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Chiral Ionic Liquid that Functions as Both Solvent and Chiral Selector for the Determination of Enantiomeric Compositions of Pharmaceutical Products

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We have successfully synthesized both enantiomers of a novel chiral ionic liquid, (*R*)- and (*S*)-[(3-chloro-2-hydroxypropyl) trimethylammonium][bis((trifluoromethyl)-sulfonyl)amide] ((*R*)- and (*S*)-[CHTA]$^+$[Tf$_2$N]$^-$) in optically pure form by a simple ion exchange reaction from corresponding chloride salts that are commercially available. In addition to the ease of preparation, this chiral IL has relatively high thermal stability (up to 300 °C), is liquid at room temperature (glass transition temperature of −58.4 °C), and exhibits strong enantiomeric recognition. The high solubility power and strong enantiomeric recognition ability make it possible to use this chiral IL to solubilize an analyte and to induce diastereomeric interactions for the determination of enantiomeric purity. In fact, we have successfully developed a novel method based on the near-infrared technique with this chiral IL serving both as solvent and as a chiral selector for the determination of enantiomeric purity. Enantiomeric compositions of a variety of pharmaceutical products and amino acids with different shape, size, and functional groups can be sensitively (milligram concentration) and accurately (enantiomeric excess as low as 0.6%) determined by use of this method.

Chiral analysis is an important subject in science as well as in technology. Enantiomeric forms of many compounds are known to have different physiological and therapeutic effects.[1−4] Very often, only one form of an enantiomeric pair is pharmacologically active.[1−4] The other or others can reverse or otherwise limit the effect of the desired enantiomer. Recognizing the importance of chiral effects, the FDA in 1992 issued a mandate requiring pharmaceutical companies to verify the enantiomeric purity of chiral drugs that are produced.[1−4] It is, thus, hardly surprising that the pharmaceutical industry needs effective methods to determine enantiomeric purity.

Methods currently available for the determination of enantiomeric purity are based either on separation (HPLC, GC, CE) or spectroscopy (CD, NMR, MS).[5−10] Although these methods have proven to be effective, they all have some drawbacks, including being time-consuming or destructive and having low sensitivity.[5−10] More importantly, none of them is truly universal; namely, they cannot be used for some types of compounds. However, contrary to the general belief, we have, in fact, demonstrated recently that it is possible to develop a novel method which is not only universal but also has relatively higher sensitivity and accuracy.[11,12] The method is based on the use of the NIR technique to measure diastereomeric interactions between an added carbohydrate compounds (e.g., α-, *β*-, or *γ*-cyclodextrin or sucrose) with both enantiomeric forms of an analyte, followed by partial least-squares analysis of the data.[11,12] Compared to other existing methods, this method not only has relatively higher sensitivity and accuracy but also is universal.[11,12] Specifically, it can be used to determine enantiomeric compositions of all types of compounds, including amino acids and pharmaceutical products (propranolol, atenolol, ibuprofen) with only microgram concentrations and enantiomeric excess as low as 1.5%.[11,12] It is noteworthy to add that although this method has proven to be very effective, it still has some limitations, such as the need to add a carbohydrate compound (to induce the diastereomeric interactions) and the fact that the analysis must be performed in a solvent that can dissolve both the analyte and the carbohydrate. Because of the latter requirement (and because of the different solubilities of various types of analytes), it may be necessary to perform the analysis in a variety of solvents, including water or a mixture of water and organic solvents. As a consequence, a separated calibration curve must be constructed for each set of carbohydrate−analyte in each specific solvent system. This cumbersome and time-consuming task somewhat limits the application of the method. It is, therefore, desirable to modify this method by eliminating the added carbohydrate and using only one solvent system for the analysis of all types of compounds. Chiral room temperature ionic liquid may offer a solution for this problem.

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Room temperature ionic liquids (RTILs) are a group of organic salts that are liquid at room temperature. They have unique chemical and physical properties, including being air- and moisture-stable and possessing a high solubility power and virtually no vapor pressure.[13−17] Because of these properties, they can serve as a "green" recyclable alternative to the volatile organic compounds that are traditionally used as industrial solvents.[13−17] The RTILs have, in fact, been successfully used in many applications, including replacing traditional organic solvents in (1) organic and inorganic syntheses,[14] (2) solvent extractions,[18] (3) liquid−liquid extractions,[19−21] (4) electrochemical reactions,[22,23] and (5) as a medium for enzymatic reaction.[24] Analytical applications of RTILs have also been achieved. For example, they have been used as buffers for capillary electrophoresis,[25] as solvents to enhance sensitivity of thermal lens measurements,[26] and as the stationary phase (SP) in gas chromatography.[27−29] Advances in RTILs have made synthesis of chiral RTILs a subject of intense study in recent years.[30−42] The popularity stems from the fact that it is possible to use chiral ILs as chiral solvents for optical resolutions, for asymmetric induction in synthesis, and as a chiral stationary phase in chromatography.[30−42] It may also be possible to use chiral ILs to replace the solvent as well as the added carbohydrate compound for the enantiomeric purity determination method. Specifically, the chiral IL with its high solubility power, should dissolve many different types of analytes. Its chirality may produce the needed diastereomeric interactions with both enantiomeric forms of an analyte. Unfortunately, despite their potentials, chiral ILs are not commercially available. Only a few chiral ILs have been synthesized, and the synthesis of reported chiral ILs required rather expensive reagents and elaborate synthetic schemes.[30−42] Because of these limitations, despite extensive efforts made by various groups, to date, the study and applications of chiral ILs have been severely hindered. Therefore, it is of particular importance to develop a novel synthesis method by which chiral ILs can be simply and easily prepared from commercially available reagents by chemists from various disciplines, not just by those with expertise in synthesis.

