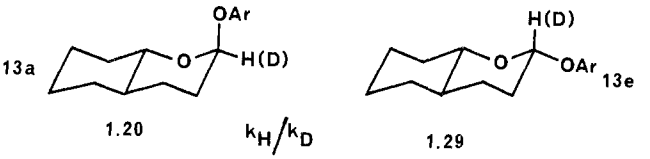
Ester **11** is an extreme, but not isolated, example of this effect, where the very long *C–O bond length expected for the ester of a strong acid and a tertiary alcohol is not observed when strongly electron-withdrawing substituents (CF_3, C=O, O) are present at C* or on the adjacent carbon atom.[20,21-22] A similar effect no doubt accounts for the very short *C–OMe bond in the methyl ether (**12**, Table II). We also describe in the following paper in this issue a detailed examination of a comparable series of acetals and glucosides, where the four substituent OH groups of the glucosides similarly inhibit the lengthening of the bond from the anomeric center to good leaving groups, OR_2.

We conclude that systems R_1–OR_2 respond to increasing electron withdrawal in the group OR_2 by electronic reorganization in the direction of the valence bond tautomer (**5**), resulting in the observed increase in the length of the R_1–OR_2 bond and charge separation in the sense $R_1^{+}\ ^{-}OR_2$. This must mean that a substantial part of the high reactivity toward heterolysis of tertiary alkyl compounds with good leaving groups derives from the substantial amount of bond breaking apparent in the ground state, compared with less reactive compounds. (Estimates of the variation of bond energy with bond length in systems of this sort are of the order of 2–300 kcal mol^{-1} $Å^{-1}$,[3,7,23] while bond length differences across a series may easily amount to 0.06 Å (Table I) or more.)

Evidently estimates of the extent of bond breaking in the transition state, which are commonly made on the basis of comparisons of reactivity over a series of compounds, should take into account the varying amounts of "bond breaking" in the ground state. Protonation of oxygen results in an enormous increase in electron demand so that much—perhaps most—of the C–O bond-breaking process in acid-catalyzed reactions of tertiary alcohol derivatives may be expected to take place as part of the preequilibrium proton-transfer step. In fact, in any comparison of transition states for a given reaction of two different compounds, it may be of crucial importance to consider the status of the bond or bonds being broken in the ground state. We showed recently in our work on acetal hydrolysis that the secondary deuterium isotope effect for the spontaneous hydrolysis of axial *p*-nitrophenyl acetal (**13a**) is significantly smaller than that of the equatorial isomer (**13e**).



It was tempting to attribute this difference to a stereoelectronic effect on transition states, though much other evidence[7] suggested that the transition states for the reactions of the two isomers were closely similar. But our X-ray structural work[4] shows clearly that the C–OAr bond of the axial isomer is expected to be substantially the longer (1.448 (4) Å for an analogue of **13a**, Ar = *p*-nitrophenyl, compared with 1.424 (4) Å for **13e**). The original state of the axial isomer is thus closer in geometry to the transition state: compared with the equatorial compound it starts farther along the reaction coordinate for C–OAr cleavage, so that the change in the character of the C–H bond between the ground and transition state is reduced. The effect is indeed stereoelectronic in origin, but it is evidently an effect on ground states.

Our results indicate, further, that it should be possible by accurate crystal structure determinations, using an appropriate series of compounds based on an oxygen probe with increasing electron demand, to explore the early stages of bond breaking in many organic reactions which are initiated by ionization to form a carbocation. (This is an extension of the approach pioneered by Bürgi and Dunitz,[1b] who found that similar changes in the lengths of the Y–M bonds of inorganic systems, YMX_3, are related to bond angle changes in the MX_3 fragment.) In principle it should be possible to observe how the carbon fragment R_1 accomodates the developing positive charge. In the following paper in this issue[4] we describe a detailed examination of bond length and reactivity in acetals and glucosides using this approach. We are currently examining several other series, particularly systems which undergo rearrangement and fragmentation reactions.

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Bond Length and Reactivity. Stereoelectronic Effects on Bonding in Acetals and Glucosides

Andrew J. Briggs,[‡] Robert Glenn,[‡] Peter G. Jones,[†] Anthony J. Kirby,*[‡] and P. Ramaswamy[‡]

Contribution from the University Chemical Laboratory, Cambridge CB2 1EW, England, and the Institut für Anorganische Chemie, D-3400 Göttingen, Federal Republic of Germany.
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Abstract: Accurate X-ray crystal structure determinations for 22 axial and equatorial tetrahydropyranyl acetals and α- and β-glucopyranosides reveal systematic changes in the pattern of bond lengths at the acetal center with changing electron demand in the exocyclic ("leaving") group. Stereoelectronic effects on bonding are analyzed and related to reactivity. Linear correlations between the pK_a of the conjugate acid of the leaving group and hence the free energy of activation for cleavage of the acetal C–O bond and the length of the bond being broken appear to be the rule rather than the exception over the range of leaving group studied.

Our recent work[1-5] on the dependence of reactivity on conformation in acetal hydrolysis has shown that the cleavage of acetals is subject to stereoelectronic control.[6,7] C–O cleavage occurs readily only when a nonbonding electron pair (lone pair) on the remaining oxygen atom of the O–C–O group is *antiperiplanar* to the bond being broken either in the ground state or in some reasonably readily accessible higher energy conformation.

[‡]University Chemical Laboratory.
[†]Institut für Anorganische Chemie.

