Positional Selectivity in an Encounter-Controlled Reaction: Base-Catalyzed Proton Exchange in Amidinium Ions

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Abstract: Kinetics of base-catalyzed proton exchange of a series of amidinium ions was studied by NMR methods, especially line broadening and saturation transfer, which could distinguish protons in different environments. In the hydroxide-catalyzed exchange of four primary amidinium ions, H_Z is observed to exchange from 25 to 100% faster than H_E. Similarly, the relative reactivities of the NH protons of the 2-amino-1-pyrrolinium ion are in the ratio 1.00:0.44:0.24. In contrast, H_E of the *N,N'*-dimethylacetamidinium ion exchanges ca. 35% faster than H_Z, and no difference could be detected in two other amidinium ions. In all cases the fastest proton is the most acidic one. The more acidic proton of the *N,N'*-dimethylacetamidinium ion was determined as H_E from the relative rates of D_2O-catalyzed exchange. The hydroxide-catalyzed exchange represents the first example of positional selectivity in an encounter-controlled proton exchange. The second-order rate constants are consistent with encounter control, as expected for the thermodynamically favorable proton transfer from amidinium ion to hydroxide. Nevertheless, the positional selectivity shows that the reaction cannot be completely encounter controlled. In part the rate-limiting step is the breaking of a hydrogen bond in an amidine hydrate (the Swain–Grunwald mechanism). Simulation shows that the observed positional selectivity is consistent with this mechanism. Substrate selectivity in encounter-controlled reactions is also established, and attributed to a variation in the encounter frequency, arising from the water structure.

The study of proton-transfer reactions[1] has greatly advanced our understanding of reactions in solution, especially fast reactions. In connection with studies of proton exchange of amides,[2] we also investigated acid-catalyzed proton exchange of some primary amidinium ions (**1**).[2f,g] These investigations took advantage of NMR methods that could distinguish diastereotopic NH protons and measure their individual rate constants. We next sought to extend our investigations to the base-catalyzed exchange of amidinium ions, especially since the only previous study[3] did not distinguish the NH protons. Indeed, except for peptides and proteins,[4] very few studies[5] have separated the exchange rates of different NH protons in the same molecule.

The hydroxide-catalyzed exchange is expected to be encounter controlled ("diffusion controlled").[6] This conclusion follows from eq 3 of ref 6, with realistic estimates of 10^{-11} s for the lifetime of an encounter pair and 10^{13} s^{-1} for the rate constant for proton transfer within the encounter complex. Proton transfer from an amidinium ion ($pK_a \sim 12$)[7] to hydroxide is thermodynamically favored. Such a proton transfer between nitrogen and oxygen is extremely rapid. Therefore, once the reactants encounter each other, it is quite unlikely that they will diffuse apart without the proton transfer occurring.

Indeed, Neuman and Hammond[3] found that hydroxide-catalyzed exchange of the acetamidinium ion (**1**, R = CH_3) is encounter controlled, with a second-order rate constant at 33 °C of 3.6×10^{10} M^{-1} s^{-1}. Notice that this is so high that a hydroxide concentration of only 10^{-9} *M*, as at pH 5, is sufficient to produce a rate detectable by NMR, by both line-broadening[8] and saturation-transfer[9] methods. Conveniently, and in contrast to amines,[10] water-catalyzed exchange is not expected to contribute, since amidinium ions are not sufficiently acidic. Indeed, as described below, the rate constant for this process is only ca. 10^{-3} s^{-1}.

We were quite surprised to find that H_Z of several primary amidinium ions (**1**) undergoes hydroxide-catalyzed exchange faster than H_E. According to the weak form of the "selectivity relationship", due to Brown and Stock,[11] intramolecular selectivity (henceforth[12] "positional selectivity") is linearly related to intermolecular selectivity (henceforth "substrate selectivity"). For a large series of electrophilic aromatic substitutions, it is observed[11,12] that as substrate selectivity vanishes, so does positional selectivity. Thus we had expected that an encounter-controlled reaction, where substrate selectivity has vanished, should show no positional selectivity. This is an assumption that has commonly been made.[13] Indeed, one exception, nitration of reactive aromatics, has been attributed to an electron-transfer mechanism.[14]

Hydroxide is a sufficiently strong base to remove an amidinium proton upon encounter. Why then does hydroxide distinguish between H_E and H_Z? We have sought to elucidate the reason for the positional selectivity by studying base-catalyzed exchange in a series of amidinium ions, including primary amidinium ions (**1**), *N,N'*-dimethylamidinium ions (**2**), which take the configuration shown,[15] and the 2-amino-1-pyrrolinium ion (**3**, *n* = 5).

