

Supplementary Material for:

Self-Consistent Electrostatic Embedding for Liquid Phase Polarization

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Codes for processing MD configurations:

These are included as stand-alone Fortran90 files: ClusterGen_3site.f90 for 3-site water models and ClusterGen_4site.f90 for 4-site models.

Script for generating proton-disordered configurations with GenIce:

```
#!/bin/bash

for i in {1..200}
do
genice --seed "$i"38"$i"73 --rep 5 5 5 1h --format gromacs > 1h_x_555_seed_"$i".gro
done
```

Keywords for processing SCEE Gaussian calculations:

Job 1 (optimization)

```
#p b3lyp/aug-cc-pvtz gfpri charge opt=(maxcycles=100,tight)
# nosymm pop=full scf=(verytight) density=current
# integral=(ultrafine,NoXCTest)
```

Job 2 (single-point in implicit solvent using geometry from Job1)

```
#p b3lyp/aug-cc-pvtz gfprint scrf=(scipcm,solvent=water,read)
# nosymm pop=full scf=(verytight) density=current
# integral=(ultrafine,NoXCCTest) guess=tcheck geom=checkpoint
eps=1.776
```

Job 3 (single-point in gas-phase using geometry from Job1)

```
#p b3lyp/aug-cc-pvtz gfprint
# nosymm pop=full scf=(verytight) density=current
# integral=(ultrafine,NoXCCTest) guess=tcheck geom=checkpoint
```

Scripts for extracting information from SCEE Gaussian calculations:

Energies from Job1

```
grep "Done" filenameJob1.out | tail -1 | awk '{print $5}'
grep " Self energy of the charges = " filenameJob1.out | tail -1 | awk '{print $7}'
grep " Nuclei-charges interaction = " filenameJob1.out | tail -1 | awk '{print $4}'
```

Multipoles from Job1

```
grep " Tot=" filenameJob1.out | tail -1 | awk '{print $8}'
grep -A1 "Traceless Quadrupole " filenameJob1.out | tail -1 | awk '{print $2, $4, $6}'
grep -A2 "Traceless Quadrupole " filenameJob1.out | tail -1 | awk '{print $2, $4, $6}'
```

Energy from Job2

```
grep "Cycle 1" filenameJob2.out -A36 | awk "NR==36{print}"
```

Energy from Job3

```
grep "Cycle 1" filenameJob3.out -A5 | awk "NR==3{print}"
```

