Monte Carlo Computer Simulation Study of the Hydrophobic Effect

Potential of Mean Force for $[(CH_4)_2]_{aq}$ at 25 and 50 °C

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A series of liquid-state computer simulations has been performed on the system $[(CH_4)_2]_{aq}$ at 25 °C as a function of the separation R between the dissolved CH_4 molecules. The potential functions for H_2O-H_2O, CH_4-H_2O and CH_4-CH_4 are based on quantum-mechanical calculations of the corresponding intermolecular interactions. The simulation was carried out by the Monte Carlo method augmented with convergence acceleration techniques involving force-bias and the method of preferential sampling. The potential of mean force $w_{ss}(R)$ for the interaction of the apolar species in water was determined using umbrella sampling procedures on four windows on the intersolute coordinate. Convergence acceleration was found to be necessary for obtaining satisfactory results. Contact and solvent-separated contributions to the statistical state of the system are discussed in terms of the radial distribution functions, quasi-component distribution functions for coordination number, binding energy and pair interaction energies. Stereographic views of significant structures are presented, and contributions of clathrate structures in the solvent are discussed. The results are discussed in the context of the experimentally observed concentration dependence of hydrophobic effects and related theoretical work on $w_{ss}(R)$ by Marcelja, Mitchell, Ninham and Scully, Pratt and Chandler, and Pangali, Rao and Berne. Prospects for quantitative study of the temperature dependence of the hydrophobic interaction and other quantitative extensions of the work are discussed.

1. INTRODUCTION

The tendency of apolar molecular species to associate spontaneously in aqueous solution is presently recognized as one of the primary organizing principles in structural biochemistry and biology, and is widely known as the hydrophobic effect. Prevalent ideas about the hydrophobic effect at the molecular level involve contact interaction of apolar groups, stabilized by entropic effects originating in the solvent water. The entropic nature of the process leads to the expectation of an inverse temperature dependence in the hydrophobic association of apolar solutes.

Recent experimental data from diverse sources indicate that the nature of hydrophobic association is possibly more complex than expected and involves competing processes. Direct experimental data on the nature of this problem at the molecular level are difficult if not impossible to obtain. This problem has currently become accessible to theoretical study at a high level of computational rigour by liquid-state computer simulation, using both the method of molecular dynamics and the Monte Carlo method. Here additional perspectives on the nature of the hydrophobic effect at the molecular level may be gained. We present herein Monte Carlo simulation results on a prototype system for study of the hydrophobic interaction, $[(CH_4)_2]_{aq}$, and discuss our results in the context of other recent theoretical and experimental work on this topic.

2. BACKGROUND

The initial physicochemical account of the hydrophobic effect and the implications thereof in structural biochemistry were advanced by Kauzmann.[1] Experimental evidence for hydrophobic effects are collected together with numerous applications in the monograph by Tanford.[2] For the brief description that follows, we employ the conventional terminology as much as possible and distinguish " hydrophobic hydration", the solvation of apolar species in water, from " hydrophobic interaction", the solute–solute association process. The latter effect is yet referred to as " hydrophobic bonding", a term which has inspired a controversy which has only been increased by current research.

There is consistent theoretical and experimental evidence that in the hydrophobic hydration of an apolar species the local solution environment of the solute is best described in terms of contributions from clathrate-like cages of water molecules not found in the pure liquid.[2] Typical experimental indices of this phenomena are the thermodynamic data of Glew[3] and the n.m.r. relaxation studies of Hertz and Radle.[4] Computer simulation studies of $[CH_4]_{aq}$ at 25 °C by Owicki and Scheraga[5] and Swaminathan et al.[6] directly implicate pentagonal dodecahedral clathrate structures in the aqueous solution of methane as shown in fig. 10 of ref. (6). Hydrogen-bond analysis showed increased structuration in the water surrounding the solvated methane.[7a] The ordered water structure is expected to be entropically unfavourable and thus consistent with the sparing solubility of apolar solutes in water. Apolar groups incorporated as functional groups in polar molecules and macromolecules must of course contend with hydrophobic hydration, and diverse clathrate structures can be formed to accommodate various sizes and shapes of solute.[7b]

The hydrophobic interaction or association of apolar groups in water has been described as a partial reversal of hydrophobic hydration,[8] entropically favoured when the solutes approach proximity and intervening clathrate water is expelled into bulk solvent. The currently prevalent textbook-level view of the hydrophobic effect has the apolar species in contact with one another, henceforth referred to as contact hydrophobic interaction (CHI).

In an extensive review article, Franks[9] collected evidence from diverse experimental points of view for an anomalous concentration dependence of observable properties of solutions of effectively hydrophobic solutes very near the limit of infinite dilution. Experimental data on partial molar volumes, partial molar enthalpies, apparent molar heat capacities and compressibilities and light scattering were among those cited. Clear physicochemical evidence that competing processes were operative in the association of hydrophobic solutes was presented. Although the nature of these processes could not be confirmed, Franks discussed the possibilities in terms of contact hydrophobic interaction and a longer-range effect which is stabilized in spite of intervening solvent. This latter situation is henceforth referred to as a solvent-separated hydrophobic interaction (SSHI).

