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Conformation of the Helix—Coil—Helix Polypeptide

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ABSTRACT: Semi-empirical energy calculations were performed to determine the conformation of the α-helix—random coil—α-helix polypeptide. The random-coil region includes only one amino acid residue in these calculations. The results are illustrated by conformational energy maps. The results indicate that the conformation of the structures is not uniquely determined, but the dihedral angles of the residue in the random region are significantly restricted.

KEY WORDS α-Helix / Steric Map / Myoglobin / Secondary Structure / Polypeptide / Protein / Conformational Energy / Helix—Coil—Helix /

It has been well recognized that the three-dimensional structure of biological macromolecules plays a crucial role in their biochemical functions. Most proteins, particularly enzymes, exist in globular conformations, and many of the complete three-dimensional structures of these molecules have been determined by X-ray crystallographic investigations in the crystalline state.

There exists a definite need for a procedure by which the functional conformations of biopolymers could be established from their primary structure. It may be possible to compute the three-dimensional conformation of protein molecule from its amino acid sequence, the positions of the disulfide bonds, and the nature of the solvent. Toward this end, methods have been reported in the literature involving the determination of the energetically favored conformations of biologically important macromolecules by computer calculations.

Typically, in these calculations, energies of interactions of atoms influenced by the conformational changes of the molecule (nonbonded interactions, torsional energies, etc.) were considered and the conformations were sought which would optimize the total energy of these interactions. Scheraga, *et al.*,[1] for instance, have applied these types of calculations to the prediction of the conformations of short peptide chains. These methods cannot yet be applied to the calculation of the conformation of entire enzymes, mainly because the large size of these molecules presents seemingly unsurmountable computational problems.

The prediction of the tertiary structure of the globular protein can be separated into two steps. The first step is to predict the regions of α-helices, loops and β-sheets, etc. (secondary structure) from the primary structure. The second step is to fold up the polypeptide chain to the compact globular structure. The prediction of secondary structure has mainly been done by the statistical analysis. Recent publications[2] confirm that α-helical regions in proteins can be predicted with reasonable accuracy.

Ptitsyn and Rashin[3] made the first attempt to predict the folding and final overall conformation of a globular protein from its amino acid sequence and known secondary (locally organized) structure. The work of Rossman and Liljas[4] confirmed the idea that sections of the backbone of more complicated proteins are bunched up locally to form subglobules within the overall globular structure of the molecules, so dividing many protein molecules into two or

more distinct lobes. The concept of interactions between secondary structure features such as α-helices leading to the formation of single compact globules is a potent one.

In this paper, we consider the interactions between α-helices using the polypeptide in helix—coil—helix conformation.

MODEL AND CALCULATION

The model chain is constructed of two α-helix regions (A, C) and a random coil region (B) as shown in Figure 1, and this structure is called the helix—coil—helix conformation. First the general feature of this conformation was determined with an L-alanine oligomer. Next, examples of this type in proteins were examined.

In this paper, we calculate the case where only one amino acid residue is included in the random-coil region, because the case is represented by only two variables, ϕ_r and ψ_r. Thus the results can be shown on a two dimensional conformational map.

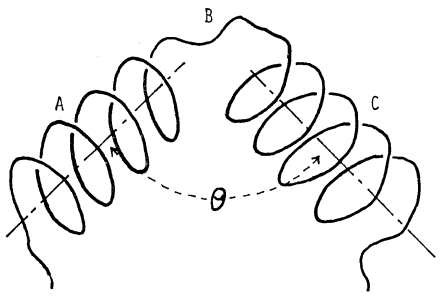

Figure 1. A schematic illustration of the model chain.

The right-handed α-helix is constructed by fixing the internal rotational angles to $\phi_h = -48°$ and $\psi_h = -57°$ for the alanine oligomers. In the case of the proteins, the values obtained from the X-ray analysis are used for internal rotation angles. The random-coil region is defined by two dihedral angles (ϕ_r, ψ_r) in which both ϕ_r and ψ_r can take all the values from $-180°$ to $180°$.

The total conformational energy was computed as the sum of nonbonded interaction, torsional, electrostatic and hydrogen bond energies. The functions and parameters for the torsional energies and the nonbonded interactions are the same as those used by Ooi, *et al.*[5] No special feature is introduced to represent hydrogen bonding. This is assumed to arise from electrostatic interaction and from a modified H---O "6—12" potential, for which the coefficients proposed by Poland and Scheraga[6] were used.

