

Why Many Semiempirical Molecular Orbital Theories Fail for Liquid Water and How to Fix Them

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Water is an extremely important liquid for chemistry and the search for more accurate force fields for liquid water continues unabated. Neglect of diatomic differential overlap (NDDO) molecular orbital methods provide an intriguing generalization of classical force fields in this regard because they can account both for bond breaking and electronic polarization of molecules. However, we show that most standard NDDO methods fail for water because they give an incorrect description of hydrogen bonding, water's key structural feature. Using force matching, we design a reparameterized NDDO model and find that it qualitatively reproduces the experimental radial distribution function of water, as well as various monomer, dimer, and bulk properties that PM6 does not. This sug-

gests that the apparent limitations of NDDO models are primarily due to poor parameterization and not to the NDDO approximations themselves. Finally, we identify the physical parameters that most influence the condensed phase properties. These results help to elucidate the chemistry that a semiempirical molecular orbital picture of water must capture. We conclude that properly parameterized NDDO models could be useful for simulations that require electronically detailed explicit solvent, including the calculation of redox potentials and simulation of charge transfer and photochemistry. © 2015 Wiley Periodicals, Inc.

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Introduction

Water is ubiquitous in nature. At the same time, water is notoriously difficult to model.^[1] This has spawned not just a multitude of models of water, but even a spectrum of classes of models of water. On the more accurate end of the spectrum are *ab initio* molecular dynamics simulations,^[2] which are robust and (at least in principle) allow for simulation of chemical reactions and photochemistry. However, these methods are expensive for all but the smallest of model systems and even these methods do not always give physical results.^[3–6] This has led to the development of many computationally inexpensive empirical molecular mechanics models for water.^[7,8] However, these methods are limited in their applicability to reactions and electronically excited systems because they do not account for electronic degrees of freedom.

Between these extremes are polarizable force fields, which seek to describe the electronic physics of water via a phenomenological treatment of molecular polarizability. These methods include charge-on-spring Drude particles,^[9–11] multipole expansions,^[12] and fluctuating charge models.^[13,14] These methods have found successful application, but each presents its own difficulties.^[15,16]

Instead of attempting to classically reproduce the effects of polarizability, we can instead use a model that contains polarizability implicitly. Semiempirical quantum chemical methods^[17] approximate the Hartree Fock method and then recover accuracy with a set of empirical parameters. Because they are still quantum-mechanical at their core, these methods contain the physics of polarizability that is difficult to capture with a phenomenological classical interaction. In addition, they are undergirded by the same underlying mature algorithms used in quantum chemistry, giving them great numerical sta-

bility. At the same time, these methods are also faster than traditional electronic structure.

Within the set of semiempirical methods, we examine the popular family of Neglect of Diatomic Differential Overlap (NDDO) methods.^[18] These methods have been widely used to describe systems that include effects that cannot be easily captured by conventional force fields—such as bond breaking and charge transfer—but that are too large for a fully *ab initio* calculation. Often, NDDO methods are used in studies of properties of water, including hydrogen bonding,^[19] solvation,^[20] the structure of water clusters,^[21] and water's role in chemical reactions.^[22,23]

With this in mind, we wanted to understand how well NDDO methods perform for the description of bulk water. As a first test, we focus on a popular NDDO method, PM6,^[24] and look at an important structural descriptor of water, the oxygen–oxygen pair distribution function (Fig. 1). We find that the PM6 method gives a very poor description of water's structure, with too short of a first nearest neighbor distance, and later neighbor peaks that are too distant, too diffuse, and with overall understructuring. The understructuring and large distance of the second and later neighbor peaks indicates poor packing of PM6 water, likely due to its incorrect description of hydrogen bond angles. Since the pair distribution function

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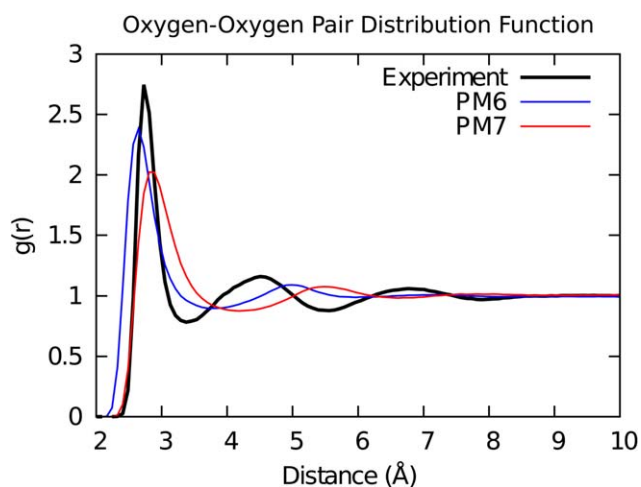


