Supporting Information for

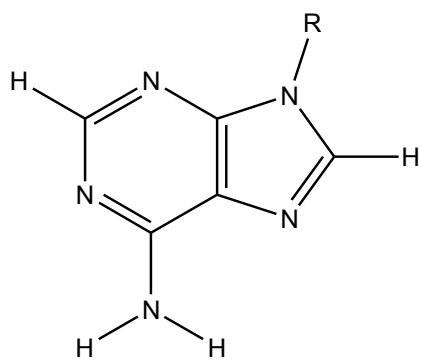# Polarizable Multipole-based Force Field for Aromatic Molecules and Nucleobases

Changsheng Zhang, David Bell, Matthew Harger, Pengyu Ren*

Department of Biomedical Engineering, The University of Texas at Austin,
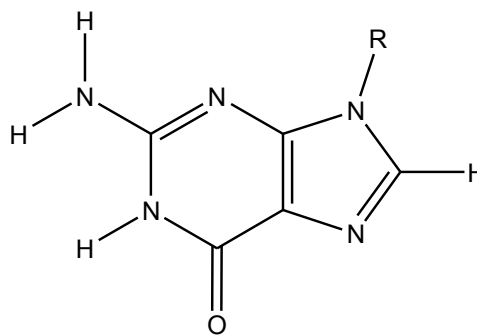
Austin, Texas 78712, United States.

Table of Contents

page #

Figure S1. The structure of the five regular nucleobases.

Adenine (Ab or Am)

Guanine (Gb or Gm)
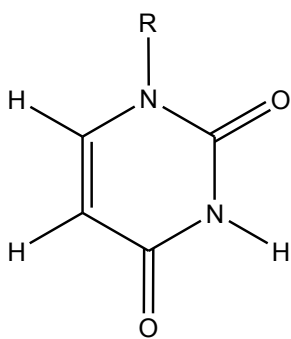
Uracil (Ub or Um)
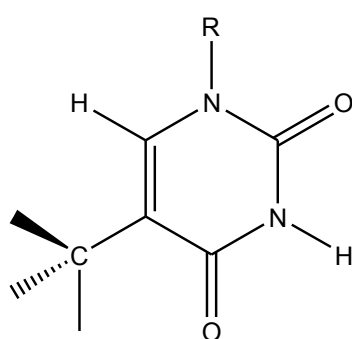
Thymine (Tb or Tm)
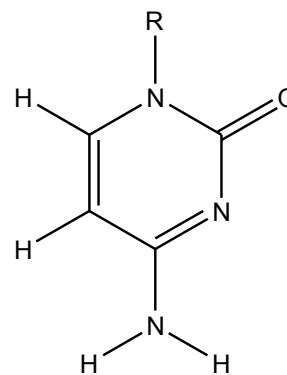
Cytosine (Cb or Cm)

R = H, or CH3

Figure S2. Nucleobases hydrogen bonding pairs used in this work. Red molecules represents the stationary base, while the black, blue, green, cyan, and magenta bases represent the corresponding (labeled) hydrogen bond pattern.

