

Table 1. Optimized Linear Expansion Coefficients Obtained for Each Model

models	C ₁	C ₂	C ₃	C ₄	C _s	C
HFED-II	-0.0338285	-0.2674625	-0.0024896	-0.0009016	0.0002941	0.0177644
OFED-II	-0.0089112	-0.1817956	-0.0075613	-0.0061214	0.0001261	0.6581843
OWLPD-II-diff	-0.0249173	-0.0856669	0.0050717	0.0052198	0.000168	-0.6404199
OWLPD-II-opt	-0.0157360	-0.0617175	0.0042068	0.0031807	0.0000924	-0.5304348

Table 2. Contributions of Each Basis Functions to Each Model

Water Solvation Free Energy, ΔG_{hyd} , HFED-II (kcal/mol)							
mol name	$\sum \sum C_1 h_1 $	$\sum C_2 h_2$	$\sum C_3 h_3$	$\sum C_4 h_4$	C _s S _s	C	ΔG_{hyd}^{cal}
1-propanol	-1.85	-5.17	-1.01	0.00	3.30	0.02	-4.72
propane	-0.12	-0.03	-0.91	0.00	3.18	0.02	2.13
1-propene	-0.20	-0.51	-0.90	0.00	3.14	0.02	1.55
toluene	-1.11	-1.91	-1.75	0.00	3.86	0.02	-0.90
propanoic acid	-2.02	-6.63	-1.03	0.00	3.33	0.02	-6.34
1-Octanol Solvation Free Energy, ΔG_{oct} , 1-OFED-II (kcal/mol)							
mol name	$\sum \sum C_1 h_1 $	$\sum C_2 h_2$	$\sum C_3 h_3$	$\sum C_4 h_4$	C _s S _s	C	ΔG_{oct}^{cal}
1-propanol	-0.49	-3.52	-3.06	-0.02	1.42	0.66	-5.01
propane	-0.03	-0.02	-2.76	-0.02	1.36	0.66	-0.81
1-propene	-0.05	-0.35	-2.72	-0.02	1.35	0.66	-1.14
toluene	-0.29	-1.30	-5.30	-0.03	1.65	0.66	-4.61
propanoic acid	-0.53	-4.51	-3.12	-0.02	1.43	0.66	-6.10
1-Octanol/Water LogP, LogP, OWLPD-II-Opt.							
mol name	$\sum \sum C_1 h_1 $	$\sum C_2 h_2$	$\sum C_3 h_3$	$\sum C_4 h_4$	C _s S _s	C	$\log P_{(w/o)}^{cal}$
1-propanol	-0.86	-1.19	1.70	0.01	1.04	-0.53	0.16
propane	-0.06	-0.01	1.54	0.01	1.00	-0.53	1.95
1-propene	-0.09	-0.12	1.51	0.01	0.99	-0.53	1.77
toluene	-0.52	-0.44	2.95	0.02	1.21	-0.53	2.69
propanoic acid	-0.94	-1.53	1.73	0.01	1.05	-0.53	-0.21

it is most crucial to have a physically realistic solvation free energy calculation method for obtaining the reliable P or $\log P$. Many computational methods have been proposed for the accurate prediction of solvation free energy of molecules. Those methods are summarized in detail elsewhere in our previous paper.¹⁰

Several $\log P$ calculation methods with 2D chemical structure have also been developed. Leo divided these methods into three categories: the whole-molecule approach, the fragment approach, and the atomic approach.¹¹ The whole-molecule approach is based on molecular properties such as charge density, molecular surface area, molecular volume and electrical properties, electrical momentum, etc., which are used as descriptors and regression parameters for the calculation of $\log P$.^{12–19} In the fragment approach, a molecule is divided into predetermined fragments and $\log P$ is calculated by the summation of the contributions from the fragments.^{20–22} In the atomic approach, $\log P$ is calculated by the summation of the contributions from the atoms in a molecule.^{23–27} Among the whole-molecule approaches, some methods employ nonlinear regression algorithm, i.e., neural network for training $\log P$ calculation model.^{28–30}

Among the calculation methods mentioned above, most methods were developed based on the additivity assumption of the contributions from the fragments or the constituting atoms in a molecule. Although those methods work very well for small rigid organic molecules, most of the methods fail to calculate $\log P$ of flexible and large molecules accurately.³¹ Those approaches have the following disadvantages: each additivity based method needs a large number of empirically derived parameters and additivity based methods cannot

describe the change in $\log P$ as the conformation of a molecule changes.

No et al. proposed the SFED model to calculate the Solvation Free Energy Density (SFED) around a molecule or a molecular cluster.¹⁰ The SFED at a point \mathbf{r} around a molecule is described as a linear combination of several basis functions which are the representations of several molecular fields, an electrostatic field, for example. The solvation free energy can be obtained by integrating the SFED around the molecule. In our previous work, Hydration Free Energy Density (HFED) was developed based on the SFED model. Several applications were performed with the SFED model. Since the $\log P$ of a molecule in a 1-octanol/water binary solvent system is the most popular descriptor for describing the behavior of the molecule in many biological systems, in this work, a $\log P$ calculation method will be developed based on the SFED model.

METHOD

1. SFED Model. The details of the SFED model are well described in our previous paper.¹⁰ In the SFED model, the solvation free energy of a solute molecule was expressed by the following equation

$$\Delta G_{sol} = \Delta G_{inter} + \Delta G_{cav} = a_l \sum_k^Q \sum_i^{N_A} f(\mathbf{r}_{ik}) + \Delta G_{cav} \quad (1)$$

where N_A is the number of atoms in the solute and \sum_Q represents the summing the grid points around the solute. a_l is a proportionality constant which depends on the grid interval, Δl . As described in Figure 1, the grid points were

