Is There Stereoelectronic Control in Hydrolysis of Cyclic Guanidinium Ions?

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Abstract: To assess stereoelectronic effects in the cleavage of tetrahedral intermediates, a series of five-, six-, and seven-membered cyclic guanidinium salts was synthesized. If stereoelectronic control by antiperiplanar lone pairs is operative, these are expected to hydrolyze with endocyclic C−N cleavage to acyclic ureas. However, hydrolysis in basic media produces mixtures of cyclic and acyclic products, as determined by ^{1}H NMR analysis. The results show that in the six-membered ring antiperiplanar lone pairs provide a weak acceleration of the breakdown of the tetrahedral intermediate, but in five- and seven-membered rings there is no evidence for such acceleration, which instead can be provided by syn lone pairs.

Introduction

Antiperiplanar Lone Pairs. Stereoelectronic control (SELC) is a topic of much current interest.[1] The term refers broadly to the positioning of lone pairs,[2] and it is certainly relevant to anomeric effects.[3] In connection with reactivity it has most widely been applied at the acetal level of oxidation, but effects are weak or elusive.[4] Consideration here is restricted to a hypothesis due to Deslongchamps that cleavage of a tetrahedral intermediate (**1**) is favored when two lone pairs on adjacent Y

1

atoms are antiperiplanar to the leaving group X.[5] This preference, often called the antiperiplanar lone-pair hypothesis (ALPH) or the kinetic anomeric effect, is supported by calculations.[6]

The role of antiperiplanar lone pairs is a fundamental aspect of the relationship between molecular structure and reactivity. It is still an area of considerable uncertainty and controversy,[7] with wide acceptance[8] and only occasional skepticism.[9] Much of the interest is for purposes of synthesis, where it offers a novel method to control stereochemistry. Customarily steric

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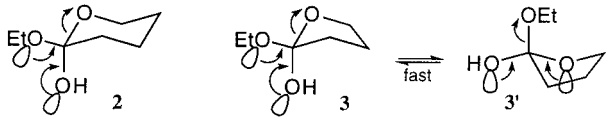
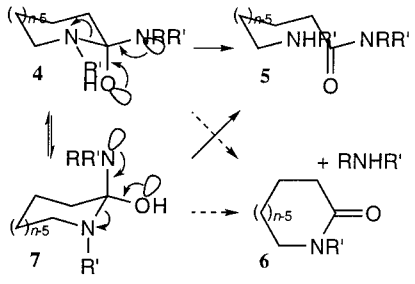
effects are used to direct an incoming nucleophile along the least hindered path to create a chiral center selectively. However, if preferential addition occurs antiperiplanar to a lone pair, this offers an alternative.[10]

To what extent is an antiperiplanar lone pair required to promote cleavage of a tetrahedral intermediate? Certainly an orthogonal lone pair is much less effective than a periplanar one.[11] The issue remaining is the effectiveness of a syn lone pair. Early evidence came from the hydrolysis of a cyclic hemiortho ester (**2**), which opens exclusively to hydroxy ester,



rather than lactone.[12] This endocyclic C−O cleavage is consistent with a preference for antiperiplanar lone pairs of 3−5 kcal/mol. Nevertheless, a serious inconsistency is that the corresponding five-membered hemiortho ester (**3**) also gives only the hydroxy ester, even though pseudorotation rapidly leads to a conformer (**3′**) that has two lone pairs antiperiplanar to the ethoxy and ought to have cleaved to lactone. Therefore it was proposed[13] that the absence of lactone from **3** must be associated simply with the well-known destabilization of lactones and of the transition state leading to them. Moreover, this same explanation may apply to **2**. If so, these product studies are uninformative regarding the necessity for antiperiplanar lone pairs.

