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Intramolecular strategies and stereoelectronic effects. Glycosides hydrolysis revisited

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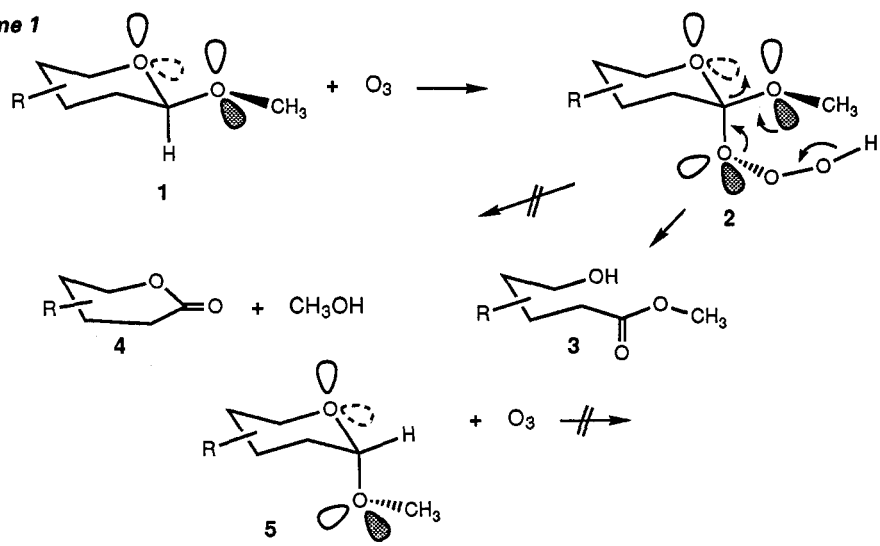
Abstract. It has been generally accepted that stereoelectronic effects play an important role in hydrolytic processes. However, the stereoelectronic theory has been criticized because the relative rates of glycosides hydrolysis could not be readily explained. Alternative mechanisms based on a synperiplanar pathway or on the principle of least motion have been proposed. A brief survey of the evidence provided by us and others which support stereoelectronic principles is presented. More recent works on the kinetically controlled spiro acetalization of hydroxy enol ethers show that spiroacetal formation takes place via an early transition state while following the antiperiplanar pathway. This approach corresponds closely to the Bürgi-Dunitz angle of attack of a nucleophile on a *pi*-system. As a result, transition states having a geometry which corresponds to the beginning of a chair form are preferred over those corresponding to a boat form. The general mechanism of reactions occurring at the anomeric center in *alpha* and *beta*-glycosides, including kinetic data for hydrolysis can be rationalized on that basis. Proposed alternative pathways are also examined.

Evidence from our laboratory that stereoelectronic effects are a key element in the understanding of the chemical reactivity of organic reactions started with the discovery of ozonolysis of acetals. In this work, it was first discovered (ref. 1) that in order to observe an oxidation, an acetal must take a conformation where each oxygen can have an electron lone pair antiperiplanar to the C—H bond. For instance, it was found (Scheme 1) that the β-glycosides **1** were selectively oxidized to the corresponding hydroxy ester **3** whereas the corresponding α-isomers **5** were found to be unreactive under the same conditions.

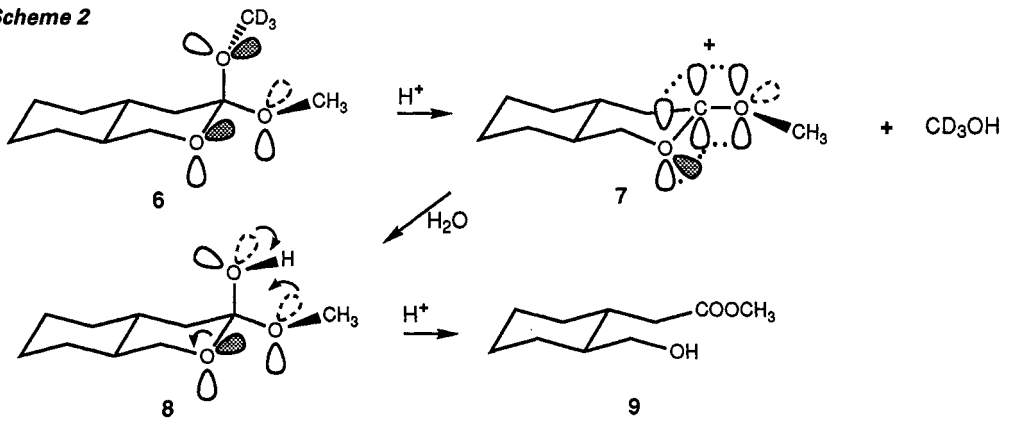
Scheme 1



The preferential formation of hydroxy-ester **3** from the hydrotrioxide tetrahedral intermediate **2** which is formed during the ozonolysis of the acetal led us to further postulate that stereoelectronic effects might be the main driving force in hydrolytic processes. In this case, it was assumed that intermediate **2** is equivalent to a tetrahedral intermediate and we postulated that specific cleavages can take place when two oxygen atoms of such a tetrahedral intermediate can have each an electron lone pair antiperiplanar to the leaving group. Under such conditions, intermediate **2**, in the chair form, can only give the hydroxy methyl ester **3**, none of the corresponding lactone **4** and methanol can be produced.

More direct experimental evidence that stereoelectronic effects (ref. 2) control hydrolytic processes were then obtained by studying the behavior of cyclic orthoesters (ref. 3). For instance, the conformationally rigid mixed orthoester **6** was shown to yield the hydroxy-methyl ester **9** following the pathway described in Scheme 2. Indeed the antiperiplanar hypothesis predicts preferential loss of the protonated axial deuterated methoxy group from **6** to yield the cyclic dioxocarbonium ion **7** which must be hydrated to give the corresponding tetrahedral intermediate **8** having an axial hydroxyl group. This intermediate can then only lead to the hydroxy methyl ester **9** (Note a).

Scheme 2

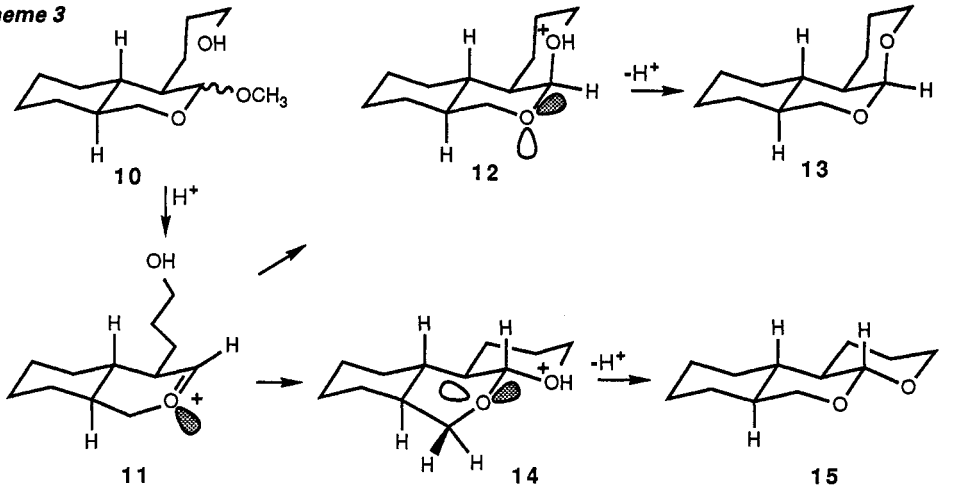


We have subsequently obtained experimental evidence that there is stereoelectronic control in the acetal formation by studying the mild acid cyclization of bicyclic hydroxypropyl acetal **10** (Scheme 3) under kinetic and thermodynamic conditions (ref. 5). Upon acid treatment (PTSA-MeOH) at room temperature, **10** gave only the *cis* tricyclic acetal **13** whereas an equilibrium mixture (45:55 ratio) of *cis* and *trans* acetals **13** and **15** was obtained after refluxing conditions. The kinetically controlled formation of **13** was then explained in the following way. Upon acid treatment, it was assumed that **10** gave first the cyclic oxocarbonium ion **11** which underwent a stereoelectronically controlled cyclization via an antiperiplanar attack to give the *cis* acetal **13** via a chair-like pathway (**11** → **12** → **13**). The formation of the *trans* acetal **15** was not observed under kinetic conditions because this compound can be produced only via a high energy twist-boat pathway (**11** → **14** → **15**) which is the result of an antiperiplanar attack of the incoming hydroxyl group.

