

Supporting Information for:**Explicitly Representing the Solvation Shell in Continuum Solvent Calculations**

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Constant terms utilized in calculations

$\Delta G_s(5H_2O)$ Poisson Boltzmann model: -15.7 kcal/mol

$\Delta G_s(5H_2O)$ IEF-PCM: -23.59 kcal/mol.

Energy for pure water clusters ($5H_2O$): -380.133 [au]

Thermal energy correction and ZPE for pure water clusters ($5H_2O$): 0.1435 [au]

Entropy for pure water clusters ($5H_2O$): 114.8 [cal/mol]

Standard state correction utilized ($RT\ln[R'T]-RT\ln(55.34/5)=-3.32$ kcal/mol

Table 3: Underlying data for Table 1, thermal corrections to the energy and continuum solvation energies for clusters calculated with the IEF-PCM model.

A ⁻	E ^a (A) [a. u.]	E ^a (A(S) ₅) [a. u.]	E ^b E _{corr} (A) [a. u.]	E ^b E _{corr} (A(S) ₅) [a. u.]	S ^c S _{total} (A) [cal/mol]	S ^c S _{total} (A(S) ₅) [cal/mol]	ΔG _s (A(S) ₅) [kcal/mol]
Cl ⁻	-459.540	-839.723	0.001	0.148	36.6	131.7	-58.7
OH ⁻	-75.376	-455.615	0.011	0.162	41.1	118.4	-60.5
CH ₃ O ⁻	-114.411	-494.635	0.041	0.192	54.8	133.2	-55.3
CH ₃ CH ₂ O ⁻	-153.455	-533.677	0.073	0.226	62.1	137.5	-53.9
C ₆ H ₅ O ⁻	-304.995	-685.183	0.102	0.251	72.6	154.9	-54.9
HCO ₂ ⁻	-188.208	-568.407	0.025	0.175	58.1	137.8	-54.5
NH ₂ ⁻	-55.518	-435.734	0.023	0.166	46.4	106.3	-57.7
HS ⁻	-398.107	-778.289	0.009	0.157	44.5	133.3	-55.2
CH ₃ S ⁻	-437.127	-817.311	0.042	0.190	57.9	144.5	-54.0
CH ₃ CH ₂ CH ₂ O ⁻	-192.491	-572.711	0.105	0.256	69.9	144.4	-54.3
(CH ₃) ₂ CHO ⁻	-192.498	-572.716	0.104	0.255	68.5	142.2	-53.7
C(CH ₃) ₃ O ⁻	-231.538	-611.755	0.135	0.286	74.2	145.7	-52.6
CH ₃ OO ⁻	-189.194	-569.411	0.048	0.199	61.6	137.4	-55.9
CN ⁻	-92.315	-472.497	0.008	0.154	47.0	133.7	-56.5
CH ₂ NO ₂ ⁻	-243.085	-623.281	0.043	0.192	63.2	139.2	-55.8
HO ₂ ⁻	-150.158	-530.379	0.017	0.167	53.7	130.8	-60.0
F ⁻	-99.419	-479.651	0.001	0.149	34.8	125.4	-58.9
Br ⁻	-2569.971	-2950.153	0.001	0.141	33.1	116.1	-57.2
HCC ⁻	-76.210	-456.393	0.018	0.164	47.1	134.4	-58.1
CH ₃ CO ₂ ⁻	-227.250	-607.449	0.055	0.205	63.5	145.6	-54.9
CH ₃ CH ₂ CO ₂ ⁻	-266.285	-646.484	0.088	0.237	75.5	151.4	-53.3
H ₂ C=CHCO ₂ ⁻	-265.100	-645.296	0.063	0.212	70.4	148.2	-54.8
C ₆ H ₅ CO ₂ ⁻	-417.780	-797.973	0.116	0.263	80.9	157.1	-55.8
H ₂ C=CHCH ₂ O ⁻	-230.343	-610.559	0.111	0.262	75.0	149.0	-55.2
C ₆ H ₅ CH ₂ O ⁻	-343.988	-724.198	0.133	0.280	80.1	151.1	-57.1
CH ₃ OCH ₂ CH ₂ ⁻	-267.341	-647.553	0.112	0.262	76.2	155.2	-59.1
C ₆ H ₅ CO ₂ ⁻	-417.780	-797.973	0.116	0.263	80.9	157.1	-55.8
<i>o</i> -CH ₃ C ₆ H ₄ O ⁻	-344.033	-724.220	0.133	0.282	79.6	153.9	-55.4
<i>m</i> -CH ₃ C ₆ H ₄ O ⁻	-344.032	-724.220	0.132	0.281	77.4	156.0	-56.2
<i>p</i> -CH ₃ C ₆ H ₄ O ⁻	-344.028	-724.220	0.133	0.282	83.6	155.5	-55.7

