Table S1. For an atom with Cartesian coordinates (0,0,0), with charge q, dipole moment $\boldsymbol{\mu}$, and traceless Cartesian quadrupole $\mathbf{Q}$, this table shows the coordinates and charges that mimic these moments. The small displacement, ε, is taken to be 0.01 Å.

Coordinates	Charge
0,0,0	q
ε,0,0	$\mu_x/2\varepsilon$
-ε,0,0	$-\mu_x/2\varepsilon$
0,ε,0	$\mu_y/2\varepsilon$
0,-ε,0	$-\mu_y/2\varepsilon$
0,0,ε	$\mu_z/2e$
0,0,-ε	$-\mu_z/2e$
ε,ε,0	$-\left(Q_{zz}-Q_{xy}\right)/6e^2$
ε,0,ε	$-\left(Q_{yy}-Q_{xz}\right)/6e^2$
0,ε,ε	$-\left(Q_{xx}-Q_{yz}\right)/6e^2$
-ε,-ε,0	$-\left(Q_{zz}-Q_{xy}\right)/6e^2$
-ε,0,-ε	$-\left(Q_{yy}-Q_{xz}\right)/6e^2$
0,-ε,-ε	$-\left(Q_{xx}-Q_{yz}\right)/6e^2$
ε,-ε,0	$-\left(Q_{zz}+Q_{xy}\right)/6e^2$
ε,0,-ε	$-\left(Q_{yy}+Q_{xz}\right)/6e^2$
0,ε,-ε	$-\left(Q_{xx}+Q_{yz}\right)/6e^2$
-ε,ε,0	$-\left(Q_{zz}+Q_{xy}\right)/6e^2$
-ε,0,-ε	$-\left(Q_{yy}+Q_{xz}\right)/6e^2$
0,-ε,-ε	$-\left(Q_{xx}+Q_{yz}\right)/6e^2$

Table S2. Absolute errors in kcal/mol between *ab initio* results and the FMO and SMFA methods for each cluster. The geometry for each cluster is given in Table S4, identified by the labels shown here.

