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Facile synthesis of ionic liquids possessing chiral carboxylates

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Abstract—The synthesis of 23 new chiral ionic liquids is achieved in high yield and purity by the reaction of an amino acid or a chiral carboxylic acid with tetrabutylammonium hydroxide in water.

1. Introduction

Ionic liquids (ILs) are generally defined as salts that melt below 100 °C to afford liquids comprised solely of anions and cations. The cations are generally bulky, asymmetric ammonium or phosphonium ions or hetero-aromatics (e.g., imidazolium and pyridinium) with a low symmetry, weak intermolecular interactions and low charge densities.[1] Typically, the anions are inorganic and include $[PF_6]^-$, $[BF_4]^-$, $[AlCl_4]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO_2)_2N]^-$. Ionic liquids exhibit a number of physical properties that may be exploited in synthetic processes, such as low viscosities, negligible vapour pressures under ambient conditions, good solubilising properties for a broad spectrum of inorganic, organic and polymeric materials, and immiscibility with many organic solvents (allowing easy separations). In addition, ILs are 'tunable' as they comprise two ions allowing for manipulation of physical properties by choosing the appropriate anion and/or cation.[1]

The synthesis of chiral ILs (CILs) has received increasing attention over the last two years. Recently, CILs comprised of imidazolium cations and amino-acid anions,[2] and tetrabutylphosphonium cations combined with amino-acid anions[3,4] have been synthesised by Fukumoto et al., while Tao et al.[5] synthesised a series of CILs in which the amino acid comprised a chiral cation. It is anticipated that the use of CILs in asymmetric organic syntheses will result in chiral induction without the use of expensive chiral metal catalysts: it has previously been shown that chiral solvents can achieve low enantioselectivities in asymmetric reactions.[6]

Commonly, ILs are prepared by anion exchange of halide salts with metal salts. This method has limitations in the preparation of pure ILs due to contamination by metal halide salts. In addition, this approach is limited by the lack of suitable commercially available metal salts. Furthermore, the use of silver salts in anion exchange reactions of ILs containing amino acids is problematic due to the formation of stable silver amino acid complexes.[7] Consequently, the development of synthetic approaches to ILs based on amino acids requires that no such metal ions are employed to avoid irreversible contamination of the desired products. Here, we describe a straightforward synthesis of a series of ILs with chiral carboxylates, utilising inexpensive, commercially available starting materials and exploiting simple acid-base chemistry, thus avoiding the use of metal salts and ion exchange.

Tetrabutylammonium hydroxide, [TBA]OH, is a strong base, which readily deprotonates the carboxylic acid moiety of amino acids and organic acids to form a carboxylate salt and water. The bulky nature of the tetrabutylammonium cation reduces intermolecular attractions, thus maximising the probability of the resulting salt being a liquid at room temperature. A large range of tetrabutylammounium salts were produced with this method and some of their physical properties are listed in Table 1. All compounds are liquids at room temperature, except for [TBA][Asn]. The salts of *N*-acetylcysteine, histidine, phenylalanine, tartaric acid and malic acid are extremely viscous oils at room temperature. The colour of the liquids ranges from colourless to orange. In the case of histidine, the isolated salt was initially

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Table 1. Physical properties and ^{1}H NMR shifts of the chiral proton of [TBA][carboxylate] salts

