and anemia. Although there are known dietary correlations, such as Fe deficiency with anemia or Zn deficiency with growth and maturation retardation, there have been no thorough studies on archaeological populations with appropriate controls to relate pathological conditions with elements other than Pb.

Conclusions and Prospectus

Sufficient data have now been accumulated to warrant the conclusion that inorganic analysis of archaeological bone provides a valid but crude measure of the ancient diet and of pathological conditions, provided that a certain protocol is followed. Skeletons must be in good condition and fully characterized according to sex, age, and, if available, status. Normally, individuals under the age of 12 should be excluded or analyzed as a distinct subgroup. For information about adult diet, tooth samples should be avoided. A given study should be limited to use of a single skeletal component, since elemental levels vary over the skeleton. Although most bones are acceptable, the cortical bones, such as the femur, are least sensitive to diagenetic effects. Samples should be ashed to remove organic material and water and to provide a common basis for comparison of analyses.

The number of samples should be large, because variance is large, on account of natural variation of elemental levels within a single bone, with the age of the individual at death, with pathological conditions, with the maternity history of females, and with other nondietary factors such as burial practices. As a possible guideline, no subgroup should have fewer than about a dozen members, so that its mean can be compared reliably with that of others. Comparison of single individuals or of statistically small groups should be avoided. It is important to obtain some information on the diagenetic status of the bone sample. Finally, as large an array of elements as possible is needed in order to have several handles on the ancient data. The elements Sr, Zn, Na, and Ca have proved to be most useful and least sensitive to diagenesis.

When studied in this manner, elemental levels can provide useful information on dietary differences between subgroups of a single culture, based for example on sex or status, or between temporally separated cultures that inhabited a single locale. Internal differences in turn may be compared on a more general basis between more distant cultures. Future studies should include a multielement comparison of juvenile and adult diet by parallel analysis of tooth enamel and cortical bone in the same population. Questions about acquired and inherited status might be answered. Multielement analysis of skeletons with observed pathologies, based on physical examination, should be useful in assessing diet-based and other health factors in ancient populations, provided statistically significant samples can be obtained.

As of the moment, the Sr–Zn two-dimensional plot offers the closest approach we have to pattern analysis. Na may provide a third dimension. Two additional advances must be made in order to achieve a better definition of the ancient diet. (1) More elements must be found that are free of diagenetic effects and have a proved dependence on diet. (2) The relationship between specific elements (Sr, Zn, Na, etc.) and specific components of the diet (leafy vegetables, nuts, meat, etc.) must be established through the use of laboratory animals. More sophisticated clustering procedures then could be used, based on the multidimensional data set of several elemental concentrations, to define more accurately the multidimensional diet of ancient populations.

Bone analysis at Northwestern has been supported by the Society of Sigma Xi and by the Northwestern University Research Committee. We also express appreciation to the small but extremely cooperative community of archaeological chemists in the United States.

Stereoelectronic Effects on Acetal Hydrolysis

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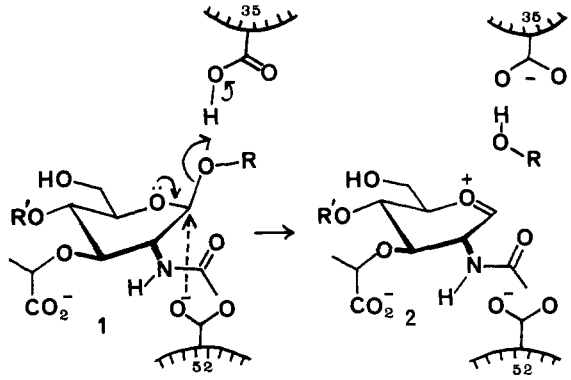
This work has its origins in the pioneering X-ray structural studies of Phillips and his co-workers on the enzyme lysozyme,[1,2] as seen in the light of the stereoelectronic theory of Deslongchamps.[3,4] From the protein crystallography emerged a uniquely detailed picture of an enzyme–substrate interaction, which has inspired a generation of mechanistic studies on acetals.[5] The stereoelectronic theory has made chemists think explicitly about the way nonbonding (lone-pair) electrons can control reactivity. I describe in this *Account* some evidence that the remarkable way lysozyme binds its substrate can be explained as a predictable response to stereoelectronic factors, which control acetal hydrolysis

A. Kirby took both B.A. and Ph.D. degrees at Cambridge, with V. M. Clark and then went on to spend a postdoctoral year with W. P. Jencks at Brandeis, where he learned the value of a systematic approach to the problems of bioorganic mechanisms in which he has alays been interested. Since 1964 he has been on the staff at Cambridge, developing major research programs in organophosphorus chemistry, intramolecular catalysis, stereoelectronic effects, and most recently, crystal structure–reactivity correlations.

(1) Imoto, T.; Johnson, L. N.; North, A. C. T.; Phillips, D. C.; Rupley, J. A. In "The Enzymes"; Boyer, P. D., Ed.; Academic Press: New York, 1972; Vol. VII, p 665.
(2) Ford, L. D.; Johnson, L. N.; Machin, P. A.; Phillips, D. C.; Tjian, R. *J. Mol. Biol.* **1974**, *88*, 349.
(3) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1983; *Tetrahedron* **1975**, *31*, 2463.
(4) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Heidelberg–Berlin–New York, 1983.
(5) Dunn, B. M.; Bruice, T. C. *Adv. Enzymol.* **1973**, *37*, 1.

