Stereoelectronic Effects at Oxygen. The Hydrolysis of 2-Aryloxy-*trans*-1-oxadecalins

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The spontaneous hydrolysis of axial nitrophenyltetrahydropyranyl acetals with one or two *trans* ring junctions is 2—3 times slower than that of the equatorial isomers. It is concluded that relative reactivity depends not on stereoelectronic effects on transition states, but on differences in ground state energies. In the acid-catalysed reaction these relative reactivities are reversed, and $k_{ax} > k_{eq}$, apparently because of an additional barrier to the cleavage of the equatorial isomer. The evidence is consistent with this additional barrier being stereoelectronic in origin, but the effects are small, and other explanations cannot be ruled out.

The key to the reactivity of orthoesters and related compounds (1; X = any leaving group, Y and Z = O or N) is the stabilisation of the derived carbonium ion (2) by the two first-row heteroatoms. Deslongchamps [1] has suggested that such reactions are subject to stereoelectronic control. Unambiguous evidence is difficult to obtain, but a substantial body of experimental results from a number of systems is at least consistent with the theory, and its basic tenets are by now rather broadly accepted.[2]

The most important of these is that the preferred mode of cleavage of a compound (1) involves a conformation (3) in which non-bonded electron pairs (lone pairs) on both remaining heteroatoms lie antiperiplanar to the leaving group. Overlap with the antibonding (σ*) orbital of the C–X bond is thus maximised, and the orbitals of the starting material are transmuted into those of the product (4) with minimal structural reorganisation.

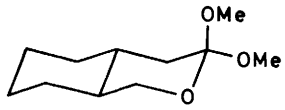
Closely similar considerations must apply to the cleavage of acetals. Substitutions at acetal centres are generally dissociative processes,[3] and though reactions involving solvent or other nucleophile participation in the transition state may be more common than is currently realised,[4] reactivity nonetheless always depends crucially on the stabilisation (5) of the developing cationic centre by the remaining oxygen atom.[3]

We have suggested that because (5), and transition states close in structure to it, are stabilised by only one π-donor, rather than by two heteroatoms as in (2), they may be even more dependent on the electron-donating capability of their single oxygen atom, including the orientation of the lone pair orbitals.[5] If the cleavage of orthoesters and related compounds is subject to stereoelectronic control, therefore, so also should be the cleavage of acetals. So a simple prediction is that acetal cleavage will be easiest when one of the lone pairs on the remaining oxygen atom is antiperiplanar to the C–O bond being broken as in (6).

The experiments described in this [5] and the following papers were designed to test this proposition. The problem is akin to that of the stereochemistry of elimination by the *E*2 (or *E*1cb) mechanism, where antiperiplanar geometry is known to be preferred, from the results of rate and product studies on a wide variety of compounds.[6] Our initial approach was based on some of this work. A major complication is that the stereochemistry of the initial product of acetal cleavage cannot normally be observed because it is a short-lived high energy species (6), so that experiments using open-chain compounds are ruled out. The most promising systems appeared to be those based on conformationally locked tetrahydropyrans. *E*2 eliminations of axial leaving groups are generally considerably faster than the reactions of the corresponding equatorial anomers from cyclohexane rings locked by an equatorial t-butyl group or a *trans*-ring junction.[7,8] Moreover, Deslongchamps has shown that the formation and cleavage of the orthoester (7) involves specifically the bond to the axial methoxy-group.[1]

We have therefore examined the cleavage reactions of a series of conformationally restricted acetals. In this paper we describe the synthesis and hydrolysis of a group of tetrahydropyranyl acetals (8) and (9). The axial anomers have a lone pair antiperiplanar to the leaving group in the ground state conformation, and can thus be cleaved with stereoelectronic control. Antiperiplanar to the leaving group of the equatorial anomers (8e) and (9e), on the other hand, are ring bonds, and here reaction in the ground state conformation is predicted to be less favourable.†

† The choice of a phenol, rather than an alcohol leaving group has important advantages. The acetals are sufficiently unsymmetrical for only one mode of cleavage to be possible (*i.e.* no ring C–O cleavage): we can follow both acid-catalysed and spontaneous reactions in some cases; the transition states for the spontaneous cleavage of compounds of this sort are particularly well understood [9] and problems of interpretation associated with the differing basicities of axial and equatorial oxygen centres are avoided.



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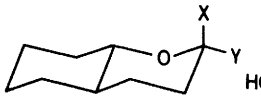
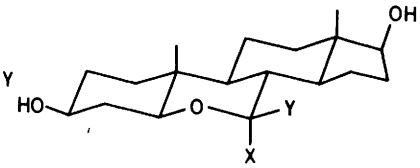


(8a) X = OAr, Y = H
(8e) X = H, Y = OAr



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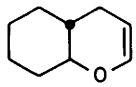
(9e) X = H, Y = OAr



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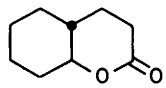

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Experimental

Materials and methods have mostly been described previously.[3,9] ^{1}H N.m.r. spectra were recorded in $CDCl_3$ on a Varian HA 100 instrument, and ^{13}C spectra in [$^2H_6$]acetone on a Varian XL 100 machine.

2-Aryloxy-*trans*-1-oxadecalins were synthesised, somewhat laboriously, as follows. [The obvious route involves the addition of the phenol to the enol ether (10), but we were unable to repeat the preparation reported by Normant-Chefney and Maitte,[10] despite repeated attempts.]

trans-Octahydrocoumarin [11] (11) was reduced to the mixture of lactols (8; X, Y = H, OH) with lithium tri-t-butoxyaluminium hydride, according to Dufey *et al.*[12] Careful reduction with lithium aluminium hydride gave the same products, and this procedure was used to make the 2-deuterio-compound.

2-*Deuterio*-2-*hydroxy*-trans-1-*oxadecalin* (8; X, Y = D, OH).—To redistilled lactone (11) (3.4 g) in dry ether (20 ml) at −20° was added a slurry of $LiAlD_4$ (0.20 g) in dry ether (15 ml). The mixture was stirred for 45 min as it warmed to room temperature, then poured onto crushed ice. After the ice had melted the mixture was extracted with ether (3 × 30 ml) and the extracts dried and evaporated to give the mixture of lactols, which slowly crystallised, m.p. *ca.* 50°, $\nu_{max.}$ 2 120 cm^{-1}, δ 3.6 (0.3 H, m), 3.05 (0.7 H, m), and 2.0—1.0 (13 H, m) the protio-compound showed additional peaks at δ 5.30br (0.3 H, s) and 4.82 (0.7 H, dd, *J* 8 and 2 Hz) for the acetal protons of the axial and equatorial isomers, respectively] (Found: C, 69.2; H, 10.4. $C_9H_{15}DO_2$ requires C, 68.8; H, 10.1%).

