Linear Relationship between Bond Length and Reactivity†

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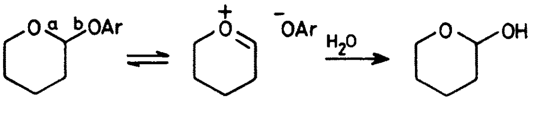
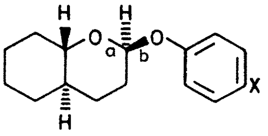
Summary The two C–O bond lengths of the acetal group in a series of compounds derived from 2-phenoxytetrahydropyran vary with the aryloxy leaving group, and are linearly related to the free energy of activation for hydrolysis.

WE have recently determined crystal and molecular structures for a series of alkyl aryl acetals derived from 2-phenoxytetrahydropyran (**1**, Ar = Ph).[1–4] When ArO^- is a good enough leaving group (nitrophenoxide or better)[5] these compounds are hydrolysed spontaneously, by way of an oxocarbonium ion (**2**), and the crystal structures show that changes in bond length in this direction are already apparent in the ground state. For compounds with the leaving group axial,‡ which can hydrolyse with stereoelectronic control,[6] the endocyclic C–O bond (**1**, a) is significantly shortened, and the bond (b) to the leaving group lengthened, by an amount which depends on the electronegativity of the exocyclic oxygen atoms.

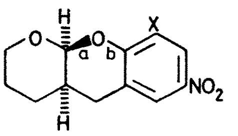


(1) (2)

We report that this variation in bond length is very simply related to the rates of hydrolysis of these acetals. A full set of crystal structures is not yet available for a suitable series of compounds based on a single structure, so we used bond lengths measured for two systems derived from 2-phenoxytetrahydropyran, the *trans*-1-oxadecalin (**3**) and the related tricyclic acetals (**4**, X = H and NO_2).



(3)



(4); X = H or NO_2

The rate constants for the hydrolysis of these three compounds cannot be compared directly, because the rate determining steps are not the same for the reactions of (**3**) and (**4**) (X = H).[6] However, it is well established that the rates of hydrolysis (log k_{hyd}) of compounds of this sort show a linear dependence on the pK_a of the leaving group when C–O cleavage is rate determining.[5] Thus a plot of bond length against the pK_a of the leaving group is equivalent to a plot against the free energy of activation for C–O cleavage in water.

This plot (Figure) shows that the lengths of the two C–O bonds of the acetal group depend linearly on the pK_a of the leaving group. The correlation is accurate ($r = 0{\cdot}9995$) for the bond (b) to the leaving group, and reasonable (0·985) for the endocyclic C–O bond (a). The lines intersect at a pK_a of 12·9, indicating that for the poor leaving groups the endocyclic C–O bond should be the longer. This is well known to be the case for sugar derivatives,[7] and data for a typical axial methyl glycopyranoside are included in the

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† No reprints available.

‡ But apparently not for the anomers, with equatorial OAr groups.[1,3]

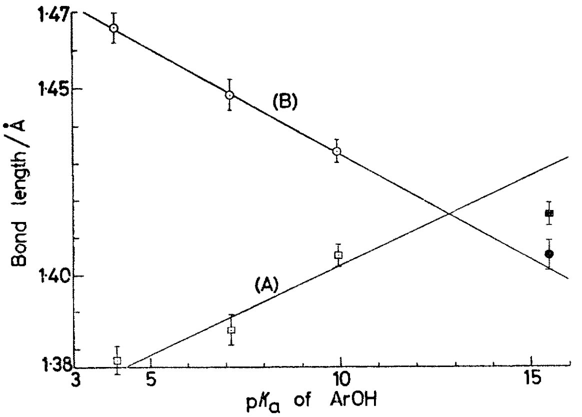

FIGURE. Plot of acetal group bond lengths a(A) and b(B) (**1**) *vs.* the pK_a of ArOH, for compounds (**3**) and (**4**) (X = H or NO_2) (open symbols). The error limits shown are standard deviations. The filled symbols represent mean values of the corresponding bond lengths for the five axial methyl glycopyranosides whose structures have been determined (see B. M. Gatehouse and B. J. Poppleton, *Acta Cryst.*, 1970, **B26**, 1761; 1971, **B27**, 654 and 871; B. J. Poppleton, G. A. Jeffrey, and G. J. B. Williams, *ibid.*, 1975, **B31**, 2400; G. A. Jeffrey, R. K. McMullan, and S. Takagi, *ibid.*, 1977, **B33**, 728).

plot. The line (B) generated by our data predicts a bond length of 1·401 Å for the C(1)–OMe bond, within experimental error of the observed mean value of 1·405 Å.

Such remarkable agreement, for four systems differing very widely in reactivity, and with different torsion angles about bond b [the tricyclic derivatives (**4**) are constrained in the *gauche–trans* conformation, the glycosides and (**3**) are *gauche–gauche*[8] acetals] suggests that the structure of the acetal group in these compounds is modified by a single dominant effect. We take this to be the overlap of the lone pair electrons of the ring oxygen atom with the σ^* orbital of the exocyclic C–O bond.[9] This interaction increases in importance as the σ^* level is lowered by increasing electron withdrawal from the oxygen atom concerned, resulting in the observed lengthening of the exocyclic C–O bond, and the shortening of the endocyclic bond.

The same process is involved in the spontaneous hydrolysis of these acetals (**1**) → (**2**) (and explains the stereoelectronic requirements for this reaction[6]). The structures of the acetal groups of compounds (**3**) and (**4**) (X = H or NO_2) can thus be regarded as successive points on the reaction co-ordinate for C–O cleavage. [The slope of the line is equivalent to a slope of about 300 kcal (1200 kJ) Å^{-1} for the dissociation curve of the C–O bond (b) in water, in this region.]

This correlation between molecular structure and reactivity extends the approach pioneered by Bürgi and Dunitz,[10] who related changes in bond lengths and angles to the pathway for the addition of nucleophiles to the carbonyl group, and allows us to infer the geometries of key species in the acetal cleavage process. For example, extrapolation of lines (A) and (B) predicts lengths for C–O bonds a and b in the conjugate acid of 2-phenoxytetrahdropyan of about 1·33 and 1·52 Å,§ respectively. For leaving groups better than phenol C–O cleavage sets in before protonation is complete,[11] so the lengths of the corresponding bonds *in the transition state* must be close to these values.

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§ A closely similar value has recently been obtained, from *ab initio* calculations, for the C–O^+ bond length in protonated dihydroxymethane, H_2O^+–CH_2OH. With the C–OH bond set at 1.43 Å, and a lone pair on the other oxygen *antiperiplanar* to the C–O^+ bond, the calculated value was 1.51 Å (G. Wipff, *Tetrahedron Letters*, 1978, 3269).

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