C

GAcisWCS

GAtransSS

GAcisWC

GAcisWCH

6

D

UAtransWCS

AUcisWCH

AUcisWC
ATcisWC

AUtransWC

H,CH₃

UAcisWCS

UAcisWCH

UAtransWCH

E

ACtransWC

CAtransWCH

7

F

CGtransWCS

GCtransWC

GCcisWC

G

GUcisWC

GUtransWC
GTtransWC

GUtransWCH

UGcisWCS

UGtransWCH

UGcisWCH

8

H

CCcisWCH

CUcisWCH

CCtransWCH

I

UUtransWC

UUtransWCH

UUcisWCH

UUcisWC
UTcisWC

9
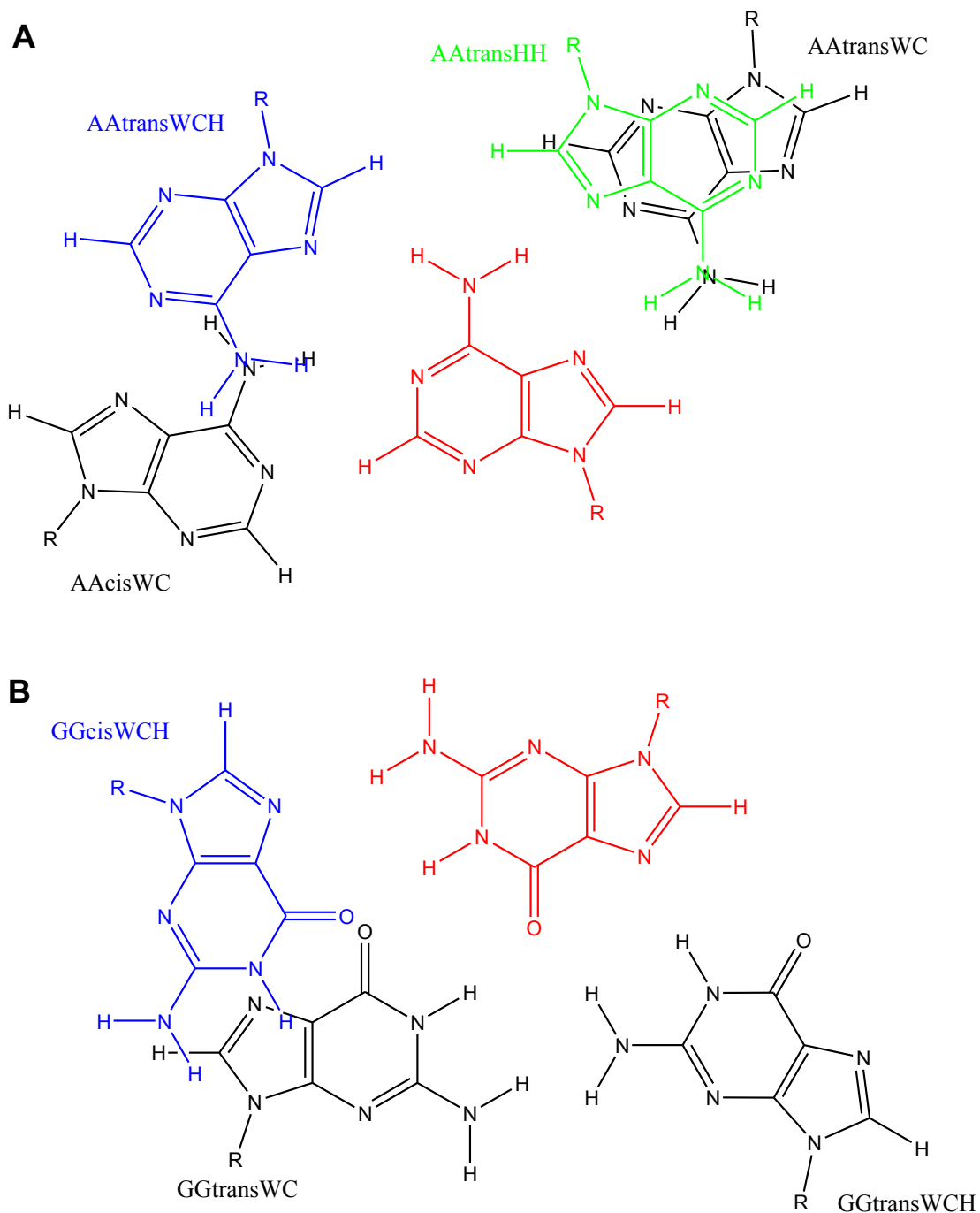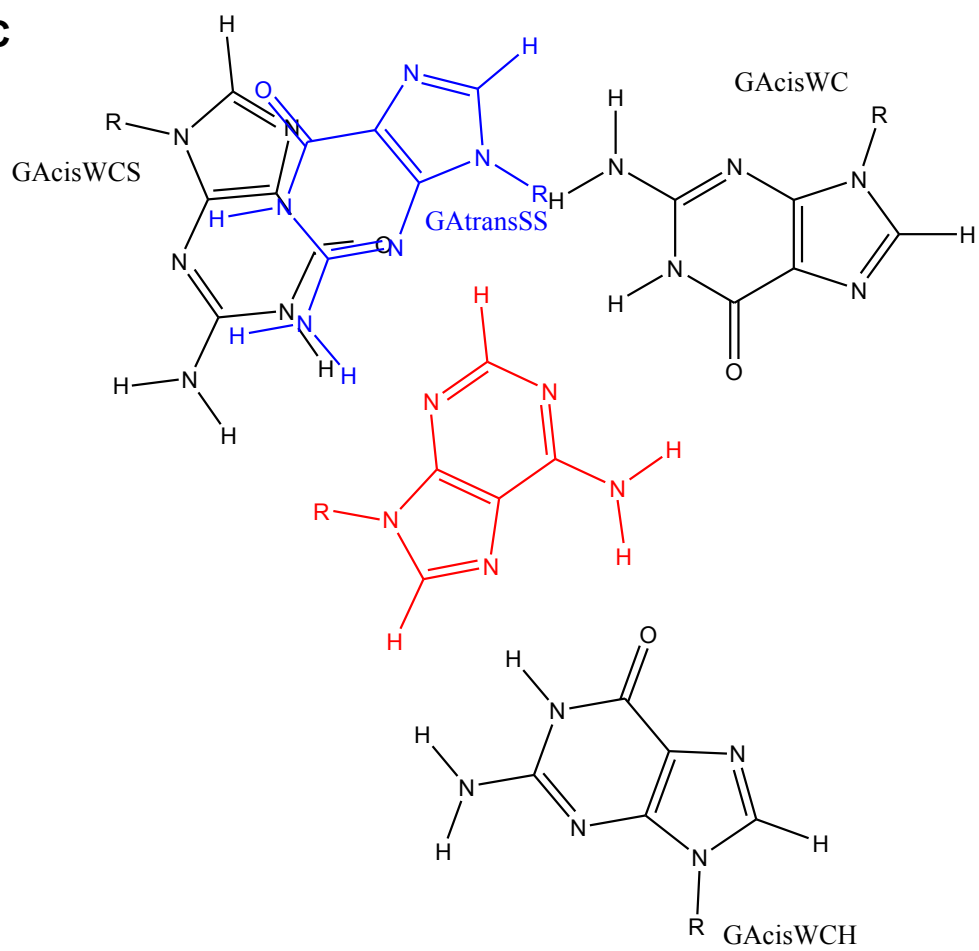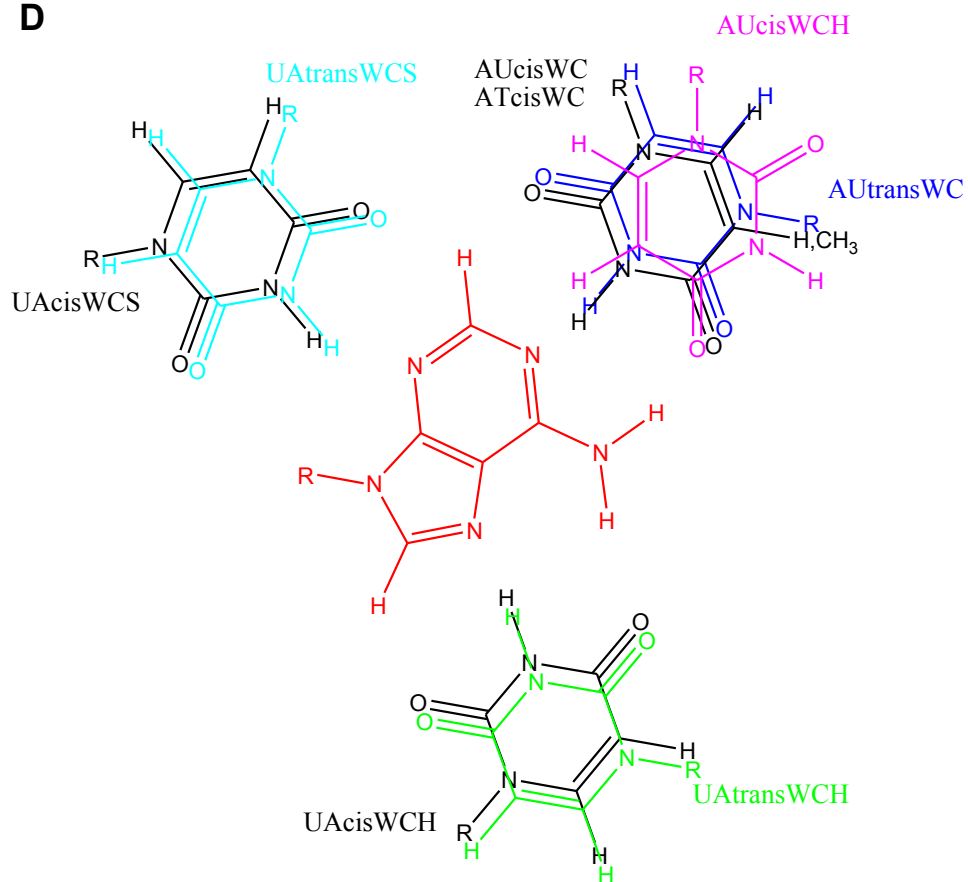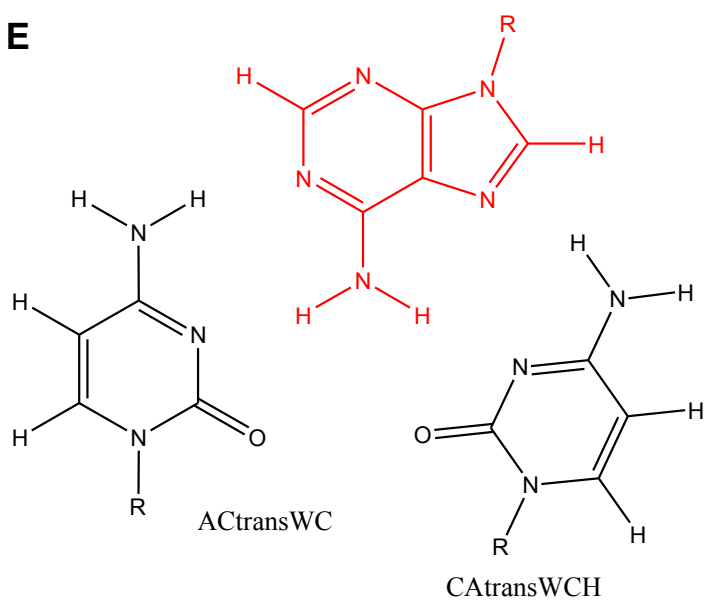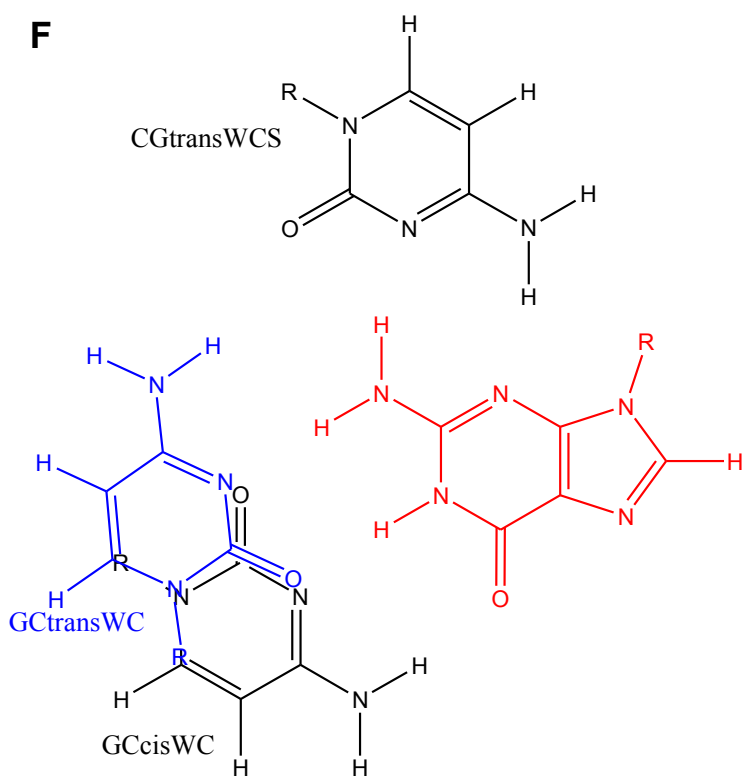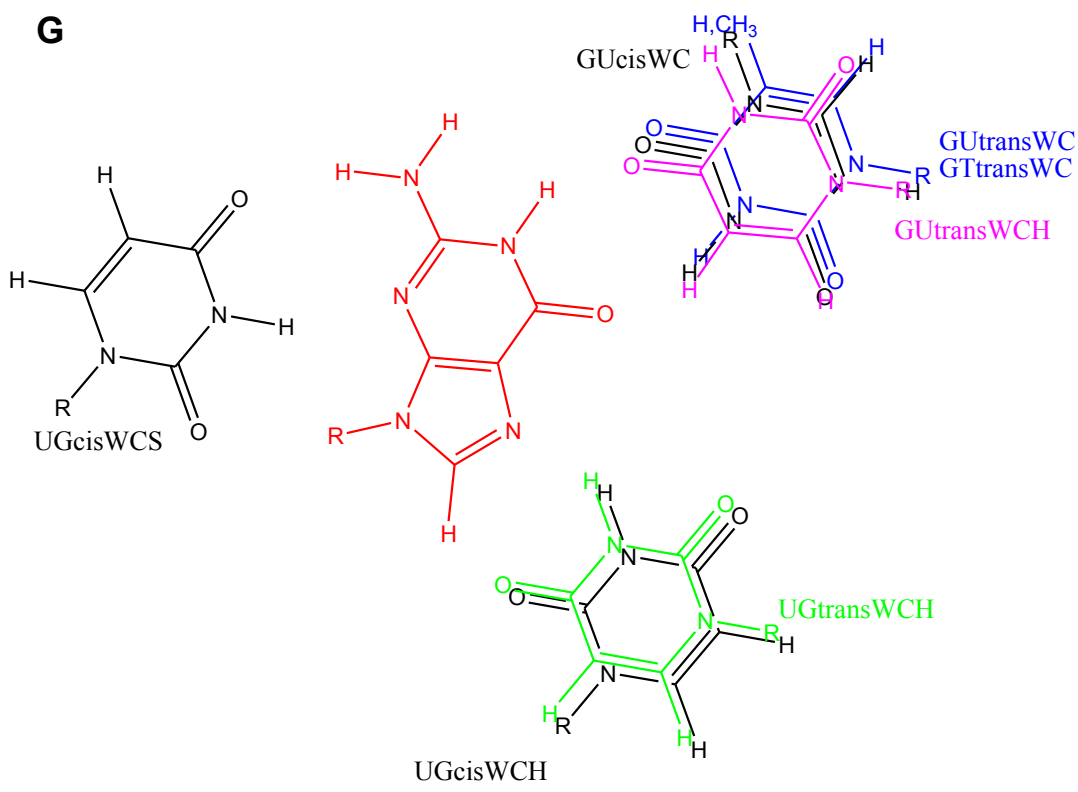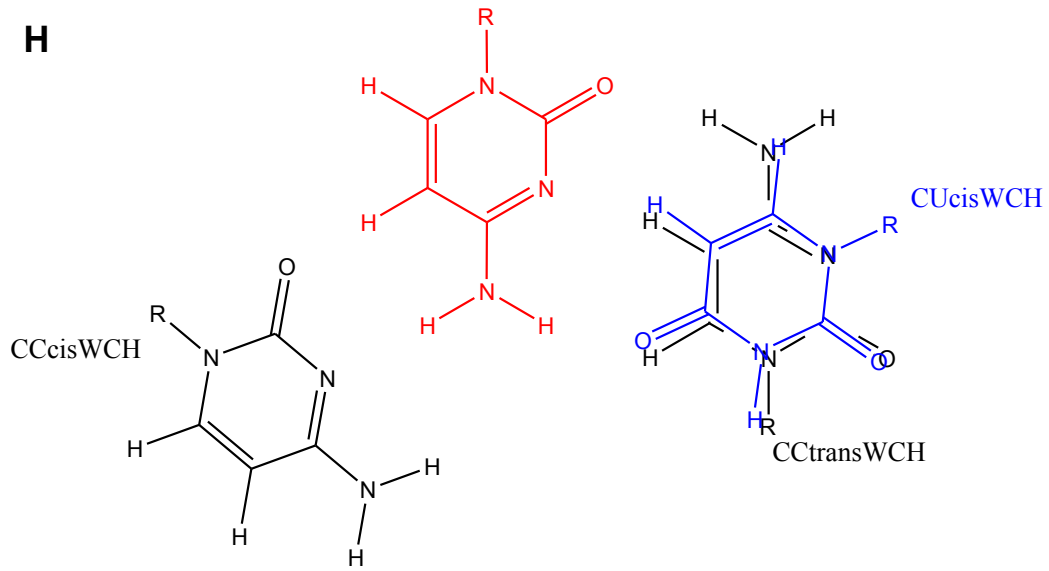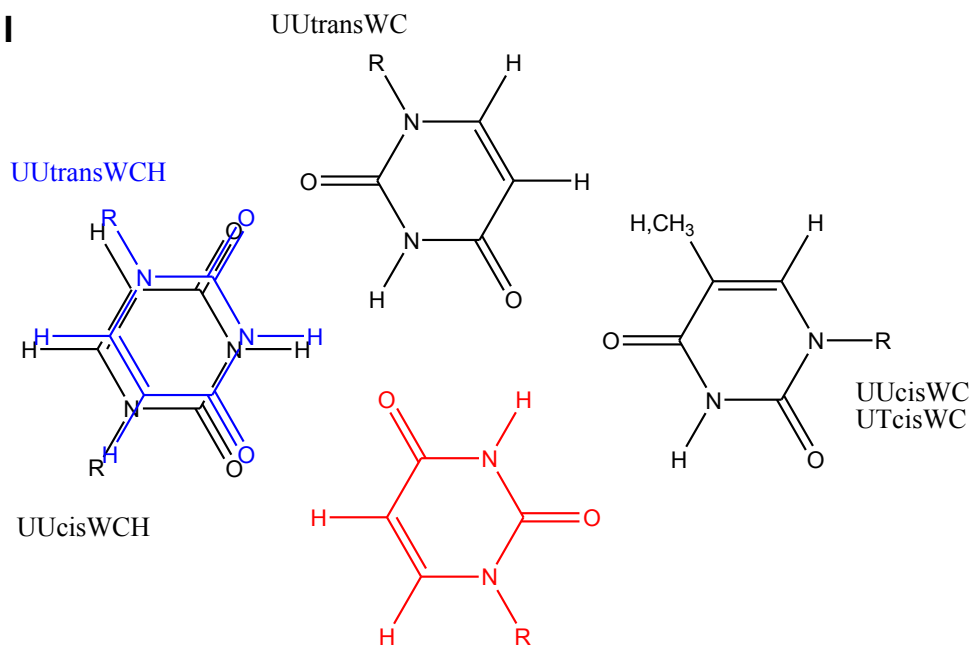
Figure S3. Water molecule positions in the aromatic molecule - water interaction study. Cones represent water molecules out of the plane of the aromatic molecule.
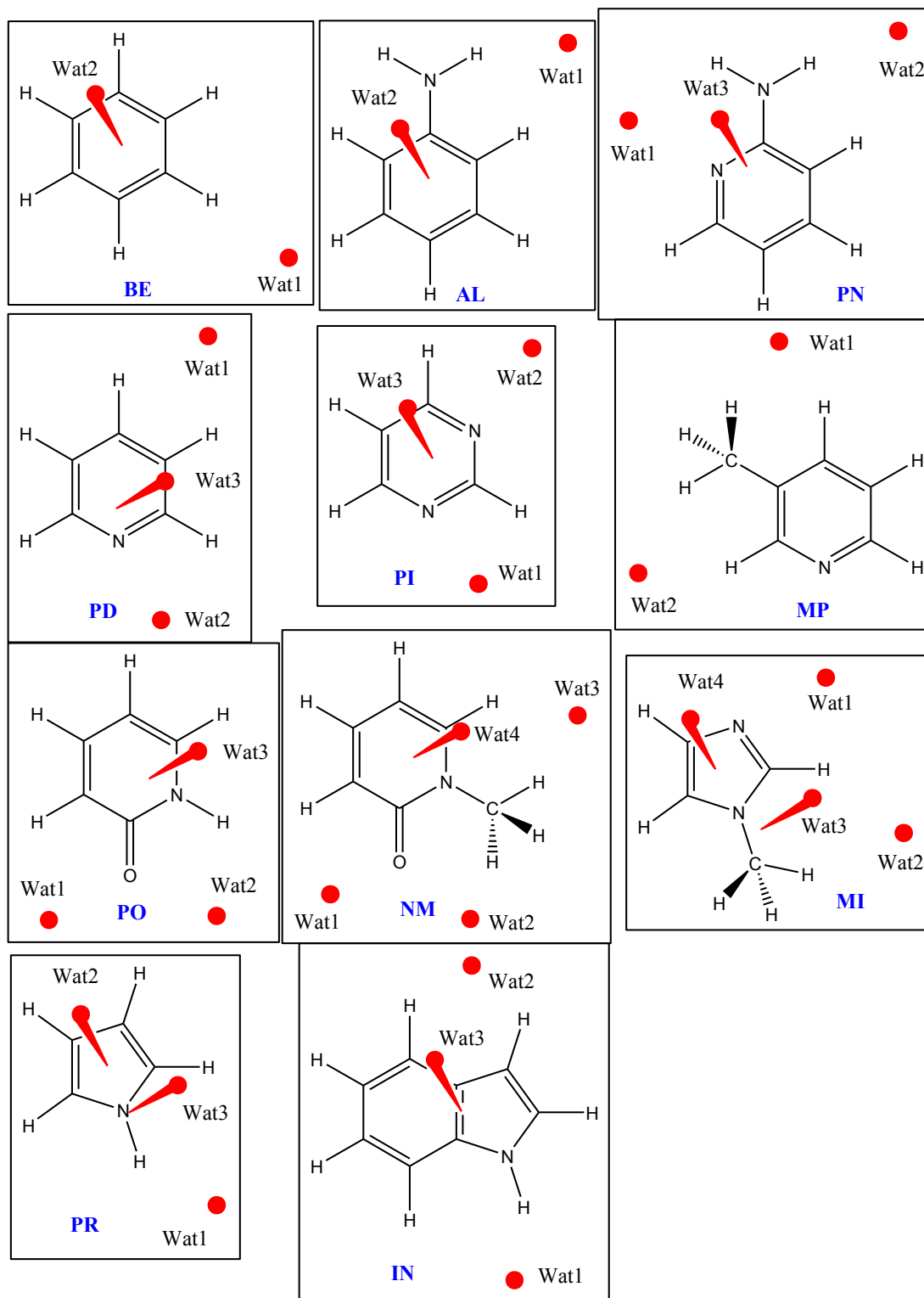
Figure S4. Aromatic molecule – water interaction energy calculated using AMOEBA and RIMP2/aug-cc-pVTZ.
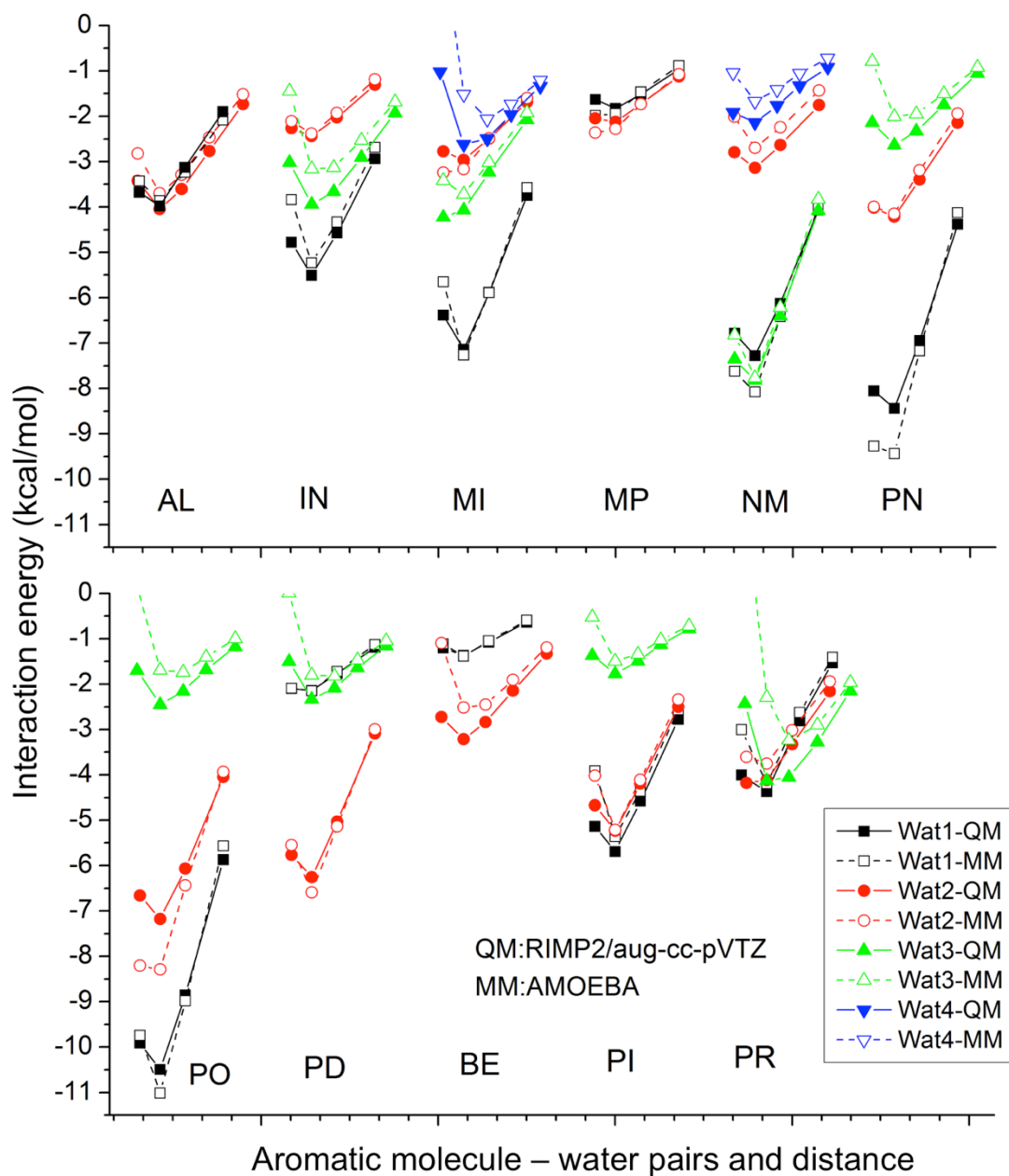
Figure S5. Aromatic ring/ring stacking conformations for interaction energy calculation.
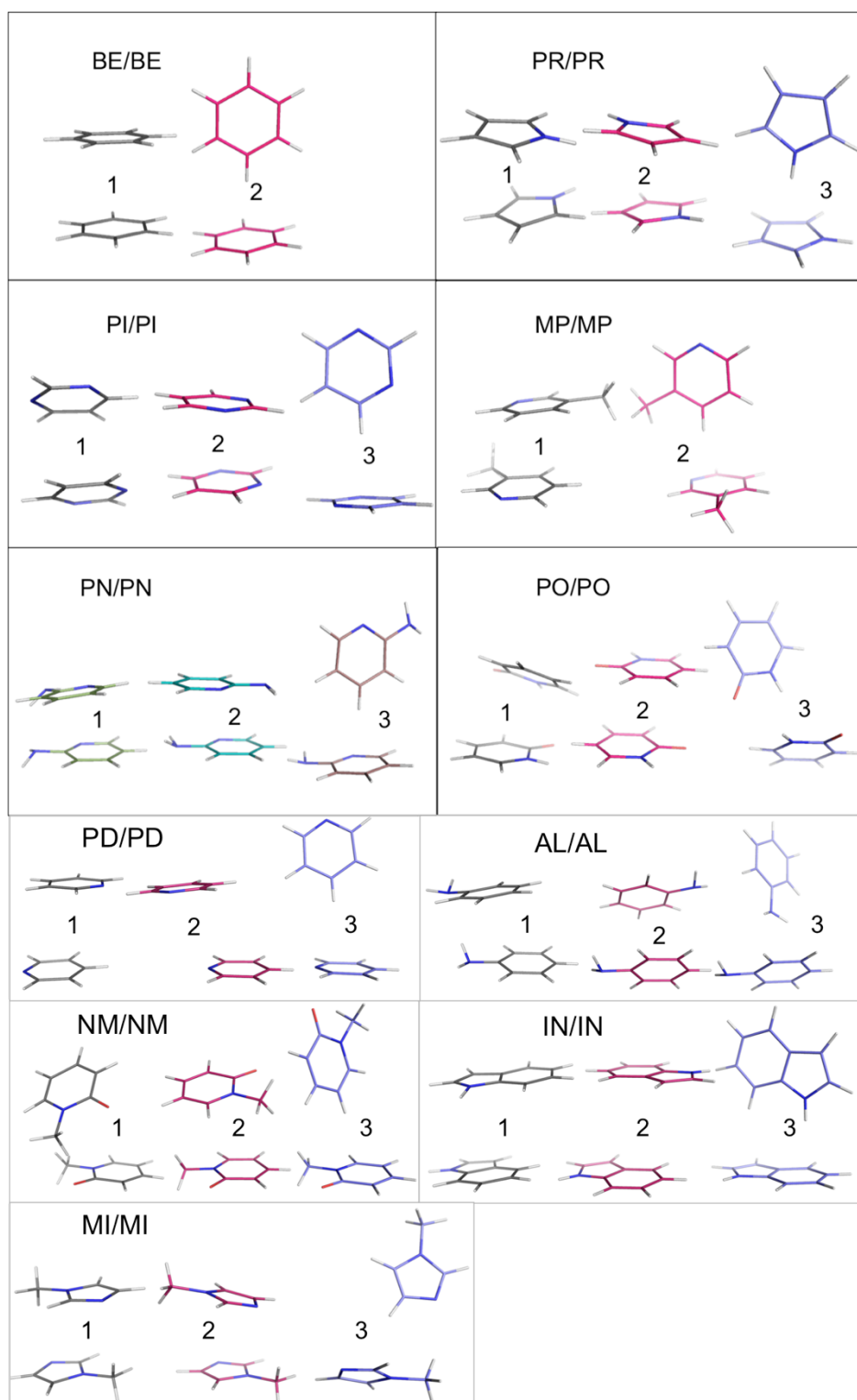
Figure S6. Aromatic ring/ring stacking energy calculated using AMOEBA and RIMP2/cc-pVTZ.
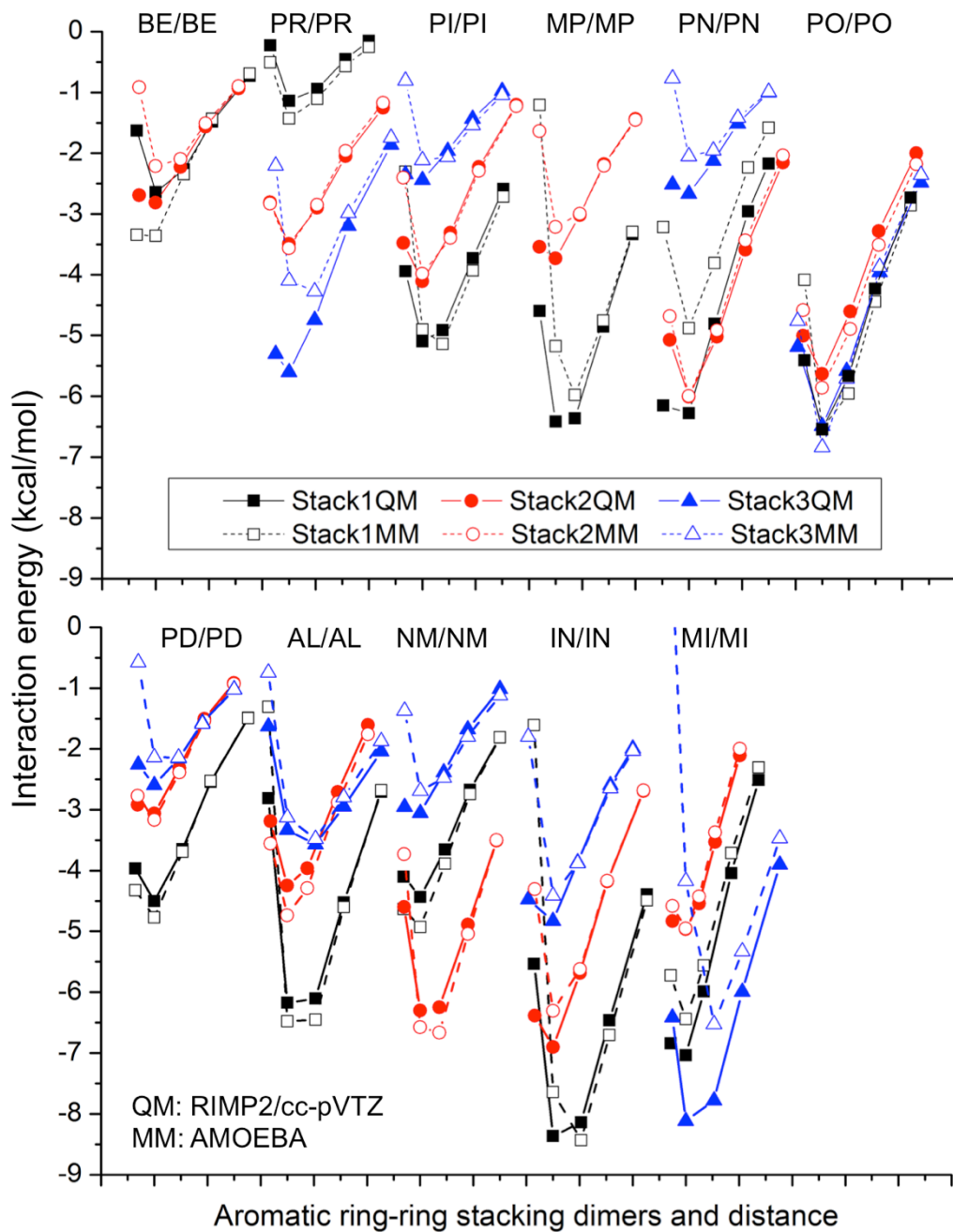
Figure S7. Distortion energy fitting results. The squared Pearson product moment correlation coefficient between AMOEBA distortion energy and QM (MP2/aug-cc-pVTZ) distortion energy is 0.920.
