most runs was 0.40–0.60. No trend in k_H/k_T with F was discernible. Error analysis showed that the relative effect of error in R_p/R_o on k_H/k_T was independent of F, but the relative effect of error in F on k_H/k_T was greater at higher F, rising slowly at first and then steeply above ca. 0.70. The chosen range of F was thus a compromise between the latter factor and the need to obtain sufficient activity in the solvent for precise counting. Three 0.2-mL samples were withdrawn by syringe for determination of the extent of reaction as described above (approximate rate constants). When the absorbance of unreacted starting material was not negligible, we corrected for it. The remainder of the solution was quenched with 1.0 N hydrochloric acid, centrifuged, and made up to 10.00 ± 0.02 mL.

Subsequent treatment varied somewhat with the nature of the substrate and solvent. In the reactions of the tosylate, 4.00 ± 0.02 mL of the solution was placed in a flask connected to a vacuum manifold, frozen in dry ice and acetone (liquid nitrogen when ethanol was the solvent), degassed by a pump–thaw–freeze–pump cycle, and distilled with the stopcock to the pump closed into a thimble cooled in dry ice and acetone (or liquid nitrogen). Remaining activity was chased into the distillate by repeating the above procedure twice after adding 2-mL portions of inactive solvent to the residue in the flask. The combined distillates were made up to 10.00 ± 0.02 mL. This procedure was shown to remove all of the active solvent within experimental error. 2,2-Diphenylethyl bromide was found to be too volatile for this procedure. Distillation of 3 mL of the total 10 mL of solution was shown by control experiments to result in no significant isotopic fractionation of the solvent (±0.25%) and no distillation of bromide. This was consequently the procedure used for experiments on the bromide.

The unreacted substrate and 1.0-mL samples of the distilled solvent from partial reaction were counted in a toluene-based scintillation cocktail to the ±0.5% (2σ) level of precision on a Beckman LS-100C liquid scintillation counter. Quench corrections were made by the external standard channels ratio method[32] using a Beckman ^{3}H set (No. 566323) of standard quenched samples to determine the quench correction curve. It was found advantageous to make a least-squares fit of the resulting data to a quadratic equation in the channels ratio to get as precise a value as possible for the percent efficiency. Counting efficiencies were close to 50% for all samples.

Position of Tritiation of Diphenylacetic Acid. In order to determine whether any tritium had been introduced into the aromic rings, we dissolved a 2.0-g sample of 2,2-diphenylethanol-*2-t* in water and treated the solution with 2.0 g of sodium carbonate and portionwise with potassium permanganate until its color persisted (ca. 10 g). After 4 h on the steam bath, the mixture was cooled, treated with sodium sulfite, and acidified to litmus. The mixture was extracted with ether and the extracts washed with sodium bicarbonate and dried. The product left upon removal of the ether was shown to be identical with authentic benzophenone (IR and 1H NMR); mp 47–48 °C (lit.[33] 48.1 °C) after recrystallization from ethanol. Its activity was only 0.083% of that of the 2,2-diphenylethanol-*2-t*, showing negligible tritium incorporation into the aromatic rings.

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Mechanism of Acid-Catalyzed Proton Exchange in Amidinium Ions

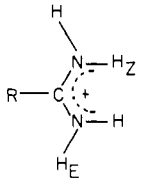
Charles L. Perrin,* Eric R. Johnston, and José L. Ramírez

Contribution from the Department of Chemistry, D-006, University of California, San Diego, La Jolla, California 92093. *Received November 28, 1979*

Abstract: In H_2SO_4, H_E of primary amidinium ions exchanges faster than H_Z, as evidenced by two different NMR techniques—line broadening and saturation transfer. This observation is interpreted according to a kinetic scheme that takes into account the competition between deprotonation of the intermediate $RC(-NH_3^+)=NH_2^+$ and rotation about its C—N single bond. Deprotonation is so fast—diffusion controlled—that it is able to compete with rotation because the intermediate is such a strong acid, with a pK_a estimated to be ca. −19. The dependence of protonation and deprotonation rates on angle of rotation is also discussed.

Introduction

In connection with studies on the mechanism of acid-catalyzed proton exchange in amides,[1,2] we were led to study the same reaction in amidinium ions (**1**). It had been observed[3] that



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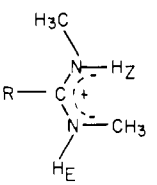

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N,N'-dimethylacetamidinium ion (**2**, R = CH_3) undergoes acid-catalyzed proton exchange in 80% H_2SO_4, via the dication $CH_3C(NH_2^+CH_3)=NH^+CH_3$, and that H_E exchanges 6.4 times as fast as H_Z. Recently this same behavior was also observed, qualitatively, in a gold-carbene complex (**2**, R = $Au_{1/2}^-$).[4] In both these studies the greater reactivity of H_E was accepted as arising from an inherently greater basicity of the nitrogen bearing H_E. Nevertheless, the 6.4-fold greater reactivity of H_E in the first example is too large to be due simply to basicity. For comparison the E/Z ratio in the isoelectronic alkene (3-methyl-2-pentene)[5] is only 1.5, and in the isoelectronic iminium ion (2-butanone *N*-methylimine in CF_3COOH) it is only 1.7 ± 0.2.[6]

We had reason to expect that H_E would exchange faster even in a primary amidinium ion (**1**), where the two nitrogens are necessarily of identical basicity. Indeed, we observed[7] that the protons of benzamidinium ion (**1**, R = C_6H_5) undergo acid-catalyzed exchange at different rates. However, this conclusion was based on only one series of spectra showing differential broadening of NH peaks already broadened by the ^{14}N quadrupole, and we were unable to ascertain that the faster proton was H_E. We now present further evidence that H_E of primary amidinium ions (**1**) does exchange faster, and the significance of that observation.

