Biophysical Chemistry 18 (1983) 339–347
Elsevier

BPC 00812

LOCAL EFFECTS IN HYDROPHOBICITY

ELECTROSTATIC INTERACTIONS IN THE RESTRUCTURING OF HIGHLY POLAR SOLVENT AROUND LESS POLAR SOLUTE

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Received 27th February 1983
Revised manuscript received 2nd July 1983
Accepted 6th July 1983

Key words: Hydrophobicity; Electrostatic interaction

Two simplifying assumptions are frequently used in the biophysical chemistry of aqueous solutions: (i) a dielectric mediates the interactions of polar and ionic molecules in aqueous phases and (ii) the dielectric constant of this medium is high and uniform up to molecular surfaces. Because of their great utility in rationalizing simple electrostatic and dielectric effects in such polar systems, it is important to examine whether these assumptions also lead to deductions that are locally consistent with the solvent restructuring observed in hydrophobic phenomena. In this paper, using a model polar fluid system, these macroscopic assumptions are applied to the rigorous, microscopic nonlinear integral equation for W_i^k, the potential of mean force between two adjacent polar molecules. In systems of high dielectric constant, linearization of Boltzmann exponentials and approximation of three-molecule potentials of mean force by superposition of two-molecule potentials permit reduction to a linear integral equation for W_i^k. It is shown that the strictly local electrostatic contributions to W_i^k exert an effect that is qualitatively similar to the global screening effect of a dielectric medium. Through the relation between W_i^k and configurational probabilities, it is further found that reducing the polarity of a molecule in a polar fluid shifts local pair probability density from energetically unfavorable to energetically favorable two-molecule configurations. This general effect, which clearly promotes local structure, would augment more specific hydrophobic mechanisms in aqueous systems. Thus, the assumptions upon which the highly successful Debye-Hückel and Onsager models are supported lead also to deductions about local structure that are consistent with hydrophobic structure enhancement.

1. Introduction

Structural reorganization of highly polar solvents vicinal to nonpolar solutes has been recognized for many years [1–3]. The effect in water is particularly interesting because of the biophysical importance of such structural changes in hydrophobic phenomena [4]. It is thought that in water a layer of enhanced solvent structure surrounds an apolar solute and that such structure formation makes an unfavorable entropic contribution to the free energy of contact between solvent and solute. Fundamental interpretation of these processes in aqueous systems remains incomplete and controversial, but it is generally agreed that hydrophobicity is a very significant and pervasive influence in biological structure and function [5]. The group of liquids exhibiting restructuring behavior includes substances as diverse as water, acetone and alcohols, so it cannot be assumed that the underlying process is the same in every case. Nevertheless, primitive effects, general within the class of highly polar fluids, could contribute to the overall change in any of the individual systems.

Either explicitly or implicitly the following two simplifying assumptions are frequently [6–9] used

0301-4622/83/$03.00

in general biophysical chemistry.

Polar or ionic molecules are assumed to interact within a dielectric medium (first assumption):

the dielectric constant of the continuum surrounding a polar molecule is assumed uniform right to the molecular surface, where it drops to a small value within the molecule (second assumption).

The first assumption is fundamental to the Debye-Hückel model of polar and ionic solutions; the second assumption is central in the Onsager theory of polar fluids. Useful conceptual descriptions of thermodynamic and dielectric properties of polar liquids have been achieved using these simple assumptions. However, it is not clear to what extent these constraints may, in principle, be more widely applied, for example, to the description of less polar or apolar molecules in polar fluids. It is therefore important to examine the consequences of a consistent application of these assumptions in the context of the local solvent restructuring described above. With regard to predictive ability, we concede at the outset the quantitative limitations imposed by the assumptions; they nevertheless continue to be widely used as convenient theoretical devices [10–13]. The main objective in the present discussion is thus not to argue the merits of the assumptions themselves but, rather, to demonstrate that the local structural deductions resulting from these assumptions are consistent in descriptive, conceptual terms with the experimentally observed 'solvophobic' behavior. A justification for presenting these simple arguments is that these assumptions are often incorporated, sometimes in generalized forms, into more elaborate approaches to solvent structure and solvent-macromolecule interaction [14–21].

A natural quantity to study in connection with local structure is the potential of average force on small numbers of molecules in fixed relative configurations within a polar fluid. This quantity determines the probabilities of occurrence of these configurations in the liquid and we will be particularly interested in the local contributions to these potentials when such contributions are constrained by the simple assumptions discussed above.

