General Base Catalysis in the Decomposition of *N*-Cl-Valine in Aqueous Solution

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Abstract

This article analyzes the kinetics of the decomposition of *N*-Cl-Valine in aqueous solution, which is formed rapidly by chlorination of Valine with sodium hypochlorite. A general-base catalyzed process not yet described is reported. The experimental evidence shows two competitive decomposition paths: an unimolecular concerted fragmentation process ($k = (1.8 \pm 0.1) \cdot 10^{-4}$ s^{-1} at 298 K) and the other one is an $E2$ elimination process whose importance increases with pH and depends on the nature and the concentration of the bases present in the medium.

Introduction

Large quantities of nitrogenated compounds are present in natural or waste waters [1,2], among these, the amino acids produced by hydrolysis of proteins can be included.

Water treatment with chlorinating agents brings about the formation of substances, at times toxic [3], with mutagenic and/or carcinogenic properties [4], and for this very reason it is advisable to carry out studies on these processes.

When the chlorination of amino acids in aqueous solution occurs, the result is the formation of unstable *N*-Cl-amino acids. In this article the kinetics of the decomposition of *N*-Cl-Valine under different experimental conditions is described and the possible decomposition pathways are discussed.

Experimental

Instrumental

The decomposition of the *N*-Cl-Valine was followed on a UV-VIS Beckman spectrophotometer (DU-70 model), equipped with a six-cell carrier where the cells are thermostatted to within ± 0.1K with water from a P Selecta Frigiterm 6000382.

pH values were measured on a Crison 506 pH-meter equipped with a combined glass electrode, which was calibrated with Beckman buffer solutions (pH = 7.00 ± 0.02 at 25°C phosphate and pH = 4.00 ± 0.02 at 25°C, phthalate).

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Ammonia analysis was carried out on an Ingold (type 15 230 3000) ammonia selective electrode.

Reagents

The hypochlorite solutions were prepared by the method of Hussain et al. [5], the stock solution was stored at 4°C and renewed weekly. Aqueous bromine solutions were obtained daily by direct dilution of Br_2 (l) in sodium hydroxide solution. The concentration of the solutions was determined spectrophotometrically as described elsewhere [6].

The pH in the range 4 to 13 was maintained constant by using different buffer solutions (dihydrogen phosphate/hydrogen phosphate, boric acid/borate, dihydrogen carbonate/hydrogen carbonate, (2,2,2)-trifluoroethanol/(2,2,2)-trifluoroethoxyde). For pH $>$ 13 sodium hydroxide solutions were used.

All the employed reagents were Merck pro analysis except (2,2,2)-trifluoroethanol, which was purchased from Sigma. The water employed was purified using a Millipore-Milli Q system.

Methodology

The *N*-X-Valine is formed in less than one second by mixing the amino acid and the hypohalite solutions (both with a pH value of approximately 9.5). The reaction was always followed at 255 nm, the wavelength at which *N*-Cl-Valine presents the maximum of absorption, this value coincides with that of most of other *N*-Cl-amino acids [7,8]. The absorption spectrum of the *N*-Cl-Valine does not vary with the pH value of the solution (between 4–14). The decomposition of *N*-Br-Valine was followed at 290 nm.

The initial absorbance is influenced by the order in which the reagents are mixed; if the buffer solution ($pH \leq 5$) is added before the hypochlorite, the initial absorbance of the mixture decreases and, occasionally the reaction cannot be followed [9].

Therefore, the mixing order always demanded the addition of the amino acid first, then the hypochlorite (both of an approx. pH value of 9.5) and finally the pH solution fixer. Unless indicated, buffer concentrations were kept as low as possible. The amino acid concentration was always in excess with respect to that of the hypochlorite (normally 90%), to avoid the formation of *N,N*-dichlorovaline [9].

The integrated first-order rate equation was fitted to the absorbance-time data obtained using a modification of the Davies, Swann, and Campey's alogorithm [10]. The reaction percentage studied was sufficiently ample (80%). When the experiments were repeated, rate constants never differed by more than 5%.

Product Analysis

In the absence of buffers *N*-Cl-Valine decomposes quantitatively to aldehyde, ammonia, chloride ion, and carbon dioxide (Scheme IIId). Whereas in the presence of buffers the reaction products are aldehyde and α-keto acid, ammonia, chloride ion and carbon dioxide (Scheme II). The ammonia production expressed as a percentage relative to the concentration of *N*-Cl-amino acid is (70 ± 15)% ($4 \leq pH \leq 14$). The aldehyde and α-keto acid analyses were carried out by generating the corresponding 2,4-dinitrophenylhydrazones as described in the literature [11]. Yields in aldehyde and in α-keto acid are dependent on the working conditions [12]. When pH $\geq$ 13 the α-keto acid is obtained in 100%.

