Bifunctional Catalysis and Apparent Stereoelectronic Control in Hydrolysis of Cyclic Imidatonium Ions

Charles L. Perrin,* Richard E. Engler, and David B. Young

Contribution from the Department of Chemistry, University of California−San Diego, La Jolla, California 92093-0358

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Abstract: To test stereoelectronic control in cleavage of tetrahedral intermediates, cyclic imidatonium ions were hydrolyzed in buffered aqueous media. In carbonate buffer >97% amino ester was observed, as previously reported. However, in borate buffers 65−91% hydroxy amide was observed from five-membered-ring imidatonium ions, except for a highly alkylated one. Selectivity is attributed to leaving-group ability. Stereoelectronic control does operate in six-membered rings but provides only 2 kcal/mol toward rate acceleration. Production of amino ester in carbonate buffers is due to the bifunctional nature of bicarbonate ion and thus cannot be used to support a large stereoelectronic contribution. The geometrical requirements for bifunctional catalysis further imply the intermediacy of conformations counter to stereoelectronic control.

Introduction

Antiperiplanar Lone Pairs. Stereoelectronic control (SELC) is a topic of much current interest.[1] The term has a broad meaning, generally involving the positioning of lone pairs,[2] frequently as applied to reactivity at the acetal level of oxidation, where kinetic effects are weak or elusive,[3] and to anomeric effects.[4] Consideration here is restricted to a hypothesis developed by Deslongchamps that cleavage of a tetrahedral intermediate (**1**) is favored when there are two lone pairs on

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adjacent Y atoms antiperiplanar to the leaving group X.[5] This preference, often called the antiperiplanar lone-pair hypothesis or the kinetic anomeric effect, is similar to the well-established stereochemistry in many β-eliminations,[6] and it is supported by MO calculations.[7]

This aspect of SELC, focusing on the role of antiperiplanar lone pairs, is a fundamental one about the interplay between molecular structure and reactivity. It is still an area of considerable uncertainty and controversy,[8] with wide acceptance[9] and only occasional skepticism.[10] Much of the interest is for purposes of synthesis, where it offers a novel method for control of stereochemistry. Customarily steric effects are used to direct an incoming nucleophile along the least hindered path. If preferential addition occurs antiperiplanar to a lone pair, this provides an alternative approach to the selective creation of a chiral center.[11] SELC has also been proposed to promote cleavage of the desired bond by enzymes and enzyme models.[12]

To what extent is an antiperiplanar lone pair required? There is no doubt that an orthogonal lone pair is much less effective

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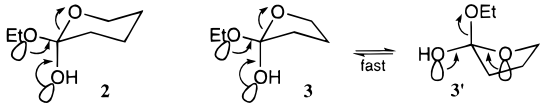
than a periplanar one.[13] The question that we address is the effectiveness of a syn lone pair. Early evidence came from the hydrolysis of a cyclic hemiortho ester (**2**), which undergoes endocyclic cleavage exclusively to hydroxy ester, rather than to lactone.[14] Such an endocyclic cleavage is consistent with the conclusion that antiperiplanar lone pairs are more effective than syn. Nevertheless, a serious inconsistency is that the corresponding five-membered hemiortho ester (**3**) also gives only the hydroxy ester, even though rapid pseudorotation provides a conformer (**3′**) that has two lone pairs antiperiplanar to the

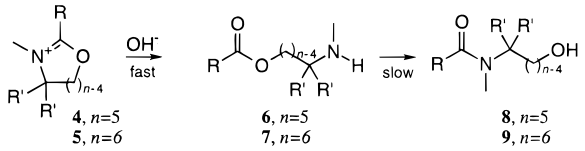


ethoxy and ought to have undergone exocyclic cleavage to lactone. Therefore it was proposed[15] that the absence of lactone in the latter case must be associated simply with the well-known greater destabilization of lactones and of the transition state leading to them. Moreover, this same explanation may apply to the former case. To the extent that this is so, these product studies do not provide any information on the need for antiperiplanar lone pairs in cleavage of hemiortho esters.

