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Kinetics of the Reaction of α-Chloro Aliphatic Acids with Aqueous Ammonia[1)]

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The kinetics of the reaction of α-chloro aliphatic acids (CAA's) with aqueous ammonia to form the corresponding α-amino acids and α-hydroxy acids have been studied by measuring the produced chloride ion. The observed rate for CAA's having COOH on a *s*-C (*s*-CAA's) is expressed as: $v=(k_1+k_2[\mathrm{NH_3}]_{\mathrm{ex}})[\mathrm{CAA}]$, while the rate for CAA having COOH on a *t*-C (*t*-CAA): $v=k_1[\mathrm{CAA}]$. These results together with previous observations indicate that the mechanism changes with substrate, *i.e.*, pure S_N2 type for chloroacetic acid to pure S_N1 type for α-chloroisobutyric acid. The exclusion of α-lactone mechanism and the effect of carboxylato group are discussed. The reactivity of ammonia toward α-chloro aliphatic acids is as twice as that of hydroxide ion.

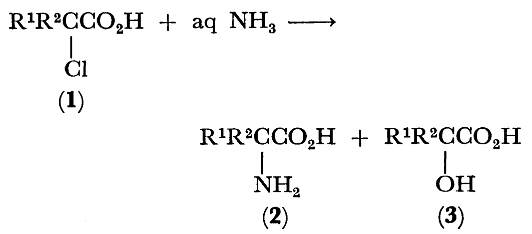
The ammonolysis of α-halo aliphatic acids is an important method for preparation of α-amino acids.[2–4)] Generally, α-chloro aliphatic acids (**1**) are treated with a large excess of aqueous ammonia to give α-amino acids (**2**) accompanied by α-hydroxy acids (**3**). (See Eq. 1.)

Cheronis and Spitzmuller[5)] have reported the effect of molar ratio, temperature, and pH on the yields for this ammonolysis, but not the kinetics and mechanism. We have reported the kinetics for the ammonolysis of chloroacetic acid, where the rate law was: $v=k[\mathrm{NH_3}][\mathrm{ClCH_2CO_2H}]$, suggesting S_N2 mechanism.[6)] But this nucleophilic mechanism may vary with the change of branching at α-position from primary to tertiary.

The present study was undertaken to obtain some information on the kinetics of the reaction of α-chloro aliphatic acids having COOH on *s*-C and *t*-C (abbreviated as *s*-CAA and *t*-CAA, respectively) with aqueous ammonia, and the change of mechanism with structure. The role of carboxylate ion is discussed.

Results and Discussion

Ammonolysis was conducted at 60 °C in aqueous ammonia, and the produced chloride ion was measured to follow the rate of reaction. The reaction gave α-amino acids (**2**) along with α-hydroxy acids (**3**). The products ratios are shown in Table 1.



$$\underset{\textbf{(1)}}{\mathrm{R^1R^2\underset{\displaystyle |\atop \displaystyle Cl}{C}CO_2H}} + \text{aq } \mathrm{NH_3} \longrightarrow \underset{\textbf{(2)}}{\mathrm{R^1R^2\underset{\displaystyle |\atop \displaystyle NH_2}{C}CO_2H}} + \underset{\textbf{(3)}}{\mathrm{R^1R^2\underset{\displaystyle |\atop \displaystyle OH}{C}CO_2H}} \qquad (1)$$

General Kinetics of the Ammonolysis. α-Chloro aliphatic acids were treated with over tenfold excess of ammonia. The rate of ammonolysis was first-order in the acid. For the determination of the order with respect to ammonia, the rate constant was measured at constant concentration of α-chloro aliphatic acid and various concentrations of ammonia. The observed rate constants are in Table 2. The plot of the observed rate constants against the initial concentrations of ammonia gave a straight line with an intercept at $[\mathrm{NH_3}]_{\mathrm{ex}}=0$. Therefore, the rate equation consists of first- and second-order terms, where $[\ \ ]_{\mathrm{ex}}$ means excess concentration to that of CAA.

