Mechanistic Study of Acid-Catalyzed Proton Exchange in Lactams

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The kinetics of acid-catalyzed proton exchange in *N*-methylacetamide and a series of lactams (5- to 8-membered ring) were studied. Kinetic data were observed by NMR line-broadening and computer simulation methods. The significant retardation in exchange rate constants of valerolactam and 2-azacyclooctanone is attributed to the high barrier of ring inversion in the *N*-protonation mechanism of lactams. It is concluded that the imidic acid mechanism is dominant in these two lactams. However, for lactams with much lower barrier of ring inversion, the acid-catalyzed proton exchange is via the *N*-protonation mechanism as predicted by the inductive effect.

Proton exchange in amides has been of special interest due primarily to its capability to provide information to questions of biochemical significance.[1-12] The reaction is both acid- and base-catalyzed. The machanism of the acid-catalyzed reaction was proposed to involve N-protonation as shown in Eq. 1.[13]

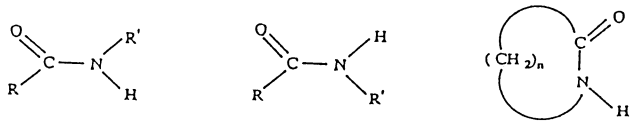
$$RCONHR' + H^+ \rightleftarrows RCONH_2R'^+ \quad (1)$$

Evidence propounded in favor of this mechanism includes the observation that electron-withdrawing substituents retard the reaction, acid-catalyzed exchange rate of H_E is faster than that of H_Z in primary amides. However, the evidence for this mechanism, is also consistent with an alternative mechanism, proposed by Martin,[14,15] proceeding by O-protonation and followed by deprotonation to the imidic acid tautomer.

$$RCONHR' + H^+ \rightleftarrows RC(OH)=NHR'^+ \rightleftarrows RC(OH)=NR' + H^+ \quad (2)$$

This mechanism, although more circuitous, is very plausible, especially in view of the well-known fact that the amide oxygen is about 10^7 fold more basic than the nitrogen.[16] Perrin and Johnston[17] have used saturation-transfer techniques to investigate the reaction mechanisms of acid-catalyzed proton exchange. By comparing intramolecular exchange to the intermolecular exchange, they concluded that both the N-protonation mechanism and the imidic acid mechanism are operative in many primary amides. Perrin and Arrhenius[3] have reported a correlation between $\log k_H$ for substituted *N*-methylacetamides and the pK_a of the corresponding RCOOH. A slope change from 0.43 for amides with electron-withdrawing substituents to about 1.84 for amides with electron-donating substituents was observed. This change has been taken as evidence for a changeover from the imidic acid mechanism to the N-protonation mechanism. For *N*-methylacetamide it is concluded that exchange occurs by the N-protonation mechanism predominantly.

Although the acid-catalyzed proton exchange in amide has been studied extensively, the exchange mechanism in lactams is still mysterious. In open-chain secondary amides, the trans conformation, I, is strongly preferred over the cis, II, as shown by dipole-moment measurements, as well as infrared, ultraviolet, and Raman spectroscopy.[18,19]



I II III

Rotation about the C–N bond is slow, the barrier to rotation being about 20 kcal mol^{-1} is ascribed to the partial double bond character of the amide C–N bond.[19] In small-ring lactams, III, with n=3—6, the amide group must adopt the cis conformation. We have been seeking to elucidate the exchange mechanism for lactams. In this report, we provide an interesting example of conformational effect on the proton exchange rate. The acid-catalyzed proton exchange in a series of lactams were examined. The perturbation of exchange mechanisms has been attributed to the ring structure of lactams.

Experimental

Chemical and Sample Preparation. *N*-Methylacetamide, 2-pyrrolidinone, valerolactam, caprolactam, and 2-azacyclooctanone were commercially available from Janssen Chemical Company and were used without further purification. Ethylene glycol, *t*-butyl alcohol, and hydrochloric acid were obtained from E. Merck Chemical Company.

