

Three- and four-site models for heavy water

Three- and four-site models for heavy water: SPC/E-HW, TIP3P-HW, and TIP4P/2005-HW

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Heavy water or deuterium oxide, D_2O , is used as solvent in various biophysical and chemical experiments. To model such experiments with molecular dynamics simulations, effective pair potentials for heavy water are required that reproduce the well-known physicochemical differences relative to light water. We present three effective pair potentials for heavy water, denoted SPC/E-HW, TIP3P-HW, and TIP4P/2005-HW. The models were parametrized by modifying widely used three- and four-site models for light water, with aim of maintaining the specific characteristics of the light water models. At room temperature, the SPC/E-HW and TIP3P-HW capture the modulations relative to light water of the mass and electron densities, heat of vaporization, diffusion coefficient, and water structure. TIP4P/2005-HW captures in addition the density of heavy water over a wide temperature range.

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I. INTRODUCTION

Water with the chemical formula D_2O is called heavy water or deuterium oxide. In heavy water, the common light hydrogen atoms (protium, 1H) are replaced with heavy hydrogen atoms (deuterium, D or 2H), a hydrogen isotope with a nucleus composed of one proton and one neutron. Despite of nearly identical equilibrium structures of H_2O and D_2O molecules, heavy and light water exhibit different physical properties.¹ Hydrogen bonds in heavy water are stronger than in light water,² which causes enhanced cluster building and thereby an increased structural order at low temperatures in D_2O .³ At higher temperatures, the viscosity and the heat capacity of D_2O are increased relative to H_2O . D_2O has an increased melting temperature compared to H_2O . The maximum density of D_2O is reached at an increased temperature of $11.2\text{ }^\circ\text{C}$ instead of $4\text{ }^\circ\text{C}$.⁴

Heavy water is used in various biophysical experiments. For instance, D_2O is used as solvent for biomolecules in small-angle neutron scattering (SANS) experiments.⁵⁻⁷ Because deuterium exhibits a largely increased neutron scattering length as compared to protium, changing the relative H_2O/D_2O concentration modulates the contrast between the biomolecule and the buffer in SANS experiments. This property may render certain biomolecular subunits invisible during so-called contrast variation experiments. Likewise, D_2O has been used for nuclear magnetic resonance (NMR) spectroscopy⁸ and Fourier transform infrared spectroscopy (FTIR)⁹. To allow accurate modelling of such experiments by molecular dynamics (MD) simulations, reliable effective pair potentials of heavy water are required.

Models for light water have been developed since decades. The simple point charge (SPC) model proposed by Berendsen *et al.* in 1981 was among the first models but remains widely used.¹⁰ The popular TIP3P and TIP4P models by Jorgensen *et al.* followed in 1983.¹¹ The TIP3P model is a three-site water model, like SPC, but it uses the experimentally observed HOH angle of 104.52° instead of the ideal tetrahedral angle of 109.47° adopted by SPC. TIP4P is a four-site model. In 1987, Berendsen *et al.* proposed the extended simple point charge model (SPC/E), a reparameterization of the SPC model with polarization corrections, thereby taking the different water dipoles in solution and in vacuum into account when comparing simulations with the experimental heat of vaporization.¹² A modified version of TIP3P for the CHARMM force field has further been implemented, which has Lennard-Jones interactions also assigned to the hydrogen atoms, in contrast to the original TIP3P model.¹³ All these models were optimized to reproduce properties such as the density, potential energy, and heat of vaporization purely for liquid water

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at 25 °C and atmospheric pressure. In 2005, Abascal and Vega proposed an optimized version of TIP4P, denoted TIP4P/2005, by taking the polarization corrections into account and by fitting against experimental data from a wide temperature and pressure range.¹⁴ The excellent agreement with experimental data over a wide temperature range came with the price of slightly worse agreement with the experimental heat of vaporization at room temperature as compared to SPC/E. Until today, the development of models for light water remains an active field, for instance with the aim to include electronic polarization¹⁵ or to model surface effects¹⁶.