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Experimental Section

Toluamidine hydrochloride[8] was prepared from the nitrile by Mr. Mike Mitchell; mp 209 °C (lit. mp 213 °C). Other amidine hydrochlorides or acetates (Aldrich), as well as solvents ethylene glycol (Mallinckrodt AR) and sulfuric acid (Mallinckrodt AR, standardized vs. NaOH), were commercially available and used without further purification. Spectra were run on solutions that were 0.1–2 M in amidinium ion. Proton FT-NMR spectra in aqueous buffers were run on a JEOL JNM-PS-100 spectrometer equipped with a frequency synthesizer for decoupling ^{14}N. Acetone-d_6 in an external, concentric 10-mm tube served for the lock signal. Spectra in ethylene glycol or aqueous sulfuric acid were run on a Varian EM390 or a Varian HR-200 FT spectrometer. These solutions are sufficiently viscous that the ^{14}N undergoes rapid relaxation without the necessity of heteronuclear irradiation, leading to N–H line widths, in the absence of exchange, of ≤10 Hz. Homonuclear double irradiation was effected with a frequency synthesizer under control of the Nicolet computer interfaced to the HR-220 spectrometer. The saturating irradiation was applied for a duration of several T_1 but was turned off during acquisition. This saturating irradiation can produce a magnetization in the xy plane, which is usually eliminated with a homospoil pulse. Instead, we chose to reject the xy magnetization by using 90° observation pulses. Owing to the high concentration of solvent protons, the high sensitivity of a 90° pulse then necessitated an additional 20–30-dB attenuation of the unmodulated signal, so as to avoid overloading the A-to-D converter. Relaxation times (T_1) of NH protons were determined by the inversion-recovery method, under conditions of selective saturation of solvent protons. Intensities for saturation transfer and T_1 measurements were simply peak heights, obtained from digitized spectra. Chemical shifts were measured relative to *tert*-butyl alcohol (δ 1.25), acetic acid (δ 2.10), or Me_4NBr (δ 3.19), and corrected to Me_4Si.

Rate constants were calculated according to equations adapted from Perrin and Johnston.[9] In particular, the saturation transfer from solvent to H_Z, $t_Z(S)$,[10] is the fractional loss of intensity, I_Z, at H_Z on saturating H_S, and this is given by eq 1, where $I_Z(S)$ and I_Z^0 are the intensities of

$$t_Z(S) = \frac{I_Z^0 - I_Z(S)}{I_Z^0} = \frac{p_S k_{SZ} + p_E k_{EZ} t_E(S)}{p_Z(k_{ZS} + k_{ZE} + R_Z)} \quad (1)$$

H_Z with and without saturation, respectively, k_{ij} is the pseudo-first-order rate constant for exchange from site i to site j, R_i is the inherent longitudinal relaxation rate constant ($=1/T_{1i}$) of protons in site i, and p_i is the relative population of protons in site i. The expression for $t_E(S)$ is analogous. Next, if apparent longitudinal relaxation rate constants of H_Z and H_E are similar, the apparent longitudinal relaxation rate constant of H_Z, while saturating H_S, is given by eq 2 and analogously for $R_E(S)$.

$$R_Z(S) = R_Z + k_{ZE} + k_{ZS} - p_E k_{EZ}/p_Z \quad (2)$$

A further simplification results from the requirement that for every exchange reaction, forward and reverse rates must be equal, or

$$p_i k_{ij} = p_j k_{ji} \quad (3)$$

If we assume that the inherent longitudinal relaxation rate constants R_E and R_Z are equal, these are four equations—four measured values $t_Z(S)$, $t_E(S)$, $R_Z(S)$, and $R_E(S)$—in four unknowns—three independent rate constants and the common longitudinal relaxation rate constant R. It is then easy to solve these equations for the rate constants of interest and analogously for k_{ES} (eq 4). It is also possible mathematically to solve

$$k_{ZS} = \tfrac{1}{2}[R_Z(S)t_Z(S) + R_E(S)t_E(S) + R_Z(S) - R_E(S)] \quad (4)$$

for k_{EZ} or k_{ZE}, but this is the difference of large numbers and subject to too large an error to be determined from these measurements.

Results

Signal Assignments. The ^{14}N-decoupled ^1H NMR spectrum of formamidinium ion (**1**, R = H) in diluted HCl shows two NH doublets, at δ 8.45 and 8.34, with coupling constants of 16 and 6 Hz, respectively. The CH is correspondingly a triplet of triplets centered at δ 7.81. Since $^3J_{trans}$ is generally greater than $^3J_{cis}$[14] we assign the high-field doublet as H_Z. This same assignment has been made in *N,N'*-dimethylformamidinium ion.[15] Similarly, acetamidinium ion (**1**, R = CH_3) in aqueous HOAc shows two NH singlets, at δ 7.97 and 8.35, with the former slightly broader, owing to unresolved coupling to the methyl hydrogens. Since $^4J_{trans}$ is often, but not always, greater than $^4J_{cis}$, we may again assign the high-field peak as H_Z. This analogy, but involving ^5J, was used[15] to make the analogous assignment in $CH_3C(NHCH_3)_2^+$ (**2**, R = CH_3). More convincing evidence for this assignment in acetamidinium ion is provided by an NOE experiment in ethylene glycol, where we find that saturating the methyl leads to a 2% enhancement of the low-field NH and no enhancement of the high-field NH.