0001-4842/84/0117-0305$01.50/0

Scheme I



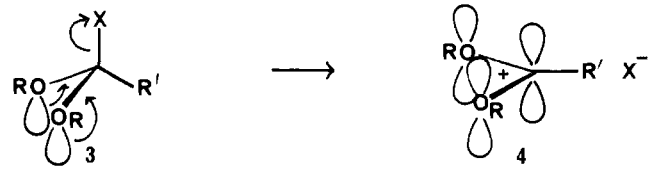
in much the same way that related factors control reactivity in the E2 reaction.

Lysozyme and the Theory of Stereoelectronic Control

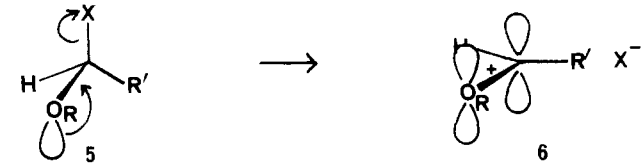
Lysozyme[1] catalyzes the hydrolysis of a polysaccharide constituent of bacterial cell walls, cleaving a β-glycosidic linkage with retention of configuration. The crystallographic results, supported by binding studies, allowed the construction of a model for the enzyme–substrate complex in sufficient detail to identify two side-chain carboxyls (glutamic acid-35 and aspartate-52) as the likely active-site catalytic groups, and an extended binding-site cleft capable of accomodating up to six residues of substrate polysaccharide, as long as one of them—the fourth from the nonreducing end—is twisted into a half-chair (or sofa[2]) conformation. This is significant, since the enzyme catalyzes the cleavage of the glycosidic bond of precisely this sugar residue.

A likely mechanism for the key C–O cleavage step is outlined in Scheme I. Glutamic acid-35 is thought to act as a general acid,[6] protonating the OR group as it leaves. The role of aspartate-52 is apparently to stabilize the developing oxocarbonium ion, though whether it does this purely electrostatically[7] or by acting as a nucleophile (dashed arrow in Scheme I)—thus introducing a glycosyl enzyme intermediate on the reaction pathway[8]—is not firmly established. But *in either case*[9] the primary driving force for C–O cleavage is electron donation from the ring oxygen atom, which thus accomodates most of the positive charge which would otherwise develop at the anomeric carbon.

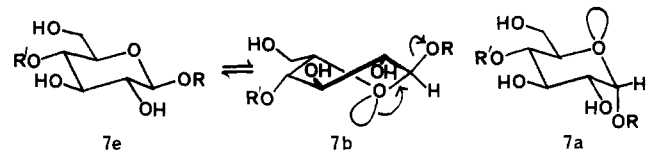
This ability of oxygen to donate its nonbonding electrons is also the key to the reactivity of ortho esters and related compounds. The theory of stereoelectronic control[3,10] proposes that such reactions are favored for conformations in which nonbonding (lone-pair) electrons on both remaining oxygen atoms lie antiperiplanar to the bond to the leaving group (X). n–σ^*_{C-X} overlap[4] with the antibonding orbital of the C–X bond is thus maximized, and the orbitals of the starting material transmuted into those of the product cation 4 with minimal structural reorganization.



The oxo carbonium ion **6** formed by the corresponding reaction of an acetal (**5**, X = OR′) is more dependent on the stabilization it receives from the single oxygen donor, so the transition state for the cleavage of an acetal should depend at least as heavily on the donor capability of the remaining oxygen atom—including the orientation of the lone pairs. So, if the Deslongchamps theory is correct, the preferred model of cleavage of an acetal or related compound will involve a conformation (**5**) in which a lone pair on the single remaining oxygen atom is antiperiplanar to the C–X bond.



This conclusion has important implications for the mechanism of action of lysozyme, or indeed of any β-glycosidase. In the ground state of a β-glycopyranoside (such as **7e**) the aglycone (OR) occupies an equatorial



position, antiperiplanar only to ring bonds, so that C–OR cleavage is predicted to be stereoelectronically unfavorable. If the stereoelectronic barrier is large enough, therefore, reaction must occur by way of some non-ground-state conformation—such as the boat (**7b**) or sofa form—in which a lone pair on the ring oxygen can be antiperiplanar to the C–OR bond.[11]

It is a reasonable assumption that enzymes do not achieve their characteristic very high rates of bond making and breaking without mobilizing *all* the factors favoring reaction—including stereoelectronic factors. So, if the relevant stereoelectronic barrier is large enough, enzyme-catalyzed cleavage of a β-glycoside substrate must involve a non-ground-state substrate conformation, *presumably from an early stage in the C–OR cleavage process* (see Conclusions).

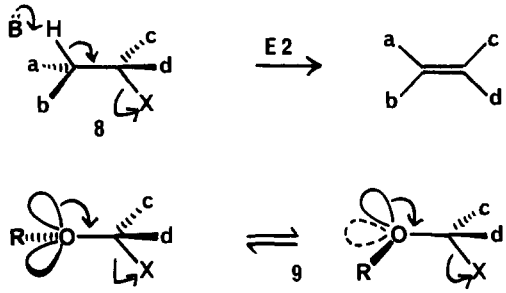
The clear implication is that lysozyme binds its substrate in a non-ground-state conformation for good stereoelectronic reasons.[12] What is needed is experi-