The lactol product was acetylated using acetic acid–pyridine,[13] and the mixture of acetates (8; X, Y = H, OAc), obtained as an oil after removing solvent and volatiles under reduced pressure, was used in the final stage of the synthesis without further purification.

General Procedure.—The mixture of acetates (8; X, Y = H, OAc) was dissolved in dry benzene and 4 equiv. of the phenol added to the solution, which was then refluxed for 4 h. The cooled mixture was washed repeatedly with 10% NaOH, then with brine. The benzene layer was dried, the solvent evaporated, and the products purified by p.l.c. on 1 mm silica plates, by repeated development with 20% CH_2Cl_2–petroleum. (b.p. 40—60°). Yields were *ca.* 80% of a mixture containing axial and equatorial isomers (8a and e), in *ca.* 3 : 1 ratios.

Equatorial 2-phenoxy-*trans*-1-oxadecalin (8e; X = H, Y = OPh) had m.p. 102—103° from CH_2Cl_2–petroleum. The structure of this compound has been confirmed by a single-crystal *X*-ray determination,[14] δ 7.1 (5 H, m), 5.09 (1 H, dd, *J* 8 and 2 Hz), 3.13 (1 H, m), and 2.0—1.0 (13 H, m).

Axial 2-phenoxy-*trans*-1-oxadecalin (8a; X = OPh, Y = H) had m.p. 98—99° from CH_2Cl_2–petroleum. The structure of this compound has been confirmed by a single-crystal *X*-ray determination,[15] δ 7.15 (5 H, m), 5.54br (1 H, s), 5.45 (1 H, m), and 2.1—1.0 (13 H, m) (Found, C, 65.0; H, 7.1; N, 5.0. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.1%).

Equatorial 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (8e; X = H, Y = $OC_6H_4NO_2$-*p*) had m.p. 108—111° from CH_2Cl_2–petroleum. The structure of this compound has been confirmed by a single-crystal *X*-ray determination,[16] δ 8.1 (2 H, d, *J* 8 Hz), 7.05 (2 H, d, *J* 8 Hz), 5.17 (1 H, dd, *J* 8 and 2 Hz), 3.17 (1 H, m), and 2.1—1.0 (13 H, m).

Axial 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (8a; X = $OC_6H_4NO_2$-*p*, Y = H) had m.p. 114—118° from CH_2Cl_2–petroleum, δ 8.1 (2 H, d, *J* 8 Hz), 7.05 (2 H, d, *J* 8 Hz), 5.66br (1 H, s), 3.35 (1 H, m), and 2.1—1.0 (13 H, m), *m/z* 277 (*M*$^+$), 276, 179, 178, 166, 165, and 139 (Found: C, 65.0; H, 6.9; N, 5.2. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.1%).

Axial 2-(4-nitrophenoxy)-2-deuterio-*trans*-1-oxadecalin (8e; X = $OC_6H_4NO_2$-*p*, Y = D), prepared similarly from the 2-deuterio-lactol, had m.p. 111—113°. The ^{1}H n.m.r. spectrum was similar to that of the protio-compound, except that the signal for the acetal proton at δ 5.17 was absent. Since this proton signal is the best guide to anomeric purity ^{13}C n.m.r. spectra were also run. The spectrum obtained was identical with that of the protio-compound, except that the signal for C(2) at δ 114.6 p.p.m. was missing, δ_C ([$^2H_6$]acetone) 143.9, 134.8, 92.5, 59.8, 50.5, 49.9, 48.4, 48.2, 44.0, and 43.3 p.p.m. (Found: C, 64.2; H, 6.8; N, 4.9. $C_{15}H_{18}DNO_4$ requires C, 64.7; H, 6.8; N, 5.0%).

Equatorial 2-(4-nitrophenoxy)-2-deuterio-*trans*-1-oxadecalin (8e; X = D, Y = $OC_6H_4NO_2$-*p*) had m.p. 107—109°. Again the ^{13}C n.m.r. spectrum showed no C(2) peak, δ_C ([$^2H_6$]acetone) 143.9, 134.8, 97.9, 59.4, 50.6, 49.9, 49.4, 48.0, 44.0, and 43.0 p.p.m. (Found: C, 64.8; H, 7.0; N, 5.0. $C_{15}H_{18}DNO_4$ requires C, 64.7; H, 6.8; N, 5.0%).

3β,17β-*Di-t-butoxy*-7-*hydroxy*-6-*oxa*-5α-*androstane* (15; R = Bu^t, R′ = H). To keto-acid (16; R = Bu^{t}O) (1 g),[17] dissolved in dry ethanol (15 ml), was added $NaBH_4$ (1.05 equiv., 91 mg) at −15°. The mixture was allowed to come to room temperature overnight, then a further 4 equiv. (0.347 mg) added, and the mixture stirred for another 24 h at room temperature. Dilute HCl was added until gas evolution ceased, and the mixture extracted with chloroform. The chloroform layer was washed with water, dried ($MgSO_4$), and evaporated to give the mixture of lactols (900 mg, 90%), δ($CDCl_3$) 5.05 (0.75 H, d, *J* 4 Hz), 4.48 (0.25 H, d, *J* 8 Hz), 3.4 (3 H, m), 1.12 (9 H, s), 1.04 (9 H, s), 0.87 (3 H, s), 0.71 (3 H, s), and 2.2—1.0 (17 H, envelope), $\nu_{max.}$ 3 330, 1 460, 1 380, and 1 365 cm^{-1}, *m/z* 422 (*M*$^+$), 404, 349, 348, and 236.

3β,7,17β-*Triacetoxy*-6-*oxa*-5α-*androstane* (15; R = R′ = Ac). The mixture of lactols (above) was deprotected by stirring for 30 min in dry acetic acid saturated with HBr gas. The solution was made slightly alkaline (1M-NaOH) and extracted with chloroform. The crude product was acetylated by stirring overnight in acetic anhydride–pyridine. Volatile components were removed by evaporation at 50° under vacuum, yield 75—80%, δ($CDCl_3$) 5.96 (0.25 H, d, *J* 4 Hz), 5.46 (0.75 H, d, *J* 8 Hz), 3.4 (3 H, m), 2.11 (2.25 H, s), 2.07 (0.75 H, s), 2.04 (6 H, s), 0.95 (3 H, s), 0.81 (3 H, s), and 2.2—1.0 (envelope).

