Mechanistic Study of Acid-Catalyzed Proton Exchange in Thioamide and Thiolactams

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The kinetics of acid-catalyzed proton exchange in a series of thiolactams (5- to 7-membered ring) and *N*-methylthioacetamide were studied. Kinetic data were observed by NMR line-broadening and computer simulation methods. The second-order rate constants of all the thiolactams and *N*-methylthioacetamide are within the same order of magnitude. It is concluded that the imidic acid mechanism is dominant in thiolactams and *N*-methylthioacetamide.

Proton transfer is one of the most fundamental chemical reactions. Proton exchange in amides including ureas has been of special interest due primarily to its capability to provide information to questions of biochemical significance.[1—13] Biochemists have employed proton exchange as a probe of static and dynamic aspects of polypeptide molecular structure. The reaction is both acid- and base-catalyzed. The mechanism of the acid-catalyzed reaction was proposed to involved N-protonation as shown in Eq. 1.[14]

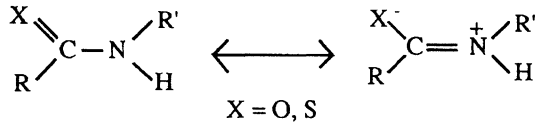
$$\mathrm{RCONHR'} + \mathrm{H^+} \rightleftharpoons \mathrm{RCONH_2R'^+} \qquad (1)$$

Evidence for 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 an alternative mechanism, proposed by Martin,[15,16] involving the imidic acid seems more reasonable, as it protonates on the amide oxygen, which is about 10^7 more basic than the nitrogen.[17]

$$\mathrm{RCONHR'} + \mathrm{H^+} \rightleftharpoons \mathrm{RC(OH){=}NHR'^+} \rightleftharpoons \mathrm{RC(OH){=}NR'} + \mathrm{H^+} \qquad (2)$$

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. They concluded that the proton exchange in *N*-methylacetamide occurs by the N-protonation mechanism predominantly.

Although the acid-catalyzed proton exchange in amides has been studied extensively, the exchange mechanism in thioamides is still mysterious. Theoretically, the proton exchange mechanism of thioamides should be similar to that of amides. However, the rotation barrier of C(S)–N bond of thioamides is much higher than that of C(O)–N bond of corresponding amides.[18—21] This is due to the 2p–3p overlap of C=S π-bonding on thioamides is much poorer than the 2p–2p overlap of C=O π-bonding on corresponding amides. Therefore, the proportion of the dipolar structure is relatively higher and the basicity of nitrogen atom is relatively weaker for thioamides.



(3)

As a result, the N-protonation mechanism will be diminished; the imidic acid mechanism is more likely to happen in thioamides.

The other interesting subject is the proton exchange mechanism of thiolactams. Wang et al.[22] have observed that the extra ring inversion during the exchange process governs the proton exchange mechanism of lactams. If the N–H proton of thiolactams exchange via the imidic acid mechanism, there should be no such ring inversion effect. In this report, the acid-catalyzed proton exchange in a series of thiolactams and *N*-methylthioacetamide are examined. The experimental observations are compared with those of lactams and *N*-methylacetamide.

Experimental

Chemical and Sample Preparation. *N*-Methylacetamide, 2-pyrrolidinone, δ-valerolactam, and ε-caprolactam were commercially available from Jansen Chemical Company. Phosphorus pentasulfide, ethylene glycol, *t*-butyl alcohol, and hydrochloric acid were obtained from E. Merck Chemical Company. Thioamide and thiolactams were synthesized from corresponding amide and lactams by literature method.[23]

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-pyrrolidinethione. To a 5 ml volumetric flask, 0.5 g of 2-pyrrolidinethione, 3 ml of ethylene glycol and certain amount of hydrochloric acid were added. Then this solution was diluted to the mark of 5 ml with distilled water. By varying the concentrations of hydrochloric acid, sample solutions with different proton exchange rate can be prepared. The concentration range of hydrochloric acid was

varied from 0.00 to 1.80 (1 M=1 mol dm^{-3}) for these 2-pyrrolidinethione 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 measure with a neat ethylene glycol sample by the method of Becker.[24] *t*-Butyl alcohol (1%, v/v) was always included to check the field homogeneity.

