lyzed by HPLC. The product yields are reported in Table III.

B. In the Presence of HBr. Equimolar amounts of a ca. 1.5×10^{-2} M solutions of Br_2 in 1,2-dichloroethane or chloroform were added dropwise to 20 mL of 3.5×10^{-2} M solutions of *cis*- and *trans*-stilbene in the same solvents, whereas HBr was bubbled through these solutions. After the addition was complete, the reaction mixtures were washed with water, dried ($MgSO_4$), and evaporated, and the crude residues were analyzed by HPLC. The results are reported in Table III.

Treatment of Dibromides with Br_2. Equimolar amounts of *meso*-**3** or *d,l* dibromide **4** and of Br_2 were mixed in 1,2-dichloroethane (ca. 3×10^{-3} M) and left at room temperature for 3 days. The solutions were then washed with saturated aqueous $NaHSO_3$ and water, dried ($MgSO_4$), and evaporated. The HPLC analysis showed that both dibromides were quantitatively recovered.

Kinetic Measurements. Bromine solutions in 1,2-dichloroethane were prepared shortly before use and the concentrations were determined from the UV-vis spectra (ϵ_{max} 211 M^{-1} cm^{-1} at λ_{max} 409 nm) and adjusted to twice the desired initial concentrations (ca. 3×10^{-3} M) in the kinetic runs. In a few runs the solvent was preventively saturated with oxygen. These solutions were prethermostated at 25 °C and mixed with equal volumes of prethermostated olefin solutions of identical concentrations in the same solvent. The reactions were followed at 25 ± 0.05 °C (Lauda MK 70 constant-temperature circulating bath) by monitoring the decrease in absorbance of Br_2 at 409 nm and recorded for more than three half-lives. The absorbance/time data were fitted to eq 3 and the third-order rate constants obtained with the usual linear least-squares procedure. The reported values are the average of four independent measurements. Errors are given as standard deviations obtained from the deviations of individual measurements from the average values.

$$1/A^2 = (2k_3/\epsilon_{Br_2}^2)t + 1/A_0^2 \quad (3)$$

Product Distribution during Bromination. A 2.5×10^{-3} M solution of *cis*-stilbene and Br_2 in 1,2-dichloroethane thermostated at 25 ± 0.05 °C was divided into two parts. One part was used to follow the reaction kinetics monitoring the absorbance of Br_2. Samples were simultaneously withdrawn at intervals from the second part, and the unreacted Br_2 was immediately reduced by adding solid $Na_2SO_3 \cdot 7H_2O$. After filtration, these samples were directly analyzed by HPLC. The amounts of unreacted olefin and of dibromide products were deduced from the absorbance measurements, while the distribution of the total olefin between *cis*- and *trans*-stilbene as well as that of the total dibromides between the meso and *d,l* isomers were calculated from the chromatograms using appropriate calibration curves. The results are reported in Table IV. Experiments carried out under identical conditions but with oxygen-saturated 1,2-dichloroethane gave the same results.

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Registry No. 1, 10368-43-1; **2**, 74892-78-7; *meso*-**3**, 13440-24-9; (*dl*)-**4**, 13027-48-0; **5**, 103-30-0; **6**, 645-49-8; HBr, 10035-10-6; Br_2, 7726-95-6.

Hydrolysis of Unsymmetrical Acetamidines: Leaving Abilities and Stereoelectronic Effects

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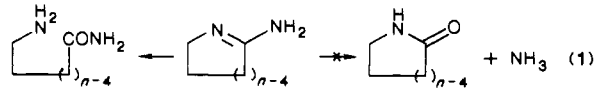
Abstract: Unsymmetrical acetamidines hydrolyze in alkaline D_2O to a mixture of two acetamides and two amines. Product ratios from three N-methylated acetamidines and five *N*-alkyl-*N'*-methylacetamidines were determined by NMR. The direction of cleavage is determined largely by the relative basicities of the two amines, rather than by the relative basicities of the two nitrogens in the tetrahedral intermediate. Steric repulsion in the product amides can also affect the product ratio, but only slightly. There is also a novel configurational effect, which favors cleavage of the nitrogen whose alkyl group is (*Z*) in the amidinium ion. This arises from a stereoelectronic preference for cleavage of a leaving group that is antiperiplanar to two lone pairs in the tetrahedral intermediate. However, it is concluded that this preference is weak. These results have guided the design of a test of this stereoelectronic preference in the hydrolysis of a set of cyclic amidinium ions where product stabilities and leaving abilities can be closely matched.

Recently the formation of aminoamide (**1**), rather than lactam + NH_3, from the hydrolysis (eq 1) of cyclic amidines (**2**, n = 5, 6), has been presented[1] as the first unambiguous evidence for



1 **2**

Deslongchamps' theory of stereoelectronic control.[2] In this reaction the products are of nearly equal stability (except for entropy, which probably does not affect the kinetics[3]), in contrast to the corresponding ortho ester hydrolysis,[4] where a lactone is appreciably less stable[5] than is an ordinary ester. Yet it is still not clear that eq 1 can be an unambiguous test of the theory. Even though product stabilities are matched, leaving abilities may not be.

