KMTISM solvation model is an implicit water solvation model developed in our group on the basis of the Movable Type (MT) method. This model places water layers centered on the solute molecule and treats the contact between the solute molecule and each water molecule as independent interaction energies, then samples the energy by evaluating a numerical integral over the solute-solvent energies for all the water layers. The solvation free energy for a solute molecule is calculated according to the following steps.

Water molecules were modeled as isotropic rigid balls with van der Waals radii of 1.6 Å. Water molecules were placed into layers outside the solute molecule, starting from the solute's water accessible surface (SASA) until 8 Å away from the solute's van der Waals surface. A 0.005 Å interval was set between every two layers. The number of water molecules accessible to each layer was calculated by comparing the maximum cross-sectional area (S_w) of a water molecule to the atomic solvent accessible surface area (S_a) in each solvent layer at r away from the solute SASA:

$$N_w(r) = \mathrm{floor}\left(\frac{S_a(r)}{S_w}\right) \tag{1}$$

As is shown in Figure 1, the maximum cross-sectional areas (Sw) of a water molecule is calculated as:

$$\begin{aligned} S_w &= \int_{\frac{\pi}{2}-\theta}^{\frac{\pi}{2}} 2\pi\left(R_a + R_w\right)R_w \sin\left(\frac{\pi-\theta}{2}\right)d\left(\frac{\pi}{2}-\theta\right) \\ &= 2\pi\left(R_a + R_w\right)R_w \cos\left(\frac{\pi-\theta}{2}\right) \end{aligned} \tag{2}$$

where R_w and R_a are the van der Waals radii for water and the atom in the solute molecule respectively.

In this study, interaction energies between each solute's atom and the water molecule at each layer was calculated using the GARF energy function employing the distance (r_i^w) between the solute's atom *i* and the water layer, and weighted by the number of water molecules at that layer, $N_w(r_i^w)$. The MT method treats all the solute's atom−water contact energies as independent variables hence the solvation ensemble energy is calculated using the numerical integral:

$$Z^{sol} = \prod_i^{N_{solute}} \left(\int_{r_i^0}^{r_i^0+8\text{Å}} \exp\left(-\frac{1}{RT} N_w(r_i^w) E_i^{sol}\left(r_i^w\right) \right) dr_i^w \right) \quad (3)$$

According to equation 3, the weighted solute-solvent interaction energy for each solute atom *i* is integrated from r_i^0, the distance between atom *i* and the water molecule at the innermost layer (SASA), to 8 Å away. The integrals are calculated independently for all solute atoms (N_{solute}) and multiplied to model the solvation ensemble energy. The solvation free energy is then approximated using the Z^{sol} generated from equation 3.

$$\Delta G^{sol} \approx -RT \ln\left[Z^{sol} \right] \quad (4)$$

In this study, we applied the KMTISM solvation model using both the GARF and KECSA energy functions for solvation free energy calculation against the same test set used in our original KMTISM paper (Zheng, Z.; Wang, T.; Pan, L.; Merz, K. M. Jr., KECSA-Movable Type Implicit Solvation Model (KMTISM). *J. Chem. Theory Comput.* **2015**, 11, 667–682), which includes 372 neutral molecules and 21 ions (10 anions and 11 cations) selected from the Minnesota Solvation Database v2012. In the original study, we also applied the MM-GBSA and

MM-PBSA methods against the same test set. Herein, we include the results using these two classical mechanics methods from our original publication as well, for the sake of comparison. All the detailed calculation results are listed in Table 1S and 2S in this Supporting Information material.

Against the neutral solute test set, the GARF-KMTISM model generated an R^2 of 0.81 and a RMSE of 1.99 kcal/mol compared to the R^2=0.79 and RMSE=2.59 kcal/mol using the KECSA-KMTISM model; R^2=0.73 and RMSE=4.62 kcal/mol using the MM-GBSA model; and R^2=0.80 and RMSE=4.64 kcal/mol using the MM-PBSA model.

Against the ion solute test set, the GARF-KMTISM model generated an R^2 of 0.72 and a RMSE of 3.85 kcal/mol compared to the R^2=0.35 and RMSE=5.77 kcal/mol using the KECSA-KMTISM model' R^2=0.00 and RMSE=11.73 kcal/mol using the MM-GBSA model; and R^2=0.80 and RMSE=10.48 kcal/mol using the MM-PBSA model.

Against all test cases including both neutral and ion solutes, the GARF-KMTISM model generated an R^2 of 0.98 and a RMSE of 2.14 kcal/mol compared to the R^2=0.97 and RMSE=2.86 kcal/mol using the KECSA-KMTISM model; R^2=0.92 and RMSE=5.26 kcal/mol using the MM-GBSA model; and R^2=0.92 and RMSE=5.13 kcal/mol using the MM-PBSA model.

From these validation studies, we found that the GARF potential outperformed the the KECSA potential, which provides evidence that the graph model based parameterization has advantage over the traditional knowledge-based scoring function. Incidentally, the GARF energy function also shows better performance compared to the two classical mechanics methods, MM-GBSA and MM-PBSA model in this solvation free energy validation study.

Table 1S. GARF-KMTISM, KECSA-KMTISM, MM-GBSA and MM-PBSA calculated solvation free energies (in kcal/mol) against 372 neutral compounds.