Figure 1. Oxygen–oxygen pair distribution function for two popular NDDO water models compared to experimental results.^[25] While we focus on the PM6 method in this work, we include the successor to PM6, PM7, to show that it does not offer an improved description of the structure of water.

serves as a proxy for important properties of water,^[25] such as hydrogen bonding and solvation, this result calls into question the utility of PM6 as a model of bulk water.

Further, we look at the hydrogen bonding structure of PM6 water since hydrogen bonding is the most important effect in organizing water.^[26] Figure 2a shows the binding potential energy between a water dimer. PM6 favors a hydrogen bond that is too long, and a bond angle far from the physical 180° . Figure 2c shows a snapshot of hydrogen bonding in PM6 water, taken from MD. It is clear that PM6 water gets the radial and angular components of hydrogen bonding wrong, and that this in turn results in an incorrect pair distribution function.

This result raises the natural question: what is wrong with PM6? The PM6 model has two components: an approximate Hamiltonian and a set of empirical parameters for that Hamiltonian. PM6 is parameterized to describe chemistry in general, with a universal set of parameters per atom; it could be the case that, similar to MM force fields, a separate set of parameters is needed for oxygen and hydrogen in water molecules than in, say, organic molecules. Conversely, it is possible that the PM6 Hamiltonian simply lacks the flexibility to describe water. Because of the minimal basis set used in PM6, it may have too little capacity for polarizability.^[27] And since this is critical to the intermolecular interactions of water, it may be that PM6 cannot get water's structure right regardless of parameters.

