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Simple Correlation between Bond Length and Reactivity. Combined Use of Crystallographic and Kinetic Data To Explore a Reaction Coordinate

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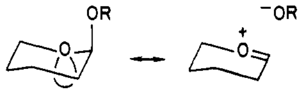
Abstract: Increasing electron demand at oxygen has been used to probe the relationship between bond length and reactivity in 11 different systems. In ten cases increasing electron demand at oxygen results in a substantial increase in both reactivity and the length of the C–OR or P–OR bond concerned. It is shown that the linear relationship observed between the length of the bond and the free energy of activation for its heterolytic cleavage implies a linear region of considerable extent on the reaction coordinate. The slope of the reaction coordinate in this region can be measured and corresponds to the energy required to extend the bond in the direction of reaction. This slope is calculated as over 600 kcal mol^{-1} Å^{-1} for the $S_N1(P)$ reaction of a series of phosphate triesters, a reaction not observed in solution, but is around 250 kcal mol^{-1} Å^{-1} for the readily observed unimolecular heterolyses of aryl tetrahydropyranyl acetals and phosphate monoester dianions.

Our analysis of crystal structure data for a large number of organic compounds containing C–O single bonds has revealed what could be a general correlation between bond length and reactivity:[1,2] the longer the bond, the more readily it is broken heterolytically. The evidence suggests that this is important in part because longer C–OR bonds are more strongly polarized in the ground state, in the sense $C^{\delta+}{-}^{\delta-}OR$. This can be expressed as a contribution to the ground-state structure of R_1OR_2 from the valence bond tautomer (**1**). The extent of this contribution is

$$R_1\text{-}OR_2 \leftrightarrow \underset{\mathbf{1}}{R_1{}^{+}\,{}^{-}OR_2}$$

more important for more stable fragments R_1^+ and R_2O^-, and thus, for a given group R_1, depends on the effective electronegativity of the oxygen atom of the group OR_2. Evidently, the greater the degree of charge separation in the ground state, the easier will be the cleavage of the C–O bond to form the ion pair **1**. We examine first the link between structure and reactivity for a single series of compounds, the axial tetrahydropyranyl acetals **2**, for which good sets of both crystallographic and kinetic data are available, and show how we can begin to explore the reaction coordinate for C–O cleavage; we then consider how general the approach might be. The C–OR bonds of acetals (**2**) show a marked lengthening as the group OR is made more electron withdrawing, accompanied by a significant shortening of the endocyclic acetal C–O bond, as expected if valence bond tautomer **3** is making an increasingly large contribution to the structure of the ground state.[2] (These changes are suppressed in the corresponding glucosides, presumably because of inductive destabilization of the developing cation (**3**).[2]) Note that these bond lengths are the first structural parameters to change in response to increasing electron demand: only for the compounds with the best leaving groups OR (lowest pK_a of ROH) are significant changes observed in the torsion angles about the ring bonds O(5)–C(1), C(1)–C(2), and C(2)–C(3) (Table I). Each of these dihedral angles decreases by 3–5° over the series of compounds we have studied (Table I), consistent with a flattening of the ring about the anomeric carbon in the direction of the oxocarbenium ion (**3**) for the compounds with the longest C–OR bonds. But for the first four or five compounds in Table I these dihedral angles do not change significantly, even though the C–OR bond (x) is already beginning to stretch. (The OCO angle at the anomeric center is also significantly smaller for the final compound in Table I, but this angle (β, Table I of the preceding paper in this issue) is restricted by the geometry of the two bicyclic members of the series, and no safe conclusions can be drawn.)



2 **3**

The bond length changes, and the flattening around C(1), are consistent with our interpretation in terms of increasing contributions from structure **3** to the ground states of compounds with better leaving groups, RO⁻. It is also reminiscent of several structure–structure correlations observed in recent years by Bürgi and Dunitz and their co-workers.[3,4] These authors have demonstrated, in favorable cases, regular relationships between one bond length or angle and another in series of compounds such as tetrahedral species YMX_3 and linear triatomics X–Y...X, which may be interpreted as defining minimum energy pathways for a particular coordination change at the given center (M or Y in the examples cited). The changes in the two acetal bond lengths, and the related flattening of the ring at the anomeric center of our axial tetrahydropyranyl acetals, may similarly be regarded as defining the pathway for the acetal cleavage reaction **2** → **3**. For our system, however, there exist sufficient kinetic as well as structural data to take the analysis a stage further.

The curves obtained by plotting d_{xy} against d_{yx} for three systems, X–Y···X, have the same general form as those available by calculation for simple linear triatomic systems like H_3 (dashed line in Figure 1) for the minimum energy pathway from H–H- - -H to H- - -H–H.[3] A similar curve (Figure 2) can be drawn through a plot of the C–OR bond length x vs. the length of the endocyclic bond n for our axial acetals (**2**), and this curve may similarly be regarded as "mapping out" a reaction coordinate for the early stages of the C–OR cleavage reaction.

