Supporting Information

For

Matching of additive and polarizable force fields for multiscale condensed phase simulations

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Supporting Methods

We illustrate here how the derivatives in Equation 3 may be obtained by simple evaluations of the electrostatic energy with appropriately chosen charges. Consider charge parameter q_r. We divide the system into 3 groups – group A is the set of atoms having charge q_r, set C is a set of atoms having charge q_N, where q_N enforces the constraint of charge neutrality, being defined in such a way as to neutralize the overall charge, and set B are all the remaining atoms. The derivative of the potential with respect to q_r is given by:

$$\frac{\partial U}{\partial q_r} = 2\sum_{\substack{i\in A\\ j\in A}} \frac{q_r}{r_{ij}} + \sum_{\substack{i\in A\\ j\in B}} \frac{q_j}{r_{ij}} + \sum_{\substack{i\in A\\ j\in C}} \frac{q_N - q_r}{r_{ij}} + \sum_{\substack{i\in B\\ j\in B}} 0 - \sum_{\substack{i\in B\\ j\in C}} \frac{q_j}{r_{ij}} - 2\sum_{\substack{i\in C\\ j\in C}} \frac{q_N}{r_{ij}}$$

We define the following sets of charges and corresponding energies: in set α, atoms in group A have charge 1, atoms in group B have their normal charge, and atoms in group C have a charge of $q_N + q_r - 1$. In set β, atoms in group A have charge 1, in B charge 0, and in group C charge -1. In set γ, atoms in group A have charge 0, in group B their normal charge and in group C charge $q_N + q_r$. Note that all these groups are overall electrostatically neutral and so their energy can be evaluated without complications using the tools in standard MD codes. The energies of each group are given by:

$$U_\alpha = \sum_{\substack{i\in A\\ j\in A}} \frac{1}{r_{ij}} + \sum_{\substack{i\in A\\ j\in B}} \frac{q_j}{r_{ij}} + \sum_{\substack{i\in A\\ j\in C}} \frac{q_N + q_r - 1}{r_{ij}} + \sum_{\substack{i\in B\\ j\in B}} \frac{q_i q_j}{r_{ij}} + \sum_{\substack{i\in B\\ j\in C}} \frac{q_j (q_N + q_r - 1)}{r_{ij}} + \sum_{\substack{i\in C\\ j\in C}} \frac{(q_N + q_r - 1)^2}{r_{ij}}$$

$$U_\beta = \sum_{\substack{i\in A\\ j\in A}} \frac{1}{r_{ij}} + \sum_{\substack{i\in A\\ j\in B}} 0 - \sum_{\substack{i\in A\\ j\in C}} \frac{1}{r_{ij}} + \sum_{\substack{i\in B\\ j\in B}} 0 + \sum_{\substack{i\in B\\ j\in C}} 0 + \sum_{\substack{i\in C\\ j\in C}} \frac{1}{r_{ij}}$$

$$U_\gamma = \sum_{\substack{i\in A\\ j\in A}} 0 + \sum_{\substack{i\in A\\ j\in B}} 0 + \sum_{\substack{i\in A\\ j\in C}} 0 + \sum_{\substack{i\in B\\ j\in B}} \frac{q_i q_j}{r_{ij}} + \sum_{\substack{i\in B\\ j\in C}} \frac{q_j(q_N + q_r)}{r_{ij}} + \sum_{\substack{i\in C\\ j\in C}} \frac{(q_N + q_r)^2}{r_{ij}}$$

With the above definitions, we have:

$$\frac{\partial U}{\partial q_r} = U_\alpha + (2q_r - 1)U_\beta - U_\gamma$$

A similar approach may be taken to the second derivatives.