The formal statistical mechanics of the interaction of apolar species in aqueous solution is described by Ben-Naim[10] in terms of a free energy $\delta A_{HI}(R)$, related to the potential of mean force $w_{SS}(R)$ or equivalently the radial distribution function $g_{SS}(R)$ for solute–solute interactions in aqueous solution. A knowledge of $w_{SS}(R)$ as a function of an intersolute coordinate R carries a full description of the association process in the hydrophobic interactions for apolar solutes in water. In an extensive study of the hydrophobic effect based on thermodynamic perturbation theory for liquids, Pratt and Chandler[11] studied prototype hydrophobic hydration and hydrophobic interaction of a hard sphere in water with the available diffraction data incor-

porated for the description of the water–water interactions. They obtained a $w_{SS}(R)$ exhibiting oscillatory behaviour, with one minimum corresponding to contact interaction and another corresponding to a solvent-separated interaction. The well depth of the solvent-separated structure was considerably less than that of the contact minimum, but since more configuration space is associated with the solvent-separated form, the relative equilibrium constant

$$K = [S \cdot W \cdot S]_{aq}/[S \cdot S]_{aq} \tag{1}$$

was found to be 1.8–4.0. Thus a solvent-separated structure could have a significant statistical weight in the description of an aqueous solution of hydrophobic solutes at infinite dilution.

Experimental data on the structure of liquid water at the molecular level have been obtained from diffraction experiments,[12] but procedures for aqueous solutions are still under development. Molecular detail in the association process at low concentrations is not readily accessible to experimental study. Thus computational chemistry and liquid-state theory have a unique vantage point on this problem. The structure of liquid water was studied by liquid-state computer simulation beginning with work by Rahman and Stillinger[13] using molecular dynamics and by Barker and Watts[14] using the Monte Carlo method. Studies on aqueous solutions of hydrophobic solutes were later reported by Owicki and Scheraga[5] and Swaminathan et al.[6]

Early work on the interaction of apolar species in water was reported by Dashevsky and Sarkisov[15] and by Marcelja et al.[16] The initial large-scale computer simulation study of the hydrophobic interaction was the molecular-dynamics calculation by Geiger et al.[17] on two neon-like Lennard-Jones solutes in ST2 water. The simulation was initiated with the solute molecules in contact. In the course of a 4.5 ps simulation, the solutes oscillated for 2.5 ps about the contact structure and moved apart for the remaining period to a solvent-separated structure. Quite recently, a large molecular-dynamics study of apolar species in water by Rapaport and Scheraga[18] surprisingly revealed no tendencies towards aggregation.

Monte Carlo calculations of hydrophobic interactions in prototype systems were reported first in terms of solvent averaged potential of mean force by Pangali et al.[19] and by Swaminathan and Beveridge.[20] Evidence for solvent-separated structures appeared in both these studies, but with larger statistical errors due to limitations in the methodology. Pangali et al.[21] extended their studies to the direct calculation of the potential of mean force for Lennard-Jones solutes in ST2 water, and confirmed the oscillatory behaviour first noted for this problem by Pratt and Chandler.[11]

In the present study we have extended simulations based on quantum-mechanical potential functions for intermolecular interaction energies to study the prototype molecular system for hydrophobic interactions, $[(CH_4)_2]_{aq}$. Improved methodologies for achieving convergence in the Monte Carlo simulation are employed. We focus on providing knowledge on the sensitivity of results to choice of potential function, the molecular nature of the contact and solvent-separated structure and the temperature dependence of the hydrophobic interaction.

3. METHODOLOGY AND CALCULATIONS

The theoretical basis for our study is the treatment of the interaction of molecules in condensed phases set forth by Ben-Naim[10] for the constant-volume ensemble. Here the work of bringing two solutes from fixed positions at infinite separation to a distance R from one another is given by the Helmholtz free-energy term

$$\Delta A(R) = E_{SS}(R) + w_{SS}(R) \tag{2}$$

where $E_{ss}(R)$ is the solute–solute potential energy of interaction and $w_{ss}(R)$ is the potential of mean force due to solvent-induced interactions between the two particles. Liquid-state theory relates $w_{ss}(R)$ to the solute–solute radial distribution function $g_{ss}(R)$,

$$w_{ss}(R) = -kT \ln g_{ss}(R) \tag{3}$$

where k is the Boltzmann constant and T is the temperature.   The quantity $w_{ss}(R)$ is identical to Ben-Naim's [10] index of hydrophobic interaction, $\delta A_{HI}(R)$.

The calculation of $w_{ss}(R)$ for the interaction of apolar solutes in water as described herein proceeds via the calculation of $g_{ss}(R)$ using Monte Carlo computer simulation along the methodological lines established by Patey and Valleau [22] and enhanced by Pangali $et\ al.$[21]   Patey and Valleau recognized that special methodology was required in order fully to sample the intersolute coordinate in a Monte Carlo simulation with only two solutes, and devised an umbrella sampling procedure for this purpose in their study of the ion–ion interactions in a dipolar fluid.   Here the $g_{ss}(R)$ were obtained for small overlapping segments or windows on the R coordinate and are subsequently combined to produce $g_{ss}(R)$ over the range of interest.   Pangali $et\ al.$ adopted this approach in their study of Lennard-Jones solutes in ST2 water, refined the methodology and introduced the idea of defining the sampling window by constraining the solute–solute separation using a harmonic restoring potential in the configurational energy expression, to be determined by trial and error.   The bias introduced by this harmonic restoring function is removed by standard procedures in umbrella sampling.

