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# Gas Phase Free Energies of Formation and Free Energies of Solution of $^{\alpha}$C-Centered Free Radicals from Alcohols: A Quantum Mechanical−Monte Carlo Study

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The gas phase free energies of formation of the $^{\alpha}$C-centered radicals of methanol (0.1 kJ mol$^{-1}$), ethanol (−11.2 kJ mol$^{-1}$), 1-propanol (−1.8 kJ mol$^{-1}$), and 2-propanol (−23.2 kJ mol$^{-1}$) were derived from a combination of experimental data and theoretical procedures. Enthalpies of formation were taken from experiment or derived from $\Delta_f H°_{(g)}$ of the parent alcohols and theoretical BDEs (radicals of 1- and 2-propanol). Entropies were obtained from B3LYP/6-31G(D) geometries and vibrational frequencies, and the rigid rotator harmonic oscillator approximation, taking account of the conformational mix of the free radicals. These results were combined with experimental free energies of formation in water to yield free energies of solution. The BOSS Monte Carlo discrete solution simulation package, combined with quantum mechanical calculations (QM+BOSS), was used to derive free energies of solution of the $^{\alpha}$C-centered free radicals of methanol, ethanol, 1-propanol, and 2-propanol in water. The absolute free energies of solution are quantitatively described by QM+BOSS with TIP4P water (in kJ mol$^{-1}$): methanol radical, expt −17.3, calc −16.2; ethanol radical, expt −11.8, calc −12.3; 2-propanol radical, expt −12.3, calc −13.3. A value is predicted for the 1-propanol radical, −15.4 kJ mol$^{-1}$. The results are not sensitive to the choice of Lennard-Jones parameters for the radical center. The recommended procedure involves geometry optimization and frequencies at the B3LYP/6-31G(D) level in the gas phase, followed by a single point SCRF−SCIPCM calculation to obtain CHELPG charges. Omission of the SCRF step yields free energies of solution that are too low compared to experiment. The radicals are less solvated than the parent alcohols. Examination of the CHELPG charges suggests that the reason lies in the lower polarity of the C−O bond and lower H-bond acceptor ability of the oxygen atom.

## Introduction

While the thermodynamic properties of C-centered free radicals are readily described in the gas phase by modern computational techniques, accurate methods for predicting their reduction potentials and other thermochemical properties in solution have not been developed as highly. Solution properties are required for an understanding of redox mechanisms and numerous other processes. For example, in the biochemical field, in addition to a variety of enzymatic radical reactions,[1] there is a great need for thermochemical information relating to the radicals created by oxidative damage that results from reactions of hydroxyl radicals and other reactive oxygen species in living cells.[2]

Oxidative damage of glycoproteins and carbohydrates occurs primarily by hydrogen abstraction at a site adjacent to an OH group. This is because the resultant C-centered free radical is stabilized by the $\pi$-donor ability of the dicoordinated oxygen atom. The (deoxy)ribose moiety of nucleic acids and the side chain of serine residues of proteins are among the sites susceptible to oxidation for the same reason. A $\pi$-donor stabilized C-centered radical necessarily has dipolar character since there is a net charge transfer from the doubly occupied $\pi$-donor orbital to the singly occupied 2p orbital at C.[3] It is reasonable that such polarity would be enhanced in a medium of high dielectric constant, such as water, and that the free energy of solution would increase with dielectric constant. The situation is compounded in the case of captodatively stabilized free radicals, for which polar resonance forms can be written. Indeed, early SCRF studies (INDO−UHF−SCRF) found that the stabilization of such radicals, relative to the gas phase, was in the range 30−120 kJ mol$^{-1}$.[4] The conclusion of such theoretical studies is that the radical, R$^{\bullet}$, should have a more negative free energy of solution than the parent, R−H, and that the difference, $\Delta\Delta G_{soln}$, would increase with polarizability of the free radical and polarity of solvent. The difference, $\Delta\Delta G_{soln}$, would be greatest in aqueous solution. Internal factors not included in these considerations, such as preferential interaction of the solvent in the form of increased hydrogen bonding and bonding of the three- or one-electron kind, would appear to exacerbate the difference, whereas external factors associated with rearranged solution structure (a decrease of solvent entropy, for example) may work in the opposite direction. In contrast, the relatively few experimental studies, which address this point, lead to the conclusion that $\Delta\Delta G_{soln}$ is close to zero. Thus, no effect of solvent polarity was found for the stabilization of captodative free radicals in a variety of polar organic solvents,[5] and a photoacoustic calorimetry study concluded that "moderately large organic molecules and their corresponding radicals are solvated to the same extent—even in water".[6] Subsequently, in the calculation of reduction potentials, $E°'$, for the process

$$R^{\bullet} + e^{-} + H^{+} = R{-}H$$

with glycine radicals, we[7,8] have assumed that the solvation free energy of the radical is the same as that of the parent species,