a: Energy of solute and solute-solvent cluster, standard state of 1 atmosphere. b: Thermal correction to the energy and zero-point energy for solute and solute-solvent cluster, standard state of 1 atmosphere. c: Total entropy of solute and solute-solvent cluster, standard state of 1 atmosphere. d: Free energy of solvation of solute-solvent cluster calculated with IEF-PCM model.

Table 4: Underlying data for Table 2, thermal corrections to the energy and continuum solvation energies for clusters calculated with the IEF-PCM model.

BH ⁺	E ^a (A) [a. u.]	E ^a (A(S) ₅) [a. u.]	E ^b E _{corr} (A) [a. u.]	E ^b E _{corr} (A(S) ₅) [a. u.]	S ^c S _{total} (A) [cal/mol]	S ^c S _{total} (A(S) ₅) [cal/mol]	ΔG _s (A(S) ₅) [kcal/mol]
H ⁺	0.000	-380.499	0.001	0.156	26.0	114.0	-65.1
NH ₄ ⁺	-56.531	-436.740	0.056	0.202	49.3	141.5	-64.4
H ₃ O ⁺	-76.291	-456.537	0.040	0.188	48.2	130.9	-63.9
K ⁺	-598.972	-979.177	0.001	0.146	36.9	141.7	-64.7
CH ₃ OH ₂ ⁺	-115.341	-495.560	0.072	0.219	58.3	143.4	-59.5
CH ₃ CH ₂ OH ₂ ⁺	-154.389	-534.601	0.103	0.250	66.0	152.8	-59.2
CH ₃ NH ₃ ⁺	-95.574	-475.772	0.089	0.235	57.8	145.8	-59.8
C ₆ H ₅ NH ₃ ⁺	-286.093	-666.287	0.146	0.294	73.1	155.8	-60.8
C ₄ H ₅ NH ⁺	-209.138	-589.324	0.107	0.253	65.8	144.1	-60.9
CH ₃ (CH ₂) ₂ NH ₃ ⁺	-173.655	-553.845	0.152	0.291	72.5	152.1	-60.0
C(CH ₃) ₃ NH ₃ ⁺	-212.700	-592.884	0.182	0.328	76.8	156.2	-56.5
(CH ₃) ₂ NH ₂ ⁺	-134.614	-514.802	0.120	0.267	65.0	148.3	-57.0
(CH ₃) ₃ NH ⁺	-173.652	-553.825	0.151	0.297	71.1	155.3	-56.5
C ₃ H ₆ NH ₂ ⁺	-172.461	-552.642	0.127	0.273	66.3	145.3	-59.0
C ₄ H ₈ NH ₂ ⁺	-211.530	-591.714	0.160	0.307	72.1	153.9	-57.0
C ₅ H ₁₀ NH ₂ ⁺	-250.575	-630.757	0.193	0.339	73.6	154.7	-56.5
CH ₃ CNH ⁺	-132.237	-512.423	0.064	0.209	60.6	143.0	-60.7
(CH ₃) ₂ OH ⁺	-154.384	-534.573	0.104	0.248	66.9	140.8	-57.7
CH ₃ C(OH)CH ₃ ⁺	-192.290	-572.477	0.108	0.108	72.2	147.0	-58.6
CH ₃ C(OH)C ₆ H ₅ ⁺	-382.827	-763.003	0.169	0.315	87.3	167.6	-58.0
(CH ₃) ₂ CHNH ₃ ⁺	-173.660	-553.849	0.151	0.298	71.4	154.3	-58.4
c-C ₆ H ₁₁ NH ₃ ⁺	-289.610	-669.799	0.224	0.371	80.3	160.2	-57.2
H ₂ C=CHCH ₂ NH ₃ ⁺	-172.462	-552.654	0.126	0.274	70.0	153.0	-59.4
C ₅ H ₁₀ NH ₂ ⁺	-266.555	-646.731	0.181	0.327	72.9	160.7	-62.0
C ₅ H ₅ NH ⁺	-247.074	-627.249	0.114	0.261	68.2	147.8	-59.6
H ₂ NNH ₃ ⁺	-111.521	-491.727	0.077	0.224	57.1	144.6	-64.6
C ₄ H ₈ ONH ₂ ⁺	-286.375	-666.556	0.167	0.313	72.6	154.1	-61.0
C ₂ H ₄ NH ₂ ⁺	-133.409	-513.596	0.094	0.241	59.8	142.6	-58.9
(C ₂ H ₅) ₂ NH ₂ ⁺	-212.695	-592.878	0.184	0.331	79.1	159.9	-55.5
(n-C ₃ H ₇) ₂ NH ₂ ⁺	-290.768	-670.950	0.247	0.394	93.9	173.8	-54.9

