

Empirical Aqueous Solvation Models Based on Accessible Surface Areas with Implicit Electrostatics

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In the current work, an empirical solvation model based on accessible surface areas was reported, which can be used to predict the solvation free energies for both organic and biological molecules very fast. This solvation model is based on atom-weighted solvent accessible surface area (SAWSA). The parameterization procedure for different kinds of atoms was performed as follows: first, the atoms in a molecule were defined to different atom types based on SMARTS language; then the solvent accessible surface area for each atom (or charged group) was calculated; finally, a genetic algorithm (GA) was applied to optimize the solvation parameters for different atom types in order to reproduce the experimental solvation free energies. The derived model possessed promising predictive ability as indicated by the good statistical significance and good prediction on the external test set. Using the solvation model based on all 377 neutral molecules, we have achieved an average unsigned error of 0.51 kcal/mol and standard deviation of 0.46 kcal/mol, which was better than the model proposed by Wang et al. The solvation model developed in the current work was applied to predict the solvation free energies of small organic molecules and proteins. For the 51 small organic molecules, the SAWSA model could give consistent results with the AM1/SM2.1 model in addition to several molecules with large conjugate systems. Moreover, the predictions from SAWSA were much better than those from SM5.0R, a solvation model based on geometry-dependent atom surface tensions. For the 18 proteins randomly selected from the Brookhaven PDB database, the solvation free energies predicted by the SAWSA model showed high linear correlation ($r = 0.99$) than those predicted by PBSA, which were much better than those given by the Ooi model and the Vial model. Finally, we have successfully applied this model to predict the relative binding free energies for four binding modes of EGFR/quinazoline. The most favorable binding mode identified by MM-PBSA could also be correctly recognized by MM-SAWSA. The relative solvation free energies calculated by SAWSA show obvious correlation with those calculated by PBSA. The SAWSA should have potential applications in QSAR, molecular docking, protein folding, free energy calculations, and so forth.

Introduction

Solvation free energies in aqueous solutions are very important for chemical and biological processes, including structural and metabolic equilibria and kinetics.^{1–4} For example, in natural biological environment, nearly all enzymes are folded and express intrinsic biological functions. But if they are dehydrated, the enzymes will be unfolded and void of biological functions. That is to say, the natural structure and the related biological functions of an enzyme are greatly determined by the solvation process. In the docking process of a drug molecule with its enzyme, the solvation effect is also very important. When the drug molecule diffuses into the active site of an enzyme, both the enzyme and the drug molecule will be partly dehydrated. Meanwhile, the water molecules around them will be rearranged. Thus, the free energies of desolvation are important contributors to the binding free energies of the protein–ligand association. So the theoretical and computational methodologies used to predict the solvation free energy would have a great impact on computational chemistry.

It is believed that the solvation free energy of a molecule is made up of two parts: the electrostatic contribution and the nonpolar contribution. The latter contribution is usually modeled as proportional to the solvent accessible surface area. For most

molecules, the electrostatic term dominates the total aqueous solvation process. Up to now, there have been many different solvation models developed to address this problem from the very simple models based on atom or fragment addition^{5,6} to methods that are treating solvent molecules explicitly. In 1975, Hine and Mookerjee developed a simple solvation model based on the assumption that the solvation free energy is fragment additive.⁵ Therefore, in their model, the solvation free energy of a given molecule is the sum of the solvation free energies of all the fragments. In 1986, Eisenberg et al. developed a simple solvation model based on the solvent accessible surface area to estimate the solvation free energies of protein.^{7,8} In 1986, Ooi et al. also developed a solvation model based on the solvent accessible surface area to predict the thermodynamic parameters of hydration of peptides. In their model, the free energy of hydration is composed of additive contribution of various functional groups, and the hydration of each group was assumed to be proportional to the accessible surface area of the group.⁹ In 1991, Vila et al. developed several hydration models for peptides and proteins based on solvent accessible surface area.¹⁰ In addition, in their models, they proposed an empirical site–site distance-dependent correction that can be used in conjunction with any of those models. In 1997, Hawkins et al. proposed a solvation model for predicting aqueous free energies of solvation based entirely on geometry-dependent atomic surface

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tensions.¹¹ In 1998, this model was extended to other solvents.¹² In 2001, Wang et al. developed a solvation model based on solvent accessible surface area, which can be used to predict the solvation free energies of both organic and biological molecules.¹³ All of the above solvation models are independent of charge computations and only need limited computational resources.

Sometimes, to estimate the solvation free energy more accurately, the electrostatic part should be treated using more physically rigorous approaches. The most widely used charge-dependent models may be divided into the following categories: the self-consistent field (SCF) solvation models,^{3,14–16} the generalized Born model (GB),^{17–19} and the Poisson–Boltzmann (PB) model.^{2,20} For the SCF solvation model, the solute charge distribution, the energetic effects of cavity formation, the dispersion interaction, and the solute-induced restructuring of water are included in the solute Hamiltonian operator for SCF calculation, so this model is time-consuming and often can only be used for small molecules. The other two models can be applied to both small molecules and biopolymers. These three solvation models only need limited parameters and can treat the electrostatic solvation effect well.

The charge-dependent models seem more physically significant, but they also bear obvious limitations. First, they are charge-dependent, so the parameter developed for one charge model may not be transferable to others. Very often, the obtained solvation free energies were different when we used different charge models. The second limitation, compared with the charge-independent models, the charge-dependent models are very time-consuming and they are very difficult to be used in some applications, such as the evaluation the solvation effects of multiple ligands in a large database docked to an enzyme.

The charge-independent models are of immense practical importance, since a fragment-additive or surface-based model can lower the required computer time enormously. In the current work, we have proposed a new solvation model based on different atom types and the atom-weighted solvent accessible surface area (SAWSA) using a large molecule set (377 neutral molecules and 38 ionic solutes). The solvation free energy is calculated using the following equation

$$\Delta G_{\text{water}} = \sum_{i=0}^n \sum_{j=0}^{m_i} w_i S_j \quad (1)$$

where m is the number of atom types for a given molecule; w_i is the solvation free energy weight of atom type i ; n_i are the number of atoms with atom type i in a molecule, and S_j is the solvent accessible surface area of atom j .

