

SMx Continuum Models for Condensed Phases

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Abstract: The SMx continuum models are designed to include condensed-phase effects in classical and quantum mechanical electronic structure calculations and can also be used for calculating geometries and vibrational frequencies in condensed phases. Originally developed for homogeneous liquid solutions, the SMx models have seen substantial application to more complicated condensed phases as well, e.g., the air-water interface, soil, phospholipid membranes, and vapor pressures of crystals as well as liquids. Bulk electrostatics are accounted for via a generalized Born formalism, and other physical contributions to free energies of interaction between a solute and the surrounding condensed phase are modeled by environmentally sensitive atomic surface tensions associated with solute atoms having surface area exposed to the surrounding medium. The underlying framework of the models, including the charge models used for the electrostatics, and some of the models' most recent extensions are summarized in this report. In addition, selected applications to environmental chemistry problems are presented.

Keywords: Solvation; Polarization; Partitioning; Solubility; Thermodynamics; Vapor pressure; Electrochemistry

1. Introduction and Underlying Physics

Many excellent reviews of the general theory and development of continuum solvation models are available [1-13], so this contribution will not attempt to provide yet another comprehensive overview of these powerful techniques. Instead, we focus specifically on the history and present status of the SMx models, which have also been reviewed [14-18], but not recently enough to include the latest developments included here. The "x" in SMx contains information about the model. Any number standing alone (e.g., 1, 2, 3, or 4) or preceding a decimal point (e.g., the "5" in SM5.42) indicates the generation of the model, and generations have typically been defined by a substantial change in the algorithmic approach undertaken for electrostatics, surface tensions, parameterization strategies, or some combination thereof as outlined in more detail below. Any number or numbers following a decimal point (e.g., the "42" in SM5.42) generally provide information about the charge models used to represent the solute charge distribution (this is also discussed in more detail below).

At the foundation of the SMx models is a partitioning of the free energy of transfer ΔG_{tr}° from the gas phase to the condensed phase into two components [19]

$$\Delta G_{tr}^{\circ} = \Delta G_{ENP}^{\circ} + G_{CDS}^{\circ} \quad (1)$$

where the first term on the right-hand-side is, at the quantum mechanical level, computed as

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$$\Delta G_{\text{ENP}}^{\circ} = \left\langle \Psi^{(1)} \left| H + \frac{1}{2} V \right| \Psi^{(1)} \right\rangle - \left\langle \Psi^{(0)} \left| H \right| \Psi^{(0)} \right\rangle \quad (2)$$

where $\Psi^{(0)}$ and $\Psi^{(1)}$ are, respectively, the wave functions that minimize the expectation values of the gas-phase Hamiltonian H and the Hamiltonian in solution; the latter adds to H one half the reaction field operator V , which represents the field acting on the solute due to the polarization of the surrounding dielectric medium by the charge distribution of the solute. The factor of $1/2$ comes from linear response theory [5] and accounts for the cost of polarizing the medium. Thus, $\Delta G_{\text{ENP}}^{\circ}$ accounts for the polarization (P) of the medium, for changes in the solute electronic (E) structure, and, if geometry reoptimization is undertaken, for changes in the nuclear (N) coordinates.

If the concentration of the solute is different in the liquid and vapor phases, eq. (1) needs another term to account for the associated entropy change. Our standard procedure is to use 1 M as the concentration in both phases, use eq. (1) as written, and then change to any other standard state that may be desired, e.g., to 1 atm standard pressure for the vapor.

In the SMx models, the reaction field operator is represented using the generalized Born (GB) equation [6,8,19-28]. In the GB approach, the charge distribution of the solute is represented by an atom-centered distribution of monopoles (i.e., partial atomic charges) and at each atom k the reaction field is defined as

$$V_k = \left(1 - \frac{1}{\epsilon} \right) \sum_{k'}^{\text{atoms}} q_{k'} \gamma_{kk'} \quad (3)$$

where ϵ is the dielectric constant of the medium, q_k is a partial atomic charge, and $\gamma_{kk'}$ is an effective Coulomb integral first suggested by Still et al. [25]

$$\gamma_{kk'} = \left(r_{kk'}^2 + \alpha_k \alpha_{k'} e^{-r_{kk'}/d_{kk'}} \right)^{-1/2} \quad (4)$$

where $r_{kk'}$ is the interatomic distance, α is an effective atomic Born radius, $d_{kk'}$ is a parameter chosen by Still et al. [25] to be 4 and by us to be either 4 or some value rather close to 4 and α is an effective Born radius.

The effective Born radius may be calculated in a number of different ways [19,25,28-36] which will not be reviewed in detail here. Conceptually, it is the radius that a spherical monatomic ion—having a charge equal to the partial charge of the atom in the solute—would need to have in order to have the same solvation free energy in the medium as does the solute atom embedded in the full, otherwise uncharged solute (the volume of which, by displacing the dielectric medium, descreens the particular atom in question). The free energy of solvation of the atom embedded in the solute is computed by solving the Poisson equation for the charged species in the dielectric medium. The necessary integration for this solution is accomplished either numerically or by using an analytical quadrature approach, and one aspect particularly worthy of attention here is that some lower limit for the integration must be chosen; in SMx models this limit for a monatomic ion is referred to as the intrinsic or atomic Coulomb radius ρ_k and the determination of robust atomic ρ values is a key aspect in parameterization.

The second term on the r.h.s. of eq. (1) refers to the free energy of cavitation (C), dispersion (D), and changes in the otherwise homogeneous solvent structure (S) induced by the solute. The SMx models assume that these various free energies may be partitioned into atomic contributions, and that each atom's contribution will depend on its atomic number, its intramolecular environment, and the extent to which it is exposed to the surrounding medium. Thus, we compute

$$G_{\text{CDS}}^{\circ} = \sum_k^{\text{atoms}} \sigma_k(\mathbf{Q}) A_k \quad (5)$$

where A_k is the solvent accessible surface area [28,37,38] of atom k and σ_k has units of surface tension and is not necessarily a simple constant for all atoms of a given atomic number but instead a function of the nuclear coordinates \mathbf{Q} and, in SM2 and SM3, on functions of the electronic density matrix as well.

We next proceed to detail how the SMx models have evolved within the general framework described by eqs. (1)–(5). We pay special attention to pointing out the details that distinguish one SMx model from another.

2. A Brief History of the SMx Models for Homogeneous Liquid Solutions

2.1. SMx models for semiempirical Hamiltonians. The first SMx models to be reported were SM1 and SM1a [19]. These two models were the first quantum mechanical continuum solvation models to be parameterized against an extensive set of experimental aqueous free energies of solvation (141 neutral compounds and 27 ions; most prior models had tended to focus on specific components of the solvation free energy that are not physical observables, or had focused on only one or a very small number of free energies of solvation for related molecules). Parameterization against increasingly large experimental data sets has been a hallmark of all SMx model development.

Both SM1 and SM1a were based on the semiempirical Austin Model 1 (AM1) Hamiltonian [39]. In these first generation models, the partial atomic charges used to define the reaction field were taken calculated from the electronic density matrix by the population analysis of Mulliken (which reduces to the description of Coulson within the context of a zero diatomic overlap model like AM1) [40]. Thus, Fock matrix elements in the self-consistent reaction field (SCRF) process were defined as

$$F_{\mu\nu}^{(1)} = F_{\mu\nu}^{(0)} + \delta_{\mu\nu} \left(1 - \frac{1}{\epsilon} \right) \sum_{k'} \sum_{v \in k'} (Z_{k'} - P_{vv}) \gamma_{kk'} \quad (6)$$

where \mathbf{F} is the Fock matrix indexed over basis functions μ and ν , δ is the Kronecker delta, Z is the AM1 valence nuclear charge, and \mathbf{P} is the density matrix. The Coulomb integral $\gamma_{kk'}$ was defined as in eq. (4) except for OO and NH atom pairs, for which an additional term was added to effectively increase the screening between these two charges.

