

Supporting Information
for

Performance of 3D-RISM-KH in Predicting Hydration Free Energy: Effect of Solute Parameters

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Table S1: Correlation coefficients (a and b) obtained from ordinary linear regression^a to calculate corrected hydration free energy as $\Delta G_{UC} = \Delta G_{GF} - a \times PMV + b$

Solute Force Filed	Solute Charge	Water Force Field	a	$-b$
UFF	M062X	SPCE2	1.3061	5.0133
UFF	LDA	SPCE2	1.3061	5.0133
UFF	B3LYP	SPCE2	1.3069	5.0026
GAFF	AM1-BCC	SPCE	0.1443	0.9343
GAFF	AM1-BCC	SPCE2	0.1383	0.9274
GAFF	AM1-BCC	TIP3P	0.1364	0.9566
GAFF	AM1-BCC	TIP4P	0.1276	1.3376
GAFF	AM1-BCC	TIP5P	0.0960	1.0042
UFF	AM1	SPCE	0.1436	3.1515
UFF	AM1	SPCE2	0.1388	3.3617
UFF	AM1	TIP3P	0.1354	3.0804
UFF	AM1	TIP4P	0.1245	3.2803
UFF	AM1	TIP5P	0.0929	2.4883
UFF	AM1-BCC	SPCE	0.1471	1.1859
UFF	AM1-BCC	SPCE2	0.1428	1.1761
UFF	AM1-BCC	TIP3P	0.1389	1.1804
UFF	AM1-BCC	TIP4P	0.1276	1.5124
UFF	AM1-BCC	TIP5P	0.0952	1.0636
UFF	AIM	SPCE	0.0703	6.2924
UFF	AIM	SPCE2	0.0549	7.4204
UFF	AIM	TIP3P	0.0644	6.1504
UFF	AIM	TIP4P	0.0612	6.7211
UFF	AIM	TIP5P	0.0418	5.1552
UFF	EQeQ	SPCE	0.0703	6.2924
UFF	EQeQ	SPCE2	0.0549	7.4204
UFF	EQeQ	TIP3P	0.0644	6.1504
UFF	EQeQ	TIP4P	0.0612	6.7211
UFF	EQeQ	TIP5P	0.0418	5.1552
UFF	QeQ	SPCE	0.0703	6.2924
UFF	QeQ	SPCE2	0.0549	7.4204
UFF	QeQ	TIP3P	0.0644	6.1504
UFF	QeQ	TIP4P	0.0612	6.7211
UFF	QeQ	TIP5P	0.0418	5.1552
UFF	QTPIE	SPCE	0.1295	1.0655
UFF	QTPIE	SPCE2	0.1209	1.1534

UFF	QTPIE	TIP3P	0.1223	1.0954
UFF	QTPIE	TIP4P	0.1122	1.5936
UFF	QTPIE	TIP5P	0.0849	1.2685
GAFF	DDEC6	SPCE	0.1519	1.2327
GAFF	DDEC6	SPCE2	0.1471	1.2376
GAFF	DDEC6	TIP3P	0.1437	1.2414
GAFF	DDEC6	TIP4P	0.1338	1.5576
GAFF	DDEC6	TIP5P	0.1010	1.1509
UFF	DDEC6	SPCE	0.1522	1.2727
UFF	DDEC6	SPCE2	0.1484	1.2916
UFF	DDEC6	TIP3P	0.1438	1.2617
UFF	DDEC6	TIP4P	0.1318	1.5593
UFF	DDEC6	TIP5P	0.0988	1.0851
UFF	CHelpG	SPCE	0.1450	0.0683
UFF	CHelpG	SPCE2	0.1408	-0.0715
UFF	CHelpG	TIP3P	0.1368	0.1149
UFF	CHelpG	TIP4P	0.1256	0.5277
UFF	CHelpG	TIP5P	0.0931	0.3506
UFF	CM5	SPCE	0.1512	0.6506
UFF	CM5	SPCE2	0.1479	0.5472
UFF	CM5	TIP3P	0.1427	0.6748
UFF	CM5	TIP4P	0.1309	0.9895
UFF	CM5	TIP5P	0.0974	0.6758
UFF	MK	SPCE	0.1440	-0.0745
UFF	MK	SPCE2	0.1396	-0.2478
UFF	MK	TIP3P	0.1358	-0.0235
UFF	MK	TIP4P	0.1247	0.3983
UFF	MK	TIP5P	0.0925	0.2224
UFF	MUL	SPCE	0.1457	0.7840
UFF	MUL	SPCE2	0.1417	0.6942
UFF	MUL	TIP3P	0.1374	0.8031
UFF	MUL	TIP4P	0.1262	1.1356
UFF	MUL	TIP5P	0.0937	0.7755
UFF	NPA	SPCE	0.1246	0.6140
UFF	NPA	SPCE2	0.1173	0.5273
UFF	NPA	TIP3P	0.1170	0.6632
UFF	NPA	TIP4P	0.1086	1.0921
UFF	NPA	TIP5P	0.0797	0.7393