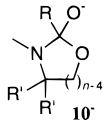
To provide an unambiguous test of SELC, hydrolysis of cyclic amidines was studied. These have the advantage that there is no bias due to product stabilities, and antiperiplanar lone pairs are again predicted to favor endocyclic cleavage. In initial studies only endocyclic cleavage was indeed observed, and the absence of lactam product was taken as evidence supporting the role of antiperiplanar lone pairs.[15] However, this was subsequently found to be due to a disparity in leaving abilities.[16] When leaving abilities are balanced, the selectivity for endocyclic cleavage is ≤93% and vanishes in five- and seven-membered rings, which produce considerable lactam.[17] Therefore it was concluded that SELC is weak even in the best case, namely six-membered rings, and absent in five- and seven-membered ones. It is slightly stronger in methanolysis of six-membered-ring ortho esters.[18]

One explanation for these results is the possibility that a syn lone pair can also be effective,[17] as is supported by computations on acetal hydrolysis,[19] The proponents of SELC have accepted the involvement of synperiplanar lone pairs in some rigid acetals where eclipsing is obligatory.[20] Yet despite numerous counterexamples to SELC,[21] the proponents continue to reject any general role for assistance by syn lone pairs in conformationally flexible systems or in cleavage of tetrahedral intermediates.[22]

Imidatonium Ions. Some evidence does seem to support SELC. Among the strongest is the observation that hydrolysis of cyclic imidatonium ions (**4** and **5**) produces only the amino esters (**6** and **7**), via C−N cleavage, rather than the hydroxy amides (**8** and **9**), which would be produced by C−O cleavage.[23]



This result is especially remarkable because the latter are more stable. This result also contrasts with the behavior of ordinary imidate esters and imidatonium ions. For example, in the hydrolysis of ethyl *N*-arylformimidate esters the yields of amine and ester decrease with increasing pH, until at pH >8 only the amide and alcohol products are observed.[24] This pH dependence is understandable: Under acidic conditions the tetrahedral intermediate, reactive as its conjugate base **10**$^-$, is protonated on nitrogen and undergoes primarily C−N cleavage because the amine is a better leaving group than the alkoxide. In base **10**$^-$ ordinarily undergoes C−O cleavage because the alkoxide is a better leaving group than a nitrogen anion.



The formation of amino ester from **4** and **5** even in base was thus interpreted in terms of SELC.[23,25] To understand its predictions, we consider the intermediate without any alkyl groups and show lone pairs only when there are two antiperiplanar to any leaving group. The intermediate is predicted to be formed as conformer **10ax**, with an axial hydroxy group and an equatorial *N*-methyl. This follows from combining SELC with the principle of microscopic reversibility, since the nucleophile should also enter antiperiplanar to two lone pairs. Since there are also two lone pairs antiperiplanar to the C−N bond, this is then predicted to cleave in preference to the endocyclic C−O bond, which has only one such lone pair (on OH or O$^-$).

Questions. It is puzzling that this behavior was seen not only in six-membered rings but also in five-membered ones. This is in sharp contrast to the hydrolysis of five-membered-ring

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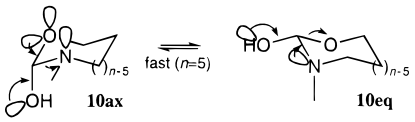
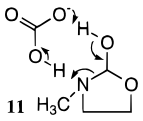


amidines, where counterstereoelectronic product was formed and attributed to participation by syn lone pairs.[17] By analogy syn lone pairs should facilitate C−O cleavage in **10ax** ($n = 5$) and lead to hydroxy amide.

Moreover, rapid pseudorotation of **10ax** ($n = 5$) must produce conformer **10eq**, in which two lone pairs are antiperiplanar to the C−O bond. Cleavage of this bond should lead to hydroxy amide. The absence of hydroxy amide is therefore doubly puzzling. It demands an explanation other than SELC.

An alternative explanation for the absence of hydroxy amide is bifunctional catalysis.[26,27] Bicarbonate ion was undoubtedly present under the conditions used previously.[23] It is known to increase the proportion of ester and amine in the hydrolysis of imidatonium ions[24,27] and imidates.[28] This catalysis is due to a simultaneous protonation of the nitrogen of **10** as the exocyclic oxygen is deprotonated, perhaps simultaneously with C−N cleavage, as illustrated in **11**. This explanation for the previous



results was raised, and it was proposed that those results can be explained without invoking orbital orientation.[29] Therefore the hydrolysis of imidatonium ions is worth reinvestigating. Besides, imidate esters are of interest for their synthetic applications.[30]

We here examine the role of buffer in the hydrolysis of cyclic imidatonium ions **4** and **5**. A comparison buffer must be operative at pH 10−12, it must not function as a bifunctional catalyst, and it should not interfere with ^{1}H NMR analysis of products. Both phenol and borate buffers have these characteristics, the latter further precluding general acid/base catalysis. We now show that elimination of bicarbonate switches the reaction toward C−O cleavage.

