

## Sequence inversion and racemization of peptides containing glycine in position 3

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### Introduction

We have observed earlier the rearrangement of the first two amino acids in the peptide chain of Leu-enkephalin and related peptides [1]. This reaction proceeds under mild conditions (pH 7, room temperature) in aqueous solution and is accompanied by decomposition resulting in DKP formation. Its velocity is slow at room temperature but increases considerably with temperature. It seemed interesting to us to study the rearrangement in peptides with Pro in the first or second position, since steric restrictions can be essential for such process.

### Results and Discussion

Results we obtained on heating aqueous solutions of Leu-Pro-Gly-NH<sub>2</sub> and Pro-Leu-Gly-NH<sub>2</sub> differed considerably from those for Leu-Enk. The main process in Leu-Pro-Gly-NH<sub>2</sub> transformation is decomposition leading to DKP and rearrangement is negligible. In the case of Pro-Leu-Gly-NH<sub>2</sub> we detected D-Pro-Leu-Gly-NH<sub>2</sub> generation in parallel with rearrangement and decomposition. Experiments with D<sub>2</sub>O as solvent have revealed that deuterium is present only in the  $\alpha$ -position of Pro and in both diastereomers (Pro-Leu-Gly-NH<sub>2</sub> and D-Pro-Leu-Gly-NH<sub>2</sub>), thus indicating racemization. Both racemization and rearrangement appear to occur simultaneously and have analogous S-shape dependencies of reaction rates on pH. A very sharp increase in reaction rate is observed quite near the pK value of the imino group of Pro. This fact can be easily explained if both reactions proceed through a DKP-like intermediate formed by nucleophilic attack of the carbonyl of the second residue by the imino group of Pro. Increasing the pH makes this group more nucleophilic and thus promotes the generation of the DKP-like structure. We suggest that all reactions observed (rearrangement, racemization and decomposition) have a DKP-like structure as the first intermediate which can split leading to DKP formation or can be bridged by nucleophilic attack of either OH or NH group of Gly<sup>3</sup> leading respectively to racemization of the first residue or rearrangement of the first two residues. Possible pathways for these transformations of peptides in aqueous solution are shown in Fig. 1.

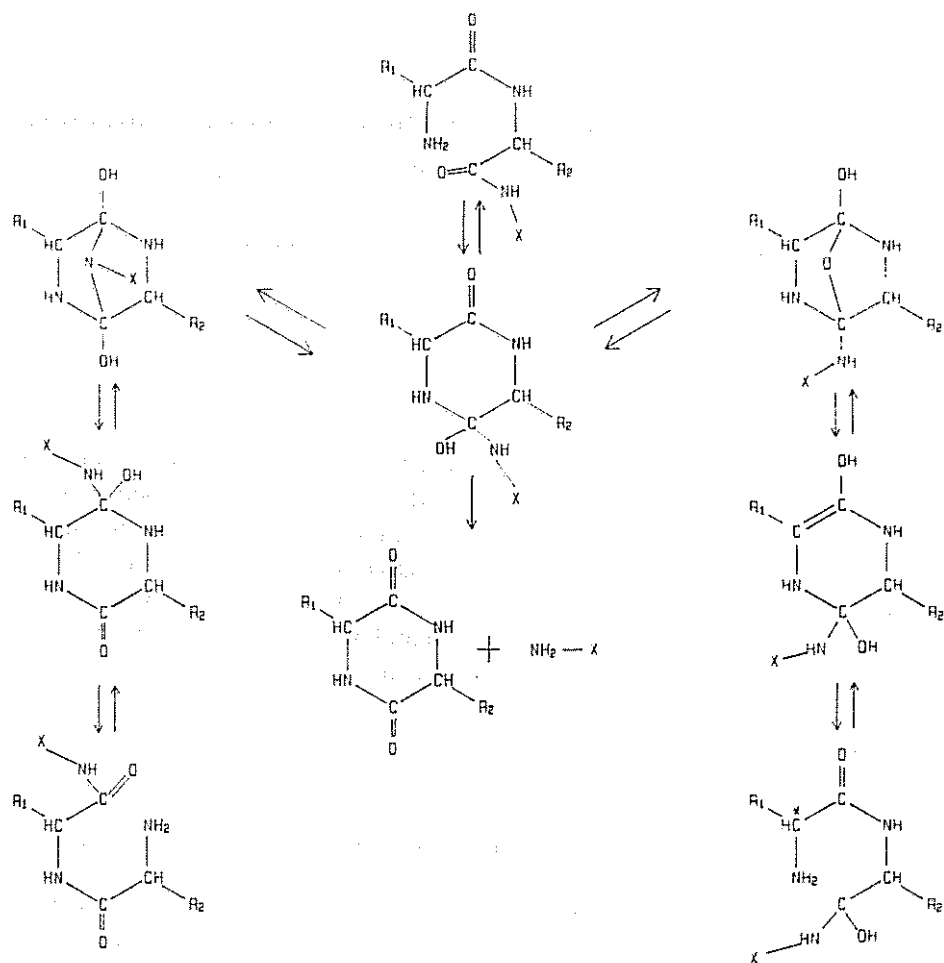


Fig. 1. Suggested pathways in the transformations of peptides in aqueous solution.  $R_1$  and  $R_2$  are the side chains of the first and the second amino acid residues,  $X = CH_2-CO- \dots -NH-CHR_n-COOH$ .

## Reference

1. Sepetov, N., Ovchinnikov, M. and Korotkov, A., Dokl. Akad. Nauk S.S.S.R., 309(1989)1014.