2. Description of the model system

The type of system in which we are interested has volume v, temperature T, and contains N molecules. Of the N molecules, $(N-1)$ have dipole moments of constant magnitude; the dipole magnitude of the one remaining molecule is controlled by a variable charging parameter κ. Because of our interest in polar solvent structure near a less polar solute, we will compare certain properties of the system in the two states $\kappa = 1$ and $\kappa < 1$. A molecule i will in general be described by three spatial and three (sometimes two) rotational coordinates which for the present purpose are represented as a combined spatial-orientational coordinate and denoted by X_i. A differential element in this combined space is $\mathrm{d}X_i = \mathrm{d}\omega_i \mathrm{d}v_i$ where $\mathrm{d}\omega_i$ and $\mathrm{d}v_i$ are elements in the rotational and Cartesian subspaces, respectively, of molecule i [22].

The potential energy of interaction $V_{ik}(X_i, X_k)$ between any two of the molecules, i and k, results from electrostatic forces and from nonpolar attractive and hard repulsive forces. As described by Kirkwood [23], the potential V_{ik} may be scaled from zero to full interaction by a coupling parameter λ_i; the potential energy shared between i and k when i is coupled to the extent λ_i is $\lambda_i V_{ik}$.

The unfavorable entropy of contact between nonpolar solute and aqueous solvent derives from strong motional constraints resulting from hydrogen bonding among water molecules closely surrounding the solute [4]. A rigorous description of hydrogen bonding in water, including cooperative effects, requires the use of quantum mechanics [24]. Coulson and Eisenberg [25], however, have shown that Coulombic interaction is the major contribution to the total energy of hydrogen bonding and, further, that dipole-dipole electrostatic interaction is approx. 75% of the total Coulombic energy. Therefore, while we do not here discuss hydrogen bonding in its most general terms, it is important, as pointed out by Deutch [26], to consider the essential features and implications of the dipole-dipole forces. In order to examine the questions raised in section 1, a greatly simplified model is used in which the molecules are impenetrable spheres containing ideal dipoles and all except electrostatic and hard-sphere interactions are ignored. Further, by introducing at the appropriate place the assumptions (section 1) regarding the dielectric medium, it is possible to reduce to three the number of molecules whose mutual interactions are explicitly considered. Thus, we do not attempt to discuss the general properties of the dipolar hard-sphere fluid model; certain aspects of this N-body problem, while not those of principal interest here, have been discussed elsewhere [27,28].

3. The potential of average force in polar liquids

The potential of average (or mean) force is a central quantity in theories of the condensed phase [29,30]. Physically, the potential of mean force $W_i^k(X_i, X_k)$ between two molecules is the free energy change within the system when they are moved from infinite mutual distance to the configuration (X_i, X_k). In theory, a potential of mean force $W_i^k(X_i, X_k, \lambda_i)$ is also defined for the same configuration when molecule i is partially coupled. Finally, the potential of mean force $W_{ik}^l(X_i, X_k, X_l)$ is the free energy change for moving molecule l from infinite distance up to molecules i and k, in configuration (X_i, X_k), to give a final configuration (X_i, X_k, X_l): the counterpart $W_{ik}^l(X_i, X_k, X_l, \lambda_i)$ is likewise defined for partially coupled i.

The differential probability $\mathrm{d}P$ for occurrence of configurations of i and k in the interval between (X_i, X_k) and $(X_i + \mathrm{d}X_i, X_k + \mathrm{d}X_k)$ is

$$\mathrm{d}P(X_i, X_k) = \left\{ e^{-W_i^k/kT} (\sigma v)^{-2} \right\} \mathrm{d}X_i \mathrm{d}X_k \tag{1}$$

In eq. 1 σ is $8\pi^2$ for nonlinear molecules and 4π for linear molecules. With the appropriate potentials of mean force and normalizing factors, the probabilities for configurations (X_i, X_k, λ_i), (X_i, X_k, X_l), and $(X_i, X_k, X_l, \lambda_i)$ are similarly defined; kT is the product of Boltzmann's constant and the absolute temperature.

