Journal of chemical & engineering data

Article

Cite This: J. Chem. Eng. Data XXXX, XXX, XXX−XXX

pubs.acs.org/jced

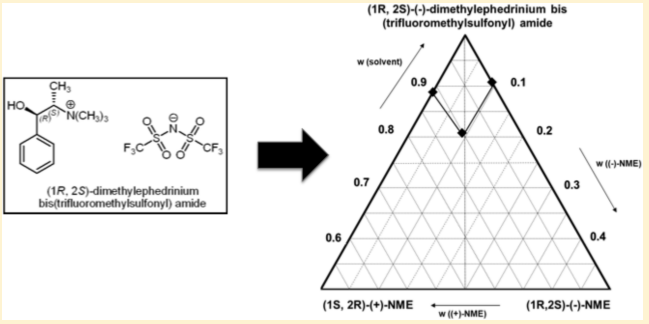
Solid−Liquid Equilibria of *N*-Methylephedrine Enantiomers and Their Mixtures in Two Chiral Ionic Liquids

Samuel Kofi Tulashie*[,†,‡] and Heike Lorenz[†]

[†]Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstrasse 1, D-39106 Magdeburg, Germany

[‡]College of Agriculture and Natural Sciences, School of Physical Sciences, Chemistry Department, Industrial Chemistry Unit, University of Cape Coast, Cape Coast 00233, Ghana

ABSTRACT: Solubility equilibria of the chiral *N*-methylephedrine species in two chiral ionic liquids, (*S*)-2-(methoxycarbonyl) pyrrolidinium bis-(trifluoromethylsulfonyl) amide ([(*S*)-2-Pro-Me][NTF_2]) and (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide, have been systematically studied. Solubility measurements were performed for [(*S*)-2-Pro-Me][NTF_2] at temperatures between 278 and 308 K and (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide at 308 K, both with different initial enantiomeric compositions of *N*-methylephedrine. Methanol as a cosolvent was used to decrease the viscosity of [(*S*)-2-Pro-Me][NTF_2]. The solubilities in [(*S*)-2-Pro-Me][NTF_2] increased with temperature increments. A considerable asymmetry was observed in the ternary solubility phase diagram of the chiral *N*-methylephedrine and (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide system. The accuracy of the solubility data for *N*-methylephedrine in (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide at 308 K was ascertained by evaluating the mean absolute error.



INTRODUCTION

Mostly, chemical synthesis or drug discovery of chiral substances leads to 50:50 mixtures of the two enantiomers that are typically recognized as racemates or racemic mixtures.[1] Usually, the enantiomer with the preferred features has to be retrieved consequently in pure form before it is marketed. Hence, for the pharmaceutical manufacturing, the production of the chiral pure substances is of particular importance.

On the background of the significance of the pure enantiomers and the huge available chiral market, a proficient production of single enantiomers would be extremely lucrative. Therefore, enantioselective crystallization is seen as a suitable method for the separation of enantiomers. Unfortunately, all efforts channeled in our previous work into the application of chiral solvents in direct enantioselective crystallization from solution as a possible way for the separation of the *N*-methylephedrine enantiomers have been proven to be unsuccessful.[2−4] Therefore, there is the need to apply a suitable solvent that would be able to promote chiral recognition (asymmetry in the ternary solubility phase diagram) in the *N*-methylephedrine system. Recently, Vasiloiu et al.[5] reported that chiral ionic liquids can demonstrate strong chiral interactions, and also Reichert et al.[6] examined the prospect of applying complex solvents such as ionic liquids for crystallization processes. Additionally, González et al.[7] and Chen et al.[8] demonstrated examples of an enantioselective asymmetric synthesis using chiral ionic liquid as a reaction medium. Hence, it appears worthwhile to use chiral ionic liquids as solvents in enantioselective crystallization of the *N*-methylephedrine chiral system.

N-Methylephedrine (NME) as a selected exemplary system belongs to the class of ephedrines. Ephedrines are potential central nervous stimulant drugs that are widely used in several pharmaceutical preparations.[9,10] In contemporary medicine, it is being applied for the treatment of asthma and bronchitis and similarly for the mitigation of symptoms related with cold and flu.[11,12]

This current work is focused on the determination of the ternary solid−liquid phase equilibria of *N*-methylephedrine enantiomers in the two chiral ionic liquids: (*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide ([(*S*)-2-Pro-Me][NTF_2]) and (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide. For the first solvent, data was measured over a wider temperature range between 278 and 308 K. For the latter solvent, data was determined at only one temperature 308 K because of the inadequate available amount of the solvent. The ternary solubility phase diagrams were derived from the obtained data for the two solute−solvent systems and discussed.

