the residue was recrystallized from 5 ml of 95% ethanol resulting in 0.28 g of III, mp 107–108°. An analytical sample, mp 108–109°, followed by solidification and remelting at 112–113°, was prepared by recrystallization from alcohol: infrared absorption (Nujol mull) at 5.57, 5.75, 7.40 (shoulder), 7.65, 7.88, 8.03, 8.13, 8.33, 8.43, 8.70, 9.15, 9.30, 9.85, 10.20, 10.33, 10.85, 11.95, 13.20 μ; nmr spectrum ($CDCl_3$), a doublet at τ 5.18, a triplet at 8.62, a quartet at 5.70, and complex multiplets at 6.7 and 7.3 with peak area ratios of 1:6:4:1:6.

Anal. Calcd for $C_{14}H_{12}O_8$: C, 53.50; H, 5.77; mol wt, 314. Found: C, 53.24; H, 5.76; sapon equiv × 4, 316.

Reaction Intermediate.—To a solution of 2 g of I in 20 ml of 95% ethanol was added 20 ml of 1 *M* hydrochloric acid. After 2 min, the solution was added to 1750 ml of water and extracted three times with chloroform. The aqueous phase was neutralized with 40 ml of 1 *M* dipotassium phosphate and extracted three times with chloroform. The chloroform extract of the neutralized solution was dried over sodium sulfate and concentrated to 31 ml under reduced pressure. A 3-ml aliquot was evaporated to dryness under reduced pressure, dissolved in 2 ml of $CDCl_3$, evaporated, and dried for 10 min under oil pump vacuum. The residue (0.15 g) was immediately dissolved in $CDCl_3$ for determination of the nmr spectrum (Figure 1b). Absence of the τ 2.78 and 4.65 furanoid proton bands indicates that I is not present in this material. The infrared spectrum of the chloroform extract shows intense absorption at 5.62, 5.80, and 5.98 μ. Purification of the extracted material by crystallization or by thin layer chromatography was not successful. The remainder of the chloroform solution was evaporated, dissolved in 10 ml of dioxane, and treated with 15 ml of 0.8 *M* hydrogen chloride in deuterium oxide. After 15 min the solution was concentrated until an oil separated. After recrystallization from a mixture of chloroform and carbon tetrachloride, 0.35 g of product, mp 93–94°, was obtained. The nmr spectrum was identical with that of II.

Hydrolytic Dimerization of I in Deuterium Oxide.—To a solution of 1.7 g of I in 17 ml of dioxane was added 25 ml of 0.8 *M* deuterium chloride in deuterium oxide. After 15 min at room temperature, the solution was cooled at −10° for 1 hr. The yield of recrystallized product, mp 91–92°, was 0.7 g. The nmr spectrum was determined in $CDCl_3$ (Figure 1c). The peaks at τ 2.51 (triplet), 3.65 (doublet), and 6.55 (singlet) have relative areas of 1:0.33:1.

Ultraviolet Absorption Studies.—A solution of 0.624 g (4.03 mmol) of I in 10 ml of 95% ethanol was prepared. A 1-ml aliquot was added to 1 ml of 1 *M* hydrochloric acid in a 25-ml volumetric flask. After the desired reaction period, the solution was diluted to 25 ml with 1 *M* dipotassium phosphate. After diluting 1:100 with water, the ultraviolet absorption spectrum was determined. The half-life of I under these conditions is 0.5 min. The formation of a reaction intermediate is indicated by the appearance of a peak at 208 mμ. After a 15-min reaction period, only end absorption characteristic of II remains.

Hydrolysis Studies.—Hydrolysis of the amine group during the hydrolytic dimerization of I was determined by liberation of ammonia using the Van Slyke aeration procedure.[10] To a solution of 30 mg of I in 0.5 ml of 95% ethanol was added 0.5 ml of 1 *M* hydrochloric acid. Separate runs were made and in each run 5 ml of 1 *M* sodium hydroxide was added after the desired reaction period. Nitrogen was passed through the solution at 0.5 ft^3/hr for 90 min. The ammonia was absorbed in 10 ml of a 2% boric acid solution containing bromcresol green indicator and was titrated with 0.02 *N* sulfuric acid. The yields of ammonia after 0.5-, 1-, 2-, 5-, and 15-min reaction periods are 32, 40, 44, 57, and 77%.

