N-Halo Derivatives III: Stabilization of Nitrogen–Chlorine Bond in *N*-Chloroamino Acid Derivatives

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Abstract □ The chlorination of α-amino acids and their related derivatives was investigated. A kinetic study of the stability of these *N*-chlorinated products led to an elucidation of the factors that significantly influence the stability and reactivity of the nitrogen–chlorine bond in these *N*-chloramines. From the kinetic investigations, a series of low chlorine potential, soft antimicrobial *N*-chloramines was developed based on derivatives of α-aminoisobutyric acid and related compounds.

Keyphrases □ *N*-Chloroamino acid derivatives—synthesis, kinetic stability study □ *N*-Halo derivatives—synthesis of *N*-chloroamino acid derivatives, kinetic stability study □ Antimicrobial agents—*N*-chloroamino acid derivatives, synthesis, kinetic stability study

Recently, the effect of chlorine directly bonded to nitrogen in *N*-chloramines was examined by photoelectron spectroscopy (1). The study was undertaken to define the interaction between the nitrogen and chlorine lone pairs in the *N*-chloro function. As a result of that investigation, the stability of the nitrogen–chlorine bond toward hydrolytic displacement and the antimicrobial activity of the *N*-chloramines could be correlated with the ionization potential of the nitrogen lone pair in the *N*-chloramines. For the *N*-chloramines investigated, the orbital energy (ionization potential) of the nitrogen lone pair was indicative of the degree of polarization in the nitrogen–chlorine bond. This observation suggested that the ionization potential of the nitrogen lone pair in *N*-chloramines would be a sensitive method for comparing the "chlorine potentials" (2, 3) of structurally different *N*-chloramines.

In continuing the investigation of the relationship between the antimicrobial activity of *N*-chloramines and the degree of polarization of the nitrogen–chlorine bond, a series of low chlorine potential *N*-chloramines was designed and investigated. It was hypothesized that the bactericidal action of *N*-chloramines was a manifestation of a chemical reaction involving the direct transfer of a positive chlorine from the *N*-chloramine to an appropriate receptor in the cell. This chemical reaction can effectively destroy or inhibit an enzymatic or a metabolic cell process, which results in the expiration of the organism.

By decreasing the polarity of the nitrogen–chlorine bond, the chemical reactivity of the *N*-chloramine would be minimized. These low chlorine potential *N*-chloramines would be less readily deactivated by extraneous reaction with denaturing agents and, therefore, would exhibit a high degree of antimicrobial activity against a broad spectrum of microorganisms. As a result, the low chlorine potential *N*-chloramines could more effectively exert their antimicrobial effect relative to higher chlorine potential *N*-chloramines.

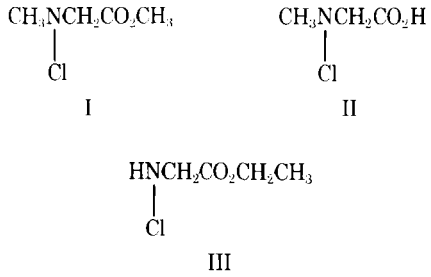
In addition to decreasing the polarity of the nitrogen–chlorine bond, it was of interest to develop these low chlorine potential *N*-chloramines as "soft" antimicrobial agents. The soft nature of the *N*-chloramines rested primarily upon the mechanism of their antimicrobial action and the transient character of the *N*-chloramine precursor to generate nontoxic degradation products. If it is assumed that the transfer of positive chlorine from the *N*-chloramine to an appropriate receptor in the cell is primarily responsible for the antimicrobial effect of the *N*-chloramine, detoxification of the microorganism ultimately regenerates the parent molecule from which the *N*-chloramine is derived. By judiciously selecting the *N*-chloramine precursor from nontoxic entities and selectively incorporating specific functional groups susceptible toward hydrolysis, the inherent toxicity of the soft *N*-chloramine antimicrobial agents could be effectively controlled.

In the present study, a rational and systematic approach to the preparation of a class of low chlorine potential, soft antimicrobial *N*-chloramines was investigated. Based on the low polarity of the nitrogen–chlorine bond and the soft nature of the *N*-chloramines desired, the chlorination of α-amino acids and their related derivatives was examined. The results elucidated the factors that significantly influence the stability of these *N*-chloramines and other low chlorine potential *N*-chloramines in general. The stability and reactivity of a number of homologous *N*-chloroamino and *N,N*-dichloroamino derivatives were also investigated.

RESULTS AND DISCUSSION

The formation of *N*-chloro derivatives of amines has been accomplished principally by treatment of a solution of the amine (primary or secondary amine) with a source of "active" chlorine such as sodium hypochlorite or molecular chlorine. Although the degree of chlorination of the nitrogen atom can be controlled by the stoichiometric quantities of amine and/or chlorinating agent used in the synthesis, the reaction product can be influenced by factors such as the pH of the reaction medium and the concentration of the *N*-chloramine in solution. The *N*-chloroamino derivative tends to predominate in basic solution (pH > 9) whereas the *N,N*-dichloroamino derivative is favored in acidic solution (pH 4–6).

