Diffusion of Solvent around Biomolecular Solutes: A Molecular Dynamics Simulation Study

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ABSTRACT Effects of the macromolecular solute on the translational mobility of surrounding solvent water, and Na^+ and Cl^- ions are investigated by molecular dynamics (MD) simulation. Using MD trajectories of myoglobin and $d(C_5T_5) \cdot d(G_5A_5)$ DNA decamer of high quality and length, we determine the average diffusion coefficients for all solvent species as a function of distance from the closest solute atom. We examine solvent mobility in the directions parallel and perpendicular to the solute surface and in proximity to three different classes of solute atoms (oxygens, nitrogens, and carbons). The nature and the magnitude of the solute effects on water diffusion appear to be very similar for protein and DNA decamer. The overall diffusion rate at the interface is lower than in the bulk. The rate is higher than the average in the direction parallel to the solute surface, and lower in the direction normal to the surface, up to 15 Å away from the solute. The rate is also lower in the solvation shells of the macromolecules, producing characteristic depressions in the radial profiles of the diffusion coefficient that can be correlated with peaks in the corresponding radial distribution functions. The magnitude of these depressions is small compared to the overall change in solvent mobility at the interface. Similar features are observed in the radial profiles of the diffusion coefficient of sodium and chlorine ions as well.

INTRODUCTION

It is well known that both mobility and structural organization of solvent in the immediate vicinity of biological macromolecules differ from those of the bulk solvent. This has been shown by x-ray crystallography (Teeter, 1991; Jiang and Brünger, 1994; Phillips and Pettitt, 1995; Burling et al., 1996) and NMR (Brunne et al., 1993), as well as in a number of theoretical studies, particularly molecular dynamics (MD) simulations (Wong and McCammon, 1987; Teeter, 1991; Beveridge et al., 1993; Phillips and Pettitt, 1995). The diffusion coefficient is a measure of solvent mobility, which is often used in such studies (Phillips and Pettitt, 1995). Because there are experimental values for both the self-diffusion coefficient of neat water (Hertz, 1973) and of certain common ions in water (Tyrrell and Harris, 1984), the accuracy of simulations may readily be tested.

The diffusion coefficient D is related to the slope of the mean square displacement of solvent molecules by the Einstein relation (Allen and Tildesley, 1987), which in N dimensions reads

$$D = \frac{1}{2N} \lim_{t\to\infty} \frac{d}{dt} \langle |\vec{r}_i(t) - \vec{r}_i(0)|^2 \rangle \qquad (1)$$

where $\vec{r}_i(t)$ is the position vector of the solvent molecule i at time t, and the brackets $\langle\rangle$ indicate that the average is taken over both the time origins and solvent molecules. Use of the Einstein relation (Eq. 1) for the determination of D presumes a linear increase of the mean square atomic displacement with time. This condition is usually fulfilled for most homogeneous isotropic three-dimensional liquids on time scales longer than a few picoseconds (Bizzarri et al., 1996). Here we shall not consider the short time periods during which molecular motion is non-Brownian and the Einstein relation does not hold. However, a linear dependence of the mean square displacement in time should be always verified (Abseher et al., 1996; Bizzarri et al., 1996).

Despite its conceptual simplicity, determination of D from molecular dynamics data has pitfalls. Conflicting results are reported for the value of the self-diffusion coefficient of bulk water for different commonly used water models (Berendsen et al., 1981; Jorgensen et al., 1983; Teeter, 1991; Lau et al., 1994). The experimental value of the water diffusion coefficient is 0.23 $Å^2$/ps (Hertz, 1973). A correct reproduction of this experimental value is an important test for validating existing water models (Berendsen et al., 1981; Jorgensen et al., 1983; Lau et al., 1994). Although a favorable agreement exists in many cases, some water models apparently fail this test (Jorgensen et al., 1983; Lau et al., 1994; Lounnas et al., 1994). Commonly used approximations, for example, the use of cutoffs and switching functions in the treatment of long-distance electrostatic interactions, were shown to affect the water diffusion coefficient (Smith and Pettitt, 1991; Alper et al., 1993a,b; Lau et al., 1994). Additional irregularities in the water diffusion calculations may be introduced by finite system size and periodic boundary conditions (Lau et al., 1994). Thus even when the bulk D value found in a particular simulation actually matches that obtained experimentally, such agreement may be artifactual (Lau et al., 1994).