Received: December 23, 2018
Accepted: June 11, 2019

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

Table 1. Description of Materials Used

name	source	CAS no.	mass fraction purity	analysis method
(1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide[a]	synthesis		0.990	^{1}H NMR
(*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide[a]	synthesis		0.990	^{1}H NMR
(1*S*,2*R*)-2-(dimethylamino)-1-phenylpropan-1-ol	Sigma-Aldrich	42151-56-4	0.990	HPLC
(1*R*,2*S*)-2-(dimethylamino)-1-phenylpropan-1-ol	Sigma-Aldrich	552-79-4	0.990	HPLC
methanol	Merck KGaA	67-56-1	0.999	HPLC
2-propanol	Merck KGaA	67-63-0	0.999	HPLC

[a](*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide and (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide were synthesized by the group of Prof. Dr. Jürgen Klankermayer and Prof. Dr. Walter Leitner from RWTH Aachen, and Institute of Technical and Macromolecular Chemistry, Aachen, Germany, and the group of Dr. Peter Schulz and Prof. Dr. Peter Wasserscheid from Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute of Chemical Reaction Engineering, Germany, respectively.

EXPERIMENTAL SECTION

Materials. (1*S*,2*R*)-(+)-*N*-Methylephedrine ((1*S*,2*R*)-2-(dimethylamino)-1-phenylpropan-1-ol, CAS no. 42151-56-4) (**1**) and (1*R*,2*S*)-(−)-*N*-methylephedrine ((1*R*,2*S*)-2-(dimethylamino)-1-phenylpropan-1-ol, CAS no. 552-79-4) (**2**) were procured from Sigma-Aldrich with mass fraction purities of ≥0.99 and used as is. As solvents, (*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide ([(*S*)-2-Pro-Me][NTF_2]) (**3**) and (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide (**4**) were synthesized by the groups of Prof. Walter Leitners at RWTH Aachen and Prof. Peter Wasserscheids at Friedrich-Alexander-Universität, Erlangen-Nürnberg, respectively. In the case of the high-performance liquid chromatography (HPLC) analysis, 2-propanol from Merck KGaA, Darmstadt, with a mass fraction purity of ≥0.999 was applied. Methanol used for analytical purposes and partly as a cosolvent component was of HPLC grade from Merck KGaA with a mass fraction purity of ≥0.999. Table 1 gives a summary description of materials used in this work.

Figure 1 illustrates the chemical structures of the two chiral ionic liquids: (*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide ([(*S*)-2-Pro-Me][NTF_2]) and (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide.

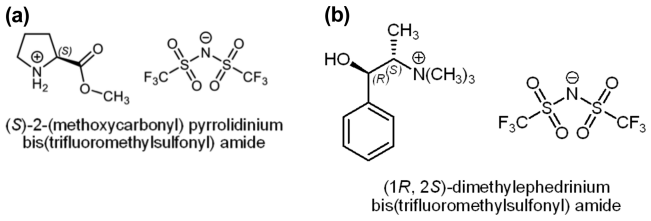


Figure 1. Chemical structures of the two chiral ionic liquids: (a) (*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide ([(*S*)-2-Pro-Me][NTF_2]) and (b) (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide.

Dissolution Kinetics Experiments. Dissolution kinetics experiments were conducted for a racemic mixture of the *N*-methylephedrine enantiomers and (1*S*,2*R*)-(+)-*N*-methylephedrine in the two chiral ionic liquid solvents, (*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl) amide/MeOH (70:30, v/v) at 278 K and (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide at 308 K, to estimate the minimum time needed to ascertain thermodynamic equilibrium in solubility measurements. Liquid phase samples were collected at specific time intervals from the suspension, and the concentrations were analyzed by HPLC. Equilibria for the two chiral ionic liquids were attained after about 9 and 12 h, respectively. Therefore, the equilibration time was established adequately beyond these values for at least 24 h.

Solubility Measurements. A standard isothermal method was employed for the determination of solubilities of chiral NME at temperatures in the range between 278 and 308 K in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) (solvent 1 in the following) and at 308 K in (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide (solvent 2 in the following). Methanol as a cosolvent was used to decrease the viscosity of the [(*S*)-2-Pro-Me][NTF_2]. The 70:30 ratio was ascertained by checking the optimum viscosity of the [(*S*)-2-Pro-Me][NTF_2] chiral ionic liquid. The method used to perform the solubility equilibria was published in our previous articles.[2,4] It signifies an isothermal method, where a mixture comprising a 5 mL solvent and a considerable excess of the solid phase (weighing of the solid phase with an analytical balance, resolution of balance: ±0.01 mg) was placed into a thermostated vial, which was agitated by a magnetic stirrer and maintained at isothermal conditions (with an uncertainty: ±0.1 K, thermostat, RC6 CP Lauda, Germany) until equilibrium was attained. Subsequently, the solid and liquid phases were separated with a glass filter (pore size, 10 μm) and analyzed. The liquid phase compositions were attained by means of HPLC after dilution with 2-propanol. Initial compositions of the NME enantiomers covered the full compositional range for solvent 1 and racemic mixture as well as the enantiomers for solvent 2.