The calculations described herein are intended as a direct extension of the earlier studies from this laboratory on hydrophobic hydration to the problem of hydrophobic interactions.   The potential functions used for the evaluation of the water–water contributions to the configurational energy was that of Matsuoka $et\ al.$[23] based on quantum-mechanical calculations.   The characteristics of this function used in Monte Carlo simulations for the description of liquid water have been treated in earlier papers from this laboratory and elsewhere; in summary this function produces a $g_{ss}(R)$ in agreement with that observed from diffraction experiments and gives most thermo-dynamic variables in reasonable agreement with the experiment considering that the cooperative effects are neglected.   The most serious problem with this potential in computer simulations is the inflated value computed for the pressure of the liquid, indicating problems in describing the curvature of the potential in the equilibrium region.

Methane–water interactions are treated by means of a quantum-mechanical potential function developed for this study by refitting the data base used in earlier work to a functional form with a more suitable long-range behaviour.   The details of the determination of this function and related functions are described by Marchese et $al.$[24] in a current paper.   The equilibrium binding energy in the methane–water potential function is -1.32 kcal mol^{-1}, attributed mainly to dipole–induced-dipole interactions.   The parameters for the methane–methane interaction are taken from the transferable methane–water potential.[24]

Monte Carlo computer simulations in these studies were carried out using the Metropolis method augmented with convergence acceleration procedures.   Monte Carlo simulations applied to aqueous solutions and, by inference, for interactions in aqueous solutions are subject to convergence problems above and beyond those encountered in pure liquids, due primarily to the loss of a significant statistical factor in the determination of configurationally averaged quantities referenced to the solute.   A recent study from this laboratory by Mehrotra $et\ al.$[25] demonstrated that this difficulty can be overcome by the joint application of force-bias sampling and

preferential sampling technique in addition to the Metropolis method in computer simulations on aqueous solutions. In the present study, all simulations reported involve Metropolis, force-bias and preferential sampling procedures. The full details of the calculations follow the description given by Mehrotra et al.[25]

The calculations described herein are aimed at producing $g_{ss}(R)$ and $w_{ss}(R)$ for the intersolute coordinate in the system $[(CH_4)_2]_{aq}$. The system for study consists of two methane molecules and 214 water molecules configured under face-centred cubic periodic boundary conditions with a spherical cutoff treatment of the potential. Four points of origin on the intersolute coordinate were chosen, defined as 3.9, 5.3, 6.07 and 6.8 Å. Harmonic constraining functions with a force constant of 1.5 kcal $Å^{-2}$ were used to define the four windows used in the umbrella sampling procedure. The density of the system was computed from the experimental measurements of partial molar volumes of methane and water. Calculations for all four windows were carried out at $T = 25$ °C and, for reasons described below, at $T = 50$ °C for the window centred at 5.3 Å. For each window that was studied, a total of 3×10^6 configurations were sampled, of which the first 1.5×10^6 configurations were treated as equilibration. All the properties reported are the ensemble averages from the second 1.5×10^6 configurations.

4. RESULTS AND DISCUSSION

The $g_{ss}(R)$ for the four windows studied at 25 °C are shown in fig. 1. For window 1, the point of origin was chosen at 3.9 Å to coincide with the solute–solute contact
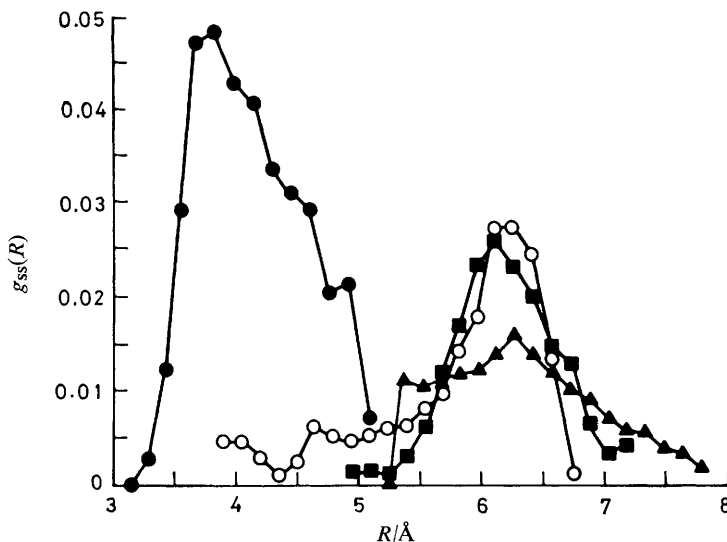

FIG. 1.—Calculated radial distribution function $g_{ss}(R)$ plotted against intersolute separation R for each of the four windows of umbrella sampling for $[(CH_4)_2]_{aq}$ at 25 °C. ●, Window 1; ○, window 2; ■, window 3; ▲, window 4.

interaction based on $R = 1.92$ Å, estimated from the position of the first peak in $g_{ss}(R)$. In this realization, the intersolute region from 3.2 to 5.2 Å is sampled. The maximum falls at 3.9 Å, with a bias in the distribution in favour of longer distances.