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Table I. Geometry at the Acetal Center of Axial Tetrahydropyranyl Acetals

compound	bond lengths, Å				bond angles			dihedral angles		ref
	a	*n*	*x*	*d*	α	*b*	γ	D_1	D_2	
5a, Ar = Ph	1.448 (3)[a]	1.405 (3)	1.433 (3)	1.378 (3)	114.0	111.6	118.9	64.6	66.9	11
3, Ar = 4-chlorophenyl	1.430 (3)	1.398 (3)	1.427 (3)	1.369 (3)	113.7	111.7	119.6	55.1	64.3	16
6a, X = H	1.436 (5)	1.385 (4)	1.448 (4)	1.364 (4)	114.1	105.9	119.6	67.5	158.1	14
3, Ar = 2,5-dinitrophenyl	1.445 (5)	1.383 (5)	1.458 (5)	1.354 (5)	113.8	110.1	118.8	66.2	55.1	26
6a, X = NO_2	1.433 (5)	1.377 (4)	1.466 (4)	1.351 (4)	114.9	105.4	118.6	69.2	164.0	15
3, Ar = 3,5-dinitrobenzoyl	1.414 (6)	1.379 (7)	1.476 (7)	1.328 (4)	113 8	106.6	117.1	−69.9	−110.8	29

[a] Numbers in parentheses represent standard deviations in the final figure quoted. Structural parameters are defined in the text and in formula **9**.

Table II. Geometry at the Acetal Center of Equatorial Tetrahydropyranyl Acetals

compound	bond lengths				bond angles			dihedral angles		ref
	a	*n*	*x*	*d*	α	β	γ	D_1	D_2	
2, R = *N*-phthalimidomethyl	1.418[a] (4)	1.419 (4)	1.392 (4)	1.417 (4)	111.5	107.3	114.1	178.7	71.4	30
5e, Ar = Ph	1.437 (3)	1.411 (3)	1.415 (3)	1.386 (3)	111.4	107.0	117.4	−177.4	76.8	12
5e, Ar = 4-nitrophenyl	1.448 (4)	1.412 (4)	1.424 (4)	1.374 (4)	110.3	107.2	118.2	176.8	−66.9	13
7e, R = 2,4-dinitrophenyl	1.449 (4)	1.411 (5)	1.448 (5)	1.350 (5)	110.6	105.7	123.2	175.9	68.8	17
7e, R = 3,5-dinitrobenzoyl	1.447 (3)	1.416 (3)	1.468 (3)	1.330 (3)	111.3	98.0	121.1	−179.4	176.0	27
7e, R = $P(O)(OPh)_2$	1.465 (3)	1.408 (3)	1.457 (2)	1.565 (3)	110.6	105.2	127.2	178.2	−44.7	31
	1.461 (3)	1.413 (3)	1.456 (2)	1.567 (3)	110.5	104.9	127.0	178.4	−49.2	
7e, R = SO_2Me	1.458 (3)	1.403 (3)	1.478 (3)	1.568 (2)	110.6	106.7	125.9	176.1	34.4	32

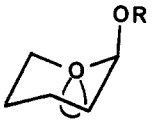
[a] Numbers in parentheses represent standard deviations in the final figure quoted. Structural parameters are defined in the text and in formula **9**.

Table III. Geometry at the Acetal Center of α-Glucopyranosides[a]

compound	bond lengths				bond angles			dihedral angles		ref
	a	*n*	*x*	*d*	α	β	γ	D_1	D_2	
8a, X = H, R = Me	1.434 (4)	1.414 (4)	1.411 (4)	1.430 (4)	114.0	112.6	113.0			*b*
	1.428 (2)	1.414 (2)	1.401 (2)	1.422 (2)	113.5	113.0	113.9	59	63.0	*c*
8a, X = Ac, R = Me	1.435 (5)	1.427 (7)	1.371 (9)	1.458 (8)	112.9	113.0	112.8	54.3	62.1	*d*
8a, X = H, R = Ph	1.436 (4)	1.407 (5)	1.419 (5)	1.386 (4)	115.0	112.5	117.0	−67.3	86.2	18
8a, X = H, R = 4-nitrophenyl	1.447 (3)	1.415 (3)	1.415 (3)	1.371 (3)	114.4	111.7	119.6	57.6	−61.2	20
	1.440 (4)	1.414 (4)	1.420 (3)	1.372 (3)	112.8	111.3	117.7	85.6	−71.3	
8a, X = R = Ac	1.422 (4)	1.403 (4)	1.431 (4)	1.354 (4)	114.6	110.2	118.2	−54.6	80.4	24
8a, X = Ac, R = 2,4-dinitrophenyl	1.429 (7)	1.411 (7)	1.417 (7)	1.352 (7)	114.8	110.0	120.8	−61.6	−69.8	33

[a] Structural parameters are defined in the text and in formula **9**. [b] Berman, H. M.; Kim, S. H. *Acta Crystallogr., Sect. B* **1968**, *B24*, 897. [c] Neutron diffraction data: Jeffrey, G. A.; McMullan, R. K.; Takagi, S. *Acta Crystallogr., Sect. B* **1977**, *B33*, 728. [d] No data are available for tetra-*O*-acetyl methyl α-glucopyranoside. These are data for the corresponding 6-methylsulfinyl compound (methyl tri-*O*-acetyl-6-deoxy-6-methylsulfinyl (*S*)-α-D-glucopyranoside of : Lindberg, K. B. *Ibid.* **1976**, *B32*, 2017.

Thus, axial tetrahydropyranyl acetals **1**, which have such a lone pair on the ring oxygen, are readily hydrolyzed with loss of the OR group, whereas the equatorial isomers (**2**) are very stable if—but only if—their conformation is fixed.



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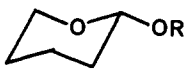
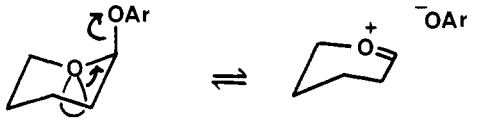


2

We chose to work with aryl tetrahydropyranyl acetals **3** because they are electronically unsymmetrical. The sp^2-hybridized oxygen atom of the OAr group is effectively more electronegative than the oxygen atom of the ring and thus a poorer π donor and a better σ acceptor. Hence, cleavage of the ring (O)C–O bond is suppressed and that of C–OAr is favored, to such an extent that compounds with electron-withdrawing substituents in the Ar group undergo spontaneous cleavage in aqueous solution.[8] As part of this work we measured crystal structures of a small number of axial and equatorial tetrahydropyranyl acetals and observed that the C–OAr bond lengths in axial compounds (**3**) are remarkably sensitive to the nature of the OAr group.[9] This effect appeared to be absent not only in the equatorial series (**2**) but also in aryl glycosides,[10] which are much less reactive than 2-(aryloxy)-tetrahydropyrans.