The information presented is, indeed, provocative and clearly demonstrates that it is possible for a chiral IL to serve as a solvent as well as an added chiral selector for the enantiomeric determination method. Such considerations prompted us to initiate this study, which aims (1) to synthesize both enantiomers of a novel chiral IL with a simple ion exchange reaction from the corresponding chloride salts which are commercially available, (2) to use various spectroscopic methods (NMR, CD, DSC, TGA) to characterize the chiral IL, and (3) to explore its use as both the solvent and added chiral selector for the enantiomeric determination.

EXPERIMENTAL SECTION

Chemicals. (*R*)-(+)- and (*S*)-(−)-4-[2-hydroxy-3-[(1-methylethyl)amino)propoxy]benzenacetamide) (i.e., (*R*) and (*S*)-atenolol), (*R*)-(+)- and (*S*)-(−)-1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol ((*R*)- and (*S*)-propranolol), D- and L-alanine (D- and L-Ala), D- and L-phenyl alanine (D- and L-Phe), (*S*)-(−)- and (*R*)-(+)−(3-chloro-2-hydroxypropyl)trimethylammonium chloride ($CHTA^+Cl^-$), and *N*-lithiotrifluoromethane sulfonamide ($Li^+Tf_2N^-$) were purchased from Aldrich Chemical (Milwaukee, WI). (*R*)-(−)-, and (*S*)-(+)- 4-isobutylphenyl) propionic acid) ((*R*)- and (*S*)-ibuprofen) were purchased from BIOMOL Research Laboratories Inc. (Plymouth Meeting, PA).

Synthesis of (*R*)- and (*S*)-(3-Chloro-2-hydroxypropyl)-trimethylammonium Tf_2N^-. A 1.88-g (10 mmol) portion of (*S*)-(−)-(3-chloro-2-hydroxypropyl) trimethylammonium chloride (or (*R*)-(−)-(3-chloro-2-hydroxypropyl)) and 2.87 g (10 mmol) of *N*-lithiotrifluoromethanesulfonimide were dissolved in water separately. Two solutions were then mixed together and stirred for 2 h at room temperature. The mixture separated into two layers. The bottom layer was separated and washed several times with water and then dried under vacuum overnight. 2.83 g (65%) of colorless product was obtained. ^{1}H NMR (300 MHz, CD_3CN) δ 3.119 (s, 9H), 3.376 (d, J = 5.4, 2H), 3.589 (dd, J1 = 5.25, J2 = 1.5, 2H), 3.972 (d, J = 4.8, 1H), 4.372 (m, 1H). (NMR spectrum is shown in Figure S1 of Supporting Information)

Instrumentation. *NMR Experiments.* ^{19}F NMR was carried out to evaluate the chiral recognition ability of this ionic liquid. The experimental procedure is similar to those used previously.[31,32] Specifically, 0.6 g (1.3868 mmol) of the optically active (*R*)- or (*S*)-$CHTA^+Tf_2N^-$ was mixed with 0.35 mL of CD_2Cl_2. Into this solution, 15 mg of (0.0585 mmol) of racemic Mosher's sodium salt in 0.4 mL of D_2O was added. The mixture was vigorously shaken for about 2 h and then allowed to equilibrate into two clear

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Table 1. Molar Ratios and Relative Concentrations of Tf_2N^-, $CHTA^+$, and Anion of Mosher's Salt in the D_2O and CH_2Cl_2 Layer

	anion of Mosher's salt: Tf_2N^-	anion of Mosher's salt: $CHTA^+$	Tf_2N^- mmol	$CHTA^+$ mmol	anion of Mosher's salt, mmol
D_2O layer	1.0:2.42	1.0:1.52	0.063	0.0395	0.026
CH_2Cl_2	1.0:40.68	1.0:41.44	1.324	1.3473	0.0325

layers. The two layers were separately transferred to two NMR tubes for the subsequent ^1H NMR and ^{19}F NMR measurements.

On the basis of the fact that the cation ($CHTA^+$) of the ionic liquid has hydrogens and no fluorines, the anion (Tf_2N^-) has fluorines and no hydrogens, and the anion of the Mosher's sodium salt has both hydrogens and fluorines, the relative concentrations of the IL and the Mosher's salt in each layer can be calculated from the integration of ^1H NMR and ^{19}F NMR spectra. ^1H NMR spectra of the top layer (i.e., D_2O layer) and the bottom layer (CH_2Cl_2) layer are shown in Figure S2A and S2B of the Supporting Information. On the basis of these spectra, the molar ratio of anion of Mosher's salt to the cation of the IL (i.e., $CHTA^+$) for the a D_2O and the CH_2Cl_2 layers was calculated to be 1.0:1.52 and 1.0:41.44, respectively. From the ^{19}F NMR spectra of the D_2O and the CH_2Cl_2 layer (Supporting Information Figure S2C and S2D), the molar ratio of the anion of Mosher's salt versus the anion of the IL (i.e., Tf_2N^-) was found to be 1.0:2.42 and 1.0:40.68, respectively. Since the total concentration of $CHTA^+Tf_2N^-$ ionic liquid and the Mosher's salt were known (1.3868 mmol for ionic liquid and 0.0585 mmol for Mosher's salt), the relative concentrations of Tf_2N^-, $CHTA^+$, and anion of Mosher's salt in both layers can be calculated. Results obtained, listed in Table 1, clearly show that most of the cation and anion of the IL were in the CH_2Cl_2 layer (97 and 95% for $CHTA^+$ and Tf_2N^-, respectively). In addition, at least 55% of the anion of the Mosher's salt was in this layer as well.

