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Alkoxide-Promoted Decomposition of N-Halo-α-Amino Acids in Aqueous Medium.

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Abstract: a kinetic study of the alkoxide-promoted decomposition of N-halo derivatives of glycine and sarcosine in aqueous solution has been carried out. The deuterium isotope effect and the leaving group effect, together with an analysis of the data in terms of the cross interaction parameter p_{xy} and of the More O'Ferrall-Jencks diagram suggest that the reaction takes place through a concerted non-synchronous mechanism.

Introduction.

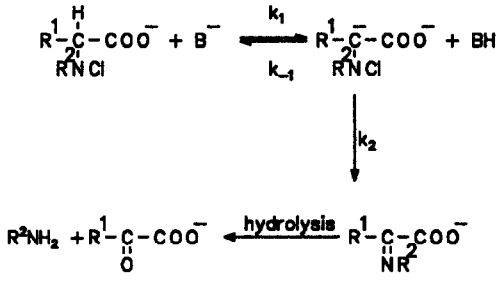
The decomposition of N-Cl-amino acids has undoubted interest due mainly to the potential carcinogenic activity of the N-chlorinated compounds, which may be generated in any water chlorination process (a common water disinfection practise).

In neutral or slightly acidic medium N-halo-α-amino acids are not stable and decompose to yield halide ions, carbon dioxide, aldehydes or ketones, and amines or ammonia[1,2] depending on the structure of the N-halo-α-amino acid. In alkaline medium the decomposition leads to the formation of α-keto acids[3,4,5,6] which in turn are precursors of undesirable products, such as trihalomethanes and other non-volatile organic compounds[7,8]. The study of this reaction in the presence of bases has the added interest of dealing with an elimination reaction leading to imine formation, a process less studied than that in which olefins are generated.

Usually it has been accepted that the decomposition of N-Cl-α-amino acids in alkaline medium takes place through carbanion formation[3,4,5] as depicted in Scheme 1.

In a previous paper[6] we pointed out that in the presence of hydroxide ions the process cannot take place through this mechanism, thus concluding that the only mechanistic alternatives are either a stepwise process or a concerted one, between which it is difficult to distinguish.

Scheme 1.



The main aim of this paper is to clear up this last point. To do so the influence of alkoxide ions ((2,2,2)-trifluoroethoxide and (1,1,1,3,3,3)-hexafluoro-2-propanoxide) concentration on the decomposition of the N-Cl and N-Br derivatives of glycine and sarcosine has been studied.

Experimental.

The preparation of the reagents (Merck® *p.a.*, unless otherwise indicated), and the kinetic study were carried out following the procedure described in other papers[6,9]. The concentration of alkoxide ions was obtained by adding to the reaction mixture different volumes of the (2,2,2)-trifluoroethanol and (1,1,1,3,3,3)-hexafluoro-2-propanol solutions prepared straight from the commercial product (Sigma®), the concentrations being determined by using the expression:

$$[B] = \frac{[B_t]}{1+10^{(pK_a-pH)}} \qquad [1]$$

where [B] and [B_t] are the concentrations of alkoxide and total alcohol respectively, and pK_a corresponds to the alcohol.

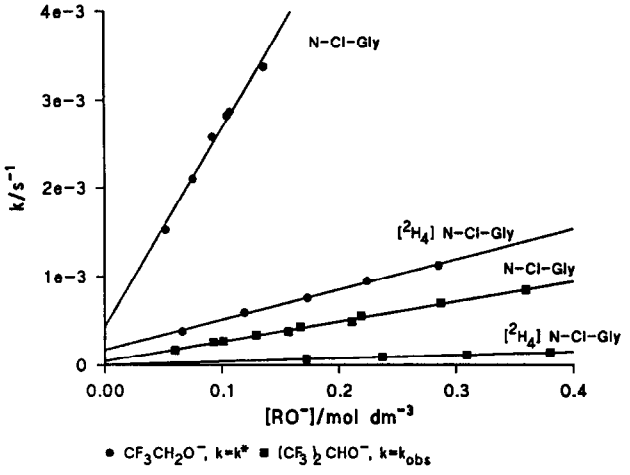


Figure 1: influence of alkoxide ion concentration. [N-Cl-Gly]=[N-Cl-$^2H_4$-Gly]=$1.4 \cdot 10^{-3}$ mol·dm^{-3}. T=298.0 K.

