Supporting information for:

LICHEM: A QM/MM Program for Simulations with Multipolar and Polarizable Force Fields

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1 Notes

This SI document contains energies and geometries for the water clusters discussed in the main paper. Due to the large size of some of the files, Monte Carlo trajectories, optimization trajectories, and DNA polymerase structures are not included in the SI. Additional data can be requested by contacting the authors.

2 Multipole accuracy

Table S1 reports the percent errors of the point–charge representation of the multipole–multipole interactions for the ten water dimer structures. All errors are less than 1% of energies calculated with TINKER. The errors were calculated for both the 2003 and 2014 parameterizations of the AMOEBA model[S1,S2] and the results are similar. The largest error was found to be 0.028 kcal/mol for dimer number 3. It is clear from Table S1 and the results reported by Devereux et al.[S3] that the point–charge conversion is highly accurate.

Table S1: Water dimer multipole–multipole interaction errors introduced by the point–charge representation of the multipoles. All errors are less than 1% of the multipole–multipole interaction energies.

Dimer	Error (%)	
	AMOEBA03	AMOEBA14
1	0.04	0.51
2	0.23	0.54
3	0.34	0.57
4	0.19	0.27
5	0.14	0.32
6	0.06	0.33
7	0.01	0.28
8	0.23	0.19
9	0.08	0.22
10	0.02	0.22

3 QM/MM binding energies

Tables S2–S17 list the QM/MM dimer and trimer binding energies calculated at several different levels of theory. Values are given for every possible division of the cluster into QM and MM regions. The values are an average of two QM/MM permutations where the identities of the QM and MM regions are swapped.

Table S2: Water dimer binding energies from PBE0/aug-cc-pVTZ (BSSE corrected) and PBE0/aug-cc-pVTZ/AMOEBA.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.2109	-0.1934
2	-0.1857	-0.1720
3	-0.1833	-0.1705
4	-0.1652	-0.1338
5	-0.1505	-0.1076
6	-0.1467	-0.0993
7	-0.1219	-0.1110
8	-0.0480	-0.0503
9	-0.1145	-0.1092
10	-0.0802	-0.0862

Table S3: Water dimer binding energies from PBE0/6-311++G(d,p) (BSSE corrected) and PBE0/6-311++G(d,p)/AMOEBA.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.2355	-0.2197
2	-0.2111	-0.1972
3	-0.2117	-0.1962
4	-0.1981	-0.1534
5	-0.1821	-0.1265
6	-0.1789	-0.1187
7	-0.1460	-0.1281
8	-0.0541	-0.0579
9	-0.1530	-0.1332
10	-0.1122	-0.1041

Table S4: Water dimer binding energies from HF/aug-cc-pVTZ (BSSE corrected) and HF/aug-cc-pVTZ/AMOEBA.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.1548	-0.2088
2	-0.1389	-0.1867
3	-0.1397	-0.1854
4	-0.1156	-0.1453
5	-0.1080	-0.1188
6	-0.1081	-0.1106
7	-0.0879	-0.1179
8	-0.0290	-0.0529
9	-0.0836	-0.1180
10	-0.0630	-0.0932

Table S5: Water dimer binding energies from HF/6-311++G(d,p) (BSSE corrected) and HF/6-311++G(d,p)/AMOEBA.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.1782	-0.2309
2	-0.1629	-0.2081
3	-0.1665	-0.2075
4	-0.1457	-0.1614
5	-0.1374	-0.1349
6	-0.1390	-0.1275
7	-0.1108	-0.1320
8	-0.0358	-0.0591
9	-0.1183	-0.1383
10	-0.0929	-0.1087

Table S6: Water dimer binding energies from PBE0/aug-cc-pVTZ (BSSE corrected) and PBE0/aug-cc-pVTZ/TIP3P.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.2109	-0.2597
2	-0.1857	-0.2414
3	-0.1833	-0.2442
4	-0.1652	-0.1776
5	-0.1505	-0.1592
6	-0.1467	-0.1549
7	-0.1219	-0.1390
8	-0.0480	-0.0619
9	-0.1145	-0.1647
10	-0.0802	-0.1333