a: Energy of solute and solute-solvent cluster, standard state of 1 atmosphere. b: Thermal correction to the energy and zero-point energy for solute and solute-solvent cluster, standard state of 1 atmosphere. c: Total entropy of solute and solute-solvent cluster, standard state of 1 atmosphere. d: Free energy of solvation of solute-solvent cluster calculated with IEF-PCM model.

Table 5: Calculated solvation free energies for anions with with zero-point energy, thermal correction to the energy and IEF-PCM continuum solvation model. All data in kcal/mol.

A ⁻	$\Delta G_{\text{solv}}^{\text{Exp. a}}$	$\Delta G_{\text{solv}}^{\text{Calc}^b}$	Error	$\Delta G_{\text{solv}}^{\text{Calc}^c}$	Error	$\Delta G_{\text{solv}}^{\text{Calc}^d}$	Error
Cl ⁻	-74.5	-78.3	-3.8	-76.2	-1.7	-77.5	-3.0
OH ⁻	-104.7	-105.4	-0.7	-107.4	-2.7	-106.6	-1.9
CH ₃ O ⁻	-95	-93.4	1.6	-93.4	1.6	-92.3	2.7
CH ₃ CH ₂ O ⁻	-90.7	-88.0	2.7	-90.2	0.5	-87.8	2.9
C ₆ H ₅ O ⁻	-71.9	-68.7	3.2	-71.5	0.4	-71.5	0.4
HCO ₂ ⁻	-76.2	-78.0	-1.8	-77.2	-1.0	-76.9	-0.7
NH ₂ ⁻	-92.2 ^f	-101.2	-9.0	-85.7	6.5	-89.3	2.9
HS ⁻	-72.1	-77.9	-5.8	-70.5	1.6	-70.9	1.2
CH ₃ S ⁻	-73.8	-76.0	-2.2	-69.5	4.3	-69.6	4.2
CH ₃ CH ₂ CH ₂ O ⁻	-88.3	-87.0	1.3	-89.0	-0.7	-87.6	0.7
(CH ₃) ₂ CHO ⁻	-86.3	-84.3	2.0	-87.0	-0.7	-85.5	0.8
C(CH ₃) ₃ O ⁻	-82.3	-80.8	1.5	-83.9	-1.6	-82.4	-0.1
CH ₃ OO ⁻	-93.2	-88.4	4.8	-88.7	4.5	-87.7	5.5
CN ⁻	-70.2	-75.1	-4.9	-70.9	-0.7	-72.2	-2.0
CH ₂ NO ₂ ⁻	-76.5	-77.1	-0.6	-75.7	0.8	-75.2	1.3
HO ₂ ⁻	-97.3	-95.2	2.1	-96.0	1.3	-95.5	1.8
F ⁻	-104.4	-107.7	-3.3	-106.1	-1.7	-107.1	-2.7
Br ⁻	-68.3	-78.2	-9.9	-70.1	-1.8	-75.8	-7.5
HCC ⁻	-76.5	-76.9	-0.4	-73.7	2.8	-75.1	1.4
CH ₃ CO ₂ ⁻	-77.6	-79.0	-1.4	-78.9	-1.3	-78.2	-0.6
CH ₃ CH ₂ CO ₂ ⁻	-76.2	-75.6	0.6	-75.1	1.1	-74.7	1.5
H ₂ C=CHCO ₂ ⁻	-74	-75.1	-1.1	-75.3	-1.3	-75.1	-1.1
C ₆ H ₅ CO ₂ ⁻	-71.2	-73.5	-2.3	-73.9	-2.7	-75.4	-4.2
H ₂ C=CHCH ₂ O ⁻	-86.6	-84.3	2.3	-87.5	-0.9	-86.2	0.4
C ₆ H ₅ CH ₂ O ⁻	-85.1	-81.6	3.5	-84.4	0.7	-85.4	-0.3
CH ₃ OCH ₂ CH ₂ O ⁻	-89.4	-88.8	0.6	-88.1	1.3	-89.0	0.4
C ₆ H ₅ CO ₂ ⁻	-71.2	-73.5	-2.3	-73.9	-2.7	-75.4	-4.2
<i>o</i> -CH ₃ C ₆ H ₄ O ⁻	-70.2	-66.6	3.6	-69.9	0.3	-69.9	0.3
<i>m</i> -CH ₃ C ₆ H ₄ O ⁻	-71.1	-68.3	2.8	-72.2	-1.1	-71.8	-0.7
<i>p</i> -CH ₃ C ₆ H ₄ O ⁻	-72.0	-68.5	3.5	-71.9	0.1	-72.0	0.0
Shift		-5.7		-12.0		-15.3	
UAE		2.8		1.6		1.8	
RMSD		3.5		2.1		2.4	

