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A Semiempirical Quantum Mechanical Solvation Model for Solvation Free Energies in All Alkane Solvents

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Using a linear fit of the solvent-ordering part of the microscopic surface tension to experimental macroscopic surface tensions, the Generalized Born/Surface Tension solvation model presented previously for *n*-hexadecane (called Solvation Model 4 or SM4), is extended to include all alkanes as solvents, including normal, branched, and cyclic alkanes. The general SM4 alkane model is applicable to any alkane solvent for which the macroscopic dielectric constant and surface tension are either known or estimable. It treats electrostatic effects, including polarization of the solute by a reaction field, in terms of a continuum dielectric model of the solvent, uses element-based surface tension terms to account for first-solvation-shell effects, and uses an element-independent surface tension to account for solvent-ordering effects that extend further into solution. The electrostatic terms are based on the recently developed Charge Model 1 (CM1) for computing atomic partial charges. This charge model allows the development of a single set of parameters which is applicable to both the AM1 and PM3 Hamiltonians and also to any other electronic structure method that provides reasonably accurate geometries and partial charges.

1. Introduction

Reaction rates in solution can change by several orders of magnitude depending on solvent characteristics.¹ Particularly large effects, even changes in mechanism, may be anticipated when comparing alkane solvents to more polar solvents, e.g., water, methanol, ethanol, etc. Alkanes are archetypal nonpolar solvents and, as such, play an important role in a wide variety of chemical processes. At 25 °C, alkane solvents have dielectric constants of about 2 compared to 78.3 for water. Alkanes are nonprotic. They do not donate nor do they accept hydrogen bonds. Alkanes are frequently used as models for hydrophobic interiors of lipid bilayers or other cellular material²⁻⁶ or for the nonpolar active site of an enzyme or receptor. In such models, the partition coefficient of a solute between an alkane solvent and water provides some indication of how likely it is to penetrate the bilayer or bind to the nonpolar site in (or on) the protein. In addition, the alkane/gas partition coefficient of a solute can be used along with the water/gas partition coefficient to calculate the solubility of a solute in biological liquids and tissues.⁷

The partition coefficient of a solute between solvents A and B can be calculated by⁸

$$\ln K_{B/A}(X) = \ln \frac{[X]_B}{[X]_A} = - \frac{\Delta G_{S_B}^o(X) - \Delta G_{S_A}^o(X)}{RT} \quad (1)$$

where $\Delta G_{S_Y}^o(X)$ is the free energy of transfer of X from the gas phase into solvent Y (free energy of solvation), R is the ideal gas constant, and T is the temperature. Hence, when the free energy of solvation for a solute in each of two solvents is known, the partition coefficient for that solute *between* those two solvents can be calculated. Using any combination of experimental data or theoretical estimates for free energies of solvation

in water and an alkane, one can in principle calculate any water/alkane partition coefficient. Examples of prior theoretical models from which aqueous estimates could be taken include the SMx series of solvation models (SM1,⁹ SM1a,⁹ SM2,¹⁰ and SM3¹¹).

In previous work,¹² we presented a solvation model called SM4 for calculating free energies of solvation in *n*-hexadecane, and in this paper we extend this model to treat all alkanes including straight-chain, branched, and cyclic alkanes. In particular, the extension is accomplished by employing the appropriate experimentally measured dielectric constant for the alkane of interest and by making a single parameter in the SM4 alkane models be a function of the macroscopic surface tension of the alkane solvent. The SM4 model for alkanes is a dielectric-continuum-based¹³ model, with the solute polarized self-consistently via the generalized¹³⁻²³ Born^{24,25} equation. Partial charges are calculated using Charge Model 1 (CM1).^{12,26} Atomic-number-based surface tensions (presented here) are included to account for short-range solute–solvent interactions that do not fit within the dielectric continuum framework, and a single atomic-number-independent surface tension is used to treat intermediate-range interactions.¹²

2. Theory

The SM4 alkane models described herein are extensions of our previously presented SM4 *n*-hexadecane solvation model.¹² We therefore begin with a review of the essential elements of that model. The free energy of solvation is written as

$$\Delta G_S^o = G_{(sol)}^o - G_{(g)}^o \quad (2)$$

where $G_{(sol)}^o$ is the standard state free energy of the solute in solution, and $G_{(g)}^o$ is the standard state free energy of the solute in the gas phase. We have chosen a concentration of 1 mol L⁻¹ and a temperature of 298 K as the standard state in both the gas phase and solution. The free energy of solvation is partitioned in the SM4 model as follows:

$$\Delta G_S^o = \Delta E_{EN} + G_p + G_{CDS}^o \quad (3)$$

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In eq 2, ΔE_{EN} is the difference between the solute electronic kinetic and electronic–nuclear Coulombic energies in the gas and solution phases. G_P is the polarization free energy associated with the solvation process, and G_{CDS}^o accounts for those contributions to the solvation free energy that are assumed to correlate with the size of the first solvation shell of the solute. The SM4 models are semiempirical quantum mechanical models that use either the AM1^{27–29} or the PM3³⁰ Hamiltonian to calculate ΔE_{EN} . The parameters of the SM4 *n*-hexadecane model¹² are applicable to both the AM1 and PM3 Hamiltonians.

G_P is calculated using the generalized Born equation,^{14–23}

$$G_P = -\frac{1}{2}\left(1 - \frac{1}{\epsilon}\right)\sum_{k,k} q_k q_{k'} \gamma_{kk'} \quad (4)$$

In eq 4, γ is a Coulomb integral, which is modeled by the dielectric screening algorithm of Still *et al.*,²² ϵ is the dielectric constant of the solvent at 298 K, and q_k is the partial atomic charge of atom k . In the SM4 formalism, q_k is calculated using Charge Model 1.²⁶ The CM1 model maps partial charges obtained by Mulliken population analysis to a new set of Class IV²⁶ charges. The mapping parameters in CM1A, used for AM1 wave functions, and those in CM1P, used for PM3 wave functions, were developed empirically so that partial charges calculated in gas-phase calculations accurately reproduce experimental dipole moments and also partial charges derived from high-level *ab initio* calculations.²⁶ Because G_P depends on the solute density matrix, it is included self-consistently^{9–14,16–20,23} in the neglect of diatomic differential-overlap (NDDO) Fock matrix of the AM1^{27–29} and PM3³⁰ Hamiltonians. The use of CM1 to give high-quality partial charges for use in the calculation of G_P allowed us to produce parameters for *n*-hexadecane that are independent of the specific level of theory or parametrization used for the solute. That is, the SM4 *n*-hexadecane parameters are applicable to any electronic structure calculation that yields reasonably good atomic partial charges and geometries.¹²

The final term in eq 2, G_{CDS}^o , is further separable in the SM4 formalism as

$$G_{CDS}^o = G_{CD} + G_{CS} \quad (5)$$

G_{CDS}^o models those interactions which are assumed to correlate with the size of first solvation shell of the solute. The most energetically important of these interactions are assumed to be the formation of a solute cavity, solute–solvent dispersion interactions, and solvent structural rearrangement brought about by introduction of the solute. Of these, dispersion is a short-range interaction, falling off as r^{-6} . Solvent structural rearrangement, on the other hand, certainly extends out into solution for a longer range. Thus, we have proposed that the size of the “first solvation shell” must depend on the type of interaction being considered.¹²

In the SM4 alkane models, we consider G_{CD} to be the net favorable free energy resulting from cavitation and dispersion and G_{CS} to result from unfavorable cavitation and solvent structural rearrangement terms. Because the formation of a cavity involves changes in both dispersion and solvent structure, it is included in both terms.¹² We model G_{CDS}^o as

$$G_{CDS}^o = \sum_{\lambda} \sum_n \sigma_n^{\lambda} A_n^{\lambda} \quad (6)$$

where λ is the type of CDS interaction being modeled ($\lambda = CD$ or CS), σ_n^{λ} is a surface tension, and A_n^{λ} is that portion of the

solvent-accessible surface area associated with λ -type solvent interactions with atom n . The solvent-accessible surface area^{31,32} is calculated by rolling a solvent sphere of radius R_S^{λ} over the surface of the solute created by centering a sphere on each atom with a radius, R_k , that depends on the atomic number of the atom k . The center of the solvent sphere traces out a surface with area $\sum_n A_n^{\lambda}$. R_S^{λ} is chosen on the basis of physical properties of the solvation process and determines the effective size of the first solvation shell.

In the SM4 model for *n*-hexadecane, we set R_S^{CD} equal to 2.0 Å and R_S^{CS} equal to 4.9 Å,¹² and we wrote G_{CDS}^o more explicitly as

$$G_{CDS}^o = \sum_k \delta_k^{CD} A_k^{CD} + \sigma^{CS} \sum_k A_k^{CS} \quad (7)$$

Furthermore, we modeled δ_k^{CD} as

$$\delta_k^{CD} = \begin{cases} \sigma_k^{CD} & k \neq H, C \\ \sum_k \sigma_{kH}^{CD} B_{kk'} & k = H \\ \sigma_k^{CD} + \sum_{k=C} \sigma_{CC}^{CD} B_{kk'}^3 & k = C \end{cases} \quad (8)$$

Hydrogen was given a surface tension which varies according to the type of atom to which it is bonded, and this surface tension depends on the bond orders to other atoms; this allows the surface tension of each hydrogen to change during the course of a reaction such as a hydrogen transfer reaction in which the environment of the hydrogen changes. Furthermore, the surface tension of each carbon was made to depend on its bond order to other carbons. We will retain eqs 2–5, 7, and 8 in the present work without changing their form and—with two exceptions—without changing the numerical values of the parameters.

Further details of the SM4 model for *n*-hexadecane are presented in our previous paper.¹²

3. Parametrization

Data. The solvents considered in the present study are listed in Table 1 (along with some data that will be useful below). We note that these solvents represent essentially the full range of liquid alkanes since *n*-butane and isobutane are gases at room temperature and *n*-octadecane is a solid.³³

Except where noted, all experimental free energy of solvation data used in this paper come from the MedChem database of Leo and Hansch.³⁴ In particular, if A denotes an alkane solvent and W denotes water, we obtained the free energy of solvation of solute X either by

$$\Delta G_{S_A}^o(X) = -RT \ln K_{A/W}(X) + \Delta G_{S_W}^o(X) \quad (9)$$

or by

$$\Delta G_{S_A}^o(X) = -RT \ln K_{A/\text{air}}(X) \quad (10)$$

where $K_{A/W}(X)$ and $K_{A/\text{air}}(X)$ were taken from the MedChem database³⁴ and $\Delta G_{S_W}^o(X)$ was taken from one of the standard compilations.^{34–37} In only one case, 3,3-dimethylbutanone, a value for $\Delta G_{S_W}^o(X)$ was found by combining $K_{H/\text{air}}$ with $K_{H/W}$, where H denotes *n*-hexadecane. When data were available to use both eqs 9 and 10, we averaged the results.

Solutes used for the present parametrizations were chosen in the following manner. A tentative solute set was made by

TABLE 1: Physical Properties of the Liquid Alkane Solvents at 298 K

	dielectric constant ^a ϵ	internal pressure, ^b cal cm ⁻³	surface tension, ^c cal mol ⁻¹ Å ⁻²	density, ^d g mL ⁻¹
n-pentane	1.843 ^e	53.8 ^f	22.3	0.621
n-hexane	1.882	57.1	25.7	0.655
n-heptane	1.911	61.1	28.3	0.680
n-octane	1.941	63.6	30.4	0.698
n-nonane	1.960	66.0	32.2	0.714
n-decane	1.985	66.9	33.6	0.726
n-undecane	1.991		34.8	0.737
n-dodecane	2.006	69.6	35.9 ^g	0.745
n-tetradecane	2.028	71.7 ^f	37.6	0.759
n-pentadecane	2.033		38.3 ^h	0.765
n-hexadecane	2.060 ⁱ	73.6 ^f	38.9	0.770
2-methylbutane	1.837	54.7	20.8	0.615
3-methylpentane	1.878		25.3	0.660
2,2,4-trimethylpentane	1.936	56.4	26.4	0.688
cyclohexane	2.016	77.9	35.4	0.774
methylcyclohexane	2.016 ^k	71.0	33.5	0.765
cis-decalin	2.214 ^l		31.6 ^{l,m}	0.893
trans-decalin	2.178 ^l		29.4 ^{l,m}	0.866

^a Except where noted, calculated from temperature-dependent data in the latest edition of the CRC Handbook of Chemistry and Physics.³³

^b Data at 293 K from CRC Handbook of Solubility Parameters.⁴¹

^c Experimental macroscopic surface tension. Except where noted, from CRC Handbook of Chemistry and Physics.³³ ^d Data from Rossini.⁵³

^e No temperature-dependent data given, calculated from fit to remaining n-alkanes. ^f Average of two experimental numbers.⁴¹ ^g Data from Riddick.⁶⁴ ^h Calculated by fit to temperature-dependent data from Timmermans.⁶⁵ ⁱ Direct measurement listed in CRC Handbook of Chemistry and Physics.³³ ^j Estimated from data for smaller n-alkanes.

^k No temperature-dependent data given, but listed value at 293 K is the same as cyclohexane at 293 K,³³ so assigned the same value as cyclohexane at 298 K. ^l Value used in model is average of cis and trans values. ^m Calculated from fit to data of Seyer *et al.*⁵⁶

combining the solute training sets for the water models²³ and the SM4 n-hexadecane model.¹² Ten additional solutes were added for which a large number of measurements exist in the MedChem database for solvents of interest. This set of compounds will be referred to as the meta set, and it contains 222 compounds. For each alkane solvent, compounds in the meta set were chosen for use in the present study if (i) an alkane/air partition coefficient exists in the MedChem database or (ii) an alkane/water partition coefficient exists in the MedChem database and a free energy of solvation in water is available. The compounds in the meta set conforming to either criterion i or ii will be referred to as the solvent test set where "solvent" is the name of the solvent of interest. Complete listings of the molecules used in the individual solvent test sets and the free energies of solvation in alkane solvents are given in the supplementary material, along with the predicted AM1-SM4 and PM3-SM4 alkane free energies of solvation. Not all solutes have data available for every solvent. Columns 1 and 2 in Table 2 list all alkane solvents and the number of solutes in each solvent test set.