Table S7: Water dimer binding energies from PBE0/6-311++G(d,p) (BSSE corrected) and PBE0/6-311++G(d,p)/TIP3P.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.2355	-0.2828
2	-0.2111	-0.2607
3	-0.2117	-0.2649
4	-0.1981	-0.1954
5	-0.1821	-0.1741
6	-0.1789	-0.1707
7	-0.1460	-0.1588
8	-0.0541	-0.0662
9	-0.1530	-0.1928
10	-0.1122	-0.1558

Table S8: Water dimer binding energies from HF/aug-cc-pVTZ (BSSE corrected) and HF/aug-cc-pVTZ/TIP3P.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.1548	-0.2737
2	-0.1389	-0.2533
3	-0.1397	-0.2568
4	-0.1156	-0.1874
5	-0.1080	-0.1669
6	-0.1081	-0.1630
7	-0.0879	-0.1468
8	-0.0290	-0.0637
9	-0.0836	-0.1746
10	-0.0630	-0.1418

Table S9: Water dimer binding energies from HF/6-311++G(d,p) (BSSE corrected) and HF/6-311++G(d,p)/TIP3P.

Dimer	E_{bind} (eV)	
	QM	QM/MM
1	-0.1782	-0.2929
2	-0.1629	-0.2695
3	-0.1665	-0.2743
4	-0.1457	-0.2021
5	-0.1374	-0.1792
6	-0.1390	-0.1764
7	-0.1108	-0.1633
8	-0.0358	-0.0670
9	-0.1183	-0.1984
10	-0.0929	-0.1610

Table S10: Water trimer binding energies from PBE0/aug-cc-pVTZ (BSSE corrected) and PBE0/aug-cc-pVTZ/AMOEBA.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.4670	-0.3924
uud 2	-0.4642	-0.3961
uud 3	-0.4834	-0.4073
uuu 1	-0.4512	-0.3702
uuu 2	-0.4512	-0.3707
uuu 3	-0.4512	-0.3707

Table S11: Water trimer binding energies from PBE0/6-311++G(d,p) (BSSE corrected) and PBE0/6-311++G(d,p)/AMOEBA.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.4977	-0.4324
uud 2	-0.4942	-0.4363
uud 3	-0.5218	-0.4514
uuu 1	-0.4859	-0.4124
uuu 2	-0.4859	-0.4128
uuu 3	-0.4859	-0.4129

Table S12: Water trimer binding energies from HF/aug-cc-pVTZ (BSSE corrected) and HF/aug-cc-pVTZ/AMOEBA.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.3246	-0.4202
uud 2	-0.3208	-0.4235
uud 3	-0.3493	-0.4351
uuu 1	-0.3227	-0.3979
uuu 2	-0.3227	-0.3983
uuu 3	-0.3227	-0.3983

Table S13: Water trimer binding energies from HF/6-311++G(d,p) (BSSE corrected) and HF/6-311++G(d,p)/AMOEBA.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.3521	-0.4533
uud 2	-0.3478	-0.4566
uud 3	-0.3850	-0.4717
uuu 1	-0.3540	-0.4333
uuu 2	-0.3540	-0.4337
uuu 3	-0.3540	-0.4338

Table S14: Water trimer binding energies from PBE0/aug-cc-pVTZ (BSSE corrected) and PBE0/aug-cc-pVTZ/TIP3P.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.4670	-0.4742
uud 2	-0.4642	-0.4724
uud 2	-0.4834	-0.4932
uuu 1	-0.4512	-0.4626
uuu 2	-0.4512	-0.4626
uuu 3	-0.4512	-0.4626

Table S15: Water trimer binding energies from PBE0/6-311++G(d,p) (BSSE corrected) and PBE0/6-311++G(d,p)/TIP3P.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.4977	-0.4972
uud 2	-0.4942	-0.4961
uud 2	-0.5218	-0.5249
uuu 1	-0.4859	-0.4847
uuu 2	-0.4859	-0.4847
uuu 3	-0.4859	-0.4847

Table S16: Water trimer binding energies from HF/aug-cc-pVTZ (BSSE corrected) and HF/aug-cc-pVTZ/TIP3P.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.3246	-0.4936
uud 2	-0.3208	-0.4917
uud 2	-0.3493	-0.5156
uuu 1	-0.3227	-0.4795
uuu 2	-0.3227	-0.4795
uuu 3	-0.3227	-0.4795

Table S17: Water trimer binding energies from HF/6-311++G(d,p) (BSSE corrected) and HF/6-311++G(d,p)/TIP3P.