a: Experimental free energies of solvation at 298K. b: Free energy of solvation calculated with zero-point energy, thermal correction to the energy and PB continuum solvation model. c: Free energy of solvation calculated without zpe and thermal correction. Calculated with IEF-PCM continuum solvation model. c: Free energy of solvation calculated with zero-point energy, thermal correction to the energy and IEFPCM continuum solvation model.

Table 6: Calculated solvation free energies for cations with with zero-point energy, thermal correction to the energy and IEF-PCM continuum solvation model. All data in kcal/mol.

BH ⁺	$\Delta G_{\text{Exp.}}^{\text{a}}$	$\Delta G_{\text{Calc}}^{\text{b}}$	Error	$\Delta G_{\text{Calc}}^{\text{c}}$	Error	$\Delta G_{\text{Calc}}^{\text{d}}$	Error
H ⁺	-265.9	-267.2	-1.3	-272.1	-6.2	-267.3	-1.4
NH ₄ ⁺	-85.2	-92.1	-6.9	-90.6	-5.4	-91.2	-6.0
H ₃ O ⁺	-110.3	-110.7	-0.4	-111.2	-0.9	-111.1	-0.8
K ⁺	-86.0	-91.0	-5.0	-92.5	-6.5	-93.9	-7.9
CH ₃ OH ₂ ⁺	-93.0	-91.3	1.7	-90.3	2.7	-90.2	2.8
CH ₃ CH ₂ OH ₂ ⁺	-88.4	-85.1	3.3	-86.1	2.3	-85.7	2.7
CH ₃ NH ₃ ⁺	-76.4	-80.3	-3.9	-78.1	-1.7	-78.0	-1.6
C ₆ H ₅ NH ₃ ⁺	-72.4	-71.1	1.3	-75.2	-2.8	-74.4	-2.0
C ₄ H ₅ NH ⁺	-61.4	-67.4	-6.0	-69.0	-7.6	-69.3	-7.9
CH ₃ (CH ₂) ₂ NH ₃ ⁺	-71.5	-75.7	-4.2	-71.4	0.1	-76.2	-4.7
C(CH ₃) ₃ NH ₃ ⁺	-67.3	-63.1	4.2	-63.5	3.8	-63.3	4.0
(CH ₃) ₂ NH ₂ ⁺	-68.6	-69.6	-1.0	-67.5	1.1	-67.3	1.3
(CH ₃) ₃ NH ⁺	-61.1	-61.3	-0.2	-58.5	2.6	-58.7	2.4
C ₃ H ₆ NH ₂ ⁺	-67.7	-64.8	2.9	-63.9	3.8	-64.1	3.6
C ₄ H ₈ NH ₂ ⁺	-66.0	-64.4	1.6	-64.6	1.4	-64.2	1.8
C ₅ H ₁₀ NH ₂ ⁺	-64.2	-62.3	1.9	-62.8	1.4	-62.6	1.6
CH ₃ CNH ⁺	-75.3	-73.8	1.5	-69.9	5.4	-71.1	4.2
(CH ₃) ₂ OH ⁺	-79.7	-71.1	8.6	-66.1	13.6	-68.0	11.7
CH ₃ C(OH)CH ₃ ⁺	-77.1	-68.6	8.5	-65.9	11.2	-67.5	9.6
CH ₃ C(OH)C ₆ H ₅ ⁺	-64.5	-59.0	5.5	-60.5	4.0	-61.0	3.5
(CH ₃) ₂ CHNH ₃ ⁺	-69.6	-69.0	0.6	-69.8	-0.2	-69.5	0.1
c-C ₆ H ₁₁ NH ₃ ⁺	-68.7	-65.7	3.0	-67.6	1.1	-67.1	1.6
H ₂ C=CHCH ₂ NH ₃ ⁺	-72.0	-71.8	0.2	-72.4	-0.4	-71.8	0.2
C ₅ H ₁₀ NH ₂ ⁺	-66.0	-65.7	0.3	-66.3	-0.3	-66.6	-0.6
C ₅ H ₅ NH ⁺	-61.1	-60.8	0.3	-61.0	0.1	-61.0	0.1
H ₂ NNH ₃ ⁺	-84.6	-88.0	-3.4	-87.9	-3.3	-87.6	-3.0
C ₄ H ₈ ONH ₂ ⁺	-69.6	-67.0	2.6	-66.6	3.0	-66.9	2.7
C ₂ H ₄ NH ₂ ⁺	-70.9	-71.4	-0.5	-68.9	2.0	-69.0	1.9
(C ₂ H ₅) ₂ NH ₂ ⁺	-63.4	-62.3	1.1	-62.2	1.2	-61.9	1.5
(n-C ₃ H ₇) ₂ NH ₂ ⁺	-60.5	-59.6	0.9	-61.0	-0.5	-60.6	-0.1
