PrS)Fl⁻, 85535-30-4; 9-(C_6H_5S)Fl⁻, 71805-72-6; 9-(*p*-BrC_6H_4S)Fl⁻, 73838-77-4; 2-Br-9-(C_6H_5S)Fl⁻, 73838-76-3; Pz⁻, 76069-04-0; 2-ClPz⁻, 79990-93-5; 3,7-Br_2Pz⁻, 79990-94-6; 9-(*p*-$MeSO_2C_6H_4$)Fl⁻, 73872-44-3; 9-(*o*-MeC_6H_4)Fl⁻, 85535-26-8; 9-MeFl⁻, 31468-21-0; 2-Br-9-$PhCH_2$Fl⁻, 103422-01-1; 9-$PhCH_2$Fl⁻, 53629-11-1; 9-phenyl-9-(*p*-nitrophenyl)-fluorene, 103437-36-1; 9-benzyl-9-(*p*-nitrophenyl)fluorene, 103422-02-2; 9-benzyl-9-(*p*-cyanophenyl)fluorene, 103422-03-3; *N*-(*p*-nitrophenyl)-phenothiazine, 19606-94-1.

Absence of Stereoelectronic Control in Hydrolysis of Cyclic Amidines

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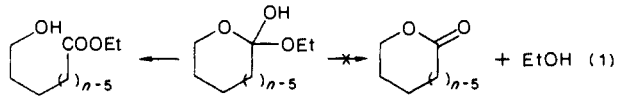
Abstract: According to Deslongchamps' theory of stereoelectronic control, preferential cleavage of a tetrahedral intermediate occurs when there are two lone pairs antiperiplanar to the leaving group. For reasons presented (Perrin and Arrhenius, *J. Am. Chem. Soc.* **1982**, *104*, 2839), product studies of hydrolysis of cyclic amidines can test this theory, and initial results supported it. However, those results are ambiguous, owing to a mismatch of leaving abilities. We now find that hydrolysis of three six-membered ring amidines bearing matched leaving groups produces predominantly aminoamide, the product of ring cleavage, and only 3–9% lactam, as expected from the theory. In contrast, hydrolysis of three five- or seven-membered ring amidines produces substantial (ca. 50%) lactam. Despite attempts to accommodate these results to the theory, it is concluded that there is no general requirement for two lone pairs antiperiplanar to the leaving group and that stereoelectronic control, even in six-membered ring amidines, contributes less than 2 kcal/mol.

According to Deslongchamps'[1] theory of stereoelectronic control, preferential cleavage of a tetrahedral intermediate occurs when there are two lone pairs antiperiplanar to the leaving group. This is certainly a plausible theory, supported by MO calculations,[2] X-ray data (from acetal derivatives),[3] and the Principle of Least Motion.[4] The experimental evidence is contained in a notable series of papers by Deslongchamps and his co-workers.[5] The key result is the observation (eq 1)[6] that a cyclic hemiorthoester (**1**,



2 **1** **3**

n = 5, 6) cleaves only to the hydroxy ester **2**, rather than to the lactone **3**. Recently we have concluded[7] that this evidence is ambiguous, both because it requires an unwarranted[8] assumption that conformational interconversion even in the five-membered ring is slower than cleavage and because the observation can be rationalized more simply on the basis of the well-known[9] instability of lactones and E esters. The many other observations claimed[10] as evidence for stereoelectronic control can likewise be attributed[7] to this instability. Deslongchamps[1,11] has referred to this instability as a "secondary stereoelectronic effect," but this begs the question of whether there is any "primary" effect. Although the theory has been generally accepted,[12] and there is good evidence[13] for stereoelectronic control at the aldehyde level of oxidation (but considerable controversy[14] for stereoelectronic control in reactions at phosphorus), only few objections have been raised,[15] most notably Capon and Grieve's reinvestigation[16] of the hydrolysis of **1**, where they found substantial formation of **3**.

In view of the importance of the theory for permitting the selective creation or destruction of a chiral center[17] and for en-

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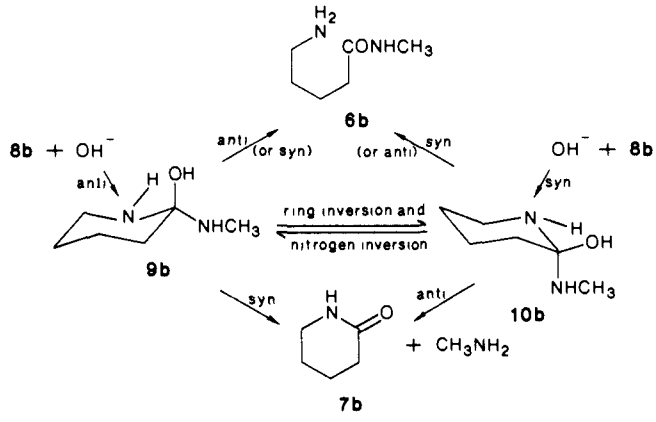
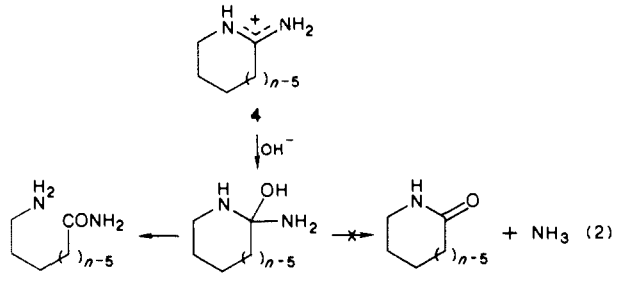
Scheme I. Stereoelectronic Control in Hydrolysis of Cyclic Amidinium Ions



zymatic hydrolysis of peptides,[18] we have sought to test it. Our initial attempt[7] involved the hydrolysis of cyclic amidinium ions, **4a,b**, via the hemiorthoamide **5** (eq 2). In contrast to hemi-

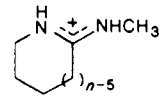


a, $n = 5$; **b**, $n = 6$

orthoester hydrolysis (eq 1), this reaction avoids the issue of lactone instability. We observed that the kinetic product is solely (≥98:2) the aminoamide **6** rather than the lactam **7** even though the latter product is more stable, owing to the entropy of liberating a molecule of NH_3. According to Scheme II of ref 7, this is exactly the result predicted by the theory of stereoelectronic control. Accordingly, this was presented as the first unambiguous evidence in support of the theory.

