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## Abstract

## Full Text

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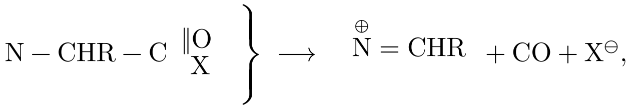
# THE INFLUENCE OF CONFORMATION ON THE FRAGMENTATION OF SOME DERIVATIVES OF $\alpha$-AMINO ACIDS

*(Presented by Academician B. A. Kazanskii, 4 V 1962)*

In recent years reports have appeared ($^{1-6}$) on transformations of various derivatives of $\alpha$-amino acids, for the interpretation of which one and the same scheme is proposed:



$$\left.\mathrm{N-CHR-C}\begin{matrix}\Vert\mathrm{O}\\ \mathrm{X}\end{matrix}\right\}\longrightarrow \overset{\oplus}{\mathrm{N}}=\mathrm{CHR}+\mathrm{CO}+\mathrm{X}^{\ominus},$$

where X is an electronegative substituent, and R is a hydrocarbon radical.

In the preceding communication ($^{4}$) we considered a reaction proceeding according to this scheme as an example of fragmentation and analyzed the influence of the electronegativity of substituent X on this reaction. However, in the fragmentation of derivatives of $\alpha$-amino acids one should also take into account the influence of conformation, which in the case of $\alpha$-amino acids with a tertiary nitrogen atom is apparently the most important factor in the reaction. We studied the fragmentation of some $\alpha$-amino acids with a tertiary nitrogen atom under the action of $PCl_5$ under standard conditions, permitting a qualitative comparison of the tendency of the substances toward decomposition. The equation of the reaction studied has the following form:

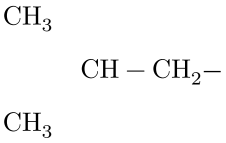
$$\mathrm{R_2NCHR'COOH}+\mathrm{PCl_5}\rightarrow\mathrm{R_2NCHR'COCl}\rightarrow$$
$$\rightarrow[\mathrm{R_2}\overset{\oplus}{\mathrm{N}}=\mathrm{CHR'}]\,\mathrm{Cl}^{\ominus}+\mathrm{CO};$$
$$\downarrow\ \mathrm{H_2O}$$
$$\mathrm{R_2NH}\cdot\mathrm{HCl}+\mathrm{R'CHO}$$

In all cases dialkyl- (or diaralkyl)amines were identified; in most cases aldehydes and CO were identified. Table 1 gives the substances studied and the yields of the isolated amines, determined by weighing the isolated crystalline amine or its hydrochloride; these yields are not maximal. Under other conditions we previously obtained a quantitative yield of dibenzylamine hydrochloride from dibenzylleucine ([3]).

Apparently, under the conditions used by us, the amine formed as the final product or the intermediate Schiff base is partially decomposed; thus, in the case of bis-*p*-nitrobenzyl-$\alpha$-alanine, *p*-nitrobenzyl chloride was isolated as a by-product under the action of $PCl_5$. Nevertheless, the amine-yield data presented in Table 1 clearly show that the reaction proceeds mainly in the indicated direction and that substituents R, differing in their electronegativity, do not exert a significant influence.

**Table 1**

Decomposition of compounds of the type $R_2NCHR'COOH$ under the action of $PCl_5$ at 30-40°

| R′ | R | Amine yield, % |
|---|---|---|
| $CH_3-$ | $C_6H_5CH_2-$ | 65 |
| $CH_3-$ | $(n)CH_3C_6H_5CH_2-$ | up to 80 |
| $CH_3-$ | $(n)O_2NC_6H_5CH_2-$ | 50 |
| $CH_3-$ | $C_2H_5-$ | 55 |
|  $(CH_3)_2CH-CH_2-$ | $C_6H_5CH_2-$ | 80 |
| $C_6H_5CH_2-$ | $C_6H_5CH_2-$ | 76 |