Calculational Procedure. An intrinsic characteristic of the solvation models considered here is that the electronic wave function and geometry are optimized in solution. The former effect is the more important of the two, and the deviation from the gas-phase minimum energy geometry is much smaller in n-alkane solutions than in water solutions. Furthermore, the difference between optimizing geometries in various alkanes is even smaller and is generally negligible. Some examples of the geometry optimization effect for n-alkane solutions are given in Table 3. To simplify the present calculations, unless specified all calculations presented here were carried out with previously available geometries optimized in n-hexadecane.

TABLE 2: Results for the SM4 Alkane Models

solvent	no. of solutes	$\sigma_{(opt)}^{CS}$, mol ⁻¹ Å ⁻²	σ^{CS} , cal mol ⁻¹ Å ⁻²	rms error, ^a kcal/mol
n-pentane	26	16.71	16.70	0.34
n-hexane	41	16.81	16.81	0.46
n-heptane	46	16.90	16.90	0.37
n-octane	32	16.96	16.97	0.40
n-nonane	27	17.01	17.03	0.38
n-decane	34	17.05	17.07	0.38
n-undecane	12	<i>b</i>	17.11	0.23
n-dodecane	7	<i>b</i>	17.15	0.22
n-tetradecane	3	<i>b</i>	17.21	0.37
n-pentadecane	5	<i>b</i>	17.23	0.38
n-hexadecane ^c	153	17.25	17.25	0.41
2-methylbutane	1	<i>b</i>	16.65	0.63
3-methylpentane	1	<i>b</i>	16.80	0.73
2,2,4-trimethylpentane	32	16.78	16.83	0.54
cyclohexane	60	17.09	17.14	0.45
methylcyclohexane	2	<i>b</i>	17.07	0.45
decalin ^d	21	<i>b</i>	16.97	0.72

^a rms error over AM1-SM4 and PM3-SM4 results for the solvent test set. ^b Not calculated. ^c Results from ref 12. ^d Data for cis and trans isomers combined.

TABLE 3: AM1-SM4 Free Energies of Solvation (kcal/mol) in n-Pentane as a Function of the Medium in Which the Geometry Is Optimized

solute	geometry optimized in		
	gas phase	n-hexadecane	n-pentane
1-butanol	-0.953	-0.988	-0.992
phenol	-1.979	-2.154	-2.154
butanone	-1.267	-1.416	-1.422
ethyl ethanoate	-0.693	-0.817	-0.824
ammonia	-2.014	-2.208	-2.212
propylamine	-0.723	-0.756	-0.762
aniline	-1.849	-1.975	-1.975
ethanonitrile	-1.836	-2.129	-2.130
2,2,2-trifluoroethanol	-2.427	-2.745	-2.750
1,1,1,3,3,3-hexafluoropropan-2-ol	-1.917	-2.112	-2.114
p-bromophenol	-2.011	-2.219	-2.219

The solvation free energies for all compounds in each solvent test set were predicted using both AM1 and PM3. This was done to ensure that the SM4 parameters for alkanes were insensitive to choice of either AM1 or PM3. Because each solute is calculated with both AM1 and PM3, the number of data points in each solvent test set is twice as large as the number of solutes.

Overview of Parameters. Section 2 described three different components that contribute to the free energy of solvation: G_p , G_{CD} , and G_{CS} . In the present section, we describe the changes necessary to extend the SM4 n-hexadecane model to all alkane solvents. In developing the new solvent models, the parametrization of each component was examined to determine how it depends on the characteristics of the new solvent. Ideally, the changes in the parameters should follow naturally from the changes in solvent properties.

The first term described in section 2 was G_p . Equation 4 has three kinds variables: ϵ , q_k , and γ_{kk} . The first, ϵ , is the dielectric constant of the pure solvent at 298 K. The dielectric constants used here are given in Table 1. The atomic partial charges, q_k , are calculated from the NDDO density matrix with the CM1 algorithm. Because CM1 is optimized²⁶ to yield charges that agree with experimental gas-phase dipole moments and high-level *ab initio* partial charges, the parameters in both CM1A and CM1P do not depend on solvent characteristics. The Coulomb integrals, γ_{kk} , depend on a set of charge-dependent and atomic-number-dependent parameters called Coulomb radii.^{9-12,23} The atomic Coulomb radii were optimized for the

TABLE 4: R_k and Cavity-Dispersion Surface Tensions for all SM4 Alkane Models

atom	R_k , Å	σ_k^{CD} , cal mol ⁻¹ Å ⁻²	σ_{kk}^{CD} , cal mol ⁻¹ Å ⁻²
H	1.20	^a	^a
C	1.60	-76.80	-50.21, ^b 1.19 ^c
N	1.55	-36.29	-56.29 ^b
O	1.52	-39.18 ^d	-56.13 ^b
F	1.47	-37.42	^a
S	1.80	-59.77	-54.64 ^b
Cl	1.75	-55.35	^a
Br	1.85	-59.79	^a
I	1.98	-62.58	^a

^a Not a parameter. ^b $k' = \text{H}$. ^c $k' = \text{C}$. ^d Not recommended for oxygen in nitro groups. See text.

n-hexadecane model¹² and were used unchanged for all other alkane solvents. The only change from the *n*-hexadecane SM4 model in the calculation of G_P for other alkane solvents is to use the experimentally measured dielectric constant in eq 4.

The second term described in section 2 was G_{CD} , which depends on R_k , R_s^{CD} , and δ_k^{CD} . Values of R_k used in this work are the same as in *n*-hexadecane and are given in Table 4. In particular, all values of R_k are taken from the van der Waals radii suggested by Bondi,³⁸ with the exception of carbon, for which we used 1.60 Å. The dominant effect modeled by the G_{CD} term is considered to be dispersion interactions. Dispersion interactions fall off so quickly with distance that it is likely that only those parts of the solvent molecule actually in van der Waals contact with the solute will experience dispersion interactions with the solute. Because of this, it is assumed, when modeling this term, that all alkane solvents act like a collection of methylene groups, and therefore dispersion interactions will be quite similar on a per methylene basis. The value of R_s^{CD} was chosen to be 2.0 Å using experimental molecular beam data for the radius of methane.^{39,40} Because dispersion interactions are expected to be nearly identical in all alkane solvents, the values of R_s^{CD} and all δ_k^{CD} are taken to be the same here as in the *n*-hexadecane model. The values of σ_k^{CD} and σ_{kk}^{CD} (see eq 8) are given in Table 4.

The final term discussed in section 2 was G_{CS} . This term models unfavorable free energy effects such as solvent structure rearrangement and the enthalpy of cavity formation. Because these effects are dependent on the solvent characteristics and the size of the solute but not necessarily on the type of the solute, σ^{CS} has been taken as independent of the atom types in the solute. The variables required in the calculation of G_{CS} are R_k , R_s^{CS} , and σ^{CS} . R_k is the same for G_{CS} as for G_{CD} ; thus, as discussed above, R_k remains the same in all alkane solvents. R_s^{CS} was also taken to have the same value for all alkane solvents, namely 4.9 Å; this is discussed further in section 4. In the SM4 alkane models, σ^{CS} is the only parameter that changes for each alkane solvent and is not taken directly from an experimental measurement. The values of σ^{CS} were fit to a two-parameter linear function of the macroscopic surface tension of the bulk liquid solvents. The optimization of σ^{CS} is presented in greater detail in the rest of this section.

Parametrization of σ^{CS} . An examination of the experimental data for various solutes for which data are available in a large number of straight-chain alkane solvents reveals a persistent trend. For a given solute, the free energy of solvation becomes less negative as the length of the alkane solvent chain increases (Figure 1). Although the trend is small—about 0.4 kcal/mol difference between *n*-pentane and *n*-hexadecane—and is often somewhat obscured by experimental error, it is a definite trend. This runs counter to what would be expected from examining the dielectric constants of the pure solvents. Equation 4 reveals

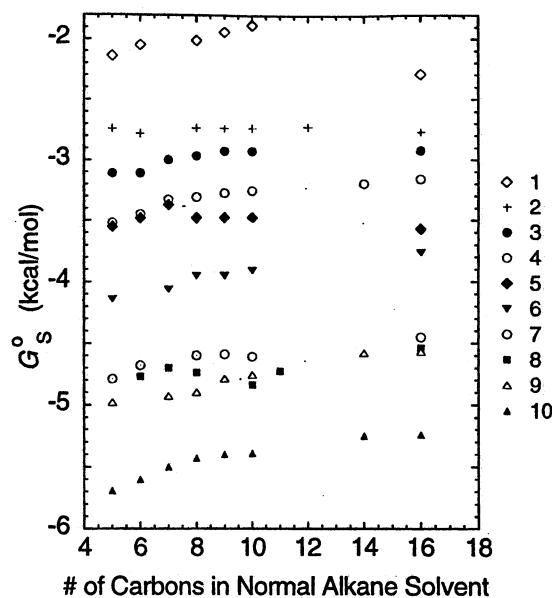


Figure 1. For a number of solutes, a comparison of the free energy of solvation in different normal alkane solvents. The abscissa is the number of carbons in the chain of the solvent. The ordinate is the free energy of solvation. The solute numbers are (1) ethylamine, (2) 1-propanol, (3) propylamine, (4) ethyl ethanoate, (5) butylamine, (6) 2-pentanone, (7) 2-hexanone, (8) toluene, (9) butyl ethanoate, and (10) pentyl ethanoate.

that, all else being equal, smaller dielectric constants will yield less negative polarization free energies. Table 1 indicates that this would lead to less negative free energies of solvation in *n*-pentane than *n*-hexadecane, which is the opposite of the observed experimental trend. Table 1 also lists the experimental values for the internal pressure,^{1,41} macroscopic surface tension, and density for each solvent. These three columns of data show that the intermolecular interactions between solvent molecules grow stronger as the length of the solvent chain increases, as is intuitively obvious since the lightest alkanes are gases and the heaviest are solids. This type of interaction should surely be modeled with the G_{CD}^0 term, although it may not be obvious whether this effect should be modeled with G_{CD} or G_{CS} . However, we consider favorable solute–solvent interactions and favorable solvent cavitation entropy terms to be included in G_{CD} and unfavorable terms such as the enthalpy of cavitation and structure rearrangement to be included in G_{CS} . While it is certainly possible that the increased intermolecular interactions in the pure solvent could lead to increased favorable solute–solvent dispersion interactions in *n*-hexadecane compared to *n*-pentane, this effect, if present, is overcome by the loss of favorable solvent–solvent interactions. For this reason, we model this trend with the CS surface tension.

As can be seen in Table 2, *n*-hexadecane is the only solvent for which we have data for more than 60 solutes (the *n*-hexadecane data were taken from sources other than the MedChem database^{37,42–45}), and cyclohexane is the only other solvent which has a solvent test set larger than 50 molecules. The relative paucity of data for the other alkanes made their parametrization more difficult. In sample sizes such as are shown in Table 2, one or two compounds with high experimental error could skew the entire fit unphysically. In addition, an unequal distribution of functional groups among the various solvents could skew the parametrization in favor of the more populated groups at the expense of poor treatment of functional groups which only have one or two representative compounds or are not represented at all. It was clear that a direct parametrization by optimizing σ^{CS} in each solvent, while

TABLE 5: Solutes in the Reduced Test Set and Their Experimental Free Energies of Solvation (kcal/mol) in *n*-Octane and *n*-Hexadecane

solute	<i>n</i> -octane	<i>n</i> -hexadecane
toluene	-4.74	-4.54
butanone	-3.30	-3.12
2-pentanone	-3.95	-3.76
2-hexanone	-4.60	-4.45
methyl ethanoate	-2.86	-2.61
ethyl ethanoate	-3.31	-3.16
butyl ethanoate	-4.90	-4.57
pentyl ethanoate	-5.43	-5.24
propylamine	-2.97	-2.92
3,3-dimethylbutanone	-4.23	-3.98
2-heptanone	-5.31	-5.13
propyl ethanoate	-4.12	-4.02
methyl hexanoate	-5.58	-5.47
methyl pentanoate	-4.88	-4.71

minimizing errors over each solvent test set, would not necessarily yield robust, physical values for σ^{CS} that would apply to compounds beyond the solvent test sets.

In an effort to achieve a robust parametrization, we decided to base the parametrization on the *n*-hexadecane model. The *n*-hexadecane model was developed using 153 solutes that included a wide variety of functional groups. Our goal was to create a parametrization that captured the trend in the difference between each specific alkane solvent and *n*-hexadecane. The first step was to temporarily reduce the solvent test sets so that the remaining compounds did not suffer from significant experimental error. Examination of the data in Table 1 seems to imply that the strength of intermolecular interactions should be a fairly smooth function of the number of carbons in a straight-chain alkane solvent; thus, we would expect that the free energy of solvation should also be a smooth function of the number of carbons in a straight-chain alkane solvent. Free energy data which differed significantly from this expectation were considered less reliable, and solutes for which the free energy data showed such deviations were not included in the next step. In addition, in order to help examine the trend in how the solvation energy changes with respect to solvent characteristics, it was necessary to choose solutes that were measured in a large number of the alkane solvents. Finally, because of the comparison which is described next, all compounds selected for the reduced test set were required to have an experimental ΔG_s° in *n*-hexadecane. The solutes chosen using these criteria will be referred to as the reduced test set. Because of the lack of data in other straight-chain alkane solvents, the only solvents considered were the unbranched alkanes from *n*-pentane to *n*-decane and also *n*-hexadecane. Originally, nine solutes were chosen for the reduced test set. These nine are the first nine compounds in Table 5. For each solute in each solvent, the difference between the experimental free energy of solvation in *n*-hexadecane and that solvent was calculated. From this, for each compound, the difference in polarization energy using the AM1-SM4 models between *n*-hexadecane and the solvent was subtracted. A very similar result would be obtained using the PM3-SM4 models. Since G_{CD} is independent of solvent in the SM4 alkane models, we may write

$$\Delta G_{\text{CS}} = \Delta \Delta G_{\text{S}_{(\text{exp})}}^\circ - \Delta G_p \quad (11)$$

where the Δ at the beginning of each term implies a difference between *n*-hexadecane and the solvent under consideration. For each solvent, σ^{CS} was then optimized to best fit the ΔG_{CS} values between that solvent and *n*-hexadecane. That is, the

