

## CONCERTED BASE-PROMOTED ELIMINATION IN THE DECOMPOSITION OF *N*-HALO AMINO ACIDS

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*N*-Chloroamino acids are unstable in aqueous solution and decompose through different pathways depending on the reaction conditions, yielding precursors of carcinogenic and/or mutagenic compounds. One of these pathways is a 1,2-elimination process, which has scarcely received any attention and for which no systematic analysis is available. The process is first order relative to the *N*-chloroamino acid and to that of hydroxide ion. The use of 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoropropan-2-ol buffer solutions established that the process is general-base catalysed. The reaction rate is affected by the presence of a methyl group on the nitrogen atom and the nature of the leaving group. The results show an important steric effect due to the alkyl substituents on the  $\alpha$ -carbon. With bulky alkyl substituents on the  $\alpha$ -carbon, and in particular in the case of *N*-alkylamino acids, the catalytic effect increases as the base strength decreases. To characterize the transition state, Brønsted's  $\beta$  and  $\beta_{\text{lg}}$  were used. A More O'Ferrall–Jencks diagram shows the transition state structure changing from carbanion-like to nitrenium-like, a large perpendicular effect being evident. The reaction proceeds through a concerted mechanism  $A_{\text{sh}}D_{\text{H}}D_{\text{N}}$  instead of the stepwise  $A_{\text{sh}}D_{\text{H}}^{\ddagger} + D_{\text{N}}$  proposed earlier.

### 1. INTRODUCTION

Amino acids, found in significant quantities in waste-water and drinking water, undergo a fast chlorination reaction in near-neutral conditions<sup>1</sup>. In contrast to the primary and secondary chloramines, *N*-chloroamino acids are not stable in aqueous solution and decompose readily.<sup>2</sup> Different decomposition paths have been suggested depending on the acidity of the medium.<sup>2,3</sup> A concerted Grob fragmentation has been shown to be the main decomposition pathway<sup>2</sup> at pH values around 7, the reaction products being chloride ion, carbon dioxide, the corresponding carbonyl compound with one carbon atom less than the parent *N*-chloroamino acid and ammonia (if there is no substituent on the nitrogen atom, otherwise primary amines are formed). When the process takes place in more basic media, the reaction products are chloride ion, ammonia (or primary amines if the compound is *N*-substituted) and  $\alpha$ -keto acids,<sup>4</sup> the latter being precursors of undesirable products such as trichloroacetic acid (in neutral medium) and chloroform (in alkaline medium).

Little or no systematic work on these reactions has been carried out at pH 10. The traditionally accepted reaction mechanism is a stepwise  $\beta$ -elimination ( $A_{\text{sh}}D_{\text{H}}^{\ddagger} + D_{\text{N}}$  or, according to Ingold's nomenclature, *E1cB*), in which a carbanion intermediate is formed by proton abstraction from the  $\alpha$ -carbon and the initially formed product is an azomethine acid, which quickly hydrolyses to an  $\alpha$ -keto acid.<sup>5</sup> Recently, we carried out a study of the decomposition of the *N*-chloro and *N*-bromo derivatives of glycine and sarcosine in alkaline medium, the experimental results of which suggested an  $A_{\text{sh}}D_{\text{H}}D_{\text{N}}$  (*E2*) concerted mechanism.<sup>6,7</sup>

The study of the decomposition of several *N*-haloamino acids in the presence of hydroxide, trifluoroethoxide and hexafluoropropoxide ions has allowed to obtain a deeper insight into the base-promoted decomposition mechanism. The influence of alkyl substituents on the  $\alpha$ -carbon and the nitrogen atoms is analysed from a physical organic point of view.

### EXPERIMENTAL

All reagents were of the best available grade and were used without further purification.

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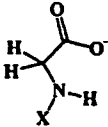
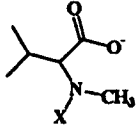
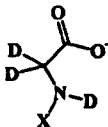
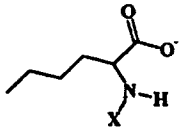
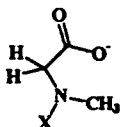
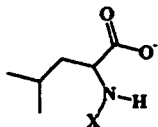
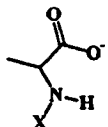
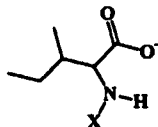
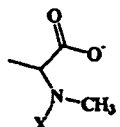
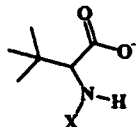
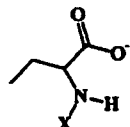
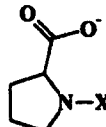
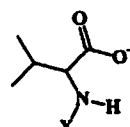
*N*-Haloamino acids. The *N*-haloamino acids (see Table 1) were generated *in situ* by simultaneous mixing of similar volumes of amino acid and hypochlorite or hypobromite solutions.<sup>1</sup>

The UV-visible absorption spectra of the *N*-chloroamino acids show a maximum around  $\lambda = 255$  nm whereas the *N*-alkyl-substituted analogues show a

maximum around  $\lambda = 267$  nm. The *N*-bromoamino acids give an absorption maximum near  $\lambda = 288$  nm that shifts to  $\lambda = 300$  nm when there is an alkyl group on the nitrogen.

