Calculation of the solvent contribution to the potential of mean force between water molecules in fixed relative orientation in liquid water

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(Received 5 June 1989; accepted 25 October 1989)

The contribution of the solvent molecules to the potentials of mean force between two water molecules in selected fixed relative orientations was calculated as a function of the interoxygen distance using the probability ratio method with adaptive umbrella sampling in Monte Carlo computer simulations.

I. INTRODUCTION

In the course of a recent examination of the solvent effects on protein folding and protein association,[1,2] we came to the conclusion that an important contribution to the solvent-induced interaction could arise from correlation between two hydrophilic groups attached to the biopolymer. We have estimated that the free-energy change for bringing two functional groups such as –OH or $>$CO, that could form hydrogen bond with water, from infinite separation to the final configuration similar to second-nearest neighbors in ordinary ice, is about -3 kcal/mol. This estimate is much larger than the corresponding interaction free energy between two hydrophobic groups,[3] routinely invoked to explain macromolecular association and folding.

We have therefore decided to examine this question by Monte Carlo computer simulations on a system of 216 water molecules in which two of the waters are held at fixed position and orientation (see below). The OH groups on these fixed waters would serve as models for the hydrophilic groups on two approaching biomolecules.

II. METHODOLOGY

This work required to move a system in the configuration space along a path described by a configurational parameter R is called the potential of mean force. In other words, the potential of mean force along R is the configurational free energy as a function of R. For the problem treated here, R is simply the interoxygen distance of the waters whose relative orientation is held fixed.

The potential of mean force along R is related to the probability of occurrence of the parameter R, $P(R)$ as

$$W(R) = -kT\ln P(R) + \text{const.} \tag{1}$$

where k is the Boltzmann constant and T is the absolute temperature.[4] The unspecified constant in Eq. (1) reflects the freedom in choosing the origin of the energy scale. To calculate $W(R)$ from computer simulation, R has to be a simulation variable itself. This, however, requires in most cases that the simulation be performed in a non-Boltzmann ensemble, where the Hamiltonian $E'(X^N,R)$ is replaced by a modified Hamiltonian $E(X^N,R)$:

$$E'(X^N,R) = E(X^N,R) + E_W(R). \tag{2}$$

The potential of mean force corresponding to the Boltzmann average can be recovered as

$$W(R) = W'(R) - E_W(R), \tag{3}$$

where $W'(R)$ is the potential of mean force calculated using the modified Hamiltonian of Eq. (2). This technique, introduced by Patey, Valleau, and Torrie, is usually referred to as umbrella sampling.[5,6] Most previous calculations using umbrella sampling used an empirical approach to determine the non-Boltzmann bias. In particular, Pangali, Rao, and Berne introduced the harmonic weighting function.[7]

Paine and Scheraga[8] and Mezei[9] have shown that $E_W(R)$ can also be determined iteratively, based on the recognition of the fact that the best choice for $E_W(R)$ is $W(R)$. For use in aqueous solutions, the technique has to deal with "dynamic" matching of iterations with large statistical noise (e.g., provide for revision of the calculated normalization constants on the probability distributions calculated in successive iterations), recognition of equilibration phase, guiding the simulation to undersampled regions, and others.[9] Using this iterative scheme is called adaptive umbrella sampling. The adaptive umbrella sampling proved to be significantly more reliable than the use of the harmonic weighting function for the calculation of the conformational free energy of the dimethyl phosphate anion.[10] Recent work suggested some enhancements to the technique[11] and those have also been incorporated into the present work.

For the calculation of the solvent contribution to the potential of mean force between two waters, the water dimer was treated as a single "solute" molecule. When the solute was moved, an attempt was also made to change the interoxygen distance. Thus, the changes in R did not result from the general motion of the two waters around each other, explaining the absence of an R^2 factor from Eq. (1). Furthermore, as no energetic consequence of the change in the interoxygen distance was included into the simulation, only the solvent contribution to $W(R)$ was obtained. This is the quantity that is of relevance if the present calculation is to be considered as a model for the association of macromolecules with hydrophilic groups in water. The complete $W(R)$ can be recovered simply by adding to the $W(R)$ calculated here, the interaction energy $E_I(R)$ between the two waters at R, since eliminating the energy contribution from the two solute wa-

0021-9606/90/021359-03$03.00

ters is equivalent to replacing $E_W(R)$ by $E_W(R) - E_I(R)$ and the prescription to recover the unbiased $W(R)$, Eq. (3), would then simply add back $E_I(R)$ to $W(R)$.

