Mechanisms of Acid-Catalyzed Proton Exchange in *N*-Methyl Amides

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Abstract: Kinetics of acid-catalyzed proton exchange in an extensive series of *N*-methyl amides, $RCONHCH_3$, were followed by NMR line-shape analysis in aqueous solution. Electron-withdrawing substituents retard the reaction, but the only good correlation is between log k_{H^+} for substituted *N*-methyl acetamides and the pK_a of the corresponding RCOOH. The correlation shows a change in slope, from 0.43 for amides with electron-withdrawing substituents to ca. 1.84 for other amides. This change is taken as evidence for a changeover from the imidic acid mechanism to the N-protonation mechanism. In particular, it is concluded that peptides and proteins represent amides with electron-withdrawing substituents, so that the NH protons of their backbone exchange predominantly via the imidic acid. The difference in slopes and the changeover in mechanism, as well as the comparison between primary and secondary amides, are rationalized in terms of substituent effects and transition-state structures.

Proton exchange in amides,[1-10] including ureas,[11] has long been of considerable interest, especially since proton-exchange kinetics of amides, peptides,[12] and proteins can provide information about the structure of peptides and proteins in solution.[13,14] The mechanism of the acid-catalyzed exchange has long been accepted[1b-d,2-4,10b,15] as involving N-protonation:

$$RCONHR' + H^+ \underset{k_d}{\overset{k_p}{\rightleftharpoons}} RCONH_2{}^+R' \qquad (1)$$

It is not possible to disprove this mechanism as requiring a step faster than the diffusion-controlled limit; from observed rates for *N*-methylacetamide and an estimate[7c,16] of the pK_a of the N-protonated intermediate, k_d need be only 2×10^{10} s^{-1}, which is reasonable for a diffusion-controlled deprotonation.[5,7c,17] Evidence adduced in favor of this mechanism includes the fact that the second-order rate constant for this reaction is greater than that for the base-catalyzed exchange,[1a] the observation that electron-withdrawing substituents retard the reaction,[2c,5,12e,13c,e] and the similarity between these rates and the rates of acid-catalyzed rotation in tertiary amides,[1a,16] as well as the effects of ortho substituents on this comparison.[9]

Nevertheless, this evidence is quite consistent with an alternative mechanism proceeding via the imidic acid:

$$RCONHR' + H^+ \underset{K_a^O}{\rightleftharpoons} RC(OH){=}NHR'^+ \underset{k_i}{\overset{k_{-i}}{\rightleftharpoons}} RC(OH){=}NR' + H^+ \qquad (2)$$

O-Protonation acidifies the NH proton so that it can be removed. The rate-limiting step cannot be the first one,[14a] since the OH acidity of the intermediate is ca. 10^8 times its NH acidity.[16] This mechanism might be questionable, since observed rates for *N*-methylacetamide and estimates[19] of the pK_as of the O-protonated

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intermediate require that k_i be (2–3) × 10^{11} M^{-1} s^{-1}, which is faster than the diffusion-controlled limit. However, the discrepancy is too small to be conclusive; it could be due merely to an imperfection of the imidate ester model, or it could vanish with substitution. Besides, this mechanism, although more circuitous, is more attractive, since it avoids protonating the amide on nitrogen, which is ca. 10^7-fold less basic than the oxygen.[16] Indeed, Martin[6] has favored the imidic acid mechanism on the basis of discrepancies between the rate of acid-catalyzed proton exchange in $RCONHCH_3$ and the rate of acid-catalyzed rotation in $RCON(CH_3)_2$, although this conclusion depends on an implicit assumption that may not be valid.[20] (The equivalent conclusion for thioamides[21] probably is valid.)

We have been seeking to elucidate the mechanism(s) of acid-catalyzed proton exchange in amides and related compounds. In primary amides, $RCONH_2$, we have attributed[20,22] the greater reactivity of H_E (the proton anti to oxygen), relative to H_Z, to the operation of the N-protonation mechanism, but with the additional feature that deprotonation of $RCONH_3^+$ is competitive with rotation about its single bond, and we have provided further evidence for this feature in the acid-catalyzed proton exchange of amidinium ions.[23] More recently, we,[20,24] and also Redfield and Waelder,[10a] have used saturation-transfer techniques to show that the occurrence of acid-catalyzed intramolecular proton exchange, compared to intermolecular exchange, is strong evidence for the N-protonation mechanism in many primary amides. Moreover, we[20,24] have found that intramolecular exchange in amides with electron-withdrawing substituents is significantly slower than intermolecular exchange, and we have interpreted this result as the first unambiguous evidence for the imidic acid mechanism.

