Supplementary Information for: "GEM*: A Molecular Electronic Density–Based Force Field for Molecular Dynamics Simulations"

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I. FITTING MOLECULAR ELECTRONIC DENSITIES

GEM* includes terms that rely on the use of fitted molecular densities obtained from the Gaussian Electrostatic Model (GEM) model. GEM relies on the use of Hermite Gaussian auxiliary basis sets (ABSs) to fit the molecular electronic density of molecular fragments

$$\tilde{\rho}(r) = \sum_k c_k k(r). \tag{1}$$

The expansion coefficients c_k for the fitted densities $\tilde{\rho}$ can be determined by an analytical or a numerical procedure as described in detail in [1–3]. In the analytical procedure the fitting coefficients may be obtained by minimizing the self–energy of the error in the density [4–7]:

$$E_{self} =< \rho(r) - \tilde{\rho}(r)|\hat{O}|\rho(r) - \tilde{\rho}(r) >, \tag{2}$$

where $\hat{O}$ can take several forms including the overlap operator $\hat{O} = 1$, the Coulomb operator $\hat{O} = 1/r$ or the damped Coulomb operator $\hat{O} = erfc(\beta r)/r$ [8]. The coefficients are obtained by minimizing Eq. 2 with respect to the expansion coefficients c_k.

Alternatively, it is possible to calculate molecular properties on a grid of points and perform a linear (on non–linear) optimization by minimizing the following fitting function:

$$\chi^2 = \sum_i W(r_i) \left(y(\mathbf{r}_i) - \tilde{y}(\mathbf{r}_i, c_k)\right)^2, \tag{3}$$

where $y(\mathbf{r}_i)$ denotes the *ab initio* molecular property of interest at point i and $\tilde{y}(\mathbf{r}_i, c_k)$ is the same property evaluated with the kth ABS element at the same point on the grid. Finally, $W(r)$ is the weighting function for the point on the grid, which can be defined in several ways [9, 10]. Our implementation employs a modified weighting function proposed by Hu *et al*, which decays smoothly close to the cores and at long distances [10, 11]. Our numerical fitting method uses the molecular electrostatic potential evaluated on spherical (Becke) grids [12].

One added advantage of performing the fit using Hermite Gaussians is that this results in a natural method to obtain distributed multipoles (GEM–DM) [1]. We have previously shown that these multipoles can be used directly in the AMOEBA force field [3].

II. GEM* FUNCTIONAL FORM

The functional form for GEM* combines terms that employ the fitted GEM densities, $\tilde{\rho}$, with terms from the AMOEBA potential resulting in:

$$E_{Total} = E^{GEM}_{Coulomb} + E^{GEM}_{exch-rep} + E^{AMOEBA}_{polarization} + E^{AMOEBA}_{VdW} + E^{AMOEBA}_{bonded}, \tag{4}$$

where the Coulomb term is given by

$$E^{GEM}_{Coulomb} = \sum_{A>B} \frac{Z_A Z_B}{r_{AB}} + \sum_{A>B} \int \frac{Z_A \tilde{\rho}^B(r_B)}{r_{AB}} dr + \sum_{A>B} \int \frac{Z_B \tilde{\rho}^A(r_A)}{r_{AB}} dr + \sum_{A>B} \int \frac{\tilde{\rho}^A(r_A)\tilde{\rho}^B(r_B)}{r_{AB}} dr \tag{5}$$

The second term corresponds to the exchange–repulsion and is calculated by means of the charge density overlap following the Wheatley–Price overlap model:

$$E^{GEM}_{exch-rep} = K \sum_{A>B} \int \tilde{\rho}^A(r_A)\tilde{\rho}^B(r_B). \tag{6}$$

Due to the explicit exchange, it has been necessary to modify the original AMOEBA function dealing with the Van der Waals (VdW) interactions. In this case, we have modified the buffered Halgren function (modHalgren) by removing the repulsive term as follows:

$$E_{modHalgren} = -\epsilon_{ij} \left[\frac{1.07 R^*_{ij}}{(R_{ij} + 0.07 R^*_{ij})} \right]^7 . \tag{7}$$

Finally, the polarization and bonded terms are the same as those in the original AMOEBA implementation [13].

III. FITTING DETAILS

For the present model of water with GEM* the reference QM density was obtained from a water monomer at the equilibrium AMOEBA geometry [13]. The molecular electronic density was calculated using Gaussian 09 [14] at the MP2/aug–cc–pVTZ level to be consistent with the original AMOEBA model. The relaxed one–electron density matrix was fitted using two different auxiliary basis sets (ABS), A1 and A2 [15, 16]. The fitting coefficients and exponents are given in Figures S1 and S2.

Figure S1: A1 fitting coefficients and ABS for the water molecule

```
Hydrogen
prim_num        expon        order          coeffs
  1            45.000          1         -0.483006141553E-02
  2             7.500          1          0.851223435024E-01
  3             1.500          1          0.345679637003E+00
  4             0.300          1          0.108019638661E+00
Oxygen
prim_num        expon        order          coeffs
  1          2000.000          1         -0.496654293880E-02
  2           400.000          1          0.974070793238E-01
  3           100.000          1          0.629276738366E+00
  4            25.000          1          0.906987607632E+00
  5             7.800         10          0.123692196059E+01
                                          0.173053987685E-10
                                          0.113135912059E-14
                                         -0.145083404615E-01
                                          0.131739243946E-01
                                          0.189952827371E-01
                                          0.156629432165E-01
                                         -0.188238738965E-15
                                         -0.979300209221E-10
                                          0.303411828773E-15
  6             1.560         10          0.429707234839E+01
                                         -0.260751723883E-08
                                          0.929739383815E-14
                                          0.773451102392E-02
                                          0.357177014179E+00
                                          0.355593956093E+00
                                          0.353749901384E+00
                                         -0.175232883222E-15
                                         -0.135396038424E-08
                                          0.127252601276E-14
  7             0.390         10          0.176931769314E+01
                                          0.134542272951E-07
                                         -0.280757434691E-13
                                          0.318089994212E+00
                                          0.259404214134E+00
                                          0.439401692008E+00
                                          0.398680231403E+00
                                          0.228804470810E-13
                                          0.144318034043E-07
                                         -0.276699153077E-15
```

