A Study on the Effective Dielectric Constant in Water Cavity Surrounded by Protein

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SUMMARY

Dielectric property in water cavity surrounded by protein is investigated with Tanford and Kirkwood formula. In the calculation, radius of the cavity is fixed at 5 Å and 32Å, and the dielectric constants of water and protein are taken to be 81 and 4, respectively. When the two charges embedded deeply in the water cavity of radius 5Å(32Å) are separated by about 3Å, which is a distance of hydrogen bonding, the effective dielectric constant between the two charges is about 7(30) due to the effect of surrounding protein with low dielectric constant. If the distance becomes longer, the value of this constant reduces down to 4. When the distance between the two charges becomes shorter, the value of the effective dielectric constant increases to 81 due to the decreasing effect of the surrounding protein. Further, effective dielectric constant in the globular protein surrounded by water is investigated with the same method for references.

INTRODUCTION

Electrostatic forces are an essential factor of protein structure and stability. However, despite of this obvious importance, it has not generally been clear how they should be treated. A major problem has been how to account for solvent effect in even a qualitatively reasonable fashion. In the current treatment of protein structure, electrostatic effects are calculated by summing the pair wise coulombic interactions between partial charges whose atomic coordinates are known from the crystal structure. The dielectric properties of the protein are described with a continuum model in which the protein is assumed to be a low dielectric medium. As a calculational technique taking account of solvent effects, the distance-dependent dielectric constant was introduced in the conformational calculation(1). While these approximations may be useful in many cases, they are not based on a well defined physical model.

Another approach to the study of dielectric property taking account of solvent effect was introduced by Tanford and Kirkwood(2). They treated a protein as a spherical region of low dielectric constant surrounded by a solvent of high dielectric constant and estimated solvent effect on the interactions between point charges within the protein. Their method was applied to evaluate the interactions between ionizable sites on the surface of hemoglobin and between the charges located on the surface and inside of hemoglobin(3).

Hemoglobin(Hb) is a globular protein composed of four subunits. In the interior of Hb,

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there exists a water cavity surrounded by the four subunits. Large number of serines and threonines face the cavity and some ionizable sites jut out into the water of the one. The water molecules in the cavity seem to have a role of screening the charges in the cavity. The dielectric property in the water cavity has not been studied while those property in the protein has been studied extensively. Then, it will be valuable to investigate the effective dielectric constant between charges in the water cavity surrounded by protein. In the present work, the effective dielectric constant is estimated between the two charges in the spherical water cavity surrounded by protein as a simple model, although the one found in Hb is not spherical.

METHOD

The work done in charging sites on a globular protein is given by Kirkwood[4]. The formula is

$$W(\xi_1, \xi_2, \cdots\cdots, \xi_m)=\frac{e^2}{2}\sum_{k=1}^{m}\sum_{l=1}^{m}\xi_k\xi_l A_{kl}-\frac{e^2}{2b}\sum_{k=1}^{m}\sum_{l=1}^{m}\xi_k\xi_l B_{kl}-\frac{e^2}{2a}\sum_{k=1}^{m}\sum_{l=1}^{m}\xi_k\xi_l C_{kl} \tag{1}$$

where

$$A_{kl}=\frac{1}{D_l r_{kl}} \tag{2}$$

$$B_{kl}=\frac{1}{D_l}\sum_{n=0}^{\infty}\frac{(n+1)(D-D_l)}{(n+1)D+nD_l}\left(\frac{r_k r_l}{b^2}\right)^n P_n(\cos\theta_{kl}) \tag{3}$$

The C_{kl} is complicated function and this term is small for the usual ionic strength. Then, the full expression for C_{kl} is not written here. In the equations, P_n $(\cos\theta_{kl})$ represents ordinary Legendre polynomials, and r_k, r_l, r_{kl}, and θ_{kl} are as shown in Fig. 1. D_l and D are the dielectric constant of protein and solvent, respectively, b the radius of the protein, a the radial distance to which the salt ions in the solvent are excluded, and $\xi_k e$ the charge on the k-th sites (hence ξ_k takes the value 0 or +1 for cationic site, 0 or -1 for anionic ones). The first term (A term) is the direct electrostatic interaction between the charges in the protein, the second term (B term) the energy arising from the fact that the globular protein is surrounded by solvent of higher dielectric constant D, and the third term (C term) the interaction with the ions in the solvent. The effective dielectric constant D_E between two charges $\xi_k e$ and $\xi_l e$ is defined as

$$W(\xi_k, \xi_l)=\frac{\xi_k\xi_l e^2}{D_E r_{kl}} \tag{4}$$

Then, according to the equations (1)−(4),

$$\frac{1}{D_E}=\frac{1}{D_l}-\frac{r_{kl}}{bD_l}\sum_{n=0}^{\infty}\frac{(n+1)(D-D_l)}{(n+1)D+nD_l}\left(\frac{r_k r_l}{b^2}\right)^n P_n(\cos\theta_{kl}) \tag{5}$$