3 4

Our preliminary conclusion, therefore, was that this was an effect on ground-state structure related to reactivity and subject to similar stereoelectronic factors.[9] Moreover, our initial small set of data showed a simple correlation between reactivity in the hydrolysis reaction (for which the rate determining step is C–OAr cleavage, **3** → **4**) and the length of the bond being cleaved.[9] We report here a more extensive investigation of the pattern of bond lengths at the acetal center for a much larger set of axial and equatorial aryl tetrahydropyranyl acetals. We have also measured crystal structures for the corresponding series of α- and β-aryl glucosides, since published structures for aryl glucosides referred to derivatives of a miscellaneous selection of sugars.[10]

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Table IV. Geometry at the Acetal Center of β-Glucopyranosides

compound	bond lengths				bond angles			dihedral angles		ref
	a	*n*	*x*	*d*	α	β	γ	D_1	D_2	
8e, X = H, R = Me	1.440 (2)	1.433 (2)	1.379 (2)	1.430 (2)	111.5	108.1	113.1	173.9	−73.2	*b*
8e, X = Ac, R = Me	1.427 (5)	1.431 (5)	1.385 (5)	1.443 (5)	112.6	107.3	112.6	173.9	−76.7	*c*
8e, X = H, R = Ph	1.437 (6)	1.434 (5)	1.394 (6)	1.388 (5)	111.8	107.4	118.0	179.7	82.5	19
8e, X = H, R = 2-nitrophenyl	1.436 (4)	1.411 (3)	1.409 (4)	1.368 (3)	111.3	106.9	118.8	−177.1	−77.3	21
8e, X = H, R = 3,4-dinitrophenyl	1.435 (5)	1.405 (5)	1.405 (4)	1.364 (4)	111.3	107.4	119.3	−179.9	−78.1	
	1.431 (4)	1.397 (5)	1.410 (4)	1.355 (4)	112.2	107.4	117.8	−179.1	−87.3	22
8e, X = Ac, R = 3,4-dinitrophenyl	1.435 (6)	1.395 (6)	1.400 (6)	1.375 (6)	110.3	109.1	117.8	−172.9	−82.3	23
8e, X = R = Ac	1.421 (8)	1.426 (7)	1.408 (8)	1.344 (9)	111.9	105.8	117.5	177.6	−92.1	25

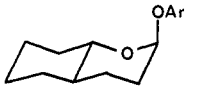
[a] Structural parameters are defined in the text and in formula **9**. [b] Neutron diffraction data: Jeffrey, G. A.; Takagi, S. *Acta Crystallogr., Sect. B* **1977**, *B33*, 738. [c] Zugenmaier, P.; Rappenecker, G. *Ibid.* **1978**, *B34*, 164.

Results

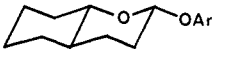
So far we have measured accurate crystal structures at room temperature for over 25 acetals. The source, or preparation and characterization, of each of these compounds has been described elsewhere, and crystal data and structural parameters have been published or will appear shortly.[11-32]

Selected data describing the geometry at the acetal center are collected in Tables I–IV. The choice of compounds for an investigation of this sort is limited by their availability as single crystals of good quality and reasonable stability. In the series of axial aryl tetrahydropyranyl acetals (Table I), for example, the phenyl derivative **1** (R = Ph) is stable but a liquid at ambient temperatures, while the 2,4-dinitrophenyl derivative is too reactive to prepare. So we used the oxadecalin derivative **5a** in the former case and the bicyclic system **6a** (X = NO_2) in the latter, because these compounds are solid and stable, respectively, by virtue of the presence of the second ring.

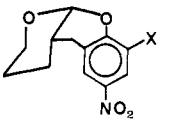
The equatorial series (Table II) presented a more serious problem because simple tetrahydropyranyl acetals generally prefer the axial conformation (the anomeric effect[6]). An exception turned out to be **2** (R = *N*-phthalimidomethyl), which was an intended addition to the axial series but in fact crystallized in the equatorial form (it exists in the axial conformation in solution).[30] But all the other equatorial compounds necessarily have their conformations fixed, either by a trans ring junction (**5e**) or by a 1,3-trimethylene bridge (**7e**). This latter system is extraordinarily



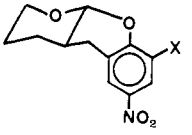
5a



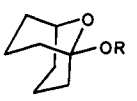
5e



6a



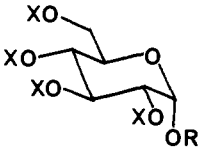
6e



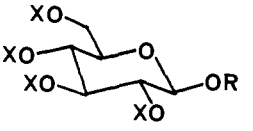
7e

unreactive,[5] even the mesylate (R = SO_2Me) being stable in the crystal for a few days at room temperature, so that a very wide range of oxygen substituent could be studied.

All the relevant glucosides are stable solids, with the exception of 2,4-dinitrophenyl α-D-glucopyranoside (**8a**, R = 2,4-dinitrophenyl, X = H), which is not a known compound. In this case



8a



8e

we used the tetraacetate (X = Ac). It was not obvious how the four additional acetate groups would affect the detailed geometry at the acetal center, but structural data are available for both α- and β-methyl glucosides and for the tetraacetate of the β isomer, and these are included in Tables III and IV. We were also able to measure directly the effects of peracetylation on a β-glucoside (**8e**) with a good leaving group, by comparing the structures of 3,4-dinitrophenyl β-D-glucoside and its tetraacetate, made available by Professor B. Capon. In the equatorial series we were unable, despite intensive efforts, to grow suitable crystals of 4-nitrophenyl β-D-glucopyranoside, so we used the 2-nitrophenyl derivative in its place.

