Computation of Hydration Free Energies Using the Multiple Environment Single System Quantum Mechanical/Molecular Mechanical (MESS-QM/MM) Method

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TABLE S1: SM8 hydration free energies in kcal/mol for SAMPL4 molecules using using five density functionals and the 6-31G* basis set. MSE' and RMSE' are computed for molecules 2 through 21.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
1	-20.43	-20.64	-20.93	-20.35	-21.08
2	-1.37	-1.53	-1.84	-1.28	-1.90
3	-4.13	-4.24	-4.61	-4.22	-4.55
4	-4.45	-4.57	-5.02	-4.57	-4.94
5	-3.52	-3.62	-4.21	-3.38	-4.16
6	-5.54	-5.74	-6.31	-5.73	-6.25
9	-8.00	-7.90	-8.06	-7.07	-8.18
10	-5.15	-5.24	-5.54	-5.08	-5.57
11	-8.08	-7.95	-8.14	-7.20	-8.19
12	-2.38	-2.35	-2.41	-1.72	-2.55
13	-3.17	-3.28	-3.65	-3.27	-3.58
14	-3.27	-3.21	-3.27	-2.37	-3.43
15	-3.51	-3.55	-3.66	-2.91	-3.82
16	-2.04	-2.10	-2.18	-2.10	-2.22
17	-1.96	-1.93	-1.93	-1.35	-2.09
19	-2.42	-2.65	-3.44	-2.88	-3.21
20	-1.20	-1.42	-2.10	-1.64	-1.93
21	-6.73	-6.96	-7.60	-6.94	-7.59
22	-5.25	-5.58	-6.26	-5.80	-6.19
23	-5.13	-5.34	-6.08	-5.40	-5.93
24	-4.85	-5.11	-5.95	-5.30	-5.74
MSE	1.23	1.12	0.72	1.33	0.73
RMSE	1.62	1.50	1.19	1.64	1.20
R2	0.95	0.95	0.96	0.96	0.96
MSE'	0.84	0.76	0.43	1.03	0.42
RMSE'	1.04	0.96	0.75	1.21	0.72

TABLE S2: SM12MK hydration free energies in kcal/mol for SAMPL4 molecules using using five density functionals and the 6-31G* basis set. MSE' and RMSE' are computed for molecules 2 through 21.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
1	-21.06	-22.51	-22.98	-23.67	-23.54
2	-1.11	-1.71	-2.14	-2.11	-2.28
3	-4.08	-4.60	-5.11	-5.14	-5.18
4	-3.81	-4.32	-4.88	-4.92	-4.94
5	-4.36	-5.18	-6.07	-6.07	-6.13
6	-6.86	-7.76	-8.68	-8.71	-8.76
9	-8.01	-8.76	-9.00	-9.13	-9.26
10	-5.68	-6.25	-6.65	-6.80	-6.80
11	-7.63	-8.23	-8.56	-8.54	-8.70
12	-2.61	-3.13	-3.30	-3.17	-3.47
13	-3.48	-4.00	-4.57	-4.53	-4.63
14	-3.11	-3.75	-4.07	-3.90	-4.22
15	-2.83	-3.33	-3.50	-3.35	-3.66
16	-2.16	-2.47	-2.56	-2.70	-2.71
17	-1.54	-1.94	-1.93	-1.87	-2.11
19	-3.94	-4.83	-6.20	-5.93	-6.08
20	-3.23	-4.21	-5.60	-5.37	-5.52
21	-8.99	-10.07	-11.20	-11.09	-11.34
22	-6.01	-6.90	-7.94	-7.88	-7.96
23	-7.26	-8.28	-9.55	-9.39	-9.54
24	-6.13	-7.06	-8.35	-8.18	-8.29
MSE	0.69	-0.04	-0.69	-0.67	-0.79
RMSE	1.19	1.02	1.47	1.41	1.47
R2	0.95	0.95	0.92	0.93	0.92
MSE'	0.46	-0.19	-0.75	-0.71	-0.85
RMSE'	0.99	1.07	1.58	1.54	1.60