Figure S2: A2 fitting coefficients and ABS for the water molecule

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Hydrogen
prim_num        expon           order           coeffs
  1                 45.000        1              -0.483006141553E-02
  2                  7.500        1               0.851223435024E-01
  3                  1.500        1               0.345679637003E+00
  4                  0.300        1               0.108019638661E+00
Oxygen
prim_num        expon           order           coeffs
  1               2000.000        1              -0.496654293880E-02
  2                400.000        1               0.974070793238E-01
  3                100.000        1               0.629276738366E+00
  4                 25.000        1               0.906987607632E+00
  5                  7.800       10               0.123692196059E+01
                                                  0.173053987685E-10
                                                  0.113135912059E-14
                                                 -0.145083404615E-01
                                                  0.131739243946E-01
                                                  0.189952827371E-01
                                                  0.156629432165E-01
                                                 -0.188238738965E-15
                                                 -0.979300209221E-10
                                                  0.303411828773E-15
  6                  1.560       10               0.429707234839E+01
                                                 -0.260751723883E-08
                                                  0.929739383815E-14
                                                  0.773451102392E-02
                                                  0.357177014179E+00
                                                  0.355593956093E+00
                                                  0.353749901384E+00
                                                 -0.175232883222E-15
                                                 -0.135396038424E-08
                                                  0.127252601276E-14
  7                  0.390       10               0.176931769314E+01
                                                  0.134542272951E-07
                                                 -0.280757434691E-13
