= 6.8 Hz, $J_{8,Me}$ = 3.6 Hz, CH_3), 2.2 (m, 1, H-7), 2.65 (anti epimer **1b**) 2.70 (syn epimer **1a**) (m, 2, H-1), 4.80 (q×d, 1, $J_{9,Me}$ = 6.8 Hz, $J_{8,9}$ = 5 Hz, H-9), 4.98 (d×q×d, 1, $J_{8,9}$ = 5 Hz, $J_{8,Me}$ = 3.6 Hz, $J_{7,8}$ = 3.0 Hz, H-8), and 5.87 (syn epimer **1a**), 6.03 (anti epimer **1b**)[9] (t, 2, $J_{1,2}$ = 2 Hz, H-2); mass spectrum *m/e* (rel intensity) 146 (28), 131 (88), 118 (25), 117 (92), 105 (45), 93 (45), 91 (100). High resolution mass spectrum: calcd for $C_{11}H_{14}$, 146.110; found, 146.110. Anal. ($C_{11}H_{14}$): C, H.

Pyrolysis of 7-(1,2-Butadienyl)bicyclo[2.2.1]hept-2-ene (1). Several pyrolyses of the epimeric mixture of allenes **1a** and **1b** were carried out as follows. Samples were placed in 20 × 250 mm Pyrex Carius tubes and deoxygenated by six or seven cycles of evacuation and filling with helium. The tubes were then sealed at 10^{-2} torr and placed in a potassium nitrate–sodium nitrite (1:1) bath maintained at various temperatures. To minimize wall effects, the tubes had been treated with concentrated aqueous HCl followed by 5% EDTA in concentrated ammonium hydroxide. They were then rinsed with copious amounts of water and dried at 200 °C.

Following pyrolysis, samples were recovered as ether solutions and analyzed by VPC (160 °C). For those samples heated below 250 °C for 3 h or less, only the peak corresponding to the **1a/1b** allene mixture (retention time = 21.5 min) could be detected. For samples heated at 275 °C for 5 h or more, a single new peak (retention time = 33.5 min) was observed. A preparative scale pyrolysis using 0.6 g of the **1a/1b** mixture was performed at 275 °C for 24 h. It yielded 0.17 g of the new compound by preparative VPC. The VPC trace showed no residual allene or the presence of any other product. The high-resolution mass spectrum of this compound had its molecular ion (M) peak at *m/e* 146.110 ($C_{11}H_{14}$; calcd *m/e* 146.110) and in addition exhibited prominent peaks at *m/e* (rel intensity, formula) 117 (100, C_9H_9), 115 (53, C_9H_7), and 91 (46, C_7H_7).[15]

1-Ethylindan was prepared by the method of Khalaf and Roberts,[10] and its IR and ^1H NMR spectra were found to be identical with those recorded for the rearrangement product obtained above: IR (neat) 3090, 3040, 2975, 2940, 2875, 1480, 1460, 1380, 1160, 1090, 1020, 930, 760, 750, 740 cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (t, 3 H), 1.1–2.4 (m, 5 H), 2.9 (m, 2 H), 7.1 (s, 4 H).

Acknowledgment. We are grateful for the financial support provided by the Research Corporation and for grants to Reed College by the Andrew W. Mellon Foundation and the National Science Foundation, the latter through their Undergraduate Research Participation Program. We also thank the Olin Foundation for their generous gift of a Varian Associates EM-360L nuclear magnetic resonance spectrometer, as part of a major capital gift to Lewis and Clark College.

Registry No. 1a, 81141-97-1; **1b**, 81141-98-2; **7**, 4830-99-3; 3-bromo-1-butyne, 18668-72-9; *syn*-7-bromonorbornene, 20047-65-8.

(15) The peak at *m/e* 91 probably arises from an initial intramolecular rearrangement followed by loss of a neutral C_4H_7 radical component.

