
Parameterization and Evaluation of a Flexible Water Model

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ABSTRACT

The thermodynamic, dielectric, and dynamic properties of a newly parameterized flexible water model are studied using molecular dynamics simulations. The potential function developed is based on the popular simple point charge (SPC) rigid model with the addition of appropriate harmonic and anharmonic energy terms for stretching and bending. Care was taken to account for the self-polarization and gas-phase monomer energy corrections during the parameterization, which have typically been ignored in past studies. The results indicate that an increased Lennard-Jones repulsive coefficient and slightly scaled partial charges are required when adding flexibility to the rigid model potential to reliably reproduce the experimental density, energy, and O...O radial distribution function of water at 298 K and 1 atm. Analysis of the power spectrum derived from the H-velocity autocorrelation function allowed the water potential to be evaluated further and refined by adjusting the valence forces to fit the vibrational frequencies of the gas and liquid. Once a consistent set of parameters was determined, the static dielectric properties of the water model were calculated at two temperatures using the reaction field method to treat long-range forces and correlations. The dielectric constant of 75 ± 7 calculated at 300 K is in good agreement with the experimental value of 78.5. The Kirkwood g factor was also examined for temperature dependence and showed the correct increasing behavior with decreasing T . As a final check of the water potential, the free energies of solvation of a flexible water molecule and neon were predicted using thermodynamic perturbation methods. The calculated solvation energies of -7.0 ± 0.8 for water and 2.7 ± 0.7 for neon are both consistent with the experimental values of -6.3 and 2.7 kcal/mol. Comparisons are made throughout the study with the results of previous rigid and flexible model simulations. © 1995 by John Wiley & Sons, Inc.

Introduction

Although there have been an overwhelming number of molecular dynamics simulations performed on condensed phase systems over the years, very few of these have employed water models that include intramolecular vibrations. The rigid approximation has dominated both developmental efforts and applications in explicit water calculations.¹⁻⁴ It is becoming increasingly apparent, however, that flexible water potentials may in fact be better suited to simulating the physical properties of water and those of hydration (which is true by default if we are interested in vibrational analyses).⁵⁻⁷ Although the benefits to dynamic and dielectric properties have been known for some time, flexible water potentials and parameters have undergone minimal refinements, especially when compared to rigid models. For the most part, existing rigid-model potentials have been simply augmented with an intramolecular potential with little or no adjustments.^{5,6,8,9} In the limited number of parameterizations performed, the results have been mixed, with each model showing some type of deficiency in reproducing the structural, vibrational, or thermodynamic properties of water. Often, the model is simply not applied across a wide enough range of physical properties to evaluate the utility fully.

In this study, we describe and parameterize a simple and efficient flexible water potential to be of general applicability in molecular dynamics studies. This is accomplished using relatively long molecular dynamics simulations (0.2 to 1 nanosecond) to evaluate the suitability of the potential for simulating an unprecedented number of experimental properties, including dielectric. Our approach is further distinguished from previous model studies in that we also account for corrections due to the self-polarization energy inherent in the potential,¹⁰ as well as the necessary correction from the average monomer energy upon going from gas to liquid.^{11,12} This latter correction is typically considered negligible in rigid model studies, but certainly should not be ignored here. This has also been noted in an informative research note by Barrat and McDonald, in which the role of flexibility in water simulations is discussed in detail.¹² Our study is similar to others, however, in that we chose the popular rigid SPC model as

the starting point for refinement.¹³ This model is not only well proven for simulating the thermodynamic properties of solvation for both proteins and small molecules but is also the most extensively applied potential in flexible model studies. Barrat and McDonald,¹² Dang and Pettitt,⁸ Yip and co-workers,⁶ and Toukan and Rahman⁵ have all used flexible SPC models with varying degrees of success in past studies.

In the following sections, we outline the model potential and simulation techniques, describe the development of the parameters, and apply the water model to calculate the static thermodynamic, structural, and dynamic properties of water. Care is taken in this work to average over sufficient time lengths to ensure that the measurements are reasonably well converged. The evaluation criteria include experimental density, internal energy, specific heat, vibrational spectra, radial distribution functions, self-diffusion, and free energy of hydration. The static dielectric properties of the water model were also studied at two temperatures using the reaction field method to capture long-range forces. The effect of these added contributions to the free energy of hydration of two simple solutes is also investigated by direct comparisons of the results with and without the continuum applied. Finally, the results are analyzed with respect to previous simulations of flexible and rigid water.

