Structure and Dynamics of the TIP3P, SPC, and SPC/E Water Models at 298 K

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Molecular dynamics simulations of five water models, the TIP3P (original and modified), SPC (original and refined), and SPC/E (original), were performed using the CHARMM molecular mechanics program. All simulations were carried out in the microcanonical NVE ensemble, using 901 water molecules in a cubic simulation cell furnished with periodic boundary conditions at 298 K. The SHAKE algorithm was used to keep water molecules rigid. Nanosecond trajectories were calculated with all water models for high statistical accuracy. The characteristic self-diffusion coefficients D and radial distribution functions, g_{OO}, g_{OH}, and g_{HH} for all five water models were determined and compared to experimental data. The effects of velocity rescaling on the self-diffusion coefficient D were examined. All these empirical water models used in this study are similar by having three interaction sites, but the small differences in their pair potentials composed of Lennard-Jones (LJ) and Coulombic terms give significant differences in the calculated self-diffusion coefficients, and in the height of the second peak of the radial distribution function g_{OO}.

1. Introduction

Liquid water, the most important solvent in nature, has many special and unusual properties. Many of these special properties are due to the ability of water molecules to form hydrogen bonds with other water molecules in three-dimensional networks. The macroscopic properties of liquid water have been thoroughly studied and are now well-known, but the microscopic forces that define water structure are not completely understood.[1] Microscopic properties can be analyzed by different experimental techniques, such as X-ray scattering[2,3] and neutron diffraction,[2,4] which measure the structure of liquid water and aqueous solutions. Neutron diffraction with isotopic substitution (NDIS) has been used to measure intermolecular partial pair correlation functions for liquid water.[5−7] The self-diffusion coefficient of pure water has been measured to be 2.3 ($\times 10^{-9}$ m^2 s^{-1}) at 298 K using the diaphragm-cell technique[8] or the pulsed-gradient spin echo (PGSE) NMR method.[9] The three radial pair distribution functions for H_2O, g_{OO}, g_{OH}, and g_{HH}, have generally been used together with the self-diffusion coefficient to characterize the structure and dynamics of water at different temperatures.[6,7,10] Simultaneously several theoretical methods have been developed to describe the properties of water and aqueous solutions. Experimental and theoretical methods are continuously being developed to give more detailed views of the microscopic properties of liquid water, thus increasing our knowledge. In this study we use one of the theoretical methods, molecular dynamics simulations, to calculate the bulk properties for models of liquid water.

Many different potential functions for the water monomer and liquid water have been developed over the last 30 years.[11−23] The water monomer can be treated as rigid or as flexible, allowing all degrees of freedom for the OH bonds and HOH bond angle. In rigid models the SHAKE algorithm[24] is generally used to constrain the bond lengths, including a fictitious H−H bond, thus making the model rigid. All water models used here, the TIP3P (transferable intermolecular potential 3P) (original[11] and modified[12]), SPC (simple point charge) (original[13] and refined[14]), and SPC/E (extended simple point charge) (original[15]) can be described as effective rigid pair potentials composed of Lennard-Jones (LJ) and Coulombic terms. All of these water models have three interaction sites and are similar in nature, but the Lennard-Jones (LJ) and Coulombic terms differ (see Table 1) and give significant differences in calculated bulk properties for liquid water.

In molecular dynamics simulations Newton's equations of motion are numerically integrated for all atoms, which requires the evaluation of the atomic forces at each time step. The force evaluation is dominated computationally by the large number of nonbonded interactions, and in particular by the long-range electrostatic interactions. Even with fast computers simplifying approximations are needed to reduce the computational time to an acceptable level. The necessity to use a system of finite size means that boundary conditions must be chosen, which may also introduce artifacts. The fast multipole expansion method[25] allows relatively efficient handling of long-range interactions, and for periodic systems the Ewald summation technique[25−27] as commonly implemented may be used to compute the Coulomb interactions exactly; in nonperiodic, spherical, systems, Coulombic effects of the neglected surroundings may be treated by a reaction field.[26] Still the most commonly used method to achieve a reasonably cost-effective computation is to use a spherical cutoff, which reduces the number of pair wise interactions by neglecting all interactions between particles separated by a distance larger than the cutoff.[26,28]

In this paper, we compare calculated bulk properties for the TIP3P (original[11] and modified[12]), SPC (original[13] and refined[14]), and SPC/E[15] water models at 298 K. All simulations were performed under exactly the same conditions and using the same system size with 901 water molecules. The system size with 901 water molecules was defined large enough to be used also in future simulations of small biomolecules, such as amino acids or nucleic acid fragments. The nonbonded interactions were truncated using force shifting,[28] where the calculated forces and

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TABLE 1: Nonbonded Parameters, Geometry, and Electrostatic Properties of the Three-Point Water Models

parameters	and units	TIP3P original	TIP3P modified	SPC original	SPC refined	SPC/E original
dipole	(debye)	2.347	2.347	2.274	2.237	2.351
r_0^{OO}	(Å)	3.5365	3.5365	3.5533	3.5257	3.5533
ϵ^{OO}	(kcal mol^{-1})	0.1521	0.1521	0.1553	0.1553	0.1553
r_0^{HH}	(Å)	0.449	0	0	0	0
ϵ^{HH}	(kcal mol^{-1})	0	0.046	0	0	0
r_0^{OH}	(Å)	0	1.993	0	0	0
ϵ^{OH}	(kcal mol^{-1})	0	0.084	0	0	0
q^{O}	(*e* units)	−0.834	−0.834	−0.82	−0.8068	−0.8476
q^{H}	(*e* units)	0.417	0.417	0.41	0.4034	0.4238
b_0^{OH}	(Å)	0.9572	0.9572	1.0	1.0	1.0
θ_0^{HOH}	(deg)	104.52	104.52	109.47	109.47	109.47
K_b	(kcal mol^{-1}Å^{-2})		450.0			
K_θ	(kcal mol^{-1}rad^{-2})		55.0			

energies are smoothly shifted to zero at the cutoff distance. This scheme has been found[29] to give similar structural and dynamic properties for bulk water as when Ewald summation is used.

