Absence of Stereoelectronic Control in the Hydrolysis of Fully and Partially *N*-Alkylated Cyclic Amidinium Ions

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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. Yet substantial amounts of lactams were produced from hydrolysis of cyclic amidines, through cleavage of the exocyclic C–N bond that is antiperiplanar to only one lone pair and syn to the other. It may be that proton transfer catalyzes nitrogen inversion, leading to an intermediate with two antiperiplanar lone pairs, such that the product distribution is indeed consistent with stereoelectronic control. To exclude this possibility, three cyclic amidinium ions (**1a,b,c**) with methyl groups at both nitrogens were synthesized, and their hydrolysis products in $NaOD/D_2O$ were analyzed by NMR. Although stereoelectronic control favors ring opening to amino amide **3**, substantial amounts (40–90%) of lactam **4** are again produced. To exclude the possibility that lactam formation is due to a steric effect, hydrolysis of a cyclic *N,N'*-dimethyl amidine (**2**) was also studied, and 26–35% lactam is still produced. These results cannot be rationalized by assuming reaction via a boat conformer, since the lone pair of the ring nitrogen does not become antiperiplanar even in the boat form. Thus stereoelectronic control is not operative in amidine hydrolysis.

Introduction

Stereoelectronic Control. Chemical reactivity can be affected not only by steric bulk of substituents but also by the orientation of nonbonding lone pairs of electrons. For example, it is a tautology that a lone pair cannot be orthogonal to the orbital with which it must bond in order to promote the reaction.[1] More problematic is Deslongchamps' hypothesis of stereoelectronic control,[2] sometimes known as the "antiperiplanar lone-pair hypothesis",[3] which states that preferential cleavage of a tetrahedral intermediate occurs when there are two lone pairs antiperiplanar to a leaving group. This is consistent with a preference for anti E2 elimination,[4] and MO calculations support the hypothesis.[5] For some transition states, the energetic benefit due to two lone pairs antiperiplanar to the leaving group has been estimated to be at least 5 kcal/mol.[6] This hypothesis has been widely accepted, with limited but spirited opposition[7] and occasional counterexamples.[8]

A key piece of evidence presented in support of this hypothesis was the observation that a cyclic hemiorthoester cleaves the endocyclic bond to give exclusively the hydroxy ester rather than the lactone.[9] Nevertheless this observation[10] and this interpretation have been challenged.[11] In five-membered rings conformational changes known to be rapid[12] ought to have led to the lactone, which is not observed (except in acid[10]). Therefore an alternative explanation based on the well-known destabilization[13] of lactones was proposed.[11] It was further concluded that all the observed results from hydrolyses of acetals, amides, and imidates can be explained on the basis of lactone instability, the instability of anti (*E*) esters, or steric effects, without ever requiring stereoelectronic control.

An unambiguous test is required. It is essential to design proper tests for the hypothesis, especially since it is an important one that offers power in stereoselective organic synthesis[14] as well as understanding of enzymatic processes.[15]

A more reliable test for stereoelectronic control is the hydrolysis of a cyclic amidine, via a hemiorthoamide intermediate. The mechanism is shown in Scheme I. If the hypothesis of stereoelectronic control is correct, then it is a corollary of the principle of microscopic reversibility that there is a preference for initial OH^- attack on the amidinium ion to occur antiperiplanar to two nitrogen lone pairs, to produce **A** as the initial intermediate. After (rapid) rotation about the exocyclic C–N bond, this intermediate has two lone pairs antiperiplanar to the endocyclic C–N bond but only one lone pair antiperiplanar to the exocyclic bond. According to the hypothesis, this geometry favors cleavage of the endocyclic bond and formation of the ring-opened product, the amino amide **B**. Cleavage of the exocyclic bond and formation of the lactam **C** could utilize the antiperiplanar lone pair on the oxygen and the syn lone pair on the ring nitrogen. In contrast to hemiorthoesters, ring inversion, leading to conformer **D**, 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 **E**. Even though this conformer could cleave to the lactam, it is inaccessible during the lifetime of the intermediate because nitrogen inversion is slow compared