Nevertheless, this result is still ambiguous, owing to a mismatch of leaving abilities. Hydrolysis of unsymmetrical amidines is known[19a] to cleave preferentially the more basic amine, and methylamine is a better leaving group than ammonia in aminolysis of imidate esters.[19b] Basicity governs cleavage because a nitrogen anion is so poor a leaving group that the nitrogen must be protonated either prior to or concerted with cleavage. (The evidence for such proton transfer is the observation[20] of general-base catalysis.) Thus it may be that **6** is formed simply because a primary amine is substantially (>1 pK unit) more basic than ammonia. Indeed, we have found[21] that ammonia is a poor leaving group in hydrolyses of unsymmetrical acetamidines.

We therefore have undertaken a study of the hydrolysis of amidinium ions **8**, where the leaving abilities of methylamine and of the primary amine that results from ring cleavage are closely matched. The match is not exact, but methylamine was chosen to facilitate NMR analysis of the products. Any mismatch is quite small, since the basicities are so similar. Indeed, hydrolysis[21] of *N*-butyl-*N'*-methylacetamidine produces a 54:46 ratio of methylamine to butylamine. Nor does any mismatch arise from the entropy difference (estimated[22] as 10.5 kcal/mol) due to liberating a molecule of CH_3NH_2, since hydrolysis of amides shows no acceleration over lactams;[23] apparently the leaving group is hardly liberated at the stage of the transition state. According to the theory of stereoelectronic control (Scheme I, illustrating $n = 6$), addition of OH^- antiperiplanar ("anti") to the lone pairs of both nitrogens of **8** leads to **9**, whereas addition synperiplanar ("syn") to the lone pair of the ring nitrogen leads to **10**. If ring inversion or nitrogen inversion is slower than cleavage of **9** and **10**, these will not interconvert. Formation of lactam **7** requires elimination of CH_3NH_2 syn to the lone pair of the ring nitrogen of **9** or anti to that of **10** whereas aminoamide can be formed by either syn or anti elimination from **9** or **10**. If both addition and elimination must occur anti to the two lone pairs, as proposed by Deslongchamps, only aminoamide **6** can be formed. Even if both must occur syn, only aminoamide can be formed. In previous studies[24] hydrolysis of **8a** or of a four-membered ring analogue gave very good yields of lactam. However, this is the product to be expected if thermodynamic equilibrium was established under the reaction conditions. It is necessary to determine the kinetic product. We now report that hydrolysis of **8b** and related ions does produce predominantly aminoamide, but hydrolysis of **8a**, **8c**, and related ions produces substantial (ca. 50%) lactam.



8

a, $n = 5$; **b**, $n = 6$; **c**, $n = 7$

Experimental Section

NMR spectra were obtained on an Oxford 360-MHz magnet interfaced to a Nicolet 1180E computer. The probe temperature was 22 °C. Some experiments (hydrolysis of five-membered ring amidines) were performed on a Varian EM390 90-MHz spectrometer at 34 °C. Chemical shifts are reported relative to tetramethylsilane (δ 0.00); for aqueous solutions *tert*-butanol (δ 1.25) was used as internal standard.

Reactants were commercially available substances from Aldrich, Eastman, Alfa, or Mallinckrodt, and used without further purification. Solutions of DCl were prepared from acetyl chloride or chloroacetyl chloride + D_2O. Methylamine was distilled through $CaCl_2$ from 40% aqueous solutions.

Synthesis of Amidines. For definiteness and simplicity each amidine is denoted by a single name, although it is a mixture of two tautomers. 2-(Methylamino)-1-pyrroline (**11a**) was prepared from 2-methoxy-1-pyrroline plus methylamine, according to Etienne and Correia:[25] mp 95–98 °C (hygroscopic) (lit.[25] 95 °C); NMR ($CDCl_3$) δ 1.95 (m, 2 H), 2.40 (t, 2 H), 2.89 (s, 3 H), 3.65 (t, 2 H); NMR (DCl/D_2O) δ 2.88 (s, 2.8 H), 2.94 (s, 0.2 H). Similarly 2-(benzylamino)-1-pyrroline (**12**) was prepared from 2-methoxy-1-pyrroline plus equimolar benzylamine: mp 79–81 °C (hygroscopic) (lit.[26] 81–82 °C); NMR ($CDCl_3$) δ 1.92 (m, 2 H), 2.40 (t, 2 H), 3.74 (t, 2 H), 4.40 (s, 2 H), 4.90 (s, 1 H), 7.30 (s, 5 H). 2-(Methylamino)-3,4,5,6-tetrahydropyridine (**11b**) was prepared from 2-methoxy-3,4,5,6-tetrahydropyridine[27] plus 50% excess methylamine in absolute ethanol: bp 95–96 °C (12 mmHg), mp 65–68 °C (hygroscopic) (lit.[28] bp 104–105 °C (14–16 mmHg)); NMR ($CDCl_3$) δ 1.78 (m, 4 H), 2.12 (t, 2 H), 2.75 (s, 3 H), 3.48 (t, 2 H); NMR (DCl/D_2O) δ 2.85 (s, 2.9 H), 2.90 (s, 0.1 H).