A Critical Test of the Theory of Stereoelectronic Control

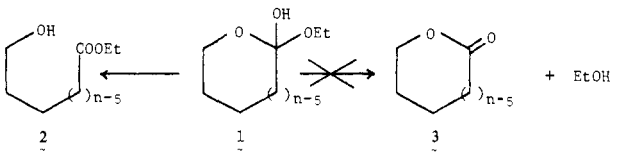
Charles L. Perrin* and Gloria Meichia L. Arrhenius

Contribution from the Department of Chemistry, D-006, University of California, San Diego, La Jolla, California 92093. *Received August 27, 1981*

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. However, it is concluded that the experimental evidence is ambiguous, because it requires an unreasonable assumption regarding rates of ring inversion and because there is a simpler explanation for the observations. Nevertheless, the theory is a plausible one, deserving unambiguous evidence to support it. The hydrolysis of cyclic amidines (**4**), via the hemiorthoamide (**5**), can provide a suitable test. It is observed that 2-amino-1-pyrroline (**4**, *n* = 5) and "2-iminopiperidine" (**4**, *n* = 6) hydrolyze in base solely to the amino amide (**6**), which is converted under the reaction conditions to the thermodynamically more stable lactam (**7**). This result is the first unambiguous evidence for stereoelectronic control, and it also shows that cleavage of the intermediate (**5**) is fast compared to nitrogen inversion.

Introduction

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, since anti elimination is generally preferred,[2] and since involvement of *both* lone pairs is required to produce the resonance stabilization of the ester or amide product. Indeed, MO calculations[3] support the theory. The experimental evidence is contained in a notable series of papers by Deslongchamps[1] and his co-workers. The key result is the "unexpected" observation[4] that a cyclic hemiorthoester (**1**, *n* = 5, 6), produced by two independent routes, cleaves only to the hydroxy ester (**2**), rather than the lactone (**3**).



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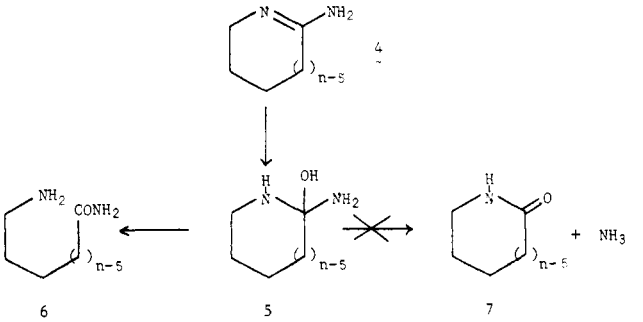
Nevertheless, for reasons presented below, this evidence is ambiguous. In contrast, for reasons presented below, the hydrolysis of cyclic amidines (**4**, *n* = 5, 6) can provide unambiguous evidence



for the theory of stereoelectronic control. According to this theory, plus a supposition regarding nitrogen inversion, a cyclic hemiorthoamide (**5**, *n* = 5, 6) should cleave only to the amino amide (**6**), rather than the lactam (**7**). Despite several previous reports of a high yield of lactam (**7**, *n* = 5,[5a,b] 6[5c]) from amidine hydrolysis, we now report that the kinetic product from **4** (*n* = 5, 6) is indeed the amino amide.

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Table I. Chemical Shifts of Amidines and Their Hydrolysis Products

	δ (n = 5)			δ (n = 6)		
	NCH_2	CH_2CH_2	$CH_2C(=X)$	NCH_2	$CH_2CH_2CH_2$	$CH_2C(=X)$
amidine (4)	3.48	1.98	2.53	3.28	1.71	2.46 ±0.04
amino amide (5)	2.61	1.71	2.29	2.60	1.60, 1.45	2.28
lactam (6)	3.43	2.19	2.35	3.28	1.77	2.32
amino acid, $H_2N(CH_2)_{n-2}CO_2^-$	2.58	1.67	2.19	2.59	1.55, 1.42	2.18