Hydrolysis of an unsymmetrical amidine, via the hemiortho amide and its conjugate base (**3**), cleaves preferentially the more basic amine,[6] although there may be exceptions.[7] Basicity governs

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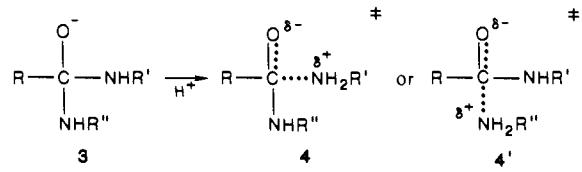

3 **4** **4'**

cleavage because a nitrogen anion is so poor a leaving group that (except for some extreme cases[8]) it must acquire a proton[9] either prior to cleavage or concerted with it. Consequently the transition state, **4** or **4'**, bears a partial positive charge on the nitrogen that is cleaved. It may then be that **1** is formed merely because a primary amine is more basic than ammonia, and therefore a better leaving group.

However, it is not certain that leaving abilities are mismatched in eq 1. Although a primary amine is appreciably more basic than ammonia (by ≥ 1 pK unit), why must the relevant basicity be that of the cleaved amine? The transition state (**4** or **4'**) resembles intermediate **3** more than it resembles the product amine, $R'NH_2$ or $R''NH_2$. It seems more appropriate to focus not on the product basicities but on the basicities of the two nitrogens in the intermediate. For the particular case of eq 1 (via **3**, R' = alkyl, R'' = H), the comparison is between a primary amine and a secondary amine, which are closer to each other in basicity. If this is the proper comparison, the leaving abilities are indeed matched in eq 1. Previous studies[6] do not make this distinction, since most involve comparison between alkylamine and arylamine, and the alkylamine is the better leaving group regardless of whether its own basicity is involved or its basicity in the intermediate (**3**, R' = alkyl, R'' = aryl). Only in the aminolysis of imidate esters can it be inferred[10] that an alkylamine may be a better leaving group than ammonia, but this is opposite to the conclusion[11] that the less basic amine should be the better leaving group in this reaction. Accordingly we have undertaken a systematic study of relative leaving abilities in hydrolysis of unsymmetrical acetamidines. This study enables us to devise a proper test[12] of the controversial theory of stereoelectronic control, which seems to be widely accepted[13] despite frequent objections.[1,14]

Experimental Section

Synthesis of Acetamidines. *N*-Methylacetamidinium chloride (**5**·HCl) was synthesized from methyl *N*-methylacetimidate[15] plus equimolar NH_4Cl; it was recrystallized three times from absolute ethanol–benzene; mp 143–146 °C (hygroscopic), lit.[16] mp 147–149 °C. NMR (D_2O) δ 2.28 (s, 3 H), 2.92 (s, 2.8 H), 3.00 (s, 0.2 H). *N,N*-Dimethylacetamidinium chloride (**6**·HCl) was synthesized from ethyl acetimidate hydrochloride and equimolar dimethylamine and recrystallized from methanol; mp 154–156 °C, lit.[17] mp 158–159 °C. NMR (Me_2SO-d_6) δ 2.32 (s, 3 H), 3.15 (s, 3 H), 3.20 (s, 3 H). *N,N,N'*-Trimethylacetamidine (**7**) was synthesized from methyl *N*-methylacetimidate[15] plus equimolar dimethylamine [bp 30–35 °C (8 mmHg), lit.[18] bp 61 °C (60 mmHg); NMR ($CDCl_3$) δ 1.82 (s, 3 H), 2.80 (s, 6 H), 2.88 (s, 3 H)] or as the hydrochloride (recrystallized from absolute ethanol–benzene) from dimethylcarbamyl chloride and *N*-methylacetamide[18] [mp 143–146 °C (hygroscopic); NMR (D_2O) δ 2.29 (s, 3 H), 2.85 (s, 0.06 H), 3.04 (s, 3 H), 3.09 (s, 3 H), 3.25 (s, 3 H)].

N-Isopropyl-*N'*-methylacetamidinium chloride (**8**·HCl) was prepared by mixing equimolar portions of methyl *N*-methylacetimidate[15] and isopropylamine in absolute ethanol. After 24 h the solvent was evaporated, the residue was taken up in dry ether, and dry HCl was passed through the solution to precipitate the hydrochloride, which was recrystallized from absolute ethanol–benzene: yield 0.25 g (29%); mp 90–95 °C (hygroscopic); NMR (DCl/D_2O) δ 1.20 (d, 2.8 H), 1.28 (d, 3.2 H), 2.28 (s, 1.6 H), 2.30 (s, 1.4 H), 2.85 (s, 1.4 H), 3.00 (s, 1.6 H), 3.8 (m, 1 H). Similarly were prepared *N*-*n*-butyl-*N'*-methylacetamidinium chloride (**9**·HCl) [mp 70–75 °C (hygroscopic); NMR (DCl/D_2O) δ 0.95 (t, 3 H), 1.50 (m, 4 H), 2.32 (s, 3 H), 2.95 (s, 1.44 H), 3.10 (s, 1.56 H), 3.25 (t, 1.04 H), 3.45 (t, 0.96 H)], *N*-methyl-*N'*-neopentylacetamidinium chloride (**10**·HCl) [mp 142–145 °C (hygroscopic); NMR (DCl/D_2O) δ 0.95 (s, 3.5 H), 1.06 (s, 5.5 H), 2.32 (s, 1.17 H), 2.38 (s, 1.83 H), 3.02 (s, 1.17 H), 3.10 (s, 1.83 H), 3.15 (s, 1.2 H), 3.30 (s, 0.8 H)], and *N*-benzyl-*N'*-methylacetamidinium chloride (**11**·HCl) [mp 123–125 °C (hydroscopic); NMR (DCl/D_2O) δ 2.12 (s, 1.8 H), 2.24 (s, 1.2 H), 2.93 (s, 1.8 H), 2.95 (s, 1.2 H), 4.45 (s, 0.8 H), 4.55 (s, 1.2 H), 7.40 (m, 5 H)].