Table 3. Experimental and Calculated Hydration Free Energy, ΔG_{hyd}

solute name	ΔG_{hyd}^{expa}	ΔG_{hyd}^{cal}	solute name	ΔG_{hyd}^{expa}	ΔG_{hyd}^{cal}
methane	2.00	2.00	2,3-dimethylnaphthalene	-2.79	-2.53
ethane	1.83	2.07	2,6-dimethylnaphthalene	-2.64	-2.43
propane	1.96	2.13	1-ethylnaphthalene	-2.41	-2.37
butane	2.08	2.19	methanol	-5.11	-4.93
pentane	2.33	2.31	ethanol	-5.01	-4.61
2,2-dimethylbutane	2.59	2.02	1-propanol	-4.83	-4.72
2-methylpropane	2.32	2.20	2-propanol	-4.76	-4.54
2,2-dimethylpropane	2.50	2.10	2-methyl-1-propanol	-4.52	-4.58
3-methylpentane	2.51	2.08	2-methyl-2-propanol	-4.52	-4.36
ethene	1.27	1.46	1-butanol	-4.74	-4.72
1-propene	1.27	1.55	2-butanol	-4.58	-4.36
1-butene	1.38	1.63	3-methyl-1-butanol	-4.44	-4.78
1-pentene	1.66	1.62	2-methyl-2-butanol	-4.45	-4.27
benzene	-0.87	-0.85	1-pentanol	-4.47	-4.69
toluene	-0.89	-0.90	2-pentanol	-4.39	-4.48
ethylbenzene	-0.79	-0.82	3-pentanol	-4.35	-4.33
propylbenzene	-0.53	-0.86	formaldehyde	-2.77	-3.11
isopropylbenzen	-0.30	-0.78	3-methylbutan-2-one	-3.26	-3.49
<i>o</i> -xylene	-0.90	-1.05	cyclopentanone	-4.72	-3.80
<i>m</i> -xylene	-0.84	-0.96	acetone	-3.80	-3.65
<i>p</i> -xylene	-0.81	-0.94	2-butanone	-3.64	-3.56
2-ethyltoluene	-1.04	-1.00	2-pentanone	-3.53	-3.55
4-ethyltoluene	-0.96	-0.82	3-pentanone	-3.41	-3.46
1,2,3-trimethylbenzene	-1.22	-1.19	acetophenone	-4.58	-5.12
1,2,4-trimethylbenzene	-0.86	-1.05	propanal	-3.44	-3.29
1,3,5-trimethylbenzene	-0.90	-0.96	butanal	-3.19	-3.26
naphthalene	-2.39	-2.27	2,5-dimethyltetrahydrofuran	-2.93	-1.84
1-methylnaphthalene	-2.45	-2.40	tetrahydrofuran	-3.49	-2.31
1,3-dimethylnaphthalene	-2.48	-2.47	dimethyl ether	-1.90	-2.10
1,4-dimethylnaphthalene	-2.83	-2.48	diethyl ether	-1.64	-1.46
di- <i>n</i> -propylether	-1.15	-1.50	butanamine	-4.26	-3.63
di- <i>n</i> -butyl ether	-0.83	-1.34	dibutylamine	-3.33	-1.38
methyl- <i>n</i> -propyl ether	-1.66	-1.78	dimethylamine	-4.29	-1.81
methyl- <i>tert</i> -butyl ether	-2.21	-1.60	diethylamine	-4.07	-1.48
diisopropylether	-0.53	-1.18	dipropylamine	-3.66	-1.38
aceticacid	-6.70	-6.54	pyridine	-4.70	-5.64
propanoicacid	-6.47	-6.34	3,5-dimethylpyridine	-4.84	-5.99
butanoicacid	-6.38	-6.34	3-methylpyridine	-4.77	-5.76
ethyl acetate	-3.10	-3.32	4-methylpyridine	-4.96	-5.89
<i>n</i> -propyl acetate	-2.86	-3.32	chloromethane	-0.55	-0.79
isopropyl acetate	-2.65	-3.22	chloroethane	-0.63	-0.66
methylpropanoate	-2.94	-3.39	1,2-dichloropropane	-1.27	-0.88
acetamide	-9.75	-12.27	1,3-dichloropropane	-1.89	-1.95
propionamide	-9.42	-12.10	bromomethane	-0.82	-0.56
dimethylacetamide	-8.54	-9.01	bromoethane	-0.74	-0.49
methanamine	-4.56	-3.86	fluorobenzene	-0.80	-2.28
ethaneamine	-4.50	-3.71	1,1-difluoroethane	-0.10	-2.87
propanamine	-4.39	-3.62	absolute mean error	0.47	

^a ΔG_{hyd}^{exp} are taken from ref 37.

located between the solvent accessible surface (SAS) and a defined distance from the SAS area, namely, R_{shell} . The space between the SAS and the outer surface corresponds to the "solvation shell". The SAS of the solute is defined by summing the area of the atomic SAS's except where they overlap. The atomic SAS is the spherical surface. The radius of the sphere is the sum of its *van der Waals* radii, R_{vdw} , and the effective solvent shell thickness, R_w . The optimum values of Δl , R_w , and R_{shell} were taken as a compromise between the computing time and the accuracy of the calculation.

The quantity $f(\mathbf{r}_{ik})$ is described by a linear combination of m functions, $h(\mathbf{r}_{ik})$:

$$f(\mathbf{r}_{ik}) = \sum_j^m C_j h_j(\mathbf{r}_{ik}) \quad (2)$$

The cavitation free energy contribution was expressed with the solvent accessible surface area (S_s) of the solute as follows:

$$\Delta G_{cav} = C_s S_s + const \quad (3)$$

The final formula for the SFED computation of a solute is

$$\Delta G_{sol} = \sum_k^Q \sum_j^m C_j (\Delta l, R_{shell}) h_j^o(\mathbf{r}_{ik}) + C_s S_s + const \quad (4)$$

The coefficients C 's are a function of both Δl and R_{shell} . The solvent accessible surface S_s is approximately proportional to the number of grid points in the shell.

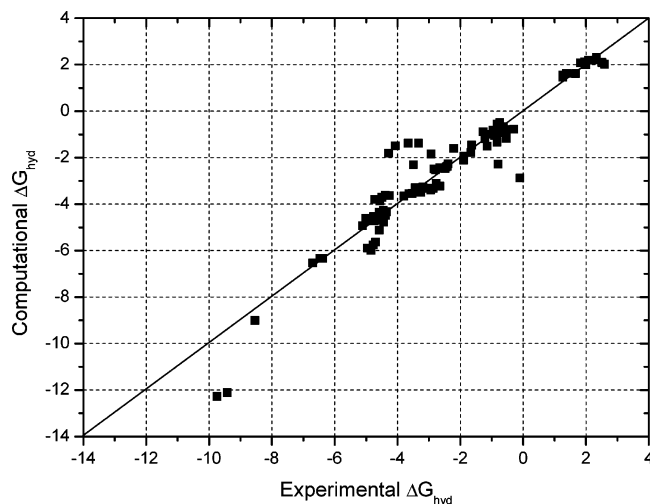


Figure 2. ΔG_{hyd}^{cal} calculated with HFED-II of 95 molecules are plotted against ΔG_{hyd}^{exp} (kcal/mol).