*Kinetics.* Immediately after the formation of the *N*-halo amino acid (which takes place almost instantaneously),

Table 1. Amino acids used in this study (X is Cl or Br)

| ( <i>N</i> -X)- $\alpha$ -amino acid               | Structure                                                                           | ( <i>N</i> -X)- $\alpha$ -amino acid | Structure                                                                             |
|----------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------|
| ( <i>N</i> -X)-Gly                                 |    | ( <i>N</i> -X), ( <i>N</i> -Me)-Val  |    |
| ( <i>N</i> -X)-[ <sup>2</sup> H <sub>4</sub> ]-Gly |    | ( <i>N</i> -X)-Ahx                   |    |
| ( <i>N</i> -X)-Sar                                 |    | ( <i>N</i> -X)-Leu                   |    |
| ( <i>N</i> -X)-Ala                                 |  | ( <i>N</i> -X)-Ile                   |  |
| ( <i>N</i> -X), ( <i>N</i> -Me)-Ala                |  | ( <i>N</i> -X)-Tle                   |  |
| ( <i>N</i> -X)-Abu                                 |  | ( <i>N</i> -X)-Pro                   |  |
| ( <i>N</i> -X)-Val                                 |  | —                                    | —                                                                                     |

the hydroxide or alkoxide solution was added to achieve the desired conditions.<sup>6</sup> The reaction was followed at the above wavelengths, recording the values of the absorbance at different times until the band disappeared. A Beckman DU-70 UV-visible spectrophotometer equipped with a thermostated cell carrier was used to follow the kinetics. The temperature was kept constant to within  $\pm 0.05$  K by water circulation using a Frigiterm 6000382 thermostat. The *N*-halo amino acid concentrations in the reaction mixtures were  $ca\ 1.2 \times 10^{-3}$  and  $2.4 \times 10^{-3}$  mol dm<sup>-3</sup> for *N*-chloro- and *N*-bromo-amino acids, respectively. A twofold excess of  $\alpha$ -amino acid was used to prevent the formation of *N,N*-dihalo- $\alpha$ -amino acids.

The integration method was used to determine the pseudo-first-order rate constants, a modification of the Davies-Swann-Campey algorithm being used.<sup>8</sup>

**Acidity measurements.** pH measurements were made with a Crison 506 pH meter and an M-7598 glass electrode. When buffer solutions of 2,2,2-trifluoroethanol were used, the pH meter was calibrated to a value of pH 12 with a glycine-glycinate buffer. To avoid errors due to Na<sup>+</sup> ions, KCl was used as the electrolyte for the reference electrode and potassium hydroxide as a base. Owing to the slow response of the electrode in solutions of potassium hydroxide,<sup>9</sup> the same time (*ca.* 5 min) was allowed to elapse before taking any reading. The concentration of alkoxide in the reaction mixture was determined from

$$[B] = \frac{[B]_T}{(1 + 10^{(pK - pH)})} \quad (1)$$

where  $[B]$  and  $[B]_T$  are the concentrations of alkoxide and total alcohol, respectively, and the  $pK$  is the  $pK_a$  of the alcohol.

The concentration of hydroxide ion was determined by means of a pH meter calibrated with a standard solution of potassium hydroxide.

The ionic strength was maintained at 0.5 mol dm<sup>-3</sup> by using sodium chloride or potassium chloride in the studies with hydroxide ion or alkoxides, respectively.

## RESULTS

### Product analysis

As already stated, the reaction products of the decomposition of *N*-chloroamino acids in aqueous solution are chloride ion, carbon dioxide, ammonia (or methylamine), aldehyde and  $\alpha$ -keto acid. Ammonia was determined with an Ingold 152303000 selective electrode.  $\alpha$ -Keto acids were determined as their corresponding 2,4-dinitrophenylhydrazones.<sup>10</sup>

Table 2 shows the results obtained for the analysis of the reaction products. The expected value is recorded with the yield of  $\alpha$ -keto acid; it has been assumed that the elimination process leads to 100% formation of  $\alpha$ -

Table 2. Yields of ammonia and  $\alpha$ -keto acid in the hydroxide-promoted decomposition of *N*-chloroamino acids in aqueous solution at  $T = 298.0$  K

| <i>N</i> -Chloroamino acid | Ammonia (%) | $\alpha$ -Keto acid (%) |          |
|----------------------------|-------------|-------------------------|----------|
|                            |             | Observed                | Expected |
| <i>N</i> -Cl-Gly           | 66          | 100                     | 99       |
| <i>N</i> -Cl-Ala           | 99          | 100                     | 93       |
| <i>N</i> -Cl-Abu           | 83          | 65                      | 86       |
| <i>N</i> -Cl-Val           | 73          | 51                      | 47       |
| <i>N</i> -Cl-Leu           | 66          | 64                      | 59       |
| <i>N</i> -Cl-Ile           | 94          | 48                      | 35       |
| <i>N</i> -Cl-Sar           | 0           | 100                     | 99       |

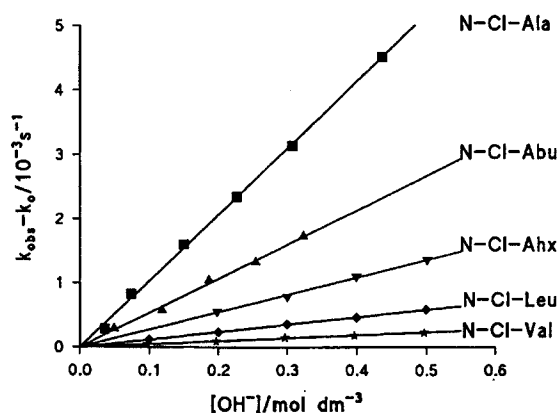


Figure 1. Influence of hydroxide ion concentration on the decomposition of *N*-chloro- $\alpha$ -alkylamino acids. [Amino acid] =  $3.0 \times 10^{-3}$  mol dm<sup>-3</sup>;  $[ClO^-] = 1.4 \times 10^{-3}$  mol dm<sup>-3</sup>;  $I = 0.5$  mol dm<sup>-3</sup>;  $T = 298$  K