Window 2 has the point of origin at 5.3 Å and was observed to sample a quite broad range of the intersolute coordinate from $R = 4.0$ Å to almost 7 Å. The maxi-

mum in the probability distribution for this window was found at 6.4 Å. The remaining two windows, $R = 6.07$ and 6.8 Å, both sample ca. 3.5 Å of the intersolute coordinate and find their maxima in the region of 6.2 Å.

The probability distributions for the four windows were matched on the basis that the points in the overlapping region should coincide and the solute–solute radial distribution function $g_{ss}(R)$ was generated. The corresponding potential of mean force $w_{ss}(R)$ was generated using eqn (2) and is plotted in fig. 2. The oscillatory
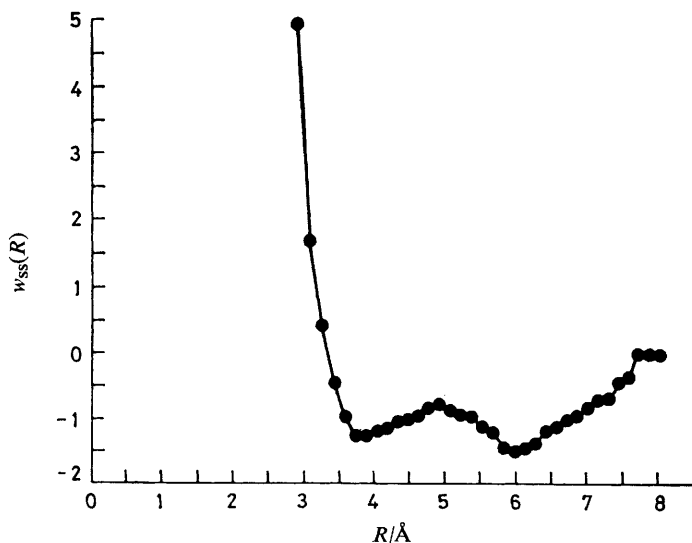
FIG. 2.—Calculated potential of mean force $w_{ss}(R)$ as a function of R, after matching, for $[(CH_4)_2]_{aq}$ at 25 °C.

behaviour in $w_{ss}(R)$ noted previously by Pratt and Chandler [11] and Pangali et al.[21] is clearly evident.   Two distinct minima, one at $R = 3.9$ Å and the other at $R = 6.0$ Å, are found.   The former corresponds to the contact hydrophobic interaction and the latter to a solvent-separated structure.

The results of Pratt and Chandler (P.C.) and Pangali et al. (P.R.B.) are included in fig. 3 for comparison and contrast.   Two essential points of difference are noted: (a) the positions of the minima in our study occur at slightly shorter intersolute separations and (b) the solvent-separated minima in our study are deeper than the minima for the contact interaction, whereas in the previous studies the contact minima were deeper.

The difference in position of the minima in $w_{ss}(R)$ is due primarily to a difference in the solute–water potential.   The P.C. and P.R.B. studies both assume a Lennard-Jones form for the solute–water potential, which lacks the granularity expected when the molecules interact with one another.   The quantum-mechanical potential used herein contains a more detailed description of this interaction and this is reflected in the positions of the calculated minima in $w_{ss}(R)$.

The discrepancies in relative depth of the contact and solvent-separated minima in $w_{ss}(R)$ can also be traced back to differences in the potential function.   The methane–water binding energy is negligible in the P.C. and P.R.B. studies, whereas our function exhibits an equilibrium binding energy of -1.32 kcal mol^{-1}.   The description of the water–water interactions varies among the studies as well, but since there is such close agreement between P.C. [using the experimental $g_{oo}(R)$] and P.R.B.
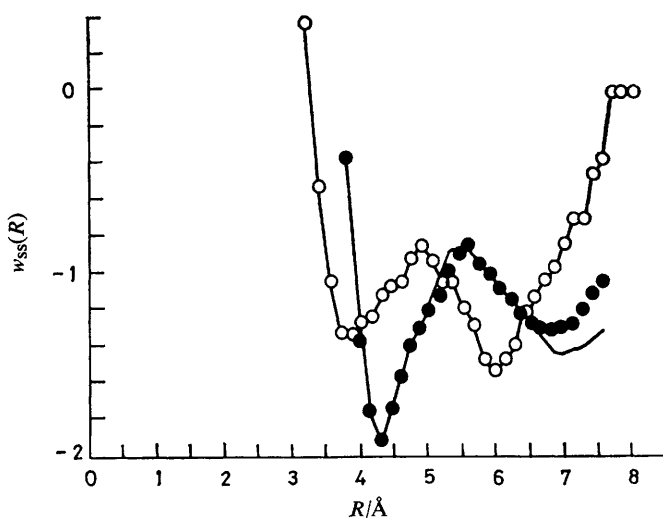
FIG. 3.—Comparison of the calculated $w_{ss}(R)$ in this work (— ○ —) with that computed by Pangali *et al.* [21] (●) and Pratt and Chandler [11] (—).