3β,17β-*Diacetoxy*-7α-(4-*nitrophenoxy*)-6-*oxa*-5α-*androstane* (15; R = Ac, R′ = 4-$NO_2C_6H_4$). The crude triacetate (above) was refluxed in the presence of 4 equiv. *p*-nitrophenol in dry benzene for 16 h. On cooling, the solution was washed repeatedly with 1M-NaOH to remove excess of phenol, and the crude product purified by p.l.c. on silica using CH_2Cl_2 (R_F 0.5). This fraction was found to contain *p*-nitrophenyl acetate, and a second p.l.c. was necessary (5% ether in CH_2Cl_2), yield 45%, δ($CDCl_3$) 8.16 (2 H, d, *J* 8 Hz), 7.14 (2 H, d, *J* 8 Hz), 5.36 [1 H, d, *J* 3 Hz, equatorial acetal proton at C(7)], 4.6 (2 H, m), 3.58 (1 H, m), 2.04 (3 H, s), 1.99 (3 H, s), 1.01 (3 H, s), 0.85 (3 H, s), and 2.2—1.1 (17 H, envelope).

3β,17β-*Dihydroxy*-7α-(4-*nitrophenoxy*)-6-*oxa*-5α-*androstane* (9a; Ar = 4-$NO_2C_6H_4$). The purified diacetate was dissolved in dry methanol containing hydrazine (2M). T.l.c. showed that reaction was complete after 15 h. After adding ether the solution was extracted with dilute HCl and then water. The organic layer was dried and evaporated to give a product which was chromatographically pure, m.p. 165—167°, δ($CDCl_3$) 8.17 (2 H, d, *J* 8 Hz), 7.17 (2 H, d, *J* 8 Hz), 5.39 (1 H, d, *J* 3 Hz), 4.24 (2 H, s, OH), 3.6 (3 H, m), 1.0 (3 H, s), 0.79 (3 H, s), and 2.1—1.0 (17 H, envelope) (Found: C, 62.85; H, 7.3; N, 2.75. $C_{24}H_{33}NO_6$,1.5H_2O requires C, 62.9; H, 7.85; N, 3.05%).

3β,17β-*Di-t-butoxy*-7α- *and* -7β-(2,4-*dinitrophenoxy*)-6-*oxa*-5α-*androstane* [15; R = Bu^t, R′ = 2,4-$(NO_2)_2C_6H_3$]. To the protected lactol mixture (15; R = Bu^t, R′ = H) (0.9 g) in ether (20 ml) was added n-butyl-lithium (2 equiv., 2.7 ml) in hexane. The solution was stirred for 15 min at room temperature then 2,4-dinitrofluorobenzene (1.4 g, 4 equiv.) was added. The mixture was refluxed for 2 h, cooled, water added, and extracted with chloroform. The chloroform extracts were washed repeatedly with 1M-NaOH, then water, then dried ($MgSO_4$), and evaporated. The products were separated by p.l.c. on 1 mm silica plates. The fastest running band (of eight) contained the mixture of axial and equatorial acetals (plus some impurities). These were separated by further p.l.c. using 10% ethyl acetate in CCl_4 (the best of a large number of solvents tried). The R_F values were 0.3 and 0.4 for the axial and equatorial anomers, respectively, and the total yield was 25%, based on the lactol mixture: axial acetal, δ($CDCl_3$) 8.78 (1 H, d, *J* 3 Hz), 8.43 (1 H, dd, *J* 3 and 8 Hz), 7.48 (1 H, d, *J* 8 Hz), 5.55 (1 H, d, *J* 3 Hz, equatorial proton at acetal centre), 3.6 (3 H, m), 1.14 (18 H, s), 0.98 (3 H, s), 0.75 (3 H, s), and 2.1—1.0 (17 H, envelope); equatorial acetal, δ($CDCl_3$) 8.65 (1 H, d, *J* 3 Hz), 8.35 (1 H, dd, *J* 3 and 8 Hz), 7.31 (1 H, d, *J* 9 Hz), 4.99 (1 H, d, *J* 8 Hz), 3.5 (3 H, m), 1.21 (9 H, s), 1.11 (9 H, s), 0.99 (3 H, s), 0.78 (3 H, s), and 2.0—1.0 (17 H, envelope).

These compounds were produced only in amounts sufficient for kinetic studies, after a number of attempts to remove the t-butyl groups selectively had failed. [Acidic conditions generally led to loss of dinitrophenol, even in the presence of a large excess of the phenol, with formation of the enol ether (18).] A few measurements showed that the ratio of the rates of hydrolysis of the axial and equatorial isomers was similar to that found for the oxadecalin *p*-nitrophenol acetals (8a and e; Ar = 4-$NO_2C_6H_4$). So no detailed investigation was carried out, and the compounds were not fully characterised. There is, however, no doubt about their structure, in view of the n.m.r. data, and the fact that both compounds behave as expected for acetals, each releasing one equiv. of 2,4-dinitrophenolate in a pH-independent reaction at the predicted rate.

Kinetic Methods and Results.—Reactions were followed by monitoring the release of the phenol or phenolate ion under pseudo-first-order conditions, in the thermostatted cell-holder of a Zeiss PMQ II spectrophotometer. Details have been described.[9] Measurements were mostly at 39.0°, and the aqueous medium contained 30% v/v dioxane for solubility reasons, plus sufficient KCl to bring the ionic strength to 0.1M. The high extinction coefficient of the *p*-nitrophenolate anion allowed measurements in water for the spontaneous reaction of the *p*-nitrophenyl acetals, and thus direct comparison with previous data for the hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran.

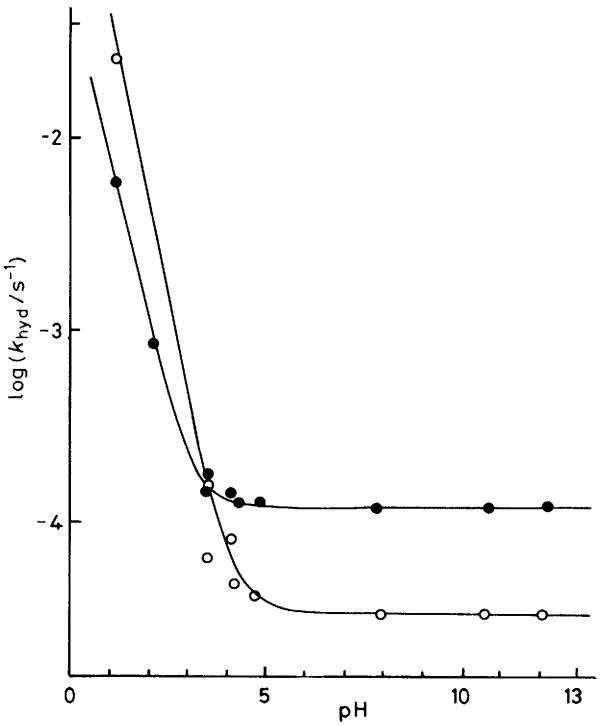


Figure 1. pH–Rate profiles for the hydrolysis of axial (open circles) and equatorial (filled circles) 2-(4-nitrophenoxy)-*trans*-1-oxadecalin, in 30% dioxane–water at 39.0°. The curves are calculated from the rate constants given in Table 1