In addition, depending upon the concentration of the *N*-chloramine in solution, the *N,N*-dichloroamino derivative may be preferentially formed *via* the *N*-chloroamino derivative through a disproportionation process. Although iodometric analysis for positive chlorine is an insufficient criterion for product homogeneity, Metcalf (4) demonstrated that the *N*-chloroamino and *N,N*-dichlo-



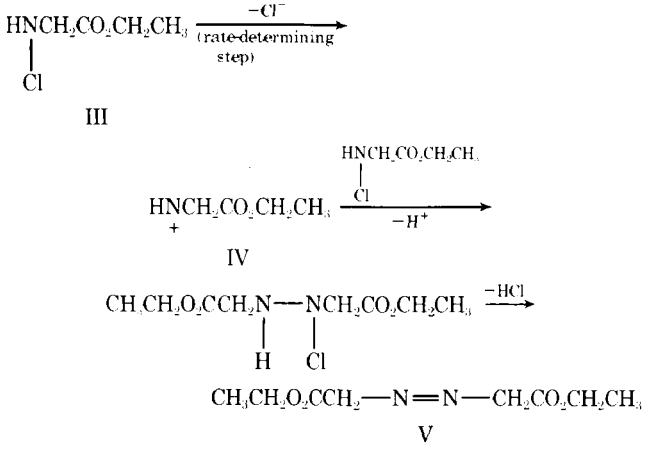
roamino derivatives have well-defined, characteristic UV absorption spectra, which can be used to determine product compositions.

To investigate a pure monochloroamino derivative from the chlorination of α-amino acids and their related derivatives, the initial studies concerned the preparation of methyl *N*-chlorosarcosinoate (I) and *N*-chlorosarcosine (II). The *N*-chloramines I and II were prepared by reaction of methyl sarcosinoate hydrochloride and sarcosine hydrochloride, respectively, with an aqueous solution of sodium hypochlorite. Compound I was isolated as a pale-yellow liquid whose UV absorption spectrum had a maximum absorbance at 264 nm, $\epsilon = 340\ M^{-1}\ cm^{-1}$. Compound I also gave satisfactory elemental analysis for positive chlorine, which was determined iodometrically. However, shortly after isolation, the *N*-chloramine underwent a spontaneous exothermic decomposition. Therefore, both I and II, as well as ethyl *N*-chloroglycinate (III), were prepared and their stability was investigated *in situ*.

The stability of the *N*-chloramines in solution was examined by following the rate of change in the concentration of positive chlorine iodometrically and/or monitoring the rate of change in absorbance at the wavelength of maximum absorption of the *N*-chloramine. The kinetic data obtained could be interpreted as first-order kinetic processes. The stability of the *N*-chloramines under the experimental conditions was characterized using the observed rate constant and the reaction half-life. Determination of the kinetic reaction constants for the *N*-chloramines was independent of the analytical method. That is, the observed rate constant and reaction half-life determined for the *N*-chloramine iodometrically were comparable to those determined spectrophotometrically.

Examination of the stability data for I–III (Table I) indicates several interesting observations. Comparison of the kinetic data for III relative to I indicates that the stability of the monochloroamino derivatives is not significantly influenced by the presence or absence of the N—H bond. Although the stability of I and III both appear to exhibit first-order behavior, the kinetic data for III are independent of the buffer concentration whereas the kinetic data for I are directly influenced by the buffer concentration.

The dichotomy of observing simple first-order kinetics for III and pseudo-first-order kinetics for I can be rationalized by considering that the monomolecular decomposition of III involves, as its rate-determining step, the loss of chloride ion from III to form the ion (IV). Subsequently, this reactive species can couple with another molecule of III to form the azo derivative (V) as suggested by Pinchuk *et al.* (5) (Scheme I).



Scheme I

Table I—Stability of *N*-Chloroamino Acids and Related Derivatives

Compound	Buffer Concentration, M[a]	Rate Constant[b] $\times 10^{-2}$, min^{-1}	Half-Life, min	Correlation Coefficient[c]
I	0.1	1.12	61.9	0.999
	0.2	2.39	29.0	0.999
	0.25	3.02	22.9	0.999
	0.3	3.59	19.3	0.999
	0.4	4.77	14.5	0.999
	0.5	5.82	11.9	0.999
II	0.1	2.60[d]	26.7	0.998
	0.2	1.93[d]	35.9	0.999
	0.3	2.32[d]	29.9	0.992
	0.4	2.17[d]	31.9	0.999
	0.5	2.10[d]	33.0	0.999
III	0.25	13.2	5.3	0.999
	0.3	16.4	4.2	0.999
	0.4	18.0	3.9	0.999
	0.5	15.6	4.4	0.999

[a] Sodium dihydrogen phosphate, pH 7.0. [b] Rate constants were determined at 25° unless noted otherwise. [c] Correlation coefficients based on a linear regression analysis of the experimental data. [d] Rate constants were determined at 37°.