The nonbonded list size and updating time are important when simulations at constant energy (NVE) are performed. If the size or updating frequency of the nonbonded list is underestimated, energy conservation is violated and the system temperature increases, which may necessitate some kind of temperature control, commonly implemented via velocity rescaling.

It should be noted that the discontinuities introduced in the velocities by this rescaling may affect dynamic properties such as the self-diffusion coefficient. Simulations with and without velocity rescaling were compared using all five water models. Velocity rescaling effects in molecular dynamics simulations in general have been studied and reported in the literature.[30]

Our interest in this work concentrated on the bulk water structure and dynamics, as characterized by the radial distribution functions, g_{OO}, g_{OH}, and g_{HH} and self-diffusion coefficient D. In general, the three-site potentials provide too little structure in g_{OO} when compared with more complicated models, and specifically the TIP3P water model is lacking the second peak.[11,21] The radial distribution functions, g_{OO}, g_{OH}, and g_{HH} for all water models used in this study, except the refined SPC, are reported in the literature.[11,13,15,17,21] Self-diffusion coefficients have been reported for the original TIP3P water model between 5.2 and 7.0 ($\times 10^{-9}$ m^2 s^{-1}),[31] for the modified TIP3P water model between 2.3 and 5.2 ($\times 10^{-9}$ m^2 s^{-1}),[32−36] for the original SPC water model between 3.6 and 5.2 ($\times 10^{-9}$ m^2 s^{-1}),[31] and for the SPC/E water model between 2.2 and 4.4 ($\times 10^{-9}$ m^2 s^{-1}),[31] but the self-diffusion coefficient for the refined SPC water model was never reported in the literature. The self-diffusion coefficient *D* should be easy to calculate from molecular dynamics data,[37] but the conflicting results for the same water model reported in the literature show that is not the case, and a set of long simulations performed and analyzed under identical conditions is necessary to accomplish a meaningful comparison.

In this work, our first goal was to calculate the self-diffusion coefficient and radial distribution functions for these water models under identical conditions. We also estimate the statistical accuracy of the commonly used method to calculate the self-diffusion coefficient *D*, the Einstein relation.[37] Long simulations (0.6−4.1 ns) with all five water models were used to calculate the mean value, and the variance of the mean, for the self-diffusion coefficient. Finally we present the effects of velocity rescaling when used as temperature control method. This work, together with recently reported work by van der Spoel et al.[31] and experimental data for liquid water,[5,8] is an important test for validating all these five commonly used water models.

TABLE 2: Systems Simulated

simulation	water model	simulation period (ns)	temperature^e (K)	temperature control^f
1^a	TIP3P original	0.6^c/ 0.5^d	301.4 (1.7)	yes 42/500ps^g
2^b	TIP3P original	0.6 /0.5	297.0 (0.9)	no
3^a	TIP3P modified	1.1 /1.0	301.2 (1.8)	yes 95/1000ps
4^b	TIP3P modified	1.7 /1.0	299.2 (1.0)	no
5^a	SPC original	0.6 /0.5	301.0 (1.7)	yes 33/500ps
6^b	SPC original	1.0 /0.5	298.6 (1.1)	no
7^a	SPC refined	1.1 /1.0	301.0 (1.8)	yes 66/1000ps
8^b	SPC refined	1.2 /1.0	297.7 (1.2)	no
9^a	SPC/E	4.1 /1.0	300.4 (1.9)	yes 40/1000ps
10^b	SPC/E	4.1 /1.0	298.2 (1.4)	no

[a] Nonbonded list 1 (see Methods). [b] Nonbonded list 2 (see Methods). [c] Total time. [d] Time used for analysis. [e] Average calculated over the analyzed part of the simulation, standard deviation (in parentheses). [f] Velocity rescaling (see Methods). [g] Number of velocity rescaling events over the analyzed part of the simulation.

2. Simulation Procedures

All different water models, the TIP3P (original, modified), SPC (original, refined), and SPC/E (original) were compared using identical microcanonical (NVE) or NVT simulations. For convenience the interaction parameters and geometries of the models are given in Table 1. All simulations were performed at 298 K using a solvent density of 0.998 g/cm^3 with periodic boundary conditions in a cubic box with side length 30.0 Å. The box contained 901 H_2O molecules and all simulations were started with the same initial coordinates and the same initial velocity assignments (i.e., the same seed was used for the random number generator) for the water molecules. In the NVT simulations the temperature was allowed to vary ±5 K around 298 K. If the average temperature since the last velocity scaling, with the average being taken over at least 2 ps, drifted outside the 10 K window atom velocities were scaled to give a temperature of 298 K again. The SHAKE[24] algorithm was used to keep water molecules rigid. Newton's equations of motion were integrated with the Verlet leapfrog algorithm with a time step of 0.002 ps.[26,37] The dielectric constant was 1.0 and the nonbonded interactions energies and forces were smoothly shifted to zero at cutoff of 12.0 Å. The shifting function was applied on an atom-by-atom basis using the force shift method.[28] Two different nonbonded lists were used: (1) 13.0 Å cutoff for the list and updated every 20 steps or (2) 14.0 Å cutoff for the list and updated when necessary using a heuristic test. A total of 10 simulations were performed (Table 2). For the analysis, coordinate sets for every 0.4 ps were used. All MD simulations and analysis were performed with the CHARMM program.[38]