The n-σ^*_{C-OR} interaction[2] responsible for the changes in these bond lengths, as presented by **2** ↔ **3**, is also the interaction involved in the cleavage of the C–OR bond, which is the rate-determining step in the spontaneous hydrolysis of the axial tetrahydropyranyl acetals **2**. The interaction is strongest, and the bond length changes greatest, in the ground states of those compounds with the best leaving groups, which are also the most reactive. There is,

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(1) Allen, F. H.; Kirby, A. J. *J. Am. Chem. Soc.*, first paper in this series in this issue.

(2) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) Dunitz, J. "X-Ray Analysis and the Structure of Organic Molecules"; Cornell University Press: Ithaca, NY, 1979; p 337 ff.

(4) Bürgi, H. B. *Inorg. Chem.* **1973**, *12*, 2321.

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Table I. Dihedral Angles within the Tetrahydropyran Ring for Axial Tetrahydropyranyl Acetals (**2**)[a]

pK_a of ROH	bond lengths		ring torsion angles[b] about					
	n	*x*	O(5)-C(1)	C(1)-C(2)	C(2)-C(3)	C(3)-C(4)	C(4)-C(5)	C(5)-O(5)
15.5	1.428	1.411	54.0 (5)	50.3 (5)	52.7 (5)	57.5 (5)	60.3 (5)	59.3 (5)
9.95	1.405	1.433	55.3 (3)	52.0 (3)	51.6 (3)	53.9 (3)	56.3 (3)	57.3 (3)
9.38	1.398	1.427	55.1 (4)	53.3 (4)	52.3 (4)	53.6 (4)	55.6 (5)	56.4 (4)
7.14	1.385	1.448	55.5 (3)	52.3 (4)	50.7 (4)	52.9 (4)	55.3 (4)	57.0 (4)
5.22	1.383	1.458	52.3 (3)	50.3 (3)	50.9 (3)	54.4 (3)	56.2 (3)	55.1 (3)
4.11	1.377	1.466	52.8 (4)	51.1 (4)	52.0 (4)	55.0 (4)	55.4 (5)	55.0 (5)
2.80	1.379	1.476	50.2 (7)	46.0 (8)	48.8 (8)	54.9 (9)	58.5 (7)	57.3 (6)

[a] Fuller data, structures, and references are given in Table I of the preceding paper in this issue[2] except for the first compound listed (**5**), which represents new work.[23] [b] Absolute values.

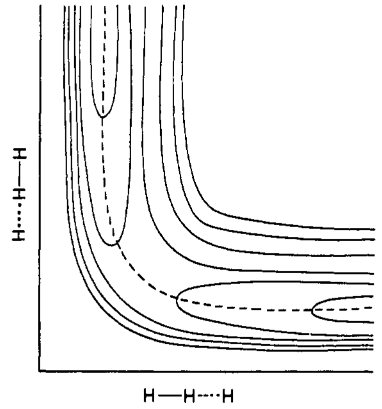


Figure 1. Typical potential energy surface calculated for the linear H_3 system. See, for example: Liu, B. *J. Chem. Phys.* **1973**, *58*, 1925.

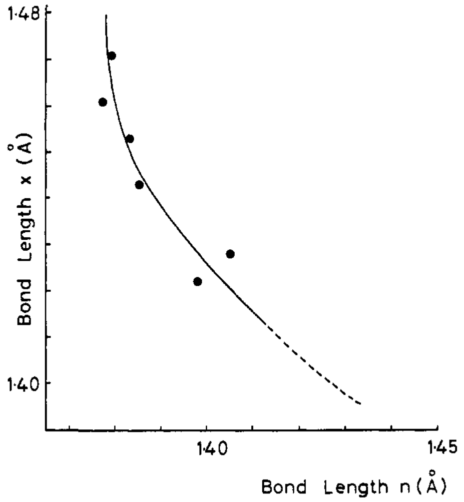


Figure 2. Correlation plot (see Dunitz, ref 3) for bond lengths at the acetal center of axial aryl tetrahydropyranyl acetals (**2**). Data are from Table I in the preceding paper in this issue.[2]

therefore, a basis for a correlation between bond length and reactivity in this series, and it is of some interest to define the form of this correlation and hence perhaps to explore the energy coordinate of the contour plot implied in Figure 2.

The form of the correlation turns out to be very simple. As shown in Figure 1 of the preceding paper in this issue,[2] there is a good linear relationship ($r = 0.985$) between the length of the C-OR bond for our series of six axial tetrahydropyranyl acetals and the pK_a of the conjugate acid of the leaving group ROH. Since log k_{hyd} has been shown also to be a linear function of the pK_a of ROH for this series of compounds,[5] this is equivalent to a linear correlation between the length of the C-OR bond and the free energy of activation for its cleavage.