                                                  0.318089994212E+00
                                                  0.259404214134E+00
                                                  0.439401692008E+00
                                                  0.398680231403E+00
                                                  0.228804470810E-13
                                                  0.144318034043E-07
                                                 -0.276699153077E-15
```

All intermolecular interaction reference values were calculated at the MP2(full)/aug–cc-pVTZ corrected for BSSE with the counterpoise method using Gaussian09 [14]. For the energy decomposition analysis the Coulomb interaction was calculated with an in–house program that employs relaxed 1–electron density matrices for the monomers. In all cases the reference Coulomb calculations were done at the same level of theory as above. The exchange–repulsion and polarization interactions were calculated with the restricted variational space (RVS) method at the HF/aug-cc–pVTZ level as implemented in GAMESS [17, 18]

The density fit was done with the A1 and A2 ABS for water [15, 16]. Initially both the analytical and numerical fitting procedures were employed (see Figure S4). In both cases there is one parameter that can be used to control the noise in the fit. This corresponds to the λ parameter in the Tikhonov regularization. In all cases, the λ parameter has been optimized so that the error in the intermolecular Coulomb interactions from the GEM Hermites is minimized with respect to *ab initio* reference calculations for the canonical water dimer at different distances. After the comparison of energies and forces with the QM reference it was observed that the analytically fitted parameters gave better results and these are the ones that were employed for the subsequent calculations. The optimized fitting coefficients for the A1 and A2 ABS obtained with the analytical fit are shown in Figures S1 and S2.

Once the Hermite coefficients (and distributed multipoles) were determined, a linear least squares fit was done to obtain the exchange–repulsion factor (K in Eq. 3). To this end, the factor was obtained by fitting using reference exchange–repulsion data from RVS over the range of 1.7–3 Å. For the A1 ABS, the exchange–repulsion factor is 5.5702. For both models with the A2 ABS the factor corresponds to 6.3559.