Self-diffusion coefficients were calculated from the mean square displacement (MSD) of all oxygen atoms using the

TABLE 3: Self-Diffusion Coefficients (10^{-9} m^2 s^{-1}) for Three Water Models Using Different Parts of the Slope of MSD(t) vs t

part of the slope (ps)	TIP3P^a modified	TIP3P^b modified	SPC/E^a original	SPC/E^b original	SPC^a refined	SPC^b refined
4−100	5.88	5.88	2.88	2.79	4.44	4.31
100−200	5.96	5.86	2.87	2.77	4.33	4.31
200−300	6.12	5.75	2.88	2.77	4.31	4.40
300−400	6.29	5.83	2.94	2.70	4.23	4.43
400−500	6.23	5.91	3.02	2.74	4.18	4.42

[a] Nonbonded list 1 (see Methods). [b] Nonbonded list 2 (see Methods).

Einstein relation[37]

$$\lim_{t\to\infty} \langle |\mathbf{r}(t' + t) - \mathbf{r}(t')|^2 \rangle = 6Dt$$

where $\mathbf{r}(t)$ is the position of the oxygen atom of the water molecule at time t, D is the self-diffusion coefficient, and the brackets denote averaging over all water molecules and time origins t'.

The self-diffusion coefficient was estimated from the slope of the linear part at long times of the mean square displacements vs time plot. The initial part of the line is influenced by inertial effects and should not be included in this calculation. To make sure that the self-diffusion coefficient calculations were not affected by the inertial effects, different parts of the slope of MSD vs time were tested (Table 3). When choosing a range the need to avoid the inertial regime has to be contrasted with the statistics of the data; for long time-separations there are only very few points available in the trajectory and the statistics for these points therefore are not as good. For the simulations without velocity scaling the results are very similar for all the tested intervals, including the shortest at 2−10 ps. Since D is temperature dependent, and the simulations do not run at exactly the same temperature, we also adjusted the observed diffusion coefficients to the standard temperature 298 K by using experimental results at different temperatures.[8] The self-diffusion coefficients were thus adjusted according to

$$D(298) = D(T) + 0.06 \times 10^{-9}\ \mathrm{m}^2\ \mathrm{s}^{-1}\ \mathrm{K}^{-1}(298 - T)$$

where T is the actual temperature during the simulation.

3. Results

The temperature in a molecular dynamics simulation is computed from the kinetic energy of the moving atoms, which may exhibit both fluctuations and drift. For a precise determination of temperature-dependent properties, such as the self-diffusion coefficient, the temperature must be stable during the simulation, and a number of methods to control the temperature have been described in the literature.[26] A temperature drift may be caused by approximations or deficiencies in the simulation protocol. We will in this section first examine the temperature stability of our water simulations, and how the stability is influenced by different updating schemes for the nonbond list. In the following sections the self-diffusion coefficient D and radial distribution functions ($g(r)$) are calculated. Here we also monitor how D and $g(r)$ are influenced by temperature control in the form of velocity scaling.

3.1. Temperature, Stability, and Equilibration. The temperature and potential energy as a function of time are shown in Figure 1 for all five water models, and with two different nonbond list updating schemes. In the simulations using updated scheme 1, where the nonbonded list is slightly too small so that atoms not on the list may fall within the cutoff distance without actually interacting for some time until the next list update, energy conservation was violated, and the system temperature was increasing. The temperature was controlled using velocity rescaling in all simulations performed using scheme 1. With scheme 2, when a bigger nonbonded list size was used together with updating when necessary, energy conservation was not violated and the system temperature stabilized close to the target temperature (298 K). In general, no velocity rescaling was needed to control the temperature with scheme 2, except when the SPC (original and refined) water models were used. In the SPC systems, the temperature was decreasing slightly in the beginning of the simulation and infrequent velocity rescaling was needed to scale-up the temperature to the target value, before the trajectories without velocity rescaling were produced. For the SPC (refined) water model the temperature was allowed to vary ±10 K around 298 K when the trajectory without velocity rescaling was produced.

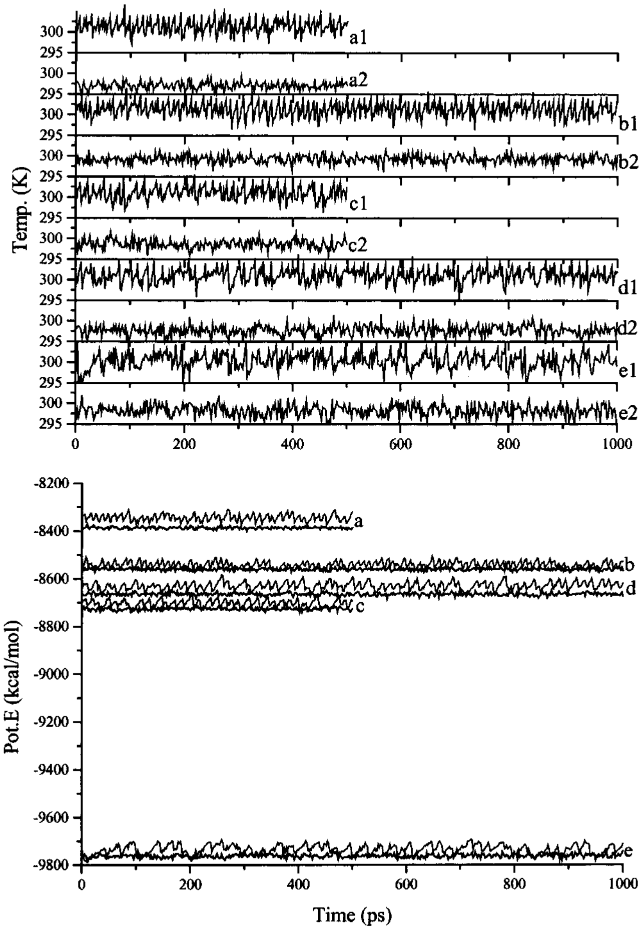

Figure 1. The temperature and potential energy as a function of time for all five water models using two different nonbonded updating schemes 1 and 2 (see Methods). (a) TIP3P (original), (b) TIP3P (modified), (c) SPC (original), (d) SPC (refined), (e) SPC/E (original). The potential energy in the lower panel is plotted in a thin line for scheme 1 and a thick line for scheme 2.