Compound ID	Exp. ΔGsolv	GARF-KMTISM	KECSA-KMTISM	MM-GBSA	MM-PBSA	Solute Name	Formula
0001met	2	0.47	1.02	-0.05	2.57	methane	H4C1
0002eth	1.83	0.86	1.39	0.69	2.65	ethane	H6C2
0003pro	1.96	1.19	1.67	0.93	2.72	n-propane	H8C3
0004nbu	2.08	1.49	1.95	1.15	2.9	n-butane	H10C4
0005npe	2.33	1.78	2.18	1.36	3.09	n-pentane	H12C5
0006nhe	2.49	2.07	2.45	1.57	3.33	n-hexane	H14C6
0007nhe	2.62	2.36	2.71	1.8	3.57	n-heptane	H16C7
0008noc	2.89	2.65	3.01	2.02	3.79	n-octane	H18C8
0010met	2.32	1.47	1.83	0.88	2.8	2-methylpropane	H10C4
0011dim	2.5	1.71	1.88	1.05	2.87	2,2-dimethylpropane	H12C5
0012met	2.52	1.97	2.28	1.32	3.22	2-methylpentane	H14C6
0013dim	2.88	2.18	2.35	1.31	3.4	2,4-dimethylpentane	H16C7
0014tri	2.85	2.34	2.39	1.45	3.39	2,2,4-trimethylpentane	H18C8
0016cyc	0.75	0.44	1.63	0.51	2.48	cyclopropane	H6C3
0017cyc	1.2	0.82	2.03	1.21	1.92	cyclopentane	H10C5
0018cyc	1.23	1.02	2.19	1.38	2.03	cyclohexane	H12C6
0019met	1.71	1.30	2.35	1.39	2.26	methylcyclohexane	H14C7
0020cis	1.58	1.51	2.46	1.38	2.37	cis-1,2-dimethylcyclohexane	H16C8
0021eth	1.27	1.18	-0.96	-0.34	1.98	ethene	H4C2
0022pro	1.27	1.08	-0.06	-0.03	2.03	propene	H6C3
0023str	0.61	2.04	-1.35	-0.78	1.37	s-trans-1,3-butadiene	H6C4
0024met	1.16	1.37	0.67	-0.01	2.03	2-methylpropene	H8C4
0025buta	1.38	1.37	0.29	0.24	2.19	1-butene	H8C4
0026cyc	0.56	0.61	0.7	0.08	0.89	cyclopentene	H8C5
0027pen	1.66	1.67	0.57	0.49	2.44	1-pentene	H10C5
0028Epe	1.34	1.33	1.23	0.6	2.44	E-2-pentene	H10C5
0029hex	1.68	1.97	0.84	0.71	2.65	1-hexene	H12C6
0030eth	-0.01	-0.51	-1	-1.07	-0.68	ethyne	H2C2
0031pro	-0.31	-0.56	-0.09	-1.06	-0.74	propyne	H4C3
0032but	-0.16	-0.15	0.28	-0.71	-0.38	1-butyne	H6C4
0033pen	0.01	0.20	0.63	-0.44	-0.08	1-pentyne	H8C5
0034hex	0.29	0.50	0.8	-0.2	0.13	1-hexyne	H10C6
0035ben	-0.87	-0.79	-1.59	-2.59	-1.77	benzene	H6C6
0036tol	-0.89	-0.57	-0.74	-2.34	-1.45	toluene	H8C7
0037eth	-0.8	-0.20	-0.34	-1.96	-1.09	ethylbenzene	H10C8
0038oxy	-0.9	-0.41	-0.09	-2.12	-1.28	o-xylene	H10C8

0039mxy	-0.84	-0.34	0.11	-2.02	-1.08	m-xylene	H10C8
0040pxy	-0.81	-0.39	0.16	-2.01	-1.06	p-xylene	H10C8
0041nap	-2.39	-1.94	-2.08	-4.31	-4.59	naphthalene	H8C10
0042ant	-4.23	-2.95	-2.54	-5.68	-6.98	anthracene	H10C14
0044met	-5.11	-4.97	-5.8	-8.2	-7.35	methanol	H4C1O1
0045eth	-5.01	-4.19	-4.96	-7.45	-6.83	ethanol	H6C2O1
0046eth	-9.3	-7.84	-11	-15.6	-16.12	1,2-ethanediol	H6C2O2
0047pro	-4.83	-3.60	-4.6	-6.97	-6.47	1-propanol	H8C3O1
0048pro	-4.76	-3.50	-4.2	-7.01	-6.23	isopropanol	H8C3O1
0049but	-4.72	-3.21	-3.98	-6.71	-6.23	1-butanol	H10C4O1
0050met	-4.51	-2.89	-3.29	-6.34	-5.62	t-butanol	H10C4O1
0051cyc	-5.49	-3.18	-3.62	-6.5	-6.87	cyclopentanol	H10C5O1
0052pen	-4.47	-2.93	-4.25	-6.43	-6.04	1-pentanol	H12C5O1
0053phe	-6.62	-4.75	-7.41	-11.11	-10.47	phenol	H6C6O1
0054hex	-4.36	-2.64	-3.93	-6.18	-5.79	1-hexanol	H14C6O1
0055ocr	-5.87	-4.26	-5.74	-10.38	-9.57	o-cresol	H8C7O1
0056mcr	-5.49	-4.50	-6.85	-10.67	-9.98	m-cresol	H8C7O1
0057pcr	-6.14	-4.57	-6.43	-10.78	-10.17	p-cresol	H8C7O1
0058hep	-4.24	-2.35	-3.63	-5.96	-5.5	1-heptanol	H16C7O1
0060dim	-1.92	-2.59	-2.92	-2.24	-1.85	dimethylether	H6C2O1
0061tet	-3.47	-2.59	-2.92	-2.25	-1.85	tetrahydrofuran	H8C4O1
0062dio	-5.05	-4.11	-7.22	-3.64	-6.01	1,4-dioxane	H8C4O2
0063die	-1.76	-1.44	-1.52	-1.27	-0.91	diethylether	H10C4O1
0064met	-1.66	-1.52	-1.1	-1.33	-0.93	methylpropylether	H10C4O1
0065met	-2.01	-1.49	-0.83	-1.53	-0.98	methylisopropylether	H10C4O1
0066dim	-4.84	-4.51	-4.24	-4.66	-5.9	1,2-dimethoxyethane	H10C4O2
0067but	-2.21	-1.05	-0.32	-1.37	-0.79	t-butylmethylether	H12C5O1
0068ani	-2.45	-2.74	-3.65	-4.3	-4.02	anisole	H8C7O1
0070eth	-3.5	-2.29	-5.19	-6.76	-4.99	acetaldehyde	H4C2O1
0071proa	-3.44	-1.72	-4.09	-6.05	-4.44	propanal	H6C3O1
0072but	-3.18	-1.36	-4.56	-6	-4.42	butanal	H8C4O1
0073pen	-3.03	-1.00	-3.63	-5.51	-3.98	pentanal	H10C5O1
0074ben	-4.02	-4.76	-6.61	-8.56	-7.55	benzaldehyde	H6C7O1
0075pro	-3.85	-2.92	-4.13	-6.06	-4.51	acetone	H6C3O1
0076but	-3.64	-2.29	-3.19	-5.51	-3.91	2-butanone	H8C4O1
0077cyc	-4.68	-1.53	-4.08	-5.23	-4.62	cyclopentanone	H8C5O1
0078pen	-3.53	-1.85	-2.93	-5.22	-3.66	2-pentanone	H10C5O1
0079pen	-3.41	-1.67	-1.92	-4.95	-3.31	3-pentanone	H10C5O1
0080hex	-3.29	-1.51	-2.62	-4.96	-3.43	2-hexanone	H12C6O1
0081dim	-2.89	-1.37	-2.77	-4.99	-3.36	3,3-dimethylbutanone	H12C6O1
0082hep	-3.04	-1.22	-2.45	-4.72	-3.18	2-heptanone	H14C7O1
0083hep	-2.93	-0.79	-1.59	-4.43	-2.65	4-heptanone	H14C7O1
0084met	-4.58	-4.38	-5.46	-7.94	-7.16	acetophenone	H8C8O1

