Concerted Grob Fragmentation in *N*-Halo-α-amino Acid Decomposition

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The Grob fragmentation of *N*-halo-α-amino acids in aqueous solution has been studied, being first order in *N*-halo-α-amino acid and pH-independent. The substituents on the C_2 and N atoms strongly affect the reaction rate. Structure reactivity correlations for C_2 substituents provide ϱ^* values of −3.9 and −4.1 for *N*-Cl and *N*-Br compounds, respectively. The same correlations for N substituents lead to ϱ^* values of −2.1 and −1.9 for *N*-Cl and *N*-Br compounds. The transition state (TS) can be generally described as product-like, its structure and characteristics being significantly affected by the substituents on the C_2 and on the N atoms. In conclusion, the reaction is a D_ED_N concerted and slightly nonsynchronous two-stage process.

Introduction

Heterolytic fragmentation reactions[1-3] form a widespread and yet largely unappreciated group of rearrangements, even though they have several interesting synthetic applications.[4,5] According to the definition proposed by Grob and Baumann,[6] a fragmentation process implies the breaking of a molecule a—b—c—d—X into three fragments, a—b, c=d, and X, their charge and structure depending on the characteristics of the initial compound. The a—b fragment is called "electrofuge", while X is called "nucleofuge", these names referring to the way in which the bond cleavage process takes place. It is worth using these names provided that in this reaction there are two leaving groups.[7] Some cases are known in which only two fragments are formed and other cases in which the initial molecule has up to seven reactive centers, yielding four fragments. From the point of view of the most common reaction products, one can talk about olefin-, alkyne-, azoxetine-, carbonyl-, isocyanate-, and nitrogen-forming fragmentations, each of them showing different mechanistic possibilities.

These fragmentation reactions must be clearly distinguished from 1,2-eliminations, where the electrofuge is only one atom or an organometallic fragment, and also from other "breaking" processes like homolytic fragmentations (this name being often given to those taking place in mass spectrometers).

Fragmentation reactions can be classified according to criteria similar to those employed in the case of 1,2-elimination reactions, depending on whether the bond breaking of b—c and d—X and the double bond making of c=d take place simultaneously, almost simultaneously, or successively, although the sequence of microscopic events is different in each of these cases.

One of the well-known fragmentation processes yields azometines from substrates like a—b—C—N—X or a—b—N—C—X. Among these processes is the fragmentation of *N*-X-α-amino acids,[8] which are unstable in aqueous solution, decomposing to yield ammonia or amines, halide ions, carbon dioxide, and aldehydes or ketones, the rate of this decomposition depending on the structure of the substrate.

N-X-α-amino acids are formed during water halogenation and have received some attention.[9-13] Several toxic compounds have been detected between the reaction products of *N*-X-α-amino acids, some of them being characterized as carcinogenic and/or mutagenic.[14,15]

In this paper a study about *N*-X-α-amino acids fragmentation is presented, in order to analyze and discuss the detailed mechanism for the reaction.

Experimental Section

Reagents. Aqueous chlorine solutions were obtained every 3 or 4 days by bubbling Cl_2 (g) through a sodium hydroxide solution and spectrophotometrically titrated daily ($\lambda_{max}(H_2O)$ = 292 nm, $\epsilon \simeq 350$ L·mol^{-1}·cm^{-1} for ClO^- when pH > 12).[16] Aqueous bromine solutions were obtained daily by direct dilution of Br_2 (l) in sodium hydroxide solution and spectrophotometrically titrated ($\lambda_{max}(H_2O)$ = 331 nm, $\epsilon \simeq 326$ L·mol^{-1}·cm^{-1} for BrO^- when pH > 12).[17] Acetic acid/acetate, dihydrogen phosphate/hydrogen phosphate, boric acid/borate, and hydrogen carbonate/carbonate were used as buffer solutions. The total buffer concentration was about 0.02 mol·L^{-1} in all cases. Ionic strength was kept constant (I = 0.5 mol·L^{-1}) using $NaClO_4$. The structures of the employed α-amino acids are shown in Table 1 together with their corresponding three-letter sytem nomenclature[18] (where available). All chemicals were supplied by Merck (p.a. quality) except for *N*-Me-Ala