Another feature of SM1 and SM1a was that the atomic Coulomb radii were made to vary as a function of partial atomic charge. In particular, we used

$$\rho_k = \rho_k^{(0)} - \rho_k^{(1)} \left[\frac{1}{\pi} \tan^{-1} \left(\frac{q_k + q_k^{(0)}}{q^{(1)}} \right) + \frac{1}{2} \right] \quad (7)$$

where $\rho_k^{(0)}$, $\rho_k^{(1)}$, and $q_k^{(0)}$ are atom-specific parameters, and $q^{(1)}$ was a universal parameter set to 0.1. The idea of charge-dependent radii has some intuitive conceptual appeal, and such a treatment persisted through SM4. However, the approach was abandoned in favor of constant Coulomb radii beginning with SM5-type models. There were several reasons for this choice. First, atomic partial charges tend to cluster in discrete, narrow regions, making it difficult to develop switching functions between those regions that are not fairly arbitrary. Unfortunately, while such arbitrariness may not affect typical stable molecules, there may be much more significant effects on transition-state structures, where atoms may be passing between standard hybridizations and charges, so the consequences for reaction dynamics may be large. In addition, because SM1 and SM1a were designed for use at the semiempirical level, it was not terribly expensive to carry out numerical geometry optimizations. However, in order to compute analytic derivatives it is quite inconvenient to have the Coulomb radii, and thus the effective Born radii, depend on density matrix elements in a particularly complicated way. In unpublished work preceding the development of the SM6 solvation model, we (C. Kelly, C. J. Cramer, and D. G. Truhlar) revisited the issue of whether more accurate models could be obtained by letting the intrinsic Coulomb

radii depend linearly or quadratically on particular atomic charges, but the gain in accuracy was insignificant.

With respect to G_{CDS}° , SM1 used the simplest possible approach for defining σ_k in eq. (6): the surface tension depended only on the atomic number of atom k . SM1a, on the other hand, parameterized surface tensions based on atom “types”, much as in molecular mechanics, and was designed to be used only for neutral molecules. Thus, the user would assign a type for each atom (e.g., ether oxygen or nitrile nitrogen) and the surface tension would be chosen accordingly. Over the parameterization training set of neutrals, SM1 and SM1a exhibited root-mean-square (rms) errors of 1.52 and 0.78 kcal/mol, respectively. Over the ionic training set, the rms error for SM1 was 4.4 kcal/mol. The models were defined for molecules containing H, C, N, O, F, S, Cl, Br, and I.

The next two SMx models to be reported, SM2 [26,41] and SM3 [26,42], were also aqueous solvation models based on semiempirical Hamiltonians. SM2 was designed for use with AM1 and SM3 for use with the Parameterized Model 3 (PM3) of Stewart [43]. The key difference between SM2 and SM3 and their precursor SM1 is in the determination of G_{CDS}° . In essence, recognizing the significant improvement SM1a offered over SM1, some of the heuristic principles by which a chemist assigns atom types were encoded into algorithms that assigned surface tension not only on the basis of atomic number, but also based on the number of attached hydrogen atoms, which were taken to have zero atomic radius in the computation of G_{CDS}° . In essence, then, SM2 and SM3 are united-atom models where heavy-atom properties are modified based on the hydrogen atoms attached to them.

Heavy atom surface tensions were defined as

$$\sigma_k = \sigma_k^{(0)} + \sigma_k^{(1)} [f(B_{kH}) + g(B_{kH})] \quad (8)$$

where $\sigma_k^{(0)}$ and $\sigma_k^{(1)}$ are atom-specific parameters and f and g are functions of the bond order matrix \mathbf{B} [44,45], the first being defined as

$$f(B_{kH}) = \tan^{-1}(\sqrt{3}B_{kH}) \quad (9)$$

and the second being a function targeted only to oxygen and nitrogen and designed to correct for otherwise systematic errors in H_2O , NH_3 , and primary oxonium and ammonium ions. Note that the bond order matrix is a function of the electronic density matrix [45].

Eq. (8) permits substantial distinction between different functional groups, and its adoption caused SM2 and SM3 to be much more accurate for the prediction of the free energies of solvation for hydrophobic species. The parameterization set for SM2 and SM3 was also extended by 9 molecules compared to SM1, which permitted P to be added to the list of allowed atoms in solute molecules, although parameterizations for P were not entirely reliable until SM5.42. Over the neutral set, SM2 and SM3 had rms errors of 0.9 and 1.3 kcal/mol, respectively, and over the ionic set these errors were 3.9 and 5.6 kcal/mol, respectively. The larger errors exhibited by SM3 are associated in part with the now well known poor quality of PM3 partial charges on N atoms [26].

Because of their ready availability in the free code AMSOL [46] and the commercial code SPARTAN [47], the SM2 and SM3 models saw substantial use after their introduction [48-92]. Subsequent to their original development, improvements were made in the numerical stability of certain aspects of the calculation (e.g., the quadrature scheme used for integration in determining effective Born radii, the analytical approach used for the computation of molecular surface area, and the updating scheme used in construction of the Fock matrix including the reaction field operator), and more robust versions of SM2 and SM3 were produced and called SM2.1 and SM3.1, respectively [28]; results from these models were practically unchanged compared to their precursors. The numerical improvements introduced into SM2.1 and SM3.1 have been incorporated into all subsequent SMx models as well. SM2, SM3, SM2.1, and SM3.1 are no longer recommended since several models in the SM5 series

discussed below are parameterized more broadly and more accurately for AM1 and PM3 as well as the equally inexpensive Modified Neglect of Diatomic differential Overlap (MNDO) model.

The SM4 models were the first to introduce a significant change in the calculation of $\Delta G_{\text{ENP}}^{\circ}$. These models continued to be founded on the semiempirical Hamiltonians AM1 and PM3, but instead of using Mulliken partial atomic charges in the reaction field operator, they made use of Charge Model 1 (CM1) to compute Class IV partial atomic charges [93]. The CM1 partial atomic charge is defined as

$$q_k^{\text{CM1}} = q_k^{(0)} + B_k \Delta q_k - \sum_{k' \neq k} B_{kk'} \Delta q_{k'} \quad (10)$$

where $q_k^{(0)}$ is a reference charge (e.g., a semiempirical Mulliken charge), $B_{kk'}$ is the covalent bond order (also called bond index) [45] between atoms k and k' , B_k is the sum of all bond orders from atom k to all other atoms, and Δq_k is defined as

$$\Delta q_k = c_k q_k^{(0)} + d_k \quad (11)$$

where c and d are an empirically optimized scaling parameter and offset, respectively, for atom k . The form of eq. 10 ensures that total molecular charge is conserved in the CM1 mapping procedure. The parameter vectors \mathbf{c} and \mathbf{d} for all atoms are optimized so that molecular dipole moments computed from the distributed partial atomic charges best fit an experimental data set for neutral molecules, and partial atomic charges computed from electrostatic potentials for select charged molecules [93]. CM1 charges are much more accurate than semiempirical Mulliken charges for the computation of molecular electrical moments, leading to a more physical partition of the total solvation free energy into ENP and CDS components when they are used in the GB procedure (note that by the nature of the parameterization of the surface tension terms, errors in the ENP component are perforce absorbed—as well as possible—into the CDS component).

The first SM4 model to be reported was not for water as solvent, but instead for *n*-hexadecane [94] (a solvent for which many data are available because it can be used as a stationary phase in capillary gas chromatography). For the hexadecane model, another new feature was also introduced into the SM4 model, namely, the use of different *solvent* radii to compute solvent accessible surface areas associated with different physical components of the CDS term. In particular, a CD area and a CS area were identified separately and the full CDS term was computed as

$$G_{\text{CDS}}^{\circ} = \sigma^{\text{CS}} \sum_k A_k^{\text{CS}} + \sum_k \sigma_k^{\text{CD}}(\mathbf{Q}) A_k^{\text{CD}} \quad (12)$$

where σ^{CS} is an empirically optimized molecular surface tension associated with a large solvent probe radius to generate the molecular surface area A^{CS} and σ^{CD} is an atom-specific surface tension that may either be an empirically optimized constant, or a function of empirical constants and bond orders between atom k and other atoms. In the latter case, the spirit of the approach taken in SM2 and SM3 was preserved, but the united atom model was abandoned in favor of a situation in which each H atom had a surface tension influenced by the atom attached to it, rather than vice versa. Atomic CD surface areas were computed with smaller probe radii, under the assumption that dispersion interactions occur over a much shorter range than do changes in the solvent structure when a solute is introduced.

Preliminary AM1-SM4 and PM3-SM4 models for *n*-hexadecane were parameterized against data for 153 neutral molecules. However, their parameters and performances were so similar to one another (because the CM1 charge mapping results in charge distributions that are effectively independent of the underlying Hamiltonian) that a single set of parameters was optimized for use with either Hamiltonian and taken to define SM4-hexadecane. The rms error of this model over the 306 data derived from combining the AM1 and PM3 calculations was 0.41 kcal/mol (for comparison, the dispersion in the reference data was 2.05 kcal/mol).