The basic idea of the solvation model in this paper is indeed not novel, and it has been used by Eisenberg et al., Ooi et al., and Wang et al.^{7,10,13} But we think there exist two obvious differences of our model compared with the others. First, the atom types used here are different from those reported by the other models. In our model, we elaborately defined many atom types, especially for the polar atoms. Moreover, our parameterization was based on a very large training set. The large training set and the careful atom typing rules may allow the electrostatic solvent effect to be better represented. Second, we have used a probe radius of 0.5 Å to generate the solvent accessible surface, where Eisenberg–MaLachlan’s model and Ooi’s model used a probe radius of 1.4 Å, and Wang’s model used a probe radius of 0.6 Å.

The first goal of this paper is to describe a set of parameters that can be applied for both small organic molecules and

proteins. Moreover, we want to discuss the potential applications of the solvation model in small molecules, proteins and free energy calculation. Finally, we want to design a program that can be used to estimate solvation free energies of a single molecule or multiple molecules as an automatic fashion.

Material and Methods

Atom Typing and Solvent Accessible Surface Area Calculations. The molecules used for parameterizations were collected from different references.^{1,5,11,21} The molecular geometries of all compounds in Table S1 in Supporting Information were modeled using the Cerius² molecular simulation package.²² The initial structures were fully minimized using molecular mechanism with MMFF force field.²³ Conformational analyses were performed for some molecules with flexible chains in order to find the global minimum geometries. For each molecule, only the global minimum conformation was used in the solvent accessible surface (SAS) calculation and the subsequent parameterization.

Here, the atom types were defined using the SMARTS language.²⁴ SMARTS is a language that allows you to specify substructures using rules that are straightforward extensions of SMILES.²⁵ In fact, almost all SMILES specifications are valid SMARTS targets. As with SMILES, in SMARTS one can use atomic and bond symbols to specify a graph. However, in SMARTS the labels for the graph’s nodes and edges (its “atoms” and “bonds”) are extended to include “logical operators” and special atomic and bond symbols; these allow SMARTS atoms and bonds to be more general. Using SMARTS, flexible and efficient substructure-search specifications can be made in terms that are meaningful to chemists. In the current work, a parameter file was used to store the SMARTS chains defined for all atom types. If we want to add some new typing rules or modify the typing rules, we only need to make some modifications to this parameter file. So, in this paper, the definitions of the atom types may be more complicated and efficient than those in the other work.

Molecular solvent accessible surface areas were calculated using the MSMS program,²⁶ and the probe radius was set to 0.5 Å with density of 3.0 vertex/Å². In the calculations, the surface component for each atom was output. For each molecule, the atomic SAS with the same atom type were added together. Then, the solvation parameter for each atom type was determined by using the automatic genetic algorithm (GA) fitting program developed in our group.^{27–29}

GA Fitting Procedure. In the current work, the GA was applied to derive the solvation parameter, w_i in eq 1.^{27–29} There are two different procedures to perform the fittings: it is possible to derive all the parameters simultaneously or derive them step-by-step. For the latter, one first obtains a set of parameters of a certain compound class, such as hydrocarbons, and the developed parameters are transferred to other compound classes without change during the subsequent fittings. In many complicated applications, such as for example, force field development, we often use the latter fitting process. But for the relatively simple applications, the former fitting procedure may be preferred, because it needs only one fitting process and avoids the biases aroused from the order in which the compound classes are fit. So, here, the first fitting process was applied.

In the current work, the fitting procedure was based on the GA, which was under development in our laboratory.^{27–29} The brief fitting process based on the GA involves four steps: creation of the initial population, selection operation, crossover operation, and mutation operation. According to the genetic

algorithm, an individual should be represented as a linear string, which plays the role of DNA for the individual, so the solvation parameters for all atom types were treated as a string. The initial population was generated by randomly generating the initial solvation parameters. Then these individuals were scored according to their fitness scores. After some cycles of the selection, crossover, and mutation operations, the model with the highest fitness score was obtained. In this study, the fitness function was defined as the multiple linear regression coefficient (r). More detailed description of the fitting process based on the GA can be found in our previous work.^{27–29}

Using the first fitting procedure, we worked out the parameters for three different solvation models. It should be noted that all models developed in this paper do not consider the dielectric constants, so the parameters developed for water cannot be transferred to the other solvents. In model I, the whole data set was divided into a training set with 291 molecules and a test set with 86 molecules. All the molecules considered in this fitting process are neutral molecules. The solvation parameters were determined based on the training set, and the actual prediction ability was validated by the test set. In model II, the parameters were developed by the data set with all neutral molecules. In model III, the parameters were developed using all the molecules including the 38 charged ones available in this work.

Solvation Free Energies of Small Organic Molecules and Proteins. The small molecules in the data set in Table S1 are too simple. As with most organic molecules, especially the drug molecules, the structures of them are much more complicated than those in Table S1. So in order to investigate the predictive ability of the SAWSA model, 41 molecules were selected (see Table S2 in Supporting Information).³⁰ Lombardo et al. have examined this set of molecules and found an obvious linear correlation between the ratio of brain–blood partitioning and the computed solvation free energy in water.³⁰ Since many of the molecules used in this study are quite flexible, systematic conformational analyses were applied to find the energy-lowest conformers of the studied molecules. Here, only the global minimum conformations were recorded and used for the calculations of the solvation free energies. The conformational analyses were conducted using the Cerius2 molecular simulation package.²²

Eighteen proteins were randomly selected from the Brookhaven Protein Data Bank (PDB) to evaluate the prediction of the SAWSA model for biopolymers. For these proteins, all crystallographic water molecules were eliminated from the structures. Some missing hydrogen atoms were added using the molecular design software InsightII,³¹ with a neutral sp³ N terminus and a carboxylic (COOH) C terminus assigned at neutral pH. Here it should be noted that all residues in the studied proteins are neutral forms. Before calculations, these structures were minimized using the AMBER force field to remove any steric overlap with a restraint of the main chain.³² The solvation free energies based on solving the Poisson–Boltzmann equation (PB) and molecular surface area estimation (SA) were compared with those from the SAWSA model. The electrostatic contribution to the solvation free energy was calculated using the DelphiII software package,² which solves the Poisson–Boltzmann equation numerically and calculates the electrostatic energy according to the electrostatic potential. The grid size was defined as 0.8 Å. The radius of the probe molecule was set to 1.4 Å. The partial charges used in the PB calculations were taken from the CFF91 force field. The radii of atoms were also taken from the CFF91 parameter set.³³ The iterative Delphi calculations were run for

1000 steps. The solvent accessible surface (SAS) was calculated using the MSMS program.²⁶ The nonpolar contribution to the desolvation free energy was calculated as $0.00542 \times \text{SAS} + 0.92$ kcal/mol. Moreover, here, the solvation free energies for these eighteen proteins were calculated using the Ooi model and the Vila model as a comparative study.^{9,10} The calculations of the solvation free energy using the Ooi model and the Vila model were performed using the Solvation module in InsightII.³¹

Relative Binding Free Energy Calculation with SAWSA.

