Stereoelectronic Control of the Hydrolysis of a Conformationally Locked Acetal

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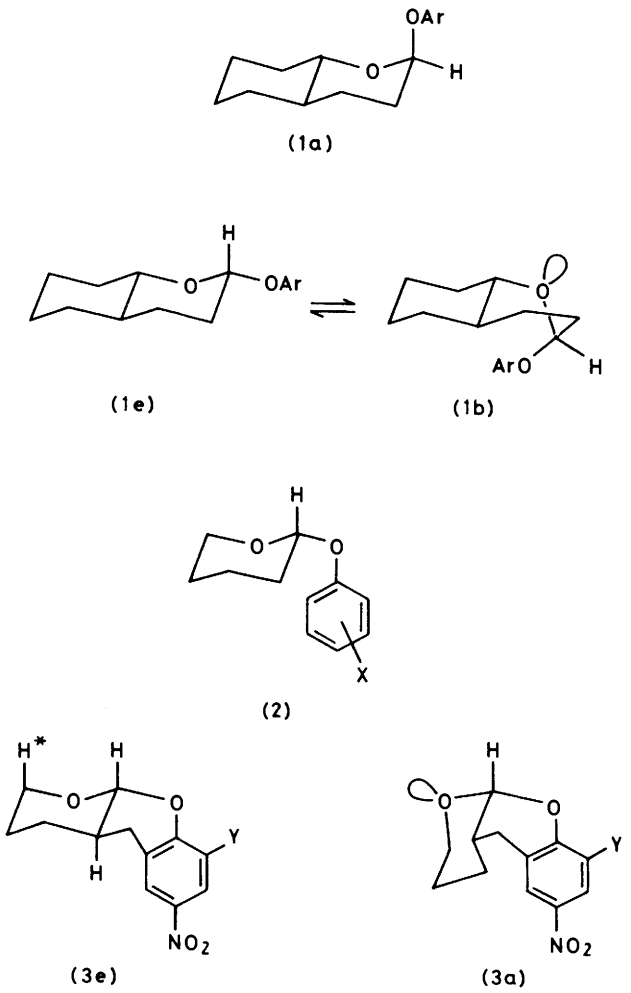
The hydrolysis of the nitrophenyltetrahydropyranyl acetal (3e; Y = H), with leaving group fixed equatorial by the *trans*-ring junction, is substantially slower than expected for a comparable conformationally flexible acetal. It is also slower than the hydrolysis of the axial isomer, by a factor of 60 in acid, but only 2 for the spontaneous reaction. It is suggested that both reactions of (3e) are slow because there is a stereoelectronic barrier to the departure of an equatorial leaving group, not readily overcome in a system where the conformation at the acetal centre is fixed by a *trans*-ring junction. The spontaneous hydrolysis of (3a) appears to be slow for a different reason: rapid internal return from the initial product of C–O cleavage enforces a change in rate-determining step, to hydration of the oxocarbonium ion, as shown by the solvent deuterium isotope effect for this reaction.

We have shown [1] that the H_3O^+-catalysed hydrolysis of axial 2-aryloxy-*trans*-1-oxadecalins (1a) is faster than that of the equatorial isomers (1e), as expected if there is an additional, stereoelectronic, barrier to the reaction of the equatorial compounds. But the rate factor involved is not large, and the evidence that the barrier is stereoelectronic in origin is less than compelling.

This is most likely because (1e) can react by way of a readily accessible higher energy conformation close to (1b), with a lone pair on the ring oxygen antiperiplanar to the C–OAr bond. Our analysis of the reactions of these acetals (1)[1] suggests that the stereoelectronic effect on rates in systems of this sort can never be large, as long as the conformational barrier (B in Figure 2 in the preceding paper) separating the equatorial acetal from a reactive conformation [*e.g.* (1b)] is lower than the transition state for its cleavage. (In terms of Figure 2 in the preceding paper,[1] as long as $E_B < E_C$.) When $E_B > E_C$ the equatorial isomer may still react by way of the higher energy conformation, but if $E_B \gg E_A$ the rate-determining step becomes the conformational change, and the reaction may be substantially slower than that of the axial isomer. Only in the extreme case, where the equatorial isomer is conformationally quite rigid, is the reaction expected to proceed without assistance from the non-bonding electrons on the ring oxygen, and the stereoelectronic effect on rates to approach the full magnitude of the stereoelectronic barrier (dashed curve in Figure 2 of ref. 1).