A Jasco 720 spectropolarimeter was used to record CD spectra. Differential scanning calorimetric (DSC) measurements were performed using a TA Instruments model Q100 differential scanning calorimeter.

Thermal gravimetric analysis (TGA) was carried out using a Cahn model TG 131 instrument. To avoid any possible reaction between ionic liquids and the sample crucible made from quartz or aluminum at elevated temperature,[43,44] we lined the quarts crucibles with silver foil before placing the sample into it. The sample size was in ~40 to 60 mg range. Measurements were performed under a flowing nitrogen atmosphere (at a flow rate of 80 mL/min) at a scan rate of 20 °C/min from 20 to 700 °C. All TGA results are the average of at least three measurements. The temperature reproducibility of the TGA is ±3 °C, and the error range of nonvolatile fraction at 700 °C is ±3%.

NIR spectra were taken on the home-built NIR spectrometer based on an acousto-optic tunable filter. Information on this NIR spectrometer was described in detail in our previous papers.[11,12]

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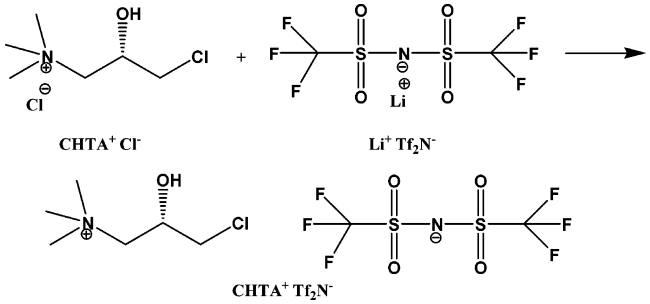
Scheme 1



Normally, each spectrum of a sample (in 5-mm path length cell) was an average of 50 spectra taken at 1-nm intervals from 1450 to 2450 nm. Multivariate analysis of data was performed using Unscrambler version 8.0 (Camo ASA), similar to the procedures used in our previous publications.[11,12]

RESULTS AND DISCUSSION

Synthesis and Characterization of Novel Chiral IL. As shown in Scheme 1, both (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl) trimethylammonium Tf_2N^- can be synthesized by a simple ion exchange reaction from corresponding (*R*)- and (*S*)-(3-chloro-2-hydroxypropyl)trimethylammonium chloride, which are available commercially.

The reaction readily proceeded in water at room temperature and completed in less than 2 h to yield (*R*)- or (*S*)-(3-chloro-2-hydroxypropyl)trimethylammonium Tf_2N^- (*R*)- or (*S*)-$CHTA^+$-Tf_2N^-) with relatively high yield (>65%). (*R*)- and (*S*)-$CHTA^+Tf_2N^-$ are liquid at room temperature, and results from differential scanning calorimetric (DSC) measurements indicate that they have glass transition temperature at −58.4 °C. It is noteworthy to add that $CHTA^+$ with other anions, including Cl^-, BF_4^-, and PF_6^-, are solid at room temperature. Results from thermal gravimetric analysis (TGA) (Figure 1) show that this chiral IL has high thermal stability. As illustrated, it remains stable at 300 °C, and loses only 1% of its weight at 326 °C. Even at a temperature as high as 437 °C, it still retains 50% of its mass.

The enantiomeric purity of (*R*)-$CHTA^+Tf_2N^-$ and (*S*)-$CHTA^+$-Tf_2N^- is confirmed by circular dichroism (CD) measurements. Figure 2A shows CD spectra of (*R*)-$CHTA^+Tf_2N^-$ and (*S*)-$CHTA^+$-Tf_2N^-, measured as neat solutions in a 0.5-mm path-length cell and plotted with the signal of the empty cell subtracted. As illustrated, (*R*)-$CHTA^+Tf_2N^-$ exhibits a positive CD band at ~217 nm, with a maximum of ~3.4 mdegree. The fact that (*S*)-$CHTA^+$-Tf_2N^- has a similar but negative CD band at the same wavelength and similar magnitude further confirms the optical purity of both chiral ionic liquids.

As described above, this IL is thermally stable to at least 300 °C. Because it is a chiral IL and chiral compounds are known to undergo thermal recemization, it is important to assess the chiral stability of this IL at elevated temperature. Accordingly, we measured CD spectra of three (*S*)-$CHTA^+Tf_2N^-$ samples: a freshly prepared sample and samples which has been in an oven for 15 h at either 100 °C (sample 2) or 150 °C (sample 3). The CD spectra of these three samples are shown in Figure 2B. As illustrated, these three samples have the same CD spectra. The results clearly