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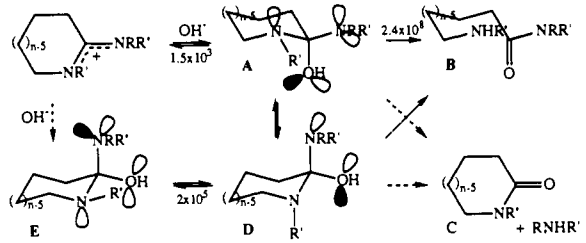
Scheme I. Stereoelectronic Control in Hydrolysis of *n*-Membered-Ring Amidines.[a]



[a] Two lone pairs antiperiplanar to a leaving group are shown as open lobes. Reactions where there is only one antiperiplanar lone pair, shown as a filled lobe, are designated with a dashed arrow.

to the rate of cleavage. Thus if stereoelectronic control is operative, the amino amide **B** is predicted to be the kinetic product.

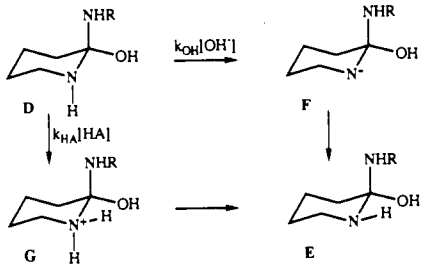
Amidine hydrolysis has a further advantage. In reactions that create or destroy acetals, the faster reaction syn to a lone pair on oxygen has been rationalized by assuming reaction via a boat conformer.[16] Then one of the oxygen's two lone pairs becomes antiperiplanar to the attacking nucleophile or the leaving group. However, in the hemiorthoamide intermediate in amidine hydrolysis, the ring nitrogen has only one lone pair, which does not become antiperiplanar even in the boat form. Therefore this rationale is not available.

Initial experiments with R = H = R′ showed that the amino amide is indeed the sole product in the hydrolysis of amidines,[11] thereby supporting stereoelectronic control. Unfortunately, this result too is ambiguous, owing to a mismatch of leaving abilities.[17] This can be overcome by methylation at the exocyclic nitrogen (Scheme I, R′ = H, R = CH_3). Again, if stereoelectronic control is operative, the product is expected to be the amino amide **B**. Yet experimentally,[18] substantial amounts (>50%) of five- and seven-membered-ring lactams **C** are observed, implying that stereoelectronic control is not operative in these systems. It is operative but weak in six-membered rings, where 93% amino amide is produced.

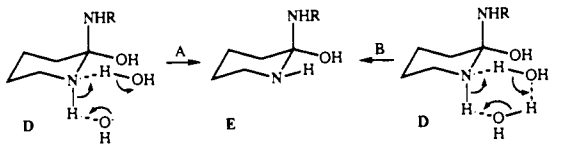
This study depends crucially on the assertion that nitrogen inversion is slow. The rate of nitrogen inversion was taken from experimental values on tertiary amines, rather than secondary amines as in intermediate **D** (R′ = H, R = CH_3). There are additional proton-transfer mechanisms for nitrogen inversion in secondary amines. It has long been recognized that trace acids can interchange the proton and the lone pair, thereby catalyzing nitrogen inversion.[19] Indeed, Deslongchamps[20] has assumed (perhaps by mistaken analogy to hydroxyl proton exchange) that nitrogen inversion is fast, so that lactam formation would be consistent with his hypothesis.

There are four proton-transfer mechanisms for nitrogen inversion, two stepwise and two concerted. The stepwise mechanisms are shown in Scheme II. The first of these is deprotonation followed by reprotonation, but this involves an unstable aminide anion **F**, so it would be far too slow. Alternatively, the order of the two steps can be reversed, and protonation can be carried out by either H_2O or H^+ as acid, with a total rate constant $k_dK_w/K_a + k_p[H^+]$, where K_a is the acidity constant of **G**, $K_w = [H^+][OH^-] = 10^{-14}$, and k_d and k_p are diffusion-controlled rate constants for deprotonation by OH^- and for protonation by H^+. Since $[H^+] < 10^{-7}$ M in alkali and K_a can be estimated[21] as 10^{-8}, it follows

Scheme II. Mechanisms for Nitrogen Inversion via Stepwise Proton Exchange



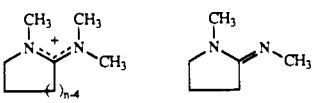
Scheme III. Mechanisms for Nitrogen Inversion via Concerted Proton Exchange



that, even if k_d and k_p are 10^{10} M^{-1} s^{-1}, the total rate constant is only 10^4 s^{-1}. Thus this mechanism is also too slow to contribute.