High-Performance Liquid Chromatography. The concentrations of the solution and enantiomeric excess were analyzed with chiral HPLC: an Agilent HP 1100 unit with an Eurocel OD column (Knauer, 250 × 4.6 mm/5 μm) was applied. The column temperature was 25 °C with a flow rate of 1 mL/min, and an injection volume of 5 μL. A UV diode array detector was applied for peak detection at a wavelength of 254 nm. The eluent compositions were as follows: 85% *n*-hexane, 15% 2-propanol, and 0.1% diethylamine.

X-ray Powder Diffraction. The solid phases of all samples were performed under X-ray powder diffraction (XRPD) to verify for any crystalline modification (solvates and/or polymorphs) and guarantee that no new phases were produced. A PANalytical X'Pert Pro diffractometer (PANalytical GmbH, Germany) with Cu Kα radiation was applied. The samples were made on Si sample holders, and the diffraction angle range was set to 3−40° with a step size of 0.017° and a counting time of 50 s per step.

Viscosity. A DV-III ultra rheometer from Brookfield Company, U.S.A. with a cone spindle CPE 40 was employed to determine the viscosity of the two chiral ionic liquids: (*S*)-2-(methoxycarbonyl) pyrrolidinium bis(trifluoromethylsulfonyl)

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

amide and (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide. It has uncertainties such as: a temperature accuracy of ±0.1 K and a viscosity accuracy of ±1.0% of full-scale range for a particular spindle running at a definite speed. Fundamentally, the internal friction of the fluid sample is measured. Extremely viscous fluids require greater force to move than less viscous materials. Hence, viscosity can be expressed mathematically as

$$\eta = \frac{\tau}{\gamma} \tag{1}$$

where η denotes the viscosity, τ is the shear stress, and γ signifies the shear rate. The viscosity (in mPa·s) of the solvents was determined.

The mass fraction solubility of a component i (w_i) is expressed as

$$w_i = \frac{m_i}{\sum_{i=1}^{z} m_i} \tag{2}$$

where m_i represents the mass of the constituent i; in our case, the summation encompasses at all times the two enantiomers and either of the chiral ionic liquid as solvent and also methanol as a cosolvent.

The reproducibility of the solubility measurements was ascertained by replicating two experiments under the same conditions. Measurements were repeated two times only due to inadequate amount of the chiral ionic liquid available. Therefore, it was impossible to perform standard deviation analysis on the obtained solubility data. However, in Tables 2 and 3, summaries of two experiments conducted and their evaluated mean values are shown. This gives a primary impression of the accuracy of the solubility data obtained in this work because the value from each experiment (experiments 1 and 2) does not differ much from the other.

RESULTS AND DISCUSSION

The analytical technique and sample preparation applied for determining concentrations and enantiomeric compositions (ee) in the different solvents are described above. Figure 2 and 3 show typical chromatograms of racemic *N*-methylephedrine in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) and (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide, respectively. The separation factor (α) was determined according to eq 3, which provides an extent of the separation or the selectivity between the enantiomers.

$$\alpha = \frac{k_2}{k_1} = \frac{t_{R2} - t_0}{t_{R1} - t_0} \tag{3}$$

where k_1 is the capacity factor of component 1 (corresponding to peak 1), k_2 is the capacity factor of component 2 (peak 2), and t_0 is the dead time.

t_{R1} and t_{R2} are the roughly estimated retention times of the maximum signal for both components 1 and 2, respectively. The separation factor was estimated to be 1.5 and 1.6, respectively; approximately, a baseline separation was achieved. As seen, the (−)-enantiomer elutes before the (+)-enantiomer in both solvents.

The attained solubility measured data are summarized in Tables 2 and 3. Figure 4 illustrates the mean values of the measured solubilities of (1*S*,2*R*)-(+)-*N*-methylephedrine and the racemic mixture of *N*-methylephedrine in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) as a function of temperature.