Table S2: Summary of the performance of different force field parameters in predicting SFEs by the 3D-RISM-KH molecular solvation theory

Solute Force Filed	Solute Charge	Water Force Field	RMSE (Train)	RMSE (Test)	RMSE (All)	MAD (Train)	MAD (Test)	MAD (All)
		CPCM	2.4	2.8	2.5	1.8	2.0	1.8
		SMD	2.0	2.7	2.2	1.1	1.3	1.1
UFF	M062X	SPCE2	8.5	11.6	9.4	3.5	4.0	3.7
	LDA	SPCE2	8.3	14.2	10.1	3.5	4.3	3.7
	B3LYP	SPCE2	8.3	14.6	10.2	3.5	4.2	3.7
GAFF	AM1-BCC	SPCE	2.3	2.8	2.4	1.4	1.5	1.4
		SPCE2	2.6	3.1	2.7	1.6	1.7	1.6
		TIP3P	2.3	2.7	2.4	1.3	1.5	1.4
		TIP4P	2.2	2.6	2.3	1.3	1.4	1.3
		TIP5P	2.0	2.4	2.1	1.3	1.4	1.3
UFF	AM1	SPCE	3.4	3.8	3.5	2.5	2.9	2.6
		SPCE2	3.5	3.9	3.6	2.5	2.9	2.6
		TIP3P	3.4	3.8	3.5	2.5	2.9	2.6
		TIP4P	3.4	3.8	3.5	2.5	2.9	2.6
		TIP5P	3.4	3.7	3.5	2.5	2.9	2.6
UFF	AM1-BCC	SPCE	2.5	2.8	2.5	1.7	2.0	1.8
		SPCE2	2.4	2.8	2.5	1.7	1.9	1.7
		TIP3P	2.5	2.8	2.5	1.8	2.0	1.8
		TIP4P	2.5	2.8	2.6	1.8	2.0	1.9
		TIP5P	2.6	2.9	2.7	1.9	2.2	2.0
UFF	AIM	SPCE	11.9	11.5	11.8	9.0	8.8	8.9
		SPCE2	12.7	12.4	12.6	9.8	9.5	9.7
		TIP3P	11.5	11.2	11.5	8.7	8.5	8.6
		TIP4P	10.6	10.3	10.5	7.9	7.7	7.8
		TIP5P	9.4	9.0	9.3	6.7	6.7	6.7
UFF	EQeQ	SPCE	11.9	11.5	11.8	9.0	8.8	8.9
		SPCE2	12.7	12.4	12.6	9.8	9.5	9.7
		TIP3P	11.5	11.2	11.5	8.7	8.5	8.6
		TIP4P	10.6	10.3	10.5	7.9	7.7	7.8
		TIP5P	9.4	9.0	9.3	6.7	6.7	6.7
UFF	QeQ	SPCE	11.9	11.5	11.8	9.0	8.8	8.9
		SPCE2	12.7	12.4	12.6	9.8	9.5	9.7
		TIP3P	11.5	11.2	11.5	8.7	8.5	8.6
		TIP4P	10.6	10.3	10.5	7.9	7.7	7.8
		TIP5P	9.4	9.0	9.3	6.7	6.7	6.7
UFF	QTPIE	SPCE	4.8	5.4	4.9	3.5	3.7	3.5
		SPCE2	5.7	6.3	5.8	4.2	4.3	4.2
		TIP3P	4.5	5.1	4.7	3.3	3.5	3.3
		TIP4P	4.2	4.7	4.3	3.0	3.2	3.1