Shift		-7.4		-5.5		-7.3	
UAE		2.8		3.2		3.1	
RMSD		3.7		4.5		4.2	

a: Experimental free energies of solvation at 298K. b: Free energy of solvation calculated with zero-point energy, thermal correction to the energy and PB continuum solvation model. c: Free energy of solvation calculated without zpe and thermal correction. Calculated with IEF-PCM continuum solvation model. d: Free energy of solvation calculated with zpe, thermal corr. to the energy and IEFPCM continuum solvation model.

Simulation Details

The molecular dynamics (MD) simulations were isothermal-isobaric simulations (nPT) with periodic boundary conditions at 298K and 1 bar. The particle-mesh Ewald procedure was used to handle long-range electrostatic interactions. Temperature was controlled by Langevin dynamics, while pressure was controlled by weak coupling to an external bath. The time-step in the simulations was set to 0.002 ps. Solute molecule geometries were fully constrained during simulations. Solute coordinates were restrained with a harmonic potential. The restraining weight was set at 5 kcal/mol Å². The nonbonded cutoff was set to 8 Å for all simulations. Bonds length involving hydrogen atoms were maintained by use of a SHAKE algorithm. The systems were equilibrated in nPT simulations for 800 ps before geometries were extracted. Cluster geometries were extracted from the MD trajectory every 2 ps. These clusters consisted of the solute and the 5 closest solvent molecules.

Water solvent was represented with the TIP3P force field.¹ The number of solvent molecules in simulations for a given solute varied from 200 and 500. The solutes geometries were obtained from HF/6-31+G(d) calculations in vacuum. Solute charges were calculated with the CM2 model.²

The force field Lennard-Jones parameters were drawn from force fields reported in the scientific literature. We selected the force fields that appeared to have the most detailed parameterization for a given solute. For many ionic species no special force field have been developed, and in these cases we drew on atomic parameters for neutral species. For atoms where no force field stood out in terms of parameterization we drew on the GAFF force field.³ GAFF would be our recommended default when no solute specific force field is available. Below are given the Lennard-Jones parameters utilized in the present work.