Table 2. Solubility in Mass Fraction w_i of (1*S*,2*R*)-(+)-*N*-Methylephedrine (1) and (1*R*,2*S*)-(−)-*N*-Methylephedrine (2) in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) (3) under 101 kPa at Different Enantiomeric Excesses (ee) [ee = $|w_1 - w_2|/(w_1 + w_2)$] in the Liquid Phase and for Different Temperatures[a]

ee	$(w_1 + w_2)$	w_1	w_2	w_3
T = 278 K				
1.0000	0.3122	0.3122	0.0000	0.6878
0.4906	0.3600	0.2683	0.0917	0.6400
0.0002	0.4283	0.2142	0.2141	0.5717
0.4970	0.3630	0.0913	0.2717	0.6370
1.0000	0.3137	0.0000	0.3137	0.6863
T = 288 K				
1.0000	0.3400	0.3400	0.0000	0.6600
0.3962	0.3882	0.2710	0.1172	0.6118
0.0000	0.4556	0.2278	0.2278	0.5444
0.4359	0.3900	0.1100	0.2800	0.6100
1.0000	0.3358	0.0000	0.3358	0.6642
T = 298 K				
1.0000	0.3900	0.3900	0.0000	0.6100
0.3580	0.4542	0.3084	0.1458	0.5458
0.0001	0.5261	0.2631	0.2630	0.4739
0.3198	0.4384	0.1491	0.2893	0.5616
1.0000	0.3836	0.0000	0.3836	0.6164
T = 303 K				
1.0000	0.4163	0.4163	0.0000	0.5837
0.4497	0.4674	0.3388	0.1286	0.5326
0.0000	0.5558	0.2779	0.2779	0.4442
0.4444	0.4647	0.1291	0.3356	0.5353
1.0000	0.4100	0.0000	0.4100	0.5900
T = 308 K				
1.0000	0.4323	0.4323	0.0000	0.5677
0.5000	0.5000	0.3750	0.1250	0.5000
0.0000	0.5900	0.2950	0.2950	0.4100
0.5000	0.4978	0.1244	0.3734	0.5022
1.0000	0.4319	0.0000	0.4319	0.5681

[a]Standard uncertainties are $u(w)$ = 0.006, $u(T)$ = 0.1 K, and $u(P)$ = 1 kPa.

Table 3. Solubility in Mass Fraction w_i of (1*S*,2*R*)-(+)-*N*-Methylephedrine (1) and (1*R*,2*S*)-(−)-*N*-Methylephedrine (2) in (1*R*,2*S*)-(−)-Dimethylephedrinium Bis(trifluoromethylsulfonyl) Amide (4) under 101 kPa at Different Enantiomeric Excesses (ee) [ee = $|w_1 - w_2|/(w_1 + w_2)$] in the Liquid Phase and for a Temperature of 308 K[a]

experiments	ee	$(w_1 + w_2)$	w_1	w_2	w_4
1	1.0000	0.1115	0.1115	0.0000	0.8885
2	1.0000	0.1126	0.1126	0.0000	0.8874
mean	1.0000	0.1121	0.1121	0.0000	0.8879
1	0.0535	0.1908	0.1005	0.0903	0.8092
2	0.0535	0.1944	0.1024	0.0920	0.8056
mean	0.0530	0.1926	0.1014	0.0912	0.8074
1	1.0000	0.0926	0.0000	0.0926	0.9074
2	1.0000	0.0929	0.0000	0.0929	0.9071
mean	1.0000	0.0928	0.0000	0.0928	0.9072

[a]Standard uncertainties are $u(w)$ = 0.006, $u(T)$ = 0.1 K, and $u(P)$ = 1 kPa.

Generally, an increasing trend of the solubility with increasing temperature is observed. Further, the solubility of the racemic

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

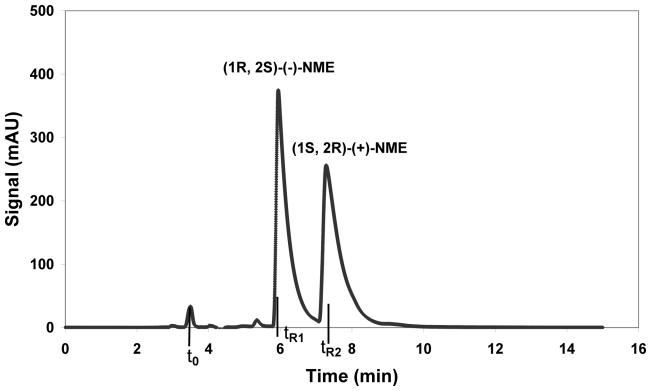


Figure 2. Chromatogram of racemic NME in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v).

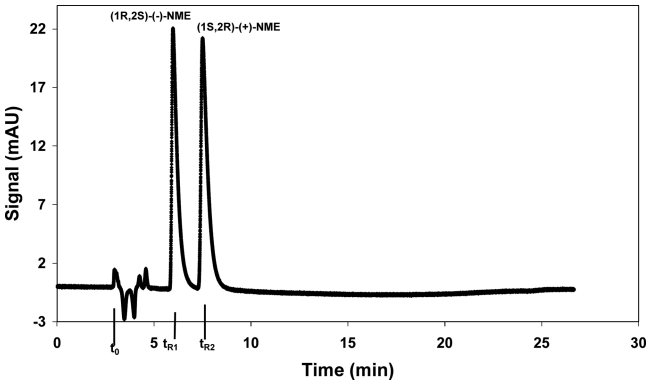


Figure 3. Chromatogram of racemic NME in (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide.

