

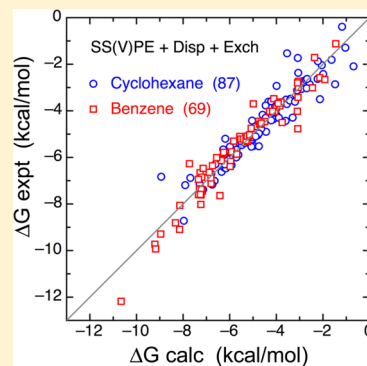
New Implicit Solvation Models for Dispersion and Exchange Energies

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S Supporting Information

ABSTRACT: Implicit solvation models provide a very efficient means to estimate solvation energies. For example, dielectric continuum models are commonly used to obtain the long-range electrostatic interactions. These may be parametrized to also include in some average manner short-range interactions such as dispersion and exchange, but it is preferable to instead develop additional implicit models specifically designed for the short-range interactions. This work proposes new models for dispersion and exchange interactions between solute and solvent by adapting approaches previously developed for treatment of gas-phase intermolecular forces. The new models are formulated in terms of the charge densities of the solutes and use only three adjustable parameters. To illustrate the performance of the models, electronic structure calculations are reported for a large number of solutes in two nonpolar solvents where short-range interactions dominate and different balances pertain between attractive dispersion and repulsive exchange contributions. After empirical optimization of the requisite parameters, it is found that the errors compared to experimental solvation free energies are only about 0.4 kcal/mol on average, which is better than previous approaches in the literature that invoke many more parameters.



INTRODUCTION

Weak short-range interactions between molecular species play an important role in chemistry and biology. For example, short-range attractive and repulsive intermolecular forces often govern protein folding, molecular recognition, and conformational preferences, and their competition can be responsible for the high sensitivity, selectivity, and reversibility of many chemical processes in complex biological systems. Proper accounting of these interactions may be important even for qualitative understanding of such behavior, as well as for quantitative evaluation.

Short-range interactions are also important in the context of solvation, the topic of this Article. They are nonnegligible even for polar solutes in polar solvents, where solvation energies are generally dominated by long-range electrostatic interactions (which we understand here to include induction), and can become dominant if the solute and/or the solvent is nonpolar. We particularly identify and treat here short-range dispersion and exchange contributions to solvation energies. Several excellent reviews consider the literature on various aspects of these and other related phenomena.^{1–5}

Because of the computational expense of treating a large number of solvent molecules explicitly, the use of implicit models has become very popular for efficient and often accurate treatment of solvation energies. In particular, dielectric continuum models are quite successful in treating the long-range electrostatic interactions between solvent and solute. Dielectric continuum models are usually based on solution of the Poisson equation,^{6,7} alternatively the Poisson–Boltzmann equation for salt solutions,⁸ or on an approximate analytic solution known as the generalized Born equation.^{9,10} To implement this, one imagines that the charge distribution of a

solute in a cavity of appropriate size and shape produces an electric field that polarizes a surrounding classical continuum solvent. The polarized solvent generates a reaction field whose electrostatic interaction with the solute leads to an attractive interaction energy. Refined treatments further allow the solute to be back-polarized by the solvent, with both polarizations being iterated until mutual self-consistency is achieved.

By themselves, dielectric continuum models do not explicitly incorporate short-range nonelectrostatic interactions between solute and solvent. However, by taking advantage of the fact that the solvation energy is sensitive to the size of the solute cavity, it is possible (and not uncommon) to account in some average manner for short-range effects by varying parameters that determine the cavity size to reproduce experimental solvation energies. A price paid by this approach is that proper description of the long-range electrostatic interactions will likely be distorted, so that poor results may be obtained for solutes having electronic structures somewhat different from those in the training set used for parametrization. Clearly, then a better approach is to add on top of the dielectric continuum description additional implicit solvation models that are specifically designed to account for the other interactions that may pertain. In doing this, it is particularly important to pay careful attention to the balance between electrostatic and nonelectrostatic contributions in any particular implicit solvation model.^{11–13}

It is generally believed that dispersion and exchange contributions to solvation energies are of comparable

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magnitudes, and being of opposite signs there is considerable cancellation to produce a result that is significantly smaller in magnitude than either contribution alone. This motivates a general approach in which physical models of the separate effects are eschewed, developing instead empirical implicit models of the combined effects of dispersion and exchange. One simple approach to this asserts the combined dispersion and exchange energy to be linearly related to the solvent-accessible portions of the surface areas of those solute atoms that are partially in contact with solvent.^{2,9}

Dispersion and exchange interactions actually have disparate physical origins and different ranges of interaction. To facilitate accurate treatment of solutes having diverse electronic structures, it would therefore seem preferable to develop separate theoretically based models for each that are accurate enough to successfully survive the partial cancellation. In this vein, we propose and test in this work simple and effective new models for dispersion and exchange contributions to solvation energies that are based on sound theoretical considerations and consequently have clear interpretations. It is also our personal philosophy to strive to keep the number of adjustable parameters in the models as small as possible to minimize any unphysical overfitting and to enhance wide applicability.