To provide a more conclusive test of ALPH, hydrolysis of cyclic amidines was studied. These have the advantage that there is no bias from product stabilities, since lactams do not share the destabilization of lactones. Reaction proceeds via a hemiorthoamide intermediate, with **4** as the initial conformer. After rotation about the exocyclic C−N bond, two lone pairs are antiperiplanar to the endocyclic C−N bond, which can cleave to form the aminoamide (**5**). Cleavage of the exocyclic bond and formation of the lactam (**6**) could utilize the antiperiplanar lone pair on O but would require the syn lone pair on the ring N. In contrast to hemiortho esters (**2**, **3**), although ring inversion of **4** can produce conformer **7**, a second lone pair is not created antiperiplanar to the exocyclic C−N, so this too cannot cleave to lactam. Conformers that could cleave to the lactam are inaccessible because their formation requires nitrogen inversion, which is slow. Thus if stereoelectronic control is operative, the aminoamide **5** is predicted to be the kinetic product.



In initial studies only endocyclic cleavage was observed, consistent with ALPH.[13] However, the absence of **6** was subsequently found to be due to a disparity in leaving abilities.[14] When these are balanced, five- and seven-membered rings produce considerable lactam **6**, counter to ALPH.[15] Even in six-membered rings, where **5** predominates, stereoelectronic control is weak. It is slightly stronger in methanolysis of six-membered-ring ortho esters.[16]

One explanation for these results is the involvement of a syn lone pair,[15] as is supported by computations on acetal hydrolysis.[17] The proponents of ALPH have accepted the involvement of synperiplanar lone pairs in some rigid acetals where eclipsing is obligatory.[18] Yet despite numerous counterexamples to ALPH,[19] the proponents continue to reject any general role for assistance by syn lone pairs in conformationally flexible systems or in cleavage of tetrahedral intermediates.[20] Instead they maintain that "decomposition of the intermediate is determined by the orientation of the lone pair orbitals on the heteroatoms, specific cleavage of a carbon−oxygen or carbon−nitrogen bond being allowed only if the other two heteroatoms (oxygen or nitrogen) of the tetrahedral intermediate each have an orbital oriented antiperiplanar to the leaving *O*-alkyl or *N*-alkyl group".[21]

The hypothesis can be extended to reactions with an additional heteroatom, as in the hydrolysis of guanidinium ions **8**. Although this was thought to proceed by addition of water to the guanidine,[22] the kinetics are equally consistent with rate-limiting addition of OH^-, as in hydrolysis of amidines,[23] to form a tetrahedral intermediate that cleaves as its conjugate base. Endocyclic C−N cleavage produces acyclic urea **10**, whereas exocyclic cleavage produces cyclic urea **11**. In either case the leaving group is a primary amine CH_3NH_2 or RCH_2NH_2, so leaving abilities are balanced. Furthermore the two sets of products are matched for stability. The 2-fold statistical bias toward **10** can be corrected for by expressing the preference for endocyclic cleavage over exocyclic as [**11**]/2[**10**].

The predictions of ALPH for the behavior of **9** are straightforward. According to the principle of microscopic reversibility, addition of OH^- proceeds anti to three nitrogen lone pairs, to

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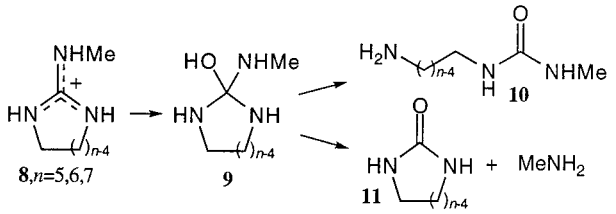
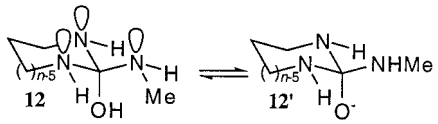
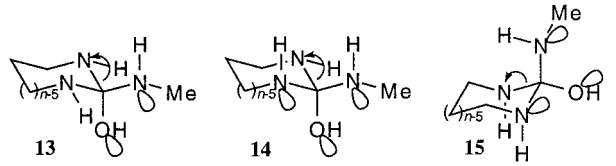


form **12** as initial conformer. Its conjugate base, **12**$^-$, might



undergo C−N cleavage, with prior or simultaneous protonation of the leaving N. The original formulation of ALPH did not consider acceleration due to three lone pairs,[5] but a logical extension is that cleavage is favored if there are at least two lone pairs anti to a leaving group.[24] Rotation about the exocyclic C−N bond produces **13**, with two lone pairs antiperiplanar to the endocyclic C−N bond, which can cleave to produce **10**. Nitrogen inversion in **13** produces **14**, with three antiperiplanar lone pairs, and cleavage again produces **10**. Alternatively, ring inversion of **13** produces **15**, also with three lone pairs