A significant influence on this reaction is exerted by the hydrogen on nitrogen. Until very recently there were no literature data on the susceptibility to decomposition of acid chlorides of $\alpha$-amino acids with a primary or secondary amino group. Quite recently a paper appeared ([6]) reporting that the N-carboxyanhydride of leucine in hydrogen fluoride is capable of partial decarbonylation (by 5%). The authors describe this reaction by the following scheme, which almost completely coincides with our scheme for the decomposition of derivatives of dibenzyl-$\alpha$-amino acids (cf. ([4])):

$$RCH-C(=O)F \longrightarrow RCH=NH_2^{\oplus} + CO$$

Thus, the fragmentation reaction may be regarded as a general property of $\alpha$-amino acids, but the ease with which this reaction proceeds depends on a number of conditions. One such condition proves to be the presence of tertiary nitrogen. And in our case this condition is more essential than the electronegativity of the substituent on nitrogen.

Indeed, the substituents R listed in Table 1 have either greater or lesser electronegativity in comparison with hydrogen. Thus, the ethyl group is more nucleophilic than hydrogen, since the basicity increases upon N-alkylation of $\alpha$-amino acids ($^{7}$). In dibenzyl-$\alpha$-amino acids, according to our data, the basicity of the amino group is lower than in primary $\alpha$-amino acids; i.e., the benzyl group proves to be more electrophilic than hydrogen. This applies all the more to the nitrobenzyl group. Introduction of benzyl and nitrobenzyl groups should hinder the course of the reaction by the proposed mechanism.

**Fig. 1.** Photographs of models of N,N-diethyl-$\alpha$-alanine:
*a* –the nitrogen electron pair, the atoms N, $C_\alpha$, and the COOH group lie in a plane perpendicular to the plane of the figure and in the vertical direction;
*b* –the same plane is almost in the plane of the figure.
Notation: *fr. el. p.* –free electron pair.

Therefore, in this reaction it is necessary to take into account other factors, not simply connected with the electronegativity of substituent R on nitrogen, which can explain the special influence of tertiary nitrogen. One factor that is of essential importance is a favorable conformation ($^{8}$). Conformational effects on the fragmentation reaction had previously been studied only for cyclic systems ($^{8,9}$).

Examination of Stuart models of $\alpha$-amino acids with a tertiary nitrogen atom (see Fig. 1) shows that in these compounds rotation about the bond

$C_\alpha$–N is not free. The van der Waals volumes of the first $CH_2$ group of the substituent on nitrogen "graze" the carboxyl carbon during rotation about the $C_\alpha$–N bond, and in fact, when even one substituent is present on nitrogen, complete rotation of the amino group (through 360°) without deformation of the valence angles proves impossible. When two substituents are present, the freedom of rotation is limited to 180°. When a substituent is present on the $\alpha$-C atom ($R = CH_3$, etc.), additional steric effects arise, which ultimately lead to the $C_\alpha$–N bond becoming almost rigid, as, for example, in the N-methyl-N-isopropylvaline described in the literature. Thus, in a separate portion of the molecule, owing to the close packing of atoms, fixation of some definite conformation becomes possible. This should probably lead to an analogy in some properties with cyclic systems, where the conformations are fixed.

Indeed, the rotational power of $\alpha$-amino acids increases sharply upon N-alkylation ($^{10,11}$). Here, just as for cyclic systems, the influence of conformation on rotation proves significant ($^{12}$). The particular conformation in which an N,N-dialkyl-$\alpha$-amino acid exists (models show that two such conformations are possible, but in one of them the alkyl substituents on nitrogen and the radical R of the amino acid are very close to each other and therefore it is less probable) is a conformation favorable for fragmentation, since in it the following conditions are fulfilled: the electron pair of nitrogen, the nitrogen atom, the $C_\alpha$ atom, and the carboxyl carbon atom lie in one plane. In primary $\alpha$-amino acids the amino group rotates very freely and therefore, although fragmentation is not completely excluded, since a favorable conformation is possible, its probability is much lower.

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*Note: Figure translations are in progress. See original paper for figures.*

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