In our previous work, it was found that four basis functions (h_j^o) and S_s contribute significantly to ΔG_{sol} .¹⁰ The basis function vector $\vec{X} = \{h_1^o, h_2^o, h_3^o, h_4^o\}$ is

$$\vec{X} = \left\{ \left| \sum_{i=1}^{N_A} \frac{q_i}{r_{ik}} \right|, \sum_{i=1}^{N_A} \frac{q_i^2}{r_{ik}}, \sum_{i=1}^{N_A} \frac{\alpha_i}{r_{ik}^3}, \sum_{i=1}^{N_A} \frac{C_i}{r_{ik}^6} \right\} \quad (5)$$

where q_i are atom-centered net atomic charges and were calculated with an empirical net atomic charge calculation method, Modified Partial Equalization of Orbital Electronegativity (MPEOE) method.^{32,33} The atomic polarizabilities, α_i , were calculated from an empirical formula, in which the effective atomic polarizability in a molecule was described as a function of its net atomic charge, Charge Dependent Effective Atomic Polarizability (CDEAP).³⁴ The dispersion coefficients, C_i , were proportional to the square of the α_i , α_i^2 .

The basis functions work well for the compounds introduced in our previous work. However, if we include highly polarizable atoms, chlorine or bromine, for example, the fourth term contributes too much, and the solvation free energies of chlorine or bromine containing molecules are overestimated. In this work, we will modify the fourth term through a basis function selection procedure proposed in our previous work.¹⁰

2. Partition Coefficient Calculation. The logarithm of the partition coefficient, $\log P$, between a solvent and water in a binary solvent system was expressed as

$$\log P = -\frac{1}{2.303RT} (\Delta G_{sol} - \Delta G_{hyd}) \quad (6)$$

In SFED model, ΔG_{oct} and ΔG_{hyd} are expressed as

$$\Delta G_{oct} = \sum_k \sum_j^Q C_j^{oct}(\Delta l, R_{shell}) h_j^o(\mathbf{r}_{ik}) + C_s^{oct} S_s^{oct} + C^{oct} \quad (7)$$

$$\Delta G_{hyd} = \sum_k \sum_j^Q C_j^{water}(\Delta l, R_{shell}) h_j^o(\mathbf{r}_{ik}) + C_s^{water} S_s^{water} + C^{water} \quad (8)$$

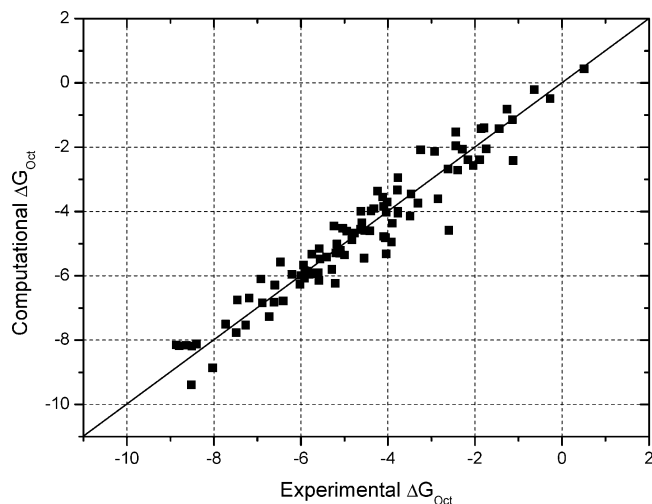


Figure 3. ΔG_{oct}^{cal} calculated with OFED-II of 95 molecules are plotted against ΔG_{oct}^{exp} (kcal/mol).

Thus, eq 6 becomes

$$\log P = -\frac{1}{2.303RT} \left\{ \sum_k \sum_j^Q \left[C_j^{oct}(\Delta l, R_{shell}) - C_j^{water}(\Delta l, R_{shell}) \right] \times h_j^o(\mathbf{r}_{ik}) + (C_s^{oct} S_s^{oct} - C_s^{water} S_s^{water}) + (C^{oct} - C^{water}) \right\} \quad (9)$$

If we assume that the solvent accessible surfaces of 1-octanol and water are the same, at constant temperature, the above equation becomes

$$\log P = -\frac{1}{2.303RT} \left\{ \sum_k \sum_j^Q C_j^{\log P}(\Delta l, R_{shell}) h_j^o(\mathbf{r}_{ik}) + C_s^{\log P} S_s + C^{\log P} \right\} \quad (10)$$

To obtain the preference of the solute at a position \mathbf{r}_{ik} between 1-octanol and water, the $\log P$ density function (LPDF) is defined as

$$LPDF(\mathbf{r}) = \sum_k \sum_j^Q C_j^{\log P}(\Delta l, R_{shell}) h_j^o(\mathbf{r}_{ik}) + \{C_s^{\log P} S_s + C^{\log P}\} \quad (11)$$

We will obtain the coefficients $C_j^{\log P}$ s in two ways: (i) using eq 9 and (ii) through the optimization procedure using experimental $\log P$ data as constraints, using eq 10.

3. Determination of the Linear Expansion Coefficients. The coefficients, $C_j(\Delta l)$, C_s , and C of each model, in eqs 7, 8, and 10, were determined by minimizing the following function:

$$F = \frac{\sum_N W_N |X_N^{cal} - X_N^{exp}|}{\sum_N W_N} \quad (12)$$

Table 4. Experimental and Calculated 1-Octanol Solvation Free Energy, ΔG_{oct}

solute name	ΔG_{oct}^{expa}	ΔG_{oct}^{cal}	solute name	ΔG_{oct}^{expa}	ΔG_{oct}^{cal}
methane	0.51	0.44	2,3-dimethylnaphthalene	-8.80	-8.18
ethane	-0.64	-0.21	2,6-dimethylnaphthalene	-8.64	-8.16
propane	-1.26	-0.81	1-ethylnaphthalene	-8.40	-8.12
butane	-1.86	-1.42	methanol	-4.10	-3.84
pentane	-2.29	-2.06	ethanol	-4.60	-4.35
2,2-dimethylbutane	-2.62	-2.68	1-propanol	-5.17	-5.01
2-methylpropan	-1.44	-1.42	2-propanol	-4.83	-4.88
2,2-dimethylpropane	-1.74	-2.05	2-methyl-1-propanol	-5.56	-5.47
3-methylpentane	-2.40	-2.71	2-methyl-2-propanol	-5.00	-5.35
ethene	-0.27	-0.49	1-butanol	-5.94	-5.66
1-propene	-1.14	-1.14	2-butanol	-5.41	-5.41
1-butene	-1.89	-2.39	3-methyl-1-butanol	-6.02	-6.26
1-pentene	-2.16	-2.39	2-methyl-2-butanol	-5.66	-5.91
benzene	-3.77	-3.99	1-pentanol	-6.60	-6.29
toluene	-4.95	-4.61	2-pentanol	-5.92	-6.07
ethylbenzene	-5.09	-5.21	3-pentanol	-6.00	-5.99
propylbenzene	-5.60	-5.91	formaldehyde	-3.25	-2.08
isopropylbenzen	-5.29	-5.80	3-methylbutan-2-one	-4.41	-4.60
<i>o</i> -xylene	-5.16	-5.27	cyclopentanone	-5.24	-4.45
<i>m</i> -xylene	-5.20	-5.28	acetone	-3.47	-3.45
<i>p</i> -xylene	-5.11	-5.29	2-butanone	-4.04	-4.03
2-ethyltoluene	-5.85	-5.85	2-pentanone	-4.77	-4.67
4-ethyltoluene	-5.91	-5.84	3-pentanone	-4.53	-4.59
1,2,3-trimethylbenzene	-6.21	-5.95	acetophenone	-6.73	-7.27
1,2,4-trimethylbenzene	-5.72	-5.93	propanal	-4.24	-3.37
1,3,5-trimethylbenzene	-5.80	-5.95	butanal	-4.39	-3.98
naphthalene	-6.89	-6.84	2,5-dimethyltetrahydrofuran	-4.63	-4.55
1methylnaphthalene	-7.73	-7.50	tetrahydrofuran	-4.12	-3.55
1,3-dimethylnaphthalene	-8.51	-8.19	dimethyl ether	-2.04	-2.57
1,4-dimethylnaphthalene	-8.86	-8.15	diethyl ether	-2.85	-3.60
di- <i>n</i> -propylether	-3.92	-4.95	butanamine	-5.58	-5.15
di- <i>n</i> -butyl ether	-5.21	-6.23	dibutylamine	-7.19	-6.69
methyl- <i>n</i> -propyl ether	-3.31	-3.74	dimethylamine	-3.77	-2.95
methyl- <i>tert</i> -butyl ether	-3.49	-4.14	diethylamine	-3.77	-4.05
diisopropylether	-2.60	-4.58	dipropylamine	-5.75	-5.33
aceticacid	-6.47	-5.57	pyridine	-5.59	-6.14
propanoicacid	-6.92	-6.10	3,5-dimethylpyridine	-7.27	-7.53
butanoicacid	-7.46	-6.75	3-methylpyridine	-6.41	-6.78
ethyl acetate	-4.10	-4.77	4-methylpyridine	-6.62	-6.82
<i>n</i> -propyl acetate	-4.55	-5.45	chloromethane	-1.79	-1.40
isopropyl acetate	-4.04	-5.31	chloroethane	-2.44	-1.96
methylpropanoate	-4.06	-4.81	1,2-dichloropropane	-4.02	-3.70
acetamide	-8.03	-8.86	1,3-dichloropropane	-4.62	-3.99
propionamide	-8.52	-9.39	bromomethane	-2.44	-1.53
dimethylacetamide	-7.49	-7.77	bromoethane	-2.93	-2.13
methanamine	-3.78	-3.33	fluorobenzene	-3.90	-4.36
ethaneamine	-4.32	-3.91	1,1-difluoroethane	-1.12	-2.42
propanamine	-5.04	-4.52	absolute mean error	0.43	

^a The experimental log*P*s that were used for ΔG_{oct}^{exp} calculation are taken from refs 38 and 39. ΔG_{oct}^{exp} s were obtained from the thermodynamic relationship as $\Delta G_{oct} = 2.303RT \log P - \Delta G_{hyd}^{35}$

W_N is the weight factor of the *N*th data value, and it depends on the reliability of the data and the frequency of the data's appearance in a system of biological molecules. If the solute molecule is rigid, a large value of W_N is assigned; for flexible molecules, smaller weight factors are assigned. It is assumed that the geometry of the solute molecule does not change upon solvation.

We expanded our model to calculate halide compounds in this work without the addition of any basis functions. For determining the coefficients in eqs 7 and 12, 95 neutral molecules that encompass a variety of organic functional groups with H, C, N, O, F, Cl, and Br atoms were introduced as constraints in this work. The molecules which were used as constraints for determining the coefficients and the functional form in the SFED were chosen using two criteria: (i) the molecules should appear frequently as

fragments of biomolecules and (ii) the molecules should be rigid. If the molecule is flexible, its conformation may change significantly upon solvation. Though the comparison of experimental free energies of solvation in neat 1-octanol with those in water saturated 1-octanol showed some difference in their two values,³⁵ the 1-octanol solvation free energy from eq 6 was used as the constraint for fitting the models.

The geometry of the molecule was obtained by energy minimization in the gas phase using CFF force field in Cerius2.³⁵

RESULTS AND DISCUSSION

1. Revised SFED Model (SFED-II). The basis function set for the SFED model was modified to overcome the

Table 5. Experimental and Calculated 1-Octanol/Water Partition Coefficient by Free Energy Difference, OWLPD-II-diff