In our previous work, we applied molecular dynamics (MD) simulations combined with MM/PBSA to determine the correct binding mode of the quinazoline type inhibitor with EGFR for which no ligand–protein crystal structure exists.³⁴ To proceed, we define the following procedure: three hundred picosecond molecular dynamics simulations were first performed for the four binding modes suggested by DOCK 4.0^{35,36} and manual docking, and then MM/PBSA³⁷ was carried out for the collected snapshots. The most favorable binding mode identified by MM/PBSA has a binding free energy about 10 kcal/mol more favorable than the second best one. The most favorable binding mode identified by MM/PBSA can give satisfactory explanation of the SAR data of the studied molecules and is in good agreement with the contour maps of CoMFA. In this work the solvation free energy contributing to the binding free energy was recalculated using the SAWSA model developed in this paper.

Results and Discussion

Atom Typing Rules. In charge-dependent methods, the electrostatic part contributing to the solvation free energy, is usually calculated using finite difference Poisson–Boltzmann (FDPB),² dielectric screening Poisson–Boltzmann (DSPB),³⁸ and the Generalized Born (GB) models.^{17–19} The nonpolar part can be simply estimated by using the total solvent accessible surface area. In the charge-independent methods, for example, the methods based on molecular surface areas, the electrostatic part is actually taken into account implicitly using different atom types. In principle, different atoms bear different partial charges. But if two atoms are in similar chemical environments, the partial charges should be quite similar. For this reason, in some force fields the atom-based partial charges are even used.

According to the above assumption, the definition of atom types may be the most important thing in charge-independent solvation models. In principle, if we define enough atom types and can obtain the solvation parameters for them, the electrostatic contribution may be well estimated. But unfortunately, the chemical environments in organic molecules are really very complicated, and it is very difficult for us to define unlimited atom types to differentiate all chemical environments. Moreover, the data set with experimental solvation free energies is very limited. The limited data do not allow us to define enough atom types to avoid overfitting. Based on the above discussions, we defined the atom types listed in Table 1.

For the definition of the atom typing rules, we think two aspects should be considered. First, the atom types for the elements N and O should be carefully defined, because these two kinds of elements bear strong polarity and relatively complicated chemical environments. In addition to the elements C and H, the elements N and O may be the most important constituents of composition in drug molecules. Second, we should carefully define the atom types in the conjugate systems. The atom types in the conjugate systems show obvious irregularity due to the charge flow along the conjugate systems. For example, each compound from 315 to 336 in Table S1

TABLE 1: Atom Typing Rules Used in Solvation Free Energy Calculations

no.	atom type	description	no.	atom type	description
1	CT3	sp ³ carbon	31	OOH	sp ² oxygen in ester
2	CD2	sp ² carbon	32	OP2	sp ² oxygen connected to phosphate
3	CS	sp carbon	33	OP1	sp ³ oxygen connected to phosphate
4	CO	carbon in carbonyl function group	34	SH	S in thiols
5	CA	carbon in aromatic ring	35	SS	S in sulfide
6	F	fluoride	36	SP	sp ² S connected to phosphate
7	Cl	chloride	37	NT3	sp ³ nitrogen
8	Br	bromide	38	NT2	sp ² nitrogen
9	I	iodide	39	NT	sp nitrogen
10	HT	hydrogen connected to sp ³ carbon without electron withdrawn group	40	ND2	nitrogen in heteroring with two connected atom
11	HT1	hydrogen connected to sp ³ carbon with one electron withdrawn group	41	ND3	nitrogen in heteroring with three connected atom
12	HT2	hydrogen connected to sp ³ carbon with two electron withdrawn groups	42	NO	nitrogen connected to oxygen
13	HT3	hydrogen connected to sp ³ carbon with three electron withdrawn groups	43	NG	sp ² nitrogen connect to carbon with a double bond
14	HE	hydrogen connected to sp ² carbon without electron withdrawn group	44	N6	one of the two conjugated nitrogen atoms in six-member heteroring
15	HE1	hydrogen connected to sp ² carbon with one electron withdrawn group	45	N5	one of the two conjugated nitrogen atoms in five-member heteroring
16	HE2	hydrogen connected to sp ² carbon with two electron withdrawn groups	46	P4	phosphate with four atoms
17	HO1	hydrogen connected to oxygen in alcohol	47	NH4+	sp ³ nitrogen cation with four connected hydrogen atoms (united-atom type)
18	HN	hydrogen connected to N of amine or imine	48	NH3+	sp ³ nitrogen cation with three connected hydrogen atoms (united-atom type)
19	HM	hydrogen connected to N of amide	49	NH2+	sp ³ nitrogen cation with two connected hydrogen atoms (united-atom type)
20	HS	hydrogen connected to S of thiol	50	NH+	sp ³ nitrogen cation with one connected hydrogen atoms (united-atom type)
21	HO2	hydrogen connected to O of enol or phenol	51	NC+	sp ² nitrogen cation with two connected hydrogen atoms in guanidinium ion (united-atom type)
22	HC	hydrogen connected to O of carboxyl	52	ND+	sp ² nitrogen cation with one connected hydrogen atom in imidazolium ion (united-atom type)
23	HA	hydrogen connected to aromatic carbon	53	NE+	sp ² nitrogen cation with one connected hydrogen atom in pyridinium ion (united-atom type)
24	HCS	hydrogen connected to sp carbon	54	O-	acetate ion and propionate ion
25	HO3	hydrogen connect to O of HCOO	55	OA-	oxygen cation connected to benzene ring
26	ON	oxygen in nitro group	56	COO-	oxygen cation in carboxyl ion
27	OH	hydroxyl oxygen in alcohol	57	S-	sulfur ion connected to sp ³ carbon
28	OC	ether oxygen	58	SA-	sulfur ion connected to benzene ring
29	O	oxygen in carbonyl function group			
30	OS	sp ³ oxygen in ester			

possesses a small conjugate ring. In the old atom typing rules, we only defined one atom type “ND2” for nitrogen in a heteroring with two connected atoms. It is interesting to find that the solvation free energies for the pyridine compounds were obviously overestimated, while those for the pyrazine compounds were obviously underestimated. The unsigned mean error for compounds with nitrogen in heterorings is 1.46 kcal/mol.