	MP2/6-31G(d)					MP2/6-31++G(d,p)					MP2/6-311++G(3df,2p)				
16	SMFA	SMFA	SMFA			SMFA	SMFA	SMFA			SMFA	SMFA	SMFA		
Waters	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3
c1b	3.79	0.08	-0.05	-3.35	1.41	-5.90	-1.72	-0.49	2.95	0.71	-9.41	1.48	-0.37	11.48	0.45
c1c16	5.23	0.22	0.02	-3.73	1.29	-2.77	-0.70	-0.11	2.80	0.49	-5.99	1.42	-0.04	11.03	0.26
c1c	8.08	0.42	0.01	-4.00	1.25	2.62	0.32	-0.02	2.68	0.56	-0.13	0.89	-0.03	10.70	0.51
cage	7.05	-0.33	0.10	-3.81	1.34	-0.65	-1.13	0.12	2.48	0.28	-2.16	0.31	0.17	11.07	0.21
cie	3.36	-0.22	0.07	-3.90	1.19	-4.05	-1.33	0.14	3.07	0.28	-5.97	0.58	-0.07	10.93	0.24
d2d	0.75	0.80	-0.01	-6.33	1.45	-13.14	-2.12	-0.69	2.97	-1.63	-14.35	1.51	-0.70	10.22	-1.32
s43	7.50	2.88	0.10	-6.84	1.67	-5.68	4.72	-0.15	2.65	-1.85	-8.38	5.68	-0.39	10.22	-1.14
20	SMFA	SMFA	SMFA			SMFA	SMFA	SMFA			SMFA	SMFA	SMFA		
Waters	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3
p3a	6.21	0.57	0.08	-5.73	1.58	-5.86	0.88	-0.12	4.66	0.17	-10.47	2.49	0.06	15.24	-0.06
p3b	6.81	-0.06	0.01	-5.85	1.61	-5.18	-1.33	-0.37	4.04	0.26	-10.49	1.79	-0.57	13.90	-0.02
pps_c	3.69	0.51	-0.04	-5.40	1.82	-11.49	-2.95	-0.78	4.03	-0.10	-15.51	2.09	-0.79	14.42	-0.20
pps_d	7.93	0.13	0.09	-6.68	1.73	-5.05	-1.57	-0.01	3.93	-0.14	-10.18	0.90	-0.23	13.23	-0.33
pps_e	7.94	0.85	0.01	-5.36	1.81	-3.92	-1.64	-0.34	3.83	-0.16	-6.35	1.24	-0.38	14.16	0.04
pps_f	10.70	0.43	0.22	-5.58	1.66	1.29	1.35	0.68	3.95	-0.06	-0.79	1.12	0.54	14.45	0.06
s4d2	0.09	0.79	0.18	-8.32	1.81	-19.11	-3.48	-0.48	4.16	-2.18	-20.91	1.37	-0.67	13.07	-2.00
32	SMFA	SMFA	SMFA			SMFA	SMFA	SMFA			SMFA	SMFA	SMFA		
Waters	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3
32_1	14.54	0.29	2.42	-10.68	3.36	-3.89	-0.30	3.08	11.80	2.21	-19.67	-9.76	0.75	26.83	0.98
32_2	13.33	1.66	2.53	-10.43	3.50	-6.13	0.82	4.15	12.37	2.53	-23.56	-9.69	1.13	27.34	1.30
32_3	17.80	4.00	3.12	-10.50	3.16	-4.00	2.53	4.21	11.45	1.92	-20.89	-5.21	1.19	24.57	1.18
32ab	13.69	1.30	2.48	-10.42	3.51	-5.51	0.10	4.08	12.48	2.53	-23.16	-10.45	1.11	27.38	1.30
32ad	17.14	4.17	2.40	-11.06	3.69	-0.36	3.16	4.29	11.77	2.55	-15.95	-7.74	1.30	25.75	1.04
32h	12.79	1.31	2.52	-10.32	3.48	-6.43	-0.01	4.13	12.30	2.48	-24.00	-10.68	1.00	27.27	1.23
32o	13.21	1.08	2.51	-10.33	3.51	-5.90	-0.56	4.13	12.46	2.49	-184.33	-11.19	1.07	27.32	1.26
32z	9.30	2.79	2.84	-9.64	3.26	-11.41	3.25	4.37	12.44	2.33	-28.43	-6.93	0.96	28.00	1.25
64	SMFA	SMFA	SMFA			SMFA	SMFA	SMFA							
Waters	L1	L2	L3	FMO2	FMO3	L1	L2	L3	FMO2	FMO3					
a	39.52	7.93	2.10	-22.08	6.41	9.12	14.77	9.02	27.72	3.37					
b	39.85	8.00	2.14	-22.05	6.40	9.95	15.05	9.06	27.75	3.36					
c	37.98	7.93	2.25	-21.81	6.36	7.76	14.53	9.37	27.54	3.29					
d	42.93	8.79	1.98	-22.23	6.43	13.37	16.78	8.65	27.66	3.30					
e	41.81	7.20	1.95	-22.32	6.47	12.59	16.80	8.35	27.21	3.29					
f	42.98	7.67	1.97	-22.79	6.55	14.32	17.47	8.71	27.36	3.15					
g	40.37	8.04	2.16	-22.14	6.34	11.22	14.87	9.06	27.69	3.35					

Table S3. The SMFA error in the total energy is compared to the total dispersion energy for each cluster (in kcal/mol).

