
Optimization of Solute Cavities and van der Waals Parameters in *Ab Initio* MST-SCRF Calculations of Neutral Molecules

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Received 16 July 1993; accepted 25 October 1993

ABSTRACT

The cavity used to represent the solute/water interface in Miertus–Scrocco–Tomasi self-consistent reaction field (MST-SCRF) calculations of neutral molecules has been optimized by fitting to experimental data. The study is focused on the refinement of the van der Waals radii of polar and apolar hydrogens and of the van der Waals parameters used to compute the dispersion/repulsion contribution to the total free energy of hydration. When a scaling coefficient of 1.25 is used to build the solute cavity, comparison of 6-31G*/MST results with experimental data demonstrates that the optimum van der Waals radii for hydrogens are around 1.2 Å (apolar) and 0.9 Å (polar). The optimization of the solute cavity and the refinement of the van der Waals parameters lead to root mean square deviations in the computed free energy of hydration of only 0.9 kcal/mol for the 23 molecules considered in this study. © 1994 by John Wiley & Sons, Inc.

Introduction

The theoretical simulation of chemical processes in solution is difficult due to the large

number of solvent molecules to be considered. This impedes a pure quantum mechanical (QM) approach to the study of solvated systems and makes necessary the use of simplified methods. Among

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them, the most popular are (1) classical (force-field-derived) models, (2) the hybrid QM-classical models, and (3) self-consistent reaction field (SCRF) methods. Classical models¹ represent both solute and solvent by means of classical Hamiltonians (force field), which permit a fast calculation of solvation free energies using molecular dynamics (MD) or Monte Carlo (MC) techniques. QM-classical models²⁻⁶ describe the solute at the QM level (usually using a semiempirical Hamiltonian), whereas the solvent is treated at the classical level. Finally, SCRF methods (for review see ref. 7) use a QM description of the solute (either at the *ab initio* or semiempirical levels) and a "quasi" continuum representation of the solvent.

SCRF methods are based on the theory of electrostatic interactions in fluids. They assume that the solvent is a continuum dielectric, which reacts against the solute charge distribution, generating a reaction field. The effect of this reaction field is introduced into the solute Hamiltonian by means of a perturbation operator (\hat{V}_R) according to eq. (1), where \hat{H}^0 stands for the unperturbed gas phase Hamiltonian:

$$(\hat{H}^0 + \hat{V}_R) \Psi = E \Psi \quad (1)$$

SCRF methods provide a fast representation of solvent effects and allow one to consider explicitly polarization effects, which are neglected or only partially considered in classical and QM-classical calculations. However, SCRF methods are approximate since the solvent is assumed to be a continuum medium. In addition to this source of uncertainties, the quality of any SCRF model depends on (1) the definition of the reaction field (the perturbation operator), and (2) the shape of the surface used to simulate the solute/solvent interface.

Miertus, Scrocco, and Tomasi developed a rigorous SCRF model (MST).⁸ This method makes a precise description of the perturbation operator in terms of the molecular electrostatic potential (MEP),⁹ thus avoiding the use of truncated expansions of the solute charge distribution. A molecular-shaped algorithm is also used to define the cavity,¹⁰ which represents an improvement with respect to early models that use a spherical cavity to describe the solute/solvent interface. The model permits one to derive the properties of the solute in solution from the solvated wave function [eq. (1)]. Moreover, it gives the free energy of hydration (see Methods), which is computed as the addition of an electrostatic term accounting for the charge interactions between solute and water, and a steric

contribution accounting for the expansion work, the van der Waals interactions, and the work needed to disrupt the solvent structure and build the solute cavity (cavitation).