The concerted mechanisms involve simultaneous protonation and deprotonation, catalyzed by OH^- (A in Scheme III) or by *n* water molecules (B in Scheme III, with *n* arbitrarily equal to 2). Indeed, the OH^--catalyzed mechanism was postulated by Deslongchamps for the intermediate in hydrolysis of amides.[22] These are interesting mechanisms that have only recently been detected.[23] Thus one possible explanation for lactam formation is that nitrogen inversion is catalyzed by concerted proton exchange at the endocyclic nitrogen. This would produce conformer **E** of Scheme I (R′ = H), whose cleavage to lactam would still be consistent with the hypothesis of stereoelectronic control. It is important to determine whether previous results that seem to contradict the hypothesis might have overlooked these mechanisms for nitrogen inversion.

This Investigation. Proton-transfer mechanisms for nitrogen inversion can be blocked by substituting a methyl group for the hydrogen of the endocyclic nitrogen. To maintain balance between the leaving abilities of the two nitrogens, it is also necessary to add a second methyl to the exocyclic nitrogen. Therefore we have determined the product distribution from the base-catalyzed hydrolyses of 1-methyl-2-(dimethylamino)pyrrolinium (**1a**), 1-methyl-2-(dimethylamino)-3,4,5,6-tetrahydropyridinium (**1b**), and 1-methyl-7-(dimethylamino)-3,4,5,6-tetrahydro-2*H*-azepinium (**1c**) iodides in D_2O. In the hemiorthoamide intermediates derived from these amidinium ions, uncatalyzed nitrogen inversion is slow, nitrogen inversion by proton transfer is blocked, leaving abilities are matched, and there is no enthalpic preference for either of the products. Thus predominant formation of amino amide would support the hypothesis of stereoelectronic control, whereas formation of any substantial amount of lactam would represent a counterexample to this hypothesis.



1a, *n*=5
1b, *n*=6
1c, *n*=7

2

Also, as a control to eliminate the possible influence of steric repulsions, we have studied the product distribution from hydrolysis of 1-methyl-2-(methylimino)pyrrolidine (**2**), even

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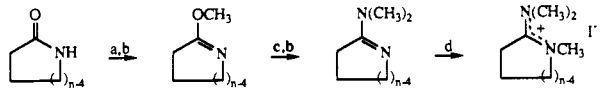
Scheme IV.[a] Synthesis of Cyclic *N,N',N'*-Trimethylamidinium Iodides **1a–c** (n = 5, 6, 7)



[a] (a) $(CH_3O)_2SO_2$, benzene, 65 °C. (b) aqueous NaOH. (c) $(CH_3)_2NH_2^+$ Cl^-, methanol. (d) CH_3I, acetonitrile.

though this does not have balanced leaving abilities. In this case both stereoelectronic control and leaving abilities ought to favor amino amide formation, so lactam formation would be even more devastating to the hypothesis.

This study complements a recent one on the kinetics and products of hydrolysis of some amidinium ions with four-membered rings, related to penicillins.[24] Besides, hydrolysis of amidinium ions is of interest, since the amidinium functionality is a recognition element in a self-replication system,[25] benzamidine derivatives behave as inhibitors of serine proteases,[26] cyclic amidines are anthelmintic and antibacterial agents,[27] and an amidine analog of glucose is an inhibitor of glycosidases.[28]

Experimental Section

Materials. The following compounds were used without further purification: γ-butyrolactam, *N*-methylbutyrolactam, *N*-methylvalerolactam, *N*-methylcaprolactam, dimethylamine hydrochloride, and D_2O (Aldrich), δ-valerolactam (Lancaster), ε-caprolactam (Matheson, Coleman, and Bell), dimethyl sulfate (Eastman), methyl iodide, K_2HPO_4 (Mallinckrodt), $K_3PO_4 \cdot 3H_2O$ (Merck), and sodium hydroxide (Fisher). All melting points were determined on samples in sealed tubes.