On the other hand, the direct relationship observed between the rate constants determined for I and the concentration of the buffer species suggests that the primary mechanism of decomposition proceeds through a bimolecular reaction between I and the phosphate buffer in a dehydrochlorination across the carbon–nitrogen bond in the *N*-chloramine. Graphical analysis of the kinetic data for I gives a rate constant equal to $0.15 \times 10^{-2}\ min^{-1}$ at zero buffer concentration (Fig. 1). Although two different hydrogen atoms adjacent to the nitrogen–chlorine bond are available for the elimination process, the dehydrochlorination is preferentially facilitated by the electron-withdrawing effect of the carbomethoxyl group in the *N*-chloramine (Scheme II).

In addition to the kinetic evidence supporting this mechanistic pathway for the decomposition of I, the decomposition product VII of I also was investigated indirectly. A solution of I that had undergone decomposition was examined spectrophotometrically and was found to be transparent in the 220–350-nm UV region. Addition of approximately a threefold excess of sodium hypochlorite, based on the initial concentration of I, to the decomposed so-

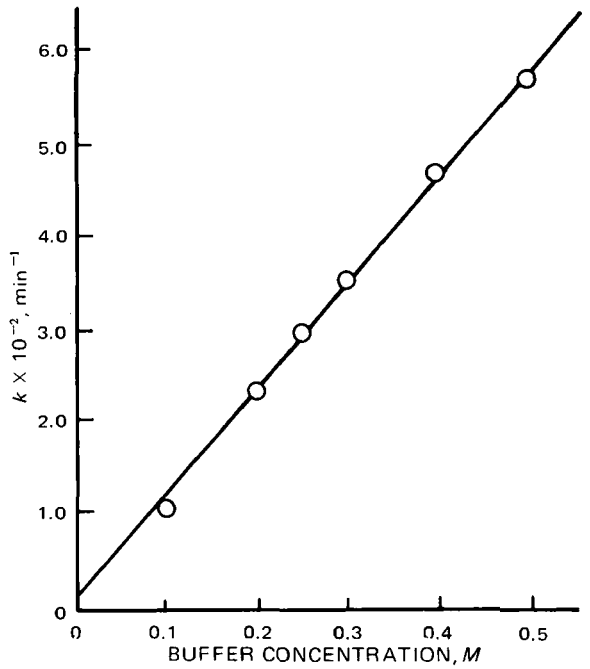
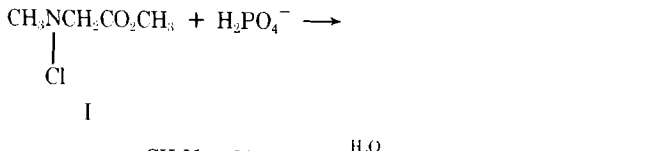


Figure 1—*Plot of the observed rate constant for the decomposition of I as a function of sodium dihydrogen phosphate concentration at pH 7.0 and 25°.*



Scheme II

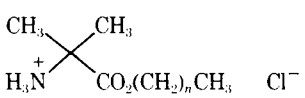
lution resulted in a product with an absorption maximum at 305 nm. This wavelength is characteristic for an *N,N*-dichloroamino species and is consistent with chlorination of methylamine (VII) to *N,N*-dichloromethylamine, λ_{max} 303 nm (4). Methylamine (VII) was formed *via* hydrolytic cleavage of the intermediate imine (VI), which had been initially formed in the dehydrochlorination (Scheme II).

The stability of *N*-chlorosarcosine (II) was investigated spectrophotometrically. Unlike the kinetic behavior observed in the decomposition of I, the reaction constants determined for the decomposition of II were independent of the buffer concentration. Therefore, the primary mechanistic pathway for the decomposition of II must proceed through a unimolecular degradation of II. This process also can be accounted for by a dehydrochlorination process. However, in this case, the dehydrochlorination of II is mediated by the decarboxylation of II itself. This mechanism is consistent with the buffer-independent rate constants observed for the decomposition of II.

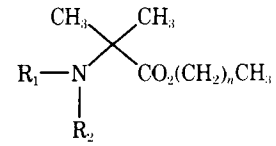
Under the experimental conditions, II exists predominantly in the ionized carboxylate form. The ionization of the carboxyl group decreases the electrophilic character of the carbonyl group in II relative to I. Consequently, the importance of the α-hydrogen elimination pathway for the decomposition of the *N*-chloramine can be decreased. In summary, the kinetic behavior observed for the stability of I–III can be accounted for by changes in the mechanistic pathway through which the positive chlorine is lost in each *N*-chloramine.