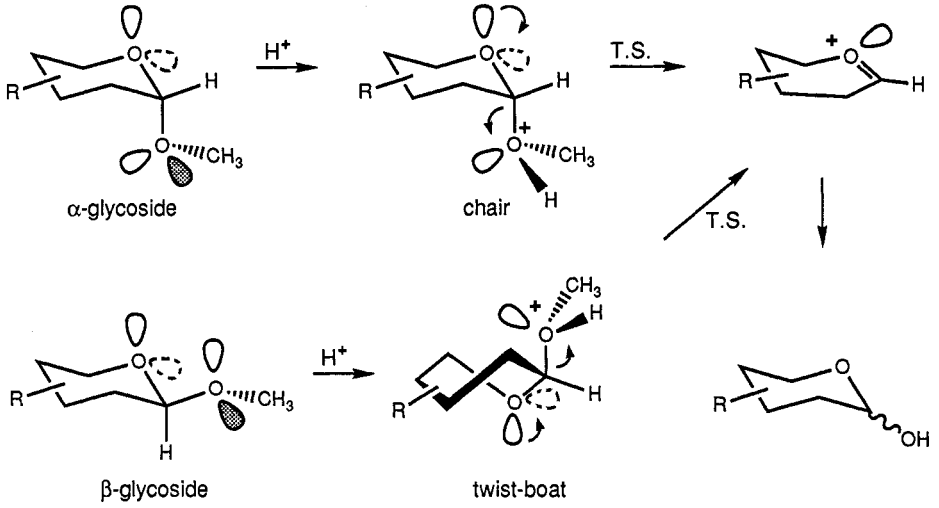
On that basis, we further postulated (ref. 2) that α-glycosides (axial anomer) must hydrolyze via their ground state conformation whereas β-glycosides (equatorial anomer) must first assume a boat conformation in order to fulfill the stereoelectronic requirement of the antiperiplanar hypothesis as shown in Scheme 4. It follows that if one assumes that the hydrolysis takes place via an early transition state

[a] Compound **6** is also formed stereospecifically by the addition of CD_3O^- to the cation **7** under aprotic conditions. It is also produced stereospecifically when the corresponding dimethyl orthoester undergoes acid-catalyzed exchange with CD_3OH in methanol-d_4-dichloromethane (ref. 4). The exchange of the equatorial OCH_3 group is much slower (~100 times).

Scheme 3



Scheme 4

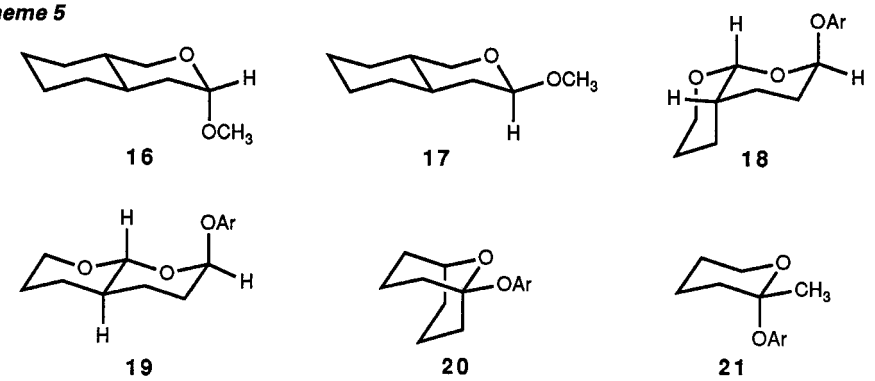


which resembles the reactive conformation of the protonated acetal rather than the cyclic oxocarbonium ion, the hydrolysis of α-glycosides via a chair-like transition state should be faster than that of β-glycosides which must proceed via a twist-boat transition state.

The rate of hydrolysis of α and β-glycosides have been measured and it does not agree with the above hypothesis, the β-anomers being generally hydrolyzed at a slightly faster rate (up to 2 or 3 times). Eikeren (ref. 6) has measured the relative rate of hydrolysis of the conformationally rigid bicyclic acetals **16** and **17** (Scheme 5) and found that the axial anomer **16** is hydrolyzed slightly faster by a factor of 1.5. Since α and β-glycosides bear additional hydroxyl groups which are likely to influence (Note b) the rate of hydrolysis, compounds **16** and **17** are better models for comparing the reactivity of α and β-anomers. Eikeren measured the activation parameters for the hydrolysis of **16** and **17** and found a slightly larger entropy term for the axial anomer and this observation led him to postulate an early

[b] By comparison, D-glucopyranosides and 2-deoxy-D-arabino-hexapyranosides are hydrolyzed at 10^{-7} and 10^{-3} times the rate of tetrahydropyranyl ethers respectively (ref. 7).

Scheme 5



transition state for the equatorial anomer with less C—O bond cleavage, and a slightly later transition state for the axial anomer with more extensive C—O bond cleavage. However, since the difference in rate between model compounds **16** and **17** is so small, it is clear that these results cannot be explained by the antiperiplanar hypothesis while assuming an early transition state along the reaction coordinates. This topic will be rediscussed later.

A large body of experimental evidence showing that the hydrolysis of acetals is governed by stereoelectronic effects has also been reported by Kirby and his co-workers. This work has been explained in details in his book (ref. 8) and in two recent reviews (ref. 4): The most convincing results were obtained by studying the spontaneous hydrolysis of conformationally restricted aryloxytetrahydropyranyl acetals **18** and **19** (Scheme 5). Isomer **18** underwent hydrolysis 200 times faster than **19**. More strikingly, the completely rigid bicyclic acetal **20** was found to hydrolyze 1.2×10^{13} times less rapidly than the tetrahydropyranyl acetal **21**. In this last case, the oxygen atom can only destabilize the cation through an inductive effect, since its lone pair electrons are not properly aligned to provide the stabilization which is normally observed by electronic delocalization.

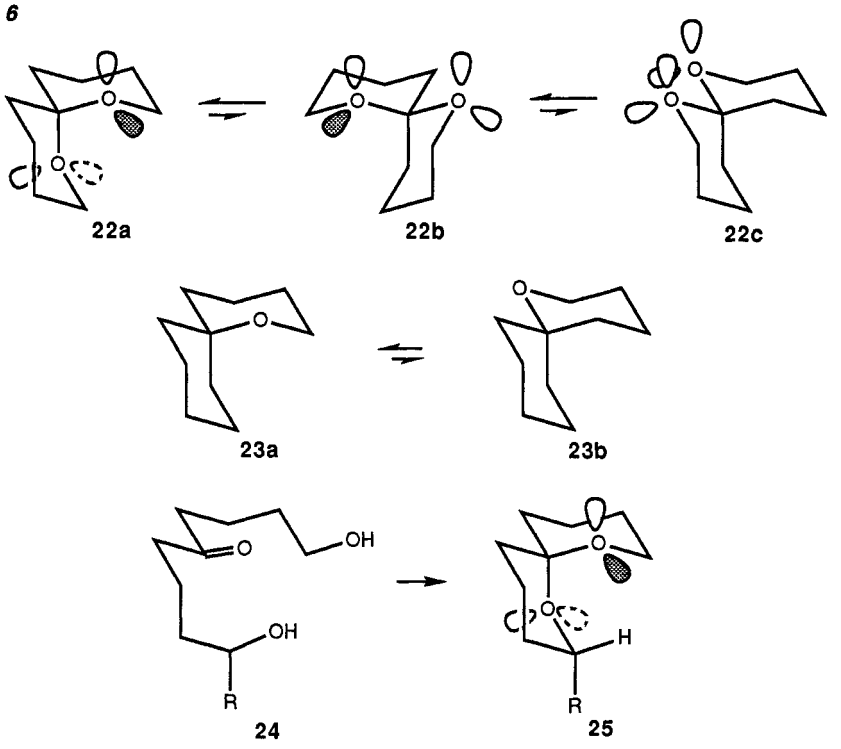
Kirby and his collaborators (ref. 4) have also obtained rigorous evidence by making accurate crystal-structure determination of a series of aryloxytetrahydropyranyl acetals which revealed a striking and systematic patterns of changes in the bond lengths at the anomeric center. They found that in axially oriented aryloxytetrahydropyrans, the endocyclic C—O bond is significantly shortened and the C—OAr bond lengthened by an amount which depends on the electronegativity of the leaving group. They further noticed that the variation in bond length is related to the rate of hydrolysis of these acetals in a simple manner. Indeed, the rate of hydrolysis shows a linear variation with the pKa of the leaving group when the C—O cleavage is rate determining.

Since the relative rate of hydrolysis of α and β-glycosides could not be explained by the antiperiplanar hypothesis along with an early transition state, alternative proposals have been put forward. Fraser-Reid and his collaborators (ref. 9) have recently proposed that the hydrolysis (or formation) of glycosides could take place in some cases by a synperiplanar rather than an antiperiplanar lone pair pathway. Another pathway which is based on the principle of least motion but completely ignores stereoelectronic principles has also been strongly advocated by Sinnott (ref. 10) in recent years. We will examine these alternative rationalizations in detail toward the end of this article. However, the yet non totally general acceptance of the stereoelectronic theory has convinced us to reinvestigate the mechanism of acetal formation and hydrolysis. It appeared to us that it was necessary to establish firmly the position of the transition state along the reaction coordinate in order to better understand the mechanism of acetal hydrolytic processes. This work is now described.