Fewer studies focused on models for heavy water. As the simplest approach, merely the mass of the hydrogen atoms has been doubled to investigate vibrational spectra of heavy water¹⁷ or to simulate heavy water permeation across aquaporins¹⁸. However, this approach cannot account for the modified properties of D₂O as compared to H₂O. Therefore, a model for heavy water on the basis of the SPC/E model has been suggested, denoted SPC/HW¹⁹. To model the larger dipole of heavy water, SPC/HW uses an increased negative partial charge of $q_O = -0.87e$ for the oxygen atom as compared to $-0.8476e$ used by SPC/E, while leaving all other parameters except for the hydrogen mass unchanged. The SPC/HW model has been employed to study the effect of heavy water on lipid membrane properties²⁰, the membrane-water interface²¹, structure and dynamics of anions²², and structure and stability of nanocrystals²³. However, with several versions of the Gromacs simulation software²⁴ (4.6 and newer) we could not reproduce the diffusion coefficient, heat of vaporization, or density reported in Ref. 19, irrespective of the chosen cutoffs for Lennard-Jones (LJ) interactions, Coulomb method (particle-mesh Ewald or plain cutoff), scheme for neighbor lists, corrections for missing dispersion interactions behind the LJ cutoff, or temperature coupling scheme. Properties of SPC/HW obtained with a current Gromacs version are presented below. This discrepancy prompted us to develop new models for heavy water.

We present three effective pair potentials for liquid heavy water developed on the basis of highly used three- and four-site water models for light water: SPC/E, TIP3P, and TIP4P/2005.^{11,12,14} Our strategy was not to parameterize new models from scratch, but instead to modify these H₂O models as little as possible, only to the extent needed to reproduce experimental properties of D₂O. This way, we aimed to maintain the specific characteristics of these popular H₂O models, and we aimed to improve the transferability of the new D₂O models to applications beyond pure-water systems, in particular towards biomolecular systems. We denote the new models SPC/E-HW, TIP3P-HW, and TIP4P/2005-HW.

II. METHODS

A. Simulation systems and parameters

MD simulations were carried out with the Gromacs software²⁴, version 2019.6 and 2020.3. Cubic boxes with 3 nm box length were created and subsequently filled with water molecules. For SPC/E¹², SPC/HW¹⁹, SPC/E-HW, TIP3P¹¹, and TIP3P-HW, the box contained 884 water molecules. For TIP4P/2005¹⁴ and TIP4P/2005-HW, the box contained 909 molecules. The energy of each simulation system was minimized within 500 steps with the steepest decent algorithm. Subsequently, the systems were equilibrated for 100 ps. The simulations were carried out at temperatures 276.95 K, 283.15 K, 288.15 K, 293.15 K, 298.15 K, 303.15 K, 308.15 K, 313.15 K, 318.15 K, 323.15 K, 333.15 K, 343.15 K, 353.15 K, 363.15 K, and 373.15 K. The temperature was controlled using velocity rescaling ($\tau = 0.1$ ps).²⁵ The pressure was controlled with the Berendsen barostat ($\tau = 1$ ps)²⁶ and with the Parrinello-Rahman barostat ($\tau = 5$ ps)²⁷ during equilibration and production simulations, respectively. Whereas the experimental data used here for validation was partly reported for 1 bar and partly for 1 atm, we simulated with 1 bar throughout this study for simplicity. The geometry of water molecules was constrained with the SETTLE algorithm.²⁸ Lennard-Jones (LJ) potentials with a cut-off at 1 nm were used to describe dispersive interactions and short-range repulsion. The pressure and energy were corrected for missing dispersion interactions beyond the cutoff. We found that, owing to the applied dispersion corrections, using a longer LJ cutoff had only a small effect on the computed water properties. Neighbor lists were updated with the Verlet scheme. Electrostatic interactions were computed with the smooth particle-mesh Ewald method (PME)^{29,30} using a Fourier spacing of approx. 0.12 nm, which was optimized by the Gromacs mdrun module at the beginning of each simulations. Systems at 298.15 K, for which the compressibility was computed, were simulated for 150 ns with a 0.5 fs integration time step. All other systems were simulated for 20 ns with a 1 fs time step. Simulations were carried out in single precision on Intel Xeon E-2136 processors, while all nonbonded interactions including PME were offloaded to an Nvidia GTX 1070Ti graphics card.

Statistical errors were computed for simulations at 298.15 K by binning the trajectory into 15 ns time blocks. The physical properties were computed for each block. The values reported below represent the average and standard error over the blocks.

TIP4P/2005-HW was optimized with the ForceBalance software.^{31,32} Simulations submitted

within the ForceBalance framework were carried out with Gromacs, version 2019.6. MD parameters were chosen as described above, except that simulations were carried out for 20 ns for all temperatures listed in the reference data in Table I. During the optimization steps, ForceBalance used a variant of the Newton-Raphson algorithm with a trust radius between 0.025 and 0.25. An additional penalty, which corresponds to ridge regression, was applied to prevent large steps in parameter space. The maximum number of iterations was set to 10 000.