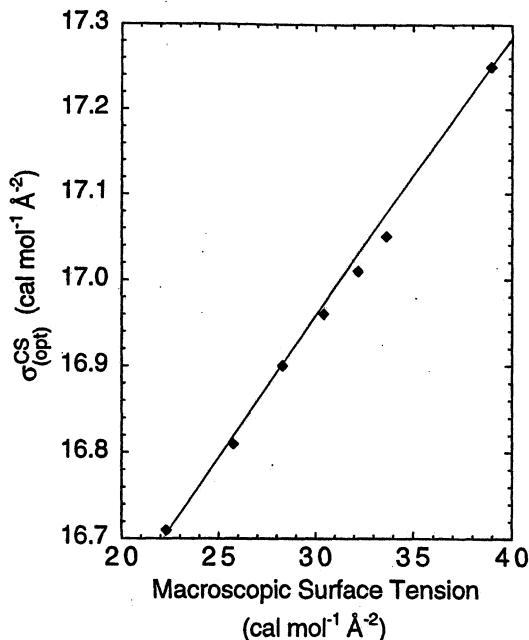


Figure 2. Plot showing the value of $\sigma_{(\text{opt})}^{\text{CS}}$ versus the experimental macroscopic surface tension for the six normal alkane solvents from *n*-pentane to *n*-decane and also *n*-hexadecane. The best fit line to this data constrained to the *n*-hexadecane value of $\sigma_{(\text{opt})}^{\text{CS}}$ is shown. The equation for this line is eq 13 and yields the SM4 values of σ^{CS} .

root-mean-square (rms) error in

$$\Delta G_{\text{CS}} = (\sigma_{(\text{n-hexadecane})}^{\text{CS}} - \sigma_{(\text{alkane})}^{\text{CS}}) \sum_n A_n^{\text{CS}} \quad (12)$$

was minimized, where $\sigma_{(\text{n-hexadecane})}^{\text{CS}}$ is σ^{CS} from the *n*-hexadecane model¹² and $\sigma_{(\text{alkane})}^{\text{CS}}$ is σ^{CS} in the alkane solvent under consideration. Because such a small number of compounds were used in the developing the σ^{CS} parameter, we tested our results by adding five other compounds (the final five compounds in Table 5) to the reduced test set. The same procedure just described was repeated. The resulting optimal σ^{CS} values differed by no more than 0.02 cal mol⁻¹ Å⁻² from the values that resulted from the original nine compounds and so were used throughout the rest of the parametrization.

Although this procedure yielded σ^{CS} values—which we will call $\sigma_{(\text{opt})}^{\text{CS}}$ —that produced low rms errors when applied to the entire parametrization set for each solvent in this process, it did not provide a method for extending the model to include all alkane solvents. This extension, however, is easily accomplished if σ^{CS} is a function of some common, experimentally measurable property. Figure 2 shows that $\sigma_{(\text{opt})}^{\text{CS}}$ is an almost linear function of the macroscopic surface tension. The best fit line to the data, constrained to the value of σ^{CS} previously optimized for *n*-hexadecane,¹² 17.25 cal mol⁻¹ Å⁻², is

$$\sigma^{\text{CS}} = 0.03332\gamma + 15.95 \text{ cal mol}^{-1} \text{ Å}^{-2} \quad (13)$$

where γ is the experimental macroscopic surface tension. The values of σ^{CS} that result from this fit differ by no more than 0.02 cal mol⁻¹ Å⁻² from $\sigma_{(\text{opt})}^{\text{CS}}$. The values resulting from this fit are defined to be the SM4 σ^{CS} values for each alkane solvent and are given in Table 2.

The above procedure yields a model for all straight-chain alkanes which are liquid at 298 K. The next step was to evaluate whether branched alkanes and ring alkanes fit into this model or need to be handled separately.

The only branched alkane solvent for which more than one solute from the meta set was measured is 2,2,4-trimethylpentane, commonly known as iso-octane. Only four of the 14 solutes in the reduced test set have data available for iso-octane; the value of $\sigma_{(opt)}^{CS}$ using those four compounds is $16.78 \text{ cal mol}^{-1} \text{ Å}^{-2}$. The value obtained using eq 13 is $16.83 \text{ cal mol}^{-1} \text{ Å}^{-2}$. Table 2 shows that using the value of $16.83 \text{ cal mol}^{-1} \text{ Å}^{-2}$ with the entire iso-octane test set of 32 compounds yields an rms error in line with other solvents. It appears that, within the constraints of available data, eq 13 is valid even for highly branched alkanes.

There were two alkane ring solvents for which a considerable amount of data existed in the partition coefficient database, cyclohexane and decalin.³⁴ Examination of Table 1 shows that ring compounds have properties that often fall outside the range of properties of the other alkane solvents. Indeed, Abraham's analysis indicates that solvation in cyclohexane is unique compared to other alkane solvents, and he explains this by invoking the greater polarizability of cyclohexane compared to *n*-hexane.⁴⁶ Another way in which the cyclic alkanes differ significantly from straight-chain alkanes is that cyclohexane is difficult to treat as a solute, as indicated by the fact that our previous solvation models^{9–12,23} consistently undersolvate saturated five- and six-membered saturated rings by about 1 kcal/mol. For these reasons, it was not obvious that cyclohexane or any ring compound would fit into the SM4 model without modifications. Furthermore, using the 14 compounds in Table 5 and eq 12, $\sigma_{(opt)}^{CS}$ is found to be $16.86 \text{ cal mol}^{-1} \text{ Å}^{-2}$, whereas using eq 13, σ^{CS} is $17.14 \text{ cal mol}^{-1} \text{ Å}^{-2}$. Although the two values are in reasonable agreement, the difference between $\sigma_{(opt)}^{CS}$ and σ^{CS} was enough to warrant further consideration.

We decided to optimize a new σ^{CS} over the entire cyclohexane test set of 60 compounds while simultaneously optimizing a scale factor on the G_{CD} term. The scale factor on G_{CD} was based on the fact that although we do not expect any different types of intermolecular interactions in cyclohexane than other alkane solvents, the greater polarizability may lead to stronger interactions. However, the optimum scale factor turned out to differ negligibly from unity—by about 1%—so we eliminated it and optimized σ^{CS} over the entire cyclohexane test set of 60 compounds while keeping G_{CD} the same as in all other solvents. The resulting σ^{CS} was $17.09 \text{ cal mol}^{-1} \text{ Å}^{-2}$, in very good agreement with the value from eq 13. Thus, we retain the value of $17.13 \text{ cal mol}^{-1} \text{ Å}^{-2}$ that is systematically derived from that equation.

Decalin presents a special case for ring solvents because there are two distinct isomers, *cis* and *trans*. The two conformers, while similar, have slightly different properties as shown in Table 1. Unfortunately, many of the references^{47–52} for decalin measurements used in the MedChem database³⁴ do not specify which conformer was used. However, the two conformers differ so slightly in their relevant physical properties—dielectric constant and surface tension—that it is reasonable to treat all data as if they were measured in a mixture of the two solvents. To accomplish this, we took the average of the two dielectric constants and the two macroscopic surface tensions to treat the solvent as if it were a mixture of the two compounds. Although not theoretically rigorous, this method is probably accurate to well within the error of the model. As shown in Table 2, we achieve reasonable agreement with experiment using eq 13.

We now have a model which is able to predict free energies of solvation for any alkane (straight chain, branched, or cyclic) by determining one surface tension in the model from an equation that relies on experimental data.

TABLE 6: Selected PM3–SM4 Calculations of the Free Energy of Solvation in kcal/mol and Its Three Components

solute	ΔG_{ENP}	G_{CD}	G_{CS}	$\Delta G_{\text{s}}^{\circ}$
n-Pentane Solvent				
methane	0.00	-10.24	9.97	-0.27
<i>n</i> -decane	0.06	-26.38	19.06	-7.26
1-butanol	-0.99	-16.28	13.71	-3.56
phenol	-1.71	-17.38	13.61	-5.47
diethyl ether	-0.47	-16.80	14.05	-3.22
benzaldehyde	-1.70	-18.13	14.21	-5.62
butanone	-1.43	-15.51	13.37	-3.56
2-hexanone	-1.31	-19.16	15.30	-5.17
ethyl ethanoate	-0.48	-17.10	14.17	-3.41
aniline	-1.57	-18.18	13.82	-5.93
fluorobenzene	-0.69	-16.52	13.48	-3.73
ammonia	-1.15	-9.54	9.54	-1.15
water	-1.35	-8.26	9.19	-0.42
Cyclohexane Solvent				
methane	-0.02	-10.24	10.20	-0.06
<i>n</i> -decane	0.07	-26.38	19.50	-6.81
ammonia	-1.29	-9.54	9.76	-1.07
water	-1.48	-8.26	9.43	-0.31

Table 6 gives results calculated with the final parameters for the PM3–SM4 *n*-pentane and cyclohexane models for some compounds that will be interesting for the discussion (whether or not used for parametrization); full tables of results for all molecules in the solvent test sets are given in the supplementary material. The total number of solute/solvent pairs included in the solvent test sets is 506. The mean unsigned errors in solvation free energies averaged over all these pairs is 0.34 kcal/mol for AM1–SM4, 0.33 kcal/mol for PM3–SM4, and 0.34 kcal/mol for the two models combined. Corresponding root-mean-square errors are 0.45, 0.45, and 0.45 kcal/mol, respectively. Table 7 shows that the data are fit about as well in the alkane models presented here as in the highly optimized *n*-hexadecane model.

4. Discussion

Polarization. The range of dielectric constants in Table 1 leads to as much as 20% difference in the factor $(1 - 1/\epsilon)$ appearing in eq 4 for the polarization free energy. This effect can change the polarization free energy by as much as 0.4 kcal/mol between two alkane solvents. An example of this effect is provided by the polarization free energy of 1-butanol as calculated using the AM1–SM4 model. Table 8 shows that the calculated polarization free energy for 1-butanol in *n*-pentane is -1.04 kcal/mol. This is 28% of the total experimental solvation free energy. For comparison, this polarization free energy is -1.19 kcal/mol in *n*-hexadecane, which represents 34% of the overall solvation free energy. We can analyze the contributions to the polarization free energy by doing the calculation in three steps. The first step is to freeze the gas-phase electronic wave function and geometry and calculate the polarization free energy without relaxation in the presence of the solvent. In *n*-pentane, this yields a polarization free energy of -0.95 kcal/mol. In the second step, we allow the electronic wave function to relax from the gas-phase optimum to the solution-phase optimum self-consistently in the presence of the reaction field. This yields an additional polarization free energy of -0.08 kcal/mol. The final step is to allow the wave function and the geometry to self-consistently relax in the presence of the solvent dielectric field. This final step causes very little change, contributing an additional -0.01 kcal/mol to the total polarization free energy of -1.04 kcal/mol.

Tables 9 and 10 give the increase in dipole moment and polarization energy for 20 solutes upon relaxation of the wave function and geometry in solution. In the unrelaxed case, the

TABLE 7: Errors (kcal/mol) in the SM4 Alkane Solvation Models

no. of solvent-solute pairs	AM1-SM4		PM3-SM4		combined ^a	
	unsigned	rms	unsigned	rms	unsigned	rms
this paper ^b	353	0.36	0.47	0.34	0.35	0.47
n-hexadecane ^c	153	0.29	0.40	0.29	0.29	0.41
all alkanes ^d	506	0.34	0.45	0.33	0.34	0.45

^a Combined AM1-SM4 and PM3-SM4 results. Total number of datapoints is twice the number of the solvent-solute pairs. ^b All solvents in Table 2 except for n-hexadecane. ^c From ref 12. ^d All solvents listed in Table 2.

TABLE 8: Polarization Energy of 1-Butanol in kcal/mol by the AM1-SM4 Alkane Models

wave function/geometry	G_P	
	n-pentane	n-hexadecane
gas phase/gas phase	-0.95	-1.08
relaxed/gas phase	-1.03	-1.17
relaxed/relaxed	-1.04	-1.19

TABLE 9: PM3-SM4 Dipole Moment (D) in n-Heptane

	unrelaxed		relaxed	
	CM1	Ψ	CM1	Ψ
methanol	1.6	1.5	1.7	1.6
ethanol	1.6	1.4	1.7	1.6
1-propanol	1.5	1.4	1.7	1.5
1-butanol	1.6	1.6	1.8	1.7
phenol	1.2	1.1	1.5	1.3
benzaldehyde	2.8	2.7	3.4	3.1
propanone	2.9	2.8	3.4	3.2
butanone	2.8	2.7	3.3	3.1
acetophenone	3.0	2.8	3.6	3.3
diethyl ether	1.1	1.2	1.3	1.2
methyl ethanoate	2.0	1.8	2.4	2.1
ethyl ethanoate	2.1	1.9	2.5	2.2
propylamine	1.2	1.4	1.3	1.5
pyridine	1.6	1.9	2.0	2.2
aniline	1.5	1.3	1.6	1.4
ethanone	3.9	3.2	4.6	3.7
benzonitrile	4.4	3.6	5.2	4.3
fluorobenzene	1.6	1.6	2.0	1.8
chlorobenzene	1.6	1.0	1.9	1.2
<i>o</i> -dichlorobenzene	2.4	1.4	3.0	1.8
iodobenzene	1.5	0.8	1.8	1.0
average % increase		16		14

geometry and the wave function remain fixed at the gas-phase minimum. In Table 9, the CM1 dipole moments are point-charge dipole moments, while the column headed Ψ contains the dipole moment calculated from the continuous wave function. (We emphasize that the latter quantity is presented here only for discussion purposes and is not used in any way in the calculations.) Since the wave function is polarized in solution using the CM1 partial charges through eq 4, it is reasonable that the average increase in the two dipole moments is similar.

Table 10 shows that polarization free energy increases at a percentage rate roughly twice that of the dipole moment on average. However, the increase in polarization free energy is not well correlated with the increase in the dipole moment. The two molecules (both esters) which experience the largest increase in the polarization energy have increases in the dipole moments that are only average. The two molecules (pyridine and fluorobenzene) that have the largest percentage increase in the CM1 point-charge dipole moment have below average increases in the polarization energy. It appears that molecules relax not only to increase charge separation but also to take advantage of the ability of the solvent to screen unfavorable charge interactions such as the O-O ester interaction.

