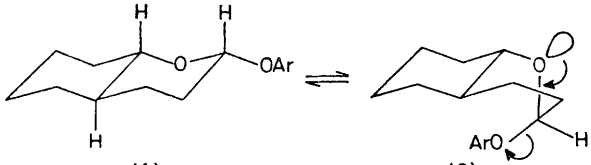
Stereoelectronic Control of Acetal Hydrolysis†

By ANTHONY J. KIRBY* and ROBERT J. MARTIN
(*University Chemical Laboratory, Cambridge* CB2 1EW)

Summary The free energy of activation for the hydrolysis of the acetal (**3**), which has no readily accessible conformation with a lone pair orbital antiperiplanar to the leaving group, is 7 kcal (29 kJ) mol^{-1} greater than that of the oxadecalin (**1**).

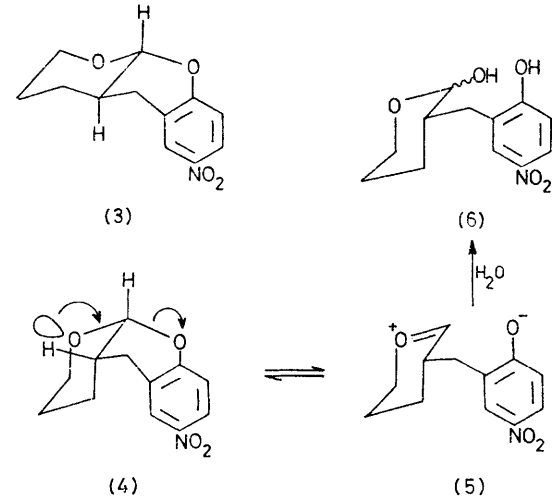
WE showed recently[1] that equatorial 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (**1**, Ar = $C_6H_4NO_2$) is hydrolysed faster than the corresponding axial anomer, even though neither lone pair orbital on the ring oxygen is antiperiplanar to the leaving group in the ground state conformation. This could mean that acetal cleavage is not subject to stereoelectronic control,[2] or that reaction occurs through a high energy conformation (*e.g.*, **2**) with a lone pair in the appropriate position.‡ We report evidence that acetal cleavage is subject to stereoelectronic control, and an estimate of the magnitude of the effect in one system.



The tricyclic acetal (**3**)§ also has no lone pair orbital antiperiplanar to the (*p*-nitrophenol oxygen) leaving group, but now the conformation about the acetal centre is locked by the *trans* ring junction. We have measured the rates of the spontaneous and acid-catalysed cleavage of (**3**), by following the appearance of the *p*-nitrophenolate chromophore at 400 nm. For comparison we have measured the same reactions of the isomer (**4**)§ with a *cis* ring junction, which does have a lone pair orbital antiperiplanar to the leaving group.

As expected for a 2-aryloxytetrahydropyran, (**4**) is rapidly hydrolysed in 0·1 M HCl (half-life 7·7 min at 39 °C). The hydrolysis of (**3**) was still not complete after several weeks under these conditions, and must be at least 3000 times slower.¶

On the other hand, the *spontaneous* hydrolysis of (**4**) ($t_{\frac{1}{2}}$ = 10·3 h at 100 °C in carbonate buffer, pH 9·0¶) is over 1000 times slower than the hydrolysis of similar compounds (*e.g.*, **1**) with exocyclic leaving groups. This is simply explained if the recyclisation of (**5**), to regenerate (**4**) is faster than attack by water, so that the hydration of (**5**) becomes rate determining. It is not unexpected that the



intramolecular addition of *p*-nitrophenoxide to the oxocarbonium ion should be faster than the intermolecular addition of water, and we find a significant solvent deuterium isotope effect [$k(H_2O)/k(D_2O)$ = 1·8 at 100 °C] for the reaction, consistent with rate determining hydration but not C–O cleavage.

If the same (hydration) step were rate determining, the spontaneous hydrolysis of the *trans* compound (**3**) would be expected to be faster than that of (**4**), since we know that (**4**) is more stable in the ground state (it is the predominant isomer at equilibrium, by 4:1 in benzene and in trifluoroacetic acid). In fact (**3**) is hydrolysed 3·4 times more slowly than (**4**) at pH 9·0, indicating that the rate determining step in this case is still C–O cleavage. (The negligible solvent deuterium isotope effect, k_H/k_D = 1·03, is consistent with this interpretation). We cannot therefore compare directly the rates of spontaneous hydrolysis of (**3**) and (**4**), since the rate determining steps are not the same. The most appropriate comparison for (**3**) is then the oxadecalin (**1**), which has essentially the same leaving group, in the same (equatorial) position in the ground state, and is also hydrolysed at pH 9 with rate determining C–O cleavage.[1] The hydrolysis of (**1**) at 39 °C is 20 times faster than that of (**3**) at 100 °C, equivalent to a factor of over 10^4 at 100 °C. This rate difference is a direct consequence of the rigid geometry of (**3**), which has no reasonably accessible conformation in which a lone pair orbital lies antiperiplanar to the leaving group. We can therefore

† No reprints available.

‡ The enthalpy of activation for the cleavage of (**1**), and of its axial anomer, is close to 25 kcal (104 kJ) mol^{-1}, much greater than the barrier to ring inversion, which is of the order of 10 kcal (41 kJ) mol^{-1}.

§ The (probably ionic) reaction of 2-hydroxy-5-nitrobenzyl bromide with dihydropyran in dimethyl sulphoxide at room temperature gives (**4**) (m.p. 100—102 °C) in 30% yield. Acid catalysed equilibration of (**4**) (in benzene saturated with HCl, sealed tube, 100 °C) produces a mixture containing 21% of (**3**) (m.p. 168—170 °C). The isomers are readily distinguished by ^{1}H n.m.r. spectroscopy; the acetal proton is a doublet in each case, with coupling constants of 8 Hz for (**3**) (δ 4·83 in $CDCl_3$) and 3 Hz for (**4**) (δ 5·44).

¶ Hydrolysis gives an equilibrium mixture of (**3**) and/or (**4**) and the open-chain compound (**6**). In acid the tricyclic acetal predominates, but in alkali (the anion of) (**6**) is the major component.

estimate the stereoelectronic barrier to C–O cleavage in this system as almost 7 kcal (29 kJ) mol^{-1}.[1] This result affects fundamentally the way we think about acetal cleavage, particularly the hydrolysis of β-glycosides, suggesting, for example, that the distortion of the substrate on bonding to lysozyme is for stereoelectronic reasons.[3]

(*Received*, 28*th June* 1978; *Com.* 688.)

[1] S. Chandrasekhar and A. J. Kirby, *J.C.S. Chem. Comm.*, 1978, 171.
[2] P. Deslongchamps, *Tetrahedron*, 1976, **31**, 2463.
[3] D. G. Gorenstein, J. B. Findlay, B. A. Luxon, and D. Kar, *J. Amer. Chem. Soc.*, 1977, **99**, 3473.