



## Aggregation behaviour of chiral ionic liquids

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### ABSTRACT

The diastereomeric ionic liquid (IL) (1*R*,2*S*)-ephedrinium (*RS*)-methoxytrifluorophenylacetate **1** was synthesized and its aggregation behavior and diastereomeric interaction were investigated using two independent methods. The aggregation number of the IL in methylene chloride was determined by diffusion ordered NMR spectroscopy. Furthermore the concentration dependence of the signal split of the two diastereomeric ILs (1*R*,2*S*)-ephedrinium (*R*)-methoxytrifluorophenylacetate and (1*R*,2*S*)-ephedrinium (*S*)-methoxytrifluorophenylacetate was measured and could be linked to the aggregation number.

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### 1. Introduction

Chiral ionic liquids (CILs) are a versatile and interesting subclass of ionic liquids (ILs). They have been successfully used in analytical applications such as stationary phases in gas chromatography,<sup>1,2</sup> or as electrolytes in capillary electrophoresis,<sup>3–6</sup> as well as in asymmetric synthesis. Prominent examples are the Diels–Alder reaction,<sup>7–9</sup> the Baylis–Hillman reaction,<sup>10–12</sup> Michael additions,<sup>13</sup> and asymmetric hydrogenations.<sup>14–16</sup> CILs have also been used as effective organocatalysts.<sup>17–19</sup>

### 2. Results and discussion

All these examples suggest that high stereocontrol is obtained when ionic transition states are present during the reaction in question and that the chiral induction from a charged species to a neutral intermediate is much less effective. The understanding of specific cation–anion interactions is therefore crucial for designing a system in which the transfer of chiral information is maximized. A very elegant possibility to investigate these interionic interactions in ILs is diffusion ordered NMR spectroscopy (DOSY-NMR). This method, which has been successfully applied to a variety of ILs in the recent years,<sup>20–25</sup> provides access to the individual self-diffusion coefficients of cation ( $D^+$ ) and anion ( $D^-$ ) of an ionic liquid.

As the self-diffusion coefficient of an ion is to a large extent a function of its size and shape, it is possible to estimate its hydrodynamic radius  $r_H$  from the measured coefficients via the Stokes–Einstein-Equation:

$$D = kT/c\pi\eta r_H \quad (1)$$

in which  $k$  represents the Boltzmann-constant,  $T$  is the temperature,  $c$  is a numerical factor, and  $\eta$  is the viscosity of the solution. While

the temperature and viscosity can be easily measured,  $c$  has to be evaluated in a more complex procedure. An acceptable semiempirical approach to estimate  $c$  through Eq. (2) has been developed by Wirtz et al. using microfriction theory:<sup>26,27</sup>

$$D = kT[1 + 0.695r_{\text{sol}}^{2.234}/r_H]/6\pi\eta r_H \quad (2)$$

Here  $r_{\text{sol}}$  is the hydrodynamic radius of the solvent and  $r_H$  is the hydrodynamic radius of the solute. Next,  $c$  is determined via iteration with the calculated radius of the solute as a starting value.

A simplified procedure for metallorganic ionic species has recently been described.<sup>28</sup> We adapted this procedure to an ionic liquid solution. Provided that the hydrodynamic radius  $r_H^{\text{st}}$  of the solvent in which the ionic liquid is dissolved is known and can be used as an internal standard, the Stokes–Einstein-Equation largely simplifies to:

$$D^{\text{sa}}/D^{\text{st}} = c^{\text{st}}r_H^{\text{st}}/c^{\text{sa}}r_H^{\text{sa}} \quad (3)$$