Cavitation Energy. It is interesting to estimate the energy required to form a cavity in n-pentane and compare it to the

TABLE 10: PM3-SM4 Polarization Energy, G_P , (kcal/mol) and Percentage Increase upon Allowing the Wave Function and Geometry To Relax

	unrelaxed	relaxed	% increase
methanol	-1.25	-1.38	11
ethanol	-1.16	-1.29	10
1-propanol	-1.11	-1.22	10
1-butanol	-0.99	-1.09	10
phenol	-1.63	-1.90	17
benzaldehyde	-1.63	-1.98	22
propanone	-1.51	-1.93	28
butanone	-1.34	-1.70	27
acetophenone	-1.58	-1.98	25
diethyl ether	-0.44	-0.49	11
methyl ethanoate	-0.33	-0.67	102
ethyl ethanoate	-0.27	-0.63	136
propylamine	-0.54	-0.60	11
pyridine	-1.12	-1.39	24
aniline	-1.50	-1.77	18
ethanone	-2.10	-2.93	40
benzonitrile	-1.62	-2.16	34
fluorobenzene	-0.64	-0.81	26
chlorobenzene	-0.56	-0.68	22
<i>o</i> -dichlorobenzene	-0.57	-0.77	34
iodobenzene	-0.57	-0.68	19
average % increase			30

energy required for cavity formation in n-hexadecane. One method of estimating the energy requirement for cavity formation in a solvent is based on the internal pressure of a liquid, π , which is the energy required per unit volume for a small isothermal expansion of the liquid. For liquids such as alkanes in which repulsions, dispersion, and weak dipole interactions predominate, π is roughly equivalent to the energy of cavity formation.⁴¹ As can be seen from the π values given in Table 1, it takes 19.8 cal/cm³ more energy to make a cavity in n-hexadecane than in n-pentane. If the cavity volume for a specific solute is known, than we can compute the difference in cavitation energies between n-pentane and n-hexadecane solutions of the solute.

There are numerous ways to estimate the cavity size of the solute. (Note that the cavity boundary of the solute is different from the solvent-accessible surface area in that the solvent-accessible surface area passes through the centers of the solvent molecules in the first hydration shell, and the cavity boundary does not contain any solvent.) We chose two methods. The first is to calculate the molecular volume from the experimental density of the pure solute at 298 K.⁵³ The second is to calculate the volume of a single molecule using the van der Waals radii of Bondi³⁸ at the solution optimized geometry. For this method, we used the geometry optimized in n-hexadecane using the PM3-SM4 method.¹² The volume was calculated using the GEPOL⁵⁴ algorithm. For this calculation only, the value of Bondi was used for the radius of carbon. The two methods yield significantly different results, and since it is not obvious which method is better, we present the results for both calculations using ethylamine and 2-hexanone as sample solutes. For ethylamine, the density method of computing the molecular volume yields a cavity size of 66 Å³, while the van der Waals method yields 34 Å³. In the first case, the differential cavitation

energy is 1.3 kcal/mol. In the second case it is 0.68 kcal/mol. These values may be compared with the PM3-SM4 difference in the CS free energy term of 0.38 kcal/mol. For 2-hexanone, the two volumes are 124 and 70 Å³, respectively. These volumes give energetic differences of 2.4 and 1.4 kcal/mol compared to the PM3-SM4 free energy difference of 0.44 kcal/mol.

The above discussion shows that the PM3-SM4 free energies are much less sensitive to the size of the solute than are the estimates based on the internal pressure. The PM3-SM4 trend agrees with the experimental data in that (as shown in Figure 1) the increasing solvation energy trend is similar in size for solutes of a wide range in size and functional group and is much less than a full kcal/mol for even the largest solutes, but more on the order of 0.4 kcal/mol. Using the molar activation enthalpy for solvent viscous flow,⁵⁵ Nikolić estimates that the difference in the cavity formation enthalpy is 1.6 cal·mol⁻¹ cm⁻³ more exothermic in *n*-pentane than in *n*-hexadecane (12.0 vs 13.6 cal mol⁻¹ cm⁻³). This enthalpic contribution is presumably included in the G_{CS} term of our model. However, this reference also estimates that solute/solvent dispersion interactions become more favorable at almost the same rate, so the overall effect from these two terms is nearly zero. While it appears that our model is correct in predicting that the energetics of cavitation do become more unfavorable as the length of the alkane solvent chain increases, this effect appears to be accompanied by some increase in the favorable solute/solvent dispersion interactions. Although the absolute magnitudes of the separate effects are hard to disentangle, what is clear from the experimental data is that the increasing unfavorable effects are not completely canceled by the gain in favorable interactions and that our model approximately captures the magnitude of this effect.

R_s^{CS} . The choice for the solvent radius associated with the intermediate-range solvation effects is not unambiguous. The original value¹² of 4.9 Å comes from a sphere containing the same volume as that of an *n*-hexadecane molecule as calculated from the liquid density. The effect on the results of the present paper of changing the size of R_s^{CS} was small as long as the value was over 4 Å, so we decided to retain 4.9 Å for all alkanes. As an alternative to this approach, we might have calculated the value of R_s^{CS} from the liquid density of each solvent as was done in *n*-hexadecane. However, for smaller alkanes, this would bring the value of R_s^{CS} down well below 4.0 Å, e.g., the value calculated for *n*-pentane this way is 3.6 Å. We found that the use of such a small radius resulted in a systematic size-dependent error in the model. That is, small solutes were oversolvated (predicted ΔG_s^o too negative) and large solutes were undersolvated.

The initial impetus behind the addition of the CS term to model intermediate-range interactions is that a straight-line fit to solvation effect vs solvent-accessible surface area calculated with only a single λ in eq 6 has a nonzero intercept.¹² We have argued that an intercept is not physical as it loses a clear meaning in the limit of a vanishingly small solute.¹² In the language of many-body theory, models with intercepts (i.e., models in which a constant term is added to equations like (6), (7), and (12)) are not size extensive (i.e., not "size consistent") in that if one has two molecules of A so far apart that their interactions are negligible, one gets a different result if the system is treated as A₂ than if it is treated as A. Our interpretation of the need for the second sum in eq 7 and the large value of its associated effective solvent radius is that there are interactions that occur on a range scale sufficiently large that the size of the solute has only a small or no effect on the size of the solvation shell when the solute is significantly smaller than the solvent. The inclusion

of the G_{CS} term gives G_{CDS}^o an ability to fit data which appear to require an intercept when modeled with a single radius, but our model retains a physical basis in the limit of very small solutes. A value of 4.9 Å is large enough that the importance of solute size is diminished, while small enough to still be physically reasonable; for example, the length of an extended *n*-pentane chain as calculated by AM1 is nearly 7 Å long. Jiang and Blanchard have recently reported measurements of the rotational (reorientational) diffusion time of perylene in *n*-alkanes that show that local solvent ordering exists on a length scale much less than 10 Å,⁵⁶ and the viscosity dependence of these relaxation times is consistent with a chain-length-dependent component to the solvent ordering in the vicinity of the solvent.⁵⁷ Thus, we are satisfied that retaining the value of 4.9 Å for R_s^{CS} in all alkane solvents is physically reasonable.

Dispersion Forces. Table 6 shows that the nonelectrostatic component of the solvation free energy results from considerable cancellation between a large negative dispersion term and a large positive structural term. This is consistent with recent work of Tuñón *et al.*,⁵⁸ who calculated, for example, that the dispersion contribution for aqueous solvent increases in strength from -2.9 kcal/mol for methane to -16 kcal/mol for *n*-decane. We can compare these effects to our results for alkanes because water and methylene groups would be expected to have roughly comparable (within a factor of 2 larger for methylene) polarizabilities. We find a comparable increase in G_{CD} for alkane solvents, with this term increasing in strength from -10 to -26 kcal/mol. See Table 6. Thus, it seems reasonable to attribute a large part of this 16 kcal/mol shift to dispersion forces.

Amovilli⁵⁹ has also recently estimated the dispersion energy contributions to solvation free energies in water. He estimates -4.2, -3.9, and -3.4 kcal/mol for methane, ammonia, and water (as solutes), respectively. Table 6 shows that the shifts in these values are about 2.4 times smaller than the shift in G_{CD} in our model for the same solutes which is similar to the difference in polarizability of water and methane, which is a factor of 1.8.³³ This is encouraging for the physical reasonableness of our model, but we emphasize that G_{CD} includes more than just the effect of dispersion interactions.

Cyclohexane. As shown in section 3, although it was anticipated that cyclohexane would perhaps require separate treatment, cyclohexane can be treated with this model without any special parameter(s). This is because the experimental solvation data for cyclohexane are not very different from other alkanes. An examination of the 33 solutes included in both the cyclohexane and *n*-hexane test sets reveals that the experimental free energies of solvation are on average 0.03 kcal/mol less negative in cyclohexane than in *n*-hexane with a standard deviation in the differential free energies of solvation of 0.25 kcal/mol. Removal of the only significant outlier changes the average difference to 0.06 kcal/mol. The average difference is much smaller than the experimental error, which from examination appears to be at least 0.15 kcal/mol and becomes irrelevant when the standard deviation is considered. Using the same 33 solutes, the AM1-SM4 model predicts that the free energy of solvation is, on average, 0.18 kcal/mol less negative in cyclohexane than in *n*-hexane with a standard deviation in the difference of 0.05 kcal/mol.

The data of Abraham *et al.*⁴⁶ provide a more complete comparison. For 122 solutes, ΔG_s^o in cyclohexane is 0.13 kcal/mol more negative than in an alkane solvent with a standard deviation of 0.21 kcal/mol. Removal of all outliers greater than two standard deviations away from the mean changes the mean difference in ΔG_s^o to 0.11 kcal/mol and the standard deviation to 0.18 kcal/mol. Abraham *et al.* do not distinguish between

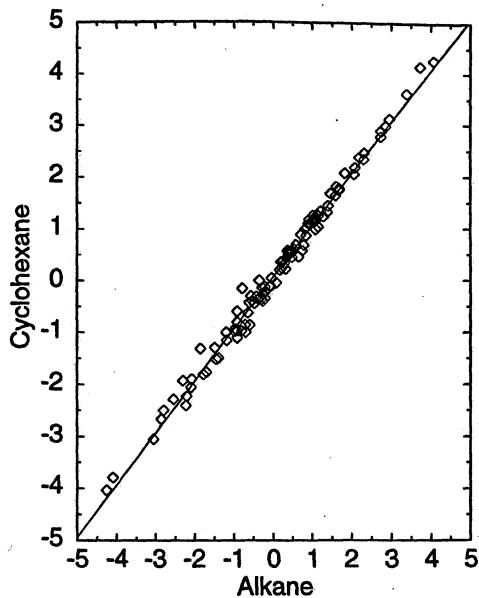


Figure 3. Comparison of the water/solvent partition coefficients for cyclohexane and alkanes for 122 solutes as described in section 4. Data are from Abraham.⁴⁶ The equation of the best fit line is $y = 1.0x + 0.09$, $R = 0.995$.

various noncyclic alkane solvents. In the comparison between cyclohexane and all alkane solvents, only *n*-hexadecane is listed separately. These data imply—to the extent that differences smaller than the typical experimental error have any significance—that solvation in cyclohexane should be only slightly more favorable than in the “average” noncyclic alkane. Figure 3 is a plot of the experimental partition coefficients between water and cyclohexane plotted against the experimental partition coefficients between water and *n*-hexane for the same compounds. The data are the same data as were used to calculate the above numbers and have been sorted in order of increasing partition coefficient. Although the data presented above show that the overall ΔG_s^o is similar in cyclohexane compared to other alkanes, it is possible (even probable) that this involves some cancellation of different effects. The greater polarizability of cyclohexane could lead to larger solute/solvent dispersion terms; however, it would also lead to stronger solvent/solvent interactions, making cavitation more unfavorable. Abraham *et al.*, using the data that led to the result above, find that cyclohexane yields a different LSER equation than the alkanes, implying that while the overall result is quite similar, the effects leading to the final result may differ slightly.⁴⁶ This is somewhat reinforced by the data of Leahy and co-workers.⁶⁰ For 20 compounds containing a benzene ring, they find that solvation is 0.20 kcal/mol more favorable in cyclohexane than in alkanes with a standard deviation of 0.15 kcal/mol. Although 20 solutes is small sample size, it shows that the polarizable aromatic ring may be able to more favorably interact with the polarizable cyclohexane molecules. The above arguments suggest that overall free energies of solvation are not significantly different in cyclohexane than in other alkanes, and, if anything, our model suffers slightly from being based on a property (macroscopic surface tension) in which cyclohexane differs from the smaller *n*-alkanes.

There is little doubt in the literature that 2,2,4-trimethylpentane (TMP, isoctane) is quite similar to other alkane solvents.^{37,60,61} As a check, for the 11 solutes that were used in both the 2,2,4-trimethylpentane and *n*-octane test sets, we note that the experimental free energy of solvation on average is 0.09 kcal/mol less negative in *n*-octane compared to the branched alkane with a standard deviation of 0.18 kcal/mol. For these

same 11 solutes, our PM3–SM4 model predicts an average free energy of solvation that is 0.11 kcal/mol less negative in *n*-octane than isoctane with a standard deviation of 0.01 kcal/mol. Considering the size of the data set, the size of the standard deviation, and the size of experimental error, this difference between solvation energies in *n*-octane and isoctane is insignificant both experimentally and in our model.

Alcohols. Most of the data on alcohols in the MedChem database³⁴ come from a single source.⁶² It is unfortunate that while measurements were made for methanol through 1-heptanol in 26 different solvents, very few significant figures, at times only one, were reported in the measurements. Because of this, it is impossible to observe any trend in the data between solvents. Deviations from a flat line in Figure 1 for alcohols occur only because of data from other sources. Due to the lack of sensitivity to solvent in the alcohol data, alcohols were not included in the reduced solvent set used in the parametrization of $\sigma_{(opt)}^{CS}$. Nevertheless, alcohols were included in the solvent test sets used to calculate the rms errors listed in Table 2 as the data represent “average” solvation free energies.

Carboxylic Acids. Carboxylic acids were not included in the parametrization set because of experimental difficulties. For example, carboxylic acids are known to dimerize in nonpolar solvents. In addition, most carboxylic acids are deprotonated in water, and because they exist in different forms in the two solvents, the interpretation of the partition coefficient becomes less straightforward.