N-*tert*-Butyl-*N'*-methylacetamidinium chloride (**12**·HCl) was prepared by treating recrystallized *N*-*tert*-butylacetamide[19] with trimethyloxonium tetrafluoroborate in CH_2Cl_2, neutralizing the mixture with aqueous NaOH, and distilling the methyl *N*-*tert*-butylacetimidate: bp 40–42 °C (20 mmHg); NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.92 (s, 3 H), 3.46 (s, 3 H). This was reacted with equimolar methylamine in absolute ethanol for 48 h. The solvent was removed under vacuum, and the residue was taken up in ether and treated with HCl to produce the hydrochloride (0.12 g, 60%), which was recrystallized from absolute ethanol–benzene: mp 180–182 °C (hygroscopic); NMR (DCl/D_2O) δ 1.32 (2, 7.65 H), 1.41 (s, 1.35 H), 2.15 (s, 2.55 H), 2.34 (s, 0.45 H), 2.82 (s, 0.45 H), 2.95 (s, 2.55 H).

Methods. NMR methodology, sources of reagents, and sample preparation were as described previously.[12] Product studies were generally carried out on a Varian EM390 spectrometer, at a probe temperature of 34 °C. Some FT spectra were obtained with a 360-MHz Oxford magnet interfaced to a Nicolet 1180E computer and pulse programmer.

Chemical shifts of the acetamidines in D_2O with NaOH are listed in Table I. For simplicity each amidine is written as a single tautomer, rather than as a mixture of two. Chemical shifts of the hydrolysis products are listed in Table II. These chemical shifts were assigned by adding each authentic amine and at least one of the product amides to the solution after hydrolysis was complete. Product ratios were determined by integrating the *N*-alkyl peaks of both amines and also of both amides and averaging the two ratios. As can be seen from Tables I and II, all peaks were well-separated. Each experiment was performed three times, and the values were averaged. Where necessary, ratios were corrected for small amounts of product present as impurity in the reactant amidine. Product ratios were constant even to 100 half-lives, so there is neither transamination of the amides nor further hydrolysis. Stereo-

Table I. Chemical Shifts of Acetamidines $CH_3C(NRMe)=NR'$ in NaOH/D_2O

amidine	R	R'	CH_3C	NMe	R, R'
5	H	H	1.98 (s)	2.78 (s)	
6	Me	H	2.17 (s)	3.00 (s)	3.00 (s)
7	Me	Me	1.98 (s)	3.13 (s)	3.13 (s), 3.00 (s)
8	H	*i*-Pr	2.23 (s)	3.03 (s)	3.92 (m) (CH)
9	H	*n*-Bu	2.00 (s)	2.82 (s)	3.70 (t) (α-CH_2)
10	H	neoP	2.30 (s)	2.97 (s)	2.99 (s) (CH_2)
11	H	$PhCH_2$	1.90 (s)	2.81 (s)	4.20 (s) (CH_2)
12	H	*t*-Bu	2.00 (s)	2.98 (s)	1.41 (s)

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Table II. Chemical Shifts of Hydrolysis Products of Acetamidines

	$CH_3CONRMe + R'NH_2$			$CH_3CONHR' + RNHMe$		
amidine	CH_3C	NMe	R, R'	CH_3C	NMe	R, R'
5	2.00 (s)	2.70 (s)		1.92 (s)	2.28[a] (s)	
6	2.18 (s)	2.99 (s)	3.15 (s)	1.92 (s)	2.23 (s)	2.23 (s)
7	2.10 (s)	2.96 (s)	3.10 (s), 2.36[a] (s)	2.00 (s)	2.36 (s)	2.36 (s), 2.76 (s)
8	2.10 (s)	2.70 (s)	3.02 (m) (CH)	2.05 (s)	2.30[a] (s)	3.70 (m) (CH)
9	1.98 (s)	2.73 (s)	2.59 (t) (CH_2)	1.98 (s)	2.30[a] (s)	3.17 (t) (CH_2)
10	1.93 (s)	2.70 (s)	2.33 (s) (CH_2)	1.98 (s)	2.30[a] (s)	2.80 (s) (CH_2)
11	1.89 (s)	2.70 (s)	3.68 (s)	1.96 (s)	2.29[a] (s)	4.29 (s)
12	1.99 (s)	2.75 (s)	1.23 (s) (*t*-Bu)	1.98 (s)	2.32[a] (s)	1.27 (s) (*t*-Bu)

[a] $\delta_{CH_3NH_2}$ varies from 2.28 to 2.45 with pH and course of reaction.