2-(Methylamino)-4-methyl-3,4,5,6-tetrahydropyridine (13). 4-Methyl-δ-valerolactam[29] was prepared by hydrogenation of ethyl 3-

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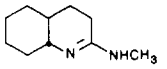
Table I. Chemical Shifts of Cyclic Amidines **16** in $NaOH/D_2O$

amidine	*n*	R	R′	X	NHR	CHN=	$CH_2C{=}N^a$
11a	5	CH_3	H	CH_2	2.92 (s)	3.65 (t)	2.78 (t)
12	5	$PhCH_2$	H	CH_2	4.39 (s)	3.46 (t)	2.51 (t)
15	5	OCH_3	H	O	3.80 (s)	4.30 (t)[b]	2.85 (t)
11b	6	CH_3	H	CH_2	2.77 (s)	3.35 (t)	2.42 (t)
13	6	CH_3	CH_3	CH_2	2.73 (s)	3.45 (t)	2.62 (t)[c]
11c	7	CH_3	H	CH_2	2.70 (s)	3.37 (m)	2.48 (m)
14					2.80 (s)	2.97 (m)	2.56 (m)

[a] Intensity decreases owing to D_2O exchange. [b] CH_2ON, pD = 9; at pD = 13.5 the hydrolysis is too fast for the amidine to be observed. [c] R′ at δ 0.98 (d).

Table II. Chemical Shifts of Hydrolysis Products of Cyclic Amidines

	lactam		amine	aminoamide		
amidine	$CH_2C{=}O^a$	CHN	$RNH_2{}^b$	NHR	CHN	$CH_2C{=}O^a$
11a	2.36 (t)	3.44 (t)	2.28 (s)	2.73 (s)	2.63 (t)	2.26 (t)
12	2.30 (t)	3.41 (t)	3.80 (s)	4.38 (s)	2.60 (t)	2.27 (t)
15	2.80 (t)	4.25 (t)[c]	3.53 (s)	3.53 (s)	3.92 (m)[c]	2.23 (m)
11b	2.33 (t)	3.28 (t)	2.28 (s)	2.74 (s)	2.58 (t)	2.25 (t)
13	2.38 (m)	3.30 (m)	2.29 (s)[d]	2.72 (s)	2.60 (m)	2.25 (m)[e]
11c	2.46 (m)	3.25 (m)	2.25 (s)	2.72 (s)	2.60 (t)	2.24 (t)
14	2.40 (m)	2.95 (m)	2.28 (s)	2.72 (s)	2.33 (m)	2.23 (m)

[a] Decreased intensity owing to D_2O exchange of the corresponding amidine. [b] Varies with concentration and pD during course of hydrolysis. [c] CH_2ON. [d] R′ at 1.00 (d). [e] R′ at δ 0.90 (d).

methyl-4-cyano-3-butenoate[30] over Rh/Al_2O_3. Reaction with equimolar dimethyl sulfate produced 2-methoxy-4-methyl-3,4,5,6-tetrahydropyridine [bp 55–58 °C (8 mmHg); NMR ($CDCl_3$) δ 1.00 (d, 3 H), 1.85 (m, 5 H), 3.50 (m, 2 H), 3.62 (s, 3 H)]. This was reacted for 48 h at room temperature with 35% excess methylamine in absolute ethanol to produce 0.5 g (84% yield) of **13**: bp 100–105 °C (10–12 mmHg), mp 70–74 °C (hygroscopic); NMR ($CDCl_3$) δ 0.92 (d, 3 H), 1.80 (brm, 5 H), 2.69 (s, 3 H), 3.45 (m, 2 H).

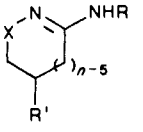
7-(Methylamino)-3,4,5,6-tetrahydro-2*H*-azepine (11c). This was prepared (3 g, 92%) from *O*-methylcaprolactim[31] plus 15% excess methylamine: mp 100–102 °C; NMR ($CDCl_3$) δ 1.52 (m, 6 H), 2.22 (m, 2 H), 2.66 (s, 3 H), 3.32 (m, 2 H).

***trans*-2-(Methylamino)-3,4,5,6,7,8,9,9a-octahydroquinoline (14).** *trans*-3,4,5,6,7,8,9,9a-Tetrahydro-2-quinolone[32] was reacted with dimethyl sulfate to produce *trans*-2-methoxy-3,4,5,6,7,8,9,9a-octahydroquinoline [bp 102–105 °C (10 mmHg); NMR ($CDCl_3$) δ 1.45 (m, 11 H), 2.15 (m, 2 H), 2.80 (m, 1 H), 3.60 (s, 3 H)]. This was reacted for 48 h at room temperature with 65% excess methylamine. After evaporation of solvent, the residue (0.4 g, 83% yield) crystallized: mp 124–125 °C; NMR ($CDCl_3$) δ 1.20 (m, 6 H), 1.72 (m, 4 H), 2.05 (m, 1 H), 2.25 (m, 2 H), 2.72 (m, 1 H), 2.79 (s, 3 H).

3-(Methoxyamino)-2-isoxazoline (15). NMR studies[33] showed that trimethyloxonium fluoroborate methylates 3-isoxazolidone[34] exclusively on oxygen in contrast to other methylating agents, which lead to a mixture of O- and N-methylation,[35] but subsequent treatment with amines causes demethylation. Accordingly, 3-isoxazolidinone was reacted with triethyloxonium tetrafluoroborate in CH_2Cl_2. After evaporating the solvent, 3-ethoxyisoxazolinium tetrafluoroborate was obtained as a viscous oil [NMR (D_2O) δ 1.13 (t, 3 H), 2.80 (t, 2 H), 3.50 (q, 2 H), 4.45 (t, 2 H)]. This was treated with equimolar methoxyamine in methanol. After evaporating the solvent, a solid (0.4 g, 69% yield) was obtained: mp 155–157 °C (hygroscopic); NMR (Me_2SO-d_6) δ 2.50 (m, 2 H), 3.73 (s, 1.1 H), 3.90 (s, 1.9 H), 4.30 (m, 2 H); NMR (DCl/D_2O) δ 3.92 (s, 1.86 H), 3.70 (s, 1.14 H). The tetrafluoroborate salt was not converted to **15** free base but was used directly.

