Pure & Appl. Chem., Vol. 59, No. 12, pp. 1605–1612, 1987.
Printed in Great Britain.

Stereoelectronic effects on bond length and reactivity

Anthony J. Kirby

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England

Abstract - Systematic studies of crystal structures allow a unique glimpse of the early stages of heterolytic reactions of simple systems - in a sense, visualising the chemist's curly arrows. There are strong correlations between the length of a bond and the rate at which it breaks in solution. In 1-arylethanol derivatives ArCHMeOX the C-OX bond length depends also on the dihedral angle controlling π-σ^*_{C-OX} overlap, and we observe changes in geometry as well as conformation which can be identified unmistakeably as the early stages of the S_N1 reaction.

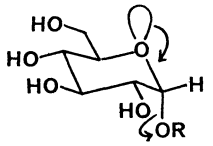
INTRODUCTION

A fundamental problem for the mechanistic chemist is understanding how bonds are made and broken. Conventional mechanism studies can delineate pathways for particular reactions, and in favourable cases can provide qualitative descriptions of rate determining transition states. But the information available from kinetic investigations is by its nature limited to such accessible maxima on reaction coordinates: the ultimate objective being the description of transition states in as much detail as is possible for ground states and products (ref. 1).

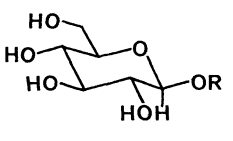
We now know that valuable, complementary, mechanistic information is available in suitable systems from the systematic study of crystal structures. The pioneering work of Dunitz and his group (ref. 2,3) on crystal structure correlations has already had a profound effect on the way we think about reaction pathways: for example, by mapping out a convincing trajectory for the attack of a nucleophile on a carbonyl group (ref. 4). Our own work is concerned primarily with bond-breaking processes, where the length of the bond being broken turns out to be a key parameter.

STEREOELECTRONIC EFFECTS ON BOND LENGTHS IN ACETALS

Our interest in this area developed out of our work on stereoelectronic effects on the reactivity of acetals. The classical crystallographic work of the Phillips group on the structure and mechanism of action of the enzyme lysozyme suggested that the cleavage of the glycosidic bond of the substrate is preceded by a change of conformation, which was proposed to be an integral part of substrate binding (ref. 5). This conclusion became of particular interest with the development of Deslongchamps' theory of stereoelectronic control (ref. 6). Extended to glycosides, this predicts that α-anomers should readily lose their axial leaving groups (OR in 1a) with assistance from the (antiperiplanar) axial lone pair on the ring oxygen. β-Glycosides (1e) like the polysaccharide substrate of lysozyme, and related compounds with equatorial leaving groups, on the other hand, have only ring bonds antiperiplanar to the C-OR bond: as a result C-OR cleavage cannot be assisted by π-donation from the lone pairs of the ring oxygen, unless there is first a change of conformation (ref. 7,8).



1a

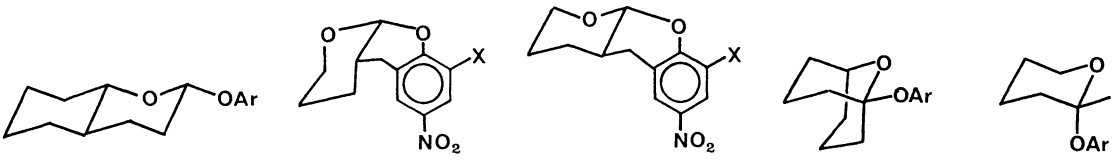


1e

We looked for evidence of this predicted difference in reactivity of axial and equatorial anomers by studying the rates of hydrolytic cleavage of aryl tetrahydropyranyl acetals (2a). These compounds prefer the axial conformation, for stereoelectronic reasons (the anomeric effect); (ref. 9) so equatorial isomers (2e) are available for comparison only in systems where the chair conformation cannot invert.

