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Acid-Base Equilibria and Decomposition of Secondary (N-Cl)-α-Amino Acids.

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Abstract: the decomposition of (N-Cl)-Sarcosine, (N-Cl),(N-Me)-Alanine, (N-Cl)-Proline, (N-Cl),(N-Me)-Valine, and (N-Cl)-2-piperidine carboxylic acid (Pipecolic acid) was studied under acid conditions. The results suggest the participation of the four possible species of the (N-Cl)-α-amino acid. A reaction mechanism is proposed which allows us to estimate the rate constant for the decomposition of each species, as well as the yet unknown macroscopic, microscopic and tautomeric equilibrum constants. The relation between the different rate and equilibrium constants is also analyzed.

Introduction.

In the framework of an extensive project in relation to water disinfection, some work has been done on the way in which nitrogenated compounds react with chlorine[1,2,3] and how the so-formed (N-Cl)-compounds decompose[4,5,6,7,8,9,10]. Up-to-date, no studies are available concerning the decomposition of (N-Cl)-α-amino acids in acid media ($pH<3$), mainly due to the favoured disproportionation reaction taking place in these conditions to yield (N,N)-di-Cl-α-amino acids that subsequently decompose.

Taking into account that in the case of the secondary (N-Cl)-α-amino acids the disproportionation reaction

$$(N\text{-}Cl)\text{-}\alpha\text{-}amino\ acid + (H\text{-}N\text{-}Cl)^{+}\text{-}\alpha\text{-}amino\ acid \rightarrow$$

$$\rightarrow (N,N)\text{-}di\text{-}Cl\text{-}\alpha\text{-}amino\ acid + \alpha\text{-}amino\ acid + H^{+}$$

is impeded, we have studied the decomposition of (N-Cl)-Sarcosine, (N-Cl),(N-Me)-Alanine, (N-Cl)-Proline, (N-Cl),(N-Me)-Valine, and (N-Cl)-2-piperidine carboxylic acid in order to propose a mechanism for their decomposition in acid media.

Experimental.

Reagents.

All the α-amino acids were supplied by Sigma® except Sarcosine that was Merck®. Water was obtained from a Millipore®-Milli Q purification system.

The chlorinating agent was prepared weekly by bubbling Cl_2 (g) through NaOH solution, daily brought to pH *ca* 9 and spectrophotometrically titrated ($\lambda_{max}(H_2O) = 292$ nm, $\epsilon \approx 350$ $dm^3 \cdot mol^{-1} \cdot cm^{-1}$ for ClO^- when $pH > 12$).

H_3PO_4 / $H_2PO_4^-$ and $H_2PO_4^-$ / HPO_4^{-2} mixtures were used as buffer solutions, the overall buffer concentration being 0.02 $mol \cdot dm^{-3}$. The acid media were generated by adding the appropriate amount of previously titrated acid, which was $HClO_4$ except where indicated. The values of proton activity were corrected according to the H_0 acidity function[11].

The ionic strength was kept constant at $I = 1.0$ $mol \cdot dm^{-3}$ using sodium perchlorate.

Equipment.

A Vis-UV Beckman® DU-70 spectrophotometer was used to follow the kinetic runs. The temperature was kept constant to within ±0.1K using water flow from a Colora® thermostat.

The pH was measured with a combined glass electrode previously filled with sodium chloride as internal electrolyte and calibrated with Crison® buffer solutions ($pH = 4.01 \pm 0.01$, potassium hydrogen phtalate / potassium phtalate, and $pH = 7.00 \pm 0.01$, potassium dihydrogen phosphate / potassium hydrogen phosphate at 298.0 K). The achieved accuracy for pH measurements was ±0.02 pH units.

Procedure.

Aqueous chlorine ($pH \sim 9$) was mixed with the α-amino acid ($pH \sim 9$) and the appropriate amount of $NaClO_4$ to reach the desired ionic strength. Working in this way, the chlorination takes place near its maximum rate value[1,7]. An excess of 100% α-amino acid was always employed. Eventually, the adequate amount of buffer or mineral acid solution was added to reach the desired pH, so that the chlorination and the decomposition processes were clearly separated.