The next two sections respectively introduce our new implicit models of dispersion and exchange contributions to solvation energies in the context of previous treatments in the literature. Sections follow on numerical techniques implemented to evaluate the required integrals and on details of the computational methods used to test the models. The next section illustrates the utility of the new models by reporting calculated solvation energies for a number of solutes in the two nonpolar solvents cyclohexane and benzene, these solvents being chosen because competing long-range electrostatic interactions are small, the short-range dispersion and exchange interactions have different balances, and substantial experimental results are available for comparison. The following section describes some further explorations in various directions to gain more insight into the workings of the new models. This Article ends with a section giving some concluding remarks.

■ DISPERSION

Physically, dispersion is a quantum mechanical effect due to correlations between the instantaneous oscillating multipole moments of the interacting partners. The dispersion energy appears in the second order of the perturbation theory for the interaction. For ground-state species, the dispersion energy is always negative; that is, it corresponds to attraction, although in excited states it may become repulsive.

The exact quantum mechanical expression for the second-order dispersion energy can be written as a formal sum over terms involving transition energies and oscillator strengths to the complete set of excited states of the unperturbed species.¹⁴ At large distances, the coulomb interaction between electrons in the two species can be developed into an inverse power series in their separation R . The leading term of this series is the dipole–dipole term $\sim 1/R^6$, and interactions among higher multipoles provide additional terms with higher inverse powers of R to produce a series that is strictly only asymptotically convergent. At short distances, these terms are often damped to prevent unphysically large results. It is further not uncommon to include only the leading dipole–dipole term, although often with the associated proportionality constant adjusted to

approximately incorporate contributions from the higher order terms. Several implicit models have been proposed in the literature to adapt this formalism for application to solvation energies.

A reaction field approach for the leading term based on the picture of oscillating dipole moments has been developed for the case of a point dipole in a spherical cavity.^{15,16} The dispersion free energy is expressed in terms of the mean square fluctuation of the solute dipole moment and the reaction field it produces in a polarizable continuum solvent. Invoking mean excitation energies of solute and solvent allows closure of the infinite sum over excited states and leads to a result depending also on the solute polarizability and the high frequency dielectric constant of the solvent. This formalism has been generalized to include higher multipole terms and for an elliptical cavity.^{17,18} It has also been generalized for a cavity of arbitrary shape by reexpressing the volume integral over the solvent region as a surface integral over the cavity,¹⁹ and the required solute polarizability has been evaluated with a variational approximation.²⁰

Some approaches to dispersion approximate the formal sum over excited states directly with single excitation configuration interaction (SCI) calculations. For the case of a spherical cavity, this has been done with SCI calculations of both the solute and the solvent excitation energies and dipole oscillator strengths to a finite number of excited states, together with sum rule corrections.²¹ A related approach applicable to general shaped cavities utilizes SCI calculations of only the solute excited states along with heuristic development of a reaction field formulation for treating the solvent response, with the further approximation of a single representative excitation energy of the solute to simplify the final result.^{22–24}

Another procedure treats the dispersion as a sum of potentials of $1/R^6$, $1/R^8$, and $1/R^{10}$ form arising from each of the solute atoms, with an approximate averaging of the potential over the solvent region for a general shaped cavity.^{25–27}

Recent work on gas-phase intermolecular forces based on a plasmon model within the context of nonlocal density functional theory relates the local plasma frequency to the charge densities of the interacting partners.²⁸ This approach has been further generalized to also include contributions from the charge density gradients.²⁹