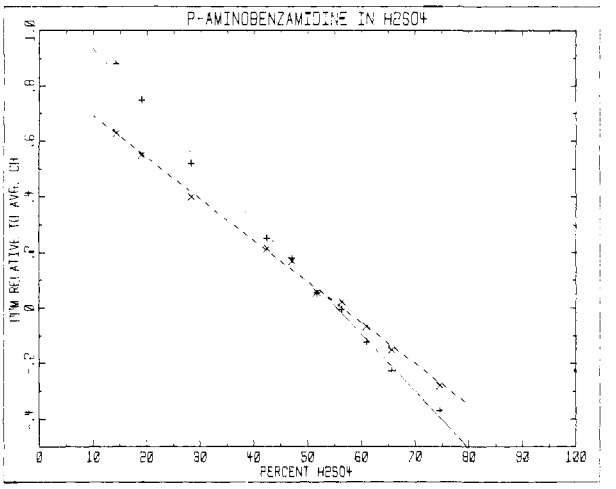

Figure 1. NH chemical shifts of *p*-aminobenzamidine in aqueous H_2SO_4, relative to the average of the aromatic CH shifts: H_E(+), H_Z(×).

In aqueous acid, benzamidinium ion (**1**, R = C_6H_5) shows NH singlets at δ 8.41 and 8.68, and *p*-aminobenzamidinium ion (**1**, R = *p*-$H_3N^+C_6H_4$) shows amidinium NH singlets at δ 8.49 and 8.72. We are unable to obtain direct evidence for assigning these NH signals, since long-range couplings are negligible and NOE and shift-reagent experiments were unsuccessful. However, by analogy to formamidinium ion and acetamidinium ions, we assign the higher-field NH as H_Z. It is quite unlikely that the aromatic ring reverses the chemical shifts, since no such reversal is seen in primary or tertiary amides, where the Z substituent is always assigned to higher field.[14,16,17]

However, solvent-induced shifts in sulfuric acid change these assignments. The NH peaks of amidinium ions shift upfield with increasing sulfuric acid concentration, and H_E, the low-field peak, is affected more, so that the two peaks move toward each other. In acetamidinium ion (**1**, R = CH_3) these peaks merge at around 70% H_2SO_4, and the chemical shifts remain coincidentally the same as the acidity is increased further. Other aliphatic amidinium ions show the same merging. Aromatic amidinium ions show a similar merging, but in stronger acid the two peaks are again separated. It is difficult to follow the course of the NH peaks, because they are obscured under the huge solvent peak in 30–40% H_2SO_4, and they may be obscured under the aromatic multiplet in 50–60% H_2SO_4, just when the peaks merge. Fortunately, a para-substituted amidine gives a simple enough aromatic region that the NH protons can be discerned. Figure 1 shows NH chemical shifts, relative to the average (aromatic) CH shift, for *p*-aminobenzamidine. The good linearity of chemical shifts with vol % H_2SO_4 is evidence for a crossover of chemical shifts, rather than a rebound of one off the other. Therefore we conclude that in moderately concentrated H_2SO_4, H_E of aromatic amidinium ions becomes the higher-field NH.

Rates. Figure 2 shows the NMR spectrum of benzamidinium ion (**1**, R = C_6H_5) in aqueous H_2SO_4. It is clear not only that

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(10) There is no accepted notation for saturation transfer, and we propose $t_i(j)$, analogous to the nuclear Overhauser enhancement, $f_i(j)$.[11] Both are measured by the same experiment, but they arise by different mechanisms and ought not[12] be designated by the same symbol.[9,11,13]
(11) Noggle, J.; Schirmer, R. "The Nuclear Overhauser Effect", Academic Press: New York, 1972.
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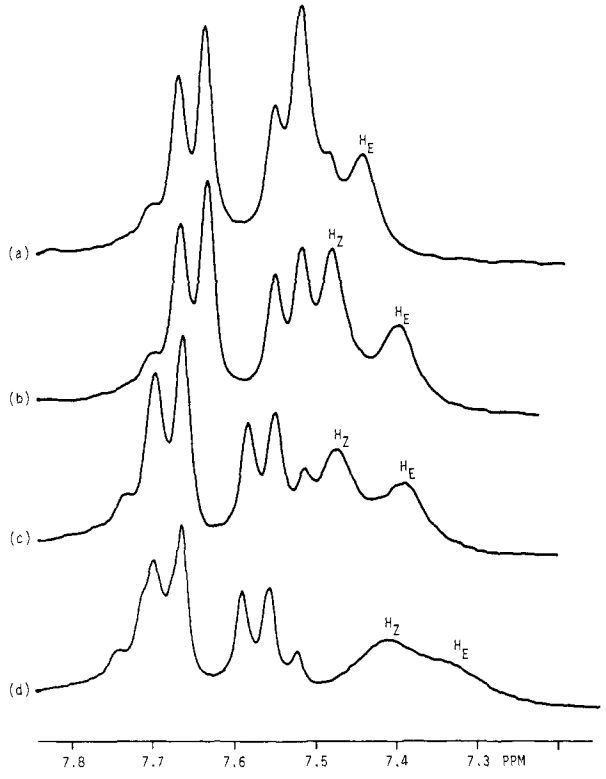

