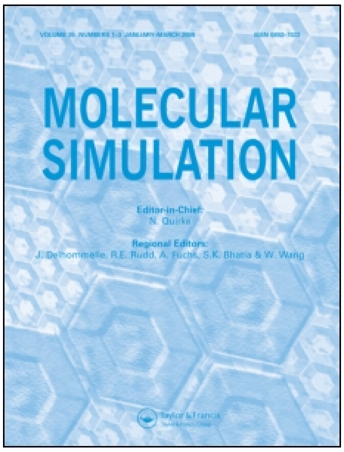

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SOLUTE-INDUCED WATER STRUCTURE: COMPUTER SIMULATION ON A MODEL SYSTEM

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Two series of Monte Carlo simulations have been carried out on a system consisting of 125 water molecules, one of which is kept fixed to simulate a water molecule whose mobility is restricted by a solute. The results are checked against similar simulations without restrictions, used as a control, and they show how the blocked molecule helps increase both the structural order and the connectivity of the hydrogen bond network. Cooperativity originating from proton polarizability of H-bonds and/or from many-body terms of interaction potentials cannot be involved since we use a rigid water model and ab initio pair potentials. The present findings are interpreted as indicative of a motion-dependent effect which is triggered by the blocked molecule and propagates along H-bonds. As has already been proposed, this effect might play a role in water-mediated solute–solute interactions.

KEY WORDS: Water molecules, Monte Carlo, computer simulation, solute–water interaction, hydration

INTRODUCTION

In the first protein hydration layer water is strongly bound [1]. Although high resolution MNR data suggest that it is not "ice-like" even at temperatures well below freezing [2], its mobility is restricted. Indeed, experiments indicate orientational times longer than in bulk water (up to 10^{-10} – 10^{-9} s rather than 10^{-12} s) [3, 4]. Thus, the water–water interaction field in the vicinity of a solute may be stronger than in the bulk water, where a larger motional averaging of that field occurs. One might then expect that the reduced mobility of the water molecules pinned to solutes or whose motional freedom is limited by solute hydrophobic surfaces, can affect the structure of the surrounding water. This and analogous effects have been considered to explain experimental results concerning different physical systems [5–8 and References therein].

In the present paper we report findings of Monte Carlo simulations performed on a system of 124 water molecules surrounding a water molecule whose position and orientation are kept fixed to simulate a water molecule pinned to a solute molecule. Our work aims to explore the possibility that solutes affect the structure of the solvent water via the reduced mobility of proximal water molecules. Using as a "solute" a blocked water molecule rather than an actual solute with its specific potentials offers the advantage of singling out effects that are motion-dependent, while keeping the rest unaltered.

The water molecules are modelled as rigid bodies and the water–water interaction is described in terms of ab initio atom–atom pair potentials. These assumptions enable us to discriminate between effects enhanced by reduced mobility, from others either related to many-body terms of the water–water potentials [3] or induced by proton polarizability of hydrogen-bonds [9].

RESULTS AND DISCUSSION

Two series of Monte carlo (MC) simulations have been conducted on a DEC VAX-11/750 computer using both Metropolis [10] and Preferential Sampling (PS) [11] algorithms. The system consisted of 125 water molecules confined within a cubic volume of side 15.53 Å (density 1 *g/cm*^{3}). The simulated temperature was 300 K. Periodic boundary conditions were used to model the condensed-phase environment and the configurational energy of the system was evaluated under the minimum image convention by assuming the ab initio (CI-SCF-LCAO-MO) pair potential MCY [12 and appendix A] for the water–water interaction.

In Figure 1, we report for the first series of simulations the evolution of the configurational energy of the system, each value being averaged over 2*10^5 successive configurations. The whole series is 3.2*10^7–moves long and includes five phases. After the equilibration phase, *a*, three phases follow in which the water molecule nearest to the center of the sample is kept blocked (*b*, *c*, and *e*) and one, *d*, in which all the