antiperiplanar to the endocyclic C−N, which again can cleave to **10**. Nitrogen inversion in **15** produces **16**, which now has two lone pairs antiperiplanar to the exocyclic C−N bond and can cleave to produce **11**. Inversion of both nitrogens in **15** produces a conformer **17** that has three lone pairs antiperiplanar to the exocyclic C−N bond and can also cleave to **11**. The time scale for these processes is limited by the rate constant for cleavage of a bond anti to two lone pairs, which was estimated to be 10^8−10^9 s^{-1},[25] and which is consistent with another estimate.[15] Rotation about the exocyclic C−N bond is sufficiently rapid, with a rate constant of $>10^{10}$ s^{-1}.[26] Rate constants for ring inversion are either slow, 10^5−10^6 s^{-1} for simple cyclohexanes, or fast, for cyclopentanes and cycloheptanes where this becomes a rapid pseudorotation with a rate constant $>10^{12}$ s^{-1}.[27] Nitrogen inversion is slow in aqueous solution, with a rate constant near 3×10^5 s^{-1}, depending somewhat on ring size.[28] Therefore during the lifetime of the intermediate, only conformer **13** is accessible, and also **15** for $n = 5$ or 7. Conformers **16** and **17** are inaccessible because they require not only ring inversion, which is sufficiently fast for $n = 5$ or 7, but also nitrogen inversion, which is too slow.

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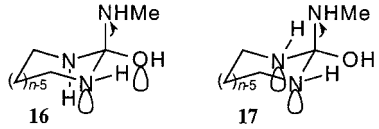
Table 1. Base Solutions

solution	base	[buffer], M
A	Na_3PO_4, 1:1	0.16
B	Na_3PO_4, 25:1	0.56
C	Na_3PO_4, 80:1	1.60
D	NaOH	0.050
E	NaOH	0.10
F	NaOH	1.0

Therefore only acyclic urea **10** should be produced, if antiperiplanar lone pairs are required.



We now report that cyclic ureas **11** are nevertheless produced, especially from five- and seven-membered rings.

Experimental Section

Synthesis. The procedure for synthesis of cyclic guanidinium iodides is simply methylation of the cyclic thiourea with methyl iodide, followed by reaction with methylamine.[29] The guanidinium iodide, **8**·I^- (n = 5), was obtained as a crystalline solid: mp 180−181 °C (lit. mp 178−181 °C); ^{1}H NMR (D_2O) δ 3.68 (s, 4H, CH_2), 2.83 (s, 3H, CH_3); ^{13}C NMR (D_2O) δ 161.7, 43.6, 29.4.

The six-membered-ring thiouronium iodide[30] was converted to the guanidinium salt by heating for 6 h in 40% aqueous methylamine, followed by concentration under vacuum. The iodide, **8**·I^- (n = 6), was obtained as a hygroscopic solid: mp 101−103 °C; ^{1}H NMR (D_2O) δ 3.32 (t, J = 6 Hz, 4H, CH_2(NH)), 2.74 (s, 3H, CH_3), 1.92 (q, J = 6 Hz, 2H, CH_2(CH_2)$_2$); ^{13}C NMR (D_2O) δ 153.8, 38.3, 26.8, 19.6.

The seven-membered-ring thiouronium iodide[31] was converted to the guanidinium iodide, **8**·I^- (n = 7), by refluxing for 6 h in methanol with excess 40% aqueous methylamine, followed by concentration under vacuum. A hygroscopic solid was produced: mp 131−132 °C; ^{1}H NMR (D_2O) δ 3.24 (m, 4H, CH_2(NH)), 2.80 (s, 3H, CH_3), 1.66 (m, 4H, CH_2(CH_2)$_2$); ^{13}C NMR (D_2O) δ 161.5, 44.2, 28.3, 26.9.