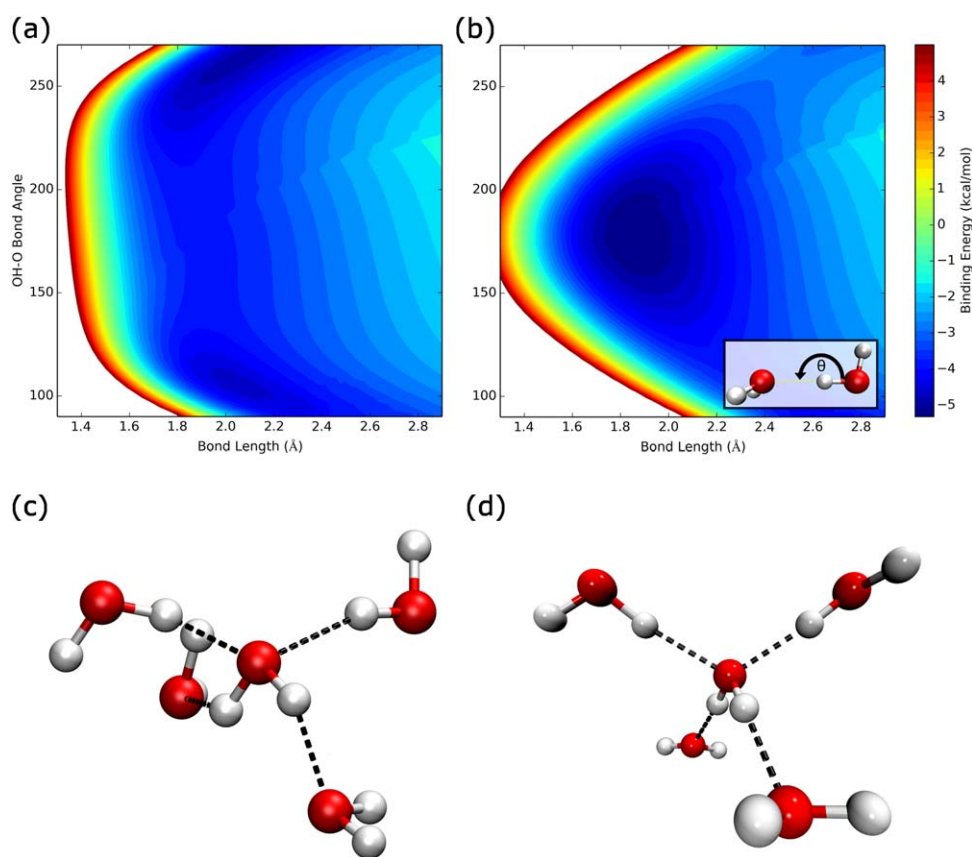


Figure 2. a) and b): Binding potential energy for a water dimer of PM6 and this work, respectively. The OH–O bond angle refers to the angle formed by the oxygen and hydrogen participating in the bond and the oxygen attached to said hydrogen. See inset of (b) for the definition of this angle. c) and d): Illustrative hydrogen bonding structures of water in bulk for PM6 and this work, respectively. PM6 water adopts hydrogen bonding geometry between the tetrahedral and see-saw configurations, while the force-matched model prefers the physical tetrahedral configuration. Further, the force-matched water has OH–O bond angles around 180° , while the PM6 hydrogen bond angles are more disordered. These structures were taken directly from MD simulation discussed in Comparison to Experiment section.

To answer this question, we reparameterize the PM6 Hamiltonian specifically for water, an approach that has been explored recently.^[28,29] We first discuss the force-matching method for parameterization. Next, we present the properties of bulk water using our reparameterized PM6. Finally, we discuss the key differences between our parameters and those of the original PM6 model, and explain how reparameterization fixes the errors in PM6.

Reparameterizing PM6 for Water

Force matching

Force matching^[30,31] uses a set of *ab initio* structures and attempts to fit a model to reproduce the energies and forces of those structures. Explicitly, this amounts to minimizing an objective function, χ^2 , which we define as the average residual of the force and energy, \mathbf{X} , for model parameters k , over some distribution of coordinates P . The energy and force are given weights w and $1 - w$, respectively. This amounts to:

$$\chi^2 = \int P(\mathbf{r}; k) |\mathbf{X}(\mathbf{r}, k; w)|^2 d\mathbf{r} \quad (1)$$

$$|\mathbf{X}(\mathbf{r}, k; w)|^2 = \Delta \mathbf{Y}(\mathbf{r}, k)^T \text{Cov}(\mathbf{Y}_{\text{QM}})^{-1} \Delta \mathbf{Y}(\mathbf{r}, k) \quad (2)$$

$$\Delta \mathbf{Y} = \begin{pmatrix} w(E_{\text{MM}}(\mathbf{r}, k) - E_{\text{QM}}(\mathbf{r})) \\ \frac{1-w}{3N} (F_{\text{MM}}^{(1)}(\mathbf{r}, k) - F_{\text{QM}}^{(1)}(\mathbf{r})) \\ \frac{1-w}{3N} (F_{\text{MM}}^{(2)}(\mathbf{r}, k) - F_{\text{QM}}^{(2)}(\mathbf{r})) \\ \vdots \\ \frac{1-w}{3N} (F_{\text{MM}}^{(3N)}(\mathbf{r}, k) - F_{\text{QM}}^{(3N)}(\mathbf{r})) \end{pmatrix} \quad (3)$$

$$\text{Cov}(\mathbf{Y}_{\text{QM}}) = \langle \mathbf{Y}_{\text{QM}} \otimes \mathbf{Y}_{\text{QM}} \rangle \quad (4)$$

where N is the number of atoms, $F^{(i)}$ is the force on the i th coordinate, Cov denotes the covariance matrix, and \mathbf{Y} is a vector of weighted energy and force components. Improving on previous work,^[32] we account for energy–force covariance in our residual, anticipating that it will give a more statistically rigorous objective function.

We use the PM6^[24] Hamiltonian for our model. We chose this semiempirical method over the more recent PM6-DH+^[33] and PM7^[34] methods because initial tests showed that these gave worse results for the radial distribution function (RDF) of water and because they are both slower than PM6. We also found that the greater flexibility of the PM6 model gave better results than the older, well-established PM3^[35] model.

We fit the parameters of the PM6 model to match quantum chemical forces and energies for clusters of 18 water molecules. *Ab initio* data were calculated at the RI-MP2^[36,37]/aug-cc-pVTZ^[38] level of theory using the frozen core and dual-basis^[39] approximations. *Ab initio* calculations were performed using the Q-Chem^[40] quantum chemistry package. Semiempirical calculations were performed using the Mopac^[41] package. Five thousand hundred structures were sampled from the Boltz-

mann ensemble at 300 K by running molecular dynamics on the force field of Wang and Jordan^[32] with a harmonic restraining potential in the Gromacs^[42] package. Samples were separated in time by 1 ps to reduce statistical correlation. The energy and force were given equal weight. Local minimization of the objective function was performed using the Broyden–Fletcher–Goldfarb–Shanno (BFGS)^[43] algorithm with finite difference first derivatives starting from the original PM6 parameters.^[24]

Another model was created in which the energy, force, and net dipole moment of the clusters were all fit with equal weight, but the parameters and properties of this model did not change significantly. Because it offers no improvement, and the energy and force matching is conceptually simpler and has fewer parameters, we will use the energy and force matched PM6 parameters for the remainder of this discussion.