2e 2a

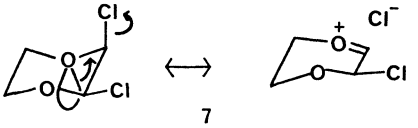
This work has been reviewed (ref. 10). Our conclusion was that there is indeed a substantial stereoelectronic barrier to the cleavage of the C-OR (C-OAr) bond of compounds (2e) with leaving groups in the equatorial conformation, but that this affects observed reactivity only when the conformation is rather firmly fixed. Given enough conformational flexibility (e.g. 3e) reaction can occur through non-ground-state conformations. But systems with the conformation at the acetal centre fixed, for example by a trans-ring junction (e.g. 4e) are substantially less reactive than the corresponding axial anomers (4a). And in the extreme case (5e) where π-donation from the ring oxygen is geometrically impossible even in the oxocarbonium ion produced, the difference in reactivity, this time compared with an analogue (6a) rather than an anomer, is enormous.



3e 4a 4e 5e 6a

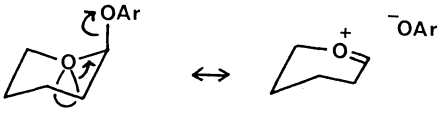
As part of this work we carried out crystal structure determinations (ref. 11) of a number of our compounds, which allowed us to confirm that they do in fact exist in the predicted conformations. But we were stuck by a remarkable, and apparently systematic, variation in the pattern of bond lengths at the acetal centre. For many years a standard 1.43Å was accepted as the length of the C-O single bond, (ref. 12) though the wide availability of accurate structural data had shown that small differences from this mean value are not unusual. In a series of acetals (2a, 3a, 4a) having in common the aryl tetrahydropyranyl structure (2a), but with varying leaving groups OAr, we observed a well-defined dependence of the exocyclic C-O bond length x (2a) on the leaving group. For more electron-deficient Ar, and thus better leaving groups ArO^-, this bond was substantially lengthened, and the endocyclic C-O bond (n) at the acetal centre shortened. Over the full range of structures now available x varies by almost one tenth of an Ängstrom unit (ref. 13).

Qualitatively this effect is similar to the bond length differences observed many years ago by Altona (ref. 14) for 2,3 and 2,5-dichloro-1,4-dioxanes, where axial C-Cl bonds are substantially longer than equatorial. Altona's explanation was in terms of a stabilising n-σ^* interaction (7) between the lone pair electrons of the ring oxygen and the antibonding orbital



7

of the C-Cl bond. A similar ($n\text{-}\sigma^*_{C\text{-}O}$) interaction (8), stronger for more electronegative OAr groups because the $\sigma^*_{C\text{-}OAr}$ energy level is lower, can also account for our observations.



8

Now this is the same interaction that leads to C-O cleavage in these compounds. Alkyl aryl acetals like (2-4a) are cleaved spontaneously in polar solvents, with loss of ArO^- when this is a good enough leaving group, and the free energy of activation for this reaction is linearly related to the basicity of ArO^-, as measured by the pKa of its conjugate acid ArOH.

There is thus a basis for a relationship between the C-OAr bond length - a simple structural parameter - and the rate at which it is broken in solution - the simplest measure of reactivity. And when we investigated possible forms of such a bond length-reactivity correlation we found that the simplest possible relationship applies: the free energy of hydrolysis (or log k_{hyd}) is a linear function of the pKa of ArOH (Figure 1) (refs. 8,15) (Note that a similar, though less accurate, correlation applies to the shortening of the endocyclic C-O bond.)