(6) Craze, G.-A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 61.
(7) Warshel, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5250.
(8) Craze, G.-A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 357.
(9) The transition state for the (very rare) S_N2 reaction at an acetal center is "S_N1-like" and involves a substantial build up of positive charge, which is stabilized by electron donation from the "spectator" oxygen.[8]
(10) The theory of stereoelectronic control (TSTC), also known as the antiperiplanar Lone-Pair hypothesis (ALPH), though first clearly enunciated by Deslongchamps, is hinted at in the work of earlier authors: most intriguingly, least clearly, but certainly earliest (1797) in the poem "Kubla Khan", by the English romantic poet Samuel Taylor Coleridge (STC!). Some undistinguished work on opium apart, bioorganic chemistry was not a major preoccupation for Coleridge, but his poem "Glycine's Dream" is still read, and "Kubla Khan" is studded with coded references to the subject of this *Account*. ALPH (*the sacred river*) is mentioned explicitly and arises from *that deep romantic chasm...with ceaseless turmoil seething*—the finest description in all poetry of an active-site cleft. There is even an unmistakeable reference, *caverns measureless to man*, to the problems associated with kinetic measurements in the area.
(11) This is presumably what happens in the acid-catalyzed hydrolysis of β-glucosides (**7e**). In some cases these are hydrolyzed a few times *faster* than the α-anomers (**7a**), which have a lone pair antiperiplanar to the C–OR bond and can therefore react in the stereoelectronically favored mode in the ground-state conformation.

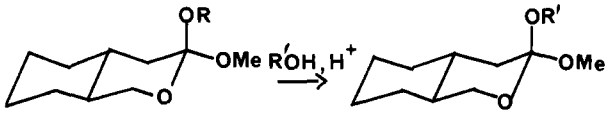
mental evidence that stereoelectronic factors *can* control reactivity in systems like **5** and **7** and, in particular, some idea of the possible magnitude of these factors.

Systems Development

The problem is akin to that of the stereochemistry of elimination by the E2 mechanism, where antiperiplanar geometry (**8**) is known to be preferred, from rate and product studies on a wide variety of compounds.[13] Our initial approach was based on some of this work. Major complications are that the stereochemistry of the initial product of acetal cleavage cannot be observed, because it is a short-lived high-energy species (**6**), and that in an acylic system (**9**) either lone pair of oxygen[14] can act as a donor.



Deslongchamps has had most success with tetrahydropyran derivatives, such as **10**, where product



10

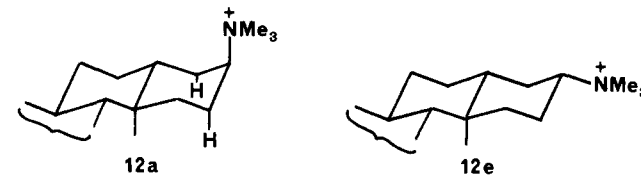
studies can give relative rates of axial, equatorial, and endocyclic C–O cleavage.[3,15] But unambiguous evidence for primary stereoelectronic effects at oxygen is difficult to obtain,[4] and product ratios are in any case notoriously unreliable as a measure of large rate differences. So we set out to measure directly rates of hydrolysis of conformationally locked axial and equatorial tetrahydropyranyl acetals.[16]

Oxadecalin Acetals

We chose to work with electronically unsymmetrical acetals, such as **11**. This has the advantage of eliminating competition from endocyclic C–O cleavage and for good leaving groups (with electron-withdrawing substituents in the aromatic ring) allows us to follow spontaneous C–OAr cleavage, as well as the usual acid-catalyzed reaction. The aryloxy group is also a model for the partially protonated aglycone of a glycoside hydrolyzing with general acid catalysis[17] (Scheme I).

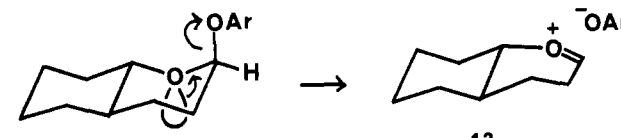
11a 11e

We were naive enough to be surprised that the spontaneous hydrolysis of the axial acetal (**11a**, Ar = 4-nitrophenyl), with a lone pair on the ring oxygen antiperiplanar to the bond to the leaving group (OAr), is actually 3 times *slower* than that of the equatorial isomer (**11e**), which has not.[18] This is in sharp contrast to the evidence for stereoelectronic control in E2 reactions. The Hofmann elimination of trimethylamine from (axial) 3α- and 6β-(trimethylammonio)cholestanes, for example, is much faster than from the corresponding equatorial epimers[19] (compare part structures **12a** and **12e**).



12a 12e

In fact there are at least two good reasons why the spontaneous cleavage of the acetal system is a much less favorable vehicle for demonstrating stereoelectronic effects. Whereas the Hofmann elimination from a system like **12** is expected to be a concerted process, with a fairly "central" transition state (both H–C and C–N bond breaking moderately well advanced),[20] for the spontaneous cleavage of an acetal such as **11a** the transition state is very late, close in energy, and thus presumably in geometry also, to the oxo carbonium ion **13**.[21]



11a 13

The ion pair produced from the equatorial isomer **11e** differs from **13** only in that ArO^- is formed initially on the opposite face of the planar oxo carbonium system, so is of very similar energy. The late transition states leading to the two ion pairs will therefore be of very similar energies also, and the relative rates of cleavage of **11a** and **11e** thus determined almost entirely by their ground-state energies. Since the axial isomer **11a** is more stable (anomeric effect) this can account for its slower rate of spontaneous hydrolysis.