Experimental Section

N,N-Dimethylacetamidine hydrochloride (mp 163 °C (lit.[16] mp 158.5–160.5 °C)), *N,N'*-dimethylacetamidine hydrochloride (**2**, R = CH_3, mp 224 °C (lit. [15a] mp 214.5–215.5, 218 °C)), *N,N'*-dimethylbenzamidine hydrochloride (**2**, R = Ph, mp 260 °C (lit.[17] mp 255–256

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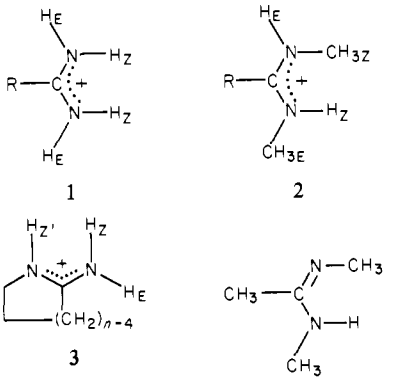

1 2

3 4

°C)), 2-amino-1-pyrroline hydrochloride (**3**, n = 5, mp 165–169 °C (lit.[18] mp 169–171 °C)), and 2-amino-$\Delta^{1,2}$-tetrahydroazepine hydrochloride (**3**, n = 7, mp 161–163 °C (lit.[19] mp 159.5–160.5 °C)) were prepared by standard procedures. Other amidine hydrochlorides were commerically available samples (Aldrich, Fluka, Crescent), used without further purification. Buffer solutions (acetate, phosphate, formate, or HCl) in water or ethylene glycol were prepared from reagent chemicals; DCl in D_2O was conveniently prepared by adding redistilled acetyl chloride to D_2O (99.8%, Bio-Rad). Spectra were run on samples that were 0.4 to 1.0 M in amidinium ion. Line widths in the absence of exchange were determined in solutions containing added acetic acid, where exchange is slow.

Proton NMR spectra of primary amidines in aqueous buffers were run on a JEOL JNM-PS-100 spectrometer with ^{14}N decoupling. Spectra of primary amidines in ethylene glycol and of N,N'-dimethylamidines in aqueous buffers were run on a Varian EM 390 or on a Varian HR-220 or 360-MHz FT spectrometer, with homonuclear irradiation where necessary for saturation-transfer studies. The use of viscous solvents to sharpen NH resonances, the decoupling and saturation methods, and the details of the saturation-transfer technique and of the calculation of rate constants and errors have been presented.[2c,g,9c] Kinetics of equilibration in D_2O were followed by rapidly dissolving the amidine hydrochloride in D_2O and immediately acquiring FT–NMR spectra by repeated pulsing every 10 to 60 s. Rate constants for equilibration were then calculated by least squares from the intensities (peak heights) of the $NHCH_3$ doublet and the $NDCH_3$ singlet. Steady-state kinetics were simulated on a CalData computer.

Peak assignments for most of the amidinium ions were made previously.[2g,15,20] With the exception of the azobis(isobutyramidinium) ion (**1**, R = $(H_2N)_2{}^+CC(CH_3)_2N{=}NC(CH_3)_2$), the upfield proton or methyl was assigned as Z, and we assume that this generalization also holds for the N,N-dimethylacetamidinium and N,N'-dimethylbenzamidinium ions. In contrast, the downfield NH of the cyclic amidinium ions (**3**, n = 5, 6, 7) in $CDCl_3$ has been assigned[21] (without any rationale) as the endocyclic NH, $H_{Z'}$. We have verified this assignment with an ^{14}N-decoupled spectrum of the aqeuous 2-amino-$\Delta^{1,2}$-tetrahydroazepinium ion (**3**, n = 7), which shows a downfield NH triplet (J = 5.6 Hz) at δ 8.68 and NH singlets at higher field. We can then conclude, by analogy to primary ions, that the highest-field proton is H_Z. We further assume that these assignments also hold for the 2-amino-1-pyrrolinium ion (**3**, n = 5), where all NH peaks are singlets.

The observed pseudo-first-order rate constants were converted to second-order rate constants, k^B, by dividing by the OH^- or lyate concentration, as calculated from the buffer ratio, the pK_a of the buffer acid,[22,23] and K_S, the autoprotolysis constant of the solvent.[22,24] Strictly, the lyate concentration is given by eq 1, but the ratio of activity coefficients may be expected to be close to unity, even in ca. 1 M amidinium chloride. Thus this value for the lyate concentration is more reliable than one based on the measured pH.

$$[OS^-] = \frac{K_S}{K_a^{BH}} \frac{[B^-]}{[BH]} \frac{\gamma_{B^-}}{\gamma_{OS^-}\gamma_{BH}} \qquad (1)$$