Supporting Figures

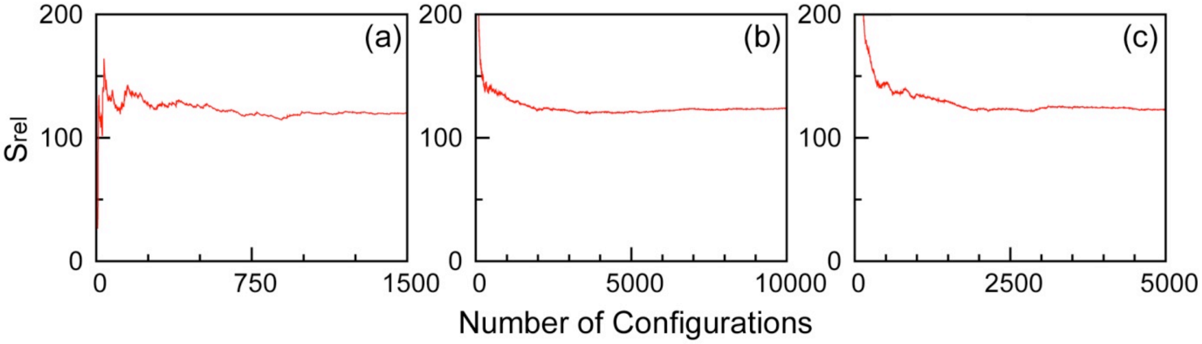

Figure S1. Measuring the number of configurations that must be included to achieve a converged value of S_{rel} for (a) water, (b) acetamide and (c) cyclohexane. S_{rel} is calculated using Equation 6.

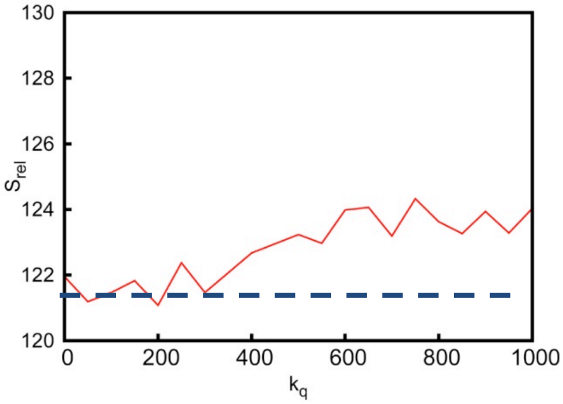

Figure S2. The final value of S_{rel} for acetamide, obtained from the optimization of S_{rel}' (Equation 9) as function of the restraint force constant k_q. At each value of k_q, S_{rel}' was optimized using the Monte Carlo Simulated Annealing protocol. Dashed line indicates optimal range of S_{rel}.

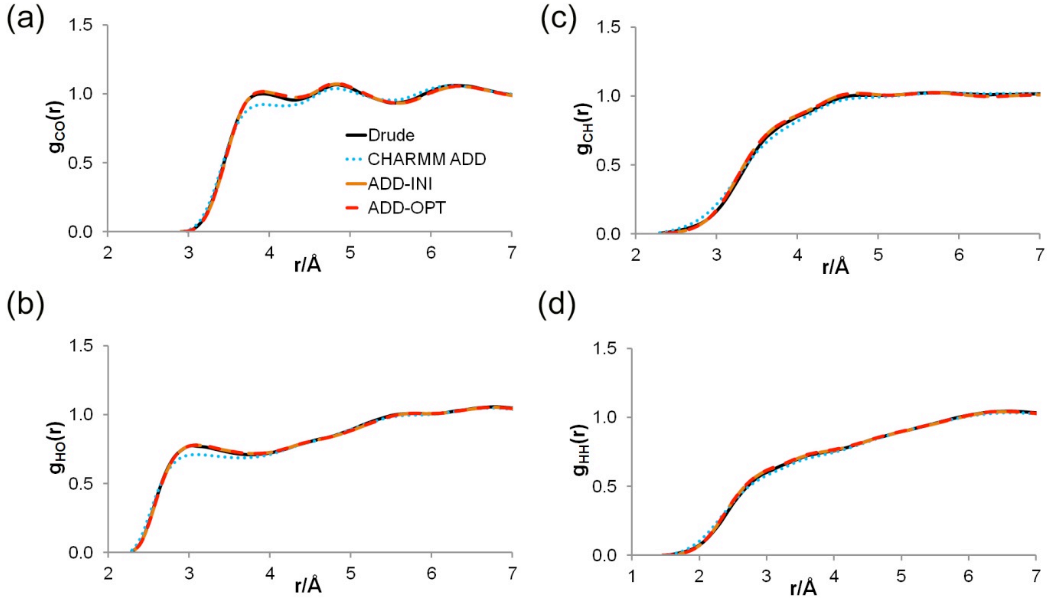

Figure S3. Radial distribution functions obtained from simulations of cyclohexane in water, calculated using various force fields. Radial distribution functions are described as $g_{ab}(r)$, where a represents the cyclohexane atom type, and b represents the water atom type.