	MP2/6-31gd					
	Level 1		Level 2		Level 3	
16 Waters	E(disp)	L1 error	E(disp)	L2 error	E(disp)	L3 error
c1b	-4.49	6.05	-0.95	0.13	-0.03	-0.08
c1c16	-4.43	8.34	-0.95	0.35	-0.03	0.03
c1c	-4.29	12.88	-0.94	0.66	-0.03	0.02
cage	-4.35	11.24	-0.95	-0.52	-0.03	0.15
cie	-4.40	5.36	-0.94	-0.34	-0.03	0.11
d2d	-5.09	1.19	-1.03	1.28	-0.05	-0.02
s43	-4.90	11.96	-1.02	4.60	-0.05	0.16
20 Waters						
p3a	-6.38	9.90	-1.53	0.91	-0.07	0.12
p3b	-6.32	10.85	-1.52	-0.09	-0.07	0.02
pps_c	-6.27	5.89	-1.40	0.82	-0.07	-0.06
pps_d	-6.50	12.64	-1.36	0.20	-0.07	0.14
pps_e	-6.12	12.66	-1.40	1.35	-0.07	0.02
pps_f	-6.13	17.05	-1.43	0.69	-0.07	0.35
s4d2	-6.82	0.15	-1.45	1.27	-0.08	0.28
32 Waters						
32_1	-15.10	23.17	-4.08	0.46	-1.43	3.86
32_2	-15.54	21.24	-4.37	2.65	-1.54	4.03
32_3	-14.80	28.37	-3.83	6.37	-1.32	4.97
32ab_2b	-15.49	21.81	-4.36	2.07	-1.54	3.96
32ad_2b	-15.70	27.32	-4.51	6.65	-1.57	3.82
32h_2b	-15.53	20.38	-4.37	2.08	-1.54	4.02
32o_2b	-15.53	21.05	-4.36	1.72	-1.54	4.01
32z_2b	-15.33	14.82	-4.11	4.44	-1.48	4.53
64 Waters						
a	-35.03	62.98	-10.93	12.64	-2.93	3.34
b	-35.00	63.50	-10.91	12.75	-2.92	3.41
c	-35.06	60.53	-10.94	12.64	-2.92	3.59
d	-34.89	68.42	-10.90	14.01	-2.92	3.16
e	-33.62	66.63	-9.82	11.48	-2.86	3.10
f	-33.76	68.50	-9.90	12.23	-2.88	3.14
g	-35.04	64.33	-10.94	12.81	-2.92	3.44
	MP2/6-31++G(d,p)					
	Level 1		Level 2		Level 3	
16 Waters	E(disp)	L1 error	E(disp)	L2 error	E(disp)	L3 error
c1b	-7.27	-9.40	-0.95	-2.73	-0.05	-0.79
c1c16	-7.24	-4.42	-0.95	-1.11	-0.06	-0.18

c1c	-7.11	4.17	-0.94	0.51	-0.06	-0.03
cage	-7.21	-1.04	-0.95	-1.81	-0.05	0.20
cie	-7.21	-6.45	-0.94	-2.12	-0.06	0.23
d2d	-8.37	-20.93	-1.03	-3.38	-0.07	-1.11
s43	-8.34	-9.05	-1.02	7.52	-0.07	-0.24
20 Waters						
p3a	-10.48	-9.34	-1.53	1.40	-0.12	-0.20
p3b	-10.40	-8.25	-1.52	-2.11	-0.12	-0.60
pps_c	-10.15	-18.31	-1.40	-4.70	-0.12	-1.24
pps_d	-10.82	-8.05	-1.36	-2.50	-0.12	-0.02
pps_e	-10.02	-6.25	-1.40	-2.62	-0.12	-0.54
pps_f	-10.11	2.05	-1.43	2.15	-0.12	1.09
s4d2	-11.14	-30.46	-1.45	-5.55	-0.13	-0.76
32 Waters						
32_1	-25.21	-6.20	-8.55	-0.47	-2.57	4.91
32_2	-25.89	-9.76	-9.16	1.31	-2.76	6.62
32_3	-24.68	-6.38	-7.94	4.02	-2.31	6.71
32ab_2b	-25.84	-8.79	-9.14	0.16	-2.76	6.50
32ad_2b	-26.02	-0.57	-9.41	5.04	-2.77	6.84
32h_2b	-25.85	-10.25	-9.16	-0.02	-2.77	6.58
32o_2b	-25.85	-9.40	-9.16	-0.88	-2.76	6.58
32z_2b	-25.35	-18.19	-8.63	5.18	-2.66	6.97
64 Waters						
a	-57.72	14.53	-18.27	23.54	-5.05	14.37
b	-57.68	15.85	-18.24	23.99	-5.05	14.43
c	-57.71	12.37	-18.28	23.16	-5.03	14.93
d	-57.68	21.31	-18.26	26.74	-5.05	13.79
e	-55.65	20.06	-16.47	26.78	-4.93	13.30
f	-55.87	22.82	-16.58	27.84	-4.95	13.88
g	-57.74	17.87	-18.28	23.70	-5.05	14.43