B. Calculation of physical properties

Following previous work³³, we approximated the heat of vaporization with

$$\Delta H_{\text{vap}} \approx -E_{\text{pot}} + RT, \quad (1)$$

where E_{pot} is the average potential energy per water molecule, R the gas constant, and T the temperature. This approximation is valid at atmospheric pressures. For SPC/E, SPC/E-HW, TIP4P/2005, and TIP4P/2005-HW, the potential energy averaged over the simulations was corrected by adding the polarization energy¹²

$$\Delta E_{\text{pol}} = (\mu - \mu_0)^2 / 2\alpha, \quad (2)$$

with the dipole moment of the model μ , the dipole moment of an isolated water molecule $\mu_0 = 1.85$ D, and the isotropic scalar polarizability^{12,34} $\alpha = 1.60810^{-40}$ F m. For TIP3P or TIP3P-HW, no correction owing to the polarization energy was applied, following the original parameterization scheme.¹¹ The self-diffusion coefficients were computed from the slope of the mean-square displacement of water molecules, using a least-square fit to the interval between 5 ps and 50 ps. The number of hydrogen bonds (H-bonds) was obtained with the Gromacs module gmx hbond. A cutoff of 30° was used for the hydrogen-donor-acceptor angle and of 0.35 nm for the donor-acceptor distance.

The isothermal compressibility was calculated via¹⁴

$$\kappa_T = \frac{\langle V^2 \rangle - \langle V \rangle^2}{k_B T \langle V \rangle}, \quad (3)$$

where V is the simulation box volume, k_B the Boltzmann constant, and $\langle \cdot \rangle$ denotes the average over the simulation frames. The compressibilities computed here for light water models agree with the literature.^{35,36}

Electron densities were computed from the mass densities using the molar mass.

Table I. Experimental parameters of liquid heavy water used for the ForceBalance optimization of the TIP4P/2005-HW water model.

Temperature (K)	Pressure (atm)	Density ⁴ (kg/m ³)	$\Delta H_{\text{vap}}^{37}$ (kJ mol ⁻¹)	Thermal expansion coefficient ³⁹ (10 ⁻⁴ K ⁻¹)	Isothermal compressibility ³⁸ (10 ⁻⁶ atm ⁻¹)	Isobaric heat capacity ³⁹ (cal/mol/K)
278.15	1.0	1105.5	45.942		51.49	
283.15	1.0	1105.7	45.746	-0.27	49.74	20.25250
288.15	1.0	1105.6	45.546		48.38	
293.15	1.0	1105.0	45.343	1.21	47.37	20.30520
298.15	1.0	1104.4	45.138		46.52	
303.15	1.0	1103.4	44.926	2.42	45.88	20.29560
308.15	1.0	1101.9	44.712		45.37	
313.15	1.0	1100.1	44.495	3.43	45.1	20.25730
318.15	1.0	1097.9	44.275		44.97	
323.15	1.0	1095.7	44.051	4.28	44.91	20.19985
328.15	1.0	1093.1	43.823		44.98	
333.15	1.0	1090.5	43.591	5.02	45.16	20.13760
338.15	1.0	1087.5	43.356		45.51	

C. Parametrization strategy for SPC/E-HW and TIP3P-HW

The SPC/E and TIP3P models were adjusted with the aim to match physical properties of heavy water molecules as well properties of liquid heavy water, as follows. The mass of the deuterium atoms was adjusted to set the D₂O mass to 20.0275 g/mol.⁴⁰ The O–H bond length and H–O–H angles were taken from the respective H₂O models. The partial charges of oxygen and deuterium were adjusted to match the experimental ratio between the dipole moments μ of light and heavy water, which was reported as $\mu_{\text{D}_2\text{O}}/\mu_{\text{H}_2\text{O}} = 1.01$ both in a benzene solution and in the gas phase.^{3,41}

Next, to refine the Lennard-Jones (LJ) parameters, we ran 20 ns MD simulations and systematically varied the σ and ϵ parameters of the oxygen atom close to the LJ parameters of the respective

light water model. Finally, σ and ϵ were selected to (i) closely match the experimental density, (ii) closely match the change of H_{vap} of heavy relative to light water, (iii) to reasonably match the diffusion coefficient, and (iv) to remain close to the parameters of the light water in order to preserve the characteristics of the light water model.

D. Parametrization strategy for TIP4P/2005-HW

The mass of the deuterium atoms was again chosen to match the D_2O mass of 20.0275 g/mol.⁴⁰ The H–O–H angle and O–H distance were taken from TIP4P/2005. All other parameters were optimized with the ForceBalance software^{31,32}, with the aim to match experimental data over a wide temperature range between 287.15 K and 338.15 K. We adapted the charge of the dummy atom q_M , the distance between the oxygen and the dummy atom r_{OM} , and the Lennard-Jones parameters σ and ϵ of the oxygen atom. More restrictive optimization protocols, for instance with fixed partial charges, did not yield acceptable water densities over a wide temperature range. The reference data used by ForceBalance is listed in Table I. We carried out several ForceBalance runs with slightly different weights for the target data, trust radius, and convergence criteria, which converged to different parameter sets. We selected a parameter set that well reproduced the experimental density and, simultaneously, reasonably well reproduced the heat of vaporization, diffusion coefficient, dipole moment, and the radial oxygen–oxygen distance distribution.

