Pressure and pH Dependence of the Kinetics of Decarboxylative Dechlorination of N-Chloro-l-Alanine

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ABSTRACT

The kinetics of decarboxylative dechlorination of N-chloroalanine were studied at 25° in aqueous HCl solutions covering the pH range 1.4 to 2.8. These data were compared with literature results, and were interpreted in terms of first-order reactions of the cationic, uncharged, and anionic forms of the reactant. Pressure effect studies on the reaction of the anionic species yielded a volume of activation estimate of $+50 \pm 3$ cm^3 mol^{-1}. This result is consistent with a concerted fragmentation process.

INTRODUCTION

Treatment of an α-amino acid with a chlorinating agent such as hypochlorous acid or chlorine in aqueous solution, with the amino acid in excess, very rapidly yields the *N*-monochloro-α amino acid, which then undergoes decarboxylation and dechlorination according to the overall process shown in eq. (1).

$$\mathrm{RCH(NHCl)COOH + H_2O \longrightarrow RCHO + NH_3 + HCl + CO_2} \quad (1)$$

Under the conditions commonly used, the carboxylic acid is in its anionic form. An intermediate imine generates the carbonyl product through hydrolysis, as shown in eqs. (2) and (3).

$$\mathrm{RCH(NHCl)COO^- \longrightarrow Cl^- + CO_2 + RCH{=}NH} \quad (2)$$

$$\mathrm{RCH{=}NH + H_2O \longrightarrow RCHO + NH_3} \quad (3)$$

This reaction (and the closely related reaction of *N*-bromo amino acids) has been carefully studied because of its synthetic utility [1–3], and because in natural waters treated with chlorinating agents for purification it is highly likely that *N*-chloroamines will form [4–7]. Several mechanisms have been proposed, but for the reaction shown as eq. (2), opinion seems to have converged on a concerted unimolecular decomposition with a delocalized transition state shown as structure I [5–10].

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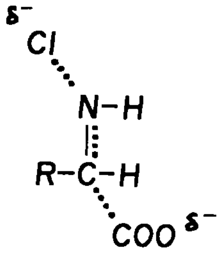


Structure I

Our interest in this reaction arises neither from its synthetic value nor its environmental importance, but rather because it possesses certain features that are advantageous to an experimental program in our laboratory. We have developed a phenomenological theory of solvent effects, and have applied this theory to solvent effects on solubilities [11–13], surface tension [14], absorption spectra [15], and molecular complex formation [16], including cyclodextrin inclusion complexes [17,18]. In order to investigate the applicability of the theory to reaction rates we sought a reaction whose kinetic solvent effects would not be confounded by secondary influences, such as solvent effects on pH. The decomposition of *N*-chloro-α-amino acids in the neutral solution range possesses the following features, very attractive for our purposes: (1) the kinetics are first-order, and the reaction is unimolecular; (2) the reaction rate is independent of pH over the approximate range 4 to 13 [5,7,8]; (3) the rate-determining step of the process is not a solvolysis; and (4) the reaction is known to display a sensitivity to solvent composition [8]. In support of the solvent effect work, we have conducted further mechanistic studies, which we report here. This new work, on the decomposition of *N*-chloroalanine in aqueous solution, extends the pH-rate profile down to pH 1.36, and provides an estimate of the volume of activation from measurements of the effect of pressure on the reaction rate.

EXPERIMENTAL

Apparatus

Absorption measurements were made with an OLIS-modified Cary 14 spectrophotometer fitted with a water-jacketed cell compartment maintained at 25°C. Pressure studies were carried out with a motorized, automated piston and cylinder apparatus connected to a computer via a controller (Advanced Pressure Products, Ithaca, New York) that regulated the pressure to ± 2%. This system was connected to a high-pressure cell fitted with sapphire windows (SLM-Aminco, Ithaca, New York). A Gilford Model 240 spectrophotometer constituted a light source for analysis. The detector was an end-on photomultiplier tube. PMT voltages were collected by an OLIS spectrophotometer Operating System (Bogart, Georgia). The pH meter was an Orion Model 701A.