Subsequent work extended the SM4 model to other alkanes [95]. A data set of 350 solute/solvent combinations, where the solvents spanned 16 different alkanes, was constructed and added to the *n*-hexadecane data set. Since the alkanes would be expected to behave very similarly with one another when it comes to dispersion interactions with a solute, and since the dielectric constants are known, it was assumed that the only model parameter that one might assume to vary as a function of solvent would be σ^{CS} in eq. (12). The free energy of cavitation/structural rearrangement was assumed to be proportional to the *macroscopic* surface tension γ of the *solvent* and empirical optimization established that for all alkanes

$$\sigma^{\text{CS}} = 0.03332\gamma + 15.95 \text{ cal/mol}\cdot\text{\AA} \quad (13)$$

provided an excellent fit to all of the experimental data (eq. (13) was constrained to reproduce SM4-hexadecane exactly). Values of σ^{CS} computed from eq. (13) differed from values optimized on a solvent-by-solvent basis by no more than 0.02 cal/mol $\cdot\text{\AA}$. Again, a single set of parameters was found to be equally applicable to both the AM1 and PM3 Hamiltonians, and the rms error over all data was 0.45 kcal/mol.

An aqueous SM4 model for water was never developed. In two cases, preliminary work was reported for solutes containing C, H, and O atoms. However, those cases were not general parameterizations, but were instead restricted to certain classes of compounds for use in modeling aqueous solvation effects on the Claisen rearrangement [14] and sugar conformational analysis [96]. Careful analysis of work accomplished up to that point indicated that the dependence of surface tensions and Coulomb radii on bond orders and partial atomic charges led to instabilities associated with the difficulty of properly including these terms in Fock matrix updates as part of the SCRF equations. A decision was taken to alleviate this problem by eliminating such dependencies, and the resulting new protocol was referred to as SM5.

In practice, the term “SM5” does not refer to any specific model, but instead represents a general functional form wherein (i) all Coulomb radii are taken to be independent of partial atomic charge, (ii) Eq. (4) holds for all pairwise atomic combinations without exception, (iii) the van der Waals radii of Bondi [97] together with a solvent probe radius are used for the calculation of solvent-accessible surface area for use in computing G_{CDS}° , and (iv) all atomic surface tensions are taken to depend only on atomic number and local solute geometry, *not* on bond orders. Except for H, all Coulomb radii are taken to be constant. For H atoms bonded to N and O, a somewhat smaller radius is assigned based on a geometric function that identifies such bonding. The dependence of atomic surface tensions on molecular geometry is, ultimately, simply a more computationally convenient and unambiguous way of encoding the heuristic rules so successfully used for assigning atomic types in the SM1a model, but with the advantage that the rules are smooth and differentiable functions of atomic coordinates, making quantum calculations on unusual species and reaction coordinates entirely feasible.

With respect to specific models, SM5 models are always identified by additional characters in their names. When CM1 Class IV charges are used in the computation of $\Delta G_{\text{ENP}}^{\circ}$, and surface tensions are optimized for the corresponding G_{CDS}° , the model is referred to as SM5.4. When Class II semiempirical Mulliken charges and the resulting associated surface tensions are used, the model is designated SM5.2. When $\Delta G_{\text{ENP}}^{\circ}$ is ignored completely, and the total solvation free energy is assumed to be computable entirely from eq. (5), the model is named SM5.0. In addition, during the course of the development of *all* of the SMx models, it was observed that reoptimization of geometries typically contributes at most 5% to a total solvation free energy. As a result, computation of SCRF solvation free energies at gas-phase geometries is an efficient alternative, and when geometries are restricted to the gas phase, the model may be identified by appending an “R” to the model name, e.g., SM5.0R. Later work at Hartree-Fock (HF) and density functional theory (DFT) levels, however, has tended to adopt instead the usual “double-slash” notation (where levels for energies are specified prior to the double slash and geometries are specified afterwards, e.g., SMx/HF/6-31G//HF/6-31G).

Another suffix that may be added to the SM5 notation is PD, for “pairwise descreening” [30,98]. At semiempirical levels, solution of the SCF equations is sufficiently fast that the computation of effective Born radii can become the slowest step in the SCRF calculation. Pairwise descreening approximates

the difficult integral involved in computing the atomic solvation free energy with a parametrically scaled combination of pairwise, analytic integrals between the atom in question and all other atoms. This scheme speeds up the calculation considerably, and indeed the PD approach² has been widely employed in *classical* GB schemes (where atomic partial charges are force field parameters) in order to take advantage of its greater speed, especially for calculations on biopolymers [99,100]. At the HF and DFT levels the computation of effective Born radii no longer comprises a significant fraction of the effort, so most modern SMx calculations do not adopt the PD approach, although it remains an efficient scheme for large- or multi-scale molecular dynamics calculations. The original report [30] of the PD approach reoptimized surface tensions for SM2.1 within the context of PD descreening and named a preliminary version of this method SM2.2; subsequent work completed this parameterization and adopted the PD suffix [98].

Given that overall framework, the first SM5 model to be published [101] described the SM5.4A and SM5.4P aqueous solvation models (designed for use with AM1 and PM3, respectively); their rms errors over an expanded test set of 215 aqueous solvation free energies of neutral molecules were 0.72 and 0.62 kcal/mol, respectively. Over 34 ions their rms errors were 5.7 and 5.4 kcal/mol, respectively. A key advance accomplished at the SM5 level was the extension of the model to organic solvents (briefly called OSM5.4 to emphasize its “organic” nature, although this nomenclature is no longer used) [102,103]. This extension was done in a general way such that the model was (and still is) referred to as being “universal”. As in all SM5 models, the ENP term is computed using the normal GB formalism and the appropriate dielectric constant for the solvent. The CDS term, on the other hand, is computed from eq. (12) using solvent probes of 1.7 and 3.4 Å for the CD and CS surface areas, respectively, but the CD and CS surface tensions themselves are made to be linear functions of macroscopic *solvent* descriptors. In particular

$$\sigma_k^{\text{CD}} = \sum_{\lambda=n,\alpha,\beta} \sigma_k^{\text{CD},\lambda} \quad (14)$$

where all parameters implicit in each $\sigma_k^{\text{CD},\lambda}$ are empirically optimized over a data set comprising free energies of solvation into multiple organic solvents, n is the solvent index of refraction, α is Abraham’s hydrogen bonding acidity $\sum \alpha_2^{\text{H}}$ [104], and β is Abraham’s hydrogen bonding basicity $\sum \beta_2^{\text{H}}$ [104]. For the molecular surface tension, we took

$$\sigma^{\text{CS}} = \sum_{\lambda=n,\gamma} \sigma^{\text{CS},\lambda} \quad (15)$$

where all symbols have been described above.

Over a data set of 1786 free energies of solvation for 206 different solutes in 90 different organic solvents, the SM5.4/AM1 and SM5.4/PM3 models achieved mean unsigned errors of under 0.5 kcal/mol after parameterization. For chloroform [105] and benzene and toluene [103], refined models were described where solvation free energies for solutes into these solvents were heavily overweighted in the optimization of the parameters implicit in equations (14) and (15). Systematic errors in these solvents were eliminated in this fashion, although the magnitude of these errors was less than 1 kcal/mol in terms of mean unsigned error.

Aqueous solvation models using the SM5 functional forms for surface tensions but combining these with $\Delta G_{\text{ENP}}^{\text{O}}$ computed from Class II Mulliken charges in combination with pairwise descreening were reported for the AM1 and PM3 Hamiltonians and referred to as SM5.2PD models [98]. Aqueous pairwise descreening models SM5.4PD were also developed [98]. All of the models achieved similar overall accuracies, but the partitioning between ENP and CDS components is presumably more realistic with Class IV charges and without adopting the PD approximation. Subsequently, SM5.2

² This is sometimes referred to in the literature as the HCT approximation, for Hawkins, Cramer, and Truhlar.

organic models were developed for AM1, PM3, MNDO, and MNDO/d [106-109], again achieving accuracy similar to SM5.4 analogs at reduced cost (primarily because of simpler coding) but with some loss of physicality.

At the extreme end of sacrificing physicality for speed, it was discovered that eliminating the computation of $\Delta G_{\text{ENP}}^{\circ}$ altogether and computing the full aqueous free energy of solvation using only SM5 surface tension functionals led to a model, SM5.0, that, was essentially as accurate as any of the other SM5 aqueous models for neutral solutes [110]. The SM5.0 model does not require any electronic structure calculations, so it is extraordinarily fast, although molecular geometries must be chosen in some fashion, of course. The SM5.0 model was subsequently extended in a universal way to the organic parameterization set [111] and a freely distributed code, OMNISOL [112], was created incorporating these models. Another model, SM5.05, was also described [110] that was designed to permit an extension of aqueous SM5.0 to include the charged groups found in protein side chains at neutral pH, e.g., imidazolium ions, carboxylate anions, primary ammonium cations, and guanidinium ions.