Registry No.—I, 15856-35-6; II, 15814-68-3; IIa, 15814-69-4; III, 15856-36-7.

Acknowledgments.—The authors are grateful to Mr. Benjamin Stevenson for the preparation of compound I, to Mr. Grant Gustin and Mr. Marvin Tefft for the microanalyses, and to Mrs. Patricia Curtis for the nmr spectra.

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Kinetics of the Reaction of Chloroacetic Acid with Ammonia in an Aqueous Solution[1]

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The kinetics of the consecutive reactions between chloroacetic acid and ammonia in aqueous solutions to form glycine and iminodiacetic and nitrilotriacetic acids have been studied by following the produced chloride ion. The observed second-order rate law, $v = k$[chloroacetic acid][amino compound], together with the relation between the rate constant and the pH of the solution confirms the ordinary S_N2 mechanism involving an attack of free ammonia or amino group on the chloroacetate ion. The reactivities of amino compounds are discussed in terms of their rate constants, activation parameters, and basicities of amino groups.

Treatment of chloroacetic acid with ammonia gave glycine, iminodiacetic acid, and nitrilotriacetic acid.

$$NH_3 + ClCH_2COOH \xrightarrow{-HCl} H_2NCH_2COOH \xrightarrow[-HCl]{ClCH_2COOH}$$

$$HN(CH_2COOH)_2 \xrightarrow[-HCl]{ClCH_2COOH} N(CH_2COOH)_3$$

A large excess (*ca.* 60-fold) of ammonia was found to be favorable for the preparation of glycine.[2-4] Cheronis and Spitzmuller have studied qualitatively the effect of pH of the solution on the yield of glycine; they suggested that the formation of secondary and tertiary amino compounds was reduced at pH below 10 and that the reactive species are probably free ammonia and chloroacetate ion.[5] Iminodiacetic acid has been prepared by the reaction of boiling aqueous chloroacetic acid with ammonia.[6] However, no report has appeared on the preparation of nitrilotriacetic acid from these materials. Few kinetic studies have been reported for this type of reaction.[7,8]

The present study was undertaken to obtain some information on the kinetics of the formation of glycine and iminodiacetic and nitrilotriacetic acids from chloroacetic acid and ammonia together with the effect of pH

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(1) Contribution No. 101.

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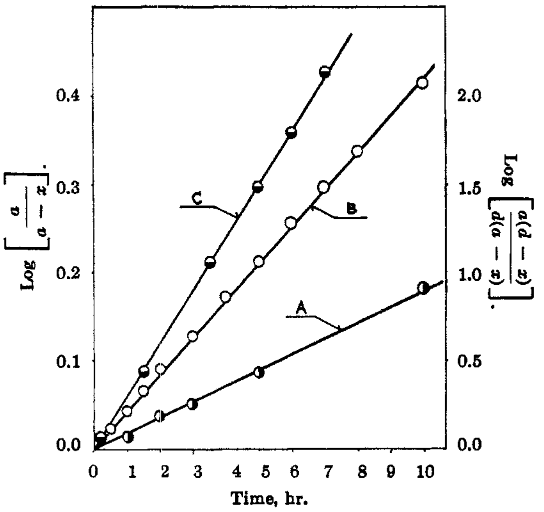

Figure 1.—Pseudo-first-order kinetics (left side of vertical axis) for the reaction of chloroacetic acid with ammonia (A) and with glycine (B) and second-order kinetics (right side of vertical axis) for the reaction of chloroacetic acid with iminodiacetic acid (C) in aqueous buffer solutions at 30 ± 0.1°. Initial concentrations were (A) chloroacetic acid, 0.1 *M*, ammonia, 2.0 *M*; (B) chloroacetic acid, 0.05 *M*, glycine, 0.50 *M*; (C) chloroacetic acid, 0.099 *M*, iminodiacetic acid, 0.05 *M*. The symbol *a* represents the initial concentration of chloroacetic acid and *d*, the initial concentration of iminodiacetic acid. All of the reaction were followed up to over 70% and all plots lie on good straight lines up to this high conversion.

on the rate for the clarification of the reaction mechanism.