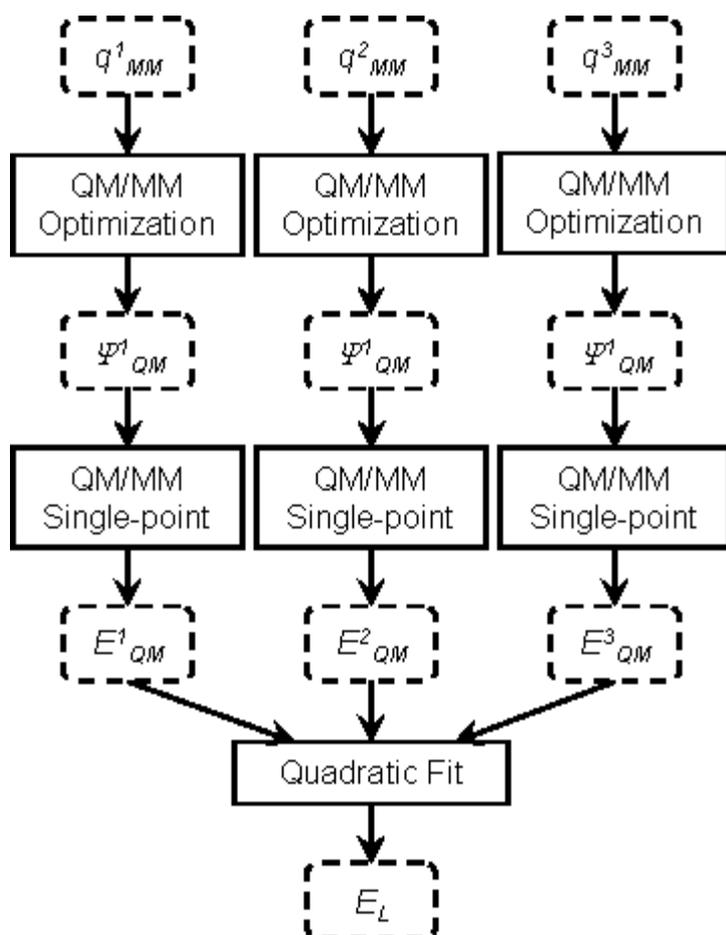


Figure S1 – Schematic flowchart explaining the procedure for calculating different polarization energy components from SCEE results. The dashed boxes denote inputs to each particular procedure (rectangles). In the fast version of SCEE (see Figure 1b in the main paper), three QM/MM optimizations of a central water molecule with electrostatic embedding are carried out for three different values of the point charges (and hence dipole moments) of the surrounding MM molecules. The self-consistent liquid phase dipole moment is then obtained from a quadratic fit over the results of those calculations. To calculate energies, the optimized wave function (Ψ_{QM}) from each of the three individual calculations is extracted and used in a single-point calculation in a different environment (e.g. to obtain the distortion energy, the wave function is placed in vacuum), from which the corresponding energy is obtained. Finally, as in the SCEE approach, a quadratic fit is applied to the three energies, which is then used to compute the energy (E_L) that corresponds to the converged liquid-phase dipole moment (μ_L).

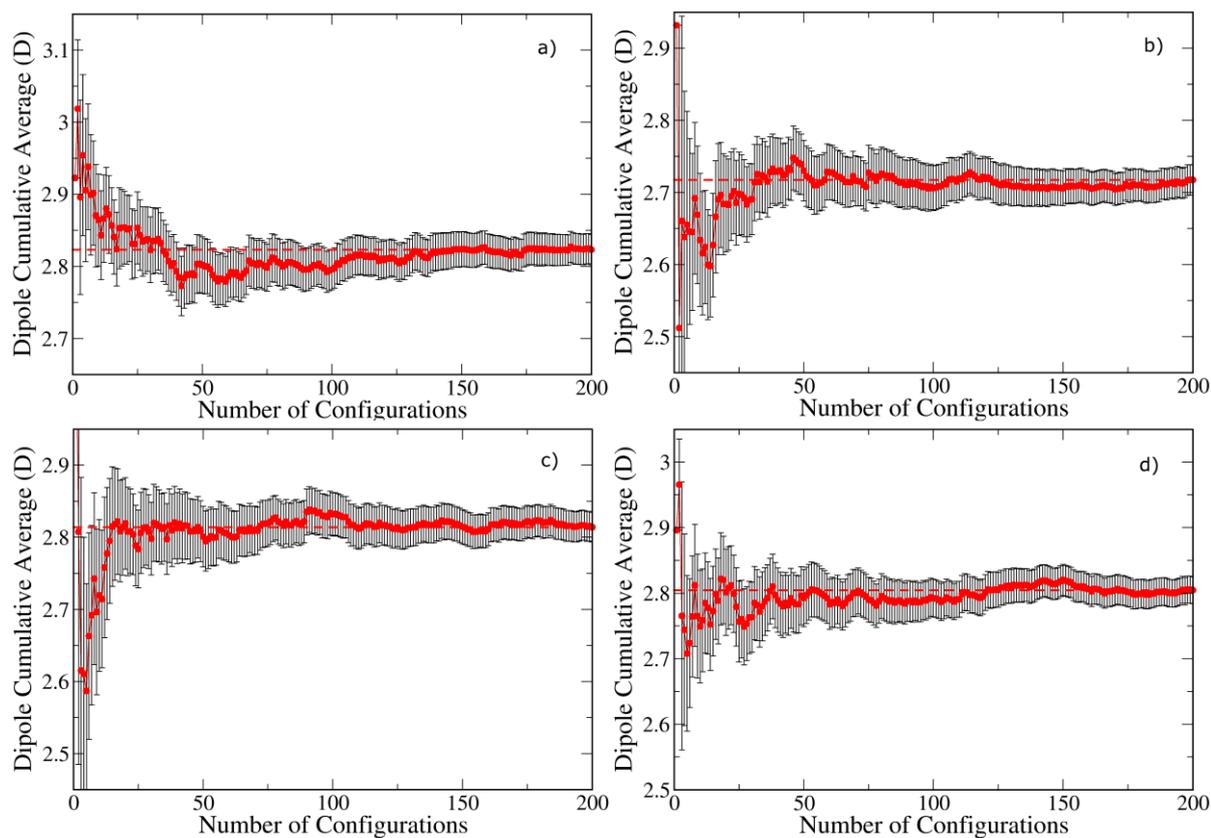


Figure S2 – Cumulative average of the liquid phase dipole moment as a function of the number of MD configurations sampled for: (a) the SPC/E model; (b) the TIP3P model; (c) the TIP4P2005 model; (d) the TIP4P-FB model. The SPC/E calculations were done at the M06-2X/PTZ level of theory, while those for the other three models were done at the B3LYP/DTZ level. All MD simulations were carried out in the NPT ensemble. The error bars in the figures represent the standard error of the mean, while the dashed red line shows the converged value.