We believe that the inverse errors of the predictions for these two types of compounds are deduced by the conjugate effect. In a pyridine ring there is only one nitrogen atom. While in a pyrazine ring there are two conjugate nitrogen atoms. If we only define one atom type for the nitrogen atoms in pyridine ring and pyrazine ring, the nitrogen atoms in these two rings are actually forced to be equivalent, and the contribution of the nitrogen atoms in pyrazine to the solvation free energy is two times of that of one nitrogen in pyridine. But in fact, due to the conjugate effect, the partial charges on the nitrogen atoms in pyrazine are quite different from those on the nitrogen atom in pyridine. We used the Hartree–Fock method with the 6-31G* basis set applied in the Gaussian 98 program to determine partial charges fitted from the electrostatic potentials (ESP).³⁹ After calculations, the ESP charge on the pyridine nitrogen is observed to be -0.66 |e|, while that on the pyrazine nitrogen is only

-0.45 |e|. So it is obvious that the nitrogen atoms in pyridine and pyrazine should be defined as different atom types.

Thus we defined a new type “N6” to represent the nitrogen atom in a conjugate six-ring with two nitrogen atoms. Using the new atom typing rules, the unsigned mean errors for compounds 315–337 are only 0.70 kcal/mol, which are much better than those only using one atom type for nitrogen. The above analyses show that the atom types in the conjugate system should be carefully defined. But unfortunately, in the studied data set, the molecules with conjugate systems are so limited. Meanwhile, the conjugate systems studied here are very simply. We think that insufficient consideration of the conjugate systems may be the most important factor which affects the quantity of the SAWAS model. The predictive ability of the SAWSA model to molecules with large conjugate systems will be further discussed below.

For the charged ions in Table S1, we defined several united-atom types including sp³ nitrogen cation in ammonium, sp² nitrogen nitrogen cation in imidazolium ion, sp² nitrogen cation in pyridinium ion, and sp² nitrogen cation in guanidinium ion. For each united atom type, the nitrogen cation and the connected hydrogen atoms were defined together.

Probe Radius. In most solvation models such as GBSA and PBSA, a probe radius of 1.4 Å is usually applied to calculate

TABLE 2: Aqueous Solvation Models Using Different Probe Radius Based on the 377 Neutral Molecules

	1	2	3	4	5
probe radius (Å)	0.30	0.35	0.40	0.50	0.60
training set ($n = 291$)					
r	0.98	0.98	0.98	0.98	0.98
SD	0.62	0.65	0.64	0.64	0.66
unsigned mean error	0.45	0.48	0.48	0.49	0.50
test set ($n = 86$)					
r	0.95	0.96	0.96	0.95	0.95
SD	0.95	0.83	0.88	0.89	0.91
unsigned mean error	0.64	0.62	0.63	0.65	0.68
data set ($n = 377$)					
r	0.97	0.97	0.97	0.97	0.97
SD	0.71	0.69	0.70	0.70	0.72
unsigned mean error	0.49	0.51	0.51	0.51	0.55

the solvent accessible surface areas. In Wang's work, a probe of 0.6 Å was applied.¹³ To investigate the influence of the probe radius to the calculated results, different probe radii from 0.3 to 0.6 Å were used for calculations (Table 2). When the probe radius is smaller than 0.5 Å, the shift of the unsigned mean errors and the standard deviations was not very obvious. It seems that the prediction of SAWSA becomes better as the probe radius becomes smaller. The results are in good agreement with those in Wang's work.¹³ The reason is that the molecule can be described more precise when using a smaller probe radius. In fact, all atoms, especially the atoms near the molecular surface, contribute to the solvation free energy. If we use a large probe radius, the contributions of some interior atoms without accessible surface areas are neglected. Only from the unsigned mean errors of the solvations models is the probe radius of 0.3 Å the best. But considering that for the MSMS program, the probe radius ranging from 0.5 to 10 Å should pose no problem, a probe radius of 0.5 Å was applied for SAS calculations in the current work.

Solvation Models. The predicted solvation free energies for three SAWSA models are listed in Table S1. In model I, the whole data set of neutral molecules was divided into a training set with 291 molecules and a test set with 86 molecules. The training set was used to generate the solvation model. As shown in Table 2 and Table 3, the unsigned average error for the training set is 0.49 kcal/mol, and that for the test set is 0.65 kcal/mol.¹³ In total, the average error for the whole data set is 0.52 kcal/mol, which is better than that obtained by Wang et al (0.54 kcal/mol).¹³ The good prediction for the test set means that the obtained model is reliable and not overfitting.

In model II, the whole data set was used in fitting (see Table 3). We achieved an average error of 0.51 kcal/mol, which is a little better than the fitting based only on the training set. For the neutral molecules, the number of atom types used in our work is the same as those in Wang's work, but our fittings are obviously better than those reported by Wang et al.¹³ We think the reason is that the atom typing rules used here are more appropriate than those used in Wang's work.¹³

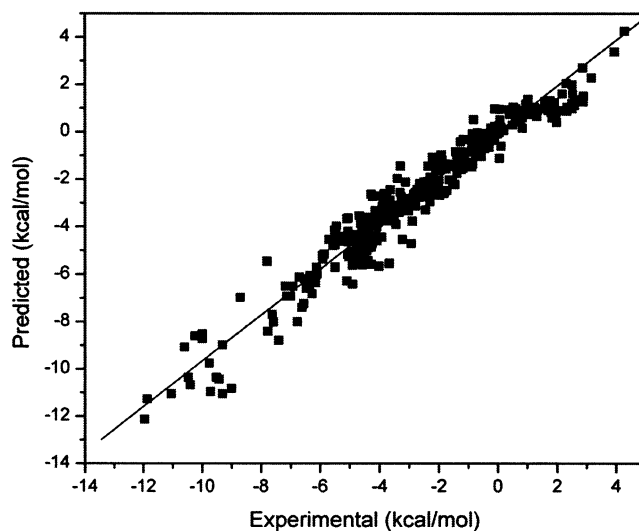
In model III, 38 ions were added for fitting. Compared with models I and II, the obtained average error of model III was increased obviously, which is 0.65 kcal/mol. It should be noted that those 38 ionic solutes have also been used in the SM5.05R model reported by Hawkins et al., and a mean unsigned error of 4.41 kcal/mol was obtained.¹¹ In the current work, the mean unsigned error for the ionic solutes is only 1.94 kcal/mol, which is much better than that using SM5.05R/AM1.