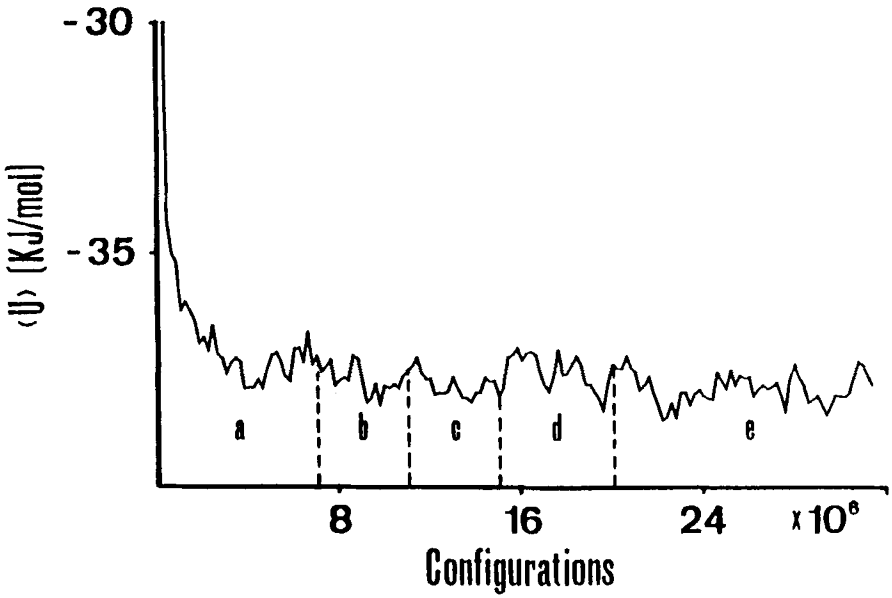

Figure 1 Evolution of the mean configurational energy, ⟨U⟩, for MC simulations of 125 water molecules at 300 K and density 1 g/cm^3, using MCY pair potentials. Each energy value was averaged over 2*10^5 moves. During *b*, *c* and *e* phases the central molecule was kept blocked; during *d* phase all molecules were left free to move. Preferential sampling was used in phase *b*.

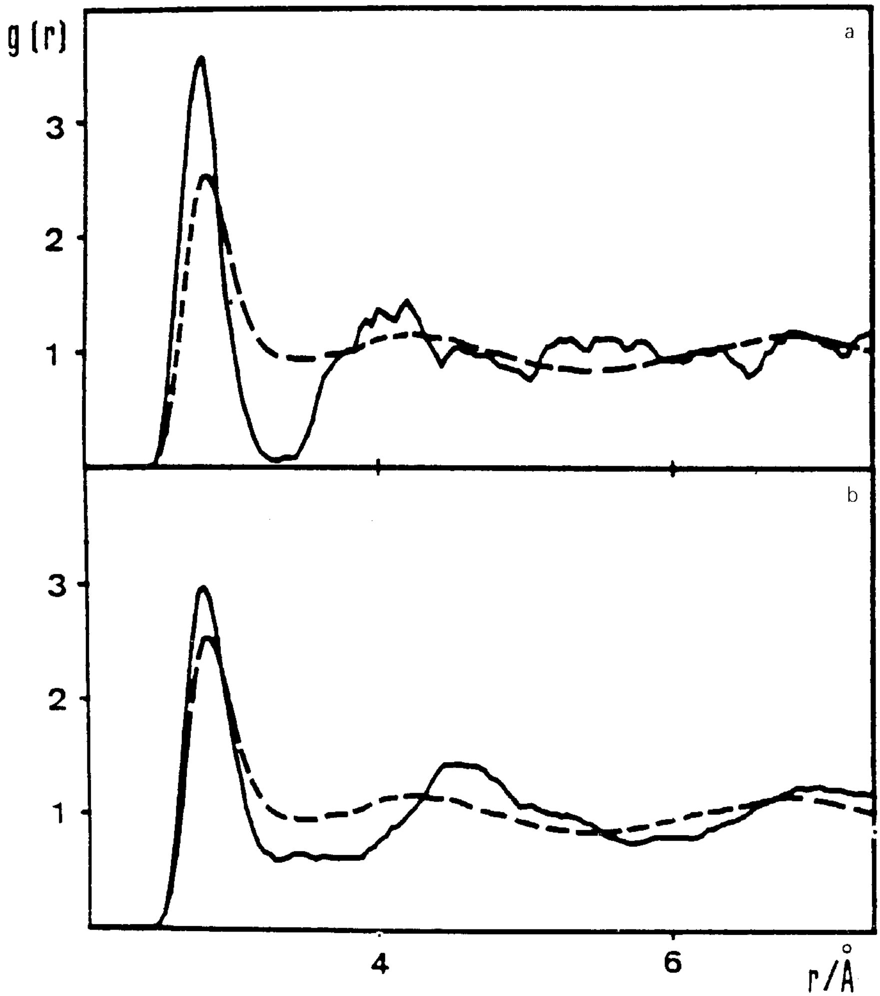

Figure 2 Oxygen-oxygen radial distribution functions (RDFs) relative to the first series of MC simulations a) RDF for the blocked water molecule (———); "total" g(r), which has been averaged over all the molecules of the sample (— — —). b) RDF averaged over the water molecules belonging to the first coordination shell of the fixed molecule (———) and averaged over all molecules of the sample non belonging to this shell (— — —), respectively.

molecules are free to move. During the *b* phase the PS scheme is used.

In Figure 2, oxygen–oxygen radial distribution functions (RDFs) are reported that have been evaluated over the last million configurations of phase *e*. In Figure 2a, we show the RDF relative to the water molecule that has been kept blocked (full curve) and the "total" RDF, which has been averaged over all the molecules of the system