Experimental Section

2-Amino-1-pyrroline hydrochloride (**4**·HCl, $n = 5$) was prepared according to Etienne and Correia[6] and recrystallized from acetonitrile: mp 165–169 °C, lit.[7] 169–171 °C. 2-Iminopiperidine hydrochloride (**4**·HCl, $n = 6$) and authentic lactams and amino acids were commercial substances (Aldrich, Eastman-Kodak), used without further purification. Solutions of the amidine hydrochlorides in dilute acid, where they are stable, showed no impurities detectable by NMR. Solutions for hydrolysis studies were prepared by neutralizing the amidine hydrochloride with 1 equiv. of NaOH, to produce a D_2O solution 0.5 M in amidine, and <0.01 M in excess OH^-. The use of D_2O avoided detector overload by a strong H_2O signal; 0.25% *tert*-butyl alcohol (δ 1.25) served as internal standard for chemical shift measurements.

Reactions proceeded at 25 °C and samples were analyzed by 360-MHz FT proton NMR, where signals are well enough separated that each substance can be distinguished. Table I lists chemical shifts for all substances under the reaction conditions. With the one exception indicated, values differed by no more than ±0.02 ppm from sample to sample. The chemical shifts of the two amino amides were assigned by a process of elimination. No other peaks (<1%) were observed, except for a set at δ 1.84, 2.21, and 3.21 at long reaction times, which may be due to 5–10% of polymeric γ-aminobutyric acid.

Results

The principal products from hydrolysis of the cyclic amidines **4** ($n = 5, 6$) are the amino amide **6** and the lactam **7**. However, the ratio of lactam to amino amide increases as the reaction proceeds, and extrapolation to time zero indicates that the initial ratio is zero (≪1/50). Therefore *the kinetic product of hydrolysis is solely the amino amide*, and the lactam is a secondary product formed from the amino amide. No amino acid (<2%), from further base-catalyzed hydrolysis, was detected in either reaction mixture. From NMR peak heights, a crude kinetic analysis, according to successive first-order reactions (eq 1), gave $k_1 = 3$

$$\text{amidine (4)} \xrightarrow{k_1} \text{amino amide (6)} \xrightarrow{k_2} \text{lactam (7)} \quad (1)$$

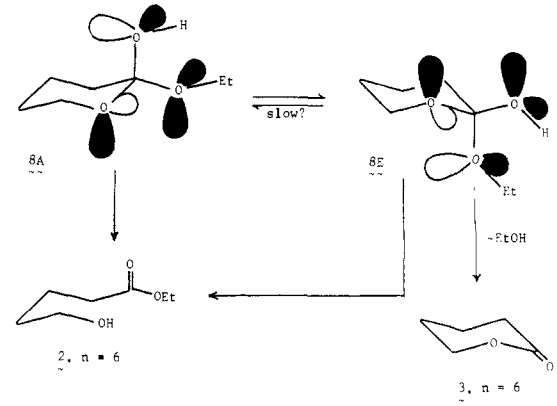
$\times 10^{-5}$ s^{-1}, $k_2 = 0.8 \times 10^{-5}$ s^{-1} ($n = 5$), and $k_1 = 2 \times 10^{-3}$ s^{-1}, $k_2 = 2 \times 10^{-5}$ s^{-1} ($n = 6$). The greater reactivity of the six-membered ring amidine is analogous to the ca. 50-fold greater reactivity of cyclohexanone vs. cyclopentanone,[8] and the faster closure of amino amide to the six-membered lactam has also been observed qualitatively with ornithine.[9] However, the salient result is that the lactam is a secondary product, and that the kinetic product of amidine hydrolysis is >98% amino amide (**6**).