We propose here to adapt these latter developments in gas-phase intermolecular forces^{28,29} to obtain a new implicit dispersion model for solvation. Specifically, we take the formulation that includes dependence on charge densities and their gradients²⁹ and adapt it by replacing the electronic charge density of the solvent by a constant $\bar{\rho}_{\text{solvent}}$, incorporating a shift parameter δ to damp the electron–electron interaction factor at short distances, and introduce a proportionality constant A to arrive at a result that can be written in atomic units (au, in which \hbar , e , m_e , and $1/4\pi\epsilon_0$ each have a value of unity) as

$$\Delta G_{\text{disp}} = A \int_{\text{solute}} d^3\mathbf{r} \frac{\rho(\mathbf{r})}{\sqrt{\rho(\mathbf{r}) + \frac{3C}{4\pi} \left| \frac{\nabla \rho(\mathbf{r})}{\rho(\mathbf{r})} \right|^4} \left[\sqrt{\rho(\mathbf{r}) + \frac{3C}{4\pi} \left| \frac{\nabla \rho(\mathbf{r})}{\rho(\mathbf{r})} \right|^4} + \sqrt{\bar{\rho}_{\text{solvent}}} \right]} I(\mathbf{r}; \delta)$$

with

$$I(\mathbf{r}; \delta) = \int_{\text{solvent}} d^3\mathbf{r}' \frac{1}{|\mathbf{r} - \mathbf{r}'|^6 + \delta^6}$$

The integral over the solute region here covers the interior of the cavity, and also the exterior to the extent that the solute electronic charge density $\rho(\mathbf{r})$ remains nonnegligible outside the cavity, while the integral over the solvent region is strictly over all space outside the cavity. The constant C is taken over unchanged from the value 0.0089 that was optimized to fit a test set of gas-phase intermolecular interaction energies,³⁰ and the solvent average electron density $\bar{\rho}_{\text{solvent}}$ is taken from experiment. The proportionality constant A and the damping shift distance δ are parameters to be determined empirically. This general form of the damping has been proposed before in studies of gas-phase intermolecular dispersion energies³¹ and has been found to compare favorably to other commonly used forms.³² We will also consider some results adapted from a related simpler formulation²⁸ that can be obtained from the above expression by omitting the contributions from $\nabla\rho(\mathbf{r})$.

■ EXCHANGE

The exchange interaction is a quantum mechanical effect arising from the antisymmetry of the total wave function to interchange of indistinguishable electrons between the interacting partners that is required by the Pauli exclusion principle. It is important only if there is significant overlap between the partners, and is repulsive by nature. Several implicit models have been proposed in the literature to include this effect in solvation energies.

One procedure treats the exchange repulsion as a sum of potentials of exponential form arising from each of the solute atoms, with an approximate averaging of the potential over the solvent region.²⁶

For interactions between two atoms in the gas phase, it has been shown that the exchange repulsion is approximately proportional to their density overlap.³³ This concept is readily adapted to the case of solvation. If the solvent density is taken to be a constant outside the cavity and zero inside the cavity, then the exchange energy would be simply proportional to the amount of solute charge density penetrating outside the cavity into the solvent region. In fact, such a proposal has been made, although motivated by different arguments, and an explicit formula for the proportionality constant has been suggested.²³ This latter formulation has also proven useful to describe molecules under very high pressure.³⁴

An interesting approach represents the asymptotic exchange energy between two one-electron gas-phase atoms as a surface integral for the flux of exchanging electrons.^{35,36} Although originally developed to only be applicable at large distances, a review of later work shows that generalizations of this approach have been quite accurate even at relatively short distances well into the overlap region.³⁷

We propose here a new implicit exchange model for solvation that is adapted from the latter developments in gas-phase intermolecular forces.^{35–37} Starting from the surface integral expression for the exchange energy of two interacting ground-state hydrogen atoms,^{35,36} one can work out an analogue for the case of a one-electron solute nominally in a cavity and surrounded by a one-electron solvent. Approximating the total two-electron wave function as a product of the one-electron solute and solvent wave functions, replacing these wave functions for the many-electron case by the square roots of the respective one-electron charge densities, and assuming

the solvent charge density to be a constant outside the cavity and zero inside the cavity then motivates an expression for the exchange energy given in au by

$$\Delta G_{\text{exch}} = B \int_{\text{solvent}} d^3\mathbf{r} |\nabla\rho(\mathbf{r})|$$

with $\rho(\mathbf{r})$ the solute electronic charge density. We note that any unconstrained quantum mechanical calculation on the solute will automatically produce a tail of $\rho(\mathbf{r})$ that penetrates outside the cavity nominally containing it, thereby making this integral nonzero. The proportionality constant B is a parameter to be determined empirically. We will also consider some results obtained with $|\nabla\rho(\mathbf{r})|$ inside the integral replaced by $\rho(\mathbf{r})$ in the above expression, as has been used previously.²³

■ IMPLEMENTATION

To evaluate the proposed expressions for dispersion and exchange, we utilize a simple single-center integration method. It is necessary that the center be chosen at a position in the solute where an observer can “see” the entire cavity surface without being blocked by some other part of the surface. The default for this center is taken as the center of solute nuclear charge, although in some cases of highly nonspherical solutes this must be changed manually to find a satisfactory alternate center. In a few cases of severely nonspherical cavities, this approach fails, and the corresponding solute cannot be treated with this simple integration scheme.