Comparison to experiment

To validate our water model, we compare its monomer, dimer, and bulk liquid properties to experimental data. Monomer and dimer properties were calculated at the model's equilibrium geometry using Mopac. Liquid water properties were averaged over structures sampled using NVT molecular dynamics in a version of the Gromacs package modified to interface with Mopac for energy and force calculations. Ten independent trajectories of 115 waters were simulated with periodic boundary conditions for 100 ps with a 1 fs time step. To allow for equilibration, samples were taken only after the first 5 ps. Simulations were run at 300 K using the Nos-Hoover thermostat^[44,45] at a density of 999.50 kg/m³ (corresponding to a square cell 1.51 nm on a side). (We note that Mopac has an outstanding bug causing its forces to lack the DH+ correction in bulk PM6-DH+ calculations. Bulk energies and nonbulk energies and forces are not affected.)

Figure 3 shows the RDF for our model as compared to neutron scattering experiments.^[25] Table 1 provides a comparison between our model and experimental data for a variety of water properties. Results for the PM6,^[24] dispersion and hydrogen bonding corrected PM6-DH+^[33] and PM7^[34] models are also included to provide a baseline for comparison. Finally, Figure 2b shows the dimer binding potential for our model and Figure 2d shows a sample taken from bulk simulation to illustrate its hydrogen bonding structure.

These observables break down into two classes: structural parameters that include the geometry of each water molecule as well as the geometry of hydrogen bonding, and electronic properties such as polarizabilities, dipoles, and dielectric constants. Our model shows consistent improvement of the former and scattered improvement of the latter. We note that none of the properties in these figures and tables were fit directly; they all arise as a consequence of force matching.

Our model does well for the simplest structural parameters of water, the gas phase bond length and angle. Often, these parameters are fit directly in force fields, but our force matching produces the same result. Figure 2 shows that the basic hydrogen bonding structure is correct in our model, with 180°