Discussion

Evidence for Stereoelectronic Control. Scheme I summarizes Deslongchamps'[1,4] key piece of evidence, and his reasoning. Under stereoelectronic control the hemiorthoester **1** ($n = 6$) is formed in conformation **8A**, with the hydroxy group axial. This hydroxy is antiperiplanar to two lone pairs, so it can cleave back to its precursor, but this does not lead to product. The ring oxygen is also antiperiplanar to two lone pairs, so it can cleave to produce the hydroxy ester **2** ($n = 6$). In contrast, the ethoxy is antiperiplanar to only one lone pair, so its cleavage, to lactone **3** ($n = 6$), would be equivalent to a syn elimination and thus disfavored.[2]

The absence of lactone product is thus the chief evidence for stereoelectronic control. This seems to be an especially strong

Scheme I. Stereoelectronic Control in the Cleavage of a Hemiorthoester (The Two Lone Pairs That Are Antiperiplanar to Any Leaving Group Are Shaded)



piece of evidence because the lactone is the "expected" product, on the basis of the entropic driving force for liberation of a molecule of ethanol. Subsequently, additional results in similar systems—amide hemiacetals,[10a,b] esters and amides,[10c] hemiorthothiolesters,[11] and a hemiorthoamide[12]—seem to provide confirmatory evidence for the theory of stereoelectronic control.

Ambiguity of the Evidence. Essential to Deslongchamps'[1] argument is the requirement that ring inversion of the intermediate **1** be slow relative to its cleavage. Otherwise ring inversion (labeled "slow?" in Scheme I) would produce conformation **8E**, with the hydroxy group equatorial. Now the ethoxy is antiperiplanar to two lone pairs, so it can cleave to produce the lactone **3** ($n = 6$). Since no lactone is formed, Deslongchamps is forced to assume that cleavage of the intermediate is fast relative to ring inversion. Since the rate constant for ring inversion in cyclohexanes[13] is 10^5 to 10^6 s^{-1}, the rate constant for cleavage would need to be $>10^6$ s^{-1}. Such a rate constant is quite possible,[14] except that rate constants down to ca. 10 s^{-1} have recently been observed for several hemiorthoesters,[15] so that the theory of stereoelectronic control has been questioned.[15,16] Admittedly, these hemiorthoesters may be unusually slow because they may lack two lone pairs antiperiplanar to any possible leaving group. If so, intermediates such as **8A** would be much more reactive, and Deslongchamps' assumption could then hold.

In contrast, *the assumption cannot hold for the five-membered*

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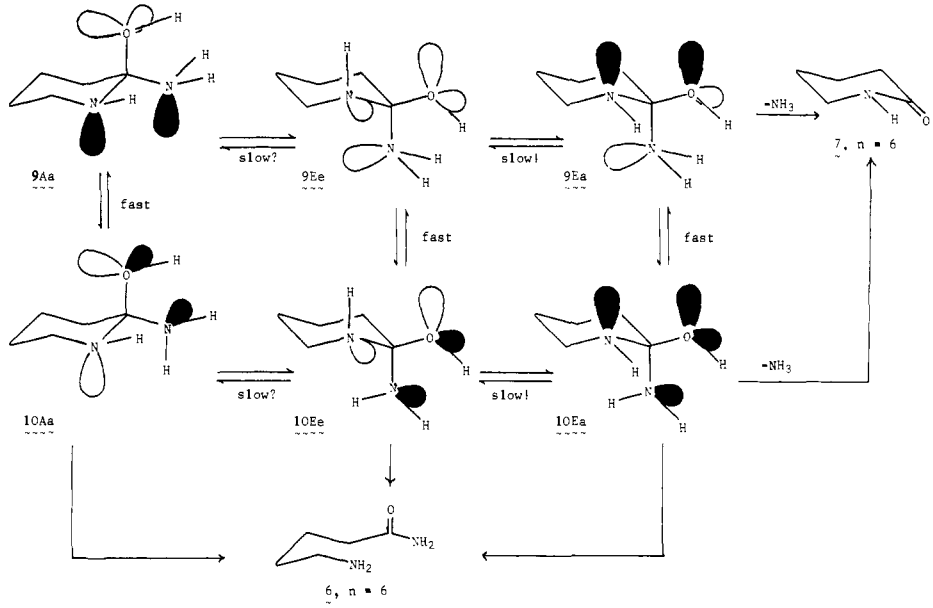
Scheme II. Stereoelectronic Control in the Cleavage of a Hemiorthoamide (The Two Lone Pairs That Are Antiperiplanar to Any Leaving Group Are Shaded)