Table 5: Force Field Parameters.

Atoms	Sigma [Å]	Epsilon [kcal/mol]	Reference
Cl	4.400	0.1	Chowdhuri and Chandra ⁴
O(OH ⁻ , H ₃ O ⁺)	3.104	0.152	TIP3P water. ¹
O (alcohols)	3.021	0.2104	GAFF ³
N	3.202	0.17	GAFF ³
C	3.349	0.1094	GAFF ³
C (aromatic)	3.349	0.086	GAFF ³
S	3.73	0.4945	Kristof and Lizli ⁵
H	2.435	0.0157	GAFF ³
H(N)	2.435	0.0157	GAFF ³
H (aromatic)	2.561	0.015	GAFF ³

References

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QM/PB Continuum Solvent Model

In the PB models, the solution is characterized as a charge distribution of the solute in a cavity mimicking the molecular shape which is surrounded by a continuous dielectric representing the solvent. The solvent is polarized by the solute and the solvent polarization generates an electrostatic field called the reaction field. The electrostatic potential of the reaction field can be described by the Poisson-Boltzmann equation:

$$-\nabla \cdot (\epsilon(\mathbf{r}) \nabla \phi(\mathbf{r})) - \frac{q^2}{4\pi\epsilon_0} \phi(\mathbf{r}) = -4\pi \rho(\mathbf{r}) \quad (1)$$

The $\rho(\mathbf{r})$ is the charge distribution of the solute calculated via semiempirical QM methods.

The $\phi(\mathbf{r})$ is the electrostatic potential that is to be obtained. The $\epsilon(\mathbf{r})$ is the dielectric function describing the dielectric discontinuity and it usually only has two values: ϵ_{out} for the region outside of the cavity and ϵ_{in} for the space within the (molecular) cavity. The $\kappa(\mathbf{r})$ is a modified Debye-Huckel parameter that reflects the salt concentration and temperature. When the charge density on the solute is low and the ionic strength is low, the $\kappa(\mathbf{r})$ term can be approximated via a linear term yielding the so-called linear Poisson-Boltzmann equation:

$$[\nabla \cdot (\epsilon(\mathbf{r}) \nabla \phi(\mathbf{r})) - \kappa^2(\mathbf{r}) \phi(\mathbf{r})] = -4\pi \rho(\mathbf{r}) \quad (2)$$

Even for the linearized PB equation, analytical solutions can only be obtained for systems defined by a simple dielectric boundary, *e.g.*, a sphere. For a boundary as complex as that of a protein or DNA molecule, the finite difference approach (among others) substitutes for the analytical differential equation solution yielding a numerical solution of the PB equation.

The electrostatic potential of the reaction field generated by a fixed set of $\rho(\mathbf{r})$ will, in turn, polarize the solute charge distribution and generate a new $\rho'(\mathbf{r})$ (*i.e.* distort the gas phase

wave function). Thus the gas phase solute Hamiltonian, H^0 is perturbed by a potential energy operator coming from the interaction between the solute and the reaction field:

$$H' = H^0 + V_{\text{int}} \quad (3)$$

$$V_{\text{int}} = \int_s ds \frac{c(r')}{|r - r'|} \quad (4)$$

The equation 4 is an integral over all the virtual surface charges, and r' is the coordinates of the surface charges. The virtual surface charges (σ) are calculated from the converged electrostatic potential of the reaction field. And the full set of virtual surface charges should generate an electrostatic field which is identical to the reaction field. Thus, the perturbation (V_{int}) due to the reaction field could be accurately calculated by equation 4, where r is the coordinates of each solute atom and r' loops through all the virtual surface charges. After the QM SCF converges with the perturbed H' , the perturbed wave function is used to obtain a new solute charge distribution $\rho(\mathbf{r})$ using CM1 or CM2 methods. A new PB equation constructed with the updated $\rho(\mathbf{r})$ which then needs to be solved self-consistently again. This iterative calculation of QM and PB defines the so-called self-consistent reaction field (SCRF) calculation. The solvation free energy of the solute is obtained via equation 5 after the SCRF converges.