The average pressure and standard deviation (in parentheses) for the original TIP3P water model was 514.5 (109.6) bar, and 442.8 (98.5) bar with schemes 1 and 2, respectively. For the original SPC the corresponding values were 709.1 (106.9) bar with scheme 1 and 660.8 (123.1) bar with scheme 2.

3.2. Self-Diffusion Coefficient D. Self-diffusion coefficients evaluated using different ranges of the slope of MSD vs time calculated from averaging over the 901 water molecules and the 1.0 ns trajectories (Figure 2) are shown in Table 3. It can be seen from Figure 2 that there is more noise at long times,

TABLE 4: Self-diffusion Coefficients ($\times 10^{-9}$ m^2 s^{-1}) for the Modified TIP3P Water Model Using Three Different Lengths of the Slope of MSD(*t*) vs *t*

part of the trajectory (ps)	slope 1.9−9.6 (ps)	slope 4.0−20.0 (ps)	slope 10−50 (ps)	slope 10−50 (ps)	temperature(K)
700−800	5.93	5.97	6.08		298.9 (0.8)
800−900	5.78	5.77	5.91	5.99[a]	299.3 (0.9)
900−1000	5.82	5.82	5.85		299.2 (1.1)
1000−1100	5.72	5.78	5.92	5.86[a]	299.1 (1.0)
1100−1200	5.90	5.86	5.70		299.3 (1.0)
1200−1300	5.77	5.74	5.67	5.76[a]	299.2 (0.9)
1300−1400	5.82	5.94	6.07		299.2 (1.1)
1400−1500	5.90	5.95	6.33	6.05[a]	299.3 (0.9)
1500−1600	5.86	5.82	5.90		299.2 (0.9)
1600−1700	5.81	5.80	5.82	5.90[a]	299.2 (1.0)
average std dev	5.83 (0.07)	5.85 (0.08)	5.93 (0.2)	5.91 (0.11)	299.21 (0.96)

[a] The analyzed part of the trajectory, 200 ps.

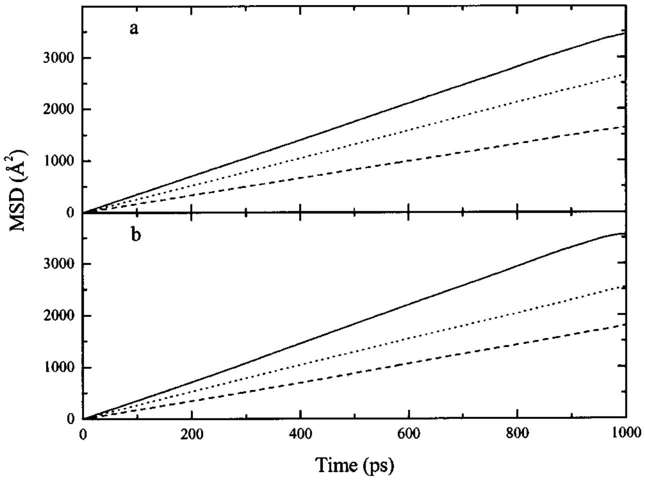

Figure 2. MSD vs time calculated from averaging over the 901 water molecules and the 1.0 ns trajectories. TIP3P (modified) line, SPC (refined) dot, and SPC/E (original) dash. (a) Nonbonded scheme 2 and (b) nonbonded scheme 1.

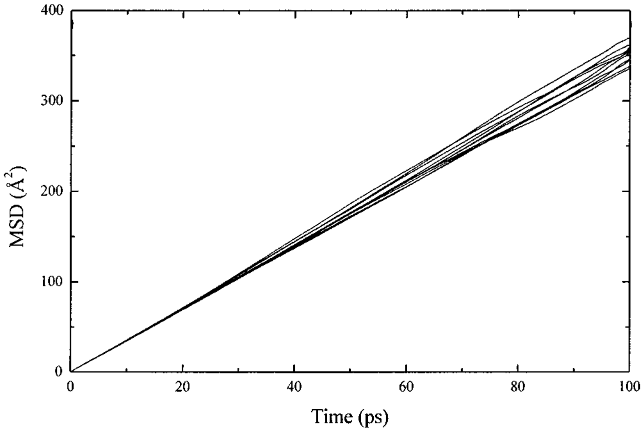

Figure 3. MSD vs time for 10 separate 100 ps blocks of the stable simulation of TIP3P (modified).

and we can also see from Table 3 that, in the simulations with the slight temperature drift and velocity rescaling (Figure 2b), there is a pronounced deviation from linearity. The variation in *D* obtained from these different ranges of the slope is 2% for the stable simulations (Figure 2a) and 7% for the simulations with velocity rescaling (Figure 2b).