We have started looking for experiments where acetals could be produced in specific configurations under kinetically controlled conditions. For that we have reexamined the formation of 1,7-dioxaspiro[5.5]undecanes, *i.e.*, spiroacetals.

We have previously reported (ref. 11) a study which revealed that the unsubstituted 1,7-dioxaspiro[5.5]undecane exists exclusively in conformation **22a** (Scheme 6) even at room temperature. This experimental observation was explained by the fact that conformation **22a** is stereoelectronically and sterically more stable than conformations **22b** and **22c** which were estimated to be less stable respectively by a value of 2.4 and 4.8 kcal/mol (Note c). This result was further confirmed experimentally by comparing the behavior of 1-oxaspiro[5.5]undecane which was shown to exist as an equilibrium mixture of two conformers, **23a** and **23b** in a 4:1 ratio (ref. 12).

Scheme 6



We have also showed (ref. 11) that the acid cyclization of ketodiols **24** led only to thermodynamically controlled conditions producing substituted 1,7-dioxaspiro[5.5]undecanes **25** having a conformation corresponding to that of **22a**. For instance, 2-methyl-1,7-dioxaspiro[5.5]undecane was formed as isomer **30** (Scheme 7), none of isomer **31** (which corresponds to conformation **22b**) was observed from the acid cyclization of the ketodiol precursor. Similarly, the tricyclic spiroacetal isomer **35** was produced exclusively under similar conditions, none of isomer **36** being formed.

We have recently found a method to produce spiroacetals under kinetically or thermodynamically controlled conditions (ref. 13). This method involves the acid cyclization of hydroxy-enol ethers.

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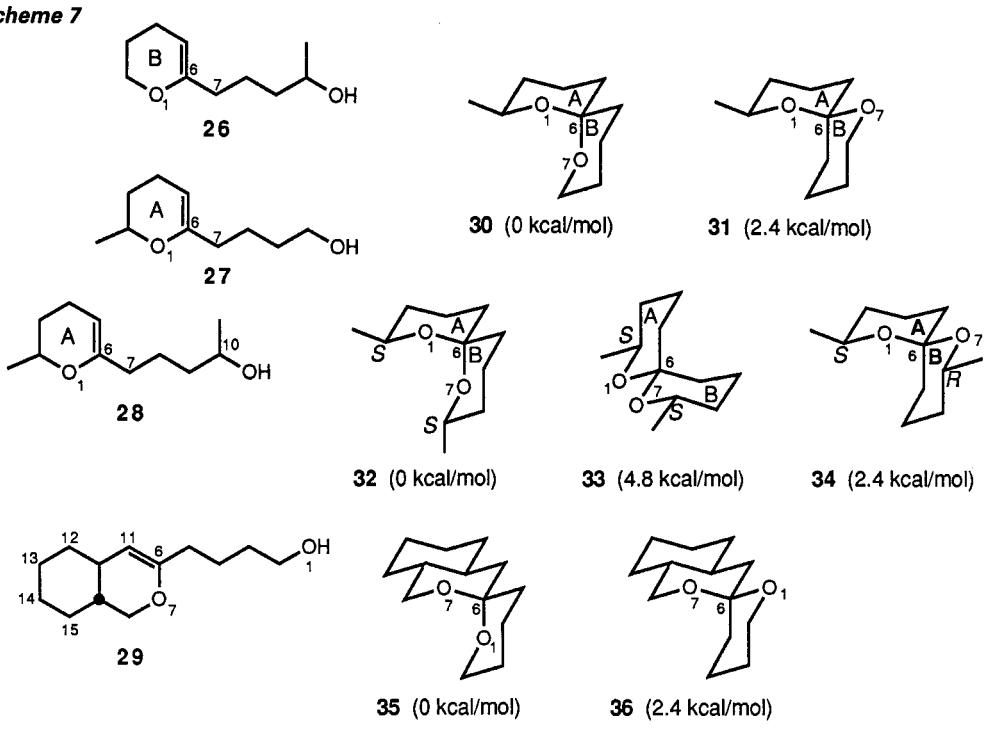
[c] The relative energy of 0, 2.4 and 4.8 kcal/mol for **22a**, **22b**, and **22c** was estimated by using the following values: anomeric effect (e) = -1.4 kcal/mol; steric effect: gauche form of *n*-butane (CC) = 0.9 kcal/mol, gauche form of CH_2—CH_2—CH_2—O (CO) = 0.4 kcal/mol and gauche form of CH_2—O—CH_2—O (CO) = 0.4 kcal/mol. Conformer **22a** = 2e + 4 CO = -1.2 kcal/mol, conformer **22b** = 1e + 2 CC + 2 CO = 1.2 kcal/mol and conformer **22c** = 4 CC = 3.6 kcal/mol.

Scheme 7



Cyclization of hydroxy-enol ether **26** (Scheme 7) with trifluoroacetic acid / benzene was complete in two hours and gave the known spiroacetal **30** (ref. 11) in quantitative yield. On the other hand, treatment of hydroxy-enol ether **26** with acetic acid / benzene during 19 hours gave a 1:1 mixture of spiroacetals **30** and **31**. This ratio was shown to remain unchanged under these mild acidic conditions. It was also observed that the mixture of spiroacetals **30** and **31** was equilibrated (<2 h) upon treatment with trifluoroacetic acid / benzene to give only spiroacetal **30**. These results show rigorously that acetic acid / benzene and trifluoroacetic acid / benzene provide respectively kinetically and thermodynamically controlled cyclization conditions. Repeating similar experiments with hydroxy-enol ether **27** gave again under thermodynamic control (TFA/benzene, 2 h) only spiroacetal **30**. Under kinetic control (AcOH/benzene, 19 h), compound **27** provided a 3:2 ratio of spiroacetals **30** and **31**.

Analogous results were obtained with bicyclic hydroxy-enol ether **29**. Under thermodynamic conditions (TFA/benzene, 2 h), the known (ref. 11) tricyclic spiroacetal **35** was formed exclusively whereas under kinetically controlled conditions (AcOH/benzene, 10 h), a 3:2 ratio of isomeric spiroacetals **35** and **36** was observed. Again, upon treatment with trifluoroacetic acid / benzene (<2 h), the mixture **35** and **36** underwent equilibration to give exclusively spiroacetal **35**.

The acid cyclization of hydroxy-enol ether **28** which is a 1:1 mixture of diastereoisomeric racemic pairs due to the presence of the two secondary methyl groups, was next examined. Cyclization of the diastereoisomeric mixture **28** with trifluoroacetic acid / benzene gave a 1:1 mixture of spiroacetals **32** and **34**. On the other hand, cyclization of **28** with acetic acid / benzene provided a mixture of three spiroacetals **32**, **33**, and **34** in a relative ratio of 3:2:5. Upon treatment with trifluoroacetic acid / benzene, this mixture was converted into a mixture of spiroacetals **32** and **34** in a 1:1 ratio.

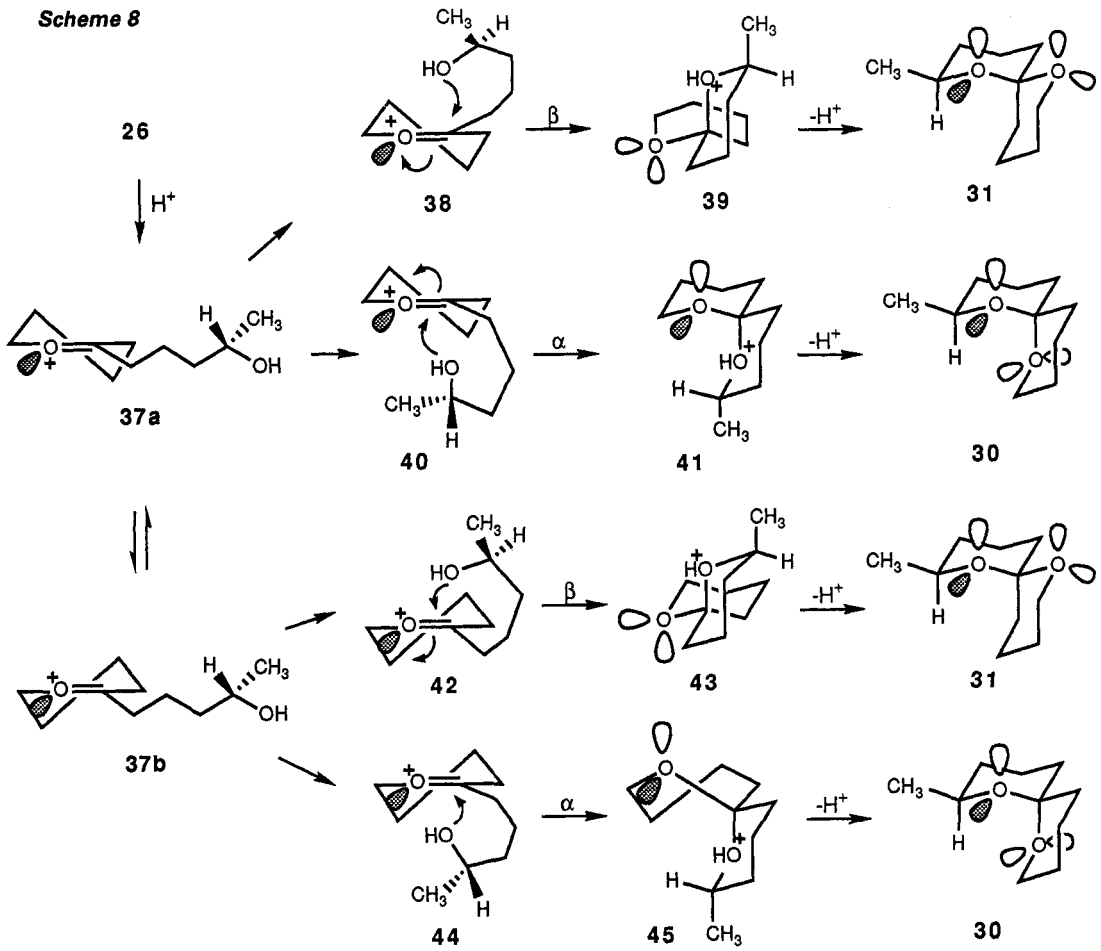
As previously discussed, a spiroacetal exists in conformation **22a** unless there is a severe 1,3-diaxial steric interaction between the substituents and the ring skeletons. In such a case, the compound will normally adopt conformation **22b** unless there is again severe 1,3-diaxial steric interaction which will force the compound to adopt conformation **22c**.