The accuracy of the results obtained in MST calculations will depend in practice on several factors: (1) the quality of the basis set in the SCF procedure, (2) the cavity used to simulate the solute/solvent interface, and (3) the reliability of the method used to represent steric effects (cavitation and van der Waals interactions). The criteria used for the selection of the basis sets are the same as those used to compute MEPs^{11a,b} and those which might be applicable for the particular system. In general, the *ab initio* 6-31G* basis set is expected to provide reasonable representations of hydration effects for neutral molecules at a moderate computational cost.¹²

Unfortunately, the criteria for the selection of the cavity size and for the calculation of steric contributions are not so clear. Particularly, the proper selection of the cavity size is crucial in MST-SCRF calculations: A cavity that is too large will underestimate the solvent effect, whereas a cavity that is too small will overestimate such an effect. Recently, we suggested that the solute cavity should be defined in such a way that it mimics approximately the first hydration shell.^{11c} From MD simulations we determined that the cavity for neutral molecules should be placed typically at around 1.20–1.25 times the van der Waals radii (C: 1.5 Å, N: 1.5 Å, O: 1.40 Å). Unfortunately, these studies did not allow us to determine key points like what are the optimum van der Waals radii for hydrogens and whether unique van der Waals radii for hydrogen should be enough to represent both polar and nonpolar hydrogens.

In this article, a 6-31G*/MST study of the free energy of hydration of 23 small prototypic bioorganic molecule is presented. According to these calculations, the best van der Waals radii for polar and nonpolar hydrogens were determined, and the optimum procedure to build the solute cavity for neutral molecules was defined. Finally, different algorithms to account for the steric contribution were examined, and the empirical parameters used to compute it were optimized.

Methods

SCRF calculations were performed using the MST model,⁸ which places the solute in a molecule-

shaped cavity embedded in an infinite polarizable dielectric medium. The polarization of the solvent by the solute charge distribution, $\rho^0(r)$, induces a surface charge distribution, $\sigma(s)$, on the solute/solvent interface. The reaction field generated from $\sigma(s)$ is included in the *in vacuo* molecular Hamiltonian (\hat{H}^0) by means of the perturbation operator \hat{V}_R [eq. (2)]. If the solute/solvent interface is divided into M elements S_i small enough to consider the charge distribution $\sigma(s_i)$ constant inside them, eq. (2) can be rewritten in a more useful way [eq. (3)], where q_i are the polarization charges on the cavity surface.

$$V_R = \int_S \frac{\sigma(s)}{|r_0 - r|} dS \quad (2)$$

$$V_R = \sum_{i=1}^M \frac{\sigma(s_i)S_i}{|r_0 - r|} = \sum_{i=1}^M \frac{q_i}{|r_0 - r|} \quad (3)$$

Evaluation of the charge density at the different surface elements ($\sigma(s_i)$) was performed by solving the Laplace equation [eq. (4)], where V_T is the total electrostatic potential, which includes contributions of both solvent (V_σ) and solute (V_ρ) charge distribution [eq. (5)]. A dielectric constant of 78.5 was used here to mimic the properties of pure water at $T = 298$ K.

$$\sigma(s_i) = -\frac{\epsilon - 1}{4\pi\epsilon} \left(\frac{\partial V_T}{\partial n} \right)_n \quad (4)$$

$$V_T(r) = V_\rho(r) + V_\sigma(r) \quad (5)$$

As noted earlier, MST is an iterative algorithm, and convergence is usually achieved in three to five cycles. This method is slightly more expensive from a computational viewpoint than other SCRF methods, but the use of a rigorous expression of the molecular charge distribution and the consideration of molecular-shaped cavities¹⁰ guarantee *a priori* the goodness of the method.

The algorithm used to build up the cavity defines each atomic sphere in terms of a pentakisdodecahedron, whose faces are progressively divided in triangles, defining in this way a sequence of levels of approximation (see ref. 10 for more details). Present calculations have been carried out at the largest surface cavity definition (level 5 in ref. 10). Alternative definitions or refinements are discussed in the literature.¹³ The cavity was determined from the atomic van der Waals radii multiplied by a scaling factor. Standard van der Waals radii for heavy atoms were used: C:1.5 Å, N:1.5 Å, O:1.4 Å, S: 1.75 Å. Different values for the van der

Waals radii of the hydrogen atom were examined (from 1.0 to 1.4 Å and from 0.7 to 1.2 Å for apolar and polar hydrogens, respectively). Scaling factors of 1.20 and 1.25 were considered.