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**TABLE 1: Thermodynamic Data at 298.15 K (Gas phase 1 atm; Aqueous Phase 1 M)**[a]

| molecule | $S^\circ_{(g)}$,[b] J K$^{-1}$ mol$^{-1}$ | $n$ | $S^\circ_{(g)}$,[c] J K$^{-1}$mol$^{-1}$ | $\Delta_f H^\circ_{(g)}$ kJ mol$^{-1}$ | BDE$_{(g)}$ kJ mol$^{-1}$ | $\Delta_f G^\circ_{(g)}$ kJ mol$^{-1}$ | $\Delta_f G^\circ_{(aq)}$ kJ mol$^{-1}$ |
|---|---|---|---|---|---|---|---|
| methanol | 237.7 | 1 | 237.7 | −200.7$^{d}$ | **401.9**$^{e}$ | **−162.0**$^{d}$ | **−175.3**$^{d}$ |
| | | | 239.8$^{d}$ | −201.6$^{f,g}$ | 393.7$^{h}$ | | |
| methanol radical | 239.6 | 2 | 245.4 | | | | **−9.2**$^{i}$ |
| | | | **244.2**$^{j}$ | **−17.8** ± 1.3$^{f,j}$ | | **0.1** | |
| | | | 255.6$^{k}$ | −17.1$^{e}$ | | | |
| ethanol | 270.0 | 3 | 278.5 | **−235.1**$^{d,g}$ | 396.3$^{l}$ | **−168.5**$^{d}$ | **−181.6**$^{d}$ |
| | | | **282.7**$^{d}$ | −234.8$^{f,m}$ | 386.8$^{h}$ | −167.9$^{m}$ | |
| | | | 281.6$^{m}$ | | | | |
| ethanol radical | 276.3 | 4 | **287.6** | −56.8$^{n}$ | | **−11.2** | **−15.1**$^{i}$ |
| | | | | **−56.9** ± 3.8$^{o}$ | | | |
| | | | | −63.6 ± 4$^{f,p}$ | | | |
| 1-propanol | 302.7 | 9 | 319.1 | −255.4$^{q}$ | **397.3**$^{l}$ | | |
| | | | **322.6**$^{m}$ | **−255.1**$^{g,m}$ | | **−159.7** | |
| 1-propanol radical | 309.5 | 12 | **328.9** | **−75.8**$^{n}$ | | **−1.8** | |
| 2-propanol | 298.0 | 3 | 307.1 | −272.8$^{g,q}$ | **393.2**$^{l}$ | | |
| | | | **309.2**$^{m}$ | **−272.6**$^{f,m}$ | | −173.2 | |
| 2-propanol radical | 322.8 | 2 | **328.6** | **−97.4**$^{n}$ | | **−23.2** | **−27.6**$^{i}$ |
| | | | | −111.3 ± 4.6$^{p}$ | | | |

[a] Definitions of table heading: $S^\circ_{(g)}$ entropy in the gas phase; $n$, number of conformers; $\Delta_f H^\circ_{(g)}$, enthalpy of formation in the gas phase; BDE$_{(g)}$, gas phase bond dissociation enthalpy; $\Delta_f G^\circ_{(g)}$ and $\Delta_f G^\circ_{(aq)}$, Gibbs free energy of formation in the gas and aqueous phase, respectively. [b] Calculated by rigid rotator−harmonic oscillator model. [c] Includes average entropy of $n$ conformers and entropy of mixing. [d] Reference 12. [e] Reference 14; see also Reference 34 (402.3 kJ mol$^{-1}$) and Reference 35 (401.1 kJ mol$^{-1}$). [f] Reference 36. [g] Reference 37. [h] Reference 38. [i] Reference 19. [j] Reference 11. [k] Reference 39. [l] Calculated from HCR$^1$R$^2$OH + $^\bullet$CH$_2$OH = $^\bullet$CR$^1$R$^2$OH + CH$_3$OH with $\Delta_f H^\circ_{(g)}(\mathrm{H}^\bullet) = 218$ kJ mol$^{-1}$. [m] Reference 40. [n] Calculated using BDE and $\Delta_f H^\circ_{(g)}$ of parent. [o] Reference 15. [p] Reference 41. [q] Reference 13.