From mechanistic work on the spontaneous hydrolysis of these compounds[5,6] we know that the transition state for C–OR cleavage is late and, thus, close in energy, and also in geometry, to the oxocarbenium ion pair (**3**). For a compound for which the

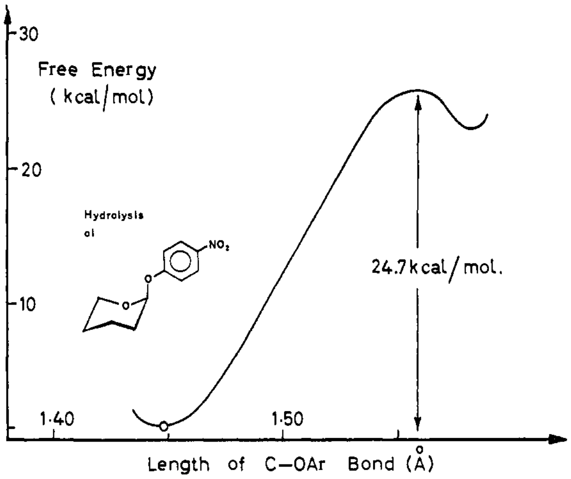
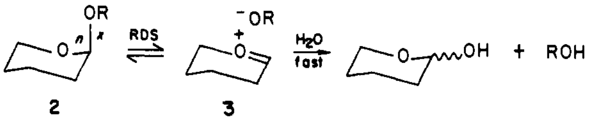


Figure 3. Rudimentary energy profile diagram for the hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran in water. Kinetic data from ref 5. See the text.



necessary structural and kinetic data are available, therefore, it is possible to construct an energy profile diagram with some accuracy. Figure 3 shows such a plot for the loss of *p*-nitrophenoxide from **2**, R = 4-nitrophenyl, using as the reaction coordinate the length of the C–OR bond (*x*) being broken. (The geometry data summarized in Table I suggest that this may be a good approximation in the early stages of the C–O cleavage.)

As usual in such plots, only differences in energy between states are known, in this case between the ground and transition states. For the difference in energy between the transition state and the intermediate we have assumed a value of 3 kcal (12 kJ) mol^{-1}, of the order of the activation energy for a diffusion-controlled reaction, since the recombination of an oxyanion and an oxocarbenium ion such as **3** is expected to be diffusion controlled, at least for poor leaving groups, RO^- (see below). Along the abscissa, the length of the C–OR bond is known only in the ground state, so the shape of the curve drawn is arbitrary. We now attempt to define the shape of the reaction coordinate more closely.

A curve of this type (Figure 3) can be constructed for any axial tetrahydropyranyl acetal for which crystal data are available, because reactivity data which have not been measured can readily be derived from the well-established linear free energy relationship between the rate constant for hydrolysis and the pK_a of the conjugate acid of the leaving group. The next stage is to put this family of curves on a common scale, and this can be done, approximately, as follows. We take as a reference point the ion pair intermediate **3**. The free energy of this species will be practically

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(5) Craze, G.-A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 354.

(6) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970**, *92*, 1681.

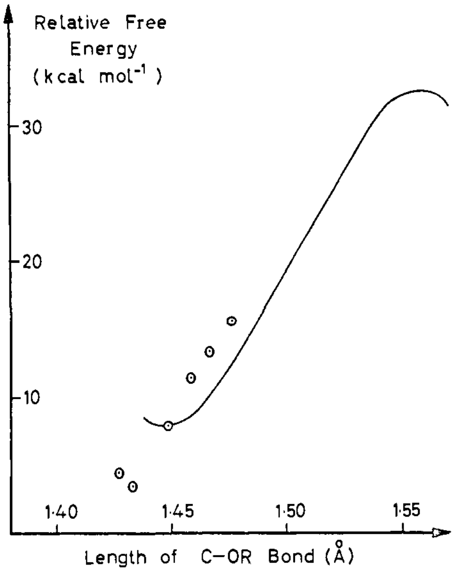
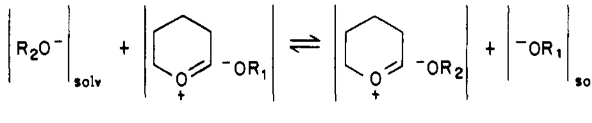


Figure 4. Data for five other axial tetrahydropyranyl acetals (**2**) normalized onto the plot of Figure 3 for the *p*-nitrophenol derivative. See the text.

independent of the group $^-$OR as long as the pH of the medium is high enough for ROH to be fully ionized. (In other words, the equilibrium constant for the exchange reaction



will be close to unity.) The transition state for C–OR cleavage is known to be late and thus close in energy to the ion pair; so as a working hypothesis we assume a constant reaction coordinate between the transition state and the ion pair and hence a constant transition-state energy and geometry.

This is equivalent to assuming that the rate of recombination of the ion pair **3** is independent of the basicity of the anion RO$^-$. The combination reactions of solvent-separated anions and relatively stable carbocations do show some selectivity for the anion, which can be correlated by Ritchie's N_+ values;[7] but N_+ values do not depend primarily on basicity[8] and probably reflect rather the solvation properties of the nucleophile, suggesting that the activation energy for the recombination of the ion pair (**3**) is indeed no more than about 3 kcal mol^{-1}, as assumed in Figure 3. An extremely weak dependence on the basicity of the nucleophile is also found in the "S$_N$1-like" substitution reactions of oxyanions with two systems of $MeOCH_2X$ (X = 2,4-dinitrophenoxy[9] and Me_2N^+Ph[10]). So what little evidence is available from studies of related reverse reactions suggests that our assumption is not far from the truth.

