Orientation-Averaged Benzene–Benzene Potential of Mean Force in Aqueous Solution

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Abstract: The potential of mean force as a function of the distance between two benzene molecules in aqueous solution has been calculated. Statistical mechanical averages were performed over the translational and rotational degrees of freedom of the solvent molecules as well as over the rotational degrees of freedom of the benzene molecules. The minimum of the potential of mean force was found to be –2.1 kJ mol^{-1} at 5.0-Å separation, at which the benzene molecules are preferentially perpendicularly oriented with respect to each other. At smaller separations the benzene molecules are forced to be more parallel, but the probability of these separations is small. Finally, the convergence of the average over the benzene orientations is considerably slower than that of the average over the solvent molecules, and this discrepancy will become more severe for more nonspherical or less symmetric solutes.

Introduction

Since the experimental investigations by Tucker and Christian[1] and Tucker et al.,[2] there has been a continued interest in theoretical investigations of the benzene dimer in aqueous solution. Important reasons for this interest are that this system is considered prototypical for hydrophobic interaction in aqueous solution[3] and that close aromatic side groups are expected to play a role in protein stability.[4]

The potential of mean force (pmf) is a central quantity for describing the interaction among solutes in solution and for relating theoretical predictions to experimental data. The pmf represents the solute–solute interaction averaged over the translational and rotational degrees of freedom of the solvent (later referred to as solvent average) and, for nonspherical solutes, also averaged over the rotational degrees of freedom of the solute (later referred to as orientation average).

Rossky and Friedman showed in 1980 that a solvent- and orientation-averaged benzene–benzene pmf consisting of a core repulsion and a solvation cosphere overlap term could result in agreement with the data of Tucker and Christian by choosing reasonable parameters of the solvation overlap term.[5] Later, more extensive investigations of the benzene dimer in aqueous solution based on molecular simulation techniques were performed, and these investigations included calculations of the pmf as a function of the benzene separation. In particular, Ravishanker and Beveridge[6] computed the pmf for the stacked dimer, Jorgensen and Severance[7] obtained an orientation-averaged pmf, and this author[8] considered the pmf for a stacked and T-shaped dimer as well as a conversion between these two.

In the present investigation, the benzene dimer in aqueous solution is again examined by means of molecular simulation and the orientation-averaged pmf is calculated. A different set of intermolecular potentials is used as compared with that used in the similar investigation by Jorgensen and Severance.[7] The present results agree better with experimental data, and furthermore, the simulation length is more extended. In addition, a comparison with the previous investigation with fixed benzene orientations[8] is made which provides further insight into the importance of the different benzene orientations to the pmf function.

Calculations of pmf functions are computer intensive, since complete simulations of a series of closely separated solvent pairs are required. In the case of spherical symmetric solutes, the simulation time is determined by the requirement of a proper average over the solvents. However, in the case of orientation averaging of nonspherical solutes, such as benzene, the averaging over the orientational degrees of the solutes governs the length of the simulation. A comparison of the simulation time for obtaining pmf functions with fixed benzene orientations and with orientation average is also included, and the simulation time for the latter case is related to the reorientation time of a benzene molecule.

Model System and Simulation Methodology

The organization of the present investigation follows closely that of the previous one.[8] Here, only a brief account for the model and simulation technique is given. Molecular dynamics (MD) simulations were carried out on a model system consisting of two benzene and 500 water molecules. All interactions were evaluated explicitly assuming pairwise additivity, and all molecules were kept rigid. The benzene–benzene and the benzene–water intermolecular potentials used were obtained from ab initio quantum chemical calculations,[9] whereas the empirical TIP4P potential was used for the water–water interactions.[10] The MD simulations were performed with the MOLSIM package.[11] Newton's equations of motion were integrated with a time step of 1.0 fs and with the constraint of fixed separation between the center of masses of the benzene molecules. Thus, the benzene molecules were free to rotate according to the torques acting on them. The simulation box was a parallelpiped with edges approximately 22 × 22 × 32 Å, and periodical boundary conditions were used together with a spherical molecular cutoff of 10.0 Å. The temperature and pressure was kept constant at 298 K and 0.103 MPa, respectively. The pmf function was obtained from 14 separate simulations, where each was performed at a given benzene separation and comprised 100 ps of averaging. The simulations were performed on an IBM RS/6000 32H workstation, and each simulation of 100 ps required 125 CPU hours.