pH–Rate profiles for the hydrolysis of the *p*-nitrophenyl acetals (8a and e; X = $OC_6H_4NO_2$-4, Y = H) are shown in Figure 1; rate constants for the spontaneous reaction appear in Table 1 and for the acid-catalysed hydrolysis in Table 2. The reaction is catalysed by the acid component of the low pH buffers, and the points on the pH–rate profile represent extrapolations to zero buffer concentration where necessary. The second-order rate constants for the H_3O^+-catalysed hydrolysis of axial and equatorial 2-phenoxy-*trans*-1-oxadecalin (1a and 2; Ar = Ph) under the standard conditions used (30% dioxane–water, 0.01M-HCl, 39°, mean of 2 and 3 runs, respectively) were k_{ax} 1.46 ± 0.03 and k_{eq} 3.63 ± 0.05 × 10^{-1} dm^3 mol^{-1} s^{-1}. Thus k_{ax}/k_{eq} is 4.0, not significantly different from the ratio (4.1, data from Table 2) for the H_3O^+-catalysed reaction of the 4-nitrophenyl compounds at 39°. The absolute rates for the axial isomer are in the region expected from the work of Fife and his co-workers,[18,19] who studied the same reactions of a series of 2-aryloxytetrahydropyrans.

First-order rate constants for the hydrolysis of the steroid derivatives, 3β,17β-di-t-butoxy-7α- and -7β-(2,4-dinitrophenoxy)-6-oxa-5α-androstane [15; R = Bu^t, R′ = 2,4-$(NO_2)_2C_6H_3$] are given in Table 3. This reaction was measured in 50% aqueous dioxane (v/v) for solubility reasons. The unprotected *p*-nitrophenol acetal (9a; Ar = 4-$NO_2C_6H_4$) was soluble enough for measurements in water (this was the

Table 1. First-order rate constants (s^{-1}) for the spontaneous hydrolysis of axial and equatorial 2-(4-nitrophenoxy)-*trans*-1-oxadecalins in 30% dioxane–water [a]

	Axial isomer	Equatorial isomer	*Runs*
k_0/s^{-1} at 28.9°	$8.64 \pm 0.02 \times 10^{-6}$	3.34×10^{-5}	4,4
33.6°	1.59×10^{-5}		4
33.8°		6.07×10^{-5}	4
39.0°	3.44×10^{-5}	1.22×10^{-4}	4,4
44.8°	7.24×10^{-5}	2.49×10^{-4}	4,4
$\Delta H^{\ddagger}$/kcal mol^{-1}	25.1 ± 0.3	23.5 ± 0.4	
kJ mol^{-1}	105 ± 1	98 ± 2	
$\Delta S_{39}^{\ddagger}$/cal K^{-1} mol^{-1}	1.4 ± 1.9	-1.1 ± 2.3	
J K^{-1} mol^{-1}	5.9 ± 7.5	-4.6 ± 9.6	
k_0 for 2-D compound at 39.0°	2.86×10^{-5}	$9.50 \pm 0.02 \times 10^{-5}$	2,2
k_H/k_D	1.20	1.29	
k_0 in water at 39°	1.58×10^{-4}	5.68×10^{-4}	2,2

[a] Errors quoted are standard errors from least-squares slopes. Where no errors are given σ is better than ±1 in the last digit quoted.

Table 2. Second-order rate constants (dm^3 mol^{-1} s^{-1}) for the acid-catalysed hydrolysis of axial and equatorial 2-(4-nitrophenoxy)-*trans*-1-oxadecalins (1a and e) in 30% dioxane–water

	k_{ax}	k_{eq}	Runs
Specific acid catalysis			
k_H at 25.0°	9.40×10^{-2}	2.16×10^{-2}	10,4
31.2°	0.162	3.83×10^{-2}	5,4
39.0°	0.321	7.77×10^{-2}	3,6
46.2°	0.636	0.161	8,5
$\Delta H^{\ddagger}$/kcal mol^{-1}	16.4 ± 0.1	17.2 ± 0.1	
kJ mol^{-1}	68 ± 1	72 ± 1	
$\Delta S_{39}^{\ddagger}$/cal K^{-1} mol^{-1}	-8.2 ± 0.8	-8.6 ± 0.8	
J K^{-1} mol^{-1}	-34 ± 4	-36 ± 4	
General acid catalysis (Data at 39°, unless otherwise stated)			
Acid (% HA, pH)			
Acetic (80, 4.76)	1.04×10^{-4}	1.63×10^{-4}	3,6
2-Chloropropionic (80, 4.10)	1.95×10^{-4}	3.44×10^{-4}	6,6
Formic (50, 4.21)	8.83×10^{-4}	5.68×10^{-4}	3,6
Formic (83, 3.50)	8.21×10^{-4}	5.86×10^{-4}	3,6
Chloroacetic (50, 3.48)	1.78×10^{-3}	1.58×10^{-3}	6,6
Chloroacetic at 25.2°	5.14×10^{-4}	3.78×10^{-4}	9,3
Chloroacetic at 30.7°	8.74×10^{-4}		12
30.95°		7.26×10^{-4}	3
Chloroacetic at 49.5°	5.31×10^{-3}		9
49.7°		4.32×10^{-3}	6
$\Delta H^{\ddagger}$/kcal mol^{-1}	17.6 ± 0.2	18.3 ± 0.1	
kJ mol^{-1}	74 ± 1	77 ± 1	
$\Delta S_{39}^{\ddagger}$/cal K^{-1} mol^{-1}	-14.7 ± 1.2	-12.8 ± 0.4	
J K^{-1} mol^{-1}	62 ± 5	54 ± 2	
Brönsted coefficient, α	0.70 ± 0.04	0.52 ± 0.01	

original reason for having hydroxy-groups in positions 3 and 17), where it hydrolysed spontaneously with a rate constant of 1.3×10^{-6} s^{-1} at 39° and ionic strength 0.1M (mean of two runs in 0.05M-carbonate buffer, pH 9.08). The hydrolysis of the oxasteroid acetals is much slower than that of the corresponding tetrahydropyran or oxadecalin acetals, but a comparison of the data for the axial *p*-nitrophenyl and 2,4-dinitrophenyl oxasteroid derivatives shows a similar dependence on the leaving group. {Correcting by a factor of 48 for the retardation in 50% dioxane compared with water [data of Fife and Brod [19] for 2-(4-nitrophenoxy)tetrahydropyran] the difference in spontaneous hydrolysis rate is 1.4×10^4; equivalent to a ρ value of 2.9, compared with the value of 2.7 measured for 2-aryloxytetrahydropyrans in water.[9]}