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When one considers the interface between water and a solute of high molecular weight, it may be necessary to treat diffusion coefficient as a local property due to heterogeneity of the solute surface. This is especially true for such macromolecular solutes as proteins (Lounnas et al., 1994), biological membranes (Raghavan et al., 1992; Alper et al., 1993b; Chiu et al., 1995), and nucleic acids, but may be also useful for small molecules (Wang et al., 1996). One may choose to compute the local diffusion coefficient in the volume elements around specific sites on the solute surface (Brooks and Karplus, 1989; Komeiji et al., 1993; Wang et al., 1996), report average values in radial shells or flat slabs of varying thickness (Abseher et al., 1996; Alper et al., 1993b), or create radial profiles (Wong and McCammon, 1987; Ahlström et al., 1988; Tirado-Rives and Jorgensen, 1990; Raghavan et al., 1992; Hartsough and Merz, 1993; Lounnas et al., 1994; Norin et al., 1994; Chiu et al., 1995; Muegge and Knapp, 1995; Bizzarri and Cannistraro, 1996; Bizzarri et al., 1996). In some cases the components of D that are parallel and perpendicular to the solute surface are reported (Ahlström et al., 1988; Raghavan et al., 1992; Chiu et al., 1995; Bizzarri and Cannistraro, 1997). Alternatively, it is possible to calculate a distribution of local diffusion coefficient values on a rectangular grid (Lounnas et al., 1994).

There have been a number of attempts to investigate the influence of different solute surface chemical groups on the mobility of the surrounding solvent, in particular, whether the water diffusion is faster in proximity to polar, charged, or apolar protein groups (Levitt and Sharon, 1988; Brooks and Karplus, 1989; Teeter, 1991; Komeijii et al., 1993; Wang et al., 1996). No definite conclusions about such influence have been made, because results reported for different simulations are in conflict with each other (Levitt and Sharon, 1988; Brooks and Karplus, 1989; Teeter, 1991; Rocchi et al., 1997), and in other cases no general trend has been found (Komeijii et al., 1993; Wang et al., 1996).

However, when spatial distributions of the local diffusion coefficient values are considered, many interesting effects become evident. First, the solvent mobility in the vicinity of the solute is restricted. This is particularly easy to see in the radial profiles of the local diffusion coefficient (Wong and McCammon, 1987; Ahlström et al., 1988; Tirado-Rives and Jorgensen, 1990; Hartsough and Merz, 1993; Lounnas et al., 1994; Norin et al., 1994; Muegge and Knapp, 1995; Bizzarri and Cannistraro, 1996; Bizzarri et al., 1996). In other simulations, it has been found that translational diffusion in the first solvation shell of a typical globular protein is retarded to between a third (Abseher et al., 1996) and a fourth (Knapp and Muege, 1993) that of bulk water. Similar observations hold with regard to the rate of solvent diffusion in the directions parallel and perpendicular to the solute surface: diffusion perpendicular to the surface is slower (Chiu et al., 1995; Bizzarri and Cannistraro, 1997), whereas lateral diffusion as almost as fast as in the bulk (Muegge and Knapp, 1995), or even somewhat faster (Chiu et al., 1995). Some relative reduction of the solvent mobility in the hydration shell of small molecules occurs as well, although to a lesser degree, as has been shown for α-maltose by Wang et al. (1996).

Another feature present in many earlier simulations is the apparent existence of hypermobile water in the 7–10-Å range away from solute (some older work reviewed by Teeter, 1991; Ahlström et al., 1988; Hartsough and Merz, 1993; Lounnas et al., 1994; Norin et al., 1994; Raghavan et al., 1992; Tirado-Rives and Jorgensen, 1990). This elevated water mobility is always observed in the same range as the electrostatics cutoff and is appearently a simulation artifact caused by truncation of the electrostatic forces (Alper et al., 1993a). It is eliminated when significantly long cutoffs or Ewald summation is used (Abseher et al., 1996; Alper et al., 1993a).

Water mobility in the immediate vicinity of the protein may be perturbed to such a degree that the motion of tightly bound surface water molecules can no longer be described as diffusive. In the simulation of fully hydrated ubiquitin (Abseher et al., 1996), water in the first hydration shell did not achieve the diffusive regime within 100 ps. Apparent deviations from the Einstein relation have also been observed in the MD simulations of fully and partially hydrated plastocyanin (Bizzarri and Cannistraro, 1996, 1997; Bizzarri et al., 1996). These effects are especially evident for a partially hydrated protein (Bizzarri and Cannistraro, 1996, 1997; Bizzarri et al., 1996). It has been suggested that spatial (protein surface roughness) and temporal disorder (distribution of water residence times) intrinsic to such systems is responsible for this behavior (Bizzarri et al., 1996; Bizzarri and Cannistraro, 1997).