We can now locate the energy level of the ground state for each of our series of compounds relative to the constant transition-state energy and thus bring the complete set of data together on the same plot (Figure 4). Each point on this plot represents the ground-state minimum of a reaction coordinate similar to that plotted for the 4-nitrophenyl compound, and the figure illustrates clearly how the ground states of compounds with good leaving groups, which are closer in energy to the transition state, are closer in geometry also.

The full set of curves is brought together in Figure 5, where they are related to the (hypothetical) reaction coordinate for the spontaneous C–OR cleavage reaction of a parent 2-alkoxytetrahydropyran (**2**, R = alkyl). The lower part of the curve (broken line) represents an extrapolation, but to the extent that the shapes of the reaction coordinates are similar in the region of the ground state it is apparent that the points for our series of compounds map out not the reaction coordinate itself but a curve approximately parallel to it, for the cleavage of the parent acetal.

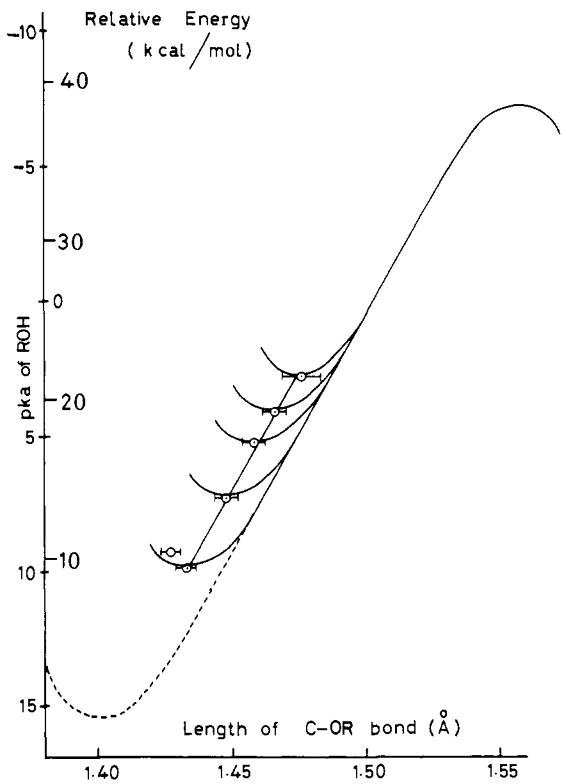
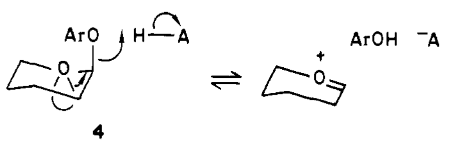


Figure 5. Reaction coordinates for six axial aryl tetrahydropyranyl acetals (**2**) normalized onto the same scale (see text) and compared with the curve for a "parent" 2-alkoxytetrahydropyran (begins as dashed curve).

Note that the ordinate (Figure 5) is drawn with two separate scales, representing alternatively relative free energy and the pK_a of the conjugate acid of the leaving group ROH. These are of course related by the linear free energy relationship correlating the kinetic data[6] but allow independent estimates of the relative energies of the ground and transition states. So far we have used measured energies of activation, together with the assumption that the transition-state level is constant.

Alternatively, the pK_a of the conjugate acid of the leaving group *at the transition state* can be estimated as follows. The acid-catalyzed hydrolysis of 2-alkoxytetrahydropyrans is known to be a specific acid-catalyzed reaction,[11] as is that of 2-phenoxytetrahydropyran. But for 2-(aryloxy)tetrahydropyrans with electron-withdrawing groups in the aromatic ring the mechanism changes to general acid catalysis.[11] Apparently as O-protonation becomes progressively more enegetically unfavorable, and C–OR cleavage becomes easier, the two steps become concerted, establishing the conditions for general acid catalysis (**4**).



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There is probably no sharp dividing line between the mechanism of **4** and the preequilibrium protonation mechanism, but for leaving groups better than PhOH, with conjugate acid pK_a's below about −7, it is clear that the transition state for C–OAr cleavage is reached before proton transfer to oxygen is complete. This locates the transition state, approximately, in terms of the pK_a of the conjugate acid of the leaving group, and it is encouraging that there is good agreement (Figure 5) between the two scales over

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(7) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.
(8) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1973**, *95*, 1882.
(9) Craze, G.-A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 357.
(10) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789.
(11) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 4081.

the whole range susceptible to observation.

Discussion

The main curve drawn in Figure 5 is a conventional representation of the energy profile diagram for the ionization of a 2-alkoxytetrahydropyran (**2** → **3**). The detailed shape of such a curve is usually arbitrary: in particular we normally have no information about the C...OR distance at any point except that corresponding to the ground state.