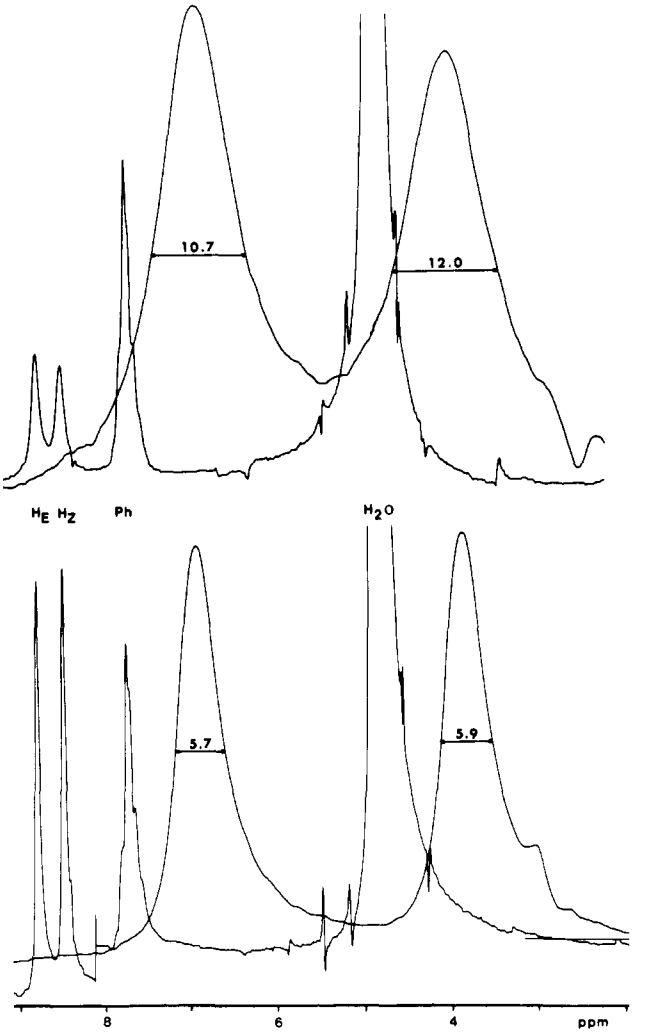

Figure 1. 100-MHz NMR spectrum of the benzamidinium ion, with ^{14}N-decoupling; expanded-scale spectrum superimposed, with NH peak widths in Hz. Bottom spectrum, in aqueous HOAc. Top spectrum, in acetate buffer.

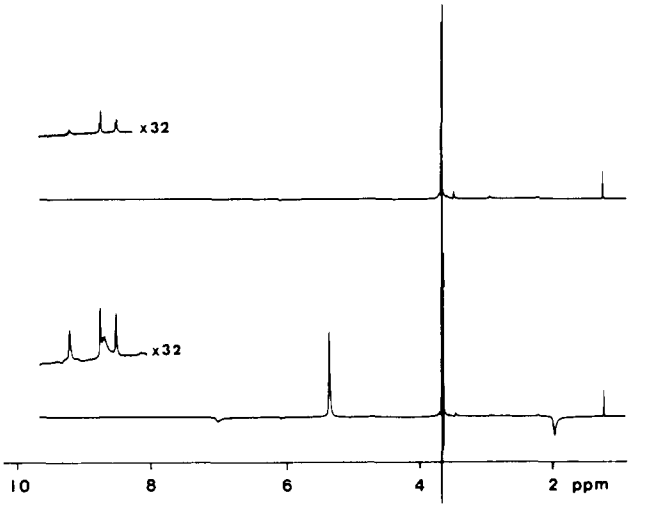

Figure 2. 360-MHz NMR spectrum of the 2-amino-1-pyrrolinium ion (**3**, n = 5) in buffered ethylene glycol. Bottom spectrum, peaks from left to right are: $NH_{Z'}$, NH_E, (third-order intermodulation product from strong solvent peaks), NH_Z, OH, CH_2, t-BuOH reference. Top spectrum, same, but with OH saturated.

Results

Figure 1 shows NMR spectra of the benzamidinium ion in aqueous buffers. The broadening of the NH peaks and the greater

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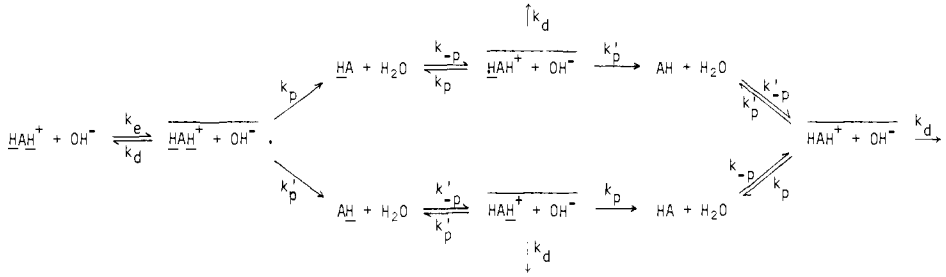
Table I. Rates of Base-Catalyzed Proton Exchange of Amidinium Ions