Figure 3 shows MSD vs time for 10 separate 100 ps blocks of the stable simulation, without velocity rescaling, of TIP3P (modified). These plots become noisy as time increases, because fewer data points are available of the points used to calculate MSD at long times. For a given system size the accuracy of the self-diffusion coefficient calculation depends on which part of the slope is used and how long the trajectory is. When the self-diffusion coefficient is calculated with a standard deviation of the order $\approx 0.1(\times 10^{-9}$ m^2 s$^{-1})$, as in this study, the upper limit of the range of the slope of MSD vs time has to be restricted to about 20% of the analyzed trajectory length. This can be seen from Table 4, where different ranges of the slope of MSD vs time have been used to calculate the self-diffusion coefficient. Similar mean values and standard deviations were obtained when the upper limit of the range of the slope of MSD vs time was limited to $\approx$ 20% of the analyzed trajectory length. The self-diffusion coefficient 5.85 ($\times 10^{-9}$ m^2 s^{-1}) with a standard deviation of 0.08 ($\times 10^{-9}$ m^2 s^{-1}) was obtained from 100 ps trajectory pieces with the upper limit of 20 ps. When the upper limit of the used range of the slope was increased to 50 ps, the analyzed trajectory length had to be increased to 200 ps for similar accuracy. The self-diffusion coefficients determined in this manner were similar, with similar standard deviations, and there was no drift with time (Table 4). A similar self-diffusion coefficient was also obtained from 1.0 ns (Table 3) trajectory when the upper limit of the range of the slope of MSD vs time was limited to 20% of the analyzed trajectory length. It is also evident from Table 4 that 100 ps is a long trajectory when compared to all relevant relaxation processes in the system. These evaluations of *D* can be treated as independent and we thus expect the standard error of *D* computed from the full 1 ns trajectory to decrease by $1/\sqrt{10} \approx 0.3$, to about 0.5%. The simulations with the SPC/E water model were extended to 4.0 ns, with very similar results when compared with the shorter 1.0 ns simulations. The 300 ps delay needed for convergence of the self-diffusion coefficient reported by van der Spoel et al.[31] is likely due to their method of estimating the convergence of *D*, which does not use the slope of the plot of MSD(*t*) vs *t*, but instead uses the ratio MSD(*t*)/6*t*. This corresponds to computing the slope starting from $t = 0$, which means that the slope calculated in this way is influenced by the initial, inertial phase of the MSD, an influence which apparently persists for long times, whereas if the short-time part of MSD(*t*) is neglected, the self-diffusion coefficient can be reliably computed in 100 ps or less, depending on the system size. The resulting self-diffusion coefficients for all five water models at 25 °C are given in Table 5. All five water models give rather high values for *D* when compared with the experimental value,[8] and the TIP3P, SPC, and SPC/E, respectively, correspond to real water around 74, 55, and 33 °C, rather than to the simulation temperature of 25 °C. The modified versions of TIP3P and SPC are both slightly more fluid than the original versions (Table 5), and we also note that the difference, 0.1×10^{-9} m^2 s^{-1}, is only observable in a simulation

TABLE 5: Self-diffusion Coefficients ($\times 10^{-9}$ m^2 s^{-1}) for All Water Models Using Two Different Lengths of the Slope of MSD(*t*) vs *t*

water model	slope (1.9−9.6 ps)	slope (4.0−20.0 ps)	temperature[c] (K)	*D* (25 °C)[f]
TIP3P original[a]	5.88[d] (0.10)[e]	5.87[d] (0.09)[e]	301.4[d](1.7)[e]	5.67
TIP3P original[b]	5.59 (0.06)	5.59 (0.08)	297.0 (0.9)	5.65
TIP3P modified[a]	5.92 (0.09)	5.92 (0.11)	301.2 (1.8)	5.73
TIP3P modified[b]	5.83 (0.07)	5.85 (0.08)	299.2 (1.0)	5.78
SPC original[a]	4.39 (0.05)	4.40 (0.06)	301.0 (1.7)	4.22
SPC original[b]	4.22 (0.06)	4.24 (0.08)	298.6 (1.1)	4.20
SPC refined[a]	4.49 (0.08)	4.48 (0.08)	301.0 (1.8)	4.30
SPC refined[b]	4.26 (0.07)	4.24 (0.10)	297.7 (1.2)	4.26
SPC/E original[a]	2.90 (0.06)	2.89 (0.08)	300.4 (1.9)	2.75
SPC/E original[b]	2.78 (0.04)	2.77 (0.06)	298.2 (1.4)	2.76
exptl[8,9]				2.30

[a] Nonbonded list 1 (see Methods). [b] Nonbonded list 2 (see Methods). [c] Temperature of the MD simulation. [d] Mean values. [e] Standard deviations. [f] Self-diffusion coefficients adjusted to 25 °C, using the slope 4.0−20.0 ps.

with 900 water molecules which is run for 0.5 ns (or longer if fewer water molecules are used). The self-diffusion coefficients calculated in this study are in good agreement with the values reported by van der Spoel et al.[31] (see Table 6) for the original TIP3P, SPC, and SPC/E water models, but the self-diffusion coefficient for the modified TIP3P water model is higher than the values reported in the literature.[32−36]

3.3. Radial Distribution Functions, g_{OO}, g_{OH}, and g_{HH}. The radial distribution functions, g_{OO}, g_{OH}, and g_{HH} are commonly used when the structure of the liquid water is studied. These intermolecular partial pair correlation functions for liquid water at 25 °C were determined from neutron diffraction data by Soper et al.[5,7] The old[5] and new[7] results for g_{OO}, g_{OH}, and g_{HH} are in good agreement, except that the first O−H peak at 1.8 Å is increased by about 14% compared to that of previous analysis. The differences probably represent the currently available accuracy in determining the site−site pair correlation functions for water. The radial distribution functions, g_{OO}, g_{OH}, and g_{HH} are easy to calculate from molecular dynamics data and are generally used when different water models are compared with experimental data.