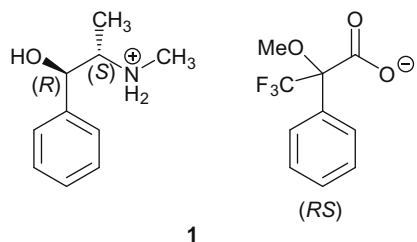
in which the suffix sa stands for the sample and st for the standard value. As the diffusion coefficients are measured and  $c$ -values determined via iteration, the hydrodynamic radius of the sample molecule can be easily determined. Under the assumption of spherical species, the volume of the diffusing species can now be determined. Furthermore, the so determined volumina can be compared to those obtained from the theoretical approaches. In the case of an ionic liquid the ratio of the measured volume of the anion or cation to the calculated volume of the ion pair  $V_{\text{calc}}^{\text{IP}}$  can thus be determined, representing the average aggregation numbers  $N^-$  and  $N^+$ , respectively.

$$N^{-/+} = V^{-/+}/V_{\text{calc}}^{\text{IP}} \quad (4)$$

An aggregation number of  $N = 1$  consequently describes a contact ion pair, a value of  $N = 0.5$  isolated and solvated ions, whereas higher numbers,  $N > 1$ , can be interpreted as the formation of higher aggregates.

We have investigated the dissociation and aggregation behavior of the doubly chiral ionic liquid (1*R*,2*S*)-ephedrinium (*RS*)-meth-

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**Figure 1.** (1*R*,2*S*)-Ephedrinium (*RS*)-methoxytrifluorophenylacetate.

oxytrifluorophenylacetate (ephedrinium mosherate) **1** in  $\text{CD}_2\text{Cl}_2$  as described above (see Fig. 1). A concentration range from  $2.5 \times 10^{-3}$  mol/l to  $6.4 \times 10^{-1}$  mol/l was scanned, with the higher concentration being limited by the IL's solubility.

Below a concentration of  $1 \times 10^{-3}$  mol/L a DOSY-measurement is problematic due to the poor signal to noise ratio and the very rapid decay of the signal intensity with increasing gradient strength. The volume of an ion pair ( $V_{\text{calc}}^{\text{IP}}$ ) of **1** was determined as  $359.58 \text{ \AA}^3$  using a semiempirical simulation tool (Materials studio, VAMP, AM1-dataset). As can be seen from Table 1, both the aggregation numbers  $N^+$  and  $N^-$  increase when increasing the concentration of the IL above a critical concentration of  $4 \times 10^{-2}$  mol/l. This is the critical concentration at which the aggregation number of the

ionic liquid is still **1** and it starts to increase significantly with higher concentrations, which indicates the formation of aggregates. Going to lower concentrations resulted in no further significant decrease in the aggregation number. This indicates that  $\text{CD}_2\text{Cl}_2$  is not able to stabilize the single solvated ions of this specific ionic liquid (see Fig. 2).

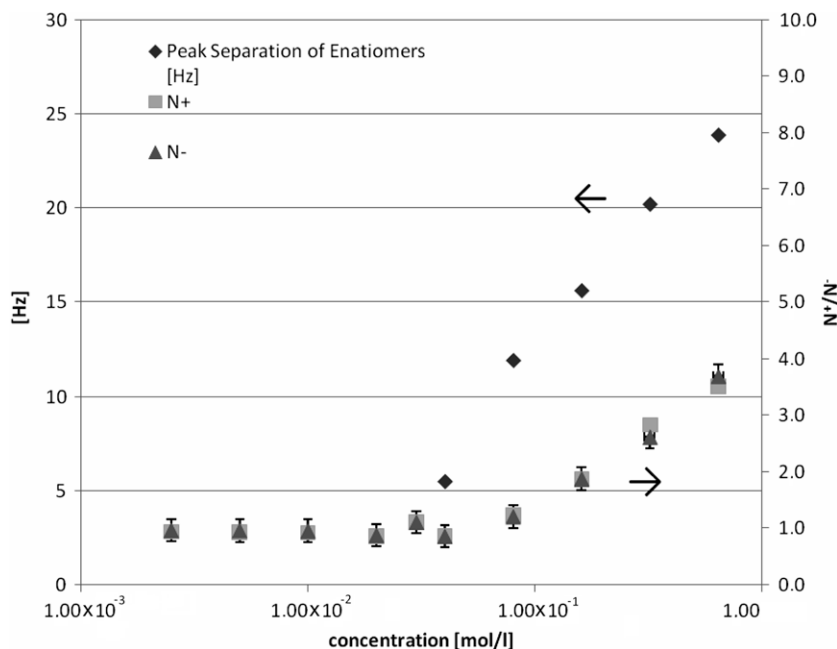
As we have shown in our earlier work,<sup>29</sup> the conjugate base of racemic Mosher's acid is a suitable probe molecule for the diastereomeric interaction between ionic species. Combining the anion of this racemic acid with an enantiopure cation gives rise to two signals of the  $\text{CF}_3$ -moiety in  $^{19}\text{F}$  NMR spectroscopy. This chemical shift difference qualitatively reflects the strength of the diastereomeric interaction between cation and anion.