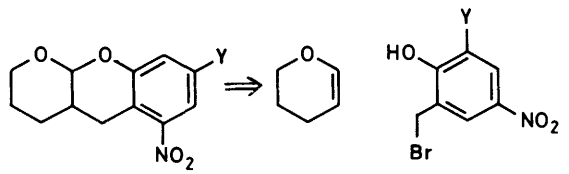
Thus we needed an aryl- (for reasons discussed previously [2]) tetrahydropyranyl acetal fixed more effectively in the equatorial conformation (2). The simplest way to prevent ring inversion to the favoured axial conformation appeared to be to incorporate an additional methylene bridge, giving system (3e), in which the conformation at the acetal centre is locked by the *trans*-ring junction. This paper describes our synthesis of, and mechanistic work with, two such compounds (3e; Y = H and Y = NO_2) and the corresponding axial isomers (3a), which show substantial differences in reactivity directly attributable to stereoelectronic effects.[3]



Experimental

Retrosynthetic analysis of the tricyclic structure (3) suggested a synthesis based on dihydropyran and a 2-hydroxybenzyl halide (4). The 5-nitro-compound (4; Y = H) is commercially available as a specific reagent for tryptophan in proteins (Koshland's reagent [4]). Its reaction with dihydropyran gave an acceptable yield of (3a; Y = H) at the first attempt. Acid-catalysed equilibration gave a mixture of isomers from which (3e; Y = H) was obtained. The dinitro-compounds (3; Y = NO_2) were prepared similarly, but in this case (4; Y = NO_2) had to be synthesized also.

3,4,4aα,10aα-*Tetrahydro*-7-*nitro*-2H,5H-[1]*benzopyrano*-[2,3-b]*pyran* (3a; Y = H).—Dihydropyran (5 g) and 2-hydroxy-5-nitrobenzyl bromide (4; Y = H) were dissolved in dry dimethyl sulphoxide (12 ml) and heated to 80 °C for 16 h. After cooling, the solution was diluted with ether and extracted



(3) (4)

repeatedly with water, then concentrated K_2CO_3 solution. The ether layer was dried ($MgSO_4$) and evaporated, and the solid product purified by p.l.c. on silica (R_F 0.55, CH_2Cl_2 as eluant). Recrystallised from CCl_4 it had m.p. 100—102 °C (Found: C, 60.8; H, 5.6; N, 6.1. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.6; N, 5.9%), *m/z* 235 (M^+), 218, 189, 176, 165, 130, 121, and 85, δ($CDCl_3$) 7.98 (2 H, m), 6.92 (1 H, d, *J* 8 Hz), 5.44 (1 H, d, *J* 2.5 Hz, anomeric H), 4.00 (1 H, m), 3.77 (1 H, dt, J_d 11, J_t 4 Hz), 3.07 (1 H, dd, *J* 17 and 6 Hz), 2.73 (1 H, dd, *J* 17 and 3 Hz), 2.23 (1 H, m), and 1.6 (4 H, m). The structure of this compound has been confirmed by a single-crystal *X*-ray structure determination.[5]

3,4,4aα,10aβ-*Tetrahydro*-7-*nitro*-2H,5H-[1]*benzopyrano*-[2,3-b]*pyran* (3e; Y = H).—HCl gas was passed through a solution of (3a; Y = H) (0.5 g) in benzene (15 ml), in a pressure tube, until it was saturated. The tube was sealed and heated to 100 °C. After 48 h equilibrium was reached, giving (n.m.r.) 21% of the equatorial (*trans*) compound. After cooling, the solution was washed with 3N-NaOH, then with water, dried ($MgSO_4$), and evaporated to dryness. The isomers were separated by p.l.c. on silica using dry CH_2Cl_2–petroleum (b.p. 40—60 °C) (60 : 40) as eluant. The plates (maximum loading 75 mg) had to be developed six times before a satisfactory separation was achieved. Total recovery was 95%, and the yield of (3e; Y = H) 19%, m.p. 168—170 °C (Found: C, 61.1; H, 5.8; N, 5.8. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.8; N, 6.1%), δ($CDCl_3$) 7.94 (2 H, m), 6.95 (1 H, d, *J* 9 Hz), 4.83 (1 H, d, *J* 8 Hz, anomeric H), 4.25 (1 H, m), 3.73 (1 H, dt, J_d 4, J_t 10 Hz), 2.85 (1 H, dd, *J* 5 and 16 Hz), 2.15 (1 H, m), and 1.9—1.3 (4 H, m).

2-*Hydroxy*-3,5-*dinitrobenzyl Chloride*.—We were unable to make the bromide (4; Y = NO_2) by nitrating the mononitro-compound (the reaction mixture proved to be explosive), or by brominating 4,6-dinitro-*o*-cresol with *N*-bromosuccinimide. So we used the corresponding benzyl chloride, made by chloromethylating 2,4-dinitrophenol, according to a German patent.[6]

A mixture of concentrated H_2SO_4 (6 ml), paraformaldehyde (9 g), and chlorosulphonic acid (15 g) was heated to 60 °C for 2 h, then added dropwise to a solution of 2,4-dinitrophenol (18.4 g) in concentrated H_2SO_4 (19 ml), maintained at 80 °C. The mixture was stirred for 3.5 h at this temperature, cooled, and poured onto crushed ice. The solution was extracted with chloroform, the combined organic layers washed with water, dried, and evaporated to give the crude chloride, δ 4.21 (2 H, s). This was used without purification in the preparation of (3a; Y = NO_2).