The orientation-averaged pmf as a function of the benzene separation was obtained by joining free energy differences from *N* separate

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(1) Tucker, E. E.; Christian, S. D. *J. Phys. Chem.* **1979**, *83*, 426.

(2) Tucker, E. E.; Lane, E. H.; Christian, S. D. *J. Solution Chem.* **1981**, *10*, 1.

(3) Isrealachvili, J. N. *Intermolecular and Surface Forces*; Academic Press: San Diego, CA, 1991; see also references given therein.

(4) Serrano, L.; Bycroft, M.; Fersht, A. R. *J. Mol. Biol.* **1991**, *218*, 465.

(5) Rossky, P. J.; Friedman, H. L. *J. Phys. Chem.* **1980**, *84*, 587.

(6) Ravishanker, G.; Beveridge, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 2565.

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(8) Linse, P. *J. Am. Chem. Soc.* **1992**, *114*, 4366.

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simulations. In each simulation the free energy difference between two close separations was calculated by using thermodynamic perturbation theory.[12,13] If we let the separations at which simulations were performed be specified by a discrete variable λ, where the smallest and largest separations are given by $\lambda_1 = 0$ and $\lambda_N = 1$, respectively, and the intermediate $N-2$ separations by $0 < \lambda_i < 1$, $i = 2, 3, ..., N-1$, then the free energy difference between separations λ_{i+1} and λ_i is given by

$$\Delta G_i = -RT \ln \langle e^{-\Delta U_i/RT} \rangle_{\lambda_i} \qquad (1)$$

where $\Delta U_i \equiv U_{\lambda_{i+1}} - U_{\lambda_i}$ denotes the difference in the total potential energy of the two separations, the symbol $\langle ... \rangle_{\lambda_i}$ an average using an equilibrium ensemble representative of the separation λ_i, R the molar gas constant, and T the temperature. The change of λ from 0 to 1 will map the path for which the pmf will be calculated, and the free energy difference between the smallest and largest separation, ΔG, becomes

$$\Delta G = \sum_{i=1}^{N-1} \Delta G_i \qquad (2)$$

For a spacial perturbation linear in λ, the benzene–benzene center-of-mass separation can be expressed as

$$r(\lambda) = r_0 + \lambda(r_1 - r_0) \qquad (3)$$

where r_0 (=3.5 Å) denotes the smallest and r_1 (=8.7 Å) the largest benzene separation. With $N = 13$ separate simulations, the difference in benzene–benzene separations between subsequent calculations becomes $\Delta r = 0.4$ Å. Since for each intermediate separation, a free energy difference was evaluated for a perturbation in either direction (smaller or larger λ), free energy differences were obtained for separations separated by $\Delta r = 0.2$ Å. Hence, 14 separate simulations were required giving 28 free energy differences and lower and upper ends of the pmf function of $r_0 = 3.3$ and $r_1 = 8.9$ Å, respectively. Finally, both benzene molecules were perturbed by an equal amount; thus each molecule was displaced 0.1 Å in the perturbation calculation.

From the set of ΔG_i, the pmf function $w(r)$ was constructed as

$$w[r(\lambda_i)] = \sum_{j=i}^{N} \Delta G_j \qquad (4)$$

now with $N = 28$. Since only relative free energies can be obtained, $w(r)$ contains an undetermined additive energy constant. It was selected such that $w(r) = 0$ at the largest separation investigated. The statistical uncertainty of quantities related to the pmf reported is one standard deviation. These uncertainties were estimated on the basis of the standard deviation of ΔG_i, $\sigma(\Delta G_i)$. The latter was obtained from a division of a simulation into subbatches according to

$$\sigma^2(\Delta G_i) = \frac{1}{n_b(n_b - 1)} \sum_{b=1}^{n_b} (\Delta G_{i,b} - \Delta G_i)^2 \qquad (5)$$

where $n_b = 10$ is the number of subbatches and $\Delta G_{i,b}$ the difference in free energy between separations λ_{i+1} and λ_i from one subbatch of 10-ps averaging. The mean of $\sigma(\Delta G_i)$, $(1/N)\sum_{i=1}^{N}\sigma(\Delta G_i)$, was 0.2 kJ mol^{-1}. Besides the statistical uncertainties, there is also a systematic error in the pmf function at large separations due to the fact that the separation comes close to the potential cutoff. It is difficult to determine this error from the present investigation only, but in the previous investigation at similar conditions, it was inferred to be limited.[8]

