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# Calculation of Alkane to Water Solvation Free Energies Using Continuum Solvent Models

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The FDPB/ $\gamma$  method and the PARSE parameter set have been recently shown to provide a computationally efficient and accurate means of calculating hydration free energies.<sup>1</sup> In this paper this approach is extended to the treatment of the partitioning of various solute molecules between the gas phase, water, and alkane solvents. The FDPB/ $\gamma$  method treats the solute molecule as a polarizable cavity embedded in a dielectric continuum. The solute charge distribution is described in terms of point charges located at atomic nuclei. Electrostatic free energies are obtained from numerical (finite difference) solutions to the Poisson (or Poisson–Boltzmann) equation, while nonpolar contributions are treated with a surface area-dependent term proportional to a surface tension coefficient,  $\gamma$ . To apply the FDPB/ $\gamma$  method to nonaqueous phases, it is necessary to derive a continuum representation of solute–solvent interactions appropriate for such systems. It is argued in this work that solute cavities in nonpolar solvents are significantly larger than in aqueous media. The physical basis for the existence of an expanded cavity in nonpolar solvents is discussed. When an expanded cavity, described in terms of increased values for atomic radii, is incorporated into the FDPB/ $\gamma$  formalism, good agreement between calculated and experimental solvation free energies is obtained. A new PARSE parameter set is developed for the transfer of organic molecules between alkanes and water which yields an average absolute error in solvation free energies of 0.2 kcal/mol for the 18 small molecules for which the parameters were optimized.

## Introduction

Many important chemical and biological processes involve the partitioning of solute molecules between aqueous and organic phases. Theoretical treatments of such transfer processes have been based primarily on statistical approaches in which experimental partition coefficients are fit to group or atom-based parameters.<sup>2–5</sup> Although methods of this type are widely used and have been quite successful in a variety of applications, they do have a number of deficiencies that reduce their effectiveness for complex molecules. In particular, they fail to properly account for pairwise interactions between polar groups or for solvation phenomena near interfaces. Continuum solvation models provide a physically more complete treatment of solvation phenomena<sup>6</sup> and are used in this paper to treat the partitioning of organic molecules between the gas phase, nonpolar solvents, and water.

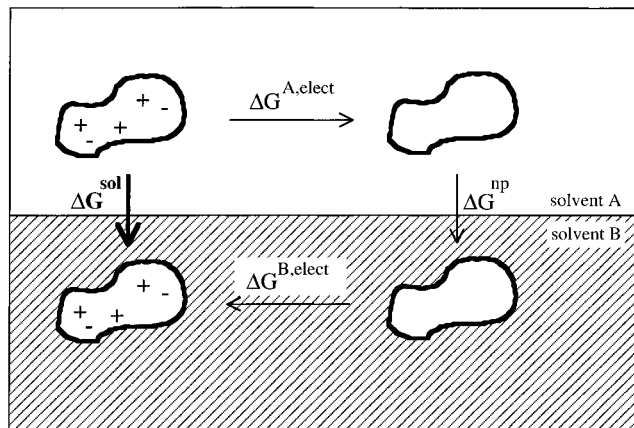
The physical model for the solvation process used in continuum models treats the solute as a low-dielectric cavity embedded in a solvent described as a medium of a given dielectric constant.<sup>7,8</sup> The solute charge distribution either is described in terms of fixed charges located at atomic nuclei<sup>9,10</sup> or is obtained from quantum mechanical calculations.<sup>11–15</sup> The fixed partial charges are often obtained from force fields derived for molecular mechanics calculations, while the cavity is defined as the volume enclosed by the molecular surface<sup>16</sup> of the solute. When identical descriptions of the solute are used, PB calculations have been shown to yield electrostatic contributions to gas phase to water solvation free energies that are in excellent agreement with the results of explicit solvent simulations, but at a fraction of the computational cost.<sup>17,18</sup> The continuum treatment of nonelectrostatic contributions to solvation free energies assumes that these are proportional to accessible surface area with a proportionality, or surface tension, coefficient,  $\gamma$ ,

derived from the solubility properties of nonpolar hydrocarbons.<sup>1</sup> When these are added to the electrostatic contributions derived from finite difference solutions to the PB equation (the FDPB/ $\gamma$  method), solvation free energies that can be compared to experiment are obtained. This approach, combined with a recently derived parameter set (e.g. PARSE<sup>1</sup> or CFF91<sup>19</sup>), yields accurate solvation free energies of small organic molecules in water. In this paper we extend the FDPB/ $\gamma$  method to alkane solvents.

Some aspects of the extension are straightforward. Solvent properties are described in terms of an appropriate dielectric constant and surface tension, while solvent effects on solute charge distribution are accounted for through the use of an appropriate solute dielectric constant<sup>20</sup> or with a quantum mechanical solute treatment.<sup>12–15,21,22</sup> However, a major complexity arises in the definition of the solute cavity size. There is of course no unique definition, at the microscopic level, of the dielectric boundary between the solute and solvent, but the choice of cavity size might be expected to depend on the size and shape of both solvent and solute molecules and on the nature of the interaction between them. Rashin and Honig demonstrated that cavity size in water could be defined in a physically meaningful way if the solute cavity was assumed to extend out to a point where the electron density of the solvent molecules becomes significant.<sup>23</sup> For polar atoms in water the atomic radii used to define the cavity correspond closely to van der Waals radii; however, this convenient result need not be true in general. Indeed, as will be shown below, it is not the case for organic solvents. This does not suggest a breakdown in continuum theory but rather is consistent with the requirement that cavity size, which is a crucial variable in continuum theory, be defined in a physically meaningful way.

Calculations are reported below for the free energy of transfer between vacuum to liquid alkane and liquid alkane to water phases for 18 small molecules containing chemical groups

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**Figure 1.** Thermodynamic cycle used to calculate the free energy of transferring a solute between solvent A and solvent B. The electrostatic ( $\Delta G^{\text{A,elect}} + \Delta G^{\text{B,elect}}$ ) and nonpolar ( $\Delta G^{\text{np}}$ ) contributions are summed to yield the total solvation free energy ( $\Delta G^{\text{sol}}$ ). The process is described in detail in the text.

present in amino acid side chains. For the majority of the molecules we find that good agreement between calculated and experimental transfer free energies can be obtained using a solvent-dependent adjustment of the cavity size which is consistent with electron density profiles obtained from *ab initio* quantum mechanical calculations. A new set of charge parameters based on the group contribution approach used in PARSE is developed to enable rapid and accurate calculation of liquid alkane to water transfer free energies for the complete set of test molecules.