The shape of the curve drawn in Figure 5 is not entirely arbitrary. As discussed above (assuming always a constant transition-state energy for the full series of **2** → **3**), to the extent that the shapes of the reaction coordinates for the cleavage of 2-(aryloxy)tetrahydropyrans are similar in the region of the ground state, the points for our series of compounds map out a curve parallel to the reaction coordinate for the cleavage of the parent acetal and thus define the *slope* of the reaction coordinate in this region. Furthermore, this is not information limited to the very early stages of bond breaking: in terms of free energy it extends to over 50% of the C–OR bond-breaking process.

The slope of the line drawn through our experimental points is 260 ± 10 kcal mol^{-1} Å^{-1} at 39 °C (the temperature of the kinetic measurements). This is a measure of the energy required to extend the C–OR bond in the direction of heterolytic cleavage (**2** → **3**) and is of the same order of magnitude as isolated previous estimates of dE/dr for C–C bonds in the normal single-bond-length region.[12] (An implicit assumption here is that the bond lengths involved do not change significantly between solid state and solution: this is consistent with the generally small differences in IR stretching frequencies between solid state and solution spectra;[13] such frequencies, and measured interatomic distances for organic molecules also, in fact, change remarkably little even on going to the gas phase.[13,14])

To explore the true reaction coordinate for the spontaneous cleavage of the C–OR bond of **2**, the next step is to attempt to relate our data to a standard potential energy curve. No theoretical treatment predicts a *linear* relationship between bond length and energy.[12,15-21] But the linear relationships we observe, between the length of a bond and the free energy of activation for its hydrolytic cleavage, must in any case be expected to hold over only a limited range of leaving group (OR). So the basic requirement for a standard potential energy curve to accommodate the data in the way suggested by Figure 5 is a substantial region of zero, or at least very low curvature, on the dissociation side of the energy minimum.

The Morse function (eq i), which describes rather successfully the dissociation of simple diatomics in the gas phase,[22] fulfills this requirement very well. A major difficulty in applying this or

$$\mathrm{PE} = D_e[1 - e^{-\beta(r-r_0)}]^2 \qquad \text{(i)}$$

related functions to our data has been that they are expressed in terms of $r - r_0$, where r is the interatomic distance (C...OR in the case of **2** → **3**) and r_0 is its value at the energy minimum. Fortunately, after many unsuccessful attempts over several years, we have very recently obtained a crystal structure for an axial 2-alkoxytetrahydropyranyl acetal **5**[23] and are now able to use an accurate experimental value (1.411 Å, Table I) for the C–OR bond length corresponding to r_0. (Note that the point for this compound does not fall on the line (Figure 5) defined by the data for our six aryl tetrahydropyranyl acetals, which predicts a bond length of 1.392 Å for a derivative of an alcohol of pK_a = 15.5.)

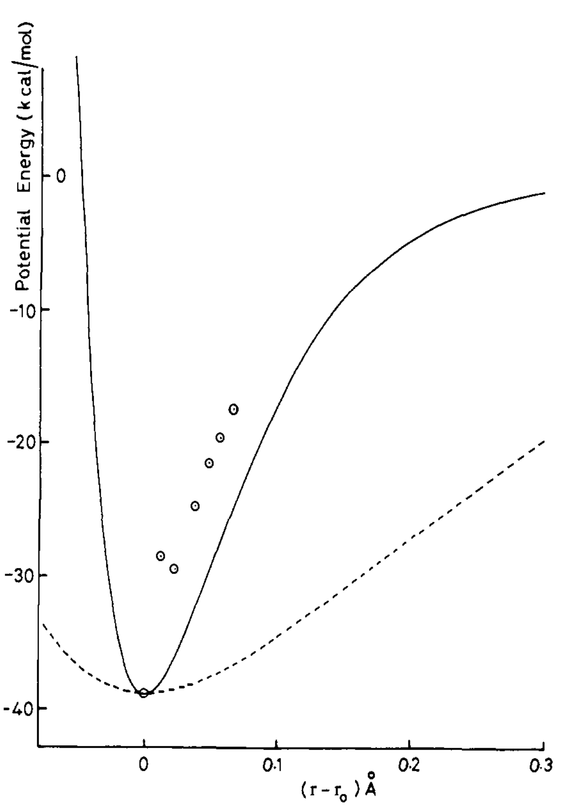
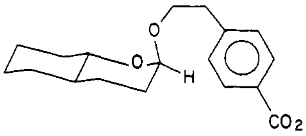


Figure 6. Morse curve (eq 1) calculated by using constants D_e = 38.85 kcal mol^{-1} and β = 13.87 Å derived (least-squares method; see text) to fit the bond length reactivity data discussed in this paper in the way suggested by Figure 5. The dashed curve shows the shallower potential function calculated for the gas-phase dissociation into the component atoms of a diatomic molecule joined by a bond with similar properties to that of the C–OR bond of a 2-alkoxytetrahydropyran derived from an alcohol ROH of pK_a 15.5.



