmolzenen Salze. Bull Acad Imper Sci (St. Petersburg) 1914:1800.
4. Seddon KR. Ionic liquids for clean technology. J Chem Technol Biotechnol 1997;68:351–356.
5. Wilkes JS. Properties of ionic liquid solvents for catalysis. J Mol Catal A: Chem 2004;214:11–17.
6. Poole CF. Chromatographic and spectroscopic methods for the determination of solvent properties of room temperature ionic liquids. J Chromatogr A 2004;1037:49–82.
7. Welton T. Room-temperature ionic liquids. Solvents for synthesis and catalysis. Chem Rev 1999;99:2071–2083.
8. Buzzeo MC, Evans RG, Compton RG. Non-haloaluminate room-temperature ionic liquids in electrochemistry—a review. Chemphyschem 2004; 5:1106–1120.
9. Tran CD. Ionic liquids for and by analytical spectroscopy. Anal Lett 2007;40:2447–2464.
10. Howarth J, Hanlon K, Fayne D, McCormac P. Moisture stable dialkylimidazolium salts as heterogeneous and homogeneous Lewis acids in the Diels-Alder reaction. Tetrahedron Lett 1997;38:3097–3100.
11. Baudequin C, Baudoux J, Levillain J, Cahard D, Gaumont AC, Plaquevent JC. Ionic liquids and chirality: opportunities and challenges. Tetrahedron-Asymmetry 2003;14:3081–3093.
12. Yu SF, Lindeman S, Tran CD. Chiral ionic liquids: synthesis, properties, and enantiomeric recognition. J Org Chem 2008;73:2576–2591.
13. Baudequin C, Bregeon D, Levillain J, Guillen F, Plaquevent JC, Gaumont AC. Chiral ionic liquids, a renewal for the chemistry of chiral solvents? Design, synthesis and applications for chiral recognition and asymmetric synthesis. Tetrahedron-Asymmetry 2005;16:3921–3945.
14. Ding J, Armstrong DW. Chiral ionic liquids: synthesis and applications. Chirality 2005;17:281–292.
15. Bica K, Gaertner P. Applications of chiral ionic liquids. Eur J Org Chem 2008;19:3235–3250.
16. Patil ML, Sasai H. Recent developments on chiral ionic liquids: design, synthesis, and applications. Chem Rec 2008;8:98–108.
17. Winkel A, Reddy PVG, Wilhelm R. Recent advances in the synthesis and application of chiral ionic liquids. Synthesis 2008;7:999–1016.
18. Chen XW, Li XH, Hu AX, Wang FR. Advances in chiral ionic liquids derived from natural amino acids. Tetrahedron-Asymmetry 2008;19:1–14.
19. Headley A, Ni B. Chiral imidazolium ionic liquids: their synthesis and influence on the outcome of organic reactions. Aldrichim Acta 2007;40:107–117.
20. Tran CD, Oliveira D, Yu SF. Chiral ionic liquid that functions as both solvent and chiral selector for the determination of enantiomeric compositions of pharmaceutical products. Anal Chem 2006;78:1349–1356.

21. Kumar V, Olsen CE, Schaffer SJC, Parmar VS, Malhotra SV. Synthesis and applications of novel bis(ammonium) chiral ionic liquids derived from isomannide. Org Lett 2007;9:3905–3908.
22. Jessop PG, Stanley RR, Brown RA, Eckert CA, Liotta CL, Ngo TT, Pollet P. Neoteric solvents for asymmetric hydrogenation: supercritical fluids, ionic liquids, and expanded ionic liquids. Green Chem 2003;5:123–128.
23. Ding J, Welton T, Armstrong DW. Chiral ionic liquids as stationary phases in gas chromatography. Anal Chem 2004;76:6819–6822.
24. Gruttadauria M, Riela S, Lo Meo P, D'Anna F, Noto R. Supported ionic liquid asymmetric catalysis. A new method for chiral catalysts recycling. The case of proline-catalyzed aldol reaction. Tetrahedron Lett 2004;45:6113–6116.
25. Bwambok DK, Marwani HM, Fernand VE, Fakayode SO, Lowry M, Negulescu I, Strongin RM, Warner IM. Synthesis and characterization of novel chiral ionic liquids and investigation of their enantiomeric recognition properties. Chirality 2008;20:151–158.
26. Chen DJ, Schmitkamp M, Francio G, Klankermayer J, Leitner W. Enantioselective hydrogenation with racemic and enantiopure binap in the presence of a chiral ionic liquid. Angew Chem Int Ed 2008;47:7339–7341.
27. Ashraf SA, Pornputtkul Y, Kane-Maguire LAP, Wallace GG. Facile synthesis of a chiral ionic liquid derived from 1-phenylethylamine. Aust J Chem 2007;60:64–67.
28. Greaves TL, Drummond CJ. Protic ionic liquids: properties and applications. Chem Rev (Washington, DC) 2008;108:206–237.
29. Aslanov LA, Valetskii PM, Zakharov VN, Kabachii YA, Kochev SY, Romanovskii BV, Yatsenko AV. Heterogeneous catalysis in ionic liquids: the heck reaction of bromobenzene with styrene over palladium supported on mesoporous carbon. Petrol Chem 2008;48:360–365.