Nitro Compounds. Because the semiempirical AM1 and PM3 Hamiltonians do not treat nitro groups very accurately,⁶³ we do not recommend treatment of nitro groups with the general parameters of the AM1–SM4 and PM3–SM4 models, and they were not included in the parametrization sets. If treatment of these molecules is desired, we recommend using PM3–SM4 with a nonstandard oxygen σ_k^{CD} of $-66.96 \text{ cal mol}^{-1} \text{ \AA}^{-2}$ for the oxygen atoms in the nitro group. This gives acceptable agreement with experiment.¹²

5. Summary

In this paper, we have presented a solvation model for all alkanes: normal, branched, and cyclic. The model is parametrized for solutes composed of H, C, N, O, F, S, Cl, Br, and I. A wide variety of functional groups were used in the parametrization, including alkanes, alkenes, alkynes, aromatics, alcohols, ethers, esters, aldehydes, ketones, amines, nitriles, pyridines, thiols, sulfides, and halocarbons.

The physical reasonableness of this model is confirmed by its generality. We are able to treat every alkane solvent by changing only two parameters, one of which is the experimental dielectric constant. The second, $\sigma_{(opt)}^{CS}$, is derived from a linear fit to experimental macroscopic surface tensions. A single set of parameters is presented; these parameters are applicable to both the AM1 and PM3 Hamiltonians, and we believe that they will work with any level of theory which provides reasonable partial charges and accurate geometries. Table 2 shows that the models have low rms errors for every solvent, and we are able to reproduce experimental trends across solvents.

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Supplementary Material Available: Tables of ΔG_{ENP} , G_{CD} , G_{CS} , and $\Delta G_{\text{s}}^{\circ}$ and experimental values of $\Delta G_{\text{s}}^{\circ}$ for all solutes in all solvents (15 pages). Ordering information is given on any current masthead page.

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Supplementary Material

**Title: A General Semiempirical Quantum Mechanical Solvation Model for Solvation
Free Energies in Alkane Solvents**

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This supplementary material consists of 15 tables. The tables list the AM1-SM4, PM3-SM4, and experimental free energy of solvation for each of the 15 solvents parameterized in this paper.

Appendix A

TABLE A-1. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-pentane test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
methanol	-1.35	-10.75	10.69	-0.06	-1.41	-1.26	-10.77	10.64	-0.13	-1.39	-1.23
ethanol	-1.27	-12.92	11.84	-1.07	-2.34	-1.16	-12.96	11.81	-1.14	-2.31	-2.09
1-propanol	-1.18	-14.66	12.81	-1.84	-3.03	-1.11	-14.72	12.79	-1.93	-3.04	-2.74
1-butanol	-0.99	-16.18	13.73	-2.45	-3.44	-0.99	-16.28	13.71	-2.57	-3.56	-3.74
1-pentanol	-0.95	-17.93	14.70	-3.22	-4.18	-0.97	-18.04	14.69	-3.35	-4.32	-4.00
phenol	-2.17	-17.34	13.64	-3.71	-5.87	-1.71	-17.38	13.61	-3.76	-5.47	-5.29
1-hexanol	0.13	-20.65	15.64	-5.01	-4.88	0.12	-20.81	15.64	-5.17	-5.05	-5.03
1-heptanol	0.13	-22.36	16.61	-5.75	-5.63	0.14	-22.57	16.61	-5.96	-5.82	-5.69
3,3-dimethylbutanone	0.18	-19.19	14.39	-4.80	-4.61	0.18	-19.40	14.40	-5.00	-4.82	-4.45
2-pentanone	-1.34	-17.31	14.34	-2.97	-4.31	-1.36	-17.43	14.34	-3.09	-4.45	-4.14
2-hexanone	-1.27	-19.03	15.31	-3.73	-4.99	-1.31	-19.16	15.30	-3.86	-5.17	-4.79
2-heptanone	0.18	-22.25	16.27	-5.97	-5.79	0.19	-22.48	16.28	-6.20	-6.01	-5.46
methyl ethanoate	-0.90	-14.87	13.10	-1.77	-2.67	-0.46	-14.98	13.09	-1.89	-2.35	-2.93
methyl propanoate	-0.65	-16.69	14.05	-2.63	-3.29	-0.23	-16.83	14.05	-2.78	-3.01	-3.69
ethyl ethanoate	-0.82	-16.95	14.19	-2.76	-3.58	-0.48	-17.10	14.17	-2.93	-3.41	-3.52
propyl ethanoate	0.12	-19.58	15.16	-4.42	-4.29	0.07	-19.30	15.15	-4.15	-4.08	-4.24
methyl pentanoate	0.08	-20.77	15.98	-4.79	-4.71	0.04	-20.53	15.99	-4.54	-4.50	-4.97
butyl ethanoate	-0.73	-20.43	16.14	-4.30	-5.02	-0.37	-20.61	16.13	-4.48	-4.85	-4.98
methyl hexanoate	-0.48	-21.89	16.95	-4.94	-5.41	0.04	-22.27	16.96	-5.31	-5.27	-5.72
pentyl ethanoate	-0.69	-22.18	17.11	-5.07	-5.76	-0.41	-22.38	17.09	-5.29	-5.70	-5.69
ethylamine	-0.82	-13.42	12.00	-1.42	-2.24	-0.57	-13.54	11.98	-1.57	-2.13	-2.14
propylamine	-0.76	-15.14	12.96	-2.18	-2.94	-0.54	-15.30	12.95	-2.35	-2.89	-3.11
butylamine	-0.71	-16.88	13.93	-2.95	-3.66	-0.52	-17.06	13.92	-3.13	-3.65	-3.55
aniline	-1.99	-18.04	13.84	-4.21	-6.19	-1.57	-18.18	13.82	-4.36	-5.93	-5.14
trichloromethane	-0.50	-15.91	12.57	-3.34	-3.84	-0.58	-15.89	12.54	-3.35	-3.93	-3.38
tribromomethane	-0.20	-18.47	13.17	-5.30	-5.50	-0.22	-17.80	12.91	-4.89	-5.11	-5.00
Mean Error	-0.11	RMS Error	0.33	Mean Error	-0.06	RMS Error	0.36				

TABLE A-2. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-hexane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	$\Delta G_{\text{S(expt)}}^0$
benzene	-0.95	-17.04	13.29	-3.75	-4.70	-0.57	-17.09	13.27	-3.82	-4.39	-3.98
toluene	-0.94	-18.61	14.24	-4.37	-5.31	-0.58	-18.66	14.21	-4.45	-5.03	-4.77
ethylbenzene	-0.84	-20.04	15.10	-4.95	-5.78	-0.53	-20.11	15.07	-5.04	-5.57	-4.88
<i>m</i> -xylene	-0.93	-20.17	15.18	-4.98	-5.92	-0.59	-20.22	15.15	-5.07	-5.66	-4.89
<i>o</i> -xylene	-0.96	-19.72	14.84	-4.87	-5.84	-0.61	-19.77	14.81	-4.96	-5.57	-5.26
<i>p</i> -xylene	-0.93	-20.17	15.19	-4.98	-5.91	-0.59	-20.22	15.15	-5.07	-5.66	-4.96
methanol	-1.39	-10.75	10.76	0.01	-1.38	-1.29	-10.77	10.71	-0.06	-1.35	-1.42
ethanol	-1.30	-12.92	11.92	-1.00	-2.29	-1.19	-12.96	11.89	-1.07	-2.26	-2.02
1-propanol	-1.21	-14.66	12.90	-1.76	-2.97	-1.14	-14.72	12.87	-1.85	-2.99	-2.78
1-butanol	-1.02	-16.18	13.82	-2.36	-3.38	-1.01	-16.28	13.80	-2.48	-3.49	-3.74
1-pentanol	-0.97	-17.93	14.80	-3.13	-4.10	-1.00	-18.04	14.78	-3.26	-4.26	-4.46
phenol	-2.23	-17.34	13.73	-3.62	-5.84	-1.75	-17.38	13.70	-3.67	-5.42	-5.11
1-hexanol	0.10	-20.65	15.74	-4.91	-4.81	0.10	-20.81	15.74	-5.07	-4.97	-5.33
1-heptanol	0.10	-22.36	16.72	-5.64	-5.54	0.11	-22.57	16.72	-5.85	-5.74	-5.93
<i>o</i> -cresol	0.20	-20.69	14.48	-6.20	-6.01	0.15	-20.25	14.45	-5.79	-5.64	-6.31
<i>p</i> -cresol	0.23	-21.31	14.67	-6.64	-6.40	0.17	-20.81	14.64	-6.17	-5.99	-5.90
benzaldehyde	-2.02	-18.41	14.31	-4.09	-6.12	-1.75	-18.45	14.29	-4.16	-5.91	-5.54
propanone	-1.66	-13.77	12.51	-1.26	-2.92	-1.65	-13.84	12.50	-1.34	-2.99	-2.53
butanone	-1.46	-15.57	13.46	-2.11	-3.57	-1.47	-15.67	13.45	-2.22	-3.69	-3.34
2-hexanone	-1.31	-19.03	15.41	-3.63	-4.93	-1.34	-19.16	15.40	-3.76	-5.10	-4.68
3,3-dimethylbutanone	0.15	-19.19	14.49	-4.70	-4.56	0.15	-19.40	14.50	-4.91	-4.76	-4.35
2-heptanone	0.15	-22.25	16.38	-5.87	-5.72	0.16	-22.48	16.39	-6.09	-5.93	-5.42
acetophenone	-2.01	-19.80	15.14	-4.66	-6.67	-1.74	-19.89	15.13	-4.76	-6.50	-6.05
methyl propanoate	-0.67	-16.69	14.14	-2.54	-3.22	-0.24	-16.83	14.14	-2.69	-2.93	-3.65
methyl ethanoate	-0.93	-14.87	13.19	-1.68	-2.61	-0.47	-14.98	13.17	-1.80	-2.28	-2.92
ethyl ethanoate	-0.85	-16.95	14.29	-2.66	-3.51	-0.50	-17.10	14.26	-2.84	-3.34	-3.45
methyl pentanoate	0.06	-20.77	16.09	-4.68	-4.62	0.03	-20.53	16.09	-4.44	-4.41	-4.96
methyl hexanoate	-0.49	-21.89	17.07	-4.82	-5.32	0.03	-22.27	17.07	-5.20	-5.17	-5.69
pentyl ethanoate	-0.71	-22.18	17.22	-4.96	-5.67	-0.43	-22.38	17.20	-5.17	-5.60	-5.60
ethylamine	-0.84	-13.42	12.08	-1.34	-2.18	-0.59	-13.54	12.06	-1.49	-2.07	-2.05
propylamine	-0.78	-15.14	13.05	-2.09	-2.87	-0.56	-15.30	13.03	-2.26	-2.83	-3.11
butylamine	-0.73	-16.88	14.02	-2.86	-3.59	-0.54	-17.06	14.01	-3.04	-3.58	-3.48
pyridine	-1.64	-15.98	13.06	-2.92	-4.56	-1.23	-16.07	13.05	-3.02	-4.25	-3.78
aniline	-2.04	-18.04	13.93	-4.11	-6.15	-1.61	-18.18	13.91	-4.26	-5.88	-5.42
fluorobenzene	-0.97	-16.67	13.58	-3.09	-4.06	-0.71	-16.70	13.56	-3.14	-3.85	-4.18

trichloromethane	-0.51	-15.91	12.65	-3.26	-3.77	-0.60	-15.89	12.63	-3.26	-3.86	-3.29
chlorobenzene	-0.95	-18.70	14.03	-4.67	-5.62	-0.61	-18.71	14.00	-4.71	-5.32	-5.19
<i>p</i> -dichlorobenzene	-0.79	-20.37	14.77	-5.59	-6.38	-0.50	-20.35	14.73	-5.61	-6.11	-6.03
tribromomethane	-0.21	-18.47	13.26	-5.21	-5.42	-0.22	-17.80	12.99	-4.80	-5.03	-4.54
bromobenzene	-1.00	-19.60	14.25	-5.35	-6.35	-0.63	-19.57	14.20	-5.36	-6.00	-5.69
<i>p</i> -bromophenol	-2.29	-19.91	14.69	-5.22	-7.51	-1.89	-19.80	14.64	-5.16	-7.05	-6.97
Mean Error	-0.25		RMS Error	0.51		Mean Error	-0.12		RMS Error	0.41	

TABLE A-3. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-heptane test set.