With a better understanding of the proposed mechanisms that have been assumed responsible for the decomposition of I–III, the development of a unique class of *N*-chloroamino acid derivatives was initiated. This new class of low chlorine potential, soft antimicrobial *N*-chloramines was designed specifically to be incapable of dehydrochlorination by the decarboxylative route as well as by α-hydrogen elimination; synthetic amino acids geminally substituted at the α-carbon atom were primarily considered. In addition to this specific structural requirement, the synthetic amino acid chosen should ideally exhibit an inherently low toxicity. Based on these objectives, the *geminal*-dimethyl substitution at the α-carbon atom in α-aminoisobutyric acid and its inherent low toxicity suggested derivatization of this amino acid as the precursor of several *N*-chloramines. The initial investigations examined the chlorination of some homologous esters of α-aminoisobutyric acid (IX*a*–IX*f*).

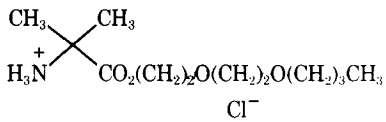
In contrast to the *N*-chlorinated products of natural α-amino acids, the *N*-chloramines based on α-aminoisobutyric acid (X*a*–X*k*) were stable and could be purified, characterized, and stored in the neat state without exothermic or extensive decomposition. In addition, chlorination of the longer chain homologs (IX*b*–IX*f*) led to the preparation of both the *N*-chloroamino and *N,N*-dichloroamino derivatives. Although the initial investigations were directed toward examining the chlorination of relatively simple homologous esters of α-aminoisobutyric acid, the extension of these concepts toward the development of other related derivatives of α-aminoisobutyric acid with specifically desired physical–chemical



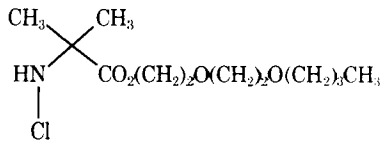
IX*a*: $n = 0$
IX*b*: $n = 5$
IX*c*: $n = 7$
IX*d*: $n = 11$
IX*e*: $n = 13$
IX*f*: $n = 17$



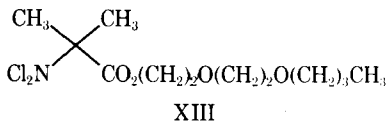
X*a*: R_1 = Cl, R_2 = Cl, $n = 0$
X*b*: R_1 = H, R_2 = Cl, $n = 5$
X*c*: R_1 = H, R_2 = Cl, $n = 7$
X*d*: R_1 = H, R_2 = Cl, $n = 11$
X*e*: R_1 = H, R_2 = Cl, $n = 13$
X*f*: R_1 = H, R_2 = Cl, $n = 17$
X*g*: R_1 = Cl, R_2 = Cl, $n = 5$
X*h*: R_1 = Cl, R_2 = Cl, $n = 7$
X*i*: R_1 = Cl, R_2 = Cl, $n = 11$
X*j*: R_1 = Cl, R_2 = Cl, $n = 13$
X*k*: R_1 = Cl, R_2 = Cl, $n = 17$



XI



XII



XIII

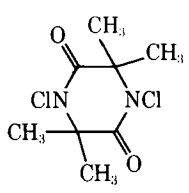
properties was equally feasible. For example, chlorination of 2-(2-*n*-butoxyethoxy)ethyl α-aminoisobutyrate hydrochloride (XI) gave the corresponding *N*-chloroamino (XII) and *N,N*-dichloroamino (XIII) derivatives.

Incorporation of the ether linkages in these *N*-chlorinated amino acid ester derivatives conferred advantageous water-solubilizing properties to XII and XIII while still retaining their surface-active characteristics. In addition to ester derivatization of α-aminoisobutyric acid, amide and peptide derivatives were considered. Representative of this approach, the 1,4-dichloro-2,2,5,5-tetramethyl-3,6-piperazinedione (XIV) was prepared. Due to the inherent low water solubility of this derivative, the *N*-chloramine could efficiently act as a sustained-release form of the active chlorine species.

The microbiological properties of these low chlorine potential, soft *N*-chloramine derivatives and other structurally related *N*-chloramine systems will be reported[1].