Experimental Section

Materials.—Aqueous ammonia, sulfuric acid, nitric acid, sodium hydroxide, sodium sulfate, and sodium nitrate used were of guaranteed reagent grade. Chloroacetic acid was redistilled under vacuum, bp 97–98° (24 mm). Commercial glycine, mp 235.2–237° (effervesces) (lit.[9] 236–239° (dec), and iminodiacetic acid, mp 224–229° (effervesces) (lit.[10] 225° dec), were recrystallized from aqueous methanol.

Rate Measurements.—A solution (5 ml) of chloroacetic acid was pipetted into an aqueous solution of amino compound (100 ml) placed in a glass-stoppered flask which had reached thermal equilibrium in a thermostat. Aliquots (5 ml) were pipetted out at regular intervals and cold dilute nitric acid was added to them to stop the reaction. The concentrations of chloride ion were determined by the Volhard method.[11]

The hydrolysis of chloroacetic acid was negligible under the kinetic conditions at pH below 12, since practically no chloride ion was detected after 8 hr in an aqueous solution of chloroacetic acid in the absence of ammonia even at pH 12 and at 30°. A report[8] that the rate of hydrolysis of chloroacetic acid in an aqueous solution at 60° is *ca.* $^1/_{30}$ of the rate of the ammonolysis under the same conditions was consistent with our observation. Therefore, the rate of appearance of chloride ion may be assumed to be equal to the rates of the corresponding formation of glycine, iminodiacetic acid, and nitrilotriacetic acid. The concentration of ammonia was determined by titration with standard hydrochloric acid.

The pH and the ionic strength of the solution were controlled by adding a mixture of sulfuric acid and sodium sulfate or a mixture of nitric acid and sodium nitrate (for the reaction of chloroacetic acid with ammonia) or by adding a mixture of sodium hydroxide and sodium nitrate (for the reaction of chloroacetic acid with glycine or iminodiacetic acid). The pH of the solution was determined by Hitachi-Horiba pH meter type M 4 which is reliable in the range of pH 0–14.

Although hydrogen chloride was a reaction product, the change in pH of the solution is very small throughout the reaction as shown in Table I.

TABLE I

RATE CONSTANTS FOR THE REACTION OF CHLOROACETIC ACID WITH AMINO COMPOUNDS IN AN AQUEOUS SOLUTION AT 30 ± 0.1°

$ClCH_2COOH$, *M*	NH_3, *M*	H_2SO_4, *M*		Initial pH	Final pH[a]	$k^b \times 10^5$, sec^{-1}
0.1	1.0	0.04		10.0	9.7	0.486
	2.0	0.11		10.2	9.8	1.09
	3.0	0.23		10.2	9.9	1.68
	4.0	0.30		10.3	10.0	2.30
	5.0	0.36		10.4	10.2	3.14
$ClCH_2$-COOH, *M*	NH_2CH_2-COOH, *M*	NaOH, *M*	$NaNO_3$, *M*	Initial pH	Final pH[c]	$k^d \times 10^5$, sec^{-1}
0.05	0.50	0.33	2.42	9.5	9.4	2.66
	0.75	0.50	2.13	9.6	9.5	4.78
	1.00	0.67	1.83	9.8	9.7	6.75
	1.25	0.83	1.55	9.8	9.7	8.45
$ClCH_2$-COOH, *M*	$NH(CH_2$-$COOH)_2$, *M*	NaOH, *M*	$NaNO_3$, *M*	Initial pH	Final pH[e]	$k^f \times 10^5$, M^{-1} sec^{-1}
0.099	0.050	0.50	2.38	13.4	13.2	19.8
	0.075	0.75	2.08	13.1	13.0	18.0
	0.100	1.00	1.78	13.3	13.1	17.4
	0.125	1.25	1.48	13.6	13.1	18.3
	0.150	1.50	1.18	13.5	13.2	18.4

[a] After 38 hr. [b] First-order rate constants for chloroacetic acid at various ionic strengths. [c] After 5 hr. [d] First-order rate constants for chloroacetic acid at ionic strength 3. [e] After 20 hr. [f] Second-order rate constants for chloroacetic acid and iminodiacetic acid at ionic strength 3.