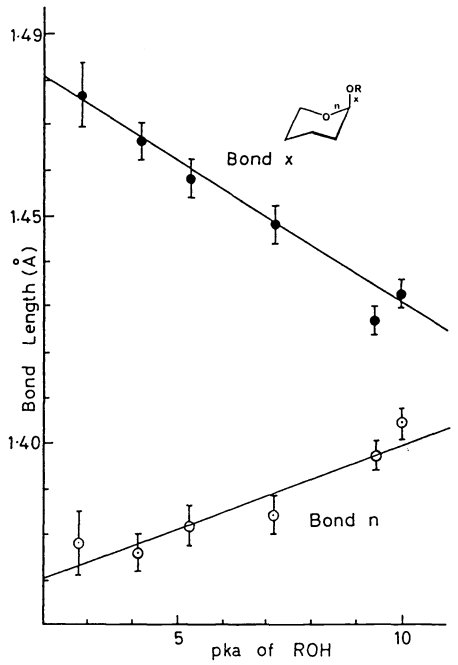


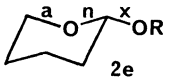
Figure 1. Dependence of C-OX bond lengths at the acetal centre of 2-aryloxytetrahydropyrans on the pK_a of the conjugate acid of the leaving group.

Insofar as the n-σ^*_{C-OAr} interaction is responsible for both observed bond length changes in the ground state and C-OAr cleavage in solution, our series of crystal structures must be 'mapping out' - in Dunitz' terms (ref. 2) - the initial stages of C-OAr bond breaking. In published work (ref. 16) we have attempted to relate the linear relationship shown in Figure 1 quantitatively to the reaction coordinate: since both bond length and reactivity are linear functions of the pKa of ArOH they can be related also to each other, and the slope of the resulting correlation calculated as 260 kcal mol^{-1} $Å^{-1}$. Here I concentrate on qualitative aspects, which are of particular interest to the organic chemist.

THE VARIABLE OXYGEN PROBE

The quantitative analysis indicates that we are not dealing with just the very early stages of reaction. In energy terms the set of compounds for which structures are available covers more than 60% of the free energy of activation for the cleavage of an alkyl tetrahydropyranyl acetal.[16] So in principle we are able to follow structural changes in detail over the greater part of the reaction, by analysing crystal structures of a series of compounds which differ only in the effectiveness of the leaving group. In the axial series based on 1a this is not especially illuminating: the only major changes in geometry over the full range of compounds being the changes in bond length summarised in Figure 1. Only for the two most reactive compounds do we observe the first stages of the flattening at the acetal centre that must be part of the C-O cleavage reaction. This is nevertheless exactly the sort of information we are interested in. And in other systems the variable oxygen probe - a series of OX substituents of varying leaving group capability - elicits much more substantial changes in geometry.

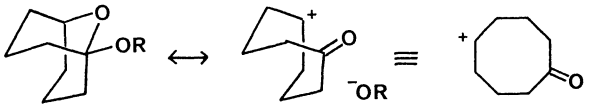
TABLE 1. Bond lengths around the acetal centre of equatorial aryl tetrahydropyranyl acetals

Compound		Bond length a	Bond length n	Bond length x
 2e	2e[a]	1.418	1.419	1.392(4)
	3e[b]	1.437	1.411	1.415(3)
	3e[c]	1.448	1.412	1.424(4)
	5e[d]	1.449	1.411	1.448(5)
	5e[e]	1.447	1.416	1.468(3)
	5e[f]	1.463	1.411	1.457(2)
	5e[g]	1.458	1.403	1.478(3)

[a]R=N-phthalimidomethyl. [b]R=phenyl.
[c]R=4-nitrophenyl. [d]R=2,4-dinitrophenyl.
[e]R=3,5-dinitrobenzoyl
[f]R=diphenylphosphonyl (mean values for two molecules of asymmetric unit).
[g]R=methanesulphonyl. Data from P.G. Jones and A.J. Kirby, J. Chem. Soc., Chem. Commun., 1982, 1365.

The first of these was the equatorial acetal series (2-5e). Here the exocyclic C-OR bond length is less sensitive to the nature of R than in the axial series, but because the bicyclic compounds 5e are so stable it is possible to use a much wider range of leaving group. The sensitivity translates into a slope of 400 kcal mol^{-1} $Å^{-1}$ for the reactivity -bond length correlation - it requires more energy to stretch the equatorial exocyclic C-O bond by a given amount - as expected if the strong n-σ^*_{C-OR} interaction is 'turned off' by the unfavourable geometry of these systems. But over the full set of compounds there is still a substantial variation in the length of the C-OR bond. The source of this bond-lengthening for better leaving groups is revealed by the pattern of bond lengths around the acetal centre shown in Table 1. This shows that the lengthening of the C-OR bond is accompanied not only by the expected shortening of the endocyclic C-O bond n, but also by a systematic lengthening of the remote C-O bond a.

