Stereoelectronic Effects on Acetal Cleavage. The Separation of the π-Donor and σ-Acceptor Properties of Oxygen

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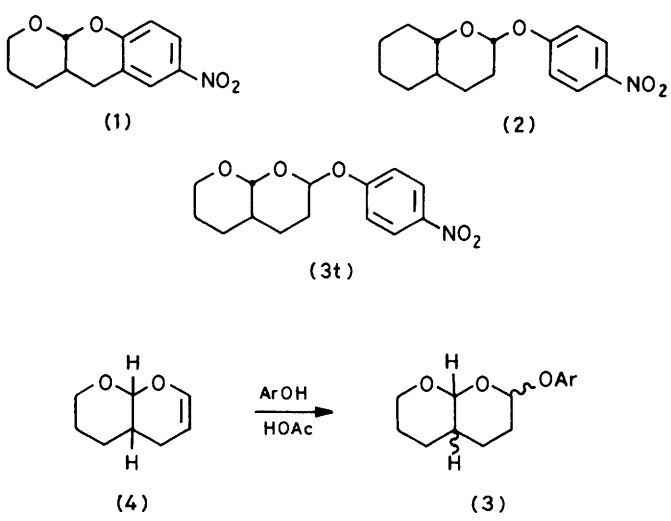
The spontaneous, general acid and H_3O^+-catalysed hydrolyses of the bis-acetals (3) are unusual, semi-concerted fragmentations in which the rate of loss of the 4-nitrophenolate leaving group is controlled by the geometry at the remote acetal centre. The hydrolysis of the *cis*-axial compound (3ca), in which the remote oxygen atom can act as a π-donor, is up to 200 times faster than that of its *trans*-isomer (3ta), in which it cannot, but acts simply as a σ-acceptor to slow C–OAr cleavage. The magnitude of the stereoelectronic effect on $\Delta H^{\ddagger}$ is of the order of 7 kcal (30 kJ) mol^{-1}.

We have shown in the preceding papers [1,2] that the hydrolysis of acetals can be subject to stereoelectronic control: the cleavage of equatorial 2-aryloxytetrahydropyrans can be substantially slower than that of the axial isomers, which have lone-pair electrons in the ring oxygen antiperiplanar to the ArO leaving group. However, this leads to observed effects on hydrolysis rates only when appropriate conformational restraints are built in, as in (1).[2] The degree of bond breaking in the transition state also appears to be a significant factor, and we have discussed the evidence that the observed effects on rates may be larger when the transition state for C–O cleavage occurs earlier, in the general acid-catalysed hydrolysis of (2).[1]

The effects observed with the oxadecalin acetals (2) are small,[1] and the larger rate differences observed with the tricyclic system (1) are to some extent concealed by kinetic complications associated with the reversibility of the initial C–OAr bond cleavage [2] although it is clear that the *trans*-ring junction is a sufficient conformational restraint when it spans the acetal centre.

In this paper we describe our results with an improved test system (3), which combines the successful features of all our previous models, a *trans*-ring junction at the acetal centre, a leaving group which leaves irreversibly, and a relatively early transition state for spontaneous cleavage.[3]



Experimental

The desired acetals (3) were readily prepared by the addition of *p*-nitrophenol to the enol ether function of (4). We were unable to find conditions for the conversion of (4) into its *trans*-isomer, but the mild acid used to catalyse the addition of *p*-nitrophenol was sufficient to effect the desired equilibration during the course of the reaction.