The Preparation of Nitrilotriacetic Acid.—Aqueous ammonia (28%, 1 mol, 70 ml), 100 ml of an aqueous solution of sodium hydroxide (15 g, 0.375 mol), and 100 ml of an aqueous solution of chloroacetic acid (38 g, 0.4 mol) were mixed in a flask equipped with a reflux condenser at room temperature. The solution was then allowed to stand for 24 hr. On heating at 100° (of bath temperature) with vigorous stirring for 3 hr the solution became yellowish. The solution was then cooled and acidified with sulfuric acid. Nitrilotriacetic acid was formed immediately as a white precipitate, which was filtered off, washed with water, and recrystallized twice from water, giving 18 g of colorless crystals of nitrilotriacetic acid, mp 240° (effervesces) (lit.[12] 242° dec); the yield after recrystallization from water was 73.4% based on chloroacetic acid.

The product was identified by similarity in paper chromatographic behavior with an authentic sample.[13] A mixture of 1-butanol–water–acetic acid (4:5:1 in volume) was employed as a developer and an ascending method was used. The R_f values (and the characteristic color) were 0.11 (violet) for the product, 0.19 (reddish violet) for glycine, 0.13 (reddish violet) for iminodiacetic acid, and 0.10 (violet) for nitrilotriacetic acid.

The Measurement of pK_a.—The ionic strength of the solution was controlled to 3 using sodium nitrate. The pK_a value of the conjugate acids of amino compounds was measured using the potentiometric titration method.[14] The pK_a values at 30° were 9.45, 9.60, and 9.15 for the conjugate acid of ammonia, iminodiacetic acid, and nitrilotriacetic acid, respectively.

Results and Discussion

Typical rate data are shown in Table I. The reactions of chloroacetic acid with ammonia to form glycine, iminodiacetic acid, and nitrilotriacetic acid are consecutive.[2–5] The straight lines in the pseudo-first-order plot in Figure 1 show that the reaction rate of chloroacetic acid with formed glycine can be neglected in a large excess (over tenfold) of ammonia. Indeed,

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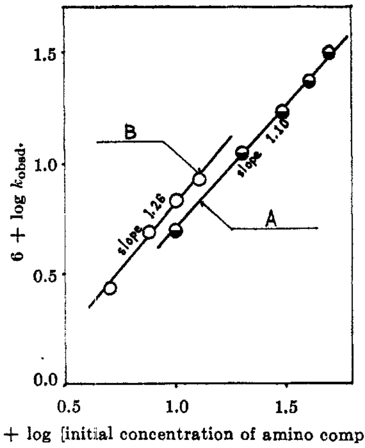


Figure 2.—The relationship between log (pseudo-first-order rate constants) and log (the initial concentration of ammonia) (A) and log (the initial concentration of glycine) (B) at 30 ± 0.1°.

although the reactivity of glycine is ten times as much as that of ammonia as observed, the reaction with glycine may be neglected even at 50% conversion of chloroacetic acid because of the high molar ratio of ammonia to glycine. It has been reported that besides glycine (a main product) only a small amount of iminodiacetic acid and nitrilotriacetic acid were obtained under these conditions.[2-5] A similar consideration may be applied to the reaction of chloroacetic acid with glycine. If the reactivity of iminodiacetic acid is almost equal to that of glycine as observed, the effect of formed iminodiacetic acid (below 5%) on the rate in a large excess (over tenfold) of glycine can be neglected even if half of the chloroacetic acid is consumed.

Kinetics of the Formation of Glycine.—Curve A in Figure 1 shows that the rate of formation of glycine is first order in chloroacetic acid. For the determination of the order with respect to ammonia, the rate was measured at constant concentration of chloroacetic acid (0.1 *M*) and at various concentrations of ammonia, *i.e.*, 1.0, 2.0, 3.0, 4.0, and 5.0 *M*. The logarithm of the observed rate constants was plotted against the logarithm of the initial concentration of ammonia (Figure 2, curve A).