Results

The process studied in this article follows first-order kinetics with respect to the N-Cl-Valine concentration, that is:

$$r = k_{obs}[N\text{-Cl-Val}] \tag{1}$$

The N-Cl-Valine complies with Beer-Lambert's Law (Fig. 1) with $\epsilon = 345 \pm 12$ mol^{-1} dm^{-3} cm^{-1} ($\lambda = 255$ nm and $4 < pH < 14$); this value was estimated by extrapolating the absorbance-time graphs to zero time and representing the initial absorbances obtained against the initial concentration of N-Cl-Valine.

pH Influence

The results obtained show that the reaction rate is independent of the acidity of the solution for the pH range 4–13 (Fig. 2), where $k_{obs} = (1.8 \pm 0.1) \cdot 10^{-4}$ s^{-1} at 298 K. When the pH values are less than 4 the reaction rate augments considerably, resulting in the impossibility of satisfactorily fitting the first-order equation to the absorbance-time data.

When pH values are greater than 13, the reaction rate increases in proportion to the pH of the solution (Fig. 3) according to:

$$r = r_0 + r_{OH^-} = k_{obs}[N\text{-Cl-Val}] = (k_0 + k_{OH^-}[OH^-])[N\text{-Cl-Val}] \tag{2}$$

where r_0 represents the term independent of the acidity, r_{OH} accounts for the dependence on the hydroxide ion concentration, k_0 is the unimolecular rate constant and

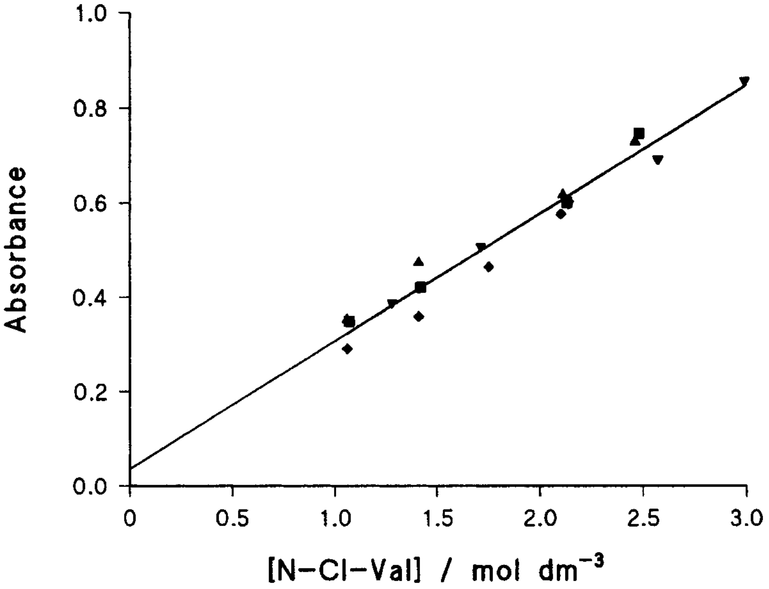


Figure 1. Absorbance-concentration graph compliance with Beer-Lambert's Law. $2 \cdot 10^{-3} < [N\text{-Cl-Val}] < 2.5 \cdot 10^{-3}$ mol dm^{-3}, I = 0.5 mol dm^{-3} (NaCl), T = 298 K, ■ pH = 4.3, ▲ pH = 7.2, ▼ pH = 10.0, and ◆ [NaOH] = 0.3 mol dm^{-3}.

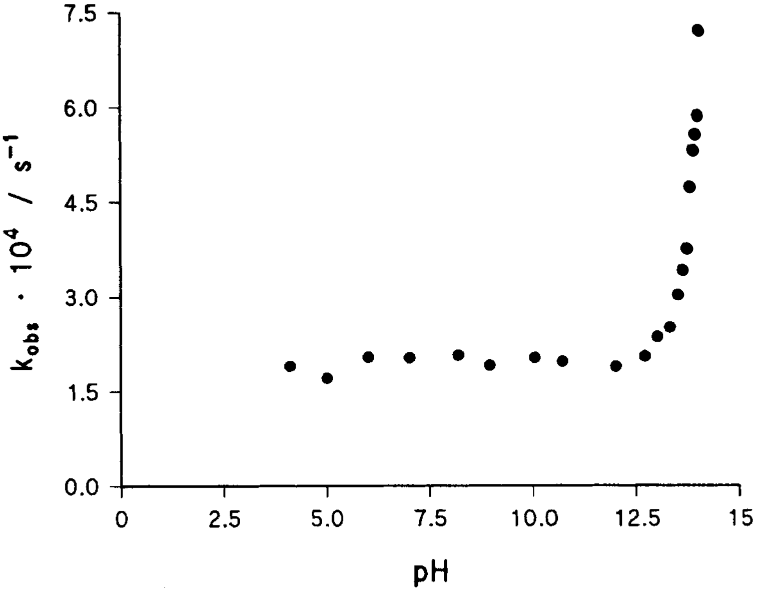


Figure 2. Influence of pH on the observed rate constant. $2 \cdot 10^{-3} < [N\text{-Cl-Val}] < 2.5 \cdot 10^{-3}$ mol dm^{-3}, $I = 0.5$ mol dm^{-3} (NaCl), and $T = 298$ K.