Exchange sample solutions were prepared by dissolving the same amount of sample in 60% ethylene glycol aqueous solutions with different concentration of hydrochloric acid. Typical procedure of sample preparation is described in the following with 2-pyrrolidinone. To a 10 ml volumetric flask, 1 g of 2-pyrrolidinone, 6 ml of ethylene glycol and certain amount of hydrochloric acid were added. Then this solution was diluted to the mark of 10 ml with distilled water. By varying the concertrations of hydrochloric acid, sample solutions with different proton exchange rate can be prepared. The concentration range of hydrochloric acid was varied from 0.00 M to 0.30 M (1M=1 mol dm^{-3}) for these 2-pyrrolidinone solutions.

Kinetics. NMR spectra were taken on a Varian EM390 90 MHz NMR spectrometer. Samples for kinetic measurement were allowed to equilibrate for 15 min to the probe temperature of 34 °C which was measured with a neat ethylene glycol sample by the method of Becker.[20] *t*-Butyl alcohol (1%, v/v) was always included to check the field homogeneity.

For *N*-methylacetamide, on which the *N*-methyl protons exhibit coupling with the NH proton, the proton exchange rate constants were estimated by the analysis of lineshape of the *N*-methyl doublet. NMR spectra of the *N*-methyl protons were simulated with a computer program employing the Bloch equation modified for chemical exchange effects.[21] The NMR absorption-mode intensity function $I(\omega)$ is equal to the imaginary part of $iC\{l\cdot[T_2+K-i\Omega+iX]^{-1}\cdot p\}$ where T_2 is a diagonal matrix containing $1/T_2$ values for the various sites, X is a constant matrix containing the frequency variable W in rad s^{-1}, Ω is a diagonal chemical shift matrix with elements ω_{ii} in rad s^{-1} for each site, K is a rate constant matrix with off-diagonal elements k_{ij} defined as the first-order rate constants for exchange from site j to site i and diagonal elements $k_{ij}=-\sum_j K_{ij}$ The diagonal elements have been omitted from all K matrices, but are added by the computer program. l and p are unit row vectors and population column vectors, respectively, and C is a scaling constant. The computer program diagonalizes $T_2+K-i\Omega$ to D by calculating transformation matrices S and S^{-1} such that $T_2+K-i\Omega=S\cdot D\cdot S^{-1}$. Substituting the expression $T_2+K-i\Omega$ into the expression above yields Eq. 3.

$$I(\omega)=\mathrm{Im}\ iC\{l\cdot S\cdot[D+iX]^{-1}\cdot S^{-1}\cdot p\} \tag{3}$$

Input parameters are fractional site population, chemical shifts in Hz, T_2 values in the absence of exchange ($T_2=1/\pi f_{1/2}$, where $f_{1/2}$ is the linewidth at half maximum height) and first-order rate constants for site interchange. Consequently the spectra of *N*-methyl doublets were simulated as a two-site exchange system with fractional population ratio 0.5000 : 0.5000. The rate constant matrix of *N*-methyl protons has the following form (Eq. 4).

$$K=\begin{vmatrix} - & k \\ k & - \end{vmatrix} \tag{4}$$

The rate constants observed have been doubled because only half of the proton exchange can cause a detectable effect.

Kinetic data for the proton exchange in lactams were observed from NMR line-broadening measurements.[22] The second-order rate constants k_H for acid-catalyzed proton exchange were determined by plotting the width of the corresponding NH peak at half-height ($f_{1/2}$, in units of Hz) against the concentration of acid. The slope of this plot $\partial f_{1/2}/\partial[H^+]$ multiplied by π yields k_H as deined in Eq. 5.

$$k_H=\pi\times\frac{\partial f_{1/2}}{\partial[H^+]} \tag{5}$$

Results

The *N*-methyl signal of *N*-methylacetamide is a doublet with 5 Hz coupling constant under non-exchange condition. Figure 1 shows the *N*-methyl signal of experimentally observed spectra and the corresponding simulated spectra. As the $[H^+]$ increased, the valley-to-peak intensity ratio of *N*-methyl signal increases significantly. By plotting the pseudo first-order rate constants k_{obsd} estimated from computer lineshape analysis vs. $[H^+]$, the second-order rate constant of acid catalysis $k_H=362\pm46\ M^{-1}s^{-1}$ is observed.