This argument suggests that stereoelectronic effects would be easier to observe if the transition state was

(12) Gorenstein, D. G.; Findlay, J. B.; Luxon, B. A.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 3477. Gorenstein et al. present calculations to support this conclusion as part of a detailed analysis of the problem which also considers the conformation around the C–OR bond.

(13) Saunders, W. H.; Cockerill, A. F. "Mechanisms of Elimination Reactions"; Wiley-Interscience: New York, 1973; pp 105.

(14) We use the organic chemist's usual description in terms of two sp^3-hybrid lone pairs. For a discussion and justification, see ref 4, p 78.

(15) Deslongchamps, P.; Chênevert, R.; Taillefer, R. J.; Moreau, C.; Saunders, J. K. *Can. J. Chem.* **1975**, *53*, 1601. We have recently shown (Briggs, A. J.; Kirby, A. J., so far unpublishable results) that the acid-catalyzed exchange of the axial OMe group of **10** (R = CH_3) for OCD_3 in methanol-d_4 is substantially (perhaps 2 orders of magnitude) faster than that of the equatorial OMe. (See: Desvard, O. E.; Kirby, A. J. *Tetrahedron Lett.* **1982**, 4163.)

(16) Conformationally unrestrained 2-alkoxy- or 2-(aryloxy)tetrahydropyrans generally prefer the conformation with the 2-substituent axial (the anomeric effect[4]).

(17) The pK_a of the conjugate acid of the leaving group, RO(H), changes from about −5 to 16 as the C–OR bond breaks. In the transition state it must lie somewhere between these extremes, perhaps in the range (4–10) of substituted phenols.

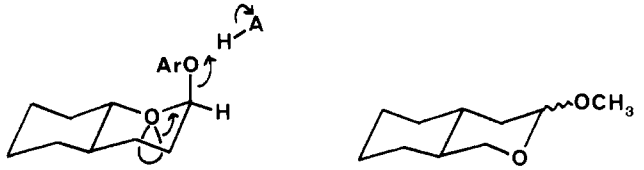
(18) Chandrasekhar, S.; Kirby, A. J.; Martin, R. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1619.

(19) Haworth, R. D.; McKenna, J.; Powell, R. G.; *J. Chem. Soc.* **1953**, 1110.

(20) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937.

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

earlier. This may account for the reversal of the relative rates of hydrolysis of **11a** and **11e** under acid catalysis.[18] The reaction is general acid catalyzed (14), so that

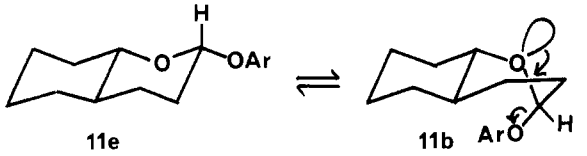


14 $\alpha_{lg} = 0.70$ 15

proton transfer must begin, and the transition state can be reached, with C–OAr cleavage less far advanced than in the transition state for spontaneous hydrolysis.

The stronger the general acid, the earlier the transition state might be expected to be reached, so it is significant that although $k_{HA}^{ax}/k_{HA}^{eq} < 1$ for the weakest general acids, the ratio increases with increasing acidity of HA, and for the H_3O^+-catalyzed reaction the axial isomer is 4 times more reactive. Similarly for the 2-oxodecalin acetals (**15**), the axial isomer is 1.5 times more reactive.[22] However, rate differences as small as this can be explained by any one, or a combination, of the many factors which determine the rates of reactions in solution.

The alternative explanation of the higher reactivity of the equatorial isomer (**11e**) in the spontaneous reaction is that it reacts by way of a non-ground-state conformation. Although one end of the tetrahydropyran ring is locked by the trans ring junction, the free end of the chair can invert, to give the chair–boat (**11b**) and related twist forms, which have a lone pair antiperiplanar to the C–OAr bond.



11e 11b

The picture is conveniently summarized by a qualitative energy profile diagram (Figure 1). The axial isomer (A) reacts in its ground-state conformation, the equatorial isomer (E) by way of the twist-boat form (B) because of the large stereoelectronic barrier ($EC^‡$) to C–OAr cleavage in its ground-state conformation. Note that **11b** is by no means a high-energy conformation, because the difference in energy between chair and flexible forms (5–6 kcal mol^{-1} in cyclohexane and tetrahydropyran[4]) will be significantly reduced by the anomeric effect.[23]

The situation is quite different for quaternary ammonium derivatives like **12e**, which are locked in the chair conformation by the bulky NMe_3^+ group as well as by the trans ring junction, making the chair–twist-boat form of **12e** a genuinely high-energy conformation.[24] In fact clear-cut stereoelectronic preferences in E2 reactions of aliphatic systems are in many cases observed *only* for bulky leaving groups.[25]