EXPERIMENTAL

Methyl *N*-Chlorosarcosinoate (I)—To a solution of 6.95 g (0.05 mole) of methyl sarcosinoate hydrochloride in 15 ml of water was added dropwise, with stirring, 65 ml (0.05 mole) of 0.78 *M* sodium hypochlorite solution. At the end of the addition, the reaction solution was adjusted to pH 7. The *N*-chloramine was extract-



XIV

[1] J. J. Kaminski and N. Bodor, to be published.

ed into ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the ethyl acetate was removed at room temperature under reduced pressure to afford 5.22 g (0.038 mole), 76%, of I as a pale-yellow liquid; UV (H_2O): λ_{max} 264 nm, $\epsilon = 340\ M^{-1}\ cm^{-1}$. The pale-yellow liquid underwent a spontaneous exothermic decomposition shortly after isolation.

Anal.—Calc. for $C_4H_8ClNO_2$: Cl, 25.8. Found: Cl, 24.8.

N-Chlorosarcosine (II)—Compound II was prepared *in situ* using a method described previously (4). Reaction of a solution of sarcosine hydrochloride buffered to pH 7 with an aqueous solution of sodium hypochlorite gave II; UV (H_2O): λ_{max} 268, $\epsilon = 310\ M^{-1}\ cm^{-1}$.

Ethyl N-Chloroglycinate (III)—Compound III was prepared *in situ* using a method described previously (4). Reaction of a solution of ethyl glycinate hydrochloride buffered to pH 7 with an aqueous solution of sodium hypochlorite gave III; UV (H_2O): λ_{max} 254 nm, $\epsilon = 339\ M^{-1}\ cm^{-1}$.

Methyl α-Aminoisobutyrate Hydrochloride (IX*a*)—To 30 ml (0.78 mole) of anhydrous methanol at −10° was added 7.9 ml (0.11 mole) of thionyl chloride at such a rate that the temperature was maintained below 0° during the addition. Then 10.3 g (0.10 mole) of α-aminoisobutyric acid was added in portions, with stirring, also at a rate such that the temperature was maintained below −5°. The reaction mixture was heated to and maintained at 58–60° for 2.5 hr. The methanol was removed under reduced pressure to afford a pale-yellow viscous liquid, which crystallized to an off-white solid on standing at room temperature. Trituration of this solid with anhydrous ether gave IX*a* as a white crystalline solid, 15.3 g (0.099 mole), 99%, mp 185–187°; IR (KBr): 1735 (C=O) cm^{-1}; PMR (D_2O): δ 1.63 (s, 6H) and 3.87 (s, 3H) ppm.

Anal.—Calc. for $C_6H_{12}ClNO_2$: C, 39.09; H, 7.88; N, 9.12. Found: C, 39.24; H, 8.01; N, 9.26.

***n*-Hexyl α-Aminoisobutyrate Hydrochloride (IX*b*)**—To 97.1 g (0.47 mole) of phosphorus pentachloride suspended in 940 ml of acetyl chloride was added 48.4 g (0.47 mole) of α-aminoisobutyric acid, and the resulting suspension was stirred at room temperature overnight. The amino acid chloride hydrochloride was removed from the reaction mixture by filtration and thoroughly washed with anhydrous ether under a nitrogen atmosphere. After drying *in vacuo* over calcium sulfate, the α-aminoisobutyryl chloride hydrochloride was obtained as a white powder, 72.96 g (0.46 mole), 98%, mp 139–141° dec.; IR (KBr): 1750 (C=O) cm^{-1}.

Anal.—Calc. for $C_4H_9Cl_2NO$: C, 30.40; H, 5.74; N, 8.89. Found: C, 31.24; H, 6.09; N, 9.15.

To 51.0 g (0.5 mole) of *n*-hexyl alcohol heated to 40° was added in portions over 10 min, with stirring, 15.7 g (0.1 mole) of α-aminoisobutyryl chloride hydrochloride, which was obtained as already described. The reaction mixture was purged with nitrogen and maintained at 75° for 3 hr. Cooling to room temperature gave a liquid mass from which the excess *n*-hexyl alcohol was removed by distillation *in vacuo*. The amino acid ester hydrochloride was crystallized by the addition of anhydrous ether and, after trituration overnight, was removed from the reaction mixture by filtration and thoroughly washed with anhydrous ether. After drying *in vacuo* over calcium sulfate, IX*b* was obtained as a white solid, 12.2 g (0.055 mole), 55%, mp 74–76°; IR (KBr): 1750 (C=O) cm^{-1}; PMR (D_2O): δ 10.7 (t, 3H), 1.3 (broad s, 8H), and 4.23 (broad t, 2H) ppm.

Anal.—Calc. for $C_{10}H_{22}ClNO_2$: C, 53.68; H, 9.91; N, 6.26. Found: C, 53.27; H, 10.06; N, 6.10.