Table III. Hydrolysis Products of Acetamidines $CH_3C(NRMe)=NR'$ in $NaOH/D_2O$

amidine	R	R'	% ZE	% $CH_3CONRMe$ + $R'NH_2$	$pK_a^{R'NH_3^+}$ [a]
5	H	H	96[b,c]	10	9.24
6	Me	H		2	10.64[d]
7	Me	Me	≤2[b]	22	10.62
8	H	*i*-Pr	54	52	10.63
9	H	*n*-Bu	52	46	10.59
10	H	neoP	61	33	10.21
11	H	$PhCH_2$	38	26	9.34
12	H	*t*-Bu	85	42	10.55

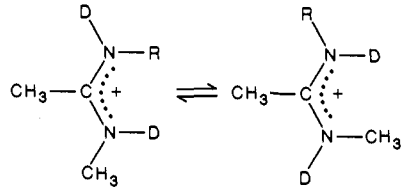
[a] From: Jencks, W. P. *Handbook of Biochemistry*, 2nd ed.; CRC: Cleveland, 1970. [b] % Z. [c] From ref 16. [d] $pK_a^{Me_2NH_2^+}$.

isomer ratios of the reactant amidinium ions in DCl/D_2O (where they were stable to hydrolysis) were determined similarly, by integrating and averaging the appropriate peaks; for most of these the two *C*-methyl peaks were well-separated and were used to check the ratios.

Results

Product ratios from hydrolysis of all the acetamidines are listed in Table III. The precision of these values is ±1–3%. The hydrolyses were performed with ca. 0.25 M amidine in D_2O in the presence of ca. 0.25 M NaOH, where the half-lives at 34 °C were ca. 10 min. In less basic media (down to pD 9) hydrolysis was slower, but the same product mixture was obtained, within experimental error.

In DCl/D_2O each amidinium ion, except **6**·H^+, is present as a mixture of stereoisomers that interconvert slowly. Both **5**·H^+ and **7**·H^+ occur as *E* and *Z* forms, whereas each *N*-alkyl-*N'*-methylacetamidinium ion (**13**) is present predominantly as *ZE* and *EZ* stereoisomers, distinguished by whether the substituent syn to nitrogen is R or CH_3, respectively. Table III also lists



13*ZE* **13*EZ***

the percent of each amidinium ion present as the *Z* or *ZE* stereoisomer. NMR signals were assigned on the basis of multiplicity, relative intensity (CH_3 vs. CH_2), splitting in H_2O (NMe_2 vs. NHMe), and the general observation[20] that an *E* alkyl is downfield of a *Z* alkyl. Usually the dominant stereoisomer of an *N*-alkyl-*N'*-methylacetamidinium ion is (*ZE*), except for **11**·D^+, where saturation of the *C*-methyl produces an 11% nuclear Overhauser enhancement of the downfield and less populated *N*-methyl, which is thereby assigned as (*E*). No enhancement could be observed for **7**·D^+, which is a single isomer, except for a barely detectable peak at δ 2.85. According to the chemical shifts the dominant stereoisomer is (*E*), and this is consistent with a large (up to 7.5 kcal/mol[21]) destabilization of the (*Z*) form due to peri methyl–methyl repulsion. Also, the 78:22 product ratio from this amidine is identical with the ratio observed[22] in an *N,N,N'*-trialkylamidine with a bicyclic ring system that holds the stereochemistry of the *N'*-alkyl to be (*E*).

Discussion

Leaving Ability and Basicity. The data in Table III show that there is a preference for cleaving the more basic amine. (The table also includes the pK_as of the conjugate acids of all amines.) The most extreme case is **6**, where there is a 98:2 preference for cleavage of dimethylamine over ammonia. A similar preference, 90:10, is shown for methylamine over ammonia from **5**. These results show that the leaving abilities of ammonia and other amines are mismatched. Consequently, observation of aminoamide **1**, rather than lactam + NH_3, in the hydrolyses[1] of eq 1 cannot be taken as evidence for the theory of stereoelectronic control.

The strong preference for cleaving methylamine or dimethylamine over ammonia is quite remarkable. It is opposite to the thermodynamics, which show[23,24] a substantial preference (13- or 500-fold, extrapolated to 34 °C from 75.8 °C data[23]) for cleavage of ammonia. The effect is clearly kinetic, due to a low leaving ability of ammonia, which is a less basic amine. The basicity of the nitrogen in the intermediate (**3**) is not relevant. Had it been, we might have expected cleavage to favor $CH_3NH_2 \sim NH_3 > (CH_3)_2NH$, since primary and secondary amines are of nearly equal basicity, but a tertiary amine is distinctly less basic. Nevertheless, this is not observed. Instead it is the basicity of the cleaved amine itself that must be considered. This is especially surprising, since the transition state for cleavage (**4** or **4'**) resembles **3** more than it resembles the protonated form of the cleaved amine. One rationale for this observation (suggested by a referee) is that alkyl substitution simply increases the nitrogen basicity in **3**, with less of the usual hindrance to solvation of the conjugate acid, which is a zwitterion.