Integration over the solute region in the dispersion equation is carried out numerically with the same set of points and weights as are used for evaluating the density functional exchange and correlation contributions to the internal energy of the solute. The inner factor $I(\mathbf{r}; \delta)$ involving integration over the solvent region is separated into integrations over a solid angular part:

$$I(\mathbf{r}; \delta) = \int d^2\Omega' D(\mathbf{r}, \Omega'; \delta)$$

that is done numerically with Lebedev points and weights,³⁸ and an inner radial part:

$$D(\mathbf{r}, \Omega'; \delta) = \int_{s'(\Omega')}^{\infty} \frac{r'^2 dr'}{(r^2 + r'^2 - 2rr'\cos\theta')^3 + \delta^6}$$

where $s'(\Omega')$ is the minimum value of r' in the direction Ω' and θ' is the angle between r and r' . The latter has been done analytically with the help of the Mathematica program³⁹ to obtain

$$D(\mathbf{r}, \Omega'; \delta) = \frac{1}{6\delta^4} \left(T_1 + T_2 + T_3 + \frac{T_4 + T_5}{q} \right)$$

with

$$T_1 = -2r \cos\theta' \ln(p^2 + \delta^2 + r^2 \sin^2\theta')$$

$$T_2 = -2 \frac{(\delta^2 - u^2)}{\sqrt{\delta^2 + r^2 \sin^2\theta'}} \arctan\left(\frac{\sqrt{\delta^2 + r^2 \sin^2\theta'}}{p}\right)$$

$$T_3 = r \cos(\xi^- + \xi^+ + 2\sqrt{3}(\eta^- - \eta^+))$$

$$T_4 = \frac{(\xi^- - \xi^+)}{2} [(u^2 - \delta^2) \cos\chi + \sqrt{3}(u^2 + \delta^2) \sin\chi]$$

$T_5 = (\eta^- + \eta^+) [\sqrt{3}(u^2 + \delta^2) \cos \chi - (u^2 - \delta^2) \sin \chi]$
where

$$p = s'(\Omega') - r \cos \theta'$$

$$q = (\delta^4 + r^4 \sin^4 \theta' - r^2 \delta^2 \sin^2 \theta')^{1/4}$$

$$u^2 = r^2(1 - 2 \sin^2 \theta')$$

$$\chi = \arctan\left(\frac{\sqrt{3} \delta^2}{\delta^2 - 2r^2 \sin^2 \theta'}\right)$$

$$\xi^\pm = \ln(p^2 + q^2 \pm 2pq \cos \chi)$$

$$\eta^\pm = \arctan\left(\frac{q \sin \chi}{p \pm q \cos \chi}\right)$$

The integration over the solvent region in the exchange equation is done with an analogous single-center integration method. The integral is separated into integrations over a solid angular part:

$$\int_{\text{solvent}} d^3\mathbf{r} |\nabla \rho(\mathbf{r})| = \int d^2\Omega E(\Omega)$$

that is done numerically with Lebedev points and weights,³⁸ and an inner radial integration:

$$E(\Omega) = \int_{s(\Omega)}^\infty r^2 dr \sqrt{\nabla \rho(\mathbf{r}) \cdot \nabla \rho(\mathbf{r})}$$

that is done numerically with Gauss–Laguerre points and weights. The exponential factor in the Gauss–Laguerre integration scheme at each solid angle Ω is determined by fitting to an exponential the radial dependence of $\rho(\mathbf{r})$ at the cavity surface.

■ COMPUTATIONAL METHODS

Charge densities of the solutes were determined by carrying out quantum mechanical electronic structure calculations with the B3LYP^{40,41} density functional method, using the version implementing the VWN5 electron gas correlation formula, together with the 6-31+G* basis set.^{42–44}

The Minnesota Solvation Database – Version 2009⁴⁵ includes optimized gas-phase geometries for all of the solutes considered. These geometries were adopted in this work and assumed to remain unchanged in solution, and it was also assumed that no changes in zero-point vibrational energy occur upon solvation, although it should be noted that some possible dangers of these assumptions have recently been emphasized.⁴⁶

Dielectric continuum methods based on solution of the Poisson equation have long been used to evaluate electrostatic contributions to solvation energies.⁷ For this we use here the SS(V)PE method,^{47–50} which notably incorporates an approximation to the volume polarization effects that arise from quantum mechanical penetration of solute charge density outside the cavity that nominally encloses it. These volume polarization effects are treated exactly in the SVPE method,^{47,51–54} and it is expected that SS(V)PE should provide results very close to SVPE for all of the calculations reported here. If implemented with the same cavity, SS(V)PE would be equivalent^{50,55} to the modified version of the IEF-PCM method^{56,57} that is often currently used. The solvent properties involved in the formulation are taken to be the experimental

values for the respective pure liquids, these being dielectric constants⁵⁸ of 2.0165 for cyclohexane and 2.2706 for benzene and average electron densities of 0.0396 au for cyclohexane and 0.0421 au for benzene.