TABLE S3: SM12CHELPG hydration free energies in kcal/mol for SAMPL4 molecules using using five density functionals and 6-31G* basis set. MSE' and RMSE' are computed for molecules 2 through 21.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
1	-21.03	-22.32	-22.74	-23.33	-23.22
2	-1.37	-1.98	-2.43	-2.38	-2.55
3	-3.73	-4.19	-4.59	-4.62	-4.67
4	-3.57	-4.04	-4.48	-4.54	-4.55
5	-4.02	-4.79	-5.59	-5.61	-5.65
6	-6.42	-7.26	-8.06	-8.13	-8.16
9	-7.58	-8.26	-8.44	-8.55	-8.69
10	-5.15	-5.66	-5.98	-6.13	-6.14
11	-7.42	-7.97	-8.22	-8.20	-8.35
12	-2.83	-3.35	-3.48	-3.38	-3.66
13	-3.44	-3.92	-4.41	-4.38	-4.46
14	-3.32	-3.93	-4.17	-4.02	-4.32
15	-3.04	-3.53	-3.64	-3.50	-3.80
16	-2.27	-2.59	-2.72	-2.82	-2.84
17	-1.80	-2.21	-2.19	-2.14	-2.36
19	-3.55	-4.33	-5.52	-5.27	-5.40
20	-2.53	-3.34	-4.50	-4.31	-4.43
21	-8.52	-9.48	-10.46	-10.35	-10.59
22	-5.73	-6.53	-7.44	-7.38	-7.46
23	-6.77	-7.69	-8.82	-8.68	-8.81
24	-5.42	-6.23	-7.36	-7.20	-7.30
MSE	0.90	0.23	-0.32	-0.31	-0.43
RMSE	1.26	0.91	1.09	1.05	1.09
R2	0.96	0.96	0.94	0.95	0.95
MSE'	0.63	0.03	-0.45	-0.42	-0.55
RMSE'	0.93	0.82	1.17	1.14	1.18

TABLE S4: SMD hydration free energies in kcal/mol for SAMPL4 molecules using using five density functionals and the 6-31G* basis set. MSE' and RMSE' are computed for molecules 2 through 21.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
1	-21.06	-23.00	-23.72	-24.45	-24.35
2	-1.30	-2.22	-3.02	-2.88	-3.10
3	-3.65	-4.40	-5.24	-5.15	-5.26
4	-3.87	-4.70	-5.69	-5.63	-5.70
5	-2.14	-3.15	-3.93	-4.07	-4.09
6	-5.29	-6.44	-7.41	-7.56	-7.56
9	-5.88	-6.93	-7.07	-7.34	-7.49
10	-3.49	-4.30	-4.67	-4.98	-4.93
11	-5.13	-5.97	-6.25	-6.35	-6.49
12	-2.19	-2.90	-3.26	-3.06	-3.41
13	-3.17	-3.89	-4.72	-4.66	-4.74
14	-1.89	-2.65	-3.10	-2.86	-3.21
15	-2.90	-3.58	-3.89	-3.64	-4.04
16	-2.03	-2.54	-2.97	-2.99	-3.05
17	-1.78	-2.38	-2.56	-2.41	-2.73
19	-1.46	-2.28	-3.61	-3.33	-3.43
20	0.15	-0.69	-1.94	-1.73	-1.81
21	-7.02	-7.95	-8.96	-8.86	-9.04
22	-3.51	-4.53	-5.67	-5.62	-5.66
23	-4.12	-5.34	-6.88	-6.65	-6.79
24	-3.21	-4.23	-5.82	-5.53	-5.64
MSE	2.07	1.16	0.38	0.41	0.28
RMSE	2.42	1.66	1.17	1.22	1.17
R2	0.92	0.93	0.94	0.94	0.94
MSE'	1.66	0.84	0.18	0.22	0.07
RMSE'	1.89	1.24	1.06	1.05	1.01