2α-(4-*Nitrophenoxy*)-3,4,4aα,6,7,8aα-*hexahydro*-2H,5H-*pyrano*[2,3-b]*pyran* (3ca; Ar = 4-$NO_2C_6H_4$).—4a,6,7,8a-Tetrahydro-4*H*,5*H*-pyrano[2,3-*b*]pyran [4] (4), (0.5 g) and an excess of 4-nitrophenol (2.5 g) were dissolved in toluene (30 ml) containing dry acetic acid (0.5 ml), and heated to 70° for 60 h. After cooling and the addition of ether the solution was extracted repeatedly with 1M-NaOH, dried ($MgSO_4$), and evaporated to dryness. P.l.c. on silica plates (eluant CH_2Cl_2) gave the *cis*-axial *acetal* (3ca), analytically pure, m.p. 84—85° (Found: C, 59.9; H, 6.3; N, 4.85. $C_{14}H_{17}NO_5$ requires C, 60.2; H, 6.1; N, 5.0%), δ($CDCl_3$) 8.3 (2 H, d, *J* 8 Hz), 7.2 (2 H, d, *J* 8 Hz), 5.8 (1 H, m, anomeric proton), 5.1 (1 H, s, bridgehead acetal proton), 3.7 (2 H, m), and 2.1—1.4 (9 H, m).

2α-(4-*Nitrophenoxy*)-3,4,4aα,6,7,8aβ-*hexahydro*-2H,5H-*pyrano*[2,3-b]*pyran* (3ta; Ar = 4-$NO_2C_6H_4$).—The *trans*-axial acetal (3ta) is obtained from the same reaction mixture, and is the main component of the slowest running spot in the original p.l.c. This was collected and replated, using ether as eluant. Slightly impure (3ta) now ran as the central spot. Final purification was on thin analytical plates using 90% CCl_4–10% MeOH as eluant, which allowed the separation of five impurity spots, and gave (3ta), m.p. 165—167° (Found: C, 59.9; H, 6.15; N, 4.85%), δ($CDCl_3$) 8.2 (2 H, d, *J* 8 Hz), 7.2 (2 H, d, *J* 8 Hz), 5.82 (1 H, m, anomeric proton), 4.48 (1 H, d, *J* 7 Hz, bridgehead acetal proton), 4.05 (1 H, m), 3.52 (1 H, dt, J_d 3, J_t 12 Hz), and 2.0—1.3 (9 H, m).

Results

Reactions were followed as described previously,[1] at 39° in water at ionic strength 1.0M (KCl), by measuring the rate of release of the 4-nitrophenolate anion at 400 nm. Rates were measured as a function of temperature for the pH-independent (spontaneous) hydrolysis in carbonate buffer between pH 9 and 10, and for the acid-catalysed reaction in dilute HCl solutions. General acid catalysis by chloroacetic and formic acids was also measured. The rate constants obtained are listed in Table 1, and the relative rates of the reactions of (3ca) and (3ta) are compared with those for the parent 4-nitrophenyltetrahydropyranyl acetal (5) in Table 2.

Discussion

General acid catalysis is observed for the hydrolysis of aryl tetrahydropyranyl acetals (5) with good leaving groups

Table 1. Rate constants for the hydrolysis of acetals (3ta) and (3ca) in water at ionic strength 1.0M [a]