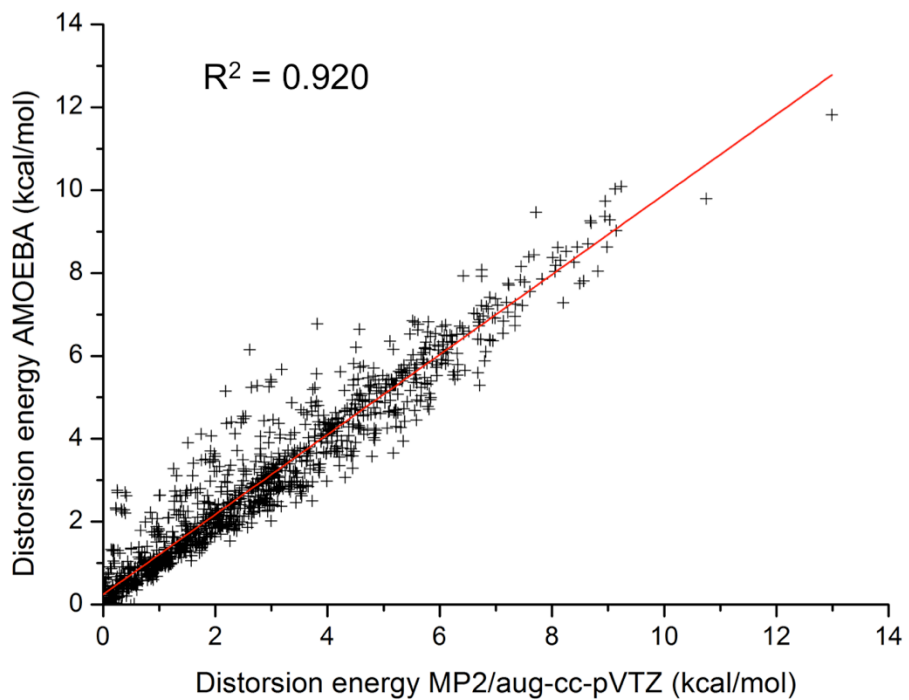
Figure S8. AMOEBA and QM values of vibrational frequencies of the 11 aromatic molecules.
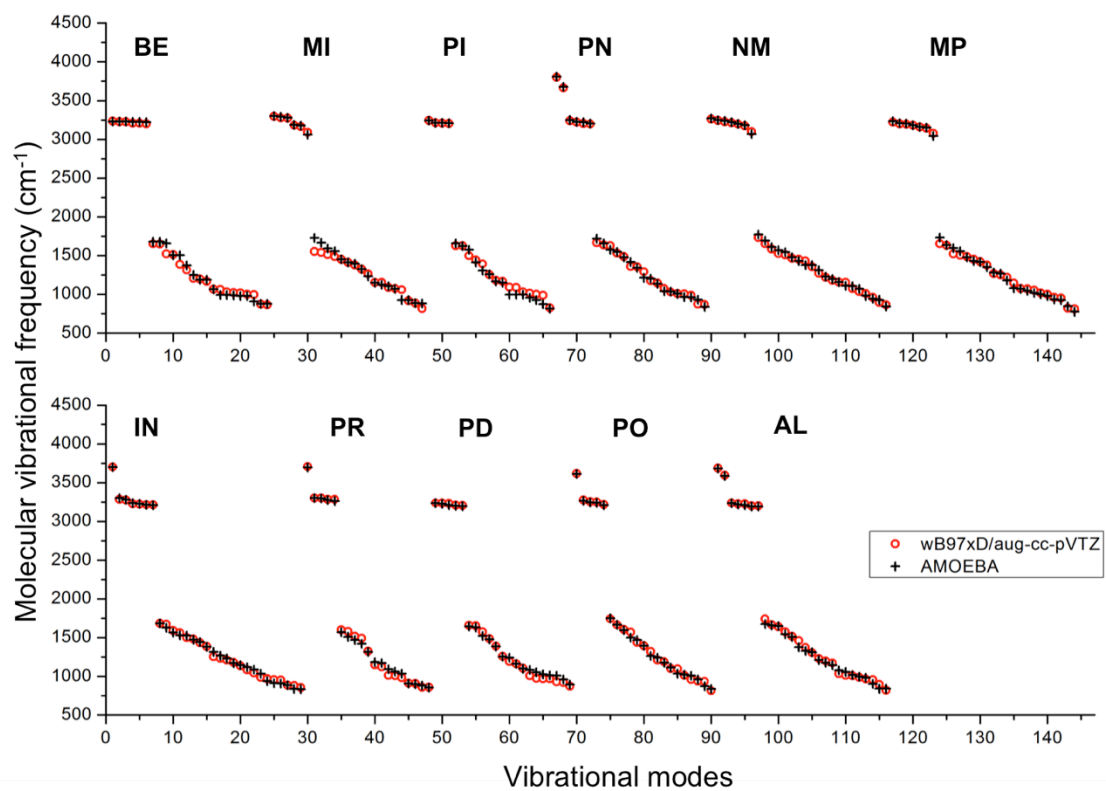
Figure S9. Benzen liquid structural properties. (A) Radial distribution function of benzene center-center distance. (B) Number distribution of benzene molecules in the first coordination shell as a function of the angle between the aromatic planes, θ (Figure 10A in maintext). The area under each curve represents the number of molecules in a given angular range for the coordination shells: 0−7.5, 0−5, and 5−6 Å. Experimental data are from Figures 4 and 11 of reference 43.
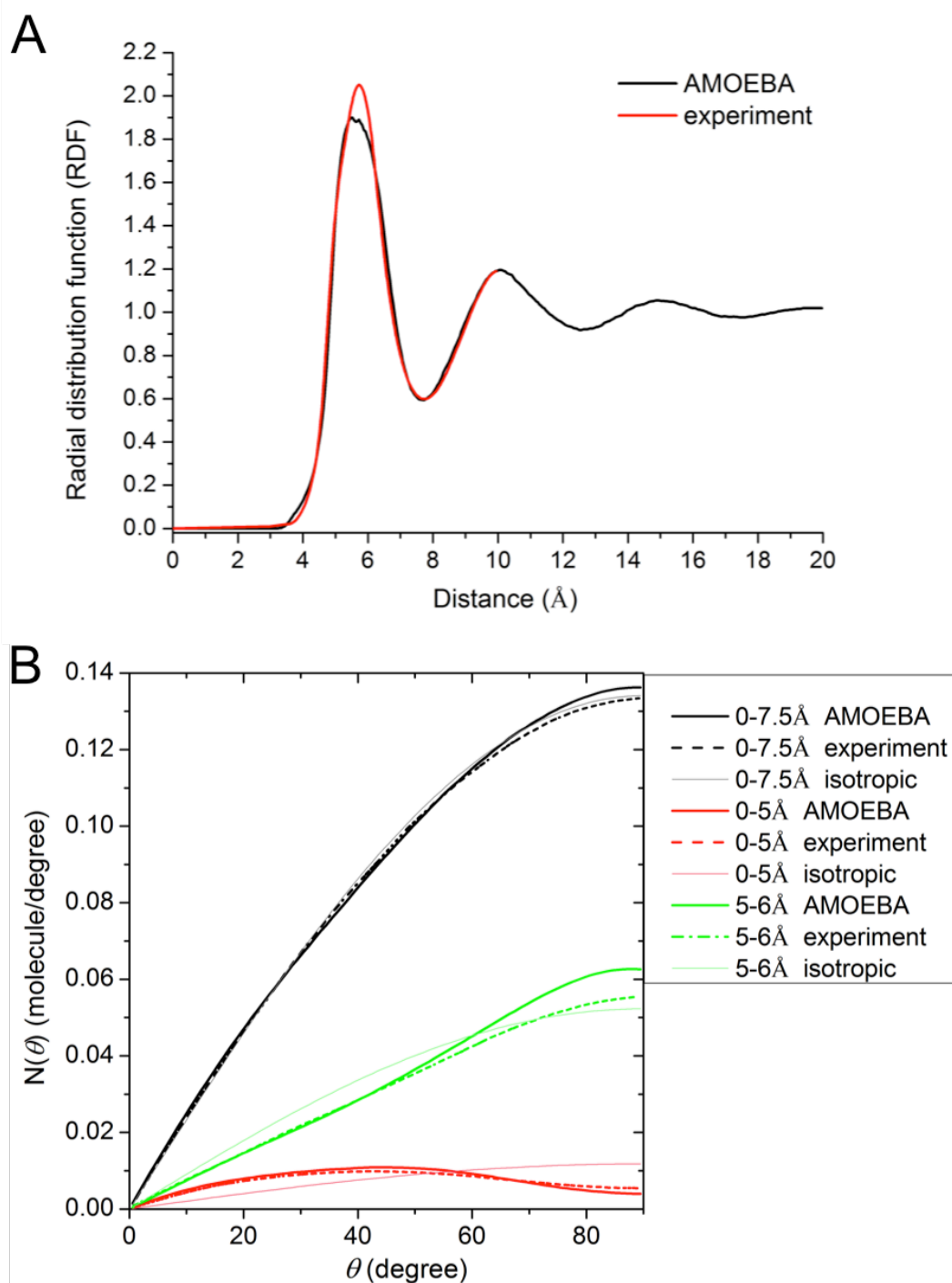
Figure S10. Comparison of stacking interaction energy computed for potential energy surfaces across rotations (Twist, Roll, Tilt) and translations (Rise, Slide, Shift) for the stacked adenine–cytosine dimer. See details about the dimer conformation in Sherrill's work (reference 35). QM results of SCS(MI)-MP2 and RIMP2 with cc-pVTZ basis set and MM force field results of AMBER FF14 and the new AMOEBA are showed.
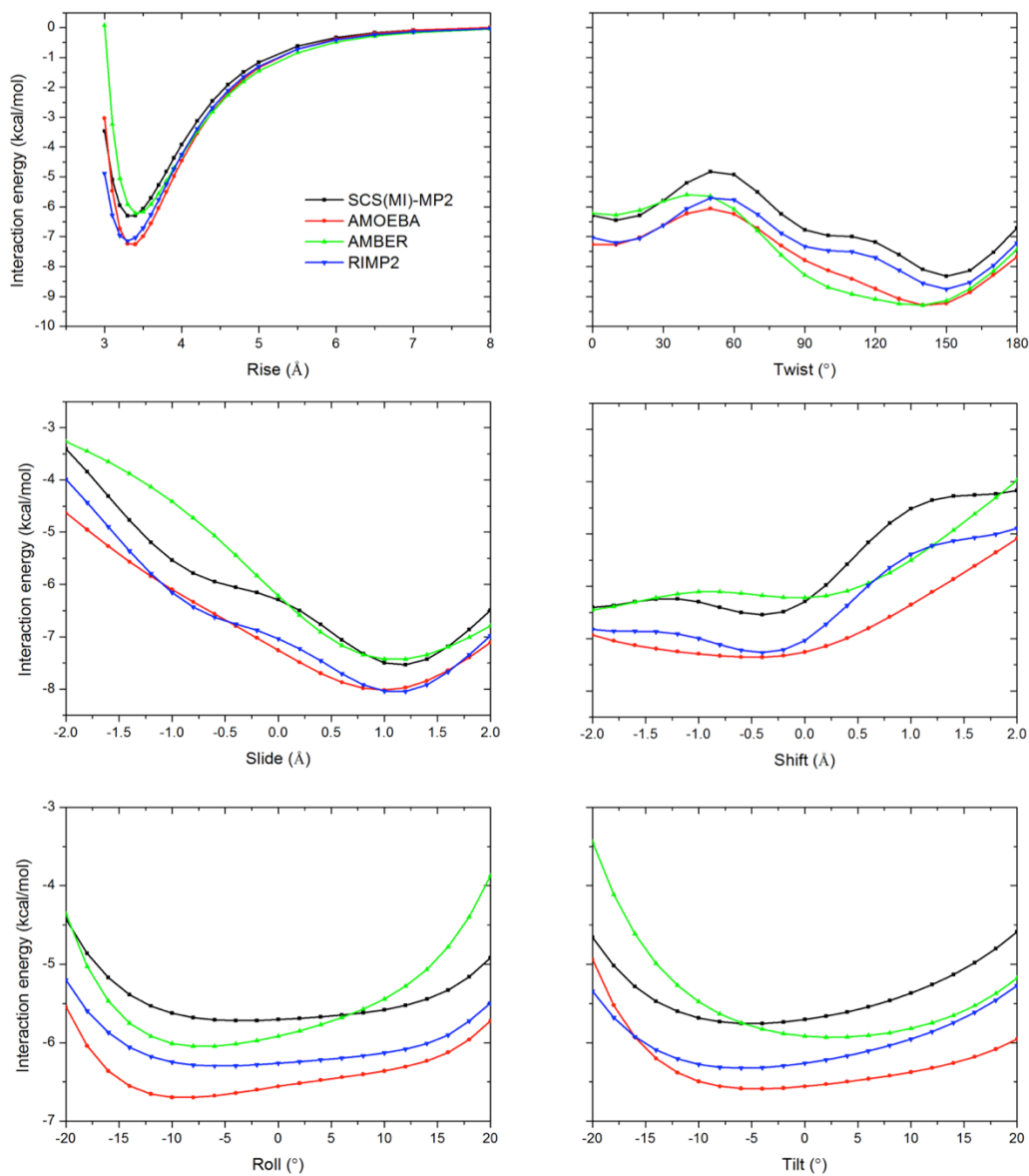
Figure S11. Base/base stacking energy using the structures in Sherrill's database. The AMOEBA and QM [SCS(MI)-MP2] interaction energies were compared for different type of conformation dimers.