TABLE S5: SM8 hydration free energies (in kcal/mol) for twelve small molecules using using five density functionals and the 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	-8.86	-8.98	-9.16	-8.95	-9.20
methanol	-4.73	-4.78	-4.94	-4.63	-4.97
ethanol	-4.38	-4.43	-4.57	-4.32	-4.60
methanethiol	-0.52	-0.50	-0.60	-0.48	-0.56
acetamide	-10.42	-10.44	-10.61	-9.78	-10.83
tetrahydrofuran	-3.18	-3.18	-3.37	-2.90	-3.39
benzene	-0.89	-1.02	-1.44	-1.14	-1.34
phenol	-4.85	-5.02	-5.50	-5.18	-5.39
aniline	-4.49	-4.60	-5.13	-4.73	-4.96
ethane	1.10	1.08	0.99	1.08	1.03
hexane	1.50	1.49	1.42	1.48	1.45
cyclohexane	0.50	0.48	0.35	0.46	0.40
MSE	-0.08	-0.14	-0.36	-0.07	-0.34
RMSE	1.09	1.09	1.08	1.06	1.11
R2	0.91	0.91	0.93	0.92	0.92

TABLE S6: SM12MK hydration free energies (in kcal/mol) for twelve small molecules using using five density functionals and the 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	-8.36	-8.85	-9.10	-9.33	-9.32
methanol	-4.96	-5.38	-5.61	-5.77	-5.76
ethanol	-4.74	-5.14	-5.35	-5.49	-5.50
methanethiol	-2.21	-2.28	-2.48	-2.34	-2.45
acetamide	-9.64	-10.43	-10.78	-10.91	-11.03
tetrahydrofuran	-2.85	-3.22	-3.43	-3.53	-3.55
benzene	-1.92	-2.46	-3.21	-3.09	-3.16
phenol	-6.46	-7.18	-8.04	-8.01	-8.05
aniline	-5.71	-6.30	-7.26	-7.06	-7.15
ethane	1.44	1.43	1.38	1.40	1.39
hexane	1.73	1.68	1.57	1.62	1.59
cyclohexane	1.20	1.18	1.10	1.14	1.12
MSE	-0.35	-0.72	-1.08	-1.09	-1.13
RMSE	0.79	1.02	1.37	1.38	1.42
R2	0.96	0.97	0.96	0.96	0.96

TABLE S7: SM12CHELPG hydration free energies (in kcal/mol) for twelve small molecules using using five density functionals and the 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	-8.35	-8.83	-9.07	-9.30	-9.28
methanol	-4.87	-5.26	-5.46	-5.62	-5.61
ethanol	-4.75	-5.13	-5.31	-5.45	-5.45
methanethiol	-1.96	-2.02	-2.17	-2.06	-2.16
acetamide	-9.58	-10.36	-10.66	-10.81	-10.92
tetrahydrofuran	-2.82	-3.16	-3.31	-3.42	-3.43
benzene	-1.81	-2.31	-3.03	-2.91	-2.98
phenol	-6.27	-6.94	-7.75	-7.72	-7.77
aniline	-5.56	-6.12	-7.03	-6.83	-6.93
ethane	1.46	1.46	1.42	1.44	1.43
hexane	1.88	1.86	1.79	1.83	1.80
cyclohexane	1.20	1.22	1.23	1.24	1.23
MSE	-0.26	-0.61	-0.92	-0.95	-0.98
RMSE	0.75	0.94	1.25	1.26	1.30
R2	0.96	0.97	0.96	0.96	0.96