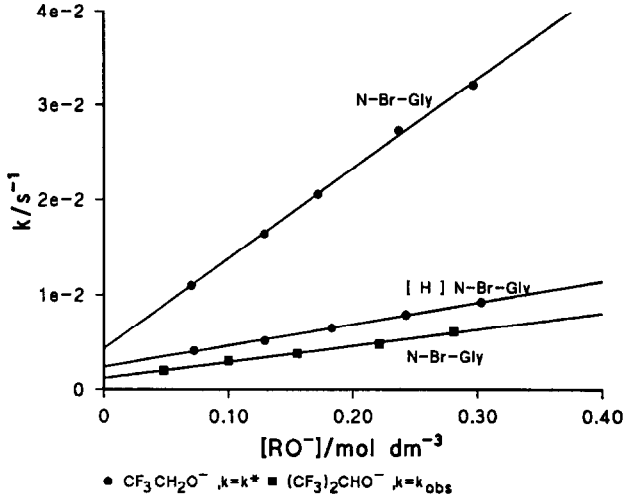


Figure 2: influence of alkoxide ion concentration. [N-Br-Gly]=[N-Br-$^2H_4$-Gly]=$2.1 \cdot 10^{-3}$ mol·dm^{-3}. T=298.0 K.

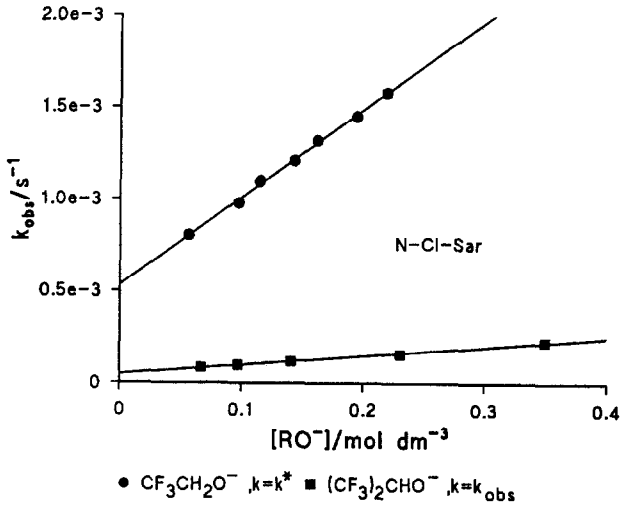


Figure 3: influence of alkoxide ion concentration. [N-Cl-Sar] = $1.4 \cdot 10^{-3}$ mol·dm^{-3}. T = 298.0 K.

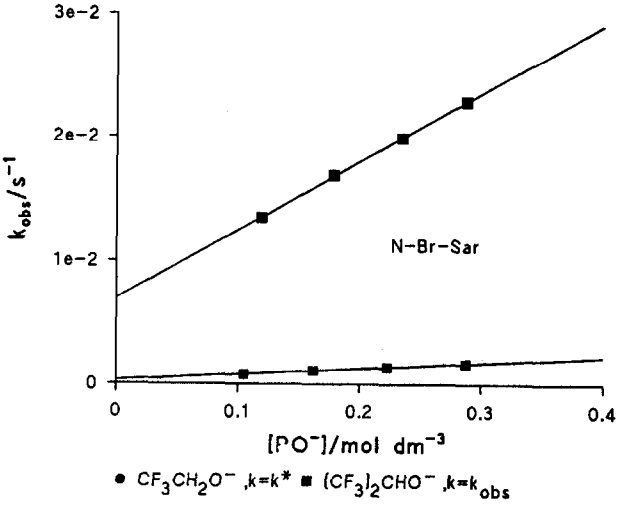


Figure 4: influence of alkoxide ion concentration. [N-Br-Sar] = $1.3 \cdot 10^{-3}$ mol·dm^{-3}. T = 298.0 K.

The ionic strength was maintained at a constant value of 0.5 mol·dm^{-3} by using sodium perchlorate (in the studies with hydroxide ion) or potasium chloride (in the studies with alkoxides). The pH values were measured with a Crison-506 pH-meter equiped with a combined glass electrode (M-7598). The concentration of hydroxide ions was determined by calibration of the electrode with a solution of potassium hydroxide (owing to the slow response of the electrode[10] in solutions of KOH, the same time was left (5 min) before taking each measurement).

All kinetic runs were followed at 298.0 K in an UV/Vis Beckman® DU-70 spectrophotometer, temperature being kept constant to within ± 0.1 K by using water flow.

Results and discussion.