We interpret this evidence in terms of an incipient fragmentation reaction (9), in which the dominant frontier orbital intermaction is between σ^*_{C-OR} and the σ-bonding orbital of the remote C-O bond (a). This σ-σ^*_{C-O} interaction is favoured by the antiperiplanar relationship of the orbitals involved, as is the n-σ^*_{C-O} interaction in the axial series; but it is weaker, explaining the reduced sensitivity of bond length to leaving group, because the σ-bonding orbital is a weaker donor that the non-bonding electron pair of the ring oxygen. This analysis is supported by the observation that



9 10

compounds 5e with very good leaving groups do in fact undergo fragmentation reactions in solution, giving rise to products derived from the cation 10. This result is of particular interest in the context of stereoelectronic effects on acetal reactivity. Not only does it confirm that it is harder to stretch the C-O bond of an equatorial tetrahydropyranyl acetal: it indicates also that when the equatorial bond does begin to stretch in the direction of reaction, it is in fact a different reaction - fragmentation rather than simple acetal cleavage.

We have explored the use of the variable oxygen probe in some 15 systems so far, and find bond length changes of the sort described in all of them, for N-O and P-O as well as C-O bonds. The sensitivity bond length to the probe appears itself to vary systematically with the reactivity of the system. For aryl α-glycosides (11), for example, which are over 10^6 times less reactive than the corresponding tetrahydropyranyl acetals, the COAr bond length varies very little, (ref. 13) while for methoxymethyl derivatives $MeOCH_2OAr$, which are of intermediate reactivity, the observed C-OAr bond length shows an intermediate sensitivity to variation in the leaving group also (ref. 17). So both the length of the bond, and how easy it is to stretch it, show a correlation with its ease of cleavage.

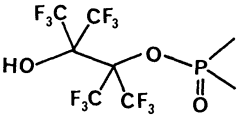
Most of our recent results involve the C-O bond, so I shall discuss C-O bond lengths first in general terms.

THE VARIABLE LENGTH OF THE C—O BOND

To set our results in context, we need to be able to define 'standard' bond lengths of some sort. We therefore searched the Cambridge Structural Database for compounds with C-O bonds, which we devided into categories as follows. Since we knew that bond length is likely to depend on leaving group in systems C-OX we defined broad classes of aliphatic (X=R) and aromatic (X=Ar) ethers, esters (X=COR) and esters of strong acids (X=P,S-oxyacid derivative). Furthermore, since we had explained the acetal results in terms of incipient heterolysis of R-OX ($\leftrightarrow R^+ \ ^-OX$) we had reason to expect bond length to depend also on the multiplicity at the carbon centre of R. The groups R were therefore separated into methyl, primary, secondary and tertiary alkyl centres, and compounds with electronegative atoms in the side-chains were also screened out. The best data available for these categories gave the results summarised in Table 2 (for 2,367 ethers and esters. There were too few data for sulphonates, phosphates etc. to justify their inclusion) (ref. 15).

TABLE 2. Mean Bond Lengths in Ethers and Esters R_1OR (Ref. 15)

R_1-	Ethers -OR	Ethers -OAr	Esters -OAcyl
CH_3	1.418(2)	1.424(1)	1.450(1)
$C-CH_2$	1.426(2)	1.437(3)	1.452(2)
C_2CH	1.432(2)	1.444(6)	1.460(2)
$C-C_2C$	1.450(2)	1.478(4)	1.475(2)



11 C-O 1.397 Å

These data confirm that the C-O bond is longer not only when the 'leaving group' is less basic, but also when the carbon atom of group R_1 can better accommodate a positive charge. The possibility that this latter effect is primarily steric, since it is greatest for tertiary alkyl groups R_1, can be ruled out: the introduction of strongly electron withdrawing CF_3 groups in 11, which does not significantly alter the steric situation, reverses the effect of the very good (phosphinate) leaving group, so that the C-O bond is actually one of the shortest we have encountered.