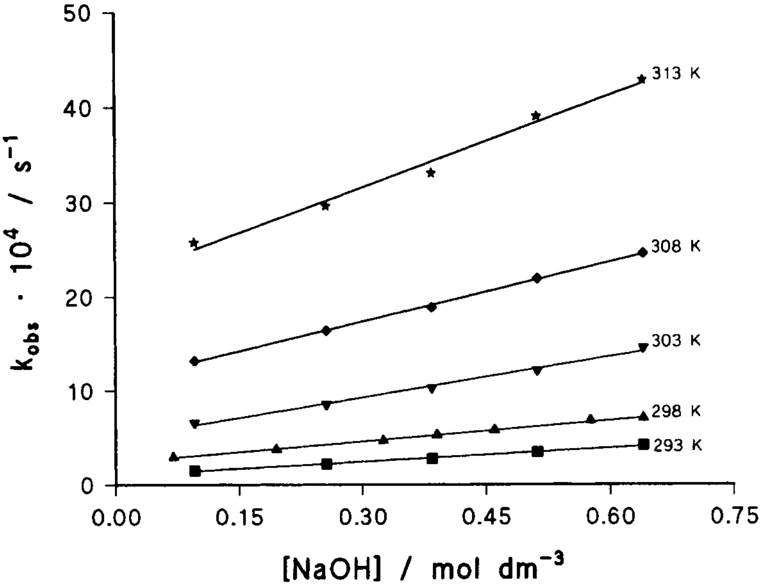


Figure 3. Influence of the sodium hydroxide concentration on the observed rate constant at different temperatures. $2 \cdot 10^{-3} < [N\text{-Cl-Val}] < 2.5 \cdot 10^{-3}$ mol dm^{-3}, and $I = 3$ mol dm^{-3} ($NaClO_4$).

coincides with the value for k_{obs} at pH < 13, and k_{OH} is the catalytic rate constant for the hydroxide ions.

Influence of the Hypochlorite and the (L)-Valine Concentration

The hypochlorite concentration does not have any influence on the rate constant on the pH range 4–14. Similarly a twofold increase in the concentrations of (L)-Valine does not modify the reaction rate.

Influence of the Ionic Strength

The results obtained show that ionic strength does not have any influence on the reaction rate over the pH range 4–13.

At pH ≥ 13 there is significant influence of the ionic strength. In fact if the sodium hydroxide is the only electrolyte, the representation of k_{obs} against [NaOH] shows a strong curvature which could be wrongly interpreted as a complex dependence with respect to the NaOH concentration. This curvature disappears when the experiments are carried out maintaining the ionic strength constant.

Influence of the Buffer Solutions

The influence of (2,2,2)-trifluoroethanol on the decomposition of the N-Cl-Valine was studied (Fig. 4) and the following dependence of the pseudo-first-order rate constant with the (2,2,2)-trifluorethoxide ion concentration (B) was found:

$$k_{\text{obs}} = k_0 + k_b[B] + k_{\text{OH}}[\text{OH}^-] \tag{3}$$

where k_0 and k_{OH} are the same as before (eq. (2)) and k_b is the catalytic rate constant for the (2,2,2)-trifluorethoxide ion.

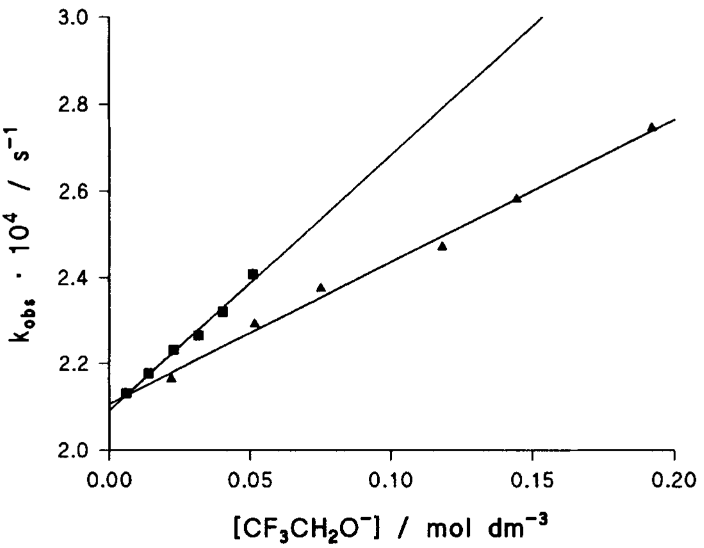


Figure 4. Influence of the trifluorethanol buffer concentration on the observed rate constant. $2 \cdot 10^{-3} < [N\text{-Cl-Val}] < 2.5 \cdot 10^{-3}$ mol dm^{-3}, $I = 1$ mol dm^{-3} (NaCl), $T = 298$ K, ■ pH = 12.7, and ▲ pH = 11.6.