Although primary amides are certainly of interest, peptides and proteins consist chiefly of secondary amides, whose mechanism(s) of acid-catalyzed proton exchange ought to be elucidated.[12b] The comparison of intramolecular exchange with intermolecular is no longer applicable to secondary amides. Fortunately we had noticed[20] a nontrivial substituent effect on rates of acid-catalyzed exchange in primary amides. The logarithms of the second-order rate constants, k_{H^+}, for $RCONH_2$ could be fit to an equation linear in the pK_a of the corresponding carboxylic acid, RCOOH, just as such correlations were obtained for the base-catalyzed exchange.[5,12a,c] However, the linearity in our case was poor, since the slope seemed to change from ca. 0.3 for amides with electron-withdrawing substituents to ca. 1 for other amides. According to this interpretation, the imidic acid mechanism is associated with a low sensitivity to the electronic effect of substituents, whereas the N-protonation mechanism shows a higher sensitivity. Thus the change of slope parallels the change of mechanism detected by the saturation-transfer measurements.

We have sought similar substituent effects to document a change in the mechanism of acid-catalyzed proton exchange of *N*-methyl amides, $RCONHCH_3$. By analogy to the primary amides, we expect such a change, but we cannot tell a priori where the change will occur. For primary amides the saturation-transfer data were not good enough to establish the change of slope. Fortunately, *N*-methyl amides have the advantage that their exchanges rates can be measured quite reliably by line-shape analysis of the *N*-methyl doublet. For three such amides it was observed[5] that log k_{H^+} is linear in the pK_a of the corresponding RCOOH, with slope 1.3. This was claimed[5,13c] as evidence for the N-protonation mechanism, since electron-withdrawing substituents would increase both K_a^O and k_{-i} (eq 2), so that the imidic acid mechanism should be relatively insensitive to substituents. However, it does not follow that the cancellation of substituent effects would be nearly complete; this is still an acid-catalyzed reaction and should be subject to some retardation by electron-withdrawing substituents. Besides, the linearity for those three amides, as well as for a series of amino acid amides,[12e] was poor. We now report kinetic studies on a more extensive series of *N*-methyl amides, where we can discern a change of slope and, by inference, a change of mechanism.

Experimental Section

Materials. Many *N*-methyl amides were commercially available (Aldrich, Eastman, Trans World, BACHEM, Polyscience), purified by vacuum distillation if necessary. Most amides were synthesized by straightforward literature procedures from the ester, anhydride, or acid chloride with ethereal or aqueous methylamine, sometimes with added NaOH. One urethane was synthesized from acetoxime plus methyl isocyanate.[25] *N*-Methyliodoacetamide was prepared from *N*-methylchloroacetamide with NaI in acetone:[26] mp 71–72 °C (EtOAc–hexane); NMR δ 2.73 (3 H, d, J = 4.8 Hz), 3.77 (2 H, s), 8.3 (br). *N*-Methylmalonamic acid was prepared by the method of Perrin and Arrhenius[27] from malonic anhydride in CH_2Cl_2 plus methylamine in ether; mp 108–110 °C (lit.[28] mp 94–108 °C (sic)).

The line width and coupling constant of an *N*-methyl doublet under nonexchange conditions were measured in water or in aqueous buffer; line widths were generally 0.5–1.0 Hz. For kinetics, aqueous solutions containing 0.02–1.0 M amide were acidified with HCl, except for *N,N'*-dimethylurea, where acetate buffer was used. For a check on field homogeneity, 1% *t*-BuOH was always included. To inhibit polymerization, hydroquinone (<1%) was included with *N*-methylacrylamide and *N*-methylmethacrylamide.