(A) Rise-twist dimers
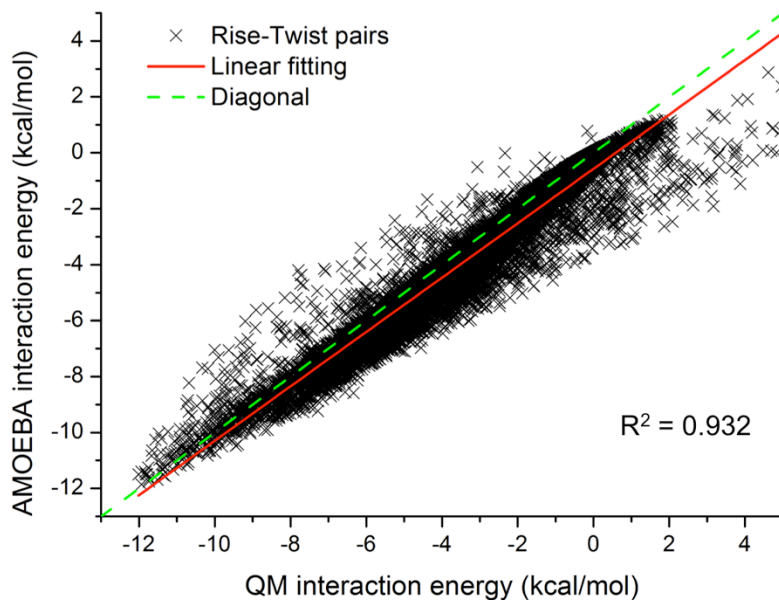
(B) Slide-shift dimers
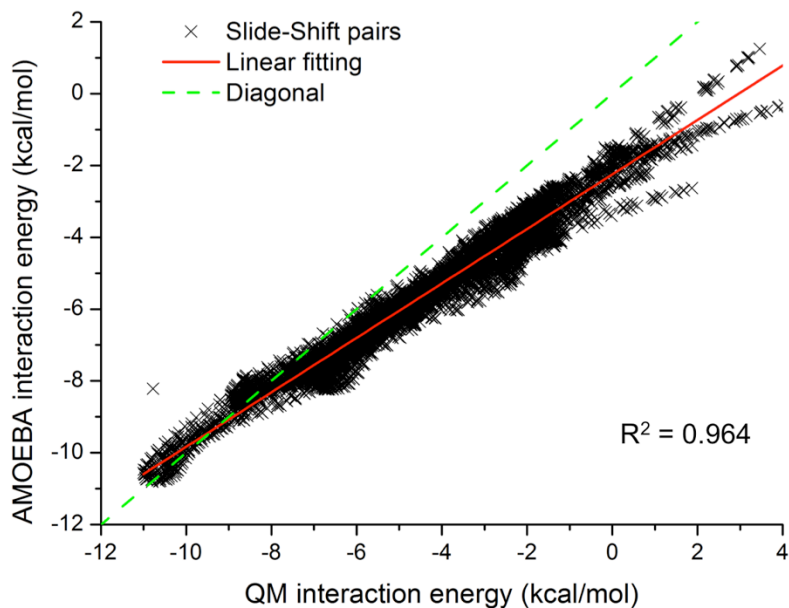
(C) Roll-Tilt dimers
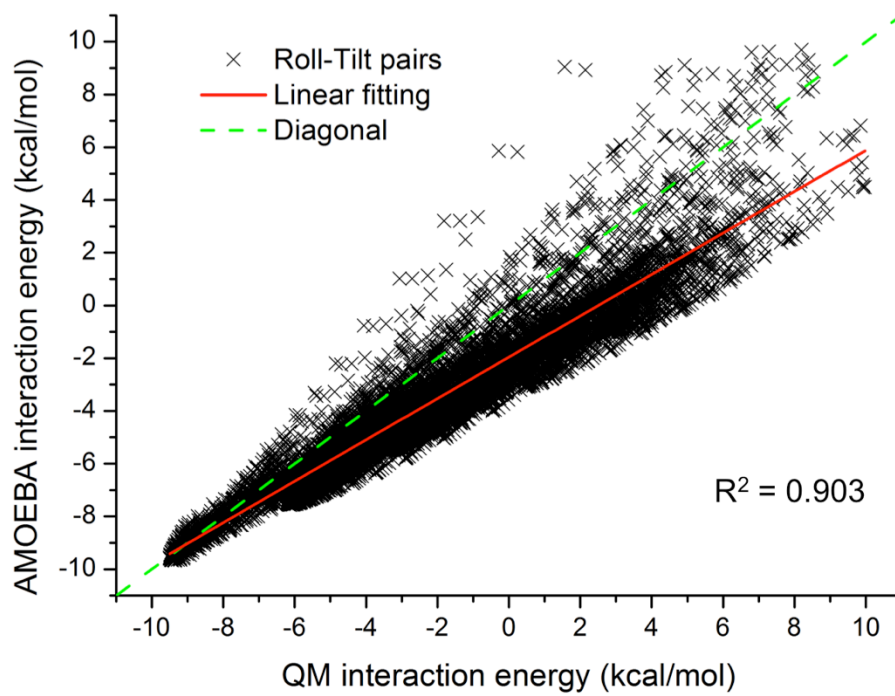
Figure S12. Nucleobases – metal ion interaction study. Na+, K+, and Mg++ are included. (A) Metal ion positions in the methylated neucleobases – metal ion dimers. (B) Interaction energy calculated using AMOEBA and MP2/6-311G**.
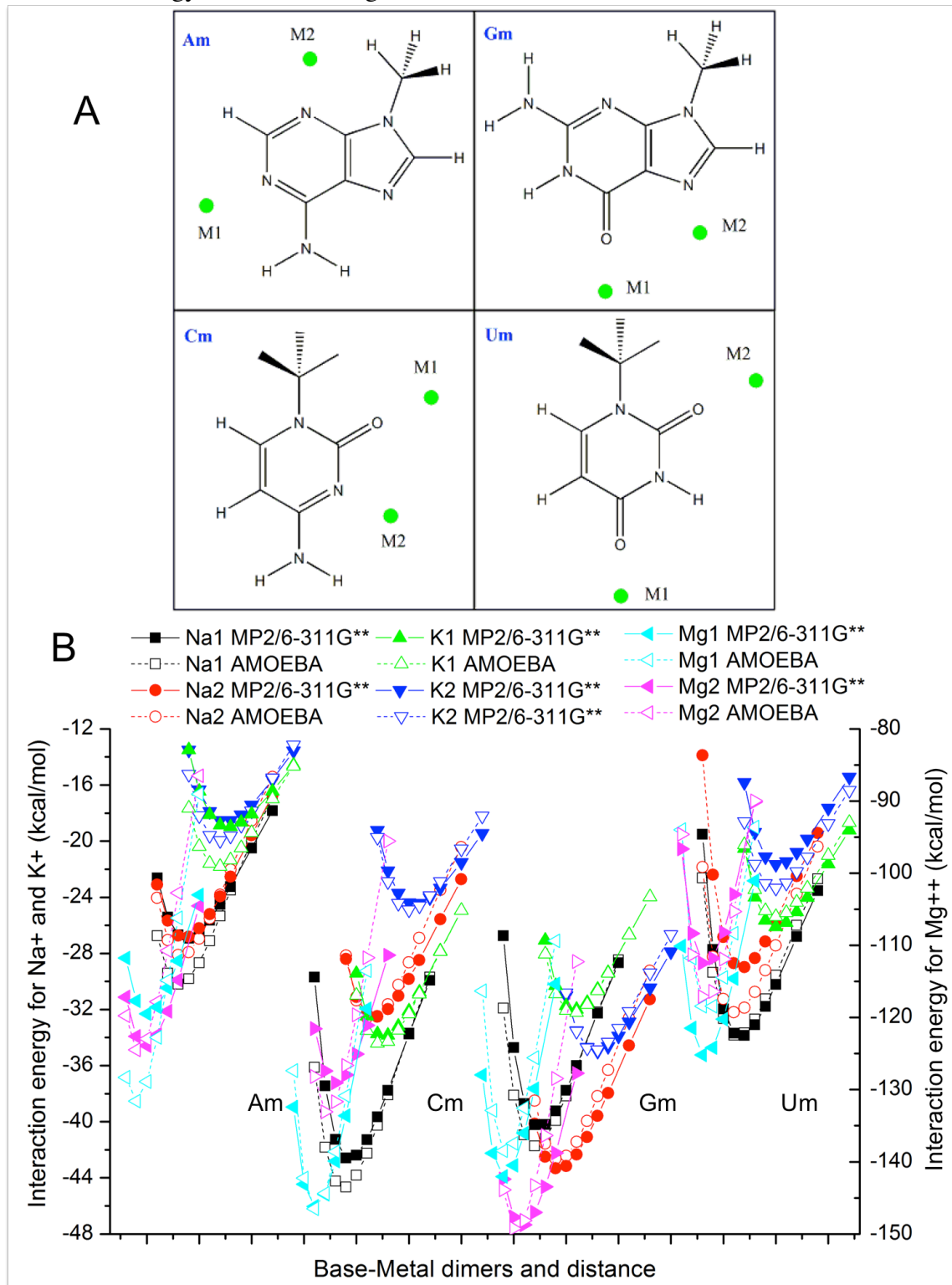
Table S1. The root mean square of the electrostatic grid potential (RMSP) between the QM and MM potential in the ESP fitting.

