SUPPORTING INFORMATION

Parameterization of Highly Charged Metal Ions Using the 12-6-4 LJ-Type Nonbonded Model in Explicit Water

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Table SI.1a. Computed HFE values for the TIP3P water model.

$R_{min}/2$ (Å)	ε(kcal/mol)	M(III) ion without C_4 term	M(III) ion with C_4 = 500 kcal/mol·Å^4	M(IV) ion without C_4 term	M(IV) ion with C_4 = 500 kcal/mol·Å^4
0.9	0.00000062	-1138.1	-2334.2	-1833.3	-3106.5
1.0	0.00001423	-1064.4	-1805.0	-1731.3	-2526.1
1.1	0.00016377	-1015.0	-1553.2	-1663.5	-2249.9
1.2	0.00110429	-949.4	-1350.1	-1575.5	-2012.2
1.3	0.00490301	-903.2	-1228.3	-1503.6	-1868.8
1.4	0.01570749	-840.2	-1106.2	-1416.3	-1707.5
1.5	0.03899838	-798.9	-1014.8	-1359.8	-1603.5
1.6	0.07934493	-761.8	-948.4	-1303.2	-1513.4
1.7	0.13818331	-725.8	-891.9	-1246.3	-1434.3
1.8	0.21312875	-693.5	-840.2	-1205.6	-1366.4
1.9	0.29896986	-663.4	-798.7	-1166.8	-1318.9
2.0	0.38943250	-638.9	-761.1	-1130.9	-1267.5
2.1	0.47874242	-616.3	-726.5	-1089.1	-1212.2
2.2	0.56252208	-592.4	-693.4	-1049.7	-1162.3
2.3	0.63803333	-569.6	-661.6	-1013.9	-1117.9

Table SI.1b. Computed HFE values for the SPC/E water model.

$R_{min}/2$ (Å)	ε(kcal/mol)	M(III) ion without C_4 term	M(III) ion with C_4 = 500 kcal/mol·Å^4	M(IV) ion without C_4 term	M(IV) ion with C_4 = 500 kcal/mol·Å^4
0.9	0.00000062	-1144.6	-2312.2	-1844.5	-3089.8
1.0	0.00001423	-1069.0	-1799.4	-1739.8	-2522.0
1.1	0.00016377	-1019.4	-1547.0	-1671.7	-2248.7
1.2	0.00110429	-955.9	-1346.8	-1585.1	-2012.7
1.3	0.00490301	-908.6	-1227.5	-1508.3	-1870.9
1.4	0.01570749	-844.7	-1106.6	-1424.0	-1710.9
1.5	0.03899838	-800.0	-1012.6	-1362.0	-1600.8
1.6	0.07934493	-761.0	-945.6	-1305.8	-1513.5
1.7	0.13818331	-724.8	-889.5	-1249.7	-1432.6
1.8	0.21312875	-692.1	-835.9	-1200.7	-1366.6
1.9	0.29896986	-661.3	-792.0	-1167.0	-1317.8
2.0	0.38943250	-635.9	-759.2	-1122.4	-1266.5
2.1	0.47874242	-612.3	-721.8	-1090.2	-1212.9
2.2	0.56252208	-587.0	-689.0	-1049.1	-1160.9
2.3	0.63803333	-565.8	-657.1	-1011.9	-1115.0

Table SI.1c. Computed HFE values for the TIP4P$_{EW}$ water model.