Ionic liquid	Colour	State at rt (mp (°C))[d]	$[\alpha]_D^{20}$[e]	δ (ppm) of α-CH in starting acid[h]	δ (ppm) of α-CH in CIL[h]
[TBA][L-Ala]	Pale yellow	Liquid	1.65	3.80	3.35
[TBA][L-Asn]	Colourless	Solid (42–44)	−4.30	4.03	3.59
[TBA][*N*-Ac-L-Cys]	Pale yellow	Oil	−41.44[f]	4.64	4.28
[TBA][L-HGlu]	Pale yellow	Liquid	−1.53	3.84	3.77
$[TBA]_2$[L-Glu]	Yellow	Liquid	1.86	3.84	3.31–3.19[i]
[TBA][D-HGlu]	Pale yellow	Liquid	1.42	3.84	3.77
$[TBA]_2$[D-Glu]	Yellow	Liquid	−2.26	3.84	3.31–3.19[i]
[TBA][L-Gly]	Pale yellow	Liquid	—[g]	3.57	3.25–3.19[i]
[TBA][L-His]	Orange	Oil	−1.68[f]	4.00	3.51
[TBA][L-Met]	Yellow	Liquid	1.22	3.89	3.36
[TBA][L-Phe]	Yellow	Oil	−0.83	4.06	3.53
[TBA][L-Pro]	Yellow	Liquid	−28.49	4.15	3.49
[TBA][L-Ser]	Pale yellow	Liquid	−0.74	3.86	3.36
[TBA][L-Thr]	Pale yellow	Liquid	−1.53	3.61	3.11
[TBA][L-Val]	Yellow	Liquid	4.10	3.62	3.07
[TBA][L-HTar][a]	Colourless	Oil	10.42[f]	4.75	4.52
$[TBA]_2$[L-Tar][a]	Colourless	Oil	11.08[f]	4.75	4.34
[TBA][D-HTar][a]	Colourless	Oil	−10.20[f]	4.75	4.52
$[TBA]_2$[D-Tar][a]	Pale yellow	Oil	−11.22[f]	4.75	4.34
[TBA][L-HMal][b]	Colourless	Oil	−2.41	4.63	4.51
$[TBA]_2$[L-Mal][b]	Pale yellow	Oil	0.90	4.63	4.42
[TBA][L-Man][c]	Colourless	Liquid	40.58[f]	5.30	4.98
[TBA][D-Man][c]	Colourless	Liquid	−39.28[f]	5.30	4.98

[a] Tar = tartrate.
[b] Mal = malate.
[c] Man = mandelate.
[d] Mp for those salts that are solids at room temperature.
[e] *c* 10, H_2O.
[f] *c* 5 in H_2O.
[g] This salt is achiral.
[h] ^{1}H NMR performed at 300 MHz in D_2O.
[i] α-H peak obscured by overlap with protons of the tetrabutylammonium counterion.

deep orange in colour; however, upon treatment with activated charcoal and filtration through silica gel, the salt was obtained as a viscous orange oil.

In the ^{1}H NMR spectra there is a clear evidence for the deprotonation of the free acid. A comparison of the chemical shifts of the α-proton in the starting acid and the subsequent CIL (Table 1) shows a clear upfield shift in the resonances. This upfield shift is consistent with the increasing electron density in the carboxylate moiety upon deprotonation and is clearly illustrated by a comparison of the ^{1}H NMR spectrum of L-tartaric acid with the spectra of the ILs [TBA][L-HTar] and $[TBA]_2$[L-Tar] (Fig. 1). In the case of the ^{1}H NMR spectrum for [TBA][L-HTar] the resonance for proton (A) is not split into the expected doublet due to a fast exchange on the NMR timescale.

The optical rotations, $[\alpha]_D^{20}$, for all of the CILs reported here were measured in aqueous solutions (Table 1). In most cases the magnitude of the optical rotation is smaller than that of the free amino acid: the one exception to this is [TBA][*N*-Ac-L-Cys] which has $[\alpha]_D^{20}$ −41.44 (*c* 5, H_2O) (cf. *N*-Ac-L-Cys $[\alpha]_D^{20}$ +5.3 (*c* 5, H_2O)). For a number of the CILs ([TBA][L-Asn], [TBA][*N*-Ac-L-Cys], [TBA][L-HGlu], [TBA][D-HGlu], [TBA][L-Phe], [TBA][L-Ser] and $[TBA]_2$[L-Mal]), the direction of rotation of the plane of the polarised light is opposite to that of the starting acid. This phenomenon has been previously observed for a variety of amino acids in the presence of an acid or a base.[8] In the case of the CILs possessing L- and D-glutamic acid, the $[\alpha]_D^{20}$ changes direction upon increasing the number of equivalents of [TBA]OH added: this has been ascribed simply to the formation of the salt and is not the result of any racemisation or inversion of the chiral centre.[8] Furthermore, the variation of the $[\alpha]_D^{20}$ of the CILs cannot be compared in any meaningful way to that of the free amino acid as ab initio calculations have shown that variations in conformational structure result in variation of the $[\alpha]_D^{20}$ values.[9,10]

