A Monte Carlo simulation of the hydrophobic interaction[a]

C. Pangali,[b] M. Rao, and B. J. Berne

Department of Chemistry, Columbia University, New York, New York 10027
(Received 24 April 1979; accepted 21 June 1979)

The hydrophobic interaction between two apolar (Lennard–Jones) spheres dissolved in a model of liquid water (ST 2 water) is simulated using the force-bias Monte Carlo technique recently devised by the authors. Importance sampling techniques are devised and used to give a relatively accurate determination of the potential of mean force of the two apolar spheres as a function of their separation. This determination shows that there are two relatively stable configurations for the spheres. In one configuration each member of the pair sits in its own water cage with one water molecule fitting between them. There is a free energy barrier separating this from the other stable configuration which is such that no water molecule sits between the spheres. This conclusion is shown to be quantitatively consistent with the recent semiempirical theory of Pratt and Chandler and is in disagreement with some previous Monte Carlo studies.

I. INTRODUCTION

The unusual properties of aqueous solutions of non-polar solutes are often attributed to hydrophobic effects.[1] It is convenient to subdivide these effects into two categories. Hydrophobic hydration refers to the structure of the water molecules in the immediate neighborhood of the nonpolar solute molecules, and to the thermodynamic properties of very dilute solutions. This is the subject of another paper.[2] The hydrophobic interaction on the other hand refers to the solvent induced interaction between two or more apolar solute molecules. These interactions are thought to be responsible for the stability of particular conformations of biopolymers in aqueous solution, the stability of micelles and membranes, and the association equilibria of many compounds in aqueous environments. Hydrophobic hydration is readily observed experimentally, but because nonpolar species are so insoluble in water, the hydrophobic interaction is not amenable to direct experiment. Investigators have therefore tried to infer details of the hydrophobic interaction from solubility data; that is, from information on hydrophobic hydration.[3] This kind of analysis is based on many assumptions and has recently been called into question. Nevertheless, it is the hydrophobic interaction that lies at the root of several important phenomena and it is exceedingly important to better understand this phenomenon. This is an area where computer simulation can provide answers that are not otherwise available.

The conventional view of the hydrophobic interaction is based on a simple picture. Because nonpolar species are relatively insoluble in water, it is assumed that there are thermodynamic forces in aqueous solution that will drive two such species together to a much greater extent than would be the case if these solute molecules were dissolved in a more accomodating solvent. It is not difficult to see where this driving force arises. It is well known that the entropy of solution of simple nonpolar solutes in water is negative. (e.g., $\Delta S_{Ar}^{\circ} = -30.2$ cal/mole deg). Most of this entropic change springs from a restructuring of the water surrounding the solute molecule—a restructuring that leads to greater order in the solvent in close proximity to the solute. Thus since two nonpolar molecules in contact will order fewer solvent molecules than when they are apart, the entropy change on bringing two solute molecules together should be positive and should thereby lower the free energy of the solution. From this follows the clustering alluded to above. Thus our observation that this is not the case should be cause for much interest.

If $g_{AA}(r)$ denotes the pair correlation function of two spherical nonpolar species (A particles) dissolved in water, then the potential of mean force

$$W_{AA}(r) = -kT \ln g_{AA}(r)$$

is a good measure of the solvent induced interactions between two A particles. $W_{AA}(r)$ is the reversible work required to bring the two A particles from infinite separation $(r = \infty)$ to r. In a constant volume ensemble, $W_{AA}(r)$ corresponds to the Helmholtz free energy change $\Delta A(r)$ for this process. In this paper, using computer simulation, we determine the potential of mean force $W_{AA}(r)$ for a model of two Lennard–Jones spheres of diameter $\sigma_{AA} = 4.12$ Å "dissolved" in 214 ST2 water molecules at 283 °K and a water density of 1 gm cm^{-3}. We find that $W_{AA}(r)$ exhibits oscillations. Each LJ sphere interacts with each water molecule with an LJ 12–6 potential ($\epsilon_{AW} = 77.82$ °K, $\sigma_{AW} = 3.43$ Å) and the simulation was carried out using the force bias Monte Carlo technique with importance sampling in the (N, V, T) ensemble with periodic boundary conditions using a spherical cutoff with truncation $r_c = 8.46$ Å.

Several computer studies have recently appeared on the topic of hydrophobic interaction.[4–6] In one study the average force exerted by the water molecules along A–A "bond" was computed from a molecular dynamics simulation[4] in which the bond length was fixed rigidly at a sequence of values. This work showed that the mean force along the bond was an oscillatory function of the bond length r, a result in qualitative agreement with the result reported here. Unfortunately, the ac-

curacy of this force was judged to be insufficient to permit the integration required to obtain the potential of mean force. It is worth mentioning in this context that Swaminathan and Beveridge[7] have very recently adopted precisely this approach for computing the mean force between two methane molecules dissolved in water using the MCY[8] potential in a Monte Carlo simulation. Because of the large errors inherent in this method they also could not determine the potential of mean force. Dashevesky and Sarkisov[6] claim to have determined the potential of mean force for two methane molecules in water using an emperical potential. They did not observe oscillation in $W_{AA}(r)$, in strong disagreement with results reported here. It is important to note that they used Monte Carlo procedure to compute the Helmholtz free energy of the whole solution as a function of the constrained distance between the methane molecules. This approach is fraught with difficulties. For a recent criticism see Ref. 9.