The simulations used the Metropolis algorithm,[12] modified by incorporating the force bias procedure[13] and preferential sampling[14] for convergence acceleration. The water–water interactions were represented by the TIP4P potential of Jorgensen and co-workers,[15,16] and one of the potentials of mean force was also calculated using the SPC model of Berendsen *et al.*[17]

III. CALCULATIONS AND RESULTS

Three different relative orientations—labeled PS, NP, and PF and shown on Fig. 1—were chosen. All three conformations allow the formation of hydrogen-bonded water bridges. The dimer PS consisted of the two waters in the same plane, with the molecular dipoles pointing in the same direction and perpendicular to the O–O line. The dimer NP represented the relative orientation of two waters that are next-nearest neighbors in Ice Ih: one of the OH bonds on each water is perpendicular to the O–O line, and these two bonds point in the same direction; while the other two OH bonds are oriented symmetrically toward a point so that the two lines connecting this point with the two oxygens form a tetrahedral angle. The dimer PF consists again of two waters in the same plane, but now the dipoles are parallel to the O–O line and the two waters are facing each other. The dimer PF is different from the other two in that it allows the formation of two hydrogen-bond bridges at favorable O–O distances. The calculation on the PS conformation was the one repeated using the SPC potential.

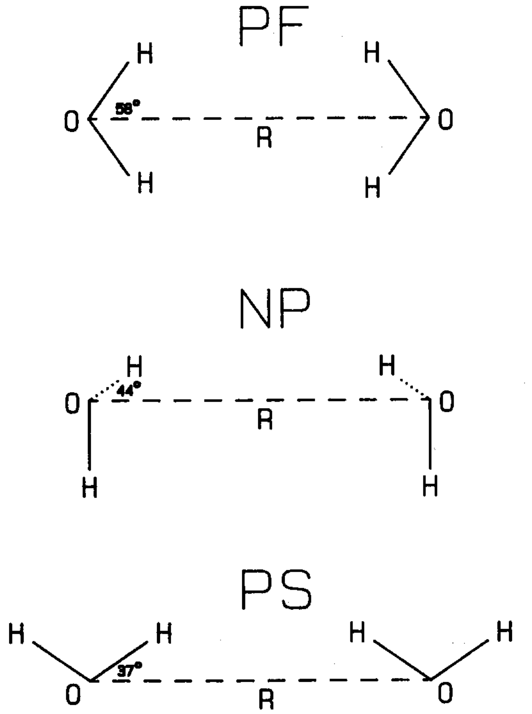

FIG. 1. The three relative orientations studied. Orientations PS and PF are planar. The O–H bonds in orientation NP drawn with dotted line are directed to a common point out of the plane. The HOO angles given refer to the experimental water geometry.

For each system, two separate calculations were performed: one covering O–O distances between 3 and 5.125 Å; the other covering O–O distances between 4.875 and 7 Å. Each calculation was run until reasonably adequate coverage of the interval was obtained. The number of attempted moves (several million) is given in Table I.

The calculated potentials of mean force (without the water–water contributions) are displayed in Fig. 2. For all calculations, there is a free-energy barrier to separate the dimer from a configuration where the O–O distance allows a third water to form a hydrogen-bond bridge. The minima are generally shallow and the maxima—the tops of the barrier—are broad. The calculated free-energy barriers, also shown in Table I, range from 1.7 to 6.0 kcal/mol, with the largest value corresponding to the conformation PF that allows two simultaneous bridges, Somewhat lower barrier height was found for the NP conformation. This conformation is different from the other two in that there are two interoxygen distances—close to each other—at which a bridged hydrogen bond can form: one bridging the hydrogens where the OH bonds are perpendicular to the O–O line; the other bridging the hydrogens where the OH bonds form an acute angle with the O–O line. Each of these bridges would in itself result in a minimum and a barrier in $W(R)$ at a different position; thus, they partially cancel each other. The relatively slow convergence of that calculation also supports this conclusion.