Samples were prepared for kinetics by weighing into an NMR tube 0.2 mmol of amidine and 0.2 mmol of freshly powdered NaOH or 0.2 mmol of Na_3PO_4 + 0.2 mmol of Na_2HPO_4. Hydrolysis was initiated by adding 0.6 mL of D_2O and shaking the tube vigorously. (The use of D_2O avoids overload of the NMR detector.) The less basic solutions could be prepared by dissolving 0.2 mmol of amidine in 0.4 mL of 0.5 M PhOD + 0.5 M PhONa or by neutralizing **15**·H^+ with NaOH in D_2O. The sample was inserted into the NMR probe and tuned, and 360-MHz FT spectra were acquired. After the reaction was completed, the pH was measured directly in the NMR tube with an Ingold thin electrode and a Corning Model 125 pH Meter, and the observed value was corrected[36] to pD. The value did not vary by more than 0.1 unit during the first half-life of the reactions.

Chemical shifts of the amidines **16** at pD ca. 13.5 in D_2O are listed in Table I. Chemical shifts of the hydrolysis products in the same medium are listed in Table II. These chemical shifts were assigned by



16

adding authentic amine or lactam to the reaction mixture or else by analogy. There were no additional signals that could not be assigned. Product ratios were determined by comparing the peak heights of the alkylamine and *N*-alkylamide singlets in the 360-MHz NMR spectrum, obtained with 1.5 Hz additional line broadening. For those amidines where the product was benzylamine or methoxyamine, whose signal was well-separated from the α-CH_2 of the aminoamide, product ratios could also be obtained by integration. Also, for **13**, the signals of the C_4-methyl doublets of aminoamide and lactam could be used to check the ratio. In no case were the exchangeable α-CH_2 signals used for product analysis. For the five-membered ring amidines at least four determinations of the product ratio were obtained after one half-life, and the values were averaged. For the other amidines the aminoamide is converted to lactam only slightly more slowly than the hydrolysis, so at least six product ratios were determined before 2 half-lives of the hydrolysis, and the values were extrapolated to time zero by a linear least-squares fit. Each experiment was performed at least 3 times.

Results

Product ratios from hydrolysis of all the amidines under various conditions are listed in Table III. Values are presented as percent lactam, even though analysis was based on the amine coproduct. The precision of all these values is ±1–3%. The reported amounts of minor products, particularly lactams, are real and not any artifact of impurities in reactant amidines, since no impurity peaks could be detected in DCl/D_2O, where the amidines are stable to hydrolysis.

Also listed in Table III are rate constants, k_h, for some representative hydrolyses. These are only approximate, since NMR

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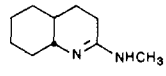
Table III. Hydrolysis of Cyclic Amidines **16**. Product Ratios and Rate Constants for Hydrolysis and for Conversion of Aminoamide to Lactam

amidine	n	R	R′	X	condtns[b]	% lactam	k_h, s^{-1}	k_c, s^{-1}
17a	5	H	H	CH_2	A	≤ 2[a]	3×10^{-5}[a]	8×10^{-6}[a]
11a	5	CH_3	H	CH_2	B	58		
					A	48	6.7×10^{-6}	slow
					C	46		
					D	39		
					E	32		
12	5	$PhCH_2$	H	CH_2	A	10		
15	5	OCH_3	H	O	B	54	fast	
					F	26		
17b	6	H	H	CH_2	A	≤ 2[a]	2×10^{-3}[a]	2×10^{-5}[a]
11b	6	CH_3	H	CH_2	B	7		5×10^{-6}
					A	4	6.2×10^{-4}	
					D	3		3×10^{-5}
					E	3		1×10^{-6}
13	6	CH_3	CH_3	CH_2	B	4		2×10^{-5}
					A	7	4.6×10^{-4}	
					D	3		3×10^{-5}
11c	7	CH_3	H	CH_2	B	56	1.3×10^{-4}	4×10^{-5}
					D	15		1×10^{-6}
14					B	9	1.0×10^{-3}	7×10^{-5}
					D	3		1.5×10^{-5}
					E	6		8×10^{-6}

[a] From ref 7. [b] A = D_2O; B = 1 equiv of NaOH; C = H_2O; D = 1 equiv of phosphate buffer, pD 13.0; E = 1 equiv of phenol buffer, pD 11.8; F = pD 9.

is not sensitive enough to allow a buffer capacity sufficient to keep the pD from decreasing slightly as amidine is converted to the less basic amines.

In separate experiments the amidine or a mixture of lactam plus methylamine in D_2O was allowed to react for several weeks, and the equilibrium constants, K = [lactam][CH_3NH_2]/[aminoamide], were determined to be 11.1 M and 5.5 M for lactam = pyrrolidone (**7a**) and piperidone (**7b**), respectively. Thus the aminoamides are not stable to conversion to lactam + amine under the hydrolysis conditions. Only for the six- and seven-membered rings did this conversion occur at an appreciable rate. Accordingly, the product ratios in Table III have been extrapolated to zero time, so they are kinetic ratios. Also listed in Table III are rate constants, k_c, for conversion of aminoamide to lactam, obtained from the slopes of plots of [lactam]/[aminoamide] vs. time. These plots were suitably linear, and it can be shown that their slope is $k_c(1 + [\text{lactam}]_{t=0}/[\text{aminoamide}]_{t=0})$. However, since this represents only an initial-rate measurement, the values are not of high accuracy.