0085non	-2.67	-0.10	-0.91	-3.89	-2.01	5-nonanone	H18C9O1
0086eth	-6.7	-6.49	-11.44	-15.99	-15	aceticacid	H4C2O2
0087pro	-6.47	-5.74	-10.12	-11.57	-10.83	propanoicacid	H6C3O2
0088but	-6.36	-5.29	-9.72	-11.26	-10.75	butanoicacid	H8C4O2
0089pen	-6.16	-4.97	-9.46	-11.02	-10.42	pentanoicacid	H10C5O2
0090hex	-6.21	-4.68	-9.37	-10.65	-10.19	hexanoicacid	H12C6O2
0091met	-2.78	-3.21	-4.28	-7.85	-6.82	methylformate	H4C2O2
0092ethb	-2.65	-2.61	-3.5	-7.23	-6.27	ethylformate	H6C3O2
0093met	-3.32	-3.06	-6.61	-6.66	-5.79	methylacetate	H6C3O2
0094met	-2.93	-2.48	-5.07	-6.06	-5.13	methylpropanoate	H8C4O2
0095eth	-3.1	-2.45	-4.88	-6.1	-5.13	ethylacetate	H8C4O2
0096met	-2.83	-2.08	-4.98	-5.68	-4.79	methylbutanoate	H10C5O2
0097pro	-2.86	-1.98	-4.55	-5.77	-4.68	propylacetate	H10C5O2
0098met	-2.57	-1.76	-4.94	-5.41	-4.59	methylpentanoate	H12C6O2
0099but	-2.55	-1.64	-4.53	-5.43	-4.38	butylacetate	H12C6O2
0100met	-2.49	-1.47	-4.54	-5.2	-4.2	methylhexanoate	H14C7O2
0101pen	-2.45	-1.34	-4	-5.2	-4.13	pentylacetate	H14C7O2
0103eth	-4.5	-4.17	-5.37	-5.65	-3.94	ethylamine	H7C2N1
0104dim	-4.29	-4.46	-1.01	-3.86	-3.75	dimethylamine	H7C2N1
0105aze	-5.56	-3.90	-1.9	-4.14	-4.48	azetidine	H7C3N1
0106pro	-4.39	-3.61	-5.25	-5.25	-3.67	propylamine	H9C3N1
0107tri	-3.23	-3.76	1.14	-1.42	-3.43	trimethylamine	H9C3N1
0108pyr	-5.48	-3.48	-1.16	-2.65	-4.26	pyrrolidine	H9C4N1
0109pip	-7.4	-7.43	-6.87	-5.62	-8.76	piperazine	H10C4N2
0110but	-4.29	-3.23	-4.7	-4.88	-3.43	butylamine	H11C4N1
0111die	-4.07	-3.09	-0.14	-1.89	-2.58	diethylamine	H11C4N1
0112Nme	-7.77	-6.64	-5.28	-3.01	-8.25	N-methylpiperazine	H12C5N2
0113pen	-4.1	-2.93	-4.51	-4.72	-3.22	pentylamine	H13C5N1
0114NNd	-7.58	-5.90	-3.27	-0.39	-7.73	N,N'-dimethylpiperazine	H14C6N2
0115dip	-3.66	-2.06	0.34	-0.96	-1.71	dipropylamine	H15C6N1
0116pyr	-4.7	-4.60	-5.22	-6.09	-5.43	pyridine	H5C5N1
0117met	-5.57	-4.72	-7.53	-9.78	-9.42	2-methylpyrazine	H6C5N2
0118ani	-5.49	-4.74	-7.7	-7.88	-6.97	aniline	H7C6N1
0119met	-4.63	-4.09	-4.4	-5.7	-4.87	2-methylpyridine	H7C6N1
0120met	-4.77	-4.27	-4.89	-5.63	-4.98	3-methylpyridine	H7C6N1
0121met	-4.94	-4.26	-4.89	-5.89	-5.16	4-methylpyridine	H7C6N1
0122Nme	-4.68	-4.25	-2.59	-6.25	-6.37	N-methylaniline	H9C7N1
0123dim	-4.86	-3.71	-3.36	-5.47	-4.51	2,4-dimethylpyridine	H9C7N1
0124dim	-4.72	-3.81	-3.5	-5.22	-4.26	2,5-dimethylpyridine	H9C7N1
0125dim	-4.6	-3.61	-2.67	-5.3	-4.23	2,6-dimethylpyridine	H9C7N1
0126eth	-3.89	-3.56	-4.93	-5.3	-4.54	acetonitrile	H3C2N1
0127pro	-3.85	-2.97	-4.62	-4.64	-3.93	propionitrile	H5C3N1
0128butb	-3.64	-2.47	-4.32	-4.35	-3.63	butanonitrile	H7C4N1