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We can now use the energy and bond length data summarized in Figure 5 to calculate the value of the coefficient β of eq i required to give a curve parallel to our experimental line. We take D_e as the free energy of activation (38.85 kcal mol^{-1}) for the spontaneous hydrolytic cleavage of the C–OR bond of an acetal (**2**) derived from an alcohol of pK_a = 15.5 (the estimated[24] pK_a of the conjugate acid of the leaving group of **5**). Then a plot of $\ln([E/D_e]^{1/2} - 1)$ vs. $r - r_0$ gives a good line (correlation coefficient = 0.987 for six data points) of slope 13.9 and intercept 0.436. Our data points thus map out a line parallel to the Morse curve defined by these values of D_e and β but displaced from it by 0.031 Å.

The calculated curve is plotted in Figure 6, together with our experimental points. The quantitative resemblance to the plot

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(12) Bartell, L. S. *Tetrahedron* **1962**, *17*, 177 and references cited therein.

(13) Jones, W. J. In "Infrared Spectroscopy and Molecular Structure"; Davies, M., Ed.; Elsevier: Amsterdam, p 159. Krimm, S. "Infrared Spectroscopy and Molecular Structure"; Davies, M., Ed.; Elsevier: Amsterdam, 1963; p 270.

(14) Beagley, B. In "Molecular Structure by Diffraction Methods"; The Chemical Society: London, 1975; Chem. Soc. Special Publication No. 3, p 52.

(15) Badger, R. M. *J. Chem. Phys.* **1935**, *3*, 710.

(16) Huggins, M. L. *J. Am. Chem. Soc.* **1954**, *75*, 4126.

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(18) Dewar, M. J. S.; Schmeising, H. N. *Tetrahedron* **1959**, *5*, 166; **1960**, *11*, 96.

(19) Johnston, H. S.; Parr, C. *J. Am. Chem. Soc.* **1963**, *85*, 2544.

(20) Hine, J. *Adv. Phys. Org. Chem.* **1977**, *15*, 1.

(21) Berces, T.; Dombi, J. *Int. J. Chem. Kinet.* **1980**, *12*, 123.

(22) Atkins, P. W. "Physical Chemistry"; 2nd ed.; Oxford University Press: London, 1982; p 585.

(23) Jones, P. G.; Briggs, A. J.; Kirby, A. J., unpublished work. **Note Added in Proof**: Data for a second oxadecalin acetal (**5**, but derived from 2,2-bis(4-chlorophenyl)ethanol), obtained still more recently, show an axial C–OR distance identical within experimental error with that for **5**, 1.406 (6) Å compared with 1.411 (6) Å.

(24) Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205. Takahashi et al. estimate the pK_a of $PhCH_2CH_2CO_2H$ as 15.48.

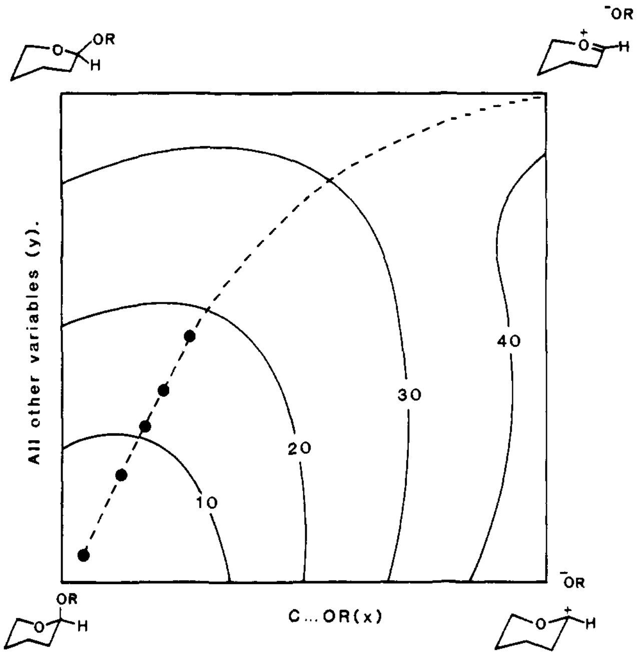

Figure 7. Speculative reaction coordinate–energy contour diagram for the conversion of **2** to **3**. The energy contour scale (in kcal mol^{-1}) is intended to give only a general indication of the shape of the surface. The reaction coordinate (dashed line) traces the minimum energy path from **2** to **3**, and the circles give an approximate indication of the location of our experimental points (see text).

of Figure 5 is striking and provides some support for the validity of this simple analysis. Particularly interesting is the value of the coefficient β derived by this treatment, which is significantly higher than β values obtained for Morse functions describing the dissociation of simple diatomic molecules in the gas phase.

In terms of molecular parameters

$$\beta = \nu_o\sqrt{2\pi^2\mu D_e}$$

When reasonable values for the C–OR stretching frequency (ν_o = 1200 cm^{-1}) and the reduced mass (μ = 10 au) are used, the value calculated for the stretching of the C–OR single bond of a relatively large molecule is β = 4.0. The Morse function calculated by using this value of β is much shallower (dashed curve of Figure 6).