Regents

l-Alanine (Aldrich, Milwaukee, Wisconsin) was recrystallized from 1 : 1 ethanol/water; l-leucine (Aldrich) was used as received. Sodium hypochlorite solution (Aldrich, 5% minimum concentration) was standardized by iodometric titration [19]. Buffer components were of analytical reagent grade. House reverse-osmosis treated water was further processed with a Sybron-Barnstead PCS system consisting of prefilter, organic, ion-exchange, and microfilter cartridges (Barnstead Co., Dubuque, Iowa).

PROCEDURES

Kinetic Studies

In a typical reaction, 0.7 mL of 0.0125 M NaOCl was added to 0.7 mL of 0.135 M alanine while swirling to mix. Then 1.4 mL of an appropriate HCl solution was added, and the solution was followed spectrophotometrically at 253 nm. The ionic strength of solutions in the acidic range was held constant at 1.1 M by the addition of NaCl. The temperature was 25°C. First-order rate constants were obtained by the method of Kezdy et al. [20,21].

Pressure Studies

The effect of pressure on the reaction rate was studied with *N*-chloroalanine at 26°C and with *N*-chloroleucine at 25°C. Aqueous solutions of the amino acid (0.06 M) and of NaOCl (0.006 M) were degassed. Equal volumes (2.0 mL) of these solutions were mixed and the resulting solution was transferred to the pressure cell. The system was pressurized, and the reaction was followed spectrophotometrically for at least one half-life, but often up to three half-lives. Occasional artifactual "spikes" in the signal, caused by activation of the pressurizing mechanism, were neglected in analyzing the spectrophotometric record to obtain the first-order rate constant. Since the reaction rate is not sensitive to pH or ionic strength throughout most of the pH range, these solutions did not contain added buffer or salts; the pH was 8.3 in these self-buffered solutions.

Table I Rate Constants for Decarboxylative Dechlorination of N-Chloroalanine in Acid Medium at 25°

pH[a]	$10^2\ k/s^{-1}$
1.36	6.88
1.57	2.62
1.59	5.15
1.68	3.35
1.75	2.57
1.83	2.35
1.97	1.54
1.99	1.54
2.17	0.97
2.35	0.853
2.69	0.323
2.78	0.268

[a] pH established with HCl; ionic strength held at 1.1 M with NaCl.

RESULTS

Kinetics in the Acid Region

The kinetics of decarboxylative dechlorination of *N*-chloroalanine were followed over the pH range 1.36 to 2.78 with HCl/NaCl solutions for pH and ionic strength control. Table I gives the results. At most pH values the rate constants listed are means of duplicate runs; the relative standard deviations were usually in the 1–2% range, though the result at pH 1.59 is much less precise.

At pH values less than 1.3 an anomalous spectral signal was seen during the reaction, suggesting complex kinetic behavior, and this observation was not pursued. Studies of the pH range 1.61 to 4.67 using citric acid buffer solutions were roughly concordant with the data in HCl solutions, but some discrepancies suggested that the caution of Armesto et al [22] concerning citrate buffers should be heeded, so these results are not reported here.

Pressure Effect Studies

The first-order rate constant for decarboxylative dechlorination of *N*-chloroalanine was studied in aqueous solution over the pressure range 1–2500 bar, 28 separate runs being made. *N*-Chloroleucine was studied in 6 runs covering the range 1–1500 bar. Because of substantial scatter in the results, they are not reported in tables, but are instead provided graphically in Figure 1 for *N*-chloroalanine; the results for *N*-chloroleucine are fragmentary, but show a change in the same direction as that in Figure 1. Despite the scatter, the incontrovertible conclusion is that the rate of reaction is decreased as the pressure is increased.

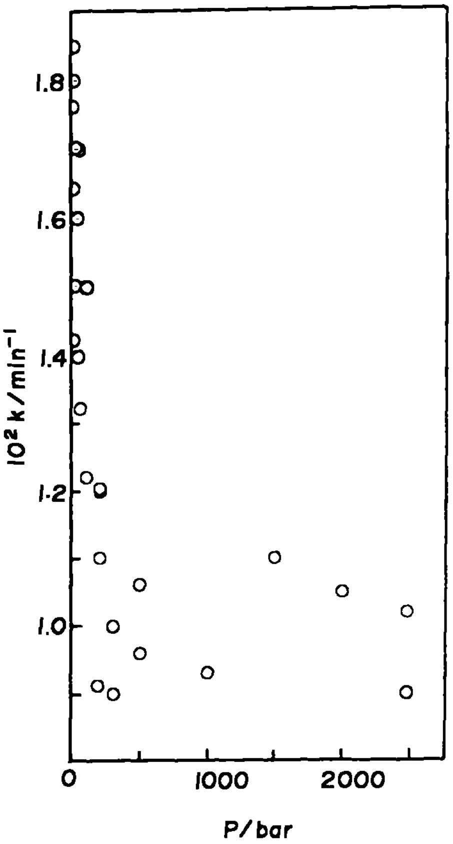


Figure 1 Effect of pressure on the decarboxylative dechlorination of *N*-chloroalanine at 26° Each point represents one run (or in some cases two runs).