Computational Methods

In developing the potential function for use in this work, we considered several simple and complex approaches to adding flexibility to the rigid SPC model. Although there has been some discussion regarding the benefits of the Morse function and cross terms for valence interactions,^{5,8} we chose a simple quadratic + cubic function for bond stretching and a single quadratic term for angle bending.¹⁴ This is a much more efficient way to include anharmonicity in the potential and, as will subsequently be shown, is effective in modeling the internal vibrations. We should add that a stretch-bend term was tested¹⁴ but failed to produce significant benefits in the model. The potential function also includes Lennard-Jones and Coulombic nonbond terms yielding the overall en-

ergy expression

$$\begin{aligned}
 E(r) = & \sum_{\text{bonds}} K_l(l - l^0)^2 + K_l K_{\text{cub}}(l - l^0)^3 \\
 & + \sum_{\text{angles}} K_\theta(\theta - \theta^0)^2 + \sum_{\nu dW} \frac{A}{r_{i,j}^{12}} - \frac{B}{r_{i,j}^6} \\
 & + \sum_{\text{charges}} \frac{q_i q_j}{r_{i,j}} \quad (1)
 \end{aligned}$$

where r is the set of atomic coordinates and $r_{i,j}$ defines the interatomic distances. (The parameters are described in detail later.) This function and its derivatives have been implemented and applied to simulate the physical properties of bulk water using molecular dynamics techniques.¹⁵ The majority of the calculations described in this work were performed on a cubic box of water containing 216 periodic molecules. This gives a box length of ~ 18.6 Å for an experimental density of 0.997 g/mL. The nonbonded pairlist was generated on a molecular basis after each step in the time integration using an O...O cutoff distance (r_c) of 8.5 Å. Pressure and temperature coupling were performed using both scaling (due to Berendsen et al.¹⁶) and stochastic collisions (due to Andersen¹⁷) to provide standard conditions for parameterizing and evaluating the model. The choice of temperature coupling methods actually depends on the potential truncation method. In this work, we have applied a residue-based switch function to conserve energy whenever possible in the simulations.^{18,19} This circumvents the need for velocity scaling to remove excess energy generated when an uncorrelated water molecule jumps into the cutoff sphere of another water molecule, allowing either Newtonian trajectories to be propagated or stochastic temperature coupling to be performed if desired. The switch interval was set from 8.0 Å to 8.5 Å, over which distance the energy is smoothed to zero.

The equations of motion were integrated using the Velocity Verlet algorithm using 1 femtosecond (fs) timesteps.¹⁸ The stability and proper functioning of the program for the system under investigation was verified by plotting the root mean square (rms) fluctuation in total energy versus the timestep squared. This relationship should be linear over suitable time steps for Verlet-based algorithms.^{11,15} Of course, a prerequisite for this behavior is energy conservation. As shown in Figure 1, this condition is met for timesteps through 1.25 fs, which is slightly greater than the value used here estimated from the O—H oscillation period (~ 10

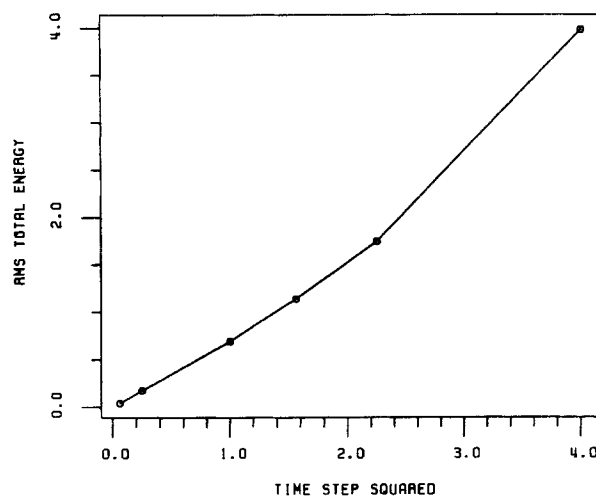


FIGURE 1. Plot of the fluctuation in total energy versus the timestep squared for 1 ps constant energy simulation.

fs). (As a general rule, an upper bound on the timestep can be approximated by 1/10 the shortest oscillation period in the system.)

The reaction field method has also been implemented in this work to calculate the dielectric properties of the water model following the protocol outlined by Neuman.²⁰ This approach has been shown to produce equivalent results when compared with lattice summation techniques but is much more efficient in implementation and calculation. The method accounts for the long-range dipolar interactions between water molecules by adding a correction term to the electrostatic component of the energy equation. In this scheme, the Coulombic potential takes the following form:

$$E_{RF}(r) = \sum_{\text{charges}} \frac{q_i q_j}{r_{i,j}} \left[1 + \frac{\epsilon_{RF} - 1}{2\epsilon_{RF} + 1} \left(\frac{r_{i,j}}{r_c} \right)^3 \right] \quad (2)$$