Sample Preparation. Concentrated (∼1:1 w/v) stock solutions of salts **8**·I^- (n = 5, 6, 7) in D_2O were prepared. Solutions **A**−**F** in D_2O with 0.1% *tert*-butyl alcohol were prepared as listed in Table 1, with heating if necessary to dissolve. Hydrolyses were carried out quite conveniently in capped NMR tubes. Each hydrolysis sample was prepared by adding 10 μL of stock solution to 0.5 mL of reaction solution, to produce a solution 0.04 M in guanidine. The sample was shaken to ensure thorough mixing, transferred to an NMR tube, and placed in an oil bath at 75 ± 2 °C. Samples were heated for ≥20 h, then allowed to cool to room temperature before NMR analysis. Each experiment was performed at least twice. The apparent pH of the solution was measured before and after hydrolysis.

To test product stability 2-imidazolidinone or tetrahydro-2-pyrimidinone **10** (n = 5, 6) was heated at 75 °C with methylamine and NaOH in D_2O for >72 h. Even after 72 h no new NMR signals were observed. This demonstrates an irreversibility of reaction, which guarantees that the measured product ratio is a kinetic ratio, not an equilibrium distribution. Also, hydrolyses in solutions **B** and **E** were continued. After 72 h no new NMR signals were observed, but after several weeks signals attributable to $H_2N(CH_2)_{n-3}NH_2$ and to $H_2N(CH_2)_{n-3}NHCO_2^-$ (n = 5, 6, or 7) were detected by ^{1}H NMR. These are products from further hydrolysis of the acyclic ureas. The identity of the diamines was confirmed by addition of authentic samples.

NMR Spectroscopy. All NMR spectra were acquired on a Varian Unity 500 spectrometer (500 MHz ^{1}H, 125 MHz ^{13}C). Chemical shifts are reported relative to *t*-BuOH (δ 1.23 or 31.2).

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Table 2. Chemical Shift Assignments for Products from Hydrolysis of **8** ($n = 5, 6, 7$)

	$n = 5$	$n = 6$	$n = 7$
10			
$-CH_3$	2.66	2.66	2.66
$-CONHCH_2$	3.14	3.12	3.08
$-CONHCH_2CH_2$	2.65	1.58	1.41−1.47
$-CONHCH_2CH_2CH_2$		2.60	1.41−1.47
$-CONHCH_2CH_2CH_2CH_2$			2.58
11			
$-NHCH_2$	3.51	3.25	3.12
$-NHCH_2CH_2$	3.51	1.83	1.69
methylamine	2.26	2.26	2.26

Table 2 lists the chemical shifts of products from hydrolyses of **8**·I^- ($n = 5, 6, 7$) in solution **F**. Nearly the same values were obtained in solutions **A**−**E**. Assignments for five- and six-membered-ring cases were confirmed by addition of authentic 2-imidazolidinone, tetrahydro-2-pyrimidinone, or methylamine to hydrolysis mixtures. Hydrolysis products from the seven-membered ring were assigned by analogy to 1,4-diaminobutane and *N*,*N*′-dimethylurea and to products from the other hydrolyses.

Integrated intensities of the ^1H NMR spectra were used to evaluate product ratios. Owing to the volatility of methylamine, its integrals were rejected. When peaks from cyclic and acyclic products overlapped, integrations from well-resolved peaks were used to determine individual contributions to the total integral. Ratios are reported as a fraction of total urea product, to exclude unreacted starting material. This also neglects any acyclic urea that has undergone further hydrolysis, for which the resulting signals are too weak to include reliably. Consequently, the apparent yield of cyclic urea was found to increase slightly at long reaction times, but those data were rejected.

Results

Reaction Rates. Some qualitative observations regarding reaction rates could be made. Decreasing the pH by 1 slows all reactions approximately 10-fold. Reaction becomes unmeasurably slow in carbonate buffers. Among the three guanidines there is only a slight variation in hydrolysis rate, with $n = 6$ reacting ~10% faster than for $n = 5$ or 7. These observations are consistent with rate-limiting hydroxide attack on the guanidinium ion. This step should proceed faster in six-membered rings because of release of torsional strain.

