The Influence of Chirality in the Amide Side Chain on the Carbonyl Orientation in Rotational Isomers of 3-Carbamoylpyridinium Halides

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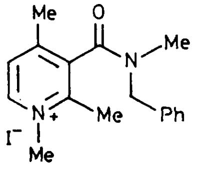
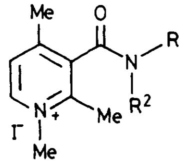
The direction of the carbonyl orientation in solid amide rotamers of 3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1,2,4-trimethylpyridinium iodide is governed by the (*R*)- or (*S*)-chirality in the amide side chain; *X*-ray structures and c.d. spectra are correlated.

In a previous communication[1] we reported the isolation of the amide rotamer (**1t**). In addition it was found by *X*-ray analysis and c.d. spectrometry that spontaneous resolution of the axially dissymmetric compound had occurred.† We then introduced additional carbon chirality in the amide side chain (arbitrarily the *R*-isomer) to study its effect on the carbonyl orientation with respect to the pyridinium ring. As for (**1**) we isolated rotamerically pure (**2c**) (*R*) and (**2t**) (*R*).

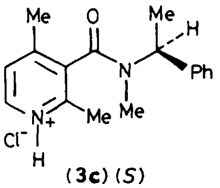
X-Ray analysis[1] revealed that in (**2t**) (*R*) the benzylic hydrogen is positioned towards the pyridinium ring. This implies a carbonyl orientation directed to the *A*-side‡ of the



(**1t**)



(**2**)



(**3c**) (*S*)

s-*cis*; (*R*): R^1 = (*R*)-CH(Me)Ph, R^2 = Me
(*S*): R^1 = (*S*)-CH(Me)Ph, R^2 = Me
s-*trans*; (*R*): R^1 = Me, R^2 = (*R*)-CH(Me)Ph
(*S*): R^1 = Me, R^2 = (*S*)-CH(Me)Ph

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† Equilibration of amide rotamers and the chromatographic separation of the enantiomers have been observed in amides of unsymmetrically substituted mesitoic acids.[2]

‡ The *A*-side of the pyridine ring is the side which faces the observer when the ring is viewed from a direction perpendicular to the plane of the ring and one travels around the ring in a counterclockwise direction when taking the shortest path from the ring N atom to the carboxamide group. The other side is the *B*-side.

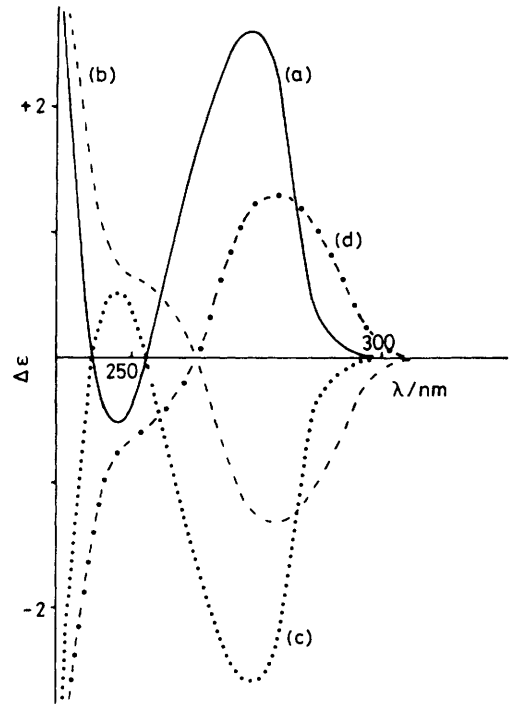

Figure 1. C.d. spectra (in MeOH) of: (a) (**2t**) (*R*); (b) (**2c**) (*R*); (c) (**2t**) (*S*), and (d) (**2c**) (*S*).

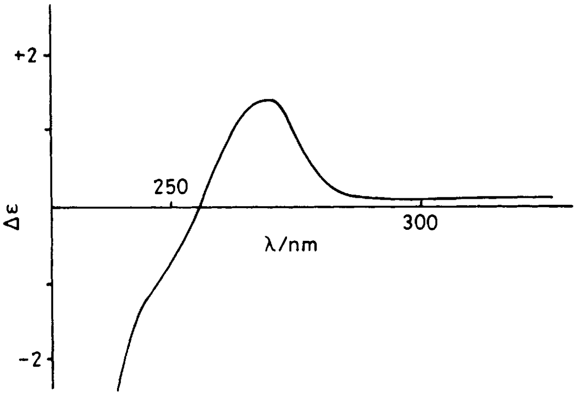

Figure 2. C.d. spectrum (in MeOH) of (**3c**) (*S*) measured on a Yobin-Yvon Mark III-S spectrometer.

pyridinium ring, according to the helicity rule[3] designated as (*M*). C.d. spectra recorded for solutions of a single crystal and a larger sample were identical. Therefore we concluded that in compounds of type (**2t**) the carbonyl orientation is governed by the chirality in the amide side chain.