ring analogue, **1** (n = 5). Ring inversion in cyclopentanes is exceedingly fast, $>10^{12}$ s^{-1},[17] far faster than the 10^8 to 10^9 s^{-1} estimated[18] for the rate constant for cleavage of such intermediates. Therefore, the conformation analogous to **8E** is immediately attained, and loss of ethoxy, to form the lactone **3** (n = 5), would occur. Only if cleavage were to occur much faster than 10^{13} s^{-1} could **8E**, and the lactone, be avoided. Thus, even according to the theory of stereoelectronic control, lactone **3** (n = 5) ought to be formed.

Nevertheless, lactone **3** (n = 5) is *not* formed, so stereoelectronic control cannot explain its absence. Furthermore, inasmuch as stereoelectronic control is not responsible for the absence of this lactone, it is not likely to be responsible for the absence of other lactones. Certainly stereoelectronic control cannot be responsible for the absence of lactone from a rigid analog of **8E**.[19] *Therefore the general absence of lactone products cannot be used as evidence for the theory.*

An Alternative Explanation. If stereoelectronic control is not always responsible for the absence of lactone products, some other explanation is required. Indeed, there is a trivial explanation: *lactones are less stable than ordinary esters*. Experimentally and theoretically, esters are Z (antiperiplanar about the C–O single bond), and the E (syn periplanar) conformer, as in lactones, is ca. 5 kcal/mol less stable.[20] Thus lactones show increased hydrolytic reactivity,[21] since some of that instability is relieved at the transition state. Correspondingly, product-development control must retard formation of lactones. Deslongchamps[10b,19] has recognized this possibility and called it a "secondary stereoelectronic effect", in order to account for the absence of lactone product from a rigid analog of **8E**. However, regardless of the name or the origin, the instability of lactones is well established.

Thus we conclude that (enthalpic) destabilization of lactones can easily account for their absence as product. Similarly, the other pieces of evidence for stereoelectronic control can be accounted for simply on the basis of the instability of the product lactones,[10,19] thionolactones,[11] or β-lactams.[12] Then, since the absence of lactones is *not* an "unexpected" result, it cannot serve as strong evidence for stereoelectronic control. Therefore we conclude that there is no evidence for stereoelectronic control that withstands critical scrutiny.

Critical Test of the Theory of Stereoelectronic Control. Since the theory is a plausible one, we have sought unambiguous evidence to support it. Any suitable system must meet two requirements that are not met by hemiorthoester hydrolysis. (1) There must be no strong enthalpic bias favoring one product over the other. (2) There must be some means whereby the stereochemistry of the intermediate can be preserved, even in the five-membered ring, so that stereoelectronic control can be exerted. Fortunately hydrolysis of cyclic amidines (**4**, n = 5, 6) meets these requirements. Scheme II summarizes the stereochemical features of this hydrolysis for the six-membered ring. For simplicity, and to maintain the similarity with Scheme I, only neutral species are shown, even though analogy with base-catalyzed amide hydrolysis[22] would suggest that cleavage occurs with proton transfer from solvent to a nitrogen of an oxyanion.