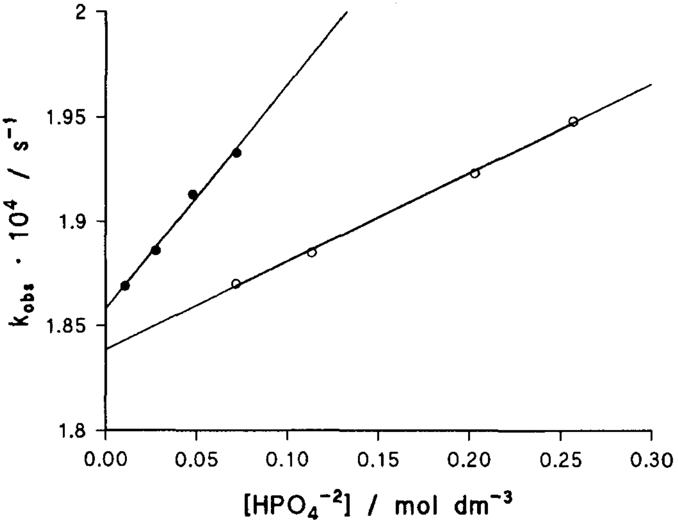


Figure 5. Influence of the phosphate buffer concentration on the observed rate constant. $2 \cdot 10^{-3} <$ [N-Cl-Val] $< 2.5 \cdot 10^{-3}$ mol dm^{-3}, $I = 1$ mol dm^{-3} (NaCl, HPO_4^{-2}, $H_2PO_4^-$), and $T = 298$ K, ● pH = 7.6, and ○ pH = 6.3.

The influence of (2,2,2)-trifluorethanol and phosphate buffers clearly shows the existence of general base catalysis (Figs. 4 and 5); i.e.:

$$k_{obs} = k_0 + \sum k_i[B] \tag{4}$$

where k_i represents the catalytic rate constant for each base present. Values for k_i are compiled in Table I.

Temperature Influence

The rate constants obtained for the *N*-Cl-Valine decomposition without buffer at different temperatures comply with the Arrhenius equation (Fig. 6). The values of the activation parameters are shown in Table II.

The study of the influence of the temperature was also carried out at pH > 13 (Fig. 3); the k_{OH} values obtained also comply with the Arrhenius equation (Fig. 6) and the activation parameters are compiled in Table II.

TABLE I. Catalytic rate constants for the base promoted-decomposition of *N*-Cl-Valine in aqueous solution at 298 K.

	$I = 1$ mol dm^{-3} (NaCl)	
Base	pK_a	$k_B \cdot 10^4$/mol^{-1} dm^3 s^{-1}
$H_2PO_4^-$	7.21	0.12
HPO_4^{-2}	12.74	1.3
$CF_3CH_2O^-$	12.43	3.6
OH^-	15.74	7.7
OH^-	15.74	74.8[a]

[a] *N*-Br-Valine.

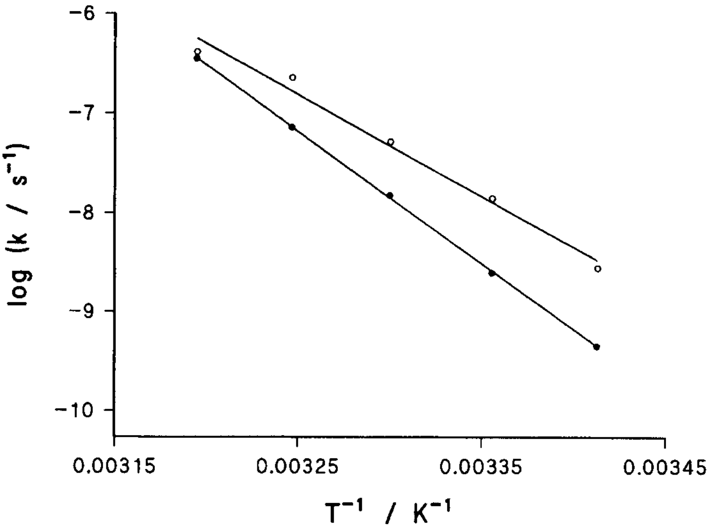


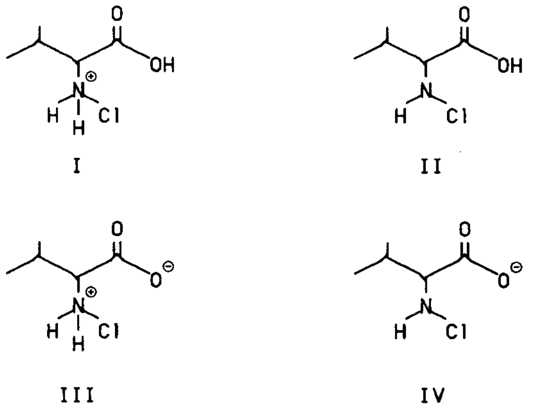
Figure 6. Arrhenius plot. ● Unimolecular decomposition and ○ Hydroxide-promoted decomposition.

TABLE II. Activation parameters for the decomposition of *N*-Cl-Valine in aqueous solution.