		TIP5P	3.2	3.7	3.3	2.3	2.6	2.4
GAFF	DDEC6	SPCE	2.2	2.7	2.3	1.5	1.8	1.6
		SPCE2	2.3	2.8	2.4	1.6	1.8	1.6
		TIP3P	2.2	2.6	2.3	1.5	1.8	1.6
		TIP4P	2.2	2.6	2.3	1.5	1.8	1.6
		TIP5P	2.2	2.6	2.3	1.6	1.8	1.7
UFF	DDEC6	SPCE	2.6	2.9	2.7	2.0	2.2	2.0
		SPCE2	2.5	2.9	2.6	1.9	2.1	2.0
		TIP3P	2.6	2.9	2.7	2.0	2.2	2.0
		TIP4P	2.7	3.0	2.7	2.0	2.2	2.0
		TIP5P	2.8	3.1	2.9	2.1	2.3	2.1
UFF	CHelpG	SPCE	2.5	3.1	2.7	1.8	1.9	1.8
		SPCE2	2.7	3.2	2.8	1.8	2.0	1.9
		TIP3P	2.5	3.0	2.6	1.8	1.9	1.8
		TIP4P	2.4	2.9	2.5	1.7	1.8	1.7
		TIP5P	2.3	2.8	2.5	1.7	1.8	1.7
UFF	CM5	SPCE	2.5	3.0	2.6	1.8	2.0	1.9
		SPCE2	2.4	3.0	2.6	1.8	2.0	1.8
		TIP3P	2.5	3.0	2.6	1.8	2.0	1.9
		TIP4P	2.5	3.0	2.7	1.8	2.1	1.9
		TIP5P	2.6	3.1	2.7	1.9	2.2	1.9
UFF	MK	SPCE	2.5	3.0	2.6	1.7	1.9	1.8
		SPCE2	2.6	3.2	2.8	1.8	2.0	1.8
		TIP3P	2.4	3.0	2.6	1.7	1.9	1.8
		TIP4P	2.3	2.9	2.5	1.7	1.8	1.7
		TIP5P	2.3	2.8	2.4	1.7	1.8	1.7
UFF	MUL	SPCE	2.9	3.3	3.0	2.3	2.4	2.3
		SPCE2	3.0	3.3	3.1	2.3	2.5	2.3
		TIP3P	2.9	3.2	3.0	2.2	2.4	2.3
		TIP4P	2.9	3.2	3.0	2.2	2.4	2.3
		TIP5P	2.9	3.2	3.0	2.2	2.4	2.2
UFF	NPA	SPCE	4.3	4.9	4.4	3.1	3.3	3.2
		SPCE2	4.8	5.3	4.9	3.5	3.7	3.5
		TIP3P	4.2	4.7	4.3	3.0	3.2	3.1
		TIP4P	3.8	4.4	4.0	2.8	3.0	2.8
		TIP5P	3.4	3.9	3.5	2.5	2.7	2.5