Figure 2. NMR spectrum (downfield region) of benzamidine in aqueous H_2SO_4: (a) 75 wt %; (b) 77 wt %; (c) 79 wt %; (d) 82 wt %. For assignments, see text.

the NH peaks are broadening owing to an increasing rate of acid-catalyzed exchange, but also that the upfield peak, assigned as H_E, shows the greater broadening and the greater exchange rate. From the extent of broadening we estimate[18] that the rate constants for exchange of H_E and H_Z are 11 and 9 s^{-1}, respectively, in 79 wt % H_2SO_4. However, these estimates are crude, since the NH peaks are broad, overlapping, and partly obscured by the more prominent aromatic peaks.

Inasmuch as the NH peaks are broadened by scalar coupling to the ^{14}N, which is undergoing quadrupolar relaxation, it might be thought that the variable broadening of Figure 2 is not due to exchange but instead to a variation in the relaxation rate, perhaps arising from the changing viscosity of the H_2SO_4. However, the increasing broadening is not simply a characteristic of 75–82% H_2SO_4 but varies with the amidine in a manner expected for substituent effects on an acid-catalyzed reaction. Thus the amidine NH peaks of *p*-aminobenzamidinium ion (**1**, R = *p*-$H_3N^+C_6H_4$) do not broaden until >90% H_2SO_4, and the NH peaks of *p*-toluamidinium ion (**1**, R = *p*-$CH_3C_6H_4$) broaden in 74 wt % H_2SO_4, as shown in Figure 3. Moreover, the upfield peak is again the broader one, so H_E is exchanging faster.

The conclusion that H_E exchanges faster does not rest only on the observation of differential line broadening, but can also be confirmed independently by the technique of saturation transfer.[13] Figure 4a shows the NMR spectrum of *p*-aminobenzamidine in 90 wt % H_2SO_4. Figure 4b is the same spectrum, but with the solvent peak saturated. Saturation transfer to the two amidinium NH peaks, at the right of the figure, is apparent, and the saturation transfer to the higher-field peak, H_E, is greater. These features are more apparent in the difference spectrum (Figure 4c). It can also be seen that there is a nuclear Overhauser enhancement[11] of the CH peaks, due to intermolecular dipole–dipole relaxation, but there is no saturation transfer to the $-NH_3^+$ protons, since these are not expected to exchange in acid.[19] Quantitatively, the extents of saturation transfer, $t_Z(S)$ and $t_E(S)$, are 0.513 and 0.636, respectively. Measurement of apparent T_1 relaxation rates, under

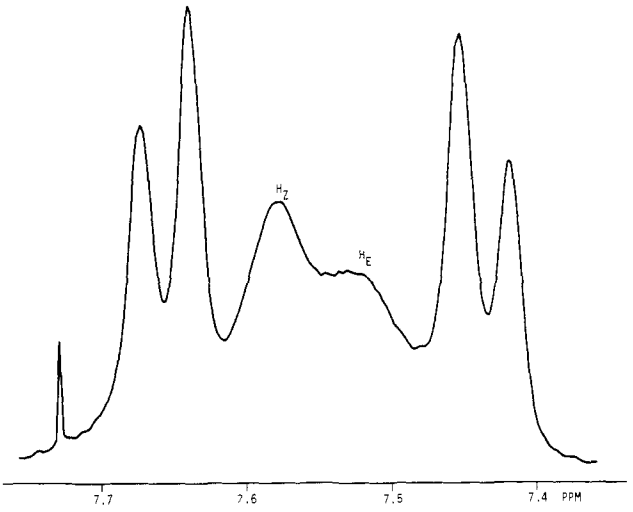

Figure 3. NMR spectrum (downfield region) of *p*-toluamidine in 74 wt % H_2SO_4.

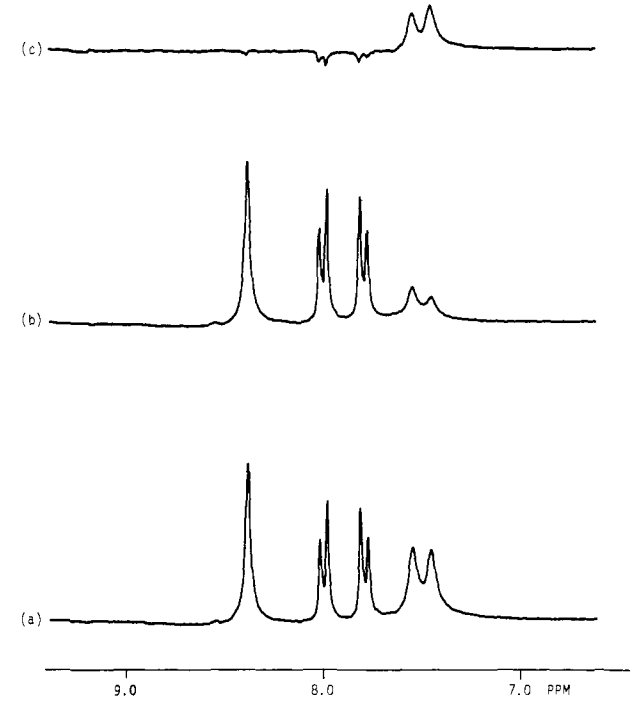

Figure 4. NMR spectrum (downfield region) of *p*-aminobenzamidine in 90 wt % H_2SO_4 (peaks, from left to right, are $-NH_3^+$, ortho CH doublet, meta CH doublet, NH_Z, and NH_E): (a) with off-resonance irradiation; (b) with solvent peak at δ 11.32 (not shown) saturated; (c) (difference spectrum, Figure 4a minus Figure 4b).