Results and Discussion

Potential of Mean Force. The calculated orientation-averaged pmf function for the benzene dimer in aqueous solution is shown in Figure 1 (filled circles). The size of the circles corresponds approximately to the local uncertainty, i.e., the uncertainty of the difference in the pmf of adjacent points. (A more detailed discussion of the statistical uncertainty is given below.) The pmf function shows a relatively gentle rise at short separation, a minimum of −2.1 kJ mol^{-1} at 5.0 Å, and a weak maximum at 7 Å. In addition, Figure 1 shows the corresponding pmf functions, where the relative orientations of the benzene molecules were kept fixed, either parallel (stacked) or perpendicular (T-shaped arrangement), obtained from the previous investigation.[8] In the parallel geometry, the C_6 axis of each molecule superimposes the intermolecular benzene–benzene vector, whereas in the perpendicular geometry one of the C_6 axes is turned to be perpendicular to the intermolecular vector.

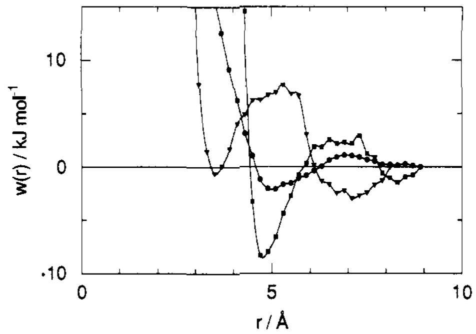

Figure 1. Benzene–benzene potentials of mean force in aqueous solution as a function of the benzene–benzene separation for the case of an average over benzene orientations, $w(r)$ (filled circles), and for fixed benzene orientations, $w(\mathbf{R})$ (parallel orientation, filled triangles; perpendicular orientation, filled squares).

An immediate conclusion is that the prominent variations in the pmf for fixed orientations due to steric and energetic factors are largely smoothed out by the averaging of the orientational degrees of freedom of the benzene molecules. In particular, the depth of the global minimum of the orientation-averaged pmf is strongly reduced as compared with that of the pmf for the perpendicular orientation. Also, the prominent minimum of the parallel pmf is 3.5 Å has no corresponding feature, not even a depression, on the orientation-averaged pmf (the orientation-averaged pmf continues to 21.2 kJ mol^{-1} at 3.3 Å). It should be remembered, however, that the parallel and perpendicular arrangements are only two points on the five-dimensionally angular space. The size of the angular space is, however, considerably reduced by the D_{6h} (near $D_{\infty h}$) symmetry of the benzene molecules.

The relative orientation of the benzene molecules was investigated by considering θ_1 and θ_2, which represent the angles between the benzene–benzene vector and the C_6 axis of the two benzene molecules, respectively, and ϕ, representing the angle formed by the two C_6 axes. Figure 2a shows the correlation of θ_1 and θ_2 at $r = 3.5$ Å and the range of the angles, 0–40°, with 20° as the mean. Thus, at this short separation, the benzene molecules are nearly parallel and undergo a wiggling motion. The angular distribution of θ_1 and θ_2 as well as that of ϕ (0–30°, not shown) leads to an increase of the benzene–benzene pair energy from −1.1 kJ mol^{-1} for the parallel geometry ($\theta_1 = \theta_2 = 0°$) to 1.5 kJ mol^{-1}, hence an excitation by $\approx RT$.

Figure 1 also shows that the primary minima of the perpendicular and orientation-averaged pmf functions coincide at 5 Å, which indicates that the T-shaped arrangement is important at this separation. Again, there is a noticeable difference in the values of the pmf at 5 Å between the perpendicular and orientation-averaged orientations. Figure 2b shows that there exists a strong correlation between θ_1 and θ_2 at $r = 5.1$ Å as well. The high probability of $\theta_1 \approx 0$ or 180° and $\theta_2 \approx 90°$, or the reverse, shows that a T-shaped arrangement is frequently occurring. However, the spread about the perpendicular geometry is broad and an L-shaped arrangement is also occurring ($\theta_1 \approx 45$ or 135° and $\theta_2 \approx 45$ or 135°). The broadening of the angle distribution due to thermal fluctuations is similarly manifested by an increase of the benzene–benzene pair energy from −10.1 kJ mol^{-1} for the perpendicular orientation (e.g., $\theta_1 = 0°$ and $\theta_2 = 90°$) to −7.4 kJ

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[12] Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420.