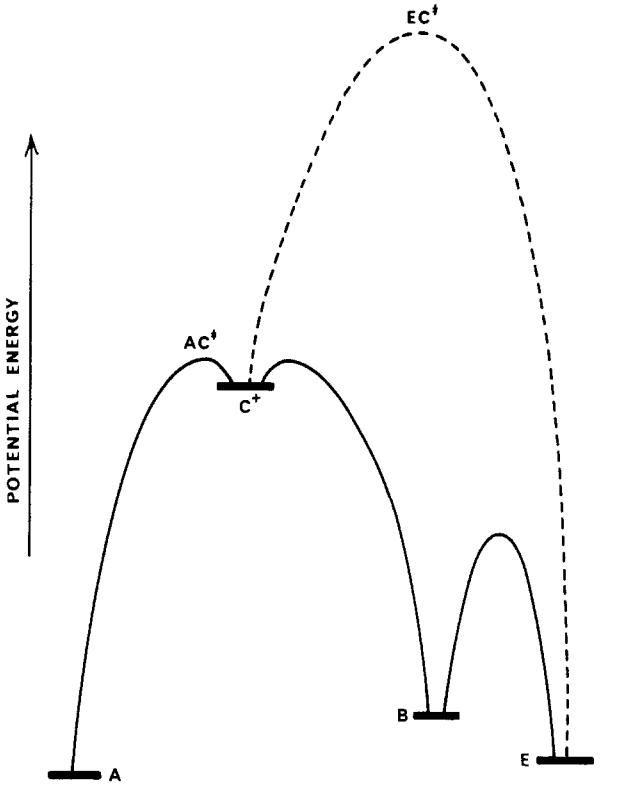
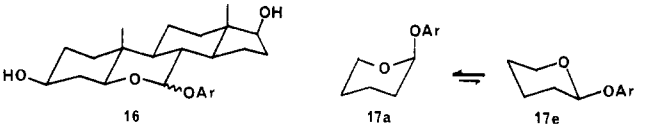


Figure 1. Schematic energy profile diagram for the C–OAr cleavage steps of axial and equatorial (A and E, respectively) isomeric aryl tetrahydropyranyl acetals (e.g., 11). B represents a flexible (twist-boat) conformation of the tetrahydropyranyl ring, $EC^‡$ the (hypothetical) transition state for C–OAr cleavage of E with the system fixed in the ground-state chair conformation.

Toward More Rigid Systems

The inference is clear, that if we want to explore the stereoelectronic barrier $EC^‡$, we must block the bypass route via B, by using a conformationally less flexible system. Our first attempt in this direction involved axial and equatorial acetals derived from the 6-oxasteroid system (**16**).

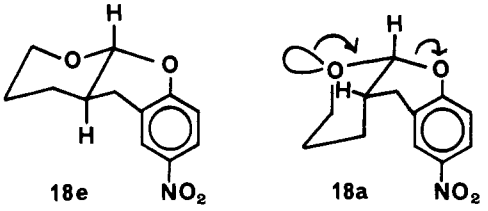


16 17a 17e

These acetals are of special interest because ring B is held in the chair conformation by two trans ring junctions, in the same positions on the tetrahydropyran ring as the four equatorial substituents of a glucoside (e.g., **7e**). Both axial and equatorial derivatives are hydrolyzed 200–300 times more slowly than the parent 2-(aryloxy)tetrahydropyrans (**17a**). This most likely reflects a decrease in torsional flexibility, which makes the transition-state conformation (close to the half-chair in both cases) less readily accessible from **16**.[26] But still the equatorial isomer is a few times more reactive than the axial form.[18]

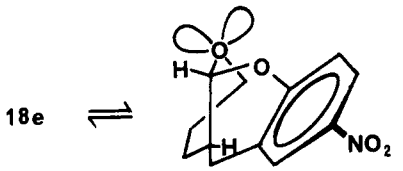
(22) van Eikeren, P. *J. Org. Chem.* **1980**, *45*, 4641.
(23) Gorenstein, D. G.; Powell, R. *J. Am. Chem. Soc.* **1979**, *101*, 4925. Gorenstein and Powell have shown recently that this effect is large enough to make the chair–twist-boat the preferred conformation of a related phosphate ester.
(24) Ortho esters **10** (ref 15) lie between these two extremes, with neither the chair–boat nor the chair–chair conformation specially favored.
(25) Reference 13, pp 121–122.
(26) The same factor may contribute to the enormous (10^6–10^7 fold) difference in reactivity[27] between glycosides **7** and the corresponding tetrahydropyranyl acetals **17**: though the major effect is undoubtedly inductive destabilization of the developing oxo carbonium ion by the four OH groups of the sugar.
(27) Dyer, E.; Claudemans, C. P. J.; Koch, M. J.; Marchessault, R. H. *J. Chem. Soc.* **1962**, 3361. Jones, C. C.; Sinnott, M. L. *J. Chem. Soc., Chem. Commun.* **1977**, 767.

Once again we presume that, even in **16**, ring B retains sufficient conformational mobility to allow C–OAr cleavage with assistance from a lone pair on the ring oxygen. To reduce this residual mobility still further we prepared the tricyclic acetal **18e**, where a trans ring junction *at the acetal center* locks the OAr group equatorial.[28]



18e **18a**

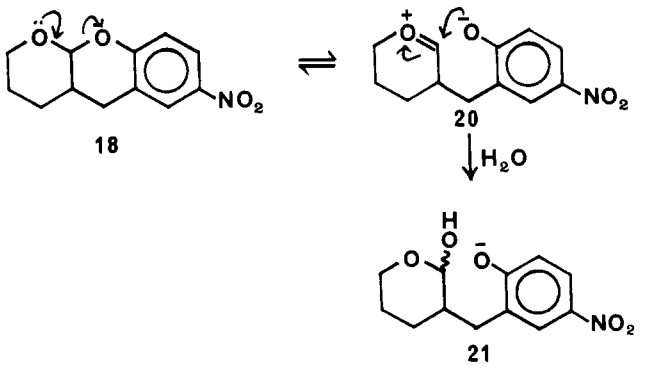
It was clear at once that the extra conformational restraint does result in a dramatic reduction in reactivity. Aryl tetrahydropyranyl acetals are generally reactive compounds, but the spontaneous hydrolysis of **18e** can only be followed at elevated temperatures and is over 10^5 times slower than that of the parent acetal (**17**, Ar = 4-nitrophenyl), extrapolated to 100 °C. It is also slower than that of the axial isomer **18a**: but here the factor is only 2, clearly negligible in terms of a major effect of conformation on reactivity. The explanation seems to be that **18e** and **18a** are unreactive for quite different reasons. We had designed **18e** to be unreactive and presume that it reacts, predictably slowly, by way of some high-energy conformation, perhaps close to **19**,