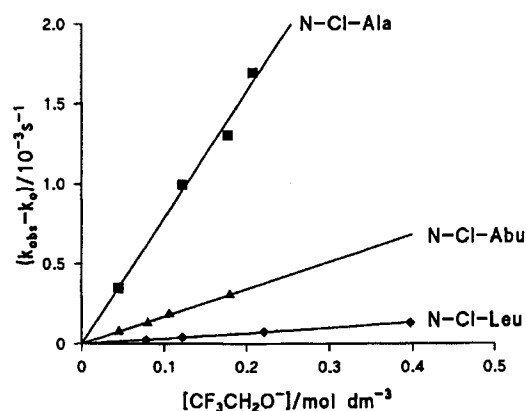


Figure 2. Influence of 2,2,2-trifluoroethoxide ion concentration on the decomposition of *N*-chloro- $\alpha$ -alkylamino acids. [Amino acid] =  $3.0 \times 10^{-3}$  mol dm<sup>-3</sup>;  $[ClO^-] = 1.4 \times 10^{-3}$  mol dm<sup>-3</sup>;  $I = 0.5$  mol dm<sup>-3</sup>;  $T = 298$  K

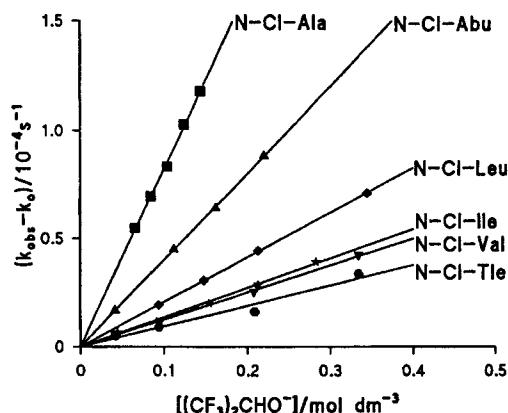


Figure 3. Influence of 1,1,1,3,3,3-hexafluoroisopropanoxide ion concentration on the decomposition of *N*-chloro- $\alpha$ -alkylamino acids. [Amino acid] =  $3.0 \times 10^{-3}$  mol dm $^{-3}$ ; [ClO $^{-}$ ] =  $1.4 \times 10^{-3}$  mol dm $^{-3}$ ;  $T = 298$  K

keto acid and should coincide with the percentage of  $k_{\text{obs}}$  that corresponds to the term  $k_{\text{OH}}[\text{OH}^{-}]$  in the equation

$$k_{\text{obs}} = k_0 + k_{\text{OH}}[\text{OH}^{-}] \quad (2)$$

that is, the percentage of expected  $\alpha$ -keto acid equals  $(k_{\text{OH}}[\text{OH}^{-}] \times 100)/k_{\text{obs}}$  and the experimental yield of  $\alpha$ -keto acid is estimated as  $([\alpha\text{-keto acid}] \times 100)/[N\text{-chloroamino acid}]_{\text{initial}}$ . As can be seen in Table 2, the expected and experimental yields are similar.

### Decomposition of *N*-haloamino acids (*N*-X-Aa)

The reaction rate shows a first order dependency on the concentration of *N*-chloroamino acid. The plot of the pseudo-first-order rate constant versus the concentration of hydroxide ion fits a straight line (Figure 1). Similar behaviour is observed in the presence of 2,2,2-trifluoroethoxide and 1,1,1,3,3,3-hexafluoroisopropanoxide ions (Figures 2 and 3). The hydrolysis of 2,2,2-trifluoroethanol causes changes in the pH value,<sup>11,12</sup> which lead to modifications in the contribution of the hydroxide ion catalysis to the value of the observed rate constant ( $k_{\text{obs}}$ ). Thus, the catalytic rate constant for 2,2,2-trifluoroethoxide ion was calculated by plotting  $k_{\text{obs}} - k_0$  versus the 2,2,2-trifluoroethoxide ion concentration. This leads to the following general rate equation:

$$r = r_0 + r_B = (k_0 + k_{\text{OH}}[\text{OH}^{-}] + k_B)[N - X - \text{Aa}] \quad (3)$$

where  $r_0$  is the contribution due to unimolecular decomposition,  $r_B$  the contribution of the base-promoted pathway,  $k_0$  the rate constant of the Grob fragmentation,  $k_{\text{OH}}$  the catalytic rate constant for hydroxide ion and  $k_B$  the catalytic rate constant for any base apart from hydroxide ion.

Although slight modifications of the pH values take place when 1,1,1,3,3,3-hexafluoropropan-2-ol buffer is used, no correction was carried out; the influence of the hydroxide ion catalysis at pH  $\approx 9$  becomes negligible. The values obtained for the catalytic rate constants of