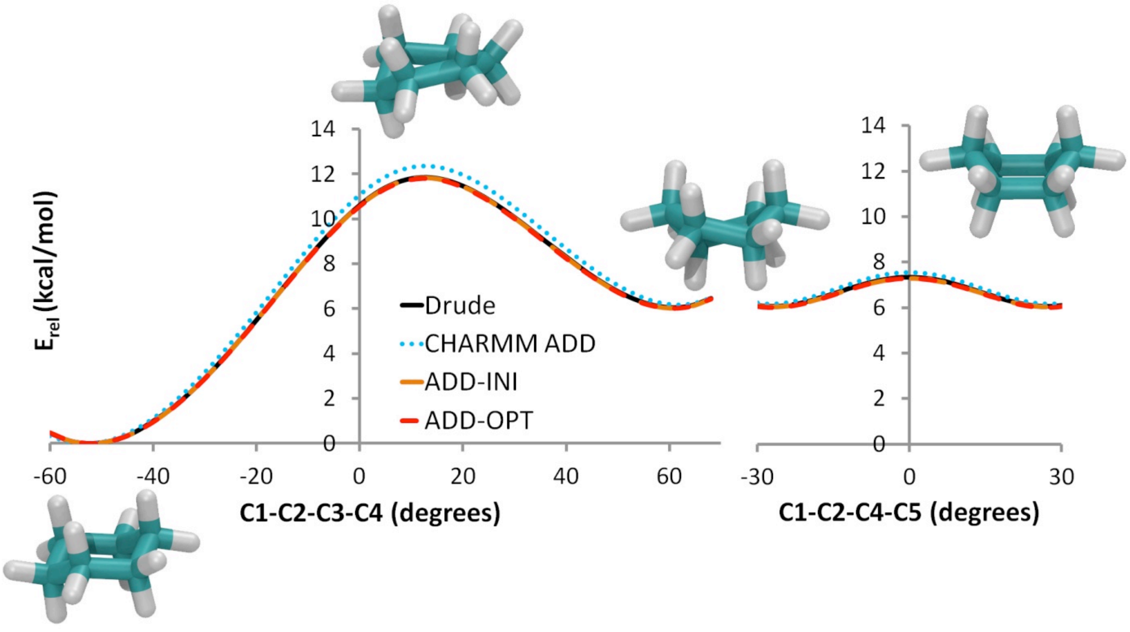

Figure S4. Dihedral angle potential energy surfaces for cyclohexane. Atom naming is as shown in Figure 1, and all energies are calculated relative to the cyclohexane chair conformation, the global energy minimum. The C1-C2-C3-C4 dihedral measures the interconversion between the chair and twist-boat conformations, via the "half-chair" transition state. The C1-C2-C4-C5 dihedral measures the interconversion between two twist-boat confomrations, via the boat transition state.

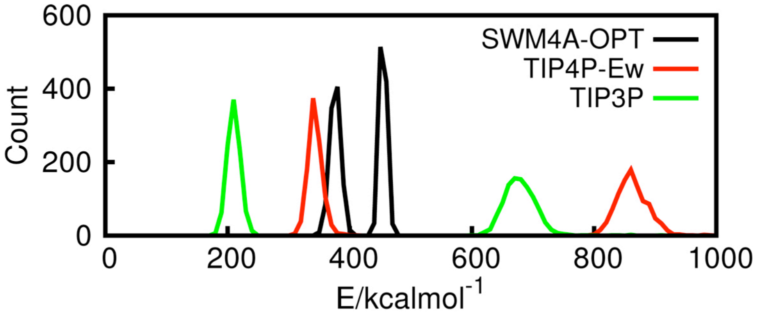

Figure S5. Overlap of energy difference distributions between the Drude SWM4-NDP model and various additive models, calculated as described for Equation 7 from simulations of liquid water. Matching colors are used to compare overlap between distributions from the simulation with SWM4-NDP model and the model noted in the key; for each pair of simulations, the distributions representing Δ_i, and Δ_j (Equation 7) are shown by lines with the same colour.