The study of the influence of the hydroxide ions, carried out in a previous paper[6], led to the following rate equation:

$$r = r_o + r_{OH^-} = (k_o + k_{OH^-}\cdot[OH^-])\cdot[N\text{-}X\text{-}Amino\ Acid] \qquad [2]$$

Figures 1 to 4 show the dependence found between the observed rate constant and the concentration of alkoxide ion. In the different kinetic runs carried out with trifluorethanol, the catalytic rate constants were obtained by plotting the corrected rate constant k^* (calculated as $k^* = k_{obs} - k_{OH^-}\cdot([OH^-] - [OH^-]_o$, where k_{OH^-} represents the catalytic rate constant for hydroxide ions), *versus* the concentration of (2,2,2)-trifluoroethoxide ion, so that the changes in hydroxide ion concentration due to the hydrolysis of the buffer are taken into account[11,12].

In the case of the study with (1,1,1,3,3,3)-hexafluoro-2-propanol, the observed rate constant was not corrected due to the negligible influence of hydroxide ions concentration (pH values close to 9).

The results are in agreement with the existence of general base catalysis, which means that equation 2 can be written as follows:

$$r = k_{obs}\cdot[N\text{-}X\text{-}Amino\ Acid] = (k_0 + \sum k_b\cdot[B])\cdot[N\text{-}X\text{-}Amino\ Acid] \qquad [3]$$

where [B] represents the concentration of any base present, and k_b the corresponding catalytic rate constant. Table 1 shows the values for such catalytic constants.

Table 1: catalytic rate constants obtained for different N-X-Amino Acids (T=298.0 K).

N-X-Amino Acid	$k_{OH^-} \cdot 10^3/mol^{-1}dm^3s^{-1}$ (Ref 6)	$k_{TFE} \cdot \cdot 10^3/mol^{-1}dm^3s^{-1}$	$k_{HFP} \cdot 10^3/mol^{-1}dm^3s^{-1}$
N-Cl-Gly	44.0±0.2	22±1	2.24±0.05
N-Cl-[$^2H_4$]-Gly	7.40±0.03	3.4±0.1	0.36±0.02
N-Br-Gly	198±8	95±2	17.1±0.8
N-Br-[$^2H_4$]-Gly	48.5±0.9	22.5±0.5	----
N-Cl-Sar	23.8±0.4	4.8±0.1	0.51±0.002
N-Br-Sar	205±6	55.4±0.6	5.5±0.3

Figure 5 represents the Brønsted plot for N-halo-Glycine derivatives, the curvature characteristic of hydroxide ions and strongly basic alkoxides can be observed[13,14,15].

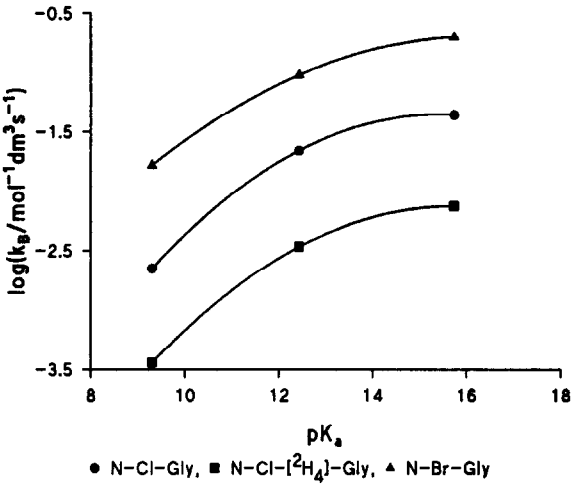


Figure 5: Brønsted plot for N-halo derivatives of Glycine.

The Brønsted parameter (β) is estimated from the isotope effect taking 7-8 as the maximum value for the latter, obtaining values between 0.39 and 0.44 for N-Cl-Gly and between 0.26 and 0.30 for the N-Br-Gly.

Figure 6 displays the Brønsted plot for the N-halo derivatives of Sarcosine, β values being 0.26 for

N-Cl-Sar and 0.24 for N-Br-Sar. It can be observed that the curvature of Figure 5 almost disappear. In this case, which may be interpreted in function to the degree of carbanionic character development in the transition state. If, as put forward by Hupe and Wu[14], the curvature is due to the destabilization of the transition state owing to the presence of solvent molecules interacting with a partially negative charged carbon atom, then the curvature would diminish as the charge diminished. The β values obtained in this study suggest that in the transition state the degree of proton transfer is greater in the N-halo derivatives of Gly than the corresponding ones for Sar, which explains the decrease in the curvature of the Brønsted plot.