[13] Beveridge, D. L.; DiCaputa, F. M. In *Computer Simulation of Biomolecular Systems. Theoretical and Experimental Applications*; van Gunsteren, W. F., Weiner, P. K., Eds.; Escom: Leiden, The Netherlands, 1989.

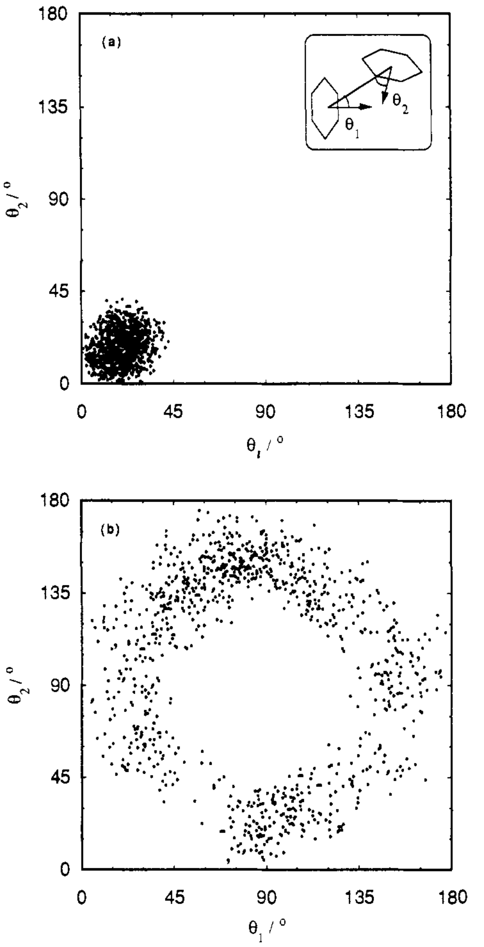

Figure 2. Correlation plot of θ_1 and θ_2 at separations r = 3.5 Å (a) and r = 5.1 Å (b). The angles θ_1 and θ_2 are formed by the benzene–benzene center-of-mass vector and the direction of the C_6 axis of the two benzene molecules, respectively [see insert of (a)]. Each of the 1000 points represents an instantaneous value of θ_1 and θ_2 separated by 0.1 ps in time.

mol^{-1}. Thus, the replacement of the very sharp rise of the pmf function obtained for the perpendicular arrangement at ≤4.5 Å (Figure 1, filled squares) by a more gentle rise of the orientation-averaged pmf (Figure 1, filled circles) is due to the fact that the perpendicular orientation ceases to occur and the parallel one starts to become more frequent at separations below ≈4.5 Å.

The low probability of finding the two benzene molecules at a short separation, e.g., 3.5 Å, in a stacked configuration needs to be discussed further. The previous investigation, in which the parallel and perpendicular arrangements were considered, showed that the perpendicular arrangement displayed the lowest free energy due to more favorable direct benzene–benzene interaction and better hydration of the π-region which outweighed the larger benzene area exposed to water. In order to make a more complete comparison, the angular spread about the two orientation arrangements must be regarded. Figure 2 indicates that the angular localization is much larger for the stacked arrangement. Thus, in addition to the free energy difference between the stacked arrangement at 3.5 Å and the T-shaped one at 4.7 Å, there is an additional entropic contribution which even more disfavors the stacked arrangement. The entropic effect contributes to the free energy discrepancy between 16 kJ mol^{-1} (the difference between the orientation-averaged pmf and the pmf for the parallel orientation at 3.5 Å) and 6 kJ mol^{-1} (the difference between the orientation-averaged pmf and the pmf for the perpendicular orientation at 4.9 Å). Thus, the free energy cost of the angular confinement also contributes to the low probability of a stacked benzene dimer at small separations.