Table 3. Summary of catalytic rate constants ( $k_{\text{OH}}$  and  $k_B$ ) for the base-promoted decomposition of *N*-haloamino acids in aqueous solution at 298.0 K,  $I = 0.5$  mol dm $^{-3}$

| <i>N</i> -Haloamino acid                           | $k_{\text{OH}} \times 10^3$<br>(mol $^{-1}$ dm $^3$ s $^{-1}$ ) | $k_{\text{TFF}} \times 10^3$<br>(mol $^{-1}$ dm $^3$ s $^{-1}$ ) | $k_{\text{HFP}} \times 10^3$<br>(mol $^{-1}$ dm $^3$ s $^{-1}$ ) |
|----------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|
| <i>N</i> -Cl-Gly <sup>6,7</sup>                    | 44.0 $\pm$ 0.2                                                  | 22 $\pm$ 1                                                       | 2.24 $\pm$ 0.05                                                  |
| <i>N</i> -Br-Gly <sup>6,7</sup>                    | 198 $\pm$ 8                                                     | 95 $\pm$ 2                                                       | 17.1 $\pm$ 0.8                                                   |
| [ $^2\text{H}_4$ ] <i>N</i> -Cl-Gly <sup>6,7</sup> | 7.40 $\pm$ 0.03                                                 | 3.4 $\pm$ 0.1                                                    | 0.36 $\pm$ 0.02                                                  |
| [ $^2\text{H}_4$ ] <i>N</i> -Br-Gly <sup>6,7</sup> | 48.5 $\pm$ 0.9                                                  | 22.5 $\pm$ 0.5                                                   |                                                                  |
| <i>N</i> -Cl-Ala                                   | 10.3 $\pm$ 0.2                                                  | 7.9 $\pm$ 0.6                                                    | 0.82 $\pm$ 0.02                                                  |
| <i>N</i> -Cl-Abu                                   | 5.3 $\pm$ 0.1                                                   | 1.70 $\pm$ 0.05                                                  | 0.40 $\pm$ 0.01                                                  |
| <i>N</i> -Cl-Ahx                                   | 2.4 $\pm$ 0.2                                                   |                                                                  |                                                                  |
| <i>N</i> -Cl-Leu                                   | 1.16 $\pm$ 0.02                                                 | 0.33 $\pm$ 0.01                                                  | 0.21 $\pm$ 0.01                                                  |
| <i>N</i> -Cl-Val                                   | 0.45 $\pm$ 0.02                                                 | 0.16 $\pm$ 0.05                                                  | 0.125 $\pm$ 0.003                                                |
| <i>N</i> -Cl-Ile                                   | 0.27 $\pm$ 0.02                                                 | 0.18 $\pm$ 0.01                                                  | 0.136 $\pm$ 0.005                                                |
| <i>N</i> -Cl-Tle <sup>a</sup>                      | 0.045 $\pm$ 0.005                                               | 0.041 $\pm$ 0.01                                                 | 0.093 $\pm$ 0.01                                                 |
| <i>N</i> -Br-Tle                                   | 1.22 $\pm$ 0.06                                                 |                                                                  |                                                                  |
| <i>N</i> -Cl-Sar <sup>6,7</sup>                    | 23.8 $\pm$ 0.4                                                  | 4.8 $\pm$ 0.1                                                    | 0.51 $\pm$ 0.02                                                  |
| <i>N</i> -Br-Sar <sup>6,7</sup>                    | 205 $\pm$ 6                                                     | 55.4 $\pm$ 0.6                                                   | 5.5 $\pm$ 0.3                                                    |
| <i>N</i> -Cl-N-Me-Ala                              | 5.7 $\pm$ 0.5                                                   | 4.4 $\pm$ 0.4                                                    | 7.2 $\pm$ 0.3                                                    |
| <i>N</i> -Br-N-Me-Ala <sup>b</sup>                 | 63 $\pm$ 5                                                      |                                                                  |                                                                  |
| <i>N</i> -Cl-N-Me-Val                              | 5.8 $\pm$ 0.1                                                   | 5.2 $\pm$ 0.1                                                    | 8.3 $\pm$ 0.1                                                    |
| <i>N</i> -Cl-Pro                                   | 23 $\pm$ 2                                                      | 19.0 $\pm$ 0.3                                                   | 5.9 $\pm$ 0.6                                                    |
| <i>N</i> -Br-Pro <sup>c</sup>                      | 61 $\pm$ 2                                                      |                                                                  |                                                                  |

<sup>a</sup> Tle was chosen as the three-letter system name for *tert*-leucine by analogy with its isomers Ile and Leu.

<sup>b</sup>  $T = 285.4$  K.

<sup>c</sup>  $T = 286.2$  K.

Table 4. Summary of rate constants for the unimolecular decomposition of the *N*-chloroamino acids in aqueous solution at  $T = 298.0\text{ K}$ ,  $I = 0.5\text{ mol dm}^{-3}$ 

| <i>N</i> -Chloroamino acid | $k_0 \times 10^4\text{ (s}^{-1}\text{)}$ |     |     |               |
|----------------------------|------------------------------------------|-----|-----|---------------|
|                            | Literature                               | HFP | TFE | $\text{OH}^-$ |
| <i>N</i> -Cl-Ala           | $2.7^2, 2.8^5, 3^{13}$                   | 3.3 | 3.1 | 4.9           |
| <i>N</i> -Cl-Leu           | $3.2^{14}$                               | 3.6 | 4   | 3.1           |
| <i>N</i> -Cl-Val           | $2.0^{15}$                               | 2.0 | 2.1 | 2.0           |
| <i>N</i> -Cl-Ile           | $1.97^3$                                 | 2.4 | 2.4 | 1.9           |
| <i>N</i> -Cl-Tle           | $2.12^3$                                 | 2.3 | 2.3 | 2.2           |

hydroxide, 2,2,2-trifluoroethanoxide and 1,1,1,3,3,3-hexafluoroisopropanoxide ions in the decomposition of several *N*-haloamino acids are collected in Table 3. (Throughout the tables and the figures we used TFE and HFP to designate 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoroisopropanoxide, or the corresponding anions.).