Unimolecular Fragmentation	Hydroxide Ion-Promoted Decomposition
E_a = (115 ± 2) kJ mol^{-1}	E_a = (74 ± 2) kJ mol^{-1}
$\Delta H^\ddagger$ = (112 ± 4) kJ mol^{-1}	$\Delta H^\ddagger$ = (71 ± 2) kJ mol^{-1}
$\Delta S^\ddagger$ = (62 ± 6) J mol^{-1} K^{-1}	$\Delta S^\ddagger$ = (−65 ± 6) J mol^{-1} K^{-1}

Discussion

Scheme I shows the different species through which the reaction can takes place. Although the pK_a values of the *N*-Cl-amino acids are unknown, it can be guessed which of the species I, II, III, and IV, is the predominant one in the solution.


I
II
III
IV

Scheme I

For species I, even considering that the pK_a values of the N-Cl-amino acid coincide with those of the amino acid, its proportion would be negligible under working conditions. It is to be expected that in species II, the presence of chlorine in the amino group forces the pK_a value of the carboxylic group to decrease slightly (to approx. 2), which permits its rejection. In species III, in tautomeric equilibrium with the latter, the pK_a of the amino group descends markedly owing to the presence of the chlorine atom [13,14], so it can be ignored.

The presence of only one species is guaranteed by the fact that neither the absorption spectrum nor the molar absortivity coefficient vary with the pH, which permits the claim of the practically exclusive existence of the ionic form IV in the pH range 4–14.

The results obtained suggest the existence of two clearly different processes: the unimolecular fragmentation and the base-promoted decomposition. Those processes correspond respectively to terms r_0 and r_B in eq. (2)

Base-Promoted Decomposition Process

Few published articles exist that a suggested show the decomposition of the N-Cl-amino acids at pH values greater than 11. Fox and Bullock [15] show that in the slow step the hydroxide ion abstract the α-hydrogen forming a carbanion and the chloride ion leaves subsequently, resulting in the formation of an imine, which rapidly hydrolyzes yielding ammonia and α-ketoacid. Antelo et al. [16] studied the decomposition of the N-Cl-Leucine at pH values greater than 12, putting forward a similar mechanism to that of Fox and Bullock.

The mechanism that is put forward for the base-promoted decomposition of the N-Cl-Valine takes place by means of a 1,2-elimination mechanism (Scheme II). Two possibilities exist: the ElcB or the $E2$ mechanism [17]. Depending on the magnitude of the rate constants k_1, k_{-1}, and k_2, three possibilities can be distinguished: ElcB reversible or $(E\text{lcB})_R$, ElcB irreversible or $(E\text{lcB})_I$ and $(\text{E1})_{\text{anion}}$.

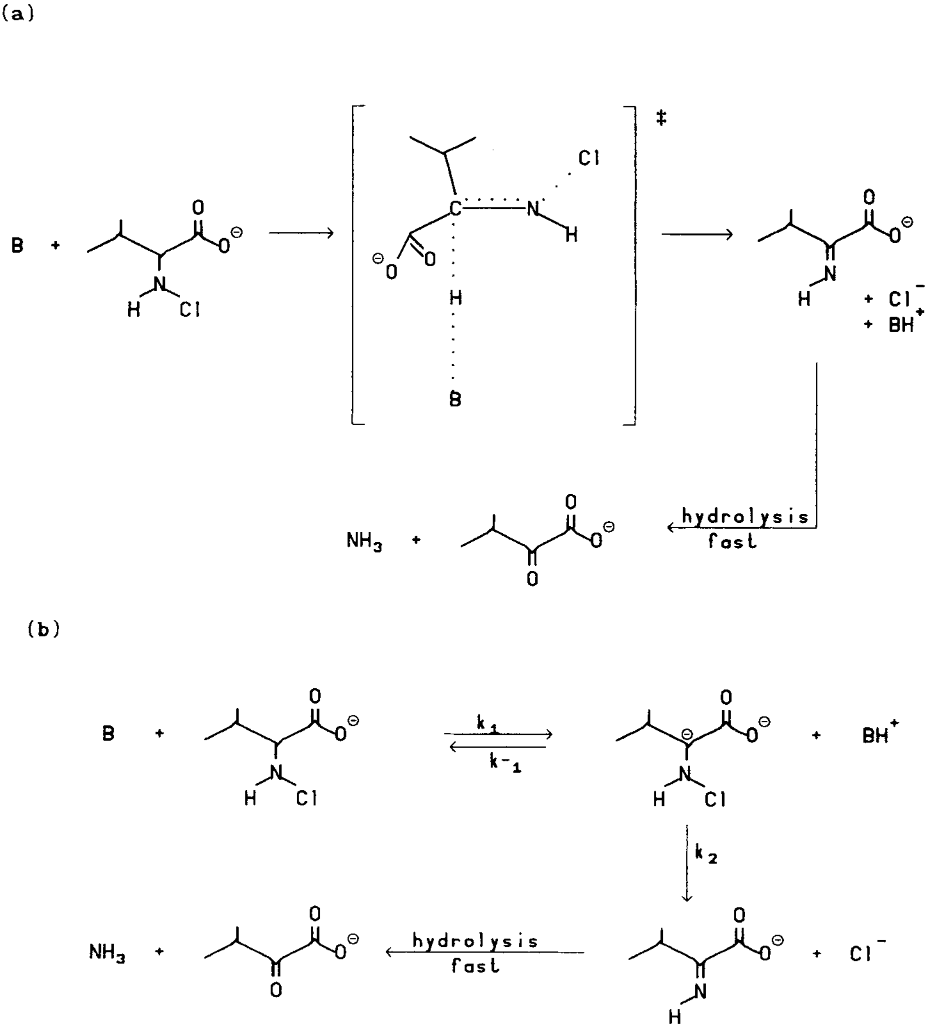
The $(\text{E1})_{\text{anion}}$ mechanism, contrary to what has been observed, is characterized by a rate law in which only the concentration of the species that undergoes the elimination figures.