solute name	$\log P^{\text{expt}}$	$\log P^{\text{cal}}$	solute name	$\log P^{\text{expt}}$	$\log P^{\text{cal}}$
methane	1.09	1.15	2,3-dimethylnaphthalene	4.41	4.14
ethane	1.81	1.67	2,6-dimethylnaphthalene	4.40	4.21
propane	2.36	2.16	1-ethylnaphthalene	4.39	4.21
butane	2.89	2.65	methanol	-0.74	-0.80
pentane	3.39	3.21	ethanol	-0.30	-0.19
2,2-dimethylbutane	3.82	3.45	1-propanol	0.25	0.22
2-methylpropan	2.76	2.66	2-propanol	0.05	0.25
2,2-dimethylpropane	3.11	3.04	2-methyl-1-propanol	0.76	0.65
3-methylpentane	3.60	3.51	2-methyl-2-propanol	0.35	0.73
ethene	1.13	1.43	1-butanol	0.88	0.68
1-propene	1.77	1.97	2-butanol	0.61	0.77
1-butene	2.40	2.95	3-methyl-1-butanol	1.16	1.08
1-pentene	2.80	2.94	2-methyl-2-butanol	0.89	1.20
benzene	2.13	2.30	1-pentanol	1.56	1.18
toluene	2.98	2.72	2-pentanol	1.12	1.17
ethylbenzene	3.15	3.22	3-pentanol	1.21	1.22
propylbenzene	3.72	3.70	formaldehyde	0.35	-0.75
isopropylbenzen	3.66	3.68	3-methylbutan-2-one	0.84	0.81
<i>o</i> -xylene	3.12	3.09	cyclopentanone	0.38	0.48
<i>m</i> -xylene	3.20	3.17	acetone	-0.24	-0.15
<i>p</i> -xylene	3.15	3.19	2-butanone	0.29	0.35
2-ethyltoluene	3.53	3.56	2-pentanone	0.91	0.82
4-ethyltoluene	3.63	3.68	3-pentanone	0.82	0.83
1,2,3-trimethylbenzene	3.66	3.49	acetophenone	1.58	1.58
1,2,4-trimethylbenzene	3.56	3.57	propanal	0.59	0.06
1,3,5-trimethylbenzene	3.59	3.66	butanal	0.88	0.53
naphthalene	3.30	3.35	2,5-dimethyltetrahydrofuran	1.25	1.99
1-methylnaphthalene	3.87	3.74	tetrahydrofuran	0.46	0.91
1,3-dimethylnaphthalene	4.42	4.19	dimethyl ether	0.10	0.35
1,4-dimethylnaphthalene	4.42	4.16	diethyl ether	0.89	1.57
di- <i>n</i> -propyl ether	2.03	2.53	butanamine	0.97	1.12
di- <i>n</i> -butyl ether	3.21	3.59	dibutylamine	2.83	3.89
methyl- <i>n</i> -propyl ether	1.21	1.44	dimethylamine	-0.38	0.83
methyl- <i>tert</i> -butyl ether	0.94	1.87	diethylamine	0.58	1.88
diisopropyl ether	1.52	2.49	dipropylamine	1.53	2.89
acetic acid	-0.17	-0.71	pyridine	0.65	0.37
propanoic acid	0.33	-0.18	3,5-dimethylpyridine	1.78	1.13
butanoic acid	0.79	0.30	3-methylpyridine	1.20	0.75
ethyl acetate	0.73	1.07	4-methylpyridine	1.22	0.69
<i>n</i> -propyl acetate	1.24	1.56	chloromethane	0.91	0.45
isopropyl acetate	1.02	1.53	chloroethane	1.43	0.95
methylpropanoate	0.82	1.05	1,2-dichloropropane	2.02	2.07
acetamide	-1.26	-2.50	1,3-dichloropropane	2.00	1.50
propionamide	-0.66	-1.99	bromomethane	1.19	0.71
dimethylacetamide	-0.77	-0.91	bromoethane	1.61	1.20
methanamine	-0.57	-0.39	fluorobenzene	2.27	1.53
ethanamine	-0.13	0.15	1,1-difluoroethane	0.75	-0.33
propanamine	0.48	0.66	absolute mean error	0.34	

^a $\log P^{\text{expt}}$ s are taken from refs 37 and 38.

shortcomings mentioned above. The functional forms of the two basis functions which were introduced in the previous SFED model, in eq 5, were modified as follows:

$$\vec{X} = \{h_1, h_2, h_3, h_4\} = \left\{ \left| \sum_{i=1}^{N_A} \frac{q_i}{r_{ik}} \right|, \sum_{i=1}^{N_A} \frac{q_i^2}{r_{ik}^3}, \sum_{i=1}^{N_A} \frac{\alpha_i}{r_{ik}^3}, \sum_{i=1}^{N_A} \frac{\alpha_i}{r_{ik}^6} \right\} \quad (13)$$

In the new basis function set, r_{ik} of h_2^o is replaced by r_{ik}^3 , and the atomic dispersion coefficient C_i of h_4^o is replaced by the atomic polarizability α_i . The optimum values for Δl , R_{shell} , and R_{SAS} , which are described in Figure 1, are determined as 0.5, 3.0, and 1.4 Å, respectively, and these optimized values are the same as those in our previous work. Further explanations on those parameters are described in our previous work.¹⁰

The hydration free energy, 1-octanol solvation energy, and $\log P$ are described with the following formula at

fixed Δl , R_{shell} , and R_{SAS} :

$$\Delta G_Y = \sum_k^Q \sum_j^m C_j^Y(\Delta l, R_{\text{shell}}) h_j^o(\mathbf{r}) + C_s^Y S_s^Y + C^Y \quad (14)$$

The optimized linear expansion coefficients, C_j s for each model, ΔG_{hyd} , ΔG_{oct} , and $\log P$, are summarized in Table 1. C_1 and C_2 of ΔG_{hyd} are larger than those of ΔG_{oct} , especially C_1 , because the major portion of solute and water interaction comes from permanent dipoles interaction. On the other hand, C_3 and C_4 of ΔG_{oct} are larger than those of ΔG_{hyd} because the major contribution comes from the polarization and dispersion interaction between the solute and 1-octanol.

Since all the basis functions have positive values and the coefficients C_1 , C_2 , C_3 , and C_4 are all negative, whereas C_s s are positive both in ΔG_{hyd} and ΔG_{oct} (Table 1), h_1 , h_2 , h_3 , and h_4 contribute to the driving force for solvation and S_s

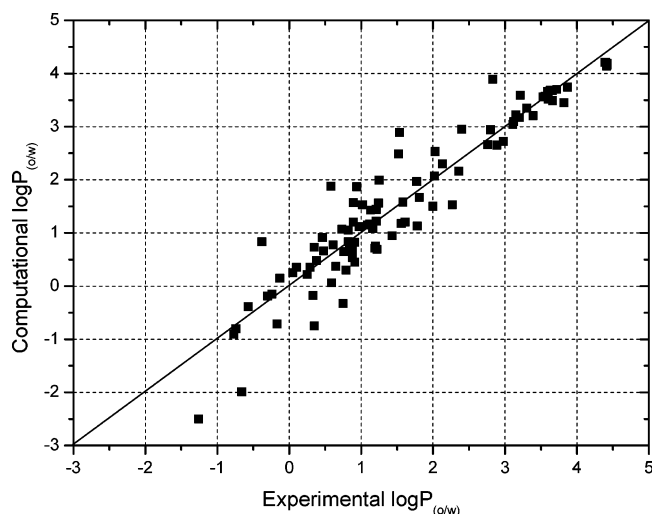


Figure 4. $\log P^{\text{cal}}$ calculated by thermodynamic relationship, OWLPD-II-diff, of 95 molecules are plotted against $\log P^{\text{exp}}$.

contributes to the driving force for desolvation. The constant C originates from the residual contribution, even for a small cavity for which S_s approaches zero. C has a positive value in both ΔG_{hyd} and ΔG_{oct} , and it is the same with $C_s S_s$.