(using ST2 water, which overemphasizes considerably the tetrahedral nature of water interactions), we feel that the origin of this discrepancy probably resides in the different solute–water binding energy. This effect was anticipated by Pratt and Chandler.[26] The interpretation of the results is significantly affected by this point. The P.C. and P.R.B. results produce an equilibrium constant, of the order of unity, indicating significant contributions from both contact and solvent-separated structures to the statistical state of the system at 25 °C. Our results predict a strong preference for the solvent-separated form. There is at present no means of deciding which result is correct, but the sensitivity of this crucial result to the choice of potential functions is
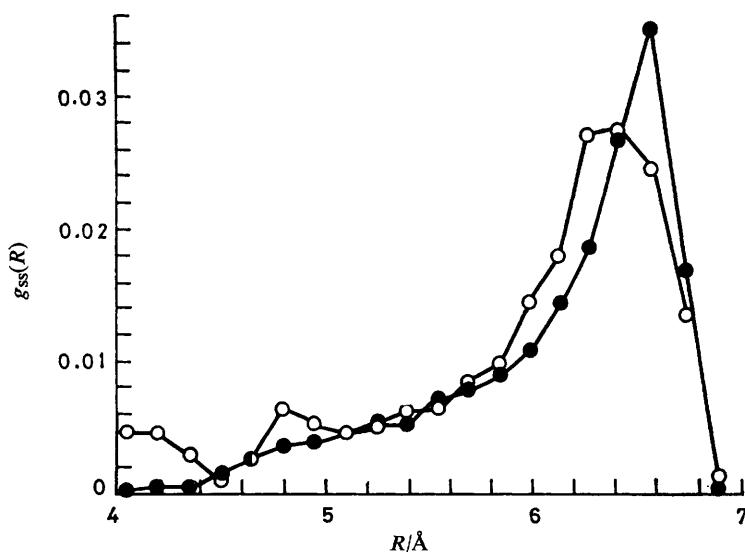
FIG. 4.—Calculated $g_{ss}(R)$ as a function of R for window 2 for $[(CH_4)_2]_{aq}$ at ○, 25 and ●, 50 °C.

notable. All studies concur in indicating that the solvent-separated structure should be considered seriously in the structural chemistry of the hydrophobic effect.

A preliminary study of the temperature dependence of the hydrophobic interaction was carried out by means of a Monte Carlo calculation on $[(CH_4)_2]_{aq}$ at $T = 50$ °C. This study was carried out for window 2 only, which was observed to span the contact and solvent-separated structures on the intersolute coordinate. The calculated $g_{SS}(R)$
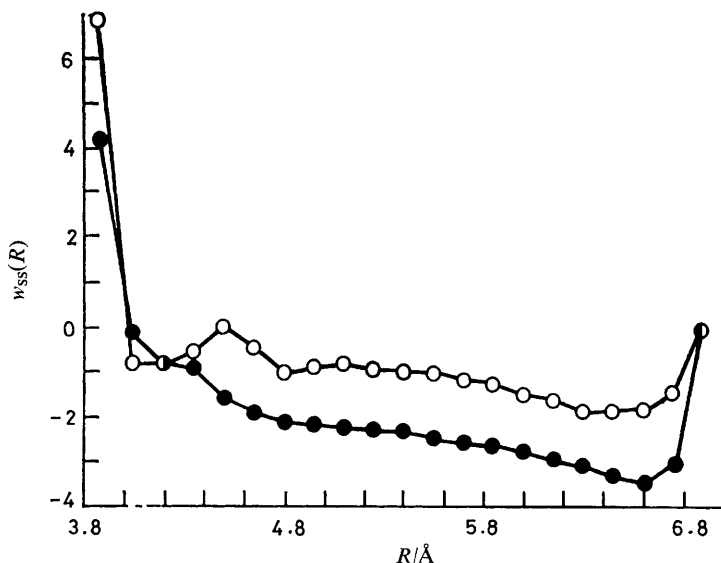
FIG. 5.—Calculated $w_{SS}(R)$ plotted against R for window 2 for $[(CH_4)_2]_{aq}$ at $\bigcirc$, 25 and $\bullet$, 50 °C.

and $w_{SS}(R)$ for 50 °C are shown in fig. 4 and 5, respectively. The minimum in $w_{SS}(R)$ corresponding to the contact interaction is no longer present and the solvent-separated structure is preferentially stabilized by the increase in temperature. Thus the inverse temperature dependence of the hydrophobic effect is accounted for by computer simulation and linked to the preferential stabilization of the solvent-separated hydrophobic interaction.