0129ben	-4.1	-4.26	-6.77	-5.56	-5.56	benzonitrile	H5C7N1
0130nit	-3.71	-5.76	-4.36	-2.35	-3.14	nitroethane	H5C2N1O2
0131nit	-3.34	-5.19	-4.02	-1.97	-2.71	1-nitropropane	H7C3N1O2
0132nit	-3.14	-4.94	-2.88	-2.26	-2.63	2-nitropropane	H7C3N1O2
0133nit	-3.08	-4.81	-3.92	-1.72	-2.4	1-nitrobutane	H9C4N1O2
0134nit	-4.12	-6.20	-6.04	-4.25	-5.69	nitrobenzene	H5C6N1O2
0135met	-3.59	-5.66	-4.18	-4.4	-5.59	2-methyl-1-nitrobenzene	H7C7N1O2
0136met	-1.24	-1.87	-2.05	-2.78	-2.09	methanethiol	H4C1S1
0137ethb	-1.3	-1.36	-1.52	-2.61	-1.95	ethanethiol	H6C2S1
0138pro	-1.05	-0.98	-1.25	-2.21	-1.62	1-propanethiol	H8C3S1
0139thi	-2.55	-2.65	-3.43	-3.82	-3.88	thiophenol	H6C6S1
0140dim	-1.54	-1.36	-0.64	-1.47	-0.51	dimethylsulfide	H6C2S1
0141dim	-1.83	-3.09	-2.04	-1.93	-1.4	dimethyldisulfide	H6C2S2
0142die	-1.43	-0.38	0.52	-1.24	-0.21	diethylsulfide	H10C4S1
0143dip	-1.27	0.37	1.05	-0.57	0.52	dipropylsulfide	H14C6S1
0144thi	-2.73	-2.13	-2.13	-2.78	-2.47	thioanisole	H8C7S1
0145pro	-5.08	-3.30	-6.25	-8	-7.23	allylalcohol	H6C3O1
0146met	-6.77	-6.75	-7.35	-9.62	-10.43	2-methoxyethanol	H8C3O2
0147met	-6.55	-6.73	-7.64	-7.33	-7.06	2-methoxyethanamine	H9C3N1O1
0148but	0.04	0.11	-1.42	-2.21	-1.61	butenyne	H4C4
0149mor	-7.17	-5.77	-5.3	-4.5	-7.22	morpholine	H9C4N1O1
0150mhy	-9.51	-9.20	-12.67	-16.65	-15.84	m-hydroxybenzaldehyde	H6C7O2
0151phy	-10.48	-9.20	-12.77	-16.85	-16	p-hydroxybenzaldehyde	H6C7O2
0153flu	-0.22	0.79	1.41	-1.77	0.04	fluoromethane	H3C1F1
0154dif	-0.11	2.13	2.01	-2.88	-0.91	1,1-difluoroethane	H4C2F2
0157flu	-0.78	-0.63	-1.14	-2.33	-1.29	fluorobenzene	H5C6F1
0160chl	-0.56	-1.00	0.21	-1.3	-0.1	chloromethane	H3C1CL1
0161dic	-1.36	-1.65	-0.59	-2.04	-1.32	dichloromethane	H2C1CL2
0162tri	-1.07	-0.79	-1.33	-1.8	-1.08	chloroform	H1C1CL3
0163chl	-0.63	-0.51	0.59	-1.04	0.1	chloroethane	H5C2CL1
0165tri	-0.25	-0.35	-0.89	-1.01	-0.42	1,1,1-trichloroethane	H3C2CL3
0166tri	-1.95	-2.34	-0.96	-3.22	-2.72	1,1,2-trichloroethane	H3C2CL3
0167chla	-0.27	-0.11	0.84	-0.71	0.35	1-chloropropane	H7C3CL1
0168chl	-0.25	-0.09	0.86	-1.1	0.27	2-chloropropane	H7C3CL1
0169chl	-0.59	-2.26	-1.38	-1.11	0.26	chloroethene	H3C2CL1
0170chl	-0.57	0.18	-0.74	-1.52	-0.17	3-chloropropene	H5C3CL1
0171Zdi	-1.17	-5.43	-1.78	-1.86	-1.19	Z-1,2-dichloroethene	H2C2CL2
0172Edi	-0.76	-3.42	-1.83	-0.81	-0.13	E-1,2-dichloroethene	H2C2CL2
0173tri	-0.39	-3.36	-1.72	-0.4	-0.1	trichloroethene	H1C2CL3
0174chl	-1.12	-1.01	-1.66	-2.27	-1.83	chlorobenzene	H5C6CL1
0175odi	-1.36	-1.21	-1.73	-1.98	-1.75	1,2-dichlorobenzene	H4C6CL2
0176pdi	-1.01	-1.14	-1.78	-1.81	-1.49	1,4-dichlorobenzene	H4C6CL2
0177bro	-0.82	-1.50	-0.38	-1.42	-0.65	bromomethane	H3C1BR1