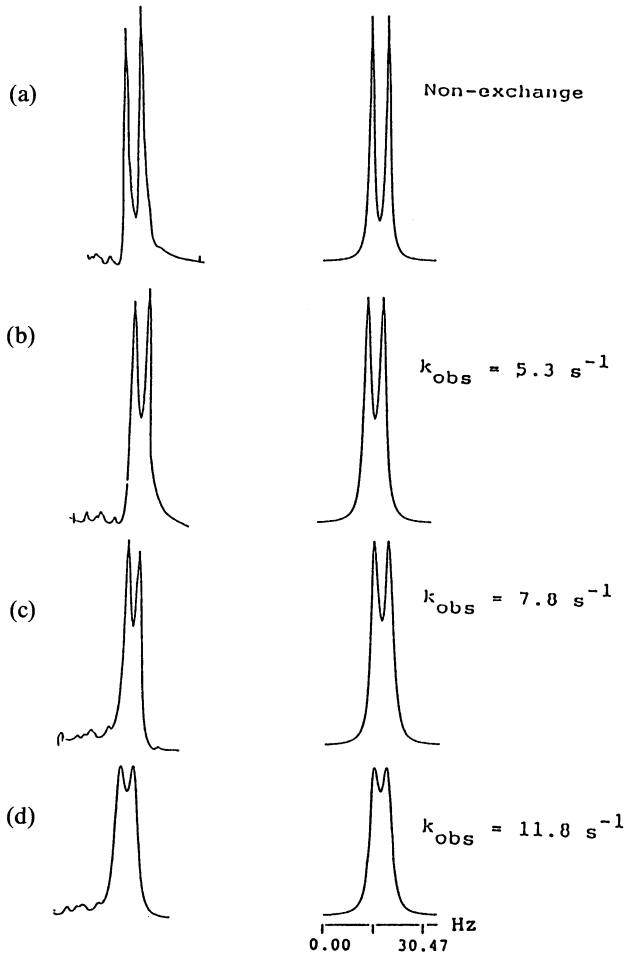


Fig. 1. Expanded spectra of *N*-methyl regions of *N*-methylacetamide.
(a) $[H^+]$=0.000 M (b) $[H^+]$=0.012 M
(c) $[H^+]$=0.021 M (d) $[H^+]$=0.030 M
Left: NMR spectra Right: Simulated spectra

Table 1. Measured NMR Linewidth at Half Height $f_{1/2}$ of 2-Pyrrolidinone N–H Proton

$[H^+]$/M	$f_{1/2}$/Hz
0.00	15.0
0.03	23.4
0.09	36.6
0.15	44.4
0.21	48.6
0.30	62.4

A typical line-broadening experiment with 2-pyrrolidinone sample solutions is shown in Fig. 2. The linewidth of NH proton is intrinsically broadened by ^{14}N quadrupolar relaxation, even under non-exchange condition. However, the broadening effect on the NH

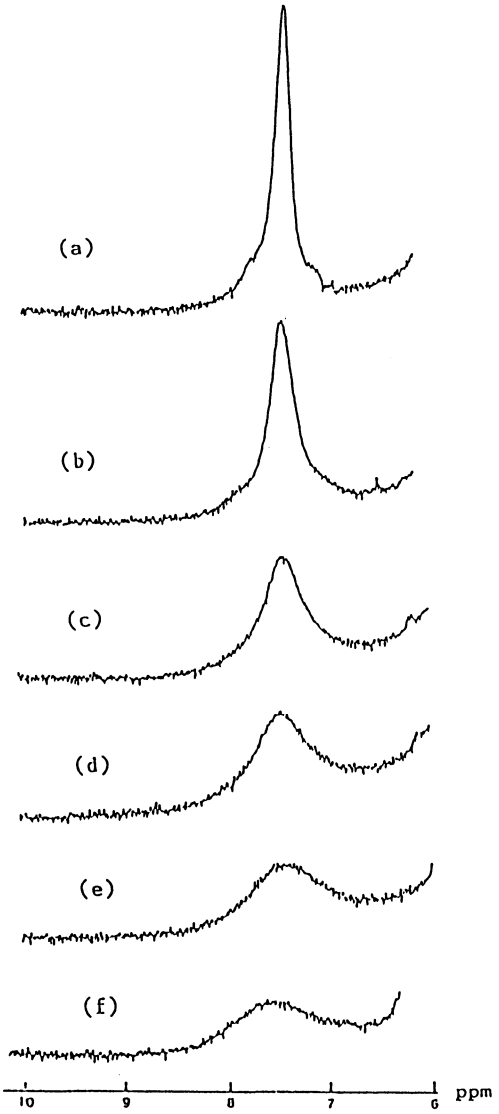


Fig. 2. NMR spectra of N–H region of 2-pyrrolidinone.
(a) $[H^+]=0.00$ M, non-exchange condition, (b) $[H^+]=0.03$ M, (c) $[H^+]=0.09$ M, (d) $[H^+]=0.15$ M, (e) $[H^+]=0.21$ M, (f) $[H^+]=0.30$ M.