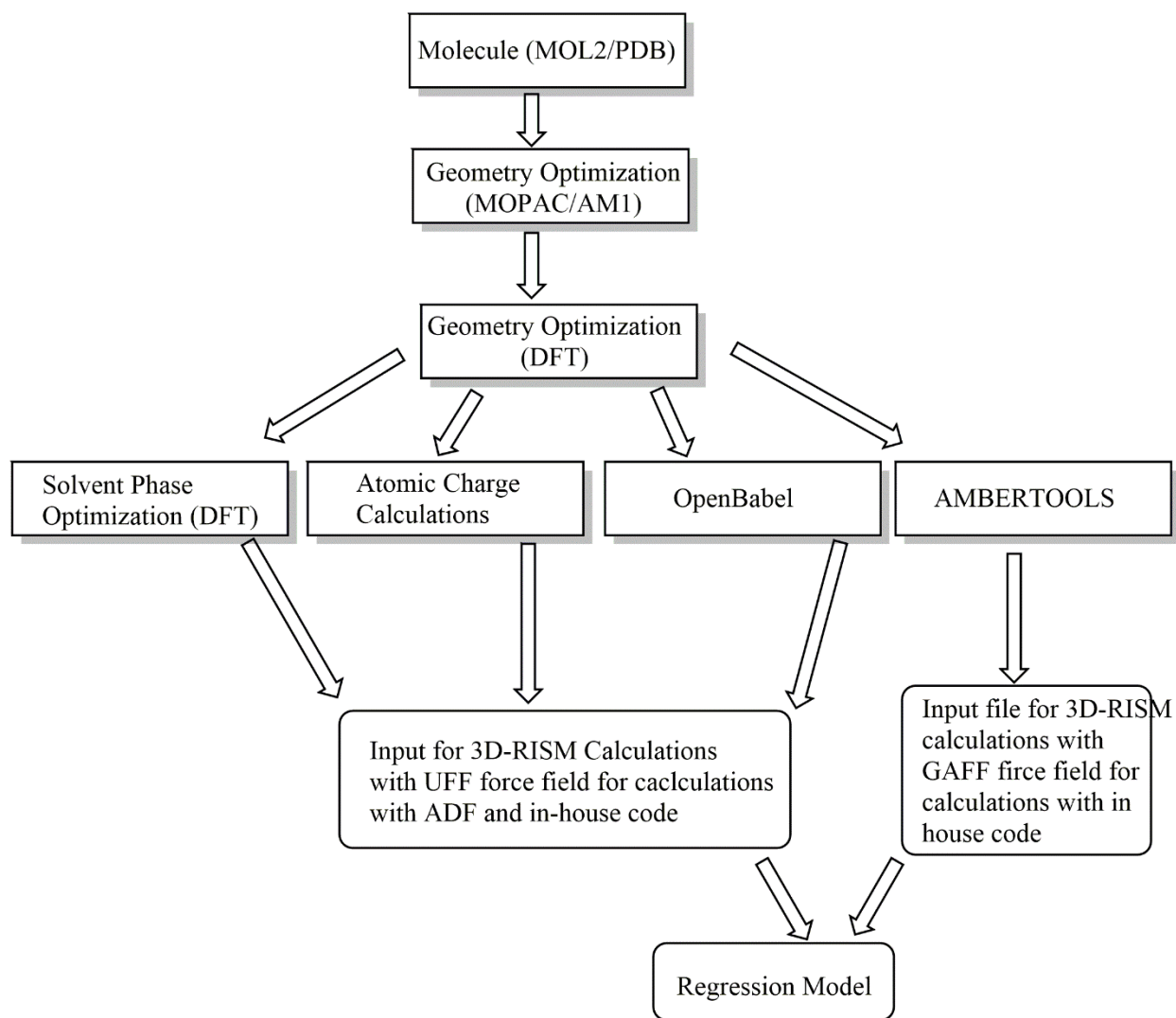


Figure S1: Workflow adopted in this manuscript for processing molecular input files for various calculations.

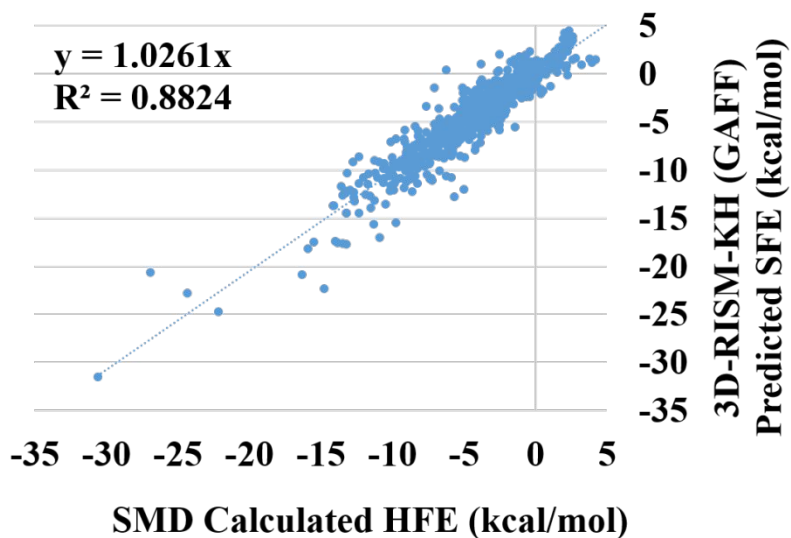


Figure S2: Correlation of the 3D-RISM-KH(GAFF) computed SFEs with that predicted by the SMD continuum solvation model.