Table 3 lists the unsigned average errors for models I, II, and III by compound class. The relationship between the solvation free energies predicted by model II and the experi-

TABLE 3: Performance of the WASAS Models by Solute Function Class^a

solute class	model I			model II			model III		
	no.	error	rms	no.	error	rms	no.	error	rms
alkanes	21	1.24	0.48	21	1.10	0.49	21	1.24	0.50
alkenes	21	0.43	0.23	21	0.41	0.18	21	0.45	0.20
alkynes	8	0.21	0.13	8	0.19	0.09	8	0.22	0.11
aromatic hydrocarbons	18	0.57	0.50	18	0.50	0.49	18	0.70	0.7
fluorides	21	0.44	0.35	21	0.47	0.35	21	0.5	0.32
chlorides	39	0.37	0.24	39	0.39	0.25	39	0.33	0.24
bromides	20	0.41	0.25	20	0.44	0.25	20	0.35	0.23
iodinates	8	0.20	0.22	8	0.19	0.24	8	0.15	0.13
alcohols	43	0.49	0.36	43	0.54	0.37	43	0.56	0.36
ethers	20	0.67	0.63	20	0.68	0.59	20	0.67	0.63
aldehydes	15	0.33	0.41	15	0.32	0.44	15	0.31	0.36
ketones	17	0.30	0.28	17	0.28	0.31	17	0.24	0.29
acids	6	0.35	0.71	6	0.20	0.19	6	0.3	0.29
esters	29	0.22	0.20	29	0.24	0.23	29	0.23	0.17
amines	28	0.60	0.47	28	0.61	0.41	28	0.60	0.44
amides	6	1.42	0.28	6	1.34	0.20	6	1.31	0.24
nitriles	5	1.18	0.64	6	1.06	0.55	6	0.99	0.84
nitro compounds	7	0.17	0.14	7	0.18	0.14	7	0.15	0.10
compounds with N in heterorings	23	0.67	0.51	23	0.70	0.58	23	0.71	0.75
compounds with S	6	0.48	0.35	6	0.51	0.31	6	0.51	0.26
compounds with P	11	0.81	0.59	11	0.88	0.83	11	0.87	0.77
ions							38	1.94	1.36
total	377	0.52	0.47	377	0.51	0.46	415	0.65	0.75

^a All the errors are in kcal/mol.

**Figure 1.** Predicted and experimental aqueous solvation free energies for the 377 neutral molecules.

mental data is shown in Figure 1. The correlation coefficient is 0.97 and the slope and intercept are 0.94 and -0.15 , respectively. Table 4 lists the solvation parameters for all atom types.

Predictive Ability of the SAWSA Model for Small Organic Molecules. Only from the prediction of the solvation model to the molecules in Table S1, the obtained solvation models are very good. It should be noted that the molecules in our research work are not usually as simple as the molecules in Table S1. We expect to know if the SAWSA model can give satisfactory prediction on more complicated molecules, so 41 molecules were selected and predicted by using model II (data in Table 4). The main reason that we selected this set of molecules is that most molecules in Table S2 bear relatively large conjugate systems. The experimental solvation free energies for these molecules in Table S2 are not reported, so it is difficult to compare the predictions using our SAWSA model with the

TABLE 4: Solvation Parameters of Different Types in Three Solvation Models

	model I	model II	model III		model I	model II	model III
1	-0.08146	-0.03628	-0.02894	30	0.12833	0.14142	0.15793
2	-0.05724	-0.04093	-0.03138	31	0.01851	0.62348	0.85386
3	-0.04232	-0.04562	-0.03850	32	-0.72903	-0.17623	-0.10629
4	-0.63387	-0.65417	-0.74537	33	0.32927	-0.07707	-0.09893
5	-0.00466	-0.01542	-0.03225	34	-0.38180	-0.40756	-0.82775
6	0.03093	0.03068	0.03027	35	-0.03673	-0.02045	-0.01057
7	-0.00156	-0.00458	-0.00498	36	-0.63822	0.10092	0.18079
8	-0.03624	-0.03752	-0.03713	37	-0.50402	-0.43494	-0.36667
9	-0.04354	-0.04574	-0.04573	38	-0.29362	-0.23863	-0.23858
10	0.00543	0.00615	0.00526	39	-0.11260	-0.13275	-0.14477
11	-0.01478	-0.01816	-0.02170	40	-0.34939	-0.35472	-0.37695
12	-0.04025	-0.02534	-0.02678	41	-0.66045	-0.60182	-0.65682
13	-0.04828	-0.04798	-0.04983	42	0.17065	0.14991	-0.06811
14	0.02090	0.01676	0.01580	43	-0.49959	-0.50292	-0.30260
15	0.00614	0.00992	0.00465	44	-0.15322	-0.15157	-0.15184
16	0.03317	0.03559	0.04435	45	-0.40689	-0.39476	-0.38912
17	-0.06468	-0.07588	-0.07476	46	-0.48593	0.03320	0.01049
18	-0.06186	-0.07044	-0.07773	47			-1.26536
19	-0.19772	-0.17986	-0.18053	48			-1.51175
20	0.26821	0.28949	0.63813	49			-2.22854
21	-0.02953	-0.03244	-0.05712	50			-4.70557
22	-0.18701	-0.54881	-0.69066	51			-1.59429
23	-0.01383	-0.00972	0.00225	52			-2.26981
24	0.02107	0.02316	0.01982	53			-2.89936
25	0.21852	0.22844	0.21497	54			-4.84185
26	-0.11253	-0.10958	-0.08021	55			-3.74973
27	-0.39931	-0.38743	-0.37282	56			-3.77908
28	-0.12451	-0.11291	-0.09372	57			-3.52476
29	-0.07559	-0.08128	-0.05361	58			-3.08527

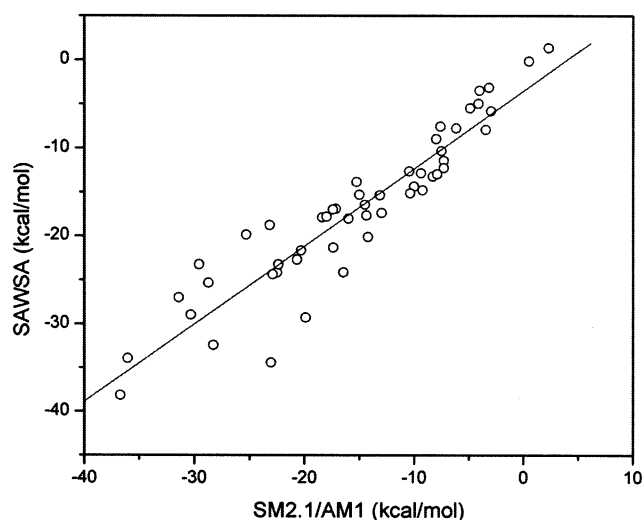


Figure 2. Comparison of the predictions using SAWSA and SM2.1/AM1 for 51 organic molecules.

experimental data. Here, we used the results predicted using the AM1-SM2.1 model as the accurate data.³ We believe that the AM1-SM2.1 model may give relatively good prediction for the molecules with conjugate systems, because in AM1-SM2.1, the redistribution of the partial charges along the conjugate systems was explicitly considered by the SCF calculations.