conditions of solvent saturation, gives $R_Z(S) = 9.16\ s^{-1}$ and $R_E(S) = 11.3\ s^{-1}$. Equation 4 then gives $k_{ES} = 7.0\ s^{-1}$ and $k_{ZS} = 4.9\ s^{-1}$; the rate ratio is 1.44. Thus the saturation-transfer results confirm the conclusion that the protons exchange at different rates. The difference is small, but it is manifested in two independent methods.

Discussion

Definitions. Since this reaction involves unusally fast processes, it is necessary to define terms and state assumptions explicitly. An intermediate is always defined[20] as a minimum on a potential-energy surface. Thus a single conformer of RC(=NH_2^+)–

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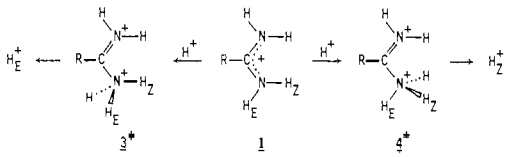

Figure 5. Concerted mechanism for acid-catalyzed proton exchange in an amidinium ion.

NH_3^+ or $RCONH_3^+$ can be an intermediate, since there is a threefold barrier to rotation of the $-NH_3^+$ group, albeit small. We do not know the height of this barrier, but we are reasoning by analogy to methyl ketones, where the barrier to rotation about the sp^2–sp^3 C–C bond is ca. 1 kcal/mol,[21] corresponding to a lifetime ca. 10^{-12} s.[22] Ketones *are* a suitable model, since according to ab initio MO calculations and some experimental results,[21,23] the barrier is not greatly affected by substitution, including replacing $-CH_3$ by $-NH_3^+$.[24] Therefore it is quite unlikely that the barrier to rotation of an $-NH_3^+$ is fortuitously so close to zero that a conformer can no longer be an intermediate. Rather it is more likely that hydrogen bonding increases the barrier. For definiteness we take 10^{-12} s as the lifetime of a conformer, but we recognize that this is only an estimate.

Implicit in this treatment is the assumption that molecular motion can be treated classically. This is adequate for a barrier of 1 kcal/mol, which is greater than the zero-point energy of the torsional motion, but not by much. On the other hand, tunneling is significant for ultrafast proton transfers in a hydrogen-bonded system.[25] Thus we do not distinguish $AH^+\cdots OH_2$ and $A\cdots HOH_2^+$ as different species. They become different only upon rotation by either the AH or the HOH_2. Such rotation is the rate-limiting step in diffusion-controlled proton transfer,[25] even strongly exothermic ones.[26] In aqueous solution the lifetime of a species that undergoes diffusion-controlled proton transfer to or from solvent (so that solvent need not diffuse to the species) is 10^{-11} [27] or 10^{-12} s.[28] In sulfuric acid[29] proton mobility is nearly as large as in water (despite the difference in viscosities). For definiteness we take 10^{-11} s as the lifetime of a species involved in diffusion-controlled proton transfer with H_2SO_4 solvent, but we recognize that this too is only an estimate.

Mechanisms for Exchange of H_E and H_Z at Different Rates. Initially we had expected that N protonation of a primary amide or amidinium ion, to produce $RCONH_3^+$ or $RC(=NH_2^+)NH_3^+$, would make the protons of the $-NH_3^+$ group equivalent, so that H_E and H_Z would necessarily exchange at the same rate. Yet the results show that H_E of aromatic amidinium ions undergoes acid-catalyzed exchange faster than H_Z. How can these protons exchange at different rates? Equivalence requires only rotation of the $-NH_3^+$ group, which ought to be exceedingly fast, requiring ca. 10^{-12} s.

Of course, rotational equivalence of the $-NH_3^+$ protons depends on the lifetime of the intermediate, $RC(-NH_3^+)=NH_2^+$. This is a strong acid, stronger even than H_2SO_4, so that proton donation to HSO_4^- is thermodynamically favorable and may be expected to be diffusion controlled.[25,30] (Although H_2SO_4 is the general acid that donates the proton,[31] in what follows we shall write the proton donor simply as H^+.) The lifetime of this intermediate in H_2SO_4 is then only ca. 10^{-11} s. In view of the uncertainties in such estimates, this is uncomfortably close to the 10^{-12} s lifetime of a conformer, especially if hydrogen bonding retards the rotation.

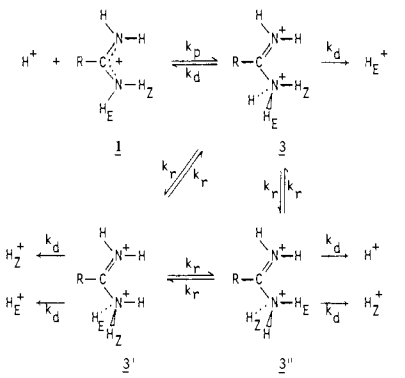

Figure 6. Mechanism of acid-catalyzed proton exchange in an amidinium ion, including competition between deprotonation and rotation of the intermediate.