	AM1					PM3					$\Delta G_{S(expt)}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{S(SM4)}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{S(SM4)}^0$	
benzene	-0.97	-17.04	13.36	-3.68	-4.65	-0.58	-17.09	13.34	-3.75	-4.33	-4.04
toluene	-0.96	-18.61	14.32	-4.29	-5.25	-0.59	-18.66	14.29	-4.37	-4.96	-4.70
naphthalene	-1.55	-21.39	15.39	-6.01	-7.55	-0.98	-21.44	15.36	-6.07	-7.05	-7.06
anthracene	-2.05	-25.74	17.40	-8.34	-10.39	-1.28	-25.78	17.37	-8.41	-9.69	-10.06
<i>m</i> -xylene	-0.95	-20.17	15.26	-4.90	-5.86	-0.60	-20.22	15.23	-4.99	-5.59	-5.57
<i>o</i> -xylene	-0.98	-19.72	14.92	-4.79	-5.78	-0.62	-19.77	14.89	-4.88	-5.50	-5.57
<i>p</i> -xylene	-0.94	-20.17	15.27	-4.90	-5.84	-0.60	-20.22	15.23	-4.99	-5.59	-5.47
methanol	-1.41	-10.75	10.82	0.06	-1.34	-1.32	-10.77	10.77	0.00	-1.32	-1.23
ethanol	-1.32	-12.92	11.98	-0.93	-2.25	-1.21	-12.96	11.95	-1.00	-2.22	-2.09
1-propanol	-1.23	-14.66	12.97	-1.69	-2.92	-1.16	-14.72	12.94	-1.78	-2.94	-2.99
1-butanol	-1.03	-16.18	13.89	-2.29	-3.32	-1.03	-16.28	13.88	-2.40	-3.43	-3.63
1-pentanol	-0.99	-17.93	14.88	-3.05	-4.04	-1.01	-18.04	14.86	-3.18	-4.19	-4.17
phenol	-2.27	-17.34	13.80	-3.54	-5.81	-1.78	-17.38	13.78	-3.60	-5.37	-4.96
1-hexanol	0.09	-20.65	15.83	-4.82	-4.74	0.07	-20.81	15.82	-4.99	-4.91	-4.93
<i>m</i> -cresol	0.19	-21.30	14.75	-6.55	-6.35	0.16	-20.83	14.71	-6.12	-5.95	-5.00
<i>o</i> -cresol	0.16	-20.69	14.56	-6.13	-5.96	0.12	-20.25	14.53	-5.72	-5.59	-6.06
<i>p</i> -cresol	0.19	-21.31	14.75	-6.56	-6.37	0.14	-20.81	14.72	-6.09	-5.95	-5.81
1-heptanol	0.08	-22.36	16.81	-5.56	-5.47	0.08	-22.57	16.81	-5.76	-5.68	-5.66
anisole	-1.44	-19.27	14.82	-4.45	-5.89	-0.93	-19.36	14.80	-4.56	-5.49	-5.37
benzaldehyde	-2.06	-18.41	14.39	-4.02	-6.08	-1.79	-18.45	14.37	-4.08	-5.87	-5.51
propanone	-1.69	-13.77	12.58	-1.19	-2.88	-1.69	-13.84	12.56	-1.27	-2.97	-2.54
butanone	-1.49	-15.57	13.53	-2.04	-3.53	-1.50	-15.67	13.53	-2.15	-3.64	-3.42
2-pentanone	-1.40	-17.31	14.51	-2.80	-4.20	-1.42	-17.43	14.51	-2.92	-4.34	-4.06
3,3-dimethylbutanone	0.12	-19.19	14.56	-4.63	-4.51	0.12	-19.40	14.57	-4.83	-4.71	-4.31
2-heptanone	0.12	-22.25	16.47	-5.78	-5.66	0.13	-22.48	16.47	-6.00	-5.88	-5.28
acetophenone	-2.04	-19.80	15.22	-4.58	-6.62	-1.78	-19.89	15.22	-4.68	-6.45	-6.14
methyl ethanoate	-0.94	-14.87	13.26	-1.61	-2.55	-0.49	-14.98	13.24	-1.73	-2.23	-2.77
ethyl ethanoate	-0.86	-16.95	14.36	-2.59	-3.45	-0.51	-17.10	14.34	-2.76	-3.27	-3.33
propyl ethanoate	0.08	-19.58	15.34	-4.23	-4.15	0.05	-19.30	15.33	-3.97	-3.92	-4.12
methyl pentanoate	0.05	-20.77	16.17	-4.60	-4.54	0.02	-20.53	16.18	-4.35	-4.33	-4.93
butyl ethanoate	-0.77	-20.43	16.33	-4.11	-4.87	-0.39	-20.61	16.32	-4.29	-4.68	-4.93
methyl hexanoate	-0.50	-21.89	17.16	-4.73	-5.23	0.02	-22.27	17.16	-5.11	-5.08	-5.68
pentyl ethanoate	-0.72	-22.18	17.31	-4.86	-5.59	-0.43	-22.38	17.29	-5.08	-5.52	-5.50
propylamine	-0.80	-15.14	13.12	-2.02	-2.82	-0.57	-15.30	13.10	-2.19	-2.77	-3.00
butylamine	-0.74	-16.88	14.10	-2.78	-3.52	-0.55	-17.06	14.09	-2.97	-3.51	-3.37

ethanonitrile	-2.25	-11.63	11.47	-0.15	-2.40	-2.48	-11.67	11.44	-0.23	-2.71	-2.03
benzonitrile	-1.89	-18.03	14.46	-3.57	-5.46	-1.87	-18.07	14.44	-3.63	-5.50	-5.34
pyridine	-1.67	-15.98	13.13	-2.85	-4.52	-1.25	-16.07	13.11	-2.95	-4.21	-4.25
aniline	-2.07	-18.04	14.00	-4.04	-6.11	-1.64	-18.18	13.99	-4.19	-5.83	-5.38
fluorobenzene	-0.98	-16.67	13.66	-3.02	-3.99	-0.72	-16.70	13.63	-3.07	-3.79	-4.17
chlorobenzene	-0.97	-18.70	14.11	-4.59	-5.56	-0.62	-18.71	14.07	-4.64	-5.26	-5.19
<i>o</i> -dichlorobenzene	-0.98	-20.05	14.68	-5.36	-6.35	-0.66	-20.03	14.64	-5.39	-6.05	-6.18
<i>p</i> -dichlorobenzene	-0.80	-20.37	14.85	-5.52	-6.31	-0.51	-20.35	14.81	-5.53	-6.04	-6.16
bromobenzene	-1.02	-19.60	14.33	-5.27	-6.29	-0.65	-19.57	14.28	-5.29	-5.93	-5.75
<i>p</i> -dibromobenzene	-0.91	-22.49	15.43	-7.06	-7.97	-0.57	-22.46	15.40	-7.06	-7.63	-7.61
iodobenzene	-0.99	-20.51	14.58	-5.92	-6.92	-0.62	-20.40	14.50	-5.89	-6.52	-6.31
Mean Error	0.22		RMS Error	0.41		Mean Error	0.06		RMS Error	0.33	

TABLE A-4. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-octane test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
toluene	-0.97	-18.61	14.38	-4.23	-5.20	-0.60	-18.66	14.34	-4.31	-4.92	-4.74
methanol	-1.44	-10.75	10.86	0.11	-1.33	-1.34	-10.77	10.82	0.05	-1.29	-1.23
ethanol	-1.35	-12.92	12.03	-0.88	-2.23	-1.24	-12.96	12.00	-0.95	-2.20	-2.09
1-propanol	-1.25	-14.66	13.02	-1.64	-2.89	-1.18	-14.72	13.00	-1.73	-2.90	-2.74
1-butanol	-1.05	-16.18	13.95	-2.23	-3.28	-1.05	-16.28	13.94	-2.35	-3.39	-3.66
1-pentanol	-1.01	-17.93	14.94	-2.99	-4.00	-1.03	-18.04	14.92	-3.12	-4.15	-4.18
phenol	-2.31	-17.34	13.86	-3.49	-5.79	-1.81	-17.38	13.83	-3.54	-5.35	-5.22
1-hexanol	0.07	-20.65	15.89	-4.76	-4.69	0.06	-20.81	15.89	-4.92	-4.86	-4.91
<i>m</i> -cresol	0.15	-21.30	14.81	-6.49	-6.33	0.12	-20.83	14.77	-6.05	-5.93	-5.18
<i>o</i> -cresol	0.13	-20.69	14.62	-6.06	-5.94	0.09	-20.25	14.59	-5.66	-5.57	-6.21
<i>p</i> -cresol	0.15	-21.31	14.81	-6.50	-6.35	0.11	-20.81	14.78	-6.03	-5.92	-6.24
1-heptanol	0.07	-22.36	16.88	-5.49	-5.42	0.08	-22.57	16.88	-5.69	-5.62	-5.64
propanone	-1.72	-13.77	12.63	-1.14	-2.86	-1.72	-13.84	12.61	-1.22	-2.95	-2.39
butanone	-1.52	-15.57	13.59	-1.98	-3.50	-1.53	-15.67	13.58	-2.09	-3.62	-3.30
2-pentanone	-1.43	-17.31	14.57	-2.74	-4.17	-1.45	-17.43	14.57	-2.86	-4.31	-3.95
2-hexanone	-1.36	-19.03	15.55	-3.48	-4.84	-1.40	-19.16	15.54	-3.62	-5.02	-4.60
3,3-dimethylbutanone	0.10	-19.19	14.62	-4.56	-4.47	0.10	-19.40	14.63	-4.77	-4.67	-4.23
2-heptanone	0.10	-22.25	16.54	-5.71	-5.61	0.10	-22.48	16.54	-5.93	-5.83	-5.31
methyl propanoate	-0.70	-16.69	14.28	-2.41	-3.11	-0.26	-16.83	14.27	-2.56	-2.82	-3.56
methyl ethanoate	-0.96	-14.87	13.31	-1.56	-2.52	-0.50	-14.98	13.30	-1.68	-2.18	-2.86
ethyl ethanoate	-0.88	-16.95	14.42	-2.53	-3.41	-0.52	-17.10	14.40	-2.70	-3.22	-3.31
propyl ethanoate	0.07	-19.58	15.41	-4.17	-4.10	0.04	-19.30	15.40	-3.90	-3.87	-4.12
methyl pentanoate	0.04	-20.77	16.24	-4.53	-4.49	0.02	-20.53	16.25	-4.28	-4.26	-4.88
butyl ethanoate	-0.79	-20.43	16.40	-4.04	-4.82	-0.40	-20.61	16.39	-4.22	-4.62	-4.90
methyl hexanoate	-0.51	-21.89	17.23	-4.66	-5.17	0.02	-22.27	17.23	-5.03	-5.02	-5.58
pentyl ethanoate	-0.74	-22.18	17.38	-4.79	-5.54	-0.45	-22.38	17.36	-5.01	-5.46	-5.43
ethylamine	-0.87	-13.42	12.20	-1.23	-2.09	-0.61	-13.54	12.17	-1.37	-1.98	-2.01
propylamine	-0.81	-15.14	13.17	-1.97	-2.78	-0.58	-15.30	13.16	-2.14	-2.72	-2.97
butylamine	-0.76	-16.88	14.16	-2.72	-3.48	-0.56	-17.06	14.15	-2.91	-3.46	-3.48
diethylamine	-0.35	-17.34	14.41	-2.93	-3.28	-0.25	-17.47	14.39	-3.08	-3.33	-3.40
2-methylpyrazine	-1.93	-16.83	14.02	-2.81	-4.74	-1.58	-16.91	14.00	-2.91	-4.49	-4.64
aniline	-2.11	-18.04	14.06	-3.98	-6.09	-1.67	-18.18	14.04	-4.13	-5.81	-4.82
Mean Error	-0.09		RMS Error	0.40		Mean Error	0.00		RMS Error	0.41	

TABLE A-5. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-nonane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	$\Delta G_{\text{S}}^0(\text{expt})$
<i>n</i> -octane	0.12	-22.69	17.47	-5.22	-5.10	0.04	-22.86	17.46	-5.40	-5.36	-5.51
toluene	-0.98	-18.61	14.43	-4.18	-5.16	-0.60	-18.66	14.40	-4.26	-4.86	-4.89
methanol	-1.45	-10.75	10.90	0.15	-1.30	-1.35	-10.77	10.85	0.08	-1.27	-1.23
ethanol	-1.36	-12.92	12.07	-0.84	-2.20	-1.25	-12.96	12.05	-0.91	-2.16	-2.36
1-propanol	-1.27	-14.66	13.07	-1.59	-2.86	-1.19	-14.72	13.04	-1.68	-2.87	-2.74
1-butanol	-1.06	-16.18	14.00	-2.18	-3.24	-1.06	-16.28	13.99	-2.30	-3.35	-3.74
1-pentanol	-1.02	-17.93	14.99	-2.93	-3.96	-1.04	-18.04	14.98	-3.06	-4.10	-4.00
phenol	-2.33	-17.34	13.91	-3.44	-5.76	-1.83	-17.38	13.88	-3.49	-5.32	-5.22
1-hexanol	0.06	-20.65	15.95	-4.70	-4.65	0.05	-20.81	15.94	-4.86	-4.81	-5.03
<i>o</i> -cresol	0.11	-20.69	14.67	-6.01	-5.91	0.08	-20.25	14.64	-5.60	-5.52	-6.26
1-heptanol	0.06	-22.36	16.94	-5.43	-5.37	0.07	-22.57	16.94	-5.63	-5.57	-5.69
1,4-dioxane	-1.35	-15.26	13.55	-1.71	-3.06	-0.97	-15.37	13.53	-1.84	-2.81	-4.12
butanone	-1.54	-15.57	13.64	-1.94	-3.47	-1.55	-15.67	13.63	-2.04	-3.59	-3.38
2-pentanone	-1.44	-17.31	14.63	-2.69	-4.12	-1.47	-17.43	14.62	-2.81	-4.28	-3.95
2-hexanone	-1.37	-19.03	15.61	-3.43	-4.79	-1.41	-19.16	15.60	-3.56	-4.97	-4.59
3,3-dimethylbutanone	0.08	-19.19	14.68	-4.51	-4.44	0.08	-19.40	14.69	-4.72	-4.64	-4.20
2-heptanone	0.08	-22.25	16.60	-5.65	-5.57	0.09	-22.48	16.60	-5.88	-5.78	-5.29
methyl ethanoate	-0.98	-14.87	13.36	-1.51	-2.49	-0.50	-14.98	13.35	-1.63	-2.13	-2.82
ethyl ethanoate	-0.89	-16.95	14.47	-2.48	-3.37	-0.53	-17.10	14.45	-2.65	-3.18	-3.28
propyl ethanoate	0.05	-19.58	15.46	-4.12	-4.06	0.03	-19.30	15.45	-3.85	-3.82	-4.11
butyl ethanoate	-0.80	-20.43	16.45	-3.98	-4.78	-0.41	-20.61	16.45	-4.16	-4.57	-4.79
methyl pentanoate	0.03	-20.77	16.30	-4.47	-4.44	0.02	-20.53	16.30	-4.23	-4.21	-4.86
methyl hexanoate	-0.52	-21.89	17.29	-4.60	-5.12	0.03	-22.27	17.29	-4.97	-4.95	-5.55
pentyl ethanoate	-0.75	-22.18	17.44	-4.73	-5.49	-0.45	-22.38	17.43	-4.95	-5.40	-5.40
ethylamine	-0.88	-13.42	12.24	-1.18	-2.06	-0.62	-13.54	12.21	-1.33	-1.95	-1.94
propylamine	-0.82	-15.14	13.22	-1.92	-2.74	-0.59	-15.30	13.20	-2.09	-2.69	-2.93
butylamine	-0.77	-16.88	14.21	-2.67	-3.44	-0.56	-17.06	14.20	-2.86	-3.41	-3.48
Mean Error	0.09	RMS Error	0.34	Mean Error	0.14	RMS Error	0.42				