Experimental Section

Sample Preparation. Methyl trifluoromethanesulfonate (methyl triflate), 2-ethyl-2-oxazoline, 2-methyl-2-oxazoline, 2-phenyl-2-oxazoline (Aldrich), methyl iodide, 2,4,4-trimethyl-2-oxazoline, trimethyloxonium tetrafluoroborate (Lancaster), D_2O, CD_3CN, $CDCl_3$ (Cambridge Isotope Labs), and buffer constituents were purchased and used without further purification, except for one batch of discolored methyl iodide that was distilled before use. 2-Methyl- and 2-phenyl-2-oxazine were prepared from 3-aminopropanol and CH_3CN or PhCN.[31]

Imidatonium salts **4a**−**5b** were prepared by mixing the parent oxazoline or oxazine with equimolar methyl triflate or trimethyloxonium tetrafluoroborate or with excess methyl iodide, removing the volatiles in vacuo, filtering the crystals, and washing with cold dry ether.[23] The intensely hygroscopic salts were stored over P_2O_5 in an evacuated desiccator. Salts that became contaminated owing to partial hydrolysis were repurified by filtering and washing. Table 1 indicates the methylating reagents used and the characteristics of the resulting salts. Generally the triflates gave the best crystals and the purest salts, but neither the reactivity nor the product ratio of **4c** or **4d** varies with counterion.

Table 1. Imidatonium Ions

ion	R	R′	reagent	mp, °C
4a	CH_3	H	CH_3OTf	112−117
4b	CH_2CH_3	H	CH_3OTf	—[a]
4c	C_6H_5	H	$(CH_3)_3OBF_4$	134−136
4d	CH_3	CH_3	CH_3OTf	91−98[b]
5a	CH_3	H	CH_3I	—[a]
5b	Ph	H	CH_3OTf	—

[a] Viscous oil. [b] Lit. mp 100−102 °C.[32]

Stock buffer solutions in D_2O were prepared from KOH, K_2CO_3, $K_2CO_3 + CO_2$, $Na_2B_4O_7$, or phenol + NaOH, and their pD values were measured or calculated and corrected for D_2O.[33] Hydrolysis samples were prepared by adding 1 mL of buffer to 10 mg of imidatonium salt, followed by immediate shaking. These proportions ensure that the pD would not decrease significantly during the hydrolysis, except with phenol, owing to solubility limitations. The solution was transferred to an NMR tube, which was quickly inserted into the spectrometer. This preparation delay, before the first acquisition, was generally ca. 2 min.

^{1}H NMR Spectroscopy. All NMR spectra were acquired on a Varian Unity 500 spectrometer at 500 MHz. The temperature was 24−25 °C. Chemical shifts in D_2O and $CDCl_3$ are reported relative to *tert*-butyl alcohol (δ 1.10) and residual $CHCl_3$ (δ 7.63), respectively. Spectral characteristics of imidatonium ions were determined from solutions in unbuffered D_2O, in which hydrolysis is slow. Spectral characteristics of amino esters were determined from those solutions after overnight hydrolysis under conditions that generated acid, followed by neutralization to verify that the chemical shifts did not change by >0.1 ppm. Spectral characteristics of hydroxy amides were determined from strongly basic solutions allowed to equilibrate overnight. Except for **9d** *E* and *Z* rotational isomers were observed, with the major isomer being 51−57% of the total, in agreement with analogous amides.[34] The assignment as stereoisomers was confirmed through coalescence of ^{1}H NMR signals at 120 °C in DMSO-d_6. Table 2 lists the chemical shifts of compounds **4**−**9**, all easily assigned from chemical-shift correlations, splittings, and relative intensities. The CH_2O signals could be assigned by analogy to **4d**, **6d**, or **8d**, allowing the CH_2N signals to be assigned by a process of elimination.