Irrespective of the definition of the local diffusion coefficient, all of these methods involve restrictions on the volume used in the calculation, inevitably leading to a substantial increase in the statistical error of the averages. In all cases where the statistical error is reported (Alper et al., 1993a,b; Komeiji et al., 1993; Muegge and Knapp, 1995; Wang et al., 1996), it is found to be relatively large, ranging from 15% (Wang et al., 1996) to 30% (Komeiji et al., 1993) to almost 100% (Muegge and Knapp, 1995) of the average D value for the particular simulation. This implies that there is a large spread in the individual values of the mean square displacement $\langle|\vec{r}_i(t) - \vec{r}_i(0)|^2\rangle$ when the calculation is restricted to a small volume of interest (on the order of 1–10 $Å^3$), and that the number of data points accumulated in the studies hitherto presented is simply not sufficient for an accurate determination of the averages. In addition, the time scale used in the most MD simulations previously studying this phenomenon (a few hundred picoseconds or less) may not be enough for a proper convergence of the structural properties of even relatively rigid solutes, such as DNA (Feig and Pettitt, 1997), which will also affect the solvent structure observed in the simulation. This leaves one with no choice but to continue the simulations for a sufficiently long period of time to achieve meaningful convergence (Feig and Pettitt, in this issue).

The goal of this paper is to carry out an analysis of solvent diffusion for different biomolecular systems and compare them. We focus on the average and global effects exerted by a macromolecular solute on the mobility of surrounding solvent rather than on the detailed description of diffusion around specific solute groups. We base our study on the two molecular dynamics simulations of high quality and duration that were performed recently by this group (Andrews et al., 1998; Feig and Pettitt, 1997). We describe a new, simple method for determination of the components of the diffusion coefficient in perpendicular and parallel directions in relation to the surface of a macromolecular solute. We then present the results of an analysis of solvent diffusion around two biologically important solutes: sperm whale myoglobin and d(CCCCCTTTTT)·d(GGGGGAAAAA) DNA decamer. Several comparisons are made between features that are similar, and differences induced by the differing chemistries of these systems are noted.

MATERIALS AND METHODS

Molecular dynamics simulations

Both molecular dynamics simulations used for this analysis have been reported in detail previously (Andrews et al., 1998; Feig and Pettitt, 1997). Therefore, only the brief accounts of the simulation set-up will be presented here. Both solutes were fitted to a consistent frame of reference before analysis.

Myoglobin

The all-atom CHARMM-23 parameter set (MacKerell et al., 1992) was used to model a single sperm whale myoglobin molecule (Protein Data Bank (Bernstein et al., 1977) entry 2 mgk; crystal structure by Quillin et al., 1993) solvated by 3717 flexible TIP3P (Jorgensen et al., 1983) water molecules in the 60.4 Å × 54.7 Å × 40.7 Å box under periodic boundary conditions. The system was prepared through a preliminary series of energy minimization and heating steps, during which the temperature was gradually increased from 50 K to 294 K over 30 ps. The heating stage was followed by equilibration at 294 K for 200 ps. Equations of motion were solved with a 0.5-fs time step without constraints. Electrostatic interactions were treated with a 13-Å cutoff and a potential-based switching function beginning at 10 Å. The trajectory was continued for a total of 1.1 ns, of which the last 900 ps was chosen for analysis.

DNA

Starting from model-built canonical A-DNA (Quanta, Molecular Simulations), the decamer d(CCCCCTTTTT)$_2$ was simulated in the number, volume, temperature ensemble at 300 K with the most recent AMBER all-atom nucleic acid force field (Cornell et al., 1995). Solvation in 2285 explicit TIP3P (Jorgensen et al., 1983) water molecules, 18 Na^+ counterions to balance the DNA charge, and 32 additional Na^+/Cl^- ion pairs resulted in a simulation box of 39.5 Å × 39.5 Å × 49.5 Å. This corresponds to ion concentrations of 1.2 M Na^+ and 0.8 M Cl^-.

The simulation program ESP was developed in this laboratory (Smith et al., 1996). It employs periodic boundary conditions, a velocity Verlet integration scheme (Allen and Tildesley, 1987), and the SHAKE algorithm (Ryckaert et al., 1977) to enforce holonomic constraints on the chemical bonds. An integration time step of 2 fs was used. Electrostatic interactions were calculated using a twin-range implementation of the exact Ewald summation (Smith and Pettitt, 1995). The direct contribution to the Ewald sum was calculated for every time step within a first cutoff of 12 Å and updated every 10 steps for distances from 12 Å to the second cutoff of 20 Å. A convergence factor α of 1.5 and 13 reciprocal space vectors achieved optimal performance. Initial equilibration included a 20-step steepest descent minimization, followed by alternating runs with either the solvent or the solute fixed, and velocity reassignment every 50 steps from a canonical Maxwell distribution at 300 K for ~200 ps. The trajectory was then allowed to continue for an additional 10 ns. Analysis presented here was performed on the last 9 ns of that trajectory.