## Theory and Methods

**Calculation of Solvation Free Energies.** The transfer of a molecule between two solvent phases is divided into a series of separate steps, as shown in the thermodynamic cycle in Figure 1. The procedure is identical to that used in previous work to calculate vacuum to water transfer free energies;<sup>1</sup> however, here the method is generalized to represent transfer between any two solvents of interest. In the first step, the molecule is discharged in solvent A, with an electrostatic free energy change  $\Delta G^{\text{A,elect}}$ . The hypothetical nonpolar molecule formed in this process is then transferred into solvent B, with a free energy change given by  $\Delta G^{\text{np}}$ . In the subsequent step, the solute is recharged in solvent B, with an electrostatic free energy change  $\Delta G^{\text{B,elect}}$ . The total solvation free energy,  $\Delta G^{\text{sol}}$ , is obtained as the sum of the free energies of the separate steps:

$$\Delta G^{\text{sol}} = \Delta G^{\text{A,elect}} + \Delta G^{\text{B,elect}} + \Delta G^{\text{np}} \quad (1)$$

**Electrostatic Contribution.** As in standard applications of the FDPB approach, the solute is represented as a collection of atomic-centered partial charges embedded in a solute-shaped cavity, surrounded by a dielectric medium representing the solvent. The solvent dielectric constant is assigned its experimental value, e.g. 1 for the gas phase, 80 for water, and 2 for liquid alkanes.<sup>24</sup> In accordance with previous work,<sup>20</sup> solute polarizability is accounted for by setting the solute dielectric constant to 2, a value consistent with the high-frequency dielectric constant of small organic molecules. The boundary between solute and solvent is defined by the distance of closest approach of the surface of a solvent-sized molecule to the solute. The input parameters to the PB equation are defined by mapping the spatially varying charge and dielectric constant onto a three-dimensional lattice. The equation is then solved for electrostatic

potential using the finite difference methods<sup>25</sup> implemented in the DelPhi program.<sup>26</sup>

The electrostatic contribution to the solvation free energy is equal to the difference in electrostatic free energy of the solute in the two solvents, A and B.

$$\Delta G_{\text{electrostatic}} = \frac{1}{2} \sum_i q_i (\phi_i^{\text{B}} - \phi_i^{\text{A}}) \quad (2)$$

where  $q_i$  and  $\phi_i$  are the atomic charges and calculated potentials at the  $i$ th grid point. Alternatively, the potentials across the solute-solvent dielectric boundary can be translated into effective charges located at the molecular surface.<sup>27</sup> This formulation increases the precision of the FDPB calculations since the effective charges at the molecular surface reduce the grid dependence of the results (A. Nicholls, unpublished results). The electrostatic contribution to the solvation free energy is then calculated through the change in interaction energy of the solute charges with the surface charges:

$$\Delta G_{\text{electrostatic}} = \frac{1}{2} \sum_{i,\sigma} \frac{q_i (q_{\sigma}^{\text{B}} - q_{\sigma}^{\text{A}})}{\epsilon_{\text{in}} r_{i\sigma}} \quad (3)$$

where  $q_i$  are the fixed charges of the solute placed at atomic nuclei;  $q_{\sigma}$  represents the induced surface charges;  $\epsilon_{\text{in}}$  is the solute dielectric constant; and  $r_{i\sigma}$  are the distances between the atomic and effective surface charges. All calculations reported in this work are based on eq 3. DelPhi runs were carried out at a resolution of 4 grids/Å. Results for molecules of the size studied here are invariant to within 0.2 kcal/mol for lattice spacings between 2 and 5 grids/Å.

**Nonpolar Contribution.** The nonpolar contribution to the solvation free energy is assumed to be proportional to the accessible surface area<sup>28-30</sup> and is given by the expression

$$\Delta G_{\text{np}} = \gamma A + b \quad (4)$$

where  $A$  is the solvent accessible surface area,  $\gamma$  is a surface area proportionality constant (referred to here as a surface tension), and  $b$  is a constant. Values for  $\gamma$  and  $b$  were obtained from least squares fits to plots of experimental transfer free energies versus calculated accessible surface areas for small alkane solutes. Recent work has suggested that there may be significant volume-dependent contributions to transfer processes involving at least one phase which consists of chainlike molecules such as linear alkanes.<sup>31,32</sup> Since molar volume is roughly proportional to accessible surface area for small molecules, molar volume effects are implicitly incorporated in the value of  $\gamma$  obtained by fitting to experimental data (see Sitkoff et al.<sup>1</sup> for further discussion of this issue). The effects of volume-dependent contributions to solubility are considered further below.

The existence of a nonzero intercept in eq 4 has been criticized on the grounds that a molecule with a zero accessible area would have a nonzero transfer free energy.<sup>33</sup> However, a nonzero intercept is in fact physically meaningful and can be associated with the transfer free energy of a "hard point" of zero volume. Such a term appears, for example, in scaled particle theory,<sup>34</sup> and there is no formal justification for its neglect. However, as has been pointed out,<sup>33</sup> use of a nonzero intercept does introduce complications for processes such as binding reactions, where the number of species on each side of an equation is different. We are not aware of a formal theory that describes how to deal with this issue, but for the single-

**TABLE 1: Organic Solvent to Water Transfer Free Energies<sup>a</sup>**

molecule	aacid	$\Delta G_{\text{total}}$			
		chx $\rightarrow$ w <sup>b</sup>	chx $\rightarrow$ w <sup>c</sup>	C <sub>6</sub> -C <sub>8</sub> $\rightarrow$ w <sup>g</sup>	CCl <sub>4</sub> $\rightarrow$ w <sup>h</sup>
<i>N</i> -propylguanidine	arg	-5.85			
acetamide	asn	-6.64			
acetic acid	asp	-4.44	-4.28, <sup>d</sup> -1.9 <sup>d</sup>	-3.88	-2.93
methylthiol	cys	1.28			
propionamide	gln	-5.54			
propionic acid	glu	-3.04	-3.45, <sup>e</sup> -3.35, <sup>d</sup> -1.09 <sup>d</sup>	-3.48	-2.31
methylimidazole	his	-4.61			
butylamine	lys	-0.38	-0.39 <sup>e</sup>		
methyl ethyl sulfide	met	2.35			
toluene	phe	2.98	3.98 <sup>d</sup>	3.89	
methanol	ser	-3.40	-3.81, <sup>d</sup> -2.50 <sup>d</sup>	-3.82, -2.03	-2.86
ethanol	thr	-2.57	-2.9, <sup>e</sup> -1.16 <sup>e</sup>	-2.91, -1.80	-2.61
methylindole	trp	2.33	2.41 <sup>f</sup>		
<i>p</i> -cresole	tyr	-0.14	-0.29 <sup>e</sup>	-0.48	
acetone			-1.31 <sup>e</sup>	-1.25	-0.46
propanol			-2.09 <sup>e</sup>	-2.05, -1.56	-1.19
butanol			-1.19 <sup>e</sup>	-1.03	-0.55
phenol			-1.07 <sup>e</sup>	-1.12	-0.61