Finally, SM5 surface tension functional forms and parameters have been optimized for use with $\Delta G_{\text{ENP}}^{\circ}$ values computed by means other than the GB formalism. In particular, SM5C [113] uses the SM5 surface tension functional form but computes $\Delta G_{\text{ENP}}^{\circ}$ at the AM1, PM3, MNDO, and MNDO/d level from the conductor-like screening model (COSMO) of Klamt and co-workers [114]. A key difference between the GB and COSMO approaches is that the latter uses the full electron density to represent the solute charge distribution instead of atom-centered point charges, and there may be instances where this more complete representation yields a more physical partitioning between electrostatic and non-electrostatic components of the full free energy of solvation. In practice, however, the accuracy of the SM5C model over the full SM5 training set is about the same as that observed for any of the other SM5-type models.

2.2. SMx models for ab initio Hartree-Fock theory and density functional theory. All of the quantum mechanical model development described for the SMx models thus far relied on underlying semiempirical QM levels of theory. Early efforts to extend the models to the HF and DFT levels made it clear, however, that the CM1 mapping scheme was not particularly well suited to these more complete levels of theory: Mulliken charges and bond orders show strong basis-set dependence and take on very unphysical values as basis sets become more saturated. In order to create a better charge mapping scheme for use at the HF and DFT levels, Charge Model 2 (CM2) was developed [115,116]. The CM2 mapping may be regarded as a more flexible and simpler extension of the CM1 model with the simultaneous adoption of pairwise specific parameters describing charge transfer between bonded atoms. The CM2 partial atomic charge is defined as

$$q_k^{\text{CM2}} = q_k^{(0)} + \sum_{k' \neq k} B_{kk'} (D_{kk'} + C_{kk'} B_{kk'}) \quad (16)$$

where the reference charge $q_k^{(0)}$ is now taken to be a Löwdin charge [117] (to reduce basis-set dependence), $B_{kk'}$ is the Mayer bond order between atoms k and k' [118,119], and $C_{kk'}$ and $D_{kk'}$ are empirically optimized parameters that change sign upon reversal of k and k' . Over a database of 211 polar molecules, CM2 models specific to level of theory/basis set combinations predict dipole moments with rms errors on the order of 0.2 D.

Subsequent SMx model development using CM2 charges led to the creation of SM5.42 models, where the "4" again denotes Class IV charges and the final "2" indicates that the Class IV charges come from CM2. At the HF level, the first SM5.42 model [120] was an aqueous model parameterized for the MIDI! basis set [121,122] based on gas-phase HF/MIDI! geometries. In short order, aqueous *and* organic SM5.42 models were described for a large number of additional HF and DFT levels /basis set combinations [123,124]. For organic solvents, eq. (15) was modified so that the summation runs over 4 solvent descriptors: the macroscopic surface tension (γ) the square of Abraham's hydrogen bonding

basicity (β^2) the square of the fraction of solvent heavy atoms that are either F, Cl, or Br (ϕ^2), and the square of the fraction of solvent heavy atoms that are aromatic carbon atoms (ψ^2). Over all solvents and solutes, mean unsigned errors in neutral solvation free energies were found typically to be on the order of 0.5 kcal/mol and the errors for ions in aqueous solution were about an order of magnitude larger. Solutes containing Si were added to the training set so that parameters for this atom could be determined [125]; predictive accuracies for the training set molecules containing Si are similar to all others.

In addition to *ab initio* levels of theory, a CM2 model was developed [126] for the INDO/S semiempirical Hamiltonian [127,128] based on a training set containing both ground- and excited-state charge distributions. An SM5.42/INDO model for ground-state molecules [129] was built upon this CM2 model, as was a two-time-scale electrostatics-only vertical excitation model (VEM4.2) designed to predict solvatochromism in UV absorption spectra [130]. This model, augmented by dispersion and hydrogen bonding terms, was used very successfully to predict the solvatochromic shifts of acetone in nine solvents.

During the course of this development effort, analytic derivatives were derived for SM5.42 solvation free energies [131], permitting efficient optimization of molecular geometries in solution. As of this date, analytic second derivatives have not yet been derived, although vibrational frequencies may be determined from numerical differentiation of the analytic first derivatives.

The SM5.42 models may be regarded as being reasonably mature, and they continue to be useful for modern research. Nevertheless, they are not the most modern members of the SM x family. In order to improve further upon the electrostatics in the GB treatment, a new Charge Model 3 [132-135] was developed that did not differ from CM2 in functional form, but was parameterized over a much more diverse test set roughly double the size of that used for CM2. In addition, a charge renormalization scheme was adopted for use with basis sets containing diffuse functions since with such basis sets Löwdin charges and Mayer bond orders were otherwise found to be less reliable [136].

SM5-type models making use of CM3 charges are referred to as SM5.43 models [137,138]. Aqueous and organic models with analytic gradients are available for the HF and B3LYP [139-142] levels with the 6-31G(d) basis set [143]. They are also available for the MPW X density functional, which corresponds to mixing $X\%$ of Hartree-Fock nonlocal exchange with $(100-X)\%$ of local mPW exchange and 100% of PW91 density functional correlation, with X taking on any value from 0 to 100% [144-146], with any of the MIDI!, 6-31G(d), 6-31+G(d), or 6-31+G(d,p) basis sets. The models are coded in the freely distributed software packages GAMESSPLUS [147], HONDOPLUS [148], and SM x GAUSS [149], and their inclusion in other codes is ongoing (updates may be found on the comp.chem.umn.edu website). Comparisons of select SM5.43 models to some of the most recent versions of the polarized continuum model (PCM; [150-155]), which is also widely used for continuum solvation calculations, are presented in Tables 1 and 2 for aqueous and organic solvents, respectively. The superior performance of the SM5.43 models is noteworthy, particularly for organic solvents.

The most recently developed SM x model is SM6, which is presently available only for water [156].

Charge model 4 (CM4) [156] was developed as part of the SM6 parameterization. The primary difference between CM3 and CM4 is that the former was judged, after detailed analysis, to sometimes predict C–H bonds to be too polar. The CM4 parameterization therefore began by optimizing the C_{CH} and D_{CH} parameters so as best to reproduce the Optimized Potentials for Liquid Simulations (OPLS; [157]) partial atomic charges for 19 hydrocarbons.³ Subsequent to that, all other parameters were optimized in the same fashion as for CM3. SM6 also has a neutral training set with some additional organic functionality not considered for SM5.43 and previous models. More importantly, however,

³ Although the OPLS partial charges are optimized for liquid phases, where dielectric screening makes bonds more polar than in the gas phase, the difference is expected to be small for C–H bonds, and we elected to use these charges as target values for gas-phase calculations.

Table 1: Mean unsigned error of the aqueous free energy of solvation (kcal/mol) of various solute classes calculated by various continuum solvation models using HF/6-31G(d)

solute class	no. data	SM5.42	C-PCM ^a	D-PCM ^a	IEF-PCM ^a	SM5.43
neutral H, C, N, O, F ^b	171	0.57	0.79	1.21	0.76	0.51
Cl, Br, S, and P neutrals ^c	86	0.49	1.64	1.69	1.64	0.48
all neutrals	257	0.54	1.07	1.37	1.06	0.50
H, C, N, O, F ions ^b	32	5.20	7.66	9.18	7.63	4.91
Cl, Br, P, S ions ^c	15	4.03	2.16	13.12	2.18	4.10
all ions	47	4.83	5.90	10.44	5.89	4.65

^aAs coded in *Gaussian 03*^bSolutes containing at most the five listed elements^cSolutes containing at least one of these elements plus, in most cases, elements from the previous row

Table 2: Mean unsigned error of the free energy of solvation (kcal/mol) of solutes in the indicated solvent calculated by various continuum solvation models with the 6-31G(d) basis set

solute class	no. data ^a	B3LYP			<i>m</i> PW1PW91	
		C-PCM ^b	D-PCM ^c	IEF-PCM ^c	SM5.43	SM5.43
acetonitrile	7	5.22	5.13	5.22	0.37	0.41
aniline	9	7.55	7.54	7.73	0.50	0.50
benzene	68	4.81	5.09	5.15	0.62	0.63
carbon tetrachloride	72	4.53	4.76	4.80	0.48	0.49
chlorobenzene	37	3.90	4.01	4.12	0.51	0.55
chloroform	96	4.56	4.75	4.82	0.53	0.55
cyclohexane	83	2.30	2.52	2.53	0.40	0.41
dichloroethane	38	3.85	3.94	4.05	0.43	0.44
diethyl ether	62	3.26	3.49	3.68	0.62	0.63
dimethyl sulfoxide	7	3.42	3.31	3.43	0.57	0.61
ethanol	8	2.17	2.45	1.87	1.30	1.35
heptane	60	2.21	2.46	2.49	0.33	0.34
methylene chloride	11	2.01	3.16	3.26	0.45	0.47
nitromethane	7	2.83	2.64	2.84	0.67	0.71
tetrahydrofuran	7	3.12	3.10	3.20	0.32	0.33
toluene	49	3.43	3.67	3.75	0.40	0.41
16 above solvents	621	3.68	3.89	3.96	0.49	0.51
all other 74 solvents	1359	n.a. ^d	n.a. ^d	n.a. ^d	0.50	0.52
self-solvation energies ^e	76 (16) ^f	(3.94)	(4.14)	(4.20)	0.50 (0.49)	0.53 (0.51)

^aNumber of experimental data in this solvent^bAs coded in *Gaussian 98*^cAs coded in *Gaussian 03*^dnot available^eStandard-state free energy of solvation of a solute in a pure liquid of the solute (i.e., equivalent to a vapor pressure).^fThe PCM-type continuum solvation models are explicitly defined for 16 of the 76 solvents used to compute the self-solvation energies and the MUEs for these 16 solvents are given in parentheses.