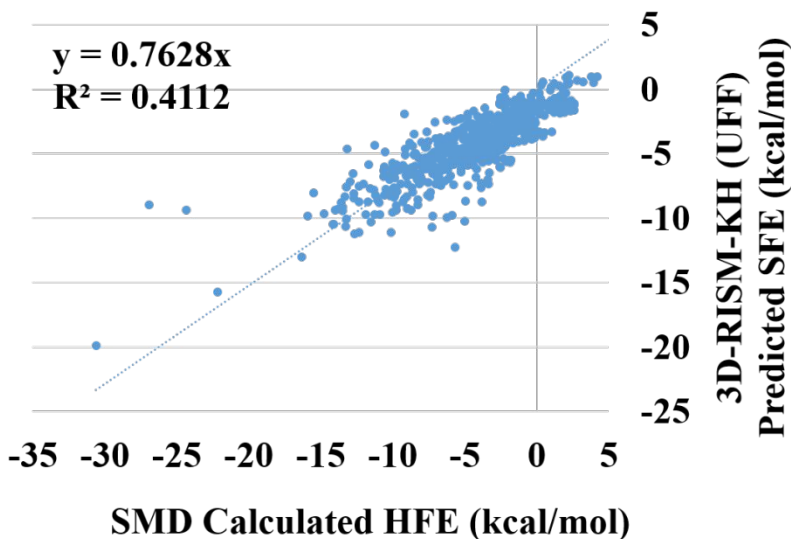


Figure S3: Correlation of the 3D-RISM-KH(UFF/AM1-BCC) computed SFEs with that predicted by the SMD continuum solvation model.

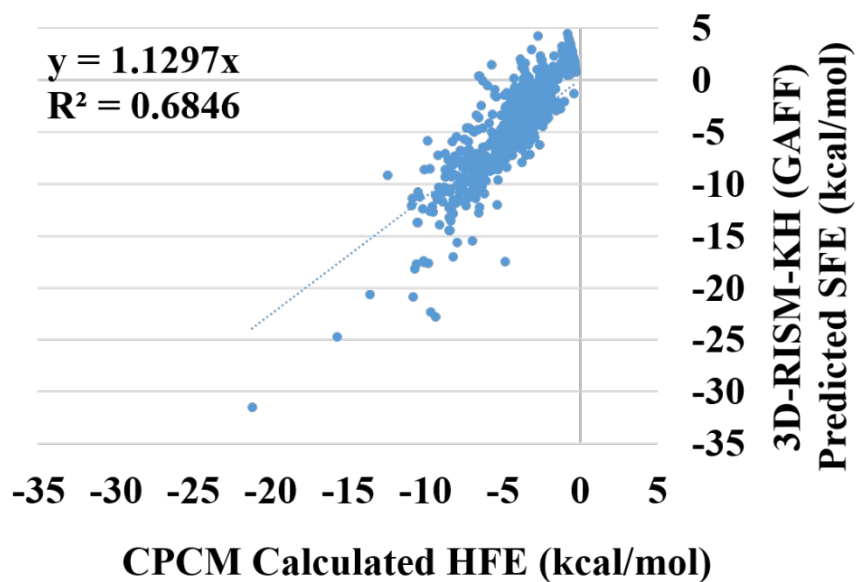


Figure S4: Correlation of the 3D-RISM-KH(GAFF) computed SFEs with that predicted by the CPCM continuum solvation model.

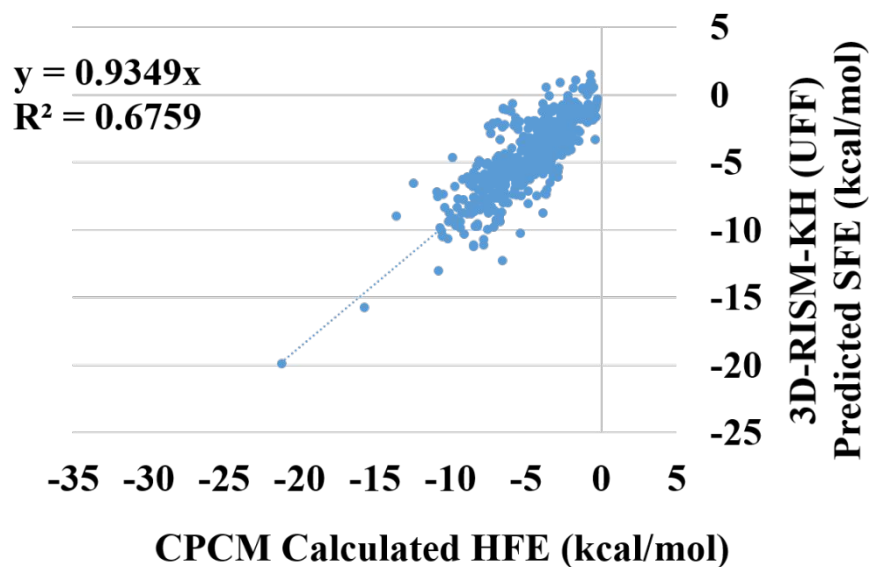


Figure S5: Correlation of the 3D-RISM-KH(UFF/AM1-BCC) computed SFEs with that predicted by the SMD continuum solvation model.

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