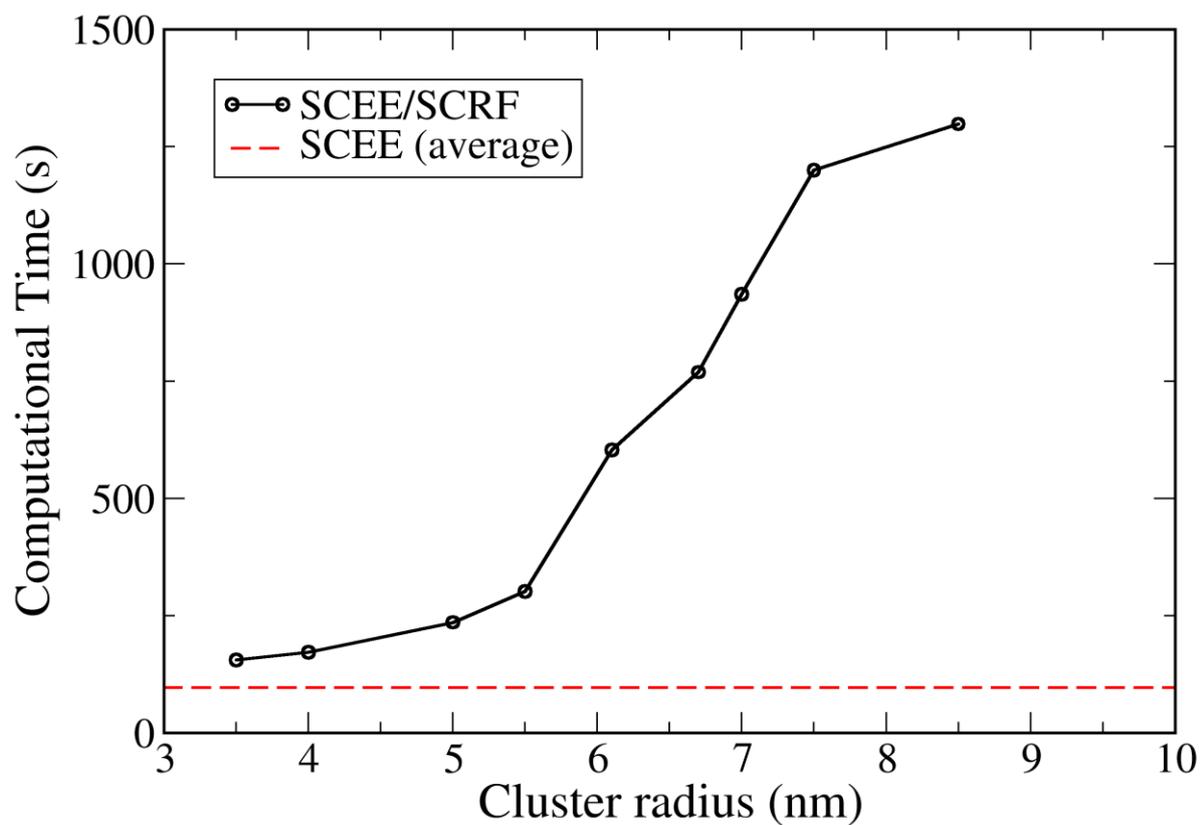


Figure S3 – Computational time for a single QM step of a SCRF calculation as a function of the radius of the cavity. For each calculation, a QM/MM cluster is contained within the SCRF cavity of the corresponding radius. The red dashed line shows the average computational time of a single step of a QM/MM calculation (i.e. without the SCRF), which is practically independent of the size of the cluster.