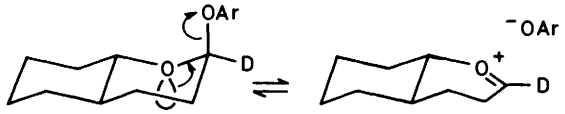
Discussion

Spontaneous Hydrolysis.—The spontaneous hydrolysis of axial 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (8a; Ar = 4-$NO_2C_6H_4$), far from being substantially faster, is actually slower than that of the equatorial isomer, by a factor of 2.8 at 39° in 30% dioxane–water (3.6 in water). This factor depends little on temperature, since the enthalpies of activation are similar (Table 1), with $\Delta H^{\ddagger}$ more favourable by 1.5 kcal mol^{-1} for the cleavage of the equatorial compound, partly offset by a slightly more favourable entropy of activation for the axial isomer.

The absolute values of these parameters are similar to those found by Fife and Brod [19] for the spontaneous hydrolysis of

Table 3. First-order rate constants for the spontaneous hydrolysis of 3β,17β-di-t-butoxy-7α- and -7β-(2,4-dinitrophenoxy)-6-oxa-5α-androstane [15; R = Bu^t, R′ = 2,4-$(NO_2)_2C_6H_3$], in 50% aqueous dioxane (v/v), 39° and ionic strength 0.1M

	Buffer (% free base)	pH	T/°C	k_{obs}/s^{-1}
Axial isomer (7α)				
	Acetate (80%)	6.70	39.0	3.71×10^{-4}
	TRIS (50%)	7.82	39.0	3.77×10^{-4}
Equatorial isomer (7β)				
	Acetate (80%)	6.67	45.4	1.91×10^{-3}
	TRIS (50%)	7.67	45.4	1.99×10^{-3}
	Acetate (80%)	6.67	39.0	1.03×10^{-3}
	TRIS (50%)	7.68	39.0	9.92×10^{-4}
	Acetate (80%)	6.76	30.8	3.90×10^{-4}
	TRIS (50%)	7.96	30.8	4.08×10^{-4}
	Acetate (80%)	6.72	25.3	2.08×10^{-4}
	TRIS (50%)	8.08	25.3	2.12×10^{-4}
		$\Delta H^{\ddagger}$/kcal mol^{-1}		20.4 ± 0.1
		kJ mol^{-1}		85
		$\Delta S_{39}^{\ddagger}$/cal mol^{-1} K^{-1}		−6.9 ± 0.5
		J mol^{-1} K^{-1}		−29



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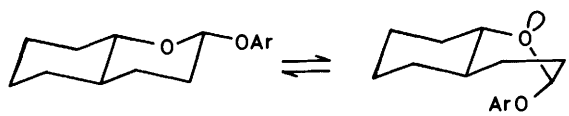


(14)

2-(4-nitrophenoxy)tetrahydropyran: this compound is expected to exist in solution predominantly in the conformation with the leaving group axial, and comparison with our data shows that the axial oxadecalin is hydrolysed at about half the rate, with $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ closely similar.

These results show clearly that the small difference in reactivity between axial and equatorial isomers observed for the spontaneous cleavage of these acetals is determined almost entirely by differences in ground state energy. (We cannot measure the equilibration of the axial and equatorial isomers under the reaction conditions, but the two are prepared as an equilibrium mixture in benzene, with the axial isomer predominating by a factor of 2—3.) The transition states for the hydrolysis of the two species must therefore be almost identical in energy.

As a more sensitive probe of transition state structure we measured the secondary deuterium isotope effect for the spontaneous hydrolysis of the *p*-nitrophenyl acetals. Both compounds show a substantial isotope effect, as expected for the late transition state characterised by previous work on similar systems.[9,19] The value for the axial compound (1.20 ± 0.01) is significantly smaller than that for the equatorial isomer (1.29 ± 0.01), but this difference also can be explained in terms of ground-state differences. Our *X*-ray structural work shows that there is significant lengthening of the bond to an axial *p*-nitrophenyl group, with concomitant shortening of the endocyclic C–O bond of the acetal group.[20] The effect is much reduced for equatorial systems, and is apparently a stereoelectronic effect on the ground state, of the same type (12) as that leading eventually to C–OAr cleavage.

The ground state of the axial isomer is thus closer in geometry to the transition state: compared with the equatorial compound it starts further along the reaction co-ordinate in the direction of C–OAr cleavage. The change in hybridisation at the acetal carbon between ground and transition states is thus smaller for the axial compound, accounting, qualitatively at least, for the smaller secondary deuterium isotope effect.

These kinetic results are clearly consistent with closely similar transition states for the spontaneous hydrolysis of the pair of axial and equatorial isomers (8a and e; Ar = 4-$NO_2C_6H_4$): there is thus no apparent stereoelectronic control of the cleavage of these conformationally locked acetals. This might be because the theory is wrong, and that stereoelectronic control of this sort does not exist, or because the system we are using to test the theory is unsuitable. In subsequent papers of this series we describe evidence that stereoelectronic control can be an important factor in the cleavage of certain related acetals, so we need here to explain how the equatorial compound is able to react in spite of the built-in conformational constraint.

Two possible explanations are of interest. The first is that the transition state, known from independent evidence to be late for this type of reaction,[9] is actually so late that stereoelectronic control is lost. Consider the extreme case, with diffusion apart of an intimate ion-pair [*e.g.* (13)] rate determining. [This cannot be so in our system (12), because the reaction shows a significant secondary kinetic deuterium isotope effect.] Since the oxocarbonium ion is the same for both isomers, the difference in rates will be determined almost entirely by differences in ground-state energy. Only while there is still significant bonding between the oxocarbonium ion and the leaving group will the exact location of ArO^- affect the energy of the system significantly. Other things being equal, therefore, an earlier rather than a very late transition state would be desirable.