This formula may be converted into a form amenable to calculation by making use of suitable properties of Legendre polynomials[5]. In this form

$$\frac{1}{D_E}=\frac{1}{D_i}-\frac{r_{kl}}{b}\left[\frac{1-2\delta}{D_i(1-2\rho_{kl}\cos\theta_{kl}+\rho_{kl}^2)^{\frac{1}{2}}}+\frac{1}{D\rho_{kl}}\ln\left\{\frac{(1-2\rho_{kl}\cos\theta_{kl}+\rho_{kl}^2)^{\frac{1}{2}}+\rho_{kl}-\cos\theta_{kl}}{1-\cos\theta_{kl}}\right\}\right] \quad (6)$$

with

$\delta=D_i/D$ and $\rho_{kl}=r_kr_l/b^2$.

The effective dielectric constant D_E between two charges within the spherical water cavity surrounded by protein is calculated by the equation (6) with the use of dielectric constants $D_i=81$ (for water cavity) and $D=4$ (for protein). Calculations are carried out with the radii of the sphere b=5Å and 32Å for the following two cases: case (1), both charges are located on the same line through the center of the cavity (θ_{kl} is set to be zero), and case (2), both charges are located at the positions of same distance from center of the spherical cavity ($r_k=r_l$).

For references, calculations are also carried out for globular protein surrounded by water solvent.

RESULTS AND DISCUSSION

The calculated results for the case (1) and case (2) with the use of dielectric constants $D_i=81$ and $D=4$, and the radius of cavity b=5Å are shown in Fig. 2.a and Fig. 2.b, respectively. In Fig. 2.a, the position of a charge is fixed at several points (r_k=1Å, 2Å,……, 5Å) and the other (r_l) is varied from center to the surface of the cavity. When the two charges are separated by about 3Å, which is the distance of hydrogen bond, D_E value is about 7 due to the effect of surrounding protein with low dielectric constant. If the distance becomes longer, the value of this constant reduces down to 4 due to the increasing effects of surrounding protein, and if the distance becomes shorter, the value increases to 81 due to the decreasing effect of the surrounding one. Angle θ_{kl} dependency of D_E is shown for several values of r_k (=r_l=1Å, 2Å,……, 5Å) in Fig. 2.b. The value of D_E decreases when the angle θ_{kl} increases. D_E value is about 4 between two charges which are separated by 3Å on the surface ($r_k=r_l$=5Å) of the spherical cavity and is about 7 in the interior of the one.

The calculated results for the case (1) and (2) with the use of $D_i=81$, $D=4$ and the radius of the sphere b=32Å are shown in Fig. 3.a and Fig. 3.b, respectively. In Fig. 3.a, the D_E curve vs r_l is shown for several values of r_k (r_k=10Å, 20Å, 30Å, and 32Å). The D_E value is about 30 for the two charges in the interior of the sphere. In Fig. 3.b, D_E vs θ_{kl} is shown for several values of r_k (=r_l=10Å, 20Å, 30Å, and 32Å). The D_E value between two charges on the surface (r_k=32Å) varies from 2.5 (for $\theta_{kl}=5°$) to 5 (for $\theta_{kl}=180°$). Such a low value is due to the great effect of the surrounding protein with low dielectric constant. In the interior of r_k=10Å (20Å), D_E is about 24(16) between the two charges separated by about 3Å.