Table I. Association Constant K_a and Osmotic Second Virial Coefficient B for Benzene in Aqueous Solution[a]

	K_a/M^{-1}	B/Å
this work[b]	0.7 ± 0.1 (a = 7 Å) 1.3 ± 0.3 (a = 9 Å)	−10 ± 500
Jorgensen and Severance[c]	2 (a = 7 Å) 5 (a = 9 Å)	−6700
experimental	0.85,[d] 0.51[e]	−1200[f]

[a] The calculated osmotic second virial coefficients were obtained according to $B = -(1/2)\int 4\pi r^2\{\exp[-w(r)/RT] - 1\}\,dr$ and the association constant from $K_a = (1/2)\int_0^a 4\pi r^2 \exp[-w(r)/RT]\,dr$, where a is a cutoff distance which defines the region of association.[7] A reasonable choice of a is 7–9 Å. [b] The uncertainties of K_a and B were obtained by simulating 10^4 pmf functions, where each function was generated from $\Delta G_i + \delta(\Delta G_i)$ instead of ΔG_i. The random quantity $\delta(\Delta G_i)$ was taken from a Gaussian distribution with a standard deviation equal to $\sigma(\Delta G_i)$ which was evaluated according to eq 5. For each pmf function, K_a and B were calculated and the uncertainties given are one standard deviation of the distributions obtained for K_a and B, respectively. [c] Reference 7. [d] Reference 1. [e] Reference 2. [f] References 1 and 5.

In their calculation of the orientation-averaged pmf function for the benzene dimer in aqueous solution, Jorgensen and Severance found a broad double minimum at 5.4 and 7.8 Å with a depth of 5–6 kJ mol^{-1} (Figure 6 of ref 7). This is a deeper and broader minimum as compared to that obtained in the present investigation. The shorter simulation (Monte Carlo simulation, 5400 configurations per molecule) makes the pmf function by Jorgensen and Severance less accurate. From Figure 7 of ref 7 it can be inferred that the statistical uncertainty of the difference in the pmf for adjacent points (Δr = 0.2 Å) is ≤2 kJ mol^{-1}, which is approximately an order of magnitude larger as compared to that of the present study.

A contact with the experimental data by Tucker and coworkers[1,2] can be established by calculating the association constant K_a for the dimerization process and the related osmotic second virial coefficient, B. These quantities have been determined for the dimerization of benzene in water from deviations of Henry's law. Table I gives the experimental data as well as those obtained from the present and Jorgensen and Severance's pmf functions. A comparison between the experimental data and those calculated from the present pmf function shows a very satisfactory agreement. Regarding the association constant, there is complete agreement (with consideration taken of the experimental spread and the uncertainty of the definition of the region of association), whereas there is a deviation in the osmotic second virial coefficient of about two standard deviations. The close agreement between experimental and simulated data indicates that there is no large systematic error in the pmf function related to the potential cutoff and system size. A similar conclusion was also inferred from the internal consistency of the pmf functions calculated with fixed benzene orientations.[8]

As expected, the more attractive pmf function obtained by Jorgensen and Severance gives a larger association constant and a far too negative osmotic second virial coefficient. However, a more detailed examination of the merits of the two sets of intermolecular potential functions used is impeded by the larger uncertainty of the pmf function of Jorgensen and Severance.

Solvent Contribution. The solvent contribution to the pmf function, w_s, is obtained by subtracting the contribution from the direct benzene–benzene interaction from the pmf function. The solvent term contains contributions from both benzene–water and water–water interactions and is zero in the gas phase. In the case of fixed benzene orientations, w_s becomes

$$w_s(\mathbf{R}) = w(\mathbf{R}) - U_{BB}(\mathbf{R}) \qquad (6)$$

where $\mathbf{R} \equiv \{r,\Omega\}$ with r being the benzene–benzene separation and Ω the five orientational degrees of freedom describing the relative benzene–benzene orientation, and U_{BB} denotes the benzene–benzene pair potential energy.

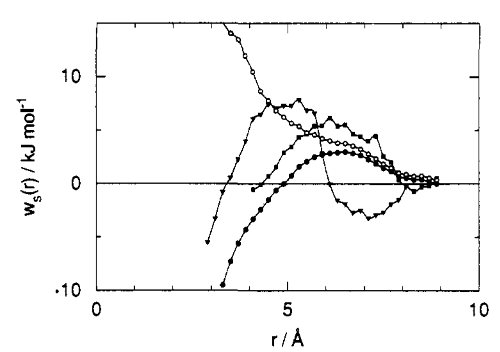

Figure 3. Solvent contribution to the potential of mean force, $w_s(r)$, defined by eq 7 (open circles), and its direct part, $w_s'(r)$ defined by eq 9 (filled circles), as well as the solvent contribution to the potential of mean force for fixed benzene orientations, $w_s(\mathbf{R})$, defined by eq 6 (parallel orientation, filled triangles; perpendicular orientation, filled squares).