As described above, the GEM fitting procedure also results in distributed multipoles that are derived directly from the Hermite Gaussians. The derived multipoles were also introduced in the GEM* model to determine the electric fields necessary for the AMOEBA polarization term. Thus resulting in a consistent representation for the Coulomb and polarization term by using Hermites and multipoles derived from the same fitted densities. For the GEM* model we reduced the Tholȇ damping parameter to 0.35 (compared to 0.39 in the original AMOEBA) in order to match the RVS polarization data. The multipoles obtained from the Hermite Gaussians for the A1 ABS correspond to the previously reported ones in [3]. For the A2 ABS, the multipoles are given in Table S1.

Table S1: GEM–DM multipoles for the A2 ABS.

	O	H
q	-0.41443768	0.20721884E+00
μ_x	-5.03193997E-09	-5.99869270E-03
μ_y	5.69869099E-14	0.00000000E+00
μ_z	-1.50290152E-02	-0.21385748E+00
θ_{xx}	0.30738046E+00	2.93619855E-02
θ_{yy}	-0.24863917E+00	2.24620404E-02
θ_{zz}	-0.05874129E+00	-5.18240255E-02
θ_{xy}	-6.10758211E-14	0.00000000E+00
θ_{xz}	-7.16347599E-10	2.15991490E-03
θ_{yz}	-2.71010148E-14	0.00000000E+00

Finally, the VdW term was fitted as the difference between the total intermolecular interaction energy from the reference calculations (E^{MP2}_{total}) and each of the previous non–bonded terms,:

$$E_{VdW} \;=\; E^{MP2}_{total} - E^{GEM*}_{Coulomb} - E^{GEM*}_{exchange} - E^{GEM*}_{polarization},$$

Thus, effectively the VdW term is not only a dispersive term. Indeed it also includes the contribution from the charge–transfer interactions and from the difference in the exchange–repulsion and polarization interactions between the HF and MP2 wave–functions since these two terms were obtained with the RVS method.

Three different parametrizations have been explored that involve different Van der Waals parameters and/or different ABS. Model 1 was fitted using only the A2 ABS for the Coulomb and exchange–repulsion, and the VdW parameters were fitted to reproduce the intermolecular interaction energies for several water dimers and oligomers (see below) and the canonical water dimer at a range of distances.