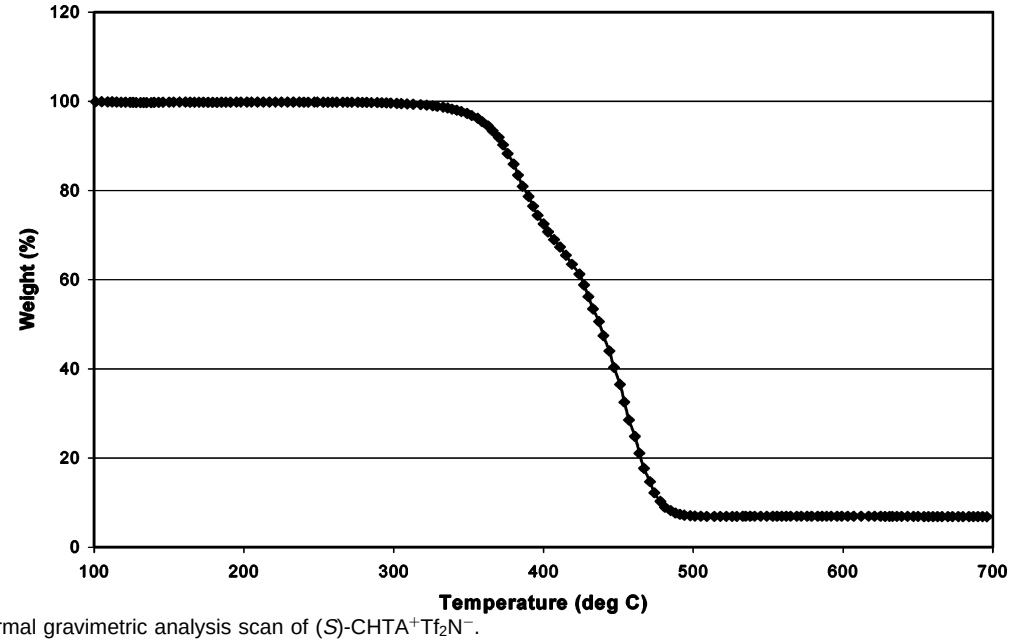


Figure 1. Thermal gravimetric analysis scan of (*S*)-CHTA$^+$Tf$_2$N$^-$.

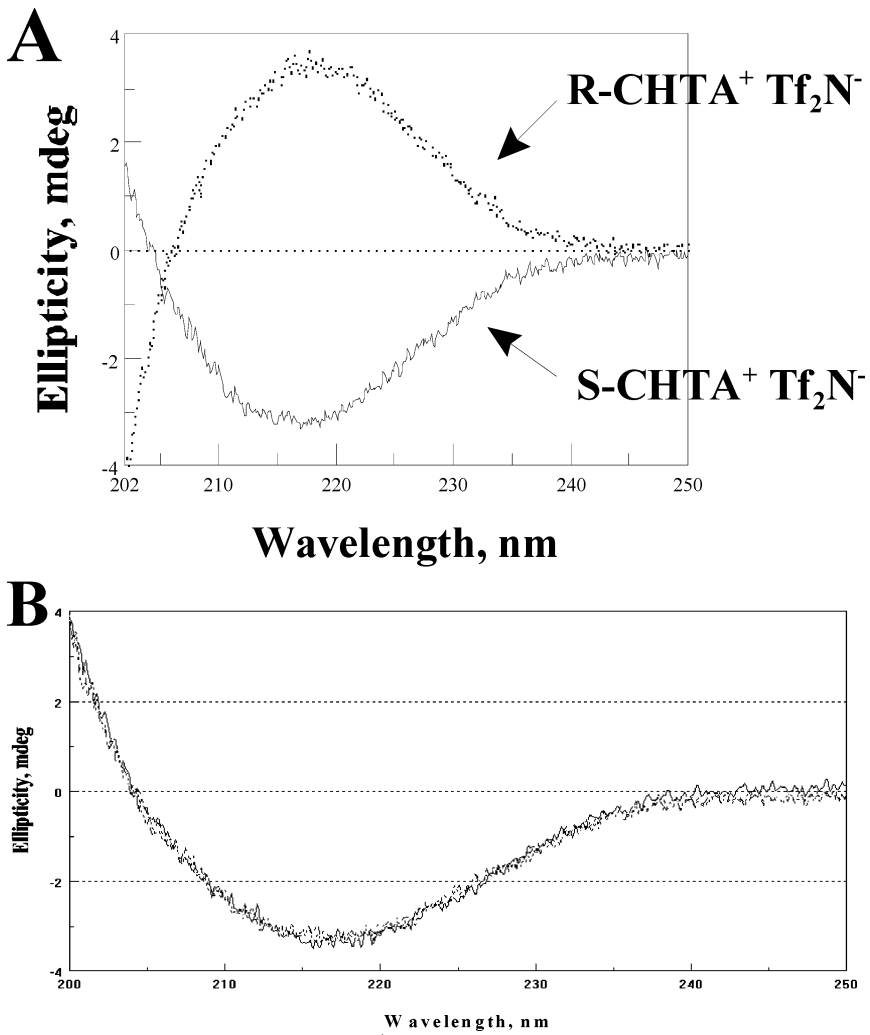


Figure 2. Circular dichroism spectra of (A) (*R*)- and (*S*)-CHTA$^+$Tf$_2$N$^-$ neat in a 0.5-mm path-length cell and (B) spectra of freshly prepared (*S*)-CHTA$^+$Tf$_2$N$^-$ sample, (*S*)-CHTA$^+$Tf$_2$N$^-$ sample which has been in a 100 °C oven for 15 h, and (*S*)-CHTA$^+$Tf$_2$N$^-$ sample which has been in a 150 °C oven for 15 h.

indicate that this chiral CHTA$^+$Tf$_2$N$^-$ ionic liquid does not undergo racemization at elevated temperature. It is, therefore, thermally stable with respect to both chemical and optical properties. These properties make this chiral IL particularly suited for applications

