Experimental evidence for the homochiral aggregation of ammonium salts in solution†

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NMR and X-ray evidence for the homochiral aggregation of chiral ammonium picrates from racemic solutions is presented.

The NMR spectra of enantiomers may be different when they are in nonracemic chiral solvents or in achiral solvents when a nonracemic chiral reactive is present. In the absence of any added nonracemic chiral substance, pure enantiomers and their racemates show identical NMR spectra only at high dilution. When the degree of solute aggregation is important they may exhibit different NMR spectra.[1] Since the first report by Williams *et al.*[2] several authors have studied the non-equivalence of the NMR spectra of enantiomers able to form relatively stable hydrogen-bonded dimers in solution.[1–3] Most of these studies are based on the assumption that dimerization reactions are rapid processes, with a fast exchange of partners on the NMR time scale. As a consequence only one set of proton signals corresponding to the weighted average peaks of monomers and dimers is usually observed for pure enantiomers or racemic mixtures.

In our studies on recognition and extraction of chiral ammonium picrates[4] we have observed that some enantiomerically pure salts show two sets of signals in their ^{1}H NMR spectra. Although this behaviour has been previously observed in non-racemic mixtures of enantiomers, to the best of our knowledge this duplicity of signals has never been reported for pure enantiomers.

The goal of this paper is to study the aggregation state of some chiral ammonium salts in solution by using NMR techniques and to determine the corresponding dimerization constants. In addition, the influence of different factors such as anion nature, steric hindrance and primary or secondary amino groups has been considered.

The ammonium picrate salts which have been studied are shown in Chart 1. These salts were easily prepared by reaction of the corresponding chiral amines with picric acid in ethanol.[4]

It has been reported that tetraalkylammonium salts in organic solvents are present as ion pairs ($R^+ \cdot X^-$) which are able to form dimers of the type $(R^+ \cdot X^-)_2$. In these cases, the dimerization process is strongly dependent on both anion and solvent characteristics.[5] However no NMR studies have been presented.

In order to elucidate the aggregation state of enantiomerically pure (*R*)-α-methylbenzylammonium picrate [(*R*)-**1**], NMR experiments were carried out with 0.016 M solutions in $(CD_3)_2CO$. The ^{1}H NMR spectrum of (*R*)-**1** is reported in Fig. 1a. This spectrum exhibits doubling of signals corresponding to two different species in a 3 : 1 ratio that were assigned to (*R*)-**1** monomeric and (*R*,*R*)-**1** homodimeric ion pairs at slow exchange on the NMR time scale (2*R* = *R*,*R*). As expected, the ratio of the integrals of the two sets of signals is concentration dependent. Dilution experiments allowed us to assign the most intense peaks to the monomer because at lower concentrations (down to 0.0016 M) the signals corresponding to the homodimer decrease steadily (Fig. 2). This behaviour suggests that only the monomer is present under high dilution conditions.

For racemic **1** all the chemical shifts as well as the coupling constants were coincident with those of the pure (*R*) enantiomer within experimental error (Fig. 1b). This result is in agreement with a slow exchange among monomers and dimers and indicates that the homodimer (*R*,*R*)-**1** is formed with preference to the heterodimer (*R*,*S*)-**1** under these experimental conditions.[6]

When ^{1}H NMR spectra were recorded at low temperatures (down to −75 °C) a steady increase in the intensity of the dimer signals was observed, as expected.

NMR experiments with different non-racemic mixtures of enantiomers (from pure (*R*)-**1** to pure (*S*)-**1**) were carried out at 25 °C in 0.016 M acetone solutions. All the recorded spectra were almost identical. No variations in the chemical shifts or coupling constants were observed and the monomer : homodimer ratio was always around 3 : 1 (Table 1). The constant ratio between both species independently of the enantiomeric