The second model, termed model 2, was fitted to reproduce the results for the canonical water dimer at different distances only using the A2 ABS. Model 3 was parametrized similarly to model 2, i.e., only to reproduce the canonical water dimer energies (and decomposition components) using the A1 ABS. For both models 2 and 3 the combining rules used in AMOEBA were maintained. Conversely, for model 1, the homo– and hetero–atomic parameters were scaled separately.

The VdW parameters for model 1 are: $\epsilon_{OO} = 0.30$, $\epsilon_{OH} = 0.70140302E-01$, $\epsilon_{HH} = -0.0345$, $\sigma_{OO} = 3.405$, $\sigma_{OH} = 3.104803$ and $\sigma_{HH} = 2.855$. The VdW parameters for model 2 are: $\epsilon_{OO} = 0.290$, $\epsilon_{OH} = 0.67831352E-01$, $\epsilon_{HH} = 0.0295$, $\sigma_{OO} = 3.405$, $\sigma_{OH} = 3.104803$ and $\sigma_{HH} = 2.655$. The VdW parameters for 3 are: are $\epsilon_{OO} = 1.1$, $\epsilon_{OH} = 0.6274834$, $\epsilon_{HH} = 0.405$, $\sigma_{OO} = 2.48$, $\sigma_{OH} = 2.246256$ and $\sigma_{HH} = 1.805$.

Once the models were obtained, they were employed to perform MD simulations on a range of water boxes containing 216, 512, 1024, 2048 and 4096 water molecules using the NVE ensemble. Prior to production calculations, the boxes were equilibrated with 20000 steps of NVT simulation at 300 K. For the performance tests, 100 steps with 1 fs time step in the NVE ensemble Particle mesh Ewald was used for long range electrostatic interactions with a direct space and Van der Waals cutoff of 8 Å [19–21]. The induced dipoles were converged to 0.00001 D RMSD and the equations of motion were integrated with a modified Beeman algorithm using a Berendsen thermostat [22].

IV. ENERGY AND FORCE ANALYSIS FOR DIMERS

Figures S3–S7 show the total intermolecular energies and each term in the GEM* decomposition for the canonical water dimer over the range of 1–7 Å for the canonical water dimers.

Figure S3 shows the total intermolecular energy for the three GEM* models compared to the MP2 reference. Figures S4–S7 present each the Coulomb, Exchange, Polarization and Van der Waals energies for the GEM* model 1 parametrization compared to its QM counterpart. Forces along each direction for each of the atoms as labeled in Figure S8 are shown in Figures S9–S17.

Tables S2 and S3 show the energy and corresponding error analysis respectively for 31 random dimers obtained from an equilibrium calculation of AMOEBA water at 298K.