$R_{min}/2$ (Å)	ε(kcal/mol)	M(III) ion without C_4 term	M(III) ion with C_4 = 500 kcal/mol·Å^4	M(IV) ion without C_4 term	M(IV) ion with C_4 = 500 kcal/mol·Å^4
0.9	0.00000062	-1068.5	-2196.5	-1726.6	-2921.2
1.0	0.00001423	-1004.8	-1710.8	-1641.4	-2393.8
1.1	0.00016377	-964.0	-1472.4	-1581.2	-2137.2
1.2	0.00110429	-905.0	-1287.2	-1504.4	-1920.8
1.3	0.00490301	-863.6	-1175.8	-1438.8	-1786.4
1.4	0.01570749	-806.4	-1061.8	-1360.3	-1637.7
1.5	0.03899838	-767.5	-975.2	-1305.3	-1540.5
1.6	0.07934493	-732.5	-913.6	-1254.5	-1457.3
1.7	0.13818331	-699.7	-859.1	-1202.2	-1380.7
1.8	0.21312875	-668.9	-810.3	-1164.9	-1318.9
1.9	0.29896986	-641.0	-770.3	-1128.8	-1274.5
2.0	0.38943250	-615.6	-736.3	-1087.0	-1226.2
2.1	0.47874242	-595.1	-703.4	-1054.0	-1174.5
2.2	0.56252208	-573.0	-671.3	-1015.7	-1127.2
2.3	0.63803333	-550.6	-641.6	-981.2	-1083.2

Table SI.2a. Simulated IOD and CN values for the TIP3P water model (The number preceding the slash is the IOD value while the one after is the CN value).

$R_{min}/2$ (Å)	ε(kcal/mol)	M(III) ion without C_4 term	M(III) ion with C_4 = 500 kcal/mol·Å^4	M(IV) ion without C_4 term	M(IV) ion with C_4 = 500 kcal/mol·Å^4
0.9	0.00000062	1.09/2.0	0.92/2.0	1.06/2.0	0.92/2.0
1.0	0.00001423	1.34/3.0	1.07/2.0	1.31/3.0	1.06/2.0
1.1	0.00016377	1.52/4.0	1.39/4.0	1.47/4.0	1.37/4.0
1.2	0.00110429	1.79/6.0	1.51/4.0	1.74/6.0	1.49/4.0
1.3	0.00490301	1.88/6.0	1.77/6.0	1.82/6.0	1.74/6.0
1.4	0.01570749	1.99/6.0	1.89/6.0	1.99/9.0	1.85/6.0
1.5	0.03899838	2.23/8.0	2.14/8.0	2.17/8.0	2.10/8.0
1.6	0.07934493	2.36/9.0	2.25/8.4	2.29/8.9	2.21/9.9
1.7	0.13818331	2.47/9.0	2.39/9.0	2.41/9.9	2.33/9.0
1.8	0.21312875	2.61/10.0	2.53/10.0	2.62/12.0	2.56/12.0
1.9	0.29896986	2.77/11.8	2.70/12.0	2.69/12.0	2.63/12.0
2.0	0.38943250	2.86/12.0	2.79/12.0	2.77/12.0	2.71/12.0
2.1	0.47874242	2.95/12.0	2.88/12.0	2.85/12.0	2.80/12.0
2.2	0.56252208	3.04/12.0	2.97/12.0	2.93/12.0	2.88/12.0
2.3	0.63803333	3.13/12.0	3.06/12.0	3.08/13.7	3.03/13.8

Table SI.2b. Simulated IOD and CN values for the SPC/E water model (The number preceding the slash is the IOD value while the one after is the CN value).

$R_{min}/2$ (Å)	ε(kcal/mol)	M(III) ion without C_4 term	M(III) ion with C_4 = 500 kcal/mol·Å^4	M(IV) ion without C_4 term	M(IV) ion with C_4 = 500 kcal/mol·Å^4
0.9	0.00000062	1.09/2.0	0.93/2.0	1.06/2.0	0.93/2.0
1.0	0.00001423	1.35/3.0	1.07/2.0	1.32/3.0	1.06/2.0
1.1	0.00016377	1.52/4.0	1.40/4.0	1.48/4.0	1.38/4.0
1.2	0.00110429	1.80/6.0	1.52/4.0	1.75/6.0	1.50/4.0
1.3	0.00490301	1.88/6.0	1.78/6.0	1.83/6.0	1.74/6.0
1.4	0.01570749	1.99/6.0	1.90/6.0	1.99/8.8	1.86/6.0
1.5	0.03899838	2.23/8.0	2.15/8.0	2.17/8.0	2.10/8.0
1.6	0.07934493	2.36/8.9	2.26/9.2	2.29/9.0	2.21/9.9
1.7	0.13818331	2.48/9.0	2.40/9.0	2.41/9.3	2.34/9.0
1.8	0.21312875	2.61/9.8	2.54/10.0	2.53/10.0	2.48/10.0
1.9	0.29896986	2.74/10.7	2.67/10.9	2.70/12.0	2.64/12.0
2.0	0.38943250	2.87/12.0	2.80/12.0	2.78/12.0	2.72/12.0
2.1	0.47874242	2.96/12.0	2.89/12.0	2.86/12.0	2.80/12.0
2.2	0.56252208	3.04/12.0	2.98/12.0	2.94/12.0	2.89/12.0
2.3	0.63803333	3.13/12.0	3.07/12.0	3.04/12.3	2.98/12.2