2. LogP Calculation Model. C_1 and C_2 of $\log P$ have negative signs whereas C_3 and C_4 of $\log P$ have positive signs. h_1 and h_2 contribute favorably to water partition, and h_3 and h_4 contribute favorably to 1-octanol partition in 1-octanol/water binary solvent. S_s and C , the quantities related to the cavity formation, contribute to $\log P$ in the opposite way: S_s contributes favorably to 1-octanol partition, and the residual cavitation free energy term C contributes favorably to water partition. Since the surface tension of water is larger than that of 1-octanol, the cavity formation in water needs more free energy destabilization than in 1-octanol. The amount of the residual cavity formation energy at the solute and 1-octanol interface is larger than that of the solute and water interface.

$\log P$ can be obtained from the difference between eqs 7 and 8 as eq 9. Another way of calculating $\log P$ is to obtain the optimum coefficients of the basis functions in eq 11 through the optimization procedure with experimental $\log P$ values. The coefficients obtained from the difference and from the optimization are compared in Table 1. For obtaining the coefficients of eq 11 through optimization procedure, the initial values for the coefficients are taken from the coefficients of eq 9. The absolute mean errors obtained with the initial input coefficient values and with optimized coefficients are 0.34 and 0.32, respectively.

Analysis of Revised SFED Model (SFED-II). In Table 2, the contribution of each basis function to each model, Hydration Free Energy Density (HFED-II) model, 1-Octanol solvation Free Energy Density (OFED-II) model, and 1-Octanol/Water $\log P$ Density (OWLPD-II) model, is summarized. $\sum |\sum C_1 h_1|$ contributes much to polar molecular hydration and significantly contributes to 1-octanol solvation of polar molecules. However, the contribution of $\sum |\sum C_1 h_1|$ to nonpolar molecular solvation is immaterial. $\sum C_2 h_2$ is the major contributing term to polar molecules solvation in both hydration and 1-octanol solvation. $\sum C_2 h_2$ contributes insignificantly to nonpolar molecular solvation. $\sum C_3 h_3$ and

the surface area, S_s , roughly linearly depend on the molecular volume. For hydration, the contribution of the residual cavitation energy, C , to hydration free energy is negligible compared with the cavity formation energy, $C_s S_s$. The residual cavitation energy significantly contributes to the 1-octanol solvation free energy.

Since the SFED method is a continuum solvent model, there is some ambiguity in the decomposition of the solvation free energy compared with the energy decomposition scheme of explicit solvent model. Even though SFED is expressed with a linear combination of analytical functions, it is difficult to give meaning to each term on solid physical ground. During the optimization procedure, it was found that the basis functions h_1 and h_2 were strongly correlated, and h_3 and h_4 were also strongly correlated. h_1 and h_2 are responsible for describing the interaction between solute dipole and the dipoles of solvent. Since the solvent dipoles are moving and the motions are temperature dependent, it is hard to describe the interaction between solute dipole and solvent dipoles with few functions. In the SFED model, this interaction is represented by the linear combination of two basis functions, h_1 and h_2 . h_3 and h_4 are responsible for describing the higher order interactions, dipole-induced dipole induced dipole-induced dipole etc.

The authors believe that the basis function set of the SFED-II model is the minimal set for describing the solvation free energy quantitatively with a continuum model. The introduction of other basis functions to the SFED-II basis function set may increase the redundancy between basis functions.

Hydration Free Energy Calculation, HFED-II. In Table 3 and Figure 2, experimental and calculated hydration free energies are summarized and compared. For hydrocarbons, alkanes, alkenes, alkylated benzenes, and alkylated naphthalenes, the calculated ΔG_{hyd} with the HFED-II model agreed very well with experimental data. Since the conformations of flexible hydrocarbons in water may be different from the optimized structure used in the HFED calculation, the calculated hydration free energies of flexible molecules have a larger deviation from experimental data compared with rigid molecules. For oxygen containing molecules, alcohols, ketones, ethers, acids, and acetates are all reasonably agreed with experimental data, except for some flexible molecules. For nitrogen containing molecules, ΔG_{hyd} of amides and alkylated pyridines are overestimated and ΔG_{hyd} of amines are less estimated. ΔG_{hyd} of dialkylated amines are especially poorly reproduced. It seems that the MPEOE point charges of dialkylated amines are physically unrealistic. The point charge and *van der Waals* radii of the nitrogens need to be modified for the hydration free energy calculation with the HFED-II model. For halogenated hydrocarbons, ΔG_{hyd} of chloroalkane and bromoalkane are reasonably agreed with experimental data. However, ΔG_{hyd} of fluorobenzene and 1-difluoroethane extremely overestimate the experimental data. This shortcoming can be improved by modifying the parameters of fluorine in MPEOE charge calculation method and introducing physically realistic *van der Waals* radii of fluorine atom.

1-Octanol Solvation Free Energy Calculation, OFED-II. In Table 4 and Figure 3, experimental and calculated 1-octanol solvation free energies are summarized and compared. Like the hydration free energy calculation, for

Table 6. Experimental and Calculated 1-Octanol/Water Partition Coefficient by OWLPD-II-Opt