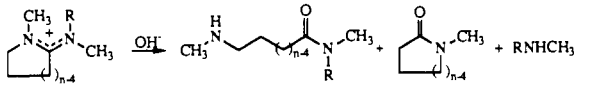
Synthesis. The trimethylamidinium salts were synthesized according to Scheme IV. Amidines were prepared from the lactams via the imino ethers according to the method of Etienne and Correia:[29] 2-(dimethylamino)-1-pyrroline bp 90–92 °C/30 Torr (lit.[29] 92–95 °C/45 Torr), 2-(dimethylamino)-3,4,5,6-tetrahydropyridine bp 100–104 °C/24 Torr (lit.[30] 70–72 °C/1 Torr), 7-(dimethylamino)-3,4,5,6-tetrahydro-2*H*-azepine bp 115–119 °C/24 Torr (lit.[30] 78–80 °C/1 Torr). The amidinium iodides were then prepared according to the procedure of McKennis and Smith.[31] Methyl iodide (13.7 g, 0.096 mol) was added to a solution of 2-(dimethylamino)-1-pyrroline (3.2 g, 0.029 mol) in 15 mL of acetonitrile. After 30 s the temperature rose to 55 °C and the solution boiled vigorously. After the reaction mixture had cooled to room temperature, it was refluxed gently for several hours. A thick orange oil formed after removal of the acetonitrile at 1 Torr. The oil was washed with five 4-mL portions of dry THF in a drybox to give white crystals of 1-methyl-2-(dimethylamino)-pyrrolinium iodide **1a** (6.3 g, 0.026 mol, 90%), which were stored in a drybox because of their extremely hygroscopic nature: mp 180–181 °C; ^{1}H NMR ($CDCl_3$) δ 2.25 (p, J = 7.8, 2 H), 3.20 (t, J = 7.8, 2 H), 3.39 (s, 6 H), 3.47 (s, 3 H), 3.90 (t, J = 7.2 Hz, 2 H). 1-Methyl-2-(dimethylamino)-3,4,5,6-tetrahydropyridinium iodide [**1b**: mp 126–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 4 H), 2.92 (t, J = 6.3 Hz, 2 H), 3.29 (s, 6 H), 3.37 (s, 3 H), 3.56 (t, J = 5.7 Hz, 2 H)] and 1-methyl-7-(dimethylamino)-3,4,5,6-tetrahydro-2*H*-azepinium iodide [**1c**: mp 100–105 °C; ^{1}H NMR (CD_3COCD_3) δ 1.81 (m, 6 H), 3.11 (m, 2 H), 3.33 (s, 6 H), 3.39 (s, 3 H), 3.68 (m, 2 H)] were prepared by exactly the same procedure.

1-Methyl-2-(methylimino)pyrrolidine (**2**) hydrochloride was prepared by heating 4-chlorobutyronitrile and 3 equiv of methylamine in absolute ethanol overnight in an autoclave: mp 161–165 °C from ethanol/ether (lit.[32] 169–170 °C); ^{1}H NMR ($CDCl_3$) δ 2.27 (p, J = 7.7 Hz, 2 H), 2.97 (t, J = 8.0 Hz, 2 H), 3.11 (d, J = 4.7 Hz, 3 H), 3.39 (s, 3 H), 3.76 (t, J = 7.4 Hz, 2 H), 10.62 (b s, 1 H).

Hydrolysis. All hydrolyses were carried out in an NMR tube. Approximately 0.2 mmol of the amidinium iodide or amidine hydrochloride and 0.3 mmol of freshly ground sodium hydroxide or $K_3PO_4 \cdot 3H_2O$ were added to an NMR tube. The reaction was initiated by addition of 1.0 mL of D_2O, chosen to avoid the necessity of suppressing solvent NMR signals. Alternatively 0.2 mmol of amidinium iodide was dissolved in 1 mL of 0.3 M DPO_4^{2-} + 0.3 M PO_4^{3-} in D_2O (measured[33] pD = 12.4). The amidinium salt or amidine was allowed to hydrolyze at 25 °C for several hours, and the ^{1}H NMR spectra of the resulting product mixture was recorded on a GE QE-300 300-MHz spectrometer or a Bruker AMX-500 500-MHz spectrometer. The water OH signal was used as internal standard (δ 4.8 ppm). Product ratios were determined by integration of several sites. Each hydrolysis was performed three to five times, and the product ratios were averaged.