Table SI.2c. Simulated IOD and CN values for the TIP4P$_{EW}$ water model (The number preceding the slash is the IOD value while the one after is the CN value).

$R_{min}/2$ (Å)	ε(kcal/mol)	M(III) ion without C_4 term	M(III) ion with C_4 = 500 kcal/mol·Å^4	M(IV) ion without C_4 term	M(IV) ion with C_4 = 500 kcal/mol·Å^4
0.9	0.00000062	1.11/2.0	0.94/2.0	1.08/2.0	0.93/2.0
1.0	0.00001423	1.37/3.0	1.08/2.0	1.33/3.0	1.07/2.0
1.1	0.00016377	1.54/4.0	1.41/4.0	1.50/4.0	1.39/4.0
1.2	0.00110429	1.82/6.0	1.53/4.0	1.77/6.0	1.51/4.0
1.3	0.00490301	1.90/6.0	1.79/6.0	1.84/6.0	1.76/6.0
1.4	0.01570749	2.01/6.0	1.91/6.0	2.02/9.0	1.87/6.0
1.5	0.03899838	2.25/8.0	2.16/8.0	2.19/8.0	2.12/8.0
1.6	0.07934493	2.38/9.0	2.28/8.4	2.31/9.0	2.23/9.9
1.7	0.13818331	2.49/9.0	2.41/9.0	2.43/9.8	2.35/9.0
1.8	0.21312875	2.63/10.0	2.55/10.0	2.64/12.0	2.58/12.0
1.9	0.29896986	2.74/10.6	2.73/12.0	2.71/12.0	2.66/12.0
2.0	0.38943250	2.89/12.0	2.81/12.0	2.79/12.0	2.73/12.0
2.1	0.47874242	2.97/12.0	2.90/12.0	2.87/12.0	2.82/12.0
2.2	0.56252208	3.06/12.0	2.99/12.0	2.96/12.0	2.91/12.0
2.3	0.63803333	3.15/12.0	3.08/12.0	3.09/13.3	3.05/13.7

Table SI.3. The estimated error for the 12-6 HFE and IOD parameter sets.

