Absence of Stereoelectronic Control in the Hydrolysis of a Conformationally Locked Acetal

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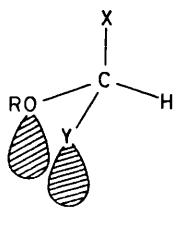
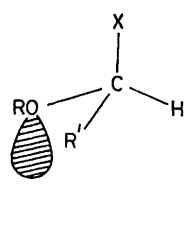
Summary The spontaneous hydrolysis of axial 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (**3a**) is slower than that of the equatorial anomer.

DESLONGCHAMPS has proposed that the direction of cleavage, and the stereospecific formation, of orthoesters and orthoamides are subject to stereoelectronic control.[1] According to this theory, the cleavage of the C–O or C–N bond requires a conformation (**1**) in which lone pair orbitals on both remaining heteroatoms (**1**; O, and Y = O or N) lie antiperiplanar to the leaving group (X = O or N).



(1)



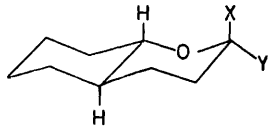
(2)

We are interested in the possible extension of the stereoelectronic theory to the cleavage of acetals. An oxocarbonium ion formed by the loss of X^- from an acetal (**2**; X = OR) will be more dependent on the stabilisation it receives from the donor oxygen atom than a doubly stabilised carbonium ion formed by the corresponding reaction of (**1**). Naively, therefore, one might expect the transition state for the cleavage of an acetal to depend more heavily on the donor capability of the oxygen atom, including the orientation of the lone-pair orbitals, than that for the similar reaction of an orthoester.

The available evidence is inconclusive. Methyl α-glycopyranosides, with axial leaving groups, are hydrolysed a few times more slowly than the β-anomers,[2] but the reverse is true for aryl glycosides.[3] In any case, rate constants for the specific acid-catalysed hydrolysis of such anomeric pairs are composite, depending not only on the ease of cleavage of the C–O bond, but also on the basicities of the leaving group oxygens, which are themselves likely to be different for the axial and equatorial isomers. Other possible sources of ambiguity are ring flipping with reaction *via* a small amount of a higher energy conformation, and, for glycosides derived from aliphatic alcohols, cleavage of the bond to the ring oxygen, leading to anomerisation, if not hydrolysis.

We have looked for evidence of stereoelectronic control in the spontaneous hydrolysis of the axial and equatorial isomers of 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (**3a** and

3e; R = 4-$O_2NC_6H_4$).† The system is conformationally locked, the position of bond cleavage is unambiguous, and the problems of interpretation associated with acid-catalysed reactions are eliminated.



(3a; X = OR, Y = H)
(3e; X = H, Y = OR)

The spontaneous reaction has been fully characterised in the tetrahydropyran series,[4] and is a unimolecular process without significant involvement of solvent. Reactivity therefore depends almost exclusively on the good leaving group, and electron-donation by the ring oxygen atom.

The spontaneous hydrolysis of the axial isomer (**3a**; R = 4-$O_2NC_6H_4$) is, as expected, pH-independent in the range pH 7—10, with a half-life of 346 min at 39 °C (30% dioxan–water, ionic strength 0·1 M).‡ The similar hydrolysis of the equatorial isomer is 3·3 times faster under the same conditions. This difference in rates can be accounted for in terms of the different ground state energies of the two isomers (the axial isomer is more stable in compounds of this sort,[5] behaviour defining the 'anomeric effect'), suggesting that the transition states for the cleavage of (**3a** and **3e**, R = 4-$O_2NC_6H_4$) differ little, if at all, in energy. Thus, in a system designed to eliminate all other factors, we find no evidence that acetal cleavage is subject to stereoelectronic control.

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† Prepared as follows. *trans*-Octahydrocoumarin [C. S. Dean, J. R. Dixon, S. H. Graham, and D. O. Lewis, *J. Chem. Soc.* (*C*),1968, 1491] was reduced with lithium tri-t-butoxyaluminium hydride (P. Dufey, *Bull. Soc. chim. France*, 1968, 4653) in ether at −50 °C to a mixture of hemiacetals (**3a** and **3e**; R = H), which were acetylated with acetic anhydride in pyridine (J. T. Edwards, P. F. Morand, and I. Puskas, *Canad. J. Chem.*, 1961, **39**, 2069). The resulting acetates (**3a** and **3e**; R = COMe) were converted into a mixture of (**3a** and **3e**; R = 4-$O_2NC_6H_4$) on heating to reflux in benzene with an excess of *p*-nitrophenol. The analytically pure axial and equatorial isomers (m.p.s. 114—118 and 108—111 °C respectively) were separated by preparative t.l.c. The stereochemistry at position 2 was assigned on the basis of the signal from the anomeric proton in the 100 MHz ^{1}H n.m.r. spectrum. This appears at δ 5·19 for the axial proton of (**3e**), as four lines characteristic of the X part of an ABX spectrum [J(ax–ax) + J(ax–eq) = 12 Hz]. The signal from the equatorial proton of (**3a**) is a partially resolved triplet, almost 0·5 p.p.m. further downfield [δ 5·66, J(eq–ax) + J(eq–eq) = 4·5 Hz] (T. L. James, 'Nuclear Magnetic Resonance in Biochemistry,' Academic Press, London, 1975, p. 113).

‡ Techniques have been described previously (ref. 4); 2-(4-nitrophenoxy)tetrahydropyran has a half life of 270 min under these conditions.

[1] P. Deslongchamps, *Pure Appl. Chem.*, 1975, **43**, 351.
[2] R. J. Ferrier and P. M. Collins, 'Monosaccharide Chemistry,' Penguin, 1972, p. 58.
[3] B. Capon, *Chem. Rev.*, 1969, **69**, 407.
[4] T. H. Fife and L. H. Brod, *J. Amer. Chem. Soc.*, 1970, **92**, 1681; T. H. Fife and L. K. Jao, *ibid.*, 1968, **90**, 4081; G. A. Craze and A. J. Kirby, *J.C.S. Perkin II*, in the press.
[5] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley-Interscience, New York, 1965, p. 376.