Some compounds crystallized as solvates. Where the solvent is water this often has the advantage of making the structure more rigid. In one case, however, the presence of cyclohexane led to unusually high thermal motion.[29] Disorder of the C(6) acetyl group was responsible for the reduced accuracy of two structures.[25,33]

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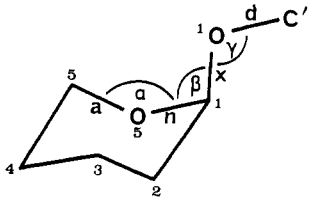
(29) Jones, P. G.; Sheldrick, G. M.; Glenn, R.; Kirby, A. J.; Ramaswamy, P. *Z. Kristallogr.* **1983**, *163*, 93.
(30) Jones, P. G.; Sheldrick, G. M.; Briggs, A. J.; Kirby, A. J. *Z. Kristallogr.* **1983**, *163*, 101.
(31) Jones, P. G.; Sheldrick, G. M.; Briggs, A. J. Kirby, A. J. *Z. Kristallogr.* **1983**, *163*, 107.
(32) Jones, P. G.; Sheldrick, G. M.; Briggs, A. J.; Kirby, A. J. *Z. Kristallogr.* **1983**, *163*, 117.
(33) Jones, P. G.; Sheldrick, G. M.; Glenn, R.; Kirby, A. J., unpublished work.

The data are organized as follows (the numbering of the atoms is that generally used to describe sugar crystal structures). We are concerned specifically with the geometry at the acetal center, and this is described in terms of the four bond lengths, three angles, and two torsion angles (**9**).



9

The bond lengths C(5)–O(5), O(5)–C(1), C(1)–O(1), and O(1)–C′ are abbreviated *a*, *n*, *x*, and *d*, respectively: the angles C(5)O(5)C(1), O(5)C(1)O(1), and C(1)O(1)C′ to α, β, and γ and the torsion angles (dihedral angles) at the acetal center C(5)O(5)C(1)O(1) and O(5)C(1)O(1)C′ to D_1 and D_2, respectively. Where two sets of figures are given, these refer to two independent molecules in the asymmetric unit, except in the case of methyl α-glucopyranoside (Table III), where they refer to separate X-ray and neutron diffraction structures. This comparison is relevant to the structure of the corresponding β-glucoside (Table IV), for which only a neutron diffraction structure is available. (Bond lengths determined by the neutron diffraction technique are generally shorter than those measured by the usual X-ray method, by up to 0.01 Å.)

In most cases the parameters of principal interest are the lengths of the endo- (*n*) and exocyclic (*x*) bonds at the acetal center. These show significant variations with the nature of the OR group in all four series. The length of bond *a* shows no systematic variation except for the equatorial tetrahydropyranyl acetals (Table II), discussed below. Bond *d* is predictably shorter, and the angle is closer to 120°, for derivatives of more acidic phenols; but angles α and β, and both torsion angles, are remarkably constant for directly comparable structures. The same is true for the tetrahydropyran rings; only for the last two compounds of Table I is any flattening of the chair conformation detectable around C(1),[29] while the glucosides all crystallized in closely similar $^4C_1$ conformations.

Sources of Error in Structure Determinations. The estimated standard deviations in molecular parameters, as calculated by routine least-squares refinement programs, represent the lower bounds of realistic error estimates. It is appropriate to discuss briefly sources of additional systematic errors and the measures we have taken to minimize them.

Cell Constants. Any errors in cell constants transmit themselves to the molecular dimensions, since intensity measurements alone provide only fractional atom coordinates (based on the cell axes).

(i) **Four-Circle Diffractometer Measurements.** The main source of error is inaccurate circle zero points, especially $2\theta_0$. We have refined all cell constants measured on our Stoe four-circle diffractometer from 2θ values derived from reflections centered at both 2θ, ω, χ, Φ and -2θ, $\omega - 2\theta$, χ, Φ; the true 2θ (independent of $2\theta_0$) is given by the difference $\omega_+ - \omega_-$.[34]

(ii) **Two-Circle Diffractometer Measurements.** Cell constants measured by conventional methods on such diffractometers are inherently less accurate, since exact alignment of the crystal along an axis is usually assumed. We have used a method based on the refinement of an orientation matrix from ω values of (typically) 100–200 reflections from positive and negative layers.[35] (In some cases the crystals were remounted on a four-circle diffractometer for cell constant determination.)

All final SHELXTL refinements were converted into tables for publication by using a locally written program; this allows (somewhat crudely) for additional cell constant errors of ca. 1 part in 1000 by increasing least-squares esd's of bond lengths and angles by 0.001 Å and 0.01°, respectively.

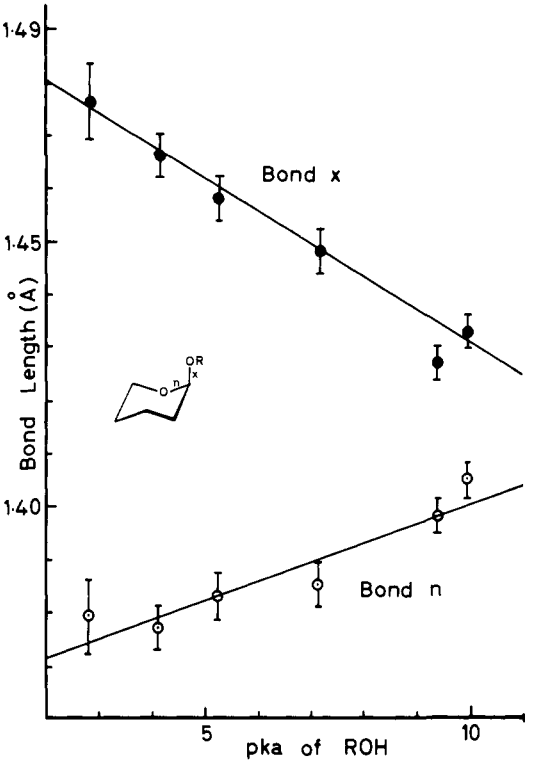


Figure 1. Plot of bond lengths vs. the pK_a of ROH for the series of axial tetrahydropyranyl acetals **1** listed in Table I. Error bars represent standard deviations in bond lengths. The equations of the lines drawn are given in the text.