Discussion

Lactam Formation and Stereoelectronic Control. The data in Table III show clearly that there is substantial lactam production in hydrolysis of cyclic N-alkyl amidines. The values range from 3–9% from six-membered ring amidines to >50% from five- and seven-membered ones. These values are in marked contrast to those obtained previously[7] for N-unsubstituted analogues (**17ab**), where <2% lactam is produced under kinetic conditions. This contrast is due to a mismatch of leaving abilities in the previous study. When the leaving abilities are matched properly, aminoamide is no longer the exclusive product.

Consequently the previous conclusions[7] must be rejected. Aminoamide production had been taken as evidence for stereoelectronic control, since only this product arises from addition of OH^- and cleavage of a leaving group anti to two lone pairs (Scheme I). Lactam production is new evidence that two antiperiplanar lone pairs are not essential for rapid creation and cleavage of a tetrahedral intermediate. In the following discussion we shall consider whether the theory of stereoelectronic control can be maintained in the face of this evidence against it. We are obligated to make an honest attempt to preserve so plausible a theory.

Leaving Abilities. The strong contrast in lactam production between **17a** and **11a** (Table III) is due to the greater leaving ability of CH_3NH_2, relative to NH_3. This may be ascribed to the greater basicity of CH_3NH_2, but steric effects or solvation effects may also be involved. A clearer measure of the basicity contribution to leaving abilities may be obtained by comparing **11a** with **12**. Here the electron-withdrawing phenyl substituent reduces both the basicity and the leaving ability of its nitrogen, so that the proportion of lactam decreases from 48% to 10%. According to eq 13 of Gilbert and Jencks,[37] the [aminoamide]/[lactam] ratio, k_A/k_L, in each of these hydrolyses is given by eq 3, where β_N and β_{lg} are the effective charges in the transition

$$\log(k_A/k_L) = (\beta_N - \beta_{lg})(pK_{exo} - pK_{endo}) \quad (3)$$

state for the remaining and leaving nitrogens, respectively, pK_{exo} is the pK_a of $CH_3NH_3^+$ or $PhCH_2NH_3^+$, and pK_{endo} is the effective pK_a of the aminoamide $-NH_3^+$, including any nonleaving ability effects, such as stereoelectronic control or entropy. This latter is unknown, but it cancels. From the observed product ratios and from the known[38] pK_as, $\beta_N - \beta_{lg} = -0.72$. Since β_N is necessarily >0, $\beta_{lg} > 0.72$. Although this value is only an uncertain estimate, it does represent a substantial positive charge developing on the nitrogen that is cleaved, and it shows the importance of basicity in determining leaving ability.

Mechanism of Amidine Hydrolysis. It has been implicitly assumed[7] that the rate-limiting and product-determining steps of amidine hydrolysis are distinct. According to Scheme I, the product-determining step is cleavage of the hemiorthoamide, which is created in conformation **9** by hydroxide addition antiperiplanar to two nitrogen lone pairs of **8**. In order for this reaction to test the theory of stereoelectronic control, that addition must be the rate-limiting step. Otherwise the addition would be reversible, and occasionally other conformers **10**, with two lone pairs antiperiplanar to the exocyclic nitrogen, could be created. Creation of such conformers would require addition of hydroxide syn to a lone pair, so it would require occasional breakdown of the theory. Then lactam could be produced even though stereoelectronic control is generally operative.

Only a study[39] of the hydrolysis of 1,3-diphenylimidazolinium (**18**, R = Ph) is sufficiently detailed to have established which step is rate-limiting. The mechanism is shown in eq 4, with $k_1 = 1.6 \times 10^4$ M^{-1} s^{-1}, $k_{-1} = 250$ s^{-1}, $pK_a = 12.75$, and $k_2 = 180$

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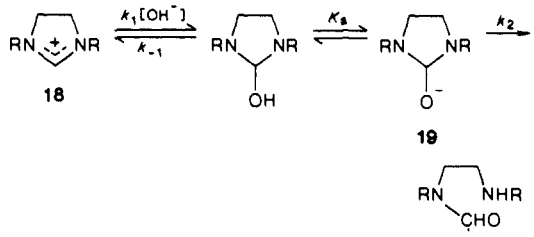


18 19

$$\text{RN(CHO)NHR} + OH^- \quad (4)$$

s^{-1}. Notice that the species that cleaves is the conjugate base **19** of the tetrahedral intermediate. These rate constants mean that the first step is rate-limiting only at pH > 12.89. Yet these values are not appropriate for the amidines studied here, where the nitrogen is much more basic. It is necessary to consider how these values might change on changing the pK of the nitrogen by 6.0 units (methylamine vs. aniline[38]).

Two lines of evidence indicate that a more basic nitrogen makes the first step more likely to be rate-limiting: (1) Alkaline hydrolysis of *N,N'*-diarylformamidines shows[40] $\rho \sim -3$ for electron-donating substituents and $\rho \sim 0$ for electron-withdrawing ones, which also show a rate term [amidinium][OH^-]^2. In contrast no such term is seen[41] for *N*-alkyl amidines at high pH. These kinetic results are most readily explained if the first step is rate-limiting when R is alkyl or electron-donating aryl. (2) Equation 5 defines the use of linear free-electron relationships

$$\beta_i = \partial \log k_i/\partial pK_{a1} + \partial \log k_i/\partial pK_{a2} \qquad (5)$$