Table 4 gives the rate constants of the unimolecular decomposition (Grob fragmentation) obtained by extrapolation to zero base concentration. As can be observed, these rate constants are in agreement with those in the literature.

## DISCUSSION

Rate constants for the hydroxide ( $k_{\text{OH}}$ ), 2,2,2-trifluoroethanoxide ( $k_{\text{TFE}}$ ) and 1,1,1,3,3,3-hexafluoroisopropanoxide ( $k_{\text{HFP}}$ ) catalysed elimination of *N*-chloro derivatives of the amino acids of Gly, Ala, Abu, Ahx, Leu, Val, Ile and Tle are given in Table 3 (amino acids are referred to by the IUPAC three-letter nomenclature, except for *tert*-leucine, for which no name has been adopted and for which Tle is used; molecular structures are shown in Table 1).

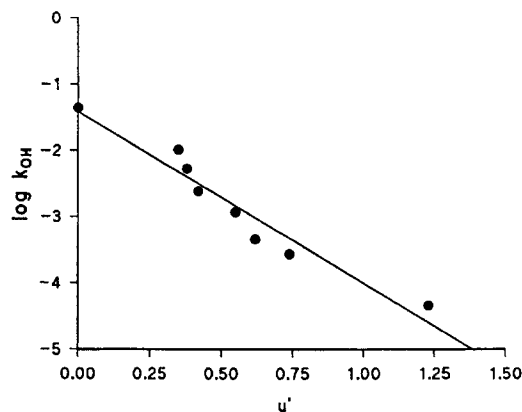
Examination of the rate constants in Table 3 shows that they decrease as substituents at the  $\alpha$ -carbon atom are made bulkier. This behaviour can be attributed either to a decrease in the acidity of the hydrogen attached to this carbon as result of inductive effects or to steric hindrance by the alkyl substituent.

A plot of  $\log k_{\text{OH}}$  versus Charton's<sup>16</sup> steric parameter  $\nu'$  is shown in Figure 4. A reasonable correlation is obtained with a slope of  $-2.59$ ; similar values have been reported.<sup>17</sup> This is consistent with a predominance of steric factors and not with differences in inductive effects of the alkyl substituents. This result agrees with those obtained by Brown and co-workers<sup>18</sup> and Charton.<sup>16</sup> Logarithms of rate constants for the reaction of the *N*-chloroamino acids with trifluoroethoxide and hexafluoropropanoxide ions were also plotted against  $\nu'$  and gave slopes of  $-2.39$  (TFE) and  $-1.17$  (HFP). The significance of these values will be discussed later.

The general importance of steric effects seems to be

confirmed by measurements for *N*-chloroproline (Table 3); the values for its catalytic rate constants are marked by than those obtained with *N*-chloroglycine. The steric hindrance in this cyclic structure should be less than that in the open-chain structures.

Brønsted plots of  $\log k_{\text{OH}}$  against the  $\text{p}K_{\text{a}}$  of the attacking base are shown in Figure 5 for the *N*-chloro derivatives of Ala, Abu, Leu, Ile and Tle. Although curvature cannot be established from three points, it can be inferred for *N*-Cl-Ala by comparison between the Brønsted plots; this curvature characteristic of the hydroxide and alkoxide ions<sup>19,20</sup> is also found for *N*-Cl-Gly<sup>7</sup> and *N*-Cl-Pro. Notwithstanding the limited number of points and the obvious non-linearity of the plots, approximate values of Brønsted exponents (Table 5) had been extracted from the data for the purpose of showing the generally small magnitude of the values and the trend towards smaller (and probably zero) slopes for the least reactive, most sterically hindered, substrates. Taking as a reference the  $\beta$  value for *N*-Cl-Gly, estimated qualitatively from the deuterium isotope effect measured in the hydroxide-promoted decomposition of *N*-Cl-Gly (see note in parentheses in footnote a in Table 5), we calculated apparent values of Brønsted's

Figure 4. Charton plot for the base-promoted decomposition of *N*-chloro- $\alpha$ -amino acids

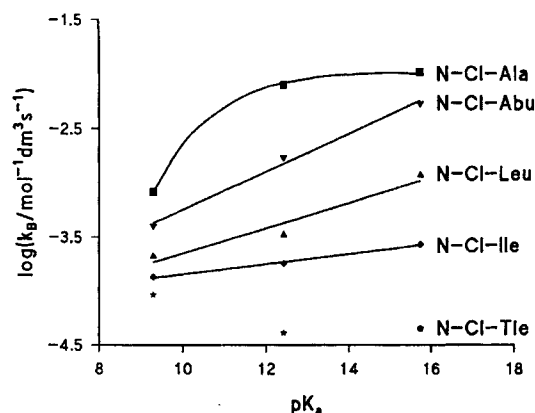


Figure 5. Brønsted plot for the base-promoted decomposition of *N*-chloro- $\alpha$ -amino acids

$\beta$  (see footnote b in Table 5) for *N*-Cl-Ala, *N*-Cl-Pro and *N*-Cl-Sar.<sup>7</sup> This procedure has been used in systems with similar behaviour.<sup>11,12</sup>

Table 6 shows the values for the effect of the leaving group, expressed as  $k_{Br}/k_{Cl}$ , on the hydroxide-promoted decomposition of *N*-haloamino acids. Two points are relevant: first, as the substituent at the  $\alpha$ -carbon is made bulkier, the leaving group effect increases, and second, the ratio  $k_{Br}/k_{Cl}$  is higher when the methyl group is on the nitrogen. The trend in those values suggests a change in the transition state as the structure of the *N*-haloamino acid is modified.