Since the plotted line has a slope of almost unity (1.10), the reaction forming glycine also follows first-order kinetics with ammonia, and the rate equation is expressed in eq 1.

$$v = k_\alpha[\text{ammonia}][\text{chloroacetic acid}] \qquad (1)$$

Effect of pH on the Rate of Formation of Glycine.—It is shown in Figure 3, curve A, that the rate of formation of glycine decreases sharply at pH below 10 and gives a line having a slope of unity at pH below 9.5.

If the rate-determining step consists of an attack of free ammonia on chloroacetate ion as postulated by Cheronis and Spitzmuller,[5] the over-all reaction is expressed in eq 2-4.

$$\text{NH}_4^+ \underset{\text{mobile}}{\overset{K_2}{\rightleftarrows}} \text{NH}_3 + \text{H}^+ \qquad (2)$$

$$\text{ClCH}_2\text{COOH} \underset{\text{mobile}}{\overset{K_3}{\rightleftarrows}} \text{ClCH}_2\text{COO}^- + \text{H}^+ \qquad (3)$$

$$\text{NH}_3 + \text{ClCH}_2\text{COO}^- \xrightarrow[\text{slow}]{k_4} \text{NH}_2\text{CH}_2\text{COO}^- + \text{H}^+ + \text{Cl}^- \qquad (4)$$

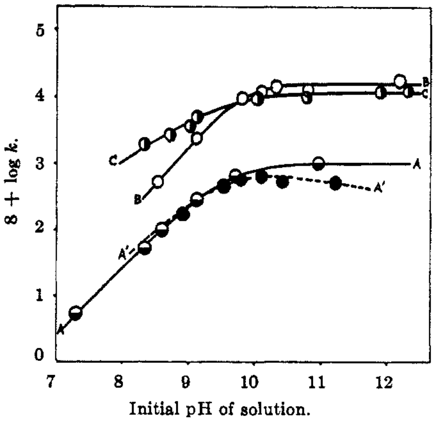


Figure 3.—The effect of pH on the rate of reaction of chloroacetic acid with ammonia (A), glycine (B), and iminodiacetic acid (C) at 30 ± 0.1° and ionic strength 3, and the effect of pH on the rate of reaction of chloroacetic acid with ammonia (A′) at 30 ± 0.1° and various ionic strengths. Initial concentrations were (A) chloroacetic acid, 0.1 *M*, ammonia, 2.5 *M*; (B) chloroacetic acid, 0.05 *M*, glycine, 0.75 *M*; (C) chlorocetic acid, 0.099 *M*, iminodiacetic acid, 0.1 *M*; (A′) chloroacetic acid, 0.1 *M*, ammonia, 5.0 *M*.

The stoichiometric concentration of ammonia $(b - x)$ is the sum of the concentrations of free and protonated amines (see eq 5). In the same way, the stoichiometric

$$(b - x) = [\text{NH}_3]\left((1 + \frac{[\text{H}^+]}{K_2}\right) \qquad (5)$$

concentration of chloroacetic acid $(a - x)$ is expressed as in eq 6. The term, $[\text{H}^+]/K_3$, may be negligible

$$(a - x) = [\text{ClCH}_2\text{COO}^-]\left(1 + \frac{[\text{H}^+]}{K_3}\right) \qquad (6)$$

under all conditions studied (pH >7), since the value of K_3 at 25° is 1.4×10^{-3} and chloroacetic acid may be almost completely anionic; hence $(a - x)$ is equal to $[\text{ClCH}_2\text{COO}^-]$. Therefore, the rate of formation of glycine may be expressed as in eq 7, where *k* and *K* are

$$v = k_4\,[\text{NH}_3][\text{ClCH}_2\text{COO}^-]$$

$$k_4\left(\frac{1}{1 + ([\text{H}^+]/K_3)}\right)(b - x)(a - x) \qquad (7)$$

rate and equilibrium constants for the subscripted step, respectively.