**TABLE 2: QM/MC and Experimental Free Energies of Solution (kJ mol$^{-1}$)**[a]

| molecule | $\Delta G^{\text{SCRF}}$ | $\Delta G_{\text{soln}}^{\text{SCRF}\ b}$ | $\Delta G_{\text{soln}}$ calc | $\Delta G_{\text{soln}}$ "expt" |
|---|---|---|---|---|
| methane | −0.38 | 8.4 (1.2) | 8.0 | 8.4$^{c}$ |
| methanol | 1.97 | −20.4 (0.6$_5$) | −18.4 | −21.3$^{c,d}$ |
| methanol radical | 2.67 | −18.8 (0.7) | −16.2 | −17.3$^{e}$ |
| ethanol | 1.37 | −18.9 (0.8) | −17.5 | −21.1$^{c,d}$ |
| ethanol radical | 2.16 | −14.5 (0.8) | −12.3 | −11.8$^{e}$ |
| 1-propanol | 1.65 | −21.7 (0.9) | −20.0 | −20.1$^{d}$ |
| 1-propanol radical | 2.30 | −17.7 (0.9$_5$) | −15.4 | |
| 2-propanol | 1.44 | −21.3 (0.9) | −19.8 | −20.1$^{d}$ |
| 2-propanol radical | 0.67 | −14.0 (1.0) | −13.3 | −12.3$^{e}$ |

[a] See Figure 1 for definition of symbols. [b] Numbers in parentheses are cumulated statistical errors relative to methane. The error for methane is relative to NOTHING. [c] Reference 12. [d] Reference 21. [e] Derived from data in Table 1.

and experimental results on the oxidation of the parent by RS$^\bullet$ radicals have borne out the predictions.[9,10]

Despite the above experimental evidence, the theoretical predictions relating to $\Delta\Delta G_{\text{soln}}$ are compelling, and further examination of the problem is obviously required. A theoretical approach with a discrete molecular modeling of the solvent would potentially avoid the difficulties with the SCRF approach. Here we have applied the BOSS (biochemical and organic simulation system) program package, combined with results derived from quantum mechanics, to investigate the solution properties of a biologically important class of free radicals. We evaluate the potential of this method, which does not require the introduction of new empirical parameters, and compare the free energies of solution, $\Delta G_{\text{soln}}$, values calculated by BOSS with results derived from experimental information.

Experimental values of $\Delta G_{\text{soln}}$ for radicals cannot be obtained by direct methods, such as vapor pressure measurements. One must therefore use radicals for which values of $\Delta_f G_{(aq)}$ and $\Delta_f G_{(g)}$ are known and obtain $\Delta G_{\text{soln}}$ from the fundamental relation:

$$\Delta G_{\text{soln}} = \Delta_f G_{(aq)} - \Delta_f G_{(g)} \qquad (1)$$

Quantitative experimental data are difficult to find. Here we have chosen the $^\alpha$C-centered radicals of methanol, ethanol, 1-propanol, and 2-propanol because values of $\Delta_f G_{(aq)}$ are available for three of them and for all of their parent alcohols. Values of $\Delta_f G_{(g)}$ were not directly available for the radicals, but they can be derived from experimental values of $\Delta_f H_{(g)}$ and standard ab initio calculations of entropies. The next section describes these calculations. A description of the BOSS calculations follows. The Results and Discussion contains the values of $\Delta G_{\text{soln}}$ obtained from eq 1 and from the BOSS calculations. Finally, there is a section on Conclusions.

## Values of $\Delta_f G_{(Aq)}$, $\Delta_f G_{(G)}$, and $\Delta G_{\text{Soln}}$ from Equation (1)

The thermodynamic results and data sources used in this paper have been summarized in Table 1. The quantities shown in bold were used to derive other dependent quantities in Table 1 and later in Table 2. For some of the parent compounds reliable values of $\Delta_f G_{(aq)}$ and $\Delta_f G_{(g)}$ exist in established databases. However, for all of the radicals and 1- and 2-propanol $\Delta_f G_{(g)}$ values had to be derived from $\Delta_f H_{(g)}$ and $\Delta_f S_{(g)}$, using the relation: $\Delta_f G_{(g)} = \Delta_f H_{(g)} - T\Delta_f S_{(g)}$. Literature values of $\Delta_f H_{(g)}$ for the radicals were assessed carefully, and in two cases values obtained by ab initio calculations with isodesmic reactions were preferred. The procedures used are described below.