III. RESULTS

As a reference, we first re-computed physical properties of the widely used H_2O models SPC/E, TIP3P, and TIP4P/2005 at room temperature (Table II).^{10,11,14} The computed results agree with the literature^{12,14,32,46} to the extent expected when using slightly different simulation parameters. The results demonstrate the previously documented strengths and weaknesses of these models. For instance, the diffusion coefficient and compressibility of TIP3P is too large as compared to experiment (cf. Table II, last column), whereas the density of TIP3P is too low. The properties of SPC/E and TIP4P/2005 reveal better agreement with experiment, although deviations are still evident. Specifically, the heat of vaporization of TIP4P/2005 is 2 kJ/mol larger than expected from experiment.

Table III presents the newly derived force field parameters for SPC/E-HW, TIP3P-HW, and

Table II. Calculated and experimental properties of H₂O at 298.15 K. Calculated properties correspond to 1 bar, experimental to 1 atm. Mass density, average potential energy during MD simulations, polarization correction, polarization-corrected potential energy, heat of vaporization, diffusion coefficient, isothermal compressibility, and average number of hydrogen bonds per molecule.

		SPC/E	TIP4P/2005	TIP3P	Expt.
Density	kg/m ³	998.810(5)	997.090(5)	985.929(5)	997.0480 ^{ax}
$-E_{\text{pot}}^{\text{MD}}$	kJ/mol	46.819(2)	47.829(2)	40.100(2)	
ΔE_{pol}	kJ/mol	5.22125	4.32095		
$-E_{\text{pot}}$	kJ/mol	41.597(2)	43.508(2)	40.100(2)	41.5 ^{bx}
ΔH_{vap}	kJ/mol	44.076(2)	45.987(2)	42.579(2)	43.990 ^{az}
D	10 ⁻⁵ cm ² /s	2.522(2)	2.104(2)	5.478(4)	2.2999 ^{cz}
κ_T	10 ⁻⁶ bar ⁻¹	46.3(2)	46.5(3)	58.3(2)	45.225 ^{dy}
$\langle \# \text{H-bonds} \rangle$		3.6025	3.66229	3.35226	3.62 ± 0.1 ^{ez}

^a Ref. 4

^b Ref. 42

^c Ref. 43

^d Ref. 44

^e Ref. 45

^x reported for 1 atm

^y reported for 1 bar

^z pressure not reported

TIP4P/2005-HW as well as, for reference, the parameters of the respective H₂O models and of the previously proposed SPC/HW model¹⁹. Simulation topology files of the D₂O models in Gromacs format are provided in the supporting material. Properties of D₂O obtained with the new models are listed in Table IV and discussed in the following.

A. Dipole moment

The experimental dipole of a D₂O molecule is approx. 1% larger as compared to an H₂O molecule.^{3,41} For SPC/E-HW and TIP3P-HW this relative increase was adopted by adjusting the partial charges. For TIP4P/2005-HW, in contrast, the dipole was not optimized but was an outcome of the ForceBalance protocol. Accordingly, the dipole of TIP4P/2005-HW is only 0.5% larger

Table III. Parameters of SPC/E, SPC/E-HW, SPC/HW¹⁹, TIP3P, TIP3P-HW, TIP4P/2005, and TIP4P/2005-HW.

	Mass O	Mass H	q_M	q_O	q_H	σ	ϵ	\angle_{HOH}	r_{OM}
		Mass D			q_D			\angle_{DOD}	
	(g/mol)	(g/mol)	(e)	(e)	(e)	(nm)	(kJ mol ⁻¹)	(°)	(Å)
SPC/E	15.9994	1.008000		-0.8476	0.4238	0.316557	0.650194	109.47	
SPC/E-HW	15.9994	2.014054		-0.8564	0.4282	0.318776	0.573885	109.47	
SPC/HW ¹⁹	15.9994	2.014054		-0.8700	0.4350	0.316557	0.650194	109.47	
TIP3P	15.9994	1.008000		-0.8340	0.4170	0.315057	0.636390	104.52	
TIP3P-HW	15.9994	2.014054		-0.8424	0.4212	0.317156	0.565396	104.52	
TIP4P/2005	16.0000	1.008000	-1.1128	0.0000	0.5564	0.315890	0.774898	104.52	0.1546485
TIP4P/2005-HW	16.0000	2.013754	-1.1220	0.0000	0.5610	0.316590	0.749730	104.52	0.1563497

relative to TIP4P/2005, which is a smaller increase than expected from experiment.^{3,41}

B. Mass and electron density

The mass densities of liquid D₂O obtained with SPC/E-HW and TIP4P/2005-HW at 1 bar and 298.15 K agree with the experimental value within less than 0.2% (Tab. IV). In contrast, the density obtained with TIP3P-HW is 1.2% below the experimental value, in line with the too low density of TIP3P by 1.1% (see Tab. II).