$$\begin{aligned} \Delta G_{\text{solv}} &= \frac{1}{2} \sum_i Z_i \cdot V_{\text{int}} + \langle \Psi' | H_M + V_{\text{int}} | \Psi' \rangle - \langle \Psi^0 | H_M | \Psi^0 \rangle + G_{\text{np}} \\ &= \left(\frac{1}{2} \sum_i Z_i \cdot V_{\text{int}} + \langle \Psi' | V_{\text{int}} | \Psi' \rangle \right) + \left(\langle \Psi' | H_M | \Psi' \rangle - \langle \Psi^0 | H_M | \Psi^0 \rangle \right) + G_{\text{np}} \quad (5) \\ &= G_{\text{rf}} + G_{\text{wfd}} + G_{\text{np}} \end{aligned}$$

The G_{rf} is the electrostatic interaction of the solute charge distribution (including core and electrons) with the electrostatic potential generated by the reaction field. It is more efficient

and accurate to calculate the G_{rf} using the virtual surface charge, (see equation 6), instead of using the electrostatic potential directly.

$$G_{rf} = \frac{1}{2} \int_v \rho(r) \int_s ds \frac{c(r')}{|r-r'|} \quad (6)$$

G_{wfd} , the wave function distortion energy is generated by the change of the gas phase wave function by the presence of solvent. It is the difference of the heat of formation calculated from polarized Fock matrix itself (without the interaction with the surface charges) and the heat of formation obtained in vacuum. G_{np} , the non-polar energy, contains contributions from cavity formation and solvent-solute dispersion-repulsion interactions. It is generally made proportional to the molecular surface area, using two surface tension parameters a & b (equation 7).

$$G_{np} = a*S + b \quad (7)$$

Figure 1 summarizes the origin of these three energy components of the solvation free energy:

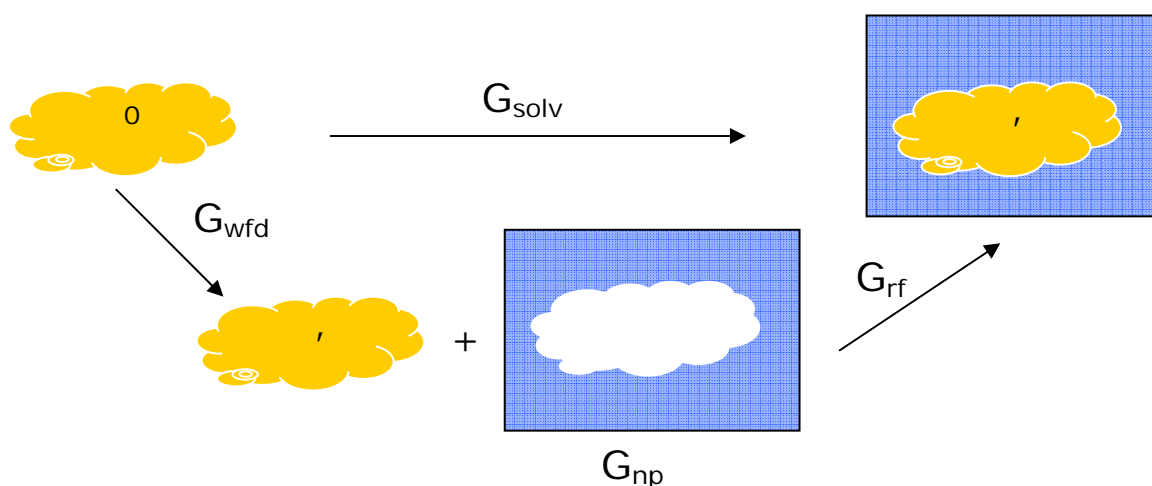


Figure 1. The components of the solvation free energy in the QM/PB model. G_{wfd} is the penalty originating from the polarization of the solute's wave function in vacuum relative to the wave function in solution. G_{np} models non-polar effects, including the entropy to make the molecular cavity in the solvent. G_{rf} is the electrostatic interaction between the polarized solute and the surrounding solvent.