In the case where averaging over the benzene orientations is performed, the solvent contribution to the pmf function is defined according to

$$w_s(r) = w(r) - w_{BB}(r) \tag{7}$$

where $w_{BB}(r) \equiv \langle U_{BB}(r)\rangle_\Omega$ is the orientation average of the benzene–benzene pair potential energy in the *absence* of the solvent (only the benzene–benzene interaction energy enters the Boltzmann weight). Two types of influences of the solvent may be distinguished, one *direct*, through interaction with the benzene molecules for a *given* orientation distribution of the benzene molecules, $w_s'(r)$, and one *indirect*, through a *perturbation* of the orientation distribution of the benzene molecules, $w_s''(r)$. Thus, we obtain

$$w_s(r) = w_s'(r) + w_s''(r) \tag{8}$$

where

$$w_s'(r) = w(r) - w_{BB}'(r) \tag{9}$$

and

$$w_s''(r) = w_{BB}'(r) - w_{BB}(r) \tag{10}$$

with $w_{BB}'(r)$ being the potential of mean force evaluated to eqs 1–4 but using ΔU_{BB} instead of ΔU in eq 1.

Figure 3 shows the solvent contribution to the pmf, w_s, as well as its direct part w_s'. The former one is purely repulsive and is dominated by its indirect part w_s''. The *indirect* part is normally strongly repulsive in any liquid, since the thermal fluctuations due to the surrounding molecules impede the solute molecules from distributing their angular orientation according to the Boltzmann weight of their pair energy. The character of the direct part $w_s'(r)$ is similar to that of $w_s(\mathbf{R})$ for fixed benzene orientations, which are also displayed in Figure 3. At short separation, $w_s'(r)$ and $w_s(\mathbf{R})$ increase with r due to an enlargement of the unfavorable benzene–water area whereas, at larger separation, $w_s'(r)$ and $w_s(\mathbf{R})$ decrease with r due to a favorable reorganization of the water molecules leading to a solvent-separated benzene dimer.[8] As for the total pmf function, the variations of $w_s'(r)$ are partly averaged out by the orientation average. For example, the mean of the forward and backward barriers between close-contact and solvent-separated configurations, which amounts to 9 and 5 kJ mol^{-1} for the parallel and perpendicular arrangements, respectively (cf. Table I of ref 8), is reduced to 3 kJ mol^{-1}.

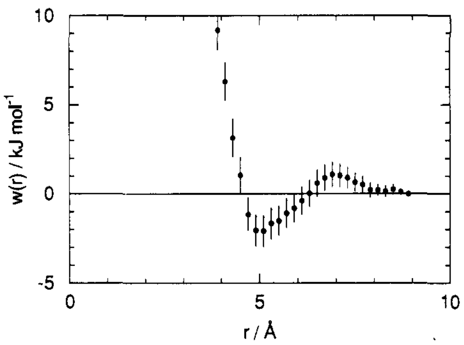

Figure 4. Potential of mean force as a function of the separation, $w(r)$, with accumulated error bars (see text for evaluation of the error bars).

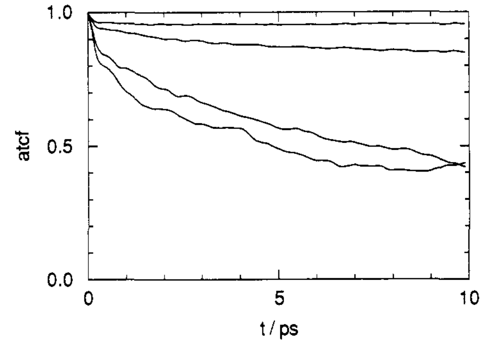

Figure 5. Angular time correlation function $\Psi(t) = \langle \mathbf{n}(0)\cdot\mathbf{n}(t)\rangle$, where $\mathbf{n}(0)$ is the direction of the C_6 axis of a benzene molecule at time zero and $\mathbf{n}(t)$ the direction at time t, at separations r = 3.5, 4.7, 5.1, and 8.7 Å (top to bottom).