Yet basicity cannot be the only factor determining leaving abilities. The product ratios from *N*-alkyl-*N'*-methylacetamidines can be fit to eq 2 (adapted from eq 13 of ref 11), but the fit is mediocre (correlation coefficient 0.915) and the slope of 0.33 does

$$\log([RNH_2]/[CH_3NH_2]) = (\beta_{lg} - \beta_N)(pK_a^{RNH_3^+} - pK_a^{CH_3NH_3^+}) \quad (2)$$

not agree with the $\beta_{lg} - \beta_N$ of 0.72 estimated previously.[12] More extreme is the case of **7**, which shows a 78:22 preference for cleavage of dimethylamine over methylamine, even though methylamine is slightly more basic (when pK_as are corrected for statistics[25]). A similar result has been obtained by Löfås and Ahlberg[22] in a bicyclic analogue.

It is necessary to consider other factors that determine the direction of cleavage of these unsymmetrical amidines. In what follows, we consider product stability, configurational effects, and stereoelectronic control, with particular interest in the last.

Product Stability. The 78:22 preference for cleavage of dimethylamine over methylamine can be attributed to an instability

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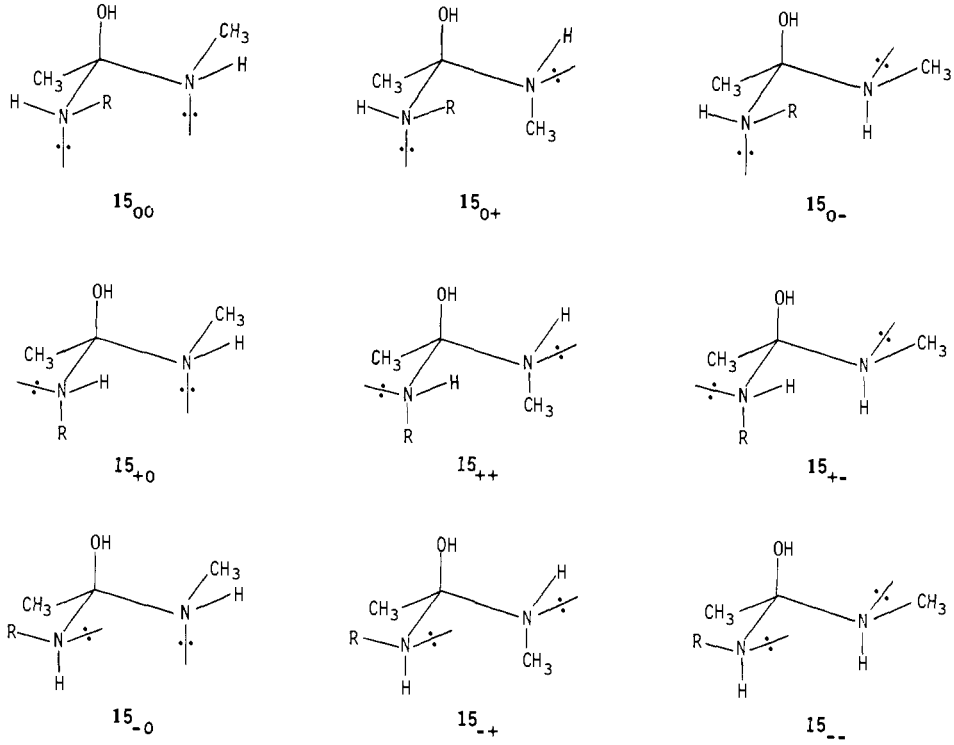


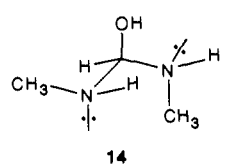
Figure 1. Nine conformers derived from the (*ZE*) stereoisomer of an *N*-alkyl-*N'*-methylacetamidinium ion (**13*ZE***). Conformers interconverted by rotation about C–$NHCH_3$ are in the same row, whereas those interconverted by rotation about C–NHR are in the same column.

of product *N,N*-dimethylacetamide. According to kinetic data[23] on formation and hydrolysis of propionamides, the equilibrium constant for eq 3, extrapolated to 34 °C, is 37. Although these

$$RCONMe_2 + MeNH_2 \rightleftharpoons RCONHMe + Me_2NH \quad (3)$$

data have been questioned[24] because they disagree with better data on formamides, this equilibrium constant is truly large, owing to steric repulsion between the alkyl group R and one of the *N*-methyls.[26] This steric repulsion is absent in formamides as well as in the preferred (*Z*) stereoisomer of *N*-methylformamide. As a result the equilibrium favors cleavage of dimethylamine, whose staying ability is reduced by steric repulsion. Leaving abilities are determined not only by basicity but also by steric repulsion in the product amide.