The reactions were spectrophotometrically followed at the wavelength of the maxima of absorption, which was previously determined to be around 267 nm in all cases.

The first order rate equation was fitted to the absorbance / time data using a modification of the non-linear optimization algorithm due to Davies, Swann and Campey[12] and of that due to Marquardt[13].

Reaction products.

Aldehydes with one less carbon atom than the (N-Cl)-α-amino acid were found as reaction products.

The analyses have been carried out for (N-Cl)-Sarcosine, (N-Cl),(N-Me)-Alanine and (N-Cl),(N-Me)-Valine by generating the (2,4)-dinitrophenyl hydrazones of the aldehydes, extracting them with hexane, and measuring the absorbance of the obtained solution at 340 nm[14] (the extinction coefficient was obtained previously following the same procedure with the pure aldehydes). Reproducibility was about 15 %.

The so-obtained results, compiled in Table 1, agree with those obtained in neutral of mild basic media for the Grob fragmentation of (N-Cl)-α-amino acids, for which the reaction products are carbonyl compounds with one less carbon atom than the (N-Cl)-α-amino acid, carbon dioxide, ammonia or primary amines and chloride ions.

Table 1: products of decomposition of secondary (N-Cl)-α-amino acids in acid media. $[(N\text{-}Cl)\text{-}\alpha\text{-amino acid}]_0 \simeq 1.2\cdot10^{-3}$ mol·dm^{-3}. Room temperature. Yields, based on the initial concentration of (N-Cl)-α-amino acid, do not consider rate constants for other pathways.

(N-Cl)-α-amino acid	% Aldehyde		
	[HCl]=0.05 mol·dm^{-3}	[HCl]=0.50 mol·dm^{-3}	8.5<pH<7.0
(N-Cl)-Sar	100	100	100 [10]
(N-Cl),(N-Me)-Ala	87	74	73 [10]
(N-Cl),(N-Me)-Val	71	100	100

Results and Discussion.

The reactions are first order relative to the concentration of (N-Cl)-α-amino acid in the pH working range. The observed rate constant is independent of both the α-amino acid and the chlorinating agent concentration.

Thus, the reaction rate is given by:

$$r = k_{obs}\cdot[(N\text{-}Cl)\text{-}\alpha\text{-}amino\ acid]$$

where k_{obs} is the observed rate constant.

The dependence of k_{obs} *versus* the acidity of the medium shows two patterns:

i) In the case of (N-Cl)-Sarcosine and (N-Cl)-2-piperidine carboxylic acid the rate constant decreases on increasing the acidity, passes through a minimum and increases again, as shown in Figure 1.

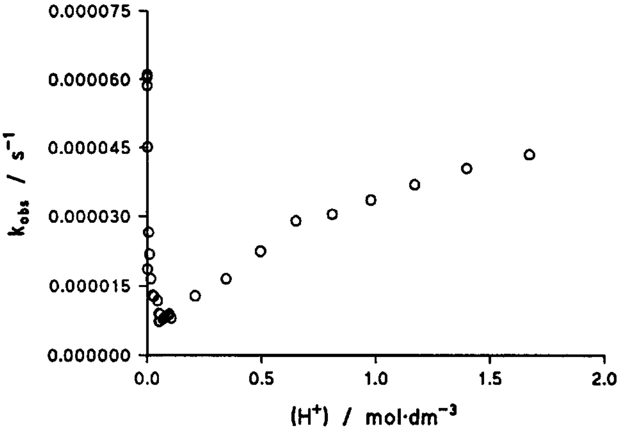


Figure 1: decomposition of (N-Cl)-Sarcosine in acid medium. [(N-Cl)-Sar]=[Sar]=$1.2 \cdot 10^{-3}$ mol·dm^{-3}; I=1.0 mol·dm^{-3}; T=298.0 K.

ii) In the case of (N-Cl)-Proline, (N-Cl),(N-Me)-Alanine and (N-Cl),(N-Me)-Valine the rate constant decreases on increasing the acidity of the medium and from certain values of proton activity it stabilizes, as shown in Figure 2.