In the ElcB mechanism the C—H bond is completely broken before the N—Cl bond (Scheme IIb), forming an intermediate. If $k_1\,[BH^+] >> k_2$, there is a rapid equilibrium where a carbanion is formed, followed by a slow elimination reaction; this mechanism is the $(E\text{lcB})_R$. Conversely, if $k_{-1}[BH^+] << k_2$ the rate determining step is the formation of the carbanion, which rapidly decomposes; this is the $(E\text{lcB})_I$ mechanism. The following equation is valid for the last two mechanisms:

$$r_B = \frac{k_1 k_2}{k_2 + k_{-1}[BH^+]}[B][N - \text{Cl} - \text{Val}] \tag{5}$$

On the other hand, in the $E2$ mechanism the proton removal and N—Cl bond-breaking take place simultaneously, forming a transition state which leads to the formation of the imine (Scheme IIa). As in the two preceding cases, the result is a theoretical rate equation with a first-order dependence both on the sodium hydroxide and on the N-Cl-amino acid concentration:

$$r_B = k_c[B][N\text{-Cl-Val}] \tag{6}$$



Scheme II

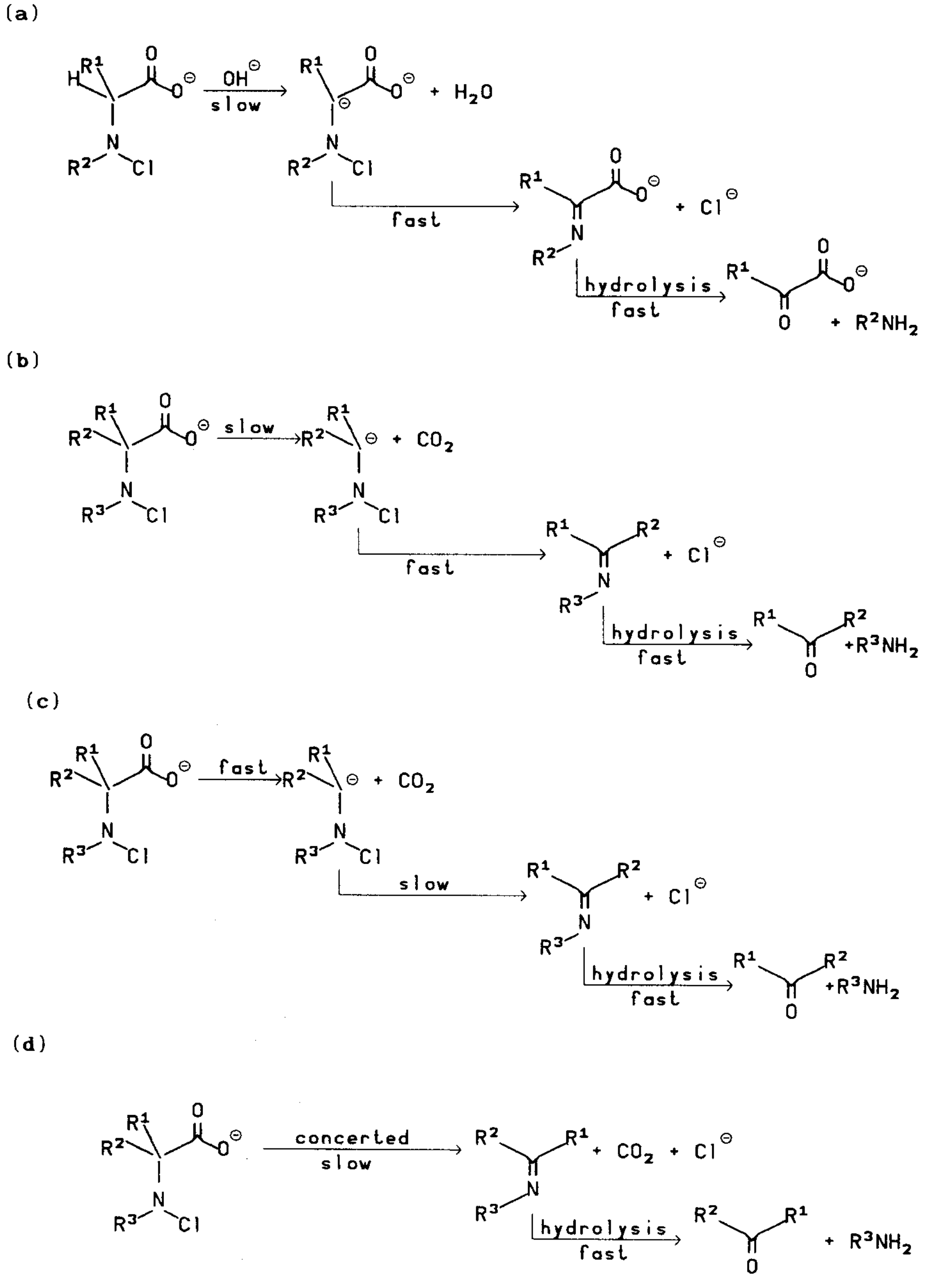
As far as the (*E*lcB)$_{\mathrm{R}}$ and (*E*1cB)$_{\mathrm{I}}$ mechanisms and the *E*2 mechanism are concerned, the theoretical rate equation corresponds with the base-promoted term of the experimental one. The magnitude of the activation parameters (Table II) and the effect of the ionic strength are consistent with either of them.