The radial distribution functions computed from our simulations for the TIP3P (modified), SPC (refined), and SPC/E water models are compared with experimental data[5] in Figure 4. Heights and positions of the peaks and minima are given for g_{OO} in Table 7 and for g_{OH} in Table 8. Our calculated radial distribution functions are in good agreement with the previously reported results in the literature. SPC/E gives the closest agreement with experiment for g_{OO}, but the first peak position occurs at too short distance when compared with experiment. SPC (refined) has similar peak positions, but the overall structure is flattened when compared with SPC/E. The modified TIP3P has the first peak position closest to the experimental position,

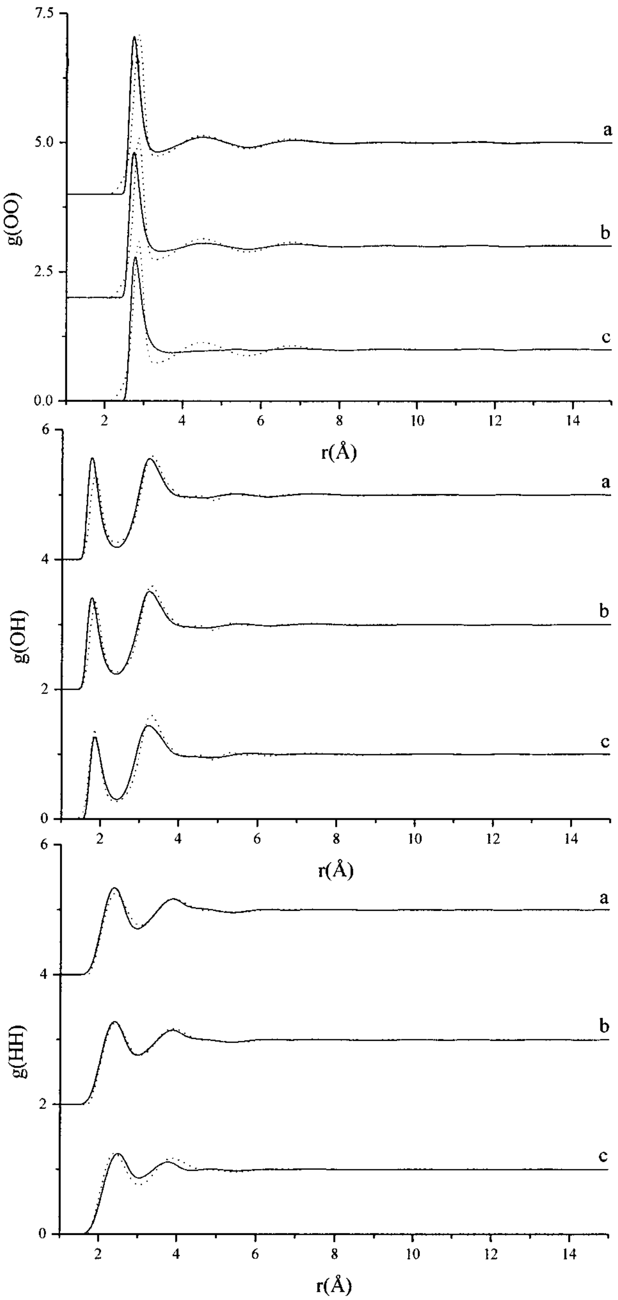

Figure 4. Radial distribution functions: (a) SPC/E (original), (b) SPC (refined), (c) TIP3P (modified) line, and the neutron diffraction data[5] dot. RDF curves are shifted by 2 units for clarity.

TABLE 6: Comparison of Different Water Properties from Two Different Molecular Dynamics Simulation Studies

model	*N*[c]	r_c (Å)[d]	E_{pot} (kJ/mol)[e]	ρ (g cm^{-3})[f]	*T* (K)[g]	*D* ($\times 10^{-9}$ m^2 s^{-1})[h]
SPC/E[a] original	820	12.0	−47.2(0.18)	1.008	301(4.4)	2.7(0.12)
SPC/E[b] original	901	12.0	−45.4(0.03)	0.998	298.2(1.4)	2.8(0.06)
SPC[a] original	820	12.0	−42.2(0.16)	0.988	301(4.4)	4.2(0.08)
SPC[b] original	901	12.0	−40.5(0.03)	0.998	298.6(1.1)	4.2(0.08)
TIP3P[a] original	820	12.0	−40.8(0.16)	1.001	301(4.4)	5.4(0.14)
TIP3P[b] original	901	12.0	−39.0(0.02)	0.998	297.0(0.9)	5.6(0.08)
TIP3P[b] modified	901	12.0	−39.8(0.02)	0.998	299.2(1.0)	5.9(0.08)
SPC[b] refined	901	12.0	−40.3(0.03)	0.998	297.7(1.2)	4.2(0.10)
exptl			−41.5[11]	0.997[40]		2.3[8,9]

[a] van der Spoel et al.[31] [b] The present study. [c] Number of H_2O. [d] Cutoff distance. [e] Potential energy. Average calculated over the analyzed part of the simulation, standard deviation (in parentheses). [f] Density. [g] Temperature. Average calculated over the analyzed part of the simulation, standard deviation (in parentheses). [h] Self-diffusion coefficient. Average calculated over the analyzed part of the simulation, standard deviation (in parentheses).