Libration Effects. Libration is the apparent shortening of bonds due to thermal motion of the atoms. Neither of the normal libration corrections[36] proved appropriate, and we therefore quote uncorrected values. The acetal groups of almost all the compounds studied (see the individual crystallographic references for details) show thermal parameters of very similar magnitude, and we consider that *trends* in uncorrected bond lengths are therefore unaffected.

Finally, we note that the overall changes in bond length observed in this work range up to many hundredths of an angstrom and that these changes (and those of bond and torsion angles) far outweigh any systematic errors.

Discussion

Axial Compounds. The trends in the lengths of the bonds at the acetal center of axial aryl tetrahydropyranyl acetals noted in our preliminary communication[9] are confirmed by the more extensive set of data shown in Table I. The compounds are listed in increasing order of effective electronegativity of the oxygen atom of the OAr group, as measured by the pK_a's of the parent phenols, ArOH, in water, and over the series show a marked lengthening of the exocyclic C–OAr bond *x*, coupled with a significant, but less pronounced, shortening of the endocyclic bond *n*. The range of leaving group is narrower than we would like, because 2-alkoxytetrahydropyrans are almost all liquids.[51] But the trend is clear, and the linear relationship between the length of the C–OAr bond (*x*) and the pK_a of the conjugate acid (ArOH) of the leaving group is now firmly established (Figure 1).

$$x = 1.493 - (6.495 \times 10^{-3})pK_a \quad r = 0.985$$

(34) Clegg, W. *Fresenius Z. Anal. Chem.* **1982**, *312*, 22.
(35) Clegg, W., Sheldrick, G. M. *Abstr. Eur. Crystallogr. Meet. 5th, 1979* **1979**, *79*.
(36) Busing, W. R.; Levy, H. A. *Acta Crystallogr.* **1964**, *17*, 142. Schomaker, V.; Trueblood, K. N. *Acta Crystallogr., Sect. B* **1968**, *B24*, 63. See also: Srinivasan, R.; Jagannathan, N. R. *Ibid.* **1982**, *B38*, 2093.
(37) Kennard, O.; Motherwell, W. D. S.; Coppola, J. C.; Griffin, B. E.; Reese, C. B.; Larson, A. C. *J. Chem. Soc.* **1971**, 1940.
(38) Stothart, P. H.; Brown, I. D. *Acta Crystallogr., Sect. B* **1973**, *B29*, 2237.

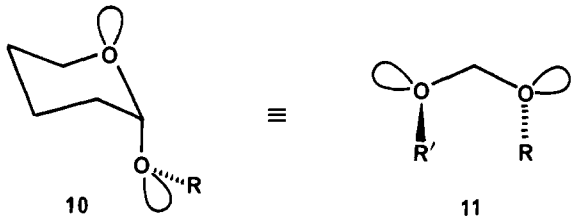
A weaker correlation

$$n = 1.364 + (3.639 \times 10^{-3})pK_a \quad r = 0.939$$

describes the associated shortening of the endocyclic C–O bond *n* (Figure 1). Note that these changes in bond lengths are apparent well before significant changes in angles appear. Only for the two most strongly electron-withdrawing OR groups listed in Table I do changes in the ring torsion angles show the onset of flattening of the chair at C(1).[29]

Since log k_{hyd} (the rate constant for spontaneous hydrolysis) is a linear function of the pK_a of ArOH for this series of compounds, these amount to linear correlations between bond lengths and free energies of activation for hydrolysis. This aspect of the results is discussed in the following paper in this issue. Here we consider specifically bonding at the acetal center, in the light of the changing pattern of bond lengths revealed by this work.

2-Alkoxytetrahydropyrans in solution (and in most cases in the crystal also) prefer the conformation **10**, with the exocyclic oxygen substituent axial. This is the anomeric effect[6,39] now generally



10 **11**

considered to arise principally from a stabilizing n–σ^* interaction between the axial lone pair on the ring oxygen and the antibonding σ^* orbital of the C–OR bond. In the *+sc, +sc* conformation **11** a similar n–σ^* interaction is possible between a lone pair on the exocyclic oxygen and the antibonding orbital of the endocyclic C–O bond of the acetal group. Both oxygens thus act as lone pair donors, and both C–O bonds are acceptors. The result is net stabilizing and apparent as a shortening and strengthening of both C–O bonds at the acetal center. (The extent of this shortening is not simply measured. A possible approach is as follows. Extrapolating from Figure 1 suggests that the two acetal C–O bonds *n* and *x* of an axial tetrahydropyranyl acetal should become equal for a derivative (**1**) of an alcohol of $pK_a \sim 13$, at 1.410 Å. Using the approximate relationship between the C–O bond length and the pK_a of ROH derived for secondary alkyl ethers in the previous paper[40] we can calculate a value for the length of the C–OR bond in R_2CH–OR of 1.438 Å for an ether derived from an alcohol ROH of $pK_a = 13$. Neither figure is likely to be very accurate, but the comparison is consistent with a significant bond shortening in the acetal. The order of magnitude (0.03 Å) lies between that observed for difluoro- and dichloromethane,[41a] and is in agreement with calculations for the difference between the internal and external C–O bond lengths of simple *+sc, +sc* acetals.[41b]) Related effects are responsible for the well-known bond shortening and low reactivity of the polyhalogenomethanes, such as CF_4 and CH_2Cl_2.[6,42]

This is the picture for an electronically symmetrical acetal. In an unsymmetrical structure, such as an aryl tetrahydropyranyl acetal, the more electron-withdrawing OAr oxygen is a poorer *n* donor, and the C–OAr bond is a better σ acceptor (lower energy σ^*_{C-O}). As a result the shortening of the endocyclic C–O bond *n* is increased, and the exocyclic C–OAr bond *x* is correspondingly lengthened. The torsion angle data in Table I show that *n* donation by the exocyclic oxygen atom must already be small for the 4-nitro derivative **6a** (X = H), since there is no discontinuity in the plot (Figure 1) of bond length against p*Ka*, even though the extra ring prevents the molecule from adopting the *synclinal* conformation