SM6 employs an ionic training set that is more than double the size of that used for prior models. In addition, ions clustered with one water molecule are included in the training set. Because ionic solvation free energies are so sensitive to atomic Coulomb radii, a good ionic training set is very important for setting this critical parameter. By using ionic cluster data, it proved possible to do a much more thorough job of determining physically realistic Coulomb radii. The performance of the SM6 model is marginally better than SM5.43 for neutral molecules, but significantly better for ions, which makes the model more accurate for properties such as those described in more detail in Section 3 of this

article, e.g., pK_a values and oxidation and reduction potentials. Development of organic solvation models within the SM6 framework is presently ongoing.

Another new frontier that is the subject of exploration is extension of the SM6 model to temperatures other than 298 K. A preliminary temperature-dependent water model that is applicable to compounds containing C, H, and O has been described [158]; the results are very encouraging.

2.3. Vapor pressures and solubilities. Another partitioning that is of special interest is that of a solute between a solvent and a pure phase of the solute itself, i.e., pure liquid or solid solute. This is of particular interest because one may relate this free energy of partitioning of a liquid or solid solute to that solute's solubility in a given phase. If we first consider a liquid species $A_{(l)}$ in equilibrium with its own vapor $A_{(g)}$



With a 1 molar standard-state and ideal behavior in both phases, the standard-state free energy of this process is

$$\Delta G_1^\circ = RT \ln \frac{P_A^\bullet}{P^\circ M_A^l} \quad (18)$$

where R is the universal gas constant, T is the temperature, P_A^\bullet is the equilibrium vapor pressure of A over pure A, P° is the pressure (24.45 atm) of an ideal gas at 1 molar concentration and 298 K, and M_A^l is the equilibrium molarity of the pure liquid solution of A, which is obtained from the liquid density of A. By rearrangement of eq. (18) one may compute the vapor pressure using models that predict ΔG_1° . The universal SM5-type models have been used for this purpose for a large number of cases where the necessary solvent descriptors are already available [137,159,160]; accuracies within a log unit are routine (cf. last line of Table 2).

Let us now consider the equilibrium between pure liquid A and an aqueous solution of A (we specify aqueous because of the importance of water, but the below analysis may be generalized to any solvent)



assuming that all activity coefficients are unity, the standard-state free energy for the phase transfer is

$$\Delta G_2^\circ = -RT \ln \frac{M_A^{aq}}{M_A^l} \quad (20)$$

where M_A^{aq} is the equilibrium aqueous molarity of solute A, i.e., its solubility in molarity units, also denoted as S . Combining eqs. (17) and (19) gives



The standard-state free energy change in this process is the standard-state aqueous free energy of solvation of solute A, $\Delta G_{S(aq)}^\circ$; and we can calculate it by adding eqs. (18) and (20), which yields

$$\Delta G_{S(aq)}^\circ = RT \ln \frac{P_A^\bullet}{P^\circ} - RT \ln M_A^{aq} \quad (22)$$

Equation (22) is based on the assumption that the aqueous solution of A obeys Henry's law, i.e., that the saturated solution behaves as though infinitely dilute. In general, then, we may predict solubility from

$$S = M_A^{\text{aq}} = \left(\frac{P_A^*}{P^o} \right) \exp \left[\frac{-\Delta G_{S(\text{aq})}^o}{RT} \right] \quad (23)$$

where the SMx models are used to compute P_A^* and $\Delta G_{S(\text{aq})}^o$. In the case of 70 organic liquids and 13 organic solids, we obtained MUEs (log units) of less than 0.4 when using the SM5.42 model for all calculations with either AM1, HF/MIDI!, or B3LYP/MIDI! as the underlying Hamiltonian [160]. The successful prediction of the solid solubilities is particularly noteworthy as we treated these compounds essentially as supercooled liquids. That is, we estimated the necessary “solvent” descriptors for use with the universal SM5.42 model and then computed vapor pressures for the solutes in equilibrium with their solid form. The solids were for the most part aromatic hydrocarbons, and this approximation is likely to be less useful for solutes that have more specific intermolecular interactions in their crystalline solid form. Nevertheless, it suggests that the computation of solid/liquid partitioning and solubility may be reasonably started from an SMx foundation.

3. SMx Models for Other Condensed Phases

Homogeneous liquid solutions are arguably the simplest condensed phases to represent with a dielectric continuum model. We may, however, expect that other condensed phases having liquid-like properties, e.g., a fluid-phase lipid membrane, might be addressable with the SMx modeling approach. Inasmuch as the SM5 organic parameterizations are designed to be universal, the data required to model *any* phase are simply the most appropriate values of ϵ , n , γ , α , and β (and ϕ and ψ if an SM5.42 or SM5.43 model is employed). Typically, of course, values for these quantities are not available. However, they may be estimated by any number of approaches (e.g., on the basis of molecular functionality also found in other molecules for which solvent parameters are available). A still more pragmatic approach for dealing with such poorly characterized systems is to treat the unknown “solvent” descriptors as being fitting parameters themselves. For all but the dielectric constant, this is particularly simple insofar as the solvation free energy depends upon them linearly. Thus, a typical approach is to make an educated guess at the dielectric constant, compute ΔG_{ENP}^o for solutes for which solvation free energies or partition coefficients (which are differences of solvation free energies between two phases, as described further below) are known, and determine the optimal values of the remaining descriptors that minimize errors in the remaining term G_{CDS}^o through multilinear regression. A final model may be determined by trial-and-error optimization of ϵ .

The first example of this approach was described for a phosphatidyl choline bilayer [17]. Available experimental data were partition coefficients P between the bilayer and surrounding aqueous solvent

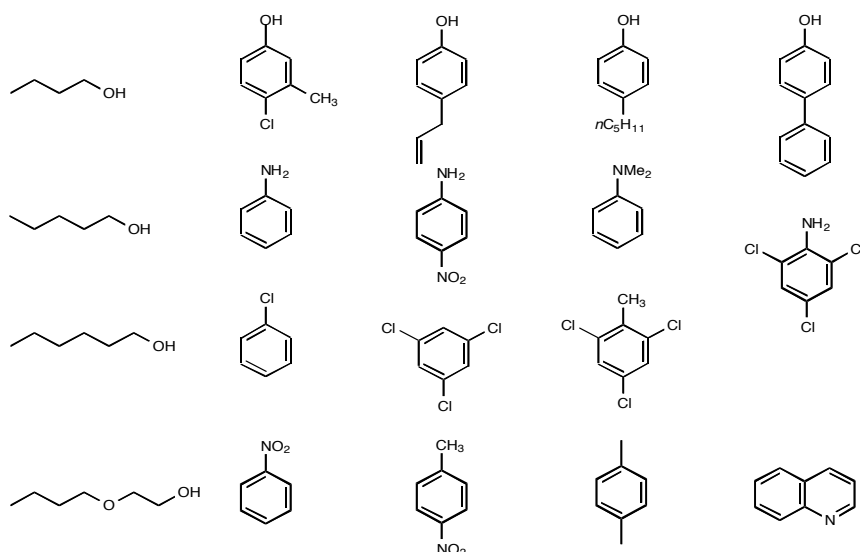


Figure 1: Solutes used in the parameterization of an SM5.4 model for phosphatidyl choline.

for the molecules shown in Figure 1. A partition coefficient depends on free energies of solvation according to

$$\log P_{A/B} = -\frac{\Delta G_{S,A}^{\circ} - \Delta G_{S,B}^{\circ}}{2.303 RT} \quad (24)$$

where A and B are the two phases between which a solute is partitioning, $\Delta G_{S,X}^{\circ}$ is the free energy of solvation from the gas phase into phase X (the quantity directly computable from an SMx model), R is the universal gas constant, and T is temperature. Using either experimental or computed aqueous solvation free energies provides target values for the solvation free energy into the phosphatidyl choline bilayer by rearrangement of eq. (17). Assuming the dielectric constant of the bilayer to be 5.0 (an estimate based on the dielectric constant of octanol), and assuming the α value to be 0.0 (as there is no significant hydrogen bond donating functionality in phosphatidyl choline), an SM5.4 model was developed by regressing the target free energies of solvation on the n , γ , and β solvent parameters. The regression provided values of 1.40, 27, and 1.15 for these parameters, which quantities are very much in the range of physically realistic values that one might have expected based on analogous molecules as solvents. In this case, the regression was also allowed to have a constant term, which was calculated to be 0.59 log units. The quality of the regression, with an R^2 value of 0.80 (Figure 2), is in the range of those typically employed for predictions of bioavailability of druglike molecules, and the specific-range-parameter (SRP) SM5.4 model may be expected to be useful when used to make predictions about molecules having functionalities not too different from those included in the training set. Of course, the introduction of significantly different functionality would likely require retraining to ensure maximum predictive accuracy.