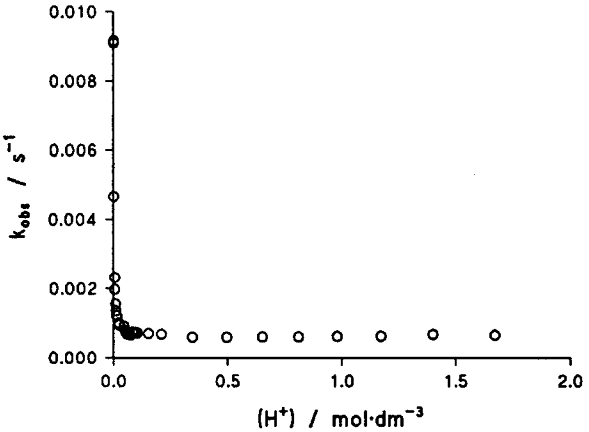
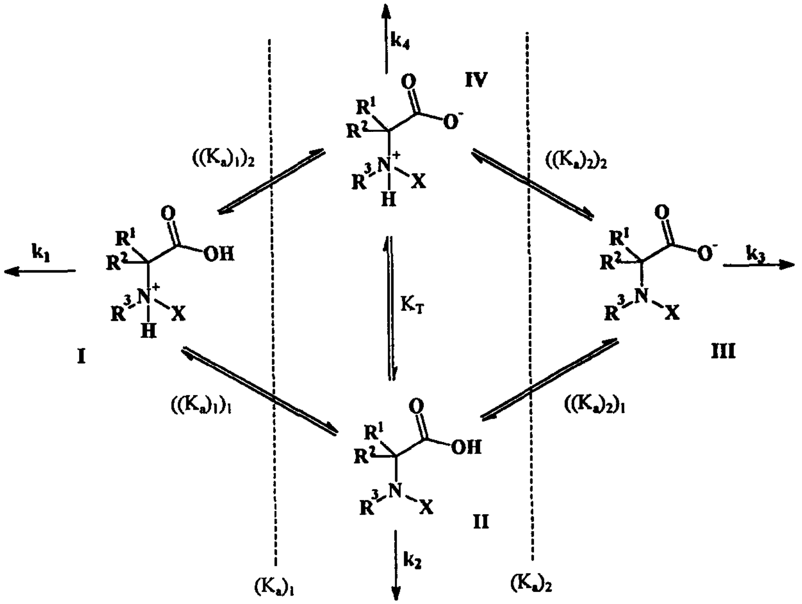


Figure 2: decomposition of (N-Cl),(N-Me)-Valine in acid medium. [(N-Cl),(N-Me)-Val] =[(N-Me)-Val]=$1.2 \cdot 10^{-3}$ mol·dm^{-3}; I=1.0 mol·dm^{-3}; T=298.0 K.

To analyze the reaction mechanism, the different possible species for the (N-Cl)-α-amino acids shown in Scheme 1 must be considered.



Scheme 1: decomposition of secondary (N-Cl)-α-amino acids in acid medium.

In near-neutral, mild acid and mild basic media it has been established that the predominant species is III, which decarboxylate through a concerted and slightly asynchronous product-like Grob fragmentation mechanism[10]. On increasing the acidity of the medium, the tautomeric species II and IV become important and, eventually, species I also plays a role. According to this, the four species can undergo decomposition.

