Is There Stereoelectronic Control in Formation and Cleavage of Tetrahedral Intermediates?

CHARLES L. PERRIN*
Department of Chemistry and Biochemistry, University of California—San Diego, La Jolla, California 92093-0358

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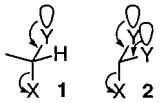
ABSTRACT
Deslongchamps' hypothesis of stereoelectronic control states that preferential cleavage of a tetrahedral intermediate occurs when a leaving group is antiperiplanar to two lone pairs. It is argued that the evidence supporting the hypothesis is suspect. An alternative explanation is that product stabilities bias the results. A more suitable test is hydrolysis of cyclic amidines and related species. Product studies show substantial cleavage of the bond that is antiperiplanar to only one lone pair and syn to the other, especially in five- and seven-membered rings. Even in the most favorable cases, six-membered rings, antiperiplanar lone pairs provide <2 kcal/mol of transition-state stabilization.

Introduction

Antiperiplanar Lone Pairs. Stereoelectronic control is a topic of much current interest.[1] The term refers to the dependence of lone-pair interactions on geometry, especially the spatial relationship between the lone pair and a chemical bond on an adjacent atom. Among its manifestations is the anomeric effect, whereby an electronegative group is stabilized when its bond is antiperiplanar (at a dihedral angle of 180°) to a lone pair, as in **1**. The effect on rates was first invoked at the acetal level of oxidation, where it is often called the kinetic anomeric effect or the antiperiplanar lone-pair hypothesis (ALPH). The claim is that cleavage of the C−X bond is facilitated by an antiperiplanar lone pair on adjacent atom Y. Although this is supported by calculations[2] and is consistent with a preference for anti E2 elimination,[3] as well as with the principle of least nuclear motion,[4] experimental evidence continues to be weak or elusive.



1 **2**

ALPH was extended to tetrahedral intermediates (**2**) by Deslongchamps.[5] Here, preferential cleavage is claimed to occur when two lone pairs on adjacent Y atoms are antiperiplanar to the leaving group X, "specific cleavage...being allowed only if the other two heteroatoms (oxygen or nitrogen) of the tetrahedral intermediate each have an orbital oriented antiperiplanar to the leaving *O*-alkyl or *N*-alkyl group".[6] This, too, is consistent with MO calculations.[7] The reduction of activation energy due to two antiperiplanar lone pairs has been estimated as ≥5 kcal/mol.[8]

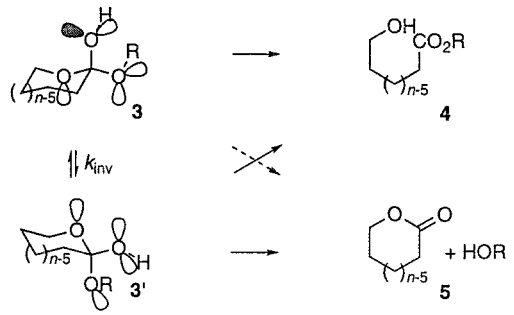


FIGURE 1. Stereoelectronic control in hydrolysis of cyclic hemiorthoesters. Two lone pairs antiperiplanar to a leaving group are shown as open lobes. A single antiperiplanar lone pair is shown shaded. Reactions that lack two antiperiplanar lone pairs are designated with a dashed arrow.

Although this hypothesis is widely accepted, it remains an area of considerable uncertainty and controversy, with occasional skepticism and numerous counterexamples. It is indisputable that an orthogonal lone pair (dihedral angle 90°) is less effective than a periplanar one (dihedral angle either 0° or 180°).[9] At issue is the effectiveness of a syn lone pair (dihedral angle < 30°). One purpose of this paper is to demonstrate that the widespread acceptance of ALPH for tetrahedral intermediates is misguided.

Significance. The role of antiperiplanar lone pairs is a fundamental aspect of the relation between molecular structure and reactivity. Much of the interest is for purposes of molecular synthesis, where it offers a novel method for selective creation of a stereocenter. Usually steric hindrance is exploited in order to direct an incoming nucleophile. An attractive alternative is to direct the nucleophile to a position antiperiplanar to an electron pair.[10] The high stereoselectivity possible (up to 99:1) implies a strong influence (a reduction of activation energy of up to 3 kcal/mol). It is important to understand the circumstances under which an electron pair governs stereoselectivity and to evaluate the preference.

Evidence for ALPH. A key piece of evidence is that hydrolysis of a cyclic hemiorthoester (**3**, $n = 6$) leads only to hydroxyester (**4**), rather than lactone (**5**).[6,11] Figure 1 presents the three predictions of ALPH. (1) There are lone pairs on the ring oxygen and the exocyclic alkoxy oxygen that are antiperiplanar to the OH, which can be cleaved. This does not lead to product but to precursor. Then, by the principle of microscopic reversibility, OH must enter antiperiplanar to those two lone pairs, to produce the

Born in Pittsburgh in 1938, Charles L. Perrin graduated from Harvard College in 1959 and received his Ph.D. in 1963 from Harvard University, under the direction of F. H. Westheimer. Following an NSF Postdoctoral Fellowship at U.C. Berkeley, he joined the founders of the new campus at U.C. San Diego, where he is now Professor of Chemistry. He has held visiting professorships in Göteborg, Paris, Padua, and Copenhagen, and he has won numerous UCSD teaching prizes. His research spans a broad range of structural and mechanistic chemistry, including anomeric effects, stereoelectronic control, proton exchange, isotope effects, dynamic NMR, and hydrogen bonding.

* E-mail: cperrin@ucsd.edu.