The total Helmholtz free energy of hydration (F_{hyd}) was determined as the addition of a steric and an electrostatic term (F_{pol}). Entropic terms and contributions due to solvent-induced changes in geometries were not considered explicitly. The steric contribution includes the expansion term ($\Delta PV = -RT$), the van der Waals interaction (F_{vw}), and the cavitation free energy (F_{cav}). Following the linear free response theory, the electrostatic free energy (F_{pol}) was computed according to eq. (6) (see refs. 8 and 14 for details), where the superscript zero stands for the gas phase environment, V_σ is the electrostatic potential generated by the solvation charges [eqs. (3–5)], and ρ_{nuc} is the nuclear charge density. According to this definition, the third term in eq. (6) is included to account for the work involved in polarizing the solvent. Alternative formalisms which include the solvent polarization work within the SCF procedure have been developed by other authors, but both formalisms exhibit a close agreement upon choice of a proper cavity definition.^{13c,15}

$$F_{\text{pol}} = \langle \Psi | \hat{H} | \Psi \rangle - \langle \Psi^0 | \hat{H}^0 | \Psi^0 \rangle - 1/2 \left(\langle \Psi | \hat{V} | \Psi \rangle + \int \rho_{\text{nuc}} V_\sigma(s) ds \right) \quad (6)$$

The cavitation free energy was determined from the scaled particle theory according to Pierotti's method.¹⁶ Two different algorithms were used to calculate the van der Waals contribution. The first method was proposed by Tomasi and co-workers¹⁷ and defines the van der Waals interaction as an expansion of polynomial and exponential terms [eqs. (7–8)]. In these equations, m and l stand for a subunit (typically atoms) of the solute (M) and of the solvent (L); ρ_L is the density of the solvent; and $g_{\text{ml}}(\mathbf{r}_{\text{ml}})$ is a correlation function, which depends on the position of solute and solvent atoms (\mathbf{r}_{ml})— $g_{\text{ml}}(\mathbf{r}_{\text{ml}})$ is equal to 0 if the solvent atom is inside the solute cavity, and 1 if it is outside (homogeneous approximation). In the potential term $V_{\text{ml}}(\mathbf{r}_{\text{ml}})$ [eq. (8)], the dispersion ($d_{\text{ml}}^{(m)}$) and repulsion ($c_{\text{ml}}, \gamma_{\text{ml}}$) coefficients can be taken from experimental data.¹⁸ In this study, we used a simplified version of eq. (8), where only the r^{-6} contribution was considered. Since the r^{-10} and r^{-8} dispersion terms cancel the repulsion contribution,¹⁷ the neglect of repulsion and r^{-10} and r^{-8} terms is expected to be

a minor source of errors for the purposes of this work. The dispersion coefficients in eq. (8) were taken directly from experimental data.¹⁸

$$F_{vw} = \sum_{i \in L} \sum_{m \in M} \int N_1 \rho_L g_{ml}(\mathbf{r}_{ml}) V_{ml}(\mathbf{r}_{ml}) d\mathbf{r}_{ml} \quad (7)$$

$$V_{ml}(\mathbf{r}_{ml}) = \sum_{n=6,8,10} -\frac{d_{ml}^{(n)}}{r_{ml}^n} + c_{ml} \exp(-\gamma_{ml} r_{ml}) \quad (8)$$

Another way to compute the van der Waals free energy contribution takes advantage of its linear relationship with the molecular surface¹⁷ [see eq. (9), where S_i is the surface assigned to atom i , and ξ_i is the corresponding van der Waals parameters]. This simple but useful relationship can be derived as a limit expression from the preceding equations when the solvent density is constant for all the series of molecules. It is obviously less rigorous than eqs. (7–8), but it permits one to optimize the atomic van der Waals parameters (ξ_i) for the different atoms in the context of SCRF calculations. It is worth noting that this linear relationship has been exploited in the literature to represent solvation effects.¹⁹

$$F_{vw} = \sum_i \xi_i S_i \quad (9)$$

The 6-31G* basis set was used in all the calculations.²⁰ Geometries were obtained from gas phase optimization at the 6-31G* level and were kept frozen during SCRF calculations. Previous SCRF studies have shown that the explicit inclusion of geometry relaxation upon the solvent effect does not lead to relevant changes in the energetics of the solvation process.²¹ Computations were performed using a modified version of the MonsterGauss computer program.²² All the calculations were carried out on the IBM 3090 of the Centre de Supercomputació de Catalunya, and on an HP/730 in our laboratory.