Aromatic molecules	RMSP (kcal/mol/e)	Nucleobases	RMSP (kcal/mol/e)
AL	0.2238	Am	0.1352
BE	0.0575	Ab	0.1328
IN	0.0693	Cm	0.2578
MI	0.0937	Cb	0.2811
ML	0.0946	Gm	0.4267
MP	0.0876	Gb	0.6637
NM	0.0867	Tm	0.1209
PD	0.0889	Tb	0.1333
PI	0.0604	Um	0.1254
PN	0.0696	Ub	0.1195
PO	0.0632		
PR	0.1021		

Table S2. Nucleic acid bases – water interaction energy comparison between QM (MP2/aug-cc-pVTZ) and AMOEBA force field model MM. (RMSE=0.69 kcal/mol). The distance value is the proportion to the equilibrium distance.

	Water	Distance	QM (kcal/mol)	MM (kcal/mol)	MM-QM
Am	Wat1	0.969	-9.774	-8.902	0.872
		1.000	-10.376	-10.039	0.337
		1.063	-10.219	-10.130	0.089
		1.126	-9.141	-8.931	0.210
		1.222	-7.073	-6.671	0.402
		1.318	-5.195	-4.745	0.450
		1.448	-3.340	-2.963	0.377
		1.578	-2.139	-1.872	0.267
	Wat2	0.970	-6.981	-7.362	-0.381
		1.000	-7.478	-8.026	-0.548
		1.060	-7.395	-7.771	-0.376
		1.121	-6.642	-6.712	-0.070
		1.212	-5.222	-4.996	0.226
		1.304	-3.940	-3.616	0.324
		1.428	-2.654	-2.349	0.305
		1.552	-1.791	-1.552	0.239
	Wat3	0.967	-8.042	-8.273	-0.231
		1.000	-8.836	-9.405	-0.569
		1.067	-8.933	-9.396	-0.463
		1.133	-8.055	-8.145	-0.090
		1.233	-6.265	-5.958	0.307
		1.334	-4.635	-4.196	0.439
		1.468	-3.039	-2.638	0.401
		1.602	-2.013	-1.713	0.300
	Wat4	0.973	-2.429	-2.156	0.273
		1.000	-2.306	-2.063	0.243
		1.054	-2.022	-1.817	0.205
		1.108	-1.739	-1.561	0.178
		1.190	-1.372	-1.225	0.147
		1.272	-1.086	-0.964	0.122
		1.382	-0.809	-0.714	0.096
		1.491	-0.618	-0.541	0.077
Cm	Wat1	0.969	-4.755	-4.397	0.358
		1.000	-5.315	-5.149	0.166
		1.062	-5.515	-5.403	0.112

		1.124	-5.105	-4.922	0.183
		1.217	-4.168	-3.909	0.259
		1.310	-3.282	-3.021	0.261
		1.433	-2.384	-2.170	0.214
		1.557	-1.771	-1.609	0.162
	Wat2	0.971	-4.871	-7.932	-3.061
		1.000	-6.160	-8.540	-2.380
		1.059	-7.050	-8.351	-1.301
		1.118	-6.774	-7.382	-0.607
		1.207	-5.634	-5.737	-0.103
		1.297	-4.427	-4.380	0.048
		1.419	-3.154	-3.107	0.047
		1.540	-2.283	-2.278	0.005
	Wat3	0.969	-9.302	-8.052	1.250
		1.000	-10.227	-9.730	0.497
		1.062	-10.429	-10.327	0.102
		1.124	-9.537	-9.318	0.219
		1.219	-7.635	-7.187	0.448
		1.314	-5.861	-5.341	0.520
		1.442	-4.080	-3.625	0.455
		1.571	-2.892	-2.549	0.343
	Wat4	0.972	-2.240	-2.456	-0.216
		1.000	-2.180	-2.333	-0.153
		1.057	-1.954	-2.022	-0.068
		1.113	-1.681	-1.710	-0.029
		1.199	-1.298	-1.312	-0.014
		1.285	-0.994	-1.013	-0.019
		1.400	-0.706	-0.733	-0.027
		1.515	-0.516	-0.547	-0.031
Gm	Wat1	0.969	-7.635	-4.567	3.068
		1.000	-8.483	-6.524	1.959
		1.063	-8.615	-7.622	0.993
		1.126	-7.721	-7.009	0.712
		1.222	-5.883	-5.279	0.604
		1.319	-4.213	-3.690	0.523
		1.450	-2.596	-2.216	0.380
		1.581	-1.577	-1.331	0.246
	Wat2	0.970	-7.052	-6.803	0.249
		1.000	-7.950	-7.834	0.116
		1.061	-8.386	-8.228	0.158
		1.123	-7.858	-7.563	0.295

		1.216	-6.475	-6.062	0.413
		1.310	-5.092	-4.685	0.408
		1.436	-3.644	-3.323	0.321
		1.563	-2.637	-2.409	0.229
	Wat3	0.966	-9.549	-6.523	3.026
		1.000	-10.621	-8.958	1.663
		1.069	-10.929	-10.398	0.531
		1.137	-10.032	-9.739	0.293
		1.240	-8.057	-7.704	0.354
		1.343	-6.194	-5.781	0.413
		1.480	-4.306	-3.932	0.374
		1.618	-3.035	-2.748	0.287
	Wat4	0.972	-6.123	-3.583	2.540
		1.000	-6.846	-5.168	1.678
		1.056	-7.039	-6.186	0.853
		1.113	-6.436	-5.875	0.561
		1.197	-5.158	-4.734	0.424
		1.282	-3.987	-3.627	0.361
		1.396	-2.824	-2.541	0.283
		1.510	-2.048	-1.832	0.216
	Wat5	0.971	-4.020	-2.632	1.388
		1.000	-3.939	-2.824	1.115
		1.057	-3.590	-2.819	0.771
		1.115	-3.155	-2.582	0.573
		1.201	-2.538	-2.139	0.399
		1.287	-2.036	-1.744	0.292
		1.402	-1.542	-1.339	0.203
		1.517	-1.195	-1.047	0.148
Tm	Wat1	0.967	-6.204	-6.190	0.014
		1.000	-6.711	-6.911	-0.200
		1.067	-6.746	-6.982	-0.236
		1.134	-6.124	-6.227	-0.103
		1.234	-4.866	-4.796	0.070
		1.334	-3.715	-3.574	0.141
		1.468	-2.571	-2.426	0.145
		1.602	-1.812	-1.694	0.118
	Wat2	0.969	-7.195	-5.559	1.636
		1.000	-8.079	-7.346	0.733
		1.062	-8.322	-8.263	0.059
		1.124	-7.568	-7.562	0.006
		1.217	-5.928	-5.765	0.163

		1.311	-4.398	-4.142	0.256
		1.435	-2.873	-2.626	0.247
		1.560	-1.876	-1.691	0.185
	Wat3	0.969	-5.686	-5.624	0.062
		1.000	-6.143	-6.179	-0.036
		1.061	-6.168	-6.128	0.040
		1.123	-5.604	-5.412	0.192
		1.215	-4.468	-4.141	0.327
		1.307	-3.429	-3.083	0.346
		1.430	-2.394	-2.101	0.293
		1.553	-1.703	-1.478	0.225
Um	Wat1	0.972	-3.420	-2.387	1.033
		1.000	-3.762	-2.978	0.784
		1.057	-3.901	-3.357	0.544
		1.114	-3.661	-3.201	0.460
		1.199	-3.085	-2.668	0.417
		1.285	-2.510	-2.141	0.369
		1.399	-1.901	-1.602	0.299
		1.514	-1.465	-1.230	0.235
	Wat2	0.969	-6.052	-6.892	-0.840
		1.000	-6.568	-7.510	-0.942
		1.061	-6.672	-7.427	-0.755
		1.123	-6.132	-6.548	-0.416
		1.215	-4.953	-4.982	-0.029
		1.307	-3.825	-3.676	0.149
		1.431	-2.666	-2.470	0.196
		1.554	-1.879	-1.710	0.169
	Wat3	0.966	-7.257	-7.281	-0.024
		1.000	-8.167	-8.761	-0.594
		1.067	-8.422	-9.190	-0.768
		1.134	-7.655	-8.156	-0.501
		1.235	-5.995	-6.073	-0.078
		1.336	-4.448	-4.313	0.135
		1.470	-2.915	-2.720	0.195
		1.604	-1.919	-1.756	0.163
	Wat4	0.967	-6.770	-5.528	1.242
		1.000	-7.684	-7.259	0.425
		1.067	-7.961	-8.110	-0.149
		1.134	-7.225	-7.385	-0.160
		1.234	-5.608	-5.590	0.018
		1.334	-4.111	-3.986	0.125

		1.468	-2.638	-2.501	0.137
		1.602	-1.690	-1.592	0.098
	Wat5	0.971	-1.658	-1.654	0.004
		1.000	-1.842	-1.928	-0.086
		1.058	-1.859	-2.002	-0.143
		1.117	-1.655	-1.792	-0.137
		1.206	-1.256	-1.367	-0.111
		1.296	-0.903	-0.995	-0.092
		1.417	-0.565	-0.641	-0.076
		1.539	-0.351	-0.413	-0.062

Table S3. Nucleic acid base pair energy comparison between QM (MP2/aug-cc-pVTZ) and AMOEBA force field model. (RMSE=1.58 kcal/mol). The distance value is the proportion to the equilibrium distance.

	Distance	QM(kcal/mol)	MM (kcal/mol)	MM-QM
AAcisWC	0.954	-4.678	-3.201	1.477
	1.000	-6.792	-7.208	-0.416
	1.061	-6.627	-7.130	-0.503
	1.138	-5.053	-5.092	-0.039
	1.255	-2.876	-2.674	0.203
AAtransWC	0.960	-10.683	-7.743	2.940
	1.000	-12.595	-12.170	0.425
	1.064	-12.322	-12.504	-0.182
	1.145	-9.777	-9.298	0.479
	1.266	-6.042	-5.226	0.816
AAtransWCH	0.960	-10.370	-7.726	2.644
	1.000	-12.231	-12.047	0.184
	1.062	-11.901	-12.158	-0.257
	1.140	-9.408	-9.069	0.339
	1.258	-5.768	-5.130	0.638
AAtransHH	0.960	-9.932	-8.914	1.018
	1.000	-11.459	-12.015	-0.556
	1.060	-11.103	-11.751	-0.648
	1.135	-8.863	-8.917	-0.054
	1.249	-5.501	-5.190	0.311
TAcisWC	0.934	-13.872	-13.941	-0.069
	1.000	-13.962	-15.125	-1.163
	1.083	-11.180	-11.616	-0.436
	1.207	-6.867	-6.630	0.237
	1.300	-4.692	-4.414	0.278
CAtransWC	0.960	-13.032	-8.386	4.646
	1.000	-15.357	-13.942	1.416
	1.058	-15.341	-15.362	-0.021
	1.133	-12.590	-12.115	0.476
	1.246	-8.274	-7.364	0.910
CAtransWCH	0.960	-13.252	-8.400	4.852
	1.000	-15.550	-14.088	1.463
	1.066	-15.421	-15.374	0.047
	1.148	-12.661	-12.220	0.441
	1.271	-8.263	-7.408	0.856

	0.960	-14.418	-10.486	3.932
GAcisWC	1.000	-16.767	-16.072	0.695
	1.069	-16.665	-17.125	-0.460
	1.157	-13.765	-13.608	0.157
	1.287	-9.179	-8.499	0.680
	0.928	-16.334	-15.453	0.881
GAcisWCH	1.000	-16.500	-16.941	-0.441
	1.090	-13.128	-12.981	0.147
	1.224	-8.051	-7.541	0.510
	1.300	-6.000	-5.548	0.452
	0.944	-11.744	-10.134	1.610
GAcisWCS	1.000	-14.088	-14.117	-0.029
	1.075	-13.691	-13.742	-0.051
	1.168	-11.230	-10.792	0.438
	1.308	-7.436	-6.749	0.687
	0.960	-6.654	-4.948	1.706
GAtransSS	1.000	-7.764	-7.201	0.563
	1.054	-7.619	-7.643	-0.024
	1.123	-5.791	-5.545	0.246
	1.230	-3.336	-2.959	0.377
	0.938	-15.116	-13.180	1.936
AUcisWCH	1.000	-15.119	-15.311	-0.192
	1.077	-12.199	-12.275	-0.076
	1.193	-7.656	-7.370	0.286
	1.250	-6.071	-5.811	0.260
	0.934	-13.978	-13.996	-0.018
UAcisWC	1.000	-14.099	-15.307	-1.208
	1.082	-11.318	-11.787	-0.469
	1.206	-6.982	-6.758	0.224
	1.300	-4.785	-4.518	0.267
	0.934	-13.503	-13.459	0.044
UAtransWC	1.000	-13.623	-14.801	-1.178
	1.083	-10.882	-11.417	-0.535
	1.207	-6.631	-6.532	0.099
	1.300	-4.504	-4.342	0.162
	0.951	-5.313	-2.954	2.359
UAcisWCH	1.000	-8.102	-8.101	0.001
	1.065	-8.111	-8.440	-0.329
	1.147	-6.400	-6.360	0.040
	1.270	-3.920	-3.667	0.253
UAtransWCH	0.938	-14.880	-13.290	1.590

	1.000	-14.899	-15.241	-0.342
	1.077	-12.004	-12.165	-0.161
	1.194	-7.509	-7.284	0.225
	1.300	-4.812	-4.592	0.220
UAcisWCS	0.946	-6.072	-4.868	1.204
	1.000	-10.067	-11.098	-1.031
	1.072	-10.173	-11.228	-1.055
	1.162	-7.840	-8.283	-0.443
	1.298	-4.481	-4.525	-0.044
UAtransWCS	0.925	-3.674	0.518	4.192
	1.000	-10.524	-10.904	-0.380
	1.068	-10.508	-11.173	-0.665
	1.154	-8.284	-8.517	-0.233
	1.282	-5.001	-4.911	0.090
CCcisWCH	0.942	-6.766	-3.357	3.409
	1.000	-10.180	-9.246	0.934
	1.078	-10.579	-10.313	0.266
	1.176	-8.833	-8.378	0.455
	1.322	-5.973	-5.422	0.552
CCtransWCH	0.938	-10.028	-9.802	0.226
	1.000	-10.130	-10.194	-0.064
	1.077	-8.674	-8.417	0.257
	1.193	-6.285	-5.798	0.487
	1.250	-5.345	-4.853	0.492
CGcisWC	0.920	-26.054	-19.398	6.656
	1.000	-27.889	-26.502	1.387
	1.100	-22.869	-21.333	1.536
	1.250	-14.901	-13.120	1.781
	1.300	-12.879	-11.207	1.672
CGtransWC	0.946	-10.731	-2.419	8.312
	1.000	-17.068	-14.518	2.550
	1.072	-17.948	-17.220	0.728
	1.162	-14.973	-14.154	0.819
	1.298	-10.007	-9.083	0.924
CGtransWCS	0.957	-15.496	-12.700	2.796
	1.000	-15.565	-14.802	0.763
	1.056	-12.824	-12.053	0.771
	1.142	-8.470	-7.518	0.952
	1.250	-6.373	-5.440	0.933
GGtransWC	0.930	-26.435	-22.381	4.054
	1.000	-26.928	-25.294	1.634

	1.088	-22.914	-21.311	1.603
	1.221	-15.632	-14.037	1.595
	1.300	-11.976	-10.588	1.388
GGcisWCH	0.920	-25.611	-20.043	5.568
	1.000	-26.927	-25.294	1.633
	1.100	-22.067	-20.440	1.627
	1.250	-14.029	-12.490	1.539
	1.300	-11.975	-10.586	1.389
GGtransWCH	0.934	-19.108	-13.511	5.597
	1.000	-19.477	-16.850	2.627
	1.082	-16.548	-14.628	1.920
	1.205	-11.670	-10.090	1.580
	1.300	-8.994	-7.674	1.320
GUtransWCH	0.942	-8.338	-2.702	5.637
	1.000	-14.015	-13.184	0.831
	1.077	-14.719	-14.828	-0.109
	1.174	-12.090	-11.698	0.392
	1.320	-7.872	-7.212	0.660
UGcisWC	0.953	-15.009	-13.238	1.771
	1.000	-15.433	-15.734	-0.301
	1.060	-12.711	-12.888	-0.177
	1.153	-8.219	-8.017	0.202
	1.250	-6.190	-6.087	0.103
UGtransWC	1.261	-16.511	-14.238	2.273
	1.000	-16.980	-17.045	-0.065
	1.060	-14.149	-14.033	0.116
	1.153	-9.404	-8.844	0.560
	1.250	-7.268	-6.848	0.420
UGcisWCH	0.929	-8.814	-7.173	1.641
	1.000	-8.801	-8.506	0.295
	1.063	-6.934	-6.871	0.063
	1.250	-4.349	-4.244	0.105
UGtransWCH	0.937	-9.386	-7.629	1.757
	1.000	-9.538	-9.229	0.309
	1.079	-7.488	-7.310	0.178
	1.198	-4.436	-4.184	0.252
	1.250	-3.479	-3.233	0.246
UGcisWCS	0.960	-12.468	-9.701	2.767
	1.000	-14.137	-13.467	0.670
	1.068	-13.785	-14.040	-0.255
	1.153	-11.258	-11.229	0.029

	1.281	-7.334	-6.903	0.431
TUcisWC	0.953	-11.189	-10.689	0.500
	1.000	-11.566	-12.375	-0.809
	1.060	-9.282	-9.824	-0.542
	1.151	-5.633	-5.726	-0.093
	1.250	-3.967	-4.120	-0.153
TGtransWC	0.953	-16.248	-13.022	3.226
	1.000	-16.672	-16.072	0.600
	1.060	-13.840	-13.346	0.494
	1.153	-9.135	-8.400	0.735
	1.250	-7.003	-6.477	0.526
CUcisWCH	0.936	-11.471	-11.082	0.389
	1.000	-11.779	-12.331	-0.552
	1.080	-9.803	-9.924	-0.121
	1.201	-6.604	-6.306	0.298
	1.300	-4.866	-4.475	0.392
UUcisWC	0.953	-11.181	-11.395	-0.214
	1.000	-11.596	-12.855	-1.258
	1.060	-9.322	-10.109	-0.787
	1.151	-5.666	-5.864	-0.198
	1.250	-3.992	-4.195	-0.203
UUtransWC	0.953	-11.527	-12.154	-0.626
	1.000	-11.957	-13.481	-1.524
	1.060	-9.641	-10.510	-0.869
	1.151	-5.897	-6.053	-0.156
	1.250	-4.187	-4.323	-0.136
UUcisWCH	0.928	-7.633	-7.170	0.463
	1.000	-8.276	-9.070	-0.794
	1.090	-6.174	-6.634	-0.460
	1.224	-3.272	-3.403	-0.131
	1.300	-2.277	-2.377	-0.100
UUtransWCH	0.944	-8.528	-8.666	-0.138
	1.000	-8.833	-9.683	-0.850
	1.070	-7.063	-7.518	-0.454
	1.177	-4.326	-4.356	-0.030
	1.250	-3.313	-3.356	-0.043

Table S4. Aromatic molecules – water interaction energy comparison between QM (MP2/aug-cc-pVTZ) and AMOEBA force field model MM. (RMSE=0.73 kcal/mol). The distance value is the proportion to the equilibrium distance.