**Free Energies of Formation in the Gas Phase.** $\Delta_f S_{(g)}$. The entropy of formation of a species, $\Delta_f S^\circ_{(g)}$, was calculated from the computed molar entropy, $S^\circ_{(g)}$, and the entropies of the elements.[12] $S^\circ_{(g)}$ was calculated for all species, because the molar entropies of the parent alcohols in the literature serve as useful checks on the validity of the procedure used. Most species of interest here exist in the gas phase as equilibrium mixtures of conformers. Conformations arise from torsions around C−C and C−O bonds and from the fact that the radical center is not planar; i.e., the out of plane bending potential has a double well. Relative energies, entropies, $S_i$, and populations (mole fractions), $x_i$, for each conformer of each species were therefore required. B3LYP calculations were used to obtain the energies, and $S_i$ values were computed in the rigid rotator−harmonic oscillator model from the B3LYP structures and vibrational frequencies (see further below for ab initio methods).

The total molar entropy is given by eq 2, where $n$ is the number of conformers and $R$

$$S^\circ_{(g)} = \sum_i^n x_i S_i - R\sum_i^n x_i \ln x_i \qquad (2)$$

is the ideal gas constant. The second term corresponds to the entropy of mixing. In Table 1, the second column gives $S_i$ for the conformer used in the subsequent BOSS calculation. The third column gives the number of conformers and the fourth the molar entropy. For each of the species, the variation in entropy among the various conformers is very small, the largest range (2.8 J $K^{-1}$ $mol^{-1}$) occurring in the case of 1-propanol. One might have assumed, as is usually done, that $\Delta S$ for a conformational change is negligibly small. However, $\Delta S_{mix}$, the entropy of mixing term (which is approximately the difference between the second and fourth columns of Table 1) is not. For instance, reasonable agreement between the calculated and experimental gas phase entropies of ethanol, and 1- and 2-propanol, could only be achieved by including $\Delta S_{mix}$. The magnitude of $\Delta S_{mix}$ is not very sensitive to the actual proportions of the components, however. It is readily verified that $R\ \ln(n)$, the entropy of mixing of $n$ equally populated conformations, provides a reasonable approximation to $\Delta S_{mix}$. As expected, the largest numbers of components occur for the most flexible species, 1-propanol ($n = 9$) and its radical ($n = 12$).

It may be noted that the double well nature of the radical bending potential is counted as giving rise to two conformations, even though in the case of $^\bullet CH_2OH$, the planar structure is lower in energy after the (harmonically approximated) ZPEs are taken into account. One may regard the "mixing" entropy of the two pyramidal forms of the radical center as compensating for the anharmonicity of the umbrella vibrational mode. The two-component treatment of $^\bullet CH_2OH$ yields a value for the entropy, 245.4 J $K^{-1}$ $mol^{-1}$, in close agreement with that obtained from a detailed analysis of the bending-torsion potential energy surface, 244.2 J $K^{-1}$ $mol^{-1}$ [11] (Table 1). The previously tabulated value[39] of 255.6 J $K^{-1}$ $mol^{-1}$ appears to be too large. The agreement between the calculated and literature values of $S^\circ_{(g)}$ for the parent alcohols is generally within 2 J $K^{-1}$ $mol^{-1}$ and satisfactory.

*$\Delta_f H_{(g)}$.* For the parent alcohols, experimental heats of formation are available (methanol,[12] ethanol,[12] 1-propanol,[13] 2-propanol[13]) and were adopted. For two of the radicals also there exist recent experimental $\Delta_f H_{(g)}$ values. In the case of $^\bullet CH_2OH$, a combined theoretical and experimental (spectroscopic) investigation has established the heat of formation to high accuracy, $-17.8 \pm 1.3$ kJ $mol^{-1}$,[11] and this is consistent with independent experimental measurements of the BDE of methanol (401.9 kJ $mol^{-1}$.[14]). A UV−PES investigation[15] has established a value for the ethanol radical, $-56.9 \pm 3.8$ kJ $mol^{-1}$, which is almost 7 kJ $mol^{-1}$ higher than previously reported values. It corresponds to an α C−H BDE of 396.2 kJ $mol^{-1}$ for ethanol. The isodesmic reaction[3] with ab initio energies computed at the G2MP2′-B3LYP level of theory,[16,17]

$$^\bullet CH_2OH + HCR^1R^2OH = {}^\bullet CH_2OH + {}^\bullet CR^1R^2OH^3 \qquad (3)$$

yields a value of 396.3 kJ $mol^{-1}$ (see Table 1). The level of agreement is excellent. Therefore the BDEs of 1- and 2-propanol in Table 1 were calculated with this isodesmic reaction using the same level of theory. The heats of formation of 1- and 2-propanol-derived radicals were calculated from them and the $\Delta_f H_{(g)}$ values of the parents. The enthalpies of the most stable parent and radical were used in eq 3. Experimentally derived BDEs *are* available for ethanol (Table 1) and 1- and 2-propanol. However, these show a greater stabilization with increased methyl substitution at the radical site than is supported by the theory. In light of earlier experience with C−H BDEs in alkylamines,[18] we consider the values from the isodesmic reactions to be more reliable.