<sup>a</sup> Energies are in kcal/mol. <sup>b</sup> Experimental values for cyclohexane to water transfer from Radzicka and Wolfenden.<sup>41</sup> <sup>c</sup> Experimental values for alkane to water transfer. <sup>d</sup> Reference 43. <sup>e</sup> Average of experimental values for cyclohexane to water transfer from ref 2. <sup>f</sup> Reference 42. <sup>g</sup> Average of experimental values for hexane, heptane, and octane to water transfer from ref 2. <sup>h</sup> Average of experimental values for carbon tetrachloride to water transfer from ref 2.

molecule transfers considered in this paper, the use of a nonzero intercept appears to be well-justified.

Accessible surface areas were calculated using a computationally efficient program which implements a modified Shrake and Rupley vertex algorithm,<sup>35</sup> using a hierarchical data structure.<sup>36</sup> The same solute radii are used in the calculation of electrostatic free energies and solvent accessible surface area. For the vacuum to water and liquid alkane to water transfer processes, a probe size of 1.4 Å was used. For the vacuum to liquid alkane process a probe radius of 2.0 Å, which approximates the radius of a methyl group, was used.

**Generating Coordinates.** Structures of 18 small organic molecules containing chemical groups related to the neutral amino acid side chains and backbone (see Table 1) were obtained via the BUILD and energy minimization tools in the Insight/Discover molecular modeling package (Biosym Technologies, Inc.). The CVFF force field and gas phase conditions were used. Geometries were considered to be invariant among the solvent phases.

**Molecular Dynamics Calculations.** To obtain an objective measure of the position of the solute/solvent boundary in aqueous versus nonpolar solvents, molecular dynamics (MD) simulations followed by a quantum mechanical calculation were used to estimate an appropriate "cavity radius" for solute atoms. A solute molecule (acetone) was built and energy minimized in the gas phase using the Insight/Discover molecular modeling package (Biosym Technologies, Inc.). The solute was then embedded in either water or methane solvent. For the case in which the solvent was water, a 5 Å thick solvent shell was built around the solute using the Insight Soak command. This procedure superimposes the solute molecule on a box of water at room temperature density and deletes water molecules that are either in van der Waals overlap with the solute or greater than 5 Å from the solute surface. The 5 Å thickness corresponds to a solvation layer of approximately two water molecules.

Molecular dynamic calculations were carried out using Discover at room temperature for 0.5 ps to equilibrate the system. The system was subsequently energy minimized using the quasi-Newton-Raphson algorithm. To model a liquid alkane solvent, the procedure was repeated except that after soaking the solute with water the water molecules were replaced with methanes. The distance from the acetone oxygen to the nearest

solvent hydrogen atom was noted for both the water and methane solvent cases.

**Quantum Mechanical Calculations.** Electron densities were obtained from the PSGVB program<sup>37</sup> with the 6-31G\*\* basis set at the GVB-PP level. Electron density was assigned to a cubic grid of spacing 0.05 Å. The use of a grid of this scale leads to recovery of electron density to within 0.05% or 0.02 electron unit of the expected value.<sup>38</sup> The electron densities for the solute and solvent molecules were subsequently placed onto a coarser grid of spacing 0.2 Å using the trilinear interpolation method and were displayed as contours using the program GRASP.<sup>39</sup>

**Experimental Data.** Transfer free energies of alkanes between vacuum and water were obtained from the expression

$$\Delta G_{v \rightarrow w} = -RT \ln(C_w/C_v) \quad (5)$$

where  $C_w$  and  $C_v$  are the measured concentrations of solute in the two phases expressed in units of molarity.<sup>40</sup> For vacuum to liquid alkane transfers, experimental free energies of vaporization from the alkane liquid were used where available.<sup>40</sup> The remaining vacuum to liquid alkane transfer free energies were calculated from measured vapor pressures through the expression

$$\Delta G_{v \rightarrow l} = -RT \ln(\rho_l/\rho_v) \quad (6)$$

where  $\rho_l$  and  $\rho_v$  are the densities in the liquid and vacuum phases, respectively. Molar volume and vapor pressure data were taken from the *CRC Handbook of Chemistry and Physics*.<sup>24</sup> Finally, for the liquid alkane to water transfer process, transfer free energies were obtained by subtracting the vacuum to water and vacuum to alkane transfer free energies. Liquid alkane to water transfer free energies also appear in the tables of Hansch and Leo;<sup>2</sup> these values agreed with those calculated here to within 0.1 kcal/mol.

Liquid alkane to water transfer free energies for the 18 molecules noted above are shown in Table 1. As a gauge of the accuracy of the values, data taken from several sources are included.<sup>2,41-43</sup> In addition, the data include transfer free energies from a range of liquid alkanes (cyclohexane, hexane, heptane, octane). In some cases, there are significant differences between the values reported by Radzicka and Wolfenden<sup>41</sup> and