Table 1. Product ratio for ammonolysis of α-chloro aliphatic acids (**1**) (See Eq. 1)

	R^1	R^2	$[\mathrm{CAA}]_0=0.1$ M	$[\mathrm{NH_3}]_{\mathrm{ex}}=5.1$ M
1a	H	Me	**2a** : **3a**	= 83 : 17
1b	H	Et	**2b** : **3b**	= 73 : 27
1c	H	*i*-Pr	**2c** : **3c**	= 39 : 61
1d	Me	Me	**2d** : **3d**	= 14 : 86

$$\frac{d}{dt}[\mathrm{Cl^-}] = (k_1+k_2[\mathrm{NH_3}]_{\mathrm{ex}})[\mathrm{CAA}] \qquad (2)$$

Here, k_1 was evaluated from the intercept of the plot and k_2 from the slope. The results are shown in Table 3. The α-amino acids and α-hydroxy acids produced in the reaction show that the ammonolysis and hydrolysis occur competitively.

s-*CAA's.* The rate equation for *s*-CAA's (**1a**, **1b**, and **1c**) can be expressed as Eq. 2. (Table 3.) The second-order rate constants decrease in the order; R^2: Me>Et≫*i*-Pr.

The order is due to inductive effect as well as steric effect. Especially, the steric effect is important for the reaction of 2-chloro-3-methylbutyric acid (**1c**). The transition state, crowded with leaving chloride ion, attacking ammonia, and carboxylato and isopropyl groups, reduced the second-order rate constants (k_2).

The accompanying hydrolysis was confirmed by the isolation of α-hydroxy acids. The rate of hydrolysis for α-chloropropionic acid (**1a**) was measured. The rate equation was expressed as

$$v = (0.35+0.76[\mathrm{OH}\ ])[\mathrm{CH_3CH(Cl)CO_2H}]\times 10^{-5} \quad \text{at } 60\ ^\circ\mathrm{C}. \qquad (3)$$

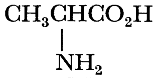
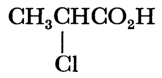
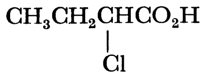
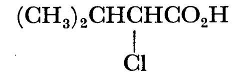
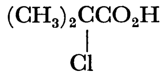
Therefore, ammonolysis of secondary α-chloro aliphatic acids is a "border line case" between S_N2 and S_N1.

t-*CAA.* In contrast to *s*-CAA's, *t*-CAA, α-chloroisobutyric acid (**1d**), has a rate independent of the concentration of nucleophiles.

$$\frac{d}{dt}[\mathrm{Cl^-}] = k_1[\mathrm{(CH_3)_2C(Cl)CO_2H}] \qquad (4)$$

The first-order rate constant is greater than that for analogous secondary substrates. α-Amino acid (**2a**) is the main product of the reaction of α-chloro-

TABLE 2. RATE CONSTANTS FOR THE REACTION OF α-CHLORO ALIPHATIC ACIDS (CAA) WITH AMINO COMPOUNDS IN AN AQUEOUS SOLUTION AT 60±0.1 °C

$[CAA]_0$ M	$[NH_3]_{ex}$[a] M	NaOH M	 $CH_3\underset{NH_2}{\underset{\vert}{C}}HCO_2H$ M	$(CH_3CHCO_2H)_2NH$ M	$k_{obsd}\times 10^5$ s^{-1}
 $CH_3\underset{Cl}{\underset{\vert}{C}}HCO_2H$ 0.10	1.2				1.7
	1.88				2.6
	2.9				3.1
	3.5				4.1
		0.12			0.35
		0.49			0.56
		0.78			0.86
		0.60	0.25		0.68
		1.1	0.50		1.6
		1.6	0.74		2.6
		2.1	1.0		3.3
		0.40		0.10	0.45
		0.55		0.15	0.62
		0.70		0.20	0.71
		1.3		0.40	1.0
		1.6		0.50	1.1
 $CH_3CH_2\underset{Cl}{\underset{\vert}{C}}HCO_2H$ 0.071	1.2				0.86
	1.8				1.4
	2.9				1.5
	4.5				2.3
		0.070			0.38
 $(CH_3)_2CH\underset{Cl}{\underset{\vert}{C}}HCO_2H$ 0.080	1.2				0.42
	2.5				0.44
	3.8				0.50
	5.1				0.52
		0.080			0.36
 $(CH_3)_2\underset{Cl}{\underset{\vert}{C}}CO_2H$ 0.087	1.2				96
	2.5				95
	3.8				96
	5.1				94
		0.090			90