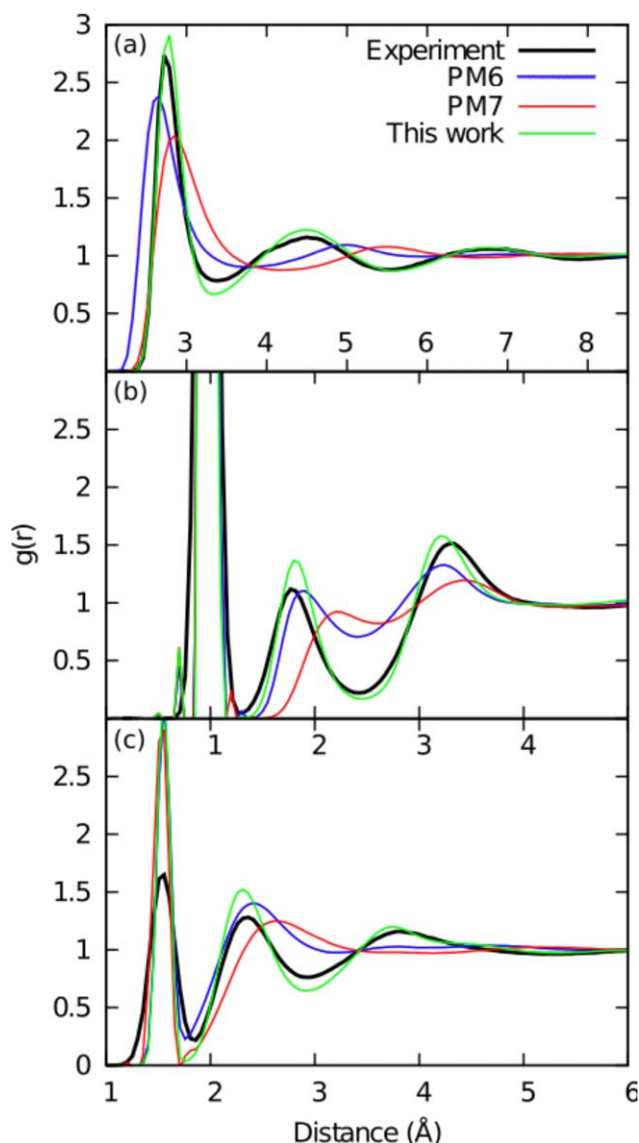


Figure 3. a) O—O, b) O—H, and c) H—H radial distribution functions for water as predicted by PM6, PM7, and this work, and as measured in Ref. [25]. Note that the horizontal scale differs between plots to show the region of interest. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

O—H...O bond angles and tetrahedral packing in the bulk liquid. Meanwhile, as mentioned before, PM6 favors bond angles closer to 100° , leading to a much more disordered hydrogen bonding network. This effect may also explain the discrepancy in self-diffusion constants: PM6 (and other NDDO methods) have too large self-diffusion constants, due to their disordered hydrogen bonding creating a weaker solvation cage around individual water molecules. Our reparameterized method, with its improved hydrogen bonding structure, has a self-diffusion constant which is lower and much closer to experiment.

The RDF shows that our model reproduces two body interactions well. The PM6 and PM7 models perform poorly in comparison, showing that our force matching is necessary to properly capture the basic structure of water. Surprisingly, the PM7 model is worse for the structure of water than PM6,

despite having more parameters. Our model shows slight overstructuring in the oxygen—oxygen RDF and larger overstructuring in the oxygen—hydrogen and hydrogen—hydrogen RDFs. Since this effect grows as we look at lighter nuclei, we attribute this overstructuring to nuclear quantum effects which are not included in our classical molecular dynamics simulations. Again we note the hydrogen bonding seems to be the key effect distinguishing our model from standard PM6. Focusing on the oxygen—hydrogen RDF (Fig. 3b), we notice that the first two hydrogen bonding peaks are understructured for PM6. This in turn explains the understructuring in the oxygen—oxygen RDF.

However, our model does not correctly describe the electronic properties of water in the gas phase, with too large dipole moments for the monomer and dimer. PM6 and NDDO methods are known to have too small a gas phase polarizability, and our method does not correct this. Despite having incorrect electronics in the gas phase, our model does reproduce the electronics of our target phase, liquid water. The low and high frequency dielectric constants are both in agreement with experiment. It is important to note that the PM6 model also does well for these observables. This supports our initial motivation to use semiempirical methods because of their built-in treatment of polarization effects.

Why PM6 fails

In light of the improvement wrought by force matching, we now ask: why is the new model better? Specifically, we wish to understand which parameters are important to this new model and how these parameters affect the physical properties of our water model. We tackle this question by performing knockout experiments where we replace one parameter in our model with its PM6 value. We then look at the effect of this knockout on two key observables, the energy RMSD of this new set of parameters (averaged over ten thousand snapshots) and the oxygen-oxygen RDF (as simulated before). We find that 14 parameters cause the RMSD to rise substantially, 14 parameters result in an unphysical RDF, and that 12 of these parameters do both, indicating that they are key to the physics of our model.

These parameters fall into two classes: half concern core-core repulsion between oxygen and hydrogen and half concern the electronic structure of oxygen. In PM6, the core-core repulsion is handled using empirical potentials. We find that parameters involving the oxygen—hydrogen core-core repulsion are important to our model, and that the modifications made these parameters in our model uniformly serve to weaken the oxygen—hydrogen repulsion. The core-core repulsion is summed pairwise and has both diatomic and monatomic parameters. The core-core repulsion between atoms i and j separated by R_{ij} is given by:

$$E_n(R_{ij}) = Z_i Z_j \left[\langle s_i s_j | \langle s_j s_j (1 + x_{ij} e^{-\alpha_{ij} R_{ij}}) + a_i^{b_i (R_{ij} - c_i)^2} + a_j^{b_j (R_{ij} - c_j)^2} \right] \quad (5)$$

where Z_i is the atomic number of atom i and x , α , a , b , and c are PM6 parameters. Of these, the diatomic parameter α_{OH} ,

Table 1. Calculated physical properties of PM6, PM6-DH+, PM7, and this work compared to experiment as well as the established AMOEBA and TIP4P/2005 force fields.