The results obtained under thermodynamically controlled conditions can be easily rationalized because we can evaluate the relative energy of the various possible conformations of the spiroacetal isomers, as well as the relative stability of the spiroacetals isomers which can be interconverted under acid conditions. Thus, since isomer **31** is 2.4 kcal/mol less stable than isomer **30**, the exclusive formation of **30** when the cyclization is carried out with trifluoroacetic acid / benzene is readily understood. Similarly, only isomer **35** was observed starting with **29** under thermodynamic conditions, because this isomer is more stable (2.4 kcal/mol) than isomer **36**. As previously discussed, hydroxy-enol ether **28** is a 1:1 mixture of two racemic diastereoisomers. One of them (racemic mixture of SS and RR) can give racemic spiroacetals **32** and **33** whereas the other (racemic mixture of SR and RS) can only lead to racemic spiroacetal **34**. However, since we know that **32** and **33** are interconvertible under acid conditions (but not **34**) and that **33** is estimated to be less stable than **32** by 4.8 kcal/mol, it follows that the cyclization of the racemic mixture **28** under thermodynamically controlled conditions should lead to a 1:1 mixture of **32** and **34** in complete agreement with the experimental results.

It remains to explain the results under kinetically controlled conditions. Under such conditions, the reaction products are independent of the relative stability of the various spiroacetal isomers, but rather depend upon the relative energy of the transition states leading to the formation of the various spiroacetal isomers.

The formation of **30** and **31** in a 1:1 ratio by the kinetic cyclization of hydroxy-enol ether **26** will first be examined. It is reasonable to assume that **26** will be protonated (ref. 7) to give an oxocarbonium ion (Scheme 8) which can exist in two rapidly equilibrating conformations **37a** and **37b**. This

Scheme 8

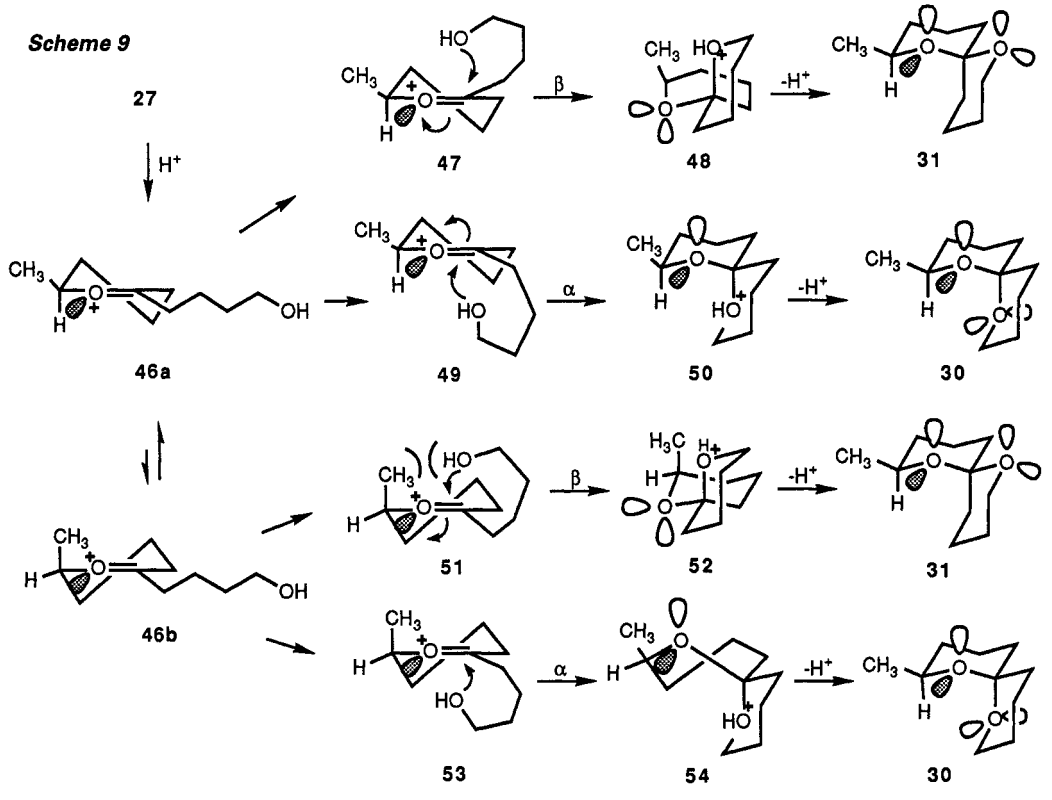


would then be followed by a stereoelectronically controlled reaction assuming an antiperiplanar attack (ref. 2). There are four possibilities, considering reactions on each face of the oxocarbonium ring leading either to a chair-like or a twist-boat-like transition state. Thus, an α-attack on conformation **37a** (**40** → **41**) and a β-attack on conformation **37b** (**42** → **43**) lead to chair-like transition states while a β-attack on **37a** (**38** → **39**) and an α-attack on **37b** (**44** → **45**) leads to twist-boat transition states. If it is assumed that transition states are late, resembling the protonated spiroacetals, the sterically disfavored twist-boats (**39** and **45**) are eliminated and it appears possible to understand the 1:1 ratio of **30** and **31** from the chair-like transition states. Indeed, stereoelectronic effects are equivalent and steric effects are relatively similar in **40** → **41** and **42** → **43**, especially if it is considered that the formation of the C—O bond is not yet completed at the transition state. If it is assumed however that the transition state is very early, resembling **38**, **40**, **42**, and **44**, steric effects appear to be close in all cases and the 1:1 ratio of isomers could be explained on that basis as well. Thus, the experimental results described so far cannot distinguish between an early or a late transition state.

Kinetic cyclization of hydroxy-enol ether **27** giving a 3:2 ratio of spiroacetals **30** and **31** will now be examined. Protonation of **27** will produce an oxocarbonium ion which can have conformation **46a** or **46b** (Scheme 9) where the former having a pseudo equatorial methyl group is more stable than the latter. In this case, there are again 4 possible modes of cyclization, since there are two chair-like (**49** → **50** and **51** → **52**) and two twist-boat-like (**47** → **48** and **53** → **54**) transition states.

We will consider first the two processes having a chair-like transition state. The first one (**49** → **50**) should produce (after loss of a proton) the more stable spiroacetal **30** whereas the second one (**51** → **52**) should give (after loss of a proton and conformational inversion of both rings) the less stable spiroacetal **31**. The first process (**49** → **50**) is essentially devoid of severe steric interactions but the second one (**51** → **52**) is severely hindered since the methyl group in **52** is in a 1,3-diaxial disposition relative to the protonated oxygen.