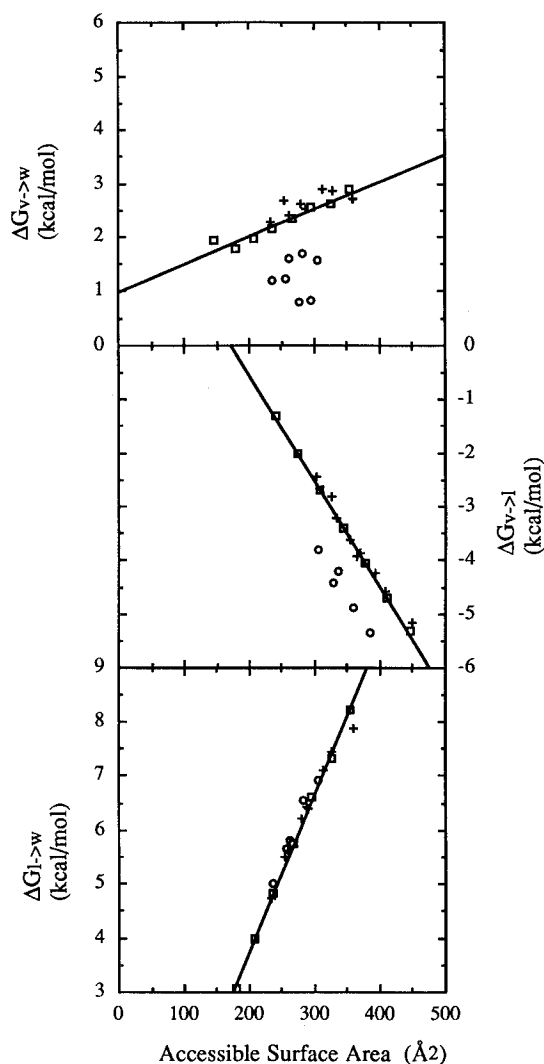
those obtained from other sources; however, with the exception of toluene, at least one of the alternate measurements is within 0.5 kcal/mol of the Radzicka and Wolfenden values. Additionally, the hexane/heptane/octane to water energies are within 0.6 kcal/mol of the Radzicka and Wolfenden, and Hansch and Leo<sup>2</sup> cyclohexane values, again except in the case of toluene, for which the discrepancy is 0.9 kcal/mol. The hexane/heptane/octane to water and the alternate cyclohexane to water values for toluene are in agreement to within 0.1 kcal/mol. We have retained both cyclohexane values in our comparisons of calculated and experimental free energies for toluene. For the remainder of the molecules, the cyclohexane transfer data from Radzicka and Wolfenden (for the 14 amino acid side chain models) or Hansch and Leo (the four remaining solutes) were used exclusively. Vacuum to cyclohexane transfer free energies were obtained by subtracting cyclohexane to water values from the vacuum to water values reported by Wolfenden et al.<sup>44</sup> and Cabani et al.<sup>3</sup>

Carbon tetrachloride (CCl<sub>4</sub>) to water transfer free energies are also shown in Table 1. As can be seen from the table, the measured values are approximately 0.5–1.0 kcal/mol less favorable than the liquid alkane to water transfer free energies. There is not sufficient experimental data (specifically transfer free energies of alkanes between CCl<sub>4</sub> and water) to determine whether the difference between CCl<sub>4</sub> and alkane solvents results from the disparity between the dielectric constants of CCl<sub>4</sub> and liquid alkanes (about 2.4 versus 2.0), differences in the nonpolar surface tension values, or other effects that may be missing from our model. However, it is important to be aware of the differences between alkane solvents and CCl<sub>4</sub> because they are sometimes used interchangeably to model the effects of a nonpolar solvent phase.

## Results

**Deriving Surface Tension Values from Alkane Transfer Data.** Transfer free energies from vacuum to water, vacuum to liquid alkane, and liquid alkane to water are plotted in Figure 2 versus accessible surface area for a series of alkanes listed in the figure caption. As has been noted previously, not all of the experimental data can satisfactorily be described with eq 4.<sup>1,45</sup> For the vacuum to water (Figure 2a) and vacuum to liquid alkane (Figure 2b) transfers, the cyclic alkanes clearly do not fall on the line that fits the linear and branched alkane data. In particular, the cyclic alkanes are more soluble in water than linear and branched alkanes with the same surface area, while in contrast, the cyclic alkanes have less negative vacuum to pure liquid transfer free energies than the other compounds. Remarkably, and probably fortuitously, the two effects appear to be of comparable magnitude and opposite sign so that liquid alkane to water transfer free energies for all compounds can be fit to a single line (Figure 2c). It is interesting that the same trends are observed on a macroscopic scale where vacuum/liquid alkane surface tensions are larger for cyclic than for linear and branched alkanes, whereas alkane/water interfacial free energies are approximately the same for all alkanes.<sup>46</sup>

That linear alkanes are more volatile than cyclic alkanes is consistent with the results of recent derivations of Flory–Huggins theory which predict that the chemical potential of any solute will be increased in phases of chainlike molecules by a factor that is proportional to the molar volume of the solute.<sup>31,32</sup> However, that cyclic alkanes are more soluble in water than linear alkanes with the same accessible surface area cannot be understood on this basis. Indeed, we are unaware of any successful attempt to explain this phenomenon. To remain consistent with previous work, we obtained values for  $\gamma$  and  $b$



**Figure 2.** Dependence of experimental vacuum to water (a, top), vacuum to liquid alkane (b, middle) and liquid alkane to water (c, bottom) solvation free energies on calculated solvent accessible surface area for alkanes of varying shapes. Molecules include methane through octane; isobutane, isopentane, neopentane, isohexane, 3-methylpentane, neohexane, 2,4-dimethylpentane, isooctane, and 2,2,5-trimethylhexane; cyclopentane, cyclohexane, methylcyclopentane, methylcyclohexane, 1,2-dimethylcyclohexane, cycloheptane, and cyclooctane: linear alkanes (□), branched alkanes (+), cyclic alkanes (○). Solid lines are the least squares fit lines to straight alkanes only:  $\Delta G(v \rightarrow w) = 0.005A + 0.92$ .  $\Delta G(v \rightarrow l) = -0.019A + 3.26$ .  $\Delta G(l \rightarrow w) = 0.028A - 1.71$ . ( $A$  = accessible surface area.) Experimental solvation data are from Ben-Naim and Marcus (1984).<sup>40</sup> Accessible surface areas were calculated using a probe radius of 1.4 Å for graphs a and c and 2.0 Å for graph b.

by fitting to linear alkane data alone. The inclusion of branched alkanes leads to changes of less than 0.1 kcal/mol in total calculated solvation energies. Values of  $\gamma$  and  $b$  (in units of cal/(mol·Å²) and kcal/mol, respectively) obtained from Figure 2 are, respectively, 5.5 and 0.92 for the vacuum to water, 27.8 and -1.71 for liquid alkane to water, and -19.3 and 3.26 for vacuum to liquid alkane transfers. Note that the values derived for liquid alkane to water are appropriate for cyclic alkanes as well since in this case the data for all molecules can be fit to a single line.