Figure 2 shows the linear correlation between the predicted values using AM1-SM2.1 and those using SAWSA. The high correlation coefficient ($r = 0.93$) shows that the predicted results using these two models are consistent. Among all those molecules, the predictions for compounds 33–35 are the worst. For these three compounds, the unsigned errors between the predictions using AM1-SM2.1 and those using SAWSA are larger than 7 kcal/mol. From the viewpoint of structures, compounds 33–35 contain large conjugate systems. Moreover, the conjugate systems are related to five kinds of elements

including H, C, O, N, and Cl, which correspond to more kinds of atom types. The large conjugate systems tend to redistribute charge. Since electrostatic interactions are included only implicitly in the SAWSA model, our results tend to represent a “typical” charge distribution across multiple classes of molecules. If there are functionalities within a molecule that cause the actual charge distribution to differ from the typical charge distribution implicit within our parameterization, the SAWSA model may tend to have more difficulty in predicting the solvation free energy.

For comparison, the SM5.0R model applied the in AMSOL program was also applied to estimate the solvation free energies in Table S2.^{11,12} The SM5.0R model is charge-independent, which predicts aqueous or organic solvation free energies based entirely on geometry-dependent atomic surface tension. From the unsigned mean errors of the predictions, the predictions using the SM5.0R model are quite worse than those using the SAWSA model. Figure 3 shows the linear correlation between the predicted values using AM1-SM2.1 and those using SM5.0R, which has a correlation coefficient of 0.82. The data in Figure 3 indicate there are totally eleven compounds of which the differences between the predictions with SM2.1/AM2 and those with SM5.0R are large than 7.0 kcal/mol. Moreover, it is interesting to find that compounds 33–35, which are greatly underestimated by SAWSA, are also underestimated by SM5.0R, and the unsigned errors between the predictions using AM1-SM2.1 and those using SM5.0R are also larger than 7 kcal/mol. That is to say, the compounds that cannot be well predicted by SAWSA are also not well predicted by SM5.0R, while some compounds that cannot well predicted by SM5.0R may be well predicted by SAWSA. It is reasonable that our model performs better than the SM5.0R model. In our model, more independent variables entered into the fitting procedure, and this number is somewhat larger than that in the SM5.0R model. Moreover, we carefully defined the atom types especially for the nitrogen and oxygen atoms, as well as the nitrogen atoms in the conjugate ring.

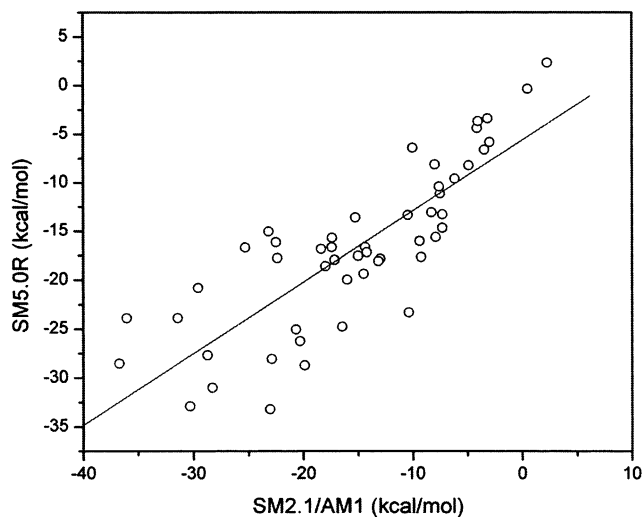


Figure 3. Comparison of the predictions using SM5.0R and SM2.1/AM1 for 51 organic molecules.

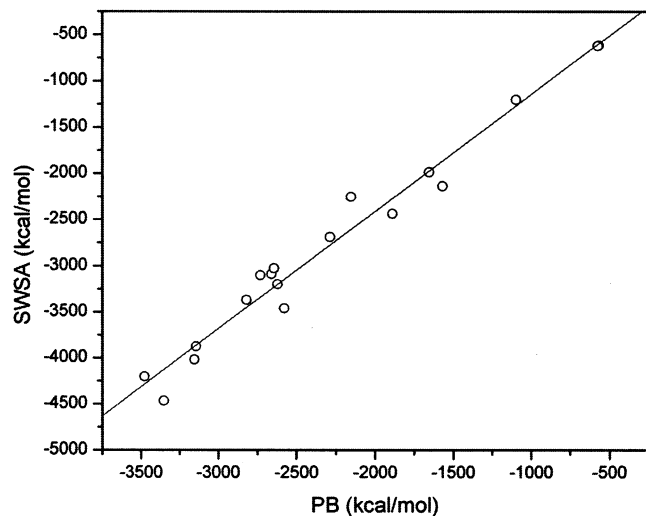


Figure 4. Comparison of the predictions using SAWSA and PBSA for 18 proteins.

We believe that the definition of enough and suitable atom types, especially for these atoms in the conjugate systems, may be the most important thing for the charge-independent solvation models. Certainly, the number of atom types is strongly limited by the available experimental data. The predicted ability of the charge-independent model may be improved by choosing a balanced training set that represents as many chemical functionalities as possible.