Comparison of the $W(R)$'s calculated in the overlapping regions gives an indication that the overall precision of the calculations is about 0.5 kcal/mol. A comparison of the $W(R)$'s calculated with the two different potentials for the PS dimer gives an indication of the accuracy of the model: the basic features have been preserved, but the minimum has shifted to shorter O–O distance with a concomittant increase in the barrier height when the potential was changed from TIP4P to SPC. Due to the shallowness of the minima, this difference is not as significant as it first may appear, indicating the general soundness of these potentials for modeling liquid water.

IV. CONCLUSIONS

The results shown in Table I confirm an earlier estimate that the hydrophilic interaction between two hydrophilic groups at fixed relative orientations similar to the second nearest neighbor configurations in ice, is about −3 kcal/mol. Two earlier harmonic umbrella sampling calculations,

TABLE I. Run lengths and free-energy barrier heights calculated for the different dimer conformations.[a]

Conformation	Water model	Length$_1$[b]	Length$_2$[b]	Barrier height[c]
PS	TIP4P	4000 K	3700 K	3.2
PS	SPC	1500 K	1500 K	3.9
NP	TIP4P	5000 K	5000 K	1.7
PF	TIP4P	3000 K	3000 K	6.0

[a] See text for definition of the PS, NP, PF, TIP4P, and SPC labels.
[b] Run lengths are given in thousands of attempted moves.
[c] Barrier height is in kcal/mol.

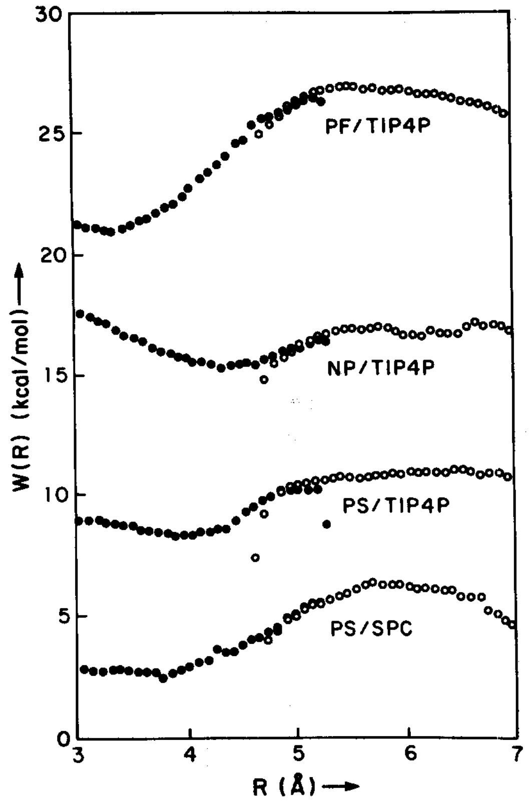

FIG. 2. Calculated potentials of mean force in kcal/mol. The points drawn by open and full circle represent the result from the calculations performed on the [3.0,5.125] and [4.875,7.0] intervals, respectively.

using rather different potentials (the ST2[18] and the MCY[19]), both estimated the strength of the hydrophobic interaction to be only 1–1.5 kcal/mol.[7,20] This comparison and the fact that both the NP and PS configurations show a minimum of the potential of mean force at a distance of 4–5 Å strengthens the belief expressed in Refs. 1 and 2 that intramolecular hydrophilic interactions might be more important than the corresponding hydrophobic interactions in various biochemical processes.

ACKNOWLEDGMENTS

This work was supported under an RCMI grant No. SRC5G12RR0307 from NIH to Hunter College and a CUNY/PSC grant. Computing resources were provided by the City University of New York, University Computing Center.

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