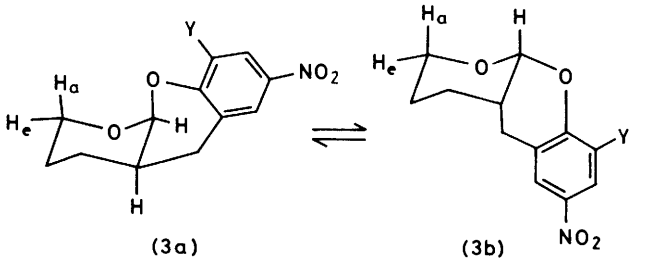
3,4,4aα,10aα-*Tetrahydro*-7,9-*dinitro*-2H,5H-[1]*benzopyrano*-[2,3-b]*pyran* (3a; Y = NO_2).—The crude chloride was dissolved in dimethyl sulphoxide (25 ml) and an excess of dihydropyran plus NaI (3 g, 0.2 mmol) added (to catalyse the reaction by forming the benzyl iodide). The mixture was heated to 80 °C for 16 h, then cooled, diluted with ether, extracted with water and concentrated K_2CO_3 solution, dried ($MgSO_4$), and evaporated to dryness. P.l.c. on a small sample of the crude product gave a u.v.-active band at R_F 0.4 (eluant CH_2Cl_2; silica plates), which was collected and crystallised on evaporation of the solvent. These crystals were used as seeds to bring about the crystallisation of the bulk material, dissolved in CCl_4 at −15 °C. The yield was 6.4 g of a mixture containing a small amount (9% by n.m.r.) of *trans*-isomer (no doubt because some acid remained in the crude benzyl chloride used). The isomers could be separated by p.l.c. on silica after repeated development with dry CH_2Cl_2–petroleum (b.p. 40—60 °C) (1 : 9). The cis-*isomer* had m.p. 118—119 °C (Found: C, 51.7; H, 4.5; N, 9.8. $C_{12}H_{12}N_2O_6$ requires C, 51.4; H, 4.3; N, 10.0%), δ($CDCl_3$) 8.50 (1 H, d, *J* 3 Hz), 8.13 (1 H, m), 5.63 (1 H, d, *J* 2 Hz, anomeric H), 4.0 (1 H, m), 3.82 (1 H, dt, J_d 12, J_t 4 Hz), 3.22 (dd, *J* 15 and 5 Hz), 2.87 (dd, *J* 15 and 4 Hz), 2.38 (1 H, m), and 1.75 (4 H, m). The structure of this compound has been confirmed by a single-crystal *X*-ray structure determination.[7]

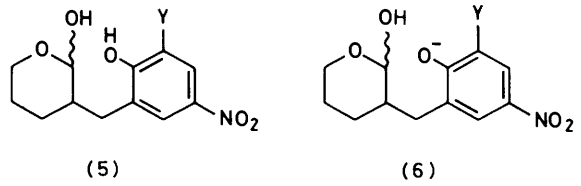
3,4,4aα,10aβ-*Tetrahydro*-7,9-*dinitro*-2H,5H-[1]*benzopyrano*-[2,3-b]*pyran* (3e; Y = NO_2).—The trans-*isomer*, separated from the predominant *cis*-compound by p.l.c., as described above, had m.p. 166—168 °C (Found: C, 51.4; H, 4.5; N, 9.8%), δ($CDCl_3$) 8.59 (1 H, d, *J* 2 Hz), 8.17 (1 H, m), 4.96 (1 H, d, *J* 8 Hz, anomeric H), 4.25 (1 H, m), 3.80 (1 H, m), 2.98 (1 H, dd, *J* 5 and 15 Hz), 2.66 (1 H, dd, *J* 10 and 15 Hz), 2.2 (1 H, m), and 2.0—1.3 (4 H, m).

2-*Hydroxy*-3-(2-*hydroxy*-3,5-*dinitrobenzyl*)*tetrahydropyran* (5). *Mixture of* cis- *and* trans-*Isomers*.—This is the initial product of hydrolysis of the tricyclic acetals (3; Y = NO_2), and is the sole product under basic conditions. The *cis*-isomer (3a; Y = NO_2) (1 g) was added to 20 ml of concentrated NaOH solution, and the suspension warmed on a water-bath. After all the starting material had dissolved the solution was cooled and neutralised with concentrated HCl. The product crystallised, and was filtered, washed with water, and dried, yield 90%, m.p. 143—144 °C (Found: C, 47.8; H, 4.6; N, 9.2. $C_{12}H_{14}N_2O_7$ requires C, 48.3; H, 4.7; N, 9.4%), $\lambda_{max.}$ 373 (ε 14 510) and 365 nm (12 800), δ($CDCl_3$) 8.90 (1 H, d, *J* 3 Hz), 8.36 (1 H, d, *J* 3 Hz), 4.92 (0.4 H, d, *J* 2 Hz, anomeric H of *cis*-isomer), 4.52 (0.6 H, d, *J* 7 Hz, anomeric H of *trans*-isomer), 4.04 (1 H, m), 3.60 (1 H, m), 3.22 (0.6 H, dd, *J* 8.5 and 14 Hz), 2.95 (0.4 H, dd, *J* 7 and 13.5 Hz), 2.8 (0.4 H, dd, *J* 7 and 13 Hz), 2.68 (0.6 H, dd, *J* 5 and 14 Hz), 2.1 (1 H, m), and 1.6 (4 H, m).