30. Tiyapiboonchaiya C, Pringle JM, MacFarlane DR, Forsyth M, Sun JZ. Polyelectrolyte-in-ionic-liquid electrolytes. Macromol Chem Phys 2003;204:2147–2154.
31. Ohno H, Yoshizawa M. Electrochemistry using ionic liquid 3. Evolution of ionic liquid as an electrolyte. Electrochemistry 2002;70:136–140.
32. Belieres JP, Gervasio D, Angell CA. Binary inorganic salt mixtures as high conductivity liquid electrolytes for > 100 degrees C fuel cells. Chem Commun 2006:4799–4801.
33. Hirao M, Sugimoto H, Ohno H. Preparation of novel room-temperature molten salts by neutralization of amines. J Electrochem Soc 2000;147: 4168–4172.
34. Greaves TL, Weerawardena A, Krodkiewska I, Drummond CJ. Protic ionic liquids: physicochemical properties and behavior as amphiphile self-assembly solvents. J Phys Chem B 2008;112:896–905.
35. Greenway FL. The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. Obes Rev 2001;2:199–211.
36. Astrup A, Buemann B, Christensen NJ, Toubro S, Thorbek G, Victor OJ, Quaade F. The effect of ephedrine/caffeine mixture on energy expenditure and body composition in obese women. Metabolism 1992;41:686–688.
37. Roth RP, Cantekin EI, Bluestone CD, Welch RM, Cho YW. Nasal decongestant activity of pseudoephedrine. Ann Otol Rhinol Laryngol 1977;86(2 Part 1):235–242.
38. Wasserscheid P, Bosmann A, Bolm C. Synthesis and properties of ionic liquids derived from the 'chiral pool'. Chem Commun 2002:200–201.
39. Thanh GV, Pegot B, Loupy A. Solvent-free microwave-assisted preparation of chiral ionic liquids from (−)-N-methylephedrine. Eur J Org Chem 2004;5:1112–1116.
40. Mukherjee DK, Ghosh N. Enantio selective phase transfer alkylation using orthopalladated complex in chiral ionic liquid. Catal Commun 2008;9:40–44.
41. Crosthwaite JM, Muldoon MJ, Dixon JK, Anderson JL, Brennecke JF. Phase transition and decomposition temperatures, heat capacities and viscosities of pyridinium ionic liquids. J Chem Thermodyn 2005;37:559–568.
42. Ohno H, Yoshizawa M. Ion conductive characteristics of ionic liquids prepared by neutralization of alkylimidazoles. Solid State Ionics 2002;154: 303–309.
43. Luo HM, Huang JF, Dai S. Studies on thermal properties of selected aprotic and protic ionic liquids. Sep Sci Technol 2008;43:2473–2488.
44. Yoshizawa M, Ogihara W, Ohno H. Design of new ionic liquids by neutralization of imidazole derivatives with imide-type acids. Electrochem Solid State Lett 2001;4:E25–E27.
45. Li M, Gardella J, Bwambok DK, El-Zahab B, de Rooy S, Cole M, Lowry M, Warner IM. Combinatorial approach to enantiomeric discrimination: synthesis and ^{19}F NMR screening of a chiral ionic liquid-modified silane library. J Combin Chem 2009;11:1105–1114.
46. Clavier H, Boulanger L, Audic N, Toupet L, Mauduit M, Guillemin JC. Design and synthesis of imidazolinium salts derived from (L)-valine. Investigation of their potential in chiral molecular recognition. Chem Commun 2004:1224–1225.
47. Rizvi SAA, Shamsi SA. Synthesis, characterization, and application of chiral ionic liquids and their polymers in micellar electrokinetic chromatography. Anal Chem 2006;78:7061–7069.
48. Schulz PS, Muller N, Bosmann A, Wasserscheid P. Effective chirality transfer in ionic liquids through ion-pairing effects. Angew Chem Int Ed 2007;46:1293–1295.
49. Tran CD, Oliveira D. Fluorescence determination of enantiomeric composition of pharmaceuticals via use of ionic liquid that serves as both solvent and chiral selector. Anal Biochem 2006;356:51–58.
50. Bwambok DK, Challa SK, Lowry M, Warner IM. Amino acid-based fluorescent chiral ionic liquid for enantiomeric recognition. Anal Chem 2010;82:5028–5037.
51. Li M, de Rooy SL, Bwambok DK, El-Zahab B, DiTusa JF, Warner IM. Magnetic chiral ionic liquids derived from amino acids. Chem Commun 2009:6922–6924.
52. Williams AA, Fakayode SO, Alpturk O, Jones CM, Lowry M, Strongin RM, Warner IM. Determination of enantiomeric compositions of analytes using novel fluorescent chiral molecular micelles and steady state fluorescence measurements. J Fluoresc 2008;18:285–296.
53. Willlams AA, Fakayode SO, Lowry M, Warner IM. A versatile chiral selector for determination of enantiomeric composition of fluorescent and nonfluorescent chiral molecules using steady-state fluorescence spectroscopy. Chirality 2009;21:305–315.