Supporting Tables

Force Field Parameters

Atom Type 1	Atom Type 2	K_b	b_0
		Water	
HT	HT	0.0	1.5139
HT	OT	450.0	0.9572
OT	LP	0.0	0.24034492
		Acetamide	
CD2O1A	CD33A	305.00	1.517
CD33A	HDA3A	322.00	1.111
OD2C1A	CD2O1A	623.00	1.239
ND2A1	CD2O1A	420.00	1.350
ND2A1	HDP1A	480.00	1.025
		Cyclohexane	
CD32A	HDA2A	309.00	1.111
CD32A	CD32A	222.50	1.530

Table S1. Bond stretching parameters used with the SWM4A-INI/SWM4A-OPT and ADD-INI/ADD-OPT models. K_b in kcal/mol/Å^2 and b_0 in Å. Atom types are taken directly from the CHARMM Drude polarizable force field, as described in Refs 1-3.

Atom Type 1	Atom Type 2	Atom Type 3	K_θ	θ_0	K_{ub}	S_0
Water						
HT	OT	HT	55.00	104.52		
Acetamide						
CD2O1A	ND2A1	HDP1A	50.00	123.50		
ND2A1	CD2O1A	CD33A	40.00	114.50		
ND2A1	CD2O1A	OD2C1A	85.00	125.00		
HDP1A	ND2A1	HDP1A	24.00	113.00		
CD2O1A	CD33A	HDA3A	42.50	111.30		
OD2C1A	CD2O1A	CD33A	73.00	121.00		
HDA3A	CD33A	HDA3A	35.50	108.40	5.40	1.802
Cyclohexane						
HDA2A	CD32A	CD32A	26.50	110.10	22.53	2.179
HDA2A	CD32A	HDA2A	35.50	109.00	5.40	1.802
CD32A	CD32A	CD32A	58.35	113.60	11.16	2.561

Table S2. Angle bending parameters used with the SWM4A-INI/SWM4A-OPT and ADD-INI/ADD-OPT models. K_θ in kcal/mol/rad^2, θ_0 in degrees, K_{ub} in kcal/mol/Å^2 and S_0 in Å. Atom types are taken directly from the CHARMM Drude polarizable force field, as described in Refs 1-3.

Atom Type 1	Atom Type 2	Atom Type 3	Atom Type 4	K_χ	n	δ
Acetamide						
HDP1A	ND2A1	CD2O1A	OD2C1A	2.000	2	180.00
HDP1A	ND2A1	CD2O1A	CD33A	2.000	2	180.00
ND2A1	CD2O1A	CD33A	HDA3A	0.070	3	180.00
OD2C1A	CD2O1A	CD33A	HDA3A	0.000	3	180.00
Cyclohexane						
CD32A	CD32A	CD32A	CD32A	0.136	5	0.00
CD32A	CD32A	CD32A	CD32A	0.078	4	0.00
CD32A	CD32A	CD32A	CD32A	0.139	3	180.00
CD32A	CD32A	CD32A	CD32A	0.083	2	0.00
CD32A	CD32A	CD32A	HDA2A	0.190	3	0.00
HDA2A	CD32A	CD32A	HDA2A	0.190	3	0.00

Table S3. Dihedral angle parameters used with the SWM4A-INI/SWM4A-OPT and ADD-INI/ADD-OPT models. K_χ in kcal/mol and δ in degrees. Atom types are taken directly from the CHARMM Drude polarizable force field, as described in Refs 1-3.

Atom Type 1	Atom Type 2	Atom Type 3	Atom Type 4	K_{ψ}	ψ_0
Acetamide					
OD2C1A	ND2A1	CD33A	CD2O1A	90.0	0.00
ND2A1	HDP1A	HDP1A	CD2O1A	4.0	0.00

Table S4. Improper dihedral parameters used with the SWM4A-INI/SWM4A-OPT and ADD-INI/ADD-OPT models. K_{ψ} in kcal/mol/rad^2 and ψ_0 in degrees. Atom types are taken directly from the CHARMM Drude polarizable force field, as described in Refs 1-3.