The existence of general base catalysis allows us to reject the (*E*lcB)$_{\mathrm{R}}$ mechanism, as it cannot be justified within its framework [18]. The choice between the (*E*lcB)$_{\mathrm{I}}$ and the *E*2 mechanisms is not straightforward, in both cases in increase of the catalytic rate constants with the pK_a is expected (see Table I). The fact that the decomposition rate of the *N*-Br-amino acids is greater than that of the corresponding *N*-Cl-amino acids [17,19] ($k_{N\text{-Br-Val}}/k_{N\text{-Cl-Val}} \approx 10$) is not easily explained by the (*E*lcB)$_{\mathrm{I}}$ mechanism, whereas the rate enhancement due to the presence of a better leaving group is characteristic of the *E*2 processes [18].

The *E*2 mechanism explains all the experimental facts satisfactorily, this mechanism is proposed to explain the base-promoted decomposition path.

Unimolecular Fragmentation Process

There are many mechanisms proposed for the unimolecular decomposition of the *N*-Cl-amino acids in aqueous solution. Fox and Bullock [15] propose a mechanism which implies the loss of the α-proton, as the rate determining step, forming an intermediate carbanion, which at a later stage loses the chlorine atom, producing an amine which hydrolyses (Scheme IIIa).



Scheme III

Awad et al. [20] found that the decomposition rate of a series of *N*-Cl-amino acids followed the order: *N*-Cl-Glycine < *N*-Cl-Alanine < *N*-Cl-Amino isobutyric acid. A mechanism similar to that of Fox and Bullock would predict a reverse order to the latter. If the formation of the carbanion were the rate controlling step, the *N*-Cl-Glycine carbanion would be more stable, and therefore, its decomposition rate would be greater, which is contrary to the experimental observations. The formation of a carbanion is possible if, in the first place, decarboxylation takes place [7] (Scheme IIIb); this mechanism is rejected for the same reasons as the latter.

The formation of an imine can also be considered as a valid rate determining step (Scheme IIIc), if the decarboxylation and dechlorination rates were different, which is contrary to what was observed by Awad et al. [20] (Table III).

The accepted mechanism [21] is a concerted fragmentation (Scheme IIId) which bases itself on: steric reasons, elevated values of the activation parameters, and the effect of the sustitutents on α-carbon. It rules out previous mechanisms comparing the decomposition rates of the *N*-Cl-Glycine, *N*-Cl-Alanine, *N*-Cl-Amino isobutyric acid, and the *N*-Cl-Sarcosine (see Table III).

However, in the literature there are three puzzling facts: (a) contradictory data for the unimolecular decomposition rate constants of the *N*-Cl-Glycine (Table III); therefore, this compound should not be used to establish comparisons to determine the mechanism; (b) the influence of the α-substituents did not appear to be so obvious [6], and (c) the reported composition of the reaction products; the decomposition of *N*-Cl-amino acids in aqueous solution leads to the production of carbon dioxide, chloride ions, ammonia, and aldehydes or ketones with one carbon atom less than the initial amino acid [22,23]. Nonetheless, the products do not render [23,24] as quantitatively as should be expected from a concerted fragmentation process. The above statements led to the suggestion of the existence of a highly destabilized intermediate reaction, nitrenium ion, [6] which might react through various paths. That intermediate might explain the rate increase when *N*-Cl-amino acid solutions are exposed to UV radiation [22].

TABLE III. Unimolecular rate constants for the decomposition of *N*-Cl-Amino acids in aqueous solution (T = 298 K).

N-Cl-amino acid	$k_0 \cdot 10^4/\text{s}^{-1}$	Ref.
N-Cl-Alanine [a]	2.7	[19]
N-Cl-Alanine [b]	2.3	[19]
N-Cl-Alanine [c]	2.5	[19]
N-Cl-2-Amino-isobutiric [a]	102	[20]
N-Cl–Sarcosine [b,c]	0.83	[19]
N-Cl-Glycine [d]	1.7	[19]
N-Cl-Glycine [a]	0.5	[23]
N-Cl-Glycine [a]	0.33	[23]
N-Cl-Glycine [a]	0.07	[21]
N-Cl-Glycine [a]	0.04	[20]
N-Cl-Valine [a]	1.8	This work
N-Br-Valine [a]	7.4	This work

[a] Spectrophotometric determination.
[b] Decarboxylation rate constant.
[c] Dechlorination rate constant.
[d] Initial rate constant.