Scheme 9



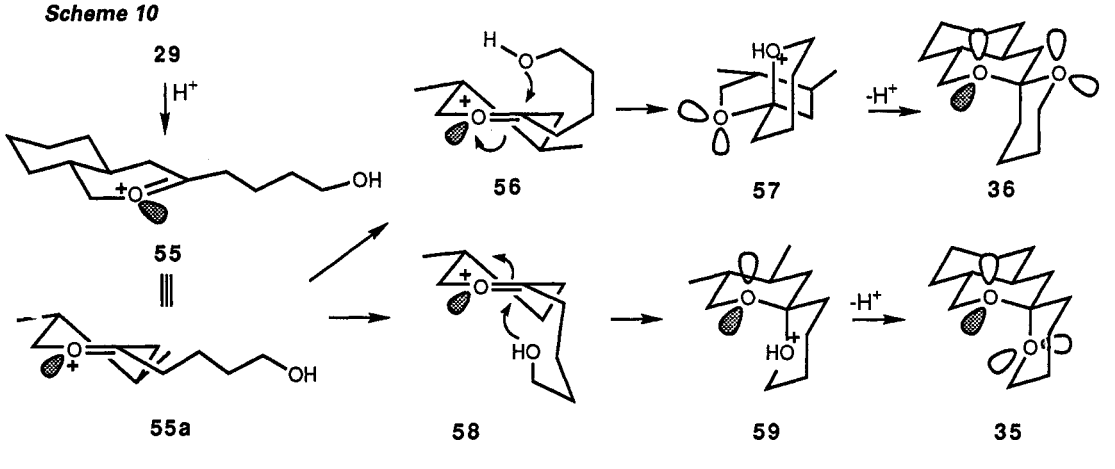
The two pathways which involve an antiperiplanar attack leading to a twist-boat intermediate are now considered. The first one is the result of a β-attack on **46a** (*i.e.* **47** → **48**) while the second one comes from an α-attack on **46b** (*i.e.* **53** → **54**). These two pathways are stereoelectronically equivalent (they are mirror images) except for the fact that the methyl group is in a pseudo equatorial orientation in the process **47** → **48** and in a pseudo axial orientation in the process **53** → **54**.

If the possibility of a late transition state is first considered for this cyclization, it becomes impossible to rationalize the rather close ratio of 3:2 in favor of spiroacetal **30**. The two twist-boat like transition states (**48** and **54**) are readily eliminated as well as the chair-like transition state **52** which experience a severe 1,3-diaxial steric interaction by comparison with **50** which is essentially sterically free. Indeed, on that basis, only spiroacetal **30** should have been produced (via **49** → **50**) under kinetically controlled conditions and this possibility is thus eliminated.

The possibility of an early transition state must next be considered. The two pathways involving the oxocarbonium ion **46b** could be disfavored because this ion is sterically less favored than ion **46a**. Furthermore, the pathways **51** → **52** must experience some steric hindrance between the pseudoaxial methyl group and the incoming OH group. On the other hand, both processes taking place on **46a** are relatively sterically free. It is therefore possible that the cyclization would take place only via **46a** where the chair-like process **49** → **50** would be very slightly favored over the twist-boat process **47** → **48** because of the very early nature of the transition state.

Examination of the results obtained with bicyclic hydroxy-enol ether **29** confirms this conclusion. Protonation of **29** produces oxocarbonium ion **55** (Scheme 10) which has a conformation (**55a**) essentially identical to that of **46a** (or **37a**) but with the difference that ring inversion is no more possible due to the *trans*-junction of the bicyclic skeleton. There are therefore only two modes of attack which respect the antiperiplanar hypothesis, the first one takes place via a twist-boat process (**56** → **57**) to give the less stable spiroacetal **36**, whereas the second one occurs via a chair-like process (**58** → **59**) to give after deprotonation the more stable spiroacetal **35**.

Scheme 10



Again, a late transition state cannot explain the experimental results since a geometry close to **57** is energetically too high by comparison with **59**. On the other hand, an early transition state can explain the fact that **56** (beginning of a twist-boat) should be slightly higher in energy than **58**. Since the 3:2 ratio is the same for the kinetic cyclization of hydroxy-enol ethers **27** and **29**, it can be concluded that the cyclization of oxocarbonium **46** probably takes place only from the ion **46a** (via the pathways **47** → **48** → **31** and **49** → **50** → **30** in a 2:3 ratio). In the case of hydroxy-enol ether **26** which produce an

oxocarbonium ion **37** which can exist in two energetically equivalent conformations (**37a** and **37b**), it can be concluded, that the four modes of cyclization are possible, with a slight preference for the chair-like processes (**40** → **41** → **30** and **42** → **43** → **31**) over the twist-boat like processes (**38** → **39** → **31** and **44** → **45** → **30**) yielding a 1:1 ratio of spiroacetals **30** and **31**.

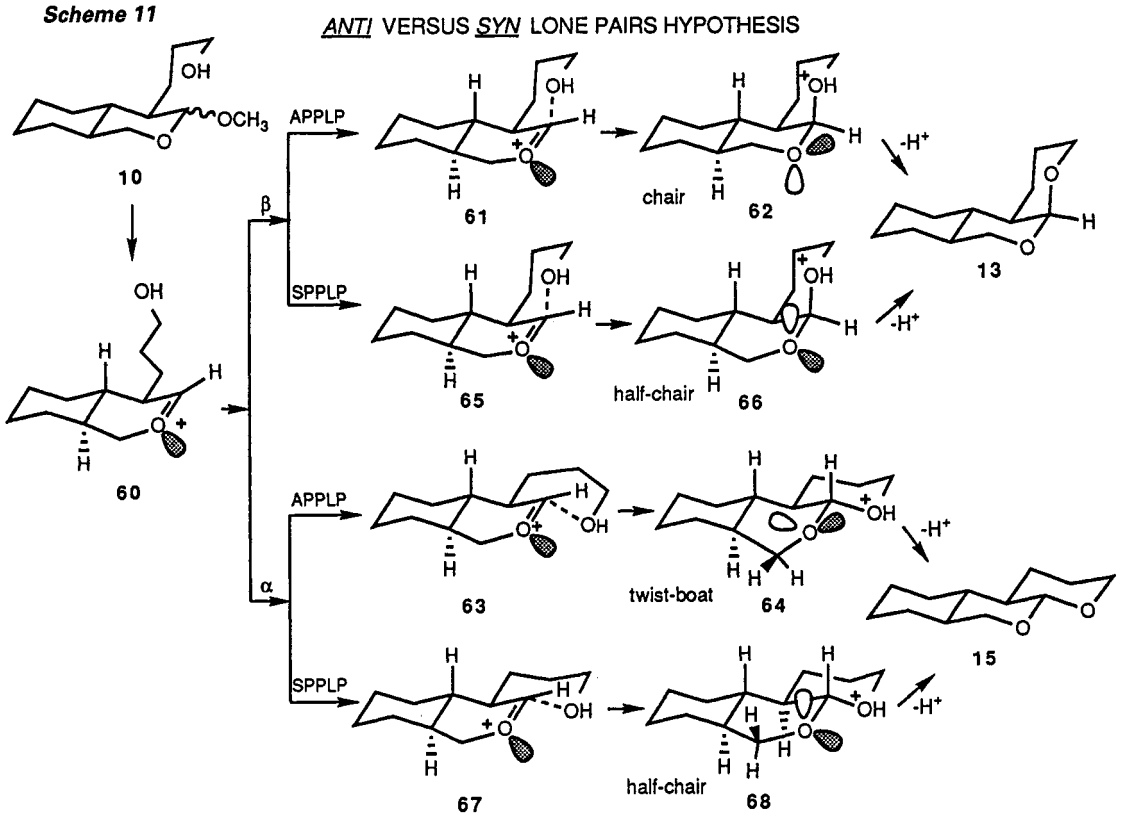
It remains to examine the cyclization of the diastereoisomeric mixture of hydroxy-enol ether **28** which gave a 3:2:5 ratio of spiroacetals **32**, **33**, and **34**. We will first discuss the formation of racemic spiroacetals **32** and **33** which come from the cyclization of the racemic SS and RR diastereoisomers of hydroxy-enol ether **28**. The formation of **32** and **33** in a 3:2 ratio is now easily explained. Taking the SS enantiomer of **28** as an example, upon protonation, it will give an oxocarbonium ion (equivalent to **46a**) which can cyclize either via a twist-boat mode or a chair-like mode where the latter would predominate over the former in a 3:2 ratio via an early transition state.

The amount of racemic spiroacetal **34** in both the kinetic and thermodynamic mixtures can be easily rationalized from the fact that in this case only one such racemic product might be obtained from the cyclization of racemic diastereoisomer RS/SR **28**. Indeed, taking the SR isomer of **28** as an example, cyclization on one face of the ring yields the enantiomer corresponding to **34** while the cyclization on the other side provides the enantiomeric form of **34**. In the light of the preceding discussion, one enantiomer of **34** must be formed preferentially over the other. Of course, a racemic mixture of **34** is finally obtained because the starting hydroxy-enol ether **28** was racemic (SR and RS mixture).