An alternative explanation is that the equatorial isomer reacts *with* stereoelectronic control, by way of a conformation other than that of the ground state. Although one end of the tetrahydropyran ring is locked by the *trans*-ring junction, the free end of the chair can still invert to give a chair-boat and related twist forms [*e.g.* (14)], which have a lone pair of electrons antiperiplanar to the leaving group. The energy of activation for such a conformational change would be much

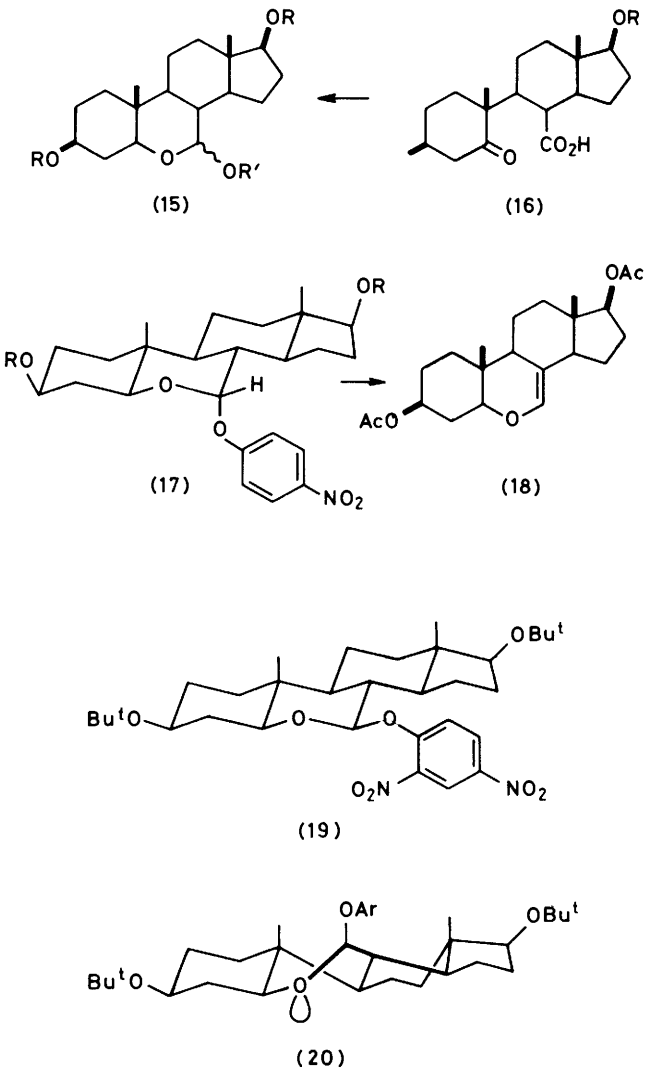
smaller than that for C–O cleavage, which is *ca.* 24 kcal (100 kJ) mol^{-1} (Table 1). The barrier to ring inversion in tetrahydropyrans is of the order of 10 kcal (41 kJ) mol^{-1},[21] similar to that in cyclohexanes. Furthermore, (14) is by no means a high-energy conformation, because the difference in energy between the chair and twist-boat forms (5—6 kcal mol^{-1} in cyclohexane [22]) will be substantially reduced by the anomeric effect.[23,24] [Gorenstein [25] has shown recently that this effect is large enough to make the twist-boat the preferred conformation of a related 2-(4-nitrophenoxy)-2-oxo-1,3,2-oxazaphosphorinane.]

We conclude that the most serious shortcoming of our test system (8a) *versus* (8e) is this residual conformational mobility around the acetal centre (possibly compounded by the lateness of the transition state). Our eventual success in overcoming this shortcoming is described in the following papers, but our first attempt to make the system more rigid was an interesting failure, described briefly below.

Since one *trans*-ring junction does not lock the conformation of our tetrahydropyran ring securely, we decided to try adding a second. The most accessible relevant system appeared to be the 6-oxasteroid lactol (15; R = R′ = H), prepared previously by Speckamp and Kesselaar.[17] We made (15; R = Bu^t, R′ = H) in near-quantitative yield from the keto-acid (16; R = Bu^t) by a two-stage low-temperature reduction with $NaBH_4$ (see Experimental section), and the *p*-nitrophenyl acetal (15; R = H, R′ = 4-$NO_2C_6H_4$) was obtained *via* the acetate in the same way as the oxadecalin acetals. In this case, however, the product was exclusively the axial compound (17; R = Ac), and we could find no way of equilibrating this acetal centre. [Under forcing conditions elimination occurred to give (probably) the enol ether (18), from (17; R = Ac).] The exclusive formation of the axial compound from the epimeric mixture of acetates (15; R = R′ = OAc, equatorial isomer predominating) is consistent with stereoelectronic control of the formation of the acetal from the oxocarbonium ion, but other explanations cannot be ruled out, and a comparison of the rates of cleavage of an axial and equatorial pair of isomers remained the crucial test.

Since we were not able to make the equatorial isomer by routes involving C–O bond formation at the acetal centre, we chose the alternative approach, of arylating the lactol mixture (15; R = Bu^t, R′ = H). This proved possible with 2,4-dinitrofluorobenzene. [We knew already that the oxasteroid system was very unreactive, from the rate of hydrolysis of (17; R = H), and so we expected the normally highly labile tetrahydropyranyl 2,4-dinitrophenyl acetal system to be reasonably stable in this case.] But now the t-butyl protecting groups of the axial and equatorial 2,4-dinitrophenyl acetals could not be removed without cleaving the acetal; so we measured the rates of hydrolysis of the two epimers [15; R = Bu^t, R′ = 2,4-$(NO_2)_2C_6H_3$] with the protecting groups still on, in 50% aqueous dioxane.

The spontaneous hydrolysis of the axial *p*-nitrophenyl acetal (17; R = H) is over 200 times slower than that of the corresponding tetrahydropyran derivative. (This we take to be a result of the increased rigidity of the ring, resulting from the two *trans*-ring junctions: these impose an additional barrier between the unstrained ground state and the transition state, which is close in geometry to the oxocarbonium ion and thus forced to adopt a half-chair conformation.) But the most important observation is that, in this system also, the equatorial isomer (19) is more reactive than the axial, by a factor (2.7 at 39° in 50% aqueous dioxane for the 2,4-dinitrophenyl acetals) very similar to that found in the oxadecalin system. Presumably a similar explanation applies: models show that the equatorial acetal is surprisingly easily converted, by a twist of ring B, into a chair-twist-boat-chair conformation



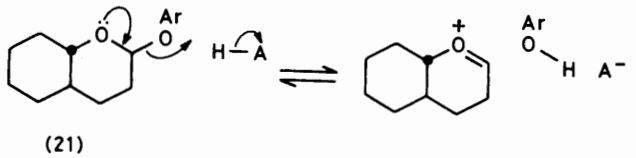
(20), which has the 2,4-dinitrophenoxy-group close to anti-periplanar to a lone pair on the ring oxygen.

