## Spontaneous Resolution of an Axially Dissymmetric 3-Carbamoylpyridinium lodide; Intrinsic Discrimination between the Enantiomeric Forms by the Introduction of a Second Chiral Element

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R<sup>2</sup>

Me (3)

The direction of the carbonyl-orientation in a solid amide-rotamer of  $3-[N-methyl-N-(R)-\alpha-methylbenzyl]$ carbamoyl-1,2,4-trimethylpyridinium iodide is governed by the (*R*)-chirality in the amide side chain; structures, as determined by *X*-ray analysis and c.d. spectra, are correlated.

Recently we reported the resolution of the nicotinamide analogue (1) into its enantiomers.<sup>1</sup> The chirality of (1) is caused by the out of plane orientation of the carboxamide group with respect to the pyridinium ring effected by two neighbouring methyl groups. Compound (1) is stable in water at 25 °C; at higher temperatures racemization occurs *e.g.* half life  $t_{0.5} = 7.5$  h (90 °C) and  $t_{0.5} = 3.1$  h (100 °C).<sup>2</sup> We now present our results with respect to isolation and structures of amide rotational isomers of the *un*symmetrically substituted pyridinium compounds (3), which are obtained by quaternization of (2).

Immediately after dissolution of compound  $(2a)^{\ddagger}$  in CDCl<sub>3</sub> its <sup>1</sup>H n.m.r. spectrum shows peaks at  $\delta$  2.68 (3H) and  $\delta$  4.80 (2H) corresponding to the *N*-methyl and *N*-methylene protons. The intensity of these signals gradually decreases and new signals appear at  $\delta$  3.12 and  $\delta$  4.27 with the same intensity ratio. As a result of the out of plane orientation of the carbonyl group the N-substituents *trans* to oxygen are situated in the shielding area of the pyridine nucleus. This affects the *N*-methyl protons in rotamer (2a) (A) and the *N*-methylene protons in rotamer (2a) (B). The more upfield lines have been assigned accordingly. Evidently rotameric pure (2a) (A) equilibrates in solution and generates to a certain extent rotamer (2a) (B). The quaternary salt (3a)<sup>‡</sup> was prepared by the reaction of compound (2a) with MeI. In the <sup>1</sup>H n.m.r. spectrum (D<sub>2</sub>O) the signals of the rotamers (3a) (A) and (3a)

NEt<sub>2</sub>

Me

(1)

† Compounds (2a) and (2b) were prepared from 2.4dimethylnicotinic acid,<sup>4</sup> via the acid chloride<sup>5</sup> and the appropriate amine. Compound (2a)(A) <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>)  $\delta$ : 2.25 (3H, s, 4-Me),<sup>6</sup> 2.47 (3H, s, 2-Me),<sup>6</sup> 2.68 (3H, s, N-Me), 4.80 (2H, s, N-CH<sub>2</sub>), 6.97 (1H, d, pyrH), 7.07–7.50 (5H, m, C<sub>6</sub>H<sub>5</sub>), 8.33 (1H, d, pyrH). M.p. 80–81 °C (toluene-hexane). Compound (2b)(A) <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>)  $\delta$ : 1.60 (3H, d, J 7 Hz, 9-Me), 2.27 (3H, s, 4-Me), 2.37 (3H, s, N-Me), 2.40 (3H, s, 2-Me), 6.20 (1H, q, 9-H), 6.87 (1H, d, 5-H), 7.23 (5H, s, Ph), 8.23 (1H, d, 6-H). M.p. 102–104 °C.

(2) **a**; (A):  $R^1 = CH_2Ph$ ,  $R^2 = Me$ 

(B):  $R^1 = Me$ ,  $R^2 = CH_2Ph$ 

**b**; (A):  $R^1 = CH(Me)Ph$ ,  $R^2 = Me$ 

(B):  $R^1 = Me$ ,  $R^2 = CH(Me)Ph$ 

‡ Compound (**3a**) <sup>1</sup>H n.m.r. (D<sub>2</sub>O)  $\delta$ : 2.48 (s, 4-Me and 2-Me, B), 2.67 (s, 2-Me, A), 2.88 (s, *N*-Me, A), 3.27 (s, *N*-Me, B), 4.20 (s, 1-Me, B), 4.27 (s, 1-Me, A), 4.47 (2 × s, CH<sub>2</sub>, B), 4.80 (2 × s, CH<sub>2</sub>, A), 6.93–7.53 (5H, m, Ph), 7.83 (1H, d, pyrH), 8.70 (1H, d, pyrH). (**3a**)(B) has m.p. 184–185 °C.