a) Excess ammonia $[NH_3]_{ex}$ means the difference in the concentrations between added ammonia and $[CAA]_0$.

TABLE 3. RATE CONSTANTS FOR THE REACTION OF α-CHLORO ALIPHATIC ACIDS WITH AQUEOUS AMMONIA AT 60±0.1 °C (See Eq. 2)

Substrate	$k_1\times 10^5$ (s^{-1})	$k_2\times 10^5$ $(M^{-1}\,s^{-1})$	$k'_1\times 10^5$ (s^{-1})[a]
1a	0.68	0.94	0.35
1b	0.48	0.40	0.38
1c	0.38	0.027	0.36
1d	95	—	90

a) k'_1: hydrolysis rate constants for α-chloro carboxylates.

propionic acid (**1a**) with aqueous ammonia, while α-hydroxy acid (**3d**) is the main product from α-chloroisobutyric acid (**1d**) with only a little α-aminoisobutyric acid (**2d**) (Table 1).

The activation parameters were calculated from k_1's at 60 and 30 °C. The energy of activation is 27.9 kcal mol^{-1} and the entropy of activation +9.3 e.u. This consistent with S_N1 mechanism, while the entropy of activation for ammonolysis of chloroacetic acid, where S_N2 mechanism operates, is −16 e.u.[6]

Grunwald and *et al.*[7] suggested α-lactone mechansim for the hydrolysis of α-bromopropionic acid on the basis of the first-order rate equation, the retention of configuration, common ion effect, and a small solvent effect. Hence, solvent effect was studied with our α-chloroisobutyric acid to examine the intermediacy of α-lactone. The results expressed as Grunwald-Winstein equation,[8] $\log(k/k_0)=mY$, are shown in Table 4.

The observed m value for the ammonolysis of α-

TABLE 4. SOLVENT EFFECT ON THE REACTION OF α-CHLOROISOBUTYRIC ACID WITH AMMONIA IN AQUEOUS METHANOL AT 30±0.1°C ($[NH_3]_{ex}=2.5$ M)

Solvent	Y value[8]	$k_1\times 10^5$ (s^{-1})
H_2O	3.493	1.4
40 vol % MeOH	2.391	0.64
80 vol % MeOH	0.381	0.19

chloroisobutyric acid ($m=0.27$) is three times larger than that for the hydrolysis of α-bromopropionic acid ($m=0.095$); *i.e.*, the former reaction is more susceptible to solvent effect than the latter.[7)]

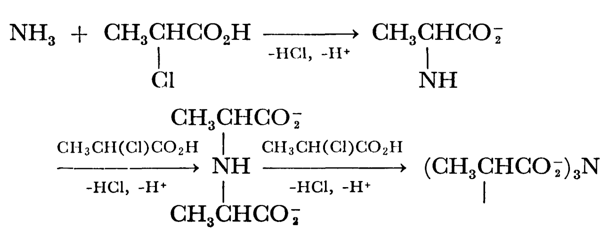
Gripenberg *et al.*[9)] proposed that a methyl group increased the unimolecular rate by a factor of 10^4 and a carboxylato group by a factor of about 10^3. Based on these values, we can expect a decrease of the unimolecular rate by a factor of 10 by substitution of carboxylato group for methyl group. Contrary to this expectation, the unimolecular rate constant for the methanolysis of α-bromopropionic acid ($5.12\times10^{-5}\,s^{-1}$ at 64.5 °C)[7)] was found to be much larger than that of isopropyl bromide ($5.0\times10^{-8}\,s^{-1}$ at 64.5 °C).[7)] This would be ascribed to the neighboring group participation of carboxylate ion in spite of the inductive rate-retarding effect of carboxylate ion. [The comparison of rate constants alone may not be appropriate to judge the participation].