	PM6	PM6-DH+	PM7	AMOEBA ^[46]	TIP4P/2005 ^[47]	This work	Experiment
Monomer properties							
O—H distance (Å)	0.949	0.949	0.955	0.957 ^[46]	0.957 ^[47]	0.958	0.9575(5) ^[48]
Bond angle	107.48	107.48	105.49	108.50 ^[46]	104.52 ^[47]	104.75	104.51 ^[48]
Dipole Moment(D)	2.071	2.071	2.128	1.773 ^[46]	2.305 ^[47]	2.104	1.85498(9) ^[49]
Polarizability (Å ³)	1.35	1.35	1.43	1.421 ^[46]	N/A	1.34	1.470(6) ^[50]
Dimer properties							
Binding energy (kcal/mol)	−3.86	−3.81	−2.85	4.96 ^[46]	−7.06	−5.35	−5.4(7) ^[51]
θ_A	47	53	39	57.2 ^[46]	77	48	58(6) ^[52]
θ_D	48	54	46	N/A	28	50	51(6) ^[52]
O—O Distance(Å)	2.88	2.79	3.00	2.892 ^[46]	2.75	2.84	2.98(1) ^[52]
Dipole moment (D)	2.095	2.817	3.359	2.54 ^[46]	3.22	3.08	2.64(5) ^[52]
Liquid properties (300 K)							
Static dielectric constant	65(2)	68.6(6)	78(2)	81.4(1) ^[53]	60 ^[47]	75(1)	78.4(1) ^[54]
High frequency dielectric constant	1.8698(6)	1.8699(7)	1.8570(7)	N/A	N/A	1.8775(7)	1.79(1) ^[55]
Diffusion constant (10 ^{−5} cm ² /s)	16.2(2)	16.7(4)	17.6(6)	2.00 ^[53]	2.08 ^[47]	2.39(7)	2.299(5) ^[56]

Liquid water properties were calculated at 300 K. Uncertainties, when appropriate, are given inside parenthesis and apply to the last significant figure.

and the monatomic parameters a_H and c_H are the most important to our force matched model. In our parameterization, α_{OH} decreases, resulting in reduced range of the oxygen—hydrogen repulsion. a_H and c_H also both decrease, creating a wider basin of attraction with a shorter radius. Since hydrogen—hydrogen core—core repulsion is not frequently encountered in liquid water, the changes in these three parameters change to correct the oxygen—hydrogen interaction. Both PM6 and our model describe the covalent OH bond well, so we conclude that this weaker and shorter cut-off core—core interaction between oxygen and hydrogen is necessary to get correct hydrogen bond energetics and geometries.

The second class of parameters concern the electronics of oxygen and determine approximate one- and two-electron integrals within the NDDO approximation. Of these, the three most important parameters to our model are G_{sp} , U_{pp} , and U_{ss} , all for oxygen. The U parameters are the one electron integrals (site energies), while G_{sp} influences two electron integrals involving the sp combination of oxygen atomic orbitals. Scanning across G_{sp} shows that large values result in a linear water geometry while small values give too acute a bond angle. In our model, G_{sp} decreases by half. Taken at face value, this corrects water's bond angle in the gas phase. Looking deeper, we also see that the electronic geometry of water becomes more tetrahedral, resulting in correct hydrogen bonding network geometry. However, G_{sp} also controls the intra-atom two electron repulsion on oxygen and the coupling between oxygen and hydrogen. When this parameter decreases, *ceteris paribus*, oxygen becomes extremely electronegative and forms ionic bonds with hydrogen. To compensate for this behavior, U_{ss} and U_{pp} increase, decreasing the electronegativity of oxygen.

Considering the effects of all of these parameters, we can now understand the results in Figure 2. PM6 forms poor hydrogen bonding networks for two reasons. First, it has too much core—core repulsion between oxygen and hydrogen, which weakens hydrogen bonds. Second, the electronic geom-

etry of oxygen is wrong, making tetrahedral hydrogen bonding networks energetically unfavorable. Parameters for our model may be found in the supporting information SI.