Kinetics. NMR spectra were determined on a Varian EM390 90-MHz spectrometer. Samples were allowed to equilibrate for 5 min to the probe temperature of 34 °C. The valley-to-peak intensity ratio of the *N*-methyl doublet was measured from replicate scans. The acidity was adjusted to produce a ratio between 0.5 and 0.8, which can be derived as being optimum for kinetics. The pseudo-first-order rate constants, including a statistical factor of 2 (since only half the proton exchanges interchange α and β spins), were then determined from an extended table[29] of this ratio as calculated from the line-shape equation,[30] without neglecting the influence of line width. This method represents a digital equivalent of a total line-shape analysis.[31] Second-order rate constants for acid-catalyzed exchange were then calculated from the pH, measured at room temperature with a miniature combination pH electrode and a Radiometer Model 26 pH meter immediately after the NMR measurements. Above 0.5 M HCl the stoichiometric $[H^+]$ was used. Reported rate constants are averages of 2–3 values determined in solutions of slightly different acidities.

Results

Table I lists all second-order rate constants for acid-catalyzed proton exchange in *N*-methyl amides. The rate constants are independent of amide concentration, as has usually been observed[1a,g,5] and as expected from the fact that amide aggregation in aqueous solutions is negligible.[32] Therefore the reaction is first order in amide.[1g] We have also assumed first-order dependence of H^+, since it is difficult to rationalize any alternative for simple amides. This has previously been demonstrated,[1a,b,2a,e,4b,5,11d,12b,e] and although there are exceptions,[4a] these may be due to systematic error in approximate line-shape analysis.[31]

Our rate constants agree well with those determined previously for six of the amides[1a,b,2a,b,3a,4a,b,d,5,6b,7c,11d,12e] if due account is taken of the temperature difference (activation energy = 14–20 kcal/mol[2,4b,12b,13c]) and of the statistical factor of 2, which is sometimes omitted.[1b,c,5,6b] However, determination of relative rates of two amides in common solution suggests that our rate constants

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Table I. Rate Constants for Acid-Catalyzed Proton Exchange in $RCONHCH_3$ at 34 °C

R	pK_a (RCOOH)[a]	k_{H^+}, M^{-1} s^{-1}	R	pK_a (RCOOH)[a]	k_{H^+}, M^{-1} s^{-1}
Cl_2CH	1.29	2.4	CH_3CHOH	3.86	220
CH_3NHCO	1.84[b,c]	7.1[d]	C_2H_5O	4.07[g,h]	6.4×10^4
$H_3N^+CH_2$	2.31	16	C_6H_5	4.20	980
$NCCH_2$	2.43	9.7	$CH_2=CH$	4.25	667
$ClCH_2$	2.86	46	$C_6H_5CH_2$	4.31	320
cis-HOCOCH=CH	2.96[e]	54	$CH_2=C(CH_3)$	4.43	2000
o-HOC_6H_4	2.98	1410	$HOCOCH_2CH_2$	4.52[e]	1210
ICH_2	3.12	67.5	$CH_3NHCOCH_2CH_2$	4.54[b]	1390[d]
o-$HOCOC_6H_4$	3.26[e,f]	145	CH_3	4.76	1310
$HOCOCH_2$	3.35[e]	90.5	CH_3CH_2	4.88	1490
$CH_3NHCOCH_2$	3.64[b]	108[d]	$(CH_3)_3C$	5.01	960
$CH_3CONHCH_2$	3.67	112	CH_3NH	5.25[b,i]	1.13×10^7[d]
H	3.77	59	CH_3CONH	?	1040
$HOCH_2$	3.83	146	$(CH_3)_2C=NO$	?	5100
o-ClC_6H_4	3.83	504			

[a] From Jencks (Jencks, W. P. In "Handbook of Biochemistry", 2 ed.; CRC Press: Cleveland, OH, 1970) or Yukawa (Yukawa, Y., Ed. "Constants of Organic Compounds", Asakura: Tokyo, 1963), unless otherwise noted. [b] Without *N*-methyl. [c] Braibante, A.; Leporati, E.; Dallavale, F. *Inorg. Chim. Acta* **1970**, *4*, 529. [d] Per NH. [e] Monoethyl ester. [f] Walker, J. *J. Chem. Soc.* **1892**, *61*, 696. [g] Without *O*-ethyl, but corrected for statistics. [h] Edsall, J. T.; Wyman, J. "Biophysical Chemistry"; Academic Press: New York, 1958; Vol. I, p 558. [i] Johnson, S. L.; Morrison, D. L. *J. Am. Chem. Soc.* **1972**, *94*, 1323.

may have errors of ±15%, perhaps from a lack of transferability of measured pH values among solutions of different amides. Fortunately, such an error is small enough that it does not invalidate the conclusions that we draw from the rates.