*$\Delta_f G_{(g)}$.* $\Delta_f G_{(g)}$ of $CH_3OH$ and $CH_3CH_2OH$ were taken from ref 12. For other species, $S^\circ_{(g)}$, was converted to an entropy of formation from the elements, $\Delta_f S^\circ_{(g)}$,[12] and combined with the best value of $\Delta_f H^\circ_{(g)}$ to obtain the $\Delta_f G^\circ_{(g)}$ values shown in column 7 of Table 1.

**Free Energies of Formation in Solution.** The values of $\Delta_f G_{(aq)}$ for three of the radicals, $^\bullet CH_2OH$, $^\bullet CH(CH_3)OH$, and $^\bullet C(CH_3)_2OH$, have been calculated from the measurement of the reduction potentials of $CH_2O$, $CH_3CHO$ and $(CH_3)_2CO$.[19] For $CH_3OH$ and $CH_3CH_2OH$ $\Delta_f G_{(aq)}$ and $\Delta_f G_{(g)}$ were taken from ref 12.

**Experimental Free Energies of Solution.** Although the values of $\Delta_f G_{(g)}$ for the radicals involved ab initio calculations of the entropies, the values of $\Delta G_{soln}$ for all species obtained in this section are referred to as *experimental free energies of solution.* For purposes of comparison with the BOSS results, $\Delta G_{soln}$ is the difference between the free energy of formation of the substance in the aqueous phase and the gaseous phase under the same conditions of temperature (298.15 K), and concentration (1 M). Since the standard state for $\Delta_f G_{(g)}$ in Table 1 was 1 atm rather than 1 M, the values obtained from eq 1 must be corrected by $-7.9$ kJ $mol^{-1}$.[20] $\Delta G_{soln}$ values calculated for the radicals by that method are given in column 5 of Table 2. The values for the four alcohols are from a review by Cramer and Truhlar.[21] For methanol and ethanol, $\Delta G_{soln}$ values derived from $\Delta_f G_{(aq)}$ and $\Delta_f G_{(g)}$ listed in Wagman et al.[12] are in agreement with these. In the case of 2-propanol, a similar value from vapor pressure data is cited by Schwartz and Dodson.[19]

## BOSS Calculations

**Ab Initio Methods.** The structures of the parent alcohols and corresponding $^\alpha C$ radicals were determined by complete geometry optimization using the B3LYP hybrid HF-DFT procedure, as implemented in the Gaussian 94 suite of programs,[22] and the 6-31G(D) basis set. Vibrational frequencies were calculated and scaled by 0.98 for the purpose of deriving zero point energies, and thermodynamic data in the rigid rotator−harmonic oscillator approximation.[23]

One conformation of each species was the "solute" of the BOSS calculations. Its gas phase entropy is shown separately and in no case differs by more than 1 e.u. from the average entropy of the components of the mixture (first term in eq 2). To simulate the state of the solute as it exists in solution, the geometry optimization, frequency analysis, and thermodynamic calculations were repeated with SCRF−SCIPCM (self-consistent isodensity polarizable continuum model),[24] at the default isodensity set to 0.0004 and the dielectric constant set to 78.5 (water). A low torsional vibrational mode in the $^\alpha C$ radical of 2-propanol in the SCRF calculation was approximated as a free internal rotor. All other internal rotations were treated as vibrations. Single point calculations at the B3LYP/6-311+G(3DF,2P) level were carried out in the presence and absence of the reaction field in order to test the effect of the basis set on the results. CHELPG (charges from electrostatic potentials, grid-oriented) charges to simulate the electrostatic potential[25] were calculated with the large and small basis sets.

**BOSS (Monte Carlo) Calculations.** Absolute free energies of solution were derived using the BOSS Monte Carlo pack-

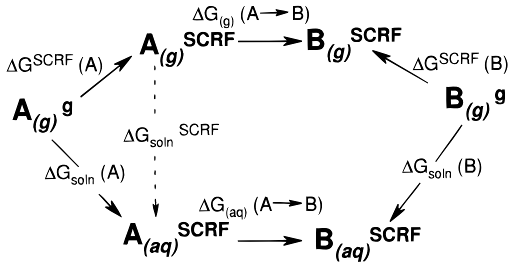

**Figure 1.** Thermodynamic cycles and definition of symbols used in the text and tables.

age,[26] following a modification of a procedure suggested by Lim and Jorgensen.[27] The SCRF structures, with charges calculated using the CHELPG procedure, were transferred to a periodic solvent box containing about 500 TIP4P[28] water molecules. The MC simulation gives information on explicit solvent structure, including a natural inclusion of hydrogen-bonding effects. Although the BOSS system permits optimization of solute structure with an internal molecular mechanical force field, in the present case, the pre-prepared ab initio SCRF structures were not permitted to change. The combination of rigid structures with frequencies and charges derived from ab initio results gives a physical model of the solute that does not rely on empirical parameters.