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(1) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.*, **1967**, *6*(1), 1–15.
(2) Grob, C. A. *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*(8), 535–546.
(3) Weyersthal, P.; Marschall, H. Fragmentation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Freming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6.
(4) Clayton, R. B.; Henbest, H. B.; Smith, M. *J. Chem. Soc.* **1957**, 1982.
(5) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254.
(6) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594.
(7) Mathieu, J.; Allais, A.; Valls, J. *Angew. Chem.* **1960**, *72*, 71.
(8) Langheld, K. *Chem. Ber.* **1909**, *42*, 2360–2374.
(9) Nweke, A.; Scully, F. E., Jr. *Env. Sci. Technol.* **1989**, *23*(8), 989–994.
(10) McCormick, E. F.; Conyers, B.; Scully, F. E., Jr. *Env. Sci. Technol.* **1993**, *27*(2), 255–261.
(11) Conyers, B.; Scully, F. E., Jr. *Env. Sci. Technol.* **1993**, *27*(2), 261–266.
(12) Hrudey, S. E.; Gac, A.; Daignault, S. A. *Wat. Sci. Technol.* **1988**, *20*, 55–61.
(13) Rook, J. J. *Water Treat. Exam.* **1974**, *23*, 234–243.
(14) Owusu-Yaw, J.; Wheeler, W. B.; Wei, C. I. *Water Chlorination (Environmental Impact and Health Effects)*; Lewis Publishers Inc.: Chelsea, 1990; Vol. 6, pp 179–191.
(15) Sen, A. C.; Owusu-Yaw, J.; Wheeler, W. B.; Wei, C. I. *J. Food Sci.* **1989**, *54*(4), 1057–1060, 1065.
(16) Morris, J. C. *J. Phys. Chem.* **1966**, *70*, 3798.
(17) Cheek, C. H.; Linnenbom, V. J. *J. Phys. Chem.* **1963**, *67*, 1856.
(18) We have used the IUPAC three-letter system names for α-amino acids (see: *Pure Appl. Chem.* **1984**, *56*, 595).

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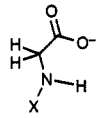
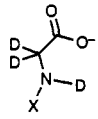
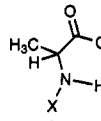
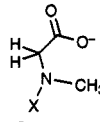
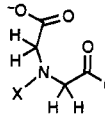
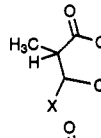
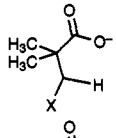
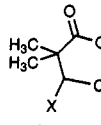
Table 1. Different Compounds Employed and Their UV Absorption Maxima

N-X-α-amino acid	structure	$\lambda_{max\ abs}$/nm N-Cl	N-Br
N-X-Gly		255	
N-X-[$^2H_4$]-Gly		255	
N-X-Ala		255	286
N-X-Sar		267	304
N-X-iminodiacetic acid		270	308
N-X-*N*-Me-Ala		267	304
N-X-Aib		255	286
N-X-*N*-Me-Aib		267	304

(Sigma) and *N*-Me-Aib (Aldrich). Water employed was obtained from a Millipore-Milli Q purification system.

Equipment. UV–vis Beckman DU-70 and Milton Roy Spectronic 3000-Array spectrophotometers were used to follow the kinetic runs. Fast reactions were followed using a SF-61 stopped-flow spectrofluorimeter from Hi-Tech Scientific. In all cases water flow was employed to keep the temperature constant to within ±0.1 K. pH measurements were carried out with a combined glass electrode filled with sodium chloride as internal electrolyte. The electrode was calibrated with commercial buffer solutions (pH = 4.01 ± 0.01, potassium hydrogen phthalate/potassium phthalate and pH = 7.00 ± 0.01, potassium dihydrogen phosphate/sodium hydrogen phosphate) at 298.0 K. Thus, the accuracy achieved in the pH measurement was within ±0.02 pH units.

Working Methodology. Reaction mixtures were prepared according to the procedure described in a previous paper.[19] A 100% excess of α-amino acid was employed. In the case of *N*-chloro-α-amino acids, the chlorinating agent (pH *ca.* 9) was always mixed with the α-amino acid and an adequate amount of inert electrolyte to maintain the ionic strength (pH *ca.* 9), adding the buffer solution to this mixture. A similar procedure was followed for *N*-bromo-α-amino acids except that in this case the brominating mixture had pH *ca.* 11. Working in this way the halogenation rate is always near its maximum value[20] and the halogenation and decomposition processes are clearly separated, hence avoiding undesirable reactions between the halogenating agent and the components of buffer solutions and minimizing the formation of *N,N*-di-X-α-amino acids.

(19) Armesto, X. L.; Canle L., M.; Losada, M.; Santaballa, J. A. *Int. J. Chem. Kinet.* **1993**, *25*, 331–339.
(20) Armesto, X. L.; Canle L., M.; Santaballa, J. A. *Tetrahedron* **1993**, *49*(1), 275–284.