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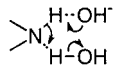
hemiorthoester initially in conformation **3**. (2) There are lone pairs on the OH and the exocyclic alkoxy oxygen that are antiperiplanar to the ring oxygen, which can be cleaved to **4**. (3) Although a lone pair on the OH is antiperiplanar to the exocyclic alkoxy group, both lone pairs on the ring oxygen are syn to that group, since there is a C−O bond in the antiperiplanar position. Ring inversion, to **3′**, would put two lone pairs antiperiplanar to the exocyclic alkoxy, but the rate constant (k_{inv}) is presumably too low. Therefore, this alkoxy group cannot be cleaved, and that is apparently why **5** is not formed.

This is a simple and elegant result, and there are many similar results with other systems. Such results have been powerfully convincing arguments for ALPH. However, to defend this hypothesis it was found necessary to postulate a novel OH^--catalyzed NH exchange (**6**).[12] This is an area where I have some experience,[13] including the knowledge that there was no evidence for such a mechanism, despite analogy to OH exchange. The necessity of an ad hoc assumption thus aroused my skepticism, and led me to consider critically the totality of the evidence. The resulting analysis and further experimental tests are a fascinating exercise in scientific logic.



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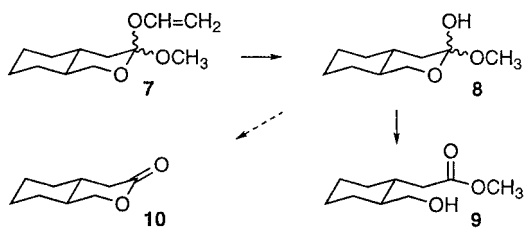
Questions. A serious inconsistency is that the corresponding five-membered hemiorthoester (**3**, $n = 5$) also gives only the hydroxyester (**4**).[6] In this case ring inversion becomes pseudorotation, with a rate constant k_{inv} in cyclopentanes of $>10^{12}$ s^{-1},[14] and anomeric effects do not retard this.[15] Since this process is faster than any possible cleavage, it immediately leads to a conformer (**3′**, $n = 5$) that now has two lone pairs antiperiplanar to the ethoxy and can cleave not only to hydroxyester but also to lactone (**5**). Since lactone is not formed, some feature other than antiperiplanar lone pairs must be responsible. The observation of hydroxyester even in five-membered rings demonstrates a logical fallacy in taking such observations as evidence for ALPH.

The same inconsistency occurs with the separate stereoisomers of 3-methoxy-3-vinyloxy-2-oxadecalin (**7**).[16] Oxidation with $KMnO_4$ leads stereospecifically to hemiorthoester (**8**). Either of these stereoisomers cleaves only to hydroxyester **9**, even though the one with OH equatorial (**8**, OH_{eq}) is analogous to **3′** and could have cleaved to lactone **10**. Thus, for both **3** and **8**, hydroxyester product cannot serve as evidence for ALPH. Admittedly, hydroxyester is consistent with ALPH, but so would lactone be, and yet it is not formed.



7 **8** **10** **9**

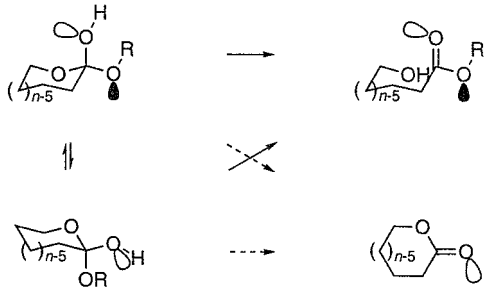
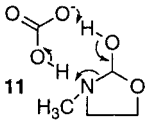


FIGURE 2. Secondary stereoelectronic effect due to additional antiperiplanar lone pair (solid) that persists to ester product but not to lactone.

An Alternative Explanation. We proposed that the absence of lactones, even from **3′** and **8** (OH_{eq}), can be associated simply with their well-known destabilization, even in polar solvents,[17] and correspondingly of the transition state leading to them.[18] This is simply a case of product-development control. Moreover, the uniformity of products, regardless of ring size, suggests that this same explanation may apply to six-membered rings. If so, these product studies are uninformative regarding the necessity for antiperiplanar lone pairs.

The absence of lactones has also been interpreted in terms of a combination of primary and secondary stereoelectronic effects in the transition state.[16,19] The primary effect is due to lone pairs antiperiplanar to the leaving group, as presented above. The so-called secondary effect is a stabilization due to lone pairs antiperiplanar to C−O bonds and that persist to product. Figure 2 shows these lone pairs. Since lactones lack one such pair present in ordinary esters, they and the transition states leading to them are disfavored. It must be recognized that this secondary effect is equivalent to the product-development control associated with destabilization of lactones. To call it a secondary effect begs the question of whether there is any primary effect. If the instability of lactones can always account for their absence, then Occam's Razor ("It is vain to do with more what can be done with fewer") makes additional explanations superfluous.[20]

It was further concluded that *all* the products from hydrolyses of orthoesters, amides, and imidates could be explained in terms of lactone instability, the instability of anti (*E*) esters, or steric effects, without ever requiring ALPH.[18] One apparent exception, the hydrolysis of imidate esters to amino esters,[8] was found to be due to bifunctional catalysis (**11**).[21] In the absence of bicarbonate, the hydroxyamide is the predominant kinetic product, owing simply to leaving-group abilities.