Yet this steric repulsion does not seem to be strong in the transition state for cleavage. The large[12] $\beta_{lg} - \beta_N$ suggests that this transition state (**4** or **4'**) is an early one, since bond breaking has not progressed so far as to substantially reduce the positive charge on the leaving nitrogen. Nor has substantial steric repulsion developed in this transition state, since **7** gives only a 78:22 product ratio, despite an equilibrium constant of 37. Further support for this notion is the observation[27] that hydrolysis of *N,N*-dimethylformamidine produces substantial amounts of (*E*)-*N*-methylformamide, even though the equilibrium constant[28] of 13.5 favors the (*Z*) isomer. This result had been interpreted[27] as evidence for stereoelectronic control, but it should be noted that **14** is the only conformer of the intermediate without gauche butane



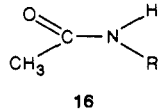
14

or other 1,4-H/H repulsions, and this can cleave only to the (*E*) amide, regardless of whether stereoelectronic control operates.

Configurational Effects and Stereoelectronic Control. Hydrolysis is complicated by the fact that each amidinium ion, except **6**-H^+, is a mixture of two stereoisomers, each of which can react. The theory of stereoelectronic control predicts the behavior of each stereoisomer. We next derive this prediction and investigate how well it accounts for the observed product ratios.

Figure 1 presents the 9 conformers that can arise from OH^- addition to the (*ZE*) stereoisomer of an *N*-alkyl-*N'*-methylacetamidinium ion (**13*ZE***), followed by rotation about C–N bonds. According to the theory of stereoelectronic control,[2] OH^- adds antiperiplanar to the lone pairs of the two nitrogens, so that conformer $\mathbf{15}_{00}$ (or its enantiomer) is formed initially. The other conformers are then obtained by rotation about C–N bonds, which conserves the absolute configuration $N_1(R)C(S)N_2(R)$ (or $N_1(S)C(R)N_2(S)$ in the enantiomers). Likewise there are 9 more enantiomeric pairs of conformers, of absolute configuration $N_1(R)C(R)N_2(R)$ and $N_1(S)C(S)N_2(S)$, arising from **13*EZ***. Each set of 9 does not interconvert with any other or with epimeric configurations such as $N_1(R)C(S)N_2(S)$. Such interconversion would require nitrogen inversion or hydroxide loss, processes which are slow[12] compared to cleavage. Therefore once conformer $\mathbf{15}_{00}$ is formed, only the 9 conformers in Figure 1 are accessible, and cleavage must occur via one or more of those.

According to the theory of stereoelectronic control,[2] only those conformers with a nitrogen lone pair antiperiplanar to a nitrogen leaving group can cleave. These are the 5 conformers $\mathbf{15}_{0-}$, $\mathbf{15}_{+0}$, $\mathbf{15}_{++}$, $\mathbf{15}_{+-}$, and $\mathbf{15}_{--}$. However, two conformers, $\mathbf{15}_{0-}$ and 15_{++}, are destabilized by 1,3-R/CH_3 repulsion. Two more conformers, $\mathbf{15}_{+0}$ and $\mathbf{15}_{+-}$, can cleave CH_3NH_2, but the *N*-alkylacetamide would be formed in its unstable (*E*) form (**16**). Above we have concluded that this destabilization is not strong in the transition state, so formation of **16** is only slightly (ca. threefold) disfavored.



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However, for simplicity we neglect this pathway. Then cleavage is expected to proceed predominantly via conformers $\mathbf{15}_{--}$ and $\mathbf{15}_{+-}$, which produce only $RNH_2 + CH_3CONHCH_3$. More generally, the theory of stereoelectronic control predicts that

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(27) Halliday, J. D.; Symons, E. A. *Can. J. Chem.* **1978**, *56*, 1463.
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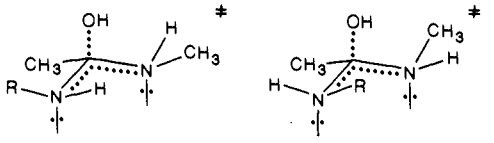
cleavage will produce only that amine whose alkyl group was *Z* in the amidinium ion. Stereoisomer **13*ZE*** should produce only RNH_2, and stereoisomer **13*EZ*** should produce only CH_3NH_2.

This prediction must be adapted to the other acetamidines. For **6**·H^+ or (*E*)-**7**·H^+ there are no stereoelectronic constraints on product formation, and each can produce a mixture of products determined only by leaving abilities and product stabilities. The (*Z*) stereoisomer of **5**·H^+ is equivalent to **13*EZ*** (R = H) discussed above, so that only CH_3NH_2 should be formed. The (*E*) stereoisomer of **5**·H^+, although equivalent to **13*ZE***, is not subject to stereoelectronic constraints, since conformers $\mathbf{15}_{+0}$ and $\mathbf{15}_{+-}$ (Figure 1, R = H) can now cleave CH_3NH_2. However, $\mathbf{15}_{--}$ (R = H) is a unique conformer with no gauche butane or other 1,4-H/H repulsions, so there may result a slight preference for cleavage of NH_3.