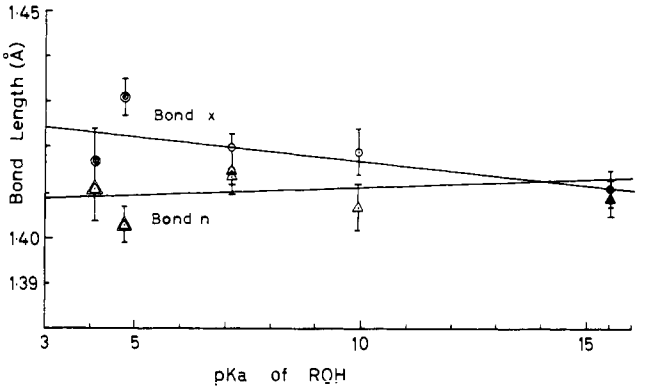
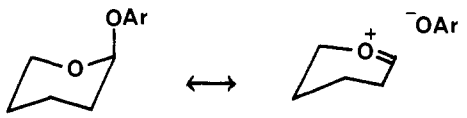


Figure 2. Bond length vs. pK_a plot for the α-glucopyranosides **8a** listed in Table III. Circles represent points for bond *x*, triangles represent bond *n*, and filled symbols represent values taken from the literature. Double symbols refer to tetraacetates. The best (least squares) line drawn has the equation $x = 1.427 - (1.02 \times 10^{-3})pK_a$ ($r = 0.626$).

about the C–OAr bond ($D_2 \sim 160°$ in compounds **6a**, compared with simple tetrahydropyran and oxadecalin acetals (**3** and **5a**), which have D_2 near 60°).

Thus, the more electronegative the OAr group—and so the poorer the donor capability of the OAr oxygen and the lower the σ^*_{O-Ar} level—the greater should be both the lengthening of the C–OAr bond and the associated shortening of the endocyclic C–O bond *n* as observed. (In valence bond terms, the greater will be the contribution of the ion pair (**4**) to the structure of the ground state of **3**.)

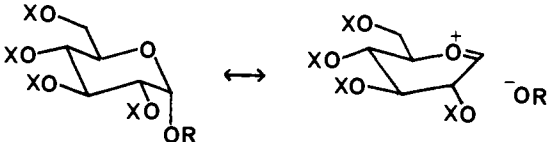


3 **4**

An extreme case would be a 2-chlorotetrahydropyran, and related effects on bond lengths were observed many years ago in the 2,3- and 2,5-dihalogeno-1,4-dioxanes: bonds to axial halogens were found to be substantially lengthened, and the adjacent endocyclic C–O bonds were shortened, though bond lengths in the O–C–hal fragment were considered normal for alkyl ethers and halides where the halogen was in an equatorial position.[43]

Remarkably, these effects on bond lengths practically disappear on going to the α-glucopyranosides (Figure 2), although the geometries at the acetal center are the same (conformations close to *+sc, +sc*, as shown by the dihedral angles in Table III). The two acetal C–O bond lengths are similar for methyl α-D-glucoside and similar also for the 2,4-dinitrophenyl derivative (tetraacetate). Statistical analysis shows that there are in fact weak trends, in the same direction as observed for axial aryl tetrahydropyranyl acetals, in the lengths of bonds *x* and *n* (Figure 2), but the sensitivity to the pK_a of ROH is smaller by about an order of magnitude.

This indicates that the contribution of the ionic form **12** to the structure of the ground state is greatly reduced in the glucosides, presumably as a result of inductive destabilization of the oxocarbonium ion by the four oxygen substituents. The same effect



8a **12**

must also account for the much reduced reactivity at the acetal center. Alkyl and aryl glucosides are hydrolyzed 10^6–10^7 times

(39) "The Anomeric Effect: Origin and Consequences," Szarek, W. A., Horton, D., Eds.; American Chemical Society: Washington, DC, 1979; ACS Symp. Ser. No. 87.
(40) Allen, F. H.; Kirby, A. J. *J. Am. Chem. Soc.*, preceding paper in this issue.
(41) Reference 6: (a) p 52. (b) p 54.
(42) Brockway, L. O. *J. Phys. Chem.* **1937**, *41*, 185.
(43) Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1967**, *4*, 39.

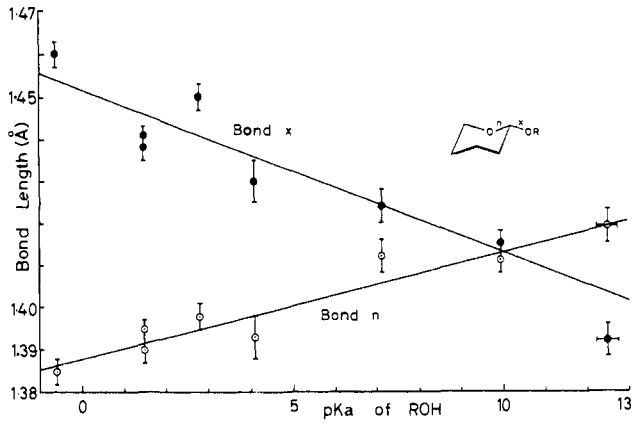


Figure 3. Bond length vs. pK_a plot for the series of equatorial tetrahydropyranyl acetals listed in Table II. The data for the four compounds with the bicyclononyl structure (**7e**, with pK_a of ROH <5) have been corrected by a factor of −0.015 Å, as described in the text, to allow for the change in multiplicity at the acetal center. The equations of the (least squares) lines drawn are $x = 1.456 - (4.76 \times 10^{-3})pK_a$ ($r = 0.945$) and $n = 1.394 + (2.14 \times 10^{-3})pK_a$ ($r = 0.911$).