Figure 1 (left) presents the mass densities of all water models considered in this study over a wide temperature range. Evidently, both TIP3P and TIP3P-HW underestimate the densities at room temperature, and the computed densities decay to rapidly with increasing temperature. In contrast, SPC/E and SPC/E-HW favorably match the experimental densities at room temperature; the temperature dependence of the densities is more realistic as compared to the TIP3P variants, yet still enhanced relative to experiment. TIP4P/2005 and TIP4P/2005-HW favorably match the experimental densities over the whole temperature range between 276.95 K and 373.15 K.

The difference of the mass densities of H₂O and D₂O is dominated by the increased mass of deuterium relative to protium. A more sensitive comparison between H₂O and D₂O is given by the electron density since H₂O and D₂O carry the same number of electrons. As shown in

Table IV. Experimental and calculated parameters of liquid D₂O at 298.15 K and 1 bar: mass density, average potential energy during MD simulations, polarization correction, polarization-corrected potential energy, heat of vaporization, diffusion coefficient, compressibility, and average number of hydrogen bonds per molecule.

		SPC/HW ¹⁹	SPC/E-HW	TIP4P/2005-HW	TIP3P-HW	Expt.
Density	kg/m ³	1125.307(5)	1106.169(5)	1103.998(5)	1092.168(6)	1104.4 ^{ay}
$-E_{\text{pot}}^{\text{MD}}$	kJ/mol	51.283(2)	48.486(2)	48.660(2)	41.215(2)	
E_{pol}	kJ/mol	6.59701	5.74264	4.51086		
$-E_{\text{pot}}$	kJ/mol	44.686(2)	42.744(2)	44.149(2)	41.215(2)	-
ΔH_{vap}	kJ/mol	47.165(2)	45.223(2)	46.629(2)	43.694(2)	45.138 ^{bz}
Diffusion coefficient	10 ⁻⁵ cm ² /s	1.370(2)	1.691(2)	1.613(2)	4.246(4)	1.87–1.9 ^{cxy}
Compressibility	10 ⁻⁶ bar ⁻¹	41.6(1)	44.2(2)	47.0(2)	57.7(3)	46.5 ^{dx}
$\langle \# \text{H-bonds} \rangle$		3.7013	3.65617	3.68684	3.403227	3.76 ± 0.1 ^{ez}

^a Ref. 4

^b Ref. 37

^c Ref. 47–50

^d Ref. 38

^e Ref. 45

^x reported for 1 atm

^y reported for 1 bar

^z pressure not reported

Figure 1 (right), the experimental electron density is slightly decreased for D₂O relative to H₂O, and this difference is closely reproduced by the TIP4P/2005-HW and TIP4P/2005 models. The SPC/E and TIP3P variants qualitatively reproduce the decreased electron density of heavy water. TIP4P/2005 and TIP4P/2005-HW capture the electron densities of light and heavy water over the whole temperature range, respectively.

C. Heat of vaporization

The experimental ΔH_{vap} of heavy water is increased by 2.6% relative to light water (Tabs. II and IV).^{4,37} This increase is, by design of our parametrization strategy, well captured by SPC/E-HW relative to SPC/E (2.60%) and by TIP3P-HW relative to TIP3P (2.61%). For TIP4P/2005-HW