In conclusion, the spiro acetalization of the four enol ethers **26-30** under kinetically controlled conditions can be explained on the basis of the antiperiplanar hypothesis while postulating an early transition state, with the early chair-like being slightly favored over the early boat-like transition state. Indeed, it explains the 1:1 ratio of spiroacetals **30** and **31** from enol ether **26**. It also provides a simple explanation for the same 3:2 ratio obtained from the spiro acetalization of the other three enol ethers **27**, **28**, and **29**.

It is now pertinent to reanalyze the previously reported mild acid cyclization of bicyclic hydroxypropyl acetal **10** (ref. 5) (Scheme 11). At room temperature, **10** gives only the *cis* tricyclic acetal **13** upon acid treatment (PTSA-MeOH). An equilibrium mixture (45:55 ratio) of *cis* and *trans* acetals **13** and **15** was obtained after a reflux under the same conditions. The kinetically controlled formation of **13** was explained in the following way. Upon acid treatment, it was assumed that **10** gave first the oxocarbonium ion **60** which can undergo a stereoelectronically controlled cyclization to give either the *cis* acetal **13** via a chair-like pathway (**61** → **62**) or the *trans* acetal **15** via a twist-boat pathway (**63** → **64**). Since, the formation of the *cis* acetal was exclusive, it was believed (ref. 5) that the transition state must be late resembling **62** rather than the less stable **64**. Nevertheless, in the light of the preceding results and other experimental evidence (refs 14-15), it is unlikely that the exclusive formation of *cis* acetal **13** comes from a late transition state. Interestingly, it is relatively easy however to understand the exclusive formation of *cis* acetal **13** via an early transition state **provided that there is a proper alignment of the incoming hydroxyl group with the π-orbital of the oxocarbonium ion.** This stereoelectronic parameter corresponds approximately to the Bürgi-Dunitz angle of attack of a nucleophile on a π-system (16). This alignment is readily achieved in **61** but not in **63**. Modeling studies on oxocarbonium species **60** also support this argument. Indeed a conformational analysis (30° steps) on all exocyclic bonds of MINDO-3 minimized **60** shows that the vast majority of the 1103 allowed conformers has the hydroxyl above the plane of the oxocarbonium ion (like in **61**) rather than underneath that plane (like in **63**). The distance from the hydroxyl oxygen to the oxocarbonium carbon covers a range between 2.63 to 6.33 Å (0.1 Å grid). An examination of those conformers having shortest distances should give an indication about the easiest path of approach between the two centers (hydroxyl oxygen and oxocarbonium

Scheme 11



carbon). Table 1 lists salient parameters for representative lowest energy conformers of both types (*e.g.* **61**-like and **63**-like), together with their heat of formation obtained from MINDO-3 semi-empirical calculations. It is easily observed that the shortest O•••C=O distance (2.65 Å) is obtained for a **61**-like conformer (entry 1, O•••C=O angle = 106°, heat of formation = 50 kcal/mol). The lowest energy **61**-like conformer (entry 4) has an O•••C=O distance of 2.85 Å, and an O•••C=O angle of 111°. Shortest O•••C=O distances in **63**-like conformers are obtained at 2.75Å and 2.95 Å. However in this case heats of formation are about 3 to 4 kcal/mol higher than in the corresponding **61**-like conformers (compare entries 2 and 6, 5 and 7). The lowest energy conformer (entry 10) has an O•••C=O distance of 3.35 Å.

TABLE 1. Representative **61**-like and **63**-like conformers

		O•••C=O Distance (Å)	O•••C=O Angle (deg.)	Heat of formation (kcal/mol)
61-like	1	2.65	106	50
	2	2.75	103	51
	3	2.85	101	51
	4	2.85	111	49
	5	2.95	101	51
63-like	6	2.75	142	54
	7	2.95	144	55
	8	3.15	152	50
	9	3.25	148	50
	10	3.35	146	48

Another point of interest is the fact that whereas O•••C=O angles of 101-111° may be readily achieved in **61**-like conformers, this is not the case for **63**-like conformers where such angles are bigger than 142°. Therefore since **61**-like conformers have shortest O•••C=O distances, lower energies and Bürgi-Dunitz O•••C=O angles, this approach path of the nucleophile (OH) should be preferred over the one starting from a **63**-like conformers. In conclusion, an early transition state situation readily explains the exclusive formation of *cis* acetal **13**.

We will now examine the two alternative mechanisms proposed respectively by Fraser-Reid and Sinnott. Taking the bicyclic hydroxyacetal **10** as an example, the synperiplanar hypothesis suggested by Fraser-Reid means that the cyclization of **60** could take place via a β-attack leading to a half-chair (**65** → **66**) in order to give *cis* acetal **13** or via an α-attack leading to a half-chair (**67** → **68**) before giving *trans* acetal **15**. Now, if these reactions take place via a very early transition state, it can be seen that **61** and **65** on one hand and **63** and **67** on the other hand are respectively virtually identical! Kinetically, they are equivalent and there is no need to discuss further the anti versus the *syn* mechanisms on that basis. Consequently, it should be noted that the experimental results on acetal cleavages reported by Fraser-Reid (ref. 9) cannot be considered as evidence in favor of the synperiplanar hypothesis because there is no reason to believe that these processes do not take place via a late transition state. On that basis, and as previously discussed in this article, these results are equally well explained by the antiperiplanar hypothesis.

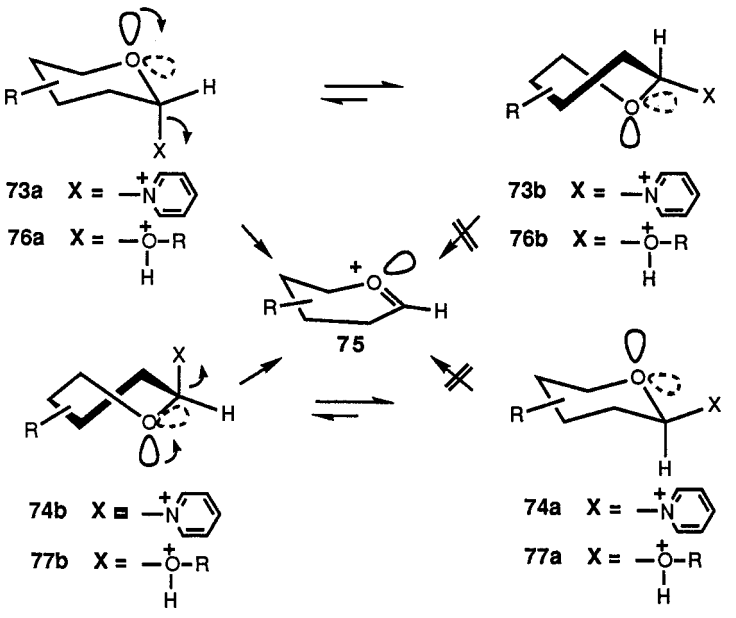
The structure of the transition state for the spontaneous hydrolysis of axial tetrahydropyranyl acetals has been estimated from experimental structural and kinetic data by Bürgi and Dubler-Steudle (ref. 17). This analysis indicates a late transition state. It follows from this work that the transition state for the proton catalyzed cleavage must also be late and therefore, it must be early for the reverse process which is consistent with the results given in the present work. Very recently, Andrews, Fraser-Reid and Bowen (ref. 18) have carried out an *"ab initio"* study of transition states in glycoside hydrolysis based on axial and equatorial 2-methoxytetrahydropyrans. This theoretical work also indicates that acetal hydrolysis takes place via a late transition state. Indeed, for the protonated axial anomer (α-glycoside), cleavage occurs via a half-chair transition state which gives a half-chair oxocarbonium ion. In the case of the protonated equatorial anomer (β-glycoside), cleavage takes place via an ^4E *endo* sofa transition state and hence via oxocarbonium ion having the same geometry. It should be pointed out that the half-chair and the sofa oxocarbonium ions have a very close geometry and similar energy, the half-chair being slightly more stable (0.15 kcal/mol).

The next question which can be asked however, concerns what happens just after the transition state; which pathway is preferred? Is the chair pathway **61** → **62** preferred over the half-chair **65** → **66** in the formation of *cis* acetal **13**? Similarly, is the *trans* acetal **15** more easily produced via the twist-boat **63** → **64** than the half-chair **67** → **68**? These questions are important, especially when the reverse process which takes place via a late transition state is considered. Indeed, in the reverse process, it becomes pertinent to know precisely which conformational change occurs in compounds **13** and **15** prior to the cleavage step.

The antiperiplanar hypothesis has received support both theoretically (refs 19-21) and experimentally (refs 2-5, 8) which indicates that electronically, it is a lower energy pathway than the synperiplanar one. Consequently, it appears safe to conclude that the antiperiplanar process is normally favored over the synperiplanar, unless unusual steric effects would prevent the former over the latter. On that basis, the chair process **61** → **62** would be preferred over the half-chair **65** → **66** based on steric and electronic reasons. For similar reasons, the process **63** → **64** should also be preferred over **67** → **68**.