The comparison of eq 7 with eq 1 leads to an expression for the apparent rate constant k_α (see eq 8). The

$$k_\alpha = k_4\left(\frac{1}{1 + ([\text{H}^+]/K_2)}\right) \qquad (8)$$

average value of rate constant, k_4, for the rate-determining step was calculated to be $1.12 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ from eq 6 at pH above 10.5 and ionic strength 3. The solid curve A in Figure 3 is the theoretical curve for log k_α-pH profile calculated from eq 8 assuming k_4 of $1.12 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ at constant ionic strength 3 and pK_2 of 9.60; the observed values of k_α lie on the curve A. The assumed value of basicity of ammonia, pK_2 = 9.60, agrees within experimental error with the observed value of pK_a (9.45) determined at 30° and ionic strength 3. This agreement shows that the above rate law is sufficient to describe the pH-rate profile.

Therefore, it is concluded that the main reactive species are not ClCH_2COOH but $\text{ClCH}_2\text{COO}^-$, at least, in this pH range.

The existence of a maximum at pH of *ca.* 10 at various ionic strengths was observed in a plot of log k_α *vs.* pH (Figure 3, curve A′). However, the fact that the salt effect is observed at high ionic strength even in the reaction between neutral and ionic species[15,16] and that the pH of the solution was prepared by adding sulfuric acid, suggests a positive salt effect. Indeed, the maximum rate disappears at constant ionic strength 3 (Figure 3, curve A). It is probable that this positive salt effect appears to be due to the reaction between chloroacetate ion and free ammonia, since a molecule of ammonia having a strong dipole may behave in a manner similar to an anion at high ionic strength.[15,16]

Kinetics of the Formation of Iminodiacetic Acid.—The rate of iminodiacetic acid formation from glycine and chloroacetic acid measured at constant ionic strength 3 follows first-order kinetics with chloroacetic acid (Figure 1, curve B) and with glycine (Figure 2, curve B), respectively. Therefore, the rate is expressed as in eq 9. The slope (1.26) of the plot of

$$v = k_\beta\,[\text{glycine}]\,[\text{chloroacetic acid}] \tag{9}$$

log k_β *vs.* log [glycine] in Figure 2 is larger than unity. This may be due to a slight increase in pH of the solution with increasing concentration of glycine and hence sodium hydroxide causes an increase in rate as stated below (Table I).

Effect of pH on the Formation of Iminodiacetic Acid.—It has been reported[5] that the formation of iminodiacetic and nitrilotriacetic acids is difficult at pH <10 and that the reaction between glycine and glucose is influenced by the pH of the solution.[17] The effect of pH on the rate of iminodiacetic acid formation may then be discussed in the same way as in the reaction between ammonia and chloroacetic acid. It is apparent in curve B of Figure 3 that the rate of formation of iminodiacetic acid sharply decreases at pH below 10 and gives a straight line having a slope of *ca.* 1 at pH below 9.

Glycine exists in an aqueous neutral solution as a zwitterion, $^+NH_3CH_2COO^-$. Considering that the solution is basic and assuming that the rate-determining step is the reaction between chloroacetate ion and glycine anion, the over-all reaction is expressed as in eq 10 and 11.

$$^+NH_3CH_2COO^- \underset{\text{mobile}}{\overset{K_{10}}{\rightleftharpoons}} NH_2CH_2COO^- + H^+ \tag{10}$$

$$NH_2CH_2COO^- + ClCH_2COO^- \xrightarrow[\text{slow}]{k_{11}} NH(CH_2COO^-)_2 + H^+ + Cl^- \tag{11}$$

As in the reaction between ammonia and chloroacetic acid, the rate equation of iminodiacetic acid formation can be derived from eq 10 and 11. The comparison of the rate equation with the observed eq 9 leads to eq 12.

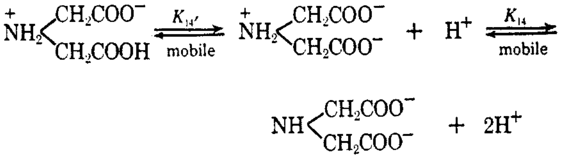
$$k_\beta = k_{11}\left(\frac{1}{1 + ([H^+]/K_{10})}\right) \tag{12}$$

The average value of the rate constants of the rate-determining step, k_{11}, was calculated to be 1.22×10^{-4} M^{-1} sec^{-1} (ionic strength 3) from eq 10 together with the observed data at pH >10. Assuming k_{11} of 1.22×10^{-4} M^{-1} sec^{-1} and pK_{10} of 9.80, curve B in Figure 3 is drawn by using the value of k_β which is a constant calculated from eq 10 at various pH. The observed rate constants at pH 8–12 lie on curve B as shown in Figure 3. The pK_{10} of 9.80 assumed here agrees with the observed value of pK_{NH^+} (9.60) determined by potentiometric titration at 30° and ionic strength 3. Therefore, it is concluded that the main reactive species in this reaction are $ClCH_2COO^-$ and $NH_2CH_2COO^-$, at least under these conditions. The rate constant of iminodiacetic acid formation was ten times as high as that of glycine formation.