A More O'Ferrall-Jencks diagram (Figure 6) can be used to show qualitatively the important modifications in the transition state as the structure of the different *N*-haloamino acids changes, the N-halogen bond breaking, except for *N*-halo-Gly, being ahead of the C—H bond-breaking ( $\beta < \beta_{lg}$ ) (the  $\beta_{lg}$  parameter<sup>21</sup> can also be used as an index of the leaving group effect;  $\beta_{lg}$  values were estimated using the values given by Bell<sup>22</sup>

for the  $pK_a$  values of HCl and HBr; although the use of  $\beta_{lg}$  when  $Cl^-$  and  $Br^-$  are leaving groups can be criticized, the work presented here is concerned with the decomposition of *N*-haloamino acids). Figure 6 clearly shows the great perpendicular effect<sup>24</sup> (the term 'perpendicular effect' is preferred to 'anti-Hammond effect' because perpendicular and Hammond effects are not opposites) induced by the increase in substitution on the  $\alpha$ -carbon and/or on the nitrogen atoms as well as by the change to a better leaving group. Perpendicular effects have been also found by Hoffman and co-workers<sup>24</sup> in their study of imine-forming eliminations in *N*-substituted-*O*-arylsulphonylhydroxylamines.

Interaction coefficients<sup>25,26</sup> provide a good description of the disturbance produced by structural changes in the transition state of a concerted process. Crossed coefficients such as  $p_{yy'}$ , and  $p_{xy'}$ , defined as

$$p_{yy'} = -\frac{\partial \beta_{lg}}{\partial \sigma} = -\frac{\partial \rho}{\partial pK_{lg}}; \quad p_{xy'} = \frac{\partial \beta}{\partial \sigma} = \frac{\partial \rho}{\partial pK_{BH}} \quad (4)$$

describe quantitatively the degree of interaction of the substituents on the  $\alpha$  carbon atom with the leaving group and the base, respectively.

The use of such parameters has no sense when, as in the present study, the alkyl substituents do not show any relevant difference in their inductive effect. In place of these parameters, the following can be defined:

$$p_{syy'} = -\frac{\partial \beta_{lg}}{\partial \nu'} = -\frac{\partial \psi}{\partial pK_{lg}}; \quad p_{sxy'} = \frac{\partial \beta}{\partial \nu'} = \frac{\partial \psi}{\partial pK_B} \quad (5)$$

where  $\nu'$  represents the Charton parameter<sup>16</sup> according to

$$\log k = \omega \nu' + h \quad (6)$$

Table 7 shows the expected and estimated values of the interaction parameters  $p_{syy'}$ , and  $p_{sxy'}$ , for different reaction pathways; the values found in this work were calculated from the variation of  $\Psi$  with  $pK_{lg}$  and  $pK_{lg}$  and  $pK_{BH}$ , respectively.

Table 5. Values of Brønsted's  $\beta$  for the base-promoted decomposition of *N*-chloroamino acids in aqueous solution at  $T = 298.0$  K

| <i>N</i> -Chloroamino acid      | $\beta$   | <i>N</i> -Chloroamino acid    | $\beta$   |
|---------------------------------|-----------|-------------------------------|-----------|
| <i>N</i> -Cl-Gly <sup>7,a</sup> | 0.35–0.40 | <i>N</i> -Cl-Sar <sup>7</sup> | 0.26      |
| <i>N</i> -Cl-Ala <sup>b</sup>   | 0.31–0.35 | <i>N</i> -Cl-Pro <sup>b</sup> | 0.16–0.19 |
| <i>N</i> -Cl-Abu                | 0.17      | <i>N</i> -Cl-Ile              | ~0        |
| <i>N</i> -Cl-Leu                | 0.12      | <i>N</i> -Cl-Val              | ~0        |

<sup>a</sup> Estimated by assuming a maximum primary deuterium isotope effect between 7 and 8 (accepting a value between 7 and 8 for the primary deuterium isotope effect when the proton is half transferred, i.e.  $\beta = 0.5$ ; a value between 0.39 and 0.44 should be a valid estimate of  $\beta$  for *N*-Cl-Gly).

<sup>b</sup> Apparent  $\beta$  values<sup>11,12</sup> calculated with respect to the *N*-Cl-Gly.<sup>7</sup> We plotted  $\log k$  for *N*-Cl-Ala and *N*-Cl-Pro [using  $OH^-$ ,  $CF_3CH_2O^-$  and  $(CF_3)_2CHO^-$  as base catalysts] versus the corresponding values of  $\log k$  for *N*-Cl-Gly. The plots are linear and from the slope and the  $\beta$  value for *N*-Cl-Gly an apparent  $\beta$  value can be estimated; these  $\beta$  values should be considered as maximum values. The method described for the determination of apparent  $\beta$  will only be valid when the degree of proton transfer within the series of parent reactions does not vary substantially.

Table 6. Values of the leaving group effect ( $k_{Br}/k_{Cl}$ ) for the hydroxide-promoted decomposition of *N*-haloamino acids in aqueous solution at  $T = 298$  K

| Amino acid       | $k_{Br}/k_{Cl}$ | Amino acid                    | $k_{Br}/k_{Cl}$ |
|------------------|-----------------|-------------------------------|-----------------|
| Gly <sup>7</sup> | 4.4             | Sar <sup>7</sup>              | 8.7             |
| Ala <sup>a</sup> | 10.0            | Tle                           | 27.5            |
| Leu <sup>a</sup> | 10.5            | <i>N</i> -Me-Ala <sup>b</sup> | 63.1            |
| Ile <sup>a</sup> | 22.9            | Proc <sup>c</sup>             | 11.0            |

<sup>a</sup>The values of  $k_{OH}$  used for the *N*-bromo derivatives are those published by Antelo and co-workers.<sup>27</sup>

<sup>b</sup> $T = 285.4$  K.