**Determination of Solute Cavity Size in Organic Solvents.** Vacuum to liquid alkane and liquid alkane to water transfer free energies were calculated using the FDPB/ $\gamma$  method and PARSE parameters for 18 small molecules representing the neutral amino acid side chains and related chemical groups. An average deviation from experiment of about 1.5 kcal/mol was

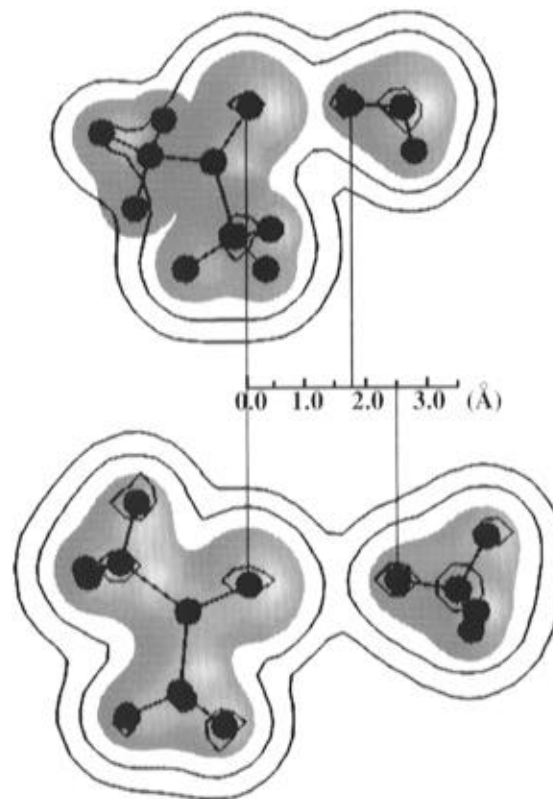
obtained, whereas for the same set of molecules, the PARSE parameters yield an average error of only 0.1 kcal/mol for vacuum to water transfer. The sign of the deviations was such that cyclohexane could be viewed as solvating polar groups less effectively than predicted from dielectric continuum theory. For example, the "experimental" electrostatic contribution to cyclohexane to water transfer free energies (obtained by subtracting calculated nonpolar transfer free energies from the total experimental transfer free energies) was, for most molecules, approximately 90% of the corresponding gas phase to water values. By carrying out solvation free energy calculations with a recently derived self-consistent quantum mechanical solute/continuum solvent treatment,<sup>15</sup> we verified that the source of the error could not be attributed to an inadequate description of the solute charge distribution. Indeed, the results using PARSE parameters or the quantum mechanical treatment were quite similar. A more likely possibility is that the size of the solute cavity is very different in different solvents.

As mentioned above, Rashin and Honig<sup>23</sup> argued that the electron density profile of solvent molecules provides a physically meaningful definition of cavity size since electron density provides a measure of the distance from the solute at which the dielectric response of the solvent can become significant. Moreover, Born radii derived on this basis yielded hydration free energies of both anions and cations that were in excellent agreement with experiment. It was shown that cavity size for a given atom type should be related to (but less than) the internuclear separation of the solute atom from the nearest solvent nucleus. Since the van der Waals radius of a methane molecule is about 0.7 Å greater than that of water, one might expect the effective cavity around each solute atom to be about 0.7 Å greater in alkane solvent than in water.

To test this idea in greater detail, we have determined the distance from the nucleus of the carbonyl oxygen in acetone at which the electron densities of a water hydrogen and methane hydrogen are equivalent. As described above, a system consisting of an acetone molecule surrounded by a 5 Å shell of water molecules was equilibrated with a brief molecular dynamics simulation followed by an energy minimization. The distances between the acetone oxygen and the closest solvent hydrogen are 1.82 and 2.50 Å for the water and methane solvents, respectively, suggesting that the cavity formed by a carbonyl oxygen in an alkane solvent is approximately 0.68 Å larger than that formed in water, a result consistent with the qualitative arguments of the previous paragraph.

We have carried out quantum mechanical calculations of electron density for acetone and the nearest solvent molecule for the energy-minimized configuration derived from the MD simulations. Electron density contour lines at 0.25, 0.0625, and 0.0125 electron/Å<sup>3</sup> are shown in Figure 3 for acetone/water and acetone/methane. Depending on which contour level is used, the distance from the oxygen nucleus increases by between 0.7 and 0.9 Å on going from water to methane. That the distance increases somewhat above the prediction based on internuclear separation alone results from a buildup of electron density in the hydrogen bond formed in the aqueous solvent and the absence of this effect in methane.

The analysis presented in this section suggests that cavity sizes in alkane solvents are significantly larger than in water. Since solute cavities are defined in terms of atomic radii, it is convenient to define a set of "cavity radii" which together produce a molecular surface which defines an effective cavity in a particular solvent. The results reported in this section indicate that cavity radii in alkane solvents should be on the order of 0.7 Å larger than in water. Thus, the relative inability



**Figure 3.** Electron density contours for acetone/water (upper panel) and acetone/methane (lower panel), calculated using PSGVB<sup>37</sup> and displayed using GRASP.<sup>39</sup> The highest electron density (0.25 electrons/Å<sup>3</sup>) is shown as a shaded 3D surface; two lower density contours (0.0125 and 0.0625 electrons/Å<sup>3</sup>) are shown in two-dimensional representation. The distance in angstroms refers to both panels.

of cyclohexane to solvate polar groups is due not only to its low dielectric constant but also to the large (relative to water) cavities formed in this solvent by polar molecules.

**Vacuum to Cyclohexane Transfer Free Energies.** To describe a solute cavity in cyclohexane in a manner consistent with the results of the previous section, all atomic radii were uniformly increased by a constant value in the range 0.6–0.9 Å. (We have preferred this simple option over the use of a different radius increment for each atom, which would have led to a significant increase in the total number of independent parameters.) The new radii were used in both the vacuum and cyclohexane phases and were used to derive new values for  $\gamma$  and  $b$ . The best fit to experimental data was obtained when all radii were increased by 0.7 Å. As shown in Table 2, calculated solvation energies are within 0.5 kcal/mol of the experimental values for all but a subset consisting of the aromatic and sulfur-containing molecules (methylimidazole, phenol, *p*-cresole, toluene and methylindole, methylthiol, methyl ethyl sulfide). Similar results were obtained using the combined quantum mechanical/continuum approach,<sup>15</sup> although in this case, optimal results were obtained with a uniform increase in atomic radii of 0.6 Å (results not shown).