Atom Type	ε	$R_{min}/2$	$\varepsilon_{,1\text{-}4}$	$R_{min}/2_{,1\text{-}4}$
Water				
OT	-0.21094325	1.78692899		
HT	-0.0000	0.0000		
LP	-0.0000	0.0000		
Acetamide				
HDA3A	-0.0240	1.3400		
HDP1A	-0.0100	0.4000		
CD33A	-0.0780	2.0400	-0.0100	1.9000
CD2O1A	-0.2300	1.8000		
OD2C1A	-0.0950	1.9000		
ND2A1	-0.2700	1.9100		
Cyclohexane				
HDA2A	-0.0350	1.3400		
CD32A	-0.0560	2.0100	-0.0100	1.9000

Table S5. Lennard-Jones parameters used with the SWM4A-INI/SWM4A-OPT and ADD-INI/ADD-OPT models. ε and $\varepsilon_{,1\text{-}4}$ in kcal/mol; $R_{min}/2$ and $R_{min}/2_{,1\text{-}4}$ in Å. Atom types are taken directly from the CHARMM Drude polarizable force field, as described in Refs 1-3.

Force Field Charge Variation

Atom	S_{rel}	Amber ff03	Selected force fields
C	0.0836	0.0844	0.0638
O	0.0736	0.0481	0.0638
N	0.0696	0.0740	0.0792
H	0.0585	0.0500	0.0143

Table S6. Standard deviation of charges on C, O, N, H atoms of the amide group in formamide (S_{rel} optimization) and in current force fields. The standard deviation for Amber ff03 is over the amides in different residues (which have different charges), while the standard deviation over multiple force fields is computed from the Alanine amide charges in Amber ff03, Amber ff94, OPLS/AA-L, CHARMM22, GROMOS G43a1 and GROMOS G53a5.

Cyclohexane Properties

	Exp.	**Drude**	**CHARMM-ADD**	**ADD-INI**	**ADD-OPT**
Monomer					
E_{rel} (chair)	0.00^{a}	0.00	0.00	0.00	0.00
E_{rel} (twist-boat)	6.60^{a}	6.06	6.18	6.02	6.01
E_{rel} (boat)	8.10^{a}	7.33	7.56	7.29	7.27
Liquid					
V_m (Å)	180.6^{b}	182.4 ± 0.8^{d}	182.7 ± 1.0^{d}	182.84 ± 0.42	182.57 ± 0.23
ΔH_{vap} (kcal/mol)	7.89^{b}	7.67 ± 0.04^{d}	7.66 ± 0.05^{d}	7.66 ± 0.02	7.69 ± 0.01
E	2.02^{b}	1.66 ± 0.00	1.02 ± 0.00	1.00 ± 0.01	1.00 ± 0.01
Aqueous Solution					
G_{hyd} (kcal/mol)	1.23^{c}	1.02 ± 0.24	1.28 ± 0.08	1.48 ± 0.18	1.47 ± 0.19

Table S7. Cyclohexane properties calculated using polarizable and initial and optimized additive models. Results obtained with the additive CHARMM force field are included for comparison. Properties in aqueous solution are calculated using the SWM4-NDP water model with polarizable acetamide; the TIP3P water model with CHARMM, and the SWM4A-OPT water model with ADD-INI and ADD-OPT cyclohexane. [a] Experimental data from Ref. 4 [b] Experimental data from Ref. 5. [c] Experimental datum from Ref. 6. [d] Simulation data from Ref. 3.

References

(1) Lamoureux, G.; Harder, E.; Vorobyov, I. V.; Roux, B.; MacKerell, A. D. J. *Chem. Phys. Lett.* **2006**, *418*, 245-249.

(2) Harder, E.; Anisimov, V. M.; Whitfield, T. W.; Mackerell, A. D., Jr.; Roux, B. *J. Phys. Chem. B* **2008**, *112*, 3509-3521.

(3) Vorobyov, I. V.; Anisimov, V. M.; Greene, S.; Venable, R. M.; Moser, A.; Pastor, R. W.; Mackerell, A. D., Jr. *J. Chem. Theory Comput.* **2007**, *3*, 1120-1133.

(4) Riehn, C.; Matylitsky, V. V.; Jarzeba, W.; Brutschy, B.; Tarakeshwar, P.; Kim, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 16455-16462.

(5) *CRC Handbook of Chemistry and Physics*; 84th ed.; Lide, D., Ed.; CRC Press Boca Raton, 2003.

(6) Kelly, C. P.; Cramer, C. J.; Truhlar, D. *J. Chem. Theory Comput.* **2005**, *1*, 1133-1152.