In a very interesting recent study A. Geiger et al.[5] studied a pair of neon atoms dissolved in 214 ST2 water molecules by the molecular dynamics method. The neon atoms were intially placed in contact, and stayed there for some time before jumping and settling into separate cages with a water molecule separating them. This work indicates that the conventional view of the hydrophobic effect may be simplistic. It also provided an interesting picture of hydrophobic interaction. It was not meant, nor could it be used, to determine the potential of mean force of the neon atoms.

In this paper we present the first accurate determination of the potential of mean force and we are able to show rather convincingly that there are indeed two relatively stable minima in $W_{AA}(r)$ for the A–A pair. In one position the A spheres are nearly in contact, whereas in the other position an H_2O molecule sits somewhere between the two A particles. The maximum in $W_{AA}(r)$ separating these two minima can be interpreted as a barrier to the transition

A–A $\rightleftharpoons$ A(H_2O)A.
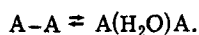
The conformation A(H_2O)A is relatively stable because the two A particles sit in two cages akin to the structures observed in the clathrate hydrates. The structure of the solvent in the neighborhood of the two A particles is discussed in detail in a separate paper. Using the determined $W_{AA}(r)$, we are able to compute the relative probability of finding the conformations A–A vs A-H_2O-A. This shows that the latter is more probable than the former by a factor larger than would be the case in a nonpolar solvent in which the solvent molecules were the same size as a water molecule (diameter 2.8 Å). This result is not consistent with the conventional picture.

Recently Pratt and Chandler[10] have proposed a semiempirical model for calculating the potential of mean force. The two apolar species are treated as hard spheres. The system is modeled by integral equations of the Ornstein–Zernicke type, which allows the solute-solute pair correlation function to be expressed in terms of the oxygen–oxygen pair correlation function $g_{OO}(r)$

for pure water. Because no accurate ab initio theory of pure water exists, Pratt and Chandler substitute the experimental x-ray diffraction data for pure water into their theory and predict a potential of mean force for the two hard spheres. Their analysis of the potential of mean force $W_{AA}(r)$, between the apolar species indicates that the HI becomes more attractive as the size of the solute particle is increased or as the temperature is decreased. Also, Pratt and Chandler[10] find that $W_{AA}(r)$ is oscillatory, suggesting that there are other free energy minima besides the one with the two apolar species in contact with each other. The second minimum corresponds to the state where the two apolar species sit in separate cages of water molecules, with one water molecule located directly between the two apolar species. We felt that a quantitative determination of $W_{AA}(r)$ would be useful at this juncture. It will contribute to our understanding of what goes on in a well-understood model (ST2) of liquid water.[1] It also allows us to test the recent Pratt–Chandler theory, a theory that gives results markedly in disagreement with the conventional picture of the hydrophobic interaction. To our surprise the simulation shows that the theory is qualitatively if not quantitatively correct.

The details of the calculation are presented in Sec. II. Using a modification of the recently devised force-bias MC technique,[12,13] we were able to determine $W_{AA}(r)$. Our approach in determining the potential of mean force is similar to that of Patey and Valleau[14] who obtained the same quantity for a pair of ions dissolved in a dipolar fluid.

Although the material of this paper is subject to criticism on the grounds that measured thermodynamic quantities for aqueous systems display a strong dependence on the type of boundary condition used for the simulation[15] we feel that the present study is justified for the following reason. The radial structure, in contradistinction to the angular structure, does not display a marked dependence on the boundary condition.[15] We therefore speculate that the radial structure arising from dissolution of spherical apolar species in water will be insensitive to the boundary condition used in the simulation. $W_{AA}(r)$ for spherical species depends only on the radial structure, and thus will be roughly independent of the boundary condition. In any case this study should be regarded as exploratory in view of the difficulties of simulating water.[15] The cost of simulation imposes severe restrictions on the size of the systems to be studied and on the length of the runs. The work described in this paper consumed over 100 hours of CPU time on the IBM 360/91.