Accuracy. The uncertainty of the free energy difference between two benzene dimer separations increases with the difference of the separation. This is a consequence of the procedure of accumulating the free energy differences in order to obtain the pmf function. Figure 4 shows the pmf function and the increasing uncertainty counted from the largest separation investigated at which the pmf is set to zero. The accumulated uncertainties were evaluated by assuming independent errors among the separate intervals according to $\sigma^2[r(\lambda_i)] = \sum_{j=i}^{N}\sigma^2(\Delta G_j)$ where $\sigma(\Delta G_j)$ is obtained from eq 5. [With the simplification $\sigma(\Delta G_i)$ = 0.2 kJ mol^{-1} for all i, we get, in general, an uncertainty of $0.5d^{1/2}$ kJ mol^{-1} Å$^{-1/2}$ for the free energy difference for two dimers with a *difference in separation* of d Å.] This analysis implies that the uncertainty of the primary minimum at 5.0 Å is 0.9 kJ mol^{-1} as compared with the depth of −2.1 kJ mol^{-1} (see Figure 4). The necessity of extended simulations is demonstrated by the consideration that if each simulation would only have extended 20 ps, the uncertainty would have increased by a factor of $5^{1/2}$ and hence the uncertainty of the minimum would have exceeded the depth of it.

The precision of the free energy differences in the former investigation of a benzene dimer with fixed orientations was also $\sigma(\Delta G_i) \approx 0.2$ kJ mol^{-1}.[8] Since the former simulations involved 18-ps averaging as compared to 100-ps here, the averaging over the orientational degrees of freedom requires an approximately 5 times longer simulation time than that required for averaging over the solvent molecules only (with similar precision). For less symmetric molecules in aqueous solution, the averaging over the orientational degrees of freedom of the solute will hence require at least an order of magnitude longer simulation time than that required for the solvent average only.

Further insight into the required simulation time can be gained by considering the rotational dynamics of the solute. Since the reorientation time *of* the C_6 axis is considerably less than that of a C_2 axis,[14] only the reorientation time of the former axis will be considered. Figure 5 shows the angular time correlation function (atcf) of the C_6 axis of the benzene molecule at separations r = 3.5, 4.7, 5.1 and 8.7 Å. For separations $r \le 4.7$ Å, the atcf levels out (at ≥0.85), showing that the C_6 axis undergoes librational motion; thus, the benzene molecule is not able to rotate freely about a C_2 axis. For larger separations, however, the atcf shows

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(14) Linse, P. *J. Am. Chem. Soc.* **1990**, *112*, 1744.

a more diffusive behavior and the diffusion coefficient[15] for rotation around a C_2 axis $\theta_\perp$ is 0.04–0.05 ps^{-1}, which is similar to that found for a single benzene molecule in water by employing the same potential under the same external conditions.[14] Thus, the length of the present simulation could also be expressed as about 5 times the inverse of the rotational diffusion coefficient for those separations at which the rotational motion was not sterically impeded.

Summary

The potential of mean force between two benzene molecules in aqueous solution has been calculated by using extended simulation of a molecular model system and thermodynamic perturbation theory. Averages were made over the solvent molecules as well as over the orientational degrees of freedom of the benzene molecules.

The calculated pmf function displayed a minimum at 5.0 Å and a depth of 2.1 kJ mol^{-1}. The orientation averaging reduced considerably the oscillatory behavior of the pmf and its solvent contribution function previously obtained for stacked and T-shaped benzene arrangements. Calculation of secondary quantities (the association constant and the osmotic second virial coefficient) gave very satisfactory agreement with experimental data. This supports the accuracy of the potential functions and the unlikeliness of a large systematic error in the pmf function related to the simulation protocol used. Furthermore, the present results also provide insights into the necessity of performing extended simulations and guidance in selecting simulation time for obtaining accurate pmf functions for nonspherical solutes.

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(15) The rotational diffusion coefficient $\theta_\perp$ was determined from $\tau_L^\parallel = 1/[L(L+1)\theta_\perp]$ with $L = 1$, where $\tau_L^\parallel$ was obtained from an exponential fit of $P_L^\parallel(t) = A^\parallel \exp(-t/\tau_L^\parallel)$ using the interval 1–4 ps of the simulated atcf given in Figure 5. For further details, see: Linse, P.; Engström, S.; Jönsson, B. *Chem. Phys. Lett.* **1985**, *115*, 95.