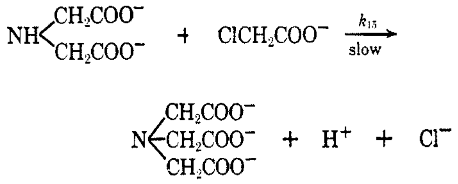
Kinetics of the Formation of Nitrilotriacetic Acid.—The reaction between ammonia and chloroacetic acid in a basic solution produces nitrilotriacetic acid in a good yield (73%). The rate of nitrilotriacetic acid formation is expressed as eq 13 derived from curve C of Figure 1.

$$v = k_\gamma[\text{iminodiacetic acid}]\,[\text{chloroacetic acid}] \tag{13}$$

Effect of pH on the Formation of Nitrilotriacetic Acid.—Considering the dissociation of reactants, the over-all reaction may be written as eq 14 and 15. Here, the



$$\overset{+}{N}H_2(CH_2COO^-)(CH_2COOH) \underset{\text{mobile}}{\overset{K_{14}'}{\rightleftharpoons}} \overset{+}{N}H_2(CH_2COO^-)_2 + H^+ \underset{\text{mobile}}{\overset{K_{14}}{\rightleftharpoons}} NH(CH_2COO^-)_2 + 2H^+ \tag{14}$$



$$NH(CH_2COO^-)_2 + ClCH_2COO^- \xrightarrow[\text{slow}]{k_{15}} N(CH_2COO^-)_3 + H^+ + Cl^- \tag{15}$$

contribution of K_{14}' is negligible, since this value is more than 10^{-3}.

The relationship between the rate constant and pH of solution expected from this scheme leads to eq 16. This equation agrees with the experimental results as shown in Figure 3. Hence the main reactive species of this

$$k_\gamma = k_{15}\left(\frac{1}{1 + ([H^+]/K_{14}) + ([H^+]^2/K_{14}'K_{14})}\right) \tag{16}$$

reaction are $NH(CH_2COO^-)_2$ and $ClCH_2COO^-$. The rate constant, k_{15}, was 1.12×10^{-4} M^{-1} sec^{-1} and pK_{14} was 9.15 at 30° and ionic strength 3. The rate constant is comparable with that of iminodiacetic acid.

The Reactivity of Amino Compounds and the Reaction Mechanism.—The rate constants for the reaction of chloroacetic acid with ammonia and amino acids were estimated at various temperatures and are shown in Table II. The activation parameters were calculated and they are listed in Table III together with the pK_a values of the conjugate acids of the amines.

Both glycine and iminodiacetic acid having a carboxymethyl group are about ten times as reactive as ammonia. On the other hand, there is little difference in reactivity between glycine and iminodiacetic acid: $NH_2CH_2COO^- \simeq NH(CH_2COO^-)_2 > NH_3$. This is

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[15] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p 151.

[16] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p 186.

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TABLE II

THE SECOND-ORDER RATE CONSTANT AT VARIOUS TEMPERATURES ($10^5 M^{-1} sec^{-1}$)

Reactants (M)	Temp, °C 60	50	45	40	35	30
$ClCH_2COO^-$ (0.1) + NH_3 (5)	...	10.0	6.13	3.25	2.17	...
$ClCH_2COO^-$ (0.055) + $NH_2CH_2COO^-$ (0.15)	209	90.0	...	36.3	...	13.3
$ClCH_2COO^-$ (0.055) + $NH(CH_2COO^-)_2$ (0.15)	223	96.7	...	28.9	...	15.1