trans-Compound (3ta)		*cis*-Compound (3ca)	
Conditions (no. of runs)	k_{obs}/s^{-1}	Conditions (no. of runs)	k_{obs}/s^{-1}
Spontaneous hydrolysis			
Carbonate buffer, pH 9.36, 54.7° (2)	3.31×10^{-6}	Carbonate, pH 9.76, 54.7° (1)	3.99×10^{-4}
Carbonate, pH 9.36, 54.6° (1)	3.32×10^{-6}		
Carbonate, pH 9.36, 49.4° (1)	1.18×10^{-6}	Carbonate, pH 9.79, 49.3° (1)	2.05×10^{-4}
Carbonate, pH 9.36, 44.0° (1)	$5.26 \pm 0.11 \times 10^{-7}$	Carbonate, pH 9.78, 44.0° (1)	1.01×10^{-4}
Carbonate, pH 9.45, 39.0° (1)	$2.34 \pm 0.03 \times 10^{-7}$	Carbonate, pH 9.37, 39.0° (1)	4.69×10^{-5}
$\Delta H^{\ddagger}$ 34.11 ± 0.22 kcal (143 kJ) mol^{-1}		$\Delta H^{\ddagger}$ 27.02 ± 0.17 kcal (113 kJ) mol^{-1}	
$\Delta S^{\ddagger}$ 20.4 ± 1.4 cal (85 J) K^{-1} mol^{-1}		$\Delta S^{\ddagger}$ 8.2 ± 1.1 cal (34 J) K^{-1} mol^{-1}	
Acid catalysis			
0.1M-HCl, 49.2 (4)	$2.55 \pm 0.02 \times 10^{-3}$	10^{-2}M-HCl, 44.4° (3)	2.45×10^{-3}
0.1M-HCl, 44.95° (4)	$1.38 \pm 0.02 \times 10^{-3}$	10^{-2}M-HCl, 39.0° (2)	1.41×10^{-3}
0.1M-HCl, 39.0° (12)	$6.94 \pm 0.03 \times 10^{-4}$	10^{-3}M-HCl, 39.0° (1)	1.60×10^{-4}
0.1M-HCl, 33.60 (3)	$2.90 \pm 0.02 \times 10^{-4}$	10^{-2}M-HCl, 34.8° (2)	$8.77 \pm 0.06 \times 10^{-4}$
		10^{-2}M-HCl, 29.6° (6)	4.60×10^{-4}
$\Delta H^{\ddagger}$ 26.13 ± 0.30 kcal (109 kJ) mol^{-1}		$\Delta H^{\ddagger}$ 20.75 ± 0.13 kcal (87 kJ) mol^{-1}	
$\Delta S^{\ddagger}$ 15.3 ± 1.9 cal (64 J) K^{-1} mol^{-1}		$\Delta S^{\ddagger}$ 3.92 ± 0.80 cal (16 J) K^{-1} mol^{-1}	
General acid catalysis			
	k_{HA}/dm^3 mol^{-1} s^{-1}		k_{HA}/dm^3 mol^{-1} s^{-1}
H_3O^+, 39.0° (12)	6.93×10^{-3} [b]	H_3O^+, 39.0° (2)	0.136 [b]
Chloroacetic acid, 39.0° (1)	$3.7 \pm 0.2 \times 10^{-5}$ [c]	Chloroacetic acid, 39.0° (7)	$1.51 \pm 0.03 \times 10^{-3}$
Formic acid, 39.0° (1)	$1.05 \pm 0.1 \times 10^{-5}$ [c]	Formic acid, 39.0° (6)	4.99×10^{-4}
Brönsted α	0.51 ± 0.09	Brönsted α	0.44 ± 0.08

[a] Errors are ±1 in last figure quoted, unless otherwise stated. [b] Calculated from rate constants quoted above, after correction for spontaneous hydrolysis. [c] From single measurements at high [HA]; 0.4M-chloroacetic acid (80% free acid, pH 2.31) and 0.486M-formic acid (83% free acid, pH 2.96); corrected for spontaneous and H_3O^+-catalysed hydrolysis.

Table 2. Relative rates of hydrolysis of (3ta), (3ca), and 2-(4-nitrophenoxy)tetrahydropyran at 39° and ionic strength 1.0M

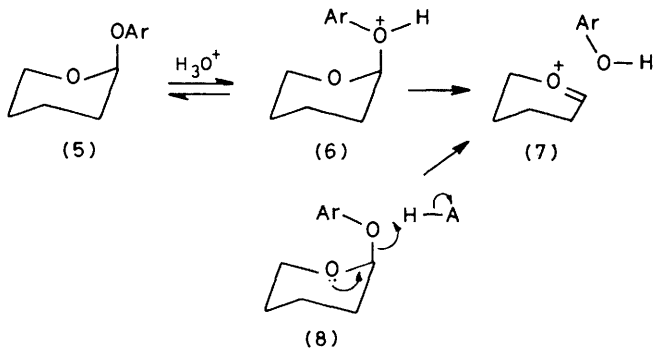
	Compound		
	(5)	(3ta)	(3ca)
Acid catalysis			
k_H	2.18 (50°) [a]	3.24×10^{-2} (50°) [b]	0.444 (50°) [b]
k_{rel}	1	1/67	1/4.9
		1	14
General acid catalysis			
Chloroacetic acid		1	40
Formic acid		1	48
Spontaneous hydrolysis			
k_{obs}	3.67×10^{-4} [c]	2.34×10^{-7}	4.09×10^{-5}
k_{rel}	1	1/1 570	1/7.8
		1	200

[a] Data from T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.*, 1970, **92**, 1681, at ionic strength 0.1M. [b] Calculated from the Arrhenius plot of k_H, using the data of Table 1. [c] Data from G.-A. Craze and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1978, 354.