We measured the peak separation as a function of the concentration of **1** in  $\text{CD}_2\text{Cl}_2$ . This study supports the findings of our earlier work as the peak separation increases when increasing the concentration. Interestingly, a significant peak separation could only be found from a minimum concentration of  $c > 4 \times 10^{-2}$  mol/l. This is the same concentration for which we have shown the aggregate formation to start.

A pronounced concentration dependency of signal splitting for diastereomeric electrolytes in solutions has often been described.<sup>29–33</sup> As a whole, these works indicate a general trend: At low concentrations, the split increases with increasing amount of electrolyte until a plateau is reached. At higher concentrations

**Table 1**  
Diffusion coefficients and aggregation numbers of **1** in  $\text{CD}_2\text{Cl}_2$

Concentration (mol/l)	Peak separation of enantiomers (Hz)	Diffusion coefficient ( $\text{m}^2/\text{s}$ )			$N^+$	$N^-$
		Cation	Anion	$\text{CD}_2\text{Cl}_2$		
$6.40 \times 10^{-1}$	23.88	$5.20 \times 10^{-10}$	$5.10 \times 10^{-10}$	$2.21 \times 10^{-9}$	3.5	3.7
$3.20 \times 10^{-1}$	20.21	$8.27 \times 10^{-10}$	$8.53 \times 10^{-10}$	$3.23 \times 10^{-9}$	2.8	2.6
$1.60 \times 10^{-1}$	15.62	$1.13 \times 10^{-9}$	$1.13 \times 10^{-9}$	$3.74 \times 10^{-9}$	1.9	1.9
$8.00 \times 10^{-2}$	11.94	$1.49 \times 10^{-9}$	$1.50 \times 10^{-9}$	$4.12 \times 10^{-9}$	1.2	1.2
$4.00 \times 10^{-2}$	5.51	$1.96 \times 10^{-9}$	$1.97 \times 10^{-9}$	$4.62 \times 10^{-9}$	0.9	0.9
$3.00 \times 10^{-2}$	None	$1.68 \times 10^{-9}$	$1.68 \times 10^{-9}$	$4.43 \times 10^{-9}$	1.1	1.1
$2.00 \times 10^{-2}$	None	$2.05 \times 10^{-9}$	$2.04 \times 10^{-9}$	$4.83 \times 10^{-9}$	0.9	0.9
$1.00 \times 10^{-2}$	None	$1.91 \times 10^{-9}$	$1.89 \times 10^{-9}$	$4.65 \times 10^{-9}$	0.9	1.0
$5.00 \times 10^{-3}$	None	$1.86 \times 10^{-9}$	$1.84 \times 10^{-9}$	$4.56 \times 10^{-9}$	0.9	1.0
$2.50 \times 10^{-3}$	None	$1.86 \times 10^{-9}$	$1.84 \times 10^{-9}$	$4.56 \times 10^{-9}$	0.9	1.0