Diffusion coefficient calculations

The diffusional mobility of water D_{uvw} at each locale *uvw* was computed according to the Einstein relation (Eq. 1), using the following finite difference expression (Lounnas et al., 1994):

$$6D_{uvw} = \frac{1}{(t_2 - t_1)}(\langle|\vec{r}(t_2) - \vec{r}(0)|^2 - |\vec{r}(t_1) - \vec{r}(0)|^2\rangle) \quad (2)$$

The values t_1 and t_2 were fixed at 1 ps and 2 ps, respectively, on the assumption that the diffusional regime would be reached after 1 ps (Brooks and Karplus, 1989; Lounnas et al., 1994), but within a time shorter than the actual residence time of water molecules within the *uvw* volume element (which is usually on the order of 10 to 10^2 ps; Brunne et al., 1993). In this work we consider the local diffusion coefficient as a function of a distance from the closest solute atom, as has been done in certain previous studies (Wong and McCammon, 1987; Ahlström et al., 1988; Tirado-Rives and Jorgensen, 1990; Raghavan et al., 1992; Hartsough and Merz, 1993; Lounnas et al., 1994; Norin et al., 1994; Chiu et al., 1995; Muegge and Knapp, 1995; Bizzarri and Cannistraro, 1996; Bizzarri et al., 1996), and leave the detailed analysis of the three-dimensional distributions of local D_{uvw} values for the forthcoming paper (Feig et al., manuscript in preparation). Averages were accumulated in layers 0.1 Å thick. Water molecules were assigned to a particular layer, depending only upon their initial positions $\vec{r}(0)$; thus the physical meaning of the local diffusion coefficient that we compute is how fast solvent is leaving a given region of space.

In addition, we have decomposed the overall diffusion coefficient into components parallel and perpendicular to the solute surface:

$$2D_\perp = \frac{1}{(t_2 - t_1)}(\langle|d_\perp(t_2) - d_\perp(0)|^2 - |d_\perp(t_1) - d_\perp(0)|^2\rangle) \quad (3)$$

and

$$4D_\parallel = \frac{1}{(t_2 - t_1)}(\langle d_\parallel^2(t_2) - d_\parallel^2(t_1)\rangle) \quad (4)$$

where $d_\perp$ and $d_\parallel$ are, respectively, the displacements perpendicular and parallel to the solute surface. The decomposition is illustrated in Fig. 1. The perpendicular displacement is determined on the basis of proximity of the center of mass of the particular solvent molecule to solute. For instance, if a solvent molecule was located at point *A* at time t_1 and at point *B* at time t_2 (see Fig. 1), and the proximal atoms on the solute surface at these times were *C* and *D*, respectively, then the displacement perpendicular to the surface would be

$$d_\perp = d_\perp(t_2) - d_\perp(t_1) = |\vec{DB}| - |\vec{DA}_1| = |\vec{DB}| - |\vec{CA}| \quad (5)$$

$$d_\parallel = |\vec{AA}_1| = |\vec{AB} - \vec{A_1B}| \quad (6)$$

To uncover the effects of the local environment on solvent diffusion, we have calculated a set of the quasicomponent radial profiles of the water diffusion coefficient, partitioned into three components for water molecules around oxygen, nitrogen, and carbon atoms of the DNA solute. Each water molecule was assigned to a particular solute atom type on the basis

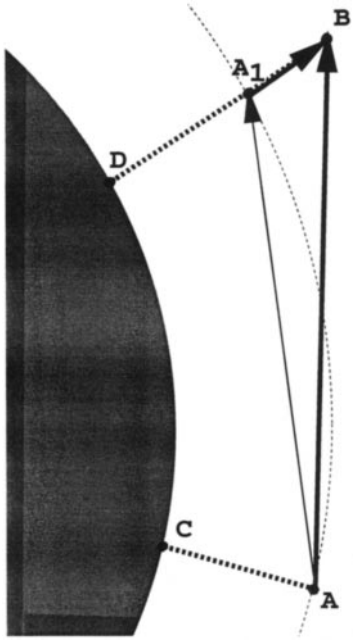

FIGURE 1 Decomposition of the overall molecular displacement of solvent into components parallel and perpendicular to the solute surface. See text for details.

of geometric proximity (Mezei and Beveridge, 1986). The solvent structure around a macromolecule can also be described using the proximity criterion, in terms of quasicomponent perpendicular radial distribution functions (pRDFs) (Mezei and Beveridge, 1986; Lounnas et al., 1994; Makarov et al., 1997). These conditional radial distribution functions take into account only the first nearest-neighbor interactions and thus depend only upon the solvent structure around a given reference atom type, but not on the exact three-dimensional structure of the solute (Mezei and Beveridge, 1986; Lounnas et al., 1994; Makarov et al., 1997). The application of proximity analysis to solvent diffusion allows us to establish a natural relation between the mobility and the structure of solvent. Because the number of ions in our simulation of DNA is much lower than the number of water molecules, the quasicomponent proximity analysis has more statistical error for the ions.