On the other hand, the observed first-order rate constant for the ammonolysis of α-chloroisobutyric acid ($1.4\times10^{-5}\,s^{-1}$ at 30 °C) was much lower than the reported value for the hydrolysis of *t*-butyl chloride ($3.3\times10^{-2}\,s^{-1}$ at 25 °C).[8)] Thus, no acceleration by neighboring carboxylate ion was observed; hence the α-lactone mechanism is excluded for the present reaction. Namely, the ammonolysis of α-chloroisobutyric acid proceeds by S_N1 mechanism, *i.e.*, rate-determing dissociation of Cl^- forming zwitter ion $Me_2\overset{+}{C}COO^-$, where carboxylate ion acts as a weaker electron-releasing group than methyl group. The change of mechanism to S_N1 in isobutyric acid may be ascribed to the high stabilization of carbonium ion by the presence of two Me and a solvated COO^-.

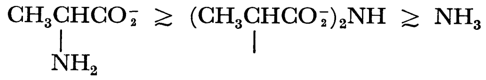
Subsequent Reaction of α-Chloropropionic Acid with Ammonia. Ammonolysis of α-chloropropionic acid is a consecutive reaction. The kinetics for the reaction of α-chloropropionic acid with α-aminopropionate or α,α′-iminodipropionate ion were studied. The rate constants are listed in Table 5.

TABLE 5. RATE CONSTANTS FOR THE REACTION OF α-CHLOROPROPIONIC ACID WITH α-AMINOPROPIONATE AND α,α′-IMINODIPROPIONATE IONS IN AQUEOUS SOLUTION AT 60±0.1 °C
$v=(k_1+k_2[\text{Amino compound}])$ [**1a**]

Amino compound	$k_1\times10^5$ (s^{-1})	$k_2\times10^5$ ($M^{-1}s^{-1}$)
NH_3	0.68	0.94
$CH_3CHCO_2^-$ $\vert$ NH_2	0.12	3.1
$(CH_3CHCO_2^-)_2NH$ $\vert$	0.33	1.7



α-Aminopropionate ion having an α-carboxylatoethyl group ($CH_3\underset{|}{C}HCO_2^-$) is about three times as reactive as ammonia in k_2, while α,α′-iminodipropionate ion is no more so stronger nucleophile than ammonia in spite of the presence of two α-carboxylatoethyl groups:

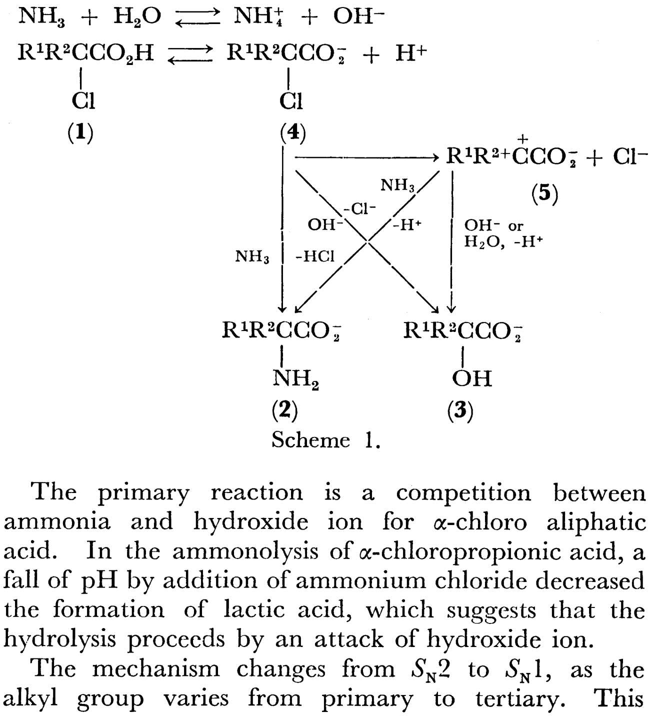


$$\underset{\substack{|\\NH_2}}{CH_3CHCO_2^-} \gtrsim (CH_3\underset{|}{C}HCO_2^-)_2NH \gtrsim NH_3$$

We reported that the reactivity toward chloroacetic acid was in the order: $NH_2CH_2CO_2^- \simeq NH(CH_2CO_2^-)_2 > NH_3$ in which the steric effect caused a slight decrease in the rate for iminodiacetate ion, compared with the rate for aminoacetate ion.[6)] Similarly, a small reactivity of α,α′-iminodipropionate ion is due to the steric effect, because α-carboxylatoethyl group is much bulkier than carboxylatomethyl group.

In aqueous solution, the hydrolysis of α-chloropropionic acid is not negligible. (Eq. 3.) The rate constant for the hydrolysis of chloroacetic acid in an aqueous solution at 60 °C ($7.67\times10^{-5}\,s^{-1}M^{-1}$) was reported to be *ca.*1/2 of that for the ammonolysis ($15.0\times10^{-5}\,s^{-1}M^{-1}$).[10)] We obtained the rate constants for hydrolysis ($0.76\times10^{-5}\,s^{-1}M^{-1}$) and for ammonolysis ($0.94\times10^{-5}\,s^{-1}M^{-1}$) of α-chloropropionic acid in an aqueous solution at 60 °C. Hence, the nucleophilicity of ammonia toward alkyl chloride is *ca.* 1.6 fold higher than that of hydroxide ion. But the relative nucleophilicity of OH^- and NH_3 may depend on the structure of RX and the solvent. Though the Swain-Scott nucleophilicity parameter for ammonia is unavailable, aniline ($n=4.49$) is twice as reactive as hydroxide ion ($n=4.20$).[11)] Ammonia seems to have the same reactivity as aniline.

Mechanism. The above observations suggest a following scheme for the reaction in an aqueous solution.



Scheme 1.

The primary reaction is a competition between ammonia and hydroxide ion for α-chloro aliphatic acid. In the ammonolysis of α-chloropropionic acid, a fall of pH by addition of ammonium chloride decreased the formation of lactic acid, which suggests that the hydrolysis proceeds by an attack of hydroxide ion.

The mechanism changes from S_N2 to S_N1, as the alkyl group varies from primary to tertiary. This result agrees with the earlier observation in the sol-

TABLE 6. CHANGE OF MECHAMISM WITH STRUCTURE

R^1	R^2	Mechanism
H	H	S_N2
H	Me	$S_N2 + S_N1$
H	Et	$S_N2 + S_N1$
H	*i*-Pr	$S_N2 + S_N1$
Me	Me	S_N1

volysis of alkyl halides.[12] The hydrolysis occurs competitively, and thus the yields of α-amino acids were lowered. The yields of α-amino acids decreased in the order: **2a**>**2b**>**2c**>**2d**. The results also support this mechanism. The hydrolysis can be suppressed on addition of ammonium chloride as was observed. In these reactions, the carboxylato group acts as a weaker electron-releasing group, but exerts no anchimeric assistance.

Experimental

Melting points were measured by a Yanagimoto micromelting point apparatus and were corrected. Boiling points were uncorrected. IR spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer, and NMR spectra on a Hitachi R-24B spectrometer.