MAPPING THE REACTION PATHWAY FOR REACTIONS TRIGGERED BY C—O HETEROLYSIS

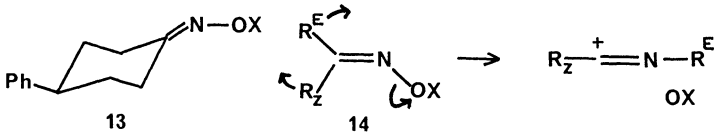
We are now confident that the C-O bond length varies in response to electronic effects. The contribution to the structure of the ground state from the ionic valence tautomer (12) is increased by factors which stabilise R^+ and OX^-, so we can in

$$R - OX \longleftrightarrow R^+ \ ^-OX$$

(12)

principle follow the development of partial positive charge on R by systematic application of the variable oxygen probe OX. We also have an indication that - at least in energy terms - we may expect to observe substantial progress in the direction of C-OX cleavage before molecules become too reactive to crystallise. We are therefore looking at a number of important reactions which involve carbonium ion intermediates - rearrangements, fragmentations and simple S_N1 reactions - in the expectation that in suitable systems we will be able to observe systematic changes in the group R as it accomodates the increasing positive charge induced by the variable oxygen probe OX.

So far we have observed systematic but small changes in a series of oximes (13), which undergo the Beckmann rearrangement when ^-OX is a good enough leaving group.



13 14

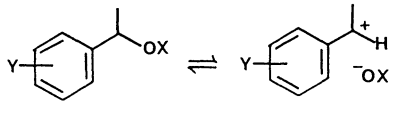
The N-O bond is very sensitive to the nature of X, lengthening from 1.429 to 1.502Å as X is changed from alkyl to arenesulphonyl, and both E and Z groups move (14) in the direction required for reaction (ref. 18). In systems where C-OX cleavage is involved

we have not so far - apart from the acetal system (5e) discussed above - observed dramatic changes consistent with incipient rearrangement or fragmentation processes (ref. 19) This says something about the timing of the various stages of such processes, since we can always see the C-OX bond stretching, but is so far essentially negative evidence.

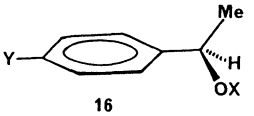
Our most illuminating recent results concern the details of the C-OX cleavage process itself, in a classical S_N1 reaction.

CRYSTAL STRUCTURE-REACTIVITY CORRELATIONS FOR 1-ARYLETHANOL DERIVATIVES

So far we have concentrated on the effects of varying the leaving group, in some 14 systems. But our developing picture of the ground state in compounds R-OX suggested that a systematic examination of the effects of R was also important. Searches of the Cambridge Structural Database (ref. 20) are normally useful only to address very general questions of this sort. For example, when we decided we should look at the behaviour of 1-arylethyl systems (15), where it is possible to vary both R and OX independently in a classical S_N1 system, we found no useful information in the database.



15



16

As for a classical physical-organic investigation we hoped to look at 'about four' substituents Y, to allow us to look for Hammett-type correlations for series with constant OX; and about four different leaving groups OX, thus in principle sixteen compounds. Unlike most physical-organic investigations, however, making the compounds is not enough: we have to produce them as single crystals of good quality, and in our experience the chances - given a solid compound - are generally about 2:1 against. Of our 16 first-choice compounds (15) we have measured crystal structures for 8, and we increased this number to 11 by minor compromises (ref. 21).

The first results showed the expected behaviour. The C-OX bond length increases, as expected, for better leaving groups ^-OX, and this increase is inhibited by electron withdrawing substituents Y. We eventually accumulated enough data to do 'Hammett' plots for two series, of four esters and three (triphenylmethyl) ethers (Figure 2). The sensitivity (slope) is higher for the more reactive esters, and the correlations are typical (r 0.993, 0.931) for Hammett plots with small numbers of points.