Results and Discussion

The free energy of hydration of 23 small prototypic molecules was computed at the MST/6-31G* level by using solute cavities defined with scaling factors of 1.20 and 1.25. Fourteen of these molecules (CH_4 , C_2H_6 , C_2H_4 , C_2H_2 , CH_3CN , CH_3OCH_3 , CH_3COH , CH_3COCH_3 , CH_3F , CH_3SCH_3 , $\text{CH}_3\text{COOCH}_3$, $\text{CH}_3\text{CH}_2\text{NO}_2$, C_6H_6 , and $\text{C}_6\text{H}_5\text{N}$ [pyridine]) have only nonpolar hydrogens (hydrogens bound to carbon), whereas the rest of

them (H_2O , NH_3 , CH_3OH , CH_3NH_2 , CH_3COOH , CH_3CONH_2 , $\text{CH}_2\text{OHCH}_2\text{OH}$, CH_3SH , and $\text{C}_6\text{H}_5\text{OH}$ [phenol]) contain polar hydrogens (hydrogens bound to heteroatoms). Atomic van der Waals radii from 1.0 to 1.4 Å and from 0.7 to 1.2 Å were considered for nonpolar and polar hydrogens, respectively (for polar molecules containing both nonpolar and polar hydrogens, a van der Waals radii of 1.2 Å was used for nonpolar hydrogens). Results for polar and nonpolar hydrogens are available upon request to the authors as supplementary material.* Since these calculations were previous to any optimization of the van der Waals parameters, an atom-independent value for ξ_i ($\xi_i = -0.077$) taken from the empirical relationships found by Tomasi and co-workers¹⁷ was used. This relationship has been very useful to represent F_{vw} in previous studies.²³ Experimental values of free energy of hydration corresponding to the transfer from the ideal 1 M state to the hypothetical ideal aqueous solution at the same concentration are taken from ref. 24.

Results clearly show the importance of a proper selection of the van der Waals radii. A small van der Waals radius for hydrogens leads to small cavities, and the free energies of hydration (in absolute value) are overestimated. Contrarily, a large van der Waals radius underestimates the free energy of hydration. The electrostatic term, but not the steric, is responsible for the dependence between the free energy of hydration and the cavity size. Accordingly, the optimum van der Waals radii for polar and nonpolar hydrogens should be determined prior to any optimization of the van der Waals parameters [ξ_i in eq. (9)].

To define the best van der Waals radii, the root mean square (RMS) deviation and the regression coefficient ($F_{\text{exp}} = c^* F_{\text{MST}}$) between experimental and theoretical free energies of hydration were determined. The average RMS and the regression coefficient as a function of the van der Waals radii of the hydrogens are displayed in Figures 1 (polar) and 2 (nonpolar). In both cases the cavities were built up by using scaling factors equal to 1.20 and 1.25.

Figures 1 and 2 confirm the dependence of the results on the proper selection of the hydrogen van

*Results available upon request are the total free energy of hydration and its electrostatic, van der Waals, and cavitation components. These values are given for each scaling factor (1.20 and 1.25) and for each van der Waals radius of the polar and nonpolar hydrogen.