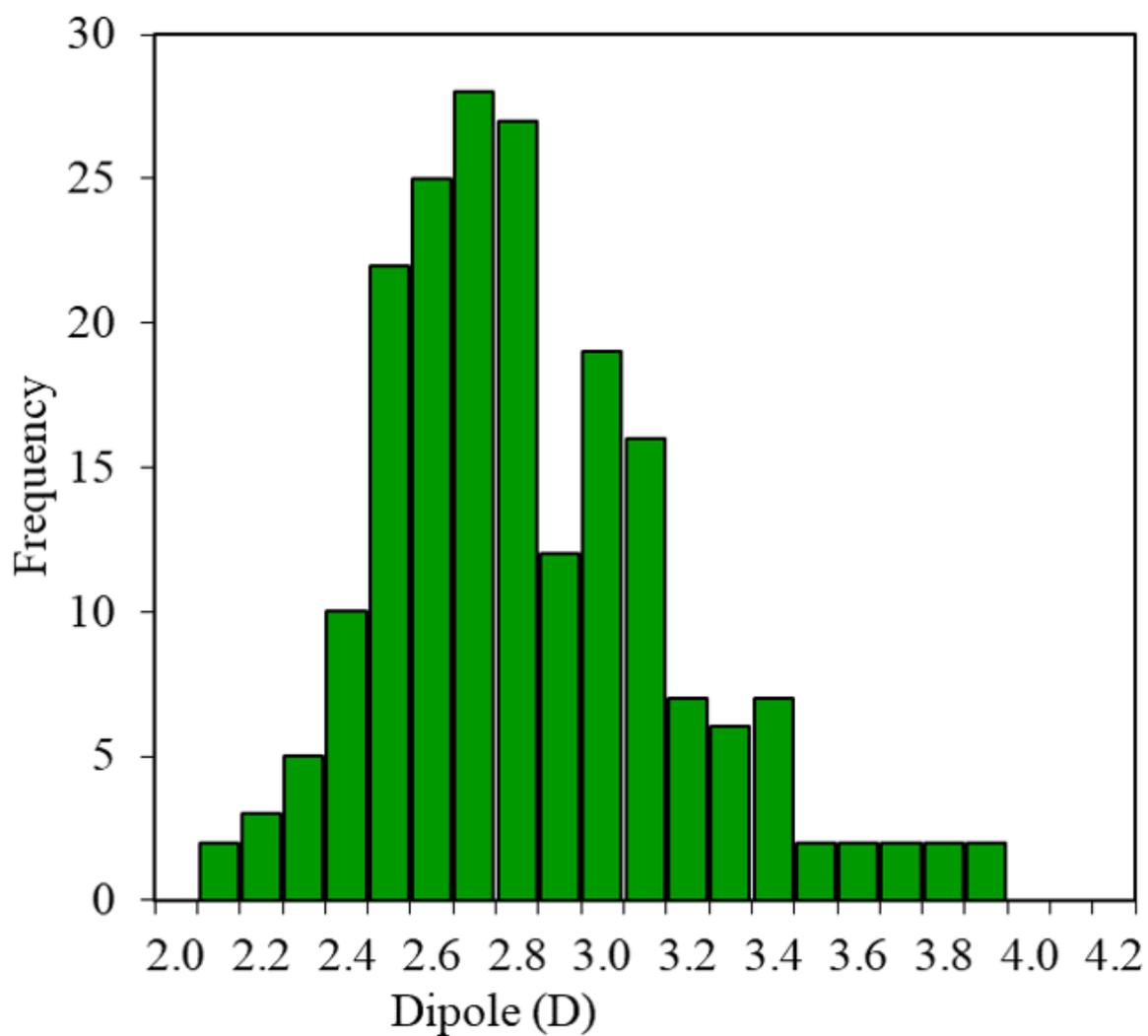


Figure S4 – Liquid dipole moment distribution over 200 MD configurations obtained at the B3LYP/DTZ QM level with hydrogen atom optimization and using the SWM4-DP polarizable water model.

Table S1 – Liquid phase multipole components and energy contributions for water obtained with each individual classical fixed-charge model. Results are averages over 200 SCEE calculations using the B3LYP/DTZ level of theory with hydrogen atom optimization.