	TIP3P		SPC/E		$TIP4P_{EW}$	
	HFE set	IOD set	HFE set	IOD set	HFE set	IOD set
Al^{3+}	-0.59(-31.4%)	180.9(-16.7%)	-0.57(-30.3%)	177.0(-16.4%)	-0.78(-41.5%)	216.5(-20.0%)
Fe^{3+}	-0.54(-26.6%)	163.0(-16.0%)	-0.52(-25.6%)	160.3(-15.7%)	-0.71(-35.0%)	194.9(-19.1%)
Cr^{3+}	-0.27(-13.8%)	81.5(-8.5%)	-0.26(-13.3%)	78.0(-8.1%)	-0.42(-21.4%)	115.3(-12.0%)
In^{3+}	-0.44(-20.5%)	129.6(-13.6%)	-0.42(-19.5%)	127.6(-13.4%)	-0.58(-27.0%)	158.5(-16.7%)
Tl^{3+}	-0.51(-22.9%)	150.2(-15.8%)	-0.50(-22.4%)	148.6(-15.7%)	-0.66(-29.6%)	177.3(-18.7%)
Y^{3+}	-0.22(-9.3%)	62.7(-7.6%)	-0.21(-8.9%)	62.0(-7.5%)	-0.33(-14.0%)	86.6(-10.5%)
La^{3+}	-0.12(-4.8%)	33.3(-4.4%)	-0.12(-4.8%)	33.6(-4.5%)	-0.21(-8.3%)	54.7(-7.3%)
Ce^{3+}	-0.20(-7.8%)	54.4(-7.1%)	-0.20(-7.8%)	54.9(-7.2%)	-0.29(-11.4%)	75.0(-9.8%)
Pr^{3+}	-0.23(-9.1%)	62.5(-8.1%)	-0.22(-8.7%)	63.2(-8.1%)	-0.33(-13.0%)	83.5(-10.8%)
Nd^{3+}	-0.19(-7.7%)	52.2(-6.7%)	-0.18(-7.3%)	52.1(-6.6%)	-0.29(-11.7%)	74.0(-9.4%)
Sm^{3+}	-0.20(-8.2%)	54.8(-6.9%)	-0.19(-7.8%)	54.6(-6.9%)	-0.30(-12.3%)	77.2(-9.7%)
Eu^{3+}	-0.24(-9.8%)	65.8(-8.2%)	-0.23(-9.4%)	65.6(-8.2%)	-0.34(-13.9%)	88.4(-11.0%)
Gd^{3+}	-0.19(-7.9%)	53.0(-6.6%)	-0.18(-7.5%)	52.4(-6.5%)	-0.29(-12.1%)	76.6(-9.5%)
Tb^{3+}	-0.22(-9.2%)	61.7(-7.6%)	-0.21(-8.8%)	61.2(-7.5%)	-0.32(-13.3%)	85.2(-10.5%)
Dy^{3+}	-0.21(-8.9%)	59.5(-7.3%)	-0.20(-8.4%)	58.8(-7.2%)	-0.32(-13.5%)	83.2(-10.2%)
Er^{3+}	-0.26(-11.0%)	73.4(-8.8%)	-0.25(-10.6%)	72.7(-8.7%)	-0.37(-15.7%)	97.3(-11.6%)
Tm^{3+}	-0.27(-11.4%)	78.2(-9.3%)	-0.26(-11.0%)	77.5(-9.2%)	-0.39(-16.5%)	102.1(-12.2%)
Lu^{3+}	-0.25(-10.7%)	72.6(-8.6%)	-0.24(-10.3%)	71.7(-8.5%)	-0.37(-15.8%)	97.3(-11.6%)
AVG	-0.29(-12.8%)	82.7(-9.3%)	-0.28(-12.4%)	81.8(-9.2%)	-0.41(-18.1%)	108.0(-12.3%)
SD	0.14(7.4%)	42.7(3.6%)	0.13(7.2%)	41.6(3.5%)	0.16(9.2%)	46.4(3.7%)
Hf^{4+}	-0.70(-32.4%)	297.7(-17.9%)	-0.67(-31.0%)	296.1(-17.8%)	-0.89(-41.2%)	342.1(-20.6%)
Zr^{4+}	-0.63(-28.8%)	268.2(-16.5%)	-0.61(-27.9%)	266.7(-16.4%)	-0.81(-37.0%)	311.5(-19.2%)
Ce^{4+}	-0.49(-20.2%)	202.4(-13.8%)	-0.48(-19.8%)	204.1(-14.0%)	-0.63(-26.0%)	238.6(-16.3%)
U^{4+}	-0.73(-30.2%)	307.6(-19.6%)	-0.72(-29.8%)	309.3(-19.7%)	-0.90(-37.2%)	343.8(-21.9%)
Pu^{4+}	-0.59(-24.7%)	248.0(-16.3%)	-0.58(-24.3%)	249.0(-16.4%)	-0.75(-31.4%)	284.9(-18.7%)
Th^{4+}	-0.34(-13.9%)	142.1(-10.2%)	-0.34(-13.9%)	143.9(-10.4%)	-0.47(-19.2%)	177.0(-12.7%)
AVG	-0.58(-25.0%)	244.3(-15.7%)	-0.57(-24.5%)	244.9(-15.8%)	-0.74(-32.0%)	283.0(-18.2%)
SD	0.15(7.0%)	62.7(3.3%)	0.14(6.6%)	61.8(3.2%)	0.17(8.2%)	65.1(3.3%)

