SOLVENT EFFECT ON SIDE CHAIN CONFORMATION OF PHENYLALANINE DERIVATIVES

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Side chain conformation of amino acid derivatives and those in peptides is considered important in understanding their biological and physicochemical properties. It is interesting how they change in environments of different polarity. Side chain rotamer population can be calculated from $^3J_{CH(\alpha)-CH(\beta)}$ values in their nmr spectra according to the Pachler's equations[1] (see the equations in Fig. 1). However, ambiguity remains about the assignment of the two prochiral protons unless stereoselectively β-deuterated amino acids are utilized. For the purpose we have exploited a method for preparing both diastereomers of phenylalanine derivatives: (2S,3R)- and (2R,3R)-PhCHD-CH(NHAc)COOR.[2]

Using the diastereomers, the present work describes the change observed in rotamer population of some phenylalanine derivatives in various solvents. Considerable change was observed when the solvent was varied from polar to apolar. Interestingly, almost linear relation was found when the relative rotamer population were plotted against log ε, where ε is the dielectric constants of the solvents (Fig. 2). The patterns of the plot for the N-methylamide (1) and the ethyl ester (2) of N-acetylphenylalanine are quite different. In the case of (1)
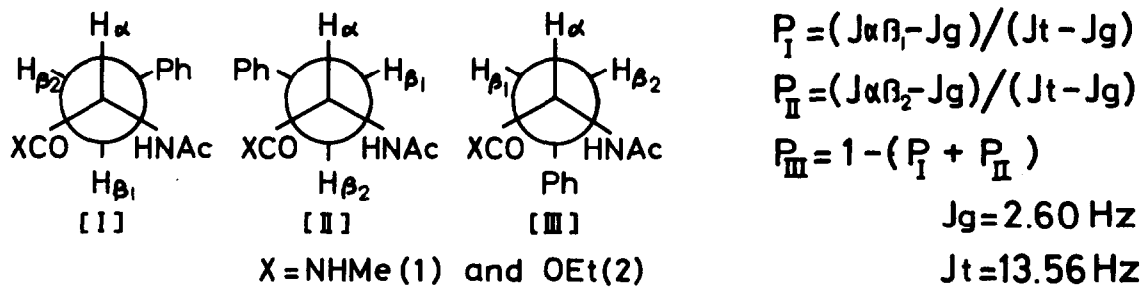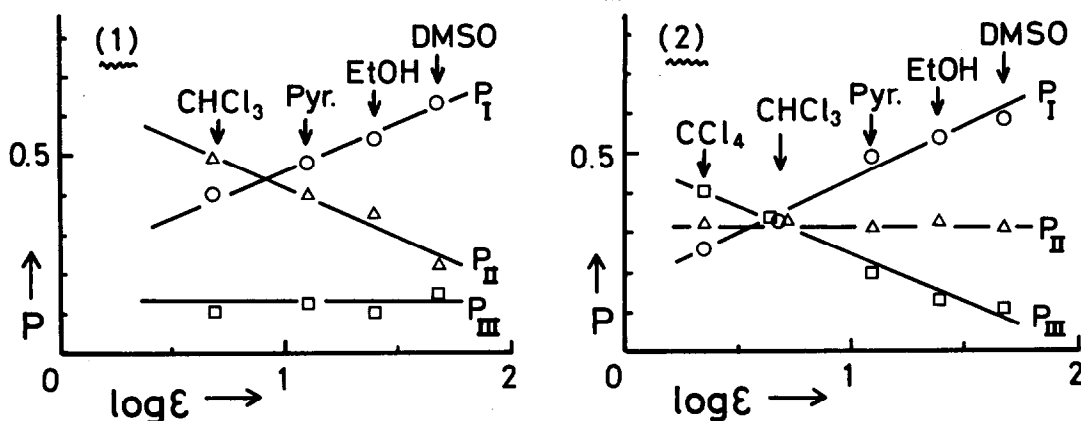

$$P_I = (J\alpha\beta_1 - Jg)/(Jt - Jg)$$
$$P_{II} = (J\alpha\beta_2 - Jg)/(Jt - Jg)$$
$$P_{III} = 1 - (P_I + P_{II})$$
$$Jg = 2.60\,Hz$$
$$Jt = 13.56\,Hz$$

X = NHMe (1) and OEt (2)

Fig. 1 Staggered rotamers of Phe derivs. and Pachler's equations.

Fig. 2   Relative rotamer population of (1) and (2) plotted against log ε.

the relative population of rotamer I (P_I) increases with increasing polarity, but P_{II} decreases, and P_{III} is constantly small.   In the case of (2) P_I increases similarly with increasing polarity, but P_{II} is constant at ca. 0.3 level, and P_{III} decreases quite rapidly.

The reason why such relations and patterns are observed cannot be understood yet.   The results, however, are very interesting from the following points of view: first, the population of the most crowded rotamer (P_{III}) is not always the lowest but can be highest in nonpolar solvent as observed for (2); second, the compounds (1) and (2) can be considered to be models of Phe residues in peptides and depsipeptides, respectively; third, since the inner part of a globular protein molecule is considered less polar than the surface, the rotamer II is expected to have higher probability of occurrence in the phenylalanine residues buried than in those on the surface, if similar tendency found for (1) is kept in protein too.

Studies on the side chain rotamer population of the phenylalanine synthetically built in some oligopeptides are in progress using phenylalanine-β-d_1. Effect of the change of the substituents are also being studied.

<div align="center">REFERENCES</div>

1. K.G.R. Pachler, Spectrochim. Acta, 20, 581 (1964).

2. U. Nagai and J. Kobayashi, Tetrahedron Lett., 2873 (1976).