conjugate acid of	T, °C	k_E, s^{-1}	k_Z, s^{-1}	$10^{10}k_E^B$, M^{-1} s^{-1}	$10^{10}k_Z^B$, M^{-1} s^{-1}
formamidine (1, R = H)	27[a]	~4.2[b]	~8.6[b]		
acetamidine (1, R = CH_3)	27[a]	8.8[b]	11.3[b]	0.66	0.84
	22[c]	3.80 ± 0.045[d]	4.81 ± 0.12[d]		
benzamidine (1, R = Ph)	27[a]	15.6[b]	19.5[b]	4.6	5.8
azobis(isobutyramidine) (1, R = $(H_2N)_2{}^+CC(CH_3)_2N{=}NC(CH_3)_2$)	27[a]	9.1[b]	18.7[b]		
N,N-dimethylacetamidine	34[c]	48[b]	48[b]	0.20	0.20
N,N'-dimethylacetamidine (2, R = CH_3)	34[a]			0.48 ± 0.04[e]	0.35 ± 0.04[e]
	−10[f]	6.8×10^{-4}	1.8×10^{-4}		
N,N'-dimethylbenzamidine (2, R = Ph)	34[a]			0.77 ± 0.04[e]	0.85 ± 0.08[e]
	22[f]	$1.8_1 \times 10^{-3}$	$1.8_4 \times 10^{-3}$		
2-amino-1-pyrroline (3, n = 5)	27[a]	2.1[b]	9.9,[b,g] 4.5[b]	0.24	1.1, 0.5
	22[c]	3.8 ± 0.1[d]	14.3 ± 0.8[d,g]		
			6.2 ± 0.2[d]		

[a] In H_2O (B = OH^-). [b] By line broadening; unless otherwise indicated, relative rates have a precision of ±10%. [c] In ethylene glycol (B = $HOCH_2CH_2O^-$). [d] By saturation transfer. [e] From the slope of line width vs. $[OH^-]$. [f] In D_2O/DCl (B = D_2O). [g] k_Z'.

Scheme I. Eigen Mechanism for Hydroxide-Catalyzed Proton Exchange of an Acid with Two Different Protons (the Protons Bound Initially Are Underlined)



broadening of the upfield NH, assigned as H_Z, are apparent. Figure 2 shows saturation-transfer spectra of the 2-amino-1-pyrrolinium ion in ethylene glycol. The transfer of saturation from solvent OH to NH, due to chemical exchange, is apparent as a diminution of intensity. The downfield NH is seen to show the greatest transfer of saturation. Rate constants for base-catalyzed proton exchange of various amidinium ions are summarized in Table I. The second-order rate constant of 3.0×10^{10} M^{-1} s^{-1} for the acetamidinium ion, summed over all four protons, is in good agreement with the value of 3.6×10^{10} M^{-1} s^{-1} obtained at 33 °C from analysis of the broadening of the water resonance.[3]

Results of control experiments were as follows: No significant effect on rates could be detected on changing the concentration of three different amidines by as much as tenfold, or of the buffer, to 0.2 *M*. This confirms the observations of Neuman and Hammond,[3] based on broadening of the water resonance, and shows that the reaction is specific-base catalyzed. The greater reactivity of H_E in the *N,N'*-dimethylacetamidinium ion was verified by a C-methyl-decoupled spectrum, even though the values in Table I are somewhat uncertain, owing to a long-range coupling which broadens the Z methyl. The twofold greater reactivity of the *N,N'*-dimethylbenzamidinium ion, relative to *N,N'*-dimethylacetamidinium, was confirmed by measurement in a common solution. Thus we may have confidence that relative values of $[OH^-]$, calculated according to eq 1, are correct, despite the high ionic strength.

The data in Table I show that with three exceptions H_Z undergoes lyate-catalyzed exchange faster than H_E. The difference in reactivities is not large—the maximum is only fourfold—but it is statistically significant and the qualitative conclusion is readily apparent, as in Figures 1 and 2. Furthermore it is obtained by two independent methods—line broadening and saturation transfer. Moreover, the relative reactivities—1.00:0.78 ± 0.01 for the acetamidinium ion and 1.00:0.44 ± 0.01:0.24 ± 0.02 for the aminopyrrolinium ion—are the same, regardless of both method and solvent. The three exceptions are the *N,N*-dimethylacetamidinium and *N,N'*-dimethylbenzamidinium ions, where no reactivity differences, beyond experimental error, could be detected, and the *N,N'*-dimethylacetamidinium ion, where it is H_E that exchanges slightly but significantly faster.

In the D_2O-catalyzed exchange, H_E of the *N,N'*-dimethylacetamidinium ion exchanges 3.8 times as fast as H_Z, whereas no such reactivity difference could be detected in the *N,N'*-dimethylbenzamidinium ion. We suggest that H_E again ought to be more reactive than H_Z, but presumably C–N rotation[15a,25] is faster than D_2O-catalyzed proton exchange, so that the reactivity difference is obscured. Thus the factor of 3.8 for the *N,N'*-dimethylacetamidinium ion must strictly be a minimum value, if C–N rotation and proton exchange are competitive.