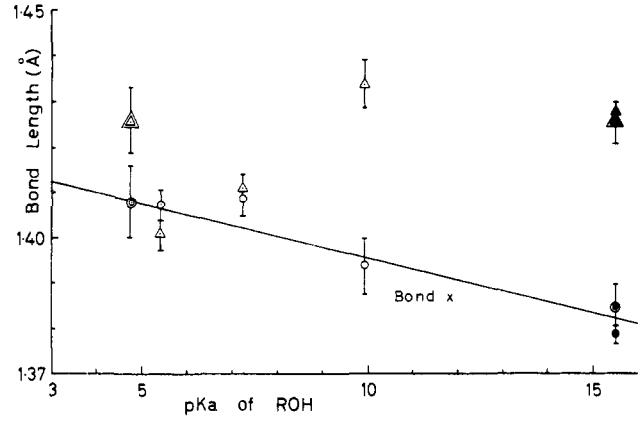


Figure 4. Bond length vs. pK_a plot for the β-glucopyranosides **8e** listed in Table IV (except that only the 3,4-dinitrophenyl derivative (mean values for two molecules in the asymmetric unit), and not its tetraacetate, is included). Symbols as in Figure 2. The equations of the (least squares) lines are $x = 1.424 - (2.85 \times 10^{-3})pK_a$ ($r = 0.962$) and $n = 1.398 + (2.50 \times 10^{-3})pK_a$ ($r = 0.662$).

more slowly than the corresponding tetrahydropyranyl acetals, when the loss of the same leaving group by the same mechanism is compared.[44,45] Apparently the electronic effects which inhibit C–OR cleavage also suppress the bond length changes observed in the tetrahydropyranyl acetals, suggesting that charge separation is significant even during the relatively early stages of bond extension.

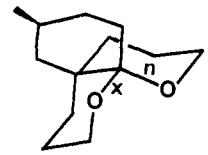
It would be useful to estimate this reduced *n*-donor capacity, or increased effective electronegativity, of the ring oxygen of α-glucosides, for example, in terms of an "effective pK_a" of its conjugate acid. This could usefully be measured in terms of the pK_a of ROH for compound **8a** for which the lengths of the endocyclic and exocyclic acetal bonds are equal. But because the correlations are so insensitive to the pK_a of ROH (Figure 2) no useful value can be extracted from the data. A good value, close to 13, is obtained in this way for the tetrahydropyranyl system from the intersection of the lines of Figure 1. This figure is itself unexpectedly low, since the pK_a of a primary alcohol is about 16. Apparently the ring oxygen atom of axial tetrahydropyran acetal **1** is for some reason an intrinsically poorer *n* donor, and the ring C–O bond *n* is a better σ acceptor, compared with the exocyclic C–OR group, when the acetal has the *+sc*, *+sc* conformation.

Equatorial Compounds. The data for equatorial tetrahydropyranyl acetals (**2**, Table II) cover a much wider range of leaving group, although only in the case of the *N*-phthalimidomethyl derivative do they refer to a simple tetrahydropyan. As in the axial series, well-defined trends are apparent in the pattern of bond lengths at the acetal center, with more electron-withdrawing OR groups associated with longer exocyclic C–OR bonds *x* and shorter endocyclic bonds *n*. The largest effects, with the most strongly electron-withdrawing groups, necessarily involve the very stable oxabicyclononyl derivatives **7**, which are ketone acetals. Since the length of the C–OR bond clearly depends on the degree of substitution at C,[40] we need to correct for the effect of the extra carbon substituent for these compounds (**7**). The mean C–OR bond length of tertiary-alkyl esters is 0.015 Å longer than that of the corresponding R_2CH–OR derivatives and appears to depend rather little on the effective electronegativity of the group OR.[40] So we have used this factor to correct the lengths of bonds *x* and *n* for acetals with structure **7** so that they can be compared directly with simpler tetrahydropyranyl acetals.

A plot of bond length (*x*, *n*) vs. pK_a of ROH for equatorial tetrahydropyranyl acetals is shown in Figure 3. It is similar in form to that (Figure 1) for the axial derivatives, but the correlation is poorer and the sensitivities of both *x* and *n* to the pK_a of ROH are smaller (least-squares slopes are 68% of those calculated for the corresponding lines of Figure 1).

This still substantial sensitivity was unexpected. The ring oxygen atom of a tetrahydropyranyl acetal **2** is prevented from acting as an efficient *n* donor by the geometry of the system, because two-electron bonding interactions of the $n-\sigma^*_{C-O}$ sort are strongest when the orbitals concerned are *antiperiplanar*.[46] But fixed antiperiplanar to the C–OR bond of **2** is the σ-bonding orbital of the ring bond C(5)–O(5). So only the exocyclic oxygen of an equatorial acetal should be able to act as a donor.

This latter effect is well-known in sugar structures, where it accounts for the short exocyclic C–OR bonds of β-glycopyranoses and methyl glycosides.[47] It has also been observed recently in the tricyclic acetal **13**, where the bond (*x*), which is equatorial to the other tetrahydropyran ring, is 0.026 Å shorter than the endocyclic bond *n*.[48] And it is comparable in the only equatorial



13

2-alkoxytetrahydropyran we have measured ($n-x = 0.025$ Å in **2**, R = *N*-phthalimidomethyl). In alkyl β-glucopyranosides the effect is larger ($n - x = 0.051$ Å in methyl β-pyranoside, 0.058 Å in the tetraacetate, Table IV), as expected if the ring oxygen is effectively more electronegative in glycosides, as discussed above.