where ϵ_{RF} is the dielectric constant of the background continuum, r_c is the nonbonded cutoff distance applied on a molecular basis, and $r_{i,j}$ is the interatomic distance (as noted earlier). The modified energy expression and its derivatives have been implemented using conducting boundary conditions ($\epsilon_{RF} = \infty$). This choice has been shown to be satisfactory for simulating the dielectric properties of polar fluids such as water and further simplifies the calculations.²⁰ As in Neuman's study, switch functions or tapering functions were not applied with the reaction field. Under these conditions, the static dielectric is de-

terminated by the following relationship:

$$\varepsilon_0 - 1 = \frac{4\pi\langle M^2 \rangle}{3VkT} \quad (3)$$

where V is the volume of the system, k is the Boltzman constant, T is the temperature, and M is the total dipole moment of the sample given by

$$M = \sum_{i=1}^{n \text{ atoms}} q_i \vec{r}_i \quad (4)$$

Another useful quantity often cited in previous reports is the finite system analog of the Kirkwood g factor, G_k , defined by

$$G_k = \frac{\langle M^2 \rangle}{N\langle \mu^2 \rangle} \quad (5)$$

where N is the number of water molecules in the sample and $\langle \mu^2 \rangle$ is the mean-squared molecular dipole moment.^{6,20} The Kirkwood g factor for an infinite system, g_k , can also be determined from these equations

$$g_k = G_k \left(\frac{2\varepsilon_0 + 1}{3\varepsilon_0} \right) \quad (6)$$

and is sometimes examined for temperature dependence. (Further details of these equations for use in water simulations can be found in refs. 6 and 20.)

Results and Discussion

The potential function was parameterized to fit both the static thermodynamic and spectroscopic (infrared) properties of liquid water on a trial-and-error basis using molecular dynamics simulations. The initial parameters reported in Table I have been taken from the rigid SPC water model and derived using a normal mode analysis of the SPC monomer to reproduce gas-phase vibrational

frequencies.^{8,14} Although we could not fit both the asymmetric and symmetric stretches of the infrared spectrum with these valence terms, the resulting force constants are reasonable estimates to begin the liquid simulations. The calculated and experimental frequencies for the monomer are given in Table II. As a first approximation, the cubic force constant was set to zero.

Refinement was accomplished in two ways. First, the intramolecular components were evaluated and adjusted according to the vibrational properties of water. Several constant-energy Newtonian trajectories were calculated for the liquid at 298 K using the initial parameter set with increasing values of K_{cub} . The power spectrum was then calculated by transformation of the hydrogen autocorrelation function to examine the parameter dependence of the vibrational frequencies.^{5,6,8} The spectrum calculated with $K_{\text{cub}} = 0$ showed the characteristic blue shift in the bending frequency upon going from gas to liquid but failed to produce the red shift in stretching.^{5,8,21} Furthermore, significant splitting of the symmetric and asymmetric stretching bands was still evident, which is also inconsistent with experiment. As $|K_{\text{cub}}|$ was increased, however, the stretching frequencies not only red shifted proportionally but also showed substantially less splitting (i.e., a small shoulder was evident). This behavior is depicted in Figure 2, which shows the power spectrum with and without the cubic stretch term applied.

In a second set of simulations, the nonbonded parameters were evaluated and adjusted to reproduce experimental density and internal energy using constant pressure/temperature molecular dynamics calculations. (See Table III for values.) We also monitored the specific heat, volume, and the O...O radial distribution function. The properties were averaged over 200-ps trajectories using the pressure and temperature coupling methods described by Berendsen et al.¹⁶ The switch function was not applied in these simulations because the physical significance of the forces computed over

TABLE I.
Initial and Final Parameter Sets of the Water Model Potential.^a

	K_f	I^0	K_θ	θ^0	K_{cub}	A	B	q_H	μ
Initial	547.5	1.0	49.9	109.5	0.0	529400.	625.47	0.41	2.27
Final	547.5	1.0	49.9	109.5	-1.65	650000.	625.47	0.413	2.29

^a See eq. (1) for functional form. Units of energy are kcal/mol, lengths and angles are Å and radians. Partial charges are in electron units.

TABLE II.
Experimental and Calculated Vibrational
Properties of Water (cm^{-1}).

	Experimental ^a	Calculated
Monomer		
Symmetric stretch	3755	3740
Symmetric stretch	3656	3669
Bend	1594	1594
Liquid		
Stretch	3557	3551 (3452–3648) ^b
Bend	1670	1661 (1629–1726)
Vibrational	597	521 (456–651)

^aMonomer ground state frequencies are given in ref. 8. Liquid frequencies are taken from ref. 21. Stretching and bending at 313 K, vibrational is for the supercooled liquid (258 K).