TIP4P water[28] consists of three Lennard-Jones atoms, an oxygen and two hydrogens, with charges of +0.52 e on the hydrogens, and a balancing charge of −1.04 e displaced 0.15 Å from the oxygen on the bisector of the H−O−H angle. This structure produces realistic radial distribution functions, reasonable densities, and reliable solvation free energies.[28]

The electrostatic contribution of the interaction with solute is through CHELPG located at the nuclear positions and the Lennard-Jones interaction through the geometric mean of solvent and solute atom-specific $\sigma$ and $\epsilon$ (Lennard-Jones) parameters. Following the recommendation within BOSS, the hydrogen atom of the OH group has zero for its Lennard-Jones parameters, while its charge still has the CHELPG value.

The free energy perturbation (FEP) technique[29,30] was used to derive accurate *relative* free energies of solution of two species, say A and B; A is converted to B in 10 steps by linearly scaling geometry, charges, and Lennard-Jones parameters. The relative free energy of solution of the two species is the sum of the changes of the 10 steps. In practice, an initial equilibration of 6 000 000 steps (where a step is the random movement and reorientation of one molecule in the box), was carried out. The first 750 000 steps of this were performed without allowing volume changes, and the rest in the NPT ensemble, at 25 °C and 1 atm pressure. Statistics were accumulated over an additional 6 000 000 steps, divided into 12 segments of 500 000 steps each. Errors were estimated as the root-mean-square of the standard deviations of each of the segments. A cutoff distance for solute−solvent interactions of 12 Å (half the width of the box) was used, with quadratic feathering of the intermolecular interactions to zero in the last 0.5 Å. For solvent−solvent interactions, the cutoff was reduced to 10 Å. Subsequent runs that continued a sequence of permutations (see below) were carried out with a total of 3 000 000 steps of initial equilibration, with the first 750 000 steps again without volume changes.

**Free Energy Perturbation.** The left- and right-hand side of Figure 1 show the free energy changes occurring between species in solution with SCRF-optimized geometries ($A_{(aq)}{}^{SCRF}$, $B_{(aq)}{}^{SCRF}$) and in the gas phase with the same geometries ($A_{(g)}{}^{SCRF}$, $B_{(g)}{}^{SCRF}$) or optimized gas phase geometries ($A_{(g)}{}^{g}$, $B_{(g)}{}^{g}$). The arrows in the middle show the changes occurring in the conversion of A into B by the FEP technique. The relative free energy of solution of species A and B, $\Delta\Delta G_{soln}$ (=$\Delta G_{soln}(B) - \Delta G_{soln}(A)$), is given by eq 4:

$$\Delta\Delta G_{soln} = \Delta G_{(aq)}{}^{SCRF}(A{\rightarrow}B) - \Delta G_{(g)}{}^{SCRF}(A{\rightarrow}B) + \Delta G^{SCRF}(B) - \Delta G^{SCRF}(A) \quad (4)$$

The last two terms correspond to the free energy change associated with the distortion of the optimized gas phase structures of the individual species to the corresponding solution structures (approximated as the SCRF-optimized structures) *in the absence of the reaction field*.[27] These are discussed below. The quantity actually calculated by BOSS is the solvent response part of the permutation of A to B, $\Delta G_{(aq)}{}^{BOSS}(A{\rightarrow}B)$, i.e.,

$$\Delta G_{(aq)}{}^{BOSS}(A{\rightarrow}B) = \Delta G_{(aq)}{}^{SCRF}(A{\rightarrow}B) - \Delta G_{(g)}{}^{SCRF}(A{\rightarrow}B) \quad (5)$$

Therefore,

$$\Delta\Delta G_{soln} = \Delta G_{(aq)}{}^{BOSS}(A{\rightarrow}B) + \Delta G^{SCRF}(B) - \Delta G^{SCRF}(A) \quad (6)$$

The quantity, $\Delta G^{SCRF}(A)$, may be represented as in eq 7:[27]

$$\Delta G^{SCRF}(A) = \Delta H^{SCRF}(A) - T(S(A_{(g)}{}^{SCRF}) - S(A_{(g)}{}^{opt})) \quad (8)$$