To determine the effect of basicity, it would be helpful to know the pH of the various solutions. From the stoichiometries there is an increase of 2 pH units from **D** to **F**. However, the pH in phosphate buffers is too uncertain, because of incomplete neutralization of guanidinium ion, the use of D_2O at 75 °C, the effect of ionic strength on the pK_a of HPO_4^{2-}, and the pH decrease during hydrolysis, owing to conversion of the guanidine to the less basic amine. Instead the effective basicities were assessed by comparing reaction rates. After 20 h hydrolysis of **8** ($n = 6$) was 65% complete in **B**, 85% complete in **C**, 75% complete in **D**, and 95% complete in **E**. These values show that the basicities of the NaOH solutions and phosphate buffers overlap. The measured pH values at 25 °C also reflect this.

Product Ratios. The results listed in Table 3 are average values from repeated experiments. Variations between samples are generally 1−2% for five- and six-membered rings. In seven-membered rings signal overlap rendered integrations less accurate, and product ratios varied by 5−10%.

Discussion

Product Ratios. The key result in Table 3 is that cyclic ureas are formed in the hydrolysis of **8** ($n = 5, 6, 7$). There are variations in product ratio with ring size. The proportion of cyclic urea is 38% for $n = 5$, 5−20% for $n = 6$, and 42−53% for $n = 7$. The ratios of endocyclic cleavage to exocyclic, corrected for statistics, are presented in Table 4.

Table 3. Percent Cyclic Urea from Hydrolysis of **8** at 75 °C

n	solution	% **11**	*n*	solution	% **11**
5	**A**	38	6	**C**	7.3
5	**B**	38	6	**D**	11
5	**C**	38	6	**E**	7.5
5	**D**	38	6	**F**	5.2
5	**F**	38	7	**A**	42
6	**A**	21	7	**B**	51
6	**B**	11	7	**D**	53
7	**E**	44			

Table 4. Direction of Bond Cleavage in Hydrolysis of **8**

n	endo/2exo
5	0.82
6	5.5
7	0.55

Both the five- and seven-membered rings yield nearly equal proportions of cyclic and acyclic ureas. Within experimental error the product ratios are independent of solution basicity. The ratio of endocyclic cleavage to exocyclic, corrected for statistics, is 0.82 or 0.55. This is definitely not a preference for endocyclic cleavage.

The six-membered ring exhibits the highest selectivity for endocyclic cleavage over exocyclic. However, this is weak, only 5.5-fold (averaged over the higher pH solutions). Moreover, there seems to be a decrease in the proportion of cyclic urea at the highest basicity, in contrast to the other rings.

Stereoelectronic Control. In the hydrolysis of these cyclic guanidines, stereoelectronic control is expected to favor endocyclic C−N bond cleavage to acyclic urea. The data in Table 3 do not show a strong preference for acyclic urea. The data in Table 4 show a preference for endocyclic cleavage in the six-membered ring but a slight preference for exocyclic cleavage in five- and seven-membered rings. This is counter to ALPH.

The exocyclic cleavages to cyclic ureas for $n = 5$ or 7 do not derive from conformers such as **16**, since these are inaccessible during the lifetime of the intermediate. Instead they derive from conformers such as **12**−**15**. These have no lone pairs on the ring nitrogens antiperiplanar to the exocyclic C−N bond. Instead only syn lone pairs are available, and the results show that they too must be capable of facilitating cleavage. Therefore anti lone pairs are not required. Indeed, it is well-known that in five- and seven-membered rings syn eliminations are quite competitive with anti.[32] It is not at all unusual that syn lone pairs can facilitate cleavage, as was seen with amidines.[15]

Stereoelectronic control should not have been expected to be so universal as to operate even in five- and seven-membered-ring guanidines. In contrast to six-membered rings, these rings are flexible enough to allow both synperiplanar and antiperiplanar relationships between lone pairs on ring nitrogens and exocyclic C−N bonds. Besides, the lone pair on a nitrogen of a nearly planar five-membered ring (**18**) is not well positioned to facilitate cleavage of the other endocyclic C−N, because the orbitals are nearly orthogonal. In the reverse reaction this is a 5-*endo-trig* ring closure, which is disfavored by Baldwin's rules,[33] but nevertheless allowed in dioxolane formation.