Evidently equilibration at the hemiacetal centre gives a mixture containing the *cis*- and *trans*-isomers, with a slight (40 : 60) preference for the latter.

The Conformation of the cis-*Compounds* (3).—Because the *cis*-ring junction is flexible, these compounds can exist in two possible conformations, with the phenol oxygen either axial (3a) or equatorial (3b). Of these the former is expected to be preferred (the anomeric effect [8]), and is indeed observed for both *cis*-compounds (3a; Y = H and NO_2) in the crystals.[5,7] That this conformation is also favoured in solution was shown by a simple experiment using the nuclear Overhauser effect. In conformation (3b) there should be a 1,3-diaxial contact between the axial alkoxy-proton (H_a) and the anomeric proton, close enough to give rise to an n.O.e. This is readily observed in the *trans*-series (3e; Y = H), where irradiation of the axial proton H* causes a 13% increase in the intensity of the anomeric proton signal. When H_a of compound (3a; Y = H) is irradiated in the same way, the intensity of the anomeric proton signal was not affected. On the other hand, when the equatorial alkoxy-proton (H_e) was irradiated, a weak long-range coupling to the anomeric proton disappeared. This is therefore identified as a W-coupling, showing that both H_e and the anomeric proton are equatorial.





Products of Hydrolysis.—The starting materials (3a and e; Y = H and NO_2) and products [*e.g.* (5)] are readily distinguished by n.m.r. because of the well resolved signals from their anomeric protons. The substrates are not soluble enough in water for measurements of product ratios by n.m.r. under the conditions of the kinetic experiments, and considerable amounts of organic solvents are needed to get them into solution. Unfortunately the addition of organic solvents alters the product ratios, at least in acid, so product ratios under kinetic conditions were estimated by the u.v. method. This worked well for the reactions of the dinitro-compounds (3; Y = NO_2), where the hydrolysis products (5) could be isolated, but the results for the mononitro-compound are less accurate.

Simplest is the spontaneous reaction of the dinitro-compound, which gives the product anion (6) as a mixture of isomers in quantitative yield at high pH. (These can be isolated in 90% yield by acidification of the product mixture, allowing characterisation of the products, as described above.) It might be expected that the hydrolysis of the mononitro-compound would also go to completion at high pH, but this appears not to be the case. The reactions were monitored at 400 nm ($\lambda_{max.}$ for 4-nitrophenolate), and the end points were consistently 62 ± 2% of the value expected for complete conversion into (6; Y = H), if the anion has the same extinction coefficient as 4-nitrophenolate at this wavelength. [It is certainly very similar. The data available for 2-methyl-4-nitrophenolate [9] show ε for this anion is 6.4% greater than for 4-nitrophenolate at $\lambda_{max.}$ 414 nm. The larger alkyl substituent on (6) should affect ε very little: thus 2-methyl-4,6-dinitrophenolate has $\lambda_{max.}$ and $\varepsilon_{max.}$ identical, within experimental error, with those measured for the isolated product anion (6; Y = NO_2).[9]] This evidence suggests that the hydrolysis of the mononitro-compounds gives an equilibrium mixture of starting material (3a; Y = H) and product anion (6; Y = H), and rate constants have been calculated on this assumption. (Even if this is not the case, and hydrolysis does go to completion, the conclusions reached below are not affected.)

In acid there is no doubt that the final product is an equilibrium mixture of starting material and hydrolysis product, with the proportion of the latter decreasing as the mole fraction of water in the solvent is reduced. For the dinitro-compound (3a; Y = NO_2) the equilibrium constant can be measured accurately in water, by the u.v. method. The same equilibrium mixture is obtained starting from either (3a; Y = NO_2) or (5; Y = NO_2), containing 26% (3a) and 74% (5), no doubt as a mixture of isomers. On the other hand, in 50% aqueous acetone (0.05M-HCl) the equilibrium mixture (n.m.r. method) can be identified as equal amounts of (3a) and the two isomers of (5; Y = NO_2) (also 1 : 1). While, when dissolved in [$^2H_6$]acetone containing four drops of 1M-DCl, the open-chain compound (5; Y = NO_2) is almost completely cyclised [90% (3a; Y = NO_2)] after 2 h at room temperature.

The mononitro-compound (3a; Y = H) gives only 20% of open-chain compound (5; Y = H) in aqueous acid, and in [$^2H_6$]acetone–0.2M-DCl (2 : 1) a mixture containing 93% of (3a) and only 7% of (5; Y = H), after equilibrating for 36 h at 39 °C. In no case in aqueous or mixed solvents is any *trans*-compound (3e) found at equilibrium, whether the starting material is (3a), (3e), or (5).