	MP2/6-31++G(3df,2p)					
	Level 1		Level 2		Level 3	
16 Waters	E(disp)	L1 error	E(disp)	L2 error	E(disp)	L3 error
c1b	-11.33	-14.99	-1.46	2.35	-0.08	-0.58
c1c16	-11.28	-9.55	-1.46	2.27	-0.09	-0.06
c1c	-11.07	-0.21	-1.45	1.42	-0.09	-0.05
cage	-11.20	-3.45	-1.46	0.50	-0.08	0.27
cie	-11.23	-9.51	-1.45	0.93	-0.09	-0.12
d2d	-13.06	-22.87	-1.59	2.41	-0.12	-1.11
s43	-13.03	-13.36	-1.57	9.05	-0.11	-0.63
20 Waters						
p3a	-16.32	-16.69	-2.35	3.97	-0.19	0.09

p3b	-16.17	-16.72	-2.34	2.86	-0.19	-0.91
pps_c	-15.81	-24.71	-2.16	3.34	-0.18	-1.26
pps_d	-16.85	-16.22	-2.09	1.44	-0.18	-0.37
pps_e	-15.61	-10.12	-2.15	1.98	-0.18	-0.60
pps_f	-15.72	-1.26	-2.20	1.78	-0.19	0.85
s4d2	-17.38	-33.33	-2.23	2.18	-0.20	-1.07
32 Waters						
32_1	-39.21	-31.35	-13.29	-15.55	-4.03	1.19
32_2	-40.26	-37.55	-14.24	-15.44	-4.33	1.80
32_3	-38.38	-33.28	-12.30	-8.30	-3.60	1.90
32ab_2b	-40.19	-36.90	-14.22	-16.65	-4.33	1.77
32ad_2b	-40.42	-25.41	-14.62	-12.33	-4.34	2.07
32h_2b	-40.20	-38.25	-14.26	-17.01	-4.35	1.60
32o_2b	-40.21	-293.75	-14.25	-17.84	-4.34	1.71
32z_2b	-39.43	-45.31	-13.43	-11.04	-4.19	1.53

Table S4. Exact *ab initio* MP2 total energies for all cluster sizes, isomers and basis sets.

16w	MP2/6-31G(d)	MP2/6-31++G(d,p)	MP2/6-311++G(3df,2p)
c1b	-1219.452518	-1219.986830	-1221.430283
c1c16	-1219.452449	-1219.986422	-1221.430122
c1c	-1219.451290	-1219.985115	-1221.428411
cage	-1219.449396	-1219.982880	-1221.427133
cie	-1219.453838	-1219.987434	-1221.431232
d2d	-1219.465796	-1219.988049	-1221.432642
s43	-1219.464310	-1219.986879	-1221.431684
20w			
p3a	-1524.332715	-1524.995331	-1526.798002
p3b	-1524.327898	-1524.991032	-1526.794256
pps_c	-1524.330607	-1524.991577	-1526.795364
pps_d	-1524.325820	-1524.983669	-1526.788159
pps_e	-1524.328649	-1524.989496	-1526.793262
pps_f	-1524.329388	-1524.989104	-1526.792911
s4d2	-1524.342855	-1524.992571	-1526.797337
32w			
32_1	-2438.924328	-2439.999083	-2442.878295
32_2	-2438.920926	-2439.998277	-2442.876899
32_3	-2438.899168	-2439.976205	-2442.855811
32ab	-2438.920568	-2439.997981	-2442.876820
32ad	-2438.911807	-2439.989907	-2442.868791
32h	-2438.920503	-2439.998068	-2442.876792
32o	-2438.919570	-2439.997437	-2442.876329
32z	-2438.922910	-2439.998974	-2442.878006
64w			
a	-4877.919876	-4880.058190	
b	-4877.918846	-4880.057063	
c	-4877.917415	-4880.057028	
d	-4877.916066	-4880.054706	
e	-4877.918720	-4880.054557	
f	-4877.918167	-4880.052526	
g	-4877.912343	-4880.051518	

Figure S1. Geometries of all clusters of 16 waters studied.