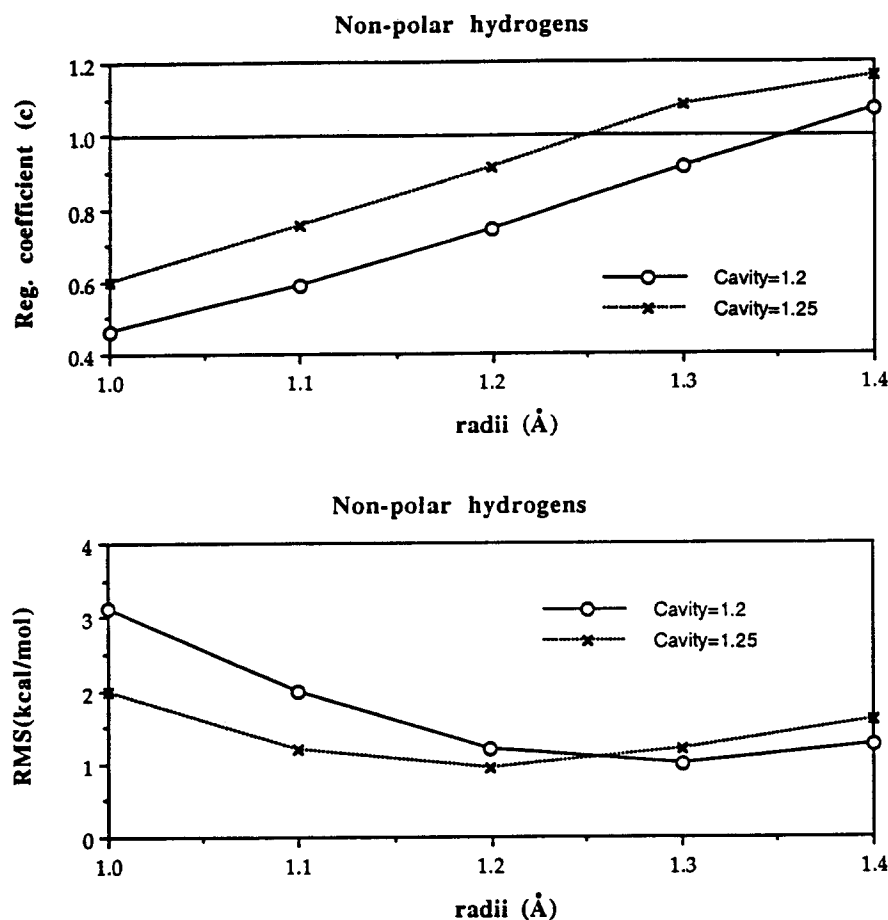


FIGURE 1. Representation of (top) the regression coefficient (c ; $F_{\text{exp}} = c \cdot F_{\text{MST}}$) and of (bottom) the RMS deviation (in kcal/mol) between 6-31G*/MST and experimental free energies of hydration for different values (in Å) of the van der Waals radii of nonpolar hydrogens. In all cases, cavities were defined by using scaling factors of 1.20 and 1.25.

der Waals radii. Different van der Waals radii should be assigned to polar and nonpolar hydrogens, in agreement with our previous suggestions^{12,25d,e} and with the most common strategy used in empirical force fields. The best fittings occur for van der Waals radii of 1.0 (polar) and 1.3 (nonpolar) Å for a scaling factor of 1.20, and of 0.9 (polar) and 1.2 (nonpolar) Å when a scaling factor of 1.25 is used. It is difficult to determine the best scaling factor (1.20 or 1.25), since good results are derived from both values. Therefore, we decided to use the scaling factor of 1.25, although it must be noted that the value of 1.20 combined with van der Waals radii of 1.0 and 1.3 Å is also a good choice.

Figures 1 and 2 emphasize the success of our previous estimates of van der Waals radii (polar: 1.0 Å; nonpolar: 1.2 Å), which were proposed from the inspection of empirical force fields. Moreover,

they show the goodness of the MST method, even previous to the optimization of the van der Waals contribution. Thus, inspection of Figures 1 and 2 shows that the 6-31G*/MST method estimates the free energy of hydration for neutral molecules with an average RMS error of only 1.3 (polar) and 0.9 (nonpolar) kcal/mol, which implies systematic deviations of 1% (polar) and 8% (nonpolar) between the experimental data and the theoretical estimates. These deviations are not larger than those provided by the free energy perturbation theory from MD and MC simulations.¹²

Optimization of the van der Waals parameters (ξ) defining the F_{vw} contribution [eq. (9)] was performed using the scaling factor of 1.25 and the corresponding set of optimum hydrogen van der Waals radii. This procedure avoids unrealistic results that might arise from the simultaneous optimization of the cavity size and the van der Waals