TABLE 7: Oxygen−Oxygen Pair Distribution Functions for All Water Models at 25 °C Using the Similar MD Simulations

water model	first maximum position (Å)	first maximum position g_{OO}	first maximum position (Å)	second maximum position (Å)	second maximum position g_{OO}	second minimum position (Å)	third maximum position (Å)	third maximum position g_{OO}
TIP3P original	2.77	2.67	(3.70)[a]	(4.50)	(0.99)	(5.80)	6.84	1.02
TIP3P modified	2.79	2.79	(3.80)	(5.40)	(1.00)	(5.94)	6.84	1.02
SPC original	2.78	2.78	3.55	4.50	1.04	5.68	6.85	1.03
SPC refined	2.75	2.80	3.45	4.50	1.05	5.68	6.85	1.03
SPC/E original	2.75	3.05	3.35	4.50	1.10	5.68	6.85	1.04
exptl[5]	2.88	3.09	3.30	4.50	1.14	5.68	6.73	1.07

[a] All numbers in parentheses are approximate values.

TABLE 8: Oxygen−Hydrogen Pair Distribution Functions for All Water Models at 25 °C Using the Similar MD Simulations

water model	first maximum position (Å)	first maximum position g_{OH}	firs minimum position (Å)	firs minimum position g_{OH}	second maximum position (Å)	second maximum position g_{OH}
TIP3P original	1.83	1.24	2.42	0.28	3.22	1.44
TIP3P modified	1.85	1.26	2.43	0.30	3.24	1.44
SPC original	1.80	1.38	2.41	0.24	3.27	1.52
SPC refined	1.77	1.41	2.41	0.23	3.25	1.51
SPC/E original	1.77	1.57	2.41	0.19	3.25	1.56
exptl[5]	1.85	1.38	2.40	0.27	3.30	1.60

but the height of the peak is too low and the structure beyond the first peak is missing. Both SPC/E and SPC (refined) have very similar peak positions also for g_{OH}. The first and the second peak positions occur at too short distances when compared with experiment. SPC/E has a too high first peak, but for SPC (refined) the peak height is similar to experiment. Both SPC/E and SPC (refined) have too low second peaks. TIP3P (modified) has the right first peak position, but the height of the peak is too low. The second peak is shifted to shorter distance and the height of the peak is too low. The SPC (refined) model gives good agreement with experiment for g_{HH}. The SPC/E has the significantly similar peak positions, but the first peak is too high when compared with SPC (refined). The modified TIP3P has a flattened structure; both peaks are shifted inward and the heights of the peaks are too low.

The oxygen−oxygen pair correlation functions are very similar when SPC (original) and SPC (refined) are compared, and TIP3P (modified) is also quite similar to TIP3P (original). The modification of the TIP3P water model changes slightly the structure of the model liquid. TIP3P (original) has the first peak at a shorter distance than TIP3P (modified) and the height of the peak is also lower. The well-documented problem for the TIP3P model, to have too little structure beyond the first peak, is similar in both models. The refined SPC water model gives slightly more structure when compared with the SPC (original), and the first peak is shifted to the same position as the SPC/E has. The position of the first peak for SPC (original) is closer to experiment, but the height of the peak is lower when compared with the SPC (refined).

By using long trajectories without velocity rescaling (continuous dynamics), it was possible to calculate the radial distribution functions, g_{OO}, g_{OH}, and g_{HH}, with high statistical accuracy and the slightly different structures for the model liquids could be compared.

4. Summary and Discussion

We have studied structural and dynamic properties of three-site water models commonly used in biomolecular simulations: TIP3P, SPC, SPC/E, and modified versions of TIP3P and SPC. These models were all parametrized using small systems with certain schemes to handle long-range electrostatic interactions. In actual biomolecular simulation applications, and also in studies of these models themselves, other schemes are often employed, which may affect the results directly through the changes introduced in the interaction potential; the effects may also be more indirect through effects on the temperature, and temperature stability, of the system. All simulations in this study were performed with a 12.0 Å cutoff and the self-diffusion coefficient may be slightly different if the long-range interactions are calculated using other methods.

With nanosecond simulations of around 1000 water molecules the self-diffusion coefficient can be determined with ∼0.5% error, if the temperature is stable. A drift in the temperature was obtained when the size and updating frequency of the nonbonded list was underestimated. We have also shown that temperature control by weak coupling to a heat bath in the form of velocity rescaling causes deviation from linearity when the slope of MSD vs time was calculated.

In the parametrization of TIP3P (original), Monte Carlo simulations were performed on 125 water molecules using a spherical cutoff at 7.5 Å. Both SPC and SPC/E were parametrized and tested using 216 water molecules with molecular dynamics simulations where the nonbonded interactions were truncated with a spherical cutoff at 9.0 Å applied on a molecule-by-molecule basis. The refinement of the SPC water model was performed by weak coupling to system pressure and potential energy per mol (the heat of vaporization)[14] using several different system sizes and cutoff distances. The bulk water structure and dynamics, as characterized by the radial distribution functions, g_{OO}, g_{OH}, and g_{HH}, and the self-diffusion coefficient D for the refined SPC were not included in that study.

In this study we have shown that different water models have significantly different properties when simulated under exactly the same conditions. Our results are in good agreement with recently reported data by van der Spoel et al.[31] (Table 6). The bulk properties of liquid water in molecular dynamics simulations are affected, for example, by the system size, the method used for truncating long-range interactions and the method used for temperature control. When our results are compared with the results of van der Spoel et al.[31] (Table 6) the differences in potential energy and in the self-diffusion coefficients are the effects of different simulation methods used.

The calculated self-diffusion coefficients are consistent with the radial distribution functions g_{OO}, g_{OH}, and g_{HH}. The SPC/E water model gives the best bulk water dynamics and structure, the SPC (original) water model gives less structure and faster diffusion, whereas the TIP3P (modified) water model gives even less structure and faster dynamics when compared with the experimental values for liquid water. The second peak is the g_{OO}, indicating the second hydration shell of water, is related to the self-diffusion coefficient, such that the water model with less defined second hydration shell has a larger self-diffusion coefficient.