Table 2. Fragmentation Products of *N*-Chloro-α-amino Acids[a]

N-chloro-α-amino acid	% CO_2	% NH_3	% carbonyl compd	% α-keto acid
N-Cl-Gly	24[b]	43[c]	56[d]	<2[25]
N-Cl-Ala	72[e]	100[f]	77[g]	<2[25]
N-Cl-Aib		82[h]	41[i]	
N-Cl-Sar		ND	100[j]	8 ± 2[25]
N-Cl-*N*-Me-Ala		ND	72[k]	
N-Cl-*N*-Me-Aib		ND	41[l]	

[a] [*N*-X-α-amino acid]$_0 \simeq 1.2 \times 10^{-3}$ mol·L^{-1}. Room temperature. Yields based on the initial concentration of *N*-Cl-α-amino acid. [b] pH = 9.01. [c] pH = 8.83. [d] pH = 8.89. [e] pH = 8.32. [f] pH = 8.12. [g] pH = 8.27. [h] pH = 8.01. [i] pH = 8.22. [j] pH = 8.54. [k] pH = 9.52. [l] pH = 9.58.

The reactions were followed at the wavelengths compiled in Table 1, which correspond to the absorption maxima of the different *N*-halo compounds. First-order rate constants were obtained from the corresponding integrated equation by using a modification of the Davies, Swann, and Campey[21] and the Marquardt[22] nonlinear optimization algorithms. All the reported rate constants correspond to those directly observed.

Reaction Products. The products of the considered fragmentation reaction depend on the structure of the *N*-X-α-amino acid: carbonyl compounds (aldehydes or ketones), carbon dioxide, and ammonia or primary amines are obtained. The analyses have been carried out for several (*N*-chloro)-α-amino acids.

The absence of "active halogen" at the end of each reaction was proved by treating the mixture with a few drops of a solution of potassium iodide buffered with acetic acid/sodium acetate and checking it did not become colored.

Ammonia analyses were carried out using an ammonia Ingold selective electrode. The amino acids with susbstituents in the nitrogen yield primary amines; hence, in these cases it was not possible to detect ammonia.

Reaction mixtures with a concentration of 10-fold the usual one were used to estimate the yield of carbon dioxide. Argon was bubbled through the mixture for 24 h, collecting the evacuated gas over a saturated barium hydroxide solution (previously prepared in fresh boiled water). The precipitate of barium carbonate was filtered, dried, and weighed to estimate CO_2 yield.[23]

Aldehyde/ketone analyses were carried out by generating the corresponding 2,4-dinitrophenylhydrazones, which were extracted with hexane, measuring the absorbance of the obtained solution at 340 nm.[24] Moreover, the carbonyl compounds were characterized by forming the corresponding dimethones and measuring their melting points, which agreed with those in the literature.[25]

No attempts were made to analyze the yields of primary amines (in the case of N-substituted compounds) or α-keto acids (for those substituted in the α carbon[26]).

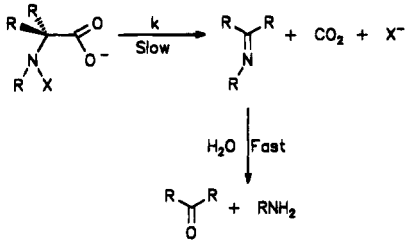
The results thus obtained are compiled in Table 2. Reproducibility was not better than 15%. The results are affected by several factors. Although the fragmentation is the main reaction in the working conditions the reactivity of these compounds allows other pathways to take place; i.e., deproportionation reaction between a *N*-X-α-amino acid and a protonated *N*-X-α-amino acid can take place in mild acid medium, while a 1,2-elimination of a proton from the C_2 of a *N*-X-α-amino acid can occur in mild basic medium. The importance of these processes increases with the initial concentration of *N*-X-α-amino acid. On the other hand, subsequent reactions of the products are not considered here,

(21) Casado, J.; Mosquera, M.; Rivas, A.; Rodríguez Prieto, M. F.; Santaballa, J. A. *Comput. Chem.* **1983**, *7*(4), 209.
(22) Marquardt, D. W. *J. Soc. Ind. Math.* **1963**, *11*, 431.
(23) Tamelen, E. E. v.; Haarstad, V. B.; Haarstad, O. R. L. *Tetrahedron* **1968**, *24*, 687–704.
(24) Lohman, F. H. *Anal. Chem.* **1958**, *30*(5), 972–974.
(25) Horning, E. C.; Horning, M. G. *J. Org. Chem.* **1946**, *11*, 95–99.
(26) Designed ahead as C_2 (C_1 for that of the carboxylate group).