There is no enthalpic bias against the lactam product (**7**), because lactams lack the dipole–dipole (or lone pair–lone pair) repulsions that destabilize lactones.[21] Indeed, lactams do not show increased hydrolytic reactivity.[23] Although the Z configuration of secondary amides is more stable than the E, the energy difference is quite small (0.5–1.5 kcal/mol) in amides free of steric repulsions.[24] Therefore lactams, which are E, are not strongly destabilized, and we might expect amino amide **6** and lactam **7** to be of comparable stability. Thus, if we omit stereoelectronic considerations, we might expect a mixture of amino amide **6** and lactam **7**. The exact composition is unpredictable, since it also depends on an entropic contribution (discussed below), the relative leaving abilities of ammonia and primary amine, the relative stabilities of primary and secondary amides or lactams, and the conformational preference of the intermediates. These effects might contribute factors of 2 or 3 to the product ratio, but there is no need to quibble over them. Certainly the "expected" result, without stereoelectronic considerations, is *some* mixture of amino amide plus lactam, rather than a single product. Indeed, hydrolysis of unsymmetrical amidines does produce a mixture of both amides and both amidines.[25]

The slowness of nitrogen inversion can preserve the stereochemistry of the intermediate hemiorthoamide **5**, so that stereoelectronic control can be exerted. Attack of hydroxide on the

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amidinium ion[26] produces the intermediate in conformation **9Aa**, with the hydroxyl group axial and antiperiplanar to two lone pairs, including an axial lone pair on the ring nitrogen. (This is a consequence of stereoelectronic control, but the reasoning is not circular because formation of other conformers would lead to lactam, which is not observed). Rapid rotation (labeled "fast" in Scheme II) about the exocyclic C–N bond produces conformer **10Aa** in which the ring nitrogen is antiperiplanar to two lone pairs, so it can cleave to produce the amino amide **6** (n = 6). Ring inversion (labeled "slow?") can lead to conformers **9Ee** and **10Ee**, in which the hydroxyl *and the lone pair on the ring nitrogen* are now equatorial. The latter conformer can undergo cleavage to the amino amide **6** (n = 6), but neither conformer can cleave with stereoelectronic control to the lactam **7** (n = 6). For cleavage to lactam, nitrogen inversion (labeled "slow!") is a prerequisite. This produces conformers **9Ea** and **10Ea** (which could also have arisen by nitrogen inversion *preceding* ring inversion, via conformers **9Ae** and **10Ae**, which have been omitted from Scheme II for simplicity), where the NH_2 is antiperiplanar to two lone pairs and can cleave with stereoelectronic control. If nitrogen inversion ("slow!") *is* slow compared to cleavage, conformers **9Ea** and **10Ea** are inaccessible and lactams cannot be formed. Although the rate of cleavage[14,15,18] is uncertain, we may suppose it to be greater than the rate of nitrogen inversion, which is 10^5 to 10^7 s^{-1}.[27] Therefore, Scheme II implies that hemiorthoamides might cleave only to amino amide and not lactam, not only for the six-membered ring system shown, but also for the five-membered ring. The contrast between hemiorthoesters (Scheme I) and hemiorthoamides (Scheme II) is that, in the former, ring inversion suffices to produce a conformer that can cleave to lactone, whereas in the latter, nitrogen inversion is also required. If nitrogen inversion ("slow!") is slow enough, then that conformer is not produced. Therefore, it becomes immaterial whether ring inversion ("slow?") is slow, as in six-membered rings, or fast, as in five-membered rings.

Thus hydrolysis of cyclic amidines (**4**, n = 5, 6) is a suitable system for testing the theory of stereoelectronic control. Two alternatives with many of the same features are hydrolysis of cyclic imidates, via amide hemiacetals[10ab,28] or amide hemiorthothioacetals,[29] or hydrolysis of lactams.[10c] Indeed, results from both cyclic and acyclic systems have been claimed[1] as evidence for stereoelectronic control, even though there is one amide hemiacetal that must have undergone cleavage *without* stereoelectronic control.[10a] Unfortunately all of these systems are complicated by a large difference in relative leaving abilities (N vs. O), which may be affected by general-acid or bifunctional catalysis and by steric effects.[30] Besides, to use these as evidence for stereoelectronic control requires a supposition about rates of conformational equilibration that is not valid for such intermediates.[16a,28] Thus all such evidence is inconclusive.