A possible explanation for the errors observed for the aromatic molecules is that the nonpolar solvation free energy contribution has been incorrectly estimated. As described above, the nonpolar contribution was calculated for all the molecules using  $\gamma$  and  $b$  parameters derived from the transfer free energies of linear and branched alkanes. However, the solvation free energies of cyclic alkanes might be a more appropriate model for the nonpolar contribution of aromatic rings. As shown in Figure 2, vacuum to liquid transfer free energies of cyclic alkanes are approximately 1.3 kcal/mol more negative than the

TABLE 2: Vacuum to Cyclohexane Solvation Free Energies<sup>a</sup>

molecule	aacid	$\Delta G_{el}$	SA	$\Delta G_{np}$	$\Delta G_{t,calc}$	$\Delta G_{t,exp}^b$	$\Delta G_{err}$
<i>N</i> -propylguanidine	arg	-1.04	467	-3.75	-4.78	-5.07	0.29
acetamide	asn	-1.46	349	-1.78	-3.25	-3.08	-0.17
acetic acid	asp	-0.82	344	-1.71	-2.53	-2.26	-0.27
methylthiol	cys	-0.36	326	-1.40	-1.76	-2.52	0.76
propionamide	gln	-1.40	390	-2.47	-3.87	-3.88	0.01
propionic acid	glu	-0.81	386	-2.41	-3.22	-3.43	0.21
methylimidazole	his	-1.50	399	-2.63	-4.12	-5.64	1.52
butylamine	lys	-0.60	426	-3.06	-3.66	-4.00	0.34
methyl ethyl sulfide	met	-0.52	411	-2.83	-3.34	-3.84	0.50
toluene	phe	-0.25	434	-3.21	-3.46	-3.74, -4.74 <sup>c</sup>	0.28, 1.28
methanol	ser	-0.70	296	-0.90	-1.60	-1.68	0.08
ethanol	thr	-0.66	339	-1.63	-2.29	-2.33	0.04
methylindole	trp	-0.73	487	-4.08	-4.80	-8.24	3.44
<i>p</i> -cresole	tyr	-0.75	452	-3.50	-4.25	-5.99	1.74
acetone		-0.80	371	-2.15	-2.95	-2.54	-0.41
propanol		-0.66	379	-2.29	-2.94	-2.76	-0.18
butanol		-0.65	419	-2.95	-3.60	-3.70	0.10
phenol		-0.75	407	-2.76	-3.51	-5.53	2.02
						av err	0.57
						av abs err	0.69
						max err	3.44

<sup>a</sup> Calculations carried out using the FDPB/ $\gamma$  method for (solute,solvent) dielectric values of (2,1) and (2,2), with PARSE charges and PARSE radii increased by 0.7 Å. Nonpolar transfer free energie ( $\Delta G_{np}$ ) were obtained using eq 4 with  $\gamma = -16.6$  cal/(mol·Å<sup>2</sup>) and  $b = 4.01$  kcal/mol.  $\gamma$  and  $b$  were derived from a least squares fit to a plot of experimental transfer free energies versus calculated accessible surface area (SA) for alkanes, as described in the Theory and Methods section, where SA was computed using PARSE radii increased by 0.7 Å and a probe size of 2.0 Å. Additional abbreviations:  $\Delta G_{el}$  = calculated electrostatic solvation free energy.  $\Delta G_t$  = total calculated or experimental transfer free energy.  $\Delta G_{err} = \Delta G_{t,calc} - \Delta G_{t,exp}$ . Energies are in kcal/mol. <sup>b</sup> Experimental values from ref 41. <sup>c</sup> Experimental value from ref 43.

transfer free energies of straight or branched alkanes of identical accessible surface area. Adding a correction of this magnitude would substantially improve the agreement between theory and experiment for aromatic molecules.

**Cyclohexane to Water Transfer Free Energies.** As demonstrated in the previous section, increasing “cavity radii” of solute atoms in cyclohexane by about 0.7 Å above their value in water is physically meaningful and, in addition, yields vacuum to cyclohexane transfer free energies that are in reasonable agreement with experiment. It is, of course, possible to obtain cyclohexane to water transfer free energies as a difference between the two corresponding gas phase transfer processes, but this has the disadvantage of requiring two FDPB calculations, using different radii for each solvent phase. Since cyclohexane to water transfer free energies are probably of the widest practical interest, it is useful to develop a single set of parameters which yields good agreement with experiment for this transfer process. Although determining a new set of cavity radii is one possible approach, we have preferred to retain standard atomic radii as used in PARSE and to determine a new set of charges that yield optimal agreement with experiment.

**PARSE Parameters for Cyclohexane to Water Transfer.** Charges were obtained by the same procedure used to derive the original PARSE parameters:<sup>1</sup> by fitting simple bond dipole moments to functional groups in a manner that optimizes the agreement between calculated and experimental solvation free energies for molecules containing those groups.

Experimental cyclohexane to water transfer free energy data were obtained from the literature<sup>2,41</sup> for a set of molecules containing a variety of chemical groups that appear in amino acid side chains. Nonpolar solvation free energy contributions were calculated using the PARSE radii, and these were subtracted from the total experimental transfer free energies to yield “experimental” electrostatic energies. Optimized charges for different chemical groups were then obtained by distributing equal and opposite charges to bonded atoms in the chemical groups (applying “bond dipole moments”) where charge magnitudes were chosen such that the calculated electrostatic

contributions best matched the “experimental” electrostatic contributions for the set of molecules containing that functional group. The rules followed in assigning charges were identical to those used in deriving the original PARSE parameters: With the object of simplicity, the fewest moments needed to obtain agreement were applied (for example, optimized charges for alcohols—methanol, ethanol, etc.—consist of identical and opposite charges placed only on the oxygen and hydrogen atoms). Charges for more complicated functional groups were built up from the parameters obtained for simpler groups (e.g. amide = ketone + amine). In some cases, charges were further adjusted to optimize agreement between calculated and experimental transfer free energies. For these cases, additional dipole moments were added. (An example is the acidic group, —COOH, whose solvation energy could not be matched using a superposition of the ketone and alcohol charges. An additional moment consisting of equal and opposite charges on the hydroxyl and the carbonyl oxygens was added.) Ambiguities in assigning multiple bond moments were resolved by choosing those which produced the best match to solvation energies, with the minimum degree of charge adjustment.

The assignment of molecules into chemical groups was identical to that used in the original PARSE parametrization with one exception. Previously, all molecules with an —NH— moiety appearing in a molecule with delocalized  $\pi$  electrons were classified into a single chemical group (e.g. methylindole, methylimidazole). In this work, to achieve better agreement with experimental data, we considered separately cases where the —NH— group is the neighbor of zero or one electron-withdrawing group. A different set of atomic charges was derived for each case.

