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# Extended Hückel MO Calculations of the Conformation of Several Amino Acids*

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The conformation of the amino acid residues, glycine, alanine, proline, and phenylalanine have been predicted from molecular orbital calculations of appropriate model compounds. Using the current main chain rotation convention ($\phi$, $\psi$) the principle conformations were found to be glycine (0°, 0°), alanine (240°, 240°), proline (120°, 330°) and phenylalanine (30°, 330°). Several secondary conformations were also found for glycine. A comparison of the predicted conformations is in good agreement with experimental data on comparable residues or model compounds.

A view is held that the major influence on the geometry of a polypeptide molecule is the conformation of the individual amino acid residues comprising the polypeptide, modified by the nonbonded interactions of side chain groups [1–3]. If the preferred conformations of individual peptides could be determined, based on the assumption that their influence on the conformation of a neighboring residue is minimal, it might be possible to predict the total conformation of a small polypeptide molecule in which there were no side chain interactions.

A method is available which has treated the preferred conformation of small molecules with a reasonable degree of success, namely extended Hückel theory [4]. We have applied this MO approach to the prediction of preferred conformations of several biologically important molecules [5–8]. The possible extension of this work to include amino acids could afford a powerful method to the theoretical treatment of polypeptide structure. In this initial study, we consider individually four amino acids in peptide form

$$H_2N–CO–CH(R)–NH–CO–R$$

and calculate the conformational preference using extended Hückel theory.

## Details of the Calculations

The molecules considered were N-acetylglycine amide, N-acetyl-proline amide, N-acetylalanine amide and N-formylphenylalanine amide. The bond lengths and angles chosen were those of Pauling and Corey [9]. Rotational increments were selected every 30 degrees. The MO parameters used were those previously employed [6].

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## Results

The results of the calculations are shown in the Table. The assignment of bonds and angles is according to the convention of Edsall [10]. In this convention, the $C_\alpha$–C bond is $\Psi$ and the N–$C_\alpha$ is $\phi$. For the conformation

$$-\mathrm{NH}\overset{\Phi}{-}\mathrm{CH(R)}\overset{\Psi}{-}\mathrm{CO}$$

$\psi = 0$, $\phi = 0$, the N, H, $C_\alpha$, C, and O atoms are coplanar. The angle $\psi$ is measured clockwise looking down the $C_\alpha$–C bond rotating the CO group. The angle $\phi$ is measured clockwise looking down the N–$C_\alpha$ bond rotating the $C_\alpha$R group.

In one case, secondary conformations were found where the total energy was less than 1 kcal above the minimum. These are included in the Table with the energy difference.

Table. *Calculated conformations of amino acid residues*

| Amino acid | $\phi$ | $\psi$ | Remarks |
|---|---|---|---|
| Glycine | 0° | 0° | |
| Secondary conformation | 300/60° | 0° | $\Delta E = 0.8$ kcal |
| Secondary conformation | 240/120° | 0° | $\Delta E = 0.6$ kcal |
| Alanine | 240° | 240° | |
| Proline | 120° | 330° | The N-acetyl CO group is directed toward the $C_\alpha$ atom |
| Phenylalanine | 30° | 330° | The phenyl ring is directed toward and is roughly coplanar with the C, $C_\alpha$, N axis |

## Discussion

A comparison was made between the calculated conformations and available experimental data on relatively small, comparable amino acid residues. A recent study has been reported on a model of glycine, N-acetylglycine-N-methylamide using infrared [11]. The results indicated that the conformation of one of two crystalline modifications was identical to one of our secondary conformations of glycine ($\phi = 120°$, $\psi = 0°$). X-ray studies of L-leucyl-L-prolyl-glycine [12] and tosyl-L-prolyl-L-hydroxyproline [13] revealed the same conformation for the prolyl residue as predicted by our calculations. Our calculations on phenylalanine are in agreement with the conformation found by X-ray analysis of glycyl-L-phenylalanyl-glycine [14]. In the case of the alanyl residue, no simple model is available with which to compare predicted values with experiments. However, our values of $\psi$ and $\phi$ are close to the values found for poly-L-alanine in a left handed $\alpha$-helix, which it is known to form [15].

The validity of these conformational predictions awaits further proof, although comparisons with available experimental evidence is certainly encouraging. The possible utility of this approach to polypeptide conformation is obvious, while the distinct limitations as far as the size of the polypeptide so treated are equally apparent. Calculations on other amino acid residues are underway in these laboratories.

## References

1. Anfinsen, C. B.: J. Polymer Sci. **49**, 3 (1961).
2. Scheraga, H. A.: In: Molecular architecture in cell physiology. T. Hayashi and A. Szent-Gyorgyi, ed. Englewood Cliffs, N. J.: Prentice Hall 1964.
3. — S. J. Leach, R. A. Scott, and G. Nemethy: Discuss. Farady Soc. **40**, 268 (1965).
4. Hoffmann, R.: J. chem. Physics **39**, 1397 (1963).
5. Kier, L. B.: Tetrahedron Letters 1233 (1967).
6. — Molecular Pharmacol. **3**, 487 (1967).
7. — J. med.Chem. **11**, 441 (1968).
8. — J. Pharmacol. exp. Therapeut.' **164**, 75 (1968).
9. Pauling,, L., R. B. Corey, and H. R. Branson: Proc. nat. Acad. Sci. USA **37**, 205 (1951).
10. Edsall, J. J.: Biopolymers **4**, 121 (1966).
11. Kayama, Y., and T. Shimanouchi: Biopolymers **6**, 1037 (1968).
12. Leung, Y. C., and R. E. Marsh: Acta crystallogr. (London) **11**, 17 (1958).
13. Fridrichsons, J., and A. Mathieson: Acta crystallogr. (London) **15**, 569 (1962).
14. Marsh, R. E., and J. P. Glusker: Acta crystallogr. (London) **14**, 1110 (1961).
15. Bamford, C. H., L. Brown, A. Elliott, W. E. Hanby, and I. F. Trotter: Nature **173**, 27 (1954).

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