Thus, the rate equation is:

$$r = k_1 \cdot [I] + k_2 \cdot [II] + k_3 \cdot [III] + k_4 \cdot [IV]$$

or, as a function of the analytical concentration of (N-Cl)-α-amino acid, the different equilibrium constants implied and the tautomerism equilibrium constant:

$$r = k_1 \cdot \frac{[(N\text{-}X)\text{-}\alpha\text{-}amino\ acid]_0}{1 + \frac{(K_a)_1}{[H^+]} + \frac{(K_a)_1 \cdot (K_a)_2}{[H^+]^2}} + k_2 \cdot \frac{K_T \cdot [(N\text{-}X)\text{-}\alpha\text{-}amino\ acid]_0}{\left(1 + \frac{[H^+]}{K_1} + \frac{K_2}{[H^+]}\right) \cdot (1 + K_T)} +$$

$$+ k_3 \cdot \frac{[(N\text{-}X)\text{-}\alpha\text{-}amino\ acid]_0}{1 + \frac{[H^+]}{(K_a)_2} + \frac{[H^+]^2}{(K_a)_1 \cdot (K_a)_2}} + k_4 \cdot \frac{[(N\text{-}X)\text{-}\alpha\text{-}amino\ acid]_0}{\left(1 + \frac{[H^+]}{K_1} + \frac{K_2}{[H^+]}\right) \cdot (1 + K_T)}$$

Hence, the pseudo-first order rate constant becomes:

$$k_{obs} = \frac{k_1}{1+\frac{(K_a)_1}{[H^+]}+\frac{(K_a)_1\cdot(K_a)_2}{[H^+]^2}} + \frac{k_2\cdot K_T}{\left(1+\frac{[H^+]}{K_1}+\frac{K_2}{[H^+]}\right)\cdot(1+K_T)} +$$

$$+ \frac{k_3}{1+\frac{[H^+]}{(K_a)_2}+\frac{[H^+]^2}{(K_a)_1\cdot(K_a)_2}} + \frac{k_4}{\left(1+\frac{[H^+]}{K_1}+\frac{K_2}{[H^+]}\right)\cdot(1+K_T)}$$

If the proposed mechanism is right, this equation must fit the experimental data. Between all the parameters included in the previous equation only k_3 is precisely known from the study[10] of the Grob fragmentation mechanism for the carboxylate anion (species III). It is possible to use the values of $(K_a)_1$ and K_T corresponding to the α-amino acids as initial estimations for $(K_a)_2$ and K_T for the (N-Cl)-α-amino acids. Concerning the value of $(K_a)_1$, taking into account the acidification of the hydrogen atoms attached to the nitrogen due to the chlorination of the amino group, an initial value for $(pK_a)_1$ around 0 can be considered. The parameters k_1, k_2 and k_4 are completely unknown.

Taking into consideration the previous statements, k_1, k_2, k_4, $(K_a)_1$, $(K_a)_2$ and K_T have been optimized, concluding that the proposed equation fits properly the experimental data, as shown in Figures 3 and 4:

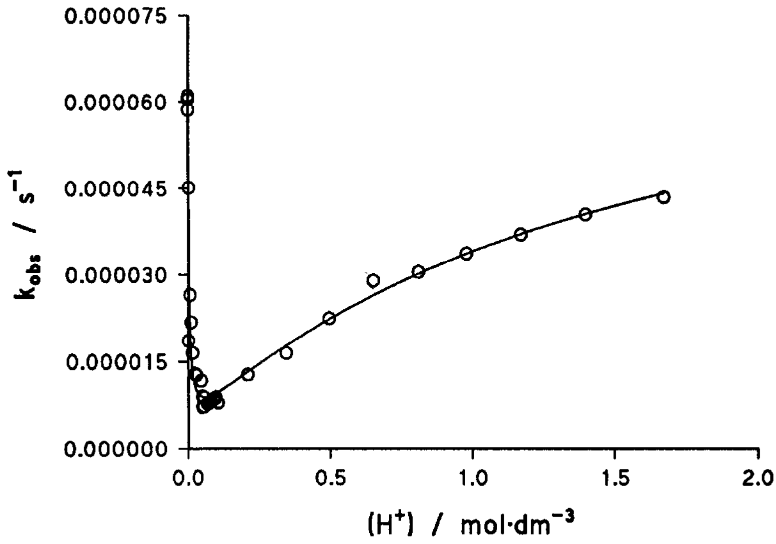


Figure 3: fitting of the equation proposed for the dependence k_{obs} *versus* (H^+) in the case of (N-Cl)-Sarcosine.