Table SI.4. Simulated HFE and IOD values for the parameters shown in Table 4.

	TIP3P			SPC/E			$TIP4P_{EW}$		
	HFE(kcal/mol)	IOD(Å)	CN	HFE(kcal/mol)	IOD(Å)	CN	HFE(kcal/mol)	IOD(Å)	CN
Al^{3+}	-1082.0	1.87	6.0	-1081.3	1.88	6.0	-1080.8	1.88	6.0
Fe^{3+}	-1019.4	2.02	6.9	-1019.2	2.02	6.8	-1020.2	2.03	6.8
Cr^{3+}	-957.8	1.95	6.0	-957.8	1.96	6.0	-957.5	1.95	6.0
In^{3+}	-951.5	2.15	8.0	-950.4	2.15	8.0	-952.2	2.15	7.9
Tl^{3+}	-948.1	2.22	8.0	-948.5	2.23	8.0	-949.7	2.22	8.0
Y^{3+}	-824.9	2.36	9.0	-824.6	2.36	9.0	-824.9	2.36	9.0
La^{3+}	-750.7	2.53	9.7	-752.1	2.52	9.2	-752.4	2.52	9.4
Ce^{3+}	-765.2	2.55	9.9	-765.1	2.55	9.7	-764.6	2.55	9.8
Pr^{3+}	-775.4	2.54	9.9	-776.6	2.54	9.7	-775.9	2.54	9.8
Nd^{3+}	-783.6	2.46	9.0	-784.3	2.47	9.0	-783.4	2.46	9.0
Sm^{3+}	-795.3	2.44	9.0	-794.8	2.44	9.0	-795.4	2.44	9.0
Eu^{3+}	-802.1	2.44	9.0	-803.4	2.45	9.0	-802.8	2.45	9.0
Gd^{3+}	-806.5	2.39	9.0	-807.2	2.39	9.0	-807.6	2.39	9.0
Tb^{3+}	-813.5	2.40	9.0	-812.2	2.40	9.0	-812.9	2.40	9.0
Dy^{3+}	-818.4	2.37	9.0	-819.0	2.37	9.0	-819.3	2.38	9.0
Er^{3+}	-834.8	2.36	9.0	-834.9	2.36	9.0	-836.2	2.36	9.0
Tm^{3+}	-840.7	2.37	9.0	-840.2	2.36	9.0	-840.6	2.36	9.0
Lu^{3+}	-839.3	2.34	9.0	-840.4	2.34	9.0	-840.9	2.34	9.0
Avg. Error	0.1	0.00	--	0.0	0.00	--	-0.3	0.00	--
SD	0.6	0.01	--	0.5	0.00	--	0.6	0.00	--
Unsigned Avg. Error	0.5	0.00	--	0.4	0.00	--	0.6	0.00	--
Hf^{4+}	-1663.9	2.16	10.0	-1663.9	2.16	8.0	-1663.3	2.16	8.0
Zr^{4+}	-1622.7	2.19	9.9	-1622.9	2.19	9.8	-1622.6	2.19	9.9

Ce^{4+}	-1462.2	2.42	10.0	-1462.1	2.42	10.0	-1462.0	2.42	10.0
U^{4+}	-1566.6	2.41	10.0	-1566.0	2.42	10.0	-1569.3	2.42	10.0
Pu^{4+}	-1519.4	2.39	10.0	-1520.3	2.39	10.0	-1520.4	2.40	10.0
Th^{4+}	-1389.3	2.44	10.0	-1388.3	2.45	10.0	-1388.0	2.44	10.0
Avg. Error	0.6	0.00	--	0.8	0.00	--	0.4	0.00	--
SD	0.4	0.01	--	0.8	0.00	--	1.2	0.01	--
Unsigned Avg. Error	0.6	0.00	--	0.9	0.00	--	1.0	0.00	--