DISCUSSION

The pH-Rate Profile

Figure 2 is a plot of the pH-rate data from Table I, supplemented with data from other sources for this same system. In the neutral region there is good agreement among all laboratories. In the acid region, however, our results disagree with those of Stanbro and Smith [4]. Our results in citrate buffers (pH 1.6 to 4.7) overlapped fairly well with the HCl-buffered data, but some significant differences led us to reject the citrate work. The HCl solutions contained NaCl to hold the ionic strength at 1.1 M, and Armesto et al. [22] have found that chloride ion seems to produce rate enhancements at low pH. This might be a kinetic (primary) salt effect or an equilibrium (secondary) salt effect, the latter possibility arising from the existence of two ionization equilibria in this pH range

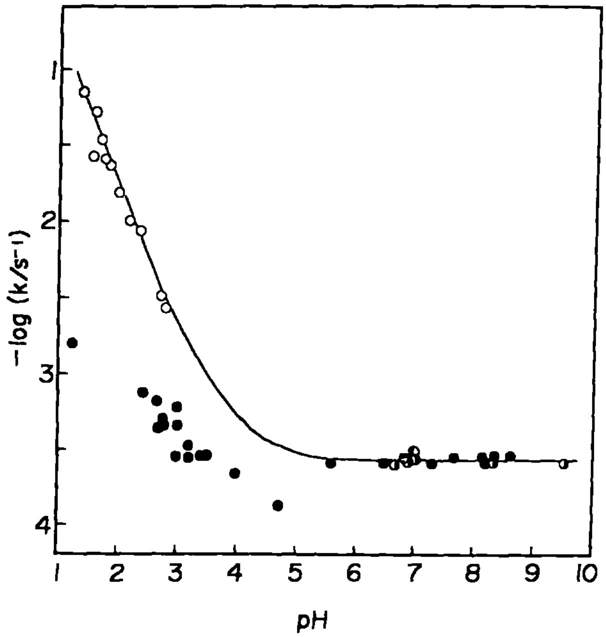


Figure 2 pH-rate profile for the decarboxylative dechlorination of *N*-chloroalanine at 25° C. Open circles, this work; filled circles, ref. [4]; and remaining points from refs. [5], [8], [22], and [26]. The smooth line was drawn with eq. (4) and values of the parameters given in the text.

(see the following paragraphs). We continue the analysis using our data, recognizing that the analysis probably applies quantitatively to only precisely the conditions we have used.

The slope of the line in Figure 2 in the very acid region is − 1.0, and a naive interpretation of the data is that this reaction undergoes a simple specific acid catalysis as well as the uncatalyzed reaction responsible for the broad flat valley in the profile. This interpretation is naive because it ignores possible ionization equilibria that may take place, and we next consider these. Abbreviating the N-chloroamino acid structure as NHCl—R—COOH, the possible ionic forms are shown in Scheme I. We agree with Stanbro and Smith [14] that the zwitterion is a much less abundant species than is the uncharged form, so the zwitterion is neglected in the following. We seek estimates of the acid dissociation constants K_1 and K_2.

Weil and Morris [23] measured (spectrophotometrically) the pK_a values of *N*-chlorodimethylamine (pK_a = 0.46) and *N*-chlorodiethylamine (pK_a = 1.02), and compared these values with the pK_a's of the parent amines. It can be concluded that replacement of a hydrogen by a chlorine on an amine reduces the basicity of the amine (i.e., increases the acid strength of the conjugate acid) by about 10 pK units. Since the pK_a of the amine group on alanine is 9.87, we estimate that pK_1 in Scheme I is about 0.0, or $K_1 \approx 1$.