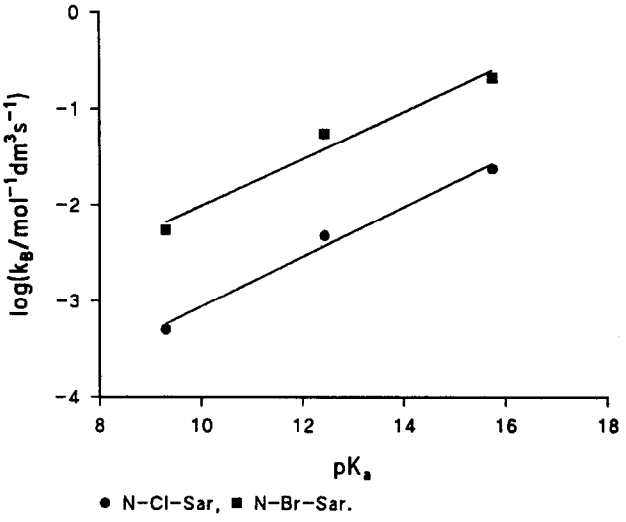


Figure 6: Brønsted plot for N-halo derivatives of Sar.

Table 2 shows the values obtained for the deuterium isotope effect with the different bases used. Table 3 shows the values for the leaving group effect expressed as β_{lg} .The isotope effect values are independent of the base strength, this behaviour has been clearly described for other systems[16] which take place through an $A_{xh}D_HD_N$ mechanism.

This behaviour has been interpreted [13] on the basis that such a modification implies mainly a decrease in the degree of breaking of the N-X bond. The results in Table 3 show this behaviour for N-X-Gly, however for N-X-Sar the β_{lg} values remain practically unaltered.

Table 2: observed kinetic isotope effect.

N-X-Aa	k_H/k_D (OH)	k_H/k_D (TFE)	k_H/k_D (HFP)
N-Cl-Gly	5.6	6.5	6.2
N-Br-Gly	4.1	4.3	---

Table 3: observed leaving group effect.

N-X-Aa	β_{lg} (TFE)	β_{lg} (HFP)
N-X-Gly	-0.32	-0.44
N-X-Sar	-0.53	-0.52

These results are consistent with an analysis carried out in the framework of the cross interaction parameter p_{XY}, defined[17] as:

$$\frac{\partial \beta}{\partial pK_{lg}} = \frac{\partial \beta_{lg}}{\partial pK_{BH}}$$

which is related to the interaction between the base and the leaving group

Although a quantitative study can not be carried out, the results obtained with the N-halo derivatives of Gly lead to a value of $p_{XY} > 0$. However, for N-Cl and N-Br-Sar both the variation of β with pK_{lg} and the variation of β_{lg} with pK_a show a value of p_{XY} close to 0, which could be considered as indicative of a change in the reaction mechanism from $A_{xh}D_HD_N$ to $D_N^{\neq} + A_{xh}D_H$. The β value obtained allows this supposition to be ruled out; p_{XY} values close to 0 for N-X-Sar can be explained on the basis of the high degree of N-X bond breaking together with the low degree of proton transfer. This implies a small interdependence between both reaction centres (base and leaving group), so a very low p_{XY} value is to be expected[18].

Table 4 shows the expected magnitude for parameters β, β_{lg} and p_{XY} in terms of the different possible mechanistic alternatives and the results obtained.

Table 4: values of β, β_{lg} and p_{XY} for different possible pathways and the observed ones.

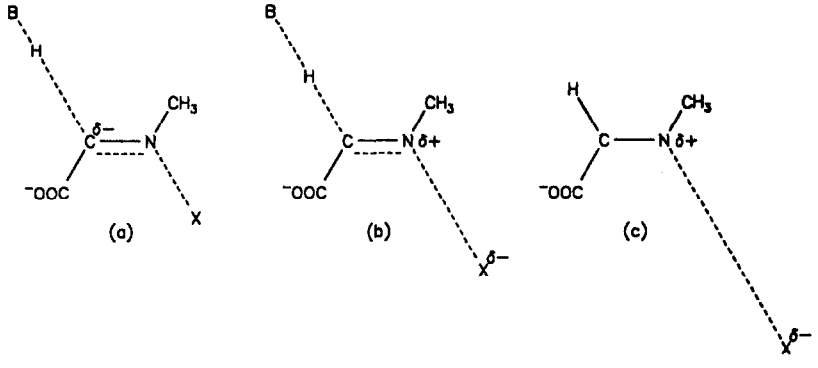
	$A_{xh}D_H^{\neq} + D_N$	$D_N^{\neq} + A_{xh}D_H$	$A_{xh}D_HD_N$	N-Cl-Gly	N-Cl-Sar
β	H	0	H - M	0.39 - 0.44	0.26
β_{lg}	0	H	H - M	0.4	0.52
p_{xy}	L	0	M - L	> 0	≈ 0

where H means "high", M "medium" and L "low".