Sinnott's opposition to the stereoelectronic theory and his attempt to rationalize the reactivity of acetals on the basis of the principle of least motion will now be examined. His conclusions were reached on the following basis. In pyridinium glycosides and due to a phenomenon called the reverse anomeric effect (ref. 22), the α-isomer is known to exist in the unusual twist-boat conformation **73b** (Scheme 12) rather than the usually more stable chair conformation **73a**, whereas the β-isomer remains in the usual chair conformation **74a**. It was then postulated that the α and β-pyridinium glycosides undergo hydrolysis directly from their ground state conformations **73b** and **74a**, respectively to yield the corresponding oxocarbonium ion **75** by simply following the principle of least motion (ref. 23) while completely neglecting the importance of stereoelectronic effects (or orbital overlap) during these processes. On that basis, Sinnott concluded that the acid hydrolysis of α and β-glycosides follows similar pathways because on protonation of the OR side chain, the β-glycosides would remain in the chair conformation **77a** whereas the α-glycosides would change from the chair **76a** to the twist-boat **76b**. Then, the formation of the oxocarbonium ion **75** would come directly from **76b** and **77a** following the principle of least motion.

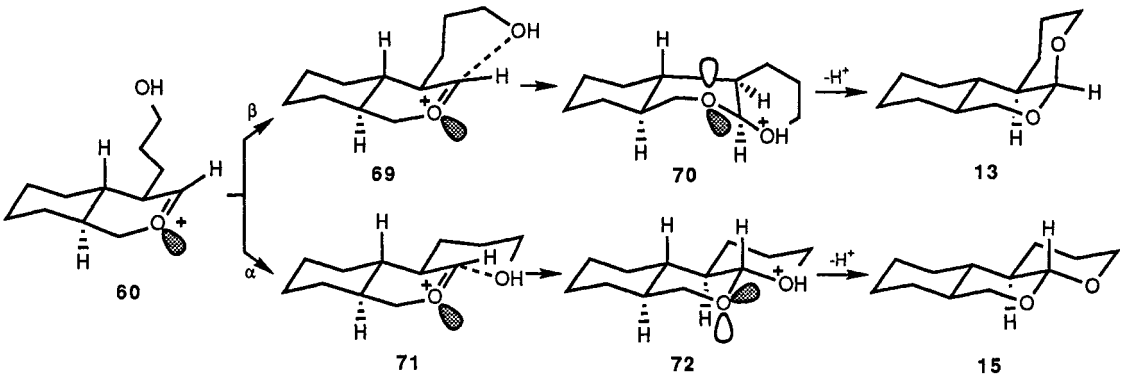
Scheme 12



This hypothesis, based on the principle of least nuclear motion, provides no driving force for the cleavage to take place, and we are convinced that it is false on the following basis. Keeping the bicyclic hydroxyacetal **10** as an example, the pathway proposed by Sinnott predicts that **10** would form *cis* acetal **13** via the twist-boat process **69** → **70** (Scheme 13), whereas *trans* acetal **15** would be formed from the chair pathway **71** → **72**. Following this hypothesis, the formation of tricyclic *trans* acetal **15** from the oxocarbonium ion **60** should take place with equal ease as the *cis* acetal **13** under kinetically controlled conditions, and hence the specific formation of *cis* acetal **13** cannot be explained.

Furthermore, *ab initio* calculations have been carried out recently (refs 20-21) on protonated species $H_nX - CH_2 - Y^+H_n$ (X and Y = O and/or N). It was found that when a lone pair of X is antiperiplanar to the C — Y^+ bond, the C — X bond shortens and the C — Y bond becomes much longer. In some cases, the tetrahedral species switch to a π-complex ($H_nX^+=CH_2 \cdots YH_n$). On the other hand, when one lone pair of X is gauche to the C — Y^+ bond, the C — Y^+ bond does not become longer. These calculations revealed also that tetrahedral intermediates having no antiperiplanar lone pairs

Scheme 13 PRINCIPLE OF LEAST MOTION HYPOTHESIS



are energetically quite stable species, indicating that the reverse anomeric effect is a stabilizing electronic effect. Furthermore, these calculations strongly suggest that the reverse anomeric effect is the result of an electrostatic attraction between the electron lone pairs of atom X and the positive charge of atom Y. Thus, in α-pyridinium glycosides, the twist-boat **73b** (Scheme 12) is more stable than the chair conformation **73a** because the N^+ is gauche to the two lone pairs of the ring oxygen. In the case of the β-isomer, it stays in the same chair conformation **74a** upon protonation, because the N^+ is already gauche to the two lone pairs of the ring oxygen.

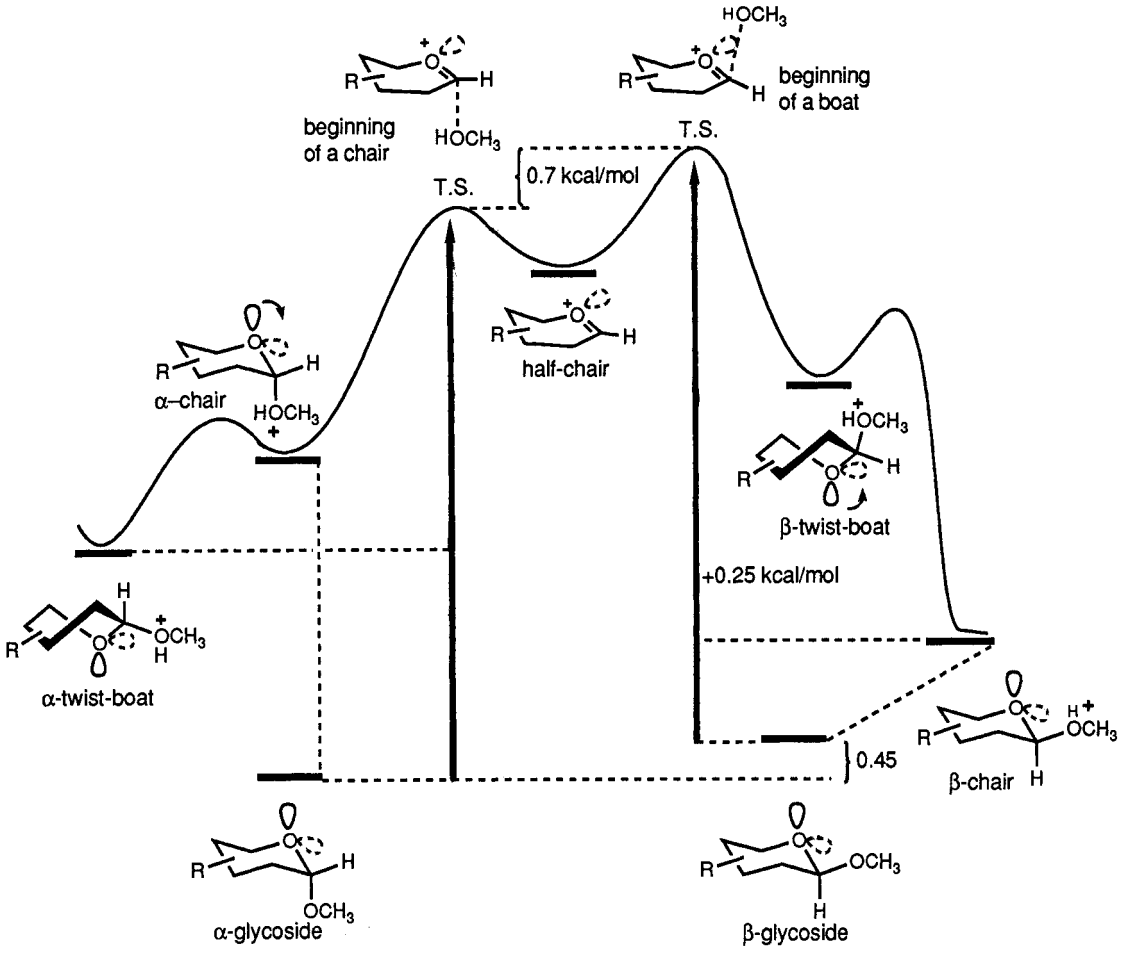
On that basis, one can postulate that although β-pyridinium glycosides exist in the ground state chair conformation **74a**, they will then undergo a conformational change to the twist-boat **74b** before reaching the transition state which will produce the oxocarbonium ion **75**. On the other hand, α-pyridinium glycosides which exist in the ground state twist-boat conformation **73b** will undergo a conformational change to the chair conformation **73a** before reaching the transition state which will eventually produce the cyclic oxocarbonium ion **75**. α and β-Glycosides would behave similarly. Upon protonation of the OR group, β-glycosides would remain in the chair conformation **77a**, but would have to undergo a conformational change to the twist-boat **77b** prior to reaching the transition state required for the formation of the oxocarbonium ion **75**. On the other hand, upon protonation, the α-glycoside would undergo a conformational change from the chair **76a** to the now more stable twist-boat **76b**. However, **76b** cannot undergo a cleavage with stereoelectronic control, and would therefore undergo a conformational change back to the chair **76a** in order to eventually reach the transition state leading to the oxocarbonium ion **75.**

The overall reaction coordinates and conformational changes occurring in the hydrolysis of glycosides are summarized in Scheme 14. Upon protonation a β-glycoside would remain in the chair conformation further stabilized by the reverse anomeric effect. Protonation of an α-glycoside would produce the protonated α-chair which can readily form a π-complex for stereoelectronic reasons. However, the protonated α-chair form can avoid the formation of the π-complex by its conversion into the protonated α-twist-boat which is stabilized by the reverse anomeric effect. The protonated α-twist-boat is however much less stable than the protonated β-chair due to their different conformation (boat versus chair, ~3-5 kcal/mol), both species having identical stereoelectronic effects.