In the case of a pure liquid of N molecules in volume v, Kirkwood's [23] equation for $W_i^k(\lambda_i)$ is

$$W_i^k(\lambda_i) = \lambda_i V_{ik} + \frac{(N-2)}{\sigma v} \int^{\lambda_i} \int^{\omega v} V_{il} \times \left\{ e^{-W_{ik}^l(\lambda_i)/kT} - e^{-W_i^l(\lambda_i)/kT} \right\} \mathrm{d}X_l \mathrm{d}\lambda_i \tag{2}$$

For present purposes, the nonlinear integral eq. 2 requires simplification. First, the exponential terms may be expanded as series. Anticipating the discussion below, retention only through linear terms is justified because the potentials of mean force W are, in the systems of interest here, of the order $(9V/4\varepsilon)$, essentially an intermolecular interaction energy divided by the dielectric constant. Our interest is in liquids of very high ε, so the $(-W/kT)$ terms become small and the linear approximations approach exactness. In practical terms relevant to water, with $\varepsilon = 80$, $T = 293$ K, dipole moments of 1.8 debye, intermolecular distance of 2.8 Å and a favorable dipolar orientation of two molecules, the quantity $(-9V/4\varepsilon kT)$ has the value 0.2 and the linear approximations are quite good. Next, a superposition approximation [23,29–31] may be used for W_{ik}^l; in this equation W_k^l is the potential of mean force between k and l when all molecules are fully coupled:

$$W_{ik}^l(\lambda_i) = W_i^l(\lambda_i) + W_k^l \tag{3}$$

Kirkwood [31] established that the terms neglected in approximating W_{ik}^l by $W_i^l + W_k^l$ are of the same magnitude as the nonlinear terms neglected in the truncations of the expanded exponentials. Therefore, when linearization and superposition are performed in eq. 2 for systems of large ε, followed by integration over λ_i from zero to unity, the resulting expression approaches exactness as a linear integral equation approximation to eq. 2 for λ_i equal to unity. Superposition of work terms (eq. 3) is used in the present argument primarily for these simplifying properties, which have been well documented and frequently applied [29,30].

$$W_i^k = V_{ik} - \frac{(N-2)}{\sigma v kT} \int^{\omega v} V_{il} W_k^l \mathrm{d}X_l \tag{4}$$

The most general form of eq. 4, appropriate to a multicomponent system, was derived by Kirkwood [23,31] in essentially the same manner. We omit from eq. 4 a term representing the potential of mean force between hard spheres; this background contribution to W_i^k remains constant throughout our present application.

The configurations (X_i, X_k) of greatest interest here are those in which molecules i and k are in, or very near, intermolecular contact. Now eq. 4 determines $W_i^k(X_i, X_k)$ for $\lambda_i = 1$ in the high ε system: the integral term in eq. 4 then gives the contribution to W_i^k from the statistical continuum surrounding i and k. All of the $(N-2)$ l-type molecules are equivalent and are of course identical to i and k. For present purposes, one of the l-type molecules will be singled out for special consideration, labeled 'j', and formally separated in eq. 5.

$$W_i^k = V_{ik} - \frac{(N-3)}{\sigma v kT}\int^{\omega r} V_{il} W_k^l \, \mathrm{d}X_l - \frac{1}{\sigma v kT}\int^{\omega r} V_{ij} W_k^j \, \mathrm{d}X_j \quad (5)$$

The last integral in eq. 5 then specifies the free energy contribution to W_i^k, and therefore through eq. 1 to the differential probability of occurrence of configuration (X_i, X_k), from the statistical distribution of the single polar molecule j. The focus of interest here is on the 'local' contribution, i.e., when j is in the immediate vicinities of both i and k, which are themselves in contact. The distance conditions of interest, r, are then $r_{ik} \simeq r_{ij} \simeq r_{kj} \simeq d$, where d is the effective molecular diameter. In order to proceed with the analysis of the local influence of j on W_i^k, definite forms are required for V_{il} and W_k^l in eq. 5. We develop in the next section what is clearly a composite approach, in that simple macroscopic concepts will be introduced into the microscopic, molecular-statistical eq. 5. The well known precedent for this strategy is the Debye-Hückel method in which the solvent molecules are represented by a dielectric medium [29]. Using this approach, the critical point we will demonstrate is that, in terms of free energy effects on W_i^k in eq. 5, the contribution from the local distribution of molecule j competes against the contribution from V_{ik}.