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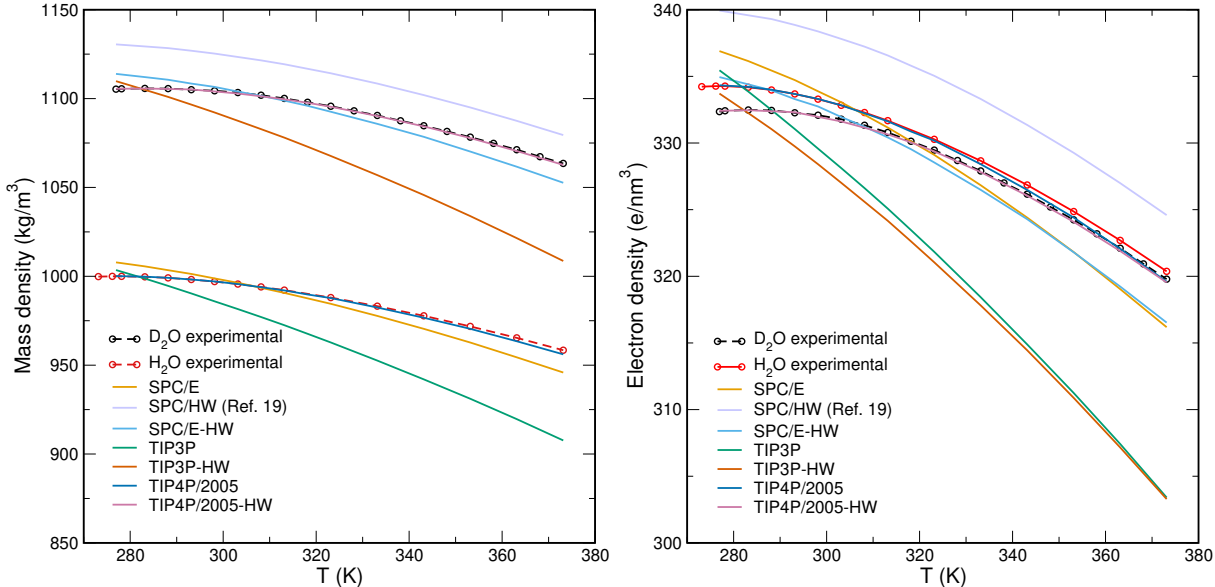


Figure 1. Mass densities (left) and electron densities (right) of liquid H₂O and D₂O as a function of temperature at 1 bar. Experimental data⁴ is shown as circles and dashed lines, calculated data as solid lines. Experimental data of H₂O and D₂O correspond to pressures of 1 atm and 1 bar, respectively. See legend for color code.

relative to TIP4P/2005, ΔH_{vap} is increased by only 1.4% since (i) we focused on reproducing the density and ΔH_{vap} over a wide temperature range rather than the relative increase of ΔH_{vap} of heavy water and (ii) ΔH_{vap} of TIP4P/2005 is already too large at room temperature (Tabs. II and IV).¹⁴ Hence, for future studies, using SPC/E-HW or TIP3P-HW may be more suitable than using TIP4P/2005-HW to study differences of thermodynamic properties between light and heavy water.

Critically, ΔH_{vap} reported in Tabs II and IV include the polarization corrections for the SPC/E and TIP4P/2005 variants, but not for the TIP3P variants, following the original force field derivations. Hence, ΔH_{vap} of both TIP3P and TIP3P-HW are in fact too low compared to experimental conditions.

D. Self-diffusion

The self-diffusion coefficient of liquid D₂O at 1 atm and 298.15 K was reported as $1.87 \times 10^{-5} \text{ cm}^2/\text{s}$ ⁴⁹ or $1.90 \times 10^{-5} \text{ cm}^2/\text{s}$ ⁴⁸. In addition, Wilbur *et al.* reported values of $1.22 \times 10^{-5} \text{ cm}^2/\text{s}$ at 283.15 K and $2.00 \times 10^{-5} \text{ cm}^2/\text{s}$ at 303.15 K, which is compatible with a value of $\sim 1.8 \times 10^{-5} \text{ cm}^2/\text{s}$ at 298.15 K assuming an approximately linear temperature dependence over this range. The self-