For *N*-methylthioacetamide on which the *N*-methyl protons exhibit coupling to the N-proton, the proton exchange rate constants were estimated by the analysis of lineshape of the *N*-methyl doublet as described in previous paper.[22]

Kinetic data for the proton exchange in thiolactams were observed from NMR line-broadening measurements.[25] The second-order rate constants k_H for acid-catalyzed proton exchange were determined by plotting the width of the corresponding N–H peak at half-height ($f_{1/2}$, in unit of Hz) against the concentration of acid. The slope of this plot multiplied by π yields k_H as defined in Eq. 4.

$$k_H = \pi \times \frac{f_{1/2}}{[H^+]}. \quad (4)$$

Results and Discussion

A typical line-broadening experiment with 2-pyrrolidinethione sample solutions is shown in Fig. 1. The linewidth of N–H proton is intrinsically broadened by ^{14}N quadrupolar relaxation, even under non-exchange conditions. However, the broadening effect on the N–H peak owing to the increasing rate of acid-catalyzed exchange is quite significant. Measured linewidth $f_{1/2}$ are listed in Table 1. The slope of $f_{1/2}$ vs. $[H^+]$ plot, as shown in Fig. 2, multiplied by π gives the second-order rate constant of $k_H = 49.2 \pm 2.9$ M^{-1} s^{-1}. Table 2 lists the observed second-order rate constant for all thiolactams.

The *N*-methyl signal of *N*-methylthioacetamide is a doublet with 3.45 Hz coupling constant under non-exchange conditions. As the $[H^+]$ increased, the valley-to-peak intensity ratio of *N*-methyl signal increases significantly. By plotting the pseudo-first-order rate constants estimated from lineshape analysis vs. $[H^+]$ the second-order rate constant of acid catalysis $k_H = 41.1 \pm 0.7$ M^{-1} s^{-1} is observed.

The proposed N-protonation mechanism for thiolactams (and lactams) is shown in Scheme 1. First, protonation of the nitrogen lone pair electrons of **I** (δ-valerolactam, for example) at a rate constant k_p gives **II**. Followed by ring inversion of **II** at a rate k_i results in **III**. Finally, loss of the axial nitrogen proton of **III** at a diffusion-controlled rate constant k_d gives **IV** and completes the exchange process. The exchange rate constant via this N-protonation mechanism is presented by Eq. 5.

$$k_H^N = k_p \frac{k_i}{k_d} \quad (5)$$

k_p is comparable to the acid catalyzed rate constant of the open-chain secondary amide *N*-methylacetamide. k_d is up to 10^{12} s^{-1}, which is faster than a diffusion-controlled rate constant.[23] k_i is the rate constant of ring inversion of **II**. We have reported that the extra ring inversion of the N-protonated lactam governs the acid-catalyzed proton exchange mechanisms of lactams.[21] For 2-pyrrolidinone and ε-caprolactam with low barrier of ring inversion (less than 1 kcal mol^{-1}), the acid-catalyzed proton exchange is via the N-protonation

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

$[H^+]$/M	$f_{1/2}$/Hz
0.00	30.0
0.30	30.6
0.60	37.8
0.90	41.1
1.50	52.8
1.80	57.0