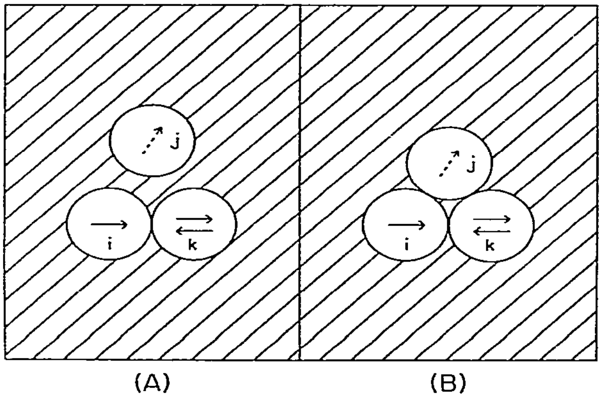

Fig. 1. Local distributions of molecule j with $r_{ik} = d$ and parallel or antiparallel orientations of electric moments in molecules i and k; orientation of moment $\kappa \boldsymbol{m}_j$ (dashed vector) varies over full 4π range. Surrounding medium has high, uniform dielectric constant ε. (A) Distances r_{ij}, $r_{kj} = 4d/3$. (B) Distances r_{ij}, $r_{kj} = d$.

4. Local contributions to the potential of mean force

In this section we impose on V_{ij} and W_k^j (a) the molecular model (dipolar hard spheres of dipole moment $\boldsymbol{m}$ and diameter d interacting within a dielectric medium) and (b) the specific conditions on ε (high and uniform up to molecular surfaces) (fig. 1). Now molecule j in eq. 5 is a particular one of the original $(N-2)$ l-type molecules of eq. 4. We further distinguish j by introducing a charging parameter κ which acts only on the electric moment $\boldsymbol{m}_j$. Initially $\kappa = 1$, but later in the discussion κ will vary toward $\kappa = 0$. Of course when $\kappa = 1$, the contribution of j to W_i^k is the same as that of any one of the $(N-3)$ remaining l-type molecules because the model and assumptions are also imposed on V_{il} and W_k^l; however, the electric moments of i, k and the $(N-3)$ l-type molecules are not functions of κ so none of the subsequent manipulations on molecule j can, under the assumed constraints (a and b above), produce change in the first integral on the right-hand side of eq. 5. The V_{ik} contribution to W_i^k in eq. 5 likewise remains constant for a specific (X_i, X_k). The potential V_{ij} is simply the unshielded electrostatic interaction between ideal dipoles and is given in eq. 6 below. The mean force potential required in the present system, W_k^j, has been rigorously analysed by Buff et al. [32]. They include in their treatment both the long-range and short-range consequences of placing two dipole-containing cavities within the continuous dielectric. They derive exact expressions for W_k^j which demonstrate the important relation between the short-range and long-range solutions. Their results and notation will be adapted to the present use. In our discussion, molecules i and k remain in contact and in fixed orientations; $r_{ik} = d$. In figs. 3 and 4 and table IV of Buff et al. [32] are given the correction factors which must be applied to the long-range, asymptotic dipolar form for W_k^j (eq. 7 below) in order to obtain the appropriate short-range expressions. These factors, called $F^{(d)}$ by Buff et al., are shown in their paper as functions of dipolar orientation as well as of S, the ratio of intermolecular distance to molecular diameter, which in the present paper is r_{kj}/d. It is found in ref. 32 that the correction factors for $S = 1.0$ can be quite large, but rapidly decrease with increasing S, becoming less than approx. 10% at $S \simeq 1.33$. We are interested for the present purpose in 'local' values of r_{kj}/d. As a practical procedure, we therefore divide our discussion into (1) the local configurations $d \leqslant r_{kj} < 4d/3$ where the short-range correction to the asymptotic form (eq. 7) must be included and (2) the local configurations $4d/3 \leqslant r_{kj}$ where the correction may essentially be neglected. For illustrative purposes we report calculations on the two specific local situations, $r_{kj} = 4d/3$ (where short-range corrections are practically negligible) and $r_{kj} = d$ (where short-range corrections are required) but there is no special significance to these distributions except that they represent two limiting local situations with regard to short-range effects.