Molecule	Water	Distance	QM (kcal/mol)	MM (kcal/mol)	MM-QM
AL	Wat1	0.920	-3.428	-3.675	-0.247
		1.000	-3.863	-3.981	-0.118
		1.100	-3.238	-3.126	0.112
		1.250	-2.086	-1.899	0.187
	Wat2	0.913	-3.425	-2.824	0.601
		1.000	-4.043	-3.696	0.347
		1.087	-3.607	-3.289	0.318
		1.196	-2.763	-2.468	0.295
		1.329	-1.735	-1.518	0.217
IN	Wat1	0.920	-4.779	-3.841	0.938
		1.000	-5.509	-5.229	0.280
		1.100	-4.573	-4.332	0.241
		1.250	-2.936	-2.687	0.249
	Wat2	0.920	-2.266	-2.106	0.160
		1.000	-2.439	-2.385	0.054
		1.100	-2.027	-1.929	0.098
		1.250	-1.303	-1.189	0.114
	Wat3	0.913	-3.019	-1.443	1.576
		1.000	-3.942	-3.157	0.785
		1.087	-3.658	-3.131	0.527
		1.196	-2.906	-2.526	0.380
		1.359	-1.923	-1.682	0.241
MI	Wat1	0.920	-6.382	-5.650	0.732
		1.000	-7.137	-7.262	-0.125
		1.100	-5.884	-5.888	-0.003
		1.250	-3.746	-3.578	0.168
	Wat2	0.920	-2.775	-3.240	-0.465
		1.000	-2.959	-3.167	-0.208
		1.100	-2.496	-2.485	0.011
		1.250	-1.693	-1.600	0.093
	Wat3	0.920	-4.224	-3.414	0.810
		1.000	-4.065	-3.718	0.347
		1.100	-3.237	-3.021	0.216
		1.250	-2.072	-1.918	0.154
	Wat4	0.907	-1.021	2.320	3.341

		1.000	-2.623	-1.520	1.103
		1.093	-2.494	-2.060	0.434
		1.187	-1.963	-1.735	0.228
		1.303	-1.338	-1.206	0.132
MP	Wat1	0.920	-1.629	-1.984	-0.355
		1.000	-1.828	-1.942	-0.114
		1.100	-1.512	-1.461	0.051
		1.250	-0.969	-0.885	0.084
	Wat2	0.920	-2.043	-2.362	-0.319
		1.000	-2.125	-2.277	-0.152
		1.100	-1.726	-1.734	-0.008
		1.250	-1.121	-1.078	0.043
NM	Wat1	0.920	-6.784	-7.620	-0.836
		1.000	-7.278	-8.075	-0.797
		1.100	-6.127	-6.414	-0.287
		1.250	-4.065	-3.986	0.079
	Wat2	0.919	-2.791	-2.009	0.782
		1.000	-3.136	-2.693	0.444
		1.101	-2.631	-2.240	0.391
		1.253	-1.756	-1.435	0.321
	Wat3	0.920	-7.354	-6.820	0.534
		1.000	-7.818	-7.759	0.059
		1.100	-6.399	-6.214	0.185
		1.250	-4.082	-3.824	0.258
	Wat4	0.913	-1.914	-1.038	0.876
		1.000	-2.143	-1.667	0.476
		1.088	-1.761	-1.409	0.352
		1.176	-1.331	-1.058	0.273
		1.287	-0.919	-0.721	0.198
PN	Wat1	0.920	-8.055	-9.271	-1.216
		1.000	-8.439	-9.434	-0.995
		1.100	-6.941	-7.171	-0.230
		1.250	-4.380	-4.124	0.256
	Wat2	0.920	-4.018	-3.998	0.020
		1.000	-4.218	-4.152	0.066
		1.100	-3.394	-3.195	0.199
		1.250	-2.145	-1.941	0.204
	Wat3	0.913	-2.136	-0.785	1.351
		1.000	-2.632	-2.001	0.631
		1.087	-2.328	-1.947	0.381
		1.196	-1.748	-1.500	0.249

		1.359	-1.056	-0.923	0.133
PO	Wat1	0.920	-9.915	-9.745	0.170
		1.000	-10.491	-11.013	-0.522
		1.100	-8.851	-8.981	-0.130
		1.250	-5.873	-5.565	0.308
	Wat2	0.920	-6.661	-8.206	-1.545
		1.000	-7.175	-8.290	-1.115
		1.100	-6.065	-6.434	-0.369
		1.250	-4.045	-3.933	0.112
	Wat3	0.909	-1.694	0.150	1.844
		1.000	-2.451	-1.686	0.766
		1.091	-2.157	-1.738	0.419
		1.182	-1.680	-1.403	0.277
		1.297	-1.179	-0.999	0.180
PD	Wat1	0.920	-2.098	-2.092	0.006
		1.000	-2.146	-2.147	-0.001
		1.100	-1.767	-1.721	0.046
		1.250	-1.189	-1.127	0.062
	Wat2	0.920	-5.764	-5.551	0.213
		1.000	-6.254	-6.593	-0.339
		1.100	-5.027	-5.140	-0.113
		1.250	-3.086	-2.996	0.090
	Wat3	0.910	-1.500	0.013	1.513
		1.000	-2.330	-1.801	0.529
		1.090	-2.086	-1.823	0.263
		1.181	-1.640	-1.468	0.172
		1.294	-1.160	-1.048	0.112
BE	Wat1	0.920	-1.203	-1.114	0.089
		1.000	-1.369	-1.383	-0.014
		1.100	-1.076	-1.050	0.026
		1.250	-0.636	-0.593	0.044
	Wat2	0.913	-2.722	-1.098	1.625
		1.000	-3.212	-2.513	0.699
		1.087	-2.837	-2.451	0.387
		1.196	-2.146	-1.909	0.236
		1.359	-1.325	-1.195	0.131
PI	Wat1	0.920	-5.136	-3.914	1.223
		1.000	-5.690	-5.360	0.330
		1.100	-4.579	-4.360	0.219
		1.250	-2.774	-2.565	0.209
	Wat2	0.920	-4.671	-4.022	0.649

		1.000	-5.230	-5.213	0.017
		1.100	-4.190	-4.113	0.077
		1.250	-2.499	-2.341	0.158
	Wat3	0.910	-1.364	-0.524	0.840
		1.000	-1.773	-1.492	0.281
		1.090	-1.492	-1.339	0.153
		1.180	-1.132	-1.028	0.104
		1.292	-0.780	-0.718	0.062
PR	Wat1	0.860	-4.004	-3.005	0.999
		1.000	-4.370	-4.199	0.171
		1.140	-2.807	-2.629	0.178
		1.326	-1.528	-1.411	0.117
	Wat2	0.920	-4.177	-3.604	0.573
		1.000	-4.117	-3.749	0.369
		1.100	-3.323	-3.016	0.307
		1.250	-2.159	-1.944	0.215
	Wat3	0.913	-2.428	2.092	4.520
		1.000	-4.124	-2.292	1.832
		1.087	-4.052	-3.239	0.813
		1.196	-3.280	-2.901	0.379
		1.359	-2.147	-1.965	0.182

Table S5. MP2/cc-pVTZ and AMOEBA energy of the ten stacked nucleobase dimers at equilibrium distance compared with the reference energy (reference 79) using a complete basis set (CBS(T)).

Stacking base pair	CBS(T)	RIMP2/cc-pVTZ	AMOEBA
AA	-8.5	-9.63	-8.95
AC	-10.2	-10.38	-10.09
AU	-9.8	-9.87	-9.93
CC	-10	-9.15	-9.35
CG	-10.6	-10.37	-10.94
CU	-10.4	-9.28	-9.40
GA	-11.4	-12.01	-11.27
GG	-12.7	-12.69	-12.72
GU	-12.1	-11.44	-11.47
UU	-7.5	-7.15	-7.87
RMSE	-	0.654	0.482

Table S6. Nucleic acid base/base stacking energy comparison between QM (MP2/cc-pVTZ) and AMOEBA force field model MM. (RMSE=1.64 kcal/mol). The distance value is the proportion to the equilibrium distance.

Stacking	Distance	QM (kcal/mol)	MM (kcal/mol)	MM-QM
AA1	0.950	-9.511	-4.202	5.309
	1.000	-11.571	-9.463	2.108
	1.072	-11.441	-11.293	0.148
	1.181	-8.864	-9.306	-0.442
	1.290	-6.185	-6.596	-0.411
AA2	0.930	-9.726	-9.235	0.491
	1.000	-11.425	-12.037	-0.612
	1.106	-9.570	-10.211	-0.641
	1.211	-6.843	-7.285	-0.442
	1.352	-4.069	-4.352	-0.283
AG1	0.913	-13.662	-9.056	4.606
	1.000	-14.889	-14.435	0.454
	1.087	-12.390	-12.626	-0.236
	1.203	-8.719	-8.930	-0.211
	1.300	-6.569	-6.705	-0.136
AG2	0.912	-8.195	-4.420	3.775
	1.000	-11.298	-11.349	-0.051
	1.088	-9.609	-10.023	-0.414
	1.205	-6.504	-6.741	-0.237
	1.300	-4.572	-4.693	-0.121
AG3	0.950	-7.665	-3.167	4.498
	1.000	-10.758	-9.537	1.221
	1.085	-10.639	-10.817	-0.178
	1.169	-8.449	-8.673	-0.224
	1.283	-5.626	-5.737	-0.111
AG4	0.916	-10.958	-9.637	1.322
	1.000	-11.224	-11.552	-0.328
	1.084	-9.077	-9.471	-0.394
	1.197	-6.147	-6.358	-0.211
	1.300	-4.330	-4.422	-0.092
GG1	0.915	-16.370	-12.241	4.129
	1.000	-16.696	-16.326	0.370
	1.086	-13.899	-14.203	-0.304
	1.200	-9.960	-10.210	-0.250
	1.300	-7.460	-7.581	-0.121
GG2	0.950	-19.041	-15.370	3.671

	1.000	-21.190	-20.493	0.697
	1.083	-20.015	-20.607	-0.592
	1.194	-15.808	-16.193	-0.385
	1.300	-12.122	-12.216	-0.094
AC1	0.920	-8.597	-8.141	0.456
	1.000	-9.063	-9.510	-0.447
	1.080	-7.417	-7.710	-0.293
	1.188	-5.087	-5.141	-0.054
	1.300	-3.482	-3.417	0.065
AC2	0.921	-7.643	-4.877	2.766
	1.000	-10.253	-10.935	-0.682
	1.079	-9.125	-10.037	-0.912
	1.183	-6.580	-7.082	-0.502
	1.300	-4.314	-4.524	-0.210
AT1	0.937	-6.618	-2.877	3.741
	1.000	-11.273	-10.723	0.550
	1.094	-11.389	-11.939	-0.550
	1.188	-9.111	-9.599	-0.488
	1.314	-6.103	-6.373	-0.269
AT2	0.915	-8.121	-6.377	1.745
	1.000	-9.722	-10.034	-0.312
	1.085	-8.098	-8.533	-0.435
	1.200	-5.432	-5.688	-0.256
	1.300	-3.898	-4.039	-0.141
GC1	0.907	-15.094	-13.149	1.945
	1.000	-15.582	-15.948	-0.366
	1.094	-12.814	-13.337	-0.523
	1.218	-8.943	-9.256	-0.313
	1.300	-7.068	-7.274	-0.206
GC2	0.912	-12.494	-10.197	2.298
	1.000	-17.023	-18.409	-1.386
	1.088	-15.438	-16.999	-1.561
	1.206	-11.552	-12.606	-1.054
	1.300	-8.985	-9.750	-0.765
GT1	0.907	-13.162	-9.524	3.638
	1.000	-14.223	-13.703	0.520
	1.093	-11.759	-11.713	0.046
	1.218	-8.224	-8.154	0.070
	1.300	-6.504	-6.400	0.104
GT2	0.925	-9.256	-5.425	3.831
	1.000	-11.986	-11.530	0.456

	1.075	-10.663	-10.853	-0.189
	1.176	-7.788	-7.921	-0.133
	1.300	-5.365	-5.457	-0.092
CC1	0.950	-13.152	-9.670	3.482
	1.000	-14.534	-13.419	1.115
	1.096	-13.645	-13.811	-0.166
	1.223	-10.420	-10.519	-0.099
	1.300	-8.572	-8.561	0.011
CC2	0.904	-7.879	-5.395	2.484
	1.000	-16.742	-18.959	-2.217
	1.096	-16.999	-18.758	-1.759
	1.223	-13.418	-13.611	-0.193
	1.300	-11.050	-10.736	0.314
CT1	0.913	-8.254	-6.176	2.078
	1.000	-11.957	-12.519	-0.562
	1.088	-10.792	-11.542	-0.750
	1.205	-7.886	-8.382	-0.496
	1.300	-6.046	-6.327	-0.281
CT2	0.923	-4.008	1.132	5.140
	1.000	-9.309	-9.375	-0.066
	1.077	-8.651	-9.893	-1.242
	1.180	-6.012	-6.995	-0.983
	1.300	-3.585	-4.238	-0.653
TT1	0.916	-4.695	-1.062	3.633
	1.000	-8.661	-9.314	-0.653
	1.085	-7.903	-9.376	-1.473
	1.199	-5.455	-6.462	-1.007
	1.300	-3.524	-4.094	-0.570
TT2	0.929	-5.089	-3.363	1.726
	1.000	-9.949	-10.920	-0.971
	1.106	-9.840	-11.008	-1.168
	1.212	-7.568	-8.243	-0.675
	1.353	-4.872	-5.150	-0.278
AU1	0.939	-6.133	-1.949	4.184
	1.000	-9.270	-8.375	0.895
	1.093	-8.801	-9.085	-0.284
	1.186	-6.788	-7.127	-0.339
	1.311	-4.402	-4.628	-0.226
AU2	0.909	-6.713	-5.409	1.304
	1.000	-7.779	-8.307	-0.528
	1.091	-6.223	-6.885	-0.662

	1.212	-3.941	-4.435	-0.494
	1.300	-2.806	-3.210	-0.404
GU1	0.912	-13.428	-11.673	1.755
	1.000	-14.516	-15.167	-0.651
	1.088	-12.078	-12.834	-0.756
	1.206	-8.493	-8.960	-0.466
	1.300	-6.372	-6.664	-0.292
GU2	0.931	-4.281	-5.328	-1.047
	1.000	-6.170	-7.398	-1.228
	1.069	-5.793	-6.610	-0.817
	1.163	-4.441	-4.811	-0.370
	1.300	-2.789	-2.934	-0.145
CU1	1.000	-9.545	-5.680	3.865
	1.084	-9.457	-9.032	0.425
	1.195	-6.577	-6.691	-0.114
	1.300	-4.175	-4.247	-0.072
CU2	0.950	-8.729	-1.885	6.844
	1.000	-11.020	-9.090	1.931
	1.089	-10.305	-10.510	-0.205
	1.208	-7.153	-7.344	-0.191
	1.300	-5.009	-5.030	-0.021
TU1	0.910	-8.501	-4.860	3.641
	1.000	-11.113	-11.394	-0.280
	1.090	-9.466	-10.272	-0.806
	1.210	-6.485	-7.068	-0.583
	1.300	-4.725	-5.116	-0.391
TU2	0.922	-6.961	-4.769	2.192
	1.000	-9.040	-9.954	-0.914
	1.079	-7.782	-9.013	-1.231
	1.184	-5.375	-6.254	-0.879
	1.300	-3.434	-4.001	-0.567
UU1	0.916	-5.196	-3.054	2.143
	1.000	-8.383	-9.155	-0.772
	1.084	-7.496	-8.581	-1.085
	1.196	-5.255	-6.032	-0.777
	1.300	-3.577	-4.105	-0.528
UU2	0.924	-4.623	-0.400	4.223
	1.000	-9.161	-9.519	-0.358
	1.077	-8.696	-10.107	-1.411
	1.181	-6.320	-7.340	-1.020
	1.300	-4.046	-4.579	-0.533

Table S7. Aromatic ring stacking energy comparison between QM (MP2/cc-pVTZ) and AMOEBA force field model. (RMSE=1.07 kcal/mol). The distance value is the proportion to the equilibrium distance.