Discussion

The data in Table I show clearly that electron-donating substituents in $RCONHCH_3$ accelerate acid-catalyzed proton exchange. Of course, such behavior is a necessary consequence of the acid catalysis, whereby positive charge develops in the transition state, so this qualitative result cannot provide any mechanistic information. It is necessary to be more quantitative, in order to assess the extent of charge development.

The best correlations of the data (log k_{H^+}) are with σ_p (ρ = −6.3, $|r|$ = 0.92, n = 23) and with σ^+ (ρ = −2.7, $|r|$ = 0.95, n = 13).[33a] The large (negative) value of ρ shows that the reaction is markedly sensitive to substituents, and the enormous reactivity of *N,N'*-dimethylurea indicates a considerable resonance component. This suggests that exchange proceeds via N-protonation, at least for ureas. Indeed, it has universally been accepted[6a] that ureas exchange via $RNHCONH_2^+R'$, and their high reactivity has been interpreted[6a,11a] in terms of a decrease in the equilibrium tautomeric ratio of O- to N-protonated forms.

Nevertheless, these correlations do not justify a conclusion that all amides exchange via N-protonation. The ρ values are large only in comparison with ρ values for reactions where substituent and reaction site are separated by a benzene ring. There are no other examples to calibrate the ρ value that would correspond to a full positive charge so close to the substituent. Besides, the correlations show considerable scatter (standard deviation in log k_{H^+} = 0.5 and 0.4, respectively), far greater than any experimental error. Evidently the high correlation coefficients are sustained merely by the extreme CH_3NH.

We therefore must seek a better correlation and one that permits an absolute measure of the extent of charge development. A most suitable parameter is the pK_a of the corresponding carboxylic acid, RCOOH. This is equivalent to Charton's inductive substituent parameter, σ_I,[33b] but scaled so that unit slope corresponds to development of unit charge at the site of the carboxylate oxygen. Unfortunately, attempts to correlate all the data have been unsuccessful. Inasmuch as the rates and the pK_as may be affected to different extents by resonance, steric, and inductive effects, it is necessary to select a subset of the data that isolates a single effect. The best correlation is obtained for substituted *N*-methylacetamides, where resonance effects are eliminated and steric effects are maintained nearly constant.

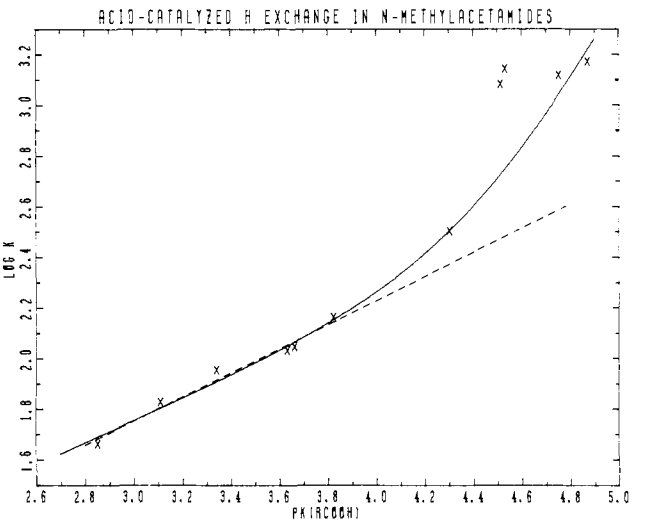

Figure 1. Correlation between log k_{H^+} for acid-catalyzed proton exchange in *N*-methylacetamides, $ZCH_2CONHCH_3$, and the pK_a of the corresponding ZCH_2COOH: dashed line, best linear fit for six amides, slope = 0.48; solid curve, $k_{H^+} = 10^{0.43pK_a+0.46} + 10^{1.84pK_a-5.88}$.