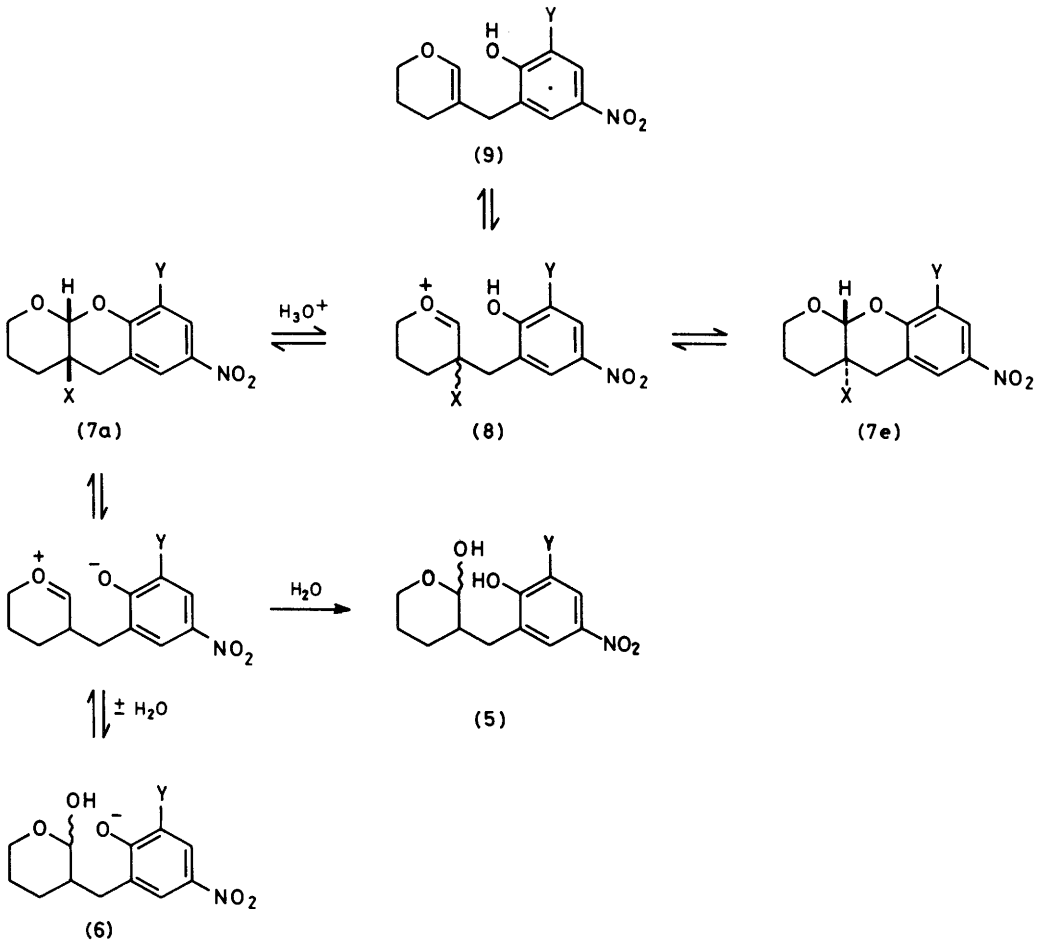
In trifluoroacetic [^{2}H]acid the *cis*-dinitro-compound (3a) ≡ (7a; X = H, Y = NO_2) rapidly exchanges one proton, for deuterium, as shown by the disappearance of one coupling each from the signals due to the anomeric proton and both benzylic protons. This must be proton X of (7) and (8), and the H–D exchange is readily explained by reversible deprotonation of the oxocarbonium ion intermediate (8) to give (9) (Scheme 1). In a subsequent, much slower process ($t_{\frac{1}{2}}$ *ca.* 5 h) a *cis*/*trans* equilibration occurs, to give a mixture containing 85% (7a) and 15% (7e) (X = D, Y = NO_2). In the case of the mononitro-compound (3a; Y = H) the relative rates of the two processes are reversed. The half-life for the *cis*/*trans* equilibration is similar [6 h, giving an 81 : 19 mixture of (7a and e: X = Y = H)]; but the H–D exchange is much slower ($t_{\frac{1}{2}}$ 25 h).

Kinetic Methods and Results.—Rates were measured under pseudo-first-order conditions in water brought to a constant ionic strength of 0.1M (KCl). The spontaneous reactions of the mononitro-compounds were followed at 100 °C (sealed tubes in a thermostatically controlled oil-bath), others at 39 °C. The hydrolysis of the mononitro-compounds was followed by monitoring the release of the nitrophenolate chromophore at 400 nm (diluting cooled samples with dilute NaOH for acid runs). For the dinitro-compounds the release of the dinitrophenoxide chromophore was followed at 365 nm for runs at pH > 7: in acid the smaller changes at 267 nm were sufficient for continuous monitoring in this case.

Pseudo-first-order rate constants observed for reactions going to an equilibrium are not simple rate constants, but represent the sum of the constants for the forward and reverse reactions. So the measured rate constants ($k_f + k_r$) were dissected using the observed product ratios (k_f/k_r) for the acid-catalysed hydrolysis of the dinitro-compounds (3a; Y = NO_2), and for all reactions of the mononitro-compounds (3a; Y = H). The reactions of the *trans*-compounds (3e) gave an equilibrium mixture containing (3a) and (5), but no (3e), so are effectively irreversible. The rate constants obtained, and the solvent deuterium isotope effects measured, are all given in the Table. Though pH–rate profiles were not measured, the evidence is clear that the reactions are substantially faster in acid, so that we are observing acid-catalysed reactions at low pH. We showed that the rate of hydrolysis of (3e; Y = NO_2) is pH independent in the range 9.07—9.79, as expected for the spontaneous cleavage. All the high-pH reactions were at least 100 times faster than those of the corresponding nitroanisoles or nitrophenetole, so no S_NAr processes are involved.