Materials. Aqueous ammonia, nitric acid, hydrochloric acid, sodium hydroxide, ammonium chloride, α-aminoisobutyric acid, and alanine used were of guaranteed reagent grade. α-Chloropropionic acid was redistilled under vacuum before use: bp 92—93 °C/15 Torr (lit,[13] 82.5—83.5 °C/12 Torr; NMR (CCl_4) δ 1.70 (d, 3H, CH_3), 4.35 (q, 1H, CH).

Preparation of the Other α-Chloro Aliphatic Acids. 2-Chloro-3-methylbutyric, α-chlorobutyric, and α-chloroisobutyric acids were prepared by α-chlorination[14] of the corresponding acids. The corresponding aliphatic acid was reacted with a gaseous mixture of Cl_2–O_2 gas in a molar ratio of 1/2 in the presence of chlorosulfuric acid and chloranil at 120 °C for 6 h. The product was then extracted with ether, the organic layer being distilled to obtain α-chloro aliphatic acid. α-Chlorobutyric acid: bp 101—111 °C/27 Torr (lit,[15] 98 °C/10.5 Torr); NMR(CCl_4) δ 4.2 (t, 1H, CH), 2.5—2.0 (m, 2H, CH_2), 1.1 (t, 3H, CH_3); IR (neat) 1730 cm^{-1} (C=O), 625 (C–Cl). α-Chloroisobutyric acid: bp 97—99 °C/27 Torr; mp 29—30 °C (lit,[16] mp 28—30 °C); NMR (CCl_4) δ 1.75 (s); IR (neat) 1720 cm^{-1} (C=O), 615 (C–Cl). α-Chloroisovaleric acid: bp 108—109 °C/15 Torr (lit,[17] 125—126 °C/32 Torr); NMR (CCl_4) δ 4.05 (d, 1H, CH), 2.5—1.8 (m, 1H, CH), 1.10 (d, 6H, CH_3); IR (neat) 1720 cm^{-1} (C=O), 620 (C–Cl).

Preparation of α-Amino Acid. A mixture of α-chloro aliphatic acids (0.01 mol) and aqueous ammonia (5.2 M, 50 ml) was heated, in the case of α-chloropropionic and α-chlorobutyric acids. A mixture of 2-chloro-3-methylbutyric acid and aqueous ammonia 50 ml (28%) was reacted at room temperature for 3 weeks. The solution was evaporated under vacuum, and α-amino acids were recrystallized from aqueous methanol. The yields of isolated products were based on α-chloro aliphatic acids. Alanine: Yield 55%; NMR (D_2O/DSS) δ 4.2—3.8 (q, 1H, CH), 1.75 (d, 3H, CH); IR (KBr) 3200—3000 cm^{-1}, 2250 (NH_2), 1600 (CO_2^-). α-Aminobutyric acid: Yield 39%; NMR (D_2O/DSS) δ 4.15 (t, 1H, CH), 2.4—2.2 (m, 2H, CH_2), 1.5 (t, 3H, CH_3); IR(KBr) 3200—3000 cm^{-1} (NH_2), 1600 (CO_2^-). Valine: Yield 17%; NMR (D_2O/DSS) δ 3.55 (d, 1H, CH), 2.2—1.9 (m, 1H, CH), 1.0 (dd, 6H, CH_3); IR (KBr) 3200—3000 cm^{-1} (NH_2), 1600 (CO_2^-).