RESULTS AND DISCUSSION

Diffusion of water and ions in the bulk

The values of the bulk diffusion coefficients of all solvent species in both simulations are listed in Table 1. Our results are in excellent agreement with the values obtained in other computer simulations under similar conditions (Jorgensen et al., 1983; Alper et al., 1993a; Smith and Pettitt, 1995), and deviations from the experimental data (Hertz, 1973; Tyrrell and Harris, 1984) follow the trends observed in these earlier simulations. In general, the rate of solvent diffusion is overestimated in all cases in comparison with the experiment. For water diffusion, the disagreement with experiment is greatest for the second simulation (DNA). This simulation was performed with Ewald electrostatics, and an elevated diffusion coefficient for the TIP3P water model is typically observed under such conditions (Alper et al., 1993a). It has been suggested that the reason for this is that the water model was originally optimized for simulations with electrostatic cutoffs (Alper et al., 1993a). The diffusion coefficients for Na^+ and Cl^- ions in our simulation are much closer to experiment than the values reported previously in molecular dynamics calculations of saline solutions with the Ewald method (Smith and Pettitt, 1995), which may be due to a recent improvement in the force-field parameters for these ions (Roux et al., 1995).

TABLE 1 Bulk diffusion coefficients of water and ions

	Simulation 1 (myoglobin)	Simulation 2 (DNA)	Experimental value (reference)
Water	0.30	0.44	0.23*
Na^+	N/A	0.17	0.12#
Cl^-	N/A	0.28	0.18#

Values are in $Å^2$/ps.
*Hertz (1973).
#Tyrrel and Harris (1984).

Statistical uncertainty in the radial distribution of D was estimated by the standard deviation of the individual 1-ns block-average distributions (Allen and Tildesley, 1987) from the overall 9-ns average. For the water diffusion coefficient distribution, this figure was below 1%. For Na^+ and Cl^- ions, the error varies between ~20% in the $R \leq 4$ Å region and ~2% thereafter.

Diffusion of water at the interface

For the analysis of solvent diffusion at the protein-water and DNA-solvent interface, we have found it convenient to normalize the values of D by a constant that equals the bulk diffusion coefficient of water in a particular simulation. This enables us to compare the relative effects caused by the solute on the mobility of surrounding water on the same scale in both simulations.

The radial profiles of the water diffusion coefficient, along with its perpendicular and parallel components for both myoglobin and DNA, are shown in Fig. 2. Both the nature and the magnitude of the effects of solute on water diffusion are very similar between myoglobin and DNA when viewed on this relative scale. This indicates that the underlying physical reasons for these effects must also be the same. There are at least three such effects.

First, the rate of water diffusion is reduced at the interface, as manifested by the decline of the curves as the surface is approached. This effect has been observed in many, if not all, molecular dynamics simulations performed in aqueous solution (Wong and McCammon, 1987; Ahlström et al., 1988; Tirado-Rives and Jorgensen, 1990; Hartsough and Merz, 1993; Knapp and Muegge, 1993; Lounnas et al., 1994; Norin et al., 1994; Muegge and Knapp, 1995; Bizzarri and Cannistraro, 1996; Bizzarri et al., 1996; Absher et al., 1996; Wang et al., 1996).

Second, the diffusion rate in the direction perpendicular to the solute surface is slower in comparison to the overall

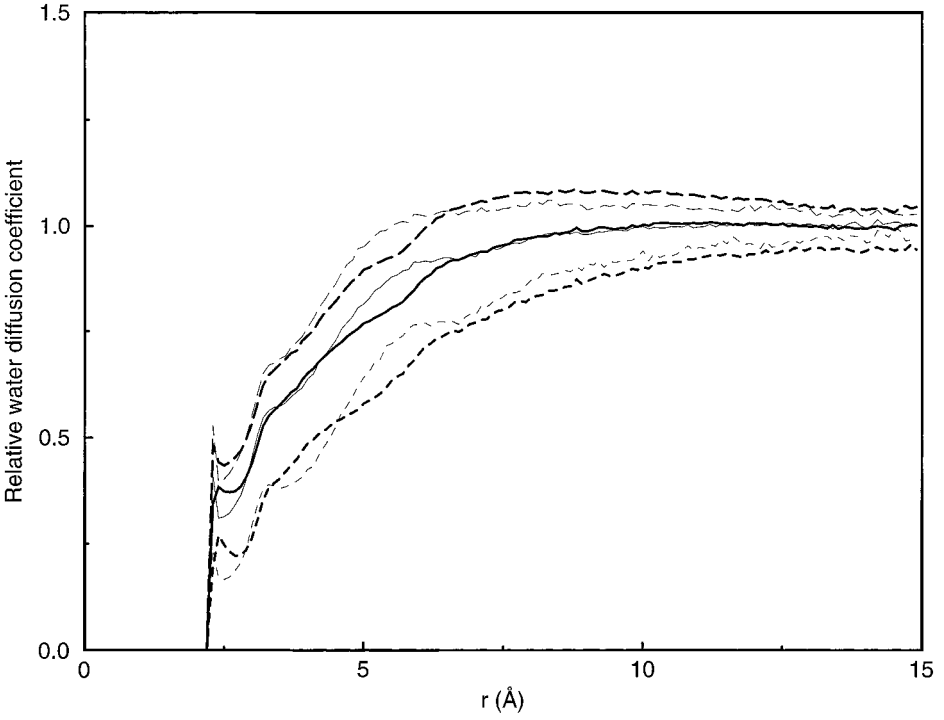

FIGURE 2 Radial profiles of the water diffusion coefficient around myoglobin (*thin lines*) and DNA (*thick lines*). The overall diffusion coefficient is shown by solid lines, and its perpendicular and parallel components by short and long dashed lines, respectively. The curves are scaled so that the bulk value corresponds to 1.