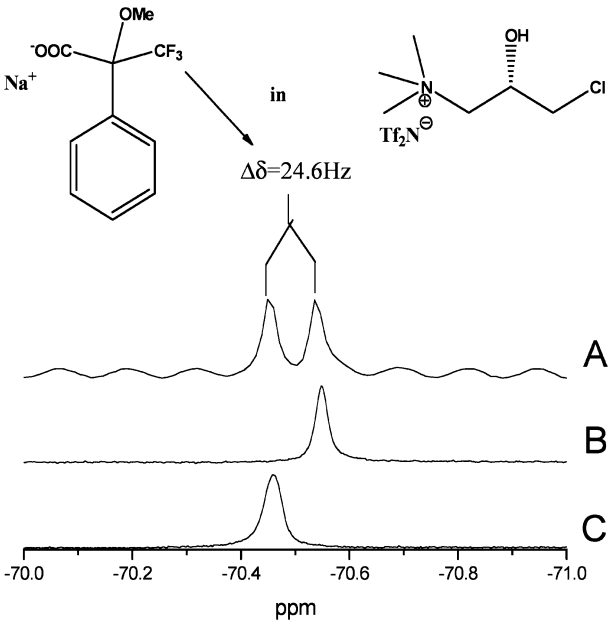


Figure 3. ^{19}F NMR spectra of (A) racemic Mosher's salt with (*S*)-CHTA$^+$Tf2N$^-$; (*S*)-Mosher's salt with (B) (*S*)-CHTA$^+$Tf$_2$N$^-$ and (C) (*R*)-CHTA$^+$Tf$_2$N$^-$.

such as a chiral stationary phase for gas chromatography and a chiral solvent for high-temperature reactions.

To be used as a chiral selector for the method to determine enantiomeric purity, a chiral IL must have enantiomeric recognition ability. We investigated the enantiomeric recognition of the chiral ILs by measuring interactions between optically active (*S*)-CHTA$^+$Tf$_2$N$^-$ ionic liquid with racemic Mosher's salt by ^{19}F NMR. Figure 3A shows the ^{19}F NMR spectrum of the racemic Mosher's salt (in the CH_2Cl_2 layer. See the experimental procedure for detailed information). It is evident that chiral (*S*)-CHTA$^+$Tf$_2$N$^-$ readily differentiates (*R*)-Mosher's salt from (*S*)-Mosher's salt, and this disastereomeric interaction resulted in the shift of the Mosher's salt fluorine signal. The difference in the chemical shifts was found to be 24.6 Hz. To further confirm the chiral recognition, we also measured ^{19}F NMR of the Mosher's salt when it interacted with either (*R*)-CHTA$^+$Tf$_2$N$^-$ or (*S*)-CHTA$^+$Tf$_2$N$^-$; however, in this case, we used not the racemic mixture but rather the optically active (*S*)-Mosher's salt. It is pleasing to see that when (*S*)-Mosher's salt interacted with (*S*)-CHTA$^+$Tf$_2$N$^-$, there was only one ^{19}F band at 70.559 ppm (Figure 3B). Similarly, there was only one band for the solution containing (*S*)-Mosher's salt and (*R*)-CHTA$^+$Tf$_2$N$^-$, but in this case, the band shifted to 70.458 ppm (Figure 3C). The difference in the chemical shifts between these two bands is 0.091 ppm or 25.7 Hz, which is, within experimental error, the same as the difference obtained above (24.6 Hz, Figure 3A) when racemic Mosher's salt interacts with (*S*)-CHTA$^+$Tf$_2$N$^-$. Two conclusions can be derived from these results. First, it is evident that (*R*)-CHTA$^+$Tf$_2$N$^-$ and (*S*)-CHTA$^+$Tf$_2$N$^-$ can provide enantiomeric recognition. In fact, because the chemical shift difference of 24.6 Hz obtained here is relatively higher than values of 10.68 and 11 Hz obtained for Mosher's salt with other chiral ILs synthesized previously,[31,32] it is expected that the chiral recognition of (*R*)- and (*S*)-CHTA$^+$Tf$_2$N$^-$ is relatively stronger than those for other reported chiral ILs.[31,32] Furthermore, because only one ^{19}F NMR band was observed when either (*R*)-CHTA$^+$Tf$_2$N$^-$ or (*S*)-CHTA$^+$Tf$_2$N$^-$ interacted with the optically active (*S*)-Mosher's salt, the results clearly and further confirm the optical purity of the chiral ionic liquids.

Table 2. Compositions of Solutions Used for Calibration

	mole fraction	
sample	(*R*)-atenolol	(*S*)-atenolol
1	0.30	0.70
2	0.40	0.60
3	0.45	0.55
4	0.50	0.50
5	0.55	0.45
6	0.60	0.40
7	0.65	0.35
8	0.70	0.30
9	0.75	0.25
10	0.85	0.15

Taken together, the results presented clearly demonstrate that both enantiomers of a novel chiral ionic liquid can be readily synthesized by a simple ion exchange reaction from corresponding chloride salts that are commercially available. In addition to the ease of preparation, this chiral IL has relatively high thermal stability (up to 300 °C) and is liquid at room temperature (glass transition temperature of −58.4 °C). Results from circular dichroism measurements indicate that both enantiomeric forms of the IL are optically pure and that the chirality of this chiral IL is thermally stable up to at least 150 °C. According to ^{19}F NMR results, this chiral IL has strong enantiomeric recognition ability. It is noteworthy to add that only a very few, not all, reported chiral ILs exhibit chiral recognition toward Mosher's salt. The fact that this chiral CHTA$^+$Tf$_2$N$^-$ ionic liquid displays not only its enantiomeric recognition toward Mosher's salt but also that it is relatively higher than the few reported chiral ILs (which were synthesized by elaborated multistep synthetic processes[31,32]) clearly indicates that this chiral IL has strong chiral recognition. although it is true that the chemical shift difference observed for this chiral IL is relatively lower than those reported for the NMR shift reagents[45,46] (and hence, indicate that this chiral IL may not be used effectively as an NMR shift reagent), it is fully expected that this chiral IL can be effectively used as a chiral selector for other various spectroscopic techniques. Such a possibility was investigated, and the results are reported in the following section.