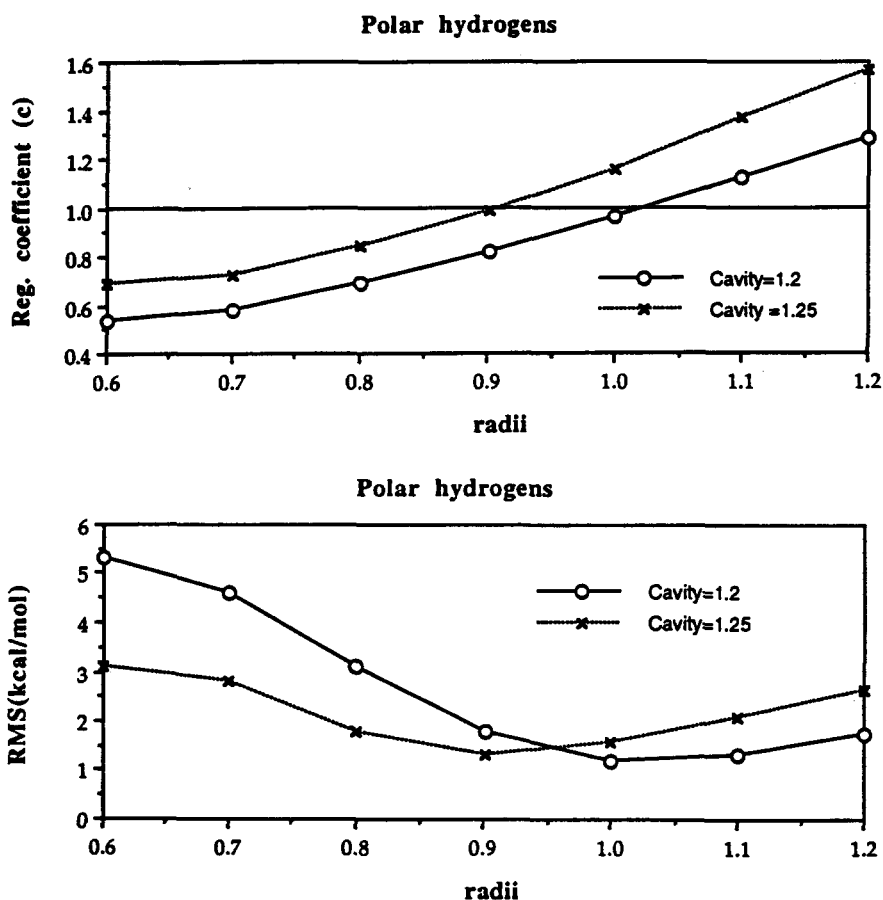


FIGURE 2. Representation of (top) the regression coefficient (c ; $F_{\text{exp}} = c \cdot F_{\text{MST}}$) and of (bottom) the RMS deviation (in kcal/mol) between 6-31G*/MST and experimental free energies of hydration for different values of the van der Waals radii (in Å) of polar hydrogens. In all cases, cavities were defined by using scaling factors of 1.20 and 1.25.

parameters. However, previous to any optimization, the suitability of eq. (9) to be used instead of eqs. (7–8) for a series of different molecules must be analyzed. Therefore, the van der Waals free energy of hydration computed from both methods was compared. For eq. (9), the atom-independent parameter (ξ) reported by Tomasi and co-workers¹⁷ was considered. With regard to eqs. (7–8), experimental values¹⁸ for the different atoms were used, but in addition a two-atom model was used for comparison (only two types of atoms were considered: hydrogen and heavy atoms, which were defined with the parameters of the carbon atom). Figure 3 demonstrates the qualitative goodness of eq. (9). Note that the accuracy of the fitting between eq. (9) and the rigorous eqs. (7–8), which is quite good, is not a matter of concern since eq. (9) will be fitted to experimental data.