	SPC/E	TIP4P2005	TIP4P-FB
μ (D)	2.81 ± 0.05	2.81 ± 0.04	2.80 ± 0.04
Q_0 (D.Å)	0.23 ± 0.02	0.26 ± 0.02	0.26 ± 0.02
Q_T (D.Å)	2.15 ± 0.03	2.12 ± 0.03	2.12 ± 0.03
E_{Dist} (kJ/mol)	32.0 ± 2.8	32.1 ± 2.3	30.5 ± 2.2
E_{Elec} (kJ/mol)	-32.7 ± 0.9	-32.8 ± 0.8	-32.4 ± 0.8
E_{Corr} (kJ/mol)	-0.7 ± 1.9	-0.6 ± 1.5	-1.8 ± 1.4
E_{Int} (kJ/mol)	-90.2 ± 5.1	-91.3 ± 4.3	-88.0 ± 4.1
E_{Stab} (kJ/mol)	-63.0 ± 5.4	-63.3 ± 4.5	-60.2 ± 4.2
E_{Pol} (kJ/mol)	-31.0 ± 6.0	-31.1 ± 5.1	-29.7 ± 4.7

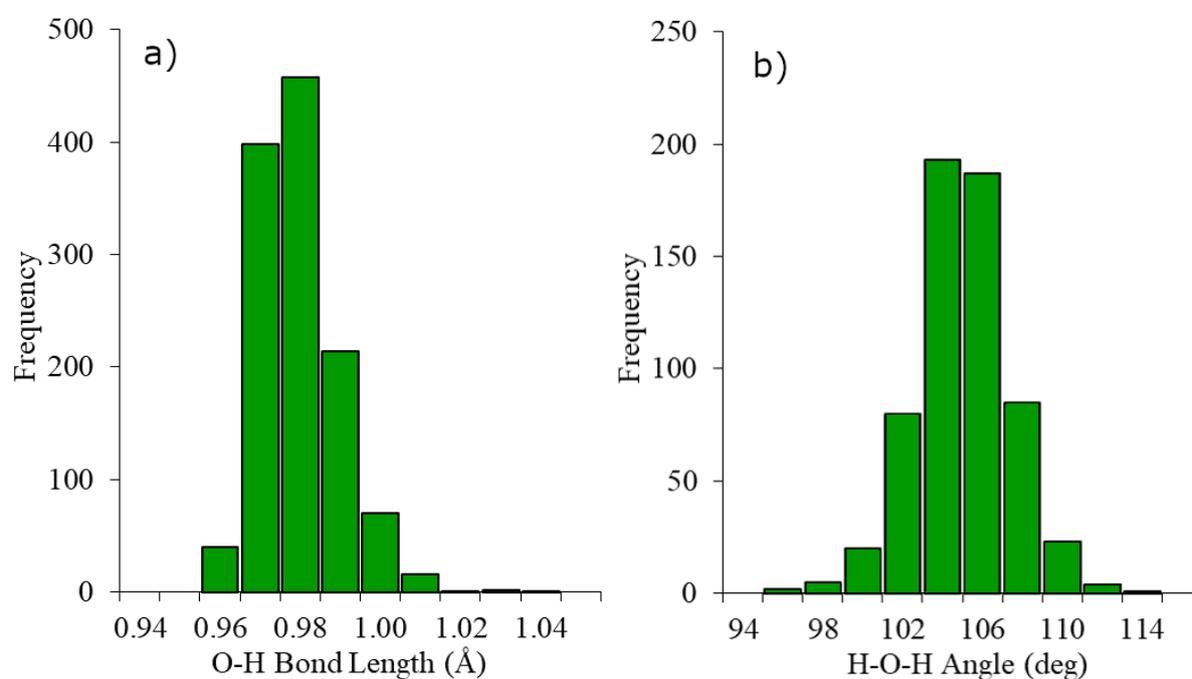


Figure S5 – Distributions of the O-H bond length (a) and H-O-H angle (b). Results were sampled over 600 configurations obtained with the SPC/E, TIP4P2005 and TIP4P-FB models, using SCEE at the B3LYP/DTZ QM level of theory with hydrogen atom optimization.