Discussion

We have not carried out a detailed mechanistic investigation of the reactions of compounds (3a and e) described in this



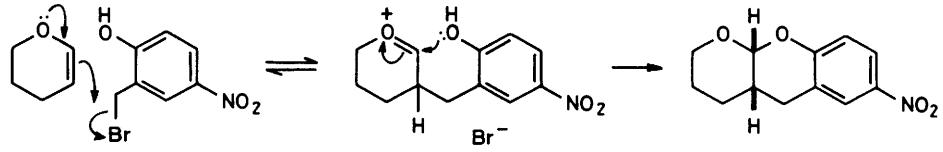
Scheme 1.

Rate constants for the hydrolysis of compounds (3a and e; Y = H and NO_2) in water at ionic strength 0.1M

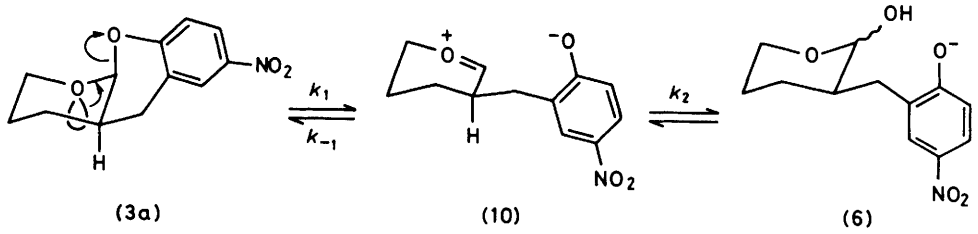
Mononitro-compound	Conditions	T/°C	k_{obs}/s^{-1}	Product ratio [a]	k_f [b]	k_r [b]	Units
(3a)	M/10 HCl	39	1.5×10^{-3}	20 : 80	3.0×10^{-3}	1.6×10^{-2}	$dm^3\ mol^{-1}\ s^{-1}$
(3e)	M/10 HCl	39	5.0×10^{-6}	20 : 80 [c]	5.0×10^{-5}		$dm^3\ mol^{-1}\ s^{-1}$
(3a)	pH 9.0 [d]	100	1.88×10^{-5}	62 : 38	1.17×10^{-5}	7.1×10^{-6}	s^{-1}
(3a)	Same buffer, D_2O	100	1.08×10^{-5}	62 : 38	(k_H/k_D 1.74)		
(3e)	pH 9.0 [d]	100	5.5×10^{-6}	62 : 38 [c]	5.5×10^{-6}		s^{-1}
(3e)	Same buffer, D_2O	100	5.4×10^{-6}	62 : 38	(k_H/k_D 1.03)		
Dinitro-compound							
(3a)	M/100 HCl	39	1.82×10^{-4}	74 : 26	1.35×10^{-2}	4.73×10^{-3}	$dm^3\ mol^{-1}\ s^{-1}$
(5)	M/100 HCl	39	1.90×10^{-4}	74 : 26	1.4×10^{-2}	5×10^{-3}	$dm^3\ mol^{-1}\ s^{-1}$
(3e)	M/100 HCl	39	2.05×10^{-5}	74 : 26	2.05×10^{-4}		$dm^3\ mol^{-1}\ s^{-1}$
(3a)	pH 9.4 [d]	100	5.32×10^{-5}	100 : 0	5.32×10^{-5}		s^{-1}
(3a)	Same buffer, D_2O	100	4.21×10^{-5}	100 : 0	(k_H/k_D 1.26)		
(3e)	pH 9.4 [d]	100	1.26×10^{-5}	100 : 0	1.26×10^{-5}		s^{-1}
(3e)	Same buffer, D_2O	100	1.04×10^{-5}	100 : 0	(k_H/k_D 1.21)		

[a] Determined by u.v. method (see text): does not distinguish (3a) from (3e). Ratio gives (5) : (3a). [b] Determined from product ratio and $k_{obs} = k_f + k_r$ (see text). Errors better than ±2 in last figure quoted. [c] Reactions of (3e) are irreversible: mixture contains only (5) + (3a) (see text). [d] Carbonate–hydrogen carbonate buffer.

paper. The mechanisms of hydrolysis of aryltetrahydropyranyl acetals are well understood, and are discussed in the preceding paper,[1] and in various references cited therein, and there is no reason to suppose that the reactions of compounds (3a and e) are mechanistically unusual. Thus we assume that the spontaneous reaction proceeds with a late transition state, as established previously,[10] and that the H_3O^+-catalysed reactions actually involve a general acid catalysis mechan-



Scheme 2.



ism; [1,11] though this has not been formally established in the present work.