Our results for the spontaneous hydrolysis of two pairs of conformationally restricted tetrahydropyran acetals thus provide no evidence to support the theory of stereoelectronic control.

Acid-catalysed Hydrolysis.—The pH–rate profiles for the hydrolysis of the 4-nitrophenyl compounds cross over near pH 4 (Figure 1), so that below this pH the axial compound *is* hydrolysed more rapidly, as predicted by the stereoelectronic theory. The actual rate difference is not large [k_H is up to 4.35 times larger for (8a; X = 4-$NO_2C_6H_4$, Y = H) at 25°] but the ground-state energy is also lower for the axial isomer. Allowing a factor of 3 for this effect gives a corrected rate factor of up to 13.

Comparison with the date of Fife and his co-workers,[18,19] shows that k_H for the axial isomers is similar [20—25% smaller for (8a; X = 4-$NO_2C_6H_4$, Y = H)] to that for the corresponding aryltetrahydropyranyl acetal. The rate difference thus appears to indicate an additional barrier to the hydrolysis of the equatorial compound.

Though small, this rate factor represents an effect on the transition state for the acid-catalysed reaction (since ground state and conformational equilibrium energies are the same as for the spontaneous reaction) and could, therefore, be



(21)

stereoelectronic in origin. So we looked for differences in the kinetic parameters for the acid-catalysed hydrolysis of four acetals (8; X and Y = Ph or 4-$NO_2C_6H_4$ and H).

Mechanistically, all the acid-catalysed reactions appear to involve general acid catalysis (21). The points for catalysis by H_3O^+ fall on the Brönsted plots for general acid catalysis by carboxylic acids, as found also by Fife and Brod [19] for the hydrolysis of 2-(4-nitrophenoxy)tetrahydropyrans: the entropies of activation are significantly negative, particularly for catalysis by chloroacetic acid (Table 2): the Brönsted coefficients, α, lie near the middle of the range 0—1: and the solvent deuterium isotope effects [k_H/k_D near 3 for the formic acid-catalysed hydrolysis of 2-(4-nitrophenoxy)tetrahydropyrans [19]] are consistent with a proton transfer being involved in the rate-determining step. So we base our discussion on the classical general acid catalysis mechanism (21).

The rate difference in favour of the axial isomers might be accounted for by differential solvation of the transition states, or in terms of electrostatic, steric, or stereoelectronic effects. It is difficult to assess how solvation or electrostatic effects might depend on whether the leaving group is axial or equatorial, and since the observed effects are not large a detailed discussion is in any case not justified. The evidence is, however, at least consistent with the stereoelectronic explanation, as we show briefly below, while a steric effect can be ruled out.

In the transition state (21) the leaving group is partially bonded to a molecule of a general acid. It is therefore effectively larger than the leaving group in the spontaneous reaction, which is otherwise identical. When the steric requirements of the transition state are greater than those of the ground state, axial compounds generally react more slowly.[26] But in the acid-catalysed hydrolysis of the oxadecalin acetals (8) the reverse is the case.

The transition state for the acid-catalysed reaction is clearly earlier, in terms of C–OAr bond breaking, than for spontaneous hydrolysis. We suggested above that, other things being equal, any stereoelectronic effect ought to be larger, the earlier the transition state. The evidence shows that the factor k_{ax}/k_{eq}, and the extent of C–OAr cleavage in the transition state, both depend on the strength of the general acid, in such a way that the rate factor is indeed higher the earlier the transition state. The highest (uncorrected) value for k_{ax}/k_{eq} (4.35 at 25°) is for the k_H, while $k_{ax} \sim k_{eq}$ for the reactions catalysed by chloroacetic and formic acids, and k_{eq} is actually greater than k_{ax} for catalysis by the two weakest general acids. (This change is reflected in the different Brönsted coefficients, α_{ax} 0.70 ± 0.04, α_{eq} 0.52 ± 0.01.) The best available indicator of the degree of bond breaking in the transition state is the Hammett ρ value. Fife and his co-workers [18,19] found that ρ is positive (0.9) for the formic acid-catalysed hydrolysis of 2-aryloxytetrahydropyrans but negative (−0.9) for the H_3O^+-catalysed reaction, consistent with C–O cleavage being more advanced in the transition state when the catalyst is a weaker acid.[18]

Thus, although the effects are small, and other explanations cannot be ruled out, the evidence is at least consistent with an additional barrier to the acid-catalysed hydrolysis of equatorial aryloxyoxadecalin acetals (8e) which is stereoelectronic in origin. This hypothetical situation is outlined in Figure 2.

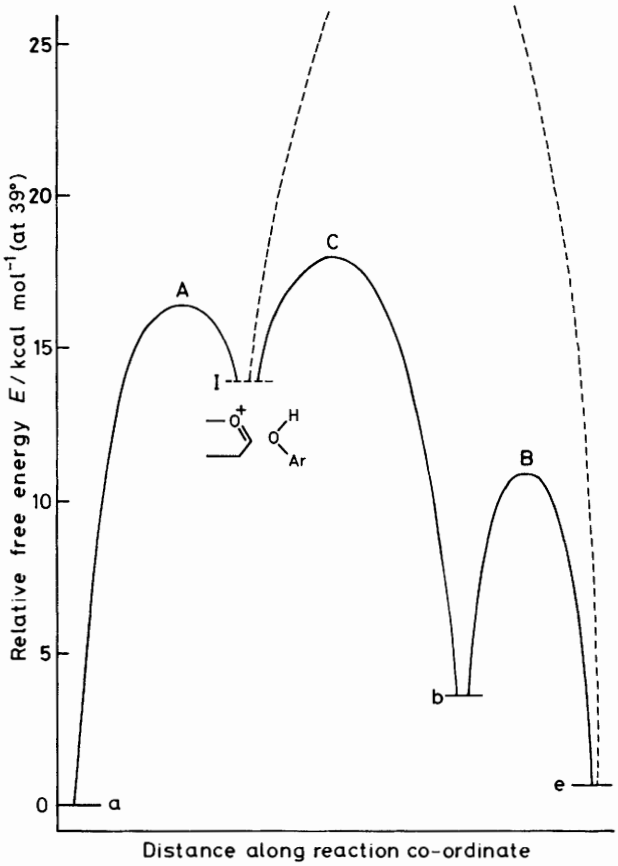


Figure 2. Energy profile diagram for the H_3O^+-catalysed cleavage of axial and equatorial 2-(4-nitrophenoxy)-*trans*-1-oxadecalin (8a and e). The energy levels specified are derived from the data in Table 2, or discussed in the text [for the conformational equilibrium (8a) ⇌ (8b), where (8b) refers to the chair-boat form (14)]: except that for the oxocarbonium ion (I), which is an estimate, not likely to be accurate to better than ±1 kcal mol^{-1}. The dashed curve represents the hypothetical pathway for cleavage of the equatorial isomer (8e) fixed in the chair conformation