The results of the simulation are described in Sec. III, together with a comparison with theoretical predictions for $W_{AA}(r)$. The work reported here supports the conclusions of Pratt and Chandler[10] and takes issue with the work of Marcelja et al.[16]

II. METHOD

In the MC simulation we considered 214 water molecules at a density of 1 g cm^3, interacting with each other through the familiar ST2 potential.[11,13]

The usual spherical cut-off convention was used, with a cutoff distance $r_c = 8.46$ Å beyond which all interactions were disregarded. The system also contained two apolar species interacting with the water molecules through a Lennard-Jones (12-6) potential with parameters $\sigma_{AW} = 3.43$ Å, $\epsilon_{AW}/k = 77.82$°K:

$$u_{AW}(r) = 4\epsilon_{AW}\left\{\left(\frac{\sigma_{AW}}{r}\right)^{12} - \left(\frac{\sigma_{AW}}{r}\right)^{6}\right\} . \qquad (2.1)$$

The apolar species also interact with each other through a Lennard-Jones (12-6) potential with $\sigma_{AA} = 4.12$ Å, $\epsilon_{AA}/k = 170.1$°K. The A-W interactions were also truncated at $r_c = 8.46$ Å.

Two apolar species labeled a and b, dissolved in water and not constrained to any fixed position, will be distributed according to the pair correlation function $g_{AA}(r)$,

$$g_{AA}(r) = \exp[-\beta W_{AA}(r)] , \qquad (2.2)$$

where $W_{AA}(r)$ is the potential of mean force for the particles a and b. It should be noted that the procedure described here could also be used in a MD simulation. As seen from Eq. (2.2), $W_{AA}(r)$ can be easily deduced from $g_{AA}(r)$. In principle this could be determined by performing a very long simulation of two solute particles in water, thereby enabling the species a and b to sample all possible separations r_{ab}. However, this approach is fraught with difficulties, the principal one being that the pair may get trapped at certain separations r_{ab} for very long times.[5] Instead we determined $g_{AA}(r)$ for small segments, or windows, of r_{ab}, and then joined the various portions of $g_{ab}(r)$ as described later in order to obtain the complete pair distribution function.

In a homogeneous system the density of molecules A at a position r with respect to a given molecule of type A,

$$\rho_A g_{AA}^{(2)}(r) = \left\langle \sum_{b \neq a}^{N_A} \delta(r - r_{ab}) \right\rangle , \qquad (2.3)$$

depends only on the distance r. Expressing the delta function in spherical polar coordinates allows us to write

$$\rho_A g_{AA}^{(2)}(r) = \left\langle \sum_{b \neq a} \frac{1}{r_{ab}^2} \delta(r - r_{ab}) \delta(u - u_{ab}) \right\rangle , \qquad (2.4)$$

where u_{ab} is a unit vector along r_{ab}. Integration of u over 4π then gives

$$P(r) \equiv 4\pi \rho_A g_{AA}^{(2)}(r) = \left\langle \sum_{b \neq a} \frac{1}{r_{ab}^2} \delta(r - r_{ab}) \right\rangle . \qquad (2.5)$$

Specializing to the case where there are only two apolar species of type A in water then gives

$$P(r) = 4\pi \rho_A g_{AA}^{(2)}(r) = \left\langle \frac{1}{r_{ab}^2} \delta(r - r_{ab}) \right\rangle , \qquad (2.6)$$

with $\rho_A = 2/V$.

In computer simulations the pair separation is treated as a discrete variable. A mesh Δr is chosen and one defines a coarse grained correlation function

$$g_{AA}(r_i) \equiv \frac{1}{\Delta r} \int_{r_i - \Delta r/2}^{r_i + \Delta r/2} dr\, g_{AA}^{(2)}(r) . \qquad (2.7)$$

This differs somewhat from the coarse graining in previous computer simulations.

Substitution of Eq. (2.6) then gives

$$g_{AA}(r_i) = \frac{1}{4\pi\rho_A \Delta r} \left\langle \frac{1}{r_{ab}^2} H_i(r_{ab}) \right\rangle , \qquad (2.8a)$$

where

$$H_i(r_{ab}) = \begin{cases} 1 , & r_i - \dfrac{\Delta r}{2} \leq r_{ab} \leq r_i + \dfrac{\Delta r}{2} , \\ 0 , & \text{otherwise} . \end{cases} \qquad (2.8b)$$

Adopting Eq. (2.8a) to the Monte Carlo simulation we find

$$g_{AA}(r_i) = \frac{1}{4\pi\rho_A \Delta r} \frac{1}{M} \sum_{\alpha=1}^{M} \frac{1}{r_{ab}^2(\alpha)} H_i[r_{ab}(\alpha)] , \qquad (2.9)$$

where $r_{ab}(\alpha)$ is the separation between the two species a and b in the αth configuration and the sum goes over all M Monte Carlo configurations. Obviously only those configurations contribute to the sum which lie in the ith cell.