By using the procedure described for the preparation of IX*b*, the following esters of α-aminoisobutyric acid were prepared.

n-*Octyl α-Aminoisobutyrate Hydrochloride* (*IX*c)—Melting point 79–82°; IR (KBr): 1750 (C=O) cm^{-1}; PMR (D_2O): δ 4.1 (t, 2H), 1.46 (s, 6H), 1.2 (broad s, 12H), and 0.7 (broad t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{26}ClNO_2$: C, 57.24; H, 10.41; N, 5.56. Found: C, 57.14; H, 10.64; N, 5.36.

n-*Dodecyl α-Aminoisobutyrate Hydrochloride* (*IX*d)—Melting point 94–96°; IR (KBr): 1750 (C=O) cm^{-1}; PMR (dimethyl sulfoxide-d_6): δ 8.8 (broad s, 3H), 4.0 (t, 2H), 1.4 (s, 6H), 1.1 (broad s, 20H), and 0.7 (broad t, 3H) ppm.

Anal.—Calc. for $C_{16}H_{34}ClNO_2$: C, 62.41; H, 11.13; N, 4.55. Found: C, 61.62; H, 11.38; N, 4.21.

n-*Tetradecyl α-Aminoisobutyrate Hydrochloride* (*IX*e)—Melting point 96–97°; IR (KBr): 1750 (C=O) cm^{-1}; PMR (D_2O): δ 4.23 (broad t, 2H), 1.63 (s, 6H), 1.3 (broad s, 24H), and 1.1 (broad t, 3H) ppm.

Anal.—Calc. for $C_{18}H_{38}ClNO_2$: C, 64.69; H, 11.33; N, 4.18. Found: C, 64.17; H, 11.26; N, 3.95.

n-*Octadecyl α-Aminoisobutyrate Hydrochloride* (*IX*f)—Melting point 75–78°; IR (KBr): 2970 (CH), 2620 (N^+H), 1750 (C=O), and 1180 (CO) cm^{-1}.

Anal.—Calc. for $C_{22}H_{46}ClNO_2$: C, 67.39; H, 11.83; N, 3.57. Found: C, 66.84; H, 12.22; N, 3.17.

2-(2-n-Butoxyethoxy)ethyl α-Aminoisobutyrate Hydrochloride (*XI*)—Melting point 55–60°; IR (KBr): 2900 (CH), 1740 (C=O), and 1175 (CO) cm^{-1}; PMR (D_2O): δ 4.3–4.9 (m, 4H), 3.4–4.0 (m, 6H), 1.7 (s, 6H), 1.2–1.8 (m, 4H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{26}ClNO_4$: C, 50.78; H, 9.24; N, 4.94. Found: C, 50.39; H, 9.53; N, 5.00.

Methyl α-*N,N*-Dichloroaminoisobutyrate (X*a*) (5)—To 750 ml of 0.76 *M* sodium hypochlorite at 0° was added dropwise, with stirring, 39.1 g (0.26 mole) of III dissolved in 75 ml of water. The reaction mixture was adjusted to pH 4–6 by addition of 1 *M* HCl, and the suspension was stirred at 0° for 0.75 hr. The *N*-chloramine was extracted with methylene chloride, and the extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the methylene chloride was removed under reduced pressure to afford a dark-yellow liquid. Distillation gave 33.48 g (0.18 mole), 69%, of X*a*, bp 34–38° (0.4 mm); IR (neat): 1750 (C=O) cm^{-1}; PMR ($CDCl_3$): δ 1.7 (s, 6H) and 3.37 (s, 3H) ppm; UV (H_2O): λ_{max} 305 nm, $\epsilon = 315\ M^{-1}\ cm^{-1}$.

Anal.—Calc. for $C_5H_9Cl_2NO_2$: C, 32.28; H, 4.88; N, 7.53. Found: C, 32.47; H, 5.03; N, 7.52.

***n*-Hexyl α-*N*-Chloroaminoisobutyrate (X*b*)**—To 65 ml of 0.75 *M* sodium hypochlorite at 0° was added 4.46 g (0.02 mole) of IV in portions over 5 min. The suspension was stirred vigorously at 0° for 1 hr. The *N*-chloramine was extracted into ether, and the extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the ether was removed under reduced pressure to afford 4.12 g (0.019 mole), 95%, of X*b* as a pale-yellow liquid; IR (neat): 3280 (NH) and 1735 (C=O) cm^{-1}; PMR ($CDCl_3$): δ 5.0 (s, 1H), 4.2 (t, 2H), 1.43 (s, 6H), 1.32 (broad s, 8H), and 0.93 (broad t, 3H) ppm.

Anal.—Calc. for $C_{10}H_{20}ClNO_2$: C, 54.16; H, 9.09; N, 6.32. Found: C, 52.29; H, 9.21; N, 5.92.