All our results can be explained in terms of these mechanisms. The new factor is a substantial additional barrier to the formation and cleavage of the *trans*-isomers (3e), with equatorial leaving groups. Under the conditions of the kinetic experiments there is no observed equilibration (3a) ⇌ (3e). Under most conditions the products are a mixture of (3a) and the hydrolysis product (5) (as a mixture of isomers), whether the starting material is (3a), (5), or (3e), showing that the hydrolysis of (3a) and the cyclisation of (5) are reversible under the conditions, while the hydrolysis of (3e) is not. This is the case also in mixed aqueous solvents, where product ratios could be studied in more detail by n.m.r.

Under more strongly acidic conditions, in the absence of water, the equilibrium (3a) ⇌ (3e) can be established, and the results are instructive. The *cis*-isomer (3a) is the sole product in the preparation of (3). Since the preparation is carried out under non-basic conditions the mechanism is presumably [for (3a; Y = H)] that in Scheme 2.

Thus (3a) is the sole kinetic product of the cyclisation of the oxocarbonium ion (8), which is the same intermediate involved in the acid-catalysed hydrolysis of (3a) [and of (3e)].

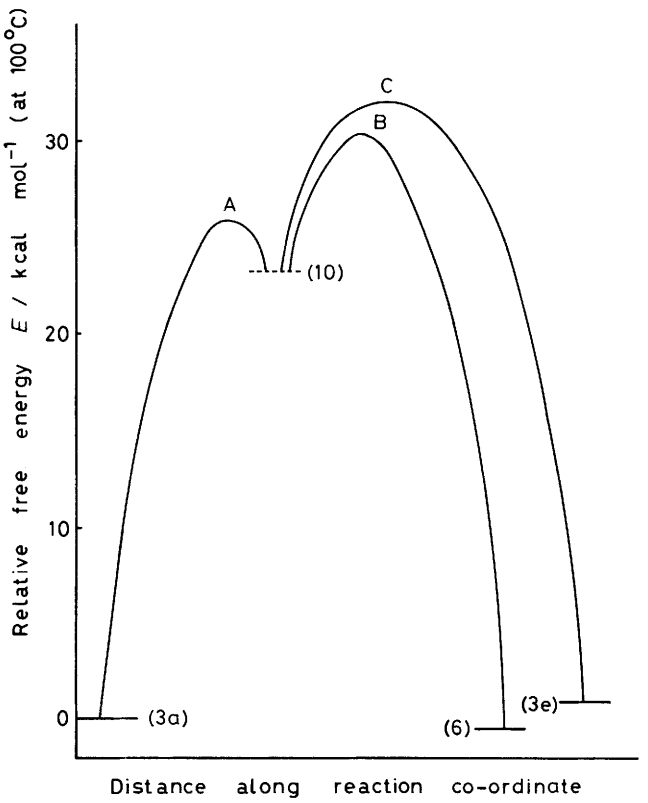
Equilibration in CF_3CO_2D provided (serendipitous) evidence about the properties of (8), which, apart from cyclising to (3a or e), can also lose a proton to give the dihydropyran (9) (see Scheme 1). In the case of the dinitro-compound (3a; Y = NO_2) this side-reaction is readily detectable as a rapid H–D exchange with solvent deuterons, much faster than cyclisation to (3e) [but much slower than recyclisation to (3a)]. In the case of the mononitro-compound (3a; Y = H) this H–D exchange is many times slower: evidently the recyclisation of (8) is much faster for the more nucleophilic mononitrophenol, and its lifetime correspondingly shorter.

The kinetic evidence is equally clearly consistent with a substantial additional barrier to the cleavage of the *trans*-compounds (3e). This evidence consists of a simple rate difference in the case of the acid-catalysed hydrolysis, but is more complicated for the spontaneous reaction.

Acid-catalysed Hydrolysis.—The observed rate of hydrolysis of (3a; Y = H) in 0.1M-HCl at 100 °C is 300 times faster than that of the compound (3e) with the leaving group axial. (This difference is smaller by an order of magnitude than the estimate in our preliminary communication.[3]) Since the reaction goes only 20% to completion, to give an equilibrium mixture of (3a) and (5) in each case, the corrected ratio of second-order rate constants for the acid-catalysed cleavage of (3a and e) is 60. This is despite the higher ground-state energy of the equatorial isomer (3e), which comprises only 19% of the equilibrium mixture of isomers in trifluoroacetic acid. Taking this into account, the transition state for loss of the equatorial leaving group from (3e; Y = H) is higher in energy by 3.4 kcal (14 kJ) mol^{-1} than that for the cleavage of the axial isomer (3a). The factors are closely similar for the acid-catalysed hydrolysis of the dinitro-compounds (3; Y = NO_2).