We restricted the range of r_{ab} sampled in a given run to a small value around r_{ab}^0 by applying a harmonic restoring potential between a and b:

$$U_H(r_{ab}) = \frac{1}{2} k_0 (r_{ab} - r_{ab}^0)^2, \qquad (2.10)$$

where k_0 is a force constant. Neither of the particles was bound to a lattice point in the box; they were allowed to wander freely within the constraints of $U_H(r_{ab})$. The two particles move in spherical shells of radius $\sim r_{ab}^0$ around each other. An alternative form for the harmonic potential is

$$U_H'(|r_{ab}|) = \frac{1}{2} k_0 |(r_{ab} - r_{ab}^0)|^2 . \qquad (2.11)$$

The potential U_H' would restrict the motion of the apolar species to a much smaller volume than does $U_H(r_{ab})$. For this reason we used U_H. Patey and Valleau[14] in their study of the hard dipolar fluid used weighting functions (instead of U_H) similar in form to $W_{AA}(r)$. Although the final form of the potential of mean force does not depend on the weighting function, a judicious choice for this function aids in the convergence of $W_{AA}(r)$. Unlike Patey and Valleau[14] we did not have a well-tested $W_{AA}(r)$ to use for the sampling and thus were forced to use a different scheme—hence $U_H(r)$. Apart from this extra constraining force the system is similar to the one used previously in the MD simulation. Of course, the temperature in a Monte Carlo walk is always constant, unlike the case of a MD simulation where it fluctuates around a mean value. In our case $T = 298.0$°K for the MC simulation.

Ensemble averages for the Monte Carlo walk can be expressed as

$$\langle A \rangle = \frac{\int dr_a\, dr_b\, dr_3 \cdots dr_N\, A\, e^{-\beta u_N}}{\int dr_a\, dr_b\, dr_3 \cdots dr_N\, e^{-\beta u_N}}$$

$$= \frac{\int dr_a \cdots dr_N\, (A/e^{-\beta u_H}) \exp[-\beta(u_N + u_H)]}{\int dr_a \cdots dr_N\, (1/e^{-\beta u_H}) \exp[-\beta(u_N + u_H)]}$$

$$\times \ \frac{\int dr_a \cdots dr_N \exp[-\beta(u_N + u_H)]}{\int dr_a \cdots dr_N \exp[-\beta(u_N + u_H)]} = \langle A/e^{-\beta u_H}\rangle_H / \langle 1/e^{-\beta u_H}\rangle_H$$

$$(2.12)$$

where u_N is the total potential energy of the system without u_H, $\langle \ \rangle_H$ denotes averages over an ensemble with u_H switched on, while $\langle \ \rangle$ denotes average with u_H switched off.

The Monte Carlo walk was performed with the force-bias method (see Ref. 13), with parameters for the translational and orientational steps for water molecules set as follows: $\Delta r = 0.6$ Å, and $\Delta \theta = 0.898$ rad. The temperature was set at 298 °K and the density of water was constrained at 1 g cm^{-3}. The solute particles were moved with much smaller steps, $\Delta r = 0.06$ Å, in order to ensure that a move involving the solute particle was nearly always accepted. As pointed out by Owicki,[9] not only does the system around the solute relax faster if the solute particle is moved with a greater probability than the solvent molecules, but the statistics for the distributions $g_{ab}(r)$ and $g_{AW}(r)$—the latter is the apolar species water distribution function—are greatly improved. This arises from the fact that a successful move of the solute will generate $1 \times (N-2)$ new pair distances for computing $g_{AW}(r)$, while a successful move of a solvent particle provides only one new pair distance for $g_{AW}(r)$. The center of mass of the A–A pair was not held fixed in the box because this would impose an unnecessary constraint on the system. Four separate runs were performed to study small regions $\Delta r_{ab} = 1.4$ Å (or windows) centered around initial A–A separations of r_{ab}^0 $= 3.88$, 5.33, 6.08, and 6.60 Å. The starting configurations were taken from the molecular dynamics study described elsewhere.[4] Each run was further equilibrated for 500 passes, after which averages were taken over trajectories of 5000 passes (1 080 000 configurations) for each window. At each pass the separation r_{ab} and $e^{-\beta u_H}$ were used to accumulate the distribution $P(r)$, see Eqs. (2.7) and (2.9). r_{ab} was binned at intervals $\delta r_{ab} = 0.15$ Å.

The procedure outlined here was first tested on a system of two Ar atoms dissolved in 214 other Ar atoms described by Lennard-Jones parameters $\sigma = 3.40$ Å, (ϵ/k)

$= 119.6$ °K at a reduced density $\rho^* = 0.77$ and a reduced temperature $T^* = 0.7$. The object was to determine roughly the length of the run needed to reproduce $g(r)$ for Ar by averaging over only the two harmonically bound particles. With run lengths of 8000 passes our $g(r)$ differed by no more than 4% from another simulation result[17] using the usual method involving $N(N-1)/2$ pairs.