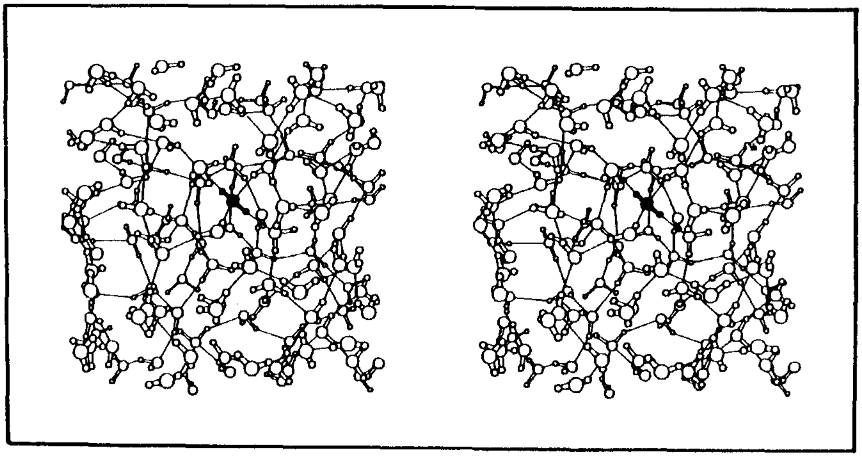

Figure 3 Stereoviews of a typical configuration taken from the phase *e* of Figure 1. The blocked molecule has been shadowed.

(dashed). In Figure 2b RDFs are shown for the molecules that belong to the first hydration shell of the blocked molecule (full curve), and for all the other molecules of the sample (dashed). As one can see, the values of the first maximum and the first minimum of the RDF relative to the blocked molecule are, respectively, higher and lower than the corresponding values of the total RDF. The same features, although less remarkable, characterize the RDF of the molecules belonging to the first hydration shell of the blocked molecule (Figure 2b). Further, the fixed molecule is found to form four hydrogen-bonds, as one can see from Figure 3, where a typical configuration is shown taken from the *e* phase. For comparison, we report in Figure 4 a typical

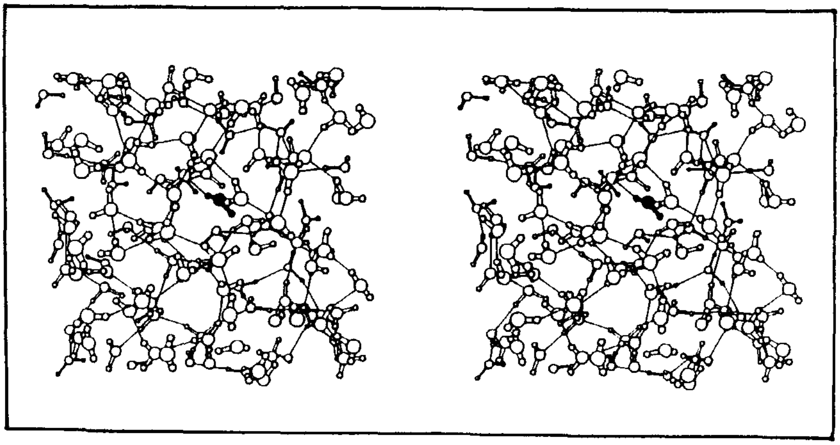

Figure 4 Stereoviews of a typical configuration taken from the last part of a $8 * 10^6$ – move MC simulation at T = 300 K and density 1 g/cm^3. The system consisted of 125 water molecules all free to move. The simulation was started from the end configuration of *e* phase of Figure 1. The shadowed molecule is the same as in Figure 3.

configuration, taken from the last part of a $8*10^6$ - move MC simulation, where all the molecules were left free to move. This simulation was started from the last configuration of *e* phase after releasing the blocked molecule. The present results suggest that an increase of structural order occurs among the molecules surrounding the blocked water molecule, as compared with the rest of the sample. This effect appears to spread, although less significantly, to the molecules belonging to the first hydration shell of the blocked molecule (Figure 2b). Also, around this molecule a region is found which is characterized by lower mean density than in the bulk water. This feature will be discussed below.

Previous analyses of the connectivity properties of MD simulated ST2 [13] water have evidenced small regions ("patches") of spatially correlated four-bonded water molecules [14]. In order to discriminate the increase of local order around the blocked molecule from a spontaneous occurrence of a small four-bonded patch, a second and independent series of MC simulations was conducted. To this purpose, two parallel $1.2*10^7$ - move simulation sequences (I and II) were performed on systems consisting of 125 water molecules at the same density and temperature as in the first series of simulations. The only difference between the two sequences was that in the sequence I the molecule closest to the center of the sample (molecule number 8) was kept blocked. The MC configurations of both sequences were generated from the *same* equilibrated configuration using the *same* series of random numbers. To accelerate the