The cavity surface was chosen here as an electronic isodensity contour ρ_0 of the solute. This automatically determines the solute shape and requires only one parameter to fix the overall cavity size. The value of ρ_0 is the only adjustable parameter in the SS(V)PE model. The value 0.001 au is most commonly used for the contour, and this has proved to be near optimal in previous studies of dielectric effects.^{59,60} In this work, we test ρ_0 values of 0.0005, 0.001, and 0.002 au. Angular integrations for the SS(V)PE, dispersion, and exchange evaluations were carried out by single-center Lebedev quadrature with 1202 grid points.

To summarize, we approximate the experimental free energy of solvation by

$$\Delta G_{\text{Expt}} \approx \Delta G_{\text{SS(V)PE}} + \Delta G_{\text{Disp}} + \Delta G_{\text{Exch}}$$

where $\Delta G_{\text{SS(V)PE}}$ gives the long-range electrostatic contribution, while ΔG_{Disp} and ΔG_{Exch} are evaluated with the new implicit models introduced here for dispersion and exchange contributions, respectively. The parameters δ , A , and B involved in the dispersion and exchange terms are optimized by minimizing the rms deviation between calculated and experimental free energies of solvation. The solvation energies are reported under the standard state convention of solute concentrations being identical in gas and solution.⁶¹ The computer code written to evaluate these quantities has been implemented in a local version of the Gamess program package,⁶² which was then used for the computations described in the next section.

■ REPRESENTATIVE CALCULATIONS

We illustrate the utility of the new models by reporting results calculated for a number of solutes in two different solvents, cyclohexane and benzene. These solvents were chosen for several reasons. Electrostatic interactions, being small in such nonpolar solvents, should not dominate the parametrization with their own uncertainties. For a given solute, these solvents should have different balances between dispersion and exchange interactions, because aromatic benzene molecules should favor dispersion interactions more than nonaromatic cyclohexane molecules, whereas they should have less distinct exchange energies because of their similar size and shape. Finally, there is considerable experimental data available on solvation energies in these solvents to aid both in parametrization of the models and in evaluation of their accuracy.

Experimental solvation energies for 91 solutes in cyclohexane and 75 solutes in benzene are available in the Minnesota Database – Version 2009,⁴⁵ which has generously been made publicly available by the Minnesota group. We were not able to treat a few of these (as detailed in the Supporting Information) because their severely nonspherical shapes defeated our simple single-center integration scheme. Several more failures were found at smaller cavity sizes than at larger cavity sizes. However, solutes similar to each of the failures were successfully treated, so there should be no significant bias in the results we obtain by omitting these few from the parametrization and evaluation process.

The dispersion and exchange contributions are evaluated only once after the self-consistency cycles for the solute internal energy and the dielectric contribution are finished. Most of the

extra effort is required for the dispersion term, whereas the exchange term can be evaluated relatively quickly. For the larger solutes in the data set, evaluation of the dispersion term approximately doubles the total time of the computation, as compared to SS(V)PE alone, while this ratio deteriorates to about 3 for medium size solutes and is nearly 10 for water, the smallest solute. These timings can presumably be improved in future work directed toward more efficient evaluation of the dispersion term.

Our new models have only three adjustable parameters, one being the linear proportionality constant A that governs the magnitude of the dispersion term, one being the linear proportionality constant B that governs the magnitude of the exchange term, and the other being the nonlinear parameter δ governing the dispersion damping. We start by examining the dependence on δ . Using the solvent cavity size contour $\rho_0 = 0.001$ au as a typical example, Figure 1 shows the mean