The possibility that the $-NH_3^+$ protons might not become equivalent during the lifetime of the intermediate then forces us to consider the reaction in more detail.

One possible mechanism for maintaining the inequivalence of H_E and H_Z is a concerted proton transfer, without any intermediate (Figure 5). Such a mechanism was suggested[27] (and rejected[26]) for acid-catalyzed proton exchange in phenol, where $C_6H_5OH_2^+$ is also a strong acid. Then the observation that $k_{ES} > k_{ZS}$ may be rationalized by the assumption that **3**‡ is of lower energy than **4**‡. However, the observed ratio of 1.44 corresponds to an energy difference of only 0.2 kcal/mol, which is less than any known threefold barrier.[21,23] Also, the observation[3] that the N methyls of *N,N'*-dimethylacetamidinium ion (**2**, R = CH_3) become a single NMR peak in 90.7% H_2SO_4 shows that the protonated species is not merely a transition state but has a finite lifetime, during which the methyls may exchange between E and Z sites. Similar behavior is also seen with tertiary amides[32] and with primary amides.[2,17] Therefore we turn to exchange mechanisms with at least one intermediate.

Protonation of an amidinium ion (**1**) should produce the dication in its most stable conformation (**3**, or its enantiomer), with a hydrogen eclipsing the double-bonded nitrogen, as shown in Figure 6. That **3** is the most stable conformation is assumed by analogy to all known examples (with one possible exception[33]) of a methyl rotor on a double bond.[21,23,24] That it is H_Z that eclipses N, rather than H or H_E, follows from the fact that the observed rate of exchange is faster than the observed rate of E–Z interchange.[34] Therefore the nitrogen does not rotate about the C–N partial double bond prior to protonation, and the conformer initially formed is **3**, not **3'** or **3''**. We shall return to these assumptions later. The intermediate **3** can lose either H^+ or H_E^+, with rate constant k_d, but it cannot lose H_Z^+, since by microscopic reversibility if a proton does not enter into the position that eclipses N, it does not leave from that position. Loss of H_Z^+ requires prior rotation, with rate constant k_r, to one of the other conformers. From the lifetimes estimated above, we might expect k_d and k_r to be ca. 10^{11} and 10^{12} s^{-1}, respectively. Solution of the kinetic scheme of Figure 6, by the steady-state approximation, leads to eq 5–7, where k_{ES} and k_{ZS} are rate constants for exchange of H_E

$$k_{ES} = k_p[H^+](k_r + k_d)/(3k_r + 2k_d) \quad (5)$$

$$k_{ZS} = k_p[H^+]k_r/(3k_r + 2k_d) \quad (6)$$

$$k_{ES}/k_{ZS} = 1 + k_d/k_r \quad (7)$$

and H_Z into solvent. Equation 7 shows the proper limiting behaviors. If rotation is rapid relative to deprotonation, as we had initially expected, then H_E and H_Z become equivalent and ex-

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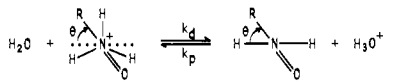
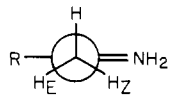


Figure 7. Rotation and protonation of an amide.

change at identical rates. If deprotonation is rapid relative to rotation, then only H_E will exchange. Experimentally neither limit is applicable, and we find that deprotonation and rotation are competitive. For *p*-aminobenzamidine (**1**, R = *p*-$H_3N^+C_6H_4$) the k_{ES}/k_{ZS} ratio of 1.44 corresponds to $k_r = 2.3k_d$. This result then suggests that the lifetimes for rotation and deprotonation are more nearly equal than our estimates of 10^{-12} and 10^{-11} s, respectively.

Redfield and Waelder[17] have recently proposed an alternative scheme for acid-catalyzed proton exchange in amides (their eq 4). Extended to amidines, this scheme would require that protonation initially produce conformation **5**, with the incoming proton



5

perpendicular to the molecular plane.[35] Conformation **5** can lose only H^+, and loss of H_E^+ or H_Z^+ requires rotation, by at least 30°, to another conformation in which that proton is perpendicular to the molecular plane. However, this mechanism assumes a sixfold barrier for rotation about the C–N bond, and it cannot account for the observation that $k_{ES} > k_{ZS}$. To do so requires the inclusion of an additional threefold barrier component, to cause the $-NH_3^+$ group of **5** to undergo preferential rotation in one direction. We choose not to introduce any sixfold component into the barrier, since these are generally extremely small[21,23] (although solvation may increase it[37]) and since the kinetic scheme based solely on the well-established threefold barrier (Figure 6) automatically leads to $k_{ES} > k_{ZS}$.

Angular Dependence of Protonation Rate. Redfield and Waelder[17] have also proposed that the incoming proton can enter the position eclipsing the double-bonded atom (their eq 7), to form **3′**. We had rejected[1] this pathway by noting that the observed rate of rotation about the C–N partial double bond[34] is too low to account for the observed rate of exchange. However, what is observable is the rate of 90° rotation, so Redfield and Waelder have suggested that protonation can occur after less than a 90° rotation, followed by continued rotation to **3′**, or else that the rotation and protonation can be concerted. This is not such an unreasonable suggestion, since a rotated amide or amidinium ion is more basic than a planar one and should be protonated more readily. We therefore consider the dependence of the rate on rotational angle, in order to estimate how much of the reaction occurs through such concerted rotations and protonations.