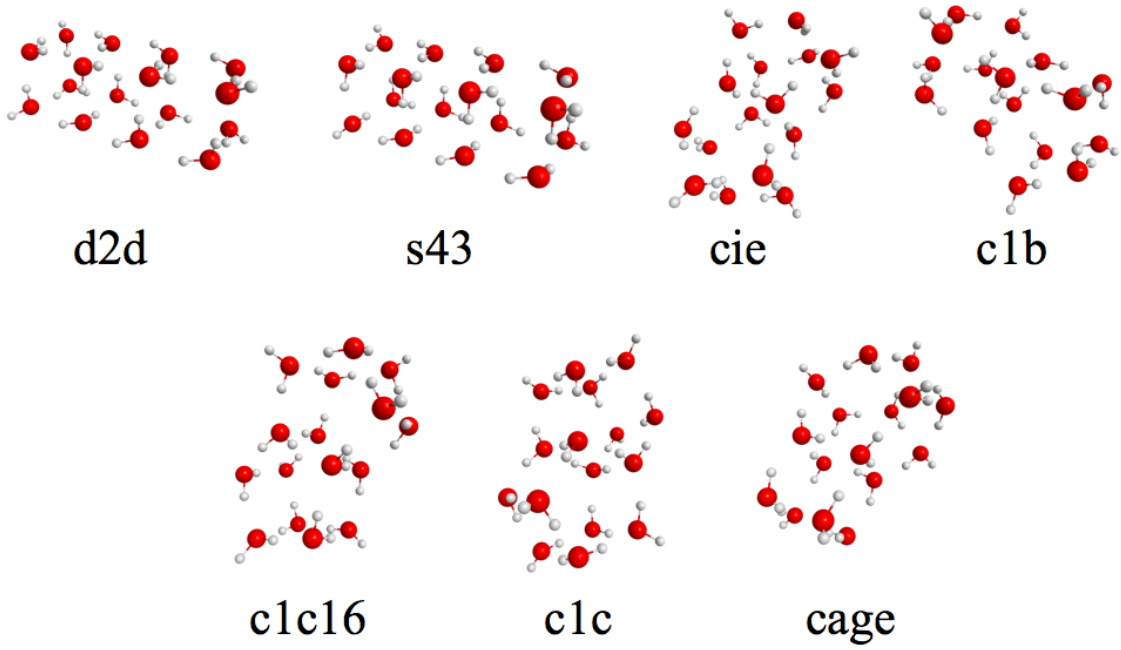

Figure S2. Geometries of all clusters of 20 waters studied.

