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Synthesis and properties of ionic liquids derived from the 'chiral pool'†

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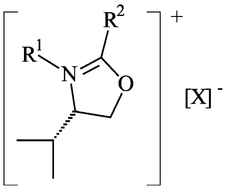
New chiral ionic liquids have been synthesised which are directly derived from the 'chiral pool' and therefore readily available in kg scale; NMR-measurements indicate that these liquids may be interesting solvents for enantioselective reactions and useful in chiral separation techniques.

Ionic liquids (ILs) are low melting (< 100 °C) salts which represent a new class of non-molecular, ionic solvents.[1–3] Nowadays, ILs are widely accepted as–often greener–alternatives to classical organic solvents in chemical transformations (for reviews see refs 1–3) and separation techniques (*e.g.* extraction,[4] chromatography[5]). Over the past few years the range of known and available ILs has been expanded so that many different candidates are accessible and even commercially available today.[6]

Surprisingly, the number of published examples for chiral ILs has been very limited so far. Howarth and co-workers described the use of chiral imidazolium cations in Diels–Alder reactions.[7] However, the synthesis of these systems required an expensive chiral alkylating agent. The use of ILs with chiral anions is somehow more obvious since some of these are readily available as sodium salts. For example, Seddon *et al.* investigated Diels–Alder reactions in lactate ILs.[8]

In the present paper, we describe for the first time ILs with chiral cations which are directly derived from the 'chiral pool'. These systems have been designed to meet the following criteria: a) easy preparation by direct synthesis in enantiopure form (up-scaling into kg scale possible); b) melting point < 80 °C; c) thermal stability up to 100 °C; d) good chemical stability *vs.* water and common organic substrates; e) relatively low viscosity.

Three different groups of chiral cations **1–3** have been identified which fulfil–at least to a large extent–these requirements.



1a: R^1= pentyl; R^2= ethyl;
$[X]^- = [PF_6]^-$

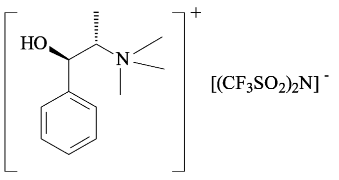
1b: R^1= methyl; R^2= ethyl;
$[X]^- = [PF_6]^-$

1

Ionic liquids of type **1** can be prepared by alkylation of the corresponding oxazoline with an alkylbromide followed by anion exchange. The oxazoline is prepared according to known procedures by reaction of the (*S*)-valinol with an aliphatic acid.[9] (*S*)-Valinol is easily accessible from (*S*)-valine by reduction with $NaBH_4$–H_2SO_4 in THF.[10,11] In this way **1a** has been obtained in 40% overall yield (referred to valine).‡ Its melting point is 63 °C (79 °C for **1b**). The enantiopurity of **1a** has been confirmed by ^{19}F-NMR spectroscopy after basic hydrolysis of **1a** and reaction with (*S*)-Mosher's acid chloride.

Even if **1a** and **1b** could be prepared in multi-gram scale, the relatively low overall yield of the four step synthesis is still a concern for the practical use of type **1** ionic liquids. Moreover, the oxazolinium cation was found to be of low stability under acidic conditions where ring opening was observed to a large extent.

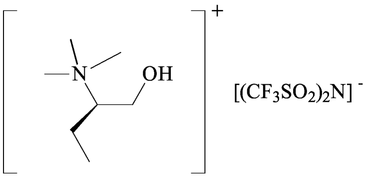
These considerations led to the development of IL **2** which is more readily obtained from the alkaloid ephedrine in a three step synthesis. Leuckart–Wallach reaction followed by alkylation with Me_2SO_4 and ion exchange in aqueous solution resulted in 80% overall yield for the synthesis of **2**.§



2

Compound **2** has a melting point of 54 °C and is stable up to 150 °C under high vacuum conditions (10^{-3} mbar). As expected, it shows a miscibility gap with water which generally allows its application for extractions from aqueous solutions.

The quest for room temperature liquid ILs with chiral cation resulted in the synthesis of IL **3**.



3

Compound **3** is obtained in a very similar manner as **2**.¶ It was prepared in 75% overall yield and is still a liquid at −18 °C. At room temperature, its viscosity is surprisingly low (η = 0.155 Pa*s at 20 °C). As **2**, this chiral IL shows good thermal stability up to 150 °C under high vacuum conditions (10^{-3} mbar). The enantiopurity of **2** and **3** has been confirmed by ^{19}F-NMR spectroscopy after esterification of **2** and **3** with (*S*)-Mosher's acid chloride. The synthesis of **3** has been carried out on a kg scale without loss in yield or enantiopurity.