Table 3. Rate Constants for Fragmentation of $R^1R^2C(NHR^3)COO^-$ and Nucleofuge Effect (NE_1) in the Indicated pH Interval (T = 298.0 K; I = 0.5 mol^{-1}-L^{-1}

R^1	R^2	R^3	$k_{N-Br} \times 10^3/s^{-1}$	$k_{N-Cl} \times 10^3/s^{-1}$	NE
H	H	H		0.0043, 6.43 < pH < 8.51 0.0042, pH = 6.85[25] 0.0333, pH = 7.25[26] 0.05, pH = 7.00[26] 0.167, pH = 7.25[26] nonconsistent data[27]	
^2H	^2H	H		0.0023, 7.10 < pH < 8.71	
CH_3	H	H	1.2, 8.61 < pH < 10.22	0.293, 4.37 < pH < 9.14	4
H	H	CH_3	0.15, 8.63 < pH < 10.00	0.070, 3.12 < pH < 6.97	2
H	H	CH_2CO_2H	0.80, 8.41 < pH < 9.01	0.155, 6.76 < pH < 9.70	
CH_3	H	CH_3	59, 7.47 < pH < 9.64	10.0, 4.08 < pH < 7.81	6
CH_3	CH_3	H	122, 8.09 < pH < 9.56	15, 2.96 < pH < 14.00	8
CH_3	CH_3	CH_3	5080, 7.52 < pH < 9.66	557, pH = 7.37	9

Scheme 1. Fragmentation of *N*-X-α-amino Acids



being a possible explanation for the low yield of ketone found in the case of *N*-Cl-Aib and *N*-Cl-*N*-Me-Aib, provided that the quite high yield of ammonia for *N*-Cl-Aib seems to imply that the process proceeds almost to completion. It is also worth noting the low yields obtained for *N*-Cl-Gly, which will be discussed later on.

Results and Discussion

The fragmentation of *N*-X-α-amino acids is a decarboxylation process with loss of halide, yielding an azomethine that quickly hydrolizes to a carbonyl compound, as shown in Scheme 1.

The reaction is first order relative to the concentration of *N*-halo-α-amino acid in all the studied cases and within the pH working range. The observed rate constant is independent both of the α-amino acid concentration and of that of halogenating agent. Ionic strength has no influence, either.

In all cases there is a reasonably large range of pH where the rate constant is independent of the acidity of the medium. This interval, which is around pH = 7, is broader for *N*-Cl compounds than for *N*-Br compounds.

According to the previous statements, the reaction rate is given by:

$$r = k_{obs}[N\text{-X-}\alpha\text{-amino acid}]$$

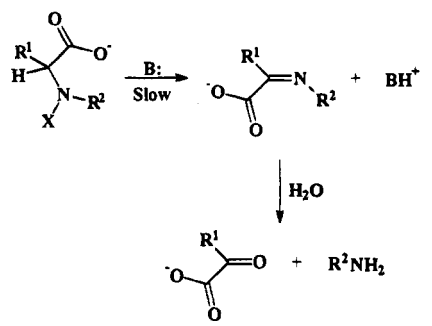
where k_{obs} is the observed rate constant.

The rate constants for the fragmentation of the different *N*-X-α-amino acids are compiled in Table 3, together with the pH conditions for each of them.

As can be observed, different values for the fragmentation rate constant of *N*-Cl-Gly,[25-27] ranging between 4.2 × 10^{-6} s^{-1} and 1.67 × 10^{-4} s^{-1} are found in the literature. This seems to advise against the use of this rate constant as a reference in the discussion of the fragmentation mechanism.

It has been proven that a general base catalysis process exists which becomes more relevant as the pK_a of the

Scheme 2. $A_{xh}D_HD_N$ Elimination for *N*-X-α-amino Acids



buffer increases, and that corresponds to an $A_{xh}D_HD_N$ process[27] (Scheme 2). This 1,2-elimination process leads to halide ion and α-keto azometines that subsequently hydrolize to α-keto acids, being the main pathway in alkaline medium.[28-30]

Considering the concentration used for the different possible catalytic species and the typical values of the catalytic rate constants for them, the influence of the elimination process on the observed rate constants for the decomposition can be neglected except in the case of *N*-X-Gly, for which the observed rate constant will comprise the elimination process as well.

The deuterium isotope effect for the $A_{xh}D_HD_N$ process is high, so the catalytic rate constants for the elimination in the case of *N*-X-[$^2H_4$]-Gly are lower than those of *N*-X-Gly. Provided that the fragmentation reaction should not show noticeable primary or secondary isotope effects, the value of the fragmentation rate constant for *N*-Cl-[$^2H_4$]-Gly would be the same than that of *N*-Cl-Gly. This is reinforced by the fact that on considering the catalytic rate constants[31] for $H_2PO_4^-$ and HPO_4^{2-} and the observed rate constant we have obtained for *N*-Cl-Gly, we can estimate a real fragmentation rate constant for *N*-Cl-Gly which is similar to that of *N*-X-[$^2H_4$]-Gly. It has not been possible to obtain the fragmentation rate constant for N-Br-Gly or for *N*-Br-[$^2H_4$]-Gly, which can be explained by the fact that the catalytic rate constants for the elimination process in *N*-Br-α-amino acids are higher than those for *N*-chloro-α-amino acids, leading to a

(27) IUPAC nomenclature has been used for the different process (see: Guthrie, R. D. *Pure Appl. Chem.* **1989**, *61*(1), 23-56).