The optimized atomic charges and corresponding cyclohexane to water transfer free energies for the small molecules used in the parametrization process are shown in Table 3. Nearly all of the cyclohexane to water charge parameters are of larger absolute magnitude than the vacuum to water PARSE charges, by 15–25%. The exceptions are the aromatic CH group, in which charges are reduced by 25%, and sulfur-containing

**TABLE 3: PARSE Group Charges and Solvation Free Energies for Cyclohexane to Water Transfer<sup>a</sup>**

chemical group	atom	crg <sup>b</sup>	aacid	molecule <sup>c</sup>	$\Delta G_{\text{el}}$	SA	$\Delta G_{\text{np}}$	calc $\Delta G_{\text{t}}$	exp <sup>d</sup> $\Delta G_{\text{t}}$	$\Delta G_{\text{err}}$
-OH	O	-0.58	ser	methanol	-6.55	158	2.68	-3.87	-3.40	-0.47
	H	0.58	thr	ethanol	-6.30	190	3.56	-2.73	-2.57	-0.16
				propanol	-6.29	220	4.40	-1.89	-2.09	0.20
				butanol	-6.26	249	5.22	-1.05	-1.19	0.14
>C=O	C	0.68		acetone	-5.67	213	4.23	-1.45	-1.31	-0.14
aromatic -CH or -C-CH <sub>3</sub>	-C	-0.10		benzene	-1.45	227	4.61	3.17	3.14 <sup>e</sup>	0.03
	H	0.10	phe	toluene	-1.42	261	5.54	4.13	2.98, 3.98 <sup>f</sup>	1.15, 0.15
	CH <sub>3</sub>	0.10		naphthalene	-2.03	292	6.40	4.37	4.59 <sup>e</sup>	-0.22
	N	-0.90	lys	butylamine	-5.67	255	5.37	-0.30	-0.38	0.08
-NH <sub>2</sub>	H <sub>1,2</sub>	0.45		benzylamine	-6.70	279	6.05	-0.65	-0.29 <sup>e</sup>	-0.36
-CONH <sub>2</sub>	C	0.58	asn	acetamide	-10.20	197	3.76	-6.44	-6.64	0.20
	O	-0.58	gln	propionamide	-10.00	228	4.62	-5.38	-5.54	0.16
	N	-0.90								
	H <sub>1,2</sub>	0.45								
-SH	S	-0.29	cys	methylthiol	-2.10	180	3.30	1.21	1.28	-0.07
	H	0.29								
-CH <sub>n</sub> -SCH <sub>n</sub>	S	-0.56	met	methyl ethyl sulfide	-2.67	243	5.06	2.39	2.35	0.04
	CH <sub>n</sub>	0.28								
-COOH	C	0.68	asp	acetic acid	-7.83	193	3.66	-4.17	-4.44	0.26
	=O	-0.62	glu	propionic acid	-7.76	224	4.53	-3.24	-3.04	-0.19
	O	-0.58								
	H	0.52								
aromatic -CH=N-CH=	C <sub>1,2</sub>	0.23		pyridine	-4.88	220	4.41	-0.47	-0.42	-0.05
	H <sub>1,2</sub>	0.10		quinoline	-4.51	288	6.29	1.79	1.71	0.08
	N	-0.66								
aromatic -C-OH	C	0.08		phenol	-6.18	240	4.97	-1.20	-1.07	-0.13
	O	-0.58	tyr	<i>p</i> -cresole	-6.12	274	5.92	-0.20	-0.14	-0.06
	H	0.50		<i>p</i> -hydroquinone	-10.76	254	5.37	-5.40	-5.49	0.09
aromatic -C-NH-CH-	N	-0.90	trp	methylindole	-4.64	301	6.67	2.03	2.33	-0.30
	H	0.45								
	C	0.225								
	CH	0.125								
	H	0.10								
aromatic -NH- next to electron-withdrawing grp	N(H)	-0.45	his	methylimidazole	-9.47	234	4.81	-4.66	-4.61	-0.06
	H(N)	0.45								
	N(C)	-0.66								
	C(NC)	0.23								
	H(C)	0.10								
-CNC-(NH <sub>2</sub> ) <sub>2</sub>	C <sub>1,2</sub>	0.33	arg	<i>N</i> -propylguanidine	-12.13	284	6.19	-5.93	-5.85	-0.09
	N	-0.66								
	N(H <sub>2</sub> )	-0.88								
	H <sub>1-4</sub>	0.44								
									av err <sup>g</sup>	0.01
									av abs err	0.21
									max err	1.15

<sup>a</sup>  $\Delta G_{\text{el}}$  = calculated electrostatic solvation free energy. SA = accessible surface area in Å<sup>2</sup>.  $\Delta G_{\text{np}}$  = calculated nonpolar solvation free energy.  $\Delta G_{\text{t}}$  = total calculated or experimental transfer free energy.  $\Delta G_{\text{err}} = \Delta G_{\text{t,calc}} - \Delta G_{\text{t,exp}}$ . All energies are in kcal/mol. <sup>b</sup> Optimized PARSE atomic charges for cyclohexane to water transfer. All unlisted aromatic C, H, and ring-substituted CH<sub>3</sub> groups were assigned as in toluene. Unlisted aliphatic C and H were assigned a charge of 0.0. Radius values are identical to those used in PARSE for vacuum to water calculations.<sup>1</sup> <sup>c</sup> Molecules used in optimization of PARSE parameter set, divided into chemical groups. <sup>d</sup> Experimental values from ref 41. <sup>e</sup> Average of hexane, heptane, and octane to water values from ref 2; cyclohexane to water values were unavailable. <sup>f</sup> Alternate experimental value from literature cited in ref 41. <sup>g</sup> Errors are calculated assuming an experimental value of 2.98 for toluene.

groups, which are nearly unchanged. Calculated and experimental transfer free energies are listed in Table 3 and plotted in Figure 4. The average error and the average error in absolute magnitude are 0.01 and 0.21 kcal/mol, respectively. The maximum error, obtained for toluene using the experimental value of 2.98 kcal/mol from Radzicka and Wolfenden,<sup>41</sup> is 1.15 kcal/mol; the error for this molecule is 0.15 kcal/mol if the alternate experimental value for toluene of 3.98 kcal/mol<sup>43</sup> is used.