5. ANALYSIS OF RESULTS

The results of the preceding section strongly implicate the solvent-separated structures in the hydrophobic interaction. In this section we inquire into the molecular nature of these structures. Two procedures are employed for this analysis: (a) examination of the distribution functions $g_{\bullet O}(R)$ and $g_{\bullet H}(R)$, describing the organization of solvent water with respect to the centre of mass ($\bullet$) of the SS complex, and (b) consideration of stereographic pictures of supermolecular structures from configurations that contribute significantly to the statistical state of the system. The $g_{\bullet O}(R)$ for window 1, fig. 6, shows successive peaks at 2.8, 4.1 and 5 Å. Assignment of these peaks to waters in the first hydration shell follows straightforwardly from a consideration of the excluded volume of methane and water molecules, as shown in the inset of fig. 6. The distribution function $g_{\bullet H}(R)$, fig. 7, is more complex because of the greater orientational possibilities, but the onset of probability at 1 Å is clearly consistent with a contact interaction. Structures representative of this type of configuration were extracted from the simulation, and a typical example is shown in fig. 8.
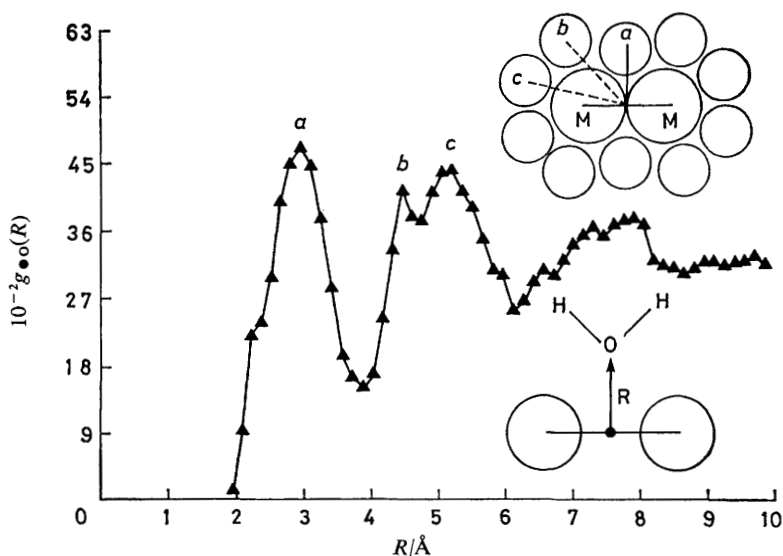
FIG. 6.—Calculated $g_{\bullet O}(R)$ for $[(CH_4)_2]_{aq}$ for window 1.

For window 2, the distribution function $g_{\bullet O}(R)$, fig. 9, shows a well developed peak at 1 Å. Examination of $g_{\bullet H}(R)$, fig. 10, shows dominant contribution from structures in which a single hydrogen atom of a water molecule intervenes between solutes, and the peak in $g_{\bullet O}(R)$ is clearly consistent with significant contributions from this structure. A structure corresponding to this configuration is shown in fig. 11.

Windows 3 and 4 are centred on solvent-separated values of the intersolute coordinate. The $g_{\bullet O}(R)$ and $g_{\bullet H}(R)$ for these two windows are very similar in appearance and we discuss here only the results from window 4. The $g_{\bullet O}(R)$, fig. 12, shows a strong peak at $R = 0$ corresponding to solvent-separated structures in which the
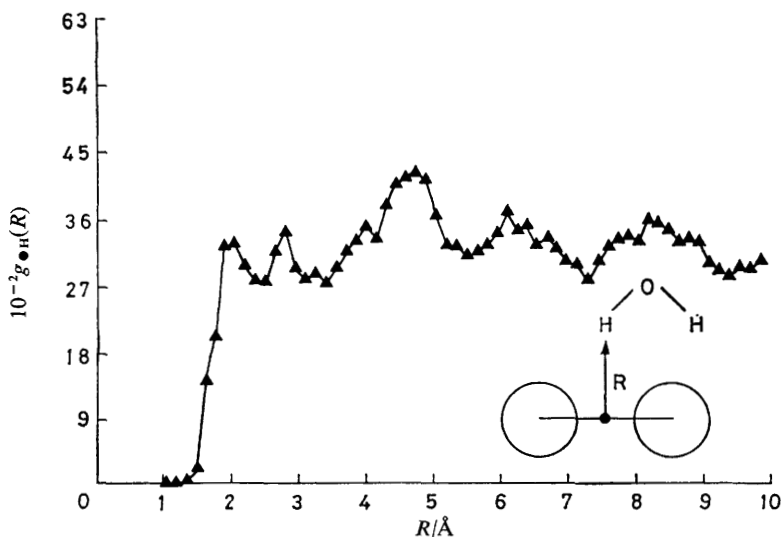
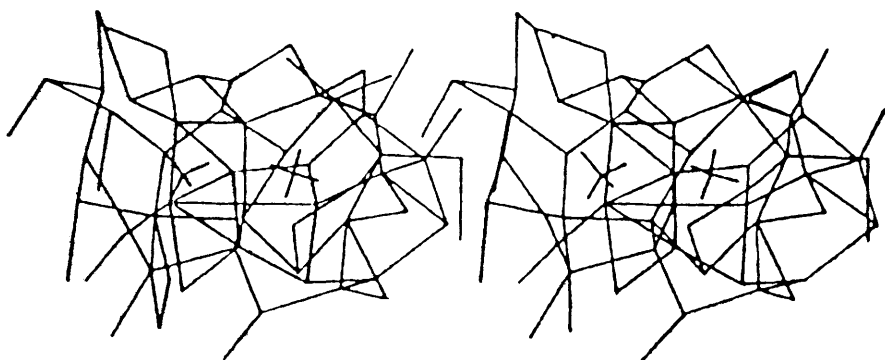FIG. 7.—Calculated $g_{\bullet H}(R)$ for $[(CH_4)_2]_{aq}$ for window 1.