The modification of the TIP3P water changed the bulk water dynamics and structure slightly when compared with the original TIP3P water model. The refined SPC water model is also quite similar to the original SPC model, but since the charges are reduced the dipole moment is also reduced, from 2.274 to 2.237 D. It should be noted that the TIP3P (original and modified) model has almost the same dipole moment as the SPC/E model, 2.347 and 2.351 D, respectively. The larger dipole moment of the SPC/E water model, when compared with the original SPC water model with similar Lennard-Jones (LJ) parameters and model structure, is the due to increased point charges. The point charges were changed when the original SPC water model was reparametrized with a polarization correction.[15] The bulk properties for the SPC/E model are closer to the experimental values of liquid water than the original SPC water model. The larger point charges also give a lower potential energy for the SPC/E model (Figure 1 and Table 6) when compared with the original SPC water model.

When all five models are compared with respect to self-diffusion coefficients or radial distribution functions it is clear that they form three different groups: TIP3P (original) and TIP3P (modified), SPC (original) and SPC (refined), SPC/E. SPC remains SPC, and TIP3P remains TIP3P, even after the modifications.

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References and Notes

(1) Neilson, G. W., Enderby, J. E., Eds. *Water and Aqueous Solutions;* Adam Hilger: Bristol, 1986.
(2) Corongiu, G.; Clementi, E. *J. Chem. Phys.* **1992**, *97*, 2030.
(3) Narten, A. H.; Levy, H. A. *J. Chem. Phys.* **1971**, *55*, 2263.
(4) Neilson, G. W.; Enderby, J. E. *J. Phys. Chem.* **1996**, *100*, 1317.
(5) Soper, A. K.; Phillips, M. G. *Chem. Phys.* **1986**, *107*, 47.
(6) Postorino, P.; Tromp, R. H.; Ricci, M.-A.; Soper, A. K.; Neilson, G. W. *Nature* **1993**, *366*, 668.
(7) Soper, A. K.; Bruni, F.; Ricci, M. A. *J. Chem. Phys.* **1997**, *106*, 247.
(8) Mills, R. *J. Phys. Chem.* **1973**, *77*, 685.
(9) Price, W. S.; Ide, H.; Arata, Y. *J. Phys. Chem. A* **1999**, *103*, 448.
(10) Soper, A. K. *J. Phys.: Condens. Matter* **1996**, *8*, 9263.
(11) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926.
(12) Neria, E.; Fischer, S.; Karplus, M. *J. Chem. Phys.* **1996**, *105*, 1902.
(13) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. In *Intermolecular Forces;* Pullman, B., Ed.; Reidel: Dordrecht, 1981, p 331.
(14) Berweger, C. D.; van Gunsteren, W. F.; Müller-Plathe, F. *Chem. Phys. Lett.* **1995**, *232*, 429.
(15) Berendsen, H. J. C.; Grigera, J. R.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269.
(16) Matsuoka, O.; Clementi, E.; Yoshimine, M. *J. Chem. Phys.* **1976**, *64*, 1351.
(17) Watanabe, K.; Klein, M. L. *Chem. Phys.* **1989**, *131*, 157.
(18) Liu, Y.; Ichiye, T. *J. Phys. Chem.* **1996**, *100*, 2723.
(19) Buch, V.; Sandler, P.; Sadlej, J. *J. Phys. Chem. B* **1998**, *102*, 8641.
(20) Levitt, M.; Hirshberg, M.; Sharon, R.; Laidig, K. E.; Daggett, V. *J. Phys. Chem. B* **1997**, *101*, 5051.
(21) Jorgensen, W. L.; Jenson, C. *J. Comput. Chem.* **1998**, *19*, 1179.
(22) Chialvo, A. A.; Cummings, P. T. *J. Chem. Phys.* **1996**, *105*, 8274.
(23) Dang, L. X. *J. Phys. Chem. B* **1998**, *102*, 620.
(24) Ryckaert, J.-P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327.
(25) Darden, T. A.; Sagui, C. *Annu. Rev. Biophys. Biomol. Struct.* **1999**, *28*, 155.
(26) van Gunsteren, W. F.; Berendsen, H. J. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 992.
(27) Ewald, P. *Ann. Phys.* **1921**, *64*, 253.
(28) Steinbach, P. J.; Brooks, B. R. *J. Comput. Chem.* **1994**, *15*, 667.
(29) Prevost, M.; Van Belle, D.; Lippens, G.; Wodak, S. *Mol. Phys.* **1990**, *71*, 587.
(30) Harvey, S. C.; Tan, R. K.-Z.; Cheatham, T. E., III *J. Comput. Chem.* **1998**, *19*, 726.
(31) van der Spoel, D.; van Maaren, P. J.; Berendsen, H. J. C. *J. Chem. Phys.* **1998**, *108*, 10220.
(32) Feller, S. E.; Pastor, R. W.; Rojnuckarin, A.; Bogusz, S.; Brooks, B. R. *J. Phys. Chem.* **1996**, *100*, 17011.
(33) Tasaki, K.; McDonald, S.; Brady, J. W. *J. Comput. Chem.* **1993**, *14*, 278.
(34) Liu, Q.; Schmidt, R. K.; Teo, B.; Karplus, P. A.; Brady, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 7851.
(35) Smith, P. E.; Blatt, H. D.; Pettitt, B. M. *J. Phys. Chem. B* **1997**, *101*, 3886.
(36) Makarov, V. A.; Feig, M.; Andrews, B. K.; Pettitt, B. M. *Biophys. J.* **1998**, *75*, 150.
(37) Allen, M. P.; Tildesley, D. J. *Computer Simulations of Liquids*; Oxford Science: Oxford, 1987.
(38) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187.