Spontaneous Hydrolysis.—Although the acid-catalysed hydrolysis of the axial compounds (3a) is considerably slower than that of similar acetals without conformational restrictions [k_{obs} for the hydrolysis of (1a; Ar = 4-$NO_2C_6H_4$) in 0.1M-HCl at 39 °C in 30% aqueous dioxane is 2.68×10^{-2} s^{-1}, compared with k_{obs} 1.5×10^{-3} for (3a; Y = H) in water, which is thus less reactive by some two orders of magnitude], these are still reactive compounds. In the case of the spontaneous hydrolysis much larger differences are observed. The half-life of 2-(4-nitrophenoxy)tetrahydropyran at 39.2 °C in water is 31.5 min.[10] Under these conditions both (3a and e; Y = H) are quite stable, and their hydrolysis has to be studied at 100 °C. We can calculate the rate of hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran under the same conditions from the data of Fife and Brod [12] to be 0.2 s^{-1}, while that of its (hypothetical) equatorial isomer should be *ca.* 3 times faster.[2] Compared with these figures (3a and e; Y = H) are respectively *ca.* 1.7×10^4 and 1.1×10^5 times less reactive. We expected a substantial factor for compound (3e) with the equatorial leaving group, which was originally designed to have a stereoelectronic barrier to hydrolysis. But the corresponding axial isomer (3a; Y = H), which can be hydrolysed with stereoelectronic control, is itself much less reactive than predicted [and only twice as reactive as (3e)]. Evidently we cannot explain the low reactivity of (3e) as a stereoelectronic effect unless the equally slow cleavage of (3a; Y = H) has a quite different explanation. There is good reason, and some evidence, to suppose that this is indeed the case.

The spontaneous cleavage of (3a) leads initially to the zwitterion (10), with the oxyanion leaving group held in close proximity to the oxocarbonium ion centre. The recyclisation of this intermediate will be rapid, and would be expected to be faster than the intermolecular addition of water to give (6): which will therefore be the rate-determining step of the reaction. Evidence that this is the case comes from the deuterium solvent isotope effect, k_{H_2O}/k_{D_2O} 1.74 at 100 °C,



Energy profile diagram for the spontaneous hydrolysis of (3a and e; Y = H). Energy levels are derived from the data given in the Table. Broken lines are used where data are not directly accessible, and levels are simply estimated

consistent with rate-determining hydration, but not with C–O cleavage. (The hydration of carbonyl compounds, and of stabilised carbonium ions in particular,[13] is general base-catalysed, and characterised by low solvent deuterium isotope effects.)

Thus we suggest that the spontaneous hydrolysis of (3a) is slow (*ca.* 10^4 times slower than expected for an axial 4-nitrophenyltetrahydropyranyl acetal) primarily because the rate-determining step of the reaction is not C–OAr bond cleavage, but the hydration of the zwitterionic intermediate (10). Efficient internal return to regenerate starting materials means that only a small proportion of the intermediate goes on to form products. (The observed $k_f = k_1k_2/k_{-1}$, where $k_2 \ll k_{-1}$.) We can set an upper limit on k_2/k_{-1} by assuming that k_1 is the same as for the hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran under the same conditions,[1] but have no way of knowing how good this assumption may be.

For the spontaneous hydrolysis of (3e), on the other hand, it is clear that hydration of the zwitterion intermediate (10) is not rate determining, since there is no solvent deuterium isotope effect (k_{H_2O}/k_{D_2O} 1.03). In this case, therefore, C–O cleavage, which is the only other step of the reaction, must be rate determining. [Hydration will still be slower than cyclisation, but cyclisation leads exclusively to (3a), as shown by the product studies. In terms of the Figure, transition state C, for the recyclisation of the zwitterion (10) to (3e), known from product studies to be higher than that (A) for the cyclisation to (3a), is evidently higher also than the transition state B for the hydration of (10) to give (6; Y = H).] Thus a direct comparison of the rates of spontaneous hydrolysis of (3e) and the corresponding parent tetrahydropyranyl acetal is valid because both reactions have the same rate-determining step.

The picture is more complicated with compounds (3; Y = NO_2). The axial isomer (3a) is a few times more reactive, as for the mononitro-compounds; and far less reactive than expected for a simple aryltetrahydropyranyl acetal (the 2,4-dinitrophenyl derivative is too reactive to be prepared [10]). But neither isomer is more than a few times more reactive than the mononitro-compound, so that C–O cleavage cannot be solely rate determining in either case,[10] as is shown also by the similar solvent deuterium isotope effects [k_{H_2O}/k_{D_2O} 1.26 and 1.21 for the hydrolysis of (3a and e; Y = NO_2), respectively]. A full analysis of the reactions of the dinitro-compounds is not possible without further evidence.

We conclude that a substantial stereoelectronic effect on the relative rates of hydrolysis of (3a and e; Y = H) is masked by the difference in rate-determining steps of the two reactions. The hydrolysis of the equatorial isomer (3e) is over 10^5 times less reactive than expected for a similar acetal with no conformational restrictions (see above), largely in consequence of the stereoelectronic barrier to the cleavage of an acetal C–O bond without unrestricted assistance from π-donation from the donor oxygen atom. That of (3a) is slow because a new step has become rate determining. To calculate the magnitude of the stereoelectronic effect in this system (approximately $E_A - E_C$ in the Figure), we need an estimate of E_A. The comparison of the rates of acid-catalysed hydrolysis of (3a) and 2-(4-nitrophenoxy)tetrahydropyran (above) suggests that the intrinsic reactivity of our tricyclic system may be up to 100 times lower. So our estimate of the stereoelectronic barrier to the cleavage of (3e; Y = H) can be only approximate: based on a rate factor of 10^3—10^5 it appears to lie in the range of 4—7 kcal (18—30 kJ) mol^{-1}.

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