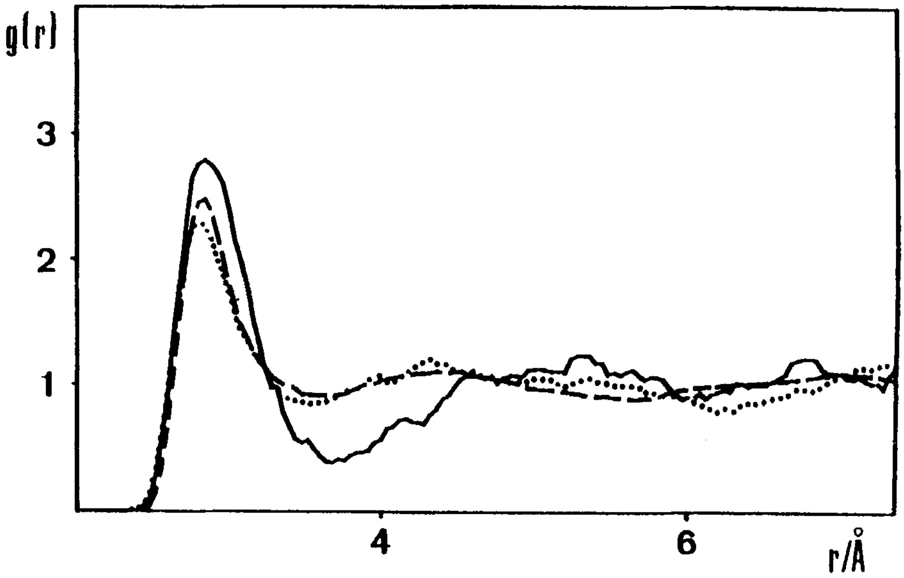

Figure 5 Oxygen oxygen radial distribution functions relative to the second series of MC simulations calculated using 10^4 configurations, equally spaced over the last four million configurations of the two parallel sequences I and II: RDF for the blocked water molecule along the sequence I (———); RDF for the same molecule left free to move along the sequence II (· · · · ·). For comparison, we report the "bulk" RDF evaluated over a 10^6 - move MC run (with all molecules free to move), whose last configuration was used to start both I and II sequences (— — —).

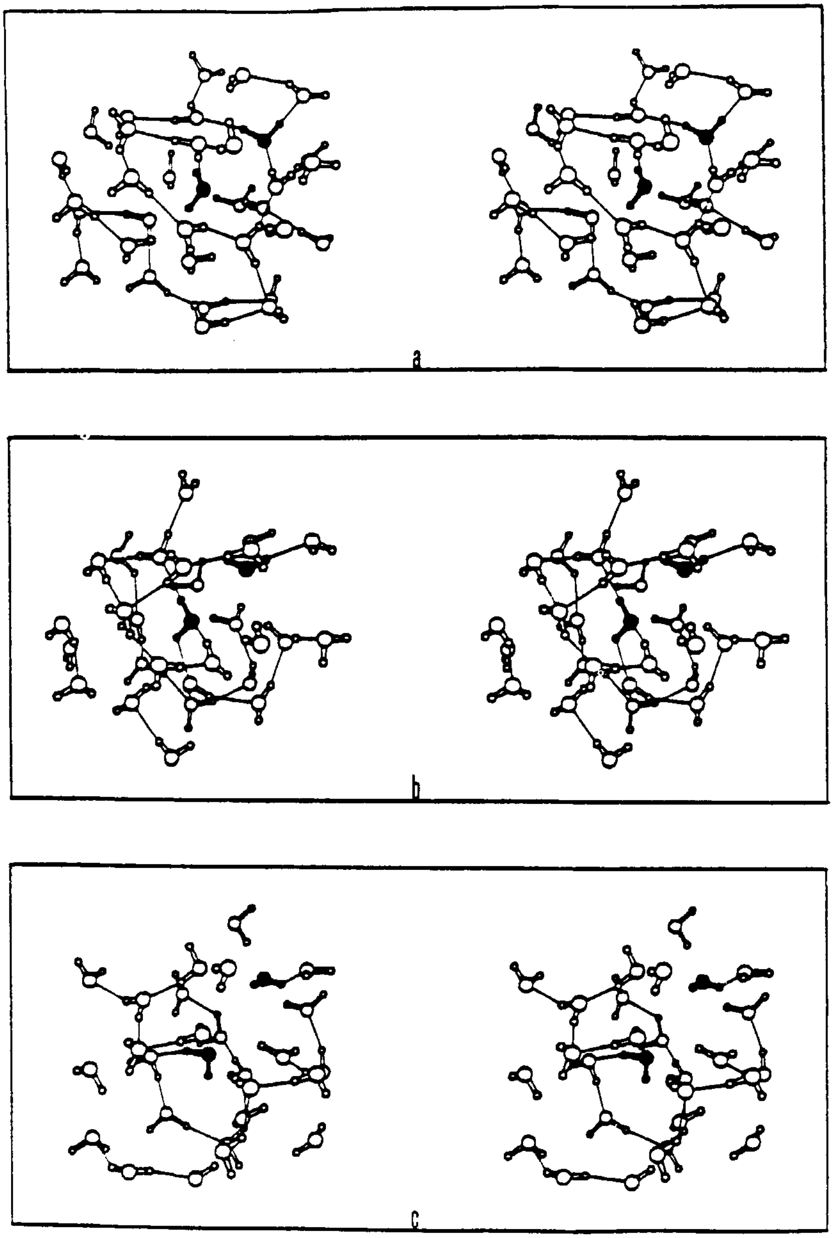

Figure 6 Stereoviews of the central region of a) the configuration from which both I and II simulation sequences were started; b) a typical configuration at the end of sequence I; c) a typical configuration at the end of sequence II. The central shadowed molecule (molecule No. 8) was kept fixed during the sequence I. The lateral shadowed molecule is the molecule No. 94 (see text for details).

simulation convergence after blocking, for both sequences the PS algorithm was used with $1/r$ weight, being r the oxygen–oxygen distance from molecule 8 (kept blocked during the simulation sequence I and left free to move during the sequence II).