A similar phase parameterization has been accomplished for soil (i.e., dirt) [161], using a training set much larger than the phosphatidyl choline case. From an environmental perspective, an important physical parameter affecting the fate of ecosystem contaminants is the soil-water partition coefficient. Because this often depends primarily on the soil's organic carbon content, measured values are usually normalized for the organic carbon (OC) content of soil, in which case the soil sorption equilibrium constant is expressed as [162]

$$K_{OC} = \frac{C_{\text{soil}}/C_{\text{soil}}^{\circ}}{C_{\text{w}}/C_{\text{w}}^{\circ}} \quad (25)$$

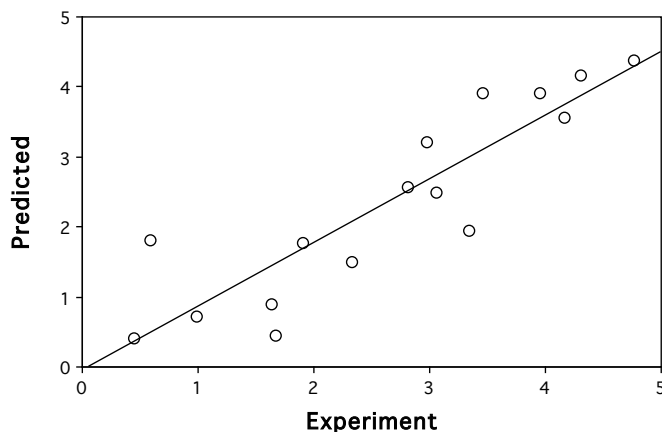


Figure 2: Predicted vs. experimental water/phosphatidyl choline partition coefficients (\log_{10} units).

where C_{soil} is the concentration of solute per gram of carbon in a standard soil, and C_w is the concentration of solute per volume of aqueous solution. The standard state concentrations C_{soil}° and C_w° are typically chosen as 1 μg solute per g organic carbon for soil and 1 μg solute per mL for aqueous solution. Although this quantity is often called the soil/water equilibrium constant for simplicity, one should note that it is actually a measure of partitioning between soil *organic matter* and water, normalized to organic carbon content.

In this instance, a database of 387 molecules containing a wide variety of organic functional groups was used for a training set. The dielectric constant for the soil phase was optimized by trial and error to a value of $\epsilon = 15$. While so high a dielectric constant may seem unusual for a solid organic phase, it should be kept in mind that the soil used in the experiment is “wet”, i.e., it is in contact with the aqueous phase and swelled by it. The optimized dielectric constant was used for the computation of electrostatics at the SM5.42/HF/MIDI!//HF/MIDI! and SM5.42/AM1//AM1 levels.

Errors in residual G_{CDS}° values were minimized by fitting the n , γ , α , and β solvent parameters as described above. For the SM5.42/HF/MIDI! level, these parameters took on values of 1.311, 45.3, 0.56, and 0.60; such values are consistent with the functionalities expected for the organic component of soil (which include aromatics, phenols, quinones, and carboxylic acids). The resulting soil partitioning model had a MUE over the training set of 0.98 kcal/mol.

A point that merits emphasis is that application of the SMx models to predict solvation or partitioning behavior can certainly be useful as a predictive exercise, but a potentially still more important feature of the models is that the free energy associated with the particular phase transfer can be decomposed into atomic or group contributions, and thus interpreted in a fragment basis [163,164]. The general form of the GB and surface tension equations should make this point clear: $\Delta G_{\text{ENP}}^{\circ}$ is computed as a sum of atomic-charge dependent terms, and G_{CDS}° is computed as a sum over atomic solvent-exposed surface areas.

For instance, Figure 3 illustrates the correlation between experimental and predicted $\log K_{\text{OC}}$ values for polychlorinated biphenyls (PCBs). There is a systematic error of about 1 log unit in the absolute accuracy of the predictions, but otherwise a fairly good correlation ($R^2 = 0.86$). Analysis of atomic contributions indicates that chlorine atoms near the biphenyl ipso carbons are less hydrophilic (owing to decreased exposure to the solvent) than chlorine atoms substituted at other positions. Such fragment analysis can be useful in drug design, where particular ranges of partitioning constants may enhance drug bioavailability.

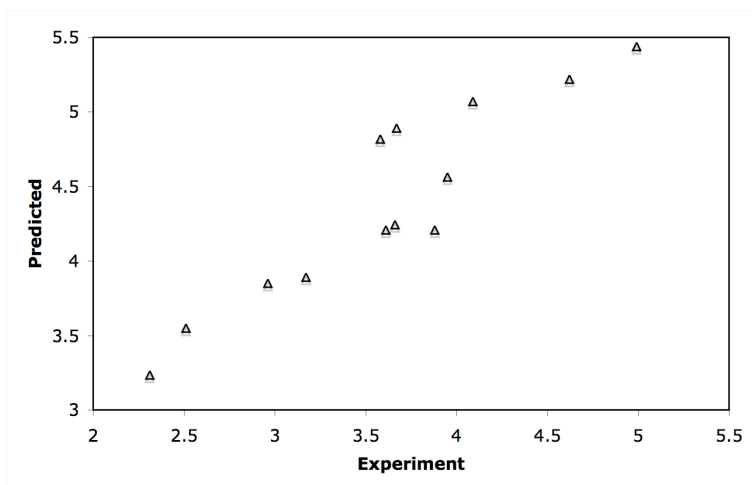


Figure 3: Predicted vs. experimental soil/water partition coefficients for PCBs (\log_{10} units).

A final example of a novel phase to which the SMx models have been extended is the surface layer of an aqueous solution that is in contact with air, i.e., the air-water interface. This is a phase that is formally two-dimensional, although at the molecular level it has some non-zero thickness. In this case the measured equilibrium constant of interest is

$$K_{i/a} = \frac{\Gamma_i}{C_a} \quad (26)$$

where Γ_i is the concentration of the adsorbed solute at the air-water interface in mol/m², and C_a is the equilibrium vapor concentration in mol/m³ of the solute. The adsorption coefficient for a molecule transferring from the gas phase to a air-water interface is related to the standard-state free energy of transfer by:

$$\ln K_{i/a} = -\frac{\Delta G_{i/a}^\circ}{RT} \quad (27)$$

However, the free energy in eq. (27) differs from all of the other free energies that have thus far been described in the sense that it contains two distinct components. The first component is the coupling free energy associated with the new interactions that a molecule in a condensed phase has in comparison to the gas phase—this is the component that the SMx models are designed to predict. In the case of $\Delta G_{i/a}^\circ$, however, there is also a term associated with the loss of entropy associated with moving from a phase of 3 dimensions to one of 2 dimensions. That is

$$\Delta G_{i/a}^\circ = \Delta G_{\text{coup}(a \rightarrow i)}^\circ + \Delta G_{3D \rightarrow 2D}^\circ \quad (28)$$

The coupling term may be computed directly, however, and depends only on the molecular weight. Thus, a particle of mass m at temperature T has a de Broglie wavelength equal to [165]

$$\Lambda = \sqrt{\frac{h^2}{2\pi mkT}} \quad (29)$$

where k is Boltzmann's constant, and h is Planck's constant. For an ideal gas molecule in M dimensions, the molecular translational partition function can be written as [165]

$$q = \left(\frac{L^\circ}{\Lambda}\right)^M \quad (30)$$

where L° is the standard-state unit of length. The molar translational partition function is then

$$Z = \frac{1}{N_A!} \left(\frac{L^\circ}{\Lambda}\right)^{MN_A} \quad (31)$$

where N_A is Avagadro's number. With this partition function and taking standard thermodynamic relationships for internal energy U , enthalpy H , and entropy S as a function of Z [165], we may compute

$$U^\circ = \frac{M}{2} RT \quad H^\circ = U^\circ + PV \quad S^\circ = R \ln \left[\frac{e^{(M+2)/2}}{N} \left(\frac{L^\circ}{\Lambda}\right)^M \right] \quad (32)$$

and thus, from

$$\Delta G_{3D \rightarrow 2D}^\circ = \Delta H_{3D \rightarrow 2D}^\circ - T\Delta S_{3D \rightarrow 2D}^\circ \quad (33)$$

we derive

$$\Delta G_{3D \rightarrow 2D}^{\circ} = \Delta(PV)_{3D \rightarrow 2D} - RT \ln\left(\frac{\Lambda}{L^{\circ}}\right) \quad (34)$$