All calculations were carried out assuming fixed bond lengths, bond angles and dihedral angles of side chains. The geometrical constants were adopted from the pertinent literature reference.[7] The nomenclature is that recommended by a IUPAC—IUB Commission.[8] The calculations reported here were carried out using the HITAC 8800/8700 computer system at the Computer Center of the University of Tokyo.

RESULTS AND DISCUSSION

Residues Contiguous to the α-Helix

The conformation of residues which are contiguous to the α-helix region receives some

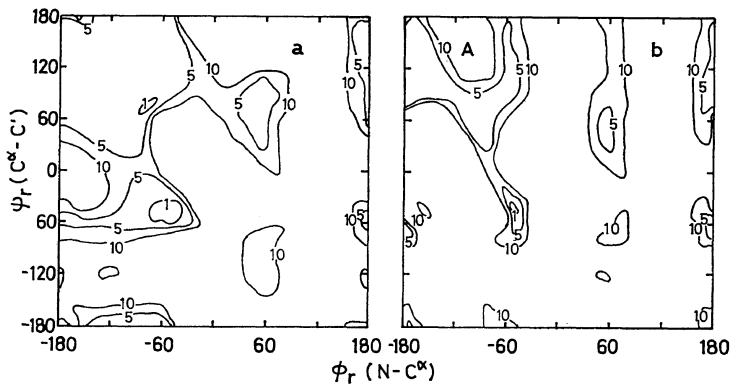

Figure 2. Energy contour maps of the contiguous residues to the α-helix: (a) preceding to α-helix; (b) following to α-helix. Contours are in kcal/mol.

restrictions from the α-helix. Residues, preceding and following to the α-helix, are subject to different restrictions. These features can be illustrated by steric maps, and are shown in Figures 2a and 2b. The various backbone conformations are generated by choosing all values from $-180°$ to 180° (in 10° steps) for the rotational angles ϕ_r and ψ_r. Comparison of these with the dipeptide map of L-alanine[7] shows the general feature of these residues. It can be seen from the steric map in Figure 2b that the region A becomes unstable because of the existence of the α-helix preceding to the residue. The residue following to the α-helix is more affected by the α-helix structure than the residue preceding to the α-helix.

The Helix—Coil—Helix L-Alanine Oligomer

The energy contour maps obtained for the helix—coil—helix L-alanine oligomer are shown in Figures 3a—d. The model of the α-helix was constructed from two to five residues. It can be seen from these steric maps that the special feature of the helix—coil—helix conformation appears when the α-helix includes three amino acid residues. This result agrees roughly with the fact that the α-helix structure has 3.6 amino acid units per turn. Then the interaction energy between two helix rods was calculated

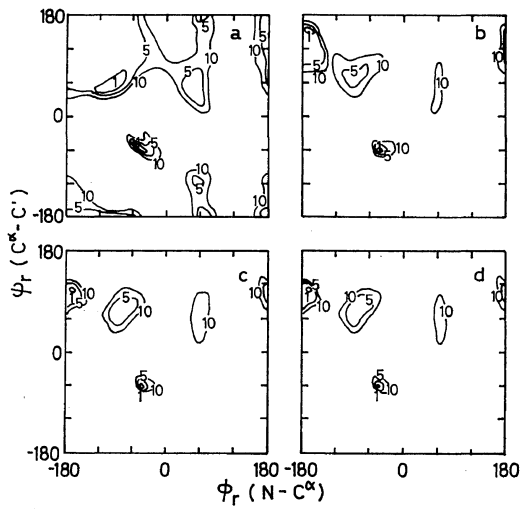

Figure 3. Energy contour maps of the helix—coil—helix alanine oligomer: (a) two; (b) three; (c) four; (d) five residues are included in α-helix. Contours are in kcal/mol.

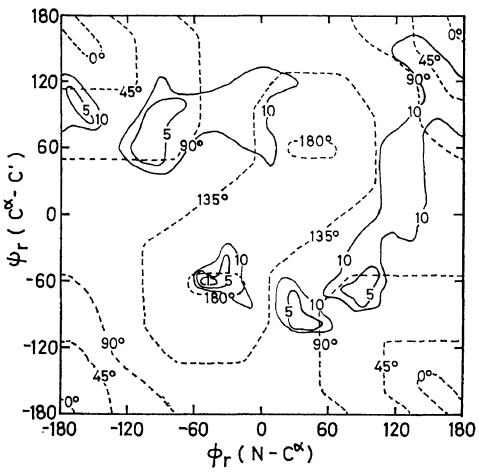

Figure 4. Energy contour map of the interhelical interaction energy of helix(5)—coil(1)—helix(5) alanine oligomer. Contours are in kcal/mol.

only at the case of the five residue α-helix (Figure 4). The angles made by the two helix axes, θ, are indicated by the numerals on the broken curves in Figure 4. The region, where the total conformational energy is less than 10 kcal/mol high than the minima, are shown as the allowed conformation in all the steric maps.