Stacking	Distance	QM (kcal/mol)	MM (kcal/mol)	MM-QM
ALAL1	0.929	-2.811	-1.367	1.444
	1.000	-6.175	-6.501	-0.326
	1.106	-6.105	-6.462	-0.357
	1.212	-4.521	-4.607	-0.086
	1.353	-2.703	-2.680	0.023
ALAL2	0.937	-3.184	-3.559	-0.375
	1.000	-4.245	-4.742	-0.497
	1.076	-3.960	-4.293	-0.333
	1.190	-2.705	-2.886	-0.181
	1.304	-1.605	-1.762	-0.157
ALAL3	0.929	-1.631	-0.752	0.879
	1.000	-3.330	-3.130	0.200
	1.106	-3.567	-3.480	0.087
	1.212	-2.945	-2.797	0.148
	1.353	-2.040	-1.877	0.164
ININ1	0.943	-6.843	-5.718	1.126
	1.000	-7.036	-6.452	0.584
	1.068	-5.989	-5.579	0.410
	1.171	-4.041	-3.724	0.317
	1.274	-2.508	-2.312	0.196
ININ2	0.950	-4.830	-4.587	0.243
	1.000	-4.965	-4.965	0.000
	1.050	-4.541	-4.438	0.103
	1.110	-3.528	-3.380	0.148
	1.203	-2.106	-2.002	0.104
ININ3	0.950	-6.417	1.193	7.610
	1.000	-8.115	-4.075	4.040
	1.106	-7.778	-6.512	1.266
	1.212	-5.991	-5.337	0.654
	1.353	-3.901	-3.474	0.427
MIMI1	0.929	-5.535	-2.029	3.506
	1.000	-8.364	-7.853	0.511
	1.106	-8.135	-8.500	-0.365
	1.212	-6.462	-6.727	-0.265

	1.353	-4.390	-4.499	-0.109
MIMI2	0.932	-6.385	-4.404	1.981
	1.000	-6.900	-6.365	0.535
	1.102	-5.685	-5.643	0.042
	1.204	-4.177	-4.178	-0.001
	1.340	-2.692	-2.689	0.003
MIMI3	0.907	-4.473	-2.030	2.443
	1.000	-4.828	-4.437	0.391
	1.093	-3.863	-3.886	-0.023
	1.216	-2.591	-2.649	-0.058
	1.300	-1.994	-2.029	-0.035
MPMP1	0.940	-4.600	-1.301	3.300
	1.000	-6.416	-5.216	1.200
	1.072	-6.360	-5.988	0.373
	1.180	-4.855	-4.750	0.105
	1.289	-3.328	-3.290	0.038
MPMP2	0.940	-3.537	-1.451	2.086
	1.000	-3.729	-3.222	0.507
	1.091	-3.017	-2.998	0.019
	1.182	-2.182	-2.205	-0.023
	1.300	-1.435	-1.453	-0.018
NMNM1	0.938	-4.099	-4.396	-0.297
	1.000	-4.430	-4.858	-0.428
	1.093	-3.654	-3.896	-0.242
	1.187	-2.674	-2.764	-0.090
	1.300	-1.808	-1.822	-0.014
NMNM2	0.940	-4.595	-3.569	1.026
	1.000	-6.300	-6.552	-0.252
	1.072	-6.251	-6.697	-0.446
	1.180	-4.891	-5.087	-0.196
	1.287	-3.507	-3.531	-0.024
NMNM3	0.941	-2.949	-1.375	1.574
	1.000	-3.049	-2.704	0.345
	1.089	-2.384	-2.488	-0.104
	1.179	-1.674	-1.809	-0.135
	1.300	-1.013	-1.124	-0.111
PNPN1	0.904	-6.152	-3.256	2.897
	1.000	-6.280	-4.871	1.409
	1.096	-4.808	-3.788	1.020
	1.223	-2.956	-2.225	0.731
	1.300	-2.170	-1.575	0.595

	0.929	-5.075	-4.693	0.382
	1.000	-6.005	-5.989	0.016
PNPN2	1.106	-5.019	-4.906	0.114
	1.212	-3.584	-3.422	0.162
	1.353	-2.155	-2.033	0.122
	0.939	-2.515	-0.779	1.736
	1.000	-2.665	-2.048	0.617
PNPN3	1.092	-2.126	-1.951	0.175
	1.184	-1.513	-1.414	0.099
	1.300	-1.003	-0.931	0.072
	0.934	-5.411	-3.719	1.692
	1.000	-6.547	-6.437	0.110
POPO1	1.099	-5.667	-5.979	-0.312
	1.199	-4.231	-4.485	-0.254
	1.332	-2.732	-2.887	-0.155
	0.929	-5.006	-4.497	0.509
	1.000	-5.635	-5.870	-0.235
POPO2	1.106	-4.603	-4.944	-0.341
	1.212	-3.281	-3.550	-0.269
	1.353	-2.003	-2.207	-0.204
	0.908	-5.188	-4.271	0.917
	1.000	-6.489	-6.736	-0.247
POPO3	1.092	-5.580	-5.715	-0.135
	1.216	-3.956	-3.891	0.065
	1.371	-2.482	-2.371	0.111
	0.929	-3.965	-4.294	-0.329
	1.000	-4.501	-4.756	-0.255
PDPD1	1.106	-3.645	-3.685	-0.040
	1.212	-2.540	-2.525	0.015
	1.353	-1.486	-1.490	-0.004
	0.938	-2.915	-2.784	0.131
	1.000	-3.061	-3.166	-0.105
PDPD2	1.094	-2.311	-2.378	-0.067
	1.188	-1.507	-1.530	-0.023
	1.300	-0.914	-0.925	-0.011
	0.940	-2.254	-0.610	1.645
	1.000	-2.591	-2.146	0.445
PDPD3	1.091	-2.156	-2.137	0.019
	1.181	-1.566	-1.584	-0.018
	1.300	-1.016	-1.021	-0.005
BEBE1	0.929	-1.627	-3.343	-1.716

	1.000	-2.639	-3.356	-0.717
	1.106	-2.264	-2.344	-0.080
	1.212	-1.481	-1.433	0.048
	1.353	-0.730	-0.691	0.039
BEBE2	0.938	-2.690	-0.914	1.776
	1.000	-2.811	-2.211	0.600
	1.093	-2.226	-2.093	0.133
	1.187	-1.562	-1.509	0.053
	1.311	-0.934	-0.902	0.032
PIPI1	0.937	-3.939	-2.194	1.745
	1.000	-5.096	-4.830	0.266
	1.076	-4.914	-5.099	-0.185
	1.190	-3.726	-3.916	-0.190
	1.304	-2.590	-2.708	-0.118
PIPI2	0.929	-3.474	-2.464	1.010
	1.000	-4.109	-3.979	0.130
	1.106	-3.307	-3.371	-0.064
	1.212	-2.228	-2.270	-0.042
	1.353	-1.206	-1.216	-0.010
PIPI3	0.937	-2.343	-0.792	1.551
	1.000	-2.440	-2.103	0.337
	1.095	-1.963	-2.051	-0.088
	1.189	-1.433	-1.540	-0.108
	1.300	-0.978	-1.040	-0.062
PRPR1	0.929	-0.230	-0.450	-0.220
	1.000	-1.140	-1.435	-0.295
	1.106	-0.944	-1.129	-0.185
	1.212	-0.452	-0.587	-0.135
	1.300	-0.154	-0.269	-0.115
PRPR2	0.929	-2.804	-2.759	0.045
	1.000	-3.493	-3.562	-0.069
	1.106	-2.898	-2.868	0.030
	1.212	-2.050	-1.980	0.070
	1.353	-1.252	-1.183	0.069
PRPR3	0.950	-5.304	-2.031	3.273
	1.000	-5.604	-4.017	1.587
	1.096	-4.746	-4.271	0.475
	1.223	-3.194	-2.995	0.199
	1.383	-1.863	-1.752	0.111

Table S8. π-orbital torsion parameters.

π-orbital torsional energy equation: $E_{\pi-tor} = w_2[1+\cos(2\varphi+\pi)]$. φ is the torsion angle between the two adjacent sp2 orbitals. The phase angle is π. The force constant w_2 of the 7 types π-orbital torsional are list in this table.

Types	Terms (atom type – atom type)	Force constant (kcal/mol)
Carbon-carbon in 6-member ring	102-102; 102-104; 104-104; 102-120;107-120;102-107;107-107	4.0
Carbon-carbon in 5-member ring	103-103; 103-105; 105-105; 103-107	6.0
Carboxyl or nitrogen related in 6-member ring	104-106; 107-106; 106-109; 104-109; 119-109	3.0
Nitrogen related in 6-member ring	107-110; 105-110	6.0
Amino group 1	102-108	2.5
Amino group 2	120-108	6.0
Amino group 3	119-108	4.0

Table S9. Structure and interaction energy comparison of nucleobase pairs between QM and AMOEBA. The energy Pearson product moment correlation coefficient is $R^2 = 0.972$ and the average RMSD is 0.11 Å.

Base-Base hydrogen bonding pairs	QM Energy Minimum (kcal/mol)	AMOEBA Energy minimum (kcal/mol)	QM-AMOEBA structure RMSD (Å)
AAcisWC	-6.792	-7.709	0.23
AAtransHH	-11.456	-11.951	0.24
AAtransWC	-12.595	-12.710	0.10
AAtransWCH	-12.231	-12.410	0.13
ACtransWC	-15.357	-15.803	0.10
ATcisWC	-13.962	-15.676	0.07
AUcisWC	-14.099	-15.911	0.05
AUcisWCH	-15.119	-15.754	0.05
AUtransWC	-13.623	-15.425	0.07
CAtransWCH	-15.550	-15.739	0.11
CCcisWCH	-10.579	-11.191	0.32
CGtransWCS	-15.656	-15.696	0.15
CUcisWCH	-11.779	-12.999	0.09
GAcisWC	-16.767	-17.191	0.15
GAcisWCH	-16.500	-16.504	0.10
GAcisWCS	-14.088	-14.104	0.09
GAtransSS	-7.764	-8.098	0.31
GCcisWC	-27.889	-27.040	0.04
GGcisWCH	-26.927	-25.371	0.17
GGtransWC	-26.928	-25.371	0.17
GGtransWCH	-19.477	-17.366	0.10
GTtransWC	-16.672	-16.468	0.08
GUcisWC	-15.433	-16.229	0.09
GUcisWCH	-8.801	-8.740	0.12

GUtransWC	-16.980	-17.558	0.08
GUtransWCH	-14.719	-15.190	0.11
UAcisWCH	-8.111	-8.752	0.09
UAcisWCS	-10.067	-12.092	0.09
UAtransWCH	-14.899	-15.787	0.05
UAtransWCS	-10.524	-11.896	0.09
UGcisWCS	-14.137	-14.931	0.20
UGtransWCH	-9.538	-9.477	0.09
UTcisWC	-11.566	-12.752	0.04
UUcisWC	-11.596	-13.332	0.06
UUcisWCH	-8.276	-9.433	0.05
UUtransWC	-11.957	-14.071	0.04
UUtransWCH	-8.833	-10.060	0.06

Table S10. Aromatic liquid density at varies temperatures. Calculated density is the average density value of a 2-ns liquid simulation.

Liquid	Temperature (K)	Experimental &std Density (g/ml)		Calculated Density (g/ml)	Error (%)
AL	267.2	1.0443	0.0013	1.0339	-1.00
	298.2	1.0174	0.0003	1.0050	-1.22
	377.8	0.9473	0.0008	0.9223	-2.64
	457.2	0.8728	0.0014	0.8319	-4.69
BE	278.8	0.8940	0.0009	0.8978	0.43
	298.2	0.8734	0.0005	0.8800	0.76
	325.6	0.8439	0.0009	0.8496	0.68
	353.4	0.8132	0.0015	0.8126	-0.07
IN	325.4	1.0741	0.0003	1.0803	0.58
	392.8	1.0348	0.0009	1.0228	-1.16
	460.0	0.9650	0.0050	0.9615	-0.36
	527.2	0.9041	0.0084	0.8880	-1.78
MI	268.8	1.0540	0.0170	1.0771	2.19
	298.2	1.0307	0.0030	1.0505	1.92
	328.0	1.0070	0.0100	1.0252	1.81
	358.0	0.9830	0.0150	0.9965	1.37
MP	255.0	0.9919	0.0025	1.0106	1.89
	298.2	0.9518	0.0002	0.9703	1.94

	357.8	0.8969	0.0009	0.9138	1.88
	417.2	0.8397	0.0020	0.8498	1.20
NM	262.0	1.1580	0.0140	1.1457	-1.06
	298.2	1.1281	0.0092	1.1231	-0.44
	412.0	1.0281	0.0097	1.0069	-2.06
	525.6	0.9135	0.0089	0.8847	-3.15
PD	254.2	1.0220	0.0012	1.0304	0.82
	298.2	0.9780	0.0002	0.9880	1.02
	343.2	0.9320	0.0005	0.9447	1.36
	388.4	0.8838	0.0011	0.8946	1.22
PI	248.0	1.1310	0.0190	1.1356	0.41
	298.2	1.0792	0.0094	1.0847	0.51
	353.0	1.0190	0.0140	1.0316	1.24
	409.0	0.9520	0.0210	0.9672	1.60
PR	249.8	1.0067	0.0017	1.0199	1.31
	298.2	0.9655	0.0002	0.9699	0.46
	350.4	0.9189	0.0013	0.9181	-0.09
	402.8	0.8680	0.0056	0.8603	-0.89

Table S11. The calculated hydration free energy and heat of vaporization of 1-methyl-2-pyridone (NM) before and after charge modification.

	Before	After	Experimental
Hydration free energy (kcal/mol)	-8.63	-10.18	-10.00
Heat of vaporization (kcal/mol)	-11.14	-11.82	-13.00

Table S12. AMOEBA stacking energy computed for potential energy surfaces across rotations (Twist, Roll, Tilt) and translations (Rise, Slide, Shift) for the stacked adenine–cytosine and guanine–uracil dimers.