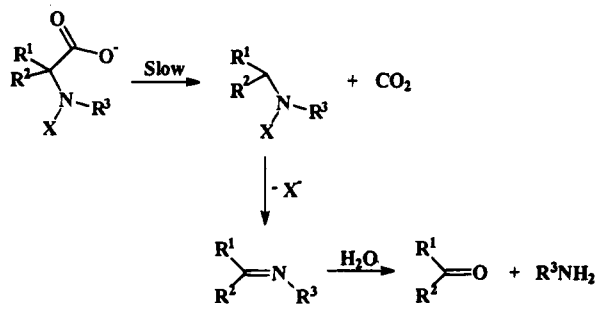
(28) Armesto, X. L.; Canle, M.; Losada, M.; Santaballa, J. A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 181-185.

(29) Losada Cabanas, M. Ph. D. Thesis, *Estudio cinético de la descomposición de N-halo-α-aminoácidos* en medio alcalino, **1992**, Departamento de Química Fundamental e Industrial, Facultade de Ciencias, Universidade da Coruña, A Coruña, Spain.

(30) Armesto, X. L.; Canle L., M.; García, M. V.; Losada, M.; Rodríguez, P.; Santaballa, J. A. *Tetrahedron* **1994**, *50*(7), 2265-2276.

(31) Abia, Ll.; Armesto, X. L.; Canle L., M.; García, M. V.; Losada, M.; Santaballa, J. A. *Int. J. Chem. Kinet.* **1994**, *26*, in press.

Scheme 3. Hypothetical Slow Decarboxylation Yielding a Carbanion



serious interference of the elimination process in the fragmentation one. Hence, we can conclude that the problem with the fragmentation rate constants of *N*-X-Gly (X = Cl, Br) lies on the existence of two competing pathways: elimination and fragmentation. Therefore, for the purpose of discussion, we shall use the fragmentation rate constant for *N*-Cl-[$^2H_4$]-Gly instead of that of *N*-Cl-Gly.

Taking into account what has been discussed in previous works[19,28,32] concerning the different possible reactive species for *N*-X-α-amino acids and the acidifying effect of the chlorine on the protons bonded to the nitrogen of the amino group, the species implied in the fragmentation process has to be the carboxylate anion corresponding to each *N*-X-α-amino acid.

The fact that there is no influence of the acidity of the medium agrees with an unimolecular decarboxylation process for the carboxylate anion.

We may consider three different pathways for this reaction, two of them would be stepwise, leading to carbanion or nitrenium ions, and the other one would be concerted.

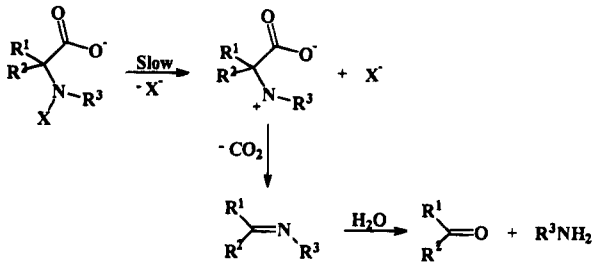
The possibility that the reaction takes place through a 1,2-elimination mechanism by abstraction of an H at the C_2 (Scheme 2) can therefore be rejected by considering the absence of influence of the acidity of the medium together with the facts that the main reaction products are always aldehydes or ketones instead of α-keto acids and that the *N*-X-α-amino acids completely substituted in C_2 also undergo fragmentation.

As the reaction rate increases when the C_2 substitution degree (changing of H by $-CH_3$) increases, the possibility of a slow decarboxylation yielding a carbanion (Scheme 3) can be rejected, since this would be less stable.

The small effect observed for the change of nucleofuge (Cl instead of Br, see Table 3) lets us rule out the possibility of a hypothetical stepwise process with formation of an intermediate nitrenium ion (Scheme 4), at least if the sample is not exposed to UV irradiation, which has been pointed out recently as a possible explanation for some puzzling results found in the literature.