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Critical Test of Stereoelectronic Control. Hydrolysis of cyclic amidines, to amides or lactams, provides a more conclusive test. The advantage is that no bias arises from product stabilities, since lactams do not share the destabilization of lactones and since the steric repulsion that

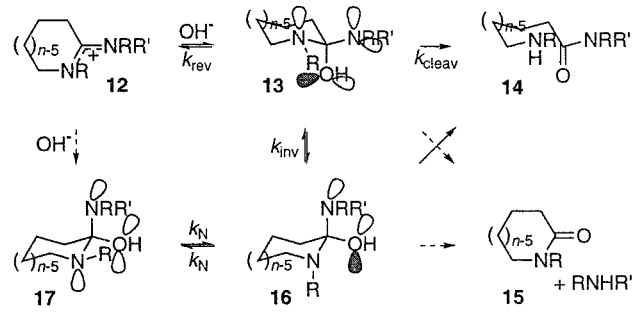


FIGURE 3. Stereoelectronic control in hydrolysis of cyclic amidinium ions. When two lone pairs are antiperiplanar to a leaving group (including one on the exocyclic nitrogen whose antiperiplanarity depends on C−N rotation), both are shown. A single antiperiplanar lone pair is shown shaded. Reactions that lack two antiperiplanar lone pairs are designated with a dashed arrow.

destabilizes cis (*E*) amides, relative to trans (*Z*), is absent in lactams. The mechanism for hydrolysis of amidinium ions (**12**) involves addition of OH^- to form an intermediate, deprotonation from oxygen, and C−N cleavage with concerted protonation (or pre-protonation) at nitrogen.[22]

Figure 3 shows the predictions of ALPH. For simplicity *O*-deprotonation is omitted, but only the conjugate base of the intermediate undergoes cleavage. As a corollary of microscopic reversibility, OH^- adds antiperiplanar to two nitrogen lone pairs of **12**, to produce **13** as the initial intermediate. After rotation about the exocyclic C−N bond, this intermediate has two lone pairs antiperiplanar to the endocyclic C−N bond but only one antiperiplanar to the exocyclic bond. According to ALPH, this geometry favors cleavage of the endocyclic bond and ring opening to the aminoamide (**14**). Exocyclic bond cleavage to the lactam (**15**) could utilize the antiperiplanar lone pair on the oxygen but would require the syn lone pair on the ring nitrogen. In contrast to hemiorthoesters (Figure 1), ring inversion, leading to conformer **16**, does not create a second lone pair antiperiplanar to the exocyclic C−N bond, so this, too, cannot cleave to lactam. The further requirement is nitrogen inversion, leading to conformer **17**. Even though this conformer could cleave to the lactam, it is inaccessible during the lifetime of the intermediate because nitrogen inversion is slow compared to the rate of cleavage. Thus, if stereoelectronic control is operative, the aminoamide **14** is predicted to be the kinetic product, via endocyclic C−N cleavage.

Results

Amidinium Ion Hydrolysis. Results are presented in Table 1, expressed as the percent of counter-ALPH product under kinetic conditions. Initial experiments showed that the aminoamide is the sole product in the hydrolysis of amidines **12** (R = H = R′).[18] These results were taken as support for ALPH, but this conclusion ignored leaving abilities. Because a nitrogen anion is a terrible leaving group, it must be protonated. Therefore, basicity is important to leaving ability, and the more basic amine is cleaved more rapidly.[23] It had been thought that the primary and secondary amine groups in the intermediates

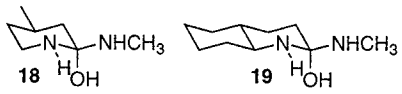
Table 1. Exocyclic Cleavage from Hemiorthoamides[a]

intermediate	R	R′	%[b]
12 ($n = 5$)	H	H	<2[c]
12 ($n = 6$)	H	H	<2[c]
12 ($n = 7$)	H	H	<2[c]
12 (n =5)	CH_3	H	32−58[d]
12 ($n = 6$)	CH_3	H	3−7[d]
12 ($n = 7$)	CH_3	H	15−56[d]
12 ($n = 5$)	CH_3	CH_3	77−81[e]
12 ($n = 6$)	CH_3	CH_3	38−72[e]
12 ($n = 7$)	CH_3	CH_3	81−92[e]
12 ($n = 5$)	H	CH_3	26−35[e]
18			3−7[d]
19			3−9[d]
22 ($n = 5$)			38[f]
22 ($n = 6$)			5−21[f]
22 ($n = 7$)			42−53[f]

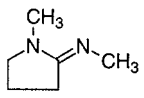
[a] Varies with pD and site monitored. [b] Lactam or cyclic urea. [c] Reference 18. [d] Reference 25. [e] Reference 26. [f] Reference 27.

of Figure 3 (R = H = R′) are of comparable basicity, regardless of the basicities of the product amines. Previous studies had not made this distinction, since they compared amines of very different basicity. Therefore, unsymmetrical acyclic acetamidines were studied, and these showed that the basicity of the product amine determines leaving ability.[24] Since ammonia is a poorer leaving group than an alkylamine, endocyclic C−N cleavage is favored, causing those initial results to be ambiguous regarding ALPH.

Therefore, the experiments were repeated with amidines **12** (R = H, R′ = CH_3), which have primary-amine leaving groups of equal basicity.[25] Consistent with ALPH, six-membered-ring aminoamide **14** is the dominant product (≥93%) from **12** ($n = 6$). In contrast, with five- and seven-membered rings, substantial amounts (>50%) of lactams **15** (n = 5, 7) are produced, along with **14**. *These results are counter to ALPH*. They are consistent with the involvement of a syn lone pair.



Additional hydrolysis studies were performed on amidinium ions **12** (R = CH_3 = R′) and amidine **20**,[26] where proton-transfer mechanisms (**6**) for nitrogen inversion in the intermediate are blocked. In all cases, substantial amounts of lactam are produced, especially with five- and seven-membered rings. This, too, is counter to ALPH.