Although the theory of stereoelectronic control predicts the products from each stereoisomer of an amidinium ion, it is not clear which stereoisomer of **13** is the reactive one. The rate-limiting step[12] is addition of OH^- to the amidinium ion, but under the hydrolysis conditions the two stereoisomeric ions interconvert rapidly, via the amidines, where C–N rotation is fast.[29] Consequently, this is a situation where the Curtin–Hammett principle[30] applies. The proportion of reaction arising from each stereoisomer of **13** depends on the energies of transition states **17** and **18**, relative to each other. Although these are not known, it is possible to



17 **18**

assume a linear-free-energy relationship (LFER) to take account of the Curtin–Hammett principle.[31] One simple model is to assume that each repulsion in each transition state is the same as in the corresponding amidinium ion (**13*ZE*** or **13*EZ***), since bond lengths and bond angles change only slightly upon OH^- addition. Then the transition states have the same relative energy as the reactants, which is equivalent to the assumption of a LFER slope of 0 or to the statement that the two stereoisomeric reactants react with the same rate constant. Another simple model is to assume that the repulsions in the two transition states (**17**, **18**) exactly balance. For example, in **17** there is a gauche $RNCCH_3$ repulsion which is quite similar to the gauche RNCNH repulsion of **18**, and likwise for each other repulsion. This is equivalent to the assumption of a LFER slope of 1 or to the statement that the two stereoisomers of **13** react at the same rate (= rate constant × concentration). Then, according to the theory of stereoelectronic control, as derived above, the product ratio RNH_2:CH_3NH_2 or $CH_3CONHCH_3$:CH_3CONHR should be identical with the *ZE*:*EZ* ratio of stereoisomeric reactants, if the first model is correct. Alternatively, the product ratio should be 1:1 if the second model is correct. For **7** these models do not apply, but it is quite likely that nearly all reaction proceeds from the dominant (*E*) stereoisomer, since a 1,3 methyl–methyl repulsion destabilizes the other transition state by ca. 1.9 kcal/mol.[32]

The product ratios in Table III do not fit either of these simple models. There is significantly less neopentylamine or benzylamine than the 61% or 38% expected according to the first model, and less of these amines than the 50% expected according to the second model. It is clear that the ratios deviate systematically. Where basicities differ, there is less of the less basic amine formed, just as expected according to leaving abilities, as discussed above.

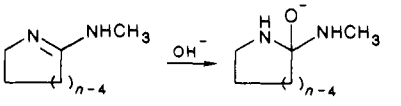
That leaving abilities also influence product ratios means that stereoelectronic control is not strong, but it can be eclipsed by other factors. This is the same conclusion as was reached in a study[12] of cyclic amidines. Even in six-membered rings the preference for anti elimination is <2 kcal/mol, and this preference ought to be reduced in acyclic systems.[33]

The second model above provides a better account of the combined action of stereoelectronic control and leaving abilities. Leaving abilities are most important for **11**, which is thereby expected to deviate most from the prediction of the theory of stereoelectronic control. If all *N*-alkyl-*N'*-methylacetamidinium ions (**13**) react 50% via each stereoisomer, this expectation is realized. The first model also does not account for the products from **5**. If nearly all reaction occurred via the dominant (*Z*) stereoisomer of **5**·H^+, only CH_3NH_2 should be formed (vide supra). The observed formation of NH_3 requires creation of (*E*)-$CH_3CONHCH_3$ or syn elimination or substantial reaction via the minor (*E*) stereoisomer of the reactant. Thus we again conclude that configurational effects and stereoelectronic control are weak.

Conclusions

Ammonia is a distinctly poorer leaving group than ordinary primary or secondary amines. This is consistent with its lower basicity, even though it is rather surprising that leaving ability is determined by the basicity of the cleaved amine, rather than by that of the nitrogen in the intermediate (**4**). Consequently eq 1 cannot serve as an unambiguous test of the theory of stereoelectronic control. The formation of aminoamide (**1**) could be due merely to the better leaving ability of a primary amine.

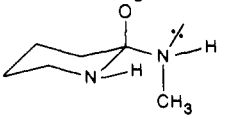
These results show how to adapt eq 1 so as to test the theory of stereoelectronic control. It is necessary only to match the leaving abilities of the two amines, as in the intermediate **19**, in the hydrolysis of **20**. Since it is the basicity of the cleaved amine that



20 **19**

determines leaving ability, the difference in basicity between the ring nitrogen and a methylcycloalkylamine, as in **19**, does not matter. The results in Table III, especially for **8** and **9**, indicate that leaving abilities of methylamine and the ring nitrogen are properly matched. Indeed we have found[12] that hydrolysis of **20** (n = 6) produces predominantly aminoamide, but hydrolysis of **20** (n = 5, 7) produces ca. 50% lactam + CH_3NH_2. The former result is as expected from stereoelectronic control, but the latter shows that stereoelectronic control is not generally operative in amidine hydrolysis.