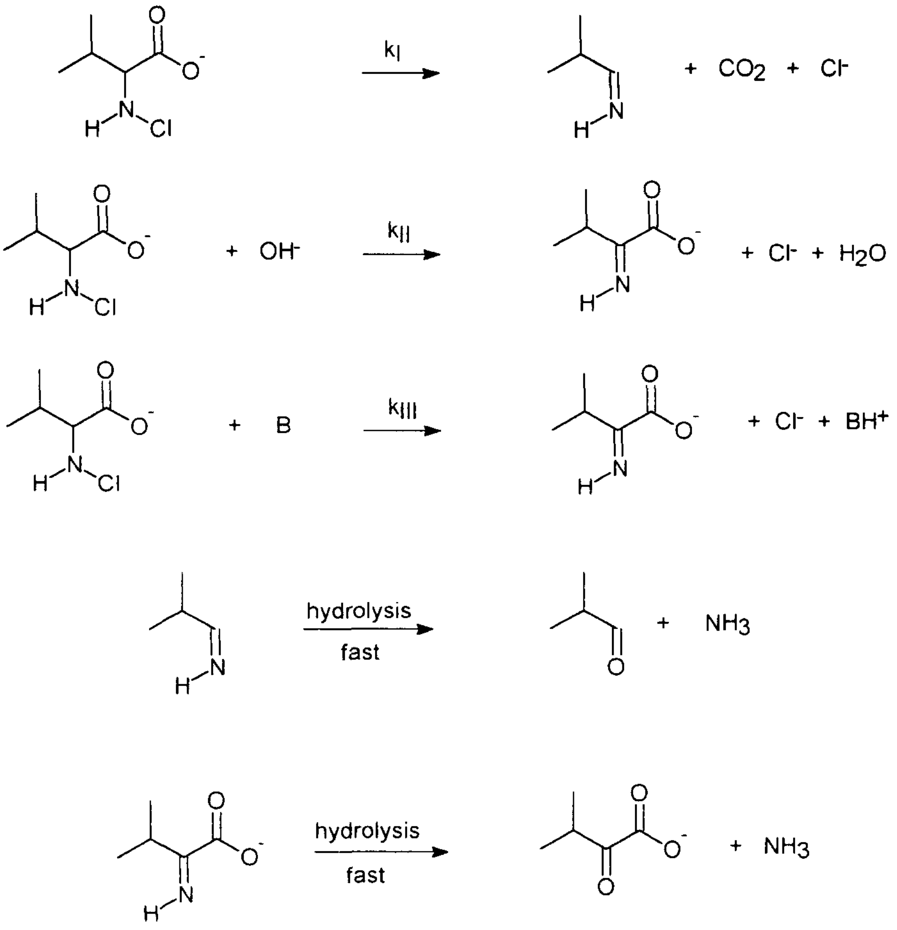
All the experimental facts, the newly explained composition of the products, the independence of the rate constant on the pH and the ionic strength, the magnitude of the activation parameters and the value 4.1 for the ratio $k_{\text{N-Br-Val}}/k_{\text{N-Cl-Val}}$, firmly support the concerted fragmentation mechanism for the unimolecular decomposition of *N*-Cl-amino acids.

Conclusion

Bearing all this in mind, the mechanism proposed for the decomposition of *N*-Cl-Valine in aqueous solution is shown in Scheme IV. From there, the theoretical rate equation is:

$$(7) \qquad \begin{aligned} r &= (k_{\mathrm{I}} + k_{\mathrm{II}}[\mathrm{OH}^-] + k_{\mathrm{III}}[\mathrm{B}])\,[N\text{-Cl-Val}] \\ &= \Big(k_{\mathrm{I}} + \sum k_j[B_j]\Big)[N\text{-Cl-Val}] \end{aligned}$$

which matches the experimental one (eqs. (3) or (4)). The composition of the reaction products becomes clear with that mechanism, the amounts of aldehyde and α-keto acid are proportional to the extension to which each pathway takes places.



Scheme IV

In summary, the decomposition of the *N*-Cl-amino acids in aqueous solution can be adequately described through two reaction paths. The first one is an unimolecular concerted fragmentation process, which is the main reaction path in the pH range 4 to 13 when the concentration of any base is low (<0.02 mol dm^{-3}). The other one is an *E*2 elimination process whose importance increases with pH and with the nature and the concentration of the bases present in the medium.

In the end, the existence of the general base catalysis process has to be considered in at least two ways: (i) the reported rate constant values for the unimolecular decomposition may be greater than the actual ones due to the buffer concentration used in their determination and (ii) the amounts of aldehyde and α-keto acid produced in the decomposition of *N*-Cl-amino acids are dependent on both the nature and the concentration of the bases present; which may be important in environmental impact studies.

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