TABLE S8: SMD hydration free energies (in kcal/mol) for twelve small molecules using using five density functionals and the 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	-7.78	-8.27	-8.53	-8.75	-8.73
methanol	-3.87	-4.33	-4.57	-4.75	-4.74
ethanol	-4.05	-4.53	-4.79	-4.95	-4.95
methanethiol	-0.96	-1.04	-1.25	-1.11	-1.21
acetamide	-7.64	-8.49	-8.83	-8.99	-9.10
tetrahydrofuran	-1.93	-2.42	-2.67	-2.80	-2.82
benzene	-0.25	-0.71	-1.39	-1.26	-1.32
phenol	-4.75	-5.46	-6.22	-6.24	-6.25
aniline	-4.28	-4.85	-5.79	-5.60	-5.66
ethane	1.89	1.84	1.72	1.77	1.75
hexane	2.61	2.52	2.28	2.39	2.33
cyclohexane	1.56	1.49	1.31	1.40	1.35
MSE	0.73	0.34	-0.04	-0.05	-0.09
RMSE	1.18	0.87	0.78	0.78	0.77
R2	0.94	0.95	0.96	0.96	0.96

TABLE S9: Gas-phase dipole moments (in Debye) for twelve small molecules using five density functionals and the 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	1.9981	2.0658	2.0991	2.1286	2.1292
methanol	1.5765	1.6705	1.7048	1.7437	1.7406
ethanol	1.5634	1.6611	1.6951	1.7359	1.7314
methanethiol	1.7139	1.7343	1.7902	1.7399	1.7901
acetamide	3.5628	3.7072	3.7461	3.7660	3.7983
tetrahydrofuran	1.6622	1.7639	1.7964	1.8339	1.8319
benzene	0.0003	0.0003	0.0004	0.0004	0.0004
phenol	1.3256	1.3494	1.3676	1.3831	1.3819
aniline	1.8002	1.7206	1.7330	1.6710	1.6891
ethane	0.0002	0.0002	0.0003	0.0002	0.0002
hexane	0.0138	0.0138	0.0136	0.0142	0.0143
cyclohexane	0.0003	0.0003	0.0004	0.0003	0.0004

TABLE S10: Gas-phase HOMO-LUMO gaps for SAMPL4 molecules using five density functionals and 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
1	0.226	0.310	0.336	0.430	0.481
2	0.178	0.243	0.259	0.338	0.394
3	0.184	0.249	0.265	0.342	0.399
4	0.188	0.251	0.268	0.345	0.402
5	0.157	0.215	0.230	0.302	0.358
6	0.153	0.210	0.224	0.296	0.352
9	0.114	0.183	0.198	0.270	0.323
10	0.158	0.216	0.231	0.302	0.358
11	0.114	0.169	0.183	0.255	0.308
12	0.142	0.222	0.240	0.332	0.379
13	0.191	0.255	0.271	0.349	0.406
14	0.121	0.199	0.216	0.295	0.349
15	0.115	0.191	0.208	0.300	0.344
16	0.253	0.334	0.358	0.444	0.500
17	0.144	0.225	0.243	0.337	0.381
19	0.175	0.231	0.245	0.315	0.374
20	0.137	0.190	0.204	0.273	0.330
21	0.155	0.214	0.229	0.302	0.361
22	0.103	0.155	0.168	0.235	0.292
23	0.136	0.205	0.218	0.300	0.352
24	0.124	0.190	0.204	0.284	0.336

TABLE S11: Gas-phase HOMO-LUMO gaps for twelve small molecules using five density functionals and 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	0.264	0.357	0.389	0.494	0.541
methanol	0.255	0.342	0.369	0.466	0.517
ethanol	0.257	0.341	0.367	0.461	0.513
methanethiol	0.197	0.266	0.285	0.364	0.423
acetamide	0.197	0.281	0.301	0.402	0.442
tetrahydrofuran	0.247	0.325	0.348	0.439	0.490
benzene	0.194	0.252	0.267	0.340	0.398
phenol	0.163	0.222	0.237	0.309	0.366
aniline	0.150	0.208	0.223	0.294	0.352
ethane	0.372	0.445	0.468	0.551	0.611
hexane	0.327	0.396	0.419	0.493	0.557
cyclohexane	0.311	0.380	0.401	0.476	0.539