Our experimental results are quite conclusive. For both amidines (**4**, n = 5 *and* 6), the amino amide is the sole kinetic hydrolysis product. Without any considerations of stereoelectronic control this would be a truly "unexpected" result, which cannot be attributed to any instability of lactams. This therefore is strong evidence for stereoelectronic control—that preferential cleavage of tetrahedral intermediates occurs when there are two lone pairs antiperiplanar to the leaving group.

Additional Comments. In comparing lactones and lactams with esters and amides, we have emphasized enthalpy, but it is also necessary to take entropy into account. For lactones the enthalpic destabilization of ca. 5 kcal/mol is less than the 10.5-kcal/mol stabilization that has been estimated[11] from the entropy of liberating a molecule of ethanol. Indeed, at longer reaction times, as equilibrium is approached, there is considerable lactone.[4b] However, it seems likely that entropy is less important kinetically, since at the transition state the ethanol is not yet liberated (whereas the dipole–dipole or lone pair–lone pair repulsions may already be considerable). Similarly, with lactams there is an entropic stabilization due to the liberation of a molecule of ammonia, but there is no appreciable enthalpic destabilization. Thus it has been possible to obtain high yields of lactams by hydrolysis of amidines,[5] by permitting the reaction to reach its entropy-driven equilibrium. However, kinetically our product is the amino amide, which is then converted to lactam. This conversion proceeds through Scheme II, including the nitrogen inversion (or a syn elimination), so it is slow. The difference between kinetic and thermodynamic products is evidence for the different influences of enthalpy and entropy on transition states and products.

In considering the rate of nitrogen inversion, we have taken values[27] for tertiary amines, rather than for secondary amines such as **9** and **10**. These latter have an additional mechanism for inversion, namely, proton exchange. However, it is readily shown that the rate constant for protonation of an amine A is equal to $k_dK_w/K_a + k_p[H^+]$, where K_a is the acidity constant of AH^+, $K_w = [H^+][OH^-] = 10^{-14}$, and k_d and k_p are diffusion-controlled rate constants for deprotonation of AH^+ by OH^- and for protonation of A by H^+, respectively. With reasonable values, $k_d = k_p = 10^{10}$ M^{-1} s^{-1} and $pK_a = 8$,[31] it is clear that this mechanism does not contribute appreciably under our reaction conditions. Therefore, inversion rates of tertiary amines are transferable. Moreover, our experimental results show that nitrogen inversion ("slow!") *is* indeed slow relative to cleavage of the intermediate hemiorthoamide. This comparison was not obvious a priori, but it is a reasonable conclusion, far more so than the assumption that cleavage of a hemiorthoester is fast relative to cyclopentane ring inversion.

Conclusions

Previous experimental evidence for the theory of stereoelectronic control has been ambiguous because it requires the unreasonable assumption that ring inversion, even in a five-membered ring, is slow relative to cleavage of the tetrahedral intermediate. Besides, that evidence is more simply rationalized in terms of the well-known destabilization of lactones. We have proposed that amidine hydrolysis can provide an unambiguous test of the theory, which predicts that a cyclic hemiorthoamide will cleave to amino amide as the sole kinetic product, and no lactam. The advantages of this test are that (1) the only additional assumption necessary is the plausible one that nitrogen inversion is slow relative to cleavage of the intermediate, and (2) the result cannot be rationalized in terms of a destabilization of lactams, because they are not destabilized. The experimental results are fully in accord with the prediction. They substantiate the theory and they also justify the assumption regarding nitrogen inversion. We conclude that although Deslongchamps was remarkably prescient to propose the theory of stereoelectronic control, this is the first unambiguous evidence in support of the theory.

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Registry No. **4**·HCl (n = 5), 7544-75-4; **4**·HCl (n = 6), 16011-96-4; **5** (n = 5), 81027-58-9; **5** (n = 6), 81027-59-0; **6** (n = 5), 3251-08-9; **6** (n = 6), 13023-70-6; 4-aminobutanoic acid ion (1–), 60-28-6; 5-aminopentanoic acid ion (1–), 764-34-1.

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