To estimate pK_2 we use a Taft equation approach described by Perrin et al [24]. For *N*-chloroalanine written as X—CHMe—COOH, the parent compound (X=Me) is isobutyric acid, and ρ^* is estimated to be 0.8. Thus we write pK_a = 4.84−0.8σ^*. If X = NH_2, $\sigma^* = 0.62$. Taking the series CH_3, CH_2Cl, $CHCl_2$, and CCl_3 as a model shows that replacement of one H by one Cl increases σ^* by about 0.9. Thus for X = NHCl we have $\sigma^* = 1.5$. Our estimate of pK_2 in Scheme I is therefore 3.6.

The simplest kinetic scheme that seems reasonable is shown in Scheme II, where the species in Scheme I are symbolized H_2A^+, HA, and A^-.

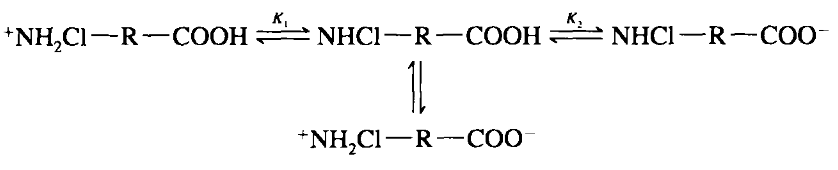
$$H_2A^+ \xrightarrow{k_+} \text{products}$$
$$HA \xrightarrow{k_0} \text{products}$$
$$A^- \xrightarrow{k_-} \text{products}$$

Scheme II

Elementary considerations [25] lead to eq. (4), where k is the observed first-order rate constant.

$$k = \frac{k_+[H^+]^2 + k_0K_1[H^+] + k_-K_1K_2}{[H^+]^2 + K_1[H^+] + K_1K_2} \tag{4}$$

We have made estimates of K_1 and K_2 above, and $k_- = 2.63 \times 10^{-4}\ s^{-1}$ from the data in Figure 2 throughout the valley region. Estimates of k_1 and k_0 from the appropriate regions of the low pH range are then adjusted by curve-fitting. The line in Figure 2



$$\begin{tikzcd}
{}^+NH_2Cl-R-COOH \arrow[r, shift left, "K_1"] & NHCl-R-COOH \arrow[l, shift left] \arrow[r, shift left, "K_2"] \arrow[d, shift left] & NHCl-R-COO^- \arrow[l, shift left] \\
& {}^+NH_2Cl-R-COO^- \arrow[u, shift left] &
\end{tikzcd}$$

Scheme I

was drawn with eq. (4) and these values of the parameters:

$k_+ = 1.65\ s^{-1}$

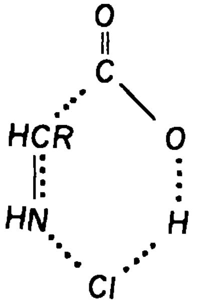
$k_0 = 1.0 \times 10^{-3}\ s^{-1}$

$k_- = 2.63 \times 10^{-4}\ s^{-1}$

$K_1 = 1.0\ M$

$K_2 = 2.5 \times 10^{-4}\ M$

Several features of this analysis are interesting. As noted in the introduction, there is widespread agreement that the reaction of species A^- occurs in a concerted fragmentation. The motivation for the present study was the expectation that protonation of the carboxylate group would "shut down" this reaction route by decreasing the abilities of Cl^- and CO_2 to function as good leaving groups. Yet we find, from the kinetic analysis, that $k_0/k_- = 3.8$; the neutral form HA reacts faster than does the anion. Fox and Bullock [3] long ago proposed the cyclic transition state II for the decomposition of this species.



Structure II

As a probe of this process, we examined the reactions of the methyl and ethyl esters of *N*-chloroalanine, but complex kinetic behavior was encountered, and it seems likely that ester hydrolysis, either prior to or concurrently with the dechlorination reaction, was confounding the issue. This approach therefore did not seem productive.

Another point of interest is the very simple appearance of the pH-rate profile for a reactant capable of undergoing ionization equilibria. Part of the reason for the apparent simplicity may be that we lack kinetic data in the region of the estimated pK_2 (3.6). That the line in the region buffered by HCl (pH 1.36 to 2.78) has a slope of unity arises because in this region $[H^+] \ll K_1$; from eq. (4), in the acid region we find [25], under this restriction,

$$k \approx \frac{k_+[H^+]}{K_1} \tag{5}$$

$$\text{or } \log k \approx \log k_+ - pH + pK_1 \tag{6}$$

Note that according to kinetic scheme II, we would not conventionally describe the rate increase in acid media as being caused by acid catalysis; there is no catalytic proton in Scheme II.