0178dib	-2.11	-2.57	-1.66	-1.54	-1.78	dibromomethane	H2C1BR2
0179tri	-1.98	-3.50	-2.89	-0.7	-1.5	bromoform	H1C1BR3
0180bro	-0.7	-0.99	0.06	-1.33	-0.55	bromoethane	H5C2BR1
0182bro	-0.56	-0.59	0.31	-1.01	-0.33	1-bromopropane	H7C3BR1
0183bro	-0.48	-0.55	0.38	-1.51	-0.43	2-bromopropane	H7C3BR1
0184bro	-0.41	-0.25	0.57	-0.76	-0.02	1-bromobutane	H9C4BR1
0185bro	-0.08	0.04	0.8	-0.54	0.22	1-bromopentane	H11C5BR1
0186bro	-1.46	-1.11	-2.14	-2.63	-2.56	bromobenzene	H5C6BR1
0187dib	-2.3	-1.26	-2.68	-2.28	-2.76	p-dibromobenzene	H4C6BR2
0197bro	1.79	-0.65	0.71	-2.81	0.23	bromotrifluoromethane	C1F3BR1
0198chl	-0.77	0.05	0.56	-3.36	-1.91	chlorofluoromethane	H2C1F1CL1
0199chl	-0.5	0.09	0.92	-4.64	-2.07	chlorodifluoromethane	H1C1F2CL1
0200tet	3.16	0.85	2.44	-3.45	1.44	tetrafluoromethane	C1F4
0201bro	-0.13	-1.42	0.13	-3.6	-1.27	1-bromo-1-chloro-2,2,2-trifluoroethane	H1C2F3CL1BR1
0202bro	-1.95	-2.26	-0.78	-2.99	-2.81	1-bromo-2-chloroethane	H4C2CL1BR1
0203bro	0.52	0.07	1.22	-4.89	-1.78	1-bromo-1,2,2,2-tetrafluoroethane	H1C2F4BR1
0204tet	0.05	-1.45	-1.64	1	0.72	tetrachloroethene	C2CL4
0205chl	0.06	-0.38	1.45	-3.94	-1.55	1-chloro-2,2,2-trifluoroethane	H2C2F3CL1
0206tri	1.77	-0.23	-0.1	-2.49	0.61	1,1,2-trichloro-1,2,2-trifluoroethane	C2F3CL3
0207tri	-4.31	-3.95	-3.7	-11.93	-9.44	2,2,2-trifluoroethanol	H3C2O1F3
0209chl	0.11	-0.50	-0.24	-9.17	-5.68	1-chloro-2,2,2-trifluoroethyldifluoromethylether	H2C3O1F5CL1
0211tri	-4.16	-3.27	-3.21	-11.26	-9.2	1,1,1-trifluoropropan-2-ol	H5C3O1F3
0212hex	-3.77	-3.04	-2.24	-15.29	-11.15	1,1,1,3,3,3-hexafluoropropan-2-ol	H2C3O1F6
0213bis	-3.92	-2.78	-1.11	-4.5	-4.61	bis(2-chloroethyl)sulfide	H8C4S1CL2
0214tri	-0.12	-2.04	-1.42	-6.06	-3.67	2,2,2-trifluorethylvinylether	H5C4O1F3
0215pbr	-7.13	-5.09	-8.04	-11.31	-11.25	p-bromophenol	H5C6O1BR1
0220tri	-8.7	-7.89	-9.38	-14.22	-14.22	trimethylphosphate	H9C3O4P1
0221tri	-7.8	-5.55	-4.67	-11.55	-11.33	triethylphosphate	H15C6O4P1
0222tri	-6.1	-4.02	-3.89	-10.3	-9.4	tripropylphosphate	H21C9O4P1
0223die	-1.63	-1.95	-0.82	-1.64	-0.81	diethyldisulfide	H10C4S2
0225pipa	-5.11	-3.07	-0.54	-2.1	-3.75	piperidine	H11C5N1
0227Nme	-6.34	-5.05	-2.72	-2.14	-6.72	N-methylmorpholine	H11C5N1O1
0228met	-4.56	-4.95	-6.22	-6.7	-4.43	methylamine	H5C1N1
0230eth	-5.51	-3.33	-7.16	-9.23	-8.71	2-ethylpyrazine	H8C6N2
0233ethb	-9.71	-7.49	-10.71	-10.89	-9.93	acetamide	H5C2N1O1
0234ENmb	-10	-6.74	-6.4	-9.08	-8.37	E-N-methylacetamide	H7C3N1O1
0235ZNmb	-10	-6.64	-6.37	-10.49	-9.48	Z-N-methylacetamide	H7C3N1O1
0236oct	-4.09	-2.06	-3.49	-5.71	-5.25	1-octanol	H18C8O1
0237oct	-2.29	-0.13	-2.72	-4.85	-3.28	octanal	H16C8O1
0238met	-2.04	-0.89	-3.72	-4.74	-3.69	methyloctanoate	H18C9O2
0239oct	-2.88	-0.93	-2.04	-4.51	-2.92	2-octanone	H16C8O1
0240met	-3.91	-4.20	-6.34	-7.83	-7.71	methylbenzoate	H8C8O2

0242dii	-0.53	-0.53	0.34	-0.81	0.21	isopropylether	H14C6O1
0244tet	-3.12	-1.46	-2.11	-1.21	-2.25	tetrahydropyran	H10C5O1
0245thi	-1.42	-1.82	-2.95	-1.95	-1.69	thiophene	H4C4S1
0246eth	-2.22	-2.15	-1.88	-3.7	-3.38	ethylphenylether	H10C8O1
0401amia	-9.63	-7.51	-10.58	-13.36	-13.74	1,1-dimethyl-3-phenylurea	H12C9N2O1
0402adn	-13.6	-11.29	-18.22	-18.38	-19.59	9-methyladenine	H7C6N5
0403thi	-10.4	-7.40	-11.48	-16.32	-17.04	1-methylthymine	H8C6N2O2
0405hex	3.94	1.04	3.13	-4.18	1.08	hexafluoroethane	C2F6
0406oct	4.28	2.46	3.54	-3.62	1.33	octafluoropropane	C3F8
0407tet	-1.15	-1.53	-1.64	-1.86	-1.51	1,1,1,2-tetrachloroethane	H2C2CL4
0408hex	-1.4	-1.30	-2.76	-0.27	0.12	hexachloroethane	C2CL6
0409clb	0.07	0.26	1.13	-0.81	0.47	2-chlorobutane	H9C4CL1
0410clp	0.07	0.52	1.34	-0.25	0.81	1-chloropentane	H11C5CL1
0411chp	0.07	0.61	1.45	-0.58	0.76	2-chloropentane	H11C5CL1
0412clt	-1.92	-1.68	-1.43	-3.54	-3.1	chlorotoluene	H7C7CL1
0413clt	-1.15	-0.79	-0.88	-2.11	-1.53	o-chlorotoluene	H7C7CL1
0414dcl	-2.73	-2.36	-2.57	-4.09	-3.48	2,2'-dichlorobiphenyl	H8C12CL2
0415dcl	-2.45	-2.48	-2.49	-3.78	-3.85	2,3-dichlorobiphenyl	H8C12CL2
0416dcl	-1.99	-2.59	-2.65	-3.63	-3.36	2,2',3'-trichlorobiphenyl	H7C12CL3
0417brp	-0.86	-0.31	-1.33	-1.73	-0.75	3-bromopropene	H5C3BR1
0418bri	-0.03	-0.21	0.53	-1	-0.09	1-bromo-isobutane	H9C4BR1
0419brt	-2.37	-2.09	-1.9	-3.89	-3.77	bromotoluene	H7C7BR1
0420pbr	-1.39	-0.92	-1.31	-2.35	-2.18	p-bromotoluene	H7C7BR1
0421dfl	1.69	-0.09	0.08	-2.01	0.71	difluorodichloromethane	C1F2CL2
0422ftc	0.82	-0.53	-1.02	-1.13	0.54	fluorotrichloromethane	C1F1CL3
0423brt	-0.93	-1.83	-2.54	0.1	0.09	bromotrichloromethane	C1CL3BR1
0424clp	2.86	0.59	2	-3.64	1.02	chloropentaflouroethane	C2F5CL1
0425dbr	-9	-8.33	-12.44	-14.7	-15.08	3,5-dibromo-4-hydroxybenzonitrile	H3C7N1O1BR2
0426dcl	-5.22	-4.43	-7.32	-4.68	-5.34	2,6-dichlorobenzonitrile	H3C7N1CL2
0427dcl	-10.81	-6.75	-8.63	-8.79	-9.44	2,6-dichlorothiobenzamide	H5C7N1S1CL2
0428ami	-11.96	-14.14	-20.64	-21.09	-22.17	4-amino-3,5,6-trichloropyridine-2-carboxylicacid	H3C6N2O2CL3
0433pho	-6.61	-9.49	-9.13	-15.3	-13.89	2,2-dichloroethenyldimethylphosphate	H7C4O4P1CL2
0437pho	-6.92	-9.68	-12.07	-18.48	-20.99	methyl3-methyl-4-thiomethoxyphenylthiophosphate	H13C9O3P1S2
0438pho	-3.86	-6.15	-4.72	-9.78	-9.82	diethyl2,4-dichlorophenylthiophosphate	H13C10O3P1S1CL2
0440pho	-7.28	-6.36	-7.4	-14.55	-13	dimethyl5-(4-chloro)bicyclo[3.2.0]heptylphosphate	H12C9O4P1CL1
0441pho	-7.62	-11.77	-20.61	-12.75	-15.07	dimethyl4-nitrophenylthiophosphate	H10C8N1O5P1S1
0442pho	-4.09	-5.08	-5.49	-12	-11.74	O-ethylO'-4-bromo-2-chlorophenylS-propylphosphorothioate	H15C11O3P1S1CL1BR1
0444pho	-5.06	-6.72	-6.02	-10.23	-10.87	dimethyl2,4,5-trichlorophenylthiophosphate	H8C8O3P1S1CL3
0445pho	-5.7	-6.81	-6.46	-10.24	-11.32	dimethyl4-bromo-2,5-dichlorophenylthiophosphate	H8C8O3P1S1CL2BR1