For $r_{kj} \geqslant 4d/3$;

$$V_{ij} = -(\kappa \boldsymbol{m}_j \cdot \boldsymbol{E}_{ij}) \tag{6}$$

$$W_k^j = \frac{9}{4\varepsilon} V_{kj} = \frac{-9}{4\varepsilon} (\kappa \boldsymbol{m}_j \cdot \boldsymbol{E}_{kj}) \tag{7}$$

In these equations, $\boldsymbol{E}_{ij}$ and $\boldsymbol{E}_{kj}$ are the electric fields, acting through the center of molecule j, which arise from the dipoles $\boldsymbol{m}_i$ and $\boldsymbol{m}_k$, respectively. In eq. 5 for the present model, $\sigma = 4\pi$ and $\mathrm{d}X_j = \mathrm{d}\omega_j \mathrm{d}v_j$; the κ-independent integral will be represented by the term $B(ikl)$. With these substitutions in eq. 5, the result is precise only for regions of v where $r_{kj} \geqslant 4d/3$; smaller r_{kj} is considered below.

$$W_i^k = V_{ik} - B(ikl) - \frac{9\kappa^2}{16\pi v k T \varepsilon} \int^{v} \int^{\omega} (\boldsymbol{m}_j \cdot \boldsymbol{E}_{ij}) \times (\boldsymbol{m}_j \cdot \boldsymbol{E}_{kj}) \mathrm{d}\omega_j \mathrm{d}v_j \tag{8}$$

Integration over orientational variables of j at constant spatial location gives

$$W_i^k = V_{ik} - B(ikl) - \frac{9\kappa^2 m_j^2}{4 v k T \varepsilon} \int^{v} (\boldsymbol{E}_{ij} \cdot \boldsymbol{E}_{kj}) \mathrm{d}v_j \tag{9}$$

Our operative assumption is that ε in eq. 9, characterizing the medium surrounding i, j and k in fig. 1, is a constant. The explicit ε and T dependence in this expression can, however, be eliminated using Onsager's [33] assumption that this medium is completely filled by molecules having the number density N/v of the pure polar liquid. The high ε form of Onsager's [33] expression for the dielectric constant may then be introduced into eq. 9:

$$\varepsilon = \frac{6\pi N m^2}{3 v \kappa T} \tag{10}$$

With this simplification, the derivative, $D_j^{\prime k}$, of W_i^k with respect to the volume distribution of molecule j, at constant T, v, ε and κ, is

$$D_j^{\prime k} = \frac{\partial W_i^k}{\partial v_j} = \frac{-9\kappa^2}{8\pi N} (\boldsymbol{E}_{ij} \cdot \boldsymbol{E}_{kj}) \tag{11}$$

We note here that, with the macroscopic quantity ε eliminated, only microscopic, molecular properties determine the behavior of $D_j^{\prime k}$. Our concern will be with the average behavior of this derivative, particularly its algebraic sign, when $r_{ik} = d$, while i and k are in certain limiting orientations and when molecule j is in those local configurations such that $r_{ij} = r_{kj} = 4d/3$ (fig. 1A).

For our purpose, with $r_{ik} = d$, the two most significant limiting orientations of i and k are end-to-end parallel (→ →, energetically most favorable V_{ik}) and end-to-end antiparallel (→ ←, energetically most unfavorable V_{ik}). These extrema are important because they generate, through the relation between eqs. 1 and 9, high and low probabilities of occurrence, respectively, for the favorable and unfavorable orientations. The locus of points for the center of j which satisfies $r_{ij} = r_{kj} = 4d/3$, when $r_{ik} = d$, is a circle whose center is the ik contact point and which lies in the plane that perpendicularly bisects the ik axis. Simple considerations of symmetry show that for all points on this locus, and for either limiting orientation of i and k, the field vectors $\boldsymbol{E}_{ij}$ and $\boldsymbol{E}_{kj}$ have equal, constant magnitudes; further, although the directions of these vectors vary individually over this locus, the angle between them remains constant for either limiting orientation. Then for either limiting orientation individually, $\boldsymbol{E}_{ij} \cdot \boldsymbol{E}_{kj}$ has the same value at all points on this locus and the difference, using eq. 11, between the $(\rightarrow \rightarrow)$ and $(\rightarrow \leftarrow)$ situations lies in the value of the angle between $\boldsymbol{E}_{ij}$ and $\boldsymbol{E}_{kj}$. Using the expressions for the dipolar fields [34] and the appropriate geometry for $r_{ij} = r_{kj} = 4d/3$ with $r_{ik} = d$, the following are derived for $D_j'^{k}$:

$$D_j'^{k}(\rightarrow \rightarrow) = \frac{-9\kappa^2 m^2}{8\pi N} \frac{\{3\cos^2(\cos^{-1} 3/8) + 1\}\cos 122°}{(4d/3)^6} \tag{12a}$$

$$D_j'^{k}(\rightarrow \leftarrow) = \frac{-9\kappa^2 m^2}{8\pi N} \frac{\{3\cos^2(\cos^{-1} 3/8) + 1\}\cos 58°}{(4d/3)^6} \tag{12b}$$