Discussion

Encounter Control. Is the lyate-catalyzed reaction really encounter controlled? Above we have presented the reasons for expecting such a thermodynamically favorable proton transfer to be encounter controlled. In support, the second-order rate constants in Table I, as well as that of Neuman and Hammond,[3] are certainly of a magnitude expected for encounter control. Our values are admittedly slightly lower than values ca 2×10^{10} M^{-1} s^{-1} customarily observed.[6,26] However, the high ionic strengths render the lyate concentrations uncertain and may also affect the mobility of the lyate ion. Therefore we conclude that the values are quite consistent with encounter control.

Nevertheless, the reaction cannot be entirely encounter controlled. Scheme I presents the Eigen[6] mechanism for an acid, HAH^+, with (for simplicity) two different acidic protons. Encounter, with second-order rate constant k_e, produces an encounter pair, $\overline{HAH^+ + OH^-}$. Next, proton transfer, with rate constant

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k_p or k_p', produces the conjugate base, HA or AH. A different proton must next be transferred to that base, and by microscopic reversibility only a water can be the proton donor, with rate constant k_{-p} or k_{-p}'. Even though a proton has been exchanged, the reaction is not yet completed. The reprotonation regenerates a hydroxide ion, within an encounter pair. In order to complete the reaction, this hydroxide must diffuse away, with rate constant k_d. *The mechanism of an exchange reaction must be symmetrical*, so if the rate is limited by diffusion of the reactants toward each other, it is also limited by their diffusion apart. Steady-state analysis of Scheme I shows that the ratio of exchange rates for the two protons is equal to $k_p(k_p' + k_d)/k_p'(k_p + k_d)$. However, since the proton transfers are thermodynamically favorable, we may expect both k_p and k_p' to be greater than k_d. This is precisely the condition for encounter control. If it holds, it then follows that the ratio of exchange rates must be 1. The two protons would exchange at equal rates because under encounter control both protons would exchange during any encounter. The observation that the rates are different thus shows that the reaction cannot be entirely encounter controlled, but must be only partially so.

Substrate Selectivity. Second-order rate constants for encounter-controlled reactions seem to vary with substrate,[6,26] and the values in Table I are no exception. However, the variability has always been small—ca. twofold—so that it was never clear that differences are real. Similarly the variability in Table I is suspect, since it is contingent on the transferability of hydroxide concentrations approximated by neglecting the activity coefficients in eq 1. Nevertheless, the twofold reactivity difference between the *N,N'*-dimethylbenzamidinium and *N,N'*-dimethylacetamidinium ions is real, since it was verified in a common solution. To the best of our knowledge, this is the first unambiguous demonstration of substrate selectivity in an encounter-controlled reaction.

How can the rate constant for an encounter–controlled reaction vary with substrate? Such variations have been attributed[27] to variations in electrostatic interactions and diffusion constants. Certainly these can affect the rate constant, but not for our reaction of OH^- with a series of cationic acids, where electrostatic interactions are constant and the diffusion constant of OH^- dominates. Such variation with substrate had also been attributed to a steric (solid-angle) effect,[6,28] whereby the probability of reaction is reduced by the fraction of encounters with the wrong orientation. Thus, for example, HS^- is only $^3/_4$ as reactive as F^- toward H^+. However, the lifetime of an encounter pair[6] and the relaxation time for molecular rotation[29] are both 10^{-10} to 10^{-11} s. Thus the encounter pair undergoes reorientation, and there are a multitude of collisions during the encounter,[23d,30] so that a wrong initial orientation does not preclude reaction. As a result, the steric effect explanation is in disrepute,[30] and besides it cannot be applicable to our comparison, where there is certainly no twofold difference in solid angle between two so similar substrates.

Another explanation for substrate selectivity invokes a hydrophobic enhancement of the water structure in the vicinity of the reaction site, such that the reacting ions need not approach as closely.[6,26b] However, it seems unlikely that the effective reaction distance can differ twofold between the *N,N'*-dimethylbenzamidinium and *N,N'*-dimethylacetamidinium ions.

We therefore wish to propose an alternative explanation, involving the water structure but not the reaction distance: It is well established that the diffusion of hydroxide ion up to the substrate occurs by a Grotthus mechanism (structural diffusion). We envision this diffusion as proceeding along preferred "channels"—chains of hydrogen bonds that are continually being made and broken. We suggest that the more "channels" there are connecting the two reactants, the more probable the encounter is. Thus the water structure, as modified by hydrophobic or other interactions, can affect the encounter frequency. Notice that this explanation can also account for the steric (solid-angle) effect, as with HS^- vs. F^-, but it is limited to reactions of H^+ and OH^- (or lyate).

Positional Selectivity. The uncertainty in the hydroxide concentrations does not affect intramolecular comparisons. Such differences in Table I are small but real. Figure 1 shows that H_Z of the benzamidinium ion is broadened to a greater extent than H_E. The broadening itself is not as apparent as the decrease in peak height, but since the areas of the two NH peaks must be equal, H_Z is indeed broader. Figure 2 shows clearly that $H_{Z'}$, the downfield NH of the 2-amino-1-pyrrolinium ion, suffers a considerably greater transfer of saturation from the OH peak than do the other two NH peaks. To the best of our knowledge, these are the first examples of positional selectivity in an encounter-controlled proton transfer.