Figure S3: Total intermolecular interaction for the canonical water dimer

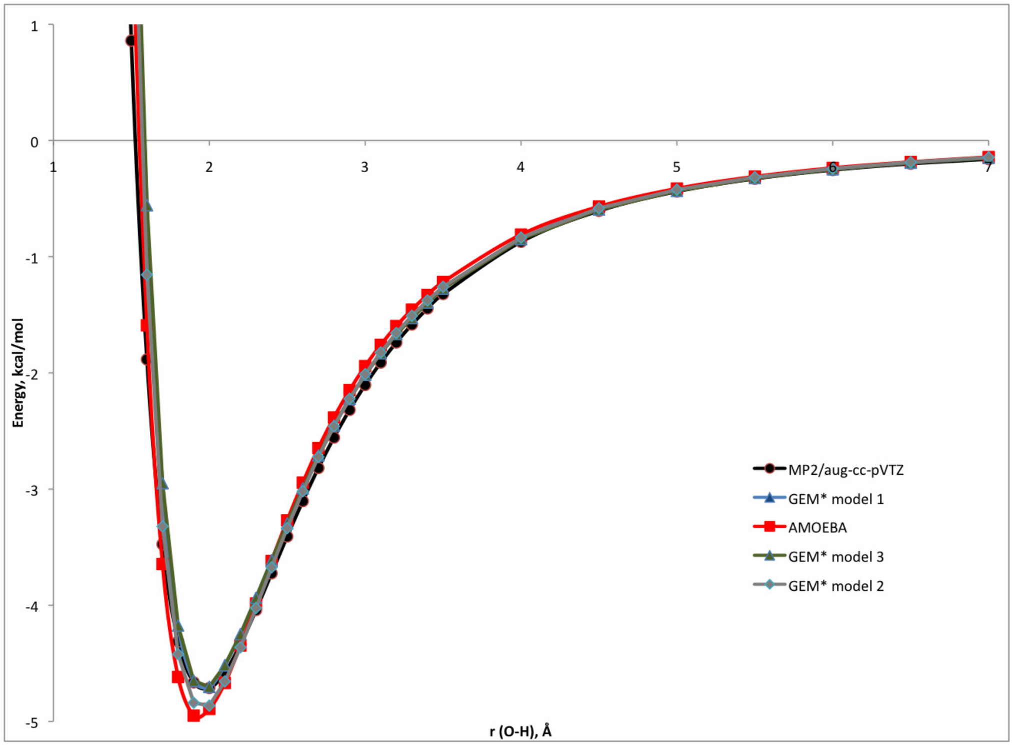


Figure S4: Intermolecular Coulomb interaction for the canonical water dimer

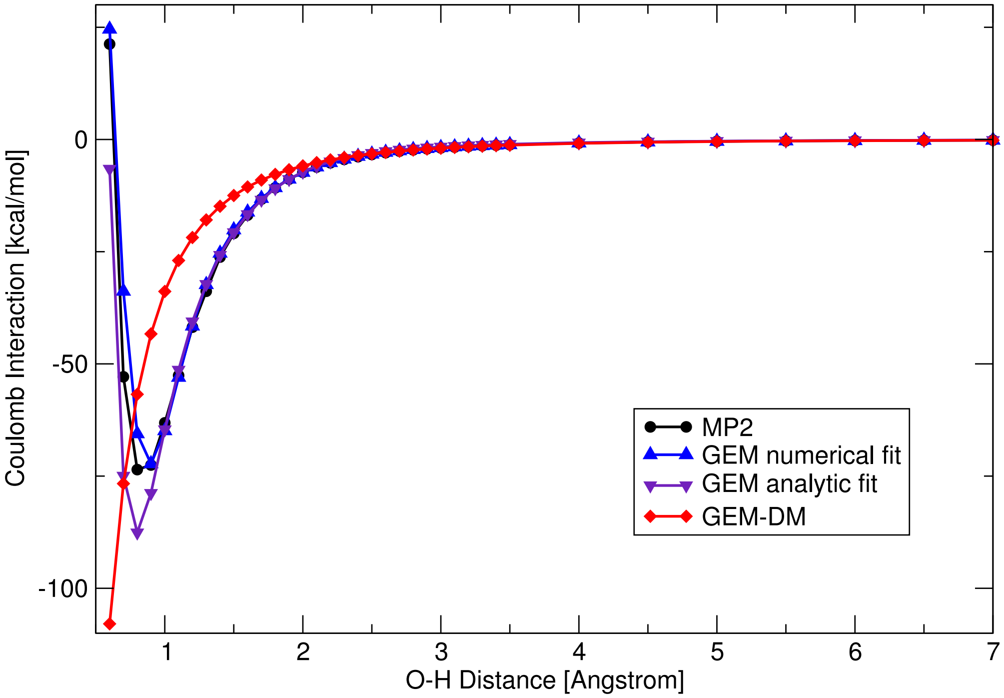


Figure S5: Intermolecular exchange–repulsion interaction for the canonical water dimer

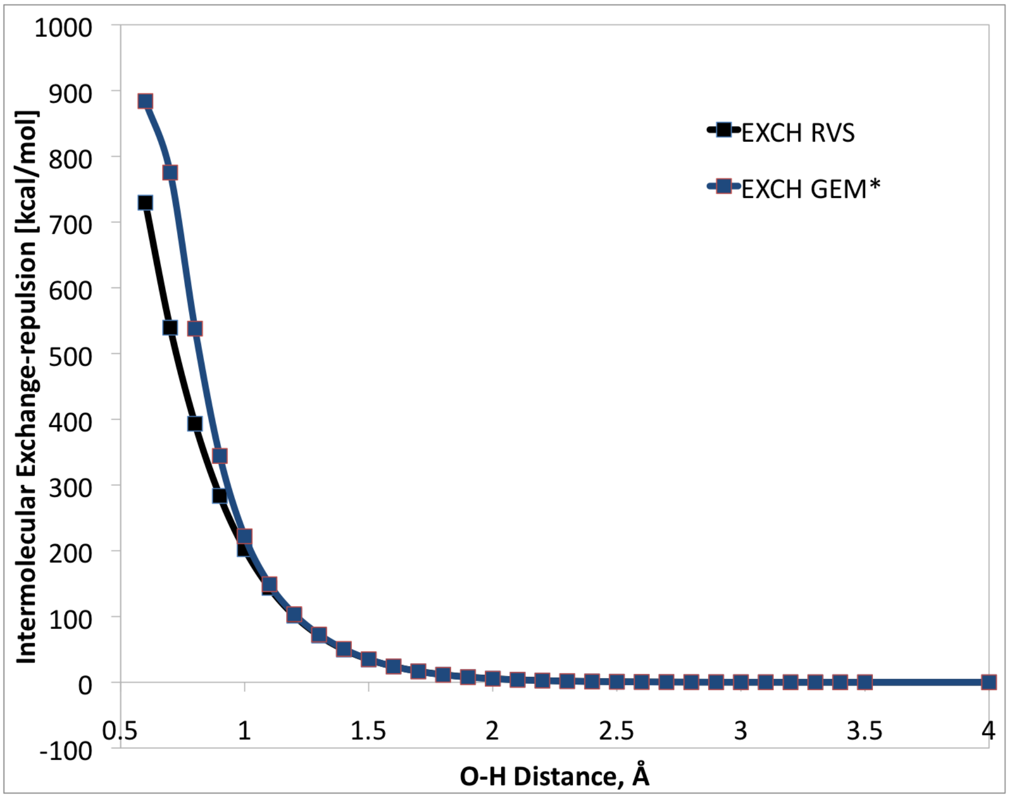


Figure S6: Intermolecular polarization interaction for the canonical water dimer

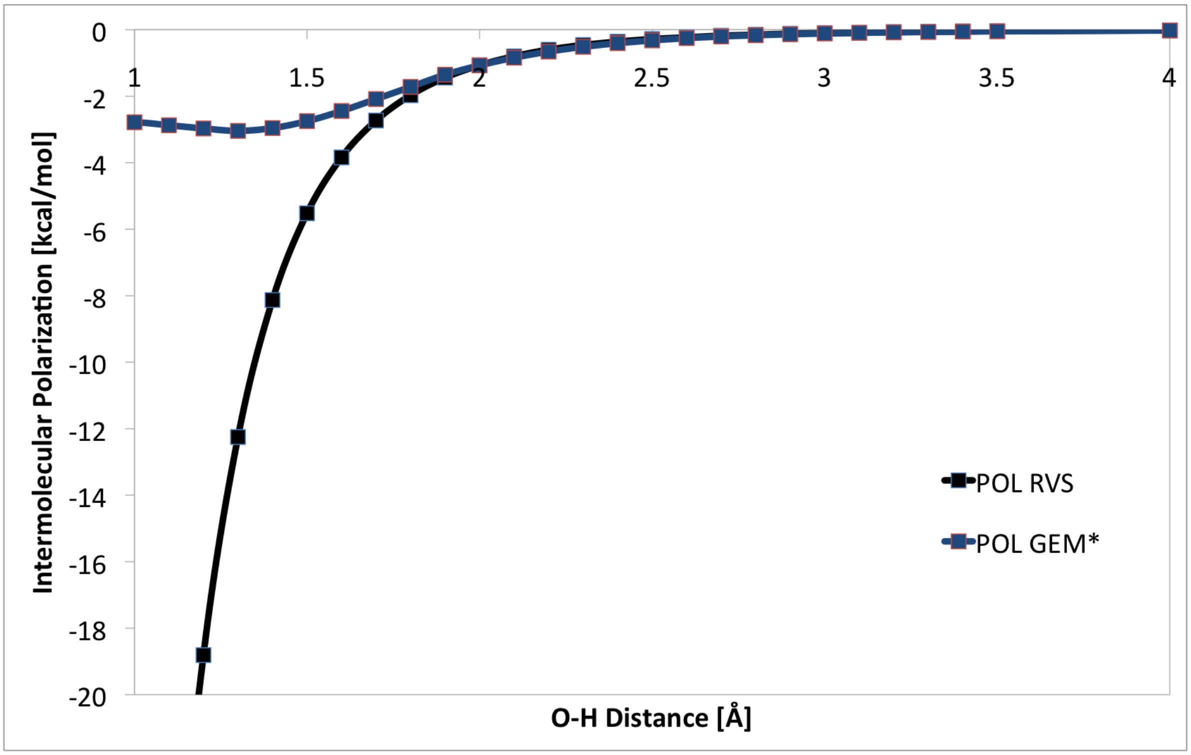


Figure S7: Intermolecular Van der Waals interaction for the canonical water dimer

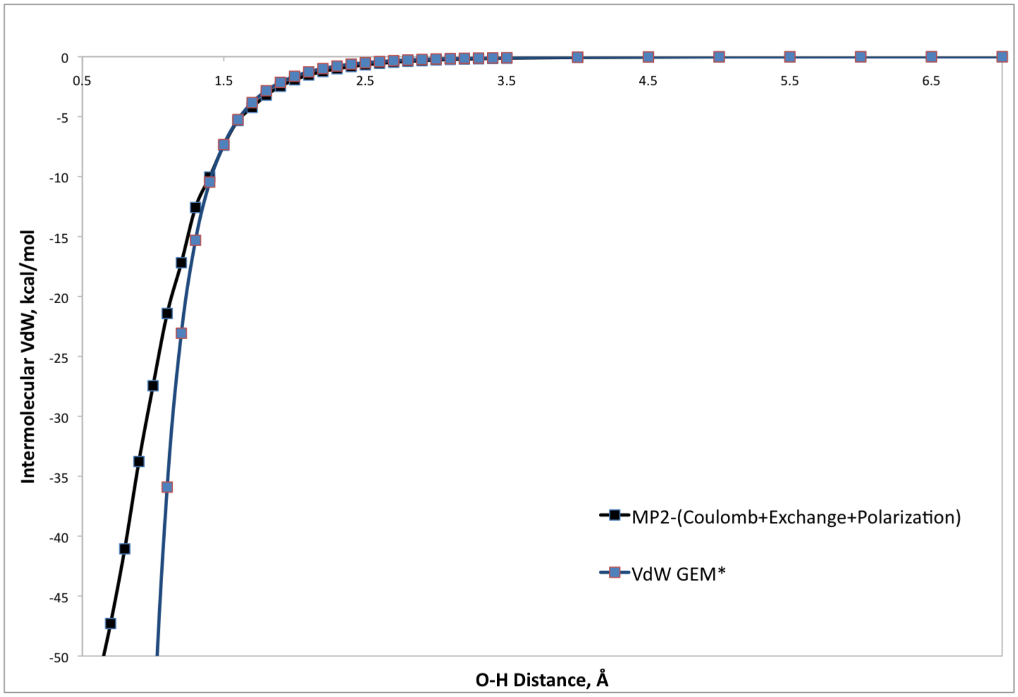


Figure S8: Canonical water dimer with labels for force analysis

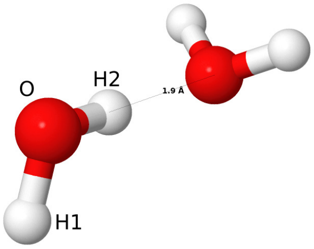


Figure S9: Force on the O atom of molecule 1 along the X direction

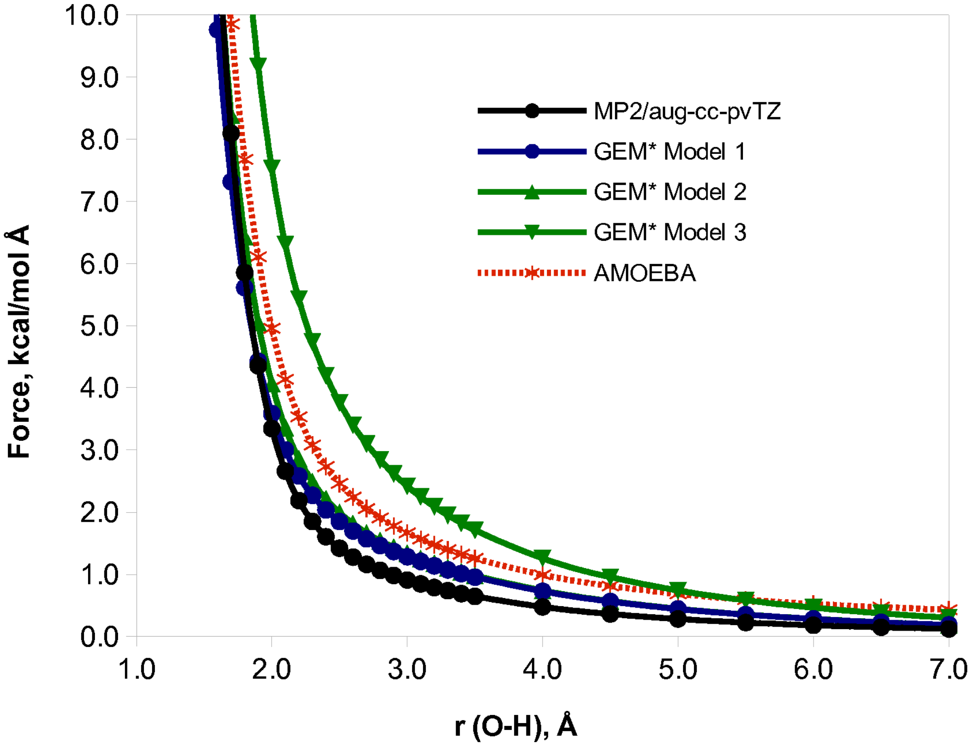


Figure S10: Force on the O atom of molecule 1 along the Y directions

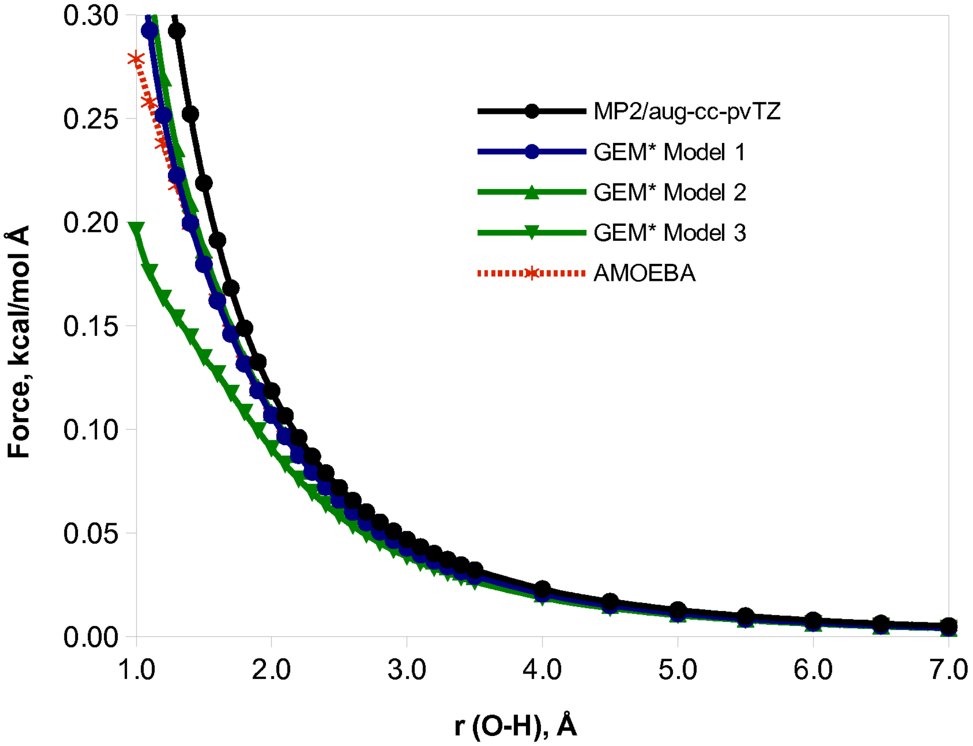


Figure S11: Force on the O atom of molecule 1 along the Z direction

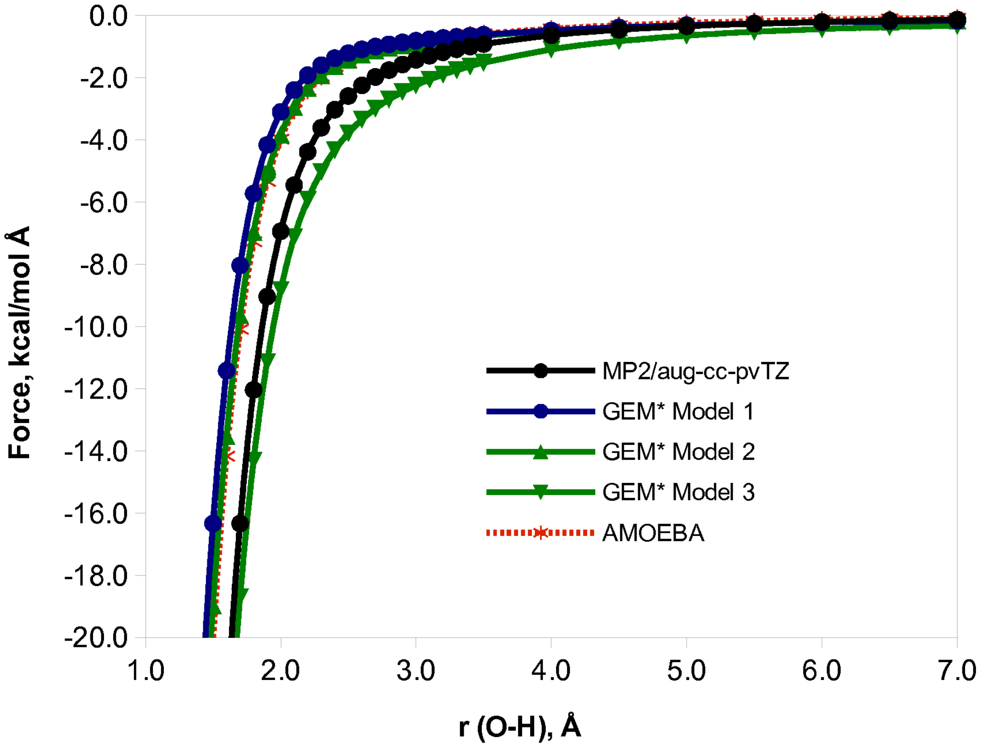


Figure S12: Force on the H1 atom of molecule 1 along the X directions

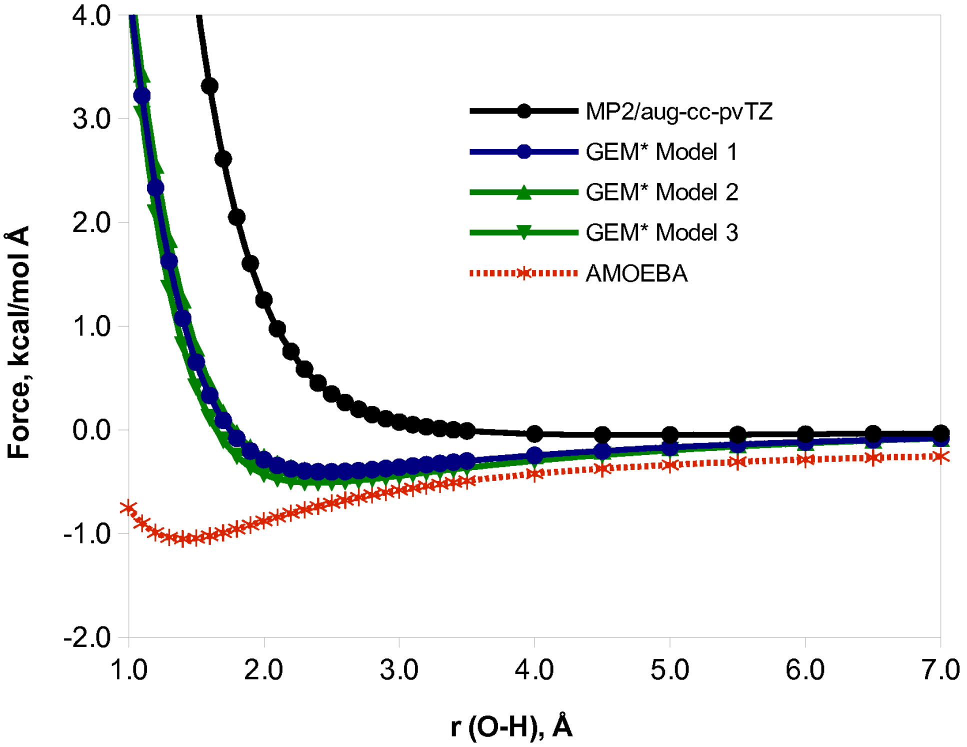


Figure S13: Force on the H1 atom of molecule 1 along the Y directions

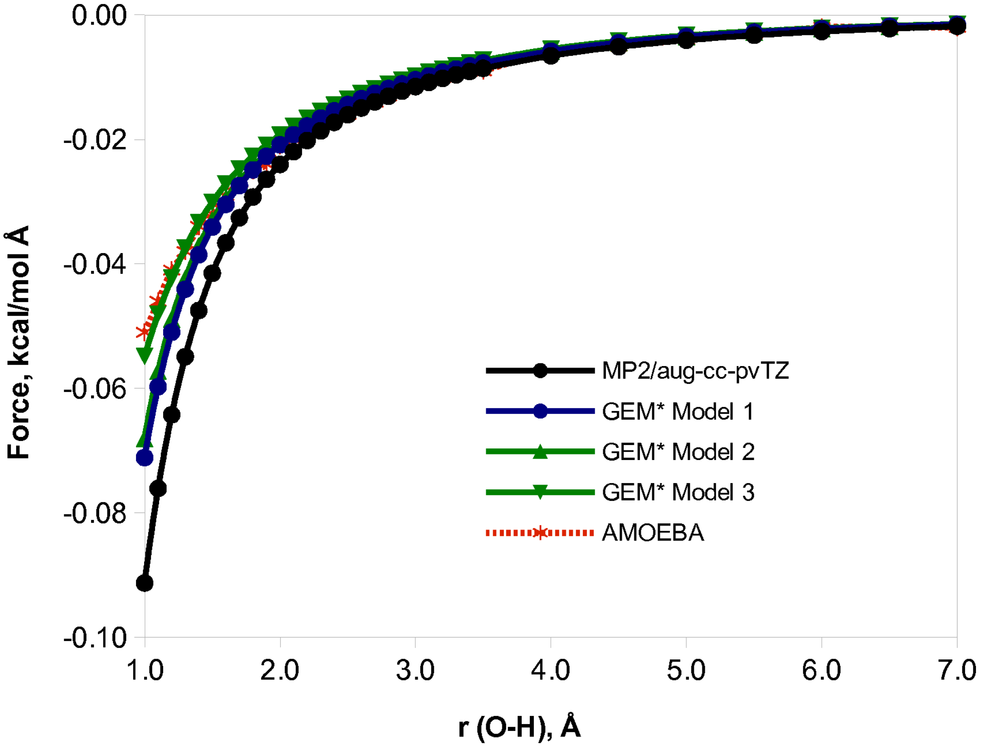


Figure S14: Force on the H1 atom of molecule 1 along the Z directions

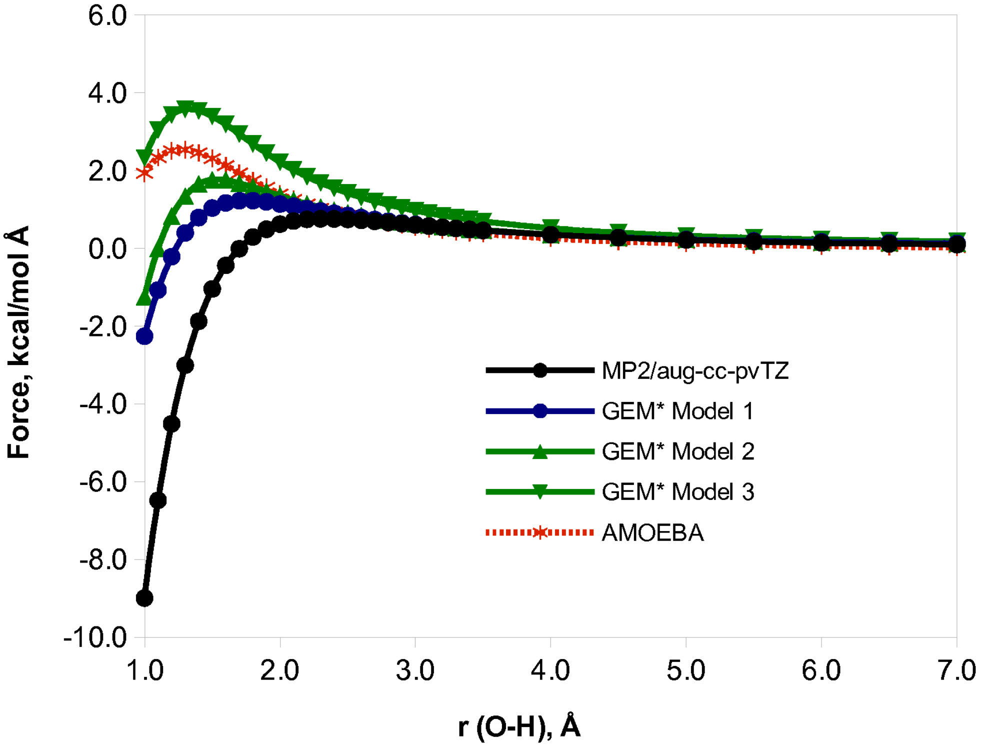


Figure S15: Forces on the H2 atom of molecule 1 along the X direction

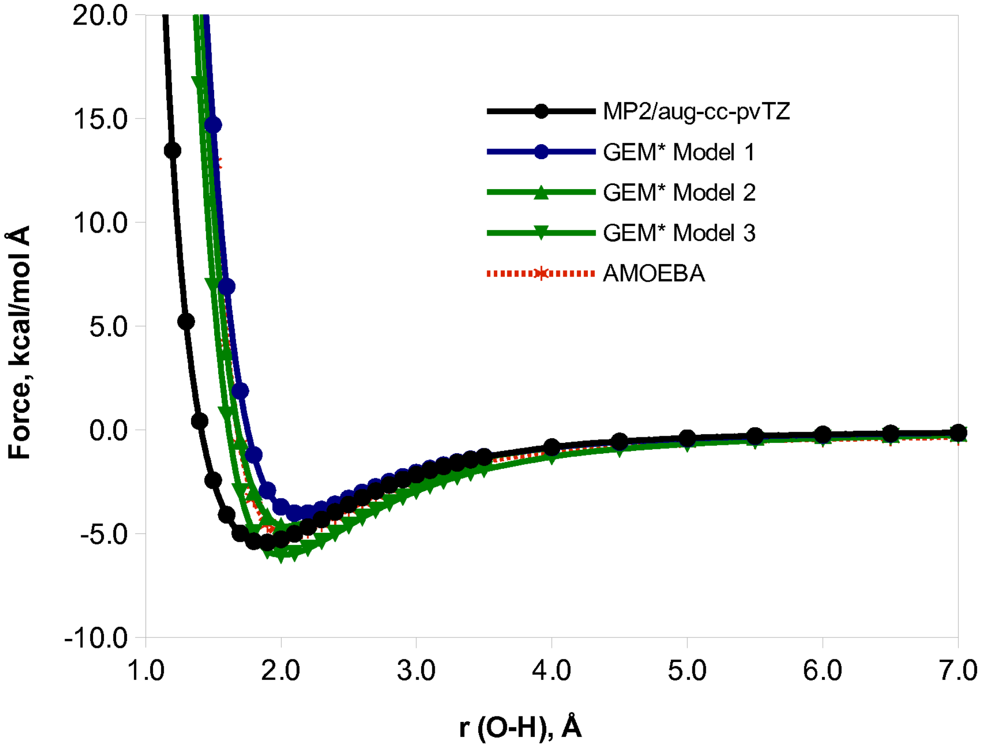


Figure S16: Forces on the H2 atom of molecule 1 along the Y direction

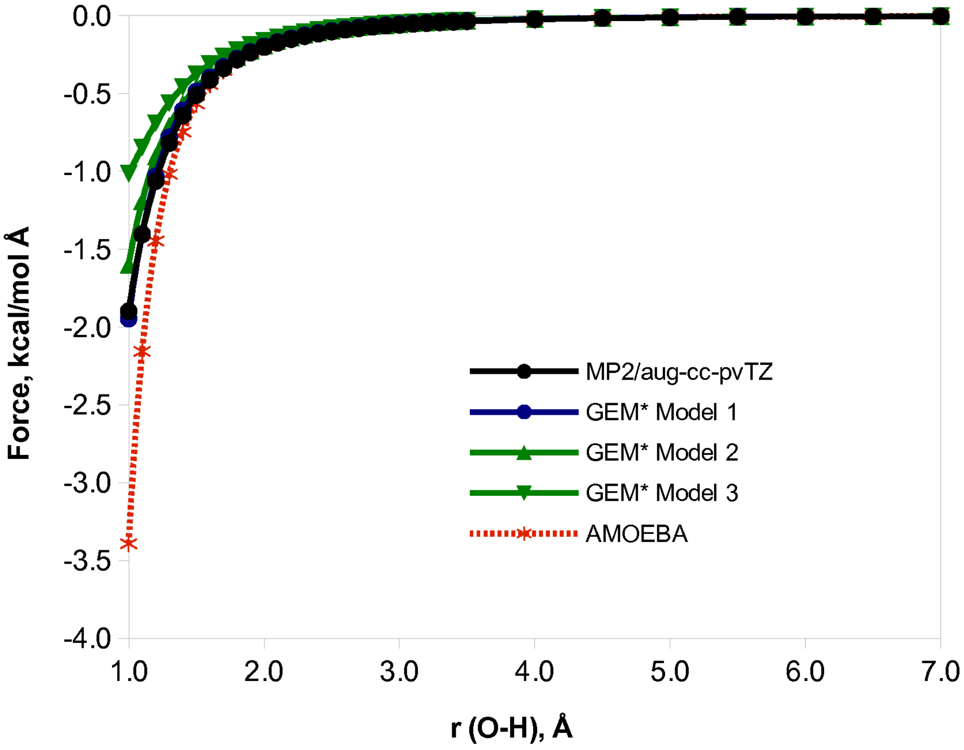


Figure S17: Forces on the H2 atom of molecule 1 along the Z direction

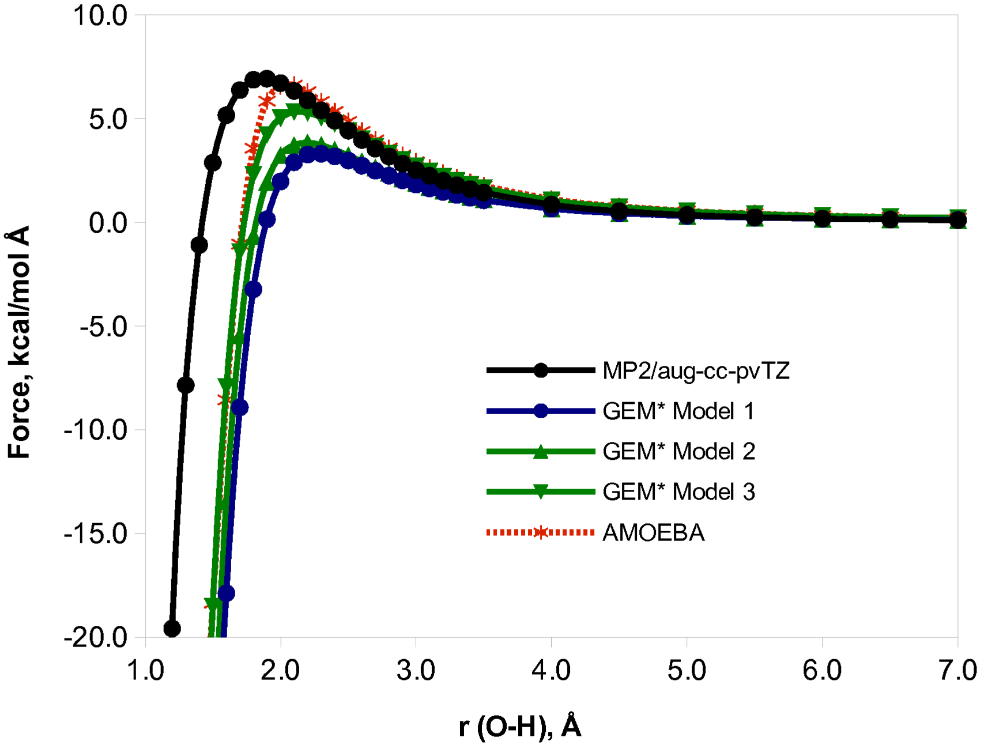


Table S2: Total intermolecular interaction energies for random dimers (in kcal/mol).

Dimer	MP2	model 1	model 2	model 3	AMOEBA
1	-1.099702442	-0.9678	-1.8708	-2.0862	-1.1711
2	0.316026162	0.2984	0.2909	0.2521	0.2583
3	-0.600048398	-0.5634	-0.5694	-0.5327	-0.5442
4	-1.213375284	-1.3065	-2.2983	-2.2505	-1.3682
5	1.110323994	1.0726	1.0641	0.9988	1.138
6	-0.151723799	-0.1348	-0.1422	-0.1507	-0.1618
7	1.160766708	1.2586	1.0051	0.8488	0.9986
8	0.269757458	0.2875	0.2764	0.2538	0.2796
9	0.44780397	0.459	0.4479	0.4203	0.4482
10	0.839622562	0.829	0.7823	0.7527	0.8543
11	-1.62643721	-1.65	-1.7239	-1.6097	-1.5456