Chiral IL Facilitates Determination of Enantiomeric Compositions of Pharmaceutical Products. Atenolol, a beta blocker drug, was found to be readily soluble in (*S*)-CHTA$^+$Tf$_2$N$^-$ ionic liquid. Ten solutions of atenolol in (*S*)-CHTA$^+$Tf$_2$N$^-$ ionic liquid having the same total concentration of 60 mM with relatively different enantiomeric compositions (see Table 2) were prepared, and their NIR spectra were taken. If the chiral ionic liquid has enantiomeric recognition toward (*R*)- and (*S*)-atenolol, the disteereomeric interactions will lead to changes in the NIR spectra. Figure 4 shows 18 NIR spectra: a spectrum of the pure (*S*)-CHTA$^+$Tf$_2$N$^-$, spectra of the 10 standard solutions of atenolol, and spectra of 7 solutions of atenolol whose compositions are to be

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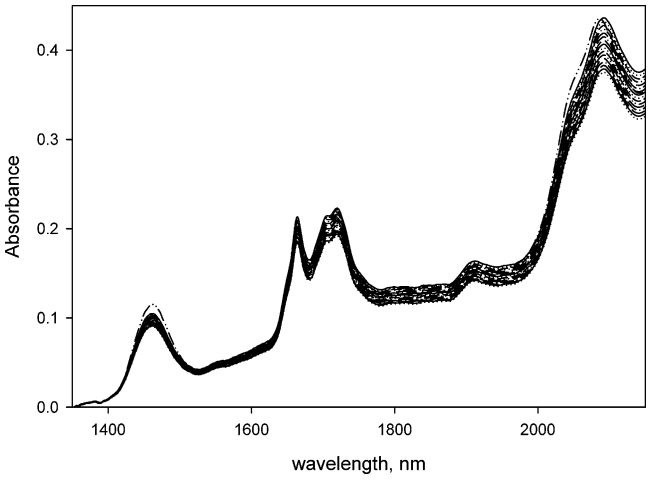

Figure 4. NIR spectra of the pure (*S*)-CHTA$^+$Tf$_2$N$^-$ and 17 solutions of atenolol with the same total concentration of 60 mM but different enantiomeric compositions.

calculated. It is evident from the figure that adding atenolol to the (*S*)-CHTA$^+$Tf$_2$N$^-$ solution leads to changes in the spectra. Of interest are the differences among the spectra of atenolol solutions. Since these atenolol solutions have the same total concentration (60 mM) but different enantiomeric compositions, the observed differences clearly indicate that, similar to cyclodextrins and sucrose,[11,12] the chiral (*S*)-CHTA$^+$Tf$_2$N$^-$ ionic liquid can differentiate (*R*)-atenolol from (*S*)-atenolol, and as expected, the diastereomeric interactions lead to changes in the NIR spectra. Similar to the procedures used in our previous studies,[11,12] a multivariate method of analysis (i.e., partial least-squares method (PLS)) was used to develop calibration models for subsequent determination of enantiomeric purity of unknown samples. Results from the PLS cross-validation show that calibration for 10 models requires a relatively small number of factors for optimal performance (12 for (*R*)-atenolol and 9 for (*S*)-atenolol). The root mean standard error of prediction (RMSEP) values are 0.122 and 0.109 for (*R*)- and (*S*)-atenolol, whereas the standard error of prediction (SEP) values are 0.120 and 0.110 for (*R*)- and (*S*)-atenolol, respectively.

To evaluate the effectiveness of this method, seven samples of atenolol with the same total concentration of 60 mM but different enantiomeric compositions were prepared, and the concentrations of (*R*)- and (*S*)-atenolol in each sample were calculated using the calibration models. Results obtained are shown in Figure 5, where the calculated concentrations of (*R*)- and (*S*)-atenolol in seven samples were plotted against actual concentrations. To illustrate the accuracy of the method, calculated concentrations of (*R*)-atenolol (in seven samples) were plotted separately from those of (*S*)-atenolol (of the same sample) (Figure 5). As expected, the calculated concentrations for both (*R*)-and (*S*)-atenolol are linearly related to actual concentrations. Furthermore, the linear relationship obtained for (*R*)-atenolol ($y = (0.97 \pm 0.09)x + (0.01 \pm 0.03)$) is, within experimental error, the same as that for (*S*)-atenolol ($y = (1.0 \pm 0.1)x + (0.01 \pm 0.09)$). In fact, both concentrations of (*R*)- and (*S*)-atenolol fit well into a single equation with $y = (1.03 \pm 0.04)x + (0.00 \pm 0.02)$ with correlation coefficient of 0.99999.