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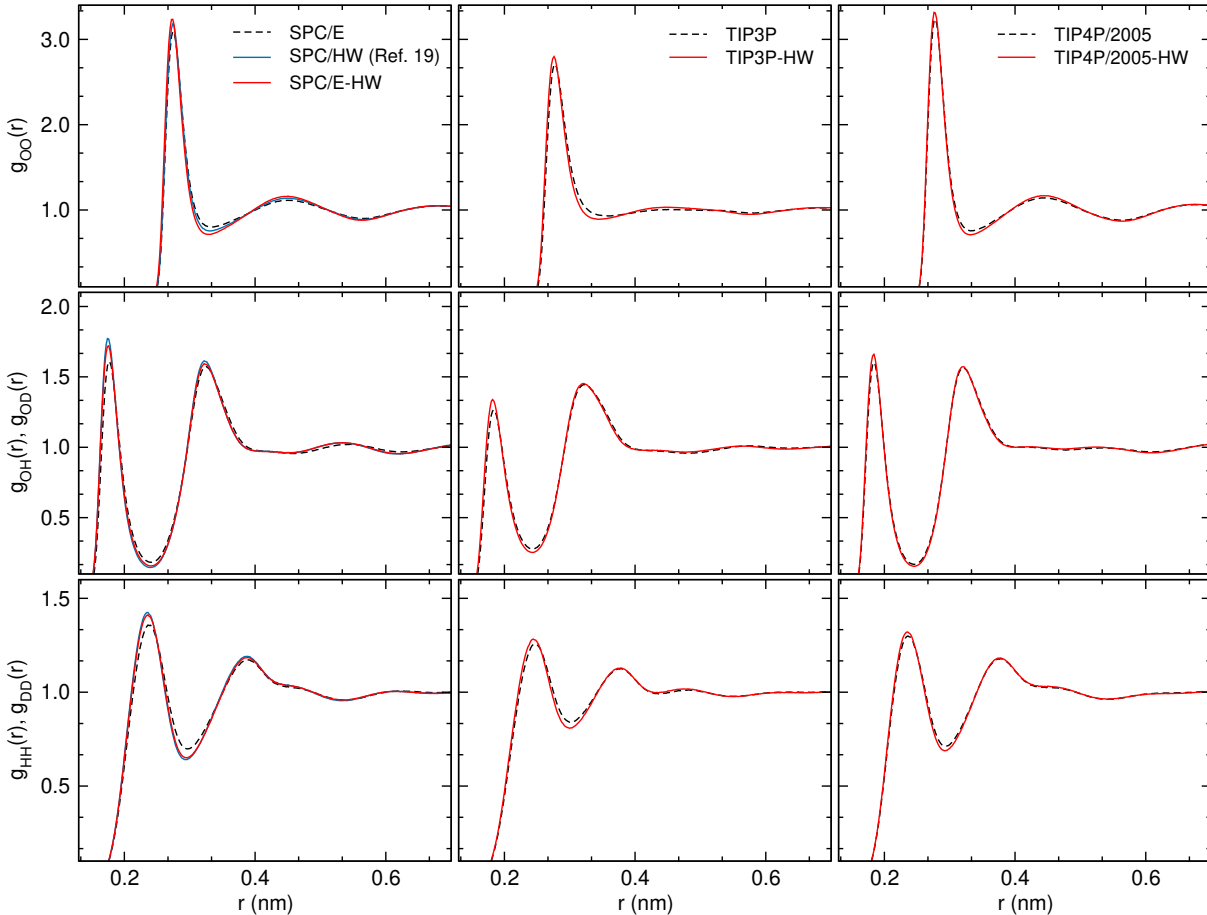


Figure 2. O–O (first row), O–H (second row) and H–H (third row) radial distribution functions for SPC/E, SPC/HW¹⁹, SPC/E-HW, TIP3P, TIP3P-HW, TIP4P/2005, and TIP4P/2005-HW water at 1 bar and 25 °C.

diffusion coefficients obtained with our D₂O models are listed in Table IV. Evidently, SPC/E-HW and TIP4P/2005-HW yield slightly too low diffusion coefficients compared to experiment. In contrast, TIP3P-HW reveals a greatly increased diffusion coefficient, in line with the increased diffusion by the TIP3P model.

E. Isothermal Compressibility

The isothermal compressibility κ_T of liquid D₂O is $46.5 \times 10^{-5} \text{ atm}^{-1}$ at 298.15 K and 1 atm, slightly increased relative to H₂O.³⁸ The calculated κ_T values of SPC/E-HW and TIP4P/2005-HW reasonably agree with the experimental value, in line with the respective H₂O models. In contrast, the compressibilities of both TIP3P and TIP3P-HW are strongly increased by $\sim 25\%$ relative to experiment.

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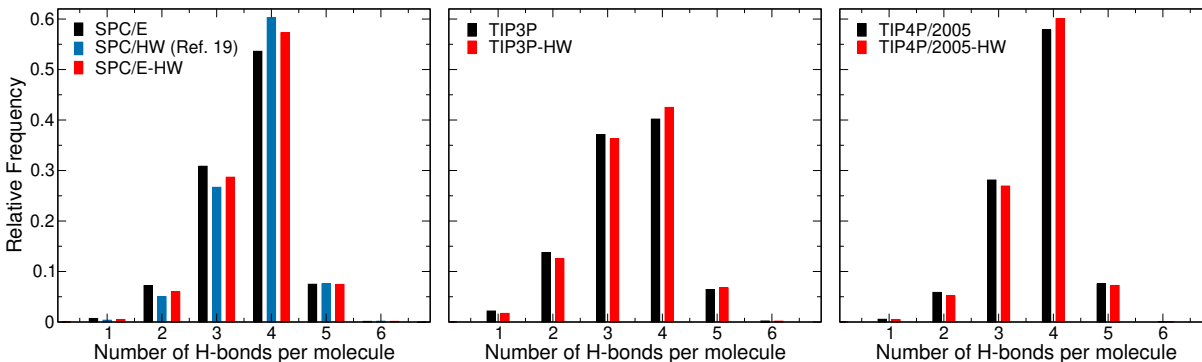


Figure 3. Probability histograms for the number of hydrogen bonds per molecule in SPC/E, SPC/HW¹⁹, SPC/E-HW, TIP3P, TIP3P-HW, TIP4P/2005, and TIP4P/2005-HW at 1 bar and 25 °C.