After having successfully established the synthesis of type **1–3** ionic liquids our interest was to evaluate the usefulness of these compounds for enantioselective reactions and separation techniques. However, instead of screening specific applications we decided to choose a more general approach. Our aim was to investigate solutions of racemic substrates in the chiral ionic liquids by NMR spectroscopy and to look for diasteriomeric interactions between substrate and IL. Obviously, those interactions would be essential for all kinds of chirality transfer from the chiral IL onto the substrate.

In detail, these interactions have been probed by ^{19}F-NMR spectroscopy using a racemic mixture of Mosher's acid sodium

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† Electronic supplementary information (ESI) available: characterisation of compounds **1a**, **2** and **3**. See http://www.rsc.org/suppdata/cc/b1/b109493a/

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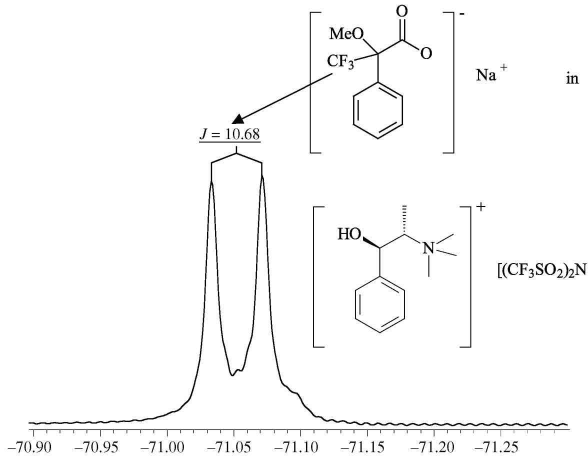

Fig. 1 ^{19}F-NMR of *rac*-Mosher's acid sodium salt in **2**.

salt as substrate and **2** as chiral ionic liquid.|| One of the recorded spectra is presented in Fig. 1.

The split of the signal related to the CF$_3$-group of the racemic substrate clearly demonstrates that the substrate has been dissolved in a chiral environment. Moreover, the extent of peak splitting can be assigned to the strength of the diastereomeric interactions. In this regard it is interesting to note that the chemical shift difference for the two diastereomeric CF$_3$-groups depends on the concentration of the ionic liquid in the NMR solvent. Moreover, the influence of water added to the chiral ionic liquid is of major influence for the extent of signal splitting (Fig. 2).

In conclusion, we could demonstrate that ILs with chiral cations can readily be prepared in enantiopure form from the 'chiral pool'. Some of the tested systems combine high thermal stability with low viscosity which makes them interesting solvent candidates for many applications in chemical synthesis and separation techniques. The general possibility of diastereomeric interactions between an enantiopure IL and a chiral substrate has been demonstrated by NMR spectroscopy.

From this starting point, more research to fully evaluate the potential of these new chiral systems in synthetic and analytical applications is actually ongoing in our laboratories. In detail, we are currently studying the use of chiral ILs in the resolution of racemates by co-crystallisation or extraction, and as solvents for asymmetric synthesis and catalysis as well as NMR spectroscopy. Furthermore, the application of chiral ILs as mobile or stationary phases in chromatography is under investigation.

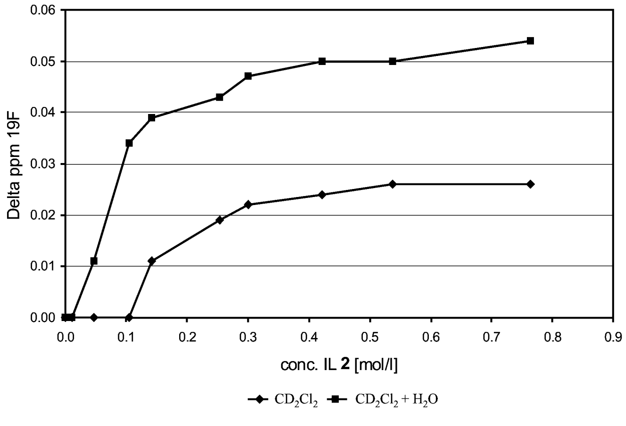

Fig. 2 ^{19}F-NMR of *rac*-Mosher's acid sodium salt in **2**–concentration dependence and influence of added water (saturated solution of **2** at 25 °C).