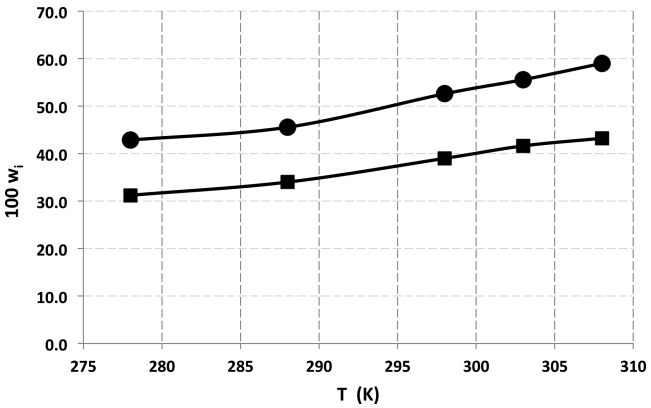


Figure 4. Average values of the mass fraction solubilities as follows: racemic mixture of *N*-methylephedrine (circle solid) and (1*S*,2*R*)-(+)-*N*-methylephedrine in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) at absolute temperatures between 278 and 308 K (box solid). The lines have been included as visualization help, and only the marked points show measured data.

mixture of *N*-methylephedrine is higher compared to the (1*S*,2*R*)-(+)-*N*-methylephedrine but not twice as proposed by Meyerhoffer[13] in the case of an ideal system. The structure of the solubility curve of the racemic mixture of *N*-methylephedrine is polynomial ($100w_i = 0.009t^2 - 4.7397t + 661.38$, with $R^2 = 0.9930$), and also for the enantiomer of (1*S*,2*R*)-(+)-*N*-methylephedrine ($100w_i = 0.0033t^2 - 1.5149t + 196.9$, with $R^2 = 0.9919$).

Figures 5 and 6 depict the derived ternary solubility phase diagrams of the *N*-methylephedrine enantiomers in the two

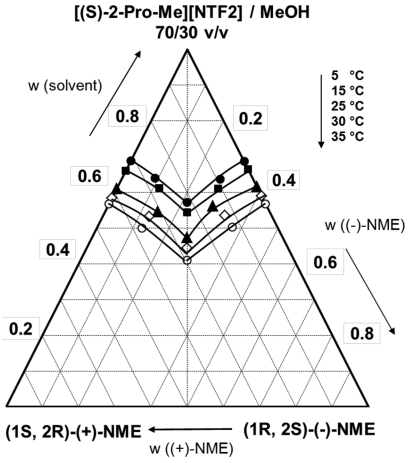


Figure 5. Ternary phase diagram of NME enantiomers in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v). The phase diagram is shown for isotherms at 278, 288, 298, 303, and 308 K. The isotherm lines are used as visualization help, and only the marked points illustrate measured solubility data.

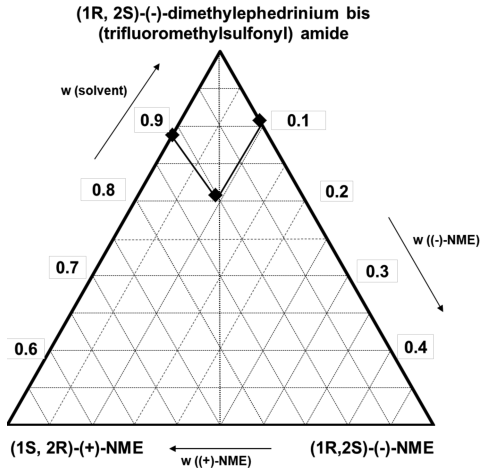


Figure 6. Ternary phase diagram of the NME enantiomers in (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide. Only the upper portion (50%) of the phase diagram is illustrated for the isotherm at 308 K. The isotherm line is applied as visualization help, and only the marked points depict measured solubility data.

solvents: [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) and (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide, respectively. Comparing the solubility values at 308 K for both solvents shows that solubilities are significantly higher in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70/30, v/v) than in (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide. This observed increment in solubility values might be attributed to the addition of a cosolvent (methanol) to reduce the viscosity (324.5 mPa·s, 25.05 °C) of the [(*S*)-2-Pro-Me][NTF_2]. Contrary, the viscosity of the (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide is very high (481.6 mPa·s, 23.10 °C) compared to [(*S*)-2-Pro-Me][NTF_2], but no cosolvent was included so as to preserve the structured nature of the chiral ionic liquid that might play a vital role in the chiral recognition process. Hence, the lower solubility values were