Guanidines. ALPH can be extended to an additional heteroatom, as in the hydrolysis of guanidinium ions **21**. Cleavage of the intermediate (**22**) may be favored if there are at least two lone pairs anti to a leaving group. In either case the leaving group is a primary amine, so leaving abilities and product stabilities are balanced. Only acyclic urea **23** should be produced if antiperiplanar lone pairs are required. Yet cyclic ureas **24** are produced, especially

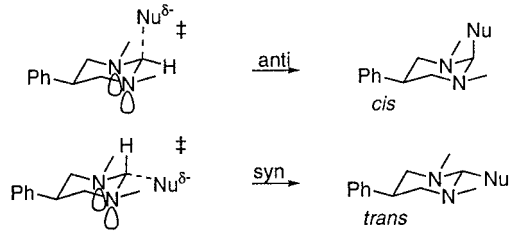
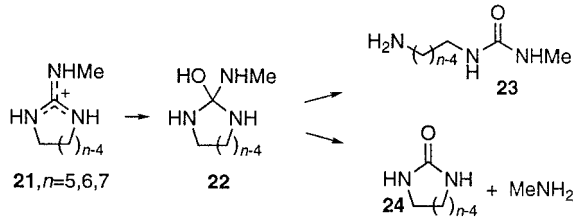


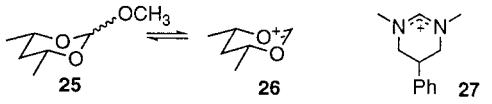
FIGURE 4. Addition paths for nucleophilic addition to **27**, anti or syn to developing lone pairs.

with five- and seven-membered rings.[27] This result, too, is counter-ALPH and attributable to the involvement of syn lone pairs.



Separation of Addition and Cleavage. In the hydrolysis of cyclic amidines, there are two steps where stereoelectronic control may operate. One is the cleavage of the tetrahedral intermediate. The other is the addition of hydroxide to form that intermediate. The counter-ALPH results could be due to the involvement of syn lone pairs in either step or in both. We had proposed that stereoelectronic control is reduced in the cleavage because a lone pair on the oxyanion provides so strong a push that a syn lone pair on the nitrogen is adequate.[25,26]

Thus, stereoelectronic control may be operative in nucleophilic addition to amidinium ions. Indeed, a stronger requirement for antiperiplanar lone pairs is seen in reactions of some orthoesters (**25**), via a dioxacarbenium ion (**26**).[28] Therefore, we examined additions to 1,3-dimethyl-5-phenyl-1,4,5,6-tetrahydropyrimidinium ion (**27**) of a wide range of nucleophiles, $NaBD_4$, $LiAlD_4$, CH_3Li, BuLi, $PhCH_2MgCl$, $CH_2{=}CHCH_2MgCl$, PhMgBr, C_6F_5MgCl, $CH_2{=}CHMgBr$, HC≡CMgBr, and PhC≡CMgBr.[29] There are two possible addition paths, shown in Figure 4, depending on whether the nucleophile enters syn or anti to the developing lone pairs on the nitrogens. According to ALPH, the latter path, leading to cis product, is favored, even though the axial substituent suffers destabilizing steric interactions. The product ratios under kinetic conditions show an anti preference between 60 and 90%. This is consistent with ALPH, whose influence though is weak, reducing activation energy by ≤1.3 kcal/mol.



In summary, there is a significant proportion of exocyclic C−N cleavage in the hydrolyses of various cyclic amidines and guanidines, especially with five- and seven-membered rings. In reactions of six-membered ring amidinium ions, there is a preference for nucleophilic addition anti to the two lone pairs on the nitrogens. We next consider the significance of these results for ALPH.

Table 2. Rate Constants (s^{-1}) for Conformational Interconversions and Reactions of Intermediates in Figure 3

process	$n = 6$	$n = 5, 7$	ref
k_{rev}[a]	1.5×10^3	1.5×10^3	25
k_{cleav}[a,b]	2.4×10^8	2.4×10^8	25
k_{rot}	$>10^{10}$	$>10^{10}$	30
k_{inv}	$\sim 10^5$	$\sim 10^{12}$	14
k_N	3×10^5	3×10^5	31

[a] Estimated from linear free-energy relationships. [b] Estimated independently[12] as 10^8−10^9.

Discussion

The exocyclic C−N cleavage in the hydrolyses of cyclic amidines and guanidines is contrary to a strong prediction of ALPH. Of course, it is necessary to consider all possible flaws in this prediction, lest exocyclic cleavage be consistent with ALPH.

Conformational Mobility. If hydrolysis of cyclic amidines is to be a valid test, product must arise only from conformers **13** and **16** (Figure 3). Conformer **17** must not be accessible during the lifetime of the intermediate. This assertion depends on relative rates of cleavage and conformational interconversion, collected in Table 2. Formation of **13** as the initial intermediate must be irreversible. Otherwise, repeated OH^- loss (k_{rev}) and eventual syn attack could equilibrate **13** with **17**. From an estimated pK_a of 13.9 for the intermediate, it then follows that cleavage becomes rate-limiting only at pD < 8.7.[25] At the high pD of these experiments, the first step is, indeed, irreversible.

The time scale for conformational interconversions is limited by k_{cleav}. Rotation about the exocyclic C−N (k_{rot}) is rapid.[30] Ring inversion (k_{inv}) is slow in six-membered rings but fast in five- and seven-membered rings.[14] Crucial is the fact that nitrogen inversion (k_N) is slow in aqueous solution.[31] Therefore, during the lifetime of the intermediate, only conformer **13** is accessible, and also **16** for n = 5 or 7. Conformer **17** is inaccessible because its formation requires not only ring inversion but also nitrogen inversion (in either order, although Figure 3 shows only one).