The essential points to note here are (i) for $(\rightarrow \rightarrow)$, the negative V_{ik} in eq. 9 is combined with a positive local $D_j'^{k}$ from eq. 12a and (ii) for $(\rightarrow \leftarrow)$, the positive V_{ik} in eq. 9 is combined with a negative local $D_j'^{k}$ from eq. 12b.

Before discussing the significance of eqs. 12a and b, we need to demonstrate that, with $r_{ik} = d$, the conclusions just noted for $r_{ij} = r_{kj} = 4d/3$ are also obtained when $r_{ij} = r_{kj} = d$ (fig. 1b). For the latter configuration the W_k^j in eq. 5 cannot be properly represented by the asymptotic dipolar form in eq. 7. This form must be corrected for short-range effects generated as r_{kj} approaches d [32]. The corrected expression is:

$$\begin{aligned} W_k^j(X_k, X_j) = {} & \frac{(m_{\mathrm{pd}}^j + m_{\mathrm{pd}}^k)^2}{4} W^{kj}(\rightarrow \rightarrow) \\ & + \frac{(m_{\mathrm{pd}}^j - m_{\mathrm{pd}}^k)^2}{4} W^{kj}(\rightarrow \leftarrow) \\ & + \frac{(m_{\mathrm{pl}}^j - m_{\mathrm{pl}}^k)^2}{4} W^{kj}(\uparrow \downarrow) \\ & + \frac{(m_{\mathrm{pl}}^j + m_{\mathrm{pl}}^k)^2}{4} W^{kj}(\uparrow \uparrow) \end{aligned} \tag{13}$$

In this equation the electric moment expressions refer to the components of the dipoles $\kappa \boldsymbol{m}_j$ and $\boldsymbol{m}_k$ which, in the arbitrary configuration (X_k, X_j) on the left-hand side, lie perpendicular (pd) and parallel (pl) to the plane of symmetry between j and k. The potentials of mean force on the right-hand side of eq. 13 are those obtained if unit dipoles are placed in k and j in the four orientations indicated; each of these potentials is obtained by correcting the asymptotic dipolar form (eq. 7), in the indicated limiting kj orientation, for short-range electrostatic effects (see the appendix).

We require the expression for $D_j'^{k}$ when $r_{ik} = r_{ij} = r_{kj} = d$. With this geometry and with V_{ij} from eq. 6 and the short-range W_k^j from eq. 13 substituted into eq. 5, the integration over rotational coordinates of j and the differentiation with respect to the distribution of j are performed as in eq. 8–11.

$$\begin{aligned} D_j'^{k}(\rightarrow \rightarrow) = {} & \frac{-9\kappa^2 m^2}{6\pi N} \frac{(3\cos^2 60° + 1)^{1/2}}{16 d^6} \\ & \times [9.617 \cos 60° \cos 161° \\ & - 4.297 \sin 60° \sin 161°] \end{aligned} \tag{14a}$$

$$\begin{aligned} D_j'^{k}(\rightarrow \leftarrow) = {} & \frac{-9\kappa^2 m^2}{6\pi N} \frac{(3\cos^2 60° + 1)^{1/2}}{16 d^6} \\ & \times [9.617 \cos 60° \cos 341° \\ & - 4.297 \sin 60° \sin 341°] \end{aligned} \tag{14b}$$

By symmetry, these local derivatives have the same value at all points on the circular locus defined by $r_{ij} = r_{kj} = r_{ik} = d$. The earlier conclusions relevant to eq. 5 are verified: When the V_{ik} component of W_i^k is negative, the local derivative $D_j'^{k}$ is positive; when V_{ik} is positive, $D_j'^{k}$ is negative. Therefore, when molecule j is located vicinal to the pair ik (fig. 1), within a roughly donut-shaped region extending from $r_{ij} = r_{kj} = d$ to at least $r_{ij} = r_{kj} = 4d/3$, the free energy contribution from j produces an effect on the probability of occurrence of the configuration (X_i, X_k) which opposes that produced by V_{ik}.