Trimer	E_{bind} (eV)	
	QM	QM/MM
uud 1	-0.3521	-0.5116
uud 2	-0.3478	-0.5102
uud 2	-0.3850	-0.5412
uuu 1	-0.3540	-0.4967
uuu 2	-0.3540	-0.4967
uuu 3	-0.3540	-0.4967

4 Solvation energies

Table S18: Pure functional QM/MM solvation energies for the $(H_2O)_5(H_2O)_{16} \rightarrow (H_2O)+(H_2O)_4(H_2O)_{16}$ system.

QM	basis	MM	E_{solv} (eV)
B97D	6-311++G(d,p)	–	-1.5239
B97D	6-311++G(d,p)	AMOEBA	-1.4663
B97D	6-311++G(d,p)	AMOEBA†	-1.2387
B97D	6-311++G(d,p)	TIP3P	-1.2817
BLYP	6-311++G(d,p)	–	-1.2731
BLYP	6-311++G(d,p)	AMOEBA	-1.3897
BLYP	6-311++G(d,p)	AMOEBA†	-1.1589
BLYP	6-311++G(d,p)	TIP3P	-1.2015
PBE	6-311++G(d,p)	–	-1.4939
PBE	6-311++G(d,p)	AMOEBA	-1.5733
PBE	6-311++G(d,p)	AMOEBA†	-1.3465
PBE	6-311++G(d,p)	TIP3P	-1.3902

† Without MM polarization

QM, MM, and QM/MM solvation energies are reported in Tables S18–S20. The tables are subdivided into *ab initio*, pure functionals, hybrid functionals, and force fields. The strong influence of the polarization energy can be seen in Table S20, where the AMOEBA solvation energy without polarization is significantly reduced.

Table S19: Hybrid functional QM/MM solvation energies for the $(H_2O)_5(H_2O)_{16} \rightarrow (H_2O)+(H_2O)_4(H_2O)_{16}$ system.

QM	basis	MM	E_{solv} (eV)
ωB97xD	6-311++G(d,p)	–	-1.6659
ωB97xD	6-311++G(d,p)	AMOEBA	-1.5909
ωB97xD	6-311++G(d,p)	AMOEBA†	-1.3697
ωB97xD	6-311++G(d,p)	TIP3P	-1.4124
B3LYP	6-311++G(d,p)	–	-1.3901
B3LYP	6-311++G(d,p)	AMOEBA	-1.4835
B3LYP	6-311++G(d,p)	AMOEBA†	-1.2560
B3LYP	6-311++G(d,p)	TIP3P	-1.2977
PBE0	6-311++G(d,p)	–	-1.5156
PBE0	6-311++G(d,p)	AMOEBA	-1.5814
PBE0	6-311++G(d,p)	AMOEBA†	-1.3575
PBE0	6-311++G(d,p)	TIP3P	-1.3999
PBE0-D2	6-311++G(d,p)	–	-1.7037
PBE0-D2	6-311++G(d,p)	AMOEBA	-1.6681
PBE0-D2	6-311++G(d,p)	TIP3P	-1.5073