In Figure 5, we report oxygen–oxygen RDFs relative to molecule 8, averaged over 10^4 configurations spanning the last four million configurations of both simulation sequences. For comparison, the RDF of "bulk" water is also reported, that was evaluated over a 10^6 – move MC run (with all molecules free to move), whose last configuration was used to start both I and II simulation sequences. As one can see, the values of the first maximum and of the first minimum of RDF relative to the blocked molecule (full line) are, respectively, higher and lower than the corresponding value of the RDF relative to the same molecule, when left free to move (dotted line). This result is in agreement with the findings of the first series of simulations (Fig. 2) suggesting an increase of local order around the blocked molecule. The position of the first minimum, however, occurs at a larger distance for the RDF of the blocked molecule than for the "bulk" RDF. Further, at the end of the sequence I the blocked molecule is most frequently found hydrogen bonded to three rather than to four molecules, as it was found at the end of the first series of simulations. These differences are probably due to the simulation being too short to induce a complete rearrangement of the molecules surrounding the blocked molecule.

The length of the simulation necessary for this restructuring is likely to depend on the environment in the initial configuration of the molecule to be blocked, and it could be remarkably long, if in this configuration a particularly stable molecular arrangement is present, which is not prone to accept the structural changes that the blocking of that molecule will induce. In Figure 6a, we show the central region of the initial configuration (common to both I and II parallel sequences). As this figure shows, the central shadowed molecule (molecule No. 8), which will be then blocked during the simulation sequence I, is singly hydrogen bonded, whereas the lateral shadowed molecule (molecule No 94) exhibits three hydrogen bonds. The molecule No. 94, which belongs to the first hydration shell of molecule 8, interacts rather repulsively (17 kJ/mol) with this molecule. In Figure 6b, the central region of the sample is shown as it appears from a statistically significant configuration at the end of the simulation sequence I. The situation is here reversed, since the blocked molecule exhibits three hydrogen bonds, whereas molecule 94 is now singly bonded. For comparison, we show in Figure 6c the central region of a statistically significant configuration taken from the end of the sequence II. These findings suggest that, although a more ordered restructuring around molecule 8 was initially not favored, it has been, at least partially, reached at the end of sequence I. It is worth noting that, as mentioned above the orientational time of water proximal to some proteins has been estimated to be of the order of 10^{-9} s [4]. The time equivalent [15] of our second series of MC simulations is less than one hundred times lower.

Further evidence supporting the view of an increased order induced by a blocked water molecule on its environment is provided by Figure 7, where we report the local density around the molecule No. 8, calculated as differences between its running coordination numbers ($n(r) = 4\pi\varrho\int g(r)\, r^2\, dr$, being ϱ the number density)

$$\Delta n(r) = n_{\mathrm{FR}}(r) - n_{\mathrm{FIX}}(r)$$

where $n_{\mathrm{FIX}}(r)$ and $n_{\mathrm{FR}}(r)$ are the running coordination number relative to the molecule No. 8 averaged over the last four million configurations of the simulation sequence I and II, respectively. As one can see, near this molecule the density is higher in the