^bRange within 30% of peak intensity.

the switch interval is questionable, especially in calculating the virial. Under these conditions local heating can be a problem, so we performed massive collisions every 2000 timesteps to ensure that this effect is kept to a minimum.* The density and interaction energy calculated using the standard SPC nonbonded parameters slightly increased beyond the experimental values with the addition of flexibility. This behavior has also been noted and examined in detail by Barrat and McDonald in a previous study of flexible and rigid SPC water.¹² The neighboring waters in the liquid induce an enhanced dipole moment and slight elongation of

*Massive collision is a variation of a stochastic collision method described in ref. 17 whereby the velocities are completely reassigned at certain intervals to give a canonical distribution of energy states.

TABLE III.
Calculated Properties of Liquid Water at 298 K and 1 atm.^a

Sim. time	E_i (kcal/mol)	E'_i	C_p (cal/deg mol)	d (g/cm ³)
200 ps	-10.03 ± 0.10	-9.99 (-9.92) ^b	18.9 (17.99)	0.997 ± 0.012 (0.997)
200 ps	-10.00 ± 0.10	-9.96	16.8	0.997 ± 0.012
200 ps	-10.00 ± 0.10	-9.96	17.4	0.995 ± 0.013
With switch function ^c				
200 ps	-10.33 ± 0.12	-10.29	23.4	1.001 ± 0.014
Energy corrections ($E'_i = E_i - E_{\text{intra}}^{\text{gas}} + E_{\text{pol}}$)				
E_{pol}	0.96			
$E_{\text{intra}}^{\text{gas}}$	0.92			

^aUncertainties are rms fluctuations in the property.

^bSee ref. 1 and citations therein for a discussion of the experimental energy.

^cSee text.

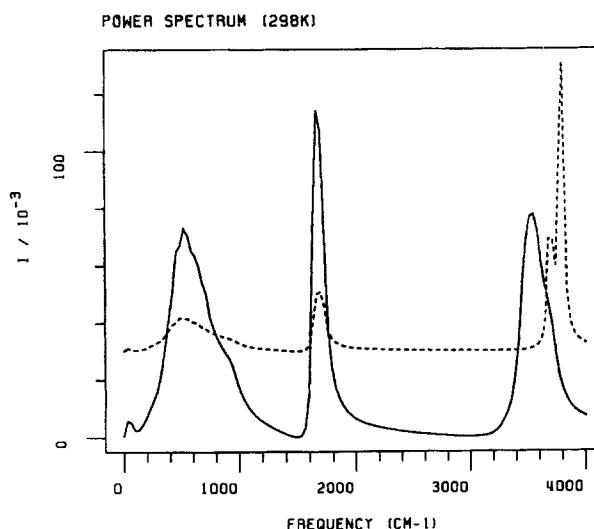


FIGURE 2. Power spectrum (ir) of liquid water at 298 K. The dotted line is the pure harmonic potential.

the bonds in the average structure, increasing the cohesive forces between water molecules. This, in turn, causes the interaction energy to become more negative and the pressure of the system to drop (or the density to increase). To balance this effect, the repulsive coefficient of the Lennard-Jones term was increased over several simulations until the density and energy approached the experimental values. This approach was not completely satisfactory and also required slight scaling of the partial charges to fit both properties.

The aforementioned calculations were performed iteratively during the latter stages of refinement to complete the parameterization. The three variables adjusted, K_{cub} , A , and q_H , were easily converged to produce consistency in the

physical properties calculated. The final parameter set is given in Table I. As might be expected from the preceding comments, the repulsive coefficient and partial charges (and therefore the molecular dipole) show slight increases over the rigid SPC model. Because the cubic term has not been used in simulating flexible water in past studies, it is difficult for us to assign significance to the value. We should point out, however, that the value arrived at here is much smaller than those used in the MM2 force field,²² suggesting that minor softening of the harmonic well is needed in water potentials to model the vibrations in the liquid.

The power spectrum of the model calculated at 298 K is shown in Figure 2 and displays the three characteristic frequency bands of liquid water corresponding to librational, bending, and stretching. A fourth peak is also noticeable at low frequency ($\approx 50 \text{ cm}^{-1}$) for the hindered translations in the liquid. The positions of these bands in the spectrum are all in good agreement with the experimental values, as indicated in Table II. As noted earlier, this figure also contains the spectra for the pure harmonic potential, which fails to show the red shift in the stretching and when compared to the gas-phase frequency. This agrees with the results of Toukan and Rahman, which also indicated that anharmonicity in the bond term is required to capture this effect in the liquid.⁵ Bending, on the other hand, shows the blue shift nearly quantitatively using the simple harmonic potential with no additional complexity. In the majority of past studies of flexible water, cross terms that couple stretching and bending have been included as well,^{5,6,8} but this does not appear necessary in the model developed here. No attempts were made to fit the librational frequency of water during the parameterization. This band arises from nonbonded interactions in the liquid and is slightly shifted lower in frequency than the experimental value ($\approx 70 \text{ cm}^{-1}$) for the supercooled liquid.²¹ The significance of this difference, however, is unclear because the librational band is known to shift to lower frequency with increasing temperature, consistent with our results.²¹