diffusion rate, whereas diffusion parallel to the solute surface is faster. A similar effect has been observed in some previous MD simulation studies (Chiu et al., 1995; Muegge and Knapp, 1995). Reduction in the perpendicular diffusion rate is due to restriction of solvent mobility at the boundary of the macromolecule, which moves as a whole at a lower rate than the solvent and thus appears as a static wall. The restriction of solvent mobility by a larger, heavier solute may also be thought of as an effective reduction of the dimensionality of space available to the solvent at the interface. A relative increase in the parallel diffusion rate can be viewed, then, as being related to the equipartition of energy principle. The magnitude of this effect decreases with distance from the solute; however, it is still present as far as 15 Å away. The increase in the parallel diffusion rate should not be confused with the hypermobile water observed in some earlier MD simulations (Teeter, 1991; Ahlström et al., 1988; Hartsough and Merz, 1993; Lounnas et al., 1994; Norin et al., 1994; Raghavan et al., 1992; Tirado-Rives and Jorgensen, 1990). In our case, this increase is only present in the parallel-*D* profile, not in the overall diffusion coefficient distribution and, unlike the artifactual hypermobile water, is not dependent upon the method of calculation of long-range electrostatic interactions. The parallel diffusion rate drops as we gradually approach the surface from 15 Å, and the decline is at least as fast as for the overall rate. This is not what one would expect for a perfectly smooth surface that imposes no restrictions on the ability of surrounding small molecules to slide over it. Thus the gradual decline of the parallel diffusion rate may be a manifestation of the solute surface roughness.

Third, there are usually three depressions found in the diffusion coefficient profile: at ~2.7 Å and 3.5 Å, and between 4.7 and 6.7 Å. The second depression is more profound in the profiles for myoglobin, and the third one is present only in the DNA profile (in comparison with the one for myoglobin; Fig. 2). Each of these depressions can be correlated with solvation structure around the macromolecule. As can be seen from a comparison of Figs. 2, 3, and 4, the first two depression regions arise because of water ordering around oxygen and nitrogen (depression number 1) and carbon atoms (depression number 2) of the solute. These relatively small depressions, which all take place in the $R \leq 5$ Å range, constitute the only difference in the diffusion rate of water around different solute atoms (Fig. 3). The third depression region occures at approximately the same distance as the second peak in the DNA-water proximal RDFs and the first minimum in the DNA-Na^+ proximal RDF (Fig. 6). It is therefore due to restriction of mobility of water molecules in the second hydration shell of the DNA. These water molecules can interact with the sodium ions that are predominantly associated with the DNA backbone and are located between the first and the second DNA hydration shells (Feig and Pettitt, manuscript in preparation). A reduction of the mobility of sodium ions in turn affects the mobility of the water molecules in their hydration shells. As our myoglobin simulation has no ions in it, there is no depression present in that region of the *D* profile for myoglobin. The initial peaks that are present in all curves are due to the steric clashes between solute and water, and are less reliable than the rest of the profile, because of the lower number of counts in that region. To our