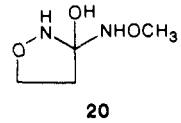
to extrapolate how each rate constant in eq 4 would change when both Rs are changed from phenyl to alkyl or hydrogen. Firstly, it is observed that k_1 decreases[41] from 1.6×10^4 M^{-1} s^{-1} to 4.3×10^{-2} M^{-1} s^{-1} or 7.5×10^{-2} M^{-1} s^{-1} on increasing the pK_as of both nitrogens by 6 (model: methylamine vs. aniline), so $\beta_1 \simeq -0.91$. To estimated β_{-1} it is next necessary to estimate how the change in basicity affects the equilibrium constant k_1/k_{-1}, which is not available. However, this equilibrium is simply the acid dissociation of a formamidinium ion ($\beta = 3.26/-4.20 = -0.78$),[42] followed by hydration of the resulting amidine, whose β may be approximated by the equilibrium β of −0.26 for imine hydrolysis.[43] Hence $\beta_1 - \beta_{-1} \simeq -1.04$, so $\beta_{-1} \simeq 0.13$. Also, β_2 is equal to $\beta_N + \beta_{lg}$. According to the result above (from eq 3), $\beta_{lg} - \beta_N = 0.72$. If we assume a conservative estimate of 0.15 for β_N, then $\beta_2 = 1.02$. From these βs we can estimate that when R = alkyl, $k_{-1} \sim 1.5 \times 10^3$ s^{-1} and $k_2 = 2.4 \times 10^8$ s^{-1}. So short a lifetime for the intermediate is supported by the pH-dependence of product ratios, as discussed below. Finally, from ρ_1–σ_1 correlations[44] pK_a may be estimated as 13.9. These values mean that the first step is rate-limiting at pD > 8.7. Even though these extrapolations are only approximate, k_2 is so much greater than k_{-1} that we are certainly justified in concluding that the first step is rate-limiting under nearly all the conditions of this study. Therefore the observed lactam formation cannot be attributed to a rapid, reversible initial step which occasionally creates a conformer with two lone pairs anti to the exocyclic nitrogen.

Ring Inversion. The data in Table III show a marked contrast between six-membered ring amidines and five- or seven-membered ones. The former class produce almost exclusively aminoamide, but the latter produce ca. 50% lactam. We interpret this result as showing that stereoelectronic control is weakly operative in the former but not at all in the latter. Before this interpretation can be accepted, it is necessary to show that lactam products do not arise because of ring inversion plus nitrogen inversion during the lifetime of the intermediate.

According to Scheme I, if the intermediate hemiorthoamide is assumed to undergo both ring inversion and nitrogen inversion prior to cleavage, then all conformers would equilibrate during the lifetime of the intermediate, including those with two lone pairs antiperiplanar to the exocyclic nitrogen **10**. The consequence would be production of lactam, as observed. However, the marked contrast between five- and six-membered ring amidines contradicts this assumption. If all conformers were to equilibrate, the product ratio would be determined by that equilibrium, which would not show such a contrast.

The simplest way to maintain the theory of stereoelectronic control for all these amidines is to associate the contrast in product ratios with ring inversion. Relative to the lifetime estimated above, ring inversion is fast in five- and seven-membered ring intermediates,[8] which would partition nearly equally to the two products. The six-membered ring intermediates would usually cleave faster than they would undergo a ring inversion that would be required to permit lactam formation. The 3–9% lactam would then represent that fraction (ca. 6–18%) of intermediates that undergo ring inversion. However, that fraction should decrease on going from **11b** to **13** to **14**, since ring inversion is either retarded by the necessity of placing a methyl group axial or prevented by the *trans*-decalin fusion. Nevertheless, no such decrease is seen. Instead, the percent lactam remains constant, within experimental error. Therefore lactam formation from six-membered ring amidines does not arise through a competition between ring inversion and cleavage. Indeed, it is especially difficult to reconcile the production of lactam from **14** with the theory of stereoelectronic control.

Nitrogen Inversion. In order for amidine hydrolysis to test the theory of stereoelectronic control, nitrogen inversion must be slow relative to cleavage of the intermediate. Otherwise conformations would become accessible that could produce lactam without violating the theory. Two lines of evidence indicate that a rapid nitrogen inversion cannot account for the observed lactam formation: (1) The rate constant of 2.4×10^8 s^{-1} estimated above for the cleavage, although uncertain, is considerably greater than the rate constant for nitrogen inversion. This latter is 2×10^5 s^{-1}, from *N,N*-dimethylbenzylamine[45a] in aqueous solution, or 1.6×10^5 s^{-1}, extrapolated from data for 4,4-difluoropiperidine[45b] at lower temperature in acetone-d_6. These rates correspond to barriers higher than customary,[46] but hydrogen bonding seems to raise the barrier. The possibility that proton exchange might provide an additional mechanism for nitrogen inversion in secondary amines has also been excluded.[7,47] (2) The data in Table III show that substantial lactam is obtained even from **15**. The oxygen substitution raises the barrier to nitrogen inversion in the intermediate **20**. According to the model compound, *N*-



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methylisoxazolidine ($\Delta G^{\ddagger}$ = 16.9 kcal/mol),[48] the rate constant for inversion may be estimated as 2×10^1 s^{-1}. This is less than 2×10^2 s^{-1}, the rate constant for cleavage estimated according to $\beta_N + \beta_{lg}$ as above. Although these estimates are again uncertain, it would be quite coincidental if the competition between inversion and cleavage would be nearly unchanged by the oxygen substitution, as would required to account for the near equality of percent lactam from **11a** and **15**. We therefore conclude that lactam formation cannot be attributed to rapid nitrogen inversion.

Ring Size and Stereoelectronic Control. The breakdown of the theory of stereoelectronic control might have been anticipated for the five- and seven-membered ring amidines. Cleavage of the intermediate **21** corresponds to an E_1cb elimination. The classic cases[49] of ionic eliminations in cyclohexanes are predominantly

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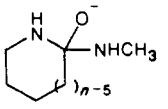

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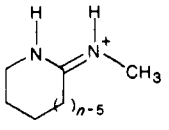
anti. In contrast, syn eliminations are quite common in five- and seven-membered rings[50] (although the stereochemistry is quite dependent on reaction conditions[51]). Indeed, the dependence of percent lactam on ring size is remarkably similar to the dependence of the percent syn elimination in cycloalkyltrimethylammonium ions: 39% (n = 5), 2% (n = 6), 30% (n = 7).[52] This similarity may be fortuitous, since, according to Scheme I, lactam formation is not necessarily due simply to syn elimination, but it could arise from a lack of stereoelectronic preference in both the OH^- addition and the cleavage.