A proton-transfer mechanism might permit faster nitrogen inversion and (together with ring inversion) render **17** accessible, which could account for lactam formation. Yet if proton transfer is blocked by *N*-methylation, as in **13** (R = CH_3, R′ = H or CH_3), lactams are still obtained.

It might be thought that six-membered rings produce less lactam because they are slower to undergo ring inversion. If the necessity for nitrogen inversion is ignored, then the observed proportion of lactam would represent the fraction of intermediates that undergo ring inversion. However, that proportion should decrease with intermediate **18**, where the equatorial methyl retards ring inversion, and even more so with **19**, where the trans-decalin fusion prohibits ring inversion. No decrease is observed.

Leaving Abilities. In the amidine hydrolyses, the formation of counter-ALPH lactam due to an imbalance of leaving abilities must be avoided. Initial results were ambiguous because leaving abilities were imbalanced. In our subsequent hydrolyses of **12** (R = H or CH_3, R′ = CH_3), the two leaving groups are either primary or secondary amines, of the same basicity. Consequently, neither product is favored through an imbalance of leaving abilities. In **20**, the leaving abilities are imbalanced because the competition is between primary and secondary amines. Since a secondary amine is a 3- to 4-fold better leaving group,[24] cleavage of the endocyclic C−N ought to be preferred. Therefore, lactam is not favored by this imbalance, so lactam formation from **20** represents a strong counterexample to ALPH.

Product Stabilities. The key evidence for stereoelectronic control had been the formation of hydroxyester in hydrolyses of hemiorthoesters, by endocyclic C−O cleavage.[6] Yet those hydrolyses are biased toward hydroxyesters because of the inherent instability of lactones.[17] Hydrolysis of amidines avoids such bias, allowing exocyclic C−N cleavage and the observation of lactams.

Steric effects are a potential complication with fully *N*-alkylated amidinium ions. Although cleavage of either C−N bond produces a tertiary amide, so that leaving abilities are balanced, endocyclic cleavage leads to an *N*,*N*-dimethyl amide where one methyl suffers repulsion. Therefore, the product stabilities of amide and lactam are not necessarily balanced. To test whether lactam is formed from amidinium ions **12** (R′ = R = CH_3) because of relief of congestion, *N*,*N*′-dimethyl amidine **20** was investigated. Cleavage of the endocyclic C−N is favored by both stereoelectronic control and the imbalance of leaving abilities. Indeed, from **20** there is only 26−35% lactam, less than the 77−81% from **12** (n = 5, R′ = R = CH_3). This is consistent with the reduction expected from leaving abilities,[24] without any appreciable role for stereoelectronic control.

In comparing stabilities of lactones, lactams, esters, and amides, it is also necessary to consider entropy, which favors exocyclic cleavage. As a result, lactone is the ultimate thermodynamic product from orthoesters, even though it is destabilized by enthalpy. Likewise, lactam is the thermodynamic product from hydrolysis of amidines.[18] If this entropy contribution were responsible for the observed formation of lactams,[25] then this observation could not be used as evidence against ALPH. However, alkaline hydrolysis of *N*-methylacetamide, where the same entropy contribution is possible, shows no rate enhancement over lactams.[32] Apparently the amine is hardly liberated at the stage of the transition state, so $\Delta S^{\ddagger}$ is quite unlikely to favor exocyclic cleavage over endocyclic in amidine hydrolysis.

Syn Lone Pairs. Thus, we find no flaws in the conclusion that exocyclic cleavage is inconsistent with ALPH. One explanation for these results is the involvement of a syn lone pair.[25,26] This is supported by computations for acetals.[33] The proponents of ALPH have accepted the involvement of synperiplanar lone pairs in some rigid acetals with obligatory eclipsing.[34] Yet they continue to reject any general role for assistance by syn lone pairs in conformationally flexible systems or in cleavage of tetrahedral intermediates.[35]

Experimentally, E2 elimination in six-membered rings shows a strong preference for anti, but in five- and seven-membered rings syn eliminations are quite competitive.[36] They are not at all unusual. The hydrolyses of amidines to lactams and of guanidines to cyclic ureas likewise demonstrate that a syn lone pair on a ring nitrogen is quite suitable for facilitating cleavage. Nobody should have expected ALPH to be so universal as to operate even in five- and seven-membered rings.

Significant amounts of lactam are produced even from the six-membered-ring amidines. This represents a further failure of ALPH. In reactions of acetals, such a failure can be avoided by assuming reaction via a boat conformer.[37] Then one of the oxygen's two lone pairs becomes antiperiplanar to the attacking nucleophile or the leaving group. In contrast, the ring nitrogen in the tetrahedral intermediate of amidine hydrolysis has only one lone pair, which is trans to the hydroxyl and cis to the other nitrogen. Conformational interconversions do not alter these relationships. Only nitrogen inversion can do so, and this is too slow. Therefore, the nitrogen lone pair never becomes antiperiplanar to the leaving group, and the failure of ALPH cannot be avoided.

Lateness of Transition States. In the hydrolysis of cyclic amidines, it is possible that ALPH is violated only in the formation of the tetrahedral intermediate or only in its breakdown. We had suggested that the less selective step is the second one, where the push of the $-O^-$ may overwhelm any benefit from the nitrogen lone pair, whether syn or anti.[25,26] This is equivalent to assuming that this second transition state is early, resembling the intermediate and with little interaction between the bond that is cleaved and the lone pair, whose stereochemistry then does not matter.