How can a reaction that is encounter controlled, or partly so, show positional selectivity? Just as with substrate selectivity, it seems intuitively reasonable to attribute positional selectivity to a steric effect,[6,28] whereby the reactivity of a proton is proportional to the solid angle through which it is accessible. However, such an explanation requires the unlikely assumption that the solid angle can vary as much as fourfold from proton to similar proton within a molecule. Alternatively, the hydrophobic enhancement of the water structure, or the "channeling" that we have proposed to account for substrate selectivity, may be operative intramolecularly as well. Indeed, it is quite likely that solvation of these ions is anisotropic, with preferred directions for hydroxide approach. Our initial results had suggested that H_Z was always more reactive than H_E, which would be consonant with preferred diffusion toward the center of positive charge. However, the counterexample of the *N,N'*-dimethylacetamidinium ion shows that the explanation cannot be so simple. Also, the invariance of rate ratios with change of solvent from water to ethylene glycol would require a fortuitous constancy of solvent structure about the ions. Besides, any argument involving accessiblity ignores the reorientation[29] within the encounter pair and the multitude of collisions per encounter.[26d,30] Were the reaction irreversible, the initial orientation of the reactants could determine reactivity, since once reaction occurs, there would be no further opportunity for reorientation and reaction at another site. However, even in nitration[31] there is reorientation within the encounter pair, so that for a reversible reaction, such as proton exchange, the direction of initial approach becomes irrelevant.

A clue to the origin of the positional selectivity is the fact that in all three cases where relative acidities are known, it is the most acidic proton that exchanges fastest. According to ab initio MO calculations,[32] the *E* configuration of formamidine is 2.94 kcal/mol more stable than the *Z*. According to IR evidence,[33] 2-amino-1-pyrroline is exclusively the amino form, not the imino tautomer. Admittedly, these results were not obtained in polar solvents, and solvation can have a marked effect on the configurational equilibria of amidines.[34] Nevertheless, if the relative stabilities persist in polar solvents, it follows by thermodynamics that the more acidic proton of the formamidinium ion (and presumably of other primary amidinium ions) is H_Z and that the most acidic proton of the aminopyrrolinium ion (**3**, $n = 5$) is $H_{Z'}$. Finally, the results in Table I show that H_E of the *N,N'*-dimethylacetamidinium ion undergoes D_2O-catalyzed exchange 3.8 times as fast as H_Z. This reaction was followed in 1 *M* DCl, where the OD^- concentration is too low to contribute to exchange and D_2O is the only base available. Since reprotonation of the amidine by D_3O^+ now becomes the encounter-controlled reaction, the relative rates of proton exchange are determined simply by the relative acidities of the protons. Thus the more acidic proton is the faster one, H_E. This reversal, relative to the formamidinium ion, may be attributed

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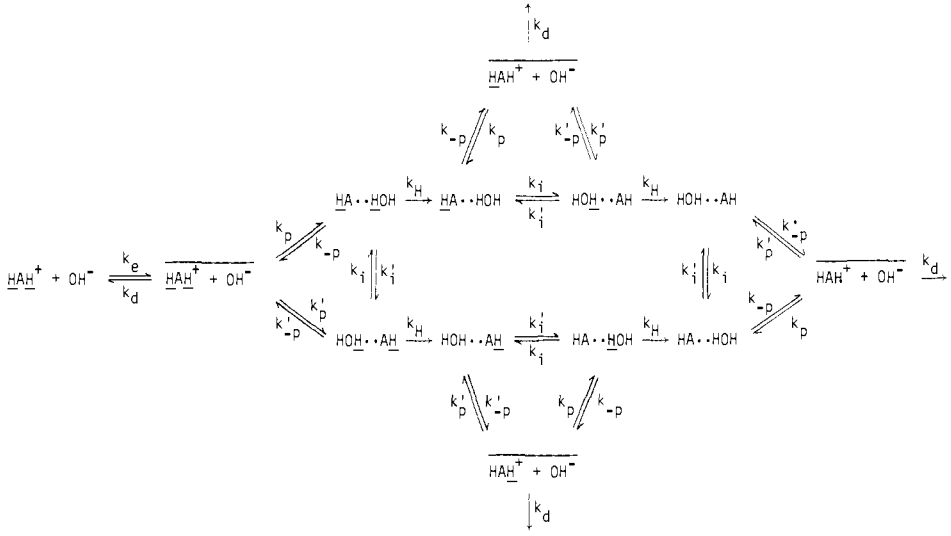
Scheme II. Swain-Grunwald Mechanism for Hydroxide-Catalyzed Proton Exchange of an Acid with Two Different Protons (the Protons Bound Initially Are Underlined)



to the relief of steric interaction in the (*Z*)-amidine (**4**), where the (*E*)-*N*-methyl can rotate out of the plane of the C-methyl. (Rotation has been demonstrated[25c] in another amidine, where steric interactions are greater. On the other hand, *N,N'*-diphenylacetamidine is predominantly *E*, according to IR evidence.[35]) Notice that in all three of our cases, the reactivity difference in the OH^--catalyzed reaction is considerably less than the difference in acidities, as measured by MO energies, IR intensities, or D_2O-catalyzed exchange rates.

