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THE ESTABLISHMENT OF OXIME ANCHIMERISM USING ISOTOPIC TECHNIQUES

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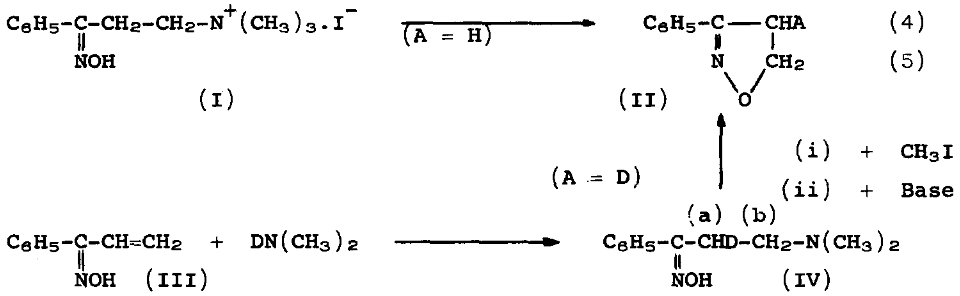
Oximate anions, while powerful nucleophiles (1), are ambident anions and undergo both O- and N- attack (2). To assign quantitative nucleophilicities to each of these sites, therefore, model oxime reactions in which only one of the nucleophilic centres is directly involved are necessary. We have described elsewhere (3) our work on the N- nucleophilicity of oxime functions. The conversion of Mannich base oximes e.g. (I) to isoxazolines (II) constitutes a possible model for exploring oxime O-nucleophilicity. On the basis of a product study, we demonstrated qualitatively some time ago (4) that this cyclization does not proceed through a vinyl, or related, intermediate. We now provide quantitative evidence that this reaction involves exclusively oxime anchimerism.



A solution of N-deuterodimethylamine was prepared by dissolving redistilled dry dimethylamine in cooled 99.8% deuterium oxide. The resulting 29% w/w solution of dimethylamine was approximately 80% deuterated. To a portion of this solution was added 1-phenyl-prop-2-en-1-one oxime (III), the resulting solution being refluxed for 30 minutes. On cooling, 94% of 2-deutero-3-dimethylaminopropiophenone oxime (IV), m.p. 108°, separated. (All our operations involving deuterated materials were carried out in an inert atmosphere box flushed with dry nitrogen.) It was originally hoped to use i.r. to gauge the extent of incorporation of deuterium by the appearance of the C-D stretching band in the 2300 cm^{-1} region. This was not possible, either in the case of the Mannich base oxime, or of the isooxazoline, due to the diffuse absorption in that region. The existence of various -CH(D) deformational bands at lower frequencies made it possible to detect the presence or absence of deuterium in the compounds concerned, but we did not use this for quantitative analysis.

The p.m.r. spectrum of the deuterated oxime (IV) (and its undeuterated analogue) had an oxime signal at -1.5 τ and an aromatic multiplet at 2.53 τ . The C-2 and C-3 methylene protons, labelled (a) and (b) above, constituted an A_2B_2 system with the C-2 methylene signal at 6.80 τ and C-3 methylene signal at 7.37 τ . Both methylenes had a triplet structure (J 7.6 c/s) complicated by second order spin-spin splitting. The methyl groups gave a singlet at 7.60 τ . The assignment of the methylene peaks was confirmed by the spectrum of the deuterated material. From an examination of the integrated spectrum of this latter material, it was calculated that the C-2 protons were 25% (atom %) deuterated, this corresponding to 50% (mass %) incorporation of deuterium at the required position.

This deuterated Mannich base oxime was quaternized by refluxing with methyl iodide for 30 minutes in dry ether, the methiodide, m.p. 190° precipitating in quantitative yield. The p.m.r. spectrum of this material (in perdeuterated DMSO) had a broad peak due to oxime OH at -1.70 τ , an aromatic multiplet at 2.40 τ and a broad envelope containing methyl and methylene protons centred around 6.60 τ . Because of lack of resolution of the methylene protons no analysis of the deuterium content of this salt was possible.

The methiodide was treated in ethanol with 1.5 equivalents of sodium ethoxide, the solution being maintained at 50° for 30 minutes. Addition of water followed by ether extraction gave a 53% yield of 3-phenyl isoxazoline, m.p. 65.5 - 66° (II). The p.m.r. spectrum of this material had an aromatic multiplet at 2.53 τ (2.58 τ) (5). The methylene protons consisted of a well defined A_2M_2 system with the C-4 proton signals at 6.80 τ (6.69 τ) (5) and C-5 protons at 5.58 τ (5.56 τ) (5). Both of these last two signals were triplets (J 10.1 c/s) with little second order splitting. Calculations based on the integrated spectrum showed that the C-4 position was deuterated to the extent of 27% (atom %) and 54% (mass %) (6). Mass spectral data (7) showed compound (II) to be 53.3%

(mass %) deuterated at position 4.

These results establish that compound (IV) was converted to the cyclic material (II) without any detectable loss of deuterium, and thus that the oxime anchimerism involved in the conversion of compounds (I), or (IV) , to (II) is quantitative (8). This reaction constitutes an excellent model for studying O-nucleophilicities of oximate anion and studies along these lines are continuing.

REFERENCES

1. See e.g., P.A.S. Smith and J. E. Robertson, J. Am. Chem. Soc. **84**, 1197 (1962), R. O'Brien, Toxic Phosphorus Esters, p. 194. Academic Press, New York (1960).
2. See e.g., E. Buchler, J. Org. Chem. **32**, 261 (1967) for some recent references.
3. F.L. Scott and F. J. Lalor, Tetrahedron Letters, 641 (1964).
4. F.L. Scott, J.C. Riordan and A. F. Hegarty, Tetrahedron Letters, 537 (1963).
5. The values in parentheses are those recorded on a 40 megacycle instrument reported by us in reference (4). In assigning the τ for the methylene triplet if one records the signal as that for the main peak then the present and previous values coincide and are identical to those recorded elsewhere; M.C. Aversa, G. Cum and M. Crisafulli, Gazz.Chim. Ital., **96**, 1046 (1966). The triplet is slightly unsymmetrical however and if the τ is recorded at the centre of gravity of the triplet then the slight differences observed are obtained.
6. The apparently higher incorporation of deuterium in the product (II) is due to the experimental error incurred in the determination of the integrated p.m.r. spectra. From an examination of a number of our materials an experimental error of ± 3% is thought to be realistic. A similar technique has been used to evaluate deuterium incorporation in some Mannich bases recently, see, J. Cymerman Craig, M. Moyle and L.F. Johnson, J. Org. Chem. **29**, 410 (1964).
7. P.m.r. spectra cited here were obtained in $CDCl_3$ (unless otherwise stated) using tetramethylsilane as internal standard, on a Varian A-60 instrument. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D mass spectrometer.

8. We have demonstrated elsewhere , F. L. Scott, R.J. MacConaill and J.C. Riordan, *J. Chem. Soc.* (C), 44 (1967) , that the oxime group is oriented in a sterically favoured position for anchimerism.