The density, internal energy, and specific heat for the water model are reported in Table III for three independent constant pressure/temperature simulations. We have also calculated correction terms for the internal energy that account for the average gas-phase intramolecular energy of the monomer ($E_{\text{intra}}^{\text{gas}}$) and the self-polarization energy (E_{pol}) of the molecule inherent in the parameterization.^{10,11} Corrections of this type have been

described in past studies but have not been routinely applied in the development of model potentials.^{2,10-12} $E_{\text{intra}}^{\text{gas}}$ was determined by simulating the box of waters with the nonbonded potential turned off. The intramolecular energy was then averaged over all monomers for 100 ps of molecular dynamics. The monomer energy calculated, $0.92 \pm 0.04 \text{ kcal/mol}$, slightly deviates from the classical value of $3/2RT$, indicating that the potential is close to harmonic in the gas phase. The self-polarization energy of the monomer was determined according to the protocol outlined by Berendsen et al.¹⁰ The energy calculated, 0.96 kcal/mol , accounts for the polarization built into the dipole of the water model (2.29 D) as compared to the gas-phase value of 1.85 D for the monomer (or, more simply, the energy to induce the dipole). Contributions to the correction term due to dipole fluctuation changes were not included here. The corrected internal energies reported, E'_i (where $E'_i = E_i - E_{\text{intra}}^{\text{gas}} + E_{\text{pol}}$) all show excellent agreement with the experimentally derived value reported in Table III. We should point out, however, that there may be contributions missing from quantum corrections to the energy which, depending on the method of calculation, range from near zero to more than a kilocalorie.^{1,2,11} The approach followed here assumes the contribution to be relatively small, which may be disputed by some but is certainly consistent with previous parameterizations of effective pair potentials for simulating water.^{1,8,10,13}

As expected from the method of parameterization, the densities reported for all three independent runs at 298 K and 1 atm are in excellent agreement with the experimental value of 0.997 g/cm^3 . Although not reported in Table III, we also simulated the water sample near the melting point to examine the temperature dependence of the density. At 275 K and 1 atm, the density increased to 1.006 g/cm^3 , consistent with the experimental trend but slightly greater than the actual value of 1.000 g/cm^3 . Considering that the parameters were not optimized for use near the melting point, this agreement is reasonable. The specific heat, C_p , reported in Table III was computed from the fluctuation in the internal energy, E_i , of the system and is therefore plagued by statistical uncertainty.^{1,15} The values include the usual $3R$ augmentation to account for the classical kinetic energy contributions of the monomer. The O...O radial distribution function was also calculated during the simulations and is given in Figure 3.¹⁵ The first peak shows the correct width and height

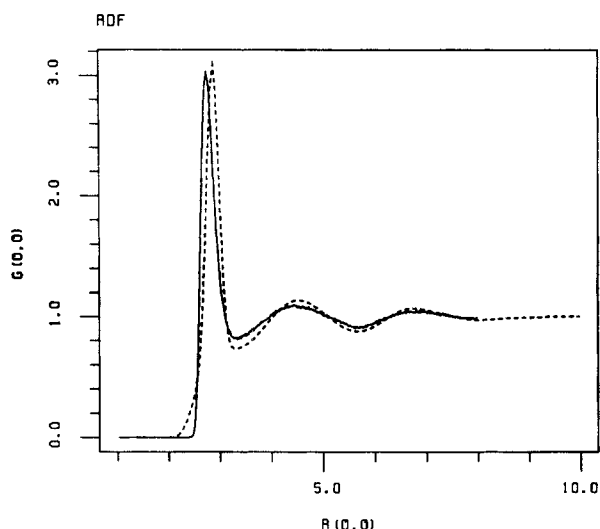


FIGURE 3. The O...O radial distribution function for liquid water averaged over a 200-ps simulation. The dashed line is the experimental distribution taken from ref. 23.

as compared with neutron diffraction data²³ but is slightly shifted toward a denser packing of the neighbors. Integration of the first peak to 3.5 Å yielded a nearest neighbor coordination number of 5.1, which also indicates tighter packing in the liquid (considering the experimental value of 5.0). Although it was possible to adjust further the characteristics of the first peak by scaling the Lennard-Jones repulsive coefficient, the structure evident at the second two peaks greatly diminished as the value of the coefficient was increased. Despite these discrepancies, the calculated radial distribution function for our flexible model shows considerably better agreement with experimental data than the majority of those reported in past studies of rigid and flexible water models.^{1,5,8}