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

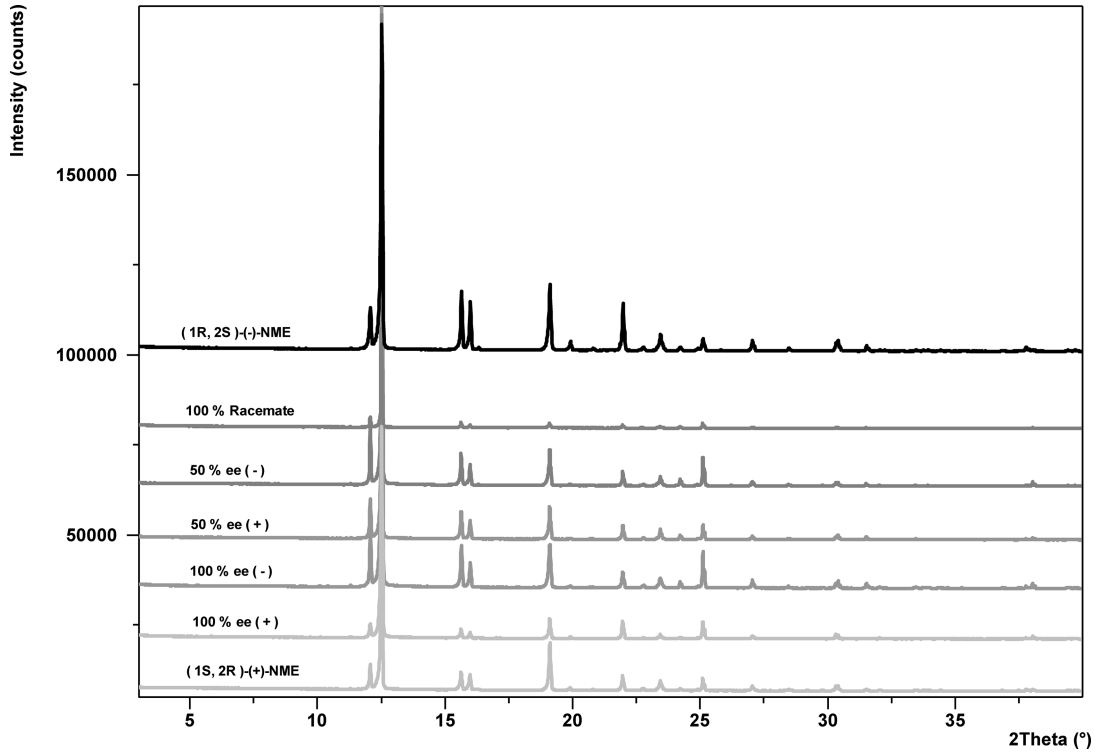


Figure 7. Experimental XRPD patterns for pure enantiomers, racemic NME, and the experimental compositions from [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) and *N*-methylephedrine at 35 °C.