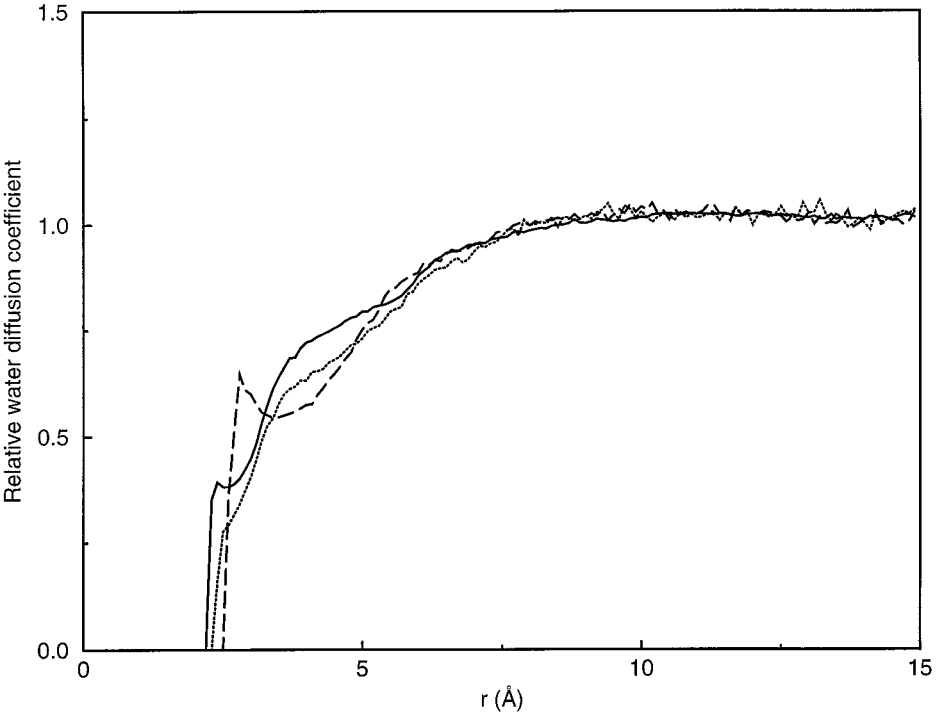

FIGURE 3 Quasicomponent radial profiles of the water diffusion coefficient around DNA, for water molecules proximal to DNA oxygens (——), nitrogens (·····), and carbons (– – –).

knowledge, this is the first report of a fine structure in the radial profiles of solvent diffusion coefficient related to specific chemical features of the macromolecule. This effect is of much lower magnitude than the other effects discussed above, which may be the reason it has not been observed before. This also may be an explanation for the controversy over the rate of water mobility around polar and nonpolar protein groups (Levitt and Sharon, 1988; Brooks and Karplus, 1989; Teeter, 1991; Komeijii et al., 1993; Wang et al., 1996; Rocchi et al., 1997).

Diffusion of ions at the interface

Analysis of ion diffusion around DNA is complicated by the high level of statistical noise in the data (Fig. 5) due to the

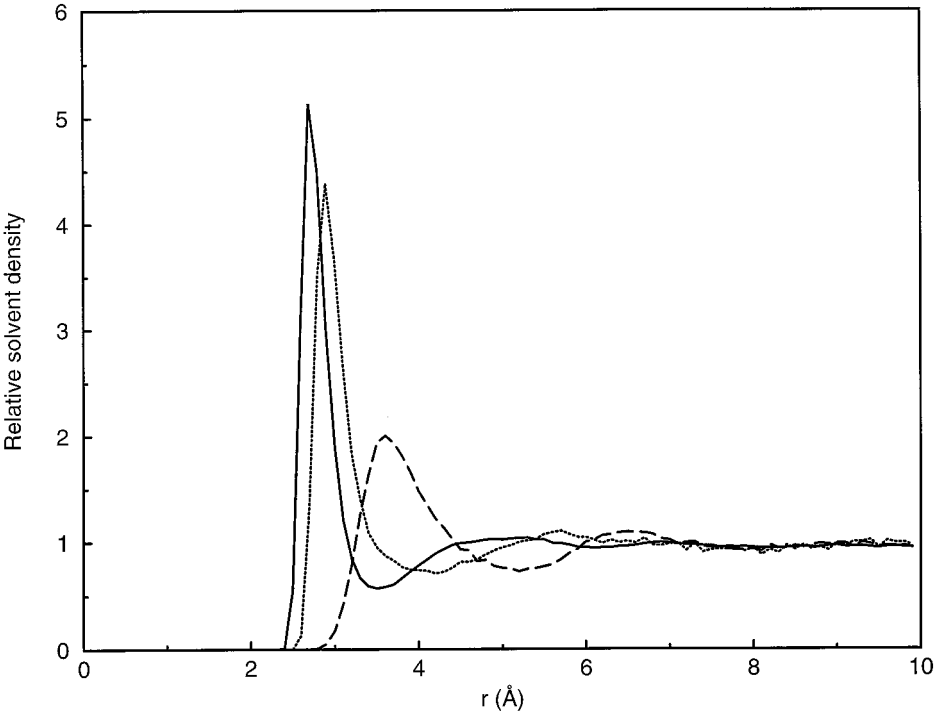

FIGURE 4 First nearest-neighbor proximal radial distribution functions for solvent water around DNA oxygens (——), nitrogens (·····), and carbons (– – –).