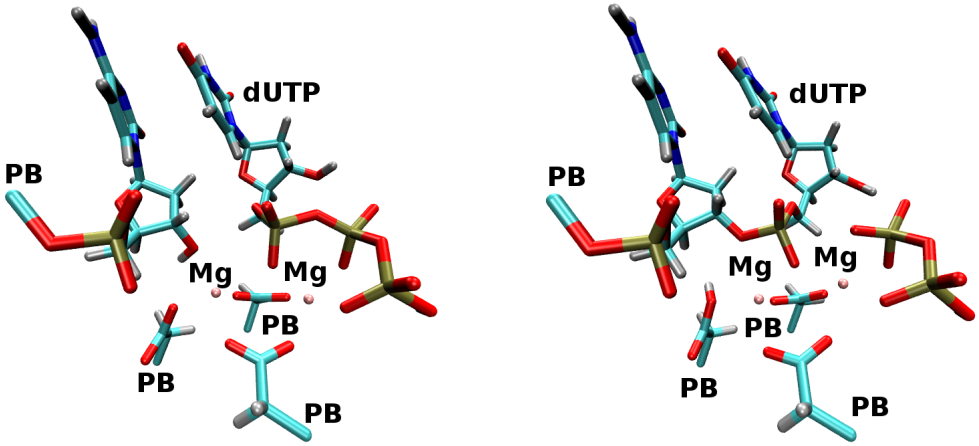
† Without MM polarization

Table S20: Wavefunction and forcefield based solvation energies for the $(H_2O)_5(H_2O)_{16} \rightarrow (H_2O)+(H_2O)_4(H_2O)_{16}$ system.

QM	basis	MM	E_{solv} (eV)
HF	6-31G(d)	–	-1.5025
HF	6-31G(d)	AMOEBA	-1.4858
HF	6-31G(d)	TIP3P	-1.2831
MP2	6-311++G(d,p)	–	-1.5730
–	–	AMOEBA	-1.5419
–	–	iAMOEBA	-1.4424
–	–	AMOEBA†	-0.5091
–	–	TIP3P	-1.1948

† Without MM polarization

5 Comparison of optimizations to crystal structures



Reactant **Product**

Figure S1: Optimized reactant and product active sites of DNA polymerase λ. For clarity, only the QM and PB were are displayed and the QM water molecules have been removed.

Non-polarizable QM/MM geometry optimizations were also performed on the reactant and product structures of a nucleotide addition reaction catalyzed by a DNA polymerase enzyme. The enzyme chosen for these simulations was human DNA polymerase λ with a dUTP added to the nascent DNA chain.[S4,S5] The geometry optimizations were performed at the ωB97xD/6-31++G(d,p)/AMBER99 level of theory. In order to make the calculations tractable, four pseudo–bonds need to bridge the QM and MM subsystems. The QM/MM system contains 101 QM atoms, 4 pseudo–bonds, 18 boundary atoms, and 18403 MM atoms. Three of the pseudo–bonds have been placed on the aspartate residues in the active site and the final pseudo–bond is on the DNA backbone (see Figure S1).

The geometry of the reactant was obtained from QM/MM simulations reported previously,[S4–S6] and the product structure was constructed by physically moving the hydrogen, phosphorous, and oxygen atoms to break the chemical bonds. The modified coordinates were specifically chosen to be far from ideal bond lengths and angles, which provides a more difficult test of the optimization algorithms. The potential energies for the optimized reactant and product structures and the root mean square deviation (RMSD) are in agreement with

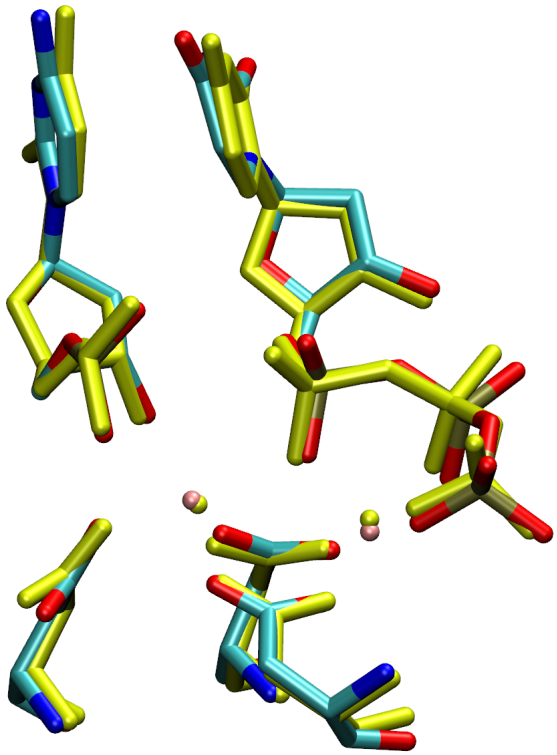


Figure S2: Superposition of the QM/MM optimized reactant and the x–ray crystal structure (PDB:2PFO, yellow). The RMSD was calculated to be 0.31 Å.

our previous results[S4,S5] and the crystals structures.[S6] RMSD between the active sites of the optimized structures and the crystal structures for the product and reactant were determined to be 0.31 and 0.42 Å, respectively. Figures S2 and S3 show the overlap between the QM/MM and x–ray structures[S6] for the reactant and product, respectively. The crystal structure is shown in yellow.