12	-0.347638003	-0.3306	-0.3361	-0.3301	-0.3569
13	-0.091738721	-0.0712	-0.079	-0.0698	-0.0516
14	-0.845484578	-0.8154	-0.8237	-0.777	-0.8045
15	-1.405839062	-1.7254	-2.0857	-1.8023	-1.4163
16	0.069540909	0.085	0.0731	0.0728	0.0927
17	0.085032107	0.1011	0.083	0.0582	0.0635
18	-1.077069723	-1.0326	-1.0454	-0.9987	-1.0491
19	-0.950525807	-0.9117	-0.9246	-0.8755	-0.8726
20	-1.305981347	-1.2443	-1.3062	-1.2363	-1.1511
21	-0.057097996	-0.2452	-0.616	-0.7243	-0.6323
22	-2.038338045	-2.3778	-2.898	-2.7624	-2.2339
23	-0.023928776	-0.0287	-0.0327	-0.036	-0.0226
24	-0.262182335	-0.2386	-0.2443	-0.2294	-0.2197
25	-0.693614193	-0.8583	-0.9234	-0.7526	-0.6862
26	0.137204325	0.1311	0.126	0.1224	0.1715
27	0.998055209	0.9622	0.952	0.8726	0.9657
28	-4.184791294	-4.2256	-4.7689	-4.1134	-3.6957
29	-0.947720286	-1.296	-2.3089	-2.3591	-1.3913
30	-0.436317018	-0.4189	-0.4234	-0.3894	-0.3828
31	-3.744861566	-3.7111	-4.157	-3.7402	-3.584

Table S3: Error in total intermolecular interaction energies for random dimers with respect to the QM reference (in kcal/mol).

Dimer	model 1	model 2	model 3	AMOEBA
1	-0.131902442	0.771097558	0.986497558	0.071397558
2	0.017626162	0.025126162	0.063926162	0.057726162
3	-0.036648398	-0.030648398	-0.067348398	-0.055848398
4	0.093124716	1.084924716	1.037124716	0.154824716
5	0.037723994	0.046223994	0.111523994	-0.027676006
6	-0.016923799	-0.009523799	-0.001023799	0.010076201
7	-0.097833292	0.155666708	0.311966708	0.162166708
8	-0.017742542	-0.006642542	0.015957458	-0.009842542
9	-0.01119603	-9.60295E-05	0.02750397	-0.00039603
10	0.010622562	0.057322562	0.086922562	-0.014677438
11	0.02356279	0.09746279	-0.01673721	-0.08083721
12	-0.017038003	-0.011538003	-0.017538003	0.009261997
13	-0.020538721	-0.012738721	-0.021938721	-0.040138721
14	-0.030084578	-0.021784578	-0.068484578	-0.040984578
15	0.319560938	0.679860938	0.396460938	0.010460938
16	-0.015459091	-0.003559091	-0.003259091	-0.023159091
17	-0.016067893	0.002032107	0.026832107	0.021532107
18	-0.044469723	-0.031669723	-0.078369723	-0.027969723
19	-0.038825807	-0.025925807	-0.075025807	-0.077925807
20	-0.061681347	0.000218653	-0.069681347	-0.154881347
21	0.188102004	0.558902004	0.667202004	0.575202004
22	0.339461955	0.859661955	0.724061955	0.195561955
23	0.004771224	0.008771224	0.012071224	-0.001328776
24	-0.023582335	-0.017882335	-0.032782335	-0.042482335
25	0.164685807	0.229785807	0.058985807	-0.007414193