The PV terms may be calculated from the microcanonical relationship [165]

$$\frac{P}{T} = \left\{ \frac{\partial S}{\partial \left[(L^{\circ})^M \right]} \right\}_{N,U} \quad (35)$$

Using S° as defined in eq. (32) gives

$$\frac{P}{T} = \frac{R}{(L^{\circ})^M} \quad (36)$$

which is the ideal gas law $PV = RT$ but expressed for volume in an arbitrary number of dimensions. Thus, ΔPV is zero for the dimensionality change and we have

$$\Delta G_{3D \rightarrow 2D}^{\circ} = -RT \ln\left(\frac{\Lambda}{L^{\circ}}\right) \quad (37)$$

When this component is removed from measured free energies of adsorption, the remaining free energies of coupling can be used as a training set for the determination of an air-water interface SMx model in the usual way.

In this case, however, there is some ambiguity associated with computing the electrostatic component of solvation. One approximation might be to assume that a molecule at the interface has half the value of $\Delta G_{\text{ENP}}^{\circ}$ that would be computed in the bulk. A more accurate model would account for preferential orientation of surface molecules. In previous work, however, we instead investigated whether an SM5.0 model (i.e., one that ignores electrostatics) would be successful in making predictions. For a training set of 85 solutes, we found that a best fit of the “solvent” descriptors for the air-water interface involved taking α , β , and γ to be 1.11, 0.59, and -144.6 , respectively [166].

These values appear to be quite physical. Various prior simulations and experimental studies [167-170] have suggested that dangling hydrogen bond sites at the air-water interface make surface water more active as a hydrogen bond donor and acceptor than bulk water (which has α and β values of 0.82 and 0.35, respectively [171]). The negative value for the surface tension is also reasonable, since for the adsorption process no free energy is being expended in order to cavitate, but instead new dispersion interactions are being added by the solute “sticking” to the surface that were not present previously. The SM5.0surf model has a MUE (log units) of 0.47 for the 85 molecules in the training set [166], many of which are functionally rich pesticides and other environmental contaminants.

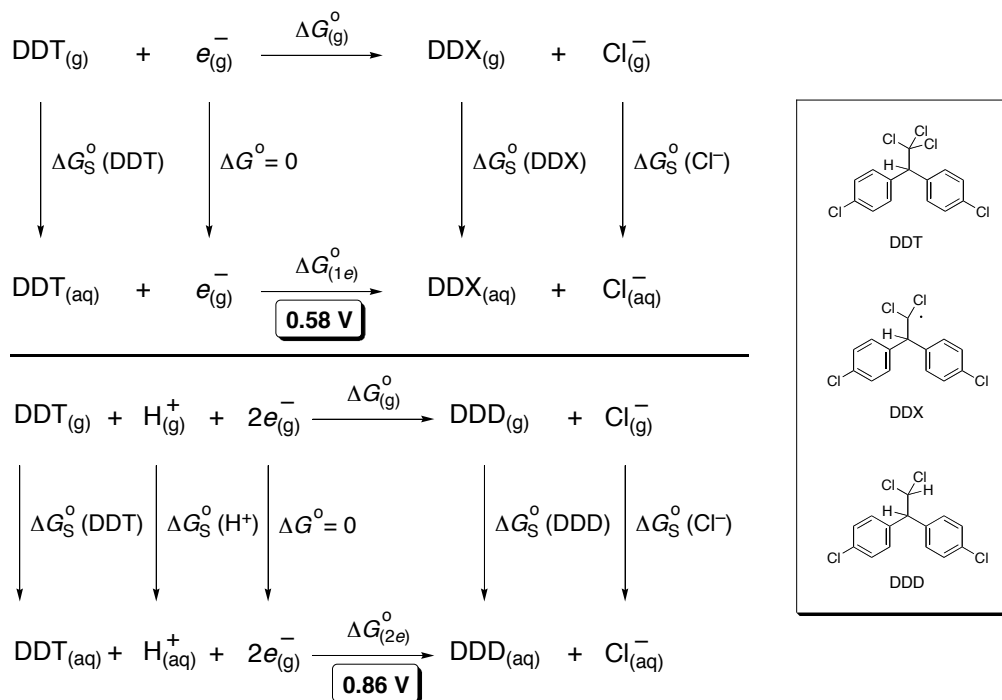


Figure 4: One- and two-electron reduction half reactions for DDT.

4. Selected Applications in Environmental Chemistry

Electron-transfer reactions play important roles in many pathways that degrade contaminants in the environment. Such electron transfers are often described with electrochemical half reactions, like those in Figure 4 for the one- and two-electron reductions of the pesticide DDT.

In order to compute the lower leg of each thermodynamic cycle, it is sufficient to compute the upper leg, which is a gas phase process, at some suitable level of electronic structure theory, and then to add the vertical legs, which quantify the differences between the solvation free energies of the various reagents. In the case of the reactions in Figure 4, calculations were carried out at the B3LYP/6-311+G(d)//B3LYP/6-31G(d) level for gas-phase energetics, the solvation free energies of the proton and chloride anion were taken from experiment [172], and the remaining solvation free energies were computed at the SM5.42/BPW91/6-31G(d)//B3LYP/6-31G(d) level [173].

The resulting free energy of reaction for a solution process $\Delta G_{\text{rxn}}^\circ$ may be converted to a potential relative to the normal hydrogen electrode (NHE) by

$$E^\circ = \frac{\Delta G_{\text{rxn}}^\circ - \Delta G_{\text{NHE}}^\circ}{nF} \quad (38)$$

where n is the number of electrons transferred, F is the Faraday constant in appropriate units, and $\Delta G_{\text{NHE}}^\circ$ is the free energy of reaction for the reference half reaction



which is 4.28 eV [173,174]. Note that this value, and the values listed in Figure 4, differ from those reported in the original reference [173] because of (i) a standard-state error made in the original reference for the solvation free energy of the proton, as explained in subsequent work [174], an

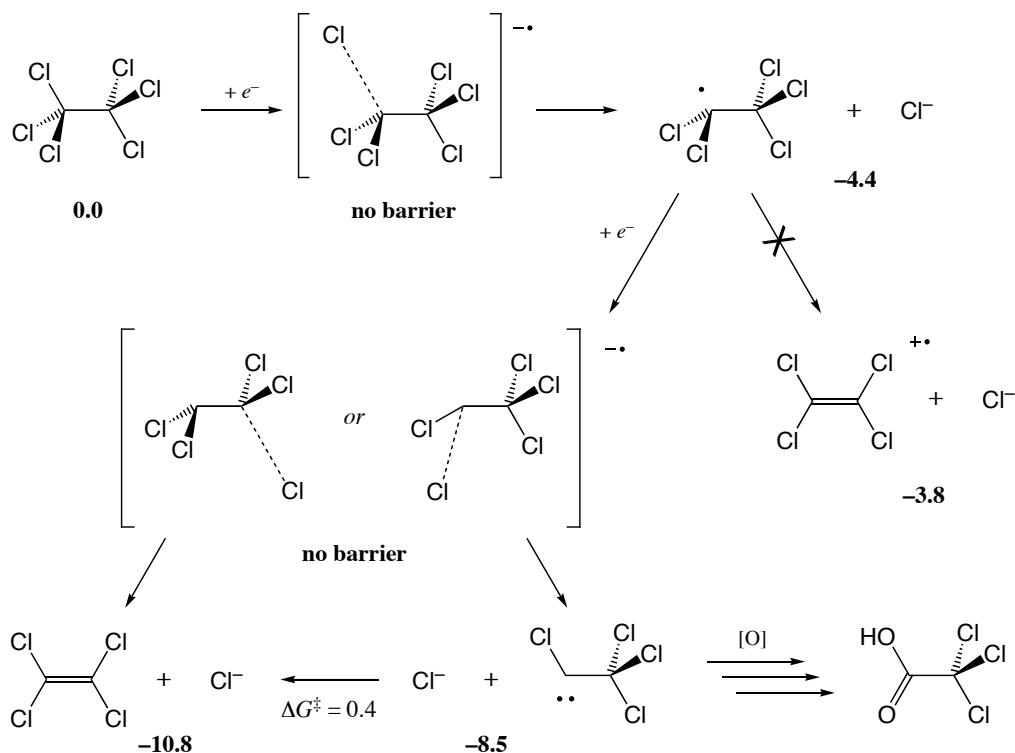


Figure 5: Steps in the reductive dechlorination of hexachloroethane in aqueous solution. Relative energies of stoichiometrically equivalent species are given in eV.

error in the 298 K free energy of the chloride anion (which should have a tabulated value of $-460.31875 E_h$ in the original reference [173]), and (iii) the use here of the experimental solvation free energy for the chloride anion instead of a computed solvation free energy (a difference of 0.1 eV).