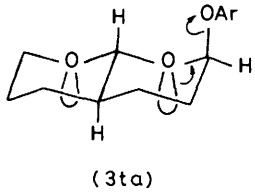
(Ar = 4-ClC_6H_4, 4-$NO_2C_6H_4$),[5] but not for the reactions of less electrophilic compounds. It is presumed that the conjugate acid (6), which is an intermediate in the specific acid-catalysed hydrolysis, becomes a prohibitively high energy species compared with the oxocarbonium ion (7) (Scheme).[6] In consequence C–O bond breaking begins before proton transfer is complete, establishing the conditions for general acid catalysis.

The departure of the aryloxy-leaving group from (3) would generate an oxocarbonium ion (9) which is an acetal with a far better (aliphatic aldehyde) leaving group. An aliphatic aldehyde is a weaker base than a phenol without strongly electron-withdrawing substituents,[7] and so (9) is itself expected to be a prohibitively high energy species compared with its cleavage product (10). Thus the second C–O cleavage is expected to begin before the first is complete, making the fragmentation of (3) a concerted process (11).

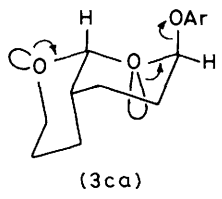
This means that the departure of the aryloxy-leaving group should be sensitive to the electron-donor capability of the remote oxygen atom, and should therefore depend on the geometry at the ring junction. We chose to work with those diastereoisomers (3ca and ta) with the leaving group axial,



Scheme.

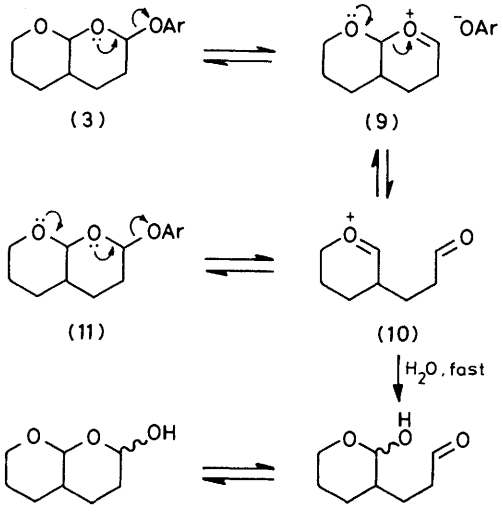


(3ta)



(3ca)

(12)



so that the intrinsic reactivity at the aryltetrahydropyranyl centre is the same. [These are in any case the major products of the preparation: only small amounts of the equatorial isomer (3te) of (3ta), and no (3ce), could be detected by n.m.r.]

As the bond to the aryloxy-leaving group breaks, positive charge develops on the oxygen atom of the first acetal centre. This triggers a response from the remote oxygen atom. In the compound (3ca) with the *cis*-ring junction this oxygen can act as a π-donor, and fragmentation to (10) proceeds smoothly, though the second C–O cleavage must clearly lag behind the cleavage of the C–OAr bond which triggers it, because two separate orbital interactions are involved. [The second n–σ* interaction is synperiplanar to the first, distinguishing the cleavage of (3ca) from a conventional concerted fragmentation (11), which requires antiperiplanar geometry throughout.[8]] The hydroxy ether [12; R = H, Ar = 2,4-$(NO_2)_2C_6H_3$], a mixture of isomers, from cyclohexane-1,3-diol and 2,4-dinitrofluorobenzene, does not break down to release 2,4-dinitrophenolate under the conditions of our spontaneous reactions. So we can rule out this mechanism for the cleavage of (3ca).