It is expected that the method is not specific to atenolol but is effective for other compounds, as well. This possibility was investigated by studying its effectiveness on other types of compounds, including two drugs (ibuprofen and propranolol) and two amino acids (alanine and phenylalanine). Figure 6A–D shows the results obtained when the calculated concentrations are plotted against actual concentrations. As illustrated, enantiomeric compositions for ibuprofen, propranolol, alanine, and phenylalanine can be accurately determined by this method. It is important to add that the five compounds studied here (atenolol, ibuprofen, propranolol, alanine, and phenylalanine) are different not only in their structures but also in their sizes, shapes, and solubility. Specifically, propranolol is probably the largest among them because it has a naphthalene ring. There is a phenyl ring in atenolol, ibuprofen, and phenylalanine, and alanine is the smallest because it does not have any aromatic ring at all. All of the compounds except ibuprofen are soluble in water. The solubility of ibuprofen in water is so poor that in our previous work (with cyclodextrins and sucrose as chiral selector[12]), instead of water,

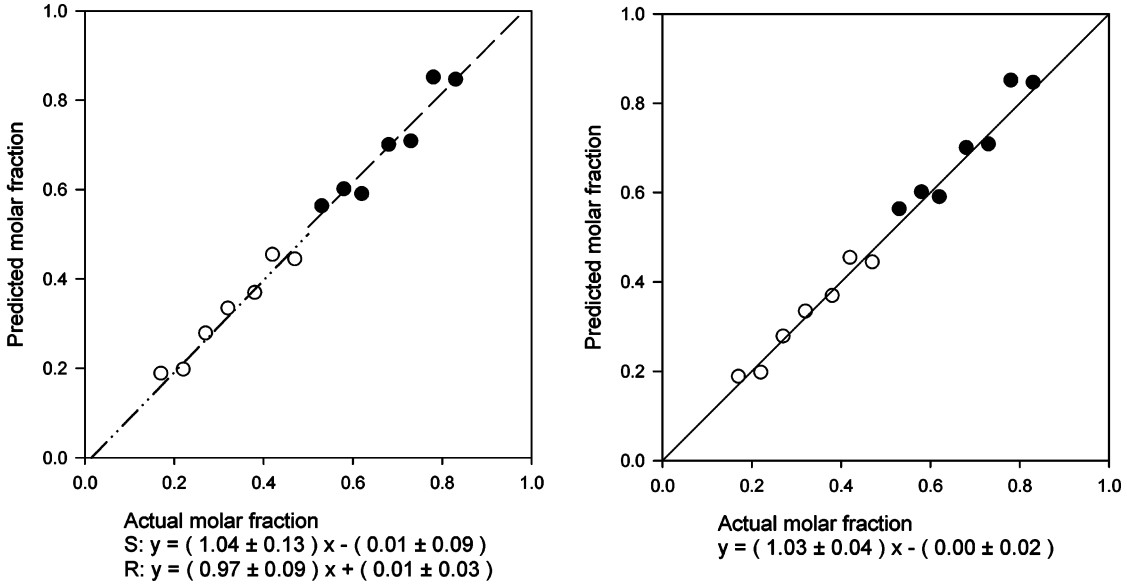

Figure 5. Predicted enantiomeric composition versus actual composition for 60 mM atenolol in (*S*)-CHTA$^+$Tf$_2$N$^-$ ionic liquid. Filled circles, (*S*)-atenolol; open circles, (*R*)-atenolol. Left: predicted (*R*)-atenolol values were plotted separately from (*S*)-atenolol; Right: (*R*)-atenolol and (*S*)-atenolol were plotted together.