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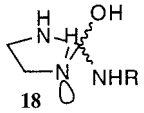

18

In contrast, the endocyclic C−N cleavage in the hydrolysis of the six-membered ring is consistent with ALPH. This parallels the strong preference for anti elimination in cyclohexane derivatives such as menthyl chloride.[34] Synperiplanar relationships in six-membered rings are possible only with high-energy eclipsed conformations. Therefore conformers **12**−**15** ($n = 6$) do not readily use syn lone pairs to cleave the exocyclic C−N. Instead they use anti lone pairs to cleave the endocyclic C−N.

Nevertheless, the preference for anti lone pairs, even in this best case, is weak. The 5.5:1 ratio corresponds to a preference of only 1 kcal/mol. This is considerably less than the 3−5 kcal/mol expected from stereoelectronic control.[5,12] However, it is difficult to assess this contribution quantitatively, since there is also an entropic contribution favoring the cyclic urea, due to liberation of a molecule of methylamine, and there may be slight differences in leaving abilities.

The weakness of stereoelectronic control in the six-membered ring and its apparent absence in five- and seven-membered rings does not mean that it does not operate. It might be operative in the cleavage step and not in the addition, or vice versa, as assumed above. Perhaps addition of OH^- syn to both lone pairs of the ring nitrogens produces **17** directly, or **16** by addition syn to only one lone pair. These could cleave to **11** with stereoelectronic control. However, it seems more likely that **11** arises because syn lone pairs are involved in the cleavage of **12**−**15**, formed by addition of OH^- anti to lone pairs. The stereoelectronic selectivity is reduced because the species that undergoes cleavage is the conjugate base of the intermediate, derived from $\mathbf{12}^-$. It has an antiperiplanar lone pair on the oxygen that provides a strong push for elimination. That may be sufficient so that even syn lone pairs on the nitrogens are adequate. This is equivalent to assuming that the transition state is early along the reaction coordinate.[20] Such a transition state resembles the intermediate and has little interaction between the lone pair and the bond to be cleaved, whose stereochemistry is then immaterial.

Variation with Basicity. The proportion of counter-ALPH cyclic urea increases at lower basicity, but only for the six-membered ring. A similar dependence was observed in the hydrolysis of some amidines.[15,35] Since C−N cleavage requires deprotonation of the hydroxyl, a reduced basicity extends the lifetime of the intermediate so that ring inversion and nitrogen inversion become competitive with product formation. Access to additional conformers such as **16** and **17** then facilitates exocyclic cleavage. However, this cannot be a major influence, since the variation is small, only 4-fold across a range of >2 pH units, where the lifetime of the intermediate varies substantially. Moreover, the product ratio from five- and seven-membered-ring guanidines is constant. In these rings there are many reactive conformers, where either syn or anti lone pairs facilitate bond cleavage, so that the lifetime of the intermediate does not affect its partitioning.

Hydrolyses were also performed in phosphate buffer to test for bifunctional catalysis. In hydrolysis of imidates, this promotes C−N cleavage when the OH and the lone pair are syn,[36] which would favor exocyclic cleavage. Yet there is no appreciable difference between NaOH and a phosphate buffer of comparable basicity.

Conclusions

Cyclic urea is formed in the hydrolysis of **8** ($n = 5, 6, 7$). The proportion is 38% for $n = 5$, 5−20% for $n = 6$, and 47% for $n = 7$. Thus both the five- and seven-membered rings yield nearly equal proportions of cyclic and acyclic ureas. The preference, corrected for statistics, is actually for exocyclic cleavage, and it is counter to ALPH. The six-membered ring does exhibit a selectivity for endocyclic cleavage over exocyclic, as expected from ALPH. However, this represents a preference of only 1 kcal/mol.

The production of cyclic ureas from hydrolysis of these guanidines is contrary to ALPH. Regardless of whether these results are interpreted in terms of a reduced selectivity, an early transition state, or the ready involvement of syn lone pairs, they show that ALPH has a low predictive power.

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