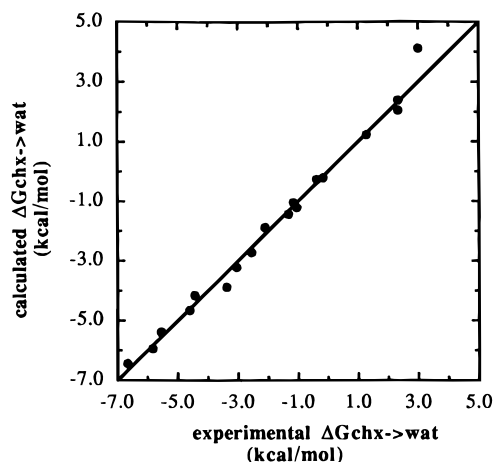
## Discussion

In this paper, we have presented a method for accurately calculating alkane to water solvation free energies for organic molecules with functional groups that are constituents of amino acids. Our strategy has been to first study gas phase to alkane and water transfer free energies and determine the physical parameters characteristic of those processes. An important

finding has been that the same charge and radius parameters that describe the solute cavity in water fail to reproduce experimental gas phase to alkane solvation free energies. In particular, the calculated electrostatic component of this process is too negative; that is, alkanes solvate polar groups less well than expected from a solvent with a dielectric constant of about 2. We attributed this effect to the use of a solute cavity size which had been assumed to be identical in size and shape to the cavity formed by the same solute in water.

The common assumption, that the properties of the solute alone define the size of the solute dielectric cavity, would imply that a given solute would form cavities of identical size in all solvents. However, the dielectric response of the medium is a property of solvent molecules, and it is their position with respect to the charge distribution of the solute that provides the most physically meaningful definition of cavity size. This point was made in the context of a reevaluation of the Born solvation





**Figure 4.** Comparison of calculated and experimental cyclohexane to water solvation free energies for amino acid side chain analogs and acetone, propanol, butanol, and phenol. Parameters used in the calculations are given in Table 3.

model, where it was found that excellent agreement between experimental and calculated hydration free energies of ions could be obtained by using "Born (cavity) radii" that extend out to a distance where the electron density of a water molecule reaches a specific value.<sup>23</sup> Related arguments have been made by Roux et al.<sup>47</sup> and by Hirata et al.,<sup>48</sup> who used the radial distribution function of solvent molecules to obtain a measure of Born radii. A particularly satisfying feature of the application of continuum methods to the aqueous phase has been that radii defined in this way yield solvation free energies that are in good agreement with experiment. If, for example, radii that were much larger than standard atomic radii were required, it is unlikely that continuum methods would have been so widely accepted since it would have been apparent that they were based on an unrealistic physical model.

It is encouraging that the extension of the continuum approach to alkane solvents can be accomplished without modifying the fundamental physical model that was used for the aqueous phase. We have shown that a consistent definition of cavity size requires that the cavity formed by a solute in the alkane phase be significantly larger than the one it forms in water. The effect corresponds to an increased distance between the solute and solvent molecules and is due, as we have shown, to a displacement of the solvent molecules from the solute. Although these effects are accounted for in part through the use of an appropriately sized solvent probe used to define the molecular surface of the solute, we have shown here that the solute radii themselves must be increased if a physically meaningful cavity size is to be obtained. The surprisingly firm linkage of macroscopic theory to microscopic parameters is demonstrated by the fact that the cavity radius increment predicted by simple geometric considerations and supported by molecular dynamics and quantum mechanical calculations leads to calculated solvation free energies that are in good agreement with experiment, without the need for further parametrization (Table 2).

In calculating transfer free energies between water and the alkane phase, we are faced with the complication that cavity sizes are different in each phase. One approach is to define a cycle involving the gas phase as an intermediate. This strategy, however, introduces a number of complications. First, it requires double the computational effort. Second, since the best fit for the nonpolar contribution is obtained for transfers from cyclohexane to water (Figure 2), it is more appealing to treat this transfer process directly so as to avoid having to deal with

the different behavior of linear and cyclic alkanes in the other transfer processes. Finally, in dealing with interfaces, for example between water and membrane, the use of different radii for each solvent would lead to complications for atoms that are located partially in each phase. Our solution to these problems has been to retain the standard radii used for gas phase to water transfer processes and to derive a set of charges appropriate for these radii. It should be emphasized that we have chosen this strategy due to expediency; the physically meaningful approach is to keep the charge distribution the same (allowing for differential polarization effects in each solvent) and to use different radii in different solvents. Thus, the partial charges listed in Table 3 have no physical meaning and constitute an alternate way to obtain accurate transfer free energies between water and organic solvents with minimal computational effort. We have retained a proper partition between electrostatic and nonelectrostatic contributions to solvation in that the electrostatic effects of changing cavity size are, in our approach, implicitly included in the PARSE charge set for alkane/water transfer.

A number of other applications of continuum methods to nonpolar solvent have been reported in the past few years. Fox and Rosch<sup>49</sup> and Luzhkov and Warshel<sup>50</sup> used combined quantum mechanical solute/continuum solvent methods to calculate solvachromic shifts in organic solvents. In each of these cases, use of solvent-specific solute radii led to significantly improved agreement between calculated and experimental values. In a recent paper, the FDPB/ $\gamma$  method was used to calculate solvation free energies of small molecules in cyclohexane.<sup>45</sup> Standard atomic radii and charges were used and the coefficient  $\gamma$  was chosen to optimize agreement with experiment. Overall, good agreement with experiment was obtained, but there were also significant discrepancies between calculated and experimental values for several molecules.

A somewhat different physical model than the one used here has been adopted by Giesen et al. in their extension of the AMSOL method to alkane solvents.<sup>33,51</sup> The electrostatic solvation component is computed via continuum solvent methods. Nonelectrostatic contributions are incorporated through a series of surface tension parameters with the additional feature that both a large and a small solvent probe with accompanying parameters are introduced to account for solvent structural changes. Giesen et al. conclude that solute-induced structural perturbations extending into solution make significant contributions to the solvation process in alkanes. The conclusions of the current work suggest a different mapping of microscopic behavior onto the language of continuum theory in that, in addition to changes in the dielectric constant, the difference in the electrostatic contributions of different solvents is determined primarily by changes in cavity size due to differences in the size and shape of solvent molecules.

## Summary

The major conclusion of this work is that the continuum solvent model as embodied in the FDPB/ $\gamma$  approach can yield accurate solvation free energies in alkane solvents. As was the case for the aqueous phase, it is possible to map the properties of both the solvent and solute onto the language of continuum theory and to obtain good agreement with experiment using parameters that have a well-defined and internally consistent physical basis. Two approaches to obtain solvation free energies are described. In one, solute cavity size is adjusted by introducing a set of "cavity radii" that provide a measure of the distance from solute nuclei where the dielectric response of the solvent becomes significant. This approach is applied to gas phase to alkane solvation free energies and in conjunction

with gas phase to water solvation free energies derived in a previous paper<sup>1</sup> allows the calculation of alkane to water solvation free energies as well. However, for the direct and simple calculation of the latter quantity we have shown that a new set of charges combined with the standard atomic radii used in the previous study also yield transfer free energies that are in good agreement with experiment.

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