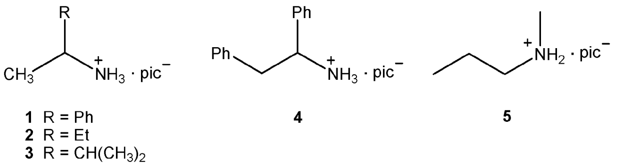

Chart 1

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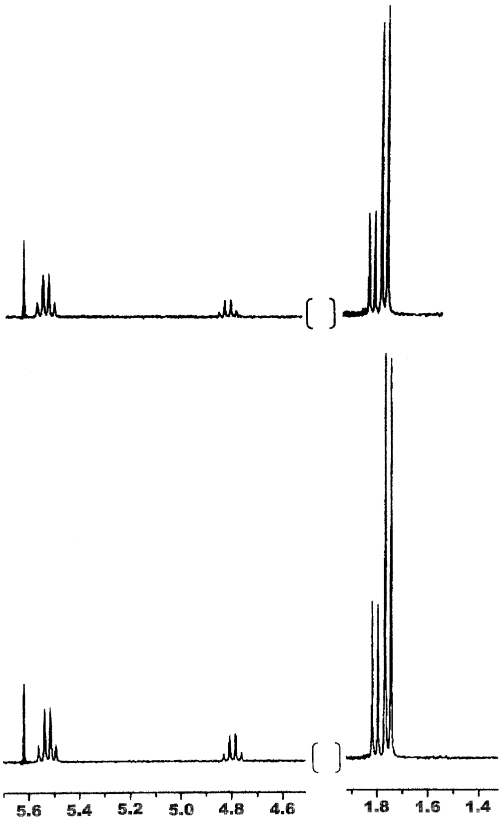

Fig. 1 ^{1}H NMR spectra (aliphatic zone) 0.016 M in $(CD_3)_2CO$ solutions of: (a) (*R*)-α-methylbenzylammonium picrate, (b) racemic α-methylbenzylammonium picrate.

composition agrees with an equilibrium between the monomers and the homodimers [(*R*,*R*)-**1** and/or (*S*,*S*)-**1**] under these conditions.

In order to obtain more information about the species present in the racemic solutions, diffusion NMR techniques were used. Diffusion NMR spectroscopy has been successfully used to define the aggregation state of different species in solution. In principle, the diffusion coefficient of a certain molecular species under given conditions depends on its size and shape, its concentration, the temperature and the viscosity of the solvent. The ratio of diffusion for two spherical molecules, provided they are in the same environment, is inversely proportional to the ratio of their radii. Thus, comparative measurements of diffusion rates can help to determinate the relative sizes of molecules in solution.[7]

Table 1 Ratios of the different species present in 0.016 M solutions of **1**, **2** and **4** in $(CD_3)_2CO$ (racemic mixtures or pure enantiomers) from their ^{1}H NMR spectra

(%) *R* : (%) *S*	**1** Homodimer : monomer	**2** Homodimer : monomer	**4** Homodimer : monomer
100 : 0	1 : 3	1 : 4	1 : 11
80 : 20	1 : 3	1 : 4	1 : 11
50 : 50	1 : 3	1 : 4	1 : 11
20 : 80	1 : 3	1 : 4	1 : 11
0 : 100	1 : 3	1 : 4	1 : 11

FT-PGSE (Fourier transform pulsed gradient spin-echo) experiments were carried out on racemic α-methylbenzylammonium picrate in acetone-d_6 at 25 °C. The relative variation of some of the NMR signal intensities, *i.e.* $\ln(I/I_0)$, is plotted as a function of the square of the gradient amplitude, G, and the slopes of the straight-line fits are directly proportional to the diffusion coefficient (Fig. 3). As can be observed, the two species present in the sample show a clear difference in slope and therefore a different diffusion coefficient, in agreement with a monomeric and dimeric ion pair system.

The influence of the counteranion was evaluated by carrying out similar experiments with the corresponding ammonium chloride salt. With this anion, the same sets of signals were obtained in the NMR spectra, but with a much higher monomer : homodimer ratio (*ca.* 6 : 1) at the same concentration, which indicates a lower aggregation degree than with the picrate anion.

It is worth noting that all these results are strongly dependent on the solvent and only have been observed in acetone-d_6. In more polar solvents (CD_3OD or DMSO-d_6) only one set of signals was observed in any case. Unfortunately, $CDCl_3$ or CD_3CN could not be used for solubility reasons.

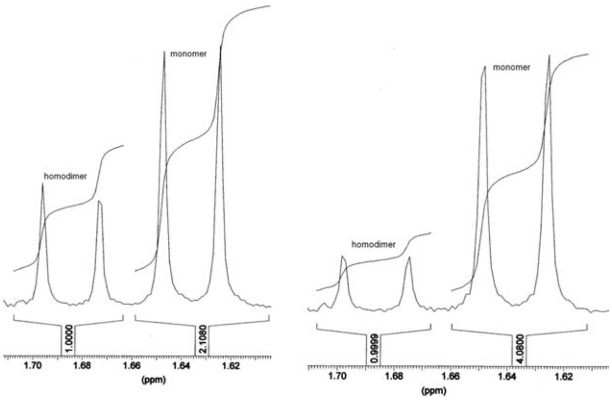

Fig. 2 ^{1}H NMR spectra (methyl signal) of (*R*)-α-methylbenzylammonium picrate in $(CD_3)_2CO$ at 0.016 M (left) and 0.0016 M concentration (right).