The residual free energy of hydration (the difference between the experimental free energy of

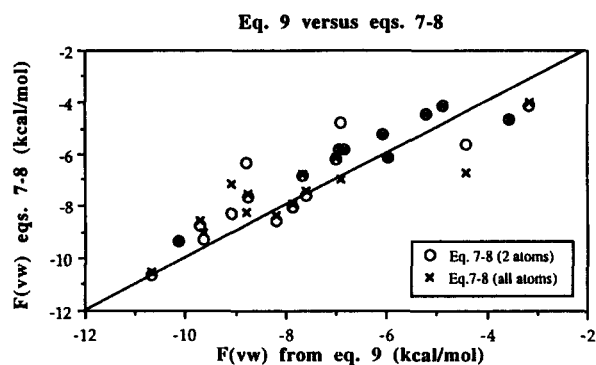


FIGURE 3. Representation of the van der Waals free energy of hydration (in kcal/mol) obtained from the polynomial-exponential expansion [eqs. (7–8)] and from the linear relationship with the cavity surface [eq. (9)]. In eqs. (7–8), both “all atoms” and “two atoms” models were used, while in eq. (9) only the atom-independent value ($\xi = 0.077 \text{ kcal/mol } \text{\AA}^2$) was considered (see text for details). A correlation line with slope = 1.00 is shown as reference.

solvation and the sum of electrostatic, expansion, and cavitation contributions) was fitted following eq. (9) by linear regression analysis in order to optimize the van der Waals parameters (ξ_i). According to this procedure, the van der Waals parameters derived from the fitting incorporate not only the dispersion and repulsion contributions, but additional energy terms (such as entropic effects arising upon transfer from the gas to aqueous phase or underlying the hydrophobic effect in the aqueous media) as well as nonelectrostatic components of hydrogen-bonding interactions.

CH_3F was excluded from the fitting, and with regard to the S parameter caution is necessary since only two molecules possess this atom. The final optimized parameters are (in kcal/mol \AA^2 ; the standard errors are given in parentheses): H (non-polar) = 0.079 (0.010), H (polar) = -0.106 (0.090), C = -0.108 (0.019), N = -0.053 (0.028), O = -0.057 (0.020), S = -0.070 (0.026). These parameters lie in the range from -0.05 to -0.10, as was expected from the previous atom-independent estimate of -0.077.¹⁷ From these van der Waals parameters, the free energy of hydration (except for CH_3F) was calculated. Results are shown in Table I, where the dipole moments obtained from gas phase and aqueous calculations are also reported.

Figure 4 displays the relationship between 6-31G*/MST and experimental free energies of hydration. The goodness of the MST results is clearly stated. Thus, the RMS deviation with respect to the experimental data is only 0.9 kcal/mol, which represents a small but significant improvement with respect to the atom-independent van der Waals parameter. Furthermore, the correlation between MST and experimental free energies of hydration is excellent, as noted by the correlation coefficient ($r = 0.95$) and the regression coefficient ($c = 1.00 \pm 0.04$), which indicates the close identity between theoretical results and experimental data. The largest deviations are found for C_2H_4 , C_2H_2 , and phenol. This can be due to the difficulty to represent carbon atoms in very different environments using a unique van der Waals parameter. Extension of this study to a more complete set of molecules, and the use of a more flexible set of van der Waals parameters, should improve the goodness of the results. However, the level of agreement of the present model is encouraging.

The effect of water on the molecular properties has been discussed extensively by us and other authors^{6c,7,11c,15,23,25,26} and is not the objective of the present work. However, inspection of Figure 5,

TABLE I.
Dipoles in Gas Phase and in Solution (in Debye), and Free Energies of Hydration.

Molecule	μ_{vac}	μ_{aq}	F_{exp}	F_{hyd}
CH_4	0.00	0.00	2.0	1.31
C_2H_6	0.00	0.00	1.8	1.69
C_2H_4	0.00	0.00	1.3	-0.03
C_2H_2	0.00	0.00	0.0	-1.99
CH_3CN	4.04	5.03	-3.9	-4.67
CH_3OCH_3	1.48	1.89	-1.9	-1.62
CH_3COH	2.98	3.84	-3.5	-4.24
CH_3COCH_3	3.12	4.13	-3.9	-4.42
CH_3SCH_3	1.79	2.33	-1.4	-0.91
$\text{CH}_3\text{CH}_2\text{NO}_2$	4.14	4.94	-3.7	-4.45
C_6H_6	0.00	0.00	-0.9	-0.97
$\text{C}_6\text{H}_5\text{N}$	2.31	3.45	-4.7	-3.62
$\text{CH}_3\text{COOCH}_3$	1.99	2.54	-3.3	-3.62
H_2O	2.25	2.56	-6.3	-7.53
NH_3	1.92	2.19	-4.3	-5.09
CH_3OH	1.87	2.23	-5.1	-4.36
CH_3NH_2	1.54	1.89	-4.6	-3.54
CH_3COOH	1.80	2.27	-6.7	-6.12
CH_3CONH_2	4.06	5.25	-9.7	-9.20
$\text{CH}_2\text{OHCH}_2\text{OH}$	0.00	0.00	-7.7	-7.73
CH_3SH	1.79	2.27	-1.2	-1.56
$\text{C}_6\text{H}_5\text{OH}$	1.63	2.07	-6.6	-4.94