Results

Chemical Shifts. The products from hydrolysis of the cyclic amidinium ions are the amino amide **3** and the lactam **4** plus dimethylamine (**5**; R = CH_3) or methylamine (**5**; R = H). The



1, R=CH_3
2·H$^+$, R=H

chemical shifts of these products in excess hydroxide are listed in Table I; shifts in phosphate buffer generally differ by only 0.1 ppm. Signal assignments are based on generally accepted chemical shifts and were confirmed by addition of the appropriate authentic *N*-methyllactam. The signals of the amino amide can then be assigned by a process of elimination. The *E* and *Z* methyl peaks of the tertiary amino amide are readily distinguished and are usually well separated from the *N*-methyl peak of the lactam. In general the amino methyl signals of the amino amide and of methylamine or dimethylamine overlap. The signal of the methylene adjacent to the carbonyl is weak owing to rapid base-catalyzed exchange of reactant with D_2O. All other methylene signals are well separated except for **1c**, where the NCH_2 overlaps with the $CH_2C{=}O$.

Stability of Product Mixtures. No quantitative study of the reaction rate was undertaken. With 1.5 equiv of NaOH, no starting material can be detected after 2 h. With 1.0 equiv or in phosphate buffer, the reaction requires several hours. For **1a–c** the product ratio changed by no more than ±3% over several hours, demonstrating that conversion of the amino amide to the more stable lactam is slow. Therefore experimental product ratios are indeed kinetically determined, and there is no need to extrapolate product ratios to time zero. This contrasts with amino amides having fewer alkyl groups on nitrogen, where there is less steric hindrance to intramolecular nucleophilic attack by amine on amide.[11,18] For **2**, amino amide slowly disappeared, and the proportion observed was extrapolated to time zero.

Product Ratios. Product ratios were determined from integration of the characteristic peaks and are tabulated in Table II. Accurate product ratios could be determined from three sites: (a) the amide methyls, (b) the methylenes α to the nitrogens, and (c) the methylenes β to the nitrogens. The overly optimistic errors reported in Table II are derived simply from replicability, ignoring systematic errors from baseline curvature or slight overlap with other peaks. Indeed, the differences among the three sites vary by as much as ±5%, and this is a more realistic estimate of the reliability of the product ratios.

It is clear that substantial amounts of lactam are produced in the hydrolysis of these amidinium ions **1a–c** and of the amidine

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Table I. Chemical Shifts of Products of Amidinium Ion or Amidine Hydrolysis

	δ (**1a**, $n = 5$)		δ (**1b**, $n = 6$)		δ (**1c**, $n = 7$)		δ (**2**, $n = 5$)	
assignment	**3**	**4 + 5**	**3**	**4 + 5**	**3**	**4 + 5**	**3**	**4 + 5**
$CONCH_3$	*Z* 2.93 (s) *E* 3.09 (s)	2.82 (s)	*Z* 2.96 (s) *E* 3.13 (s)	2.95 (s)	*Z* 2.88 (s) *E* 3.06 (s)	2.92 (s)	*Z* 2.71 (s)	2.82 (s)
$NHCH_3$	2.29 (s)	2.27 (s)	2.32 (s)	2.31 (s)	2.23 (s)	2.23 (s)	2.27 (s)	2.27 (s)
NCH_2	2.54 (t)	3.50 (t)	2.56 (t)	3.40 (t)	2.49 (t)	3.44 (t)	2.49 (t)	3.49 (t)
$CH_2C{=}O$	*a*	2.42 (t)	*a*	2.37 (t)	*a*	2.49 (m)	2.25 (t)	2.41 (t)
β-(CH_2)	1.73 (p)	2.04 (p)	1.55 (m)	1.83 (p)	1.31 (m) 1.43 (m)	1.59 (m) 1.70 (m)	1.73 (p)	2.03 (p)

[a] Weak and obscure owing to exchange with D_2O.