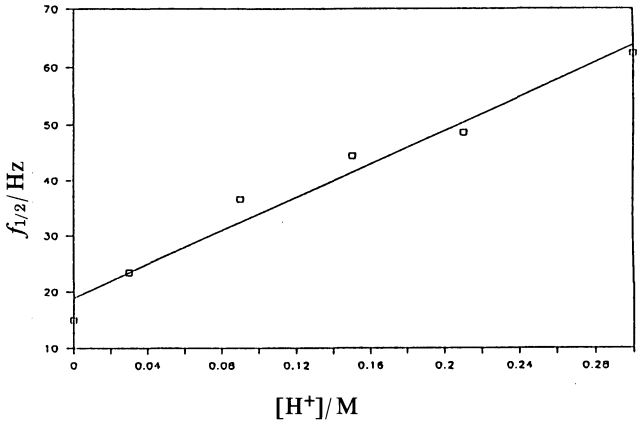


Fig. 3. Plot of $f_{1/2}$ of N–H region of 2-pyrrolidinone vs. $[H^+]$.

Table 2. Second-Order Rate Constants for Acid-Catalyzed Proton Exchange in *N*-Methylacetamide and Lactams

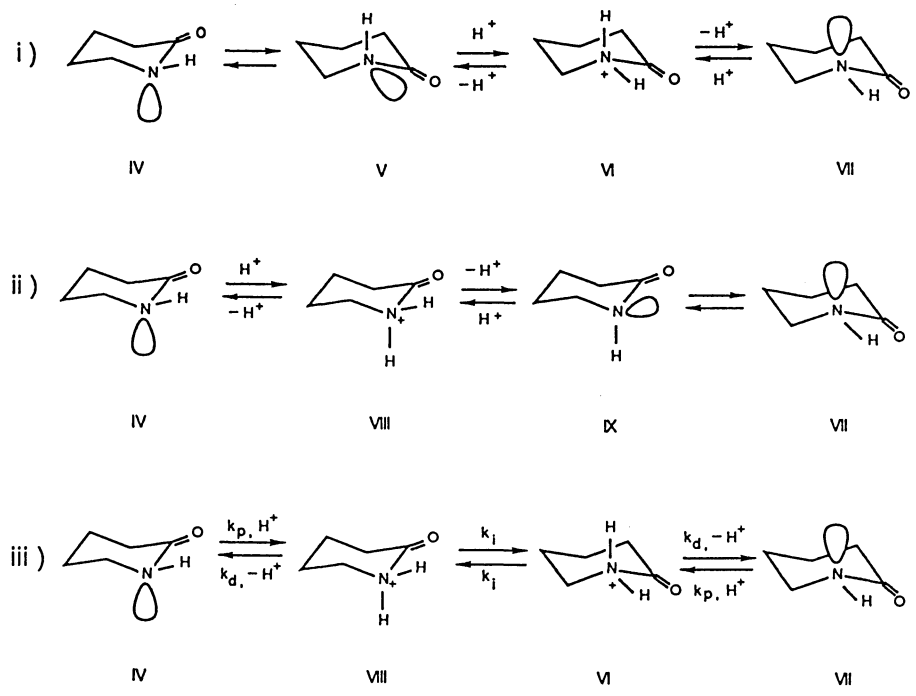
Lactam (amide)	k_H/M^{-1}s^{-1}
N-Methylacetamide	362 ±46
2-Pyrrolidinone	471 ±43
Valerolactam	39.6± 1.6
Caprolactam	392 ±27
2-Azacyclooctanone	11.0± 1.6

peak owing to the increasing rate of acid-catalyzed exchange is quite significant. Measured linewidths $f_{1/2}$ are listed in Table 1. The slope of $f_{1/2}$ vs. $[H^+]$ plot, as shown in Fig. 3, multiplied by π gives the second-order rate constant of $k_H=471\pm43$ M^{-1}s^{-1}. Table 2 lists the observed second-order rate constant for all lactams (n=3—6) and *N*-methylacetamide.