Preparation of α-Hydroxy Aliphatic Acid. An aqueous solution of α-chloro aliphatic acid (0.01 mol) and the equivalent amount of NaOH was refluxed for 24 h. The solution was acidified with HCl and extracted with ether (20 ml). The solution was evaporated to obtain α-hydroxy aliphatic acid. In the case of α-chloropropionic and α-chloroisobutyric acids, the solution was dried without acidification and α-hydroxy aliphatic acid sodium salts were obtained. Sodium lactate: NMR (D_2O/DSS) δ 4.2 (q, 1H, CH), 1.5 (d, 3H, CH_3). α-Hydroxybutyric acid: NMR (CCl_4) δ 7.10 (s, 1H, OH), 4.15 (t, 1H, CH), 2.2—1.9 (m, 2H, CH_2), 1.0 (t, 3H, CH_3); IR (KBr) 3450 cm^{-1} (OH), 1720 (C=O). 2-Hydroxy-3-methylbutyric acid: NMR (CCl_4) δ 7.15 (s, 1H, OH), 4.1 (d, 1H, CH), 2.2—2.0 (m, 1H, CH), 0.9 (dd, 6H, CH_3); IR (KBr) 3420 cm^{-1} (OH), 1720 (C=O). Sodium α-hydroxyisobutyrate: NMR (D_2O/DSS) δ 1.80 (s, CH_3); IR (KBr) 3440 cm^{-1} (OH), 1610 (CO_2^-).

The products were identified similarly by means of NMR in comparison with the authentic samples. The ratio of products of ammonolysis of α-chloropropionic and α-chloroisobutyric acids was estimated by NMR spectra of the reaction mixture after evaporation of the solvent. In the case of α-chlorobutyric and 2-chloro-3-methylbutyric acids, the reaction mixture of α-chloro aliphatic acids and aqueous ammonia was acidified with aqueous HCl and extracted with ether. After evaporation of the solvent the molar ratio of α-amino acids to DMSO was estimated by NMR spectra of the residue of the aqueous layer. Similarly, the ratio's of α-hydroxy aliphatic acids to DMSO were estimated by that of the ether extract. Then, the ratio of products of ammonolysis of α-chlorobutyric and 2-chloro-3-methylbutyric acids was obtained in this way.

Preparation of α,α′-Iminodipropionic Acid. Alanine (25 g, 0.3 mol), 100 ml of aqueous NaOH (24 g, 0.6 mol), and 50 ml of aqueous α-chloropropionic acid (32 g, 0.3 mol) were mixed in a flask equipped with a reflux condenser at room temperature. The solution was refluxed for 24 h. Then, the aqueous solution was acidified with HCl and was washed with ether (50 ml×3) to extract lactic acid. After evaporation of aqueous layer in vacuum to dryness, α,α′-iminodipropionic acid was extracted with ethanol (1.5 l), the ethanol solution being condensed in vacuum and cooled. α,α′-Iminodipropionic acid was slowly crystallized, filtered, washed with cold ethanol, and recrystallized from water-ethanol-ether (1 : 2 : 1). 5.0 g of colorless crystals of α,α′-iminodipropionic acid was obtained: mp 236—238 °C (lit,[18] 238 °C); NMR (D_2O/DSS) δ 3.90 (q, d, 2H, CH), 1.55 (d,d, 6H, CH_3); IR (KBr) 3400 cm^{-1} (NH), 1720 (C=O), 1600 (CO_2^-). Found: C, 43.07; H, 6.45; N, 8.35%. Calcd for $C_6H_{11}NO_4$: C, 44.72; H, 6.88; N, 8.69%.

Kinetics. A solution of α-chloro aliphatic acid (5 ml) was added to an aqueous solution of amino compound (45 ml) in a glass-stoppered flask, which had reached thermal equilibrium in a thermostat. Aliquots (5 ml) were pipetted out at regular intervals of time and cold dilute nitric acid was added to stop the reaction. The chloride ion concentration was determined by the Volhard method.[19]

The rate constants for the reaction of α,α′-iminodipropionate ion and α-chloropropionic acid was rather inaccurate (±10%) because of the lower initial concentration of α,α′-iminodipropionate ion and a small amount of impurity (NaCl), which could not completely be eliminated, but the content of NaCl was determined and subtracted. The initial first-order rate constants (up to 20% conversion) were calculated by the least square method (r>0.98). The

% conversion of the reaction of NH_3 or OH^- was 30—50%. Probable error in rate constants was ±5%.

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