For references, the effective dielectric constant between two charges is estimated in the spherical protein surrounded by water solvent. The dielectric constants $D_i=4$ and $D=81$ are used for protein and water solvent, respectively. The radius of the protein is taken to be 32Å which is used as a spherical radius of hemoglobin[3]. The calculated results for case (1) and case (2) are shown in Fig. 4.a and Fig. 4.b, respectively. In Fig. 4.a, r_k is fixed at several points and r_l is varied from the center to the surface of the sphere. D_E value between two charges, one on the surface ($r_k = 32$ Å) and another in the interior ($r_l < 29$ Å), is very high due to the solvent effect while D_E between two charges in the interior ($r_k = 10$ Å and 20 Å, $r_l < 29$ Å) is close to the dielectric constant of the protein with weak shielding by the solvent. In Fig. 4.b, the r_k ($= r_l$) is fixed and θ_{kl} is varied from 0° to 180°. The D_E value exceed 81 (for $\theta_{kl} > 70°$) near the surface ($r_k = 30$ Å, 32 Å) due to the great solvent effect while this value in the interior ($r_k = 10$ Å, 20 Å) is less than 30.

These figures given here will be useful in evaluating the effective dielectric constant between two charges in water cavity found in protein or in globular protein surrounded by water.

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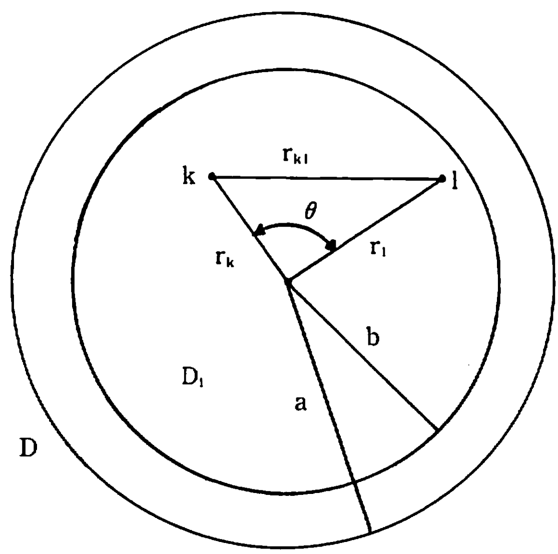
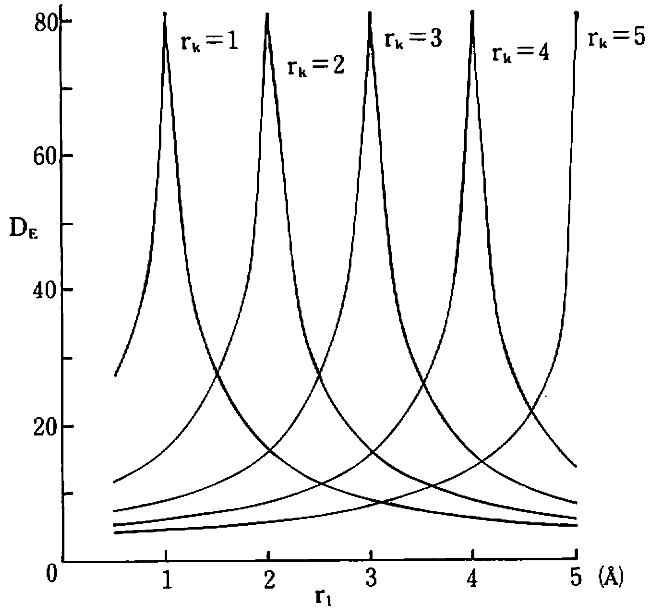
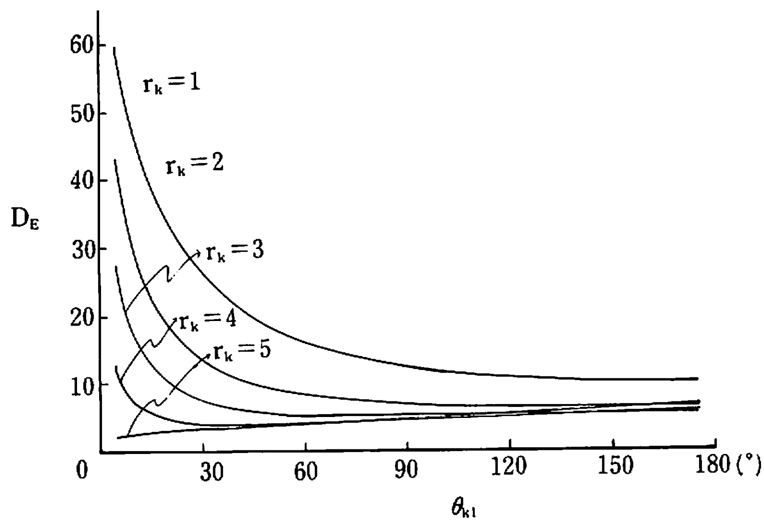


Fig. 1 Model of protein molecule. The points k and l represent the locations of the two charges. The dielectric constant is D_i within the radius b, and D outside it. Salt ions in the solvent can not penetrate within the radius a (from Kirkwood[4]).



