The Interaction Energy Calculation Between Heme Group and Globin. I. Oxyhemoglobin

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Summary

The van der Waals interaction energies and the electrostatic interaction energies between heme group and globin are calculated on the basis of the atomic coordinates of oxyhemoglobin. The results of the calculation leads to the following conclusion. The electrostatic interaction energy originated in the partial charges on all constituent atoms of hemoglobin molecule and the hydrogen bond energy are negligibly small compare with the van der Waals interaction energy. Therefore the heme groups are stabilized by the van der Waals interaction and the partial covalent bond between Fe atom and Nε atom of the proximal histidine. If the energies of the partial covalent bonds are assumed to be same both in α and β chain, the heme group in α chain is more stabilized than in β chain by about 10 kcal/mole which is originated in the van der Waals interaction.

Introduction

A great deal of work has been done to clarify the mechanism of heme-heme interaction in the oxygenation process of hemoglobin. To explaine the mechanism of heme-heme interaction, abstruct models are proposed by Monod, Wyman and Changeux [1] and by Koshland, Némethy and Filmer. [2]

Several years ago, the atomic coordinates of hemoglobin molecule have been determined with X-ray analyses by Peruts et al. [3]-[8] Moreover, Perutz proposed the stereochemical mechanism of both heme-heme interaction and Bohr effect based on the atomic coordinates. [8] But his model dose not seem to be well substantiated on the basis of energitics.

Recently, Arata and Otsuka [9] proposed a new model based on energy. Their energy calculations are carried out by taking into account van der Waals interaction, electrostatic interaction and hydrogen bond between subunits on the basis of atomic coordinates of oxy-and deoxyhemoglobin.

In the present paper, the interaction energy between heme group and globin in oxyhemoglobin are calculated to clarify the difference in energy between α and β chains by taking into account van der Waals interaction, electrostatic interaction.

The sequential and structural notation of hemoglobin conform to those of Perutz et al. [3], [7]

Atomic Coordinates used in the Present Calculation

I used the atomic coordinates determined from 2.8 Å resolution electron density map of horse oxyhemoglobin by Perutz et al. [7] in my calculation. The coordinates of hydrogen atoms, which

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had not been listed in their table, were determined with the use of the bond lengths estimated as the sums of covalent radii[10] of the participant atoms and of the bond angles shown in previous paper.[9] More rigorous selection of bond lengths and bond angles may not be needed because the atomic coordinates of hydrogen atoms are restricted to non-hydrogen atom's coordinates which are already determined.

Method of Energy Calculation

The calculations of the interaction energies between globin and heme group are carried out by taking into account electrostatic interaction, van der Waals interaction. These two types of interactions are assumed to be superposed in the evaluation of the interaction energies.

(A) Electrostatic interaction

The electrostatic interaction energies are calculated with the coulomb's low type potential function between partial charges. The equation for the electrostatic energy is given as

$$U_{el} = \sum_{all} q_i q_j / Dr_{ij}, \tag{1}$$

wheee, q_i and q_j are partial charges on atoms; r_{ij} is the distance between two charges on atoms; D is the effective dielectric constant and D=4 is used for all atom pairs. The calculation of electrostatic interaction is carried out between heme group and the globin to which the heme group belong. All the amino residues of globin are considered to be neutral because the heme group is surrounded by non-polar residues and also because the effect of charged residues, which are distributed over the surface, is shown to be small by Arata and Otsuka.[9] The partial charges for neutral amino acid have been determined by Poland and Scheraga[11] for homopolymers of the important amino acid. Their result are used in the present calculation.

It is difficult to estimate completely the partial charges on the heme plane. However, the partial charge on four N atom and Fe atom are assumed to be −0.5e, −0.5e, −0.5e, −0.5e and +2.0e, respectively. The partial charges of propionic acid side chain, methyle group and binyle group attatched to heme are determined with the knowledge of electronegativity as follows.

The electronegativity difference of the bonded atoms C-H and N-H are 0.4 and 0.9,[12] respectively. From these values the ammount of ionic character 4% and 18% are obtained for C-H, and N-H bond, respectively. Then, the partial charges of 0.04e and 0.18e are placed on the H-atoms on C and N atoms, respectively. The partial charges of carboxyl group are taken from Poland and Scheraga.[11] The used values of the partial charges on heme group are shown in Fig. 1.