The basic properties reported in Table III were also calculated with the switch function applied to examine the effect this scaling term has on the equilibrium values. The temperature coupling method was also changed to massive collisions (every 2000 steps). As can be seen in Table III, the internal energy of the system is more negative, leading to a drop in the pressure and an increase in the density. The values are still in reasonable agreement with experiment, however, so it is hard to assign significance to the minor differences reported. To explore this further, we reparameterized the water potential using the protocol described earlier with the switch function applied. The Lennard-Jones repulsive coefficient and the

hydrogen partial charge were both reduced from 650,000 and 0.413 to 649,000 and 0.41, respectively (see Table I for units), whereas all other parameters remained the same. In this light, the differences in the potential with and without the switch function appear fairly small and most likely can be disregarded in other routine calculations that require energy conservation. Perhaps the most significant effect is seen in the specific heat or the fluctuations in the energy of the system. This property shows a dramatic increase under these conditions, which we ascribe to the use of the stochastic collision method for temperature coupling. This approach is physically correct in contrast to the Berendsen method, which may damp out fluctuations in the system. Although the C_p reported is substantially larger than the experimental value, we should point out that no quantum corrections have been considered that would most likely contribute negatively to the calculated value.^{1,11} The overall uncertainty in this property, however, makes this postulate highly tentative, and the increase noted may simply reflect poor convergence in the measurement.

The self-diffusion constant of the water model was calculated at three temperatures using several constant energy/volume simulations. The system was brought to equilibrium at the appropriate temperature before calculating the Newtonian trajectories for the water molecules. The self-diffusion constant was then determined from the Einstein relation by plotting time versus the center of mass displacement squared.^{15,24} The linear (or diffusional) regime was identified in the plot and least squares fit to determine the slope of the line.²⁴ The values reported in Table IV have been averaged over a minimum of 20 independent samples to provide a reliable estimate of this dynamic property. At 300 K, the diffusion constant calculated is consistent with both the experimental value and the results of a previous study of flexible SPC water.⁶ Although a slight enhancement in the rate is evident, the agreement noted here is better than the majority of diffusion constants reported for rigid models.^{1,2} At lower temperatures, however, the disparity with the experimental values is more pronounced, which is not surprising because the potential has been parameterized at the higher temperature. The agreement is still reasonably good over a relatively wide temperature range considering the statistical errors in the calculations. It is also important to note that most previous studies of water models have not examined the

TABLE IV.
Dielectric Properties and Self-Diffusion Constants of Water.^a

Temperature	ϵ_0	G_k	g_k	$\sqrt{\langle \mu^2 \rangle}$ (D)	$D(10^{-5} / \text{cm}^2 / \text{s})$
300 K					
0.5 ns	77 ± 11	3.7 ± 0.5	2.5 ± 0.6	2.458	2.47 ± 0.32
0.5 ns	87 ± 12	4.2 ± 0.6	2.8 ± 0.7	2.458	
1.0 ns	75 ± 7	3.6 ± 0.3	2.4 ± 0.4	2.458	
Exp.	78^b 80^c		2.9^d	2.35	2.3 (298 K) ^e
270 K	—	—	—	—	1.62 ± 0.41
Exp.					1.1^f
259 K					
0.5 ns	112 ± 30	4.7 ± 1.3	3.1 ± 1.4	2.462	1.04 ± 0.41
Exp.	94^g				0.80^h

^aUncertainties are standard deviations. Statistical inefficiencies were taken from the relaxation times in the total dipole reported in ref. 6. ^bRef. 25. ^cRef. 26. ^dRef. 20. ^eRef. 27. ^fRef. 28. ^gRef. 25. ^hRef. 29.

effect of temperature on diffusion, so it is difficult to make further comparisons.

The dielectric properties of the water model have been calculated at two temperatures using the reaction field method.²⁰ Simulations of this type are known to require rather long time scales for convergence, so we have performed several independent calculations ranging from 0.5 ns to 1.0 ns to provide some measure of the overall uncertainty in the properties. Unfortunately, most previous studies have not reported multiple simulations (due to the intense demands of the computations). Because our system is smaller than those previously employed in reaction field calculations, we also checked for potential artifacts in the water structure that may adversely effect our simulations by reexamining the O...O radial distribution function.^{15, 20, 30, 31} As shown in Figure 4, the distribution is nearly identical to that previously calculated (in Fig. 3), indicating that the reaction field geometry has little effect on the water structure in our implementation.