TABLE S12: Computed λ values for SAMPL4 molecules using five density functionals and 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
1	0.830	0.890	0.900	0.960	0.980
2	0.760	0.830	0.850	0.910	0.940
3	0.800	0.860	0.870	0.930	0.960
4	0.790	0.850	0.870	0.920	0.950
5	0.700	0.770	0.790	0.850	0.890
6	0.730	0.790	0.810	0.870	0.910
9	0.710	0.780	0.800	0.870	0.900
10	0.770	0.830	0.850	0.910	0.940
11	0.750	0.820	0.840	0.900	0.930
12	0.730	0.800	0.820	0.900	0.930
13	0.790	0.840	0.860	0.920	0.950
14	0.700	0.780	0.800	0.890	0.920
15	0.690	0.780	0.800	0.880	0.920
16	0.820	0.880	0.890	0.950	0.980
17	0.740	0.810	0.830	0.910	0.930
19	0.730	0.790	0.800	0.860	0.900
20	0.740	0.810	0.820	0.880	0.920
21	0.720	0.790	0.810	0.880	0.910
22	0.770	0.840	0.850	0.920	0.950
23	0.770	0.830	0.840	0.900	0.940
24	0.770	0.820	0.840	0.900	0.930

TABLE S13: Computed λ values for twelve small molecules using five density functionals and 6-31G* basis set.

molecule	BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	0.850	0.910	0.930	0.990	1.000
methanol	0.830	0.890	0.900	0.960	0.990
ethanol	0.820	0.880	0.900	0.960	0.980
methanethiol	0.820	0.880	0.900	0.960	1.000
acetamide	0.710	0.800	0.820	0.910	0.940
tetrahydrofuran	0.800	0.860	0.870	0.930	0.960
benzene	0.750	0.810	0.830	0.890	0.930
phenol	0.770	0.830	0.850	0.910	0.950
aniline	0.820	0.870	0.890	0.940	0.970
ethane	0.860	0.920	0.940	1.000	1.000
hexane	0.860	0.920	0.930	1.000	1.000
cyclohexane	0.840	0.900	0.920	0.980	1.000

TABLE S14: Average change (in kcal/mol) in QM/MM permanent electrostatic energy (ΔE_1) and polarization energy (ΔE_2) from the BLYP functional to B3LYP, PBE0, M06-2X and ωB97X-D functionals using the 6-31G* basis set. Averaged over 10,000 frames from the first MM trajectory with frozen-gas-phase-geometry solute molecules and TIP3P water molecules.

molecule		BLYP	B3LYP	PBE0	M06-2X	ωB97X-D
water	ΔE_1	0.00	-0.65	-1.01	-1.26	-1.26
	ΔE_2	0.00	0.07	0.10	0.11	0.17
methanol	ΔE_1	0.00	-0.59	-0.90	-1.10	-1.11
	ΔE_2	0.00	0.05	0.09	0.10	0.08
ethanol	ΔE_1	0.00	-0.61	-0.93	-1.11	-1.13
	ΔE_2	0.00	0.05	0.04	0.05	0.08
methanethiol	ΔE_1	0.00	-0.04	-0.16	-0.07	-0.16
	ΔE_2	0.00	0.02	0.01	0.02	0.03
acetamide	ΔE_1	0.00	-0.96	-1.28	-1.42	-1.59
	ΔE_2	0.00	0.02	0.03	-0.05	-0.02
tetrahydrofuran	ΔE_1	0.00	-0.67	-0.95	-1.15	-1.18
	ΔE_2	0.00	0.04	0.06	0.07	0.06
benzene	ΔE_1	0.00	-0.37	-0.84	-0.76	-0.80
	ΔE_2	0.00	0.00	-0.01	-0.01	-0.01
phenol	ΔE_1	0.00	-0.71	-1.31	-1.41	-1.41
	ΔE_2	0.00	0.06	0.06	0.07	0.05
aniline	ΔE_1	0.00	-0.69	-1.52	-1.47	-1.51
	ΔE_2	0.00	0.09	0.08	0.13	0.16
ethane	ΔE_1	0.00	-0.01	-0.03	-0.02	-0.03
	ΔE_2	0.00	0.00	-0.00	0.00	0.02
hexane	ΔE_1	0.00	-0.02	-0.07	-0.05	-0.06
	ΔE_2	0.00	0.01	0.02	0.00	0.06
cyclohexane	ΔE_1	0.00	-0.01	-0.04	-0.03	-0.03
	ΔE_2	0.00	0.01	0.00	0.00	0.03