Conclusions

NDDO methods offer an attractive alternative to polarizable force fields for capturing complex electronic phenomena in condensed phases at lower cost than fully *ab initio* methods. However, these methods, specifically PM6, provide a poor description of the structure of liquid water as characterized by its pair distribution function and hydrogen bonding structure. We asked whether this result is due to a fundamental flaw in the PM6 Hamiltonian or whether the parameters for PM6 are just ill-suited for liquid water. To approach this question, we used force matching to reparameterize PM6 for liquid water. Comparing to experiment, we found that this new force-matched model had improved structural and electronic properties for water especially in the liquid phase, as well as in the gas phase. Again, we note that these high-quality properties emerge from the model; our method was fitted only to *ab initio* water clusters. This led us to conclude that the PM6 Hamiltonian is in fact capable of describing liquid water. We then looked at which PM6 parameters effected this change and looked at their physical purpose. The main changes were a decreased oxygen—hydrogen core—core repulsion and electronic modifications to oxygen that promoted a tetrahedral electronic geometry. Both of these effects produced more physical hydrogen bonding and thus a better structure for liquid water.

This study allows us to understand the physics that are important to modeling water, and to show that NDDO methods are capable of capturing such physics. This opens up the possibility of applying these semiempirical methods to the development of models that are cheaper than full *ab initio* simulations, but also capture the complex physics of water.

Because they treat electronic properties explicitly, NDDO models have great potential for describing complex condensed


phase systems. For example, these methods could be used for calculation of redox potentials, solvation energies, and even excited state properties in solution, problems that are traditionally hard for molecular mechanics. (Although we have not tested this model for these properties in particular, NDDO methods have the potential to describe them.) While NDDO does not natively provide an accurate description of the condensed phase, we have shown that it still contains the essential physics and needs only to be reparameterized.

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 Additional Supporting Information may be found in the online version of this article.