(B) Van der Waals interaction

A Lennard-Jones "6-12" potential function is used for the interaction of a pair of atom i in one subunit and atom j in another:

$$U_{ij} = d_{ij}/r_{ij}^{12} - e_{ij}/r_{ij}^{6}, \tag{2}$$

where r_{ij} is the inter-atomic distance. The used values of d_{ij} and e_{ij} for all pairs between C, N, O, and H are taken from Scott and Scheraga's paper.[13] The calculations are carried out for the following pairs of atoms; pairs of non-hydrogen atoms (C, N, and O) within 6 Å, pairs of non-hydrogen atoms and

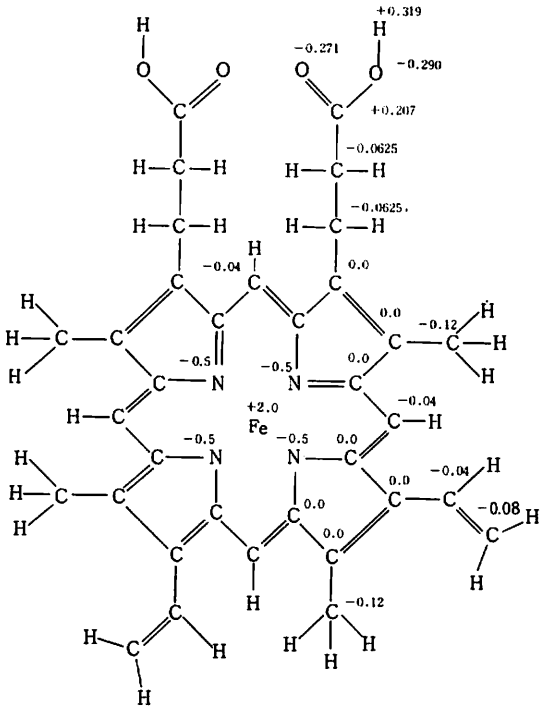

Fig. 1. The partial charges used in the present calculation on heme group. All the values of the partial charges on hydrogen atoms, which are not written on the figure, are 0.04 except for the carboxyl group. The values of charges are given in units of electronic charge e.

hydrogen atoms within 5 Å, and pairs of hydrogen atoms within 4 Å. For the pairs of atoms within the distance of the sum of the van der Waals radii, the energy value of the van der Waals-interaction for each of these pairs is assumed to be zero. The van der Waals interaction between heme and globin is evaluated by the superposition of the interactions of all the pairs of atoms mentioned above.

Result

The calculated values of the electrostatic interaction and the van der Waals interaction energies between heme group and the globin are listed in Table I for the α and the β chains. In this table, the energy values are shown in kcal/mole. In Table I, the interaction energy between Nε atom of His (F8) and Fe atom in both α and β chains are not included because of the reason mentioned in the previous section. First the main features of these interactions are taken up briefly.

(A) α chain

The van der Waals interaction between heme group and globin in α chain is outstanding in the segments CD, E, F, FG, and G. The F segment has the most strong van der Waals interaction, namely about −19

Table I. The calculated energy values of the electrostatic interaction and the van der Waals interaction between heme group and globin in oxyhemoglobin. All the residues are treated as neutral. The dielectric constant D=4 is used for all atom pairs. The energy values are given in units of kcal/mole.

α			β		
segment	van der Waals	electrostatic	segment	van der Waals	electrostatic
NA			NA		
A			A		
AB			B	− 0.6	− 0.1
B	− 0.8		C	− 3.2	− 0.3
C	− 2.8	− 0.1	CD	− 1.6	0.3
CD	− 9.4	0.4	D		
E	−11.5	− 0.5	E	−20.5	− 1.3
EF			EF		
F	−18.8	1.3	F	−15.2	2.1
FG	− 7.3	0.2	FG	− 5.6	
G	−13.3		G	− 7.9	− 0.2
GH			GH		
H	− 2.3	− 0.1	H	− 0.9	
HC			HC		
total	−66.2	1.2		−55.5	0.5

kcal/mole, between heme group in α chain. The total value of the van der Waals interaction energy in α chain ammounts to about −66 kcal/mole. The energy value of the electrostatic interaction is small and is somewhat repulsive.

(B) β chain

The segments E, F, FG and G are outstanding in the van der Waals interaction between heme group and the globin in β chain. The most strong van der Waals interaction is found between E segment and globin, and the energy value of this interaction is about −20 kcal/mole. The total value of the van der Waals interaction energy in β chain ammounts to about −56 kcal/mole. The electrostatic interaction is also small and repulsive.

Discussion

Van der Waals interaction, electrostatic interaction, covalent bond suggested dy Perutz,[8] and the hydrogen bonds are considered as the interaction between heme group and globin. In the present calculation, the covalent bonds between iron and histidine F8 in both α and β chains, one probable hydrogen bond between propionic acid carboxyls and histidine CD3(45) in α chain, and two between propionic acid carboxyls and serine CD3(44) and lysine E10(66) in β chain are not taking into account. It is difficult to calculate directly the bond energy between iron and N atom of histidine. However, this bond energy

may be gessed to be fairly large from the covalent bond energy of simple molecule. The energies of hydrogen bonds mentioned above may be small because they have contacts with water and because the number of hydrogen bonds is a few.

Table I shows that the electrostatic interaction is negligibly small in compare with the van der Waals interaction in both α and β chains. Therefore, following conclusions are derived from the present calculation. The heme groups are stabilized by the van der Waals interaction and the covalent bond between Fe atom and Nε atom of the proximal histidine. If the energies of covalent bonds are assumed to be same both in α and β chains, the heme group in α chain is more stabilized than in β chain by about 10 kcal/mole which is originated in the van der Waals interaction.

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