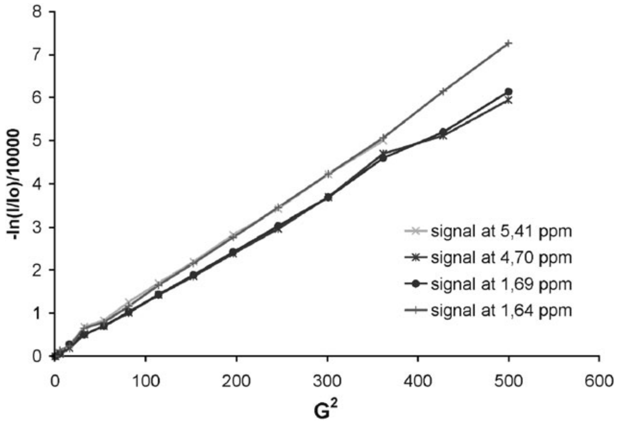

Fig. 3 Plot of $-\ln(I/I_0)$ *vs.* G^2 for different proton signals of racemic α-methylbenzylammonium picrate 0.016 M in $(CD_3)_2CO$ at 25 °C.

Table 2 Dimerization equilibrium constants at 25 °C in $(CD_3)_2CO$

Ammonium salt	**1**	**2**	**4**
K_{eq}/M^{-1}	240	15	10

The dimerization equilibrium constant could be determined for this ammonium salt due to the observation in the ^1H NMR spectrum of two separate sets of signals. The obtained value at 25 °C in $(CD_3)_2CO$ was $K_{eq} = 240\ M^{-1}$ (Table 2).

Single crystals suitable for X-ray diffraction were obtained for racemic **1**.‡ The first observation was that this compound crystallizes as a conglomerate and the studied crystal corresponds to the (*R*) enantiomer (Fig. 4).

The unit cell of the crystal consists of two molecules of methylbenzylamine and two of picric acid. The hydrogen atoms of the phenolic hydroxyl group of picric acid migrate from the picric acid to the amino group, and the distance between C(5) and O(7) (1.261(3) Å) is shorter than the normal one (1.33 Å) and similar to that observed in other picrate ammonium salts.[8] Clear hydrogen-bonding interactions between ion pairs are observed in the crystal (Fig. 5). These hydrogen-bonding interactions appear not only between the ammonium group and the phenoxy oxygen but also to the nitro groups at the *ortho* positions. These interactions would explain the clear distortion observed in the aromatic ring of the picrate moiety. Thus, C–C bond lengths C(5)–C(4) and C(5)–C(6) (1.435(3) and 1.441(3) Å, respectively) are longer than normal aromatic C–C bonds (on average 1.374 Å). These longer bonds give rise to important modifications of the bond angles: C(6)–C(5)–C(4) = 111.5(2)° is smaller than usual whereas C(5)–C(4)–C(3) = 124.5(2)° and C(1)–C(6)–C(5) = 124.6(2)° are larger than the normal sp^2 angles. These larger values allow both nitro groups in the *ortho* positions to be further away from the phenolic oxygen by closing the angles C(3)–C(4)–N(2) = 116.2(2)° and C(1)–C(6)–N(3) = 116.1(2)°. In addition both groups are twisted in relation to the aromatic rings, with dihedral angles of C(5)–C(4)–N(2)–O(5) = 34.54 (0.37)° and C(5)–C(6)–N(3)–O(4) = −38.62 (0.37)°. This type of distortion is not observed in the nitro group in the *para* position.

Similar studies were carried out with compounds **2–5**. *sec*-Butylammonium picrate (**2**) and 1,2-diphenylethylammonium picrate (**4**) show the same behaviour as previously described for **1**. Two sets of signals are again observed, corresponding to the monomeric and homodimeric ion pairs, whose integral ratios are dependent on the solute concentration but not on the relative amount of each enantiomer (see Table 1). In both cases the dimerization equilibrium constants are lower than that obtained for compound **1** very likely due to higher steric repulsions in **2** and **4** (Table 2). In this sense, **3** did not show duplication in the NMR signals. This result was expected due to the structure of this salt giving rise to stronger steric repulsions than **2** or **4**. Finally, compound **5**, a secondary ammonium salt, did not show any doubling of signals probably due to the same steric effects.