The results given in Table IV show the correct temperature dependencies in the dielectric and the Kirkwood g factor²⁰ and compare remarkably well with the data reported by Yip and co-workers for another flexible SPC model.⁶ The average dielectric and g factor computed from the table at 300 K (80 ± 6 and 2.6 ± 0.3) are also in accord with experiment, but the close agreement evident may be fortuitous give the range of the measurements. In addition, some errors may also be introduced from the use of conducting boundary conditions in the simulations ($\epsilon_{RF} = \infty$ instead of the $\epsilon_{RF} = \epsilon_0$),

which is an approximation.^{20, 31} The differences in the properties reported in previous studies, however, are small ($\sim 3\%$) and easily fall within the statistical errors of the calculations.^{20, 31} The actual dielectric of the water model, therefore, is most likely in the range of this average (74–86).

Perhaps the best estimate of the dielectric constant for the model is represented by the value derived from the 1-ns simulation. This time scale has been commonly used in past studies to determine dielectric properties to a reasonable resolution and is certainly further converged than the 0.5-ns

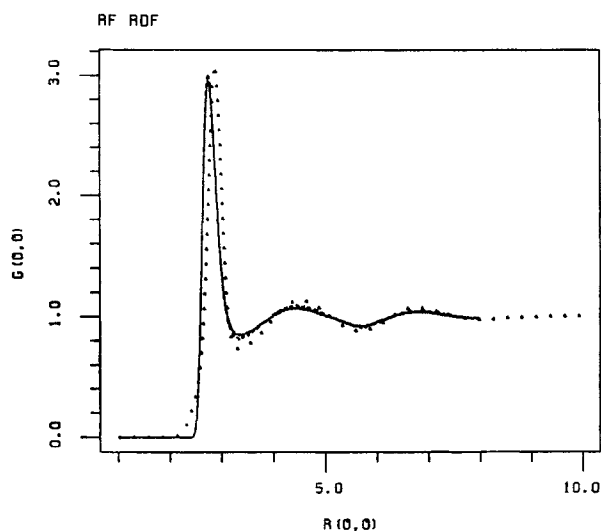


FIGURE 4. The O...O radial distribution function for liquid water with the reaction field applied. The dashed line is the distribution taken from the standard calculation. The dotted line represents the experimental data of ref. 23.

runs.^{20,31} The calculated dielectric constant of 75 ± 7 for our flexible model shows improvement over previous rigid model calculations that have typically underestimated the value as compared to experiment.^{1,20,31} Although the dielectric at 300 K is satisfactory, the low-temperature value reported in Table IV has increased too far and shows a considerable enhancement over the experimental value. The uncertainty is large, however, which is due to the long relaxation time of the total dipole moment [$\langle M^2 \rangle$ in eq. (3)] in the supercooled liquid.⁶ Convergence in the dielectric properties at 259 K would most likely require significantly longer simulation times, which are beyond the scope of this study. Given the statistical error and the fact that the parameters have been developed for simulations near 300 K, the agreement is still reasonable.

As a final evaluation of the water model, the free energy of solvation was calculated for two solute systems using thermodynamic perturbation methods.³² The details of this computational approach are discussed elsewhere and will not be repeated here for brevity.^{32,33} The calculations performed, neon to water and neon to nothing, provide an excellent basis to examine further both the thermodynamics and the general applicability of the water model for molecular simulations. We have also calculated the free-energy differences of these systems with the reaction field applied to gain insight into the effect long-range forces have on the static thermodynamics. The results given in Table V are similar to our previous calculations performed on these systems using the TIP3P water model.³⁴ The predicted free energy of solvation for the water model monomer is -7.0 ± 0.4 kcal/mol

using standard truncation versus -6.5 ± 0.5 kcal/mol with the reaction field applied. Both estimates are slightly more negative than the experimental value of -6.3 kcal/mol,³⁵ which is most likely due to the enhanced dipole moment of the monomer in the liquid. The reaction field result shows slightly better agreement, however, suggesting that the long-range interactions may contribute favorably to the free-energy sampling. The results for neon are both in reasonable agreement with experiment but once again show a slightly more positive value with the reaction field applied. At this point, the results are limited, and further work is required to determine if these differences are significant. There is also an issue of convergence in the reaction field calculations that we have not yet addressed in our work in free-energy calculations.