Spectra during hydrolysis were acquired with eight scans, each with an acquisition time of 4 s and a subsequent delay of 1 s, so that the total time per spectrum was 40 s. Delays were programmed to space the acquisitions across a 90-min period. An "infinity" point was acquired at least 20 h after mixing.

Products. No reactant imidatonium ion was detectable in any solution with adequate buffer capacity. Hydrolysis is expected to be irreversible and too fast to follow by NMR, since the lifetimes of acyclic imidatonium ions at pH >10 are <10 s.[29]

The relative amounts of amino ester and hydroxy amide were measured by integrating their *N*-methyl peaks, summed over *E* and *Z* for the latter. (The α-methyl or methylene was not suitable, owing to base-catalyzed H/D exchange.) One complication is that the amino ester may isomerize to the more stable hydroxy amide. This is the familiar aminolysis of an ester, by base-catalyzed recyclization to **10ax** or **10eq**, followed by C−O cleavage. To correct for isomerization that occurred during the preparation delay, the amount of amino ester was extrapolated to time zero, either from the course of continuing isomerization in the

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Table 2. ^{1}H NMR Chemical Shifts of Reactants and Products in D_2O

species	N−CH_3	N−CH_2−	O−CH_2−	α-CH_nCO	other
4a	3.19	4.04	4.78	2.28	−
4b	3.64	4.29	4.98	2.75	1.30
4c	3.43	4.29	4.96	7.53−8.07	−
4d	3.05	−	4.55	2.25	1.35
5a[a]	3.51	3.88	4.79	2.61	2.50
5b	3.41	3.83	4.75	7.61−7.64, 7.71−7.75	2.40
6a	2.47	3.03	4.16	1.98	−
6b	2.69	3.31	4.08	2.25	0.94
6c	2.67	3.38	4.49	7.57−7.92	−
6d	2.39	−	3.98	2.01	1.20
7a	2.72	3.15	4.18	2.09	2.06
7b	2.74	3.25	4.43	7.55, 7.71, 8.06	2.20
8a[b]	2.78, 2.95	3.62, 3.57	3.39, 3.35	1.99, 1.97	−
8b[b]	2.95, 2.79	3.57, 3.62	3.37, 3.40	2.30	0.94
8c[b]	2.87, 2.78	3.19, 3.40	3.60, 3.43	7.2	−
8d	2.45	−	3.44	1.77	1.13
9a[b]	2.89, 3.05	3.61, 3.56	3.44, 3.40	2.12, 2.09	1.76, 1.84
9b[b]	2.64, 2.82	3.22, 3.12	3.44, 3.30	7.3−7.5	1.58, 1.64

[a] In $CDCl_3$. [b] E/Z isomers, major species first.

reaction mixture or from the extent of isomerization in a sample of amino ester prepared in unbuffered D_2O and quickly mixed with stock buffer. These two methods of extrapolation gave the same values. The largest extrapolation was a 2-fold increase for **4c** in pD 10 borate buffer.

Results

Homogeneous aqueous solutions were easier to study than the water−acetonitrile used previously.[23] Although we infer that those samples appeared to be homogeneous, other researchers observed heterogeneity,[27] and we too observed two liquid phases. With homogeneous aqueous solutions there was no question about which phase was in the NMR probe. This resulted in reduced line broadening and fewer unidentified peaks.

Product ratios in the various buffers are listed in Table 3. In the OD^- and K_2CO_3 buffers imidatonium ions **4a**−**c** produce only hydroxy amide (**8**). However, independent experiments showed that amino esters **6a**−**c** are rapidly isomerized to hydroxy amide under these conditions, as had been observed previously.[23] At lower pD (10−11) isomerization is slower, typically requiring 10−30 min, thus allowing detection of amino ester, whose concentration could be extrapolated to time zero. Under these conditions there is still appreciable hydroxy amide **8a**−**c** as kinetic product, in amounts as listed in Table 3.

Hydrolysis of the highly alkylated imidatonium ion (**4d**) is unusual in that it gives only the amino ester (**6d**), regardless of pD. This is not the thermodynamic product, since it does isomerize slowly to the corresponding hydroxy amide (**8d**).