FIG. 8.—Typical structure corresponding to the most probable configuration in window 1.

water oxygen atom intervenes, and a smaller peak at $R = 1$ Å corresponding to structures in which a water hydrogen intervenes. The $g_{\bullet H}(R)$ for window 4, fig. 13, falls off more gradually than the corresponding plot for window 2, as a consequence of the significant contributions from the structures in which the water oxygen intervenes. A solvent-separated structure extracted from the configuration is shown in fig. 14.

In conclusion, some comments on the molecular structures in fig. 8, 11 and 14 are in order. In viewing these structures, keep in mind that no one structure in a simulation is necessarily representative of the statistical state of the system, and structures arbitrarily chosen may be misleading. The urge to look at structures is nevertheless irresistible, and we present them here along with a strong *caveat emptor*. The structures presented here are given as computer-drawn Dreiding models, with all oxygens closer than 3.2 Å shown as bonded. Hydrogen atoms are included only for the methanes and the solvent-separated water molecule. Only those water molecules within 6.5 Å of the methane molecules are included, which amounts to *ca.* 70.

Extensive networking is found in all three cases displayed. Three-, four- and five-
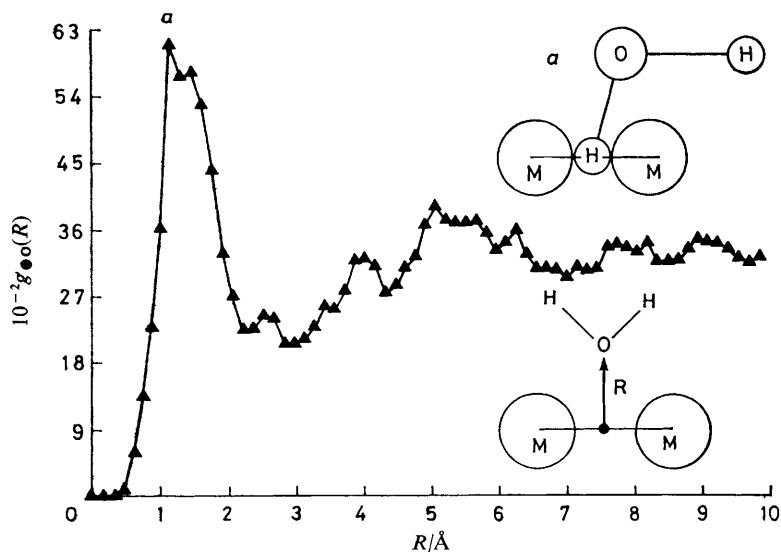

FIG. 9.—Calculated $g_{\bullet O}(R)$ for $[(CH_2)_4]_{aq}$ for window 2.