Yet ALPH is violated as well in the formation of the tetrahedral intermediate. In nucleophilic additions to **27**, the anti preference is only 60−90%.[29] Although OH^- was not a feasible nucleophile, these results with a range of other nucleophiles suggest that OH^- can add syn to the nitrogen lone pairs in the first step of amidine hydrolysis. It could be proposed that stereoselectivity is weak because this transition state is early, resembling reactant and with little interaction between the developing bond and the lone pair, whose stereochemistry then does not matter. This seems to resemble the above rationalization, except that there the assumption was that the transition state resembles the intermediate. A related attempt to rationalize counter-ALPH results assumed that they are due to the lower resonance stabilization of amidines, compared to esters and amides,[38] which ignores the fact that the reactive substrate is the amidinium ion, with greater resonance. Such assumptions, of either early or late transitions states, can be made whenever stereoelectronic control does not hold,[37] but the need to invoke ad hoc assumptions may render ALPH empty.

Ring Size. Six-membered rings are the most favorable for operation of ALPH, and hydrolysis of these cyclic amidines and guanidines does lead predominantly to endocyclic cleavage. In contrast, products from five- and seven-membered rings are balanced between endocyclic and exocyclic cleavage, facilitated by either anti or syn lone pairs. Even in six-membered rings, there is a small amount of exocyclic cleavage, 3−7% from amidinium ion **12** ($n = 6$), 5−21% from guanidine **21** ($n = 6$), and 3−9% from intermediates **18** and **19**, where lactam must come from participation of syn lone pairs and not via ring inversion and nitrogen inversion. This corresponds to a transition-state stabilization from anti lone pairs of only 2 kcal/mol. Likewise, anti additions to **27** are favored by <1.3 kcal/mol. These are not large preferences, but they can be sufficient for stereoselective synthesis in favorable cases.

Conclusions

One test of any theory of reactivity is its ability to predict products. In hydrolysis of amidinium ions and related species, the clear prediction of ALPH is for endocyclic C−N cleavage. Instead, there is substantial exocyclic cleavage, except in six-membered rings. This cannot occur through a conformer with two lone pairs antiperiplanar to the exocyclic nitrogen, since that would require rapid nitrogen inversion. Nor can it occur through conformational changes, since the lone pair of the ring nitrogen remains cis to the leaving group and does not become antiperiplanar even in the boat form. We therefore affirm that ALPH cannot always account for the reactions of tetrahedral intermediates.

These results raise further doubt about the hydrolyses of orthoesters, amides, and imidates claimed to show stereoelectronic control.[5] Since those can be explained[18] without requiring stereoelectronic control, it may be that ALPH is not widely applicable. Moreover, those apparent failures of ALPH that were rationalized by assuming reaction via a boat conformer[37] may be true failures of the hypothesis.

Even in six-membered rings, an antiperiplanar lone pair provides only 1−2 kcal/mol of stabilization of the transition state for formation or cleavage of tetrahedral intermediates. Stereoelectronic control is weak, even in this most favorable case. Fortunately, a weak control may be sufficient for stereoselective synthesis.

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References

(1) Kirby, A. J. *The Anomeric and Related StereoelectronicEffects at Oxygen*; Springer: Berlin, 1983. Juaristi, E.; Cuevas, G. Recent Studies of the Anomeric Effect. *Tetrahedron* **1992**, *48*, 5019−5087. Thatcher, G. R. J., Ed. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series; American Chemical Society: Washington, DC, 1993. Thibaudeau, C.; Chattopadhyaya, J. *Stereoelectronic Effects in Nucleosides and Nucleotides and Their Structural Implications*; Uppsala University Press: Uppsala, Sweden, 1999.

(2) Lehn, J.-M.; Wipff, G.; Bürgi, H.-B. Stereoelectronic Properties of Tetrahedral Species Derived from Carbonyl Groups. Ab Initio Study of the Hydroxymethanes. *Helv. Chim. Acta* **1974**, *57*, 493−496. Bach, R. D.; Badger, R. C.; Lang, T. J. Theoretical Studies on E2 Elimination Reactions. Evidence That Syn Elimination Is Accompanied by Inversion of Configuration at the Carbanionic Center. *J. Am. Chem. Soc.* **1979**, *101*, 2845−2848. Grein, F.; Deslongchamps, P. The Anomeric and Reverse Anomeric Effect. A Simple Energy Decomposition Model for Acetals and Protonated Acetals. *Can. J. Chem.* **1992**, *70*, 1562−1572.

(3) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3 ed.; Harper & Row: New York, 1987; pp 610−616.

(4) Sinnott, M. L. The Principle of Least Nuclear Motion and the Theory of Stereoelectronic Control. *Adv. Phys. Org. Chem.* **1988**, *24*, 113−204.

(5) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983. Deslongchamps, P. Stereoelectronic Control in the Cleavage of Tetrahedral Intermediates in the Hydrolysis of Esters and Amides. *Tetrahedron* **1975**, *31*, 2463−2490.

(6) Deslongchamps, P.; Chênevert, R.; Taillefer, R. J.; Moreau, C.; Saunders, J. K. Hydrolysis of Cyclic Orthoesters: Stereoelectronic Control in the Cleavage of Hemiorthoester Tetrahedral Intermediates. *Can. J. Chem.* **1975**, *53*, 1601−1615.