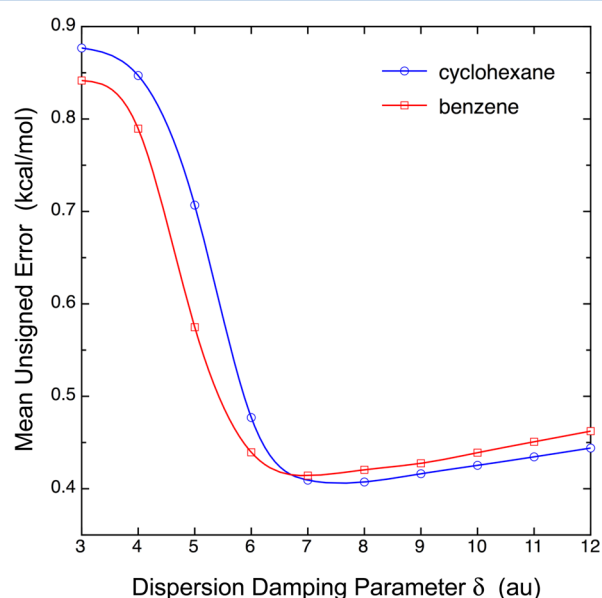


Figure 1. Dependence of mean unsigned error of calculated solvation energies on the dispersion damping parameter δ , with cavity size contour $\rho_0 = 0.001$ au.

unsigned errors (MUE) of the calculated solvation energies as a function of δ , where the parameters A and B are reoptimized at each value of δ . Spline fits join the calculated points to guide the eye. It is seen that results for the two solvents are very similar. The MUE errors are largest at small δ , as expected because the damping is least effective there, then drop off quickly to reach their minimum values, and finally rise slowly at large values of δ . It is interesting and gratifying that both solvents show minima at very nearly the same value of δ being about 7 au (i.e., about 3.7 Å), which is consonant with the range of values found in studies of gas-phase intermolecular dispersion energies.³²

Table 1 reports values for all of the optimized parameters at each cavity contour considered. The optimum value of δ is seen to be rather insensitive to the cavity size, being near 7 au in all cases. The proportionality parameters A and B are of the same order of magnitude. The B parameters for exchange are quite sensitive to cavity size, whereas the A parameters for dispersion show only small variation with cavity size. These trends are in keeping with the shorter range of the exchange interaction as

Table 1. Optimum Parameter Values and Errors As Compared to Experiment

solvent	cavity contour ^a	N^b	δ^c	A^d	B^e	MUE ^f
cyclohexane	0.0005	87	6	−0.01730	0.06039	0.35
	0.001	87	7	−0.01496	0.04380	0.41
	0.002	83	7	−0.01497	0.02742	0.58
benzene	0.0005	71	8	−0.01016	0.06533	0.52
	0.001	69	7	−0.01154	0.03442	0.41
	0.002	62	7	−0.01223	0.02377	0.40

^aCavity size isodensity contour ρ_0 in au. ^bNumber of solutes. ^cDispersion damping parameter in au. ^dDispersion proportionality parameter in au. ^eExchange proportionality parameter in au. ^fMean unsigned error in kcal/mol.

compared to the dispersion interaction. At each cavity size, the corresponding parameters are similar for cyclohexane and benzene.

Table 1 also reports the MUE results. For cyclohexane the lowest MUE is obtained with the $\rho_0 = 0.0005$ au cavity, while for benzene the lowest MUE is obtained with the $\rho_0 = 0.002$ au cavity. However, the improvements of these over the results obtained with the $\rho_0 = 0.001$ au cavity are not large, and this latter cavity gives quite good results for both solvents, whereas one or the other solvent has significantly worse results at the other cavity sizes. We conclude that the $\rho_0 = 0.001$ au cavity performs the best overall.

The SM8 model⁶³ is the latest SM x version for which analogous results have been published in sufficient detail on these same solutes and solvents to allow proper comparison. It should be noted that the SM8 results were obtained with the mPW1PW/6-31G* method for the solute electronic structure, rather than the B3LYP/6-31+G* method used here. The respective MUE results from SM8 are 0.49 kcal/mol for cyclohexane and 0.65 kcal/mol for benzene. Our MUE of 0.41 kcal/mol for both solvents obtained with the $\rho_0 = 0.001$ au cavity are somewhat better, despite the much smaller number of parameters in the models proposed here.

Figure 2 shows the individual calculated solvation energies, as determined with the cavity size contour $\rho_0 = 0.001$ au, as compared to experiment. For perfect agreement, all results would fall on the diagonal gray lines. The left panel gives results from SS(V)PE alone, which show poor agreement with experiment, having less than one-half the correct range, and large MUE of 2.91 kcal/mol for cyclohexane and 3.30 kcal/mol for benzene. The right panel gives results that also include the dispersion and exchange contributions proposed here, which have high correlation with experiment ($r = 0.955$) and small MUE of 0.41 kcal/mol for both cyclohexane and benzene.