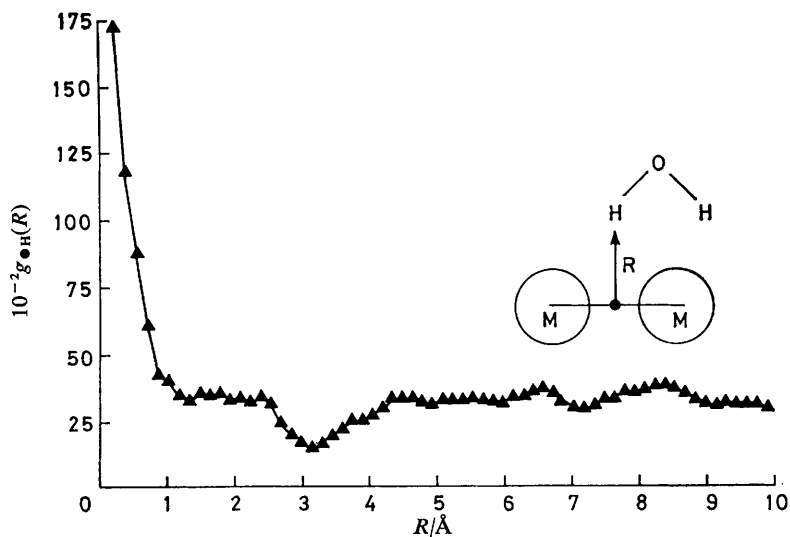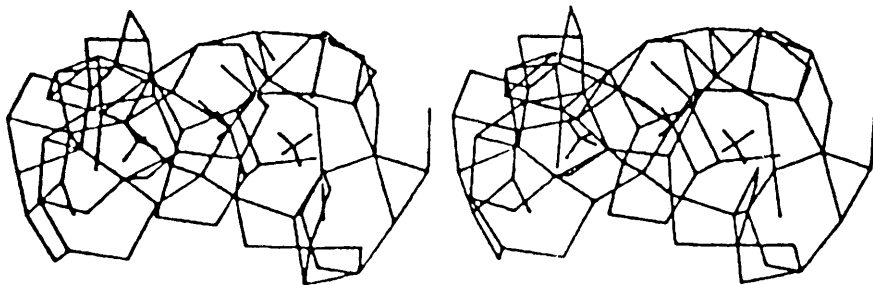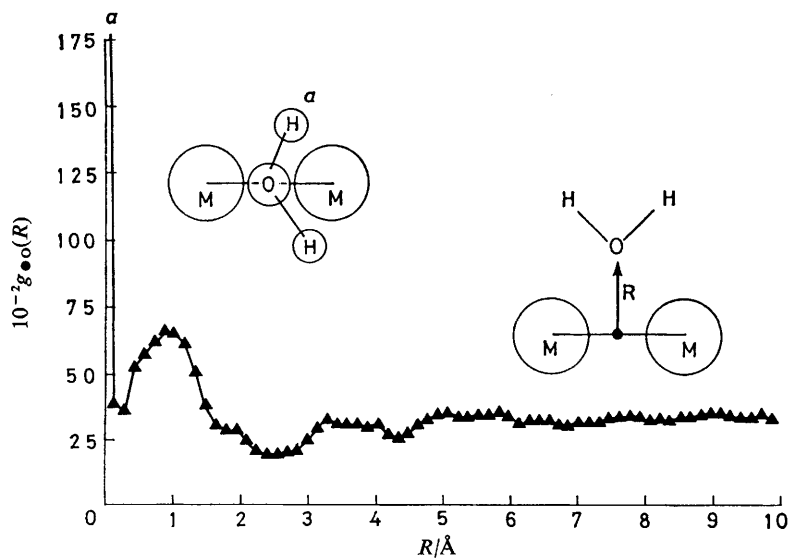FIG. 10.—Calculated $g_{\bullet H}(R)$ for $[(CH_4)_2]_{aq}$ for window 2.

FIG. 11.—Typical structure corresponding to most probable configuration in window 2.

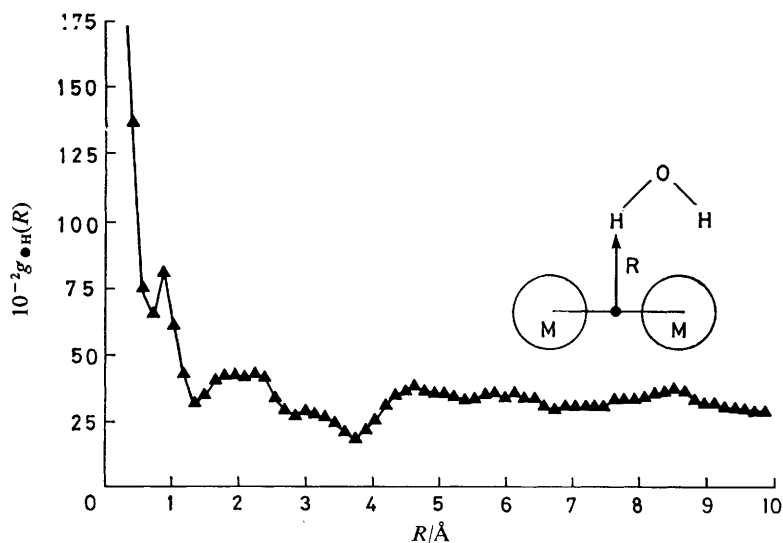FIG. 12.—Calculated $g_{\bullet O}(R)$ for $[(CH_4)_2]_{aq}$ for window 4.

FIG. 13.—Calculated $g_{\bullet H}(R)$ for $[(CH_4)_2]_{aq}$ for window 4.

coordinate waters are readily seen in all structures as expected. While the statistical indices of the calculations are consistent with the existence of clathrate-like contributions, the individual structures do not feature much which can be interpreted as regular clathrate polyhedra, although quite good individual pentagons can be found in all structures. The intervening water molecule in the solvent-separated structures in fig. 11 and 14 and the interaction of this molecule with the other waters is clearly evident.
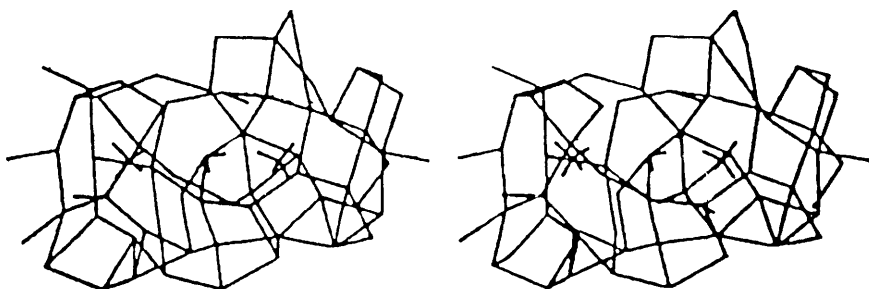

FIG 14.—Typical structure corresponding to most probable configuration in window 4.

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