Let us return to the estimates we have made of pK_1 (0.0) and pK_2 (3.6). Stanbro and Smith [4] described a decrease in the molar absorptivity in the pH 2–4 range, which they ascribe to an acid-base equilibrium. Armesto et al. [22], on the other hand, have concluded that the molar absorptivity is not pH-dependent over the pH range 2–11; apparently the order of mixing the reactants can introduce artifacts. We would not expect an important spectral change in the K_2 ionization step (the carboxylic acid function), to which we have assigned the value 3.6.

Finally we note that we have made spectrophotometric kinetic observations in the (nominal) pH range 0.13 to about 1.3 that reveal complex kinetic behavior. The reaction of the fully protonated species H_2A^+ must therefore be more complicated than is represented in Scheme II.

The Volume of Activation

From transition state theory the activation volume is related to the pressure dependence of the rate constant by eq. (7).

$$\Delta V^{\ddagger} = -RT\left(\frac{\partial \ln k}{\partial P}\right)_T \tag{7}$$

Usually the plot of ln k against P is not linear, and it is conventional to take the value of the slope at P = O (or P = 1 bar, which is practically the same thing) for use in eq. (7). Since there is no theory relating k to P, many empirical approaches have been described for extracting the desired quantity [27–29].

As can be seen from Figure 1, the data points are rather imprecise, and too few points were collected in the *N*-chloroleucine system to permit $\Delta V^{\ddagger}$ to be calculated, though its sign is obviously positive. The manner in which the rate constant becomes independent of pressure at high pressures is unusual, and suggests a possible change in mechanism. Data analysis therefore was based on the points in the pressure range 1–300 bar. Figure 3 shows a plot of ln k against P over this range, with a least-squares straight

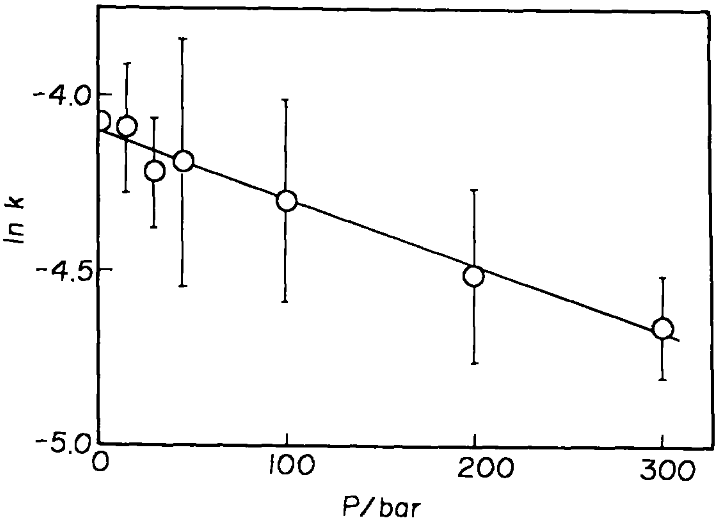


Figure 3 Plot of ln k against pressure for the decarboxylative dechlorination of *N*-chloroalanine at pH 8.3 and 26° C. The points are mean values of the data from Figure 1.

line drawn through the points. The error bars about the points are twice the standard deviation of ln k. From the slope of the line the volume of activation is found to be $\Delta V^{\ddagger} = +50 \pm 3$ cm^3 mol^{-1}.

This is a large volume of activation, though it lies within the range of commonly observed values. The $\Delta V^{\ddagger}$ evaluated here is for the reaction of the anion in the neutral region, the reaction that is considered to take place via transition state I. A positive value of $\Delta V^{\ddagger}$ is fully consistent with this concerted mechanism, for the charge dispersal will function to reverse any electrostriction effect, and bond lengthening takes place in passing from the initial state to the transition state. The large positive $\Delta V^{\ddagger}$ value found here is consistent with the large positive $\Delta S^{\ddagger}$ values observed for this process [5,30].

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