TABLE A-6. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-decane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	$\Delta G_{\text{S(expt)}}^0$
<i>n</i> -octane	0.12	-22.69	17.51	-5.18	-5.06	0.04	-22.86	17.50	-5.36	-5.32	-5.24
benzene	-1.01	-17.04	13.50	-3.55	-4.55	-0.60	-17.09	13.47	-3.61	-4.22	-3.83
toluene	-1.00	-18.61	14.46	-4.15	-5.15	-0.61	-18.66	14.43	-4.23	-4.84	-4.77
ethylbenzene	-0.89	-20.04	15.33	-4.71	-5.60	-0.56	-20.11	15.31	-4.81	-5.36	-5.14
methanol	-1.47	-10.75	10.92	0.17	-1.30	-1.37	-10.77	10.88	0.11	-1.26	-1.23
ethanol	-1.38	-12.92	12.10	-0.81	-2.19	-1.27	-12.96	12.07	-0.88	-2.16	-2.28
1-propanol	-1.29	-14.66	13.10	-1.56	-2.85	-1.21	-14.72	13.07	-1.65	-2.86	-2.74
1-butanol	-1.08	-16.18	14.03	-2.15	-3.23	-1.08	-16.28	14.02	-2.26	-3.34	-3.74
1-pentanol	-1.04	-17.93	15.03	-2.90	-3.94	-1.06	-18.04	15.01	-3.03	-4.09	-4.00
phenol	-2.37	-17.34	13.94	-3.40	-5.77	-1.86	-17.38	13.92	-3.46	-5.31	-5.13
1-hexanol	0.04	-20.65	15.99	-4.67	-4.62	0.03	-20.81	15.98	-4.83	-4.79	-5.03
<i>p</i> -cresol	0.10	-21.31	14.90	-6.41	-6.31	0.08	-20.81	14.86	-5.94	-5.87	-6.05
1-heptanol	0.05	-22.36	16.98	-5.39	-5.34	0.04	-22.57	16.98	-5.59	-5.55	-5.69
1,4-dioxane	-1.37	-15.26	13.58	-1.68	-3.05	-0.98	-15.37	13.56	-1.81	-2.79	-4.01
propanone	-1.77	-13.77	12.71	-1.06	-2.83	-1.76	-13.84	12.69	-1.15	-2.91	-2.40
butanone	-1.56	-15.57	13.67	-1.90	-3.46	-1.57	-15.67	13.66	-2.01	-3.58	-3.27
2-pentanone	-1.46	-17.31	14.66	-2.65	-4.11	-1.49	-17.43	14.65	-2.78	-4.27	-3.91
2-hexanone	-1.39	-19.03	15.64	-3.39	-4.78	-1.43	-19.16	15.63	-3.52	-4.96	-4.61
3,3-dimethylbutanone	0.06	-19.19	14.71	-4.48	-4.42	0.06	-19.40	14.72	-4.68	-4.62	-4.16
2-heptanone	0.06	-22.25	16.64	-5.61	-5.55	0.07	-22.48	16.64	-5.84	-5.76	-5.24
methyl ethanoate	-0.99	-14.87	13.39	-1.48	-2.47	-0.51	-14.98	13.38	-1.60	-2.11	-2.78
ethyl ethanoate	-0.91	-16.95	14.51	-2.44	-3.35	-0.53	-17.10	14.48	-2.62	-3.15	-3.26
propyl ethanoate	0.04	-19.58	15.50	-4.08	-4.04	0.02	-19.30	15.49	-3.81	-3.79	-4.05
methyl pentanoate	0.02	-20.77	16.34	-4.43	-4.41	0.01	-20.53	16.34	-4.19	-4.17	-4.78
butyl ethanoate	-0.81	-20.43	16.49	-3.94	-4.75	-0.41	-20.61	16.48	-4.12	-4.54	-4.76
methyl hexanoate	-0.52	-21.89	17.33	-4.56	-5.09	0.01	-22.27	17.33	-4.93	-4.92	-5.53
pentyl ethanoate	-0.76	-22.18	17.49	-4.69	-5.45	-0.45	-22.38	17.47	-4.91	-5.36	-5.39
ethylamine	-0.89	-13.42	12.27	-1.15	-2.04	-0.63	-13.54	12.24	-1.30	-1.93	-1.88
propylamine	-0.83	-15.14	13.25	-1.89	-2.72	-0.59	-15.30	13.23	-2.06	-2.66	-2.93
butylamine	-0.78	-16.88	14.24	-2.64	-3.42	-0.57	-17.06	14.23	-2.83	-3.39	-3.48
trichloroethene	-0.30	-17.32	13.49	-3.82	-4.13	-0.27	-17.22	13.43	-3.79	-4.06	-3.91
chlorobenzene	-1.01	-18.70	14.25	-4.45	-5.46	-0.64	-18.71	14.22	-4.49	-5.13	-4.97
bromobenzene	-1.06	-19.60	14.47	-5.13	-6.19	-0.67	-19.57	14.42	-5.14	-5.82	-5.46
fluorobenzene	-1.03	-16.67	13.79	-2.88	-3.91	-0.75	-16.70	13.77	-2.93	-3.68	-3.50
Mean Error	-0.07		RMS Error	0.38		Mean Error	0.02		RMS Error	0.37	

TABLE A-7. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-undecane test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
benzene	-1.01	-17.04	13.53	-3.51	-4.52	-0.60	-17.09	13.51	-3.58	-4.18	-4.08
toluene	-1.00	-18.61	14.49	-4.12	-5.12	-0.61	-18.66	14.46	-4.19	-4.81	-4.73
ethylbenzene	-0.89	-20.04	15.37	-4.68	-5.56	-0.56	-20.11	15.34	-4.77	-5.33	-5.33
trichloromethane	-0.54	-15.91	12.88	-3.04	-3.57	-0.64	-15.89	12.85	-3.04	-3.68	-3.55
1,2-dichloroethane	-0.75	-15.93	13.18	-2.75	-3.50	-0.77	-16.02	13.17	-2.84	-3.62	-3.71
1,1,1-trichloroethane	-0.58	-17.22	13.66	-3.56	-4.14	-0.52	-17.21	13.63	-3.58	-4.10	-3.79
E-1,2-dichloroethene	-0.36	-15.81	12.89	-2.92	-3.28	-0.34	-15.80	12.86	-2.94	-3.28	-3.62
trichloroethene	-0.30	-17.32	13.52	-3.79	-4.10	-0.27	-17.22	13.46	-3.76	-4.03	-3.94
tetrachloroethene	-0.03	-18.76	14.12	-4.64	-4.67	0.00	-18.65	14.07	-4.58	-4.58	-4.61
chlorobenzene	-1.01	-18.70	14.28	-4.42	-5.43	-0.65	-18.71	14.25	-4.46	-5.11	-5.16
<i>o</i> -dichlorobenzene	-1.03	-20.05	14.87	-5.18	-6.21	-0.69	-20.03	14.83	-5.20	-5.89	-6.28
tribromomethane	-0.23	-18.47	13.49	-4.97	-5.21	-0.24	-17.80	13.22	-4.57	-4.82	-5.01
Mean Error		-0.12	RMS Error		0.26	Mean Error		0.03	RMS Error		0.19

TABLE A-8. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-dodecane test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
ethanol	-1.40	-12.92	12.16	-0.76	-2.15	-1.28	-12.96	12.13	-0.83	-2.11	-2.01
1-propanol	-1.30	-14.66	13.16	-1.50	-2.80	-1.22	-14.72	13.13	-1.59	-2.81	-2.73
1-butanol	-1.09	-16.18	14.10	-2.08	-3.17	-1.09	-16.28	14.08	-2.20	-3.29	-3.44
1-pentanol	-1.05	-17.93	15.10	-2.83	-3.88	-1.07	-18.04	15.08	-2.96	-4.03	-4.13
1-hexanol	0.03	-20.65	16.06	-4.59	-4.56	0.03	-20.81	16.06	-4.75	-4.72	-4.33
1-heptanol	0.03	-22.36	17.06	-5.31	-5.28	0.04	-22.57	17.06	-5.52	-5.48	-5.48
acetophenone	-2.16	-19.80	15.45	-4.35	-6.51	-1.88	-19.89	15.44	-4.45	-6.33	-6.11
Mean Error		-0.02	RMS Error		0.24	Mean Error		-0.08	RMS Error		0.19

TABLE A-9. AM1 and PM3 calculated and experimental free energies of solvation(kcal/mol) for the *n*-tetradecane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	$\Delta G_{\text{S}}^0(\text{expt})$
phenol	-2.42	-17.34	14.05	-3.29	-5.71	-1.90	-17.38	14.03	-3.35	-5.24	-5.32
pyridine	-1.79	-15.98	13.37	-2.61	-4.40	-1.34	-16.07	13.36	-2.71	-4.05	-4.21
aniline	-2.21	-18.04	14.26	-3.78	-5.99	-1.76	-18.18	14.24	-3.93	-5.70	-5.31
Mean Error	-0.42		RMS Error	0.47		Mean Error	-0.05		RMS Error	0.25	

TABLE A-10. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the *n*-pentadecane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	$\Delta G_{\text{S}}^0(\text{expt})$
methyl propanoate	-0.74	-16.69	14.50	-2.19	-2.93	-0.43	-20.61	16.64	-3.97	-4.40	-3.34
methyl ethanoate	-1.02	-14.87	13.52	-1.35	-2.37	-0.55	-17.10	14.62	-2.48	-3.03	-2.62
ethyl ethanoate	-0.93	-16.95	14.64	-2.31	-3.24	-0.48	-22.38	17.63	-4.74	-5.22	-3.20
propyl ethanoate	0.02	-19.58	15.64	-3.93	-3.92	-0.53	-14.98	13.50	-1.48	-2.01	-3.94
methyl pentanoate	0.01	-20.77	16.49	-4.28	-4.27	-0.28	-16.83	14.49	-2.34	-2.62	-4.60
butyl ethanoate	-0.83	-20.43	16.65	-3.79	-4.61	0.00	-20.53	16.49	-4.03	-4.03	-4.58
methyl hexanoate	-0.54	-21.89	17.49	-4.40	-4.94	0.01	-19.30	15.63	-3.67	-3.66	-5.40
pentyl ethanoate	-0.78	-22.18	17.65	-4.53	-5.31	0.00	-22.27	17.50	-4.77	-4.77	-5.25
Mean Error	0.17		RMS Error	0.26		Mean Error	0.40		RMS Error	0.47	

TABLE A-11. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the 2-methylbutane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	$\Delta G_{\text{S(expt)}}^0$
ethanonitrile	2.13	-11.63	11.30	-0.32	-2.45	2.35	-11.67	11.27	-0.40	-2.75	-3.21
	Mean Error	0.77		RMS Error	na		Mean Error	0.46		RMS Error	na

TABLE A-12. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the 3-methylpentane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	$\Delta G_{\text{S(expt)}}^0$
phenol	-2.22	-17.34	13.72	-3.62	-5.84	-1.75	-17.38	13.70	-3.68	-5.42	-4.93
	Mean Error	-0.91		RMS Error	na		Mean Error	-0.49		RMS Error	na

TABLE A-13. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the 2,2,4-trimethylpentane test set.

	AM1					PM3					
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S}}^0(\text{SM4})$	$\Delta G_{\text{S(expt)}}$
<i>n</i> -pentane	0.04	-17.48	14.34	-3.14	-3.10	0.01	-17.59	14.31	-3.27	-3.27	-3.25
<i>n</i> -hexane	0.06	-19.21	15.31	-3.90	-3.84	0.02	-19.35	15.29	-4.05	-4.03	-3.12
<i>n</i> -octane	0.12	-22.69	17.26	-5.43	-5.31	0.04	-22.86	17.25	-5.61	-5.57	-5.50
propene	-0.23	-13.86	12.08	-1.78	-2.01	-0.12	-13.93	12.05	-1.88	-2.00	-1.57
1-butene	-0.17	-15.65	13.11	-2.53	-2.71	-0.09	-15.73	13.08	-2.64	-2.74	-2.29
1-pentene	-0.13	-17.38	14.09	-3.29	-3.42	-0.08	-17.48	14.06	-3.42	-3.50	-2.38
benzene	-0.98	-17.04	13.31	-3.74	-4.71	-0.58	-17.09	13.29	-3.80	-4.38	-4.04
toluene	-0.97	-18.61	14.26	-4.35	-5.32	-0.59	-18.66	14.23	-4.43	-5.02	-4.73
<i>m</i> -xylene	-0.96	-20.17	15.20	-4.96	-5.93	-0.61	-20.22	15.16	-5.06	-5.67	-5.02
ethanol	-1.34	-12.92	11.93	-0.98	-2.32	-1.23	-12.96	11.90	-1.05	-2.29	-2.35
1-propanol	-1.25	-14.66	12.91	-1.74	-3.00	-1.18	-14.72	12.89	-1.83	-3.01	-2.93
1-butanol	-1.05	-16.18	13.84	-2.35	-3.39	-1.05	-16.28	13.82	-2.46	-3.51	-3.52
1-pentanol	-1.01	-17.93	14.82	-3.11	-4.12	-1.03	-18.04	14.80	-3.24	-4.27	-4.25
phenol	-2.30	-17.34	13.74	-3.60	-5.90	-1.81	-17.38	13.72	-3.66	-5.46	-4.92
<i>o</i> -cresol	0.13	-20.69	14.50	-6.19	-6.06	0.09	-20.25	14.47	-5.78	-5.69	-5.73
<i>p</i> -cresol	0.15	-21.31	14.69	-6.62	-6.46	0.11	-20.81	14.65	-6.15	-6.04	-5.64
1,4-dioxane	-1.33	-15.26	13.39	-1.87	-3.20	-0.95	-15.37	13.37	-2.00	-2.95	-4.07
anisole	-1.46	-19.27	14.76	-4.51	-5.97	-0.95	-19.36	14.74	-4.63	-5.57	-5.22
butanal	-1.42	-15.56	13.48	-2.07	-3.50	-0.93	-15.65	13.48	-2.17	-3.10	-3.44
pentanal	-1.46	-17.24	14.53	-2.71	-4.17	-1.60	-17.34	14.51	-2.82	-4.42	-4.24
benzaldehyde	-2.09	-18.41	14.33	-4.08	-6.17	-1.81	-18.45	14.31	-4.14	-5.95	-5.45
propanone	-1.71	-13.77	12.53	-1.24	-2.95	-1.71	-13.84	12.51	-1.33	-3.04	-2.47
butanone	-1.52	-15.57	13.48	-2.10	-3.61	-1.52	-15.67	13.47	-2.20	-3.72	-3.45
2-pentanone	-1.42	-17.31	14.45	-2.86	-4.28	-1.45	-17.43	14.45	-2.98	-4.43	-4.18
2-hexanone	-1.35	-19.03	15.42	-3.61	-4.96	-1.39	-19.16	15.41	-3.74	-5.14	-4.72
acetophenone	-2.08	-19.80	15.16	-4.64	-6.72	-1.80	-19.89	15.15	-4.74	-6.54	-6.10
pyridine	-1.70	-15.98	13.08	-2.91	-4.60	-1.27	-16.07	13.06	-3.01	-4.28	-4.11
aniline	-2.11	-18.04	13.94	-4.10	-6.21	-1.67	-18.18	13.93	-4.25	-5.92	-5.20
benzonitrile	-1.92	-18.03	14.40	-3.63	-5.55	-1.90	-18.07	14.38	-3.69	-5.59	-5.46
ethanethiol	-0.66	-14.88	12.42	-2.47	-3.12	-0.51	-15.04	12.44	-2.60	-3.11	-2.97
thiophenol	-1.28	-19.36	14.20	-5.17	-6.44	-0.80	-19.48	14.22	-5.26	-6.06	-5.29
trichloromethane	-0.53	-15.91	12.66	-3.25	-3.78	-0.62	-15.89	12.64	-3.25	-3.87	-3.18
Mean Error		-0.38	RMS Error		0.59	Mean Error		-0.29	RMS Error		0.49