The effect of the methyl group on the nitrogen seems to point towards the fact that if there is an important degree of proton transfer in the transition state, Scheme 2(a), the inductive effect produced by the

methyl group will lead to a destabilization of the transition state due to the partial negative charge development on the α-carbon and the greater difficulty in the formation of the double bond. This seems to be the behaviour observed in the case of Glycine and Sarcosine N-Halo derivatives, the catalytic rate constants for Sarcosine always being minor than those corresponding to Glycine, with the exception of the N-Br derivatives in presence of hydroxide ions, where the catalytic rate constants are similar (see Table 1).

Scheme 2.



As the degree of N-X bond breaking increases, Scheme 2(b), the described effect decreases until its sign changes. At this point the inductive effect of the methyl group favours the exit of the leaving group. This would be the effect if the reaction were to proceed through an $D_N^* + A_{xh}D_H$ mechanism, Scheme2(c). Taking into consideration the obtained results, the $D_N^* + A_{xh}D_H$ mechanism can be ruled out.

Eventually, the position of the transition state in a More O'Ferrall - Jencks diagram is depicted in Figure 7, the location of the transition state fitting what is to be expected in an $A_{xh}D_HD_N$ type mechanism. The

effect of the presence of a methyl group on the N can be interpreted as a change in the location of the transition state from being central in the case of N-X-Gly to being nitrenium-like in that of N-X-Sar.

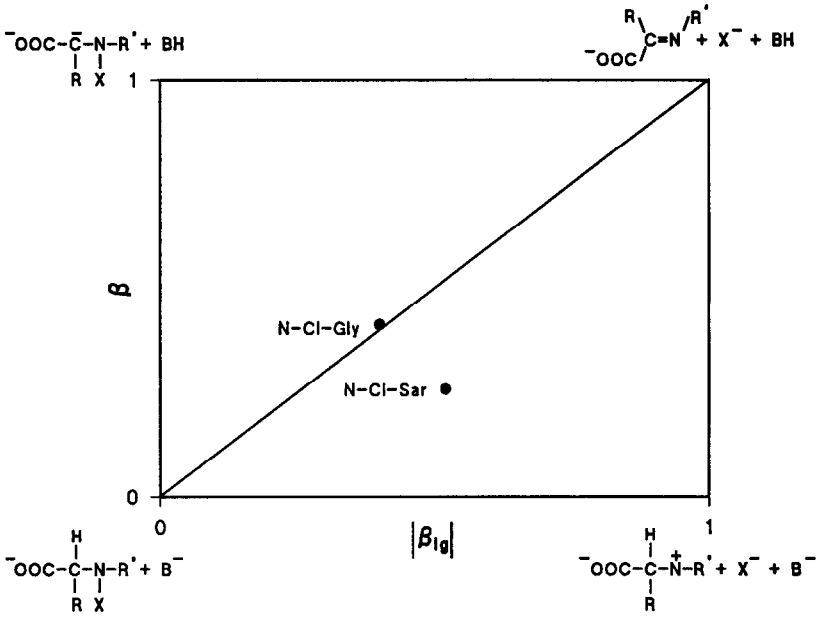


Figure 7: More O'Ferrall - Jencks diagram.

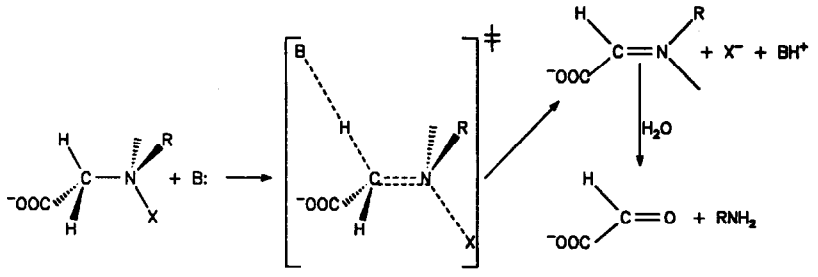
Conclusion.

The decomposition of N-Cl and N-Br derivatives of Gly and Sar in aqueous solution shows general base catalysis. The deuterium isotope effect and the leaving group effect were determined and the transition state has been characterised by the β and the β_{lg} values finding, as in all the other studies on elimination reactions leading to the formation of imines[19], a nitrenium-like character.

Experimental evidence suggests that the base-promoted decomposition of N-halo amino acids takes

place through a concerted non-synchronous $A_{ai}D_HD_N$ mechanism, as depicted in Scheme 3.

Scheme 3.



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