Why does the most acidic proton exchange fastest? Inasmuch as hydroxide is so strong a base as to remove any amidinium proton ($pK_a \sim 12$)[7] upon encounter, the acidity of that proton ought to be immaterial. However, we have concluded above that the reaction is only partially encounter controlled, even though this contradicts our expectation that k_p and k_p' in Scheme I ought to be greater than k_d. Besides, even if k_d could be competitive with k_p and k_p', the competition would be viscosity dependent, whereas relative reactivities are the same in ethylene glycol as in water.

These contradictions force us to reject Scheme I and invoke a more complicated version, Scheme II, which distinguishes proton transfer from proton exchange. This scheme is the extension of the Swain–Grunwald mechanism[10,36] to an acid, HAH^+, with two different protons. In this mechanism the rate-limiting step can be the breaking of a hydrogen bond in the hydrated base, with rate constant k_H. For simplicity we take k_H to be the same for the two isomeric bases, HA and AH. Also, for generality we allow for a nondissociative mechanism[10b,26e,27] for interconversion of the two bases, with rate constants k_i and k_i'.

Steady-state analysis of Scheme II shows that the two protons can exchange at different rates even if k_p and k_p' are equal and even if they are considerably greater than k_d. Thus it is not necessary to abandon our expectation that the reaction is encounter controlled. Table II lists some rate ratios calculated with a range of reasonable estimates for the various rate constants; for definiteness the pK_as of the two protons are taken to differ by log 3. Rate ratios are found to be quite sensitive to k_p/k_{-p} and to k_H, but not to k_i. *The values show that Scheme II can account for the observed selectivity, even though the reaction is encounter controlled, with, on the average, at least one proton exchanged per encounter.* The value of k_H that is needed to account for the observed rate ratios is somewhat lower than the 10^{9-11} s^{-1} previously reported for amines,[10] but it may be that it is more difficult to break hydrogen bonds to the more basic (or more polarizable) amidines.

Table II. Relative Rates of OH^--Catalyzed Exchange of the Two Different Protons of HAH^+, Calculated According to Scheme II, with $k_d = 1.0 \times 10^{11}$ s^{-1}, $k_p' = k_p$, $k_i = 1.0 \times 10^8$ s^{-1}, $k_{-p}'/k_{-p} = 3 = k_i'/k_i$[a]

$10^{-9} \times$	$k_H = 1.0 \times 10^8$ s^{-1}		$k_H = 4.0 \times 10^8$ s^{-1}	
k_{-p}, s^{-1}	$10^{-13}k_p =$ 0.25 s^{-1}	$10^{-13}k_p =$ 1.0 s^{-1}	$10^{-13}k_p =$ 0.25 s^{-1}	$10^{-13}k_p =$ 1.0 s^{-1}
0.25	1.18 (1.64)	1.05 (1.89)	1.05 (1.85)	1.01 (1.96)
1.0	1.56 (1.14)	1.18 (1.67)	1.18 (1.63)	1.05 (1.89)
4.0	2.21 (0.55)	1.57 (1.16)	1.56 (1.14)	1.18 (1.66)

[a] Values in parentheses are the average number of protons exchanged per encounter.

We conclude that positional selectivity in this encounter-controlled reaction arises because k_H becomes partially rate limiting. Even though k_H is much less than k_d, these are competitive owing to the position of the equilibria governed by k_p/k_{-p} and k_p'/k_{-p}'. The competition between these two diffusional processes is expected to be nearly independent of viscosity, as observed. Also, as k_H becomes rate limiting, specific base catalysis is to be expected, as we and others[3] have observed.

The analysis shows that the more acidic proton exchanges faster because there is a greater steady-state concentration of the more stable isomer, HA, of the base, as its hydrate. During an encounter, equilibrium between these isomers is approached, so that the more stable one is more likely to break a hydrogen bond. The values in Table II show that the reactivity ratio could approach the ratio of acidities if equilibration of the isomers is established (k_{-p} or $k_i \gg k_H$). It is not possible to distinguish whether equilibration occurs dissociatively or nondissociatively, since it is possible to simulate the kinetics without a nondissociative pathway.

The analysis shows also that the reactivity ratio is diminished relative to the ratio of acidities, as observed. Such a loss of selectivity is what we expected for an encounter-controlled reaction, but, except for the *N,N'*-dimethylbenzamidinium ion, it is not complete. The values in Table II show that loss of selectivity would be complete if both protons were to exchange during an encounter ($k_H \gg k_d k_{-p}'/k_p'$). Indeed, the exception of complete (within experimental error) loss of selectivity with the *N,N'*-dimethylbenzamidinium ion may arise because this is presumably more acidic (decreased k_{-p}'/k_p'), so that there is a greater likelihood

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for multiple proton exchanges during an encounter. Multiple exchange during an encounter has been observed for several proton-exchange reactions,[37a,d-f] but our data do not permit a decision as to whether the observed diminution of selectivity arises from incomplete equilibration of the isomeric bases or from multiple proton exchanges during the encounter.