solute name	$\log P^{\text{expt}}$	$\log P^{\text{cal}}$	solute name	$\log P^{\text{expt}}$	$\log P^{\text{cal}}$
methane	1.09	0.91	2,3-dimethylnaphthalene	4.41	4.30
ethane	1.81	1.45	2,6-dimethylnaphthalene	4.40	4.36
propane	2.36	1.95	1-ethylnaphthalene	4.39	4.35
butane	2.89	2.46	methanol	-0.74	-0.88
pentane	3.39	3.03	ethanol	-0.30	-0.27
2,2-dimethylbutane	3.82	3.31	1-propanol	0.25	0.16
2-methylpropan	2.76	2.47	2-propanol	0.05	0.20
2,2-dimethylpropane	3.11	2.88	2-methyl-1-propanol	0.76	0.63
3-methylpentane	3.60	3.37	2-methyl-2-propanol	0.35	0.70
ethene	1.13	1.21	1-butanol	0.88	0.65
1-propene	1.77	1.77	2-butanol	0.61	0.73
1-butene	2.40	2.78	3-methyl-1-butanol	1.16	1.08
1-pentene	2.80	2.78	2-methyl-2-butanol	0.89	1.19
benzene	2.13	2.24	1-pentanol	1.56	1.16
toluene	2.98	2.69	2-pentanol	1.12	1.16
ethylbenzene	3.15	3.20	3-pentanol	1.21	1.20
propylbenzene	3.72	3.70	formaldehyde	0.35	-0.79
isopropylbenzen	3.66	3.68	3-methylbutan-2-one	0.84	0.89
<i>o</i> -xylene	3.12	3.10	cyclopentanone	0.38	0.58
<i>m</i> -xylene	3.20	3.17	acetone	-0.24	-0.10
<i>p</i> -xylene	3.15	3.19	2-butanone	0.29	0.41
2-ethyltoluene	3.53	3.58	2-pentanone	0.91	0.91
4-ethyltoluene	3.63	3.69	3-pentanone	0.82	0.91
1,2,3-trimethylbenzene	3.66	3.54	acetophenone	1.58	1.74
1,2,4-trimethylbenzene	3.56	3.61	propanal	0.59	0.09
1,3,5-trimethylbenzene	3.59	3.69	butanal	0.88	0.57
naphthalene	3.30	3.43	2,5-dimethyltetrahydrofuran	1.25	1.98
1methylnaphthalene	3.87	3.86	tetrahydrofuran	0.46	0.88
1,3-dimethylnaphthalene	4.42	4.34	dimethyl ether	0.10	0.26
1,4-dimethylnaphthalene	4.42	4.32	diethyl ether	0.89	1.49
di- <i>n</i> -propylether	2.03	2.49	butanamine	0.97	1.10
di- <i>n</i> -butyl ether	3.21	3.58	dibutylamine	2.83	3.88
methyl- <i>n</i> -propyl ether	1.21	1.38	dimethylamine	-0.38	0.71
methyl- <i>tert</i> -butyl ether	0.94	1.83	diethylamine	0.58	1.79
diisopropylether	1.52	2.45	dipropylamine	1.53	2.84
aceticacid	-0.17	-0.75	pyridine	0.65	0.42
propanoicacid	0.33	-0.21	3,5-dimethylpyridine	1.78	1.26
butanoicacid	0.79	0.28	3-methylpyridine	1.20	0.84
ethyl acetate	0.73	1.01	4-methylpyridine	1.22	0.78
<i>n</i> -propyl acetate	1.24	1.53	chloromethane	0.91	0.38
isopropyl acetate	1.02	1.50	chloroethane	1.43	0.90
methylpropanoate	0.82	1.00	1,2-dichloropropane	2.02	2.02
acetamide	-1.26	-2.35	1,3-dichloropropane	2.00	1.53
propionamide	-0.66	-1.82	bromomethane	1.19	0.64
dimethylacetamide	-0.77	-0.73	bromoethane	1.61	1.15
methanamine	-0.57	-0.45	fluorobenzene	2.27	1.54
ethanamine	-0.13	0.10	1,1-difluoroethane	0.75	-0.40
propanamine	0.48	0.62	absolute mean error	0.32	

^a $\log P^{\text{expt}}$ s are taken from refs 38 and 39.

hydrocarbons, the calculated ΔG_{oct} with the OFED-II model agree very well with experimental data. For oxygen containing molecules, alcohols and ketones agree well with experimental data, whereas ΔG_{oct} of acids are less estimated to some degree. The calculational ΔG_{oct} of ethers and acetates are overestimated compared with the experimental ΔG_{oct} . For nitrogen containing molecules, ΔG_{oct} of amides are little overestimated and ΔG_{oct} of alkylated pyridines are reasonably agreed with experimental data.

1-Octanol/Water LogP Calculation, OWLPD-II. The coefficients of OWLPD-II were determined in two ways: (i) with eq 9, $C_j^{\log P} = C_j^{\text{oct}} - C_j^{\text{water}}$, OWLPD-II-Diff and (ii) through optimization procedure using experimental logP as constraints, eq 10, OWLPD-II-Opt. In Table 5 and Figure 4, logP calculated with free energy difference, $\Delta G_{\text{oct}} - \Delta G_{\text{oct}}$, (OWLPD-II-Diff) and experimental logP are compared. In Table 6 and Figure 5, logP obtained through the optimization

procedure (OWLPD-II-Opt) and experimental logP are compared. The standard errors of logP calculated with OWLPD-II-Diff and OWLPD-II-Opt are 0.34 and 0.32, respectively. Though the OWLPD-II-Opt model gives better estimation of experimental logP than the OWLPD-II-Diff model, the OWLPD-II-Diff model has more concrete physical ground than the OWLPD-II-Opt model. The prediction capability of the OWLPD-II-Diff model will increase when the shortcomings of the HFED and OFED models are improved.

To test the predictability of the proposed model, the logPs of the compounds set in Breindl et al. work were calculated.²⁷ The absolute mean error was obtained as 0.68. This error is larger than that of the training set (0.32) because some atom types in the test set molecules are not well defined in the MPEOE net atomic charge calculation method and the molecules in the test set are more flexible than the training

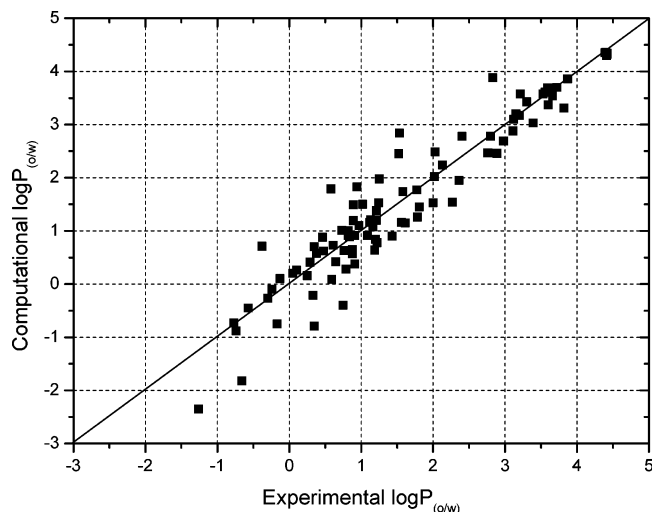


Figure 5. $\log P^{cal}$ calculated with OWLPD-II-Opt of 95 molecules are plotted against $\log P^{exp}$.