The chiral integrity of the ILs was tested by comparing the $[\alpha]_D^{20}$ of a decomposed IL with that of the parent amino acid at the same concentration (reacting [TBA][L-HGlu] or $[TBA]_2$[L-Glu] with 5 M HCl). Furthermore, the comparison of the $[\alpha]_D^{20}$ of the corresponding solutions with that of the free amino acid (in 5 M HCl) showed that no racemisation of the chiral centre had occurred during the formation of the ILs.

The CILs synthesised herein are soluble in water, acetonitrile, acetone, dichloromethane and chloroform. All of the CILs are insoluble in diethyl ether, hexane and toluene. The thermal stability of these ILs is low. The amino acid-based ILs showed significant darkening when heated to temperatures of 110 °C or more.

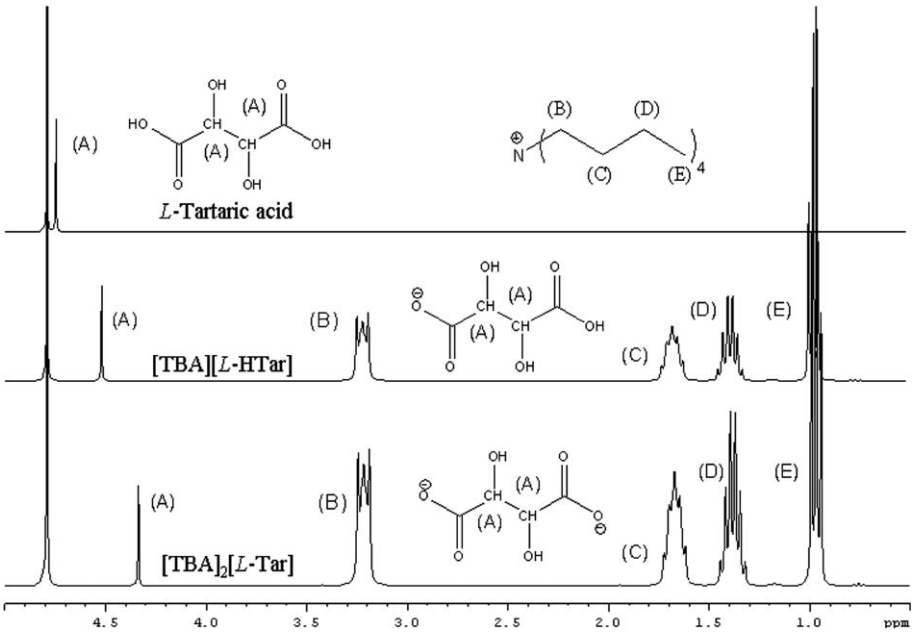

Figure 1. ^{1}H NMR (300 MHz, D_2O) of L-tartaric acid and the corresponding ILs resulting from the reaction with one and two equivalents of [TBA]OH, respectively.

However, those ILs based upon the chiral acids showed no signs of decomposition when heated at 110 °C for 24 h.

In conclusion, we have presented a straightforward route towards a series of CILs, which are expected to have a high potential as chiral solvents and in chiral separations.

2. General procedure for the synthesis of [TBA]carboxylates

An aqueous solution of tetrabutylammonium hydroxide (40% w/w, 13 mmol) was added to an aqueous suspension of the desired amino acid (13 mmol). The resultant reaction mixture was heated at 60 °C for 2 h. The water was removed in vacuo at 80 °C. The resultant residue was dissolved in CH_3CN (50 mL) and filtered to remove the unreacted amino acid. The filtrate was dried over Na_2SO_4, filtered and the solvent was removed in vacuo to afford the desired product.

3. Data for three members of the series of new compounds

3.1. Tetrabutylammonium L-alanate [TBA][L-Ala]

Yield 98%. $[\alpha]_D^{20}$ +1.65 (*c* 10, H_2O). ^{1}H NMR (D_2O): δ 3.35 (q, 1H, $^{3}J_{HH} = 7.11$ Hz, O_2C–C*H*), 3.22 (m, 8H, TBA), 1.67 (m, 8H, TBA), 1.38 (m, 8H, TBA), 1.25 (dd, 3H, $^{3}J_{HH} = 7$ Hz, H_3C–C–NH_2), 0.97 (t, 12H, $^{3}J_{HH} = 7$ Hz, TBA) ppm. $^{13}C\{^{1}H\}$ NMR (D_2O): δ 184.9, 58.74, 52.05, 23.74, 20.94, 19.76, 13.47 ppm. MS [ESI-] (*m*/*z* (%)): 88.4 ([M]$^-$, 77). Anal. Found: C, 65.51; H, 12.87; N, 8.22. Calcd for $C_{19}H_{42}N_2O_2{\cdot}H_2O$: C, 65.45; H, 12.73; N, 8.04.

3.2. Tetrabutylammonium L-histidinate [TBA][L-His]

Yield 85%. $[\alpha]_D^{20}$ −1.68 (*c* 5, H_2O). ^{1}H NMR (D_2O): δ 7.68 (s, 1H, N=C*H*–NH), 6.93 (s, 1H, *H*N–CH=C), 3.51 (dd, 1H, $^{3}J_{H1H\alpha} = 5$ Hz, $^{3}J_{H1H\beta} = 8$ Hz, OOC–C*H*), 3.20 (m, 8H, TBA), 2.98 (dd, 1H, $^{2}J_{H\alpha H\beta} = 15$ Hz, $^{3}J_{H1H\alpha} = 5$ Hz, O_2C–CH–C*H*(α)), 2.83 (dd, 1H, $^{2}J_{H\alpha H\beta} = 15$ Hz, $^{3}J_{H1H\beta} = 8$ Hz, O_2C–CH–C*H*(β)), 1.66 (m, 8H, TBA), 1.37 (m, 8H, TBA), 0.96 (t, 12H, $^{3}J_{HH} = 7$ Hz, TBA) ppm. $^{13}C\{^{1}H\}$ NMR (D_2O): δ 182.7, 136.7, 134.2, 119.2, 59.09, 57.02, 32.81, 24.10, 20.12, 13.79 ppm. MS [ESI-] (*m*/*z* (%)): 154.4 ([M]$^-$, 100). Anal. Found: C, 63.26; H, 10.86; N, 14.95. Calcd for $C_{22}H_{44}N_4O_2{\cdot}CH_3CN{\cdot}H_2O$: C, 63.24; H, 10.86; N, 15.37.

3.3. Tetrabutylammonium L-methioninate [TBA][L-Met]

Yield 96%. $[\alpha]_D^{20}$ +1.22 (*c* 10, H_2O). ^{1}H NMR (D_2O): δ 3.36 (dd, 1H, $^{3}J_{HH} = 6$ Hz, $^{3}J_{HH} = 8$ Hz, O_2C–C*H*), 3.20 (m, 8H, TBA), 2.57 (t, 2H, $^{3}J_{HH} = 9$ Hz, S–CH_2), 2.12 (s, 3H, S–CH_3), 2.10–1.78 (m, 2H, C*H*–CH_2), 1.66 (m, 8H, TBA), 1.36 (m, 8H, TBA), 0.96 (t, 12H, $^{3}J_{HH} = 7$ Hz, TBA) ppm. $^{13}C\{^{1}H\}$ NMR (D_2O): δ 181.85, 57.96, 55.01, 33.66, 29.51, 22.96, 18.97, 13.92, 12.66 ppm. Anal. Found: C, 59.62; H, 11.10; N, 11.41. Calcd for $C_{21}H_{46}N_2O_2S{\cdot}2CH_3CN{\cdot}2H_2O$: C, 60.00; H, 11.11; N, 11.01.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.007.

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