We consider that the observation of positional selectivity in this exchange reaction is strong evidence for Scheme II and for the Swain–Grunwald mechanism. This mechanism is an attractive one, which must occur, and it has been widely accepted. However, the chief evidence for it is the inhibition by acid of the proton exchange of ammonium ions,[10,38] and this inhibition is seen only in nonideal solutions. Nonideality is inherent, since >0.1 M H^+ is required in order that reprotonation of the intermediate be competitive with a process whose rate constant is above 10^9 s^{-1}. Yet inhibition by acid is a thermodynamic necessity in such nonideal solutions. It is readily shown that the simplest mechanism, without k_H, leads to an observed first-order rate constant for exchange given by

$$k_{obsd} = k_2 K_a^{AH^+}[H^+]/h_0 \quad (2)$$

where k_2 is the second-order rate constant for encounter-controlled reprotonation of amine A by H^+, and h_0 is the acidity function governing protonation of A. Since h_0 increases faster than $[H^+]$ in strong acid, k_{obsd} *must* decrease in acid, and since $[H^+]/h_0$ is a strong function of water activity,[39] a 500-fold decrease in k_{obsd} *is* consistent with a 7.4-fold decrease in water activity, despite a denial.[38a] Moreover, there is an implicit assumption that k_2 is independent of acidity, whereas proton mobility does decrease at high concentrations.[22] Thus nonideality taints the evidence for the Swain–Grunwald mechanism. Our results are also obtained in nonideal solutions, but all comparisons are intramolecular, and the only uncertainty arising from nonideality is in the second-order rate constants, whose values are immaterial so long as they are accepted as being in the range of encounter control. Thus these results are an independent confirmation of the existence of the Swain–Grunwald mechanism.

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Conclusions and Summary

To the best of our knowledge, here is the first demonstration of positional selectivity in an encounter-controlled proton exchange. These proton exchanges are so favorable thermodynamically that they are expected to be encounter controlled, and the second-order rate constants support this. However, positional selectivity forces us to conclude that the reaction is not completely encounter controlled. Even though hydroxide is a sufficiently strong base to remove all amidinium protons upon encounter, so that their acidity should be immaterial, it is always the most acidic proton that exchanges fastest. We therefore conclude that the Swain–Grunwald mechanism is operative and that the rate-limiting step is in part the breaking of a hydrogen bond in the amidine hydrate. Simulation, using reasonable rate constants, shows that the observed selectivity is consistent with this mechanism. We therefore conclude that these results represent independent evidence for the Swain–Grunwald mechanism.

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Registry No. **1** (R = H), 50676-76-1; **1** (R = CH_3), 52018-42-5; **1** (R = Ph), 53356-58-4; **1** (R = $CH_2N^+CC(CH_3)_2N{=}NC(CH_3)_2$), 79246-17-6; **2** (R = CH_3), 79734-87-5; **2** (R = Ph), 79734-88-6; **3** (n = 5), 79734-89-7; **3** (n = 7), 79734-90-0; *N,N*-dimethylacetamidinium ion, 79734-91-1.

Displacement Stereochemistry and Product-Formation Selectivities in the Solvolysis of Cyclooctyl *p*-Bromobenzenesulfonate

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Abstract: Configurational analysis by ^2H NMR of the products of solvolysis of (*E*)-cyclooctyl-*2-d* and (*E*)-cyclooctyl-*4-d* brosylate in acetic acid and 80% acetone has established that substitution without rearrangement occurs with complete retention of configuration while substitution under 1,5-hydride shift takes place with complete inversion at the migration origin. The reaction is concluded to proceed by direct initial formation of a 1,5-hydrogen-bridged cation. Solvolysis of cyclooctyl-*1-d* brosylate in several solvents has shown elimination to be favored from the C-1 over the C-5 side, whereas selectivities for competitive substitutions are similar at the two positions. Elimination is thus indicated to take place largely from first-formed tight ion pairs while displacement proceeds through more dissociated intermediates.

The cyclooctyl and other medium-ring systems are of distinctive importance to solvolysis theory by reason of their characteristic rearrangements under transannular hydride shift.[1] Cope and Gale[2] determined that net 1,5-hydride migration occurs to the extent of 53%, 60%, and ≥62% on solvolysis of cyclooctyl-*1,2,2,8,8-d*$_5$ brosylate in acetic, formic, and trifluoroacetic acid, respectively. Regioalternative rearrangements were found to be negligible.[2] Parker and Watt[3] synthesized the *cis*- and *trans*-cyclooctyl-*5-d* brosylates and deduced a 10:1 preference for transposition of a *trans*- over a *cis*-5-hydrogen in acetolysis.

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