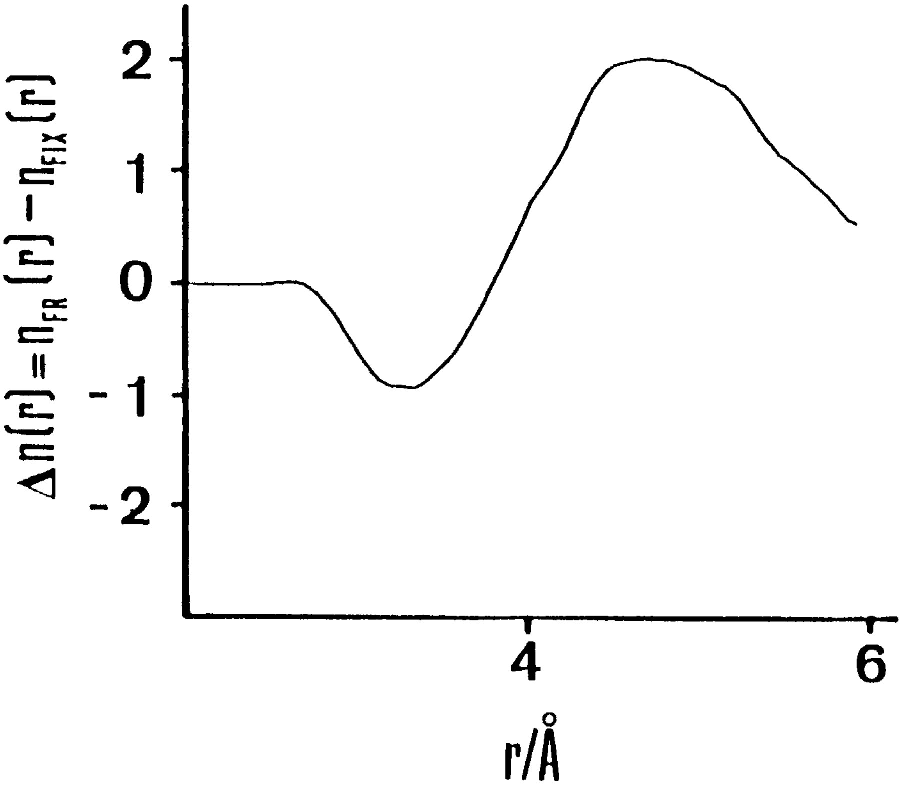

Figure 7 Difference, $\Delta n(r)$, between running coordination numbers relative to the molecule No. 8 throughout the last four million configurations of the simulation sequences II ($n_{FR}(r)$) and I ($n_{FIX}(r)$).

sequence I than in the sequence II. A larger reverse behavior takes place at larger distances, and a maximum in the mean density difference $\Delta n(r)$ occurs at ca. 4.7 Å. Analogous findings have been reported in studies of density fluctuations conncected to the occurrence in simulated ST2 water of patches of four-bonded molecules [14]. Those results were interpreted as indicating that the neighbors of a four-bonded water molecule crowd at 2.85 Å and that there are more molecules near non-four-bonded molecules than around four-bonded molecules. Similarly, the present results show that i) the surrounding molecules crowd around the blocked molecule at ca. 2.84 Å, where the first maximum of the RDF relative to the blocked molecule occurs; ii) at larger distances more water molecules are found near the molecule No. 8 when it is left free to move than when it is blocked.

ANALYSIS OF THE HYDROGEN BOND NETWORK

In order to see if and to what extent the H-bond network of the surrounding water is affected by the presence of a blocked water molecule, we followed the approach that has been developed previously to study the connectivity properties of MD simulated ST2 water [16, 17]. To decide if two molecules are hydrogen bonded, the hybrid energetic–geometric definition [17] was used, and the H-bond network characteristics were evaluated by scanning a range of 32 threshold energy values, V_{HB}, equally spaced between -4.2 and -22.8 kj/mol. To each V_{HB} value corresponds a mean number of hydrogen-bonds per molecule, n_{HB}. In finite systems, as percolation is approached, the larger clusters merge in a cluster (we shall call it "infinite" cluster) spanning the whole volume [16]. Results are reported here concerning the probability that molecules surrounding the blocked molecule belong to the infinite cluster. For both simulation sequences (I and II), values of this probability *vs*. n_{HB} are shown in Fig. 8 for molecules that throughout the last four million configurations are found inside a sphere of radius 4.7 Å centered on the molecule No. 8. As one can see, the system with the blocked molecule has a significantly higher tendency to percolate. This indicates that

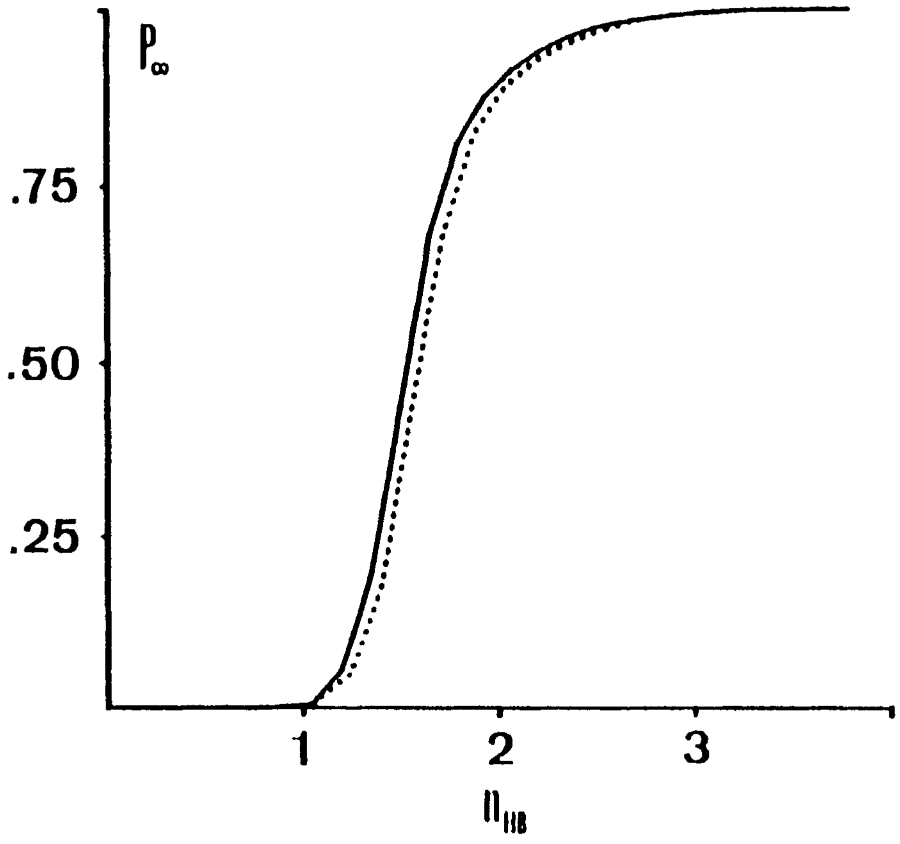

Figure 8 Probability, P_∞, *vs* the average number of H-bonds per molecule, n_{HB}, that the molecules within a sphere of 4.7-Å radius centered on molecule 8, belongs to the "infinite" cluster, as averaged over 10^3 configurations spanning the last four million configurations of simulation sequence I (———) and sequence II (· · · · ·).