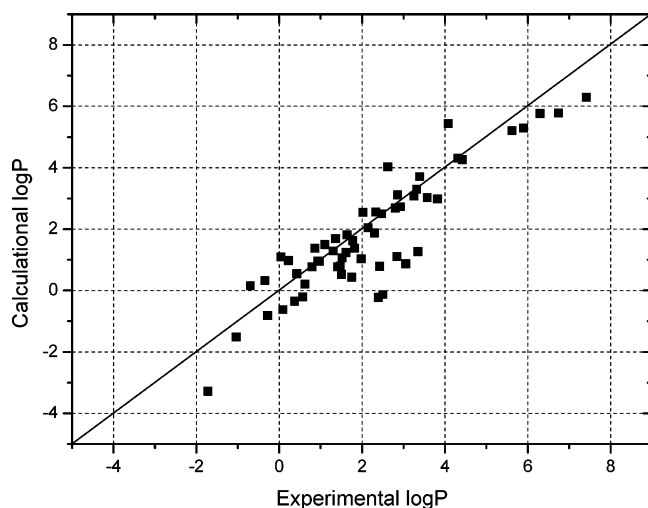


Figure 6. $\log P^{cal}$ calculated by OWLPD-II-opt of 58 molecules are plotted against $\log P^{exp}$. $\log P^{exp}$ s are taken from ref 27.

set molecules. In Figure 6, experimental and calculated $\log P$ s of the test set are compared.

CONCLUSION

In this work, the functional form of the basis functions of the SFED model was modified in order to overcome the overestimation in the hydration free energies of the molecules that have highly polarizable atoms, chlorine and bromine, for example. Based on the modified SFED model, SFED-II, the hydration free energy and the 1-octanol solvation free energy calculation methods were obtained. The logarithm of the partition coefficient between water and 1-octanol, $\log P$, was expressed with the same basis functions of the SFED-II. $\log P$ was also calculated from the free energy difference between hydration and 1-octanol solvation free energies calculated with the SFED model. The calculated hydration free energy, 1-octanol free energies, and $\log P$ are agreed well with experimental data.

Since the SFED-II gave reliable results for the prediction of experimental water and 1-octanol solvation free energies and $\log P$, the SFED-II can also be applied extensively for the solvation free energy calculations of several solvents.

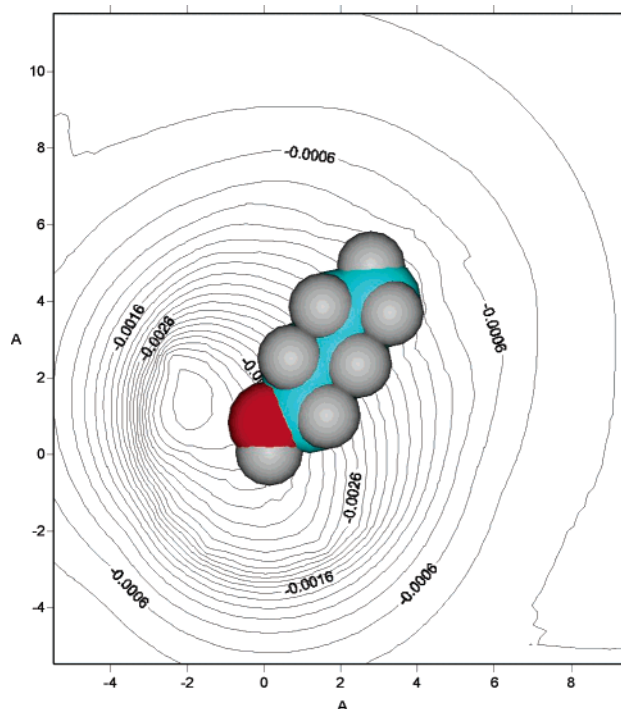


Figure 7. The ΔG_{inter} in ΔG_{hyd}^{cal} eq 1, is plotted as contours for 1-pentanol (kcal/mole).

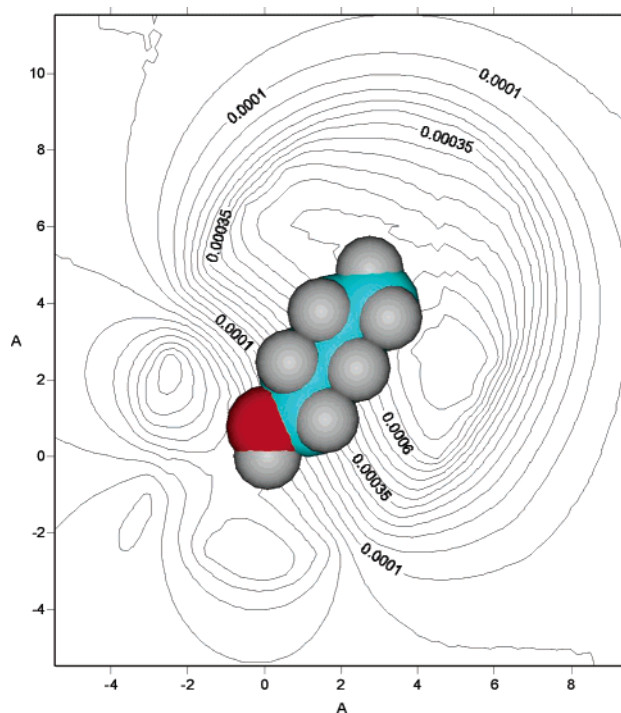


Figure 8. The OWLPD_{inter} in OWLPD-II-Opt, eq 11, is plotted as contours for 1-pentanol.

Since the SFED in the SFED model was expressed in terms of analytical functions, this can be transformed easily to other functional forms that can describe the physical properties of molecule descriptors. The SFED-II model will be used for the development of several kinds of three-dimensional descriptors. The SFED model can be used also for the interaction studies between protein and small organic molecules and between proteins in solvent, with a minor modification of the model.

With the solvation free energy density calculated around a molecule, one can easily visualize the degree of interaction between the solvent molecules and the solute molecule, shown in Figures 7 and 8.

Currently, the SFED method has a limitation of calculation because some molecules have various functional groups the atomic charges and the atomic polarizations cannot be accurately calculated. Since the atomic charge calculation method, MPEOE, was developed to calculate electrostatic interaction in protein, the net atomic charges and the atomic polarizabilities of the atom types that do not exist in proteins cannot be accurately calculated. Therefore we exclude the molecules that contain atom types that are not well defined in the MPEOE method. Now we are revising the MPEOE and the CDEAP method to include most of the organic molecules with various functional groups. Once completed, those methods will be applied to expand the SFED model to handle organic molecules with various functional groups.

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