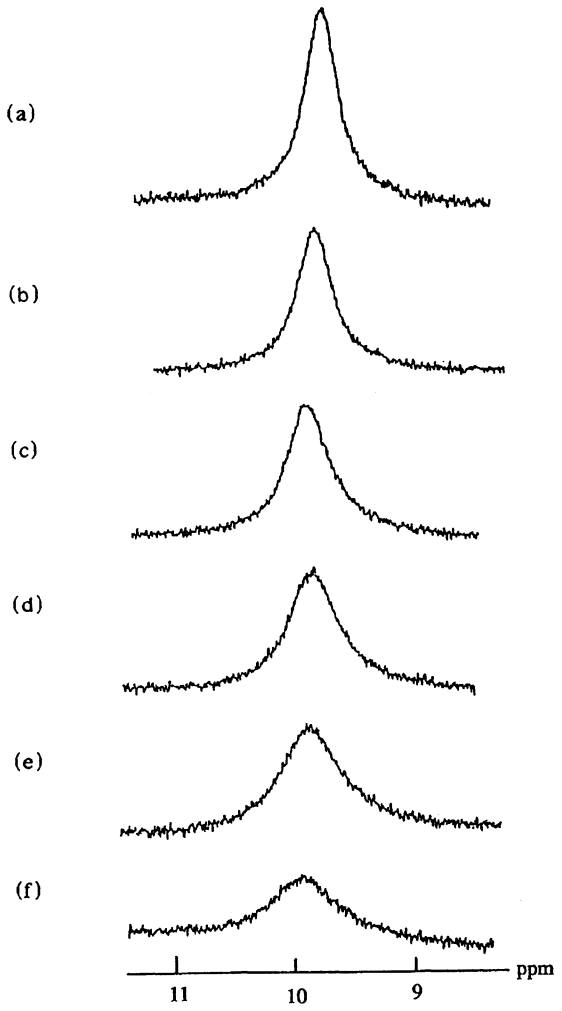
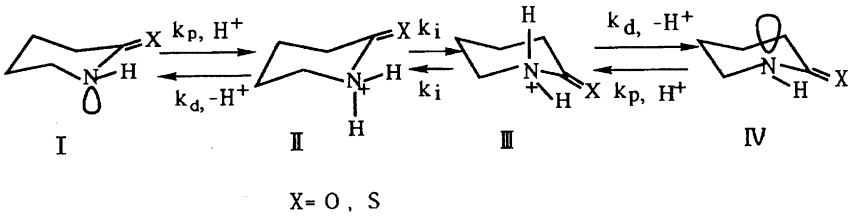


Fig. 1. NMR spectra of N–H region of 2-pyrrolidinethione. (a) $[H^+]$=0.00 M. non-exchange conditions. (b) $[H^+]$=0.30 M. (c) $[H^+]$=0.60 M. (d) $[H^+]$=0.90 M. (e) $[H^+]$=1.50 M. (f) $[H^+]$=1.80 M.

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

Thiolactams (Thioamide)	$k_H/M^{-1}\,s^{-1}$	Lactams (Amide)	$k_H/M^{-1}\,s^{-1}$ a)
N-Methylthioacetamide	41.1±0.7	*N*-Methylacetamide	362±45
2-Pyrrolidinethione	49.2±2.9	2-Pyrrolidinone	471±43
δ-Thiovalerolactam	35.4±3.9	δ-Valerolactam	39.6±1.6
ε-Thiocaprolactam	11.5±1.9	ε-Caprolactam	392±27

a) From our previous study in Ref. 22.



Scheme 1. N-Protonation mechanism for proton exchange in lactams (thiolactams).

Table 3. Chemical Shifts of N–H Proton of *N*-Methylthioacetamide, Thiolactams, and Corresponding *N*-Methylacetamide, Lactams

Thiolactams (Thioamide)	Chemical shift, δ	Lactams (Amide)	Chemical shift, δ
N-Methylthioacetamide	9.70	*N*-Methylacetamide	7.75
2-Pyrrolidinethione	9.73	2-Pyrrolidinone	7.57
δ-Thiovalerolactam	9.85	δ-Valerolactam	7.60
ε-Thiocaprolactam	9.92	ε-Caprolactam	7.55

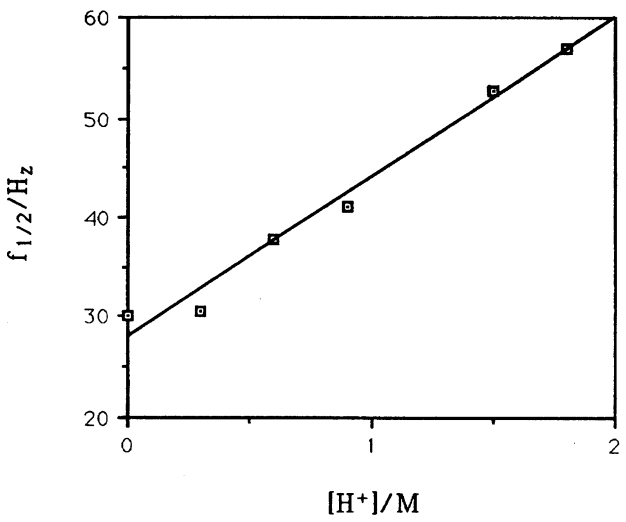
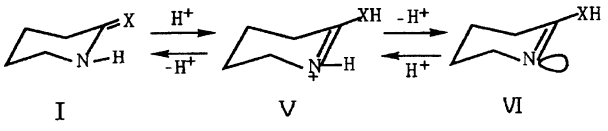