Table II. Product Ratios (% Lactam, ±2%) from Hydrolyses of Cyclic Amidinium Ions

site	**1a**[a]	**1b**[a]	**1b**[b]	**1c**[a]	**1c**[b]	**2**[a]	**2**[b]
$CONCH_3$	78	44	72	81	92	26	35
NCH_2	77	38	70	*c*	*c*	26	34
β-(CH_2)	81	38	69	83	*c*	26	34

[a] In excess NaOD (pD > 13). [b] In phosphate buffer (pD < 12.4). [c] Not determined, owing to peak overlap.

2. This agrees with hydrolyses of four-membered-ring amidinium ions,[24] despite the relief of ring strain on forming the amino amide. Lactam formation from the hydrolyis of **1b** ($n = 6$) is significantly less than from **1a** ($n = 5$) and **1c** ($n = 7$). This agrees with earlier observations[18] on hydrolyses of cyclic amidines.

Discussion

One test of any theory of reactivity is its ability to predict product distributions. In the hydrolyses of these cyclic amidinium ions there is substantial lactam formation (25–90%). Yet a strong prediction of the hypothesis of stereoelectronic control is that lactam ought not to be produced. Scheme I and the surrounding text present this prediction. However, it is necessary to consider all possible flaws in this prediction, lest lactam formation be unexpectedly consistent with the theory.

The following mechanism has been established[34] for the hydrolysis of amidinium ions under strongly basic conditions: initial attach by OH^-, deprotonation from oxygen, and finally C–N cleavage with concerted protonation at nitrogen (or possibly preprotonation at nitrogen). Scheme I shows the stereochemical aspects of this mechanism for cyclic amidinium ions, but with proton-transfer steps omitted, such that the intermediate that cleaves is actually the conjugate base of what is shown.

The key to the prediction of stereoelectronic control is that product arises only from conformers **A** and **D** and that conformer **E** is not accessible during the lifetime of the intermediate. Conformers **A** and **D** permit cleavage only to amino amide **B**, whereas only **E** has two lone pairs antiperiplanar to the exocyclic nitrogen, to permit cleavage to lactam **C**. There are two possibilities for forming **E**: (1) directly from the original amidinium ion and (2) from **A** by ring inversion plus nitrogen inversion.

Reversibility of Initial Attack. Direct formation of **E** from amidinium ion would require OH^- attack syn to the lone pair on the ring nitrogen. If instead initial attack must occur antiperiplanar to the lone pairs on both nitrogens, only **A** can be formed as the initial intermediate. This first step must be irreversible if the product distributions are to test stereoelectronic control. Otherwise repeated loss of OH^- and rare but eventual syn attack on the amidinium ion could directly produce the equilibrium mixture of conformers **A** and **E**. Although rate constants are not known for each step in these particular hydrolyses, they have been estimated by extrapolation,[18] and the values are included in Scheme I. From an estimated pK_a of 13.9 for the intermediate and the rate constants for its reversion to amidinium ion and for cleavage (of its conjugate base) to product, it follows that the first step becomes rate-limiting at pD > 8.7. Under the strongly alkaline conditions of these experiments, the first step thus seems to be irreversible.

These esimated rate constants are unlikely to be grossly in error, but they disagree with inferences from recent results on four-membered-ring amidinium ions. The rate constant for reversion of intermediate to amidinium ion has been inferred[24] as 10^9 s^{-1}, not 1.5×10^3 s^{-1}, on the basis of a slight (<5-fold) increase in rate in highly alkaline (and therefore nonideal) solutions and of the questionable assumption that the rate-limiting step at high pH is encounter-limited deprotonation of the intermediate by OH^-. If the reaction second-order in OH^- near pH 13 is real, then the first step is reversible below this pH, rather than below pD 8.7. It may be that the highly substituted four-membered-ring amidinium ions are a special case, but even if the first step is reversible, the published rate constants mean that at least 20% of the initial attacks do lead to cleavage. This is too frequent for a rare syn attack to produce conformer **E** directly. Therefore lactam formation cannot be attributed to reversibility of the initial step.