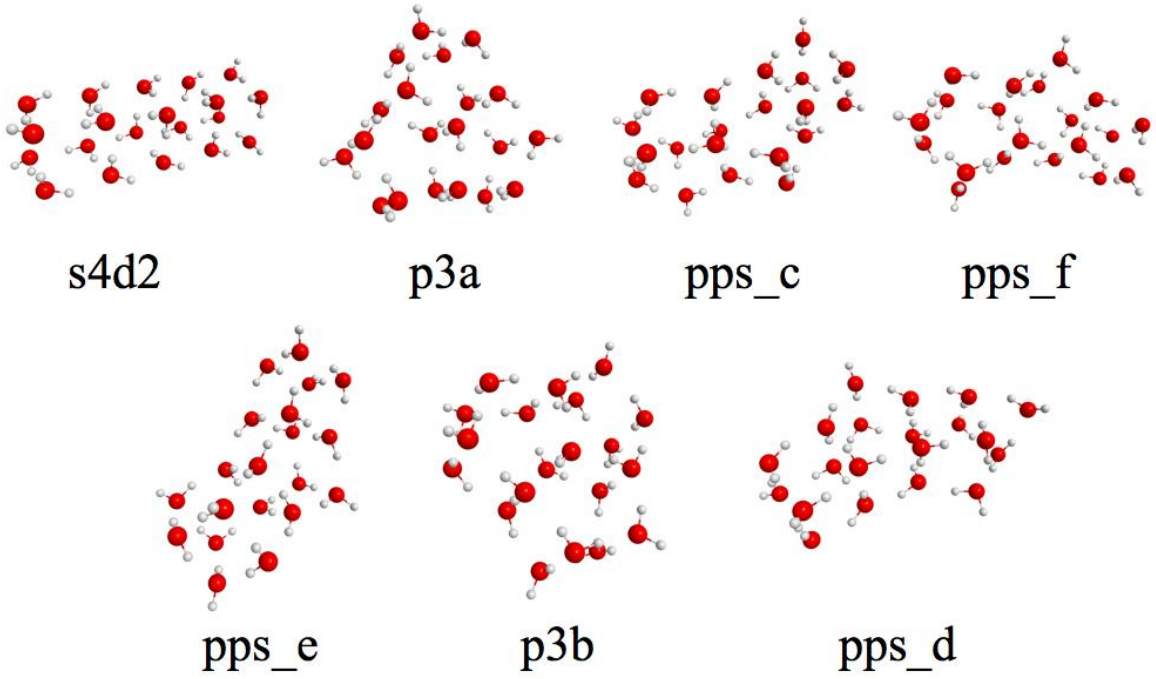

Figure S3. Geometries of all clusters of 32 waters studied.

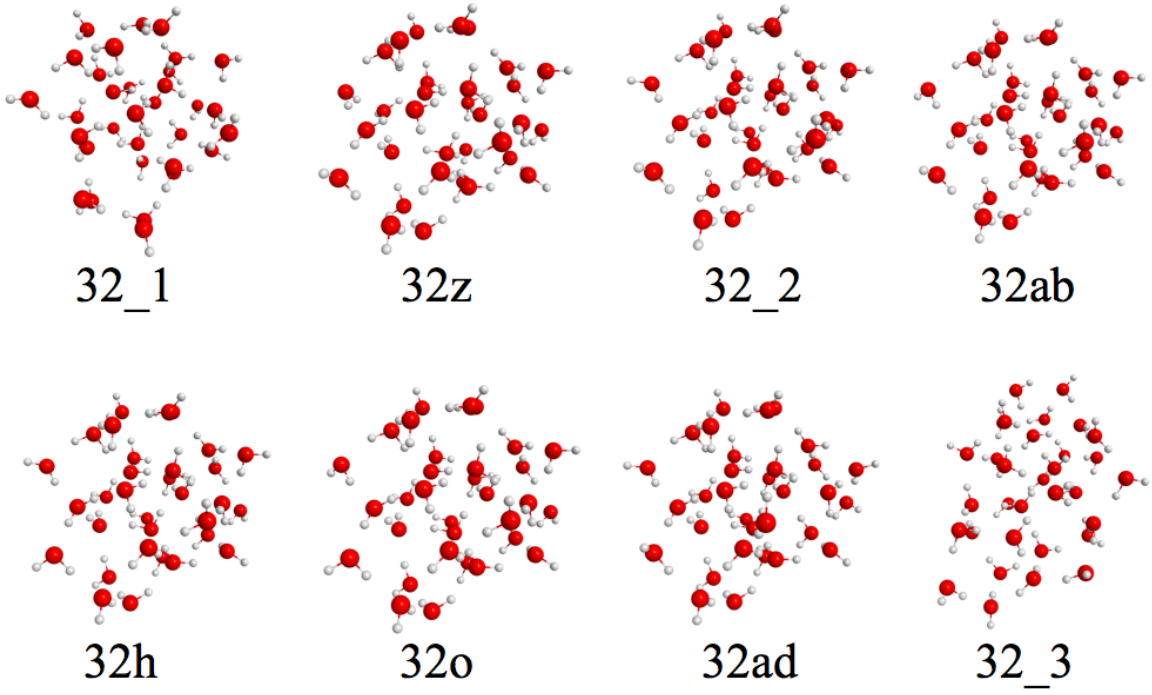

Figure S4. Geometries of all clusters of 64 waters studied.