We define the enthalpy change following Lim and Jorgensen:[27]

$$\Delta H^{SCRF}(A) = \langle \Phi^{SCRF} | H^{B3LYP} | \Phi^{SCRF} \rangle_{(g)} - \langle \Phi^{opt} | H^{B3LYP} | \Phi^{opt} \rangle_{(g)} \quad (8)$$

Values for the enthalpy change determined at the B3LYP/6-31G(D)//B3LYP/6-31G(D) and B3LYP/6-311+G(3DF,2P)//B3LYP/6-31G(D) levels are discussed below. The entropy is derived from B3LYP/6-31G(D) frequencies with and without the reaction field. The difference represents changes to rotational and vibrational terms as a consequence of the presence of the solvent modeled as a dielectric continuum. We shall see that the $\Delta S$ term is small and may be set to zero, in effect avoiding the tedious computation of vibrational frequencies in the presence of the reaction field.

## Absolute Solvation Free Energies

The *absolute* free energy of solvation of A is derived by making A disappear, i.e., setting B to NOTHING in Figure 1. Only for methane was the absolute solvation free energy determined, by permuting it to NOTHING. Methane was removed from the solvent in a two-step perturbation known as electrostatic decoupling.[31] The first step was to mutate methane into a species with the identical geometry and Lennard-Jones parameters, but without any charges on the atoms. This species only interacted with the solvent by taking up a certain volume. In a second perturbation, the C−H bonds were reduced to 0.1 Å, and the Lennard-Jones parameters were removed, leaving a tiny solute that had no effect on its surroundings. The sum of these two perturbations yielded an absolute value for the solvation free energy of methane of 8.4 ± 1.2 kJ mol$^{-1}$, exactly the same as experiment and essentially the same as in the pioneering work of Jorgensen and co-workers.[31,32]

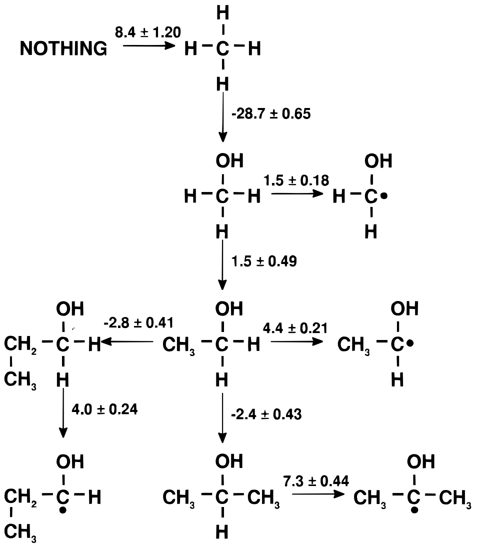

**Figure 2.** "Tree" of permutations. Each arrow corresponds to an FEP calculation. The value on the arrow is $\Delta G_{(aq)}{}^{BOSS}(A \rightarrow B)$ (eq 5) with the RMS error for that perturbation sequence.

To avoid singularities due to the close approach of solvent molecules to charged species, electrostatic decoupling was more appropriate than direct mutation when aliphatic functional groups were being added or removed. Therefore, a similar procedure was used in subsequent mutations whenever a methyl group was being added. This procedure saw first the growth of the methyl group out of a hydrogen, while maintaining the hydrogen's charge on the central carbon, and keeping all other charges constant. Second, the charges on all the atoms were mutated to their final values.

In the present work, the permutation tree shown in Figure 2 was applied. The quantities, $\Delta G_{(aq)}{}^{BOSS}(A \rightarrow B)$, for each permutation of B3LYP−SCRF/6-31G(D) structures and CHELPG are indicated on the arrows. The absolute free energy of solution of a species is the sum of all of the permutation free energy changes back to "NOTHING", and the associated error is the RMS of the individual errors. The largest single statistical error is for the permutation of methane to NOTHING.

## Results and Discussion

The computed results are summarized in Table 2. The first column of numbers corresponds to $\Delta G^{SCRF}$ of Figure 1, the free energy of distortion in the gas phase of the gas phase optimized structure to the geometry and the wave function of the solution structure (as modeled by SCRF−SCIPCM). The second column lists absolute free energies of solution that would be obtained if the gas and solution phase structures were identical and equal to the SCRF-derived species. These correspond to the vertical dashed arrow in Figure 1. The best calculated and "experimental" $\Delta G_{soln}$ values are listed in the last two columns. In Figure 3 are plotted the $\Delta\Delta G_{soln}$ values, namely the differences between the free energies of solution of the $^{\alpha}$C-centered radical and its parent alcohol by all three measures (columns 3−5 of Table 2). Table 3 and Figure 4 detail tests on the effects of basis set size and medium for optimization on methanol and its radical.