Conformational Mobility. The alternative possibility for formation of conformer **E** is that the intermediate undergoes ring inversion and nitrogen inversion. (This may occur in either order, although Scheme I shows only one.) Both inversion processes are required, since, in contrast to cyclic hemiorthoesters, ring inversion in cyclic hemiorthoamides conserves the number of lone pairs antiperiplanar to the exocyclic C–N bond. Ring inversion may be slow in six-membered rings,[35] but it is quite rapid in five- and seven-membered rings.[36] Regardless of the rate of rate inversion, the rate of nitrogen inversion in aqueous solution is especially low, about 3×10^5 s^{-1}.[37] Since this is considerably slower than cleavage, which proceeds at $>10^8$ s^{-1},[18,24] conformer **E** was considered to be inaccessible during the lifetime of the intermediate. Yet there are other mechanisms that might permit faster nitrogen inversion and render **E** accessible.

The purpose of this study was to investigate whether a proton-transfer mechanism for nitrogen inversion might account for products from previous amidine hydrolyses. In the present experiments, proton transfer has been blocked by methylation at nitrogen and yet the same products are obtained. Rapid nitrogen inversion (along with rapid ring inversion) can therefore be excluded as an explanation for lactam formation.

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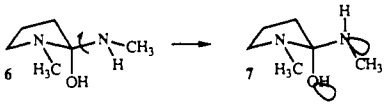
Leaving Abilities. Since a nitrogen anion is a terrible leaving group, the nitrogen must be protonated. Therefore basicity is important to leaving ability, and the more basic amine is the one that is cleaved more rapidly.[38] Early hydrolyses of cyclic amidines seemed to indicate that stereoelectronic control was operative,[11] but the result was due to a mismatch of leaving abilities.[17] When the leaving groups were primary amines of equal basicity,[18] it was possible to show that stereoelectronic control is weak or absent.

In hydrolysis of **1a–c**, the leaving groups are both secondary amines presumably of the same basicity. Consequently neither product is favored through an imbalance of leaving abilities. In **2** the leaving abilities are imbalanced because the competition is between primary and secondary amines. According to bicyclic[39] and acyclic[17] models, cleavage of the endocyclic C–N bond, leading to secondary amine, ought to be preferred by 3- to 4-fold. Therefore the imbalance of leaving groups does not favor lactam, so lactam formation here is an even stronger counterexample to stereoelectronic control.

Product Stabilities and Steric Effects. The salient evidence for stereoelectronic control had been the formation of hydroxy esters from the hydrolyses of hemiorthoesters.[2] However, these results are biased against formation of lactone because of its inherent instability.[12] Hydrolysis of amidines and amidinium ions avoids this bias. In the absence of steric repulsion, the *E* configuration of a secondary amide is only slightly (0.5–1.5 kcal/mol) less stable than the *Z*.[40] Thus the lactam **C**, which is equivalent to an *E* amide without steric repulsion, does not suffer from the instability of a lactone, so there is no thermodynamic preference against its formation.

With tertiary amides there is a potential complication from steric effects. Might lactam be formed from amidinium ions **1a,b,c** simply because exocyclic C–N cleavage relieves steric congestion? Although cleavage of either C–N bond produces a tertiary amide, endocyclic cleavage leads to an *N,N*-dimethyl amide where the *E* methyl suffers ca. 2 kcal/mol of repulsion.[40] Therefore the product stabilities of amide and lactam are not necessarily balanced.

To eliminate this steric effect, the cyclic *N,N'*-dimethylamidine **2** was also investigated. The results of its hydrolysis in base are included in Table II. The reactive species is the amidinium ion, which takes the *EZ* configuration.[41] The initial conformer resulting from OH^- attack is **6**. Rapid ($<10^{-8}$ s)[42] rotation about the exocyclic C–N bond then produces **7**, which now has two lone



pairs antiperiplanar to the endocyclic C–N bond. Cleavage of this bond produces the more stable *Z* amide, depicted in **3** (R = H). This preferential cleavage of the amine whose alkyl group is initially *Z* has been detected previously in hydrolysis of acyclic amidines.[17] However, the *N*-methyl on the ring still precludes nitrogen inversion by proton exchange; so conformers like **E** are still inaccessible, and cleavage of the exocyclic nitrogen is still prohibited. Therefore cleavage of the endocyclic C–N bond, leading to secondary amine, is favored by both stereoelectronic control and by the imbalance of leaving abilities. Indeed, there is more amino amide from **2** than from **1a**. Nevertheless there is substantial cleavage of the exocyclic C–N bond, leading to 26–35% lactam, which is not appreciably different from the 3- to 4-fold preference expected from leaving abilities. Therefore stereoelectronic control is not responsible for directing the C–N cleavage in either this amidine or the fully *N*-methylated amidinium ions.