**Figure 2.** Peak separation and aggregation numbers against concentration of **1** in  $\text{CD}_2\text{Cl}_2$ .

the split diminishes again. This behavior was interpreted as the subsequent aggregation of isolated ions to contact ion pairs and then to quadruples and/or higher aggregates. Efficient peak splitting was attributed to ion pair formation. We have now demonstrated that this is not necessarily the case. Obviously, in a contact ion pair of **1** the diastereomeric interaction is not strong enough to allow differentiation by NMR spectroscopy between the (*R,S*)(*R*)- and the (*R,S*)(*S*)-diastereomer. We suggest that a distinct arrangement of cation to anion is necessary to allow strong interaction. In the case of **1** this arrangement is enabled only in the aggregates.

### 3. Conclusion

Our work demonstrates that the concentration range that allows effective chirality transfer in synthetic applications can be rationalized by NMR spectroscopy. We anticipate that by using the herein described technique it will be possible to predict for a given reaction of a prochiral ion in a chiral ionic liquid the suitable concentration range for potential chirality transfer.

### 4. Experimental

NMR experiments were carried out with a Jeol ECX 400 MHz spectrometer with a 2-channel (HF, LF)-probe. Spectra were referenced to the solvent. The optical rotations were recorded with a Polartronic E, Schmidt + Haensch.

(1*R*,2*S*)-Ephedrinium (*RS*)-methoxytrifluoromethylphenylacetate **1** was synthesized by adding equimolar amounts of (*RS*)-methoxytrifluoromethylphenylacetic acid to (1*R*,2*S*)-ephedrine dissolved in dichloromethane. After stirring for 1 h the solvent was removed in vacuo and the product was obtained as white solid in quantitative yield.  $[\alpha]_D^{20} = +0.4$  (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, ppm): δ = 0.94 (d, 3H, CH-CH<sub>3</sub>, 3-H, <sup>3</sup>J = 6.8 Hz), 2.44 (s, 3H, OCH<sub>3</sub>), 2.99 (dq, 1H, CH-CH<sub>3</sub>, <sup>3</sup>J = 1.7 Hz, <sup>3</sup>J = 6.8 Hz), 3.51 (d, 3H, N-CH<sub>3</sub>, <sup>3</sup>J = 7.0 Hz), 5.28 (d, 1H, CH-OH, <sup>3</sup>J = 1.7 Hz), 7.23–7.33 (m, 8H, Phenyl-H), 7.62–7.67 (m, 2H, Phenyl-H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100.4 MHz, ppm): δ = 8.80 (d, CH-CH<sub>3</sub>), 30.89 (d, OCH<sub>3</sub>), 55.04 (d, N-CH<sub>3</sub>), 61.63 (d, CH-CH<sub>3</sub>), 70.24 (d, CH-OH), 85.36 (u, quart., CF<sub>3</sub>-C, <sup>3</sup>J = 26 Hz), 124.63 (CF<sub>3</sub>, <sup>1</sup>J = 287 Hz),<sup>†</sup> 125.74 (d, Phenyl-C), 127.57, 127.73, 127.79 (d, Phenyl-C), 128.20 (d, Phenyl-C), 128.43 (d, Phenyl-C), 128.91 (d, Phenyl-C), 135.26 (u, CF<sub>3</sub>-C-C), 139.84 (u, CH-C), 171.79 (u, CO). <sup>19</sup>F NMR (CDCl<sub>3</sub>, 376.3 MHz, ppm): δ = -69.78 (CF<sub>3</sub>). Anal. Calcd for C<sub>20</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>4</sub>: C, 60.14; H, 6.06; F, 14.27; N, 3.51; O, 16.02. Found: C, 60.11; H, 6.14; N, 3.40.

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<sup>†</sup> The <sup>13</sup>C-signal for CF<sub>3</sub>-moiety is not detectable with standard techniques using 1000 scans. It was detected by using a HF-HETCOR-experiment and an experiment with 10,000 scans using Fe(acac)<sub>3</sub> as a relaxation agent.