Cleavage would thus start from the protonated α-twist-boat and from the protonated β-chair respectively. In the α-series, the protonated α-twist-boat would first undrgo a conformational change back to the α-chair which is stereoelectronically allowed to reach the transition state for cleavage. The transition state would be late having a geometry corresponding to the beginning of a chair form to finally

Scheme 14

Reaction coordinate and conformational change in hydrolysis of α and β-methoxy tetrahydropyrans



produce the half chair cyclic oxocarbonium ion. In the β-series, the protonated β-chair would first undergo a conformational change to the β-twist-boat (a π-complex!) which is stereoelectronically allowed to reach the corresponding transition state. In this case, the transition state would correspond to the beginning of a twist-boat which would lead to the reaction product, the half-chair cyclic oxocarbonium ion.

The relative rate of hydrolysis of O-alkyl α and β-glycosides are explained by the difference in energy between their ground state conformation and their respective transition state. The axial and equatorial bicyclic acetals **16** and **17** can be taken as models for α and β-glycosides. The α-anomer **16** is more stable than the β-anomer **17** by 0.45 kcal/mol, on the other hand, **16** is hydrolysed faster by a factor of 1.5 (~0.25 kcal/mol) (ref. 6), the difference in energy between the two transition states should be approximately 0.7 kcal/mol (Note d). The beginning of a chair is at a lower energy level than the beginning of a twist-boat, it is therefore normal that the α is lower than the β-transition state. Then, when the difference in energy between the α- and β-ground state conformations are taken into account, the relative rate of hydrolysis (α faster than β by 1.5) is readily understood.

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[d] Andrews, Fraser-Reid and Bowen have obtained a value of the same order ($\Delta E_{T.S.}(\beta\text{-}\alpha)$ = 1.05 kcal/mol) in their 6-31G *ab initio* studies (ref. 18).

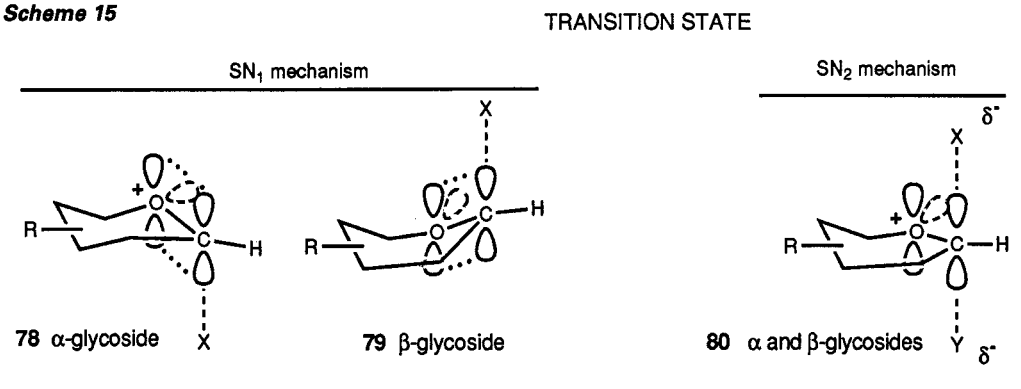
α and β-Pyridinium glycoside ground state conformations correspond respectively to the protonated α-twist-boat and β-chair of O-alkyl glycosides, their relative rate of hydrolysis should therefore be quite different than those observed for α and β-O-alkyl glycosides. As previously mentioned, the protonated α-twist-boat is at a much higher energy level than the protonated β-chair for steric reasons, it should be the same for the α and β-pyridinium glycosides. On the other hand, the relative energy of the α and β-transition states should be relatively similar to those of O-alkyl glycosides. On that basis, α-pyridinium isomers are expected to hydrolyze at a faster rate. This is indeed the case, α-pyridinium glucoside is hydrolyzed 80 times more rapidly than the β-anomer (ref. 24).

Thus, as previously pointed out by Kirby (ref. 4b), even if an antiperiplanar lone pair requirement is necessary for cleavage, it is not essential that it must be satisfied in the ground state conformation as long as some accessible appropriate conformations are available. The only criteria is simply that the conformational barrier involved should be smaller (usually the case) than the activation energy required for the cleavage reaction. Thus, the kinetic data for the hydrolysis of glycosides cannot be used against a rationalization based on stereoelectronic principles.

There are other well known organic reactions which are believed to proceed via a conformational change prior to cleavage in order to undergo stereoelectronically controlled processes. A very well known case is the reductive elimination of *trans* 1,2-dibromocyclohexane. This compound exists in the diequatorial conformation in the ground state, but it must undergo a conformational change to the less stable diaxial orientation in order to produce cyclohexene. Note that the formation of cyclohexene does not occur directly from the diequatorial conformer although this would follow the principle of least motion! Similarly, in the reverse process, the addition of bromine to cyclohexene will produce first *trans* 1,2-dibromocyclohexane in the diaxial conformation.

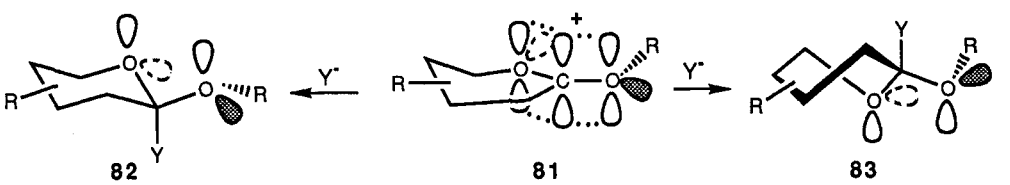
Finally, it is well known that reactions at the anomeric center in α and β-glycosides proceed in some cases with retention and in others with inversion of configuration. These reactions are explained on the basis of an SN_1 and an SN_2 process respectively. When the displacement reaction takes place via an SN_1 mechanism, it is definetely a process with a very late transition state, near the oxocarbonium ion which is a discrete species in these conditions (cf. **78** and **79** in Scheme 15). However, the results described on spiroacetal formation indicate that the geometry of the early transition state which corresponds to the beginning of a chair would be slightly preferred over that of a boat form. When the process takes place via an SN_2 mechanism, it is again a late transition state operation, but in this case, the attacking species is nucleophilic enough to start reacting before the leaving group is completely ejected (SN_1 mechanism). Recent studies by Banait and Jencks (ref. 25) on the reactivity of α-D-glucopyranosyl fluoride are in complete accord with this conclusion. The SN_2 displacement reaction must therefore have a geometry at the transition state where the C_1 and O_5 atom of the glycosides must be sp^2 hybridized (cf.

Scheme 15



80). So, these processes are also controlled stereoelectronically at the transition state level (ref. 26). In other words, the theory of stereoelectronic control (ref. 2) does not represent "an interpretation over of small and elusive least motion effects" (ref. 10), but it predicts the stereochemistry of the overall process including the transition state, although, it cannot pinpoint the position of the transition state along the reaction coordinate. The position of the transition state will of course vary depending on the nature of the substrate and the reaction conditions (nucleophile, catalyst, etc). For instance, a dioxocarbonium ion like **81** (Scheme 16) is more stable, thus less reactive than the corresponding oxocarbonium ion **75**. The hydration of **81** should therefore take place via a more advanced transition state along the reaction coordinates than that of **75**. Indeed, the transition states should now be closer to the tetrahedral intermediate, and the α-attack leading to a chair-like (**81** → **82**) should be preferred to that of a boat-like (**81** → **83**) transition state. Thus, the previous rationalization of the hydrolysis of cyclic orthoesters remains essentially as published in 1985 (refs 27-28) except for the fact that the position of the transition state is not as near the tetrahedral intermediate as previously anticipated (refs 2-3).

Scheme 16



82 **81** **83**

In conclusion, the rate of hydrolysis of α and β-glycosides are explained while assuming a late transition state following the antiperiplanar hypothesis. The geometry of transition states for α and β-glycosides corresponds to the end of a chair and of a twist-boat respectively in order to produce the half-chair cyclic oxocarbonium ion.

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