Recent studies of the highly related DNA polymerase β suggest that a third magnesium ion may be involved in the reaction mechanism.[S7] We have carried out QM/MM optimizations with a third magnesium ion located near the dUTP alpha phosphorous, as found in the experimental studies. Our preliminary results suggest that both the third ion and the entropic contribution have strong effects on the relative energies of the reactant and product. Additionally, the pseudo–bond method can readily be extended to multipolar/polarizable force fields to allow for polarizable enzymatic reactions. These three factors will be explored further in the future as they are beyond the scope of the present work.

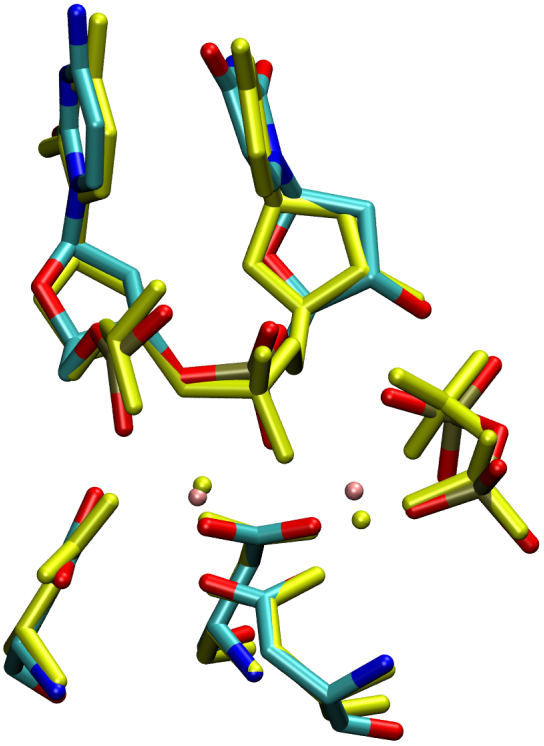


Figure S3: Superposition of the QM/MM optimized reactant and the x–ray crystal structure (PDB:2PFQ, yellow). The RMSD was calculated to be 0.42 Å.

6 Molecular structures

XYZ files for the water clusters and peptides are given below. The structures are labeled in the comment line of the XYZ file.