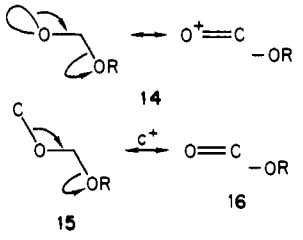
In the series of equatorial β-glucosides we have studied (Table IV) the exocyclic C–OR bond *x* is generally shorter than the endocyclic acetal bond *n*, even for relatively strongly electron-withdrawing groups R, but the difference ($n - x$) decreases for derivatives of more acidic ROH, primarily because of a steady increase in the length of the C–OR bond *x* (Figure 4). Once again there is a reasonable linear correlation between bond length (*x*) and the pK_a of ROH, with a slope 60% of that for the equatorial tetrahydropyranyl acetals. Presumably this represents the gradual disappearance of the $n-\sigma^*_{C-O}$ interaction involving the exocyclic oxygen as the donor. In α-glucosides this is largely matched by the $n-\sigma^*_{C-OR}$ interaction involving the ring oxygen as a donor, so that the exocyclic bond is subject to both bond

(44) Dyer, E.; Glaudemans, C. P. J.; Koch, M. J.; Marchessault, R. H. *J. Chem. Soc.* **1962**, 3361.
(45) Jones, C. C.; Sinnott, M.; *J. Chem. Soc., Chem. Commun.* **1977**, 767. Compare with data in ref 8.
(46) Epiotis, N. D.; Yates, R. L.; Larson, J. R.; Kirmaier, C. R.; Bernardi, F. *J. Am. Chem. Soc.* **1977**, *99*, 8379.
(47) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373.
(48) Brown, K. C.; Down, G. J.; Dunitz, J. D.; Seiler, P. *Acta Crystallogr. Sect. B* **1982**, *B38*, 1241.

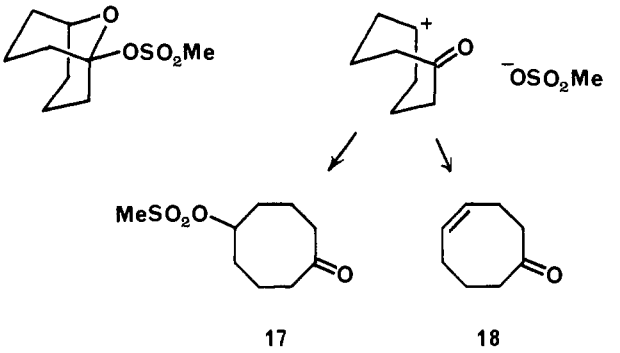
shortening and lengthening effects. In the β-glucosides only the former effect operates.

In the equatorial tetrahydropyranyl acetal series the ring oxygen is effectively less electronegative, so that all the bond length difference, $n - x$, has already disappeared at $pK_a = 10$ (R = Ph). If the increasing length of the exocyclic bond x were due here also to the gradual disappearance of the $n-\sigma^*_{C-O}$ interaction involving the exocyclic oxygen as a donor, then a lower sensitivity to the electronegativity of the OR group might be expected. In fact the slope of the line for bond x (Figure 3) is almost twice that of the corresponding plot of Figure 4. So we need to look for a new effect to explain most of the variation in bond length shown in Figure 3.

The clue to this new effect lies in the remarkable variation in the length of the remote C–O bond *a* (Table II).[49] This varies substantially more than the intermediate bond *n* (though this shows significant shortening) amounting over the seven compounds to about half that observed for the exocyclic bond x, when the full range of leaving group is taken into account. Bond *a* is *antiperiplanar* to bond x (the dihedral angles D_1 lie between 176° and 180°), just as is the lone pair on the ring oxygen which is involved in the $n-\sigma^*_{C-OR}$ interaction (**14**) responsible for the lengthening of the C–OR bond in the axial series. So the likely explanation of the pattern of bond length changes in the equatorial series (Table II) is a similar two-electron bonding interaction (**14**) between σ^*_{C-OR} and the σ-bonding orbital of the C–O bond *a*. Overlap is expected to be most efficient in the antiperiplanar orientation and to become more efficient as the σ^*_{C-OR} level is lowered by increasing electron withdrawal, leading to a shortening of bond *n* and lengthening of bonds *a* and x, as observed. (Bond *a* does not change significantly in any of the other series we have studied.)



Thus, the pattern of bond length changes at the acetal center in the series of equatorial compounds listed in Table II can be interpreted as marking progress along the reaction coordinate for a fragmentation reaction 15, the ground state for compounds with better leaving groups RO^- being closer in energy and geometry to the fragmentation products **16**, just as the pattern for the axial series (Table I) can be interpreted as mapping progress along the reaction coordinate for acetal cleavage (see the following paper in this issue[50]). This is entirely consistent with the known chemistry of these compounds. Axial tetrahydropyranyl acetals with very good leaving groups cannot be prepared because they break down too rapidly, with loss of RO^-. The corresponding equatorial compounds are much more stable (as long as their conformation is fixed), because a σ orbital is a poorer donor than a lone pair.[46] But the compound with the best leaving group in Table II (**7**, R = SO_2Me) is known to break down readily at room temperature in solution, to yield the products **17** and **18** expected from a fragmentation process.



Acknowledgment. We thank the Science and Engineering Research Council of Great Britain (A.J.B., R.G., P.S.), the Fonds der Chemischen Industrie, and the Deutscher Akademischer Austauschdienst for support and travel funds.

(49) Preliminary communication: Jones, P. G.; Kirby, A. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1365.

(50) Jones, P. G.; Kirby, A. J. *J. Am. Chem. Soc.*, following paper in this issue.

(51) Data for two nucleoside derivatives for which crystal structures are available are complicated by hydrogen bonding to one or the other of the acetal oxygen atoms,[37,38] and the only alkyl tetrahydropyranyl acetal for which we have so far been able to grow useful crystals had crystallized in the equatorial conformation.[30,52] Hydrogen bonding is not possible in the majority of our compounds, and the ring and glucosidic oxygens act as H-bond acceptors in the crystal in only two of the glucosides listed in Tables III and IV. These are 4-nitrophenyl α-D-glucopyranoside, where only one of the molecules in the asymmetric unit is involved,[20] and methyl β-D-glucopyranoside (Table IV), where the ring oxygen atom is the acceptor.

(52) **Note Added in Proof**: Since this paper was submitted we have obtained crystal structures for two axial 2-alkoxy-1-oxadecalins (**5a**, Ar = 2-(4′-carboxyphenyl)ethyl and 2,2-bis(4-chlorophenyl)ethyl). Some of the data for the first of these compounds have been included in the following paper.[50]