A likely explanation for this discrepancy lies in the simplifications implicit in the two-dimensional plots shown in Figures 5 and 6. A reaction coordinate maps out a minimum energy pathway across an energy surface, and the apparent slope depends on the vantage point of the observer. Consider the (qualitative) energy-contour map (More O'Ferrall–Jencks diagram[25]) shown in Figure 7. We have generated the three-dimensional plot by discarding the assumption that the reaction coordinate can be represented simply by C–OR bond breaking. The new third coordinate represents all the other variables, such as changes in ring conformation and the shortening of the endocyclic C–O bond, involved in going from **2** to **3**. When the reaction coordinate (dashed line) is projected onto the xz plane to generate the two-dimensional plot corresponding to Figure 6 (rather than on to the xy plane to give Figure 7), the slope of the derived curve is clearly magnified, by a factor which depends on the relative steepness of the surface along the x and y coordinates.[26]

In terms of our analysis, the observed linear relationship between bond length and reactivity appears to arise from the low curvature of the Morse function at small-to-moderate bond extensions. In the region 0.02–0.10 Å relevant to our series of compounds (**2**), the calculated potential energy (Figure 6) is an almost precisely linear function of $r - r_0$, with a correlation coefficient of 0.9995. This is an intrinsic property of the Morse function and raises the possibility that linear correlations between bond length and reactivity may turn out to be the rule.

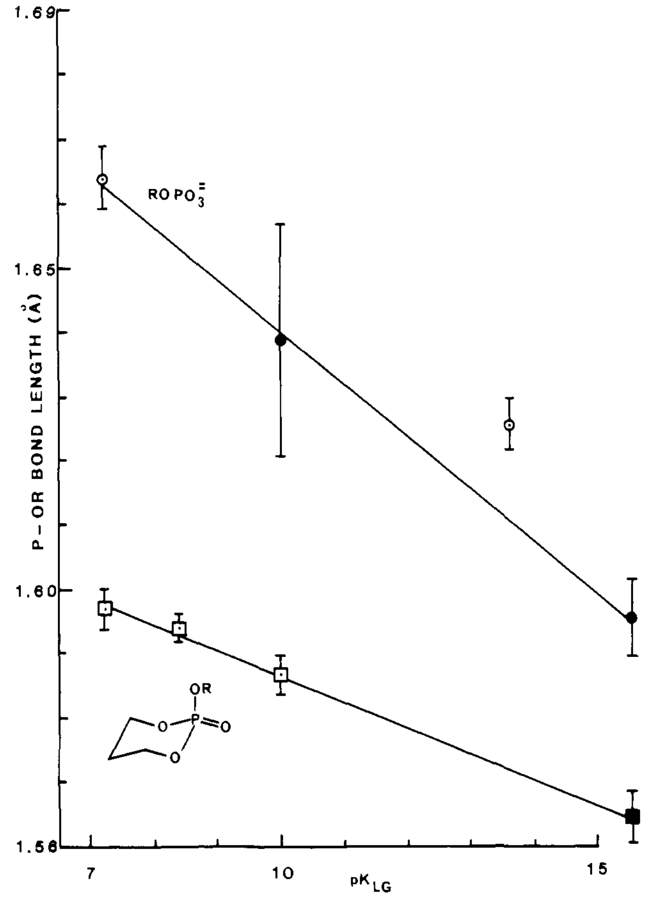

Figure 8. Plot of P–OR bond length vs. the pK_a of ROH for phosphate monoester dianions and phosphate triesters (**6**, **7**). Data are for dicyclohexylammonium 4-nitrophenyl and propargyl phosphate[31,32] (closed circles), dipotassium phenyl phosphate (Caughlan, C. N.; Haque, M.-U. *Inorg. Chem.* **1967**, *6*, 1998), and diammonium methyl phosphate (Garbassi, F.; Giarda, L.; Fegherazzi, G. *Acta. Crystallogr. Sect. B*, **1972**, *B28*, 1665). The triesters are **7**, R = 2-nitrophenyl, 3-nitrophenyl, and phenyl,[33] and (closed symbol) 5,5-dimethyl-2-methoxy-2-oxo-1,3,2-dioxaphosphorinane (Van Nuffel, P.; Lenstra, A. T. H.; Geise, H. J. *Cryst. Struct. Commun.* **1980**, *9*, 733).

The preliminary indications are that they are indeed rather general. We have so far collected or retrieved C–O bond length data for nine different systems. In the first paper of this series[1] we showed that for sets of methyl and primary, secondary, and tertiary alkyl ethers and esters, R_1–OR_2, for which accurate crystal structures are available in the literature, C–OR_2 bond lengths depend on the pK_a of R_2OH in the same sort of way as described for the more homogeneous set of axial acetals containing the structural unit **2** discussed in this paper. Our published work on acetal structures[2] shows that in three series out of four C–OR bond length data are correlated by acceptable straight lines. (The fourth set, of α-glucosides, shows very little variation of bond length with effective electronegativity of the leaving group.) And our most recent results,[23] with methoxymethyl acetals, CH_3OCH_2OR, again show a good correlation of C–OR bond length with the pK_a of ROH.