F_{exp} : experimental²⁴; F_{hyd} : derived from optimized 6-31G*/MST calculations; in kcal/mol).

which shows the relationship between gas phase and aqueous dipole moments, allows one to gain insight into the linear scaling of the dipole upon aqueous solution. The regression coefficient indicates that for these molecules water linearly increases the dipole around 28%. This value agrees

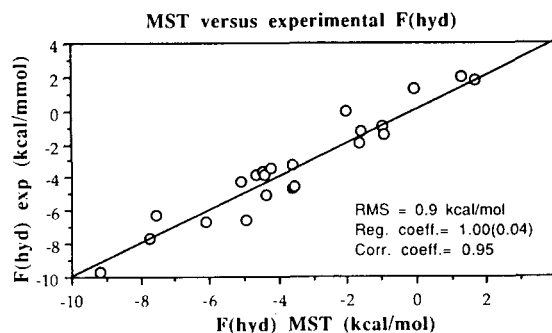


FIGURE 4. Comparison between 6-31G*/MST and experimental free energies of hydration (in kcal/mol). The straight line corresponds to the regression equation $F_{\text{exp}} = c \cdot F_{\text{MST}}$. Statistical parameters (RMS deviation, regression coefficient c , and correlation coefficient r) defining the goodness of the comparison are displayed.

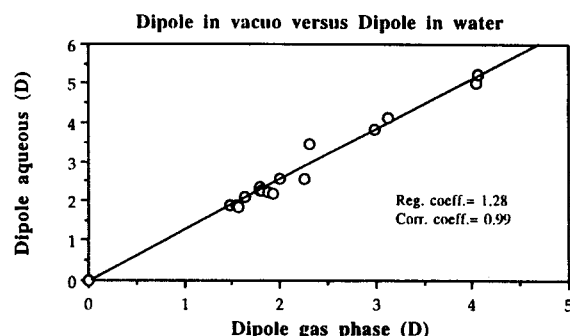


FIGURE 5. Comparison between aqueous and gas-phase dipole moments (in Debye). The straight line correspond to the regression line $\mu_{\text{aq}} = c \cdot \mu_{\text{gas}}$.

with previous estimates obtained with nonoptimized cavities²⁵ and confirms the smaller dependence of the dipole on the cavity size with regard to the free energy of hydration.

Conclusions

The optimization of the solute cavity, and of the surface parameters defining the van der Waals contribution to the total free energy of hydration in *ab initio* MST calculations, has been performed. Such an optimization stresses the necessity to use different van der Waals radii for polar (0.9–1.0 Å) and nonpolar (1.2–1.3 Å) hydrogens and confirms the suitability of the scaling factor of 1.20–1.25, which was used previously to define the cavity size. Within the MST framework, these optimized cavities and van der Waals parameters provide accurate estimates of the free energy of hydration for 23 neutral molecules. Thus, the average RMS error is less than 1 kcal/mol for the series of molecules. Moreover, the correlation coefficient between theoretical and experimental free energies of hydration of 0.95, and the regression coefficient (*c*) of 1.00, confirms the goodness of the optimized model.

Acknowledgments

M.O. is indebted to Professor W. L. Jorgensen for his hospitality and to the Fullbright commission for financial support. We also thank Professor J. Tomasi for his version of Montergauss computer program. This work has been supported by the Centre de Supercomputació de Catalunya (Mol.

Recog. Project) and by the DGICYT (PM92-0055-C02-01).

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