(A) Rise-twist dimers

Rise (Å)	AC	GU	Twist (°)	AC	GU
3.0	-3.146	-1.566	0	-7.240	-6.184
3.1	-5.528	-4.080	10	-7.249	-6.303
3.2	-6.756	-5.442	20	-7.002	-6.613
3.3	-7.234	-6.051	30	-6.591	-7.170
3.4	-7.240	-6.184	40	-6.197	-7.975
3.5	-6.963	-6.026	50	-6.028	-8.945
3.6	-6.526	-5.702	60	-6.205	-9.922
3.7	-6.012	-5.292	70	-6.681	-10.726
3.8	-5.472	-4.848	80	-7.262	-11.218
3.9	-4.939	-4.402	90	-7.755	-11.334
4.0	-4.431	-3.973	100	-8.103	-11.085
4.2	-3.524	-3.202	110	-8.396	-10.528
4.4	-2.776	-2.564	120	-8.727	-9.742
4.6	-2.177	-2.052	130	-9.069	-8.807
4.8	-1.704	-1.647	140	-9.277	-7.806
5.0	-1.331	-1.328	150	-9.215	-6.833
5.5	-0.716	-0.799	160	-8.849	-5.996
6.0	-0.378	-0.504	170	-8.277	-5.400
6.5	-0.192	-0.334	180	-7.678	-5.106
7.0	-0.087	-0.232			
8.0	0.004	-0.127			
9.0	0.031	-0.080			

(B) Roll-Tilt dimers

Angle (°)	ACRoll	ACTilt	GURoll	GUTilt
-20.0	-4.874	-5.529	-4.795	-3.733
-18.0	-5.465	-6.020	-5.332	-4.139
-16.0	-5.878	-6.334	-5.682	-4.451
-14.0	-6.158	-6.522	-5.894	-4.698
-12.0	-6.342	-6.622	-6.005	-4.899
-10.0	-6.456	-6.663	-6.043	-5.068
-8.0	-6.520	-6.665	-6.029	-5.217
-6.0	-6.550	-6.643	-5.978	-5.351
-4.0	-6.556	-6.608	-5.902	-5.475
-2.0	-6.546	-6.568	-5.808	-5.592

0	-6.526	-6.526	-5.702	-5.702
2.0	-6.499	-6.486	-5.587	-5.804
4.0	-6.467	-6.448	-5.467	-5.897
6.0	-6.432	-6.412	-5.342	-5.976
8.0	-6.393	-6.375	-5.211	-6.035
10.0	-6.349	-6.333	-5.076	-6.067
12.0	-6.299	-6.277	-4.935	-6.058
14.0	-6.239	-6.199	-4.785	-5.996
16.0	-6.164	-6.083	-4.625	-5.859
18.0	-6.069	-5.911	-4.451	-5.622
20.0	-5.947	-5.657	-4.260	-5.252

(C) Slide-shift dimers

Distance (Å)	ACSlide	ACShift	GUSlide	GUShift
-2.0	-4.614	-6.910	-7.638	-7.011
-1.8	-4.938	-7.026	-7.673	-7.014
-1.6	-5.252	-7.113	-7.641	-6.955
-1.4	-5.550	-7.181	-7.543	-6.850
-1.2	-5.825	-7.235	-7.386	-6.720
-1.0	-6.078	-7.281	-7.184	-6.589
-0.8	-6.315	-7.318	-6.954	-6.474
-0.6	-6.544	-7.341	-6.719	-6.383
-0.4	-6.772	-7.342	-6.500	-6.313
-0.2	-7.005	-7.311	-6.317	-6.252
0.0	-7.240	-7.240	-6.184	-6.184
0.2	-7.471	-7.128	-6.104	-6.091
0.4	-7.680	-6.973	-6.076	-5.961
0.6	-7.850	-6.784	-6.085	-5.787
0.8	-7.961	-6.568	-6.116	-5.573
1.0	-7.998	-6.335	-6.150	-5.324
1.2	-7.952	-6.093	-6.169	-5.052
1.4	-7.825	-5.846	-6.161	-4.767
1.6	-7.628	-5.595	-6.119	-4.480
1.8	-7.379	-5.338	-6.042	-4.197
2.0	-7.097	-5.072	-5.930	-3.921

Table S13. Special pairwise vdW parameters for metal ion interactions.

type	pairs	Distance (Å)	Epsilon (kcal/mol)
Na:lone-pair N	Na-112, Na-113	3.387	0.240
K:lone-pair N	K-112, K-113	3.676	0.290
Mg:lone-pair N	Mg-112, Mg-113	3.364	0.215
Mg:carboxyl O	Mg-113	3.172	0.182

Table S14. The AMOEBA polarization energies of dimers at equilibrium distance and the SAPT0 induction energy (correlation coefficient $R^2 = 0.842$).

Dimer	SAPT0 induction energy	AMOEBA polarization energy
ALAL1	-3.127	-1.715
ALAL2	-1.102	-0.814
ALAL3	-1.289	-0.534
ALwat1	-1.072	-0.863
ALwat2	-1.006	-0.375
ININ1	-1.253	-0.614
ININ2	-1.162	-0.540
ININ3	-2.940	-1.016
INwat1	-1.633	-1.001
INwat2	-0.401	-0.192
INwat3	-1.112	-0.392
MIMI1	-2.918	-1.348
MIMI2	-1.587	-0.715
MIMI3	-0.859	-0.598
MIwat1	-2.412	-1.861
MIwat2	-0.535	-0.346
MIwat3	-0.750	-0.330
MIwat4	-1.247	-0.659
NMNM1	-1.286	-0.349
NMNM3	-0.408	-0.229
NMwat1	-2.649	-1.967
NMwat2	-0.712	0.022
NMwat3	-2.540	-1.887
NMwat4	-0.473	0.009
PDPD1	-0.665	-0.197
PDPD2	-0.535	-0.209
PDPD3	-0.478	-0.115
PDwat1	-0.366	-0.304
PDwat2	-2.155	-1.723
PDwat3	-0.792	-0.312
BEBE1	-0.400	-0.191
BEBE2	-0.477	-0.166
BEwat1	-0.373	-0.308
BEwat2	-0.792	-0.395
PRPR1	-0.701	-0.424
PRPR2	-0.822	-0.401

PRPR3	-1.548	-0.794
PRwat1	-0.801	-0.519
PRwat2	-0.818	-0.358
PRwat3	-1.357	-0.611
MPMP1	-1.959	-0.656
MPMP2	-0.623	-0.182
MPwat1	-0.330	-0.196
MPwat2	-0.461	-0.276
PNPN1	-1.200	-0.483
PNPN2	-1.136	-0.190
PNPN3	-0.434	0.010
PNwat1	-3.460	-2.605
PNwat2	-1.033	-0.602
PNwat3	-0.650	-0.248
POPO1	-1.524	-0.416
POPO2	-1.113	-0.306
POPO3	-1.768	-0.448
POwat1	-4.453	-3.214
POwat2	-2.601	-2.111
POwat3	-0.704	-0.110
PIPI1	-1.100	-0.192
PIPI2	-0.731	-0.097
PIPI3	-0.392	-0.135
PIwat1	-1.876	-1.058
PIwat2	-1.831	-1.108
PIwat3	-0.545	-0.249

Table S15. Molecular induced dipole in different environments (pure liquid and water solution).

Molecule	Gas phase molecular dipole	Induced dipole in liquid (average & standard deviation)		Induced dipole in dilute solution (average & standard deviation)	
AL	1.360	0.941	0.377	1.250	0.457
BE	0.062	0.387	0.164	0.707	0.298
IN	2.183	0.965	0.376	1.234	0.480
NM	4.380	1.709	0.545	2.946	0.565
MI	4.335	1.424	0.367	2.223	0.456
PR	1.878	0.823	0.287	1.042	0.370
PD	2.330	0.899	0.335	1.704	0.463

Energy functions of AMOEBA force field (see details in reference 26)

Total $\quad U = U_{vdW} + U_{ele}^{perm} + U_{ele}^{ind} + U_{bond} + U_{angle} + U_{torsion}$

Bond stretching $\qquad U_{bond} = K_b(b-b_0)^2[1 - 2.55(b-b_0) + 3.793125(b-b_0)^2]$

Bond angle bending

$$U_{angle} = K_\theta(\theta-\theta_0)^2[1 - 0.014(\theta-\theta_0) + 5.6\times10^{-5}(\theta-\theta_0)^2 - 7.0\times10^{-7}(\theta-\theta_0)^3 + 2.2\times10^{-8}(\theta-\theta_0)^4]$$

Torsional $\qquad U_{tor}(\chi) = \sum_{n=1}^{3} k_{tor,n}[1 + \cos(n\chi + \phi_n)] \qquad \phi_1 = \phi_3 = 0, \phi_2 = \pi$

vdW $\qquad U_{vdw}(ij) = \varepsilon_{ij}\left(\dfrac{1.07}{\rho_{ij} + 0.07}\right)^7\left(\dfrac{1.12}{\rho_{ij}^7 + 0.12} - 2\right) \qquad \varepsilon_{ij} = \dfrac{4\varepsilon_{ii}\varepsilon_{jj}}{(\varepsilon_{ii}^{1/2} + \varepsilon_{jj}^{1/2})^2},$

$$\rho_{ij} = \frac{R_{ij}}{R_{ij}^0}, \qquad R_{ij}^0 = \frac{(R_{ii}^0)^3 + (R_{jj}^0)^3}{(R_{ii}^0)^2 + (R_{jj}^0)^2}$$

Permanent electrostatic

$$U_{ele}^{perm}(r_{ij}) = M_i^t T_{ij} M_j$$

$$M_i = [q_i, \mu_{ix}, \mu_{iy}, \mu_{iz}, Q_{ixx}, Q_{ixy}, Q_{ixz}, Q_{iyx}, Q_{iyy}, Q_{izx}, Q_{izy}, Q_{izz}]$$

$$T = \begin{vmatrix} 1 & \dfrac{\partial}{\partial x_j} & \dfrac{\partial}{\partial y_j} & \dfrac{\partial}{\partial z_j} & .. \\[2mm] \dfrac{\partial}{\partial x_i} & \dfrac{\partial^2}{\partial x_i \partial x_j} & \dfrac{\partial^2}{\partial x_i \partial y_j} & \dfrac{\partial^2}{\partial x_i \partial z_j} & .... \\[2mm] \dfrac{\partial}{\partial y_i} & \dfrac{\partial^2}{\partial y_i \partial x_j} & \dfrac{\partial^2}{\partial y_i \partial y_j} & \dfrac{\partial^2}{\partial y_i \partial z_j} & .... \\[2mm] \dfrac{\partial}{\partial z_i} & \dfrac{\partial^2}{\partial z_i \partial x_j} & \dfrac{\partial^2}{\partial z_i \partial y_j} & \dfrac{\partial^2}{\partial z_i \partial z_j} & .... \\[2mm] \dfrac{\partial^2}{\partial x_i^2} & \dfrac{\partial^3}{\partial x_i^2 \partial x_j} & \dfrac{\partial^3}{\partial x_i^2 \partial y_j} & \dfrac{\partial^3}{\partial x_i^2 \partial z_j} & .... \\[2mm] ... & ... & ... & ... & .... \end{vmatrix} (\frac{1}{r_{ij}})$$

Induced dipole $\qquad \mu_i = \alpha_i [E_i - \sum\limits_{j \neq i}^{N} T_{ij} \mu_j]$

Supplementary Method.

MATLAB programs for vdW parameter optimization

```
Fitting script:

geom= load('Geometry');
% geometry format: atom1_typ atom2_typ d H1 a1 H2 a2 a3 pair_num
interene=load('targetVDWene');
totene=interene(:,1); %total interaction energy
eleene=interene(:,2); %electrostatic energy
vdwene=interene(:,3); % tot - ele
label=interene(:,4);  % whether the distance is smaller than
                      %  equilibrium
lowene=interene(:,5); % lowest vdw ene on the vdw ene- distance curve


Ns=size(vdwene);
N=Ns(1);


weight=ones(N,1);
repul=zeros(N,1);


for i=1:1:N
    weight(i)=exp((lowene(i)-vdwene(i))/2.0);

    if  label(i)==1
        repul(i)=1;
    end
end


para0=[1    3.680     0.1290       1
2    3.700     0.1270        1
3    3.720     0.1060        1
4    3.720     0.1060        1
… ….
14    2.600     0.0200     0.88
]; % initial parameters
p0=[para(:,2)',para(:,3)',para(12:14,4)'];

% set the down and up limit of parameters
pdown([1:14])=p0([1:14])*0.95;
pdown([15:28])=p0([15:28])*0.80;
pup([1:14])=p0([1:14])*1.05;
pup([14:28])=p0([15:28])*1.20;
pup([29:31])=ones(3,1);
pdown([29:31])=p0([99:111])-0.05;
constraint=[4 1 16];
% parameter optimization with "lsqnonlin" method
[p,vdwee,resd]=lsqnonlin(@(x)vdwbasefitene(x,vdwene,geom,weight,p0,repu
l,constraint,1),p0,pdown,pup);

% draw pictures
```

```matlab
enefitted=vdwbasefitene(p4,vdwene,geom,weight,p0,repul,constraint,0);
figure;
plot(totene,'k');
hold on;
plot(enefitted+eleene,'r');
```

Objective function:

```matlab
function
vdwE=vdwbasefitene(p,vdwqm,geom,weight,p0,repul,constraint,mode)
%% p: parameter set
%% vdwqm: target vdw energy = QM total — MM electrostratic
%% geom: geometry data, including distance, angle
%% weight: the weight of every interaction dimer
%% p0: initial value of the parameter
%% repul: 0 or 1 whether the distance is smaller than equilibrium
%% constraint: constraint force constant for the three %%types of
parameters
%% mode: fitting mode (1) or vdw energy calculation mode %%(0)
s=size(geom);
n=s(1);
v=zeros(n,1);
Ns=size(vdwqm);
N=Ns(1);
vdw=zeros(N,1);

rad=ones(16,1);
rad([1:14])=p([1:14]);       % the first 14 parameters in p are radii
rad([15:16])=[3.405 2.655]; % water O and H radii
eps=zeros(16,1);
eps([1:14])=p([15:28]);      % the next 14 parameters in p are epsilon
eps([15:16])=[0.110 0.0135]; % water O and H epsilon
redu=ones(16,1);
redu([12:14])=p([29:31]);    % the last 3 parameters in p are reduction
                             %  factors for hydrogens

for i=1:1:n
    t1=geom(i,1);
    t2=geom(i,2);
    d=geom(i,3);
    a1=geom(i,4);
    H1=geom(i,5)*(1-redu(t1));
    a2=geom(i,6);
    H2=geom(i,7)*(1-redu(t2));
    a3=geom(i,8);
    v(i)=calvdw(d,a1,a2,a3,H1,H2,rad(t1),eps(t1),rad(t2),eps(t2));
end
for i=1:1:n
    m=geom(i,9);    % m is the number of the interaction pair
    vdw(m)=vdw(m)+v(i);
end
if mode==0
    vdwE=vdw;
end
if mode==1
    for i=1:1:N
        if((repul(i)==1)&&(vdw(i)<vdwqm(i)))
```

```matlab
                    vdw(i)=3*vdw(i)-2*vdwqm(i);
        end
    end

    vdwE=[(vdw-vdwqm).*weight; 2*abs(constraint(1)*((p([1:49])'-
p0([1:49])')./p0([1:49])'));2*abs(constraint(2)*((p([50:98])'-
p0([50:98])')./p0([50:98])'));2*abs(constraint(3)*((p([99:111])'-
p0([99:111])')./p0([99:111])'))];
end

function e=calvdw(d0,a1,a2,a3,H1,H2,r1,ep1,r2,ep2)
%% vdw potential energy with buffered 14-7 equation
%% d0 distance of atoms A and B
%% H1 if A is hydrogen and A linked with C, H1 is the bond length A-C
%% H2 if B is hydrogen and B linked with D, H2 is the bond length B-D
%% a1 if A is hydrogen a1 is the angle B-A-C
%% a2 if B is hydrogen a2 is the angle A-B-D
%% a3 the angle between A-C and B-D
%% r1 ep1 vdw parameters for A
%% r2 ep2 vdw parameters for B
d=sqrt(d0*d0+H1*H1+H2*H2+2*d0*H1*a1+2*d0*H2*a2-2*H1*H2*a3);
Ep=(4*ep1*ep2)/((ep1^0.5+ep2^0.5)^2);
R=(r1*r1*r1+r2*r2*r2)/(r1*r1+r2*r2);
e=Ep.*(1.07./(d./R+0.07)).^7.*(1.12./((d./R).^7+0.12)-2);
```