(7) Lehn, J. M.; Wipff, G. Stereoelectronic Properties and Reactivity of the Tetrahedral Intermediate in Amide Hydrolysis. Nonempirical Study of Aminodihydroxymethane and Relation to Enzyme Catalysis. *J. Am. Chem. Soc.* **1974**, *96*, 4048−4050. Lehn, J.-M.; Wipff, G. Stereoelectronic Properties of Tetrahedral Species Derived from Carbonyl Groups: Ab Initio Study of Aminodihydroxymethane, $CH(OH)_2NH_2$, A Model Tetrahedral Intermediate in Amide Hydrolysis. *Helv. Chim. Acta* **1978**, *61*, 1274−1286. Pullumbi, P.; Lemeune, S.; Barbe, J.-M.; Trichet, A.; Guilard, R. Experimental and Theoretical Study of Stereoelectronic and H−Bond Control of Reactivity in α- and β-Methyl D-Glucopyranoside Ozonolysis. *Theochem: J. Mol. Struct.* **1998**, *432*, 169−176.

(8) Deslongchamps, P.; Dubé, S.; Lebreux, C.; Patterson, D. R.; Taillefer, R. J. Hydrolysis of Imidate Salts. Stereoelectronic Control in the Cleavage of the Hemiorthoamide Tetrahedral Intermediate. *Can. J. Chem.* **1975**, *53*, 2791−2807.

(9) Briggs, A. J.; Evans, C. M.; Glenn, R.; Kirby, A. J. Stereoelectronic Effects at Oxygen: A Very Large Effect on the Hydrolysis of a Conformationally Locked Acetal: Implications for β-Glycosidase Mechanisms. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1637−1640.

(10) Deslongchamps, P. The Concept of Strategy in Organic Synthesis. *Bull. Soc. Chim. Fr.* **1984**, *II*, 349−361. Stevens, R. V. Nucleophilic Additions to Tetrahydropyridinium Salts. Applications to Alkaloid Syntheses. *Acc. Chem. Res.* **1984**, *17*, 289−296. Halterman, R. L.; McEvoy, M. A. Evidence of Stereoelectronic Control in Osmium-Catalyzed Cis-Dihydroxylations of Sterically Unbiased 3,3-Diarylcyclopentenes. *J. Am. Chem. Soc.* **1992**, *114*, 980−985.

(11) Deslongchamps, P.; Atlani, P.; Fréhel, D.; Malaval, A.; Moreau, C. Oxidation of Acetals by Ozone. *Can. J. Chem.* **1974**, *52*, 3651−3664. Deslongchamps, P.; Lessard, J.; Nadeau, Y. The Products of Hydrolysis of Cyclic Orthoesters as a Function of pH and the Theory of Stereoelectronic Control. *Can. J. Chem.* **1985**, *63*, 2485−2492.

(12) Deslongchamps, P.; Barlet, R.; Taillefer, R. J. Hydrolysis and Carbonyl-Oxygen Exchange in Tertiary Amides. Estimation of the Free Energy Changes for Breakdown and Conformational Changes of Tetrahedral Intermediates. *Can. J. Chem.* **1980**, *58*, 2167−2172.

(13) Perrin, C. L. Proton Exchange in Amides: Surprises from Simple Systems. *Acc. Chem. Res.* **1989**, *22*, 268−275.

(14) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York, 1990; pp 131, 142.

(15) Perrin, C. L.; Nuñez, O. Does an Anomeric Effect Raise the Barrier to Conformational Change? *J. Chem. Soc., Chem. Commun.* **1984**, 333−334.

(16) Deslongchamps, P.; Beaulieu, N.; Chênevert, R.; Dickinson, R. A. Oxidative Cleavage of Conformationally Rigid Vinyl Ortho-Esters: Evidence for Primary and Secondary Stereoelectronic Control in the Cleavage of Tetrahedral Intermediates. *Can. J. Chem.* **1980**, *58*, 1051−1058.

