

STEREOCHEMISTRY OF THE REACTIONS OF BIOPOLYMERS II.

ASYMMETRIC SYNTHESIS III.

**Kinetic resolution in the acylation of DL-alanine
ethyl ester with benzyloxycarbonylalanine peptide azides**

L. Ötvös, I. Tömösközi and T. Mohácsi

**Central Research Institute for Chemistry
of the
Hungarian Academy of Sciences
Budapest**

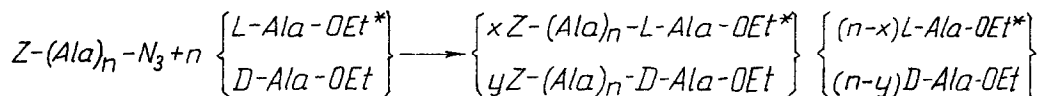
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In the course of an investigation (1) in THIS LABORATORY concerning the stereochemistry of acylation of amines and amino acid esters by amino acid and peptide derivatives, a marked change was observed in the direction and magnitude of kinetic resolution when benzyloxycarbonylalananyl azide was replaced by the corresponding protected di- and tripeptide azides.

The preferential formation of L-D (or D-L) dipeptides from L and DL amino acid derivatives has been demonstrated by several authors (2), however, little is known (3) of the extent to which a peptide of longer chain can discriminate between the enantiomers of the racemic amino acid partner to be incorporated at the N- or C-termini. Information available from studies on the kinetics of polymerization and copolymerization of L- and DL-amino acid NCA-s reflected a tendency of the growing peptide chain towards isotacticity (4).

The aim of our experiments was to check the tendency of the corresponding di-, tri- and tetrapeptides towards isotacticity by systematic stepwise asymmetric synthesis. Further, study was made on the influence

on the stereoselectivity of the configuration of amino acid residues in the peptide chain. The ratio of the enantiomers incorporated by the peptide chain was determined by a simple radioisotope technique (5) based on the equation:



where $Et^* = {}^{14}CH_2CH_3$.

Racemic alanine ethyl ester hydrochloride was prepared by mixing equal amounts of the enantiomers, either of which was labelled with ${}^{14}C$. Ester hydrochlorides were treated with triethylamine in dichloromethane and the amino acid esters liberated were reacted in situ with 0,1 equivalent of the azide. The azide solutions were prepared by nitroization at -5° from the corresponding hydrazides (6) with sodium nitrite in an aqueous hydrochloric acid - acetic acid mixture, extraction with dichloromethane, followed by washing the organic phase with H_2O , 10% $NaHCO_3$ solution and H_2O and drying (Na_2SO_4) for a few minutes in the cold. The combined azide and ester solutions were kept overnight at 20° , thoroughly washed with $N HCl$, H_2O , 10% $NaHCO_3$ solution and H_2O , dried (Na_2SO_4) and evaporated to dryness. Radioactivity of the crude products (obtained in 60-70% yield) was measured without further purification. Incorporation of the L and D enantiomers of the racemic alanine ethyl ester component, as calculated from the molar radioactivity of the products obtained in the reactions of the same azide with L^*D and LD^* esters, are shown in the Table.

TABLE

Per cent Incorporation of Ala-OEt Enantiomers by Benzyloxy-carbonyl-alanyl Peptide Azides in Dichloromethane at 20°
(expressed as percentages of the theoretical yield)

No.	Z-/Ala/ _n -N ₃	L from L ^x D	D from LD ^x
1	DL	49,37	49,57
2	L	45,81	52,70
3	L-L	86,59	12,99
4	L-D	23,30	76,77
5	L-L-L	81,35	19,12
6	L-L-D	24,86	75,39
7	L-D-L	66,13	31,36
8	L-D-D	18,74	82,11

It appears from the Table that a great, unexpected enhancement of the stereoselectivity occurs when the benzyloxycarbonyl-L-alanyl azide is replaced by di- and tripeptide azide derivatives. A further interesting fact is the altered preference of incorporation of the ester enantiomers in the case of peptides, as compared to the amino acid derivative. The striking difference between the extent of stereoselectivity of the mono- and that of the L-L dipeptide may be ascribed (7) to a decreased rotational freedom (8) of the latter and a similar view may serve to explain the data for the tripeptides. An isotactic unit (L-L or D-D) at the reaction centre increases the stereoselectivity, as compared to a syndiotactic one (L-D or D-L); the configuration of the enantiomer incorporated being determined by the configuration of

the residue next to the reaction centre. The lowest stereoselectivity was found in the case of the L-D-L tripeptide involving two syndiotactic units. It is somewhat puzzling that the L-L-L tripeptide involving two isotactic units discriminates less effectively between the enantiomers than the L-L dipeptide.

Further experiments with longer-chain peptides are in progress.

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