TABLE S15: Hydration free energies (in kcal/mol) from MESS-E-QM/MM NBB calculations with different sampling frequencies (100fs, 200fs, 500fs, and 1ps) using the BLYP functional and the 6-31G* basis set. MSE' and RMSE' are computed for molecules 2 through 21.

molecule	Expt	MESS-E-QM/MM NBB			
		100fs	200fs	500fs	1ps
1	-23.62	-18.45 ± 0.23	-18.45 ± 0.20	-18.27 ± 0.26	-18.28 ± 0.27
2	-2.49	-3.18 ± 0.13	-3.12 ± 0.11	-3.14 ± 0.23	-3.08 ± 0.32
3	-4.78	-6.03 ± 0.03	-6.01 ± 0.03	-5.99 ± 0.09	-6.00 ± 0.12
4	-4.45	-5.55 ± 0.24	-5.54 ± 0.33	-5.54 ± 0.22	-5.48 ± 0.30
5	-5.33	-4.45 ± 0.48	-4.50 ± 0.60	-4.15 ± 0.16	-4.12 ± 0.16
6	-5.26	-7.56 ± 0.45	-7.45 ± 0.27	-7.29 ± 0.34	-7.37 ± 0.31
9	-8.24	-9.38 ± 0.92	-9.18 ± 1.25	-8.88 ± 0.69	-8.70 ± 0.69
10	-6.24	-5.30 ± 0.18	-5.38 ± 0.14	-5.15 ± 0.53	-5.25 ± 0.62
11	-7.78	-7.95 ± 0.48	-7.86 ± 0.41	-7.82 ± 0.53	-7.99 ± 0.74
12	-3.75	-4.23 ± 0.18	-4.22 ± 0.21	-4.17 ± 0.38	-4.22 ± 0.44
13	-4.44	-5.04 ± 0.24	-5.05 ± 0.30	-5.16 ± 0.35	-5.09 ± 0.48
14	-4.09	-4.63 ± 0.36	-4.49 ± 0.28	-4.49 ± 0.59	-4.33 ± 0.37
15	-4.48	-5.95 ± 0.32	-6.16 ± 0.42	-6.06 ± 0.46	-6.39 ± 0.51
16	-3.20	-3.84 ± 0.28	-3.85 ± 0.29	-3.86 ± 0.31	-3.88 ± 0.35
17	-2.53	-3.62 ± 0.20	-3.65 ± 0.23	-3.64 ± 0.15	-3.66 ± 0.20
19	-3.78	-3.51 ± 0.25	-3.52 ± 0.26	-3.49 ± 0.28	-3.44 ± 0.26
20	-2.78	-2.23 ± 0.30	-2.21 ± 0.28	-2.22 ± 0.32	-2.19 ± 0.26
21	-7.63	-8.29 ± 0.32	-8.35 ± 0.35	-8.27 ± 0.34	-8.19 ± 0.56
22	-6.78	-8.09 ± 0.20	-7.89 ± 0.26	-8.02 ± 0.29	-7.95 ± 0.28
23	-9.34	-3.98 ± 0.19	-3.91 ± 0.18	-4.07 ± 0.26	-3.84 ± 0.26
24	-7.43	-5.03 ± 0.24	-5.12 ± 0.28	-4.99 ± 0.34	-5.19 ± 0.31
MSE		0.10	0.12	0.18	0.18
RMSE		1.95	1.94	1.95	1.98
R2		0.82	0.82	0.83	0.82
MSE'		-0.55	-0.54	-0.46	-0.47
RMSE'		1.02	1.00	0.99	1.02