We now describe our procedure for matching the $P(r)$'s from the different windows. Let $P_1(r)$, $P_2(r)$, $P_3(r)$, and $P_4(r)$ represent these frequency distributions corresponding to the windows around $r_{ab}^0 = 1.2\sigma$, 1.55σ, 1.75σ, and 2.01σ, respectively (see Fig. 1) obtained from our simulation on Ar. The distributions are assymetric, reflecting the shape of the pair distribution function $g(r)$. The two distributions $P_1(r)$ and $P_2(r)$ do not superpose in the overlap region because the normalization constant for the individual $P_i(r)$'s depends in a nontrivial way on the window. We therefore renormalize $P_2(r)$ to obtain a new distribution $P_2'(r)$ such that the latter is given with the same normalization as $P_1(r)$. One simple way of doing this is to require that at some point $r = r_\alpha$ both $P_1(r)$ and $P_2'(r)$ have the same numerical values, i.e.,

$$P_2'(r) = P_2(r) \times \frac{P_1(r_\alpha)}{P_2(r_\alpha)} \ . \qquad (2.14)$$

In this manner we can obtain a single distribution function $P(r)$ covering the total range of r_{ab} spanned by $P_1(r)$ and $P_2(r)$. As seen from Fig. 1, the statistics for these distributions $P_i(r)$, $i = 1, 4$ get poorer towards the tails, so that if $P_1(r)$ and $P_2(r)$ are to be matched it is essential to do so at a point where both $P_1(r)$ and $P_2(r)$ have reasonable error bars, say for $1.35\sigma \lesssim r_\alpha \lesssim 1.45\sigma$. Of course, the final function should *not* sensitively depend on where the matching is carried out.

III. RESULTS AND DISCUSSION

To assess the accuracy inherent in the method used to determine the pair correlation function, we performed a MC simulation on neat liquid argon at a temperature of 84 °K and a density given by $\rho = 0.77/\sigma^3$. In Fig. 2 we show the pair correlation function $g(r)$ for Ar obtained by
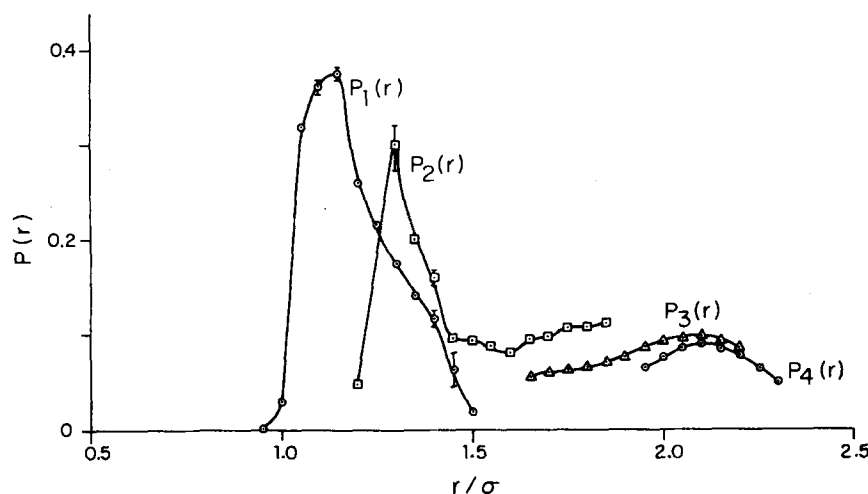

FIG. 1. The probability distribution functions $P_i(r)$ defined in Eq. (2.1) from the simulation of two labeled Ar atoms in a system of 216 Ar atoms. The two labeled atoms were held to together by a harmonic potential and their motion was used to generate the $P_i(r)$'s shown here.
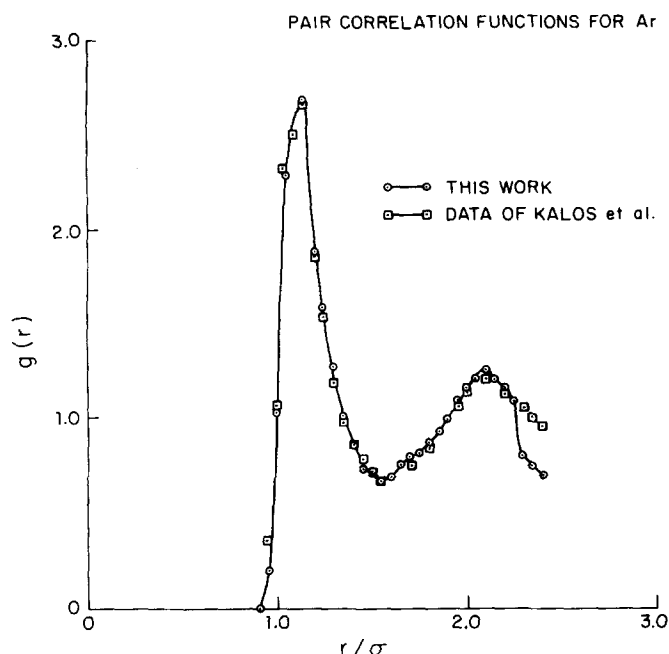
PAIR CORRELATION FUNCTIONS FOR Ar

FIG. 2. The pair correlation function obtained by matching the $P_i(r)$'s of Fig. 1. For comparison with the exact result we show the data of Kalos *et al.* (Ref. 11).