The six-membered-ring imidatonium ions **5ab** produce only almost exclusively the amino esters **7**, but in borate buffer there is definitely a small amount of hydroxy amide **9**. Isomerization of amino ester is slower, so extrapolation to time zero introduces no uncertainty.

Discussion

Five-Membered Rings. The data in Table 3 show that at pD >13 only hydroxy amide **8** is detected from hydrolysis of **4a**−**c**. This result is uninformative, since amino esters **6a**−**c** are rapidly converted to hydroxy amide under these conditions. Although it is not possible to exclude **8** as the kinetic product under these conditions, which would be counter to SELC, it is most likely that amino ester **6** was produced and isomerized before an NMR spectrum could be acquired. In support of this interpretation, amino ester was detectable in a mixed solvent,[23] where the lower polarity reduces the rate of isomerization. Since we cannot determine the kinetic product mixtures at high pD, we cannot use such experiments to study SELC.

Results in borate and phenol buffers are quite informative. Under these less alkaline conditions isomerization is slow enough that hydroxy amide **8a**−**c** can be seen to be the major kinetic product from **4a**−**c**, and amino ester **6a**−**c** represents only 9−35% of the product mixture. For **4b**,**c** there is less hydroxy amide at lower pD, as with other imidates and imidatonium ions.[24] Therefore the formation of hydroxy amide **8** is not a consequence of the lower alkalinity of the borate and phenol buffers.

In the bicarbonate buffers amino ester **6a**,**c** is the major kinetic product from **4a**,**c**. This corroborates the results that were presented as evidence for SELC.[23] Nevertheless, at the same pD in borate buffer hydroxy amide **8a**−**c** is the major product. Any stereoelectronic effect on the direction of cleavage should be independent of buffer. Therefore the formation of amino ester **6** in bicarbonate buffer, even in the earlier study, must be attributed to bifunctional catalysis (**11**), and not to SELC. The obervation that there is no significant difference between borate and phenol buffers of the same pD shows further that general acid/base catalysis is not involved, but that bicarbonate is truly operating as a bifunctional catalyst.

This observation also shows that the change in product is not due to cleavage of an intermediate resulting from nucleophilic addition of phenoxide (or bicarbonate) to **4**. Such an intermediate is likely to revert to **4**, rather than undergo cleavage to species that are less stable. Therefore even in these buffers the reactive intermediate is **10** or $\mathbf{10}^-$.

A key result is that the preference (65−91%) for hydroxy amides **8** in borate buffers contradicts the previous observation that only amino esters are formed.[23] That was the experimental evidence that had been presented for SELC but which was viewed above as a puzzle. Now the puzzle is solved by recognizing that **10eq** ($n = 5$) is indeed accessible and does cleave to hydroxy amide. The formation of hydroxy amide is simply a consequence of the greater leaving-group ability of alkoxide over a nitrogen anion, as with other imidates,[24] and the products neither support nor contradict SELC.

A Special Case. The hydrolysis of imidatonium ion **4d** is more difficult to rationalize in terms of leaving-group abilities. Only amino ester **6d** is produced under all conditions. This is opposite to the behavior of $CH_3C(OEt){=}NR_2^+$, where steric hindrance reduces the extent of C−N cleavage.[29] It is likely that the selectivity is due to steric repulsion between the pseudoaxial methyl at C4 and the pseudoaxial hydroxyl at C2, as has been proposed in similar cases.[23] If this is relieved by cleaving the C−N bond, then the nitrogen becomes a better leaving group. Relief of steric repulsion has similarly been proposed to account for preferential cleavage of the C−O bond adjacent to the axial methyl of 4,6-dimethyl-1,3-dioxanes.[23,35]

Six-Membered Rings. In bicarbonate buffer hydrolysis of imidatonium ion **5a** or **5b** produces only amino ester **7a**,**b**, confirming the previous result.[23] However, in borate buffer of the same pD there is definitely 3 or 4% of hydroxy amide **9a**,**b**. The dominant product is the one expected from SELC, but exclusive formation of this product in bicarbonate can now be recognized as a consequence of bifunctional catalysis. The stabilization attributable to two antiperiplanar lone pairs, even in this best case, is then only ca. 2 kcal/mol, not the 5 kcal/mol originally suggested.[5]

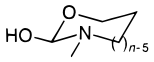
(35) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymm.* **1990**, *1*, 477. Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089.