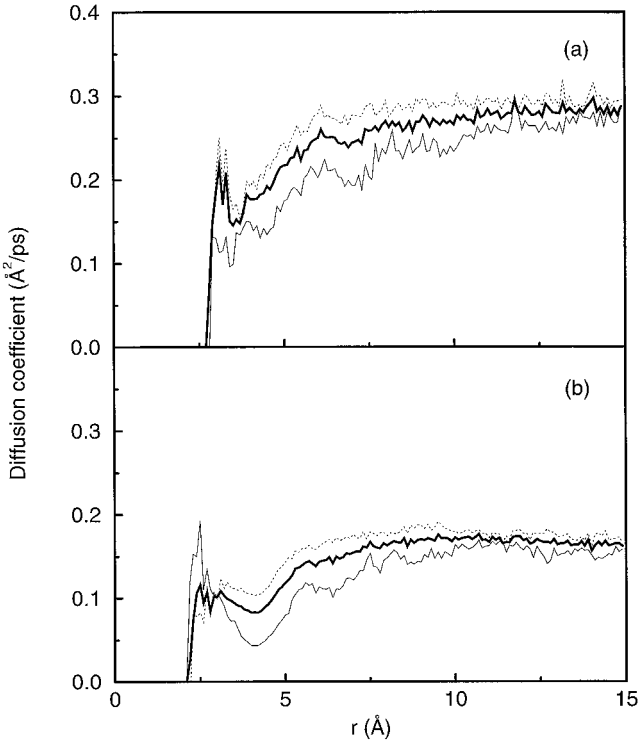

FIGURE 5 Radial profiles of the diffusion coefficient of chlorine (*a*) and sodium (*b*) ions around DNA. The regular diffusion coefficient is shown by the thick solid line, and its perpendicular and parallel components by thin solid and dotted lines, respectively.

low number of ions in the simulation. However, the overall features remain the same. We observe the overall increase in the diffusion rate of ions with the distance to the solute, the perpendicular component being slower and the parallel component faster then the overall rate. There are three depressions in the D profile for Cl^- (at ~3.5 Å, ~4.5 Å, and ~7.3 Å) and two for Na^+ (at ~4 Å and ~6.4 Å) that all relate to peaks in the corresponding radial distribution functions (Fig. 6).

CONCLUSIONS

The analysis of solvent diffusion presented above shows that the solute effects on solvent mobility are similar for two macromolecular solutes of totally different structure and shape. This indicates that the mobility of solvent in such systems is governed by a few universal physical principles. That is, the reduction of the dimensionality of space at the interface due to the presence of a heavy solute molecule produces a general decline in the rate of solvent mobility in proximity to the solute and causes the rates of diffusion in different directions (parallel and perpendicular to the solute surface) to deviate from the overall average. Additional reduction in solvent mobility comes from the solute surface roughness and solvent structuring by means of hydrogen bonding and ion solvation. There are small variations in the solvent diffusion rate around different types of solute surface atoms, all of which can be correlated with the average solvent structure around the corresponding solute atom type.

It would be interesting to perform an even more detailed study of solvent mobility and find out how site- or sequence-specific variations in solvent diffusion rate, if there are any, depend upon the local structure of a particular

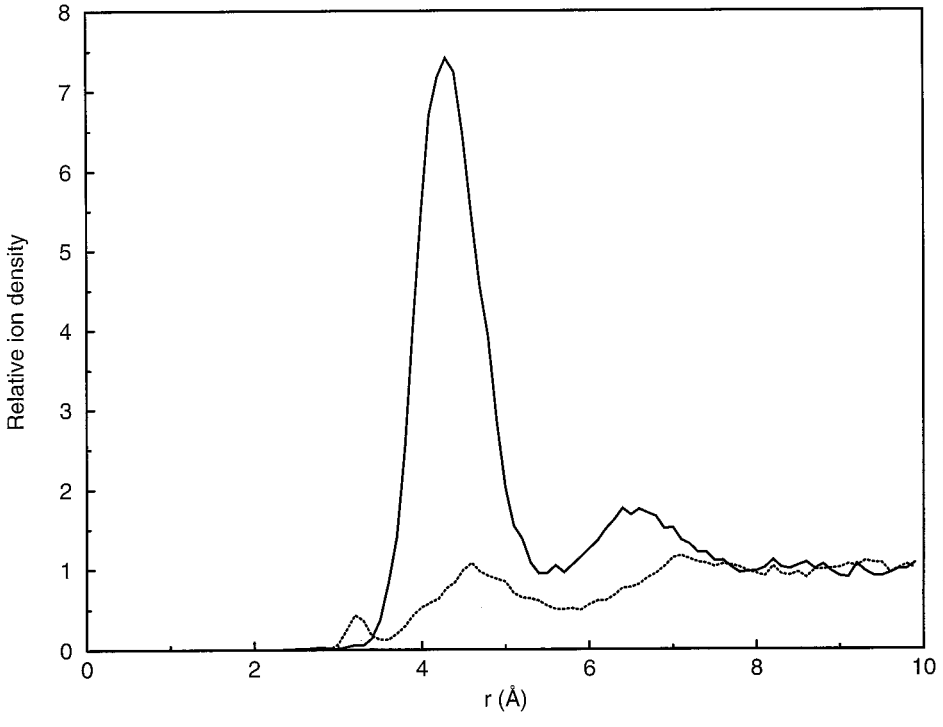

FIGURE 6 First nearest-neighbor proximal radial distribution functions for sodium (——) and chlorine (·····) ions around DNA.

solute and its solvent environment. Work in this direction is currently under way in this laboratory.

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