TABLE S16: Hydration free energies (in kcal/mol) from MESS-E-QM/MM NBB calculations with different sampling frequencies (100fs, 200fs, 500fs, and 1ps) using the B3LYP functional and the 6-31G* basis set. MSE' and RMSE' are computed for molecules 2 through 21.

molecule	Expt	MESS-E-QM/MM NBB			
		100fs	200fs	500fs	1ps
1	-23.62	-20.35 ± 0.31	-20.32 ± 0.25	-20.07 ± 0.27	-20.08 ± 0.25
2	-2.49	-3.91 ± 0.14	-3.86 ± 0.15	-3.87 ± 0.28	-3.83 ± 0.38
3	-4.78	-6.77 ± 0.04	-6.76 ± 0.05	-6.75 ± 0.09	-6.75 ± 0.10
4	-4.45	-6.29 ± 0.24	-6.27 ± 0.32	-6.26 ± 0.22	-6.21 ± 0.27
5	-5.33	-5.56 ± 0.46	-5.63 ± 0.58	-5.27 ± 0.17	-5.22 ± 0.14
6	-5.26	-8.91 ± 0.46	-8.82 ± 0.38	-8.62 ± 0.38	-8.71 ± 0.41
9	-8.24	-10.12 ± 0.87	-10.07 ± 1.10	-9.90 ± 0.81	-9.84 ± 0.92
10	-6.24	-6.08 ± 0.19	-6.11 ± 0.16	-5.92 ± 0.50	-5.98 ± 0.53
11	-7.78	-8.82 ± 0.35	-8.79 ± 0.42	-8.75 ± 0.46	-8.81 ± 0.61
12	-3.75	-5.00 ± 0.20	-4.97 ± 0.23	-4.96 ± 0.40	-5.00 ± 0.46
13	-4.44	-5.68 ± 0.22	-5.68 ± 0.23	-5.76 ± 0.27	-5.70 ± 0.32
14	-4.09	-5.24 ± 0.37	-5.11 ± 0.30	-5.15 ± 0.59	-5.04 ± 0.39
15	-4.48	-6.78 ± 0.35	-6.99 ± 0.46	-6.88 ± 0.51	-7.21 ± 0.55
16	-3.20	-4.49 ± 0.29	-4.50 ± 0.30	-4.49 ± 0.30	-4.52 ± 0.32
17	-2.53	-4.32 ± 0.22	-4.36 ± 0.28	-4.34 ± 0.16	-4.36 ± 0.23
19	-3.78	-4.17 ± 0.23	-4.18 ± 0.25	-4.18 ± 0.29	-4.11 ± 0.28
20	-2.78	-2.88 ± 0.30	-2.88 ± 0.28	-2.87 ± 0.32	-2.86 ± 0.25
21	-7.63	-9.19 ± 0.36	-9.25 ± 0.41	-9.19 ± 0.35	-9.12 ± 0.57
22	-6.78	-9.06 ± 0.20	-8.85 ± 0.29	-9.03 ± 0.35	-8.91 ± 0.35
23	-9.34	-5.10 ± 0.23	-5.05 ± 0.20	-6.11 ± 2.14	-5.01 ± 0.24
24	-7.43	-6.00 ± 0.24	-6.07 ± 0.26	-5.94 ± 0.36	-6.15 ± 0.34
MSE		-0.78	-0.77	-0.76	-0.71
RMSE		1.96	1.95	1.85	1.96
R2		0.84	0.84	0.87	0.84
MSE'		-1.35	-1.35	-1.28	-1.29
RMSE'		1.63	1.63	1.58	1.61

TABLE S17: Hydration free energies (in kcal/mol) from MESS-E-QM/MM NBB calculations with different sampling frequencies (100fs, 200fs, 500fs, and 1ps) using the BLYP functional and the 6-31G* basis set.