(a) $D_l=81$, $D=4$

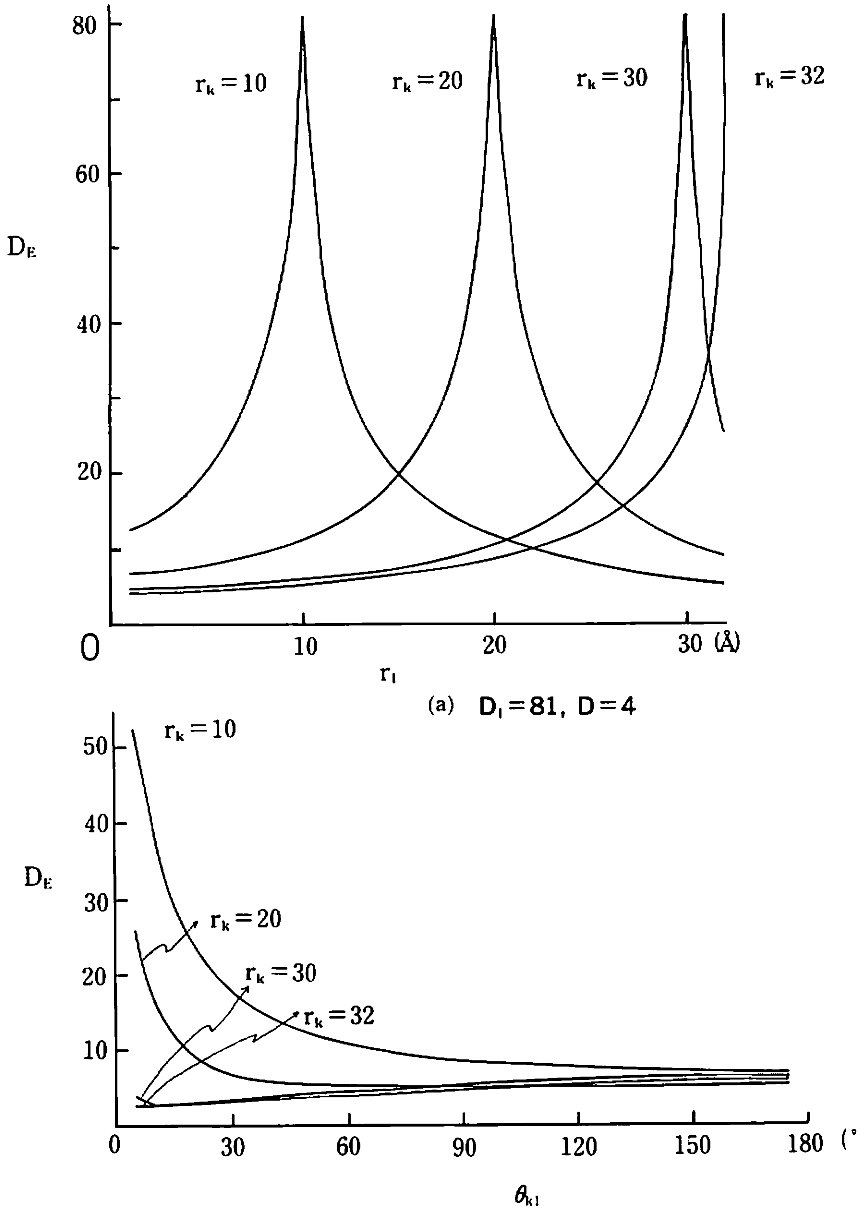


(b) $D_l=81$, $D=4$

Fig. 2 The effective dielectric constant D_E between two charges in the spherical water cavity of radius b=5Å surrounded by protein. The calculations are carried out for several values of r_k (1Å, 2Å,……, 5Å) with the use of dielectric constants $D_l=81$ and $D=4$.

(a) The two charges are located on the same line passing through the center of the sphere ($\theta_{kl}=0$). D_E is shown as a function of r_l.

(b) The two charges are located at the same distance from the center of the cavity ($r_k=r_l$). D_E is shown as a function of θ_{kl}.