To substantiate this conclusion we have now repeated the amide synthesis[1] using the (*S*)-amine to produce (**2t**) (*S*). This compound, in comparison with (**2t**) (*R*), has an identical ^{1}H n.m.r. spectrum and indeed shows an opposite Cotton effect (see Figure 1). So, the (*R*) and (*S*) isomers may be regarded as enantiomers with opposite configurations. Analogous to the preparation of (**2c**) (*R*), which was briefly mentioned,[1] we isolated (**2c**) (*S*). As expected also in the s-*cis*-series both compounds show identical ^{1}H n.m.r. spectra but opposite Cotton effects (Figure 1). Attempts to obtain single crystals from (**2c**) (*S*) to elucidate its absolute structure have so far been unsuccessful. Therefore we prepared the HCl salt (**3c**) (*S*)§ directly from the parent pyridine, which is known to possess the s-*cis*-conformation.[1] The c.d. spectrum of (**3c**) (*S*) (see Figure 2) indicates the structural similarity with (**2c**) (S) (*cf.* Figure 1).

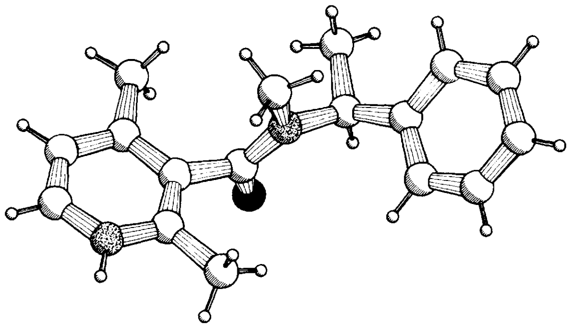

Figure 3. Perspective view of the absolute configuration of (**3c**) (*S*). Only one of the independent (nearly identical) molecules is shown. N atoms are indicated by dotted spheres and O by a black sphere.

The result of the *X*-ray analysis¶ is represented in Figure 3 n which the carbonyl orientation is directed to the *B*-side‡ of he pyridinium ring resulting in a helicity designated as (*P*).[3] Summarizing, we conclude that in compound (**2**) the absolute configuration in the amide side chain determines the absolute axial chirality which is not affected by the s-*cis*- or s-*trans*-conformation of the amide moiety.

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References

1 L. A. M. Bastiaansen, J. A. Kanters, F. H. van der Steen, J. A. C. de Graaf, and H. M. Buck, *J. Chem. Soc., Chem. Commun.*, 1986, 536.
2 K. H. Rimböck, M. A. Cuyegkeng, and A. Mannschreck, *Chromatographia*, 1986, **21**, 223; A. Mannschreck, personal communication.
3 G. Krow in 'Topics in Stereochemistry,' eds. E. L. Eliel and N. L. Allinger, Wiley–Interscience, New York, 1970, vol. 5, p. 31.

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§ Compound (**3c**) (*S*) was prepared by passing dry HCl gas through a solution of the parent pyridine in Et_2O: ^{1}H n.m.r. (D_2O) δ: 1.69 (3H, d, 9-Me), 2.70 (9H, s, 2-Me, 4-Me, N-Me), 6.08 (1H, q, 9-H), 7.55 (5H, s, Ph), 7.98 (1H, d, 5-H), 8.69 (1H, d, 6-H). Single crystals were obtained from Pr^iOH.

¶ *Crystal data* for (**3c**) (*S*): $C_{17}H_{21}ClN_2O{\cdot}H_2O$, $M = 322.83$, monoclinic, space group $P2_1$, $a = 13.667(1)$, $b = 8.585(1)$, $c = 16.106(4)$ Å, $\beta = 106.09(1)°$, $U = 1815.7(5)$ Å^3, $D_c = 1.181$ g cm^{-3}, $Z = 4$, $F(000) = 688$, Ni-filtered Cu-K_α radiation, $\lambda = 1.54184$ Å, μ(Cu-K_α) = 19.4 cm^{-1}. Intensities of 7232 reflections were collected (CAD4F; $2\theta_{max} = 140°$; $\omega/2\theta$ scan; $hkl/\bar{h}\bar{k}\bar{l}$ Friedel pairs) of which 6021 with $I > 2.5\sigma(I)$ were used in the solution and refinement. The structure was solved by Patterson and Fourier methods and refined by least-squares techniques to $R = 0.0659$. H-atoms were placed at calculated positions with X–H = 0.98 Å. The alternative absolute configuration was rejected based on the refinement of the inverted model which resulted in the significantly higher $R = 0.0776$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.