The H_3O^+-catalysed cleavage of (8a) goes smoothly, with stereoelectronic control, by way of transition state A, to the oxocarbonium ion (which is hydrated in a subsequent fast step). The direct cleavage of (8e) in its ground state conformation (dashed curve) is not assisted by π-donation from the ring oxygen, so involves a large additional, stereoelectronic, barrier. The observed ready cleavage reaction of (8e) must go by way of a higher energy, flexible conformation close to (8b): and as long as the conformational barrier B is lower than the transition state C for cleavage of (8b) the observed stereoelectronic effect will be small or non-existent. [It is given formally by $(E_C - E_A) - (E_{8e} - E_{8a})$, so must always be smaller than $(E_C - E_I)$, which is the activation energy for the addition of a nucleophile (ArOH) to a carbonium ion.]

Conclusions.—There is thus little or no evidence that the hydrolysis of 2-aryloxy-*trans*-1-oxadecalins is subject to stereoelectronic control. This is in striking contrast to the substantial body of evidence derived from similar systems which is consistent with strict stereoelectronic control in the *E*2 reaction: for example, the Hofmann elimination of trimethylamine from (axial) 3α- and 6β-trimethylammoniocholestanes, is much faster than that from the equatorial (3β and 6α) isomers.[8] It is significant that clearcut results are

generally found only for reactions involving bulky leaving groups,[7,8] because the observed differences in reactivity are determined not simply by the antiperiplanar arrangement of proton and Me_3N^+ group characteristic of the axial compounds, but also by their higher ground-state energies. The equatorial Me_3N^+ group itself contributes substantially to locking these systems in the chair form, so that the twist-boat is indeed a high-energy conformation. Thus in a concerted *E*2 reaction of an equatorial trialkylammonio compound *via* this conformation the transition state energy will be correspondingly high (true stereoelectronic effect). But even if no stereoelectronic effect were operating, the axial isomer would presumably be substantially more reactive, because of its higher ground-state energy.

In tetrahydropyranyl acetals the equatorial isomers have higher ground-state energies (the anomeric effect [2]) and react faster for this reason. Orthoesters (7) represent an intermediate case: the ground state is the same for the loss of either axial or equatorial groups; and because both axial and equatorial substituents are alkoxy-groups neither the selective stabilisation of the chair-chair form observed for equatorial trialkylammonium compounds, nor that of the chair-boat conformation characteristic of equatorial acetals [*e.g.* (8e)], is operative. In fact our recent results show that the magnitude of the apparent stereoelectronic effect on orthoester hydrolysis is also much lower than that observed for the *E*2 reaction of trialkylammonium derivatives of the decalin system.[27]

The *trans*-ring junctions of the oxadecalin (8) and oxasteroid (9) systems are thus uniquely ineffective in locking the conformations of acetals. If stereoelectronic effects are important for acetal cleavage, they are only likely to be apparent in conformationally rather rigid systems, where low energy by-pass pathways like that *via* transition states B and C in Figure 2 are not available. In the following papers [28,29] we describe the results of our further work based on this approach.

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References

1 P. Deslongchamps, *Pure Appl. Chem.*, 1975, **43**, 351; *Tetrahedron*, 1975, **31**, 2463; *Heterocycles*, 1977, **7**, 1271.
2 A. J. Kirby, ' The Anomeric Effect and Related Stereoelectronic Effects at Oxygen,' Springer-Verlag, Heidelberg–Berlin–New York, 1983.
3 G.-A. Craze and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1978, 357.
4 W. P. Jencks and M. L. Sinnott, *J. Am. Chem. Soc.*, 1980, **102**, 2026.
5 Preliminary communication, S. Chandrasekhar and A. J. Kirby, *J. Chem. Soc., Chem. Commun.*, 1978, 171.
6 W. H. Saunders and A. F. Cockerill, ' Mechanisms of Elimination Reactions,' Wiley-Interscience, New York, 1973, pp. 105*ff*.
7 Ref. 6, pp. 121—122.
8 R. D. Haworth, J. McKenna, and R. G. Powell, *J. Chem. Soc.*, 1953, 1110.
9 G.-A. Craze and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1978, 354.
10 C. Normant-Chefnay and P. Maitte, *Bull. Soc. Chim. Fr.*, 1974, 1090.
11 C. S. Dean, J. R. Dixon, S. H. Graham, and D. O. Lewis, *J. Chem. Soc. C*, 1968, 1491.
12 P. Dufëy, *Bull. Soc. Chim. Fr.*, 1968, 4653.
13 J. T. Edwards, P. F. Morand, and I. Puskas, *Can. J. Chem.*, 1961, **39**, 2069.
14 P. G. Jones, O. Kennard, S. Chandrasekhar, and A. J. Kirby, *Acta Crystallogr.*, 1978, **B34**, 3835.
15 P. G. Jones, O. Kennard, S. Chandrasekhar, and A. J. Kirby, *Acta Crystallogr.*, 1979, **B35**, 2947.
16 P. G. Jones, O. Kennard, S. Chandrasekhar, and A. J. Kirby, *Acta Crystallogr.*, 1979, **B35**, 239.
17 W. N. Speckamp and H. Kesselaar, *Tetrahedron Lett.*, 1974, 3405; H. Kesselaar, Ph.D. Thesis, University of Amsterdam, 1971.
18 T. H. Fife and L. K. Jao, *J. Am. Chem. Soc.*, 1968, **90**, 4081.
19 T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.*, 1970, **92**, 1681.
20 P. G. Jones and A. J. Kirby, *J. Chem. Soc., Chem. Commun.*, 1979, 288.
21 P. Gatti, A. L. Segre, and C. Morandi, *J. Chem. Soc. B*, 1967, 1203.
22 E. L. Eliel, ' Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 206.
23 W. F. Armarego, ' Stereochemistry of Heterocyclic Compounds,' Wiley, New York, 1977, Part II, pp. 84*ff*.
24 F. G. Riddell, ' Conformational Analysis of Heterocyclic Compounds,' Academic Press, London and New York, 1980.
25 D. G. Gorenstein and R. Rowell, *J. Am. Chem. Soc.*, 1979, **101**, 4925.
26 E. L. Eliel, ' Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 222.
27 O. E. Desvard and A. J. Kirby, *Tetrahedron Lett.*, 1982, **23**, 4163.
28 A. J. Kirby and R. J. Martin, following paper.
29 A. J. Briggs, C. M. Evans, R. Glenn, and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1637.

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