Fig. 2. Plot of $f_{1/2}$ of N–H region of 2-pyrrolidinethione vs. $[H^+]$.

mechanism.[22] For δ-valerolactam, the barrier of ring inversion is estimated around 5.2 kcal mol^{-1},[27] which gives a k_d value of 10^9 s^{-1}. Therefore, the N-protonation mechanism of δ-valerolactam is retarded by a factor of 1000 in comparison with that of *N*-methylacetamide although k_p should be comparable for these two molecules. As a result, the imidic acid mechanism as shown in Scheme 2 is dominant in proton exchange of δ-valerolactam. Evidence propounded in favor of the conclusions above includes the exchange rate constant of δ-valerolactam is of one order smaller in magnitude than those of 2-pyrrolidinone and ε-caprolactam, the rate constants of 2-pyrrolidinone and ε-caprolactam are comparable to that of the open-chain secondary amide *N*-methylacetamide (Table 2). However, the second-order rate constants of all the thiolactams and *N*-methylthioacetamide as listed in Table 2, are within the same order of magnitude. This is quite different from those observed in the corresponding lactams and *N*-methylacetamide.

Since thiolactams are isoelectronic to the corresponding lactams, both δ-thiovalerolactam and δ-valerolactam should have similar barrier of ring inversion in the N-protonation mechanism. Therefore, the exchange rate of δ-thiovalerolactam via the N-protonation mechanism is retarded by a factor of about 1000 due to the necessity of ring inversion in comparison with that of



Scheme 2. Imidic acid mechanism for proton exchange in lactams (thiolactams).

N-methylthioacetamide. According to the discussion above and the similarity in magnitude of rate constants, we conclude that the N-protonation mechanism is trivial in *N*-methylthioacetamide and δ-thiovalerolactam. Otherwise, the acid catalysis in these molecules is predominantly via the imidic acid mechanism which should have no such ring inversion effect.

As 2-pyrrolidinone and ε-caprolactam, 2-pyrrolidinethione and ε-thiocaprolactam should have very low barrier of ring inversion in the N-protonation mechanism. Therefore, k_i of these two thiolactams are much larger than that of δ-thiovalerolactam which is retarded as discussed above. Since the acid-catalyzed exchange rate constants of these thiolactams with different ring size are comparable, the exchange via the N-protonation mechanism must be negligible in comparison with that via the imidic acid mechanism.

Direct evidences for the retardation of the N-protonation mechanism in *N*-methylthioacetamide, 2-pyrrolidinethione and ε-thiocaprolactam are observed from the chemical shift of N–H protons. The ^{1}H NMR signal of N–H proton shifts from $\delta = 7.75$ in *N*-methylacetamide to $\delta = 9.70$ in *N*-methylthioacetamide (Table 3). Likewise, the chemical shifts of N–H proton of thiolactams are all downfield-shifted for more than 2 ppm in comparison with those of lactams. This deshielding effect in *N*-methylthioacetamide and thiolactams is simply due to the significant contribution of dipolar resonance form which reduces the electron density on nitrogen atoms. Therefore, the basicity of nitrogen atoms in *N*-methylthioacetamide and thiolactams are diminished. The N-protonation mechanism which depends on the basicity of nitrogen atom is retarded.

As a conclusion, the acid-catalyzed proton exchange in thioamide and thiolactams is via the imidic acid mechanism predominantly. The change over of the proton exchange mechanisms in lactams caused by the extra ring inversion is not observed in thiolactams.

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