However, when we plot the bond length data for compounds with constant aromatic substituent Y (H, NO_2) against the pK_a of HOX - the procedure which has given us good linear correlations for some 14 other systems - the plots are very obviously not linear (Figure 3). Evidently something is different about the 1-arylethyl system 15: it turns out that difference is simply its conformational flexibility.

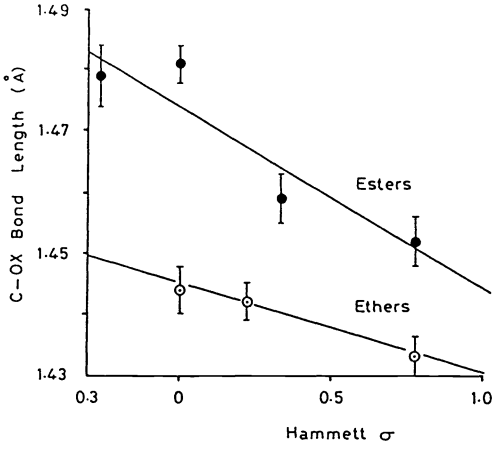


Figure 2. 'Hammett' plot of C-O bond length against for 1-arylethyl esters (X=COR) and ethers (X=R).

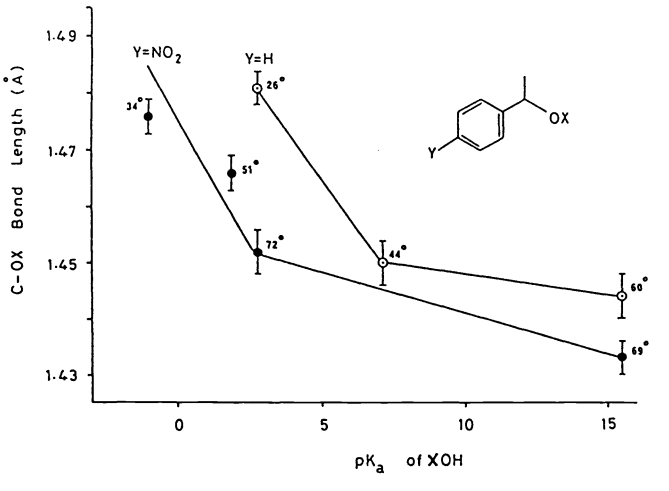
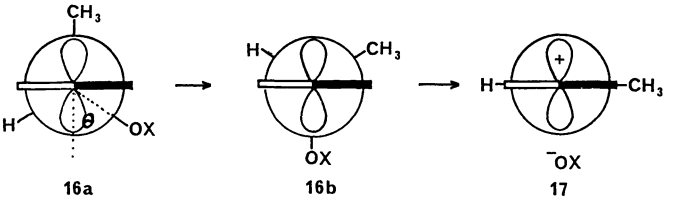


Figure 3. Dependence of C-OX bond length on the leaving group for 1-arylethyl derivatives. The conformation changes with the leaving group, as shown by the dihedral angles (θ, see formula 16) quoted for each point.

It happens that all the systems we had examined previously were conformationally homogeneous, either because the conformations were fixed for some geometrical or stereoelectronic reason, or because the data were averaged over a large number of structures, and thus conformations also. In the 1-arylethyl system (15) there is free rotation about the ring - C_α bond, and our 11 compounds do in fact crystallise in a range of conformations. The majority of compounds have the C-Me bond perpendicular to the plane of the ring (16), as expected on steric grounds (CH_3 is generally effectively larger than OX).



16a 16b 17

C-OX cleavage, on the other hand, clearly requires π-σ^*_{C-OX} overlap, to take advantage in the transition state of delocalisation of the developing positive charge onto the ring. So, not only must the C-OX bond lengthen; the conformation must also change in the direction 16a → 16b. Both these changes are apparent in the crystal structures.