molecule	Expt	MESS-E-QM/MM NBB			
		100fs	200fs	500fs	1ps
water	-6.31	-7.08 ± 0.14	-7.09 ± 0.14	-7.08 ± 0.18	-7.07 ± 0.23
methanol	-5.10	-3.81 ± 0.06	-3.83 ± 0.04	-3.81 ± 0.12	-3.75 ± 0.18
ethanol	-5.05	-3.85 ± 0.11	-3.85 ± 0.11	-3.83 ± 0.12	-3.85 ± 0.14
methanethiol	-1.24	-3.09 ± 0.33	-2.92 ± 0.28	-2.95 ± 0.55	-2.79 ± 0.51
acetamide	-9.68	-11.19 ± 0.21	-10.98 ± 0.14	-10.92 ± 0.08	-10.86 ± 0.17
tetrahydrofuran	-3.40	-3.29 ± 0.08	-3.33 ± 0.07	-3.27 ± 0.16	-3.17 ± 0.07
benzene	-0.86	-0.56 ± 0.12	-0.56 ± 0.10	-0.55 ± 0.12	-0.54 ± 0.12
phenol	-6.61	-5.92 ± 0.14	-5.86 ± 0.23	-5.83 ± 0.18	-5.80 ± 0.36
aniline	-5.49	-6.82 ± 0.34	-6.80 ± 0.46	-6.75 ± 0.26	-6.66 ± 0.31
ethane	1.83	2.04 ± 0.12	2.04 ± 0.12	2.05 ± 0.10	2.08 ± 0.11
hexane	2.48	2.16 ± 0.26	2.15 ± 0.28	2.13 ± 0.25	2.12 ± 0.27
cyclohexane	1.23	1.03 ± 0.10	1.03 ± 0.11	1.02 ± 0.10	1.02 ± 0.12
MSE		-0.18	-0.15	-0.13	-0.09
RMSE		1.00	0.95	0.95	0.92
R2		0.94	0.94	0.94	0.94

TABLE S18: Hydration free energies (in kcal/mol) from MESS-E-QM/MM NBB calculations with different sampling frequencies (100fs, 200fs, 500fs, and 1ps) using the B3LYP functional and the 6-31G* basis set.

molecule	Expt	MESS-E-QM/MM NBB			
		100fs	200fs	500fs	1ps
water	-6.31	-7.72 ± 0.15	-7.73 ± 0.15	-7.71 ± 0.20	-7.70 ± 0.25
methanol	-5.10	-4.45 ± 0.04	-4.46 ± 0.05	-4.45 ± 0.11	-4.37 ± 0.18
ethanol	-5.05	-4.50 ± 0.12	-4.52 ± 0.12	-4.47 ± 0.14	-4.51 ± 0.16
methanethiol	-1.24	-3.19 ± 0.33	-3.01 ± 0.30	-3.04 ± 0.56	-2.88 ± 0.52
acetamide	-9.68	-12.47 ± 0.23	-12.23 ± 0.15	-12.18 ± 0.05	-12.09 ± 0.24
tetrahydrofuran	-3.40	-4.12 ± 0.09	-4.16 ± 0.06	-4.09 ± 0.23	-3.96 ± 0.08
benzene	-0.86	-0.90 ± 0.12	-0.90 ± 0.10	-0.89 ± 0.11	-0.89 ± 0.12
phenol	-6.61	-6.64 ± 0.13	-6.56 ± 0.20	-6.54 ± 0.14	-6.47 ± 0.28
aniline	-5.49	-7.43 ± 0.33	-7.44 ± 0.45	-7.36 ± 0.26	-7.27 ± 0.36
ethane	1.83	2.04 ± 0.12	2.04 ± 0.12	2.05 ± 0.10	2.07 ± 0.11
hexane	2.48	2.15 ± 0.26	2.14 ± 0.28	2.12 ± 0.25	2.10 ± 0.27
cyclohexane	1.23	1.02 ± 0.10	1.02 ± 0.11	1.01 ± 0.10	1.01 ± 0.11
MSE		-0.67	-0.63	-0.61	-0.56
RMSE		1.25	1.19	1.17	1.12
R2		0.95	0.95	0.95	0.95