(B) are observed. The rotameric distribution (A/B) remains constant in  $D_2O$  for several days but appears to be affected by the method of preparation *e.g.* conducting the reaction with MeI in toluene (reflux) leads to A/B 0.3 and without a solvent (25 °C) to A/B 3.3. Evidently the A conformation of the starting substance (2a) is conserved to a greater degree at lower temperatures. On warming the solutions ( $D_2O$ ), interconversion of the rotamers occurs. So both samples are converted to give the final distribution of A/B 1.7 (60 °C). Prolonged cooling of an aqueous solution of (3a) with A/B 0.3 caused rotameric pure (3a) (B) to crystallize. In the <sup>1</sup>H n.m.r. spectrum only the signals attributed to the B conformation are found. X-Ray analysis§ revealed that (3a) (B) crystallises in



Figure 1. C.d. spectra (in MeOH) measured on a Yobin–Yvon Mark III-S spectrometer: (-----) (3a) (B) as depicted in Figure 2 and the enantiomeric form (----).

<sup>§</sup> Crystal data for (3a) (B),  $C_{17}H_{21}N_2OI$ , M = 396.27, orthorhombic, space group  $P2_12_12_1$ , a = 7.183(3), b = 8.769(2), c = 28.093(6) Å, U =1769.4(9) Å<sup>3</sup>,  $D_{c} = 1.487$  g cm<sup>-3</sup>, Z = 4,  $\lambda$ (Mo- $K_{\alpha}$ ) = 0.71069 Å,  $\mu(Mo-K_{\alpha}) = 16.73 \text{ cm}^{-1}$ . The data were collected on an Enraf-Nonius CAD-4F diffractometer using  $\omega$ -2 $\theta$  scans (2 $\theta_{max}$  = 60°). In one octant 2952 reflections were collected of which 2352 had  $I > 2.5\sigma(I)$ . Three periodically measured control reflections showed an average deviation of 1.1%. The data were corrected for Lorentz, polarisation, and absorption effects (min. transmission 0.619, max. 1.413). The structure was solved by Patterson and Fourier methods. Anisotropic, weighted full-matrix refinement on F resulted in a R-value of 0.035. All H atoms were refined with a constant isotropic temperature factor. The absolute conformation of (3a)(B) was established by refinement of the inverted model which resulted in an R-value of 0.040 and by the Bijvoet differences of a set of 20 sensitive Friedel pairs which were measured with  $Cu-K_{\alpha}$  radiation.



Figure 2. Molecular structures of (3a) (B) and of (3b) (B).



Figure 3. C.d. spectra (in MeOH) of (3b) (A) (----) and (3b) (B) (----).

the enantiomorphic space group  $P_{2_12_12_1}$  with one molecule in the asymmetric unit. This encouraged further examination of the individual single crystals using c.d. spectrometry, which showed that spontaneous resolution of the racemate had taken place. The c.d. spectra, recorded for solutions of the 3D-analysed crystal and of a crystal with opposite Cottoneffect are presented in Figure 1. The presence of the counter ion I<sup>-</sup> enabled the use of anomalous dispersion for the determination of the absolute molecular conformation, which is shown in Figure 2. We therefore had the opportunity to correlate the c.d. spectra with the absolute structure of (**3a**) (B).

These results prompted us to introduce an additional chiral element in the amide side chain of (3a) (B). With the corresponding compound (3b) (B) we were able to determine the geometrical influence of the introduced carbon chirality [arbitrarily the (R)-isomer] on the absolute location of the carbonyl moiety with respect to the pyridinium ring. For that purpose N-methyl-N-(R)- $\alpha$ -methylbenzylamine<sup>3</sup> was selected

in the preparation of the precursor, compound (2b).<sup>+</sup> In the <sup>1</sup>H n.m.r. spectrum of (2b) the same observations were made as in compound (2a). The amide-methyl signal at  $\delta$  2.37 decreases and a new signal arises at  $\delta$  3.07. On the basis of essentially the same arguments as with compound (2a) we conclude that solid (2b) has the A conformation.