(17) Huisgen, R.; Ott, H. Medium-Sized Rings. XV. Configuration of the Ester Group and the Singular Properties of Lactones. *Tetrahedron* **1959**, *6*, 253−267. Byun, K.; Mo, Y.; Gao, J. New Insight on the Origin of the Unusual Acidity of Meldrum's Acid from ab Initio and Combined QM/MM Simulation Study. *J. Am. Chem. Soc.* **2001**, *123*, 3974−3979.
(18) Perrin, C. L.; Arrhenius, G. M. L. A Critical Test of the Theory of Stereoelectronic Control. *J. Am. Chem. Soc.* **1982**, *104*, 2839−2842.
(19) Deslongchamps, P. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 1993; Chapter 3.
(20) Russell, B. *A History of Western Philosophy*; Simon & Schuster: New York, 1945; p 472.
(21) Perrin, C. L.; Engler, R. E.; Young, D. B. Bifunctional Catalysis and Apparent Stereoelectronic Control in Hydrolysis of Cyclic Imidatonium Ions. *J. Am. Chem. Soc.* **2000**, *122*, 4877−4881.
(22) Robinson, D. R. Direct Observation of a Tetrahedral Intermediate during Amidine Hydrolysis. *J. Am. Chem. Soc.* **1970**, *92*, 3138−3146.
(23) Benkovic, S. J.; Barrows, T. H.; Farina, P. R. Studies on Models for Tetrahydrofolic Acid. IV. Reactions of Amines with Formamidinium Tetrahydroquinoxaline Analogs. *J. Am. Chem. Soc.* **1973**, *95*, 8414−8420. Slebocka-Tilk, H.; Bennet, A. J.; Keillor, J. W.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. ^{18}O Exchange Accompanying the Basic Hydrolysis of Primary, Secondary, and Tertiary Toluamides. 2. The Importance of Amine Leaving Abilities from the Anionic Tetrahedral Intermediates. *J. Am. Chem. Soc.* **1990**, *112*, 8507−8514. Vincent, S.; Mioskowski, C.; Lebeau, L. Hydrolysis and Hydrogenolysis of Formamidines: *N,N*-Dimethyl And *N,N*-Dibenzyl Formamidines as Protective Groups for Primary Amines. *J. Org. Chem.* **1999**, *64*, 991−997.
(24) Perrin, C. L.; Nuñez, O. Hydrolysis of Unsymmetrical Acetamidines: Leaving Abilities and Stereoelectronic Effects. *J. Am. Chem. Soc.* **1987**, *109*, 522−527.
(25) Perrin, C. L.; Nuñez, O. Absence of Stereoelectronic Control in Hydrolysis of Cyclic Amidines. *J. Am. Chem. Soc.* **1986**, *108*, 5997−6003.
(26) Perrin, C. L.; Thoburn, J. D. Absence of Stereoelectronic Control in the Hydrolysis of Fully and Partially *N*-Alkylated Cyclic Amidinium Ions. *J. Am. Chem. Soc.* **1993**, *115*, 3140−3145.
(27) Perrin, C. L.; Young, D. B. Is There Stereoelectronic Control in Hydrolysis of Cyclic Guanidinium Ions? *J. Am. Chem. Soc.* **2001**, *123*, 4446−4450.
(28) Perrin, C. L.; Engler, R. E. Quantitative Assessment by 1D-EXSY NMR of Stereoelectronic Control in Acid-Catalyzed Exchange Between Stereoisomeric 2-Methoxy-1,3-Dioxanes and Methanol. *J. Am. Chem. Soc.* **1997**, *119*, 585−591. Desvard, O. E.; Kirby, A. J. A Measure of Stereoelectronic Control in the Hydrolysis of an Orthoester. *Tetrahedron Lett.* **1982**, *23*, 4163−4166. Eliel, E. L.; Nader, F. W. Conformational Analysis. XX. The Stereochemistry of Reaction of Grignard Reagents with Ortho Esters. Synthesis of 1,3-Dioxanes with Axial Substituents at C-2. *J. Am. Chem. Soc.* **1970**, *92*, 584−590. Eliel, E. L.; Nader, F. W. Conformational Analysis. XXI. Reduction with Metal Hydrides. XX. The Stereochemistry of Reduction of Ortho Esters with Lithium Aluminum Hydride and Mixed Hydrides. *J. Am. Chem. Soc.* **1970**, *92*, 3045−3050.
(29) Perrin, C. L.; Young, D. B. Stereoelectronic Control in Addition of Nucleophiles to an Amidinium Ion. *J. Am. Chem. Soc.* **2001**, *123*, 4451−4458.
(30) Bushweller, C. H.; O'Neil, J. W.; Bilofsky, H. S. Evidence Supporting a Common Transition State for Rotation and Inversion in *tert*-Butylbenzylmethylamine. *J. Am. Chem. Soc.* **1971**, *93*, 542−544.
(31) Saunders, M.; Yamada, F. Measurement of an Amine Inversion Rate Using Nuclear Magnetic Resonance. *J. Am. Chem. Soc.* **1963**, *85*, 1882−1882.
(32) Imming, P.; Klar, B.; Dix, D. Hydrolytic Stability Versus Ring Size in Lactams: Implications for the Development of Lactam Antibiotics and Other Serine Protease Inhibitors. *J. Med. Chem.* **2000**, *43*, 4328−4331.
(33) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. An ab Initio Study (6-31G*) of Transition States in Glycoside Hydrolysis Based on Axial and Equatorial 2-Methoxytetrahydropyrans. *J. Am. Chem. Soc.* **1991**, *113*, 8293−8298.
(34) Li, S.; Kirby, A. J.; Deslongchamps, P. First Experimental Evidence for a Synperiplanar Stereoelectronic Effect in the Acid Hydrolysis of an Acetal. *Tetrahedron Lett.* **1993**, *34*, 7757−7758. Li, S.; Deslongchamps, P. Experimental Evidence for a Synperiplanar Stereoelectronic Effect in the Ozonolysis of a Tricyclic Acetal. *Tetrahedron Lett.* **1993**, *34*, 7759−7762.
(35) Deslongchamps, P.; Dory, Y. L.; Li, S. The Relative Rate of Hydrolysis of a Series of Acyclic and Six-Membered Cyclic Acetals, Ketals, Orthoesters, and Orthocarbonates. *Tetrahedron* **2000**, *56*, 3533−3537. Deslongchamps, P.; Dory, Y. L.; Li, S. Hydrolysis of Isomeric Tricyclic Orthoesters and AM1 Molecular Modelling of the Reaction Pathway: Further Evidence for Stereoelectronic Control. *Heterocycles* **1996**, *42*, 617−624. Deslongchamps, P. Intramolecular Strategies and Stereoelectronic Effects. Glycosides Hydrolysis Revisited. *Pure Appl. Chem.* **1993**, *65*, 1161−1178.
(36) March, J. *Advanced Organic Chemistry*, 4 ed.; Wiley: New York, 1992; pp 983−990.
(37) Pothier, N.; Goldstein, S.; Deslongchamps, P. Cyclization of Hydroxyenol Ethers into Spiroacetals: Evidence for the Position of the Transition State and its Implication on the Stereoelectronic Effects in Acetal Formation. *Helv. Chim. Acta* **1992**, *75*, 604−620.
(38) Dugas, H. *Bioorganic Chemistry*, 3rd ed.; Springer: New York, 1996; p 217.

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