The Helix—Coil—Helix Structure in Myoglobin

Examples of this structure were found in myoglobin, *i.e.*, AB corner or DE corner. It is concluded from the results of alanine oligomers that the inclusion of the five amino acid residues in an α-helix region is enough to estimate the nature of the helix—coil—helix structure.

Table I. The values of dihedral angles about AB corner in myoglobin

Residue		ϕ	ψ	χ_1	χ_2	χ_3	χ_4
15	Ala	−47	−36				
	Lys	−73	−46	−109	−180	−171	179
	Val	−61	−32	60			
	Glu	−70	−30	−135	147	−128	
	Ala	−71	−35				
	Asp	ϕ_r	ψ_r	149	−121		
	Val	−48	−56	−80			
	Ala	−71	−35				
	Gly	−61	−62				
	His	−49	−52	−120	60		
25	Gly	−54	−55				

Table II. The values of dihedral angles about DE corner in myoglobin

Residue		ϕ	ψ	χ_1	χ_2	χ_3	χ_4
53	Ala	−55	−60				
	Glu	−47	−52	−68	−176	158	
	Met	−50	−60	−81	−157	−154	
	Lys	−52	−37	−60	−150	−171	179
	Ala	−61	−54				
	Ser	ϕ_r	ψ_r	−90	60		
	Glu	−70	−40	−120	−80	−86	
	Asp	−64	−41	−173	−145		
	Leu	−58	−54	−150	−60		
	Lys	−42	−79	−120	180	−53	−173
63	Lys	−45	−55	−101	−152	−171	179

The amino acid sequences or diheral angles of these oligomer are listed in Tables 1 and 2. Using the data in the literature,[9] the steric hindrance appears to be present. In order to eliminate the steric hindrance, the dihedral angles were changed. The results of these examples were shown in Figures 5a and b. From the X-ray data, the dihedral angles are $\phi_r=-149°$ and $\psi_r=69°$ in the case of AB corner and $\phi_r=-60°$ and $\psi_r=123°$ in DE corner, and these were indicated by crosses in Figures 5a and b. The minimum energy conformations are at $\phi_r=-160°$, $\psi_r=80°$ in Figure 5a and $\phi_r=-60°$, $\psi_r=-30°$ in Figure 5b. It can be seen in

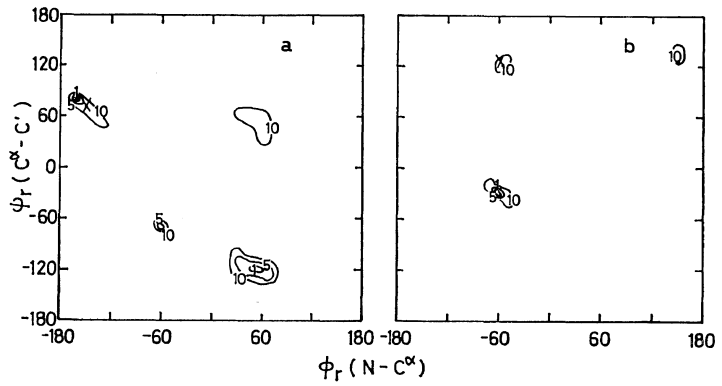

Figure 5. Energy contour maps of the examples in myoglobin: (a) AB corner; (b) DE corner. Contours are in kcal/mol.

Figures 5a and b that the sterically permissible regions are restricted to a few narrow regions, and the crosses are included in these regions. It is worth noting that the right-handed α-helix region still remains a stable region in both cases. If the whole structure is taken into these calculation, the α-helix region will become unstable. These facts indicate that helix-breaking is affected not only by the type of the amino acid residue but also by the long-range interactions.

It was reported by Ponnuswamy, *et al.*,[10] that short-range and medium-range interactions play the dominant role in determining the conformation of an amino acid residue in a protein, and longer-range interactions may be of considerably less importance. But our results suggest that the conformation of the residue is not determined uniquely by the short-range interactions.

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