Tetrahedron Letters,Vol.23,No.40,pp 4163-4166,1982 0040-4039/82/404163-04$03.00/0
Printed in Great Britain 

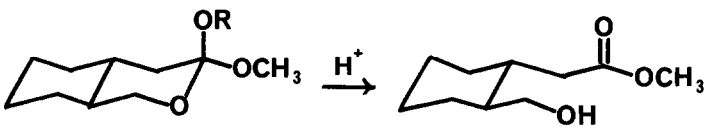
# A MEASURE OF STEREOELECTRONIC CONTROL IN THE HYDROLYSIS OF AN ORTHOESTER

Osvaldo E. Desvard and Anthony J. Kirby*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.

*The axial $OCH_3$ of 5 exchanges with solvent $CD_3OD$ up to 12 times faster than the equatorial $OCH_3$ group.*

One of the most convincing pieces of evidence for Deslongchamps' theory of stereoelectronic control[1] is his observation that the three unsymmetrical orthoesters (1, a, b, and c) are all hydrolysed to the same product (2), which has retained the $OCH_3$ group of the starting material. The selective loss of the OR group is predicted because of the three C-O bonds at the orthoester centre only the axial C-OR bond is *antiperiplanar* to lonepairs on both the other two oxygen atoms.

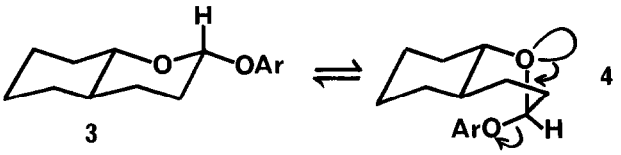



**1a** R = $CH_3$
**b** R = $CD_3$
**c** R = Et

**2**

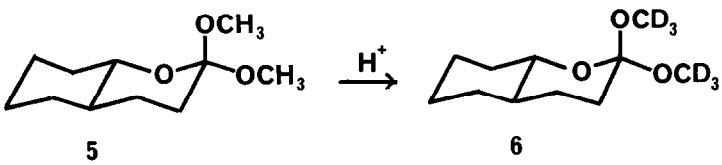
We are interested in the magnitudes of stereoelectronic effects at oxygen. These can be very large - we have shown recently[2] that one axial aryl tetrahydropyranyl acetal is hydrolysed more than $10^{14}$ times more rapidly than a comparable compound with the leaving group fixed equatorial (and thus prevented from being *antiperiplanar* to either lone pair on the ring oxygen). But the conformation of the tetrahydropyran ring of a *trans*-oxadecalin is fixed only at the ring junction, and compounds like 1 can in principle circumvent the stereoelectronic barrier by reacting through higher energy, chair-boat conformations. In the case of the equatorial acetals (3) for example, cleavage with stereoelectronic control is possible by way of conformations close to (4),

and no stereoelectronic barrier is apparent.[3]