By using the procedure described for the preparation of X*b*, the following α-*N*-chloroaminoisobutyrates were prepared.

n-*Octyl α-N-Chloroaminoisobutyrate* (*X*c)—R_f 0.21 (benzene, silica gel); IR (neat): 3300 (NH), 2960 (CH), 1750 (C=O), and 1150 (CO) cm^{-1}; PMR ($CDCl_3$): δ 5.0 (broad s, 1H), 4.2 (t, 2H), 1.4 (s, 6H), 1.37 (broad s, 12H), and 0.93 (broad t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{24}ClNO_2$: C, 57.70; H, 9.68; N, 5.61. Found: C, 58.29; H, 10.09; N, 5.50.

n-*Dodecyl α-N-Chloroaminoisobutyrate* (*X*d)—R_f 0.24 (benzene, silica gel); IR (neat): 3300 (NH), 2970 (CH), 1740 (C=O), and 1140 (CO) cm^{-1}; PMR ($CDCl_3$): δ 5.0 (broad s, 1H), 4.2 (t, 2H), 1.4 (s, 6H), 1.3 (broad s, 20H), and 0.9 (broad t, 3H) ppm.

Anal.—Calc. for $C_{16}H_{32}ClNO_2$: C, 62.82; H, 10.55; N, 4.58. Found: C, 63.79; H, 11.24; N, 4.62.

n-*Tetradecyl α-N-Chloroaminoisobutyrate* (*X*e)—R_f 0.41 (benzene, silica gel); IR (neat): 3300 (NH), 2970 (CH), 1740 (C=O), and 1140 (CO) cm^{-1}; PMR ($CDCl_3$): δ 5.0 (broad s, 1H), 4.2 (t, 2H), 1.4 (s, 6H), 1.3 (broad s, 24H), and 0.9 (broad t, 3H) ppm.

Anal.—Calc. for $C_{18}H_{36}ClNO_2$: C, 64.74; H, 10.87; N, 4.20. Found: C, 65.02; H, 11.19; N, 3.68.

n-*Octadecyl α-N-Chloroaminoisobutyrate* (*X*f)—R_f 0.25 (benzene, silica gel); IR (neat): 3300 (NH), 2970 (CH), 1750 (C=O), and 1150 (CO) cm^{-1}; PMR ($CDCl_3$): δ 5.0 (broad s, 1H), 4.2 (t, 2H), 1.4 (s, 6H), 1.3 (broad s, 32H), and 0.9 (broad t, 3H) ppm.

Anal.—Calc. for $C_{22}H_{44}ClNO_2$: C, 65.39; H, 10.98; N, 3.47. Found: C, 66.77; H, 11.67; N, 2.99.

2-(2-n-Butoxyethoxy)ethyl α-N-Chloroaminoisobutyrate (*XII*)—IR (neat): 3295 (NH), 2960 (CH), 1740 (C=O), and 1130 (CO) cm^{-1}; PMR ($CDCl_3$): δ 5.0 (broad s, 1H), 4.3 (m, 2H), 3.2–4.0 (m, 8H), 1.4 (s, 6H), 1.8–1.2 (m, 4H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{24}ClNO_4$: C, 51.15; H, 8.58; N, 4.97. Found: C, 50.99; H, 8.56; N, 4.71.

***n*-Hexyl α-*N,N*-Dichloroaminoisobutyrate (X*g*)**—To 75 ml of 0.69 *M* sodium hypochlorite at 0° was added 4.46 g (0.02 mole) of IV in portions over 5 min. The reaction mixture was adjusted to pH 4–6 by the addition of 1 *M* HCl, and the suspension was vigor-

ously stirred at 0° for 1 hr. The *N*-chloramine was extracted into methylene chloride, and the extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the methylene chloride was removed under reduced pressure to afford 3.71 g (0.015 mole), 75%, of a dark-yellow liquid. Chromatography on a magnesium silicate column with benzene–petroleum ether (75:25) (bp 30–60°) gave X*g* as a dark-yellow liquid, R_f 0.67 (benzene, silica gel); IR (neat): 2985 (CH), 1750 (C=O), and 1170 (CO) cm^{-1}; PMR ($CDCl_3$): δ 4.2 (t, 2H), 1.63 (s, 6H), 1.30 (broad s, 8H), and 0.90 (broad t, 3H) ppm.

Anal.—Calc. for $C_{10}H_{19}Cl_2NO_2$: C, 46.88; H, 7.48; N, 5.47. Found: C, 46.98; H, 7.69; N, 5.20.