pD Dependence. The results in Table II show that there is a small but significant increase in the proportion of lactam product at lower pD. This agrees with the behavior of highly substituted four-membered-ring amidinium ions.[24] However, it is opposite to that of simpler five-membered-ring amidines,[18] where it was attributed to competition between rotation about the exocyclic C–N bond and cleavage, which becomes faster in strong base. In the intermediates from the more highly alkylated amidinium ions, the rotation of the exocyclic dialkylamino group is expected to be faster. This places the lone pair of the exocyclic nitrogen where it can accept a proton from the hydroxyl, via bifunctional or one-encounter catalysis. The facilitated cleavage of this nitrogen then leads to more lactam in the buffered solutions of lower pD.

Ring Size. The preference for anti elimination has been attributed[7] to the Principle of Least Nuclear Motion.[43] However, this is only a "default" theory, applicable in the absence of knowledge about energetics, and the preference may actually be traceable to better HOMO–LUMO overlap in the transition state for anti elimination.[44] Experimentally, anti elimination in six-membered rings is indeed strongly preferred.[45] Nevertheless syn eliminations in five- and seven-membered rings are quite competitive with anti eliminations.[46] They are not at all unusual. The formation of lactam demonstrates that the syn lone pair on the ring nitrogen is quite suitable for facilitating cleavage. Stereoelectronic control should not have been expected to be so universal as to operate even in five- and seven-membered-ring hemiorthoamides.

Even in the six-membered-ring amidines, stereoelectronic control is not very strong, since substantial amounts of lactam are produced. This represents a failure of the antiperiplanar lone-pair hypothesis. In reactions that create or destroy acetals, such a failure can be avoided by assuming reaction via a boat conformer,[16] which places one of the oxygen lone pairs antiperiplanar to the attacking nucleophile or the leaving group. However, a nitrogen has only one lone pair. That lone pair in these hemiorthoamides is trans to the hydroxyl and cis to the other nitrogen, and conformational changes do not change these relationships. Only nitrogen inversion can do so, and this is too slow. Therefore the nitrogen lone pair does not become antiperiplanar to the leaving group even in the boat form, and the failure of the antiperiplanar lone-pair hypothesis cannot be avoided.

It is not certain whether stereoelectronic control is lost in the formation of the tetrahedral intermediate or in its breakdown. These results are equally consistent with OH^- addition syn to the two nitrogen lone pairs. However, we suggest that the less-selective step is the cleavage of the deprotonated hemiorthoamide, where the push of the O^- may overwhelm any stereoelectronic effect from the nitrogen lone pair. This is equivalent to assuming that this second transition state is early, resembling the intermediate and having little interaction between the bond that is

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cleaved and the lone pair, whose stereochemistry then does not matter. Such an assumption can be made whenever stereoelectronic control does not hold,[16] but invoking ad hoc assumptions may render the antiperiplanar lone-pair hypothesis empty.

Conclusions

Hydrolysis of five-, six-, and seven-membered cyclic *N*-methylated amidinium iodides in base involves substantial (25–90%) exocyclic C–N cleavage, leading to lactam. This is not the product predicted by the hypothesis of stereoelectronic control. Lactam cannot arise through a conformer with two lone pairs antiperiplanar to the exocyclic nitrogen, since that would require rapid nitrogen inversion. Nor can it arise by reaction of a boat conformer, since the lone pair of the ring nitrogen does not become antiperiplanar even in the boat form. We therefore affirm that stereoelectronic control is not operative in the cleavage of the hemiorthoamide intermediate.

These results raises general doubt about the hydrolyses of acetals, amides, and imidates claimed[2] to show stereoelectronic control. Since those can all be explained[11] without ever requiring stereoelectronic control, it may be that the antiperiplanar lone-pair hypothesis is not widely applicable. Moreover, those apparent failures of the antiperiplanar lone-pair hypothesis that were rationalized by assuming reaction via a boat conformer[16] may be true failures of the hypothesis.

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