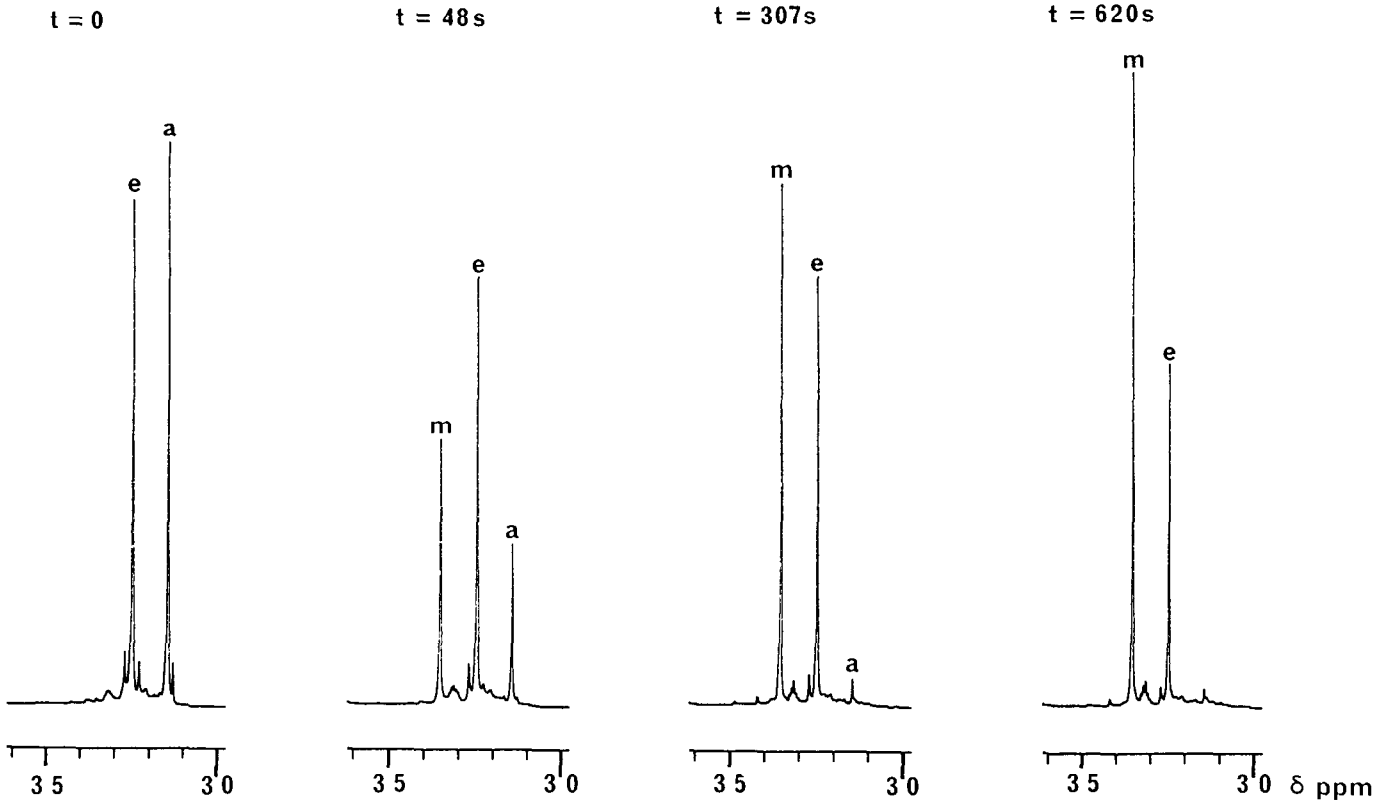

This equilibrium is particularly favourable for an acetal, because the high energy conformation (4) is selectively stabilised by the anomeric effect,[4] but cleavage by way of a chair-boat is clearly possible for an ortho-ester also. So we have carried out some simple experiments to determine the magnitude of the preference for the loss of an axial rather than an equatorial alkoxy group from an orthoester based on the oxadecalin system.

The axial and equatorial $OCH_3$ protons of the dimethyl orthoester (5)[5] are clearly resolved in the $^1H$ NMR spectrum in most solvents, though not in $CD_3OD$. In the presence of small amounts of acid $CD_3OD$ both signals rapidly dis-appeared, as the $OCH_3$ groups were exchanged for $OCD_3$ from the solvent (5 → 6). But under carefully controlled conditions (Table) the exchange reaction could be monitored by following the disappearance of the separate $OCH_3$ peaks. (A selection of the scans used to follow the reaction in $CD_2Cl_2$- $CD_3OD$ is shown in the Figure).




The results are summarised in the Table. In three different solvent systems there is a clear preference for the loss of the axial $OCH_3$ group, as predicted by the stereoelectronic theory. This preference amounts to an order of magnitude in the less polar solvent mixtures, but falls to a factor of only 2 in dimethyl sulphoxide-$d_6$-$CD_3OD$, probably reflecting a later transition state in the more polar solvent. If the loss of the equatorial $OCH_3$ group involves reaction with stereoelectronic control by way of a non-chair conformation, the magnitude of the observed preference for the cleavage of the axial C-OMe bond is determined primarily by conformational factors, and sets only a lower limit for the magnitude of the stereoelectronic effect in this system.

FIGURE Successive scans (Bruker WM-250, 250 MHz, 20°) of the $OCH_3$ region of the $^1H$ NMR spectrum of orthoester 5 in $CD_3OD$ - $CD_2Cl_2$ (5:95; for conditions see Table). Peaks are labelled a for axial, e for equatorial, m for methanol.



TABLE

Rate Constants for the $OCH_3/OCD_3$ Exchange Reaction of the Axial and Equatorial $OCH_3$ Groups of 5 at 20°

| Solvent | | $[CF_3CO_2H]$, M | $10^3 k_{ax}$ ($s^{-1}$) | $10^3 k_{eq}$ | $k_{ax}/k_{eq}$ |
|---|---|---|---|---|---|
| $CD_3OD$ - $CD_2Cl_2$ | (5:95)[a] | $1.5 \times 10^{-4}$ | 13.7 ± 0.9 | 1.29 ± 0.04 | 10.6 ± 0.7 |
| $CD_3OD$ - $C_6D_6$ | (5:95)[b] | $1.33 \times 10^{-3}$ | 23.3 ± 6.5 | 1.92 ± 0.10 | 12.1 ± 3.4 |
| $CD_3OD$ - $(CD_3)_2SO$ | (5:95)[b] | $1.56 \times 10^{-3}$ | 11.6 ± 0.2 | 6.25 ± 0.30 | 1.9 ± 0.1 |

Notes (a) Orthoester 0.25M (b) Orthoester 0.15M

Rate constants were obtained from good semi-logarithmic plots of integrated intensity of the appropriate $OCH_3$ singlets against time. The standard errors quoted derive from the fit of these lines.

ACKNOWLEDGEMENT - O.E.D. was supported by a Fellowship awarded by the Consejo Nacional de Investigaciones Cientificas y Técnicas of Argentina.

REFERENCES

1. P. Deslongchamps, *Heterocycles*, 7, 1271 (1977) : *Tetrahedron*, 31, 2463 (1975) : *Pure Appl. Chem.*, 43, 351 (1975).
2. C. M. Evans, R. Glenn and A. J. Kirby, *J. Am. Chem. Soc.*, 104 (in press)
3. S. Chandrasekhar and A. J. Kirby, *J. Chem. Soc., Chem. Commun.*, 1978, 171
4. A. J. Kirby, 'The Anomeric Effect and Related Stereoelectronic Effects at Oxygen', Springer-Verlag, 1982.
5. Prepared from the corresponding lactone (*trans*-octahydrocoumarin) according to P. Deslongchamps, R. Chênevert, R. J. Taillefer, C. Moreau and J. K. Saunders, *Can J. Chem.*, 53, 1601 (1975).

(Received in UK 15 July 1982)