Using the procedure described for the preparation of X*g*, the following α-*N,N*-dichloroaminoisobutyrates were prepared.

n-*Octyl* α-N,N-*Dichloroaminoisobutyrate* (*X*h)—R_f 0.69 (benzene, silica gel); IR (neat): 2980 (CH), 1750 (C=O), and 1160 (CO) cm^{-1}; PMR ($CDCl_3$): δ 4.2 (t, 2H), 1.7 (s, 6H), 1.3 (broad s, 12H), and 0.90 (broad t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{23}Cl_2NO_2$: C, 50.71; H, 8.16; N, 4.93. Found: C, 50.77; H, 8.50; N, 4.46.

n-*Dodecyl* α-N,N-*Dichloroaminoisobutyrate* (*X*i)—R_f 0.70 (benzene, silica gel); IR (neat): 2970 (CH), 1750 (C=O), and 1170 (CO) cm^{-1}; PMR ($CDCl_3$): δ 4.2 (t, 2H), 1.7 (s, 6H), 1.3 (broad s, 20H), and 0.90 (broad t, 3H) ppm.

Anal.—Calc. for $C_{16}H_{31}Cl_2NO_2$: C, 56.46; H, 9.18; N, 4.12. Found: C, 56.74; H, 9.51; N, 3.81.

n-*Tetradecyl* α-N,N-*Dichloroaminoisobutyrate* (*X*j)—R_f 0.75 (benzene, silica gel); IR (neat): 2970 (CH), 1750 (C=O), and 1170 (CO) cm^{-1}; PMR ($CDCl_3$): δ 4.2 (t, 2H), 1.6 (s, 6H), 1.3 (broad s, 24H), and 0.9 (broad t, 3H) ppm.

Anal.—Calc. for $C_{18}H_{35}Cl_2NO_2$: C, 58.68; H, 9.58; N, 3.80. Found: C, 58.30; H, 9.94; N, 3.29.

n-*Octadecyl* α-N,N-*Dichloroaminoisobutyrate* (*X*k)—R_f 0.75 (benzene, silica gel); IR (neat): 2970 (CH), 1750 (C=O), and 1170 (CO) cm^{-1}; PMR ($CDCl_3$): δ 4.2 (t, 2H), 1.6 (2, 6H), 1.3 (broad s, 32H), and 0.90 (broad t, 3H) ppm.

Anal.—Calc. for $C_{22}H_{43}Cl_2NO_2$: C, 62.25; H, 10.21; N, 3.30. Found: C, 61.69; H, 10.53; N, 2.80.

2-(2-n-*Butoxyethoxy*)*ethyl* α-N,N-*Dichloroaminoisobutyrate* (*XIII*)—IR (neat): 2960 (CH), 1750 (C=O), and 1150 (CO) cm^{-1}; PMR ($CDCl_3$): δ 4.4 (m, 2H), 3.3–4.0 (m, 8H), 1.7 (s, 6H), 1.8–1.2 (m, 4H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{23}Cl_2NO_4$: C, 45.58; H, 7.33; N, 4.43. Found: C, 46.05; H, 7.60; N, 4.22.

1,4-Dichloro-2,2,5,5-tetramethyl-3,6-piperazinedione (XIV)—Through a mechanically stirred suspension of 29.95 g (0.17 mole) of 2,2,5,5-tetramethyl-3,6-piperazinedione (6) in 250 ml of water at 0° was bubbled chlorine gas for 1.5 hr. The white solid was isolated by filtration, washed thoroughly with cold water, and dried *in vacuo* over calcium sulfate to yield 38.20 g (0.16 mole), 94%, of XIV, mp 176.5–178°; IR (KBr): 1680 (C=O) cm^{-1}.

Anal.—Calc. for $C_8H_{12}Cl_2N_2O_2$: C, 40.18; H, 5.06; N, 11.72. Found: C, 40.49; H, 5.18; N, 11.64.

Kinetics for the Decomposition of I–III—*Iodometric Method*—For each determination of the reaction constants for I, a stock solution of 0.8×10^{-3} *M* I was prepared by reaction of methyl sarcosinoate hydrochloride (1 m*M*) with sodium hypochlorite (0.8 m*M*) in a final volume of 100 ml using the appropriate buffer solution. Periodically, samples were removed from the stock solution and the concentration of positive chlorine in the sample was determined iodometrically using 10^{-3} *M* sodium thiosulfate. Analysis as a first-order kinetic process gave the rate constants and half-lives listed in Table I.

Spectrophotometric Method—For each determination of the reaction constants for I–III, stock solutions of 0.8×10^{-3} *M* I–III were prepared by reaction of methyl sarcosinoate hydrochloride (1 m*M*), sarcosine hydrochloride (1 m*M*), and ethyl glycinate hydrochloride (1 m*M*), respectively, with sodium hypochlorite (0.8 m*M*) in a final volume of 100 ml using the appropriate buffer solution. In each case, the decrease in the wavelength of maximum absorbance for I (λ_{max} 264 nm), II (λ_{max} 268 nm), and III (λ_{max} 254 nm) was recorded as a function of time. Analysis as a first-order kinetic process gave the rate constants and half-lives reported in Table I.

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