Each point in Figure 3 is labelled with the magnitude of the dihedral angle (θ), between the C-OX bond and the π-orbital or the adjacent ring carbon, which controls π-σ^*_{C-OX} overlap. This dihedral angle is smaller for electron-donating groups Y or better leaving groups $^-$OX, and thus for longer C-OX bonds. The effect is clearly systematic, as shown by the correlation of Figure 4, where θ is plotted against C-OX bond length, and is large enough to account for the non-linearity of the plots shown in Figure 3.

This conformational dependence means that we cannot relate reactivity towards C-OX cleavage and bond length by a simple two-parameter equation based on Hammett's σ and the pK_a of HOX, but must include also the appropriate function ($\cos^2\theta$), of the dihedral angle controlling orbital overlap. Multiple linear regression of the bond length C-OX on all three variables indicates that the direct dependence on the aromatic substituent Y is negligible, and all expressed through its effect on θ.

Thus as the C-OX bond stretches in compounds 15, the conformation (16) adjusts in the direction expected to stabilise developing positive charge at C_α, which means also towards the conformation of the transition state. The other major geometrical difference between ground and transition states in an S_N1 reaction is that C_α changes from sp^3 to sp^2 hybridisation, and substantial changes in this direction are also apparent over our series of compounds. In Figure 5 the Ar-C-Me angle is plotted against the C-OX bond length: once again we see a systematic change from below the tetrahedral angle for the least reactive compound, with the shortest C-OX bond, to almost 116° for the most reactive, with the longest. In terms of this geometry change we are once more able to map out over 60% of the reaction coordinate for the cleavage of the C-OX bond of an alkyl ether (15, X=alkyl).

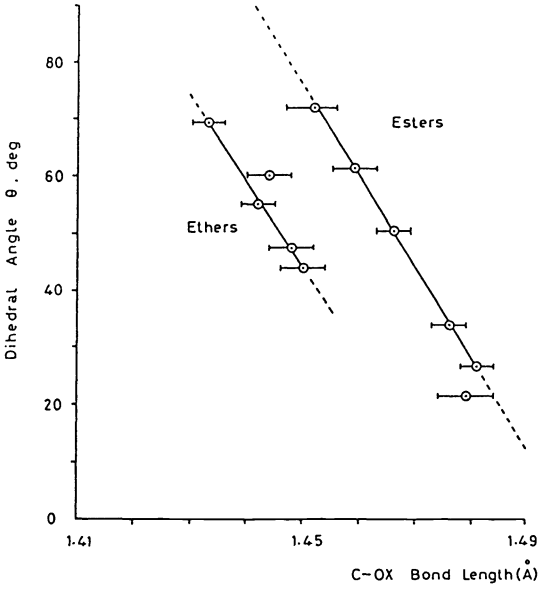


Figure 4. Correlations between C-OX bond length and interorbital angle θ (see formula **16**) for 1-arylethyl derivatives.

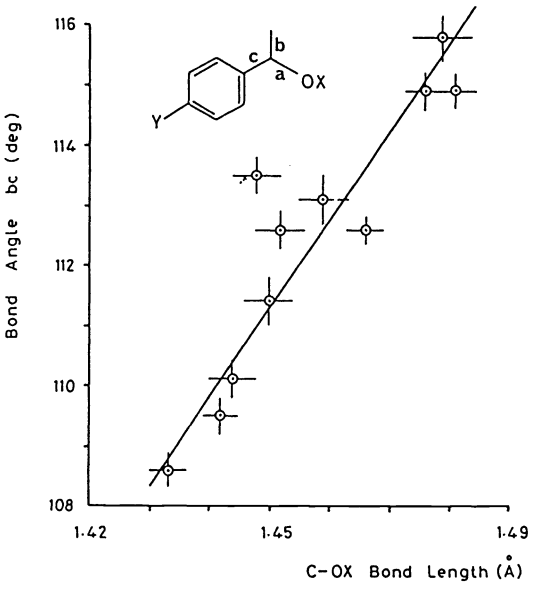


Figure 5. Changes in hybridisation at the benzylic centre associated with increasing C-OX bond length.