Table 3. Percentage of Hydroxy Amide from Hydrolyses of Imidatonium Ions **4** and **5**

buffer	pD	**8a**	**8b**	**8c**	**8d**	**9a**	**9b**
0.9 M KOD	14.9			100	0		
1.9 M K_2CO_3	13.1	100	100	100			
0.4 M borate/KOD	11.3		65 ± 3	91 ± 3			
$KDCO_3$	10.0	21 ± 7		0	0	0	0
0.6 M borate	10.0	70 ± 10	66 ± 3	52 ± 4	0	2.8 ± 0.3	4.5 ± 0.1
0.05 M phenol	≤ 10.4	78 ± 12		65 ± 3			

Stereochemistry of Bifunctional Catalysis. The observation that bicarbonate shifts the product distribution toward amino ester **6** or **7** has further implications for SELC. The transition state for bifunctional catalysis (**11**) has an eight-membered ring (including the two protons). This requires that the hydroxyl group which loses a proton and the nitrogen lone pair which accepts a proton must be syn to each other. Such a relationship is impossible with conformer **10ax**, where those functionalities are anti, with a geometry equivalent to a strained *trans*-cyclooctene.

Since bifunctional catalysis does occur, conformers of the intermediate other than **10ax** must be formed. With five-membered rings this could be **10eq**, formed by rapid pseudorotation. With six-membered ones ring inversion to **10eq** is likely to be slower than cleavage. An alternative possibility is that hydroxide attack syn to lone pairs on N and O produces conformer **12**, with the hydroxyl and the nitrogen lone pair in



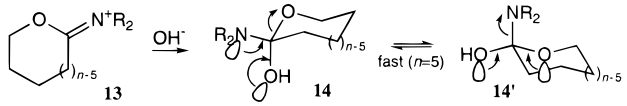
12

a syn relationship. It is not certain whether stereoelectronic control is lost in the formation of the tetrahedral intermediate or in its breakdown. It seems likely that the latter step is less selective, owing to the push of the $-O^-$.[17]

Does Stereoelectronic Control Determine Products? In contrast to amidines, where exocyclic cleavage is inconsistent with the predictions of SELC,[17] these results do not represent counterexamples to SELC. They can be attributed simply to relative leaving abilities of oxygen and nitrogen, which outweigh the influence of SELC. It had been thought that SELC dominates, but the results in carbonate solution were misleading.

The comparison of five- and six-membered rings is evidence both for and against SELC. If leaving abilities were the only determinant of product ratios, they would be independent of ring size. The major products from **5a**,**b** are amino esters **7a**,**b**, as expected from SELC, but they are not the exclusive product because leaving abilities can counter the benefit from antiperiplanar lone pairs. If antiperiplanar lone pairs were so crucial, amino esters should have been the dominant or exclusive products.

One additional piece of evidence claimed to support SELC is the observation that "syn" imidatonium ions **13** hydrolyze to hydroxy amides.[23] For six-membered rings this is admittedly consistent with SELC, since the intermediate **14** ($n = 6$) has two lone pairs antiperiplanar to the alkyl oxygen. However, in five-membered rings rapid pseudorotation of the intermediate must lead to conformation **14′** ($n = 5$), with two lone pairs



13 **14** **14'**

antiperiplanar to the C−N bond. That this did not undergo cleavage to form the amino ester (with proton transfers as necessary) means that there is another factor responsible. Indeed, these results can more consistently be attributed to the destabilization of lactones, as in ortho ester hydrolysis, without ever requiring a role for antiperiplanar lone pairs.[15]

Conclusions

The apparent preference for C−N cleavage in alkaline hydrolysis of five-membered-ring imidatonium ions was confirmed. Nevertheless, it is not due to stereoelectronic control but to bifunctional catalysis by bicarbonate ion. In the absence of bicarbonate catalysis and steric repulsion, the hydroxy amide is the predominant kinetic product (65−91%), as with other, noncyclic imidates, where selectivity is governed by leaving-group abilities. Stereoelectronic control does operate in six-membered rings and provides only ca. 2 kcal/mol toward reduction of the activation energy. This is less than the stabilization that had been inferred from product studies under conditions of bifunctional catalysis. The operation of bifunctional catalysis is further evidence for conformations counter to the predictions of stereoelectronic control.

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