Thus the cleavage of the remote C–O bond of (3ca) is expected to be less far advanced in the transition state than that of the C–OAr bond, which should break in the normal way for the hydrolysis of an aryltetrahydropyranyl acetal. In the case of the *trans*-isomer (3ta), on the other hand, the remote oxygen atom is prevented from acting as a π-donor by the geometry of the *trans*-ring junction, and will presumably behave simply as a σ-acceptor, destabilising the developing oxocarbonium ion (9), and thus inhibiting the departure of the *p*-nitrophenolate leaving group.

All these expectations are borne out in practice. The spontaneous hydrolysis of the *trans*-isomer (3ta) is 1 570 times slower than that of the parent tetrahydropyranyl acetal (5), and 200 times slower than that of (3ca).* Evidently π-donation is not sufficiently advanced in the latter case to dominate σ-withdrawal.

Smaller, but still considerable differences in reactivity, are observed for the acid-catalysed reactions. k_{ca}/k_{ta} falls from 200 for the spontaneous reaction, to *ca.* 45 for general acid catalysis by carboxylic acids, to 14 for the H_3O^+-catalysed hydrolysis. This evidence, and the small negative effect of the remote oxygen on the rate of the spontaneous cleavage of (3ta), suggests that the cleavage of the second C–O is not far advanced in the transition state, and that the magnitude of the observed stereoelectronic effect increases with increasing degree of C–O cleavage, since the degree of C–OAr bond breaking in the transition state is thought to decrease in the sequence spontaneous > general acid > H_3O^+-catalysed reaction.[3]

These rate differences are entirely accounted for by the observed enthalpies of activation (Table 1) as expected if electronic effects are involved. These are 6—7 kcal (25—30 kJ) mol^{-1} more favourable for the cleavage of (3ca), with a lone pair on the remote ring oxygen antiperiplanar to the second C–O bond to be broken, than for that of the *trans*-isomer (3ta), which has not. The entropies of activation are actually more favourable for the reactions of the *trans*-compound (3ta), and all substantially more positive than those observed for the hydrolysis of related acetals. For the spontaneous and H_3O^+-catalysed reactions of both 2-(4-nitrophenoxy)-tetrahydropyran [9] and -1-oxadecalin, for example, $\Delta S^{\ddagger}$ is near zero and *ca.* 8 cal K^{-1} mol^{-1}, respectively. The corresponding figures for (3ca) are +4 and +8, while for (3ta) both are *ca.* 20 cal (85 J) K^{-1} mol^{-1}. A likely explanation of this effect of the involvement of the second oxygen in the reaction is the release of molecules of solvation as reaction proceeds. The lone pairs of the ring oxygen atoms act as hydrogen-bond acceptors in hydroxylic solvents. As the reaction proceeds the hybridisation of these oxygens changes from sp^3 to sp^2, and they develop substantial positive charges, so that their hydrogen-bond basicity falls dramatically. When they are no longer capable of acting as hydrogen-bond acceptors the solvating water molecules will be released, and to the extent that this

* The spontaneous hydrolysis of (2; Ar = 4-$NO_2C_6H_4$) is only 2.3 times slower than that of (5),[1] so the greater rigidity of the bicyclic system does not appear to contribute significantly to the decreased reactivity of (3ta): and any such effect should be smaller still for the flexible *cis*-isomer (3ca).

process has occurred in the transition state it will be apparent as an increase in the entropy of activation.

Conclusions.—We have now observed substantial differences in reactivity between axial tetrahydropyranyl acetals, which can be cleaved with stereoelectronic control, and their equatorial isomers, in two different systems relying on *trans* ring-junctions between six-membered rings to lock the conformations. In each case the apparent stereoelectronic barrier to the reaction of the equatorial isomer can be as large as 7 kcal (30 kJ) mol^{-1}; but, as discussed previously, it is likely that this sets only, then, a lower limit to the potential magnitude of the stereoelectronic effect. In the following paper we show that much larger effects can be observed in very rigid systems.

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