TABLE III

pK_a VALUES FOR THE CONJUGATE ACID OF AMINO COMPOUNDS AND ACTIVATION PARAMETERS FOR THE REACTION OF CHLOROACETIC ACID WITH AMINO COMPOUNDS IN AN AQUEOUS SOLUTION AT 30 ± 0.1° AND IONIC STRENGTH 3

Reactants	pK_a[a]	pK_a[b]	$k^c \times 10^5$, M^{-1} sec^{-1}	E_a, kcal/mol	$\Delta S^\ddagger$, eu
$ClCH_2COO^-$ + NH_3	9.45	9.25	1.12	20.9	−16
$ClCH_2COO^-$ + $NH_2CH_2COO^-$	9.60	9.74	12.2	18.5	−17
$ClCH_2COO^-$ + $NH(CH_2COO^-)_2$	9.15	9.89	11.2	18.7	−17

[a] The acidities of protonated amines were measured at 30° and ionic strength 3. [b] The acidities of protonated amines taken at 30° and lower ionic strength. [c] Second-order rate constant.

apparent from the energy of activation, but not from the entropy of activation which is in the order $NH_2CH_2COO^- \simeq NH(CH_2COO^-)_2 < NH_3$. The observed p$K_a$ values at 30° and ionic strength 3 for conjugate acids of amines are in the order $NH_2CH_2COO^- > NH_3 > NH(CH_2COO^-)_2$, but the basicities and nucleophilicities of these amines at lower ionic strength are in the order: $NH(CH_2COO^-)_2 \simeq NH_2CH_2COO^- > NH_3$. The difference between these values may be due to the difference of ionic strength.

Therefore, the reactivities of these amino compounds depend more on the basicity or nucleophilicity of amino nitrogen. A slight decrease in rate for iminodiacetic acid, compared with the rate for glycine, may have been due to the steric effect. However, the reaction of chloroacetic acid with these amino compounds possesses comparable entropies of activation. Hence, the steric effect of the introduced carboxymethyl group seemed to be negligible.

The rate of reaction is expressed as $v = k[\text{amine}] \times [ClCH_2COO^-]$, where k depends on the basicity (and nucleophilicity) of amino nitrogen. Further, the entropy of activation is *ca.* −16 to −17 eu. These facts suggest that these reactions proceed by the SN2 mechanism.

A mechanism involving carbonium ion or α-lactone is excluded, since the rate did not decrease in spite of the accumulation of chloride ion as the reaction proceeded; *i.e.*, no common ion effect was observed, and the rate of the hydrolysis of substrates compared with ammonolysis is slow.

Registry No.—Chloroacetic acid, 79-11-8; ammonia, 7664-41-7; glycine, 56-40-6; iminodiacetic acid, 142-73-4.

A New Thermal Rearrangement of Allylic Phenylurethans[1]

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On heating to 200–240° with a catalytic amount of sodium hydride, phenylurethans of allylic alcohols rearrange, with expulsion of carbon dioxide, to N-phenylallylamines. Predominant inversion of the allyl moiety occurs and the reaction is considered to proceed by a cyclic electron reorganization process. Rearrangement of optically active Δ^2-cyclohexenylphenylurethan is accompanied by 65% retention of configuration and 35% racemization. Small amounts of imidazolidones are found as by-products and a pathway for their formation, involving base-catalyzed cyclization of N-allylureas, is proposed and supported by testing the presumed intermediates.

Of the thermal reorganization reactions which involve six-membered cyclic transition states,[2] one of the mechanistically most interesting and synthetically most useful families is that whose prototype is the Claisen rearrangement of allyl vinyl ethers (Chart I, reaction a[3]). A number of variations on this theme are known, some of which are listed in Chart I. These include the rearrangement of allylic imidates to amides (b),[4,5] the rearrangement of ketene acetals and their nitrogen analogs to esters and amides (c),[6,7] the pyrolysis of allylic acetoacetates and cyanoacetates (d),[8,9] and the rearrangement of carbanions of allylic esters to α-allyl carboxylic acids (e).[10] Similar rearrangements are observed in reactions which verge on the SNi′ type, such as the thermal isomerization of allyl esters (f),[11,12] and the recently reported conversion of allyl sulfamates into allylamines (g).[13]

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