<sup>c</sup> $T = 286.2$  K.

Although the available data are not sufficiently quantitative to justify a formal analysis in terms of interaction coefficients, these values suggest a decrease in  $\beta$  and an increase in the N-halogen bond breaking when the steric hindrance at the  $\alpha$ -carbon atom is

increased, which agrees with a concerted  $A_{xh}D_HD_N$  mechanism. For a central or carbanion-like transition state, it is expected that  $|p_{sxy'}| \gg |p_{syy'}|$ ; hence the values obtained in Table 7 support a nitrenium-like transition state.

The magnitude of the interaction parameter  $p_{sxy'}$  allows an interpretation of the magnitude of the Charton slope for the different bases. A value of  $p_{sxy'} \neq 0$  means that the slope of the Charton plot depends on the strength of the base; a negative value implies that the steric effect has less importance as base is weaker, *i.e.* the absolute value of  $\psi$  should be less. This is the observed behaviour, the absolute value of the Charton slope with the bulkier  $(CF_3)_2CHO^-$  being smaller than with  $CF_3CH_2O^-$  and  $OH^-$ .

The previous discussion does not interpret the results obtained with the *N*-chloro derivatives of Tle, *N*-Me-Val and *N*-Me-Ala, for which a greater catalytic rate constant with the weakest base is obtained. A possible explanation for this behaviour could be an interaction

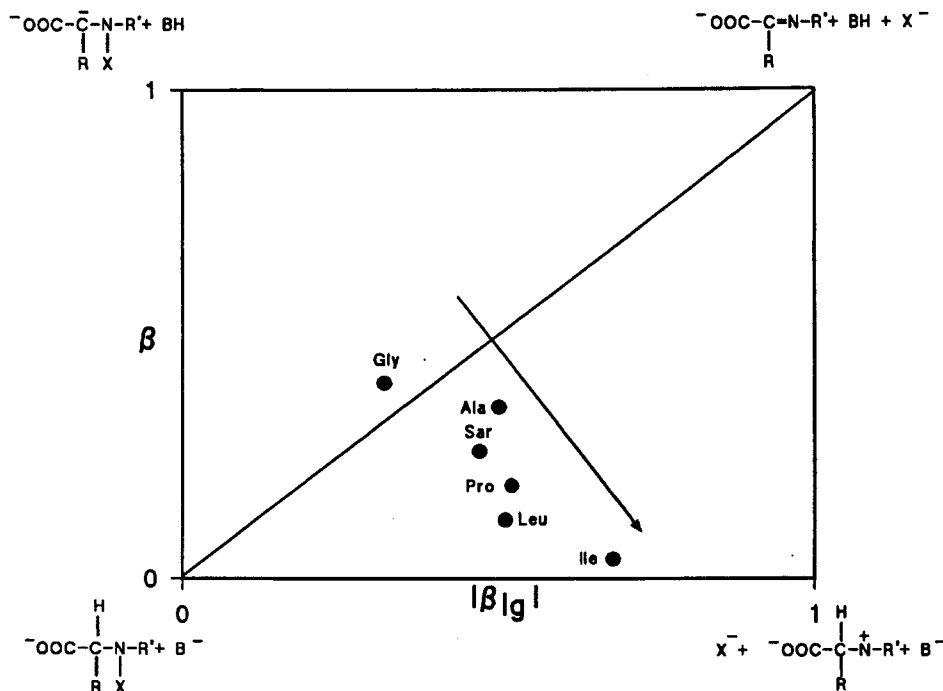


Figure 6. More O'Ferrall-Jencks' diagram for the base-promoted decomposition of *N*-chloro- $\alpha$ -amino acids

Table 7. Expected values for  $p_{syy'}$  and  $p_{sxy'}$  as a function of the reaction pathway

| Parameter  | $A_{xh}D_H^\ddagger + D_N$ | $D_N^\ddagger + A_{xh}D_H^\ddagger$ | $A_{xh}D_HD_N^\ddagger$ | This work |
|------------|----------------------------|-------------------------------------|-------------------------|-----------|
| $p_{syy'}$ | 0                          | 0                                   | $S \leftrightarrow H^a$ | 0.3       |
| $p_{sxy'}$ | H                          | 0                                   | $S \leftrightarrow H$   | -0.2      |

<sup>a</sup>S = small and H = high.

between the attacking base and the N atom, *i.e.* an  $A_{\text{N}}D_{\text{H}}D_{\text{N}}(A_{\text{N}})$  mechanism (or  $E2C$  according to Ingold's nomenclature). This mechanism has not been generally accepted but within the framework of the valence-bond configuration mixing (VBCM) model,<sup>28</sup> the  $A_{\text{N}}D_{\text{H}}D_{\text{N}}(A_{\text{N}})$  mechanism makes the observed facts understandable. However, the data are insufficient to support or reject this mechanism.