Table SI.5. Polarizability values of AMBER atom types used the 12-6-4 nonbonded model simulation of a protein system.[a]

Atom Type	Polarizability	Atom Type	Polarizability	Atom Type	Polarizability
HW	0.000	O2	0.569	CB	1.352
FE	0.264	OH	0.637	CC	1.352
H	0.387	CT	1.061	CN	1.352
H1	0.387	N	1.090	CR	1.352
H4	0.387	N2	1.090	CV	1.352
H5	0.387	N3	1.090	CW	1.352
HA	0.387	NA	1.090	OW	1.444
HC	0.387	NB	1.090	S	3.000
HO	0.387	C	1.352	SH	3.000
HP	0.387	C*	1.352		
O	0.569	CA	1.352		

a. The poarlzaibilty of Fe was calculated at the B3LYP/6-311++G(2d,2p) level of theory using Gaussian 09 Revision C.01.[1] The polarizaiblity of the water oxygen (OW) was taken from Eisenberg and Kauzmann[2] while the polarizabilities of the other atom types are adopted from Miller.[3]

Simulation protocol for the protein system:

The AMBER 12[4] and Amber Tools[4] were employed for structure modeling, minimization, molecular dynamics simulation and data analysis. Chain C in PDB entry 4BV1 was used in our simulations. The H++ web server[5] was used to add hydrogens to the protein system using a pH 7.2, a salinity of 0.15, an internal dielectric and external dielectric constant as 4 and 80 respectively. Different names of the His groups were assigned due to their pronation states. Afterwards the Cys residue binding to the iron ion was renamed as CYM while the hydrogen atom linked to sulfur was deleted. ACE and NME groups were used to cap the protein system. A TIP3P[6] water box was chosen to solvate the protein system with a thickness as 10 Å. The polarizability value of each atom type are shown in Table SI.5.

1. 2000 steps of steepest descent minimization plus 3000 steps of conjugate gradient minimization were performed for the system with the protein (except the capped residues) with the metal ion being held by a force restraint of 500 kcal/mol·Å^2.
2. 2000 steps of steepest descent minimization followed by 3000 steps of conjugate gradient minimization were carried out for the system with a 500 kcal/mol·Å^2 force constant on the heavy atoms of the protein and metal ion.
3. 10000 steps of steepest descent minimization and afterwards 10000 steps of conjugate gradient minimization were performed for the system with the backbone C, CA and N atoms of the protein where a 200 kcal/mol·Å^2 restraint was placed on them.
4. 5000 steps of steepest descent minimization with 40000 steps of conjugate gradient minimization was carried out for the entire system.

5. 400 ps of simulation using the NVT ensemble was performed to heat the system from 0 K to 300 K with the protein system and metal ion having a force restraint of 10 kcal/mol·Å^2.
6. 200 ps of simulation using the NVT ensemble was carried out to equilibrate the system at 300 K.
7. A 2 ns simulation using the NPT ensemble was performed at 300 K and 1 atmosphere to correct the density and further equilibrate the system.
8. Finally, 10 ns of simulation was performed using the NPT ensemble at 300 K and 1 atm with snapshots being stored every 2 ps. In total there were 5000 frames for further analysis.

The Langevin algorithm was used to control the temperature with a collision frequency set at 5.0 ps^{-1}. Isotropic position scaling was employed to control the pressure with a relaxation time of 2.0 ps. The cut off value was set to 10 Å. PME was used to handle long-range electrostatic interactions.[7-9] SHAKE[10] was employed during the simulation to constraint the positions of the hydrogen atoms while for water the "three-point" algorithm[11] was employed.

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