CONCLUSIONS

The systematic study of crystal structure correlations can give us access to a vast amount of information, not only about what happens when a bond begins to break, but also about conformational preferences. One great advantage of using crystal structures is that we know precisely the conformations of the systems we are discussing, so stereoelectronic factors can be confidently assessed. The correlations arising in our work on arylethyl systems, together with results from other laboratories (see, for example, references 22 and 23) show that reliable conformational trends can also be observed, and that random packing forces are often not a problem, at least if strongly polar and hydrogen-bonding groups are avoided. And in suitable systems we can see, clearly and unmistakeably, the early stages of the reaction process.

Acknowledgements

This work has relied on the expertise of my coworkers named in the references, and especially that of my colleague, Dr P.G. Jones of Göttingen, who is responsible for all the crystallographic work. We are grateful for support to the Science and Engineering Research Council of Great Britiain, and the Fonds der Chemischen Industrie.

REFERENCES

1. E.S. Lewis in A. Weissberger, ed., "Technique of Organic Chemistry", vol VIII Part I. Interscience, New York, 1961, Chapter 1.
2. J.D. Dunitz, "X-Ray Analysis and the Structure of Organic Molecules", Cornell University, Press, Ithaca, N.Y., 1979.
3. H.-B. Bürgi and J.D. Dunitz, Accts. Chem. Res., **16**, 153 (1983).
4. H.B. Bürgi, J.D. Dunitz and E. Sheffer, J. Am. Chem. Soc., **95**, 5065 (1973).
5. T. Imoto, L.N. Johnson, A.C.T. North, D.C. Phillips and J.A. Rupley in "The Enzymes", ed. P.D. Boyer; Academic Press, New York, 1972, Vol. VII, p.665.
6. P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry', Pergamon Press, Oxford, 1983; Tetrahedron, **31**, 2463 (1975).
7. D.G. Gorenstein, J.B. Findlay, B.A. Luxon and D. Kar, J. Am. Chem. Soc., **99**, 3473 (1977).
8. A.J. Kirby and R.J. Martin, J. Chem. Soc., Chem. Commun., 1978, 172.
9. A.J. Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag, Heidelberg - Berlin - New York, 1983.
10. A.J. Kirby, Accts. Chem. Res., **17**, 305 (1984).
11. 'We' means Dr P.G. Jones, Anorganisch-Chemisches Institut der Universität, Tammannstrasse 4, Göttingen.
12. L.E. Sutton, ed., "Tables of Interatomic Distances and Configuration in Molecules and Ions", The Chemical Society, London, 1965; Special Publication No. 18.
13. A.J. Briggs, R. Glenn, P.G. Jones, A.J. Kirby and R. Ramaswamy, J. Am. Chem. Soc., **106**, 6200 (1984).
14. C. Altona and C. Romers, Acta. Cryst., **16**, 1225 (1963); C. Romers, C. Altona, H.R. Buys and E. Havinga, Top. Stereochem., **4**, 39 (1967).
15. F.H. Allen and A.J. Kirby, J. Am. Chem. Soc., **106**, 6197 (1984).
16. P.G. Jones and A.J. Kirby, J. Am. Chem. Soc., **106**, 6207 (1984).
17. P.G. Jones and A.J. Kirby, J. Chem. Soc., Chem. Commun., 1986, 444.
18. M.R. Edwards, P.G. Jones and A.J. Kirby, Acta. Cryst. C, in press.
19. Unpublished work with M.R. Edwards.
20. F.H. Allen, O. Kennard and R. Taylor, Accts. Chem. Res., **16**, 146 (1983).
21. M.R. Edwards, P.G. Jones and A.J. Kirby, J. Am. Chem. Soc., submitted.
22. L.I. Kruse, C.W. DeBrosse and C.H. Kruse, J. Am. Chem. Soc., **107**, 5435 (1985).
23. C. Rüchardt and H.D. Beckhaus, Angew. Chem. Internat. Ed. Engl., **24**, 329 (1985).