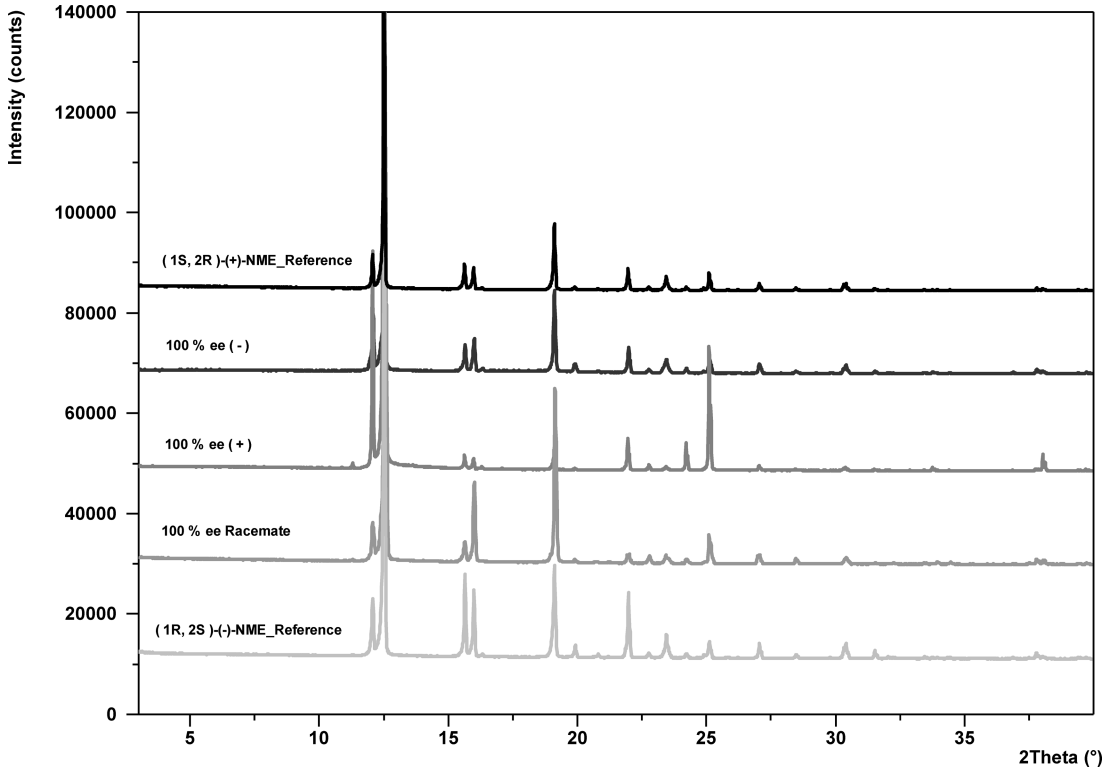


Figure 8. Experimental XRPD patterns for pure enantiomers and racemic NME from (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide and NME at 35 °C.

observed in (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide.

It is obvious that the solubility isotherms in Figures 5 and 6 relate to the normal shape of conglomerate type systems. The XRPD patterns from Figures 7 and 8 suggest conglomerate type systems, as the XRPD patterns of the different solid phase samples mimic the reference reflexes of the pure enantiomers and also similar to pattern simulated from crystal structures

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

reported for (−)-NME.[14] Furthermore, no extra or new phases (neither polymorphs nor solvates) different from those of the single enantiomers were observed from the obtained outcomes of the solid phase analysis by XRPD. Since NME in [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) clearly shows a conglomerate forming system (Figure 5), the reflexes of the enantiomers and the racemic mixture must be similar. The ternary solubility phase diagram shows a symmetrical mirror image with respect to the racemic axis rather than the expected asymmetry, which is feasible in chiral solvents. As it is established from the binary phase diagram of the chiral system, *N*-methylephedrine enantiomers do not form a racemic compound but rather a common eutectic (conglomerate) system.[15,16] This is illustrated distinctly in Figures 7 and 8 above.

However, in a closer look, Figure 6 shows an appreciable asymmetry in the ternary solubility phase diagram. The mean absolute error (MAE) was calculated to establish the level of accuracy of the measured solubility values with eq 4

$$\mathrm{MAE} = \frac{1}{n}\sum_{i-1}^{n} |x_i - x| \tag{4}$$

where n is the number of errors, and $|x_i - x|$ represents the absolute error. The evaluated MAE for (+)-*N*-methylephedrine enantiomer, (−)-*N*-methylephedrine enantiomer, and the racemic mixture of *N*-methylephedrine were 0.00015, 0.00055, and 0.0018, respectively, and negligible compared with the solubility data measured. Therefore, the corresponding solubility values in the ternary phase diagram are reliable. Since the accuracy of the solubility data in this case can be guaranteed, as the measured values are closer to the true values. This indicates that the (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide has a quantifiable chiral recognition with the NME enantiomers. The chiral ionic liquid employed here was "tailor-made" for the NME system, which means that it is task-specific to create a particular strong chiral interaction between itself and the chiral solute (NME). This observed effect might be due to the structured and "tailor-made" nature of the (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide, which can exhibit strong chiral interactions.[5] This observed asymmetry can be exploited for the enantioselective crystallization of the NME system in the (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide.

CONCLUSIONS

We studied the solid−liquid phase equilibria of the conglomerate forming system *N*-methylephedrine in both chiral ionic liquids: (*S*)-2-(methoxycarbonyl) pyrrolidinium bis-(trifluoromethylsulfonyl) amide ([(*S*)-2-Pro-Me][NTF_2]) and (1*R*,2*S*)-(−)-dimethylephedrinium bis-(trifluoromethylsulfonyl) amide. The obtained solubility data was employed to derive the ternary solubility phase diagrams. Asymmetry was observed in the solubility phase diagram of the chiral NME system in (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide. The accuracy of the solubility data for NME in this solvent was ascertained with the calculation of the mean absolute error (MAE), which indicated the reliability of the solubility values.

However, no chiral recognition was observed with regard to solubility equilibria for [(*S*)-2-Pro-Me][NTF_2]/MeOH (70:30, v/v) and NME. Therefore, in the case of [(*S*)-2-Pro-Me]-[NTF_2]/MeOH (70:30, v/v) in the NME system, the ternary solubility phase diagram is characterized by the symmetric behavior. This implies that there was no measurable chiral recognition in the liquid phase between the chiral solute and the chiral solvent molecules. This might be due to the inclusion of the cosolvent in the [(*S*)-2-Pro-Me][NTF_2]. Hence, (1*R*,2*S*)-(−)-dimethylephedrinium bis(trifluoromethylsulfonyl) amide is considered to be an appropriate solvent for a chiral separation of the studied pair of enantiomers due to the observed asymmetry in the ternary solubility phase diagram.