It is easier to estimate the dependence of the rate of deprotonation k_d on rotational angle θ, as indicated in Figure 7. For convenience we do so for amides in aqueous solution, where the data are available, but the conclusion should hold for amidines in H_2SO_4 as well. For each θ the ratio of forward and reverse constants must equal the equilibrium constant, or

$$k_d/k_p = K_a^{RCONH_3^+} \qquad (8)$$

Next we estimate how $K_a^{RCONH_3^+}$ depends on θ. For $\theta = 0°$ Fersht's eq 45[38] gives $K_a^{RCONH_3^+} = 10^{9.0}$. For $\theta = 90°$, a model ketoamine[39] gives $K_a^{RCONH_3^+} = 10^{-5.3}$. For intermediate θ we assume that the resonance energy of the amide shows a $\cos^2\theta$ dependence, and we neglect any rotational barrier in $RCONH_3^+$. Therefore $K_a^{RCONH_3^+} = 10^{14.3\cos^2\theta - 5.3}$. Next we invoke the simplifying assumption that any proton-transfer reaction that is thermodynamically favorable will occur with the same diffusion-controlled rate constant.[25,26] Therefore k_d will be ca. 10^{12} s^{-1} whenever $K_a^{RCONH_3^+} > K_a^{H_3O^+} = 10^{1.74}$, or only if $|\theta| < 45°$. On the other hand, for larger $|\theta|$ it is k_p that becomes diffusion controlled and k_d falls off rapidly with increasing θ. Figure 8 shows the dependence of log k_d on θ. However, we need the *rate* of deprotonation, which is the product of the rate constant and the concentration. The concentration of $RCONH_3^+$ rotated by an angle between θ and $\theta + d\theta$ is proportional to $e^{-V/RT}$, where V is the potential of the rotational barrier. By analogy to methyl rotors on a double bond,[21] we take $V = {}^1/_2V_0(1 - \sin 3\theta)$; for definiteness we choose $V_0 = 1.0$ kcal/mol. Then we can calculate the angular dependence of the concentration and of the rate of deprotonation, which is also shown in Figure 8. At equilibrium, rates of protonation and deprotonation must be equal, so Figure 8 also shows the dependence of the rate of protonation on θ. Notice that the rate is maximum for $\theta = 30°$, and falls off very rapidly for $|\theta| > 45°$. Therefore protonation most often produces conformation **3** ($\theta = 30°$), as was asserted previously,[1] but formation of conformation **5** ($\theta = 0°$) is only 0.4 times as likely, formation of conformation **4** ($\theta = -30°$) is still less likely, and formation of conformation **3′** ($\theta = 90°$) does not contribute to the observed rate. These conclusions do not depend very strongly on the pK_a's estimated from models, but the first one does depend on the rotational potential.

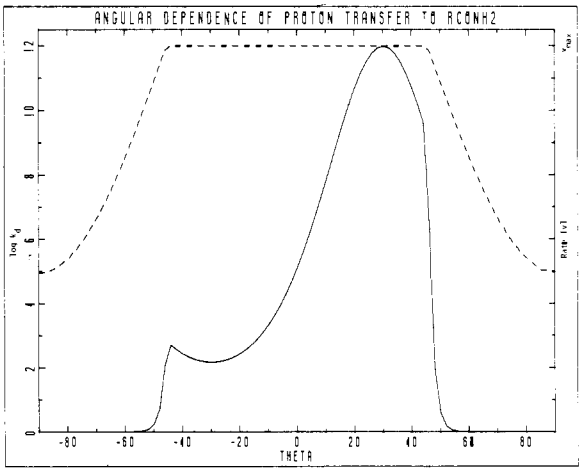


Figure 8. (a) Angular dependence of log k_d for deprotonation of $RCONH_3^+$ (---). (b) Rate of deprotonation of $RCONH_3^+$ or rate of protonation of $RCONH_2$ (—).

Acidity of the Intermediate. Finally, we may estimate how acidic the intermediate **3** really is. Since forward and reverse rates (Figure 6) must be equal, $k_p h_0[RC(NH_2)_2^+] = 2k_d[RC(NH_3^+){=}NH_2^+]$. For definiteness, since the data are available, we take H_0 as the acidity function that governs the protonation of this $-NH_2$ group, even though H_0 pertains to protonation of the $-NH_2$ group of a nitroaniline and H_+ would be more appropriate. From the observed $k_{ES} = 7.0$ s^{-1} and $k_{ZS} = 4.9$ s^{-1} for *p*-aminobenzamidine (**1**, R = *p*-$H_3N^+C_6H_4$) in 90% H_2SO_4, eq 5 and 6 give $k_p h_0 = 19$ s^{-1}. With an assumed $k_d = 10^{11}$ s^{-1} and the observed $H_0 = -8.92$,[40] we obtain $K_a^{RC(NH_3^+){=}NH_2^+} = h_0[RC(NH_2)_2^+]/[RC(NH_3^+){=}NH_2^+] = 9 \times 10^{18}$ or $pK_a^{RC(NH_3^+){=}NH_2^+} = -19$ (R = *p*-$H_3N^+C_6H_4$). Since $pK_a^{RC(NH_2)_2^+} = 11.6$ (R = C_6H_5),[41] there is a difference of 30 between the first and second pK_a's. For comparison, the differences between first and second pK_a's of H_3O^+ and $C_6H_5C(OH)_2^+$ are 17.5 and 11.4,[42] respectively. The considerably larger ΔpK_a for amidines is a reflection of the considerable resonance energy of amidinium ions and of their resistance to both protonation and deprotonation.