It is also possible to consider the formation of 1,4-oxazetidin-2-ones as intermediates (Scheme 5), but the substituent effects are not those expected, provided that the N should be more affected by charge donation than the C_2. This is a favored 4-*exo-tet* process according to Balwind's rules for ring closure reactions,[33] so the intramolecular pathway must be disfavored, maybe due to the severe distortion of bond angles and distances (specially those in which N, C_1, and C_2 atoms are implied)

Scheme 4. Hypothetical Formation of Nitrenium Ion



Scheme 5. Hypothetical Formation of a 1,4-Oxazetidine-2-one

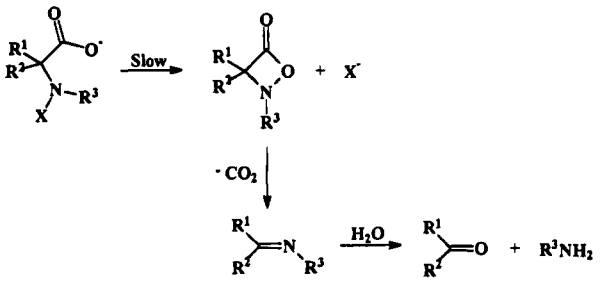


Table 4. Activation Parameters for Fragmentation of *N*-X-α-amino Acids

	$\Delta H^{\ddagger}$/kJ·mol^{-1}		$\Delta S^{\ddagger}$/J·mol^{-1}·K^{-1}	
N-X-amino acid	*N*-Cl	*N*-Br	*N*-Cl	*N*-Br
N-X-Ala	113 ± 1	97 ± 7	67 ± 1	50 ± 5
N-X-Aib	104 ± 1	95 ± 1	69 ± 2	60 ± 1
N-X-Sar	136 ± 1	125 ± 3	94 ± 2	97 ± 3
N-X-iminodiacetic acid	105 ± 5		35 ± 2	
N-X-*N*-Me-Ala	101 ± 1	101 ± 1	55 ± 4	69 ± 1
N-X-*N*-Me-Aib	98 ± 1	95 ± 1	79 ± 1	85 ± 7

necessary to achieve the convenient stereochemical configuration for the ring closure, as well as to the high strain which would exist in the TS.[34]

On the basis of these results, the mechanism for the fragmentation process must be that depicted in Scheme 1, so that the observed rate constant coincides with the unimolecular rate constant for each *N*-X-α-amino acid, *i.e.*:

$$k_{obs} = k_{uni}$$

It does not seem reasonable to expect the existence of substituent steric effects in Grob fragmentation. This hypothesis is confirmed by the fact that the rate constants for Ahx, Leu, Ile, and Tle, which are chain isomers, show no correlation.

Activation parameters have been determined as shown in Table 4. The high and positive values observed for activation enthalpy and entropy, showing the same order of magnitude for *N*-chloro- and *N*-bromo-α-amino acids, are characteristic of processes with a TS less ordered than the reactants, which fits the expected behavior for a fragmentation reaction. If the reaction were to proceed through an intermediate 1,4-oxazetidine-2-one, it should be predictable that $\Delta S^{\ddagger} \leq 0$.

(32) Armesto, X. L.; Canle L., M.; Losada, M.; Santaballa, J. A. *Int. J. Chem. Kinet.* **1993**, *25*(1), 1–8.
(33) Baldwin J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(34) We use the term "TS" to refer to the saddle point in the free energy hypersurface for the considered reaction and "transition structure" to refer to the saddle point in the potential energy hypersurface. For wider discussions on this topic, see: Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682. Williams, I. H. *Chem. Soc. Rev.* **1993**, 277–283.

The substitution of a proton by a methyl group, both on the C_2 and on the N atom, has a noticeable effect on the rate constant, as can be deduced from Table 3. The change of $-H$ by $-CH_3$ on the C_2 and on the N atom promotes the fragmentation, the acceleration in the case of the C_2-substituted compound being more important than that in the case of the N-substituted one. The fact that the first substituent has more influence on the rate constant than the second one also seems relevant; *i.e.*, the change from *N*-X-Gly to *N*-X-Ala is larger than from *N*-X-Ala to *N*-X-Aib. Provided that the methyl is a poor charge donor, it can be concluded that both reaction centers are quite sensitive to changes in electronic density.

The ϱ^* values obtained from structure–reactivity correlations for the observed influence of several alkyl groups on the C_2 and on the nitrogen have been obtained (σ^* values taken from Hansch and Leo[35] and Exner[36]). The inductive effect should have two components on the reaction center:[37] an effect through the bonds and a direct through-space electrostatic effect (field effect). Despite the strong efforts of some authors,[38] it has not been possible until now to separate these effects, although it seems that when the substituents are relatively far away from the reaction center, the field effect is the predominant one.[39] The fact that the effect of the first substituent is the higher one (at least on C_2) seems to point toward an important effect through the bonds in Grob fragmentation, while an effect through-space could be discarded on the basis of results obtained previously.