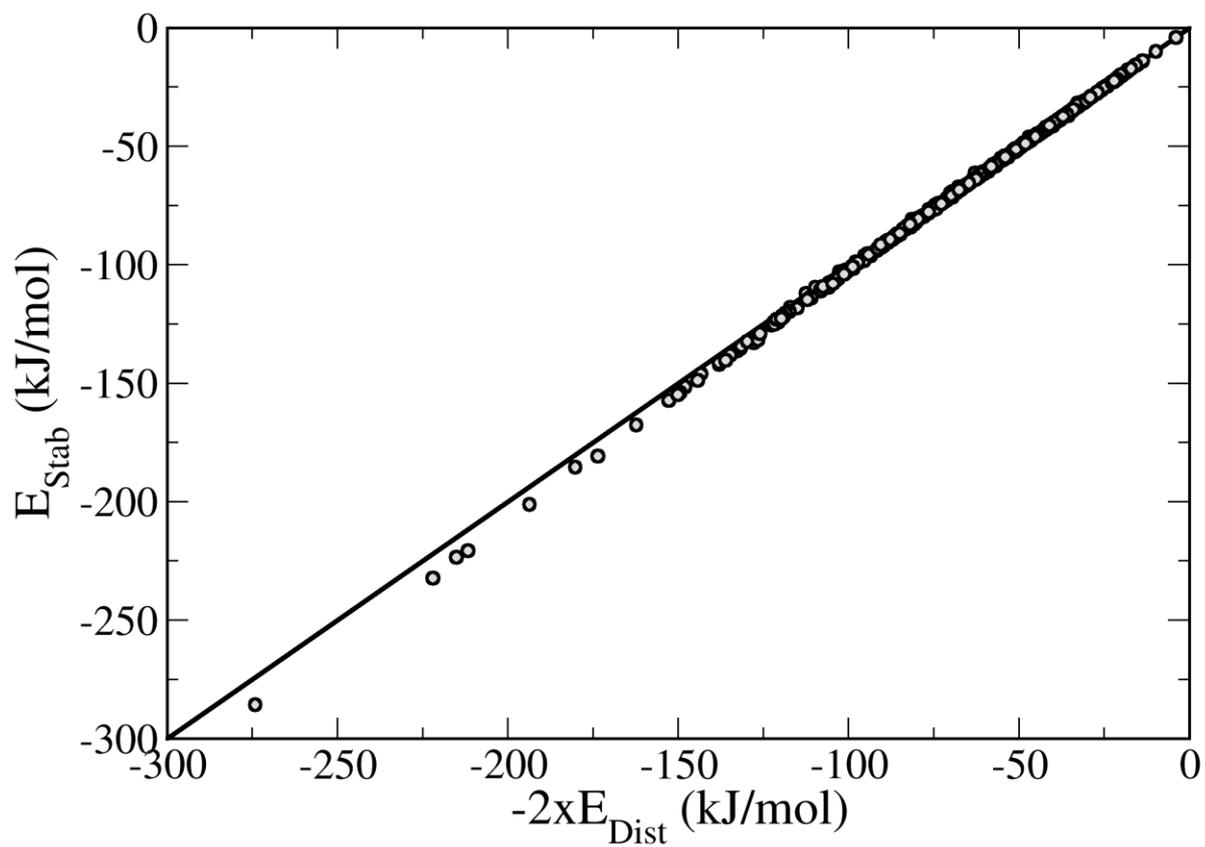


Figure S6 – Stabilization energy (i.e. the energy gained in the liquid phase by polarizing the central water molecule) vs the negative of twice the distortion energy (i.e. the energy cost from polarizing the wave function of the central molecule). The diagonal line corresponds to $x = y$, while the points are results from individual SCEE calculations.

Table S2 – Dipole moments of water in the liquid phase reported in previous QM/MM studies in the literature. For each entry, we report the QM level of theory (wave function method or DFT functional, followed by basis set when applicable), the QM/MM method (EE = electrostatic embedding; PE = polarized embedding), whether the central QM molecule was optimized or not, the classical MM model used, the ensemble used in the simulations, the reported value of the dipole moment shift (i.e. the difference between the liquid and gas dipole moments), and the corrected value of the dipole moment shift, both in Debye units. To estimate the latter, we added individual correction terms for each step of the process, as described in the main paper. These corrections are given in brackets in each relevant column of the table, also in Debye units. We excluded work done using semi-empirical methods, as they severely underestimate the liquid dipole moment. For studies that carried out multiple QM/MM calculations, we report only the most accurate estimates (see original papers for details).