AUTHOR INFORMATION

Corresponding Author

*E-mail: stulashie@ucc.edu.gh. Phone: (00233) 0207232962.

ORCID

Samuel Kofi Tulashie: 0000-0002-6744-2917

Heike Lorenz: 0000-0001-7608-0092

Funding

We are thankful to the German Academic Exchange Service (DAAD) and the Max Planck Society for the financial support.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the group of Prof. Dr. Jürgen Klankermayer and Prof. Walter Leitner at RWTH Aachen, Institute of Technical and Macromolecular Chemistry, Aachen, Germany, and the group of Dr. Peter Schulz and Prof. Peter Wasserscheid from Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute of Chemical Reaction Engineering, Germany, for providing us with the two synthesized chiral ionic liquids used in this work. Furthermore, the authors thank Prof. Andreas Seidel-Morgenstern, C. Malwade, J. Kaufmann, and L. Borchert at the Max Planck Institute in Magdeburg for their help.

REFERENCES

(1) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, racemates and resolutions*; Krieger Publishing Company: Malabar, FL, 1994.

(2) Tulashie, S. K.; Lorenz, H.; Seidel-Morgenstern, A. Solid-Liquid Equilibria of N-Methylephedrine Enantiomers and Their Mixtures in Three Chiral Solvents Distinguished by Chain Length. *J. Chem. Eng. Data* **2010**, *55*, 5824−5828.

(3) Tulashie, S. K.; Lorenz, H.; Malwade, C. R.; Seidel-Morgenstern, A. Ternary Solubility Phase Diagrams of Mandelic Acid and N-Methylephedrine in Chiral Solvents with Different Carbon Chain Lengths. *Cryst. Growth Des.* **2010**, *10*, 4023−4029.

(4) Kaemmerer, H.; Tulashie, S. K.; Lorenz, H.; Seidel-Morgenstern, A. Solid-Liquid Phase Equilibria of N-Methylephedrine Enantiomers in Two Chiral Solvents. *J. Chem. Eng. Data* **2010**, *55*, 1131−1136.

(5) Vasiloiu, M.; Gaertner, P.; Zirbs, R.; Bica, K. Coordinating Chiral Ionic Liquids: Design, Synthesis, and Application in Asymmetric Transfer Hydrogenation under Aqueous Conditions. *Eur. J. Org. Chem.* **2015**, 2374−2381.

(6) Reichert, W. M.; Holbrey, J. D.; Vigour, K. B.; Morgan, T. D.; Broker, G. A.; Rogers, R. D. Approaches to crystallization from ionic liquids: complex solvents-complex results, or, a strategy for controlled formation of new supramolecular architectures? *Chem. Commun.* **2006**, 4767−4779.

(7) González, L.; Escorihuela, J.; Altava, B.; Burguete, M. I.; Luis, S. V. Chiral Room Temperature Ionic Liquids as Enantioselective Promoters for the Asymmetric Aldol Reaction. *J. Org. Chem.* **2014**, 5356−5363.

(8) Chen, D.; Schmitkamp, M.; Franciò, 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.

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX

(9) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharnaceutical Substances: Syntheses, Patent and Applications of the most relevant APIs*; 5th Ed.; Georg Thieme Verlag KG: Stuttgart, 2009.
(10) Ma, G.; Bavadekar, S. A.; Davis, Y. M.; Lalchandani, S. G.; Nagmani, R.; Schaneberg, B. T.; Khan, I. A.; Feller, D. R. Pharmacological Effects of Ephedrine Alkaloids on Human 1- and 2-Adrenergic Receptor Subtypes. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 214−221.
(11) Bensky, D.; Gamble, A. *Chinese Herbal Medicine-Materia Medica*; Eastland Press: Seattle, WA, 1985.
(12) Duke, J. A. *The Handbook of Medicinal Herbs*; CRC Press: FL, 1995.
(13) Meyerhoffer, W. Stereochemische Notizen. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 2604−2610.
(14) Staples, R. J.; Cho, E. Crystal structure of R,S-(−)-N-methylephedrine, $C_{11}H_{17}NO$. *Z. Kristallgr.* **2005**, *220*, 543−544.
(15) Wang, X. J.; Wiehler, H.; Ching, C. B. Physicochemical Properties and the Crystallization Thermodynamics of the pure Enantiomer and the Racemate for N-Methylephedrine. *J. Chem. Eng. Data* **2003**, *48*, 1092−1098.
(16) Tulashie, S. K.; Polenske, D.; Seidel-Morgenstern, A.; Lorenz, H. Solid-Phase and Oscillating Solution Crystallization behavior of (+)- and (−)-N-methylephedrine. *J. Pharm. Sci.* **2016**, *105*, 3359−3365.

DOI: 10.1021/acs.jced.8b01245
J. Chem. Eng. Data XXXX, XXX, XXX−XXX