Predictive Ability of the SAWSA Model for Proteins. The solvation parameters for SAWSA are derived based on a set of small molecules. Certainly, the functional groups of protein can also be found in these small organic molecules, so we believe that the parameters can be extended to proteins. Figure 4 shows that the plot of predictions with PBSA versus predictions with SAWSA. The good linear correlation ($r = 0.99$) indicates that the solvation abilities of these 18 proteins can be well ranked by the predictions with SAWSA. From Figure 4, we find that some differences exist between the absolute values from SAWSA and PBSA. This is reasonable. First, the PBSA model is charge-dependent, so different partial models may tend to produce different results. Second, the PBSA model is also greatly affected by many empirical parameters, for example, the grid spacing of Delphi calculations, the dielectric constant, the probe radius, and so forth. So, the relative quantities for

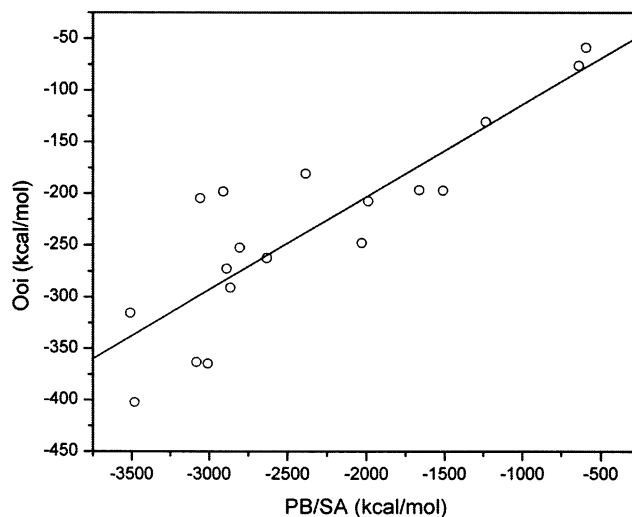


Figure 5. Comparison of the predictions using Ooi and PBSA for 18 proteins.

different systems may be the most valuable information to which we should pay attention. The above discussions show that the SAWSA model is reliable to predict the solvation ability of a neutral protein.

Here, the predictive abilities of two other models proposed by Ooi et al. and Vila et al. were also investigated. These two models have been widely used to empirically calculate solvation effect for very large molecules such as protein. The first model is from Ooi et al.⁹ They used, in part, vapor-to-water transfer free energies of small solute molecules given by Cabani et al. to find their atomic parameters. The model proposed by Ooi et al. is based on united atom and contains seven types of atoms or groups that allow the methods to be applied to a group of neutral training set. The correlation between the predictions with Ooi and those with PBSA is shown in Figure 5. There also exist significant differences between the absolute solvation free energies predicted using PBSA and the Ooi model. Not considering the difference of the absolute values between those two models, the predicted values using these two models show obvious linear correlation ($r = 0.86$). But the linear correlation is obviously worse than that shown in Figure 4. That is to say, the predictive ability of the SAWSA model for protein may be significantly better than that of the Ooi model.

The second solvation model was developed by Vila et al., which is a revised version of the model proposed by Ooi et al.¹⁰ Compared with the Ooi model, two pairwise-distance-dependent modifications were applied: the AIPD (atomic interaction using pairwise distances) modification, in which interactions between all atoms are taken into account, and the UISC (unified interacting side chains) modification, in which the side chains are represented as unified interacting groups. Figure 6 shows the correlation between the predictions with Ooi and those with PBSA. As shown in Figure 6, the data show some linear correlation, but the correlation is poor ($r = 0.67$). It seems that the Vila model cannot rank the solvation ability of the proteins effectively. The poor performance of the Ooi model and the Vila model may be simply explained by the simple atom typing rules. We think that electrostatic interactions cannot be well considered by such simple atom types.

Binding Free Energy Calculations on EGF-R/Quinazoline. The above calculations have proven that our SAWSA model can give good predictions for small organic molecules and proteins. So it is very interesting to investigate if this model can give good predictions for relative binding solvation free

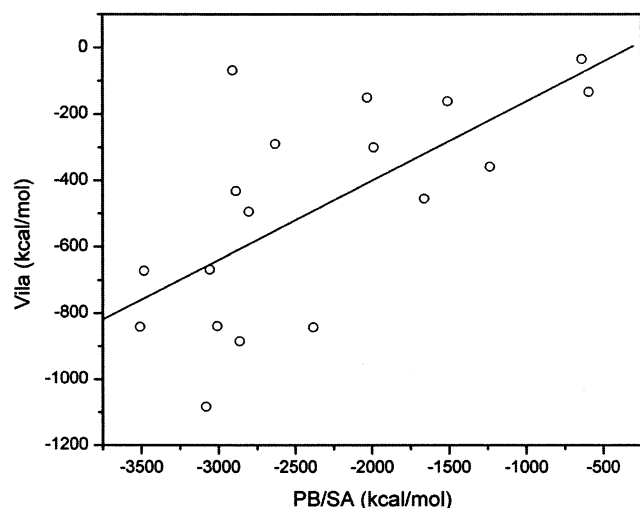


Figure 6. Comparison of the predictions using Vila and PBSA for 18 proteins.

TABLE 5: Summary of Energies from MD Simulations on EGF-R/Quinazoline^a

	model I	model II	model III	model IV
ΔE_{vdw}	-44.8 (2.3)	-42.5 (1.9)	-47.9 (2.1)	-45.4 (2.0)
ΔE_{ele}	-21.6 (3.2)	-4.7 (2.4)	-12.2 (4.9)	-22.0 (2.46)
ΔG_{PB}	48.7 (3.2)	29.7 (4.2)	42.3 (5.3)	39.5 (2.5)
ΔG_{SA}	-5.6 (0.1)	-5.2 (0.1)	-5.4 (0.2)	-5.1 (0.1)
ΔG_{WAWAS}	42.9 (2.2)	20.7 (2.7)	31.7 (3.1)	30.1 (2.1)
$-T\Delta S$	17.9 (1.5)	16.8 (1.6)	17.4 (1.5)	16.2 (1.47)
$\Delta\Delta G_1$	-5.4	-5.9	-5.8	-16.8
$\Delta\Delta G_2$	-5.6	-9.7	-11.0	-21.1

^a All the energies are in kcal/mol.

energies between small molecules and protein. Here, the binding free energy calculations on EGFR/quinazoline were used as a case study. The epidermal growth factor receptor (EGF-R) is a 170 000-dalton membrane glycoprotein.⁴⁰ The overexpression or inappropriate expression of the EGF receptor or its ligands, EGF and transforming growth factor- α , can produce loss of growth control and the unregulated cell proliferation associated with malignancy. Recently, a number of reports have shown that a broad class of 4-anilinoquinazolines are potent and highly selective inhibitors of EGF-R phosphorylation, resulting from competitive binding at the ATP site.^{41–45} Several pharmaceutical firms and research groups established programs based on these inhibitors, and now at least three such compounds have entered or will be entering clinical trials. Because the crystal structure of EGFR complexed with a quinazoline-type inhibitor is unknown, it is very meaningful to predict the binding model of EGFR with a quinazoline-type inhibitor by a theoretical approach. In previous publications, the binding modes of the quinazoline-type inhibitors in the ATP binding site of EGF-R have been reported by several groups.^{42,45,46} It is interesting to find that these reported binding modes are quite different. Several binding models have been proposed by us based on the previous reports and molecular docking calculations.^{34,47}