19

in which a lone pair on the tetrahydropyran ring oxygen can get close to antiperiplanar to the C–OAr bond, only at the expense of severe strain: and that C–O cleavage is rate determining.

18a, on the other hand, represents an unstrained, flexible conformation, and there is no obvious reason why C–OAr cleavage should be significantly slower than in the parent system (**17a**). If it is not, then the rate-determining step cannot be C–O cleavage; it must therefore be the second step of the hydrolysis reaction, the hydration of the oxo carbonium ion **20**. This is



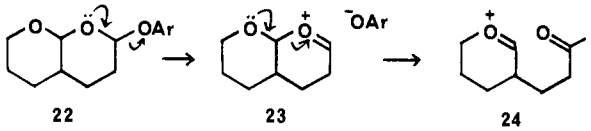
18 **20** **21**

easily rationalized: it requires simply that the nitrophenolate oxygen of **20** add back to the neighboring oxo carbonium center more rapidly than it is hydrated by solvent water. Consistent with this interpretation, the hydrolysis of **18a**—but not that of **18e**—shows a significant solvent deuterium isotope effect, k_{H_2O}/k_{D_2O} = 1.74 at 100 °C.[18]

Thus we believe that the equatorial compound (**18a**) is indeed unreactive because of the predicted stereoelectronic barrier to the cleavage of an equatorial C–O bond. The axial isomer is hydrolyzed only twice as fast because of the change in rate-determining step caused by the rapid internal return of **20** to **18a**. It might be expected that this internal return could be suppressed by protonation of the phenolate oxygen, and under acidic conditions a bigger rate difference is indeed observed, **18a** disappearing 300 times more rapidly than **18e** in 0.1 M HCl.[28] However, the reaction of **18a** does not go to completion under these conditions, but gives a 4:1 mixture of starting material and hemiacetal product **21**. The hydrolysis of **18e** gives the same mixture and is thus effectively irreversible, so that the ratio of *rate constants* for hydrolysis, k_H^{ax}/k_H^{eq}, is only 60.

Stereoelectronic Control by Remote Oxygen

These—and other[28]—results with the bicyclic system **18** can thus be explained in terms of normal acetal reactivity, if there is an additional barrier (of 4–7 kcal mol^{-1}) to C–O cleavage of the equatorial isomer (**18e**), with the trans ring junction. But the interpretation is complicated by the change in rate-determining step for the spontaneous reaction of **18a**, which conceals the major difference in the rates of C–O cleavage, and by the fact that under most conditions reaction does not go to completion. Both problems arise because the leaving group of **18** does not leave, but remains attached to the oxo carbonium ion **20** produced. Both can be solved by the further refinement of this type of system shown in **22**.



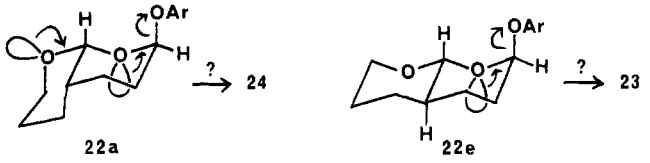
22 **23** **24**

These compounds combine the key features of a trans ring junction at the acetal center and a leaving group which leaves irreversibly, but at different acetal centers. Our reasoning was as follows.[29] The loss of ArO^- from **22** would generate cation **23**, by way of the usual late transition state, close to **23**. Now **23** is the cyclization product of aldehyde **24**, and an aldehyde oxygen is a far better leaving group than ArO^-—so good, in fact, that **23** is expected to be too unstable to exist for a significant length of time.[29] Thus cleavage of the second C–O bond, at the bridgehead acetal center, should begin before C–OAr cleavage is complete and hence, most likely, before the (late) transition state for C–OAr cleavage is reached. The rate of C–OAr cleavage is therefore expected to depend on the electron donor capability of the remote oxygen atom of ring A, which, in turn, we expect to depend on the geometry at the ring junction.

(28) Kirby, A. J.; Martin, R. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1627.

(29) Kirby, A. J.; Martin, R. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1633.

Compounds **22a** and **22e**, with the oxygen atom of ring B axial and equatorial, respectively, to ring A (but both having the leaving group, OAr = 4-(nitrophenoxy), axial) do show substantial differences in reactivity, clearly attributable to an extra barrier to C–OAr cleavage for the equatorial isomer (**22e**).[29]



The spontaneous hydrolysis of **22e** is 1570 times slower than that of the parent acetal (**17a**, Ar = 4-nitrophenyl). The effect of the extra ring per se is known to be small (under the same conditions the oxadecalin acetal **11a** is hydrolyzed only twice as slowly as **17**), so this factor is almost entirely a measure of the destabilization of the developing positive charge of **23** by the oxygen atom of ring A, no doubt by inductive electron withdrawal. The σ-acceptor properties of the ring A oxygen of **22a** are presumably similar, but this (axial) isomer is hydrolyzed 200 times faster than **22e** (and just 7.8 times more slowly than **17a**). This factor is entirely accounted for by the enthalpy of activation, which is more favorable for the hydrolysis of **22a** by 7 kcal mol^{-1},[29] though this factor is offset to some extent by a very favorable entropy of activation for the hydrolysis of **22e**.