Moreover, the results for **20** (n = 5, 6, 7) cannot be ascribed to a configurational effect in order to accommodate them to the theory of stereoelectronic control. Such an effect might arise because **20**·H^+ is predominantly the configuration with the methyl (*Z*), so that **21** (depicted for n = 6) is the only conformation that



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satisfies the requirements of stereoelectronic control—arising from OH^- addition antiperiplanar to two lone pairs as well as having two lone pairs antiperiplanar to a nitrogen leaving group. This could lead to aminoamide, but as the (*E*) stereoisomer, which is sterically destabilized. As a result, formation of lactam + CH_3NH_2 could become competitive, even though it requires the use of a syn lone pair. However, the results in Table III, particularly for **7**, show that the steric destabilization is too slight to prevent aminoamide formation. Therefore the results for **20**

(29) Halliday, J. D.; Symons, E. A.; Bindner, P. E. *Can. J. Chem.* **1978**, *56*, 1470.
(30) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(31) Perrin, C. L.; Seeman, J. I. *J. Org. Chem.* **1984**, *49*, 2887.
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(33) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. Bartsch, R. A.; Závada, J. *Chem. Rev.* **1980**, *80*, 453. Mohrig, J. R.; Schultz, S. C.; Morin, G. *J. Am. Chem. Soc.* **1983**, *105*, 5150.

(n = 5, 6, 7) do show that stereoelectronic control is quite weak. Indeed, we have concluded above that it is so weak in the acyclic amidines of Table III that it can easily be eclipsed by other factors, such as leaving abilities.

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Enantioselective Functionalization of Prochiral Diols via Chiral Spiroketals: Preparation of Optically Pure 2-Substituted 1,3-Propanediol Derivatives and Asymmetric Synthesis of Chroman Ring and Side Chain of α-Tocopherol

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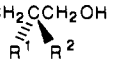
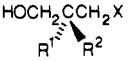
Abstract: The enantioselective functionalization of a prochiral hydroxyl group in 2-substituted 1,3-propanediols ($HOCH_2CR^1R^2CH_2OH$) is presented. The reaction of the bis(trimethylsilyl) derivative of the diol with *l*-menthone in the presence of trimethylsilyl trifluoromethanesulfonate selectively gave one of the diastereomers of the spiroketal in which the larger substituent (R^1) occupies an equatorial position. The equatorial spiroketal was treated with acetophenone enol trimethylsilyl ether in the presence of titanium tetrachloride to give the ring-cleavage product



which was produced by the selective cleavage of the equatorial C–O bond. After a proper functionalization of the hydroxyl group, the chiral auxiliary was removed under basic conditions to give the optically pure (>95% ee) derivatives **5**.



5

(X = OTHP, $OCPh_3$, SPh)

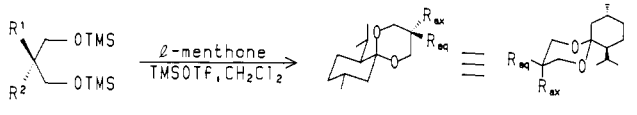
The stereoselective preparation of the axial spiroketal (R^1 = H, R^2 = Me) and its ring-cleavage are also described. The potentiality of the present method is demonstrated in an asymmetric synthesis of (2*R*,6*R*)-2,6,10-trimethylundecanol and (*S*)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol which are key intermediates in the total synthesis of naturally ocurring (2*R*,4′*R*,8′*R*)-α-tocopherol.

The enantioselective differentiation of a prochiral functional group in a symmetric difunctional compound is one of the efficient methods for creating new chiral centers. While this type of asymmetric synthesis is commonly observed in enzymatic transformations, examples of the chemical transformation are rare.[1] We report here a novel enantioselective functionalization of 2-substituted 1,3-propanediols (Scheme I)[2-4] utilizing a highly stereoselective ring-cleavage reaction of chiral spiroketals **2**.

Scheme I

Results and Discussion

A treatment of a bis(trimethylsilyl) ether **1a–c** and *l*-menthone with a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at −85 °C[5] gave selectively the thermodynamically stable equatorial isomer of spiroketal **2(a–c)-eq** (eq 1, Table I). In contrast, the catalytic hydrogenation of the



1a-d

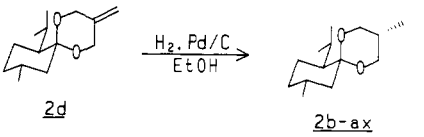
2-eq ; $R_{eq} = R^1, R_{ax} = R^2$
2-ax ; $R_{eq} = R^2, R_{ax} = R^1$

(1)

Table I. Preparation of Chiral Spiroketal

entry	starting material	products	yield (**2-eq**:**2-ax**)
1	**1a**: R^1 = Ph, R^2 = H	**2a-eq**, **2a-ax**	90% (17:1)
2	**1b**: R^1 = Me, R^2 = H	**2b-eq**, **2b-ax**	91% (5.7:1)
3	**1c**: R^1 = Ph, R^2 = Me	**2c-eq**, **2c-ax**	90% (2.6:1)
4	**1d**: R^1, R^2 = CH_2	**2d**	60%

exo methylene analogue **2d**, which was prepared by the same ketalization procedure as above, afforded the axial isomer of **2b** selectively (**2b-ax**:**2b-eq** = 20:1, 82%) (eq 2). Interestingly,



2d 2b-ax (2)

hydroboration of **2d** with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeded with an opposite stereoselectivity, and after the protection of the hydroxyl group as a benzyl ether, **2e-eq** was obtained selectively (**2e-eq**:**2e-ax** = 14:1, 88% overall yield) (eq 3). It must be noted here that **2-eq** and **2-ax** can be readily separated by a flash or medium-pressure silica gel column chromatography, and

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