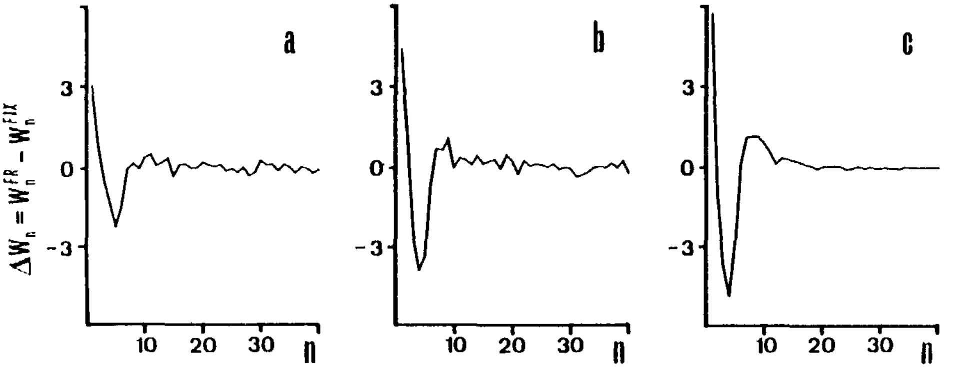

Figure 9 Percentage difference, ΔW_n, between the weight fraction of molecules belonging to nets of size n vs the cluster size, n, for molecules within a sphere of 5-Å radius centered on the molecule No. 8. The difference has been evaluated over 10^3 configurations evenly spanning the last four million configurations of the simulation sequences I (W_n^{FIX}) and II (W_n^{FR}), using the following values of energy threshold (in kJ/mol: a) -16.2; b) -17.4; c) -18.6.

the presence of this molecule perturbs the surrounding H-bond network and favours the formation of larger clusters in the surrounding region, as compared with the analogous region around the same molecule when it is left free to move. Further work is in progress to study energetic and topological features of the H-bond network, and to perform Molecular Dynamics simulations of systems including one or more water molecules with reduced mobility.

These results are confirmed by the data shown in Figure 9, where percentage differences are reported between the values of weight fractions, W_n, (i.e. the probability values that a molecule is a member of a net with n molecules [16]) evaluated over 10^3 configurations spanning the last four million configurations of sequence II (W_n^{FR}) and the corresponding values relative to sequence I (W_n^{FR}), vs. the size, n, of the net. These data refer to molecules that are found inside a sphere with 5 Å radius centered on molecule 8 and are calculated for three different values of energy threshold V_{HB}. For all of these energy values, the system with the blocked molecule exhibits a markedly higher preference to form clusters. These data together with those reported in Figure 7 suggest that the presence of a blocked water molecule triggers a mechanism that brings about a lower density packing of the surrounding molecules and a higher hydrogen bond connectivity. Similar characteristics, which become more relevant as temperature decreases, have been evidenced with MD simulations of ST2 water for patches of four-coordinated molecules [14b]. It has been argued that the local decrease of mean density and mean entropy associated with these patches could explain in terms of entropy and volume fluctuations [18, 19] the observed thermodynamic anomalies of liquid water, which become more pronounced as temperature decreases. The present results suggest that a similar behavior could be relevant even at higher temperatures, and be originated at spots or areas of solute surfaces capable of hindering the mobility of proximal water molecules. In this way, the origin of the observed positive values of solution heat capacity of solutes capable of restraining the motional freedom of vicinal water molecules [20] may find a more detailed microscopic interpretation.

CONCLUSIONS

The main conclusion one can draw from the present MC simulations of MCY water is that a blocked water molecule induces higher structural order among the surrounding water molecules. If the simulation is extended to equivalent times comparable with correlation times of water molecules pinned to solute biomolecule, the blocked molecule likely becomes four-coordinated. In any case, around this molecule, yet not very close to it, a region is found, which is characterized by lower mean density and higher hydrogen-bond network connectivity as compared with bulk water. Similar features have been evidenced for patches of four-bonded molecules in MD simulations of ST2 water spontaneously and progressively occurring as temperature is decreased [14]. The way our second series of simulations was performed rules out the possibility that the present results arise from the spontaneous occurrence of a small patch of this kind around the blocked molecule. Further, as well known, the MCY water model is less four-coordination prone that ST2.