- [1] P. Ball, *Nature* **2008**, *452*, 291.
- [2] K. Laasonen, M. Sprik, M. Parrinello, R. Car, *J. Chem. Phys.* **1993**, *99*, 9080.
- [3] J. R. Hammond, N. Govind, K. Kowalski, J. Autschbach, S. S. Xantheas, *J. Chem. Phys.* **2009**, *131*, 214103.
- [4] H.-S. Lee, M. E. Tuckerman, *J. Chem. Phys.* **2007**, *126*, 164501.
- [5] M. Sprik, J. Hutter, M. Parrinello, *J. Chem. Phys.* **1996**, *105*, 1142.
- [6] J. VandeVondele, F. Mohamed, M. Krack, J. Hutter, M. Sprik, M. Parrinello, *J. Chem. Phys.* **2005**, *122*, 14515.
- [7] W. L. Jorgensen, J. Tirado-Rives, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 6665.
- [8] B. Guillot, *J. Mol. Liquids* **2002**, *101*, 219.
- [9] G. Lamoureux, B. Roux, *J. Chem. Phys.* **2003**, *119*, 3025.
- [10] F. Wang, K. D. Jordan, *J. Chem. Phys.* **2002**, *116*, 6973.
- [11] H. Yu, W. F. van Gunsteren, *Comput. Phys. Commun.* **2005**, *172*, 69.
- [12] D. Van Belle, M. Froeyen, G. Lippens, S. J. Wodak, *Mol. Phys.* **1992**, *77*, 239.
- [13] S. W. Rick, S. J. Stuart, B. J. Berne, *J. Chem. Phys.* **1994**, *101*, 6141.
- [14] S. Rick, S. Stuart, *Rev. Comput. Chem.* **2003**, *18*, 89.
- [15] A. Warshel, M. Kato, A. V. Pislakov, *J. Chem. Theory Comput.* **2007**, *3*, 2034.
- [16] J. Chen, T. J. Martinez, In *Advances in the Theory of Atomic and Molecular Systems*, Vol. 19; P. Piecuch, J. Maruani, G. Delgado-Barrio, S. Wilson, Eds.; Progress in Theoretical Chemistry and Physics; Springer Netherlands: Dordrecht, **2009**; pp 397–415.
- [17] M. C. Zerner, In *Reviews in Computational Chemistry*, Vol. 2, Chapter 8; K. Lipkowitz, D. Boyd, Eds.; Wiley: New York, **1991**; pp 313–365.
- [18] A. K. Soper, *Chem. Phys.* **2000**, *258*, 121.
- [19] J. A. Pople, D. P. Santry, G. A. Segal, *J. Chem. Phys.* **1965**, *43*, S129.
- [20] P. A. Kollman, L. C. Allen, *J. Am. Chem. Soc.* **1970**, *92*, 753.
- [21] C. J. Cramer, D. G. Truhlar, *J. Comput. Chem.* **1992**, *13*, 1089.
- [22] M. W. Jurema, K. N. Kirschner, G. C. Shields, *J. Comput. Chem.* **1993**, *14*, 1326.
- [23] A. Gonzalez-Lafont, T. N. Truong, D. G. Truhlar, *J. Phys. Chem.* **1991**, *95*, 4618.
- [24] E. R. Kuechler, D. M. York, *J. Chem. Phys.* **2014**, *140*, 054109.
- [25] J. J. P. Stewart, *J. Mol. Model.* **2007**, *13*, 1173.
- [26] G. Jeffrey, *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, **1997**.
- [27] D. E. Woon, T. H. Dunning, *J. Chem. Phys.* **1994**, *100*, 2975.
- [28] Y. Zhou, J. Pu, *J. Chem. Theory Comput.* **2014**, *10*, 3038.
- [29] A. Marion, G. Monard, M. F. Ruiz-López, F. Ingrosso, *J. Chem. Phys.* **2014**, *141*, 034106.
- [30] F. Ercolessi, J. B. Adams, *Europhys. Lett.* **1994**, *26*, 583.
- [31] S. Izvekov, M. Parrinello, C. J. Burnham, G. a. Voth, *J. Chem. Phys.* **2004**, *120*, 10896.
- [32] L.-P. Wang, J. Chen, T. Van Voorhis, *J. Chem. Theory Comput.* **2012**.
- [33] M. Korth, *J. Chem. Theory Comput.* **2010**, *6*, 3808.
- [34] J. J. P. Stewart, *J. Mol. Model.* **2013**, *19*, 1.
- [35] J. J. P. Stewart, *J. Comput. Chem.* **1989**, *10*, 209.
- [36] F. Weigend, M. Haßer, *Theor. Chim. Acta*, **1997**, 331.
- [37] F. Weigend, A. Kohn, C. Hattig, *J. Chem. Phys.* **2002**, *116*, 3175.
- [38] T. H. Dunning, *J. Chem. Phys.* **1989**, *90*, 1007.
- [39] K. Wolinski, P. Pulay, *J. Chem. Phys.* **2003**, *118*, 9497.
- [40] Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. DiStasio, R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R. Z. Khallulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, J. Kong, A. I. Krylov, P. M. W. Gill, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172.
- [41] J. Stewart, MOPAC. Available at: <http://openmopac.net/>. Last Accessed on March 5, 2015.
- [42] B. Hess, C. Kutzner, D. van der Spoel, E. Lindahl, *J. Chem. Theory Comput.* **2008**, *4*, 435.
- [43] J. Nocedal, S. J. Wright, *Numerical Optimization*, 2nd ed.; Springer: New York, **2006**.
- [44] S. Nose, *J. Chem. Phys.* **1984**, *81*, 511.
- [45] W. Hoover, *Phys. Rev. A* **1985**, *31*, 1695.
- [46] P. Ren, J. W. Ponder, *J. Phys. Chem. B* **2003**, *107*, 5933.
- [47] J. L. F. Abascal, C. Vega, *J. Chem. Phys.* **2005**, *123*, 234505.
- [48] D. R. Lide, *CRC Handbook of Chemistry and Physics*, 93rd ed.; CRC Press, Boca Raton, Florida, USA, **2012**.
- [49] S. L. Shostak, W. L. Eisenstein, J. S. Muentner, *J. Chem. Phys.* **1991**, *94*, 5875.
- [50] W. F. Murphy, *J. Chem. Phys.* **1977**, *67*, 5877.
- [51] L. A. Curtiss, D. J. Frurip, M. Blander, *J. Chem. Phys.* **1979**, *71*, 2703.
- [52] T. R. Dyke, K. M. Mack, J. S. Muentner, *J. Chem. Phys.* **1977**, *66*, 498.
- [53] L.-P. Wang, T. Head-Gordon, J. W. Ponder, P. Ren, J. D. Chodera, P. K. Eastman, T. J. Martinez, V. S. Pande, *J. Phys. Chem. B* **2013**, *117*, 9956.
- [54] D. P. Fernandez, Y. Mulev, A. R. H. Goodwine, J. M. H. L. Sengers, *J. Phys. Chem. Ref. Data* **24**, 1995, 33.
- [55] A. D. Buckingham, *Proc. R. Soc. A* **1956**, *238*, 235.
- [56] M. Holz, S. R. Heil, A. Sacco, *Phys. Chem. Chem. Phys.* **2000**, *2*, 4740.

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