Quaternization of (2b) was carried out with MeI in toluene (reflux). Recrystallization from water afforded pure single crystals of rotamer (3b) (B).¶ The result of the X-ray analysis is represented in Figure 2. Interestingly, the structures of (3b)(B) and of the depicted form of (3a) (B) are almost superimposable. Apparently the orientation of the phenyl group with respect to the pyridinium moiety leads to a carbonyl orientation which minimizes the steric impact of the introduced methyl substituent for one of the benzylic hydrogens. The c.d. spectra (see Figure 3) of (3b) (B) taken from solutions of a separate crystal and from a weighed quantity are identical. Therefore we conclude that in (3b) (B) the carbonyl orientation is governed by the (R)-chirality in the amide side chain.

Performing the quaternization with an excess of MeI (1 °C) and recrystallization (EtOH) at 1 °C yielded pure (**3b**) (A).¶ Its c.d. spectrum is presented in Figure 3; a study of the structure is in progress.

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 $\label{eq:solution} \begin{array}{l} \mbox{(3b) (B) } \mbox{!H n.m.r. (H}_2\mbox{O} \ \& 1.60 \ (3H, d, J \ 7 \ Hz, 9 \ -Me), \\ \mbox{2.10 (3H, s, 4 \ -Me), 2.77 \ (3H, s, 2 \ -Me), 3.17 \ (3H, s, N \ -Me), 4.17 \ (3H, s, 1 \ -Me), 4.50 \ (1H, q, J \ 7 \ Hz, 9 \ -H), 7.00 \ -7.50 \ (5H, m, Ph), 7.67 \ (1H, d, 5 \ -H), 8.57 \ (1H, d, 6 \ -H). \ M.p. \ 245 \ -247 \ ^{\circ}\ C. \ Compound \ (3b) \ (A) \ ^{\circ}\ H \ n.m.r. \ (H}_2\ O) \ \& 1.67 \ (3H, s, J \ 7 \ Hz, 9 \ -Me), 2.50 \ (3H, s, 4 \ -Me), 2.53 \ (3H, s, 2 \ -Me), 2.61 \ (3H, s, N \ -Me), 4.13 \ (3H, s, 1 \ -Me), 5.90 \ (1H, q, J \ 7 \ Hz, 9 \ -H), 7.40 \ (5H, m, Ph), 7.77 \ (1H, d, 5 \ -H), 8.57 \ (1H, d, 6 \ -H). \ M.p. \ 226 \ -227.5 \ ^{\circ}\ C. \end{array}$ 

Crystal data for (3b) (B),  $C_{18}H_{23}N_2OI$ , M = 410.30, orthorhombic, space group  $P2_12_12_1$ , a = 7.209(7), b = 8.877(5), c = 28.698(1) Å, U =1836(2) Å<sup>3</sup>,  $D_c = 1.484$  g cm<sup>-3</sup>, Z = 4,  $\lambda$ (Mo- $K_{\alpha}$ ) = 0.71069 Å,  $\mu$ (Mo- $K_{\alpha}$ ) = 16.13 cm<sup>-1</sup>. The data were collected with an Enraf-Nonius CAD-4F diffractometer using  $\omega$ -2 $\theta$  scans (2 $\theta_{max}$  = 53°). In one quadrant of the reflection sphere  $h k l/h \bar{k} l$  pairs were measured sequentially so as to minimise instability effects of the system. 4148 Intensities were collected of which 3 181 were above the  $2.5\sigma(I)$  level, which were corrected for Lorentz, polarisation, and absorption effects (min. transmission 0.839, max. 1.154). Three periodically measured control reflections showed an average deviation of 1.2%. The solution of the structure and refinement proceeded as with (3a) (B). The final R-value was 0.030. The absolute configuration was established by refinement of the inverted model which resulted in an R-value of 0.035 and by the Bijvoet differences of a set of 22 sensitive h k l/h k l pairs of the (Mo- $K_{\alpha}$ ) set. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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