26	0.006104325	0.011204325	0.014804325	-0.034295675
27	0.035855209	0.046055209	0.125455209	0.032355209
28	0.040808706	0.584108706	-0.071391294	-0.489091294
29	0.348279714	1.361179714	1.411379714	0.443579714
30	-0.017417018	-0.012917018	-0.046917018	-0.053517018
31	-0.033761566	0.412138434	-0.004661566	-0.16086156

V. ENERGY ANALYSIS FOR OLIGOMERS

Tables S4 and S5 show the energy and error analysis respectively for fourteen water clusters (one dimer, two trimers, three tetramers, two pentamers and six hexamers). The water cluster geometries were obtained from reference3 [23]. The labels for the oligomers follows the same notation as in reference [23]. The reference values were calculated at the MP2/aug–cc–pVTZ level corrected for BSSE by the counterpoise method.

Table S4: Total binding energies for selected water clusters (in kcal/mol).

Dimer	MP2	model 1	model 2	AMOEBA
2-Cs	-4.775	-4.6069	-4.957	-4.9692
3-UUD	-14.828	-16.144	-16.8821	-15.0685
3-UUU	-14.469	-16.0778	-16.6457	-14.2761
4-Ci	-25.105	-26.2338	-27.3935	-26.6348
4-PY	-22.220	-24.3236	-25.3594	-22.7958
4-S4	-25.670	-26.3684	-27.7175	-27.1849
5-CA-B	-30.914	-33.3486	-34.8061	-32.794
5-CYC	-33.781	-34.2582	-35.7258	-35.8806
6-BAG	-41.551	-43.1668	-44.9979	-44.0378
6-BK-1	-42.645	-44.0384	-45.8899	-45.0546
6-BK-2	-42.338	-43.9481	-45.8489	-44.8221
6-CA	-42.828	-45.3776	-47.473	-45.1167
6-CC	-41.781	-41.8982	-43.5261	-43.9014
6-PR	-42.200	-45.3936	-47.2138	-44.8727

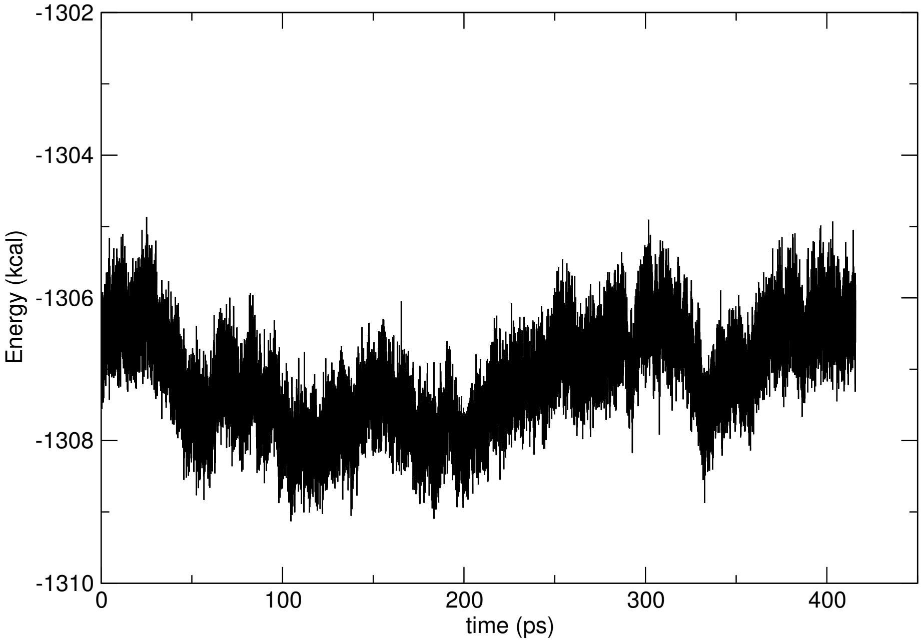
Table S5: Error in total binding energies for selected water clusters with respect to the QM reference (in kcal/mol).

Dimer	model 1	model 2	AMOEBA
2-Cs	-0.168	0.1819604726	0.194
3-UUD	1.316	2.0544826126	0.241
3-UUU	1.609	2.1768607474	-0.193
4-Ci	1.129	2.2882661641	1.530
4-PY	2.103	3.1389718911	0.575
4-S4	0.699	2.0477583326	1.515
5-CA-B	2.435	3.8925345714	1.880
5-CYC	0.477	1.9447967604	2.100
6-BAG	1.615	3.446489416	2.486
6-BK-1	1.394	3.24503119	2.410
6-BK-2	1.610	3.5112449245	2.484
6-CA	2.550	4.6450072339	2.289
6-CC	0.117	1.7449629867	2.120
6-PR	3.193	5.0135289065	2.672

VI. TOTAL ENERGY FOR 216 WATER BOX

Figure S18 shows the total energy of a 216 water box with the model 2 parametrization for an NVE simulation at 298 K.

Figure S18: Total Energy for a 216 water box, NVE ensemble at 300 K



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