The present findings may be interpreted in terms of a stereodynamic mechanism already surmised [5–8] that has stimulated a number of experiments based on solvent deuteration in order to enhance its effects [7]. The central idea is that solute molecules could help establish an order parameter in their environmental water *via* a stabilizing feedback between angular motional modes of water molecules and potentials restraining them. This feedback is thought to involve H-bond correlations and sharpening of potential wells, induced by lower motional averaging [8]. In our case, the "solute" is simulated by the blocked water molecule, so avoiding the complication of using specific solute–water potentials. Further, by modelling the water molecules as rigid bodies and the water–water interaction by ab-initio pair potentials, one can exclude cooperative effects originating from proton polarizability of H-bonds [9] and/or many-body contributions to the interaction potentials [13]. The present results can thus be interpreted as consistent with a motion-dependent effect which is triggered by blocking a water molecule and may be sustained by the above mentioned feedback mechanism. It is worth noting that, as previous MD simulations suggest [17], weak H-bond correlations can be present even if the water–water interaction is modelled by pair potentials.

It has been argued that the above mentioned feedback mechanism could be capable of playing a role in the stereodynamic behavior of water and aqueous solutions [7, 8]. In particular, it could be involved in the solute–solute water-mediated interaction. According to this view, the present results may help to understand how a solute can affect the water structure *via* the effects that motionally restricted water molecules belonging to its hydration layer induce among the surrounding molecules, and how these effects can propagate into the solvent. Moreover, since in our system the density fluctuations and the extent of the lower density regions are larger than for the patches of four-bonded molecules occurring in pure water, one might speculate that the local restructuring of water surrounding solutes could play a role in molecular recognition.

Long-lived clathrate-like cages of H-bonds are thought to exist around hydrophobic surfaces of solutes, on the grounds of large negative excess entropies of mixing [20, 21], decreased densities [22], increased viscosities [23], and computer simulations results [24–26]. These ordered structures are characterized by local low density. This perhaps suggests that the present simulations can also be representative of situations where partial immobilisation (and/or a longer residence time) of solvent molecules is imposed by hydrophobic surfaces. Recent micro- and macroviscosity studies have allowed quantitative evaluations of these structures and suggest that in the series of alcohols studied, partial pinning of a water molecule at the OH group contributes to the building-up of such structures [27].

Finally, it is here worth noting that completely inhibiting the movement of a water molecule to simulate its attachment to a pinning point of a solute molecule is not unreasonable, considering that the whole second series of the present simulations would be equivalent to a MD simulation extending to less than 10 ps [15], that is one or two orders of magnitude less than the orientational time of water molecules proximal to solutes [3, 4].

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APPENDIX

The ab initio (CI-SCF-LCAO-MO) atom-atom pair potential MCY is expressed by the following analytical form [12, 28]:

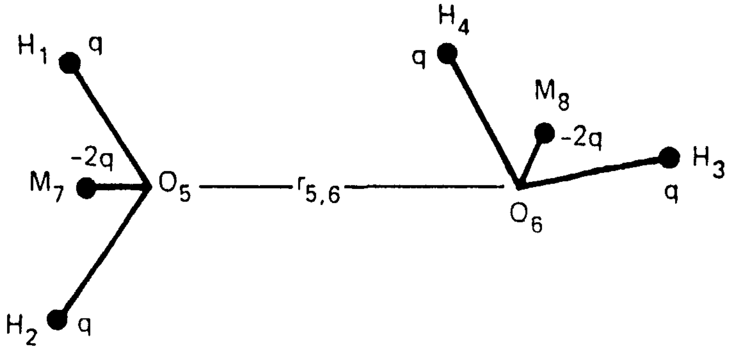
$$\begin{aligned} V(\mathrm{i,j}) = {} & q^2\,[1/r_{13} + 1/r_{14} + 1/r_{23} + 1/r_{24}] + 4q^2/r_{78} - 2q^2\,[1/r_{18} + 1/r_{28} + 1/r_{37} \\ & + 1/r_{47}] \\ & + a_1\, exp\,(-b_1 r_{56}) \\ & + a_2\,[exp\,(-b_2 r_{13}) + exp\,(-b_2 r_{14}) + exp\,(-b_2 r_{23}) + exp\,(-b_2 r_{24})] \\ & + a_3\,[exp\,(-b_3 r_{16}) + exp\,(-b_3 r_{26}) + exp\,(-b_3 r_{35}) + exp\,(-b_3 r_{45})] \\ & - a_4\,[exp\,(-b_4 r_{16}) + exp\,(-b_4 r_{26}) + exp\,(-b_4 r_{35}) + exp\,(-b_4 r_{45})] \end{aligned}$$

where the parameter values (in kcal/mol and Å) are,

$$\begin{array}{lll} a_1 = 1088213.2 & a_2 = 666.3373 & a_3 = 1455.427 \\ a_4 = 273.5954 & b_1 = 5.152712 & b_2 = 2.760844 \\ b3 = 2.961895 & b4 = 2.233264 & q^2 = 170.9389 \end{array}$$

The geometry of the water molecule is defined by

$$r_{\mathrm{om}} = 0.2677\,\text{Å} \qquad r_{\mathrm{oh}} = 0.9572\,\text{Å} \qquad h\hat{o}h = 104.5^\circ$$



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