0447pho	-6.27	-5.09	-8.29	-10.9	-12.95	diethyl4-nitrophenylthiophosphonate	H14C10N1O5P1S1
0449pho	-5.1	-8.40	-8.61	-18.15	-17.51	ethyl4-cyanophenylphenylthiophosphonate	H14C15N1O2P1S1
0471dim	-5.22	-4.01	-4.3	-5.48	-4.83	3,4-dimethylpyridine	H9C7N1
0506nit	-3.95	-6.62	-5.88	-2.73	-3.66	nitromethane	H3C1N1O2
0571dim	-4.84	-3.93	-3.99	-5.15	-4.32	3,5-dimethylpyridine	H9C7N1
0574eth	-4.74	-4.84	-6.25	-5.81	-5.93	4-ethylpyridine	H9C7N1
n005	-5.31	-4.66	-6.72	-10.54	-8.76	methylhydrazine	H6C1N2
n006	-4.48	-4.18	-6.33	-7.69	-7.75	1,1-dimethylhydrazine	H8C2N2
n007	-13.8	-12.99	-15.47	-13.57	-13.91	urea	H4C1N2O1
n008	-10.9	-8.33	-11.69	-12.24	-12.16	benzamide	H7C7N1O1
n009	-5.56	-4.25	-5.88	-7.31	-6.56	2-methylaniline	H9C7N1
n010	-5.67	-4.48	-6.78	-7.58	-6.64	3-methylaniline	H9C7N1
n011	-5.55	-4.56	-6.78	-7.46	-6.65	4-methylaniline	H9C7N1
n013	-4.62	-3.55	-1.91	-5.36	-5.6	N-ethylaniline	H11C8N1
n014	-3.58	-3.63	-0.14	-4.41	-5.86	N,N-dimethylaniline	H11C8N1
n015	-9.92	-8.65	-13.66	-13.25	-12.47	3,aminoaniline	H8C6N2
n016	-9.72	-9.06	-12.04	-11.1	-9.82	1,2-ethanediamine	H8C2N2
n018	-5.28	-4.81	-9.9	-9.89	-9.07	methylperoxide	H4C1O2
n019	-5.32	-4.10	-10.27	-9.21	-8.59	ethylperoxide	H6C2O2
n191	-16.59	-9.59	-15.77	-18.49	-19.38	uracil	H4C4N2O2
n200	-16.92	-8.82	-11.46	-18.65	-19.54	5-fluorouracil	H3C4N2O2F1
n201	-15.46	-8.67	-12.9	-21.18	-21.13	5-trifluoromethyluracil	H3C5N2O2F3
n202	-17.74	-9.58	-15.8	-18.25	-19.5	5-chlorouracil	H3C4N2O2CL1
n203	-18.17	-9.60	-15	-18.54	-20.24	5-bromouracil	H3C4N2O2BR1
test0001	-8.84	-6.51	-12.38	-18.14	-17.12	glyceroltriacetate	H14C9O6
test0004	1.07	-0.03	1.81	-6.15	-2.66	m-bis(trifluoromethyl)benzene	H4C8F6
test0005	-11.01	-7.66	-7.27	-11.19	-11.71	N,N-dimethyl-p-methoxybenzamide	H13C10N1O2
test0006	-9.76	-5.69	-9.15	-9.42	-9.29	N,N,4-trimethylbenzamide	H13C10N1O1
test0007	-4.23	-3.76	-1.5	-4.86	-5.24	bis(2-chloroethyl)ether	H8C4O1CL2
test0008	-4.97	-4.24	-9.45	-11.01	-10.87	1,1-diacetoxyethane	H10C6O4
test0009	-3.28	-2.41	-1.05	-2.97	-3.64	1,1-diethoxyethane	H14C6O2
test0011	-6	-4.31	-9.11	-10.91	-10.45	diethylpropanedioate	H12C7O4
test0012	-2.93	-4.36	-5.15	-5.06	-6.24	dimethoxymethane	H8C3O2
test0013	-6.34	-4.74	-8.81	-12.65	-12.26	ethyleneglycoldiacetate	H10C6O4
test0014	-3.54	-3.29	-0.96	-3.36	-4.4	1,2-diethoxyethane	H14C6O2
test0016	-3.82	-3.31	-5.66	-9.96	-9.14	phenylformate	H6C7O2
test0017	-9.81	-8.72	-8.7	-10.3	-10.46	imidazole	H4C3N2
test1001	-5.7	-8.89	-6.53	-5.56	-9.7	nitroglycol	H4C2N2O6
test1002	-5	-7.10	-5.57	-5.22	-9.01	1,2-dinitroxypropane	H6C3N2O6
test1003	-2.1	-4.77	-2.92	-1.64	-2.94	butylnitrate	H9C4N1O3
test1004	-1.8	-5.96	-2.15	-1.87	-2.97	2-butylnitrate	H9C4N1O3
test1005	-1.9	-3.46	-2.59	-1.72	-2.79	isobutylnitrate	H9C4N1O3