Reference	Year	QM level	Method	Optimization	MM Model	Ensemble	Reported $\Delta\mu$	Corrected $\Delta\mu$
Wei [1]	1994	LDA/TZVP+	EE (+0.14)	No (+0.08)	SPC (+0.07 ¹)	NVT (0.0)	0.66	0.95
Tuñon [2]	1995	VWN/TZP	EE (+0.14)	No (+0.08)	TIP3P (+0.07)	NVT (0.0)	0.68	0.97
Tuñon [3]	1996	VWN/DZP	EE (+0.14)	No (+0.08)	TIP3P (+0.07)	NPT (+0.02)	0.61	0.92
Chalmet [4]	2001	BP/”extended”	EE (+0.14)	No (+0.08)	TIP3P (+0.07)	NVE (0.0)	0.8	1.09
Tu [5]	1999	HF/6-311G(d,p)	EE (+0.14)	No (+0.08)	TIP3P (+0.07)	NVT (0.0)	0.65	0.94
Rocha [6]	2001	HF/6-31++G(d,p)	EE (+0.14)	No (+0.08)	TIP3P (+0.07)	NVT (0.0)	0.44	0.73
Takahashi [7]	2001	PZ/60 a.u. ²	EE (+0.14)	No (+0.08)	TIP4P (0.0 ³)	NVT (0.0)	0.73	0.95
Coutinho [8]	2003	MP2/aug-cc-VDZ	EE (+0.14)	No (+0.08)	TIP5P (0.0 ⁴)	NPT (0.0)	0.74	0.96
Georg [9]	2012	MP2/aug-cc-pV5Z	EE (+0.14)	Yes (0.0)	SPC/E (0.0)	NVT (0.0)	0.86	1.00
Jansen [10]	1996	CISD/Sadlej	PE (0.0)	No (+0.08)	PSCP (0.0)	NVT (0.0)	0.79	0.88
Moriarty [11]	1996	HF/ANO	PE (0.0)	No (+0.08)	NEMO (0.0)	NVT (0.0)	0.82	0.90
Sánchez [12]	1998	HF/6-21G**(ddp)	PE	No	TIP3P	NPT	0.74	0.91

			(0.0)	(+0.08)	(+0.07)	(+0.02)		
Sánchez [13]	2000	MP2/aug-cc-pVDZ	PE (0.0)	No (+0.08)	TIP3P (+0.07)	NPT (+0.02)	0.81	0.98
Tu [14]	2000	MP2/Sadlej	PE (0.0)	No (+0.08)	TIP3P (+0.07)	NVT (0.0)	0.77	0.95 ⁵
Poulsen [15]	2002	CAS(8,8)/aug-cc-pVTZ	PE (0.0)	No (+0.08)	PSCP (0.0)	NVT (0.0)	0.81	0.89
Kongsted [16]	2002	CCSD/aug-cc-pVQZ	PE (0.0)	No (+0.08)	PSCP (0.0)	NVT (0.0)	0.87	0.95
Kongsted [17]	2003	CCSD/aug-cc-pVTZ	PE (0.0)	No (+0.08)	PSCP (0.0)	NVT (0.0)	0.86	0.94
Osted [18]	2003	CC2/aug-cc-pVQZ	PE (0.0)	No (+0.08)	PSCP (0.0)	NVT (0.0)	0.91	0.99
Jensen [19]	2003	LDA/TZ2P+++	PE (0.0)	No (+0.08)	Thole-A (0.0)	NVT (0.0)	0.83	0.91
Osted [20]	2006	CCSD/d-aug-cc-pVTZ	PE (0.0)	No (+0.08)	PSCP (0.0)	NVT (0.0)	0.86	0.94
Millot [21]	2008	MPW1PW91/aug-cc-pVDZ	PE (0.0)	No (+0.08)	NCC (0.0)	NVE (0.0)	0.68	0.79 ⁵

¹ – The SPC model was not tested in this work, but we have approximated the correction to be the same as for TIP3P, since both methods lead to a similarly poor description of the liquid state.

² – Plane waves were used in this method, so the energy cutoff is reported instead of the basis set.

³ – The TIP4P model was not tested in this work, but we have assumed a correction of zero, as this model provides a much better description of the liquid state compared to TIP3P.

⁴ – The TIP5P model was not tested in this work, but we have assumed a correction of zero, as this model provides a much better description of the liquid state compared to TIP3P. Also, for the same reason, we did not apply a correction for the choice of ensemble, as the TIP5P density is close to the experimental value.

⁵ – An additional correction of +0.03 D was applied in this case to account for the fact that the point charges, and not the dipole moments, were iterated self-consistently. This issue is explained in more detail in the main paper.

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