TABLE A-14. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the cyclohexane test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
propane	-0.02	-13.99	12.61	-1.38	-1.40	0.00	-14.07	12.58	-1.49	-1.49	-2.12
<i>n</i> -butane	0.02	-15.74	13.61	-2.13	-2.11	0.01	-15.83	13.58	-2.25	-2.24	-2.90
<i>n</i> -pentane	0.04	-17.48	14.60	-2.88	-2.84	0.01	-17.59	14.58	-3.01	-3.00	-3.54
cyclohexane	0.02	-17.01	14.28	-2.73	-2.71	0.01	-17.12	14.26	-2.85	-2.85	-4.47
benzene	-1.03	-17.04	13.55	-3.49	-4.52	-0.61	-17.09	13.53	-3.56	-4.17	-4.23
toluene	-1.01	-18.61	14.52	-4.09	-5.10	-0.62	-18.66	14.49	-4.17	-4.79	-4.48
<i>m</i> -xylene	-1.00	-20.17	15.48	-4.68	-5.69	-0.64	-20.22	15.44	-4.78	-5.42	-5.42
<i>o</i> -xylene	-1.04	-19.72	15.13	-4.58	-5.63	-0.66	-19.77	15.11	-4.67	-5.32	-5.58
naphthalene	-1.65	-21.39	15.60	-5.79	-7.44	-1.04	-21.44	15.58	-5.86	-6.89	-7.21
methanol	-1.50	-10.75	10.97	0.22	-1.28	-1.39	-10.77	10.92	0.15	-1.24	-1.23
ethanol	-1.40	-12.92	12.15	-0.76	-2.16	-1.29	-12.96	12.12	-0.83	-2.13	-2.04
1-propanol	-1.31	-14.66	13.15	-1.51	-2.82	-1.23	-14.72	13.13	-1.60	-2.82	-2.70
2-propanol	-0.97	-14.41	12.98	-1.43	-2.40	-0.95	-14.48	12.97	-1.51	-2.46	-2.32
1-butanol	-1.09	-16.18	14.09	-2.09	-3.18	-1.09	-16.28	14.08	-2.21	-3.29	-3.49
2-methyl-2-propanol	-0.91	-15.90	13.67	-2.23	-3.14	-0.90	-15.97	13.67	-2.30	-3.20	-2.86
1-pentanol	-1.05	-17.93	15.09	-2.84	-3.89	-1.07	-18.04	15.07	-2.97	-4.04	-3.69
phenol	-2.41	-17.34	14.00	-3.35	-5.75	-1.89	-17.38	13.97	-3.40	-5.29	-5.17
1-hexanol	0.02	-20.65	16.05	-4.60	-4.58	0.01	-20.81	16.05	-4.76	-4.75	-5.37
<i>m</i> -cresol	0.05	-21.30	14.96	-6.34	-6.29	0.05	-20.83	14.92	-5.91	-5.86	-5.18
<i>o</i> -cresol	0.04	-20.69	14.77	-5.92	-5.88	0.03	-20.25	14.74	-5.51	-5.48	-6.06
<i>p</i> -cresol	0.04	-21.31	14.96	-6.35	-6.30	0.04	-20.81	14.92	-5.88	-5.84	-5.94
1-heptanol	0.02	-22.36	17.05	-5.32	-5.29	0.02	-22.57	17.05	-5.53	-5.50	-6.10
diethylether	-0.66	-17.15	14.43	-2.72	-3.38	-0.49	-17.25	14.41	-2.84	-3.33	-2.86
anisole	-1.53	-19.27	15.03	-4.23	-5.77	-0.99	-19.36	15.01	-4.35	-5.34	-5.40
benzaldehyde	-2.19	-18.41	14.60	-3.81	-6.00	-1.90	-18.45	14.58	-3.88	-5.77	-5.71
propanone	-1.80	-13.77	12.76	-1.01	-2.81	-1.79	-13.84	12.74	-1.10	-2.89	-2.61
butanone	-1.59	-15.57	13.73	-1.85	-3.43	-1.59	-15.67	13.72	-1.96	-3.54	-3.43
2-pentanone	-1.49	-17.31	14.72	-2.59	-4.08	-1.51	-17.43	14.71	-2.72	-4.23	-4.18
3-pentanone	-1.38	-17.37	14.69	-2.69	-4.06	-1.39	-17.51	14.69	-2.82	-4.21	-4.29
2-hexanone	-1.42	-19.03	15.71	-3.32	-4.74	-1.46	-19.16	15.70	-3.46	-4.92	-4.78
3,3-dimethylbutanone	0.03	-19.19	14.77	-4.42	-4.39	0.03	-19.40	14.78	-4.62	-4.59	-4.44
2-heptanone	0.03	-22.25	16.70	-5.54	-5.51	0.03	-22.48	16.71	-5.77	-5.74	-5.53
acetophenone	-2.17	-19.80	15.44	-4.36	-6.53	-1.89	-19.89	15.43	-4.46	-6.35	-6.30
methyl propanoate	-0.74	-16.69	14.42	-2.26	-3.01	-0.27	-16.83	14.42	-2.41	-2.68	-3.70
methyl ethanoate	-1.01	-14.87	13.45	-1.42	-2.43	-0.52	-14.98	13.43	-1.55	-2.07	-2.86

ethyl ethanoate	-0.92	-16.95	14.57	-2.38	-3.30	-0.54	-17.10	14.54	-2.56	-3.10	-3.39
propyl ethanoate	0.02	-19.58	15.56	-4.02	-3.99	0.01	-19.30	15.55	-3.75	-3.74	-4.40
methyl pentanoate	0.01	-20.77	16.40	-4.37	-4.36	0.01	-20.53	16.41	-4.12	-4.11	-5.06
butyl ethanoate	-0.82	-20.43	16.56	-3.87	-4.69	-0.42	-20.61	16.55	-4.05	-4.48	-5.04
methyl hexanoate	-0.54	-21.89	17.40	-4.49	-5.03	0.02	-22.27	17.41	-4.86	-4.85	-5.80
pentyl ethanoate	-0.77	-22.18	17.56	-4.62	-5.39	-0.47	-22.38	17.54	-4.84	-5.30	-5.79
ethylamine	-0.90	-13.42	12.32	-1.10	-2.00	-0.64	-13.54	12.29	-1.25	-1.89	-2.01
trimethylamine	-0.61	-15.07	13.19	-1.87	-2.49	-0.22	-15.21	13.19	-2.01	-2.24	-2.62
butylamine	-0.79	-16.88	14.30	-2.58	-3.37	-0.57	-17.06	14.29	-2.77	-3.34	-3.65
diethylamine	-0.37	-17.34	14.56	-2.78	-3.15	-0.26	-17.47	14.53	-2.93	-3.20	-3.60
pyridine	-1.78	-15.98	13.32	-2.67	-4.44	-1.33	-16.07	13.30	-2.76	-4.10	-4.26
aniline	-2.20	-18.04	14.20	-3.84	-6.04	-1.74	-18.18	14.18	-3.99	-5.74	-5.51
2-methylpyridine	-1.79	-17.87	14.39	-3.48	-5.27	-1.29	-17.96	14.37	-3.59	-4.88	-5.03
4-methylpyridine	-1.78	-17.56	14.29	-3.27	-5.05	-1.36	-17.64	14.26	-3.38	-4.74	-5.21
ethanonitrile	-2.40	-11.63	11.64	0.01	-2.38	-2.65	-11.67	11.60	-0.07	-2.72	-1.84
propanethiol	-0.60	-16.63	13.64	-2.98	-3.59	-0.48	-16.79	13.67	-3.12	-3.60	-3.14
fluorobenzene	-1.05	-16.67	13.85	-2.82	-3.87	-0.77	-16.70	13.82	-2.87	-3.65	-3.61
1,1,1-trichloroethane	-0.59	-17.22	13.69	-3.53	-4.12	-0.52	-17.21	13.66	-3.56	-4.07	-4.05
1,2-dichloroethane	-0.76	-15.93	13.20	-2.73	-3.49	-0.79	-16.02	13.19	-2.82	-3.61	-4.08
chlorobenzene	-1.03	-18.70	14.31	-4.39	-5.42	-0.65	-18.71	14.27	-4.44	-5.09	-5.15
bromobenzene	-1.08	-19.60	14.53	-5.07	-6.15	-0.68	-19.57	14.48	-5.08	-5.77	-5.58
2,2,2-trifluoroethanol	-3.07	-12.44	12.97	0.53	-2.54	-2.95	-12.44	12.92	0.48	-2.47	-1.47
<i>m</i> -hydroxybenzaldehyde	-3.47	-18.73	15.04	-3.69	-7.16	-3.09	-18.76	15.02	-3.74	-6.83	-6.86
<i>p</i> -hydroxybenzaldehyde	-3.66	-18.72	15.04	-3.68	-7.34	-3.28	-18.76	15.02	-3.74	-7.02	-7.16
water	-1.64	-8.23	9.44	1.21	-0.43	-1.48	-8.26	9.43	1.18	-0.31	-0.33

Mean Error 0.02

RMS Error 0.50

Mean Error 0.14

RMS Error 0.48

TABLE A-15. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the methylcyclohexane test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
phenol	-2.40	-17.34	13.94	-3.40	-5.80	-1.89	-17.38	13.92	-3.46	-5.35	-5.03
trichloromethane	-0.55	-15.91	12.85	-3.06	-3.61	-0.64	-15.89	12.82	-3.07	-3.71	-3.88
Mean Error	-0.25		RMS Error	0.58		Mean Error	-0.08		RMS Error	0.26	

TABLE A-16. AM1 and PM3 calculated and experimental free energies of solvation (kcal/mol) for the decalin test set.

	AM1					PM3					$\Delta G_{S(\text{expt})}^0$
	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	ΔG_{ENP}	G_{CD}	G_{CS}	G_{CDS}	$\Delta G_{\text{S(SM4)}}^0$	
toluene	-1.10	-18.61	14.38	-4.23	-4.94	-0.68	-18.65	14.34	-4.31	-4.60	-4.80
phenol	-2.62	-17.34	13.86	-3.48	-3.54	-2.04	-17.36	13.83	-3.53	-3.11	-3.30
<i>m</i> -cresol	-2.57	-18.88	14.81	-4.07	-5.65	-2.02	-18.90	14.77	-4.13	-5.37	-5.51
<i>p</i> -cresol	-2.58	-18.89	14.81	-4.08	-6.89	-2.02	-18.92	14.78	-4.14	-6.64	-6.23
anisole	-1.67	-19.26	14.88	-4.38	-6.37	-1.07	-19.36	14.86	-4.50	-6.02	-5.78
acetophenone	-2.37	-19.80	15.29	-4.51	-3.22	-2.02	-19.88	15.27	-4.61	-2.80	-3.49
methyl propanoate	-0.82	-16.68	14.28	-2.41	-2.66	-0.24	-16.81	14.26	-2.55	-2.26	-2.70
methyl ethanoate	-1.11	-14.87	13.31	-1.56	-6.39	-0.58	-14.98	13.30	-1.68	-5.97	-5.28
ethyl ethanoate	-1.01	-16.95	14.42	-2.53	-5.65	-0.44	-17.08	14.41	-2.67	-5.29	-4.65
propyl ethanoate	-0.95	-18.69	15.41	-3.28	-5.71	-0.42	-18.83	15.39	-3.44	-5.75	-5.87
methyl pentanoate	-0.67	-20.15	16.24	-3.91	-7.01	-0.15	-20.33	16.24	-4.09	-6.55	-6.00
butyl ethanoate	-0.90	-20.44	16.40	-4.04	-6.10	-0.39	-20.60	16.39	-4.22	-5.58	-5.00
methyl hexanoate	-1.93	-21.90	17.23	-4.67	-6.05	-0.12	-22.08	17.22	-4.86	-5.57	-5.01
pentyl ethanoate	-0.86	-22.17	17.38	-4.79	-5.34	-0.39	-22.35	17.37	-4.98	-4.99	-4.29
aniline	-2.39	-18.04	14.06	-3.98	-4.09	-1.89	-18.16	14.04	-4.12	-3.84	-3.46
benzonitrile	-2.20	-18.03	14.52	-3.51	-4.23	-2.18	-18.07	14.50	-3.57	-3.86	-4.08
thioanisole	-1.58	-20.60	15.23	-5.37	-4.58	-1.29	-20.82	15.28	-5.54	-4.23	-4.85
fluorobenzene	-1.14	-16.67	13.71	-2.96	-6.64	-0.84	-16.69	13.68	-3.01	-6.15	-5.10
chlorobenzene	-1.12	-18.69	14.16	-4.53	-6.65	-0.71	-18.70	14.13	-4.57	-6.15	-5.72
bromobenzene	-1.17	-19.60	14.39	-5.21	-6.59	-0.75	-19.56	14.34	-5.23	-4.98	-5.55
iodobenzene	-1.15	-20.50	14.64	-5.86	-6.96	-0.72	-20.39	14.56	-5.83	-6.83	-5.57
Mean Error	-0.62		RMS Error	0.83		Mean Error	-0.20		RMS Error	0.58	