We have seen here two functional forms for the potential of mean force. The first form, eqs. 7 and 13, furnishes a global, macroscopic, phenomenological description of the screening effect of the dielectric medium; in free energy terms, the medium attenuates both positive and negative values of V to yield W. On the other hand, if eq. 7

(long range) or eq. 13 (short range) are themselves introduced simply as expressions for the work term W_k^l needed in eq. 5, a second form for W results, eq. 9, which can be used to obtain the strictly local, microscopic, molecular contributions to W, eqs. 12 and 14. The important point is that, in eq. 9, these molecular contributions (controlled by the quantity κ) produce the same effect locally as that produced globally by the medium in eqs. 7 or 13; the local free energy contributions $D_j^{ik}\mathrm{d}v_j$, on average, oppose V_{ik} in sign and thus attenuate the effect of V_{ik} in W_i^k.

5. Discussion and conclusions

The quantity $D_j^{ik}\mathrm{d}v_j$ is the differential contribution to W_i^k when j is in $\mathrm{d}v_j$. Before discussing implications of our results, several points should be examined. First, the form of eq. 11 shows that, for $r_{ik} = d$, there are locations for j such that the V_{ik} and $D_j^{ik}\mathrm{d}v_j$ contributions to W_i^k could have the same sign. However, because of the $r_{ij}^{-3} r_{kj}^{-3}$ dependence in D_j^{ik} (eqs. 12 and 14), the largest absolute values of this derivative occur when j is near to both i and k; for these configurations, we have seen above that V_{ik} and $D_j^{ik}\mathrm{d}v_j$ oppose one another and this is thus the dominant local effect. Second, we stress that the full integration of $D_j^{ik}\mathrm{d}v_j$ over the system volume v has not been our present objective; our more modest purpose has been to characterize the essential behavior of $D_j^{ik}\mathrm{d}v_j$ where the volume elements $\mathrm{d}v_j$ are vicinal to both i and k. Next, a question might be raised as to whether the types of configurations considered here (for example, equilateral: $r_{ik}, r_{ij}, r_{kj} = d$ or isosceles: $r_{ij}, r_{kj} = 4d/3$, $r_{ik} = d$) are found as important 'structures' in a real polar liquid such as water. Now W_i^k determines structure through the ik spatial-rotational distribution function [29,30]. But W_i^k is itself determined by the integral term in eq. 2, approximated here by eq. 5. Thus, these local configurations are generated not by requirements of structure but because they are called for in the integration over states in eq. 2. Finally, we have emphasized here the end-to-end ik arrangements ($\rightarrow\rightarrow$) and ($\rightarrow\leftarrow$). With $r_{ik} = d$, the local effects of j on the side-to-side ik configurations ($\uparrow\downarrow$) and ($\uparrow\uparrow$) have also been examined. These are slightly more complex than those already considered because the quantity $\boldsymbol{E}_{ij} \cdot \boldsymbol{E}_{kj}$ is not constant on the relevant circular loci and an extra averaging over these loci is required. When this is taken into account, the same conclusions are reached regarding the local D_j^{ik}; the sign of the average $D_j^{ik}\mathrm{d}v_j$ opposes the sign of V_{ik}.