An attractive suggestion[53] has been that syn E_1cb eliminations occur by deprotonation, carbanion inversion, and then anti elimination. Such a course avoids syn elimination, which is less favored orbitally.[2b] However, it should be noted that the E_1cb elimination of amidine hydrolysis cannot involve the equivalent nitrogen inversion, which we have claimed above is slow relative to the lifetime of the intermediate. Consequently this must be an elimination that is truly syn.

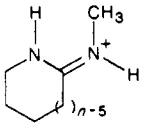
Even in the six-membered rings, the preference for anti elimination is here quite small, in contrast to the classic cases.[49] The 3–9% lactam corresponds to a preference of ≤2 kcal/mol, significantly less than the at least 5 kcal/mol estimated[54] from hydrolysis of imidates. Apparently the $-O^-$ substituent so promotes the elimination that the nitrogen lone pair is not subject to a strong stereoelectronic requirement.

The weakness of stereoelectronic control should be a warning against relying on it to predict stereochemistry or reactivity. Other effects are too likely to eclipse it. Among these have already been mentioned the instability of lactones and a mismatch of leaving abilities. These effects operate in the same direction as stereoelectronic control, so they led to results[6,7] that seemed to be evidence for the theory of stereoelectronic control. Other effects, such as reactant-energy differences,[55] steric hindrance or ring strain,[56] and the presence of boat conformations,[57] act in the opposite direction and led to results that contradict the theory.

Configurational Considerations. In DCl/D_2O separate E and Z configurations of amidinium ions (**8E**, **8Z**) can be detected. By



8E



8Z

analogy to similar species,[58] the downfield N-alkyl is assigned as the E configuration. For **8a** and **8b**, the Z configuration predominates, by 93:7 and 97:3, respectively. For **15**·H^+, the E configuration predominates, by 62:38. According to the theory of stereoelectronic control, the Z configuration is expected[21] to be biased toward lactam formation, since the aminoamide would be created in the less stable E configuration. Of course, the lactam is also an E amide, so that only the steric destabilization of an E amide could account for lactam formation. From studies of acetamidines,[21] it can be seen that such steric interactions are small (less than 1 kcal/mol) and cannot be used to maintain the theory of stereoelectronic control. Besides, no such effect can account for lactam formation from **15**, since E and Z forms of hydroxamic acids are of nearly equal stability.[59]

Still another possible way to rationalize lactam formation within the theory of stereoelectronic control is to assume that the initial product is the E aminoamide, despite the steric interactions. Indeed, hydrolysis of *N,N'*-dimethylformamidine does produce a substantial amount of (*E*)-*N*-methylformamide,[60] and hydrolysis of 1,3-diphenylimidazolinium ion (**18**, R = Ph) produces a nonequilibrium distribution of amide stereoisomers.[61] After rotation about the C_α—C=O bond, the E aminoamide could reclose to conformer **10**, which can cleave to lactam. The steric interactions that destabilize the E aminoamide would then be responsible for its high reactivity toward reclosure. However, in order to account for lactam formation, the E aminoamide must reclose faster than it isomerizes to Z. Saturation-transfer measurements[33] show that the rate constants for E-to-Z isomerization of *N*-methylacetamide and *N*-methylpropionamide are 0.1 ± 0.05 s^{-1} and 1.3 ± 0.1 s^{-1}, respectively. (The former value is in good agreement with the 0.06 s^{-1} extrapolated from higher temperature.[62]) According to Table III, the rate constants for reclosure of the Z aminoamide vary from 10^{-6} s^{-1} to 10^{-4} s^{-1}, and a $>10^4$-fold acceleration due to steric destabilization of the E aminoamide is unreasonable.

pD Dependence. According to the data in Table III, hydrolysis of **11a** and **11c** shows a slight but significant increase of percent lactam with increasing pD. The six-membered ring amidines may also show such variation, but it is so small that it is masked by experimental errors. Indeed, the variation is so small that it is difficult to account for it while maintaining the theory of stereoelectronic control. There are only two reactions that are pH-dependent: the initial hydroxide attack, whose rate does not affect the product ratio, and the ionization equilibrium of the intermediate (**9**, **10** ⇌ **21**). This latter affects the lifetime of the intermediate, since only the conjugate base **21** undergoes cleavage. As a result, this lifetime is strongly pD-dependent. Similarly, since cleavage requires proton transfer to the nitrogen leaving group, its rate should be increased in H_2O relative to D_2O. If the product ratio were determined by competition between cleavage and nitrogen inversion or ring inversion, as considered and rejected above, it too would be strongly pD-dependent. Moreover, the proportion of lactam would increase as pD decreases and the lifetime of the intermediate increases. Yet this is not observed. Nor does the ratio change from H_2O to D_2O. Therefore, the pD-dependence is due to competition between cleavage and some process whose status does not strongly affect the product.