test1006	-8.2	-12.47	-9.17	-11	-13.25	ethyleneglycolmononitrate	H5C2N1O4
test1007	-8.2	-4.61	-3.88	-10.73	-10.05	alachlor	H20C14N1O2CL1
test1008	-9.8	-8.74	-10.28	-9.53	-9.08	aldicarb	H14C7N2O2S1
test1009	-7.7	-6.04	-10.88	-9.02	-12.23	ametryn	H17C9N5S1
test1010	-10	-11.77	-15.51	-18.66	-21.58	azinphosmethyl	H12C10N3O3P1S2
test1011	-3.5	-4.92	-4.41	-4.12	-4.48	benefin	H16C13N3O4F3
test1012	-17.2	-17.75	-27.37	-33.94	-38.29	bensulfuron	H18C16N4O7S1
test1013	-9.7	-5.27	-8.09	-14.11	-14.48	bromacil	H13C9N2O2BR1
test1014	-9	-5.58	-9.95	-11.05	-11.57	captan	H8C9N1O2S1CL3
test1015	-9.5	-6.61	-9.06	-10.37	-11.08	carbaryl	H11C12N1O2
test1016	-9.6	-5.84	-6.89	-11.51	-11.81	carbofuran	H15C12N1O3
test1017	-6.5	-6.92	-5.51	-12.62	-14.79	carbophenothion	H16C11O2P1S3CL1
test1018	-3.4	-3.48	-3.03	-2.12	-2.39	chlordane	H6C10CL8
test1019	-7.1	-9.12	-5.29	-11.88	-10.82	chlorfenvinphos	H14C12O4P1CL3
test1020	-14	-14.64	-23.13	-34.54	-37.03	chlorimuronethyl	H15C15N4O6S1CL1
test1021	-1.5	-2.34	-1.85	-0.2	-1.52	chloropicrin	C1N1O2CL3
test1022	-5	-7.05	-8.21	-13.53	-13.31	chlorpyrifos	H11C9N1O3P1S1CL3
test1023	-5.7	-8.87	-10.04	-29.24	-28.85	dialifor	H17C14N1O4P1S2CL1
test1024	-6.5	-5.58	-6.6	-12.5	-12.4	diazinon	H21C12N2O3P1S1
test1025	-9.9	-8.68	-12.78	-14.15	-15.35	dicamba	H6C8O3CL2
test1027	-5.7	-6.13	-6.21	-9.11	-11.99	dinitramine	H13C11N4O4F3
test1028	-6.2	-7.91	-8.68	-11.3	-13.15	dinoseb	H12C10N2O5
test1029	-4.2	-8.36	-10.4	-10.19	-13.89	endosulfanalpha	H6C9O3S1CL6
test1030	-5.5	-3.90	-7.69	-4.32	-6.33	endrin	H8C12O1CL6
test1031	-6.1	-9.12	-2.46	-17.95	-17.98	ethion	H22C9O4P2S4
test1033	-2.6	-2.78	-3.26	-1.67	-1.97	heptachlor	H5C10CL7
test1034	-5.2	-4.04	-3.95	-5.7	-4.18	isophorone	H14C9O1
test1035	-5.4	-3.57	-1.99	-5.45	-5.47	lindane	H6C6CL6
test1036	-8.2	-9.60	-12.93	-19.82	-18.93	malathion	H19C10O6P1S2
test1037	-10.7	-9.17	-9.45	-11.74	-11.57	methomyl	H10C5N2O2S1
test1039	-15.5	-14.26	-25.61	-32.58	-35.93	metsulfuronmethyl	H15C14N5O6S1
test1040	-8	-12.16	-12.36	-15.07	-15.7	nitralin	H19C13N3O6S1
test1041	-6	-7.74	-9.54	-9.33	-10.51	nitroxyacetone	H5C3N1O4
test1043	-6.7	-10.32	-17.84	-11.03	-13.03	parathion	H14C10N1O5P1S1
test1044	-3.6	-2.56	-1.72	-4.74	-4.23	pebulate	H21C10N1O1S1
test1045	-4.4	-5.74	-2.93	-8.28	-9.2	phorate	H17C7O2P1S3
test1046	-2.5	-3.65	-3.37	-4.67	-4.76	profluralin	H16C14N3O4F3
test1047	-8.4	-5.53	-8.37	-8.31	-11.25	prometryn	H19C10N5S1
test1048	-7.8	-5.65	-4.74	-11.49	-11.46	propanil	H9C9N1O1CL2
test1049	-16.4	-7.91	-13.33	-18.79	-18.84	pyrazon	H8C10N3O1CL1
test1050	-10.2	-6.25	-11.38	-11.65	-14.63	simazine	H12C7N5CL1
test1051	-20.3	-14.02	-21.56	-30.85	-32.58	sulfometuron-methyl	H16C15N4O5S1
test1052	-11.1	-5.17	-7.5	-13.41	-14.14	terbacil	H13C9N2O2CL1