Notes and references

‡ Synthesis of **1a**: 97 g (*S*)-valinol (94% yield) was obtained from 117.15 g (1 mol) (*S*)-valine following the procedure of Masamune *et al.*[10] According to prior work,[9] 103.16 g (1 mol) valinol was reacted with 74.08 g (1 mol) propionic acid to yield 67.8 g (*S*)-2-ethyl-4-isopropyloxazolin (48% yield). 29 g (0.2 mol) of the latter was mixed with 62 g pentyl bromide (0.4 mol) and refluxed for 2 d. The remaining pentylbromide was removed under high vacuum to yield 89.2 g (0.196 mol, 98% yield) of crude (*S*)-2-ethyl-3-pentyl-4-isopropyloxazolinium bromide. 7 g (24 mmol) of the oxazolinium bromide was dissolved in 50 ml water and 6.6 ml (31 mmol) of a 65% hexafluorophosphoric acid was added. The resulting precipitate was washed with water and dried under high vacuum to give 7.8 g (91% yield) (*S*)-2-ethyl-3-pentyl-4-isopropyloxazolinium hexafluorophosphate (mp = 63 °C).^{1}H-NMR (300 MHz), CDCl$_3$–TMS: δ = 0.78–1.10 (9H), 1.18–1.33 (7H), 1.68 (m, 2H), 2.22 (m, 1H); 2.73 (m, 2H), 3.40 (m, 1H), 3.63 (m, 1H), 4.46 (m, 1H), 4.64 (m, 1H), 4.90 (m, 1H); ^{13}C-NMR (75 MHz), CDCl$_3$–TMS: δ = 7.99, 13.27, 13.45, 17.38, 19.95, 21.72, 26.04, 26.50, 28.13, 45.34, 65.53, 71.11, 178.63; ^{19}F-NMR (282 MHz), CDCl$_3$–CCl$_3$F: δ= −72.9 (d, *J* = 710 Hz); ^{31}P-NMR (121 MHz), CDCl$_3$: δ = −143.2 (hept, *J* = 710 Hz).

§ Synthesis of **2**: (−)-*N*-Methylephedrine was prepared from (−)-ephedrine according to known literature[12] in 87% yield. 17.9 g (0.1 mol) *N*-methylephedrine was dissolved in 50 ml dichloromethane and 12.6 g (0.1 mol) Me$_2$SO$_4$ was slowly added. The solvent was removed under reduced pressure and the residue dissolved in water. Addition of an aqueous solution of 31.6 g (0.11 mol) Li[(CF$_3$SO$_2$)$_2$N] led to the separation of an ionic liquid phase which was washed three times with 50 ml water. Drying of the ionic liquid phase at 100 °C under high vacuum resulted in 43.7 g (92% yield) (−)-*N*,*N*-dimethylephedrinium-bis(trifluoromethanesulfon)imidate (mp = 54 °C).^{1}H-NMR (300 MHz), DMSO–TMS: δ = 1.16 (3H, d, *J* = 6.4 Hz), 3.22 (9H, s), 3.65 (1H, dq, *J* = 6.4 Hz, *J* = 6.8 Hz), 5.41 (1H, d, *J* = 6.8 Hz), 6.06 (1H, s), 7.19–7.31 (5H, m); ^{13}C-NMR (75 MHz), DMSO–TMS: δ = 6.5, 51.5, 68.5, 73.6, 119.5 (q, *J* = 321.6 Hz), 125.8, 127.4, 128.1, 141.9; ^{19}F-NMR (282 MHz), DMSO–CCl$_3$F: δ = −79.3.

¶ Synthesis of **3**: **3** (mp < −18 °C) was prepared from (*R*)-2-aminobutan-1-ol in 75% overall yield following the method described for the synthesis of **2**.^{1}H-NMR (300 MHz), CD$_3$CN/TMS: δ = 1.03 (3H, t, *J* = 7.2Hz), 1.83 (2H, m), 3.06 (9H, s), 3.09 (1H, m), 3.4 (1H, s), 3.83 (1H,m), 4.2 (1H, m); ^{13}C-NMR (75 MHz), CD$_3$CN/TMS: δ = 11.4, 18.7, 53.2, 57.7, 77.7, 120.8 (q, *J* = 321Hz). ^{19}F-NMR (282 MHz), CD$_3$CN/CCl$_3$F: δ = −78.9.

|| NMR Experiment: 10 mg of sodium-(*S*)-2-methoxy-2-(trifluoromethyl)-phenylacetate was dissolved in 150 mg of **2**. This mixture was dissolved in 0.35 ml CD$_2$Cl$_2$ and the spectrum was recorded. For the spectrum in water-saturated IL, 0.2 ml water was added to the above mentioned mixture and the mixture was shaken. The spectrum of the IL layer was recorded.

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