### Activation parameters

Table 8 shows the activation parameters for the hydroxide-promoted decomposition of *N*-chloroamino acids. The activation parameters were estimated from plots of  $\log k_{\text{B}}/T$  versus  $1/T$ ; an example is shown in Figure 7. The variation in  $\Delta S^{\ddagger}$  values can be interpreted in terms of a changing transition state; the activation entropy increases as the degree of proton transfer decreases and the N-halogen bond breaking increases, *i.e.*  $\Delta S^{\ddagger}$  varies from negative values when the transition

state is carbanion-like (*N*-Cl-Gly) to positive values for a nitrenium-like transition state (*N*-Cl-Tle). The same trend in  $\Delta H^{\ddagger}$  and  $\Delta S^{\ddagger}$  values was observed by Cho and co-workers<sup>17</sup> in studies of imine-forming eliminations in *N*-chlorobenzylalkylamines, where the transition state is more carbanion like.

### CONCLUSIONS

The following conclusions can be drawn for the base-promoted decomposition of *N*-haloamino acids in aqueous solution:

Bulky alkyl substituents on the  $\alpha$ -carbon decrease the rate of base-catalysed catalyzed decomposition; a linear correlation is found between  $\log k_{\text{B}}$  and Charton's steric parameter.

An *N*-methyl group on the amino nitrogen of the *N*-chloroamino acid decreases the rate of base-catalysed decomposition of the amino acids bearing small substituents on the  $\alpha$ -carbon (*N*-Cl-Gly/*N*-Cl-Sar), but increases the rate of base-catalysed decomposition for *N*-chloroamino acids with bulky substituents on the  $\alpha$ -carbon (*N*-Cl-Val/*N*-Cl-*N*-MeVal) for the three bases used in this study [ $\text{OH}^-$ ,  $\text{CF}_3\text{CHO}^-$ ,  $(\text{CF}_3)_2\text{CHO}^-$ ]. For *N*-chloroamino acids with intermediate substituents (*N*-Cl-Ala/*N*-Cl-*N*-MeAla) the effect varies with base strength, resembling the case for smaller substituents with stronger bases, and the effect with larger substituents with weaker bases.

The effect of the leaving group (Br or Cl) on the  $\text{OH}^-$ -catalysed reaction changes with the size of the  $\alpha$ -substituent. The *N*-bromo compounds react more rapidly than the *N*-chloro compounds, and the difference in reactivity becomes more pronounced as the substituent on the  $\alpha$ -carbon becomes larger.

$\Delta S^{\ddagger}$  for the hydroxide promoted reaction appears to be negative in general for *N*-chloroamino acids with small  $\alpha$ -substituents and tends towards positive values for *N*-chloroamino acids with bulky  $\alpha$ -substituents.

Base-promoted decomposition of *N*-haloamino acids in aqueous solution proceeds through a concerted  $A_{\text{N}}D_{\text{H}}D_{\text{N}}$  mechanism in place of  $A_{\text{N}}D_{\text{H}}^{\ddagger} + D_{\text{N}}$  which has previously been considered valid. The degree of asynchronicity increases with increasing substitution on the  $\alpha$ -carbon and/or on the nitrogen atom and also when a better leaving group is present, covering the  $A_{\text{N}}D_{\text{H}}D_{\text{N}}$  spectrum. This variation in the structure of the transition state is a clear example of a process with a noticeable perpendicular effect.

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Table 8. Activation parameters for the hydroxide-promoted decomposition of *N*-chloroamino acids in aqueous solution<sup>a</sup>

| <i>N</i> -Chloroamino acid     | $\Delta H^{\ddagger}$ (kJ mol <sup>-1</sup> ) | $\Delta S^{\ddagger}$ (J mol <sup>-1</sup> K <sup>-1</sup> ) |
|--------------------------------|-----------------------------------------------|--------------------------------------------------------------|
| <i>N</i> -Cl-Gly               | 56 ± 2                                        | -83 ± 4                                                      |
| <i>N</i> -Cl-Ala               | 67 ± 3                                        | -57 ± 4                                                      |
| <i>N</i> -Cl-Abu               | 72 ± 5                                        | -45 ± 6                                                      |
| <i>N</i> -Cl-Ahx               | 72 ± 4                                        | -53 ± 5                                                      |
| <i>N</i> -Cl-Leu               | 77 ± 3                                        | -43 ± 4                                                      |
| <i>N</i> -Cl-Val               | 84 ± 2                                        | -28 ± 1                                                      |
| <i>N</i> -Cl-Ile               | 90 ± 3                                        | -11 ± 1                                                      |
| <i>N</i> -Cl-Tle               | 106 ± 6                                       | 27 ± 3                                                       |
| <i>N</i> -Cl-Sar               | 60 ± 3                                        | -64 ± 2                                                      |
| <i>N</i> -Cl- <i>N</i> -Me-Ala | 94 ± 4                                        | 27 ± 1                                                       |

<sup>a</sup> Errors in activation parameters were estimated from the results of the least-squares fit and considering the error in the rate constants.

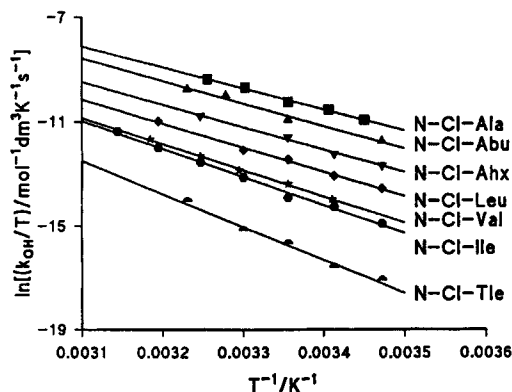


Figure 7. Influence of temperature on the hydroxide ion-promoted decomposition of *N*-chloro- $\alpha$ -amino acids



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