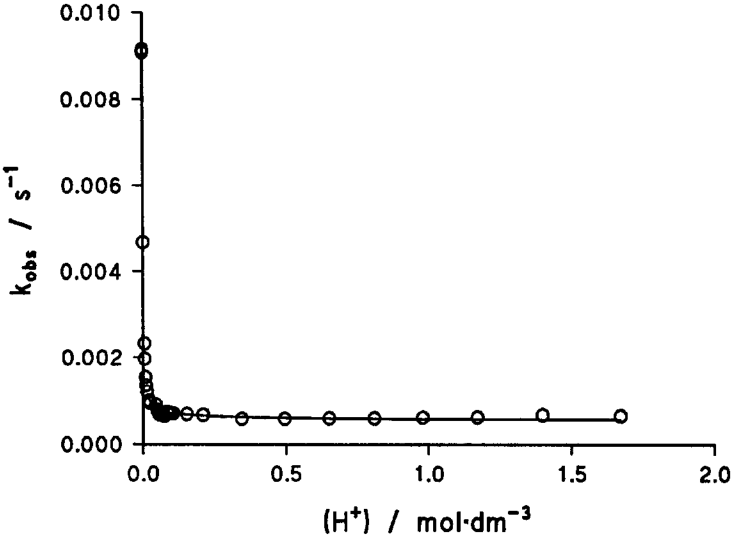


Figure 4: fitting of the equation proposed for the dependence k_{obs} *versus* (H^+) in the case of (N-Cl),(N-Me)-Valine.

Before proceeding to analyze the results it is convenient to clarify that for the (N-Cl)-derivatives of Proline, (N-Me)-Alanine and (N-Me)-Valine the obtained values must be considered only as good estimations, provided that statistically high errors arise from the optimization. Notwithstanding, this reason is not strong enough to discard them. It must be also remarked that the reproducibility of k_3, corresponding to the decarboxylation of III, was always better than 4%.

As a result of the optimization procedure, the equilibrium constants $(K_a)_1$, $(K_a)_2$ and K_T are obtained and from them the corresponding microscopic equilibrium constants can be calculated[15]. The so-obtained values are shown in Table 3.

It is worth remarking that there are no previous references to the $(pK_a)_1$ of these compounds. As can be observed, the pK_a for the (N-Cl)-amino group is 8-9 units minor than for the amino group, which can be explained on the basis of the electronegativity of chlorine.

The tautomeric constant is of the order of 10^4-10^5 towards the neutral species, this value being far away from that of the α-amino acids, which is around 10^5-10^6 towards the zwitterion. This huge difference must be attributed to:

i) the fact that the difference of acidity between the two protonation sites on the molecule is less than in the case of α-amino acids.

ii) while in the case of α-amino acids the most acidic group is the carboxylic one, in the case of (N-Cl)-α-amino acids it is the (N-Cl)-amino group.

Table 2: macroscopic, microscopic and tautomeric acid-base equilibrium constants for different (N-Cl)-α-amino acids.