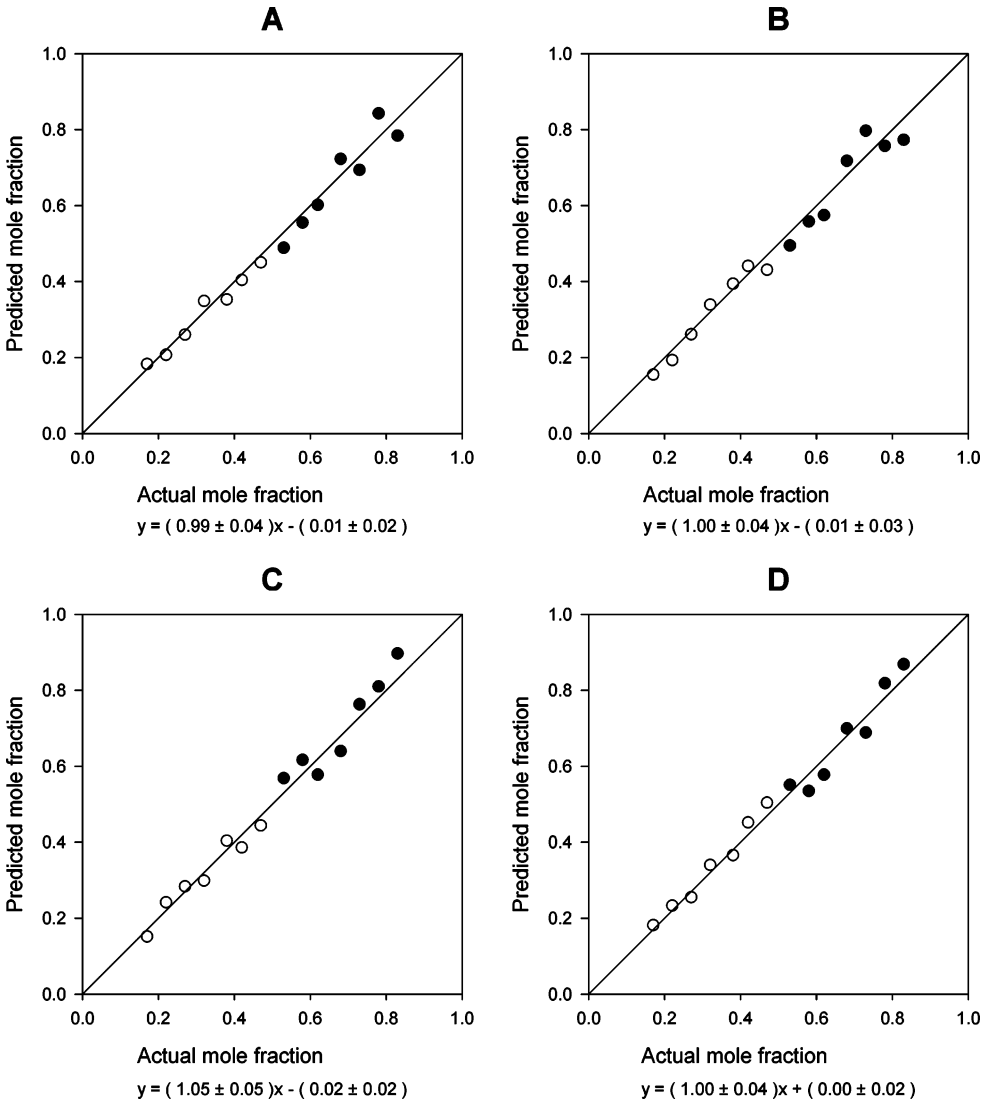

Figure 6. Predicted enantiomeric composition versus actual composition for 60 mM of (A) ibuprofen, (B) propranolol, (C) phenylalanine, and (D) alanine in (*S*)-CHTA$^+$Tf$_2$N$^-$ ionic liquid. Filled circles, *S* enantiomers for ibuprofen and propranolol and L-enantiomers for phenylalanine and alanine; open circles, *R* enantiomers for propranolol and D-enantiomers for phenylalanine and alanine.

we had to use a 30:70 ethanol/water mixture. It was not necessary to change the solvent in this case because CHTA$^+$Tf$_2$N$^-$ ionic liquid has such a high solubility power that it dissolves ibuprofen as well as it does propranolol and atenolol.

It is expected that similar to the method reported previously that is based on the use of cyclodextrins and sucrose, the present method should have a high sensitivity. Its sensitivity can be evaluated from two values: the lowest enantiomeric excess (EE % which is defined as ee% = [(*R* enantiomer − *S* enantiomer)/(*R* enantiomer + *S* enantiomer)]) that can be determined at the lowest concentration of a sample. It should be noted that these two terms are interdependent on each other; namely, the limit of detection (LOD) on ee% can be improved by increasing the sample concentration or vice versa. In an attempt to estimate the sensitivity of the method, we performed measurements on 10 samples of 10.0 mM or 2.66 mg/mL of atenolol with different ee%'s in (*S*)-CHTA$^+$Tf$_2$N$^-$. Results obtained are listed in Table 3. It is evident from the table that the method is not only effective but also very sensitive. It can accurately determine samples with concentration as low as milligrams having ee values as high as −90.00% (or +97.00%) and as low as 0.6%. Furthermore, even at an ee as low as 0.6%, the relative error was only 3.33%.

Table 3. Actual and Calculated Enantiomeric Excess of Solution of 10 mM Atenolol in (*S*)-CHTA$^+$Tf$_2$N$^-$ Ionic Liquid

	mole fraction		ee, %[a]		
sample	(*R*)-atenolol	(*S*)-atenolol	actual	calcd	rel error[b]
1	0.050	0.950	−90.00	−82.17	8.70
2	0.150	0.850	−70.00	−72.95	4.21
3	0.300	0.700	−40.00	−39.34	1.65
4	0.365	0.650	−27.00	−27.69	2.55
5	0.480	0.520	−4.00	−4.25	6.25
6	0.496	0.504	−0.80	−0.74	7.50
7	0.503	0.497	0.60	0.58	3.33
8	0.510	0.490	2.00	2.10	5.00
9	0.800	0.200	60.00	61.86	3.10
10	0.985	0.015	97.00	101.06	4.19

[a] Defined as ee (%) = [((*R*)-atenolol − (*S*)-atenolol)/((*R*)-atenolol + (*S*)-atenolol)] × 100. [b] Defined as relative error = [(actual value − calculated value)/(actual value)] × 100.

CONCLUSIONS

Collectively, the results presented clearly demonstrate that both enantiomeric forms of a novel chiral ionic liquid, (*R*)- and (*S*)-$[CHTA]^+[Tf_2N]^-$ can be readily synthesized in enantiomerically pure form by a simple ion exchange reaction from corresponding chloride salts that are commercially available. In addition to the ease of preparation, this chiral IL has a relatively high thermal stability (up to 300 °C), is liquid at room temperature (glass transition temperature of −58.4 °C), and exhibits strong enantiomeric recognition. The high solubility power and enantiomeric recognition ability of the IL make it possible to use this chiral IL to solubilize an analyte and to induce diastereomeric interactions for the determination of enantiomeric purity. In fact, we have successfully developed a new method based on the near-infrared technique with this chiral IL serving both as a solvent and as a chiral selector for the determination of enantiomeric purity. Enantiomeric compositions of a variety of pharmaceutical products and amino acids with different shape, size, and functional groups can be sensitively (microgram concentration) and accurately (enantiomeric excess as low as 0.60%) determined by use of this method. Because in this method, the chiral IL serves as both solvent and chiral selector, it is not necessary to add a carbohydrate compound or to perform the analysis in a variety of solvents. Relatively fewer and simpler calibration models are needed. As a consequence, the method will have wider applications and universal utility because it can be used for the analysis of all types of compounds with relatively shorter analysis time and easier procedure.

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SUPPORTING INFORMATION AVAILABLE

Additional information as described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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