Nearly all of the calculated solvation energies agree with experiment to within 1 kcal/mol. With the $\rho_0 = 0.001$ au cavity, the only exceptions to this (with errors noted parenthetically in kcal/mol) in cyclohexane are for *n*-pentane (−1.37), acetic acid (+1.35), *t*-butanol (+1.06), *n*-propane (−1.40), *n*-butane (−1.38), 2,2,2-trifluoroethanol (+2.00), and 3,5-dibromo-4-hydroxybenzonitrile (+2.11), while the exceptions in benzene are for methyl benzoate (+1.46), *t*-butanol (+1.29), 1,1-dimethyl-3-phenylurea (−1.52), 3,5-dimethylpyridine (−1.22), and hydrogen peroxide (−1.69). There does not seem to be any apparent common thread to be noted among the electronic structures that might explain the large errors for these particular solutes.

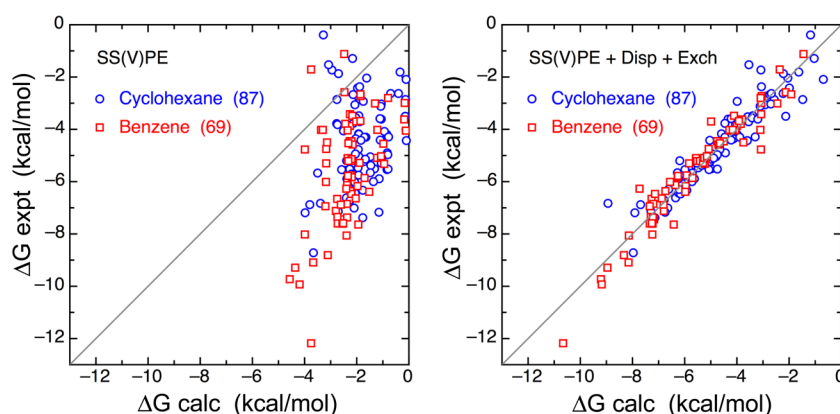


Figure 2. Experimental versus calculated free energies of solvation, with cavity size contour $\rho_0 = 0.001$ au.

As expected, the dispersion and exchange contributions partially cancel one another. For example, with the $\rho_0 = 0.001$ au cavity, the average contributions in cyclohexane are -19.2 kcal/mol for dispersion and $+16.5$ kcal/mol for exchange, and in benzene are -16.1 kcal/mol for dispersion and $+12.9$ kcal/mol for exchange. The average combined dispersion plus exchange contributions of -2.7 kcal/mol in cyclohexane and -3.2 kcal/mol in benzene are much smaller than either separate average contribution. Full details of the individual contributions to the solvation energy calculated for each solute in each solvent are provided in the Supporting Information.

FURTHER EXPLORATIONS

This section describes several explorations carried out to obtain further insight into the working of the proposed new models. In the interest of conciseness, we present these only for results obtained with the $\rho_0 = 0.001$ au cavity.

It is possible to criticize an approach that uses the same data set for parametrization as for evaluation. With such a small number of adjustable parameters and large number of solutes, this is not likely to be a concern here. Yet to put the matter to rest, we have explored this issue by dividing the data set randomly into two groups of nearly equal size and used one for parametrization and the other for evaluation, and then repeated this with the roles of the two groups reversed. For both roles, this led to optimum parameters very similar to those reported in Table 1 and changed the MUE from those in Table 1 by no more than 0.04 kcal/mol in cyclohexane and no more than 0.07 kcal/mol in benzene, thus verifying the robustness of the parametrization for these models.

The average experimental solvation energies for this data set are -4.58 kcal/mol in cyclohexane and -5.57 kcal/mol in benzene. To calibrate thinking about accuracy, we note that a blithe assumption that all solutes in a given solvent have the same solvation energy as their average would lead to MUE of 1.37 kcal/mol in cyclohexane and 1.68 kcal/mol in benzene.

The SS(V)PE model taken alone is not even as good as the assumption of constant solvation energies, having large MUE of 2.91 kcal/mol for cyclohexane and 3.30 kcal/mol for benzene. On the other hand, taking the dispersion plus exchange models alone, with reoptimized parameters but without any SS(V)PE contribution, gives better MUE of 0.51 kcal/mol in cyclohexane and 1.00 kcal/mol in benzene. These explorations clearly show that the solvation energies calculated here in these nonpolar solvents are dominated by the short-range dispersion and exchange terms, with smaller although nonnegligible contribu-

tions from the long-range SS(V)PE term. That same conclusion can be reached from examination of the individual contributions to the solvation energy for each solute in each solvent that is provided in the Supporting Information.