Bearing these points in mind, the conclusions to be drawn from our results are straightforward. In the very primitive, highly polar system examined here, the average local effect produced by a representative third molecule j, on the probability of occurrence of a fixed configuration of two other molecules i and k, is to suppress the probability if V_{ik} is favorable and to enhance the probability if V_{ik} is unfavorable. These local effects on W_i^k were obtained by using the assumptions from section 1 to specify W_k^l in eq. 5. If the functional forms of eq. 7 or 13 were used to derive W_i^k directly from V_{ik}, the global dielectric screening effect which results is qualitatively and conceptually consistent with our strictly local description developed using eq. 2 and 5. By thus introducing the constraints on the dielectric behavior at the level of the integral terms in eq. 5 rather than directly, using eq. 7 or 13, it has been possible to isolate the vicinal electrostatic effects regulating W_i^k. To this point, the κ values in eqs. 12 and 14 have been fixed at $\kappa = 1$ which, as mentioned, makes the local contribution of j to W_i^k equal to that of any of the $(N-3)$ l-type molecules in eq. 5. The objective in our discussion is to examine the local result of converting molecule j to a less polar or apolar solute by reducing κ toward $\kappa = 0$. Under the assumed constraints (first paragraph, section 4) and for a particular ik configuration, we reemphasize that reducing κ does not change the contribution to W_i^k made by either V_{ik} or the first integral in eq. 5. We are then interested in the comparative effects exerted on W_i^k by molecule j when $\kappa = 1$ and when $\kappa < 1$. In view of the earlier discussion, these comparative local effects will depend on the sign of V_{ik}: if V_{ik} is negative, reducing κ makes W_i^k more negative; if V_{ik} is positive, reducing κ makes W_i^k more positive. Therefore, by eq. 1, the change from $\kappa = 1$ to $\kappa < 1$ will be accompanied by a shift in ik pair probability density from energetically unfavorable to energetically favorable *ik* configurations. Moreover, in the primitive model used here, the amount of probability density flowing out of the unfavorable configurations, per unit change in κ, is equal to the amount transferred into the corresponding favorable configurations. Our original objective was to demonstrate that if standard assumptions regarding the dielectric behavior of the polar medium were applied (section 4), then the resulting local structural deductions would be consistent with the commonly described solvophobic structure promotion. If we accept as a measure of 'local structure formation' this enhancement of probabilities for the energetically favorable *ik* configurations at the expense of the unfavorable, then this objective has been met.

Due to the extreme simplicity of our approach, we emphasize the descriptive rather than the quantitative features of our results. However, the assumptions and model, which are primitively valid in highly polar fluids and which have proved useful in many biophysical contexts [6–13,35,36], have been systematically applied to a rigorous origin, eq. 2. The results demonstrate that the simple theoretical constructs, which are so frequently used to describe polar and ionic interactions in other biologically important situations, can also furnish a description of local electrostatic effects at biological polar-nonpolar interfaces that is consistent with current structural interpretations [3,4]. We obviously do not propose that our results give the mechanism of hydrophobic structural change; the effect described here is instead a general mechanistic contribution which would augment and act concertedly with more specific structural elements in water (for example, cooperative hydrogen bonding) to produce hydrophobicity.

Appendix

We illustrate here the derivation of the short-range potentials W^{kj} required in eq. 13. The potential $W^{kj}(\rightarrow\leftarrow)$ will be discussed in detail; the other potentials are obtained similarly. Buff et al. [32] show that $W^{kj}(\rightarrow\leftarrow)$ can be expressed as a correction, for short-range effects, to the asymptotic unit dipolar form ${}_{\mathrm{ad}}W^{kj}(\rightarrow\leftarrow)$. The correction uses a fraction $F^{(d)}$, found in figs. 3 and 4 and table IV of Buff et al. [32].

$$W^{kj}(\rightarrow\leftarrow) = (1+F^{(d)})_{\mathrm{ad}}W^{kj}(\rightarrow\leftarrow)$$

For unit dipoles with $r_{kj} = d$, eq. 7 of the present paper gives

$${}_{\mathrm{ad}}W^{kj}(\rightarrow\leftarrow) = \frac{9}{4\varepsilon}\frac{(2)}{d^3}$$

The appropriate $F^{(d)}$ from Buff et al. [32] is 0.6164 so

$$W^{kj}(\rightarrow\leftarrow) = \frac{9}{4\varepsilon}\frac{(3.233)}{d^3}$$

The other potentials in eq. 13 are derived in the same way.

$$W^{kj}(\rightarrow\rightarrow) = \frac{-9}{4\varepsilon}\frac{(1.576)}{d^3}$$

$$W^{kj}(\uparrow\downarrow) = \frac{-9}{4\varepsilon}\frac{(1.293)}{d^3}$$

$$W^{kj}(\uparrow\uparrow) = \frac{9}{4\varepsilon}\frac{(0.856)}{d^3}$$

Acknowledgments

The author acknowledges a careful, critical review of the manuscript by Dr. D.B. Millar; consultation with Professor F.P. Buff on points in ref. 32 is also gratefully acknowledged. This work was supported by Naval Medical Research and Development Command, Research Work Unit No. MR04101-004-0006. The opinions and assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the view of the Navy Department or the naval service at large.

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