Thus the rate of loss of ArO^- is sensitive to the geometry at the ring junction of **22** and specifically to the orientation of the lone pairs at the remote oxygen atom. This is consistent with our analysis of the failure of the hydrolysis of the oxadecalin acetal **11e** to show a stereoelectronic effect, in that observable differences of reactivity between axial and equatorial isomers have appeared in a system designed to fulfil *both* criteria we identified as important—conformational restriction and an earlier transition state for C–O cleavage (since bond breaking at the bridgehead acetal center must be run behind the C–OAr cleavage which triggers it).

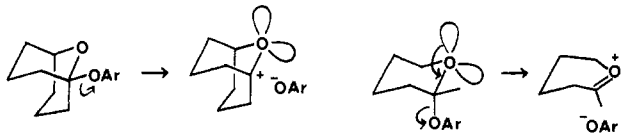
In fact it seems likely that bond breaking is still in its early stages in the rate determining transition state for the hydrolysis of **22a**. Apart from the decelerating effect of the remote (ring A) oxygen (the effect of the remaining oxygen is always to accelerate acetal C–O cleavage via late transition states), the ratio k^{ax}/k^{eq} is smaller for the (general) acid-catalyzed hydrolysis of anomers **22** than for the spontaneous reaction and smallest for the strongest acid (H_3O^+).[29] This is the opposite of what is observed in all our other systems, which involve simple C–OAr cleavage via a late transition state. Our explanation is that here the stereoelectronic effect is increasing with increasing amounts of C–O cleavage in the transition state. The overall picture is then of stereoelectronic effects being small or absent for very early or very late transition states, where relative reactivity depends primarily on ground-state energies, and reaching a maximum somewhere in between.

Exploring the Stereoelectronic Barrier: The Extreme Case

What then is the potential magnitude of the effect? Consider the energy profile diagram for the reactions of axial and equatorial isomers of a conformationally flexible system (Figure 1). If it were possible to reduce conformational flexibility sufficiently to eliminate the pathway via B altogether, the reaction of E would be forced to go over the stereoelectronic barrier $EC^‡$. In practice this appears to be impossible for any pair of axial and equatorial isomers. Conformational restraints which raise the barrier $EB^‡$ disfavor also the similar half-chair conformation preferred by the oxo carbonium ion C^+, thus raising its energy and slowing the reaction of the axial isomer also (as happens with our oxasteroids, **16**).

Even where it is possible to raise the conformational barrier ($EB^‡$) above $AC^‡$ (as may be the case for **18e**), the observed barrier to the cleavage of the equatorial isomer is primarily conformational and sets no more than a lower limit on the potential magnitude of the stereoelectronic effect. The root of the problem is that comparing transition states for C–O cleavage of axial and equatorial isomers is equivalent to looking for differences in the rates of addition of a nucleophile (ArO^- or ROH) to the opposite faces of a given oxo carbonium ion. Both reactions in this direction are rapid and involve early transition states ($AC^‡$ vs. $BC^‡$) so that large rate differences are not to be expected. The high stereoelectronic barrier (dashed curve of Figure 1) may be there, but any system flexible enough to form a stable oxo carbonium ion will also be flexible enough to find a way round it.

How then can we explore the height of this barrier directly? The answer is that we have to change our frame of reference and find a system where conformational flexibility is reduced to the practicable minimum, regardless of the effect on the stability of C^+. We have constructed such a system (**24**, Ar = 2,4-dinitrophenyl) and find that it is indeed extraordinarily unreactive.[30]



We can no longer compare the reactivity of the equatorial compound with that of an axial isomer, because the trimethylene bridge which controls the conformation at the acetal center is fixed 1,3-diaxial. So we compare the reactivity of **24** with that of the simplest axial analogue (**26**). Because compound **26** (Ar = 2,4-dinitrophenyl) is far too reactive to prepare, the comparison relies on an extrapolation. But the factor involved—our estimate is 1.3×10^{13}—is clearly enormous.[30]

This is a measure of the stabilization available from lone-pair donation to the transition state for C–OAr cleavage of **26**, which is denied the corresponding reaction of **24**.[31] Of course this factor represents primarily the vastly different stabilities of the respective cations **27**, which is planar, with unrestricted π-overlap, and **25**, with virtually none, because the geometry of the

(30) Briggs, A. J.; Evans, C. M.; Glenn, R.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1637.

(31) There is little, if any, conventional strain associated with a planar cation **25**.[30] The effect of oxygen is net destabilizing (the formation of **25** from the chloride is 3 times slower than the formation of the [3.3.1] bicyclononyl cation from the bridgehead chloride) as shown by Quinn and Wiseman. Quinn, C. B.; Wiseman, I. R. *J. Am. Chem. Soc.* **1973**, *95*, 1342. See ref 30 for leading references.

system fixes it in the perpendicular conformation.[32] But the magnitude of the effect demonstrates dramatically that acetal cleavage ordinarily requires lone-pair electrons on the remaining oxygen atom to be antiperiplanar[35] to the bond to the leaving group oxygen, either in the ground state or in some reasonably accessible conformation.