Reduction (and oxidation) potentials are useful quantities for analyzing environmental persistence in phases having either oxidizing or reducing character. Indeed, taken together with soil/water partition coefficients, which may also be computed using SMx methods, they are key components in the prediction of environmental fate constants for organic contaminants.

Solvation free energies can also be added to reagents in reactions that do not involve electron transfer. Accounting for and predicting changes in reaction pathways induced by solvation is a key application of solvation models. One interesting mechanism that we have studied [175], which involves both electron transfer steps and steps in which electrons do not appear as individual species, is the reductive dechlorination of hexachloroethane (Figure 5).

In the initial reductive dechlorination, loss of the first chloride anion is predicted to proceed without barrier subsequent to electron transfer in aqueous solution. One proposal that had been made in the literature was that a heterolytic ionization of the resulting radical might precede a second electron transfer, however this step is predicted at the SM5.42/BPW91/aug-cc-pVDZ//BPW91/aug-cc-pVDZ level of theory to be too endergonic to be important. Interestingly, chloride elimination is again predicted to proceed without barrier following the second electron transfer. However, that prediction holds true for both sets of stereochemically distinct chlorine atoms, those leading to the much more stable tetrachloroethene and those leading to the less stable chlorotrichloromethylcarbene. Rearrangement of the carbene is predicted to have a sufficiently high barrier that diffusion-controlled bimolecular processes might compete with rearrangement of the singlet carbene to the alkene. One such process involves attack of water on the carbene to generate an oxonium ylide that, upon

rearrangement would generate a chlorohydrin that could subsequently be easily oxidized to trichloromethylacetic acid. The latter species is detected in small amounts in the reductive

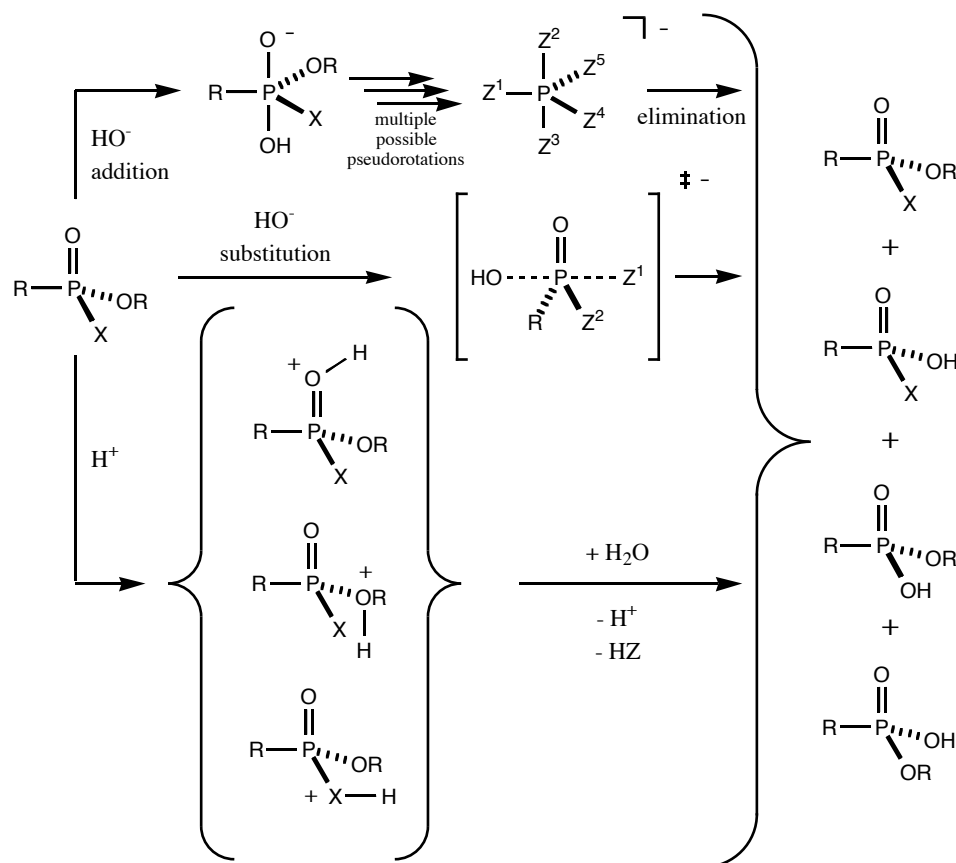


Figure 6: Possible pathways for aqueous hydrolysis of a generic phosphonate derivative.

dechlorination process, and the mechanism of its formation had not been well understood prior to our modeling efforts [175].

The prediction of pK_a values for environmental contaminants can also be particularly important because of the potentially enhanced (or retarded) activity of molecules in their conjugate acid or base forms. In the case of phosphorus-based chemical weapons agents, for example, aqueous decontamination can follow different reaction coordinates depending on aqueous pH (Figure 6).

One mechanistic pathway is the reaction of the weapons agent with hydroxide acting as a nucleophile. In the upper pathway, the addition of hydroxide to phosphorus leads to a phosphorane anion intermediate. In general, the elimination of ligands from phosphoranes is more facile from apical positions than from equatorial. Stereochemistry in the phosphorane, i.e., the energetic preference for location of individual groups in apical or equatorial positions, is controlled by a number of factors, including apicophilicity and hyperconjugative interactions between the ligands [176] and solvation effects. Interconversion between different trigonal bipyramids requires a pseudorotation, and the barriers to pseudorotation in such complex phosphoranes are not well understood and may also be subject to solvation effects.

An alternative pathway (the central one in Figure 6) is a one-step bimolecular substitution. Depending on the substituents of the original phosphonate, either or both of these two pathways may be operating.

In general, the direct substitution pathway becomes more favorable when the leaving group is the conjugate base of a strong acid.

Finally, under neutral or acidic conditions, the nucleophile may not be hydroxide but instead a water molecule (the lower path in the figure). Under these conditions, there are again two paths, addition/elimination and direct substitution, either or both of which are potentially operative.

The SM6 aqueous solvation model has recently been demonstrated to be particularly effective for the computation of pK_a values [177] (although they are still subject to errors of 1 to 2 pK units in unfavorable cases). Other SMx models have also been decisive in explaining key features in the hydrolytic detoxification of chemical weapons agents. For example, Seckute et al. [178] were able to explain the anomalous reactivity of VX-like compounds (thiophosphonates having potential neurotoxic properties) with aqueous hydroperoxide vs hydroxide, a case where solvation effects played a key role in favoring a beneficial reaction path (formation of an innocuous product) over a less useful one (formation of a long-lived toxic product).

5. Conclusions

Continuum solvation models are a critical element in the computational chemist's toolbox because of their utility for describing (i) condensed-phase effects on molecular structure and properties and (ii) the connection between gas-phase and condensed-phase potential energy surfaces. The parameterization of the SMx models against a large and diverse set of data, the broad variety of electronic structure levels with which they are compatible, e.g., semiempirical theory, ab initio Hartree-Fock theory, and density functional theory, and their incorporation into several general-purpose electronic structure packages makes them particularly attractive for modeling. Future developments designed to include temperature dependence, improve accuracy, and extend the range of condensed phases to which they may be applied, may be expected to further increase their general utility.

Acknowledgments

The authors are grateful to Daniel Liotard, David Giesen, Gregory Hawkins, Joey Storer, Candee Chambers, Jiabo Li, Tony Zhu, Paul Winget, Jason Thompson, James Xidos, Casey Kelly, and Adam Chamberlin for extensive contributions to the development of the SMx models and to Eric Weber, Eric Patterson, and Bill Arnold for collaboration on their application to environmental problems. We are also grateful to our many co-workers on the SMx models over the years, whose names grace the publications resulting from their efforts. This work was supported by the NIH training grant for Neurophysical-computational Sciences, by the U.S. Army Research Office under Multidisciplinary Research Program of the University Research Initiative (MURI) through grant number DAAD19-02-1-0176, by the Minnesota Partnership for Biotechnology and Medical Genomics, by the National Science Foundation (CHE02-03446 and CHE03-49122), and by the Office of Naval Research under grant no. N 00014-05-01-0538.

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