(N-Cl)-Amino acid	$(K_a)_1$ / mol·dm^{-3}	$((K_a)_1)_1$ / mol·dm^{-3}	$((K_a)_1)_2$ / mol·dm^{-3}	$(K_a)_2$ / mol·dm^{-3}	$((K_a)_2)_1$ / mol·dm^{-3}	$((K_a)_2)_2$ / mol·dm^{-3}	K_T
(N-Cl)-Sarcosine	1.6399	1.6399	$2.076 \cdot 10^{-5}$	0.02611	0.02611	206.20	78974
(N-Cl)-2-Piperidine Carboxylic Acid	1.2922	1.2921	$1.2554 \cdot 10^{-4}$	0.00076	0.00076	7.84	10292
(N-Cl)-Proline	0.0278	0.0278	$4.3 \cdot 10^{-7}$	0.00130	0.00130	84.27	64772
(N-Cl),(N-Me)-Alanine	0.0470	0.070	$1.04 \cdot 10^{-6}$	0.00082	0.00082	37.13	45352
(N-Cl),(N-Me)-Valine	0.1240	0.1240	$1.31 \cdot 10^{-6}$	0.00078	0.00078	73.46	94450

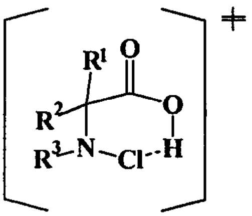
Table 3: optimized values for the decomposition rate constants of the different species of secondary (N-Cl)-α-amino acids.

(N-Cl)-Amino acid	$k_1 \cdot 10^{-4}$ / s^{-1}	$k_2 \cdot 10^{-4}$ / s^{-1}	$k_3 \cdot 10^{-4}$ / s^{-1}	k_4 / s^{-1}
(N-Cl)-Sarcosine	0.840	0.004	0.7*	0.244
(N-Cl)-2-Piperidine Carboxylic Ac.	1.557	0.127	2.8*	0.141
(N-Cl)-Proline	0.506	0.408	105*	22.826
(N-Cl),(N-Me)-Alanine	2.389	3.382	100*	36.827
(N-Cl),(N-Me)-Valine	5.585	3.392	103*	41.119

* Value fixed for the fitting.

Table 2 summarizes the values obtained for the different decomposition rate constants. As can be observed, the rate constant for the decomposition of the zwitterion (k_4) is around four orders of magnitude greater than the decarboxylation of the carboxylate anion (k_3). This noticeable increase can be attributed to the presence of the positive charge on the nitrogen. From the comparison between the rate constants k_3 and k_4 a reasonable parallelism in their tendency can be deduced. Although it is difficult to carry out a detailed study of the reaction in acid media, as for the Grob fragmentation of the carboxylate anion (species III)[10], these processes are expected to be concerted.

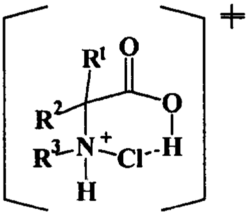
The rate constant (k_2) for the decomposition of the neutral species II is, at least, one order of magnitude less than that for the decarboxylation of the carboxylate anion (k_3). This difference becomes comprehensible considering that the carboxylic group is protonated in species II. The decarboxylation of II could imply a transition state like TS II:



TS II

hence being similar to the decarboxylation of β-keto acids[16,17,18,19].

The rate constant for the decomposition of the completely protonated species (k_1) is lower than that of the carboxylate anion (k_3) and higher than that of the neutral species (k_2). Again, the presence of the proton on the nitrogen forces species I to decompose faster than species II. As in the previous case, this process could imply a transition state like TS I:



TS I

It will be necessary to extend this study with new (N-Cl)-compounds and also with other (N-halo)-compounds, going up to higher values of acidity with the aim of determining more precisely the importance of each species and their detailed decomposition mechanism.

Conclusion.

The decomposition of secondary (N-Cl)-α-amino acids shows a complex dependence with the acidity of the medium when $pH < 3$. This behaviour has been explained on the basis of the acid-base and tautomeric equilibria, in such a way that the four possible species undergo decomposition. The theoretical rate equation has been obtained, allowing us to estimate the rate constants for the decomposition and the microscopic, macroscopic and tautomeric equilibrium constants. The pK_a for the carboxylate group of the (N-Cl)-α-amino acid is slightly above that of the corresponding α-amino acid, while for the (N-Cl)-group it is 8-9 units below that of the corresponding amino group. The tautomeric rate constant is of the order of 10^4-10^5, the neutral species being the favoured one.

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