the procedure outlined in Sec. II. In this method two argon atoms are constrained using Eq. (2.11). For a comparison with the exact result we have also presented the $g(r)$ given by Kalos *et al.*[17] in Fig. 2. The latter was obtained from a lengthy simulation of 864 Ar particles at the same density and temperature as our system, and it may be regarded as the exact result. We normalized our $g(r)$ to yield the same value of $g(r)$ as the exact result at $r = 1.10\sigma$. It is clear that the method yields a pair correlation function in fairly good agreement with the exact result, except at large separations $r/\sigma \gtrsim 2.20$; corresponding to the large r tail of $P_4(r)$, where the statistics, as we have remarked before, are poor. Since we were merely concerned with establishing the feasibility of the method with the simulation of the Ar system, we did not feel compelled to improve the statistics for $r \gtrsim 2.20$ by undertaking another run with a window centered around $r \sim 2.20\sigma$. The good agreement for $r < 2.0\sigma$ amply vindicates the procedure for computing $g(r)$.

Given the success of our study on the simpler Ar system we applied the method discussed here to a study of two Lennard-Jones spheres dissolved in water. The various distributions $P_i(r)$ were matched as described in the previous section to obtain $P(r)$. From Eqs. (2.2) and (2.3) it is clear that

$$P(r) = C_1 \exp[-\beta W_{AA}(r)] \ , \tag{3.1}$$

or, equivalently,

$$W_{AA}(r) = -kT \ln P(r) + C \ , \tag{3.2}$$

where C and C_1 are constants. The potential of mean force $W_{AA}(r)$ determined from Eq. (3.2) with a particular choice of the constant C (see next section) is shown in Fig. 3. $W_{AA}(r)$ displays an oscillation. The first

minimum occurs at a separation of 4.34 Å and corresponds to the two particles being in contact. The second minimum is located at 7.13 Å which is roughly σ_{AA} $+ \sigma_{H_2O}$. The two minima are separated by 3.0 Å, i.e., by roughly the diameter of a water molecule. The precise distribution of water molecules around the two Å particles as a function of their separation is discussed in Ref. 2. Suffice it to say here that the second minimum corresponds to a water molecule being located in the region between the two A particles. The two mimima are separated by a free energy barrier at $r_1 = 5.73$ Å. Consider the pseudoreaction

$$A-A \rightleftharpoons A - (H_2O) - A \ ,$$
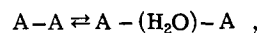
where the left side corresponds to a configuration in the first minimum and the right side corresponds to a configuration in the second minimum. The barrier height for the forward reaction is $0.95kT$ kcal/mole and for the reverse reaction it is $0.46kT = 0.27$ kcal/mole. Thus there is a free energy barrier which must be surmounted in the reaction and this corresponds in part to the removal of the intermediate water molecule.

IV. DISCUSSION AND COMPARISON WITH THEORY

The Pratt-Chandler theory[10] of hydrophobic interactions is based on the ideas of the WCA theory of dense liquids. The basic viewpoint is that the short range, strongly repulsive part of the potential determines the structure of the solution whereas the long range part of the potential gives the enthalpy of solution. The starting point is the breakup of

$$U_{AA}(r) = U_{AA}^{(0)}(r) + U_{AA}^{(1)}(r) \ , \tag{3.3a}$$
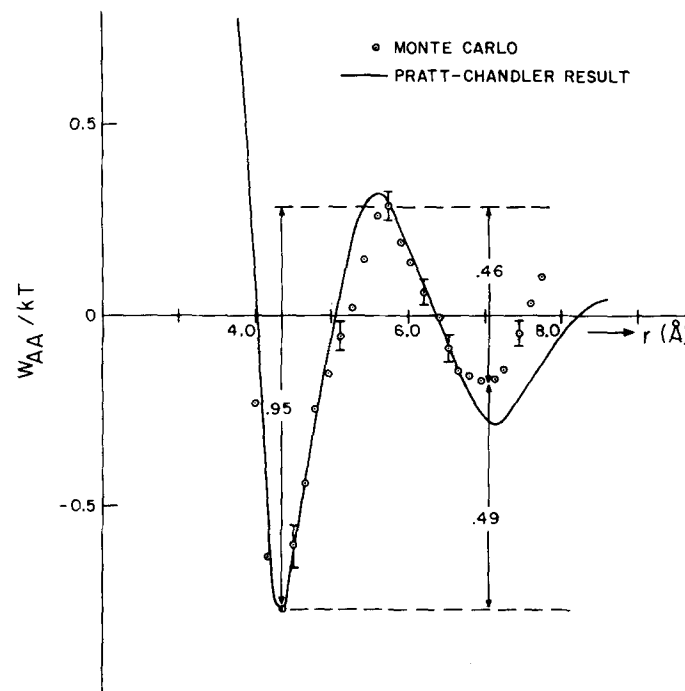

FIG. 3. The potential of mean force obtained from a simulation of two Lennard-Jones particles dissolved in 214 ST2 water molecules is shown in circles. Solid line shows the Pratt-Chandler result.