test1053	-6.7	-5.57	-9.3	-9.11	-12.2	terbutryn	H19C10N5S1
test1054	-16.2	-15.57	-25.7	-36.05	-38.78	thifensulfuron	H13C12N5O6S2
test1055	-12.7	-9.08	-11.46	-21.94	-20.41	trichlorfon	H8C4O4P1CL3
test1056	-3.3	-4.48	-3.04	-4.67	-4.99	trifluralin	H16C13N3O4F3
test1057	-4.1	-2.48	-1.81	-4.63	-3.88	vernolate	H21C10N1O1S1
test1058	-11.2	-11.69	-12.76	-13.68	-15.24	4-amino-4'-nitroazobenzene	H10C12N4O2
test1059	-7.4	-7.71	-16.38	-15.54	-18.03	1-amino-4-anilinoanthraquinone	H14C20N2O2
test1060	-8.9	-9.90	-19.45	-22.8	-25.4	1,4,5,8-tetraminoanthraquinone	H12C14N4O2
test1061	-8	-6.65	-15.57	-15.17	-15.98	1-amino-anthraquinone	H9C14N1O2
test1063	-9.4	-6.44	-4.62	-14.17	-16.19	pirimicarb	H18C11N4O2
test2001	-9.94	-8.69	-13.96	-18.92	-18.67	acetylsalicylicacid	H8C9O4
test2003	-8.72	-6.86	-10.4	-15.29	-14.73	butylparaben	H14C11O3
test2004	-12.64	-7.36	-12.01	-18.95	-21.27	caffeine	H10C8N4O2
test2006	-15.83	-9.50	-15.51	-16.25	-17.51	6-chlorouracil	H3C4N2O2CL1
test2007	-18.06	-14.29	-21.51	-22.88	-25.87	cyanuricacid	H3C3N3O3
test2010	-9.4	-9.45	-15.84	-17.33	-17.24	diflunisal	H8C13O3F2
test2011	-9.2	-7.66	-10.91	-15.96	-15.49	ethylparaben	H10C9O3
test2013	-8.42	-6.92	-11.34	-17.39	-17.03	flurbiprofen	H13C15O2F1
test2015	-2.33	-1.72	-1.93	1.26	-0.38	hexachlorobenzene	C6CL6
test2017	-7	-4.33	-9.02	-12.32	-11.75	ibuprofen	H18C13O2
test2019	-10.78	-9.50	-13.16	-19	-18.71	ketoprofen	H14C16O3
test2020	-9.51	-8.30	-12.1	-16.56	-16.51	methylparaben	H8C8O3
test2021	-10.21	-8.82	-12.96	-16.33	-17.54	naproxen	H14C14O3
test2022	-9.45	-10.16	-12.16	-10.07	-11.81	4-nitroaniline	H6C6N2O2
test2023	3.43	6.35	3.66	-2.06	1.49	octafluorocyclobutane	C4F8
test2024	-5.22	-6.71	-4.3	0.52	-2.29	pentachloronitrobenzene	C6N1O2CL5
test2025	-9.61	-7.37	-14.4	-15.14	-15.2	phthalimide	H5C8N1O2
test2026	-9.37	-7.20	-10.11	-15.53	-14.97	propylparaben	H12C10O3
test2027	-8.61	-7.91	-10.18	-13.12	-13.73	sulfolane	H8C4O2S1
test2029	-0.8	-4.55	-1.69	-5.48	-4.96	trimethylorthotrifluoroacetate	H9C5O3F3
test3001	-14.83	-10.03	-11.62	-21.72	-21.24	paracetamol	H9C8N1O2
test3002	-13.93	-9.97	-12.01	-21.56	-21.32	N-(3-hydroxyphenyl)acetamide	H9C8N1O2
test3003	-12.75	-11.06	-16.37	-25.75	-26.05	fenbufen	H14C16O3
test3004	-11.61	-6.42	-11	-21.46	-20.84	N-(2-hydroxyphenyl)acetamide	H9C8N1O2
test3005	-10.91	-7.41	-6.35	-14.26	-14.15	phenacetin	H13C10N1O2
test3007	-10.32	-8.57	-11.71	-14.69	-15.34	2-methoxybenzoicacid	H8C8O3
test3014	-9.15	-9.44	-13.25	-14.72	-15.34	4-methoxybenzoicacid	H8C8O3
test3015	-8.93	-9.43	-13.33	-14.43	-14.85	3-methoxybenzoicacid	H8C8O3
test3019	-6.71	-7.96	-10.06	-12.94	-14.18	tolfenamicacid	H12C14N1O2CL1
test3020	-6.3	-5.60	-10.92	-22.37	-21.19	diclofenacacid	H11C14N1O2CL2
test3021	-5.68	-5.94	-10.96	-16.06	-14.64	flufenamicacid	H10C14N1O2F3

Table 2S. GARF-KMTSIM, KECSA-KMTSIM MM-GBSA and MM-PBSA calculated solvation free energies (in kcal/mol) against 21 charged compounds.

Compound ID	Exp. ΔGsolv	GARF-KMTISM	KECSA-KMTISM	MM-GBSA	MM-PBSA	Solute Name	Formula
			Anions				
i058	-76.2	-84.74	-70.64	-70.46	-71.79	formicacid	H1C1O2
i059	-77.6	-78.94	-70.58	-63.33	-65.1	aceticacid	H3C2O2
i060	-76.2	-73.87	-70.91	-63.15	-64.37	propanoicacid	H5C3O2
i061	-74.6	-70.75	-71.64	-60.41	-61.92	hexanoicacid	H11C6O2
i062	-74	-70.75	-71.58	-60.06	-61.48	acrylicacid	H3C3O2
i063	-68.5	-65.97	-71.63	-63.81	-65.94	pyruvicacid	H3C3O3
i064	-71.2	-70.39	-73.01	-80.95	-82.23	benzoicacid	H5C7O2
i118	-59.3	-63.68	-67.87	-79.96	-80.54	trifluoroaceticacid	C2O2F3
i119	-69.7	-64.93	-70.83	-61.19	-63.11	chloroaceticacid	H2C2O2CL1
i120	-62.3	-62.91	-70.91	-63.45	-65.44	dichloroaceticacid	H1C2O2CL2
			Cations				
i003	-76.4	-79.52	-78.4	-62.95	-64.91	methylamine	H6C1N1
i004	-71.5	-70.04	-78.92	-91.16	-87.52	n-propylamine	H10C3N1
i008	-72	-69.16	-79.7	-86.92	-83.96	allylamine	H8C3N1
i020	-69.6	-68.85	-71.13	-84.68	-81.8	3-methylaniline	H10C7N1
i021	-69.8	-69.97	-71.18	-82.01	-79.25	4-methylaniline	H10C7N1
i023	-65.8	-73.77	-72.9	-81.93	-79.18	3-aminoaniline	H9C6N2
i047	-85.2	-89.81	-90.16	-84.38	-79.84	ammonia	H4N1
i048	-84.6	-88.29	-80.59	-80.98	-78.91	hydrazine	H5N2
i093	-71.2	-72.06	-82.26	-70.8	-67.26	4-methoxyaniline	H10C7N1O1
i125	-74.7	-69.89	-80.74	-80.29	-77.73	3-chloroaniline	H7C6N1CL1
i126	-74.1	-70.38	-80.7	-74.39	-71.6	4-chloroaniline	H7C6N1CL1