6.1 Water dimers

6

Dimer1

O 0.872736 0.000000 -1.246754

H 0.288273 0.000000 -2.010853

H 0.288273 0.000000 -0.482655

O -0.778803 0.000000 1.132683

H -0.666682 0.764099 1.706291

H -0.666682 -0.764099 1.706290

– – – – – – – – – – – ––

6

Dimer2

O 0.83717100 -0.11036500 -1.28937600

H 0.25270831 -0.11036500 -2.05347506

H 0.25270783 -0.11036500 -0.52527732

O -0.67496100 0.05571300 1.19601400

H -1.59808346 0.08932533 1.46463854

H -0.20106721 0.56727951 1.85871180

– – – – – – – – – – – ––

6

Dimer3

O 0.81155400 0.00000000 -1.31392300

H 0.22709107 0.00000000 -2.07802187

H 0.22709107 0.00000000 -0.54982413

O -0.66377500 0.00000000 1.20081300

H -0.07883416 0.00000000 1.96454608

H -1.55399554 0.00000000 1.56543801

– – – – – – – – – – – ––

6

Dimer4

O -0.09543100 -0.65652700 -1.21555100

H -0.67989369 -0.65652700 -1.97965006

H -0.67989417 -0.65652700 -0.45145232

O 0.09543100 0.65652700 1.21555100

H 0.67989417 0.65652700 0.45145232

H 0.67989369 0.65652700 1.97965006

− − − − − − − − − − − −

6

Dimer5

O -0.27044000 0.36263800 -1.29694700

H -0.85490317 0.36263800 -2.06104568

H -0.85490269 0.36263800 -0.53284794

O 0.29425600 -0.29295500 1.30953900

H 0.68054422 -0.87736854 1.96884638

H 0.83930439 -0.40368190 0.52461492

− − − − − − − − − − − −

6

Dimer6

O -0.340410 0.000000 -1.324577

H -0.924873 0.000000 -2.088676

H -0.924873 0.000000 -0.560478

O 0.340409 0.000000 1.324577

H 0.924872 0.000000 0.560478

H 0.924873 0.000000 2.088676

− − − − − − − − − − − −

6

Dimer7

O -0.624294 0.000000 1.212401

H -1.208757 0.000000 0.448302

H -1.208757 0.000000 1.976500

O 0.712130 0.000000 -1.325109

H 0.854910 -0.764099 -0.758355

H 0.854909 0.764099 -0.758355

− − − − − − − − − − − −

6

Dimer8

O 1.05351300 1.32267600 0.00000000

H 0.46905007 1.32267600 -0.76409887

H 0.46905007 1.32267600 0.76409887

O -1.05351300 -1.32267500 0.00000000

H -0.46905007 -1.32267500 -0.76409887

H -0.46905007 -1.32267500 0.76409887

− − − − − − − − − − − −

6

Dimer9

O 1.575290 0.000000 0.000000

H 0.990827 0.000000 -0.764099

H 0.990827 0.000000 0.764099

O -1.342829 0.000000 0.000000

H -1.927292 0.764099 0.000000

H -1.927292 -0.764099 0.000000

− − − − − − − − − − − −

6

Dimer10

O -1.43512200 0.00000000 0.00000000

H -2.01958493 0.00000000 -0.76409887

H -2.01958493 0.00000000 0.76409887

O 1.66947500 0.00000000 0.00000000

H 1.08501207 0.00000000 -0.76409887

H 1.08501207 0.00000000 0.76409887

6.2 Water trimers

9

uud

O 7.97080000 -1.97570000 -0.12000000

H 8.88262950 -2.25702115 -0.19521451

H 7.52075183 -2.56327557 0.48699541

O 10.76520000 -1.96030000 -0.26440000

H 10.56756541 -1.03037952 -0.15295358

H 11.28017964 -2.25357096 0.48727809

O 9.37150000 0.42000000 0.26880000

H 8.65154989 -0.20781890 0.20758636

H 9.16674089 1.17205281 -0.28682768

– – – – – – – – – – – –

9

uuu

O 17.44550000 -2.33970000 -0.14840000

H 16.82154031 -2.82261716 0.39353834

H 17.36012888 -1.40679668 0.04815788

O 18.12910000 0.34930000 0.22760000

H 18.12218955 1.01036148 0.91982959

H 18.99800570 -0.05120353 0.19876181

O 20.13750000 -1.57100000 -0.11600000

H 20.82083176 -2.00645800 0.39357421

H 19.35893063 -2.12782693 -0.11831211

6.3 Water 21

63

water21

O 11.717236 11.442052 11.798908

H 11.663986 10.558790 11.388620

H 11.433550 11.254508 12.711759

O 11.556608 15.680353 10.163047

H 10.959448 16.381017 9.895684

H 11.747781 15.838217 11.102115

O 12.071718 16.029951 12.932211

H 12.057426 16.918369 13.293295

H 11.471112 15.521790 13.512439

O 14.551422 14.674614 12.990496

H 13.749539 15.221256 12.964140

H 15.292821 15.280029 12.942212

O 14.009871 12.698504 10.998106

H 14.308390 13.326458 11.669987

H 13.232319 12.261238 11.397368

O 13.117598 13.692896 8.614162

H 12.610342 14.452298 8.921342

H 13.514149 13.337186 9.430788

O 12.050292 11.602501 7.306247

H 12.437630 12.392054 7.741134

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6.4 Peptide chains

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230

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7 Full citations

Full citations for Gaussian,[S8] PSI4,[S9] Q-Chem,[S10] and AMBER[S11] are reported below.

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