$$U_{AW}(r) = U_{AW}^{(0)}(r) + U_{AW}^{(1)}(r) \ , \qquad (3.3b)$$

where the $U^{(0)}$ and $U^{(1)}$ stand for the repulsive and attractive potentials defined in the usual WCA sense. No potential model is ascribed to the W–W interaction. Instead the measured $g_{OO}^{(2)}(r)$ function is used. One of the important approximations is that

$$g_{AA}^{(2)}(r) \cong g_{AA}^{(0)}(r) = y_{AA}^{(0)}(r) \exp[-\beta U_{AA}^{(0)}(r)] \ , \qquad (3.4)$$

where $y_{AA}^{(0)}(r)$ is the cavity function for the two A particles in a reference system in which the attractive parts in a potential, namely $U_{AA}^{(1)}(r)$ and $U_{AW}^{(1)}(r)$ are turned off. Likewise, $g_{AA}^{(0)}(r)$ is the pair correlation function in this reference system. Pratt and Chandler then approximate $y_{AA}^{(0)}(r)$ by the cavity function for two hard spheres dissolved in water, that is

$$y_{AA}^{(0)}(r) = y_{HS}(r) \qquad (3.5)$$

To compute $y_{HS}(r)$ for two hard spheres in real water, Pratt and Chandler[1] propose and solve coupled "Ornstein–Zernicke like" integral equations. This introduces several approximations. It is our aim to give a measure of the adequacy of these approximations. To this end then we note that when Eq. (3.5) is substituted into Eqs. (3.4)

$$g_{AA}^{(2)}(r) \cong y_{HS}(r) \exp[-\beta U_{AA}^{(0)}(r)] \ . \qquad (3.6)$$

Taking the logarithm then gives

$$W_{AA}^{PC}(r) = -kT \ln y_{HS}(r) + U_{AA}^{(0)}(r) \ ; \quad r > 0 \ .$$

This is the Pratt–Chandler approximation to $W_{AA}(r)$. Pratt and Chandler have computed $y_{HS}(r)$ for two spheres of variable diameter by solving their integral equations and using the radial distribution function $g_{OO}^{(2)}(r)$ obtained from x-ray diffraction studies on real water. In the computer simulation we determined $W_{AA}(r)$ for two Lennard-Jones spheres in ST2 water—a system not exactly corresponding to the model discussed by Pratt and Chandler. To make a proper comparison we should use the $g_{OO}^{(2)}(r)$ of ST2 water in the Pratt–Chandler theory. Unfortunately the computer simulation is based on a finite system and cannot be used to determine the long range correlations in $g_{OO}^{(2)}(r)$ which appear to be important in the Pratt–Chandler theory. Thus we are forced to compare the computer simulation with the same empirical model using the x-ray diffraction data. This required solving the Pratt–Chandler equations for an equivalent hard sphere diameter of $\sigma_{AA} = 4.075$ Å. This diameter was determined from the table presented by Verlet and Weiss using our Lennard-Jones diameter of $\sigma_{AA} = 4.12$ Å.

The potential of mean force, $W_{AA}^{PC}(r)$, obtained using the Pratt and Chandler theory is compared with the result of our computer simulation $W_{AA}(r)$, in Fig. 3. The arbitrary constant C in Eq. (3.2) is fixed such that $W_{AA}^{PC}(r) = W_{AA}(r)$ at the first minimum. This does not affect the shape of $W_{AA}(r)$; it merely facilitates comparison between theory and experiment. The curves appear to be in qualitative agreement. The second minimum is deeper in the PC case. The reader will notice that error bars for $W_{AA}(r)$ grow towards small r. This arises from a propagation of error from $P_i(r)$ to $P_j(r)$

when the latter is rescaled to match the former. We deliberately matched the $P_i(r)$ from right to left in order to keep the effects of errors arising from the matching of the $P_i(r)$'s to a minimum for the large r region of $W_{AA}(r)$. This is precisely the region for which different theoretical predictions exist.

It is possible to define a pseudo "equilibrium constant" for this pseudo reaction as

$$K = X_{A-(H_2O)-A}/X_{A-A} = \int_{r_1}^{r_2} dr \exp[-\beta W_{AA}(r) r^2]/$$
$$\int_0^{r_1} dr \exp[-\beta W_{AA}(r) r^2] \ ,$$

where $r_1 = 5.73$ Å is the position of the first barrier and r_2 is the position of the second barrier. In our simulation we did not locate the second barrier. We thus take $r_2 = 7.75$ Å, the maximum separation studied. Clearly the $K = 1.81$ obtained is smaller than would be the case if we had located the second barrier. It is possible to estimate the location and height of the barrier using the Pratt–Chandler theory discussed in the next section. This allows us to predict that our correct value should be $K \sim 3.0$.

In a recent paper Pratt and Chandler[18] have predicted on the basis of their theory for hard spheres in "real water" that $K = 4.0$ while hard spheres in a hard sphere solvent (with diameter 2.7 Å) gives $K = 2.90$. Attributing much significance to this difference, they concluded that water led to considerably higher fraction of $A - (H_2O) - A$ than would exist in an ordinary solvent. Given our result, we believe that caution should be exercised here.