F. Water structure: radial distribution function and number of hydrogen bonds per molecule

Using a combination of X-ray and neutron diffraction, Soper and Benmore showed that liquid D₂O is more structured than liquid H₂O, as quantified by more pronounced maxima and minima in atomic radial distribution functions (RDFs).⁴⁵ To probe the structure of our liquid D₂O models, we computed RDFs between oxygen atoms ($g_{OO}(r)$), oxygen and hydrogen atoms ($g_{OH}(r)$, $g_{OD}(r)$), and between hydrogen/deuterium atoms ($g_{HH}(r)$, $g_{DD}(r)$), as presented in Fig. 2. Notably, the RDFs of D₂O models (Fig. 2, red lines) yield more pronounced maxima and minima relative to the respective H₂O model (Fig. 2, black dashed line). Hence, the liquid D₂O models exhibit increased structure, in qualitative agreement with the experimental findings.

As a second measure for the degree of water structure, we computed the average number of hydrogen bonds (H-bonds) per water molecule. As expected from the increased water structure according to the RDFs, we find that all D₂O models yield an increased average number of H-bonds (Tabs. II and IV). These findings agree qualitatively with the diffraction data by Soper and Benmore.⁴⁵ Histograms over the average number of H-bonds per water molecule show that this shift is realized by an increased number of water molecules with four H-bonds at the cost of water molecules with only two or three H-bonds, consistently among the three D₂O model.

IV. DISCUSSION

We presented three models for liquid heavy water, SPC/E-HW, TIP3P-HW, and TIP4P/2005-HW. We parametrized SPC/E-HW and TIP3P-HW with the aim to (i) reproduce the relative differences between light and heavy water, while (ii) changing the original water models as little as possible, thereby maintaining the characteristics of original light water model. Consequently, SPC/E-HW and TIP3P-HW inherit the strengths and weaknesses of the SPC/E and TIP3P models. Specifically, both TIP3P and TIP3P-HW neglect the polarization contribution to the heat of vaporization, they exhibit too low mass densities, too large diffusion coefficients, and too large isothermal compressibilities. In addition, liquid water modeled with TIP3P and TIP3P-HW lack internal water structure as revealed by the absence of a second solvation shell in the O–O RDFs and by the reduced number of H-bonds. Nevertheless, since TIP3P is widely used in biomolecular simulations, we expect TIP3P-HW to be useful for comparative simulation studies. SPC/E and SPC/E-HW exhibit overall favorable agreement with experimental data.

TIP4P/2005-HW was parameterized with the aim to reproduce D_2O properties over a wide temperature range. Specifically, we aimed to reproduce the temperature-dependent density since the density plays a critical role in neutron scattering contrast variation experiments. The favorable agreement with experimental data at various temperatures limited the possibilities to reproduce the relative differences between D_2O and H_2O at room temperature. In consequence, the increase of the heat of vaporization of liquid D_2O relative to H_2O is not as precisely captured by TIP4P/2005-HW as compared to SPC/E-HW or TIP3P-HW.

This study was motivated by our inability to reproduce reported properties of the SPC/HW model¹⁹ with the Gromacs simulation software, irrespective of the Gromacs version and the choice of various simulation parameters. For instance, compared to Ref.¹⁹, we obtained with the SPC/HW model an increased density (Fig. 1), more negative potential energies and thereby a larger heat of vaporization, as well as smaller diffusion coefficients (Tab. IV). Therefore, we do not recommend SPC/HW¹⁹ for simulations with Gromacs.

The most appropriate choice for a heavy water model in future studies will depend on the application. For studies that focus at room temperature and involve fine balances of thermodynamic properties such as solvation free energies, we anticipate that comparative simulations with SPC/E and SPC/E-HW may be most insightful because SPC/E and SPC/E-HW (i) favorably agree with a wide range of experimental data at room temperatures and (ii) accurately capture the in-

creased ΔH_{vap} of liquid D_2O relative to H_2O . For biomolecular simulations, simulations with TIP3P and TIP3P-HW will provide a useful alternative because several biomolecular forcefields were parametrized in conjunction with TIP3P. For studies involving D_2O and H_2O a wider temperature ranges, TIP4P/2005 and TIP4P/2005-HW are recommended. Taken together, the D_2O models presented here will be useful for gaining atomic and energetic insight into phenomena and experiments involving heavy water.

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