Conclusion

Stereoelectronic effects on the cleavage of acetals and their derivatives (**9**) are thus very similar to those observed for E2 reactions of related systems. The effects are less easily observed than in E2 reactions, because of the several factors which combine to make it difficult to fix oxygen derivatives **9** in unreactive conformations and perhaps also, to some extent, because the two lone pairs on oxygen are less localized than C–H bonding orbitals.[4] But the barrier to the cleavage of a tetrahydropyranyl acetal, or β-glycoside, fixed in the equatorial conformation, is so large that it is certain that observed reactions involving C–O cleavage are finding their way round, rather than over it.

A conformation change of the sort proposed by Phillips and his co-workers for the binding of its substrate by lysozyme is thus an essential part of the cleavage of a β-glycoside. Binding the reacting sugar residue in the ground-state chair conformation would increase the already significant barrier to the conformational change necessary for reaction. We conclude that lysozyme has compelling stereoelectronic reasons for binding its substrate in a non-ground-state conformation.[36]

This work was supported by the Science and Engineering Research Council of Great Britain and done by my excellent co-workers, whose names appear in the references.

(32) Calculations[33] and some experimental evidence[34] suggest that the energy difference between planar and perpendicular conformations of a simple oxo carbonium ion, $MeOCH_2^+$, is of the order of 20 kcal mol^{-1}. The observed difference in reactivity between **24** and **26** (Ar = 2,4-dinitrophenyl) corresponds to a difference in free energy of activation of 18.4 kcal mol^{-1}.

(33) Farcasiu, D.; Horsley, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 4906.

(34) Lustgarten, R.; Brookhart, M.; Winstein, S. *Tetrahedron Lett.* **1921**, 141.

(35) As pointed out by a reviewer, a lone pair synperiplanar to the bond to the departing group would also allow the development of a planar oxo carbonium ion.

(36) The evidence that lysozyme binds its substrate in a nonground-state conformation is extensive and self-consistent, but not incontrovertible. This work, similarly, shows that binding the ground-state conformation would make the reaction more difficult—not impossible.

Polyhedral Skeletal Electron Pair Approach

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The great interest shown by chemists in materials which have symmetrical polyhedral structures far exceeds that anticipated on utilitarian grounds and seems to reflect a deeper scientific desire to understand and create objects of natural beauty. This interest in polyhedral molecules ranges from transition-metal cluster compounds, with potential as a new generation of homogeneous and heterogeneous catalysts, to boron hydrides and strained hydrocarbons.[1] The fusion of polyhedra to form extended and infinite solids is of interest to chemists investigating structural modifications of elemental boron and the lower valent halides and chalcogenides of the early transition metals—some of which show fascinating superconducting properties.[2] In each of these areas bonding models have been developed to account for their structures and reactivities.[3,4] In this *Account* we outline a scheme, the "Polyhedral Skeletal Electron Pair Approach",[5] which attempts to unify some of these areas. Such a scheme is no replacement for accurate molecular orbital calculations on specific compounds,[4] but it provides a simple way to understand the intriguing structural diversity shown by polynuclear molecules and thereby opens up new areas of chemistry at the interfaces between the various subdisciplines.

Nowhere has the aesthetic pleasure derived from the synthesis of a compound of high symmetry been expressed more flamboyantly than in the recent report of dodecahedrane, $C_{20}H_{20}$ (**1**, Chart I).[6] The synthesis of **1** ("The Mount Everest of Alicyclic Chemistry") was but the final chapter in the planned syntheses of several hydrocarbons based on polyhedra, where all the vertices

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(1) B. F. G. Johnson, "Transition Metal Clusters", John Wiley and Sons, New York, 1980, provides a good general introduction to cluster chemistry.

(2) J. D. Corbett, *Acc. Chem. Res.*, 14, 239 (1981).

(3) K. Wade, *Adv. Inorg. Radiochem.*, **18**, 1 (1976); R. Mason and D. M. P. Mingos, *M.T.P. Int. Rev. Sci., Ser. Two*, 11, 121 (1975); J. W. Lauher, *J. Organomet. Chem.*, **213**, 25 (1981); G. Ciani and A. Sironi, *J. Organomet. Chem.*, **197**, 233 (1980); D. M. P. Mingos, *J. Chem. Soc., Dalton Trans.* 133 (1974).

(4) P. T. Chesky and M. B. Hall, *Inorg. Chem.*, **20**, 4419 (1981); F. A. Cotton and G. G. Stanley, *Chem. Phys. Lett.*, **58**, 450 (1978); W. C. Trogler and M. C. Manning, *Coord. Chem. Rev.*, **38**, 89 (1981).

(5) The term *polyhedral skeletal electron pair theory* was first introduced in R. Mason, K. M. Thomas, and D. M. P. Mingos, *J. Am. Chem. Soc.*, **95**, 3802 (1973), but the basic rules were also developed in R. E. Williams, *Inorg. Chem.*, **10**, 210 (1971); K. Wade, *J. Chem. Soc., Chem. Commun.*, 792 (1971); D. M. P. Mingos, *Nature (London), Phys. Sci.*, **236**, 99 (1972); R. W. Rudolph, *Acc. Chem. Res.*, **9**, 446 (1976).

(6) L. A. Paquette, R. J. Ternansky, D. W. Balogh, and G. Kentgen, *J. Am. Chem. Soc.*, **105**, 5446 (1983).

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