

THE RELATIVE STABILITIES OF SOME POLYAMINO ACID HELICES*

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INTRODUCTION

We have recently reviewed some of our work of the past year on the calculation of polypeptide structures¹; this review and the papers cited therein give further details of the results reported here. The calculations on the relative stabilities provide information about the interactions in several polyamino acids of current interest and, at the same time, provide a test of the procedures being developed for the calculation of protein conformation from amino acid sequence.

In these calculations, the energy is expressed as a function of the coordinates of the atoms of the molecule and of the solvent, and the energy is minimized with respect to these coordinates. The most stable conformation is the one of lowest free energy; however, only the energy can be calculated for a given conformation. In order to obtain the free energy difference between two conformations, the contours of the energy surface in the region of each of these conformations must be known. In most of our calculations the assumption has been made that the dominant factor in the free energy difference for two different conformations (e.g., the right- and left-handed α -helices) will be the difference between the minimum energy values, but the problem of obtaining actual free energy differences is under investigation.

ENERGY FUNCTIONS AND PARAMETERS

In our earlier work (see, for example, ref. 2), very approximate energy expressions were used. From calculations on dipeptides², the important role of repulsive forces, in severely restricting the number of allowed conformations, was demonstrated. Recently, a more complete set of energies was included in the computations. The energy contributions taken into account are: torsional potentials, non-bonding interactions, hydrogen-bonding interactions, dipole-dipole interactions, and (only insofar as they affect the dielectric constant) solvent effects. It is a difficult problem to provide accurate expressions for these energy contributions. Therefore, we have obtained a set of energy functions only after testing them on a variety

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of small molecules³⁻⁵ and, at the same time, varying the energy parameters over a range⁵ to make sure that the conclusions reached did not depend on the particular values chosen for the parameters. Besides varying the numerical values of the energy parameters, we separated the barriers to internal rotation into contributions from orbital interactions (i.e. the torsional potentials) and from non-bonding interactions³; also attention was paid to the effect of the direction of approach of two atoms on their van der Waals contact distances⁵ and to the form of the non-bonding potential functions³⁻⁵. Therefore, these *empirical* energies represent our best estimates to date, and it is our belief that the values selected are reasonable ones. Nevertheless, we are at present improving our values⁶ by adaptation of a computer programme of Williams⁷ to the "determination" of the (known) crystal structures of small molecules.

PREFERRED CONFORMATIONS OF POLYAMINO ACID HELICES

Using the energies and procedure described above, calculations were carried out for the homopolyamino acids, polyglycine, poly-L-alanine, poly-L-valine, poly- β -methyl-L-aspartate, poly- γ -methyl-L-glutamate, and poly-L-tyrosine^{5,8,9} and for the cyclic decapeptide gramicidin-S¹⁰. In the calculations on the homopolyamino acids, the computations were restricted to regular (helical) singled-stranded structures. Thus, the calculations could be compared with experimental results in all cases except for polyglycine, which exists as an intermolecularly hydrogen-bonded β -form, polyglycine I¹¹⁻¹³, and as intermolecularly hydrogen-bonded helices, polyglycine II¹⁴. The results for polyglycine, poly-L-alanine and poly-L-valine^{5,9} were expressed as energy contour diagrams on plots of ψ vs. ϕ , the dihedral angles for rotation around the C $^{\alpha}$ -C' and N-C $^{\alpha}$ bond, respectively, of a backbone residue; the calculations for the other structures were initially limited to values of ψ and ϕ corresponding to those of the right- and left-handed α -helices, and the results expressed as energy contour diagrams on plots of χ_2 vs. χ_1 , the dihedral angles for rotation around the C $^{\beta}$ -C $^{\alpha}$ and C $^{\alpha}$ -C $^{\beta}$ bond, respectively, of the side chain⁹. In all cases, the energy was then minimized with respect to ϕ , ψ , and the χ_j 's⁹. The definitions of ϕ , ψ and the χ_j 's are given elsewhere¹⁵.

For *single-stranded* polyglycine, the most stable structures were the right- and left-handed α -helices, and each had the same energy⁵.

For poly-L-alanine^{5,9}, the right-handed α -helix was the most stable structure, and slightly more stable (by 0.4 kcal/mole/residue) than the left-handed α -helix, in agreement with experiment. The preferred position of the side-chain methyl group in the right-handed α -helix is the staggered one.

For poly-L-valine^{8,9}, the right-handed α -helix was the most stable structure, being 0.5 kcal/mole/residue more stable than the left-handed α -helix. The preferred position of the side chain is that for which $\chi_1 = 283^\circ$, i.e. rotated 17° away from the minimum of the potential function for internal rotation about the C $^{\alpha}$ -C $^{\beta}$ bond. This result was an unexpected one, since prior experiments and calculations have been interpreted to mean that poly-L-valine cannot exist in the form of an α -helix¹⁶⁻¹⁹. In fact, it has been concluded previously that branching on the β -carbon atom prevents α -helix formation¹⁶. However, by preparing a block copolymer of L-valine and

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DL-lysine⁸, it has been possible to solubilize poly-L-valine in aqueous solvents to extend the range of study of this polamino acid. In 98 per cent methanol, poly-L-valine appears to exist in the form of a right-handed α -helix⁸, according to o.r.d. data, in agreement with the above prediction. Thus, the branching of the β -carbon does not offer sufficient steric hindrance to prevent the formation of the α -helix in poly-L-valine.

In the cases of poly- β -methyl-L-aspartate, poly- γ -methyl-L-glutamate, and poly-L-tyrosine, the side chains are polar, and the side-chain dipole can interact with the dipole of the amide group of the backbone chain. The effect of this interaction, of course, depends on the relative orientations and distances of separation of the backbone and side-chain dipoles. For the tyrosyl polymer, this interaction is relatively small, and does not seriously affect the total energy, which is dominated by the non-bonding interactions, the latter favouring the right-handed α -helix for all of the polyamino acids considered here; thus, the most stable form of poly-L-tyrosine was found to be the right-handed α -helix. However, for the aspartate and glutamate polymers, the dipole-dipole interaction is considerably stronger, and differs in the two cases because of the extra methylene group between the side-chain ester group of the glutamate and the backbone. As a result, the relative orientations of the dipole of the ester group are such as to favour the right-handed α -helix of poly- γ -methyl-L-glutamate and the left-handed α -helix of poly- β -methyl-L-aspartate. This effect can readily be demonstrated by appropriate variations of the non-bonding potentials and the dielectric constant, the latter influencing the magnitude of the dipole-dipole interaction energy.

Recently¹⁰, an initial attempt was made to compute the conformation of the cyclic decapeptide gramicidin-S by combining the results of steric calculations² and more complete energy expressions⁵. At present, the problem of calculating the conformation of such a biopolymer is being approached by direct energy minimization, using the procedure previously applied to homopolymer helices⁹.

SUMMARY

Using suitable expressions for the various contributions to the total energy, and appropriate procedures for minimizing the total energy, it has been possible to determine the preferred conformations of several polyamino acid helices. These calculations are being extended to other polyamino acids, including those with multiple-stranded structures, such as polyglycine II, β -structures, etc., and to polypeptides of arbitrary amino acid sequence.

Note added in proof

Since the presentation of this symposium lecture, further progress has been reported (see, for example, refs. 20 and 21 and the references cited therein).

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