We can check the claim made earlier that dispersion and exchange should have different balances in the two solvents. For this exercise, we consider only the 53 solutes that are common to both solvents. In cyclohexane the combined dispersion plus exchange contributions for these solutes average to -2.52 kcal/mol, while in benzene they average to -3.31 kcal/mol. As expected, the balance is more negative in the aromatic solvent benzene than in the nonaromatic solvent cyclohexane.

In water solvent we have previously found that a simple correction called the FESR (Field-Extremum Short Range) model led to significant improvement over SS(V)PE alone for solvation energies.^{64,65} In keeping with its interpretation as mainly describing hydrogen bonding, the FESR correction would be expected to be small in non-hydrogen bonding solvents such as cyclohexane and benzene. Indeed, adding it as an additional correction to the models proposed here leads to a very minor improvement in the MUE of about 0.02 kcal/mol or less, even after reoptimization of the linear proportionality parameters.

Closely related alternative versions of the models for dispersion and exchange were also considered, with full reoptimization of all three parameters for each combination of models, to compare to the MUE of 0.41 kcal/mol found in both solvents with the models proposed here. Replacement of the dispersion formula by a simpler version that omits the contributions from $\nabla\rho(\mathbf{r})$ gave slightly poorer MUE of 0.47 kcal/mol for cyclohexane and 0.41 kcal/mol for benzene. Replacement of the exchange formula by a version that integrates $\rho(\mathbf{r})$ instead of $\nabla\rho(\mathbf{r})$ outside the cavity gave poorer MUE of 0.58 kcal/mol for cyclohexane and 0.46 kcal/mol for benzene. Simultaneous replacement of both terms with the alternative versions gave significantly poorer MUE of 0.88 kcal/mol for cyclohexane and 0.66 kcal/mol for benzene. It is concluded that the alternative formulas considered for dispersion and exchange are not as effective as the ones proposed here.

It is often asserted that the solvation energy should include a significant contribution from cavitation work, such as may be calculated with scaled-particle theory⁶⁶ or quasichemical theory.⁶⁷ To explore this, we have considered simple models of cavitation wherein a single constant or terms proportional to

either solute surface area or solute volume are added to the present model. In each case, a very slight improvement was found in the MUE of about 0.01 kcal/mol or less. This insensitivity may in part be due to the fact that there is not a great range in sizes of the solutes in the database used. In any case, there does not appear to be any evidence at present to favor inclusion of an additional model for cavitation beyond whatever part of it may already be implicitly included in our exchange term.

CONCLUDING REMARKS

This work has presented new implicit models for dispersion and exchange contributions to solvation energies based on sound theoretical developments of the respective interactions. They are found to work very well in illustrative calculations on the solvation energies of a large number of solutes in cyclohexane and benzene, two nonpolar solvents where short-range interactions predominate and different balances pertain between dispersion and exchange. By virtue of having only three adjustable parameters and of formulating the models explicitly in terms of the solute charge densities, there is promise that they will also be effective in other solvents for solutes having a wide variety of electronic structures.

While the present formulation seems to work quite well, there are several obvious places where still further improvement could be sought in future work. The assumption of a constant solvent charge density involved in arriving at both the dispersion and the exchange formulas is particularly harsh. Use of even a crude model of the charge density of solvent near the solute might be profitable. Either or both of the constants C and $\bar{\rho}_{\text{solvent}}$ in the dispersion formula could be taken as adjustable parameters to be optimized. As practiced by some workers, different cavities could be used to evaluate the electrostatic and nonelectrostatic interactions,^{25,68,69} and it might prove worthwhile to go even further down that path to use different cavities for dispersion and for exchange. The use of other electronic structure methods and basis sets could be explored. Being formulated as explicit functionals of the solute density, the appropriate functional derivatives could be evaluated for inclusion as additional potentials in the solute Hamiltonian to allow dispersion and exchange interactions to affect the solute electronic structure.

There is considerable interest in water as solvent. As already noted above, we have previously suggested an empirical way to add to a dielectric continuum model additional terms, dubbed as the FESR model, to account for hydrogen-bonding contributions to hydration energies.^{64,65} The FESR correction provides considerable improvement in the calculated hydration energies, especially for ions, over the stand-alone SS(V)PE model. However, dispersion and exchange interactions have so far been treated there only to the extent that their combined influence is a single constant for all solutes. Future work will incorporate the more detailed dispersion and exchange models developed in the present study to provide an improved implicit solvation model for water.

ASSOCIATED CONTENT

Supporting Information

Additional tables. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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