Discussion

According to the results in Table 2, k_H of valerolactam is equal to 39.6 ± 1.6 M^{-1}s^{-1}, which is about one order of magnitude slower than that of *N*-methylacetamide although the inductive effects of the substituents are comparable for these two molecules. This is not an exact comparison, since the Z proton of valerolatam is intrinsically different from the E proton of *N*-methylacetamide. However, the E proton is only 15% faster than the Z proton in acid-catalyzed exchange of acetamide via the *N*-protonation mechanism.[17] The substantial reactivity difference therefore can not be attributed to this explanation.

There are several possible N-protonation mechanisms for proton exchange as shown in Scheme 1, where each structure represents itself and its enantiomer, so that it is not necessary to distinguish nitrogen inversion from ring inversion in the lactam. i) Nitrogen inversion or ring inversion of IV gives V, which has the nitrogen lone pair electrons in the equatorial position. Then, protonation of V by a proton from the solvent gives VI. Finally, loss of the original nitrogen proton at a diffusion-controlled rate gives VII, which completes the exchange. ii) Protonation of the nitrogen lone pair electrons of IV gives VIII. Then, loss of the equatorial nitrogen proton of VIII gives IX. Finally, nitrogen inversion or ring inversion of IX gives VII. iii) Protonation of the nitrogen lone pair electrons of IV at a rate constant of k_p gives VIII, followed by the ring inversion of VIII at a rate constant k_i results in VI. Finally, loss of the axial nitrogen proton of VI at a diffusion-controlled rate constant k_d gives VII. Both mechanisms i) and ii) involve similar high energy intermediates, V or IX, with nitrogen lone pair electrons in the equatorial position. The resonance stabilization of the N–C–O π system in IV is lost in those intermediates. This resonance energy is around 20 kcal mol^{-1}, which is estimated from the rotational barrier of the C–N bond in amides. A maximum rate constant of 0.03 s^{-1} was estimated



Scheme 1. N-Protonation mechanisms for proton exchange in valerolactam.

according to the 20 kcal mol^{-1} energy barrier. Therefore, the contribution from these mechanisms is negligible. For mechanism iii), the exchange rate constant is presented by Eq. 6.

$$k_H^N = k_p \frac{k_i}{k_d} \quad (6)$$

k_p is comparable to the acid catalyzed rate constant of *N*-methylacetamide. k_d is up to 10^{12} s^{-1}, which is actually faster than a diffusion-controlled rate constant.[23] k_i is the rate constant of the ring inversion of VIII. According to the experimental data of cyclohexanone, this inversion barrier is about 5.2 kcal mol^{-1},[24] corresponding to k_i around 10^9 s^{-1}. As a result, the exchange rate via the N-protonation mechanism for valerolactam is retarded by a factor of about 1000 in comparison with that of *N*-methylactamide. In short, the activation energy of the N-protonation mechanism is raised by the necessity for ring inversion, and the imidic acid mechanism becomes dominant.

In the acid catalysis study of caprolactam, a k_H of 392±27 M^{-1} s^{-1} was observed. This value is comparable to that of *N*-methylacetamide in spite of the ring structure of caprolactam. However, the barriers of a series of chair–twist-chair pseudo rotations in cycloheptanone, which is isoelectronic to the N-protonated caprolactam, are extremely low (less than 1 kcal mol^{-1}).[25] Hence, the rate of ring inversion of the N-protonated caprolactam is comparable with the diffusion-controlled deprotonation process. The retardation effect in valerolactam will no longer exist here. Therefore, we conclude that, like in *N*-methylacetamide, the acid-catalyzed proton exchange of caprolactam is predominantly via the N-protonation mechanism. The rate constant for proton exchange via the imidic acid only should be close to 39.6 M^{-1} s^{-1} which is the value of k_H of valerolactam.

Similar argument can be applied to the 5-membered ring 2-pyrrolidinone, which has a k_H of 471±43 M^{-1} s^{-1}. The N-protonated 2-pyrrolidinone intermediate is isoelectronic to the cyclopentanone. Cyclopentane is well-known to have extremely fast ring inversion rate via the "pseudo rotation". Since the carbonyl functional group with sp^2 electronic structure on the 5-membered ring is intrinsically less crowded than the sp^3 methylene, the inversion rate of cyclopentanone should be even faster than that of cyclopentane. Therefore, the N-protonation mechanism is the dominant process for the acid-catalyzed proton exchange in 2-pyrrolidinone.