## Comparison of Calc vs "Expt" (Table 2)

From Table 2 it is immediately apparent that there is agreement between calculated and best experimental values of $\Delta G_{soln}$ (columns 4 and 5 of Table 2) to within an experimental accuracy of ±4 kJ mol$^{-1}$ in every case.[33] The average deviation is 1.2 kJ mol$^{-1}$, the largest being 3.6 kJ mol$^{-1}$ in the case of the ethanol parent. Within this small sample, the radical species are as well described as the parents. In Figure 3, the differential solvation, $\Delta\Delta G_{soln}$, of the $^{\alpha}$C radical and its parent alcohol is displayed. Again, there is good agreement between theory and experiment in the three cases for which comparison is possible. While the $\Delta\Delta G_{soln}$ values are small, they are significant in the context of the statistical error of the BOSS FEP calculation. They indicate that the free radical is *less* solvated than the parent. It is of considerable interest that SCRF calculations (not shown)

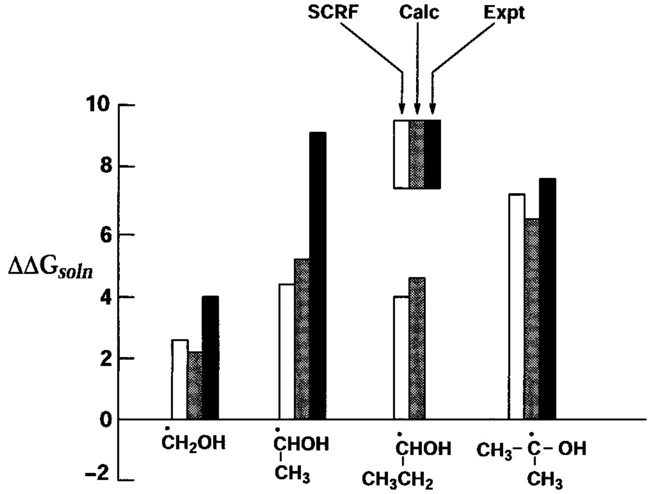

**Figure 3.** Difference in free energies of solution of the $^{\alpha}$C-centered radical and the parent alcohol. $\Delta\Delta G_{soln} = \Delta G_{soln}(\text{radical}) - \Delta G_{soln}(\text{parent})$ in kJ mol$^{-1}$. SCRF, Calc, and Expt refer to columns 3, 4, and 5, of Table 2, respectively.

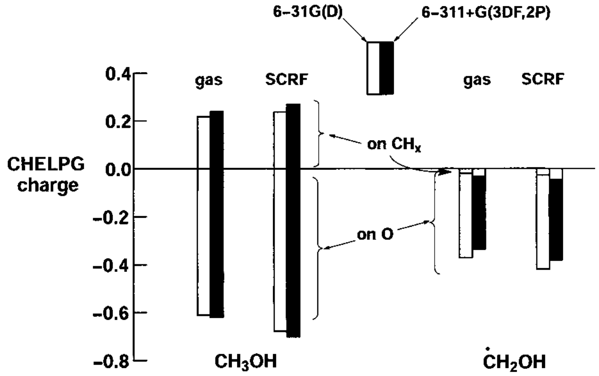

**Figure 4.** CHELPG on O and methyl/methylene groups of methanol and its $^{\alpha}$C radical with small and large basis sets. The total lengths of the bars represent the charge separation of the C−O bond.

**TABLE 3: SCRF and Basis Set Dependence of $\Delta G_{soln}$ at 298.15 K for $CH_3OH$ and $^{\bullet}CH_2OH$**

| wave function<br>basis set<br>geometry | gas<br>small<br>gas | gas<br>large<br>gas | SCRF<br>small<br>gas | SCRF<br>small<br>SCRF | SCRF<br>large<br>SCRF |
|---|---|---|---|---|---|
| $CH_3OH$ | | | | | |
| $\Delta\Delta G_{soln}$ | 7.7 | 7.8 | 0.3 | 0.0 | −0.2 |
| $\Delta G_{soln}{}^{SCRF}$ | −12.6 | −12.6 | −20.1 | −20.4 | −20.6 |
| CHELPG of H(O) | +0.393 | +0.381 | +0.440 | +0.440 | +0.432 |
| CHELPG of O | −0.611 | −0.619 | −0.677 | −0.678 | -0.700 |
| CHELPG of $CH_3$ | +0.218 | +0.238 | +0.237 | +0.238 | +0.268 |
| $^{\bullet}CH_2OH$ | | | | | |
| $\Delta\Delta G_{soln}$ | 7.9 | 9.2 | 1.0 | 0.0 | 1.2 |
| $\Delta G_{soln}{}^{SCRF}$ | −