Table 5 listed the results of energy analyses with MM/PBSA and MM/SAWSA. The calculations with MM/PBSA show that binding mode IV has the strongest binding affinity. It is encouraging to find that the MM-SAWSA also gives consistent results with MM-PBSA. The solvation free energies obtained with the two models have a high linear correlation (Figure 7) and the correlation coefficient is 0.88. But it can be found that the absolute values from these two models bear some differ-

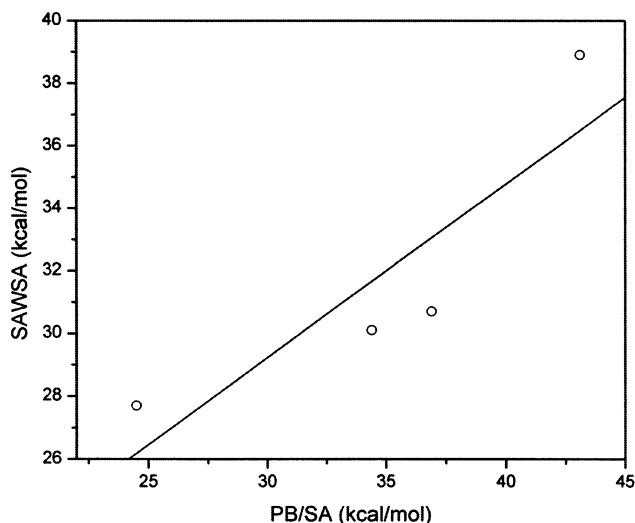


Figure 7. Relationship of the solvation free energies by SAWSA and PBSA for the four binding models of EGF-R/quinazoline.

ences, and unsigned mean errors between the binding solvation free energies used these two models are 4.5 kcal/mol. The deviations between these two models can be suggested by the neglect of the contributions of the intrinsic charges in SAWSA. The binding free energies using these two models bear obvious difference, but the best binding mode given by MM-PBSA is also correctly determined by MM-SAWSA. The high correlation shown Figure 7 indicates that the SAWSA model is somewhat meaningful if one is interested only in the relative solvation free energy. Moreover, SAWSA calculations are very time saving, being much faster than PBSA. We believe that SAWSA may be very promising in estimating the binding free energies for multiple ligands in a database.

Further Applications of SAWSA. Due to the simplicity and efficiency of the SAWSA model, it may be widely used in many fields. First, it can be used to estimate the solvation free energies for small molecules, a very important parameter in QSAR. For example, the ratio of brain–blood partitioning, $\log BB$, of CNS active drugs was found to have obvious linear correlation with the computed solvation free energies in water. Using our SAWSA model, the estimation of $\log BB$ for small molecules can be performed in high-throughput fashion.

Second, the SAWSA model has potential applications in protein folding. Our above calculations have proven that the solvation effects calculated from PBSA and SAWSA were highly correlated. In our previous work, the genetic algorithm (GA) was used to sample the conformational spaces and thoroughly search the global conformations of peptides.⁴⁸ But in our program, only the potentials of the peptides were considered. In future work, we will apply this model to calculate the solvation free energy in protein folding or the installation of side chains. We expect that the consideration of the solvation free energy will improve the performance of our method.

Finally, we will apply this model to calculate the relative binding free energy for a set of protein/ligand complexes and incorporate this model into our docking program. In our group, we have developed a different score of functions for the following two stages of conformation searching. In the first stage, surface complementarity is considered, while in the second stage only energetic complementarity is considered. In the current release of our SFDOCK program, only the van der Waals and electrostatic interactions were used to estimate the energetic complementarity.^{49–51} Soon, the SAWSA model will be incorporated into our program.

Conclusions

In the current work, several solvation models based on solvent accessible surface areas have been proposed, which can be used to estimate the aqueous solvation free energies of small molecules and proteins quickly and efficiently. The solvation free energy of a molecule can be calculated based on different atom types, corresponding solvent accessible areas, and solvation parameters. In our work, the definition of atom types was based on the SMARTS language. The prediction using the solvation model based on the entire 377-molecule set gives an average unsigned error of 0.51 kcal/mol and standard deviation of 0.70 kcal/mol.

We applied the solvation model developed in this paper to calculate the solvation free energies for 51 small organic molecules. The results are consistent with those from the AM1/SM2.1 models, in addition to several compounds with large conjugate systems. The comparison for the results from SAWSA, AM1/SM2.1, and SM5.0R shows that the calculations with SAWSA are obviously better than those with SM5.0R, another solvation model using geometry-dependent atomic surface tensions. We have also applied our model to predict the solvation free energies for 18 proteins. For the 18 proteins randomly selected from Brookhaven PDB database, the solvation free energies predicted by SWSA model bear high linear correlation ($r = 0.99$) with those predicted by PBSA model, which were much better than those given by the Ooi model and the Vial model.

Finally, we have applied SAWSA in predicting the relative binding free energies for the four binding modes of EGF-R/quinazoline. The best binding model determined by MM-PBSA was also recognized by MM-SAWSA. The solvation free energies calculated by SAWSA show high correlation with those calculated by PBSA, although some differences exist between the absolute binding free energies calculated by MM-PBSA and MM-SAWSA. Considering the simplicity and high efficiency, it can be useful to implement SAWSA to take into account the solvation effect on ligand binding.

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Supporting Information Available: The methods proposed here and all the parameters for calculations on aqueous and 1-octanol (unpublished work) have been incorporated into a computer program called SolAWSA. The SolAWSA computer code can be obtained from us freely. In SolAWSA, three sets of solvation parameters are afforded: SAWSA1.0, SAWSA2.0, and SAWSA3.0. SAWSA1.0 and 2.0 are used for solvation in water. The only difference of SAWSA1.0 and SAWSA2.0 is that SAWSA2.0 is extended to treat charged groups. SAWSA3.0 is used for solvation in 1-octanol (unpublished work). The SolAWSA program has been tested on IRIX6.5 and Linux operation systems. Also available are tables S1 (aqueous solvation free energies of organic compounds) and S2 (compounds used to validate the predictive ability of SAWSA). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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