Figure 1 is a plot of log k_{H^+} for $ZCH_2CONHCH_3$ vs. the pK_a of ZCH_2COOH. It can be seen that there is an excellent linear correlation (dotted line) for the six electron-withdrawing substituents Z = Cl, I, HOCO, CH_3NHCO, CH_3CONH, and HO (slope = 0.48, $|r|$ = 0.988, standard deviation in log k_{H^+} = 0.025). Substituents Z = H_3N^+ and NC deviate negatively, but these require 0.5–1.0 M HCl for measurable exchange. Since it is known,[34] both experimentally and theoretically, that the mechanism may change in strong acid, these two amides have been omitted. The excellence of the straight-line correlation shows that this reaction is sensitive to inductive effects in a way that is well described by pK_as of carboxylic acids. The small slope, significantly less than 1, is indicative of a mechanism that does not involve a full positive charge in the transition state. Thus this result is quite consistent with the imidic acid mechanism, just as was observed for primary amides with electron-withdrawing substituents.

The five amides with substituents that are less electron withdrawing (Z = Ph, $HOCOCH_2$, $CH_3NHCOCH_2$, H, and CH_3) all show significant positive deviations from the straight line in Figure 1. The excellence of the straight-line correlation for the six previous amides suggests that the reactivity enhancement of these five is real. By comparison with primary amides, this may

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be attributed to the availability of another mechanism—the N-protonation mechanism, which is more sensitive to substituent effects. Indeed, the data can be fit to a sum of two mechanisms, one with slope 0.43 and the other with slope 1.84. The solid line in Figure 1 shows this correlation (standard deviation in log k_{H^+} = 0.03). The two succinic acid amides deviate, perhaps because the side chain is flexible, so these have been omitted.

We conclude that these kinetic results are good evidence for a change from the imidic acid mechanism to the N-protonation mechanism. Such a change may be rationalized[20] in terms of substituent effects and transition-state structures: For both mechanisms the reverse of the rate-limiting step is a thermodynamically favorable proton transfer. Then, by Hammond's postulate,[35] the transition states occur late along the reaction coordinate so that they resemble the intermediates $RC(OH)=NCH_3$ and $RCONH_2^+CH_3$, respectively. The latter transition state, which bears a full positive charge, will be more strongly destabilized by electron-withdrawing substituents. Indeed, the high slope (ca. 1.84), significantly greater than unity, is indicative of the development of a substantial positive charge. The exact value of the slope is somewhat uncertain because various acetamides do deviate (Figure 1), and it may be that the pK_a of RCOOH is a poor model for substituent effects on $RCONH_2^+CH_3$. The smaller slope (0.43) associated with the imidic acid mechanism shows that substituent effects on K_a^O and k_{-i} (eq 2) do *not* cancel completely, as had been assumed.[5,13c]

The change of mechanism is not abrupt, but gradual. None of the amides in Figure 1 exchanges solely by one mechanism. For example, from the correlation, it can be estimated that *N*-methylacetamide exchanges predominantly by N-protonation, but 30% via the imidic acid. This is remarkably close to Martin's[6b] estimate of 68%. Similarly, *N*-acetylglycine methylamide exchanges predominantly via the imidic acid, but 6% via N-protonation. This amide is most closely comparable to peptides and proteins, except that those have an additional electron-withdrawing substituent, so that the contribution of the N-protonation mechanism is even less. We therefore conclude that *the amide NH groups of the backbone of peptides and proteins undergo acid-catalyzed exchange predominantly via the imidic acid mechanism.*

What of the other amides, not included in Figure 1? As discussed above, the strong resonance stabilization by electron-donating substituents indicates that ureas exchange by N-protonation. Similarly, the enhanced reactivity of urethanes, acrylamides, and benzamides, relative to the correlation of Figure 1, suggests that these too exchange predominantly by N-protonation. The high reactivity of salicylamides, which are vinylogous urethanes, has previously been noted.[20] Amides with strongly electron-withdrawing substituents, omitted from Figure 1, exchange quite slowly, presumably by the imidic acid mechanism in dilute acid, but tending toward N-protonation in concentrated acid.[34] The mechanism for *N*-methylformamide is indeterminate, since it is unusually slow, relative to the correlation of Figure 1. However, according to general-acid catalysis and comparison of proton exchange with *E*/*Z* isomerization,[36] both mechanisms seem to be operative.