The obtained ϱ^* value seems to point towards the fact that both the C_2 and the N play the role of eletrophilic centers, accepting charge. The values of ϱ^*_{C2} (-3.9 for *N*-chloroamino acids, -4.1 for *N*-bromoamino acids), as well as those of ϱ^*_N (-2.1 for *N*-chloroamino acids, -1.9 for *N*-bromoamino acids) agree with those found in the literature for similar processes. Provided that ϱ^*_{C2}(*N*-Br) $\sim$ ϱ^*_{C2}(*N*-Cl) and ϱ^*_N(*N*-Br) $\sim$ ϱ^*_N(*N*-Cl), it can be concluded that both the C_1-C_2 and the N–X bond-breaking processes are not very sensitive to the nucleofuge change. As $\varrho^*_{C2} > \varrho^*_N$, we can conclude that the C_1-C_2 bond breaking process goes slightly ahead of the *N*-X one.

The increases in the rate observed when introducing simple changes of substituents in the structure of the *N*-X-α-amino acids (i.e., $-CH_3$ instead of $-H$) can be considered as typical of concerted reactions.

Table 3 summarizes the effect of the nucleofuge on the reaction rate. The better the nucleofuge is, the faster the fragmentation; *i.e.*, the change of $-Cl$ by $-Br$ leads to a slight increase in the reaction rate.

Taking into account the pK_a values[40] for HCl and HBr, a value for β_n can be estimated (which is the analogous of β_{lg} in elimination reactions, "n" referring to the nucleofuge) ranging from -0.15 for *N*-X-Sar to -0.45 in the case of *N*-X-*N*-Me-Aib. Depending on the characteristics of the TS, in some cases for concerted reactions this could be interpreted as the degree of N–X bond breaking in the TS.

At this stage it is worth considering these estimations of β_n: if the TS is far away from its corresponding "nitrenium-like" structure (or from the "carbanion-like" one), the perpendicular effect will be much less important than the parallel one.[41,42] Similarly, if the TS is really far away from its "product-like" or "reactant-like" structures the perpendicular effect will be the enhanced one. These facts imply that the β_n (also β or β_{lg}) values in a concerted reaction can be strongly affected by the characteristics of the TS, so that a careful consideration of them becomes necessary.

The fact that the substituent effects are of the same order of magnitude on both reaction centers seems to point toward the fact that this process is not far away from a central concerted one. On the other hand, the change of $-H$ by $-CH_3$ on the N is always greater that of the nucleofuge (i.e., $-Cl$ by $-Br$). Hence, the TS must be quite far away from that of the virtual intermediate nitrenium ion, showing instead an important degree of double bond development. These statements lead us to believe that there could be some lack of synchronization in the bond breaking/bond making sequence.

Taking into account the previous discussion it can be considered, according to Dewar's ideas,[43] that the Grob fragmentation of *N*-X-α-amino acids is a concerted two-stage reaction in which the second step (conversion of the virtual intermediate into products) has zero activation energy. Accordingly, the bond making/bond breaking processes do not occur simultaneously and each of them shows a different degree of development when the TS is reached; *i.e.*, to some extent this is an imbalanced process.[44,45]

The previous statements are in good agreement with the principle of nonperfect synchronization;[46–48] *i.e.*, the fact that the observed rate increase when the substituents stabilize the TS allows us to assume that the C_1-C_2 bond breaking is ahead of the N–X bond breaking.

It is possible to locate approximately the TS on a More O'Ferrall[49] diagram as represented by the shaded circle in Figure 1. Assuming this as true the TS would be "product-like", which explains the small effect of the change of nucleofuge and the lack of meaning of the estimated β_n values, according to what was pointed out by Bacciocchi.[50]

In relation to this, it must be pointed out that this location of the TS is only temptative, provided that the possibility of a lack of synchronization between each of the two reaction coordinates shown in the diagram and a third one, *i.e.*, the development of the C=N double bond, is not considered.

According to the results and to the previous discussion two reaction sequences could be considered (Chart 1). Chart 1b represents the situation in which the C_1-C_2

(35) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biolog*; John Wiley & Sons, Inc.: New York, 1979.
(36) Exner, O., A critical compilation of substituent constants. In *Correlation analysis in chemistry: recent advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10.
(37) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, 1969.
(38) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(39) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1983**, *14*, 165.
(40) Bell, R. P. *The Proton in Chemistry*; Chapman & Hall: London, 1973; p 91.
(41) We shall refer to parallel effects instead of "Hammond effects" and to "perpendicular effects" instead of "anti-Hammond effects" since the term "anti-" seems to be inadequate, suggesting that the behavior is "against" the Hammond principle, which is not the case.
(42) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*(12), 2915–2927.
(43) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*(1), 209–219.
(44) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.
(45) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948.
(46) Bernasconi, C. F. *Tetrahedron* **1985**, *41*(16), 3219–3234.
(47) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119–238.
(48) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*(1), 9–16.
(49) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274–277.
(50) Bacciochi, E. *Acc. Chem. Res.* **1979**, *12*, 430–436.