Our results are in marked disagreement with the predictions of Marcelja et al.[16] and of the Monte Carlo work of Dashevsky and Sarkisov.[6] Both of them fail to see a second minimum in $W_{AA}(r)$, suggesting instead a monotonic decay of $W_{AA}(r)$ to zero after the first minimum. Indeed, conventional wisdom on the hydrophobic effect disdains the notion of apolar species separated by a molecule of water. The very term hydrophobic suggests as much. Our results demonstrate that although pairing exists, it is not the only stable condition for a pair of apolar species dissolved in water.

Ben Naim and others[3] have presented arguments supporting the idea of a net expansion of the system when apolar solutes are added to water. This suggests that (N, P, T) ensemble is more appropriate to the study of aqueous solutions on the computer than that (N, V, T) ensemble used here. We chose the latter ensemble partly because of custom and partly because of the cost: Owicki and Scheraga[9] estimate the cost for volume perturbation acquired in the (N, P, T) ensemble to be $N/2$ times the cost for a single particle move. Moreover, present model potentials for liquid water are not accurate enough to give the experimentally observed densities when used in the NPT ensemble.

The influence of boundary conditions on the properties of simulated water has been explored in Ref. 15. As pointed out there, it appears that the radial structure of water is comparatively insensitive to the boundary con-

dition used in the simulation compared to the angular structure. It is our belief, in view of this observation, that our results reported here will not be greatly changed in going to the cubic cutoff convention. However this matter should be explored before extending the implication of our results to real system. A related question is that of the size of the system. Here again we believe our system to have been sufficiently large for interference effects such as the influence of the image of b upon the structure of water around a to have been small. It is worth pointing out that previous studies of aqueous solutions of apolar species[16] have usually involved only 64–100 particles. We have studied as large a system as our budget would permit.

A question that may occur to the reader is the following: Can one use $W_{AA}(r)$ to simulate an aqueous solution of apolar species. In this connection it must be borne in mind that fluctuations are an important part of any simulation. Although the well depths of $W_{AA}(r)$ appear to be small, a pair of apolar species trapped in either of the wells will simply stay there for very long times, as observed by Geiger et al.[5] in their MD simulation on a pair of Lennard-Jones spheres in ST2 water. It appears that the breaking of a cage of water molecules is an extremely infrequent event. This information cannot be deduced from $W_{AA}(r)$ and therefore a simulation with this potential and without any extra information on the fluctuations of the system would give misleading results.

A detailed picture of how the water molecules distribute themselves around the two A particles as a function of the A–A separation is given in a companion paper.[2]

ACKNOWLEDGMENTS

[1]W. Kauzmann, Adv. Protein Chem. **14**, 1 (1959).

[2]C. Pangali, M. Rao, and B. J. Berne, J. Chem. Phys. 71, 2982 (1979).

[3]A. Ben Naim, *Water and Aqueous Solutions* (Plenum, New York, 1974). See Chap. 7.

[4]C. Pangali, M. Rao, and B. J. Berne, "Determination of the Mean Force of Two Noble Gas Atoms Dissolved in Water," in "Computer Modeling of Matter," ACS Symp. Ser. 86, 32 (1978).

[5]A. Geiger, A. Rahman, and F. H. Stillinger, J. Chem. Phys. **70**, 263 (1979).

[6]G. Dashevesky and G. N. Srakisov, Mol. Phys. **27**, 1271 (1974).

[7]S. Swaminathan and D. L. Beveridge, "Monte Carlo Computer Simulation of Hydrophobic Bonding," Preprint (1979).

[8]O. Matsuoka, E. Clementi, and M. Yoshimine, J. Chem. Phys. **64**, 1351 (1976).

[9]J. C. Owicki and H. A. Scheraga, J. Am. Chem. Soc. **99**, 7403 (1977).

[10]L. Pratt and D. Chandler, J. Chem. Phys. **67**, 3683 (1977).

[11]F. H. Stillinger and A. Rahman, J. Chem. Phys. **60**, 1545 (1974).

[12]C. Pangali, M. Rao, and B. J. Berne, Chem. Phys. Lett. **55**, 413 (1978).

[13]M. Rao, C. Pangali, and B. J. Berne, Mol. Phys. 37, 1773 (1979).

[14]G. N. Patey and J. P. Valleau, J. Chem. Phys. **63**, 2334 (1975).

[15]C. Pangali, M. Rao, and B. J. Berne, "A Monte Carlo study of structural and thermodynamic properties of water: Dependence on the system size and on the boundary conditions," Mol. Phys. (in press).

[16]S. Marcelja, D. J. Mitchell, B. W. Ninham, and M. J. Sculley, J. Chem. Soc. Faraday Trans. 2, **5**, 630 (1970).

[17]M. H. Kalos, J. K. Percus, and M. Rao, J. Stat. Phys. **17**, 111 (1977).

[18]L. Pratt and D. Chandler, Preprint (1979).