Most recently we have begun to collect data on two series of phosphate esters, to examine the variation of the P–OR bond length in the same way. Of particular interest are phosphate monoester dianions, RO–PO_3^{2-}, which, like aryl tetrahydropyranyl acetals, undergo ready S_N1-like cleavage (**6**) to RO^- and an electrophilic fragment (here monomeric metaphosphate, PO_3^-,

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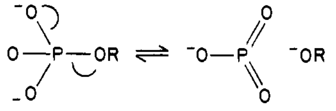
(25) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705. More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 247.

(26) This explanation was suggested to us by Dr. Ian H. Williams of this department. We are currently developing a more quantitative basis for the relationship between Figures 6 and 7 (Jones, P. G.; Kirby, A. J.; Williams, I. H., to be published).

or something very close to it).[27] This reaction also is believed to have a very late transition state, close to the high-energy intermediate, and the high sensitivity of reactivity to the leaving group must depend primarily on the ground state. For comparison we have measured crystal structures for a series of phosphate triesters (**7**).[28] These compounds react only by associative



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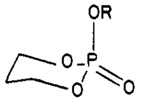

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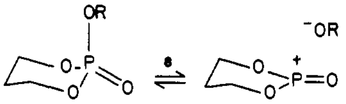
mechanisms: in the absence of the powerful internal electron donation available to the monoester dianions the P–OR bond cannot normally be broken without assistance from an external nucleophile.[29]

These differences in reactivity are clearly reflected in the patterns of P–O bond lengths in the two series. In both cases lines can reasonably be drawn through the data points when the P–OR bond length is plotted against the pK_a of ROH (Figure 8). As before, these lines represent linear relationships between the length of the P–OR bond and the free energy of activation for its cleavage. For the triesters four accurate structures define a good line of slope -3.94×10^{-3}. The data for the monoester dianions (salts of three different cations) are less accurate and less convincingly linear. But the length of the P–OR bond is clearly much more—perhaps twice as—sensitive to the nature of OR than in the series of triesters (the slope of the line drawn is -8×10^{-3}).

For the monoester dianions the slope of the kinetic plot of log k_{hyd} vs. pK_a of ROH gives a good straight line of slope -1.23,[27] so the slope of the line of Figure 8 is equivalent to a slope of 230 kcal mol^{-1} Å^{-1} for the linear region of the reaction coordinate for P–OR cleavage (**6**). For the triester the ionization (8) is not a



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known reaction in solution; but Williams[30] has estimated β_{eq} for the transfer of the neutral phosphoryl group $(HO)_2P{=}O$ between different OR groups as -1.83. This gives the slope of a plot of ground-state energies vs. pK_a of R_iOH for a series of esters $R_iOPO(OH)_2$, and this should be similar to that for triesters $R_iOPO(OR)_2$. We can thus calculate that the slope of the line for the series of triesters (Figure 8) is equivalent to a slope of 650 kcal mol^{-1} Å^{-1} for the linear region of the reaction coordinate for the early stages of reaction 8. It is clearly far more energetically expensive to stretch the P–OR bond of phosphate triesters (reaction 8) than of monoester dianions (**6**), consistent with the observed differences in reactivity between the two systems.

Conclusions

We have used increasing electron demand at oxygen as a probe to test the relationship between bond length and reactivity in, so far, 11 different systems. In ten cases the length of the bond to oxygen increases significantly with increasing electron demand and shows a linear correlation with the free energy of activation for its cleavage. This implies that there is a substantial linear region in the first half of the reaction coordinate for cleavage of this bond to oxygen and there is a correlation between the slope in this region—in effect the energy required to stretch the bond concerned—and mechanism and reactivity.

When physical organic chemists talk about structure–activity relationships they generally mean reactivity–reactivity relationships, between the logarithms of rate and equilibrium constants for reactions. The relationships developed by Bürgi and Dunitz and co-workers,[34] on the other hand, are structure–structure relationships, between geometrical parameters such as bond lengths and angles. What we have described in these three papers are genuine structure–reactivity relationships, which we hope may be developed further to be of some theoretical as well as mechanistic interest.

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Registry No. 5, 91631-42-4.

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(28) Briggs, A. J.; Jones, P. G.; Kirby, A. J., unpublished work.

(29) Khan, S. A.; Kirby, A. J. *J. Chem. Soc. B* **1970**, 1172.

(30) Williams, A. *J. Chem. Soc., Perkin Trans. 2*, in press.

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(32) Jones, P. G.; Sheldrick, G. M.; Kirby, A. J.; Abell, K. W. Y. *Acta Crystallogr., Sect. C* **1984**, *C40*, 550.

(33) Jones, P. G.; Sheldrick, G. M.; Kirby, A. J.; Briggs, A. J. *Acta Crystallogr., Sect. C* **1984**, *C40*, 1061.