Conclusions

This study has presented a fairly comprehensive approach to the development and evaluation of a flexible water potential for use in simulating the physical properties of liquid water and those of solvation. Although the potential function is simple, it is apparently well suited to model effectively both the vibrational and thermodynamic properties of water. Given the rigid SPC model as a starting point and valence forces derived from a normal mode analysis, we have shown that the model could be efficiently parameterized to simulate the liquid by iteratively adjusting three key parameters: the Lennard-Jones repulsive coefficient, the H-partial charge (i.e., molecular dipole), and the cubic stretch force constant (i.e., anharmonicity in the stretch). Although, previous force fields have applied normal mode analyses and fitting techniques to energetic properties, most, if not all, have not yet fully integrated parameterizing the intramolecular and intermolecular components as done here, especially for condensed phase work.³⁶ This also includes previous flexible water model studies.^{5-9,12} Because the vibrations show a considerable dependence on the liquid environment, a good case could be made for this approach. It is important to recognize, however, that the parameterization performed in this way is not exact due to the dependence the static properties (such as density and energy) show on the simulation conditions. The calculations performed with and without the switch function indicate that the

TABLE V.
Free Energies of Solvation Calculated Using Thermodynamic Perturbation Calculations with and without the Reaction Field.^a

		Reaction field	Exp. ^b
Neon / water	-9.7 ± 9.4	-0.4 ± 0.5	-9.0
Neon	2.7 ± 0.7	2.9 ± 0.4	2.7

^aEnergies in kcal/mol. All simulations were run using double-ended sampling in both the forward and reverse directions. The number of windows employed for each system was taken from ref. 34. Equilibration and collection periods were 1 ps and 10 ps, respectively, in all cases. Values reported are averages of the four independent estimates. Uncertainty is determined from the variance in the measurement as described in ref. 34.

^bRef. 35.

differences are minor and have a marginal effect on the intermolecular parameters ($< 1\%$).

The general applicability of our flexible water potential has also been established across a wide range of physical properties. The list is long and includes density, internal energy, specific heat, structure ($O \cdots O$ radial distribution function), vibrational frequencies, self-diffusion, dielectric, and solvation free energies. The overall agreement with experiment noted here has not been shown for most water models, flexible or rigid. The majority of rigid models show too low a dielectric and too high a self-diffusion rate.^{1, 2, 20, 31} As Watanabe and Klein have demonstrated, however, the latter can be remedied by increasing the molecular dipole moment of the model.² Unfortunately, this approach has a detrimental effect on the self-diffusion, dramatically reducing the value below experiment. In addition, the large permanent dipole of the monomer (2.6 D) produces a bifurcated water dimer structure that is too stable when compared to the cyclic form.²⁷ Flexibility in the model imparts a similar effect in the molecular dipole but as an average property in the liquid that is much less pronounced. However, the enhanced dipole is the key to reducing the diffusion and increasing the dielectric in our model over that of rigid SPC, which others have noted as well.^{2, 12}

In comparing our results to those of previous flexible models, good agreement is evident in dielectric properties and self-diffusion.^{6, 12} It is interesting to note (in light of the preceding comments) that the average molecular dipole reported by Yip and co-workers is nearly the same as ours as well.⁶ Most previous models however, have neglected to parameterize the intermolecular potential to reproduce the density of water. As we have shown, parameters taken directly from rigid models are inadequate in this regard and require further refinement to be used reliably. Given that simulations are often performed under isothermal-isobaric conditions and the dependence other static properties have on this physical property, parameterization against density would appear to be fundamentally important. In this study and in others of flexible models, considerable attention has been given to the vibrational frequencies of the gas and the liquid.^{5, 8} Although we have chosen a fairly simple intramolecular potential function, the vibrational properties (*ir* region) compare favorably with previous reports, in which more complex energy expressions were applied. Our results clearly show that the key factor in fitting the vibrational frequencies to experiment is the anharmonic

component in the bond stretching. Our approach is unique in that the softening of the harmonic well can be controlled by attenuating K_{cub} . Complex cross terms appear to be ancillary.

Overall, the results of our study provide fairly convincing evidence that the flexible water model described here is well suited for a wide variety of molecular dynamics studies of condensed phase systems. In addition to the benefits noted earlier, we have also shown that reasonable timesteps can be applied to integrate the equations of motion with this potential. Of course, one of the arguments often cited for using rigid models is algorithm or timestep efficiency. Given that our algorithms are stable up to 1.25-fs timesteps and the obsolescence of SHAKE and RATTLE to enforce the geometric and kinetic constraints,¹⁵ the advantages to the rigid approximation in practice would seem minimal; especially if we consider that 1-fs timesteps are popular in molecular dynamics simulations. Although it could also be argued that the addition of flexibility has only a minor effect on thermodynamic properties (as suggested by our free-energy calculations and those of others),³⁸ it is important to point out that the utility of the model parameterized here extends beyond static to dynamic calculations (e.g., spectroscopic and transport) of interesting chemical processes such as solvation. The ability to investigate reliably both types of properties is clearly advantageous in a molecular model and may prove invaluable for gaining new insight into the physical behavior of water and solutes in complex chemical systems.[†]

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[†]Copies of the programs applied in this work are available by anonymous FTP from the author.

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