We propose that this process is rotation about the exocyclic C–N bond. We further assume that the lone pair on the exocyclic nitrogen shows a slight preference to be anti to incoming OH^- or to leaving group. This is consistent with a preference for anti elimination in acyclic systems[51,63] and with the hydrolysis of acetamidines.[21] Then the conformer initially created by hydration of **11a** is **22**. The configuration of the ring nitrogen is unspecified, since we find no stereoelectronic control in five-membered rings,

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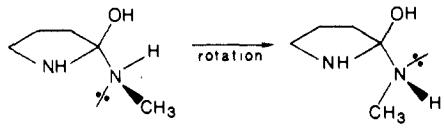


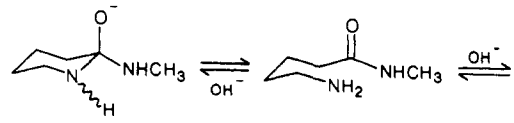
22 **23**

so OH^- can add either syn or anti to that nitrogen's lone pair. Upon deprotonation the conjugate base of this species can eliminate the exocyclic nitrogen, regardless of the configuration of the ring nitrogen. It can also eliminate the ring nitrogen, but this requires participation of the syn lone pair on the exocyclic nitrogen. In order to gain the participation of an anti lone pair on this nitrogen, rotation about the exocyclic C–N bond is required, to produce **23**. At low pD cleavage is slow relative to rotation, so **23** can produce aminoamide. At high pD the lifetime of the intermediate is shorter, **22** (as its conjugate base) is the reacting conformer, and the percent lactam increases.

This competition provides another estimate of the lifetime of the intermediate. The rate constant for cleavage must be comparable to that for rotation about the C–N bond. From the barrier in Me_3C–$NMeCH_2Ph$[64] this may be estimated as 10^8 s^{-1}, which is quite close to the estimate above.

The product ratio from **15** is also slightly dependent on pD. The above explanation cannot hold, since the lifetime of the intermediate (vide supra) is longer. This is likely to be a manifestation of a change in rate-limiting step. At pH 9 cleavage becomes rate-limiting, as with **18**, R = Ph. All conformers of the intermediate equilibrate, and the 26:74 ratio may represent the inherent relative leaving abilities (not far from 50:50) of methoxyamine and endocyclic alkoxyamine, without any influence of stereoelectronic control.

According to the data in Table III, k_c, the rate constant for conversion of aminoamide to lactam generally increases with pD, although general-base catalysis by phosphate sometimes surpasses the OH^- catalysis. Indeed, aminolysis of amides has been shown[19,65] to exhibit OH^- catalysis, as is required by the principle of microscopic reversibility from the hydrolysis of amidines. Also, *N*-arylamidine hydrolysis shows[20] general-base catalysis, with $\beta = 0.26$ in the term that corresponds to the conversion of aminoamide to lactam; for *N*-alkylamidines β ought to be <0.26. The mechanism of conversion is shown in eq 6, for the particular case of **11b**. Notice that **24**, the conjugate base of **9b**, cleaves predominantly back to aminoamide, but **25** can be formed from the aminoamide, and it can cleave to lactam. Thus the conversion is base catalyzed.



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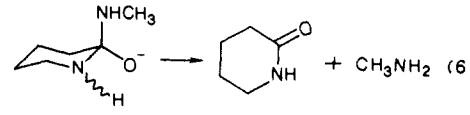

25

Conclusions

According to Deslongchamps' theory of stereoelectronic control, hydrolysis of these cyclic amidines (Scheme I) ought to produce only aminoamide. In a previous study[7] only aminoamide was observed, but those results are a consequence of a mismatch of leaving abilities. When leaving abilities are properly matched, substantial amounts of lactam are produced, especially from five- and seven-membered ring amidines. We are unable to rationalize these results within the theory of stereoelectronic control; various possibilities, involving entropy, rate-limiting cleavage, rapid ring inversion and nitrogen inversion, and configurational effects, have been considered and rejected. We therefore conclude that despite theory[2-4] stereoelectronic control is not operative in hydrolysis of five- and seven-membered ring amidines, and it is only weakly operative for six-membered ones. In the five- and seven-membered rings the absence of stereoelectronic control is not due to a preference for a syn lone pair on nitrogen. On the contrary, it hardly matters whether that lone pair is syn or anti. Even in the six-membered rings the preference for an anti lone pair is <2 kcal/mol, and this is so small an effect that it can easily be eclipsed by another. Apparently the lone pairs on the $-O^-$ are so effective at facilitating cleavage that the nitrogen lone pair is not required to be anti. Whether stereoelectronic control might be stronger if there are no $-O^-$ lone pairs to reduce selectivity is an interesting question, currently under investigation.

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Registry No. **11a**, 872-54-8; **11a** (lactam), 616-45-5; **11a** (aminoamide), 23435-12-3; **11b**, 3256-26-6; **11b** (lactam), 675-20-7; **11b** (aminoamide), 23434-27-7; **11c**, 7048-57-9; **11c** (lactam), 105-60-2; **11c** (aminoamide), 23435-13-4; **12**, 7544-88-9; **12** (aminoamide), 103621-64-3; **13**, 103621-57-4; **13** (lactam), 4720-64-3; **13** (aminoamide), 103621-66-5; **14**, 103621-58-5; **14** (lactam), 59224-99-6; **14** (aminoamide), 103621-67-6; **15**, 103621-56-3; **15**·BF_4, 103621-63-2; **15** (lactam), 1192-07-0; **15** (aminoamide), 103621-65-4; **17a**, 872-34-4; **17b**, 22780-54-7; CH_3NH_2, 74-89-5; $C_6H_5CH_2NH_2$, 100-46-9; $NCCH{=}C(CH_3)CH_2CO_2CH_2CH_3$, 66066-39-5; 2-methoxypyrroline, 5264-35-7; 2-methoxy-3,4,5,6-tetrahydropyridine, 5693-62-9; 2-methoxy-4-methyl-3,4,5,6-tetrahydropyridine, 103621-59-6; *O*-methylcaprolactim, 2525-16-8; *trans*-2-methoxy-3,4,5,6,7,8,9,9a-octahydroquinone, 103621-60-9; triethyloxonium tetrafluoroborate, 368-39-8; 3-ethoxyisoxazolinium tetrafluoroborate, 103621-62-1.

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