Compared to primary amides, *N*-methyl amides are more likely to exchange via the imidic acid. For example, in malonamide[20] the two mechanisms contribute nearly equally, but in *N*,*N*′-dimethylmalonamide the imidic acid mechanism predominates by ca. 15-fold. It would have seemed most likely that this effect of N-methylation would be exerted through stabilization of the imidic acid, just as alkyl groups stabilize olefins. However, the rate of acid-catalyzed exchange of *N*-methylcyanoacetamide is slightly *lower* than that of cyanoacetamide,[20] and *N*-methylacetamide, *N*-methylacrylamide, and *N*-methylmethacrylamide are ca. one-tenth as reactive as the corresponding primary amides. An intramolecular comparison—*N*-methylurea[11e]—is similar. This is not due to any complication resulting from the competition[23] between rotation and deprotonation in the N-protonated intermediate, since the NH proton of $RCONHCH_3$ is H_E, whose exchange does not require rotation. Therefore the shift of mechanism with N-methylation is due to a destabilization of $RCONH_2^+CH_3$, despite the methyl's electron-donating power. This presumably results from steric hindrance to solvation, since an analogous effect (less pronounced, though) is also seen in the pK_as (corrected for statistics) of $CH_3NH_3^+$ and $(CH_3)_2NH_2^+$.

Why do some amides exchange via N-protonation, despite our prejudice that the imidic acid mechanism is more attractive? The answer, based on estimated pK_as[7c,16,19] and the diffusion-controlled limit, seems to be that the N-protonated intermediate is not so unfavorable, whereas O-protonation does not quite acidify the NH proton sufficiently. However, electron-withdrawing substituents decrease k_p (eq 1) and increase K_a^O and k_{-i} (eq 2), while k_d and k_i are still subject to the diffusion-controlled limit. As a result, the N-protonation mechanism is retarded so that the imidic acid mechanism becomes predominant.

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Registry No. $Cl_2CHCONHCH_3$, 5345-73-3; $CH_3NHCOCONHCH_3$, 615-35-0; $H_2NCH_2CONHCH_3 \cdot H^+$, 83487-41-6; $NCCH_2CONHCH_3$, 6330-25-2; $ClCH_2CONHCH_3$, 96-30-0; *cis*-$HO_2CCH{=}CHCONHCH_3$, 6936-48-7; *o*-$HOC_6H_4CONHCH_3$, 1862-88-0; $ICH_2CONHCH_3$, 83487-42-7; *o*-$HO_2CC_6H_4CONHCH_3$, 6843-36-3; $HO_2CCH_2CONHCH_3$, 42105-98-6; $CH_3NHCOCH_2CONHCH_3$, 2090-18-8; $CH_3CONHCH_2CONHCH_3$, 7606-79-3; $HCONHCH_3$, 123-39-7; $HOCH_2CONHCH_3$, 5415-94-1; *o*-$ClC_6H_4CONHCH_3$, 3400-31-5; $CH_3CH(OH)CONHCH_3$, 51676-15-4; $C_2H_5OCONHCH_3$, 105-40-8; $C_6H_5CONHCH_3$, 613-93-4; $CH_2{=}CHCONHCH_3$, 1187-59-3; $C_6H_5CH_2CONHCH_3$, 6830-82-6; $CH_2{=}C(CH_3)CONHCH_3$, 3887-02-3; $HO_2C(CH_2)_2CONHCH_3$, 56269-39-7; $CH_3NHCO(CH_2)_2CONHCH_3$, 16873-50-0; $CH_3CONHCH_3$, 79-16-3; $CH_3CH_2CONHCH_3$, 1187-58-2; $(CH_3)_3CCONHCH_3$, 6830-83-7; $CH_3NHCONHCH_3$, 96-31-1; $CH_3CONHCONHCH_3$, 623-59-6; $(CH_3)_2C{=}NOCONHCH_3$, 10520-34-0.

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