Conclusions

The observation that acid-catalyzed proton exchange in amidinium ions (**1**) shows $k_{ES} > k_{ZS}$ is entirely consistent with the

(35) An analogous conformation has been invoked[36] as the first-formed intermediate in nucleophilic displacement on vinyl halides, but neither this nor **5** can be an intermediate, inasmuch as it is not a minimum-energy species.

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kinetic scheme of Figure 6 and good evidence for it. The intermediate **3** is so acidic (pK_a = ca. −19) that deprotonation, even in sulfuric acid, is diffusion controlled and is competitive with rotation about the C–N single bond. As a result, the lifetime of the intermediate is too short to permit H_E and H_Z to become equivalent. This means that, at least in part, the rate-limiting step for exchange of H_Z is a rotation, even though the rate constant for that process is $\geq 10^{11}$ s^{-1}.

How general is this conclusion? The result has been obtained only for aromatic amidines, since the coincidence of chemical shifts of H_E and H_Z of primary aliphatic amidinium ions in >70% H_2SO_4 has precluded measuring their individual exchange rates. By analogy to $RCONH_3^+$ [1] it may be expected that aliphatic R groups would increase k_r, promote rotational equivalence, and make k_{ES} and k_{ZS} more nearly equal. However, the large, 6.4-fold greater reactivity of H_E in *N,N'*-dimethylacetamidinium ion (**2**, R = CH_3)[3] suggests that deprotonation and rotation are competitive in all protonated amidinium ions.

Note Added in Proof: We have confirmed this assignment for benzamidinium ion (**1**, R = C_6H_5) with the use of anionic lanthanide-shift reagents.[43]

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Total Synthesis of (*R*)-Glycerol Acetonide and the Antiepileptic and Hypotensive Drug (−)-γ-Amino-β-hydroxybutyric Acid (GABOB): Use of Vitamin C as a Chiral Starting Material[1]

Michael E. Jung*[2] and Teresa J. Shaw

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received November 13, 1979*

Abstract: Ascorbic acid (Vitamin C) (**9**) is shown to be a useful, inexpensive chiral starting material for natural products synthesis. It is converted in high yield via two synthetic operations into (*R*)-glycerol acetonide (**7**), the more inaccessible enantiomer of glycerol acetonide. Since D-(*R*)-glyceraldehyde acetonide (**4**) and the corresponding alcohol **1** have been used in many total syntheses of a wide variety of compounds, the ready availability of the opposite enantiomers L-(*S*)-glyceraldehyde acetonide (**6**) and glycerol **7** should be of great value. As one indication of this potential synthetic utility, the hypotensive, antiepileptic compound (*R*)-(−)-γ-amino-β-hydroxybutyric acid (GABOB) (**8**) has been synthesized from ascorbic acid (**9**) via nine steps in 10% overall yield. As further evidence of the importance of these compounds in synthesis, several useful intermediates for the preparation of the highly active hypotensive agents, the aryloxypropanolamines (**5**), were prepared from Vitamin C.

Introduction

Recently great advances have been made in the total synthesis of optically active natural products from readily available chiral precursors. Especially useful as optically active starting materials have been the naturally occurring carbohydrate derivatives, particularly D-glucose.[3] Herein is reported the first use of a different inexpensive carbohydrate derivative, ascorbic acid, Vitamin C (**9**), as a chiral precursor and from it the total synthesis of the useful antiepileptic and hypotensive drug γ-amino-β-hydroxybutyric acid, GABOB (**8**). Also the utility of several intermediates, e.g., (*R*)-glycerol acetonide (**7**), for the synthesis of other interesting chiral drugs such as the aryloxypropanolamines (**5**) is described.

Background

(*S*)-Glycerol acetonide (**1**) and its derivatives have often been used as chiral intermediates for natural products synthesis.[4] The racemic form of **1** was first reported by Fischer in 1895[5] and has been prepared simply from glycerol many times.[6] For the synthesis of the optically active forms of glycerol acetonide, the naturally occurring, inexpensive polyhydroxy compound D-mannitol (**2**) was used. The bis(acetonide) of mannitol (**3**) was prepared in moderate yield and the resulting diol cleaved with lead tetraacetate to yield unstable (*R*)-glyceraldehyde acetonide (**4**).[7]

A number of biologically active compounds have been formed from **4**, including naturally occurring D-glyceraldehyde,[8] an amino acid,[9] prostaglandins,[10] and carbohydrates.[11] It has also been used to synthesize the unnatural enantiomer of the antibiotic pyridindolol.[12] However, due to its instability, (*R*)-glyceraldehyde acetonide (**4**) is usually reduced to (*S*)-glycerol acetonide (**1**) with hydrogen in the presence of a nickel catalyst.[13] This enantiomer

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