The acid-catalyzed proton exchange of 8-membered ring lactam 2-azacyclooctanone is much slower than that of 5- and 7-membered ring lactams. We conclude that the ring inversion of the N-protonated 2-azacyclooctanone must be slower than the deprotonation reaction, as a result, causing the retardation of N-protonation mechanism. The slow acid-catalyzed proton exchange (k_H=11.0±1.6 M^{-1} s^{-1}) is via the imidic acid mechanism.

As a conclusion, the extra ring inversion of the N-protonated lactam governs the exchange mechanisms. For 2-pyrrolidinone and caprolactam with low barrier of ring inversion, the acid-catalyzed proton exchange proceeds via the N-protonation mechanism. However, for valerolactam and 2-azacyclooctanone, the N-protonation mechanism is retarded significantly by the

high barrier of ring inversion, and therefore, the alternative imidic acid mechanism takes over.

References

1) C. L. Perrin, T. J. Dwyer, J. Rebek, Jr., and R. J. Duff, *J. Am. Chem. Soc.*, **112**, 3122 (1990).
2) C. L. Perrin, C. P. Lollo, and E. R. Johnston, *J. Am. Chem. Soc.*, **106**, 2749 (1984).
3) C. L. Perrin and G. M. L. Arrhenius, *J. Am. Chem. Soc.*, **104**, 6693 (1982).
4) F. Abildgaard, J. J. Led, P. Balshmidt, and F. B. Hansen, *Int. J. Pept. Protein Res.*, **34**, 340 (1989).
5) J. Zhong, J. C. Gore, and I. M. Armitage, *Magn. Reson. Med.*, **11**, 295 (1989).
6) R. Saffrich, H. R. Kalbitzer, H. Bodenmueller, P. Muhn, R. Pipkorn, and H. C. Schaller, *Biochim. Biophys. Acta*, **997**, 144 (1989).
7) G. D. Henry, J. H. Weiner, and B. D. Sykes, *Biochemistry*, **26**, 3626 (1987).
8) E. Tuchsen and C. Woodward, *Biochemistry*, **26**, 8073 (1987).
9) A. A. Rashin, *J. Mol. Biol.*, **198**, 339 (1987).
10) H. Roder, G. Wagner, and K. Wuthrich, *Biochemistry*, **24**, 7407 (1985).
11) N. R. Krishna, G. A. Heavner, and J. B. Vaughn, Jr., *J. Am. Chem. Soc.*, **105**, 6930 (1983).
12) A. D. Barksdale and A. Rosenberg, *Methods Biochem. Anal.*, **28**, 1 (1982).
13) A. Berger, A. Loewenstein, and S. Meiboom, *J. Am. Chem. Soc.*, **81**, 62 (1959).
14) R. B. Martin, *J. Chem. Soc., Chem. Commun.*, **1972**, 793.
15) R. B. Martin and W. C. Hutton, *J. Am. Chem. Soc.*, **95**, 4752 (1973).
16) A. R. Fersh, *J. Am. Chem. Soc.*, **93**, 3504 (1971).
17) C. L. Perrin and E. R Johnston, *J. Am. Chem. Soc.*, **103**, 4697 (1981).
18) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955).
19) W. E. Stewart and T. H. Siddall, *Chem. Rev.*, **70**, 517 (1970).
20) D. S. Raiford, C. L. Fisk, and E. D. Becker, *Anal. Chem.*, **51**, 2050 (1979).
21) L. W. Reeves and K. N. Shaw, *Can. J. Chem.*, **48**, 3641 (1970).
22) J. Sandstrom, "Dynamic MMR Spectroscopy," Academic Press, London (1982), p. 17.
23) Z. Luz and S. Meiboom, *J. Am. Chem. Soc.*, **86**, 4768 (1964).
24) F. R. Jensen and B. H. Beck, *J. Am. Chem. Soc.*, **90**, 1066 (1968).
25) D. F. Bocian and H. L. Strauss, *J. Chem. Phys.*, **67**, 1071 (1977).