(b) $D_l=81$, $D=4$

Fig. 3 The effective dielectric constant D_E between two charges in the spherical water cavity of radius b=32 Å surrounded by protein. The calculations are carried out for several values of r_k (10 Å, 20 Å, 30 Å, 32 Å) with the use of dielectric constants $D_l=81$ and $D=4$.

(a) Two charges are on the same line passing through the center of the sphere ($\theta_{kl}=0$). D_E is shown as a function of r_l.

(b) Two charges are at the same distance from the center of the cavity ($r_k=r_l$). D_E is shown as a function of θ_{kl}.

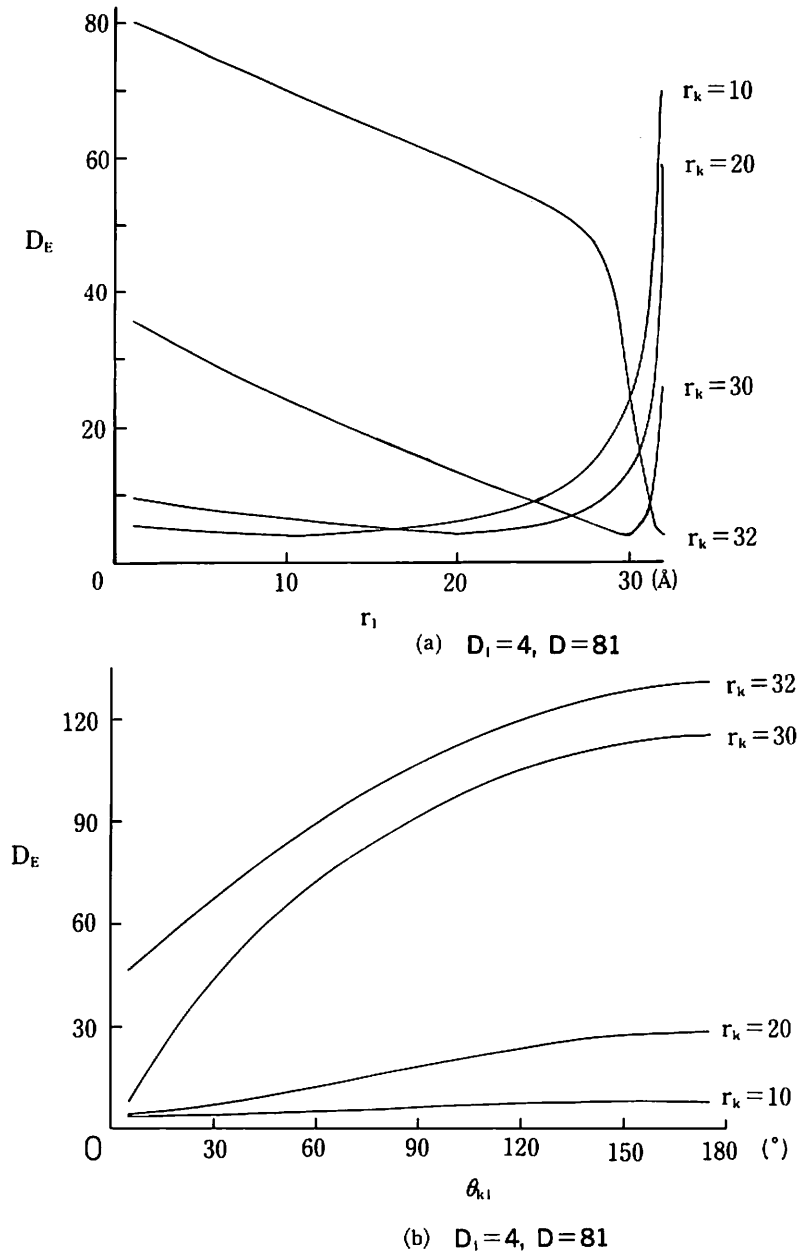


Fig. 4 The effective dielectric constant D_E between two charges in the spherical protein of radius 32 Å surrounded by water. The calculations are carried out for several values of r_k (10 Å, 20 Å, 30 Å, 32 Å) with the use of dielectric constants $D_l=4$ and $D=81$.

(a) Two charges are on the same line passing through the center of the protein ($\theta_{kl}=0$). D_E is shown as a function of r_l.

(b) Two charges are located at the same distance from the center of the protein ($r_k=r_l$). D_E is shown as a function of θ_{kl}.