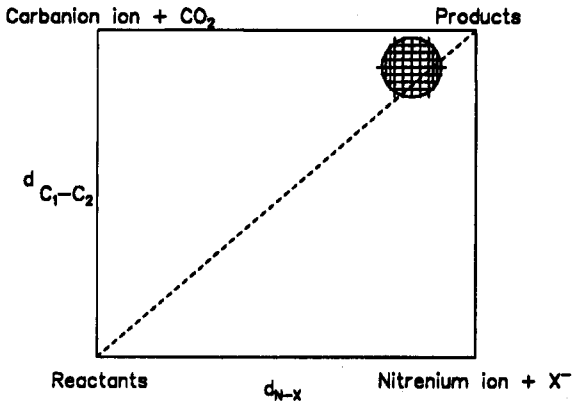
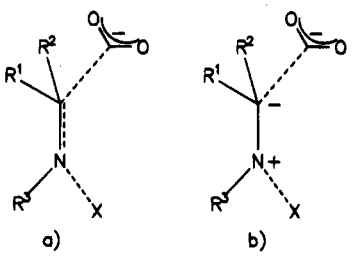


Figure 1. More O'Ferrall diagram for *N*-X-α-amino acid fragmentation.

Chart 1. Possible Reaction Sequences



and N—X bonds are broken before the double bond formation takes place leading to a hypothetical zwitterionic species; quite the contrary occurs in the other one (Chart 1a), where the C=N double bond is formed as the charge development in C_2 and N is enough. To analyze these situations one might try to visualize the position of the TS in a cube where each dimension represents a bond distance:[51] C_1—C_2, N—X, and C=N. Obviously, some species in this representation could never exist but nevertheless, it would be useful in order to emphasize that we know nothing about the C=N bond making process, which means that we have to decide whether the TS is product-like or zwitterion-like.

The fact that the influence of a methyl group on the nitrogen is higher than that of the nucleofuge agrees with the structure in Chart 1a (stabilization of the double bond). As the effects are more important on C_2, we can conclude that C_1—C_2 bond breaking begins first, which would imply a destabilization of the zwitterion in Chart 1b by electron-releasing groups on the C_2. This allows us to discard the hypothesis of the zwitterion-like TS and to conclude that it must be product-like. These facts also lead to the conclusion that the reaction shows an uphill free energy profile.

The shaded zone in Figure 1 tries to represent a possible position for the TS of an unsubstituted *N*-X-α-amino acid. Taking into account the possible influence of the change of substituents on the TS,[42,52,53] it is to be expected that the carbanion stabilizing groups would modify the TS, making it more carbanion-like and less product-like, while the nitrenium ion stabilizing substituents would make it less product-like and more nitrenium-like. The fact that ϱ^*_{C2}(*N*-Br) ~ ϱ^*_{C2}(*N*-Cl) is in agreement with these expectations; i.e., the substitution of Cl by Br leads to a very small displacement of the TS toward a position nearer to that of a central concerted and synchronous process, this effect being more noticeable for *N*-X-*N*-Me-Aib than for *N*-X-Sar due to the change induced by the methyl groups on the TS.

It is also possible to think that the fragmentation could be limited by the stereochemistry. If this were so, when the electrofuge and the nucleofuge are antiperiplanar the p orbitals could collapse easily to form the π-double bond, leading to a TS similar to that shown in Chart 1a. Should the contrary occur, *i.e.*, the electrofuge and the nucleofuge are not antiperiplanar, the TS would be similar to that in Chart 1b. This hypothesis can be readily discarded provided that the *N*-X-α-amino acids considered here must show free rotation about the C_2—N bond.

Conclusion

On the basis of the experimental results it can be concluded that the Grob fragmentation of *N*-X-α-amino acids proceeds through a concerted D_ED_N two-stage mechanism, maybe with some lack of synchronicity between C_1—C_2 and N—X bond breaking processes, the first going slightly ahead of the latter one (with an imbalanced TS). The location of the TS on the free energy surface changes significantly depending on parallel effects (stabilization/destabilization of reactives and/or products by the substituents) and perpendicular effects (stabilization/destabilization of the virtual carbanion and/or the virtual nitrenium ion by the substituents). The process is remarkably product-like beginning with the bond breaking of C_1—C_2 which induces the formation of the C=N double bond and, eventually, the subsequent N—X bond breaking.

Acknowledgment. The authors wish to thank the Xunta de Galicia for providing funds (project XUGA10301B91) and to Prof. Dr. J. Andrés Bort (Universitat Jaume I, Castelló, España) for helpful discussions.

(51) It is worth pointing out that while More O'Ferrall's diagram includes energy this one would not, so it would not be adequate to talk about reaction paths, but instead about possible theoretical structures for the TS.

(52) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.
(53) Harris, J. C.; Kurz, J. L. *J. Am. Chem. Soc.* **1970**, *92*(2), 349–355.