In conclusion, the ammonium salts **1**, **2** and **4** form homodimeric ion pair aggregates in preference to the heterodimeric species, with a slow exchange rate between monomers and dimers. For this reason doubling of signals in the NMR spectra is observed both in enantiomeric pure solutions and in racemic mixtures. This behaviour contrasts with previous observations of chiral aminoalcohols and other compounds where racemic mixtures and pure enantiomers show different behaviour to the non-racemic mixtures of enantiomers due to the formation of heterodimers as well as homodimers with a fast exchange of partners on the NMR time scale. Steric hindrance is extremely important in the dimerization process and solvent and concentration effects also influence the equilibrium behaviour of the samples. PGSE-NMR diffusion techniques have proved to be valuable in these studies by allowing differentiation between monomer and dimer species. Finally,

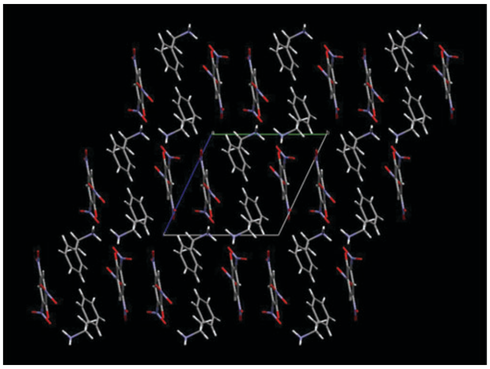

Fig. 4 Crystal packing of α-methylbenzylammonium picrate. It can be observed that: (a) chiral centres show an (*R*) configuration and (b) the unit cell comprises an ion pair dimer.

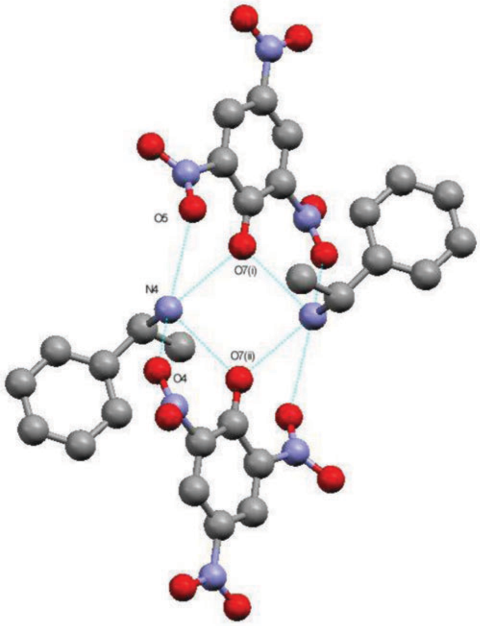

Fig. 5 Hydrogen bonds between α-methylbenzylammonium and picrate units with N···O distances of: N(4)···O(7)(i) 2.845(3) Å, N(4)···O(5) 3.049(3) Å, N(4)···O(7)(ii) 2.853(4) Å and N(4)···O(4) 3.030(4) Å, (i and ii in atom labels refer to equivalent positions (1 + *x*, *y*, −1 + *z*) and (1−*x*, 1−*y*, 1−*z*), respectively). Hydrogen atoms have been omitted for clarity.

racemic **1** crystallizes as a conglomerate of homochiral dimeric ion pairs.

Acknowledgements

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‡ Crystal data for **1**: $C_{14}H_{14}N_4O_7$, M_r = 350.29, T = 293(2) K, triclinic, space group $P\bar{1}$, a = 8.1150(3), b = 10.5080(3), c = 10.7640(5) Å, α = 113.522(1)°, β = 107.871(1)°, γ = 91.599(3)°, V = 789.01(5) Å^3, ρ_{calc} = 1.474 g cm^{-3}, μ = 0.121 mm^{-1}, Z = 2, reflections collected = 4863, independent reflections = 3433 (R_{int} = 0.0323), final R indices [$I > 2\sigma I$]: $R1 = 0.0539$, $\omega R2 = 0.1148$, R indices (all data): $R1 = 0.1349$, $\omega R2 = 0.1465$ [$\omega = 1/[\sigma^2(F_0^2) + (0.0616\ \mathrm{P})^2 + 0.13\ \mathrm{P}]$ where $P = (F_0^2 + 2F_c^2)/3$]. All hydrogen atoms were found experimentally and refined isotropically. The final residual Fourier positive and negative peaks were equal to 0.171 and −0.264 e Å^{-3}, respectively. Crystal data were collected on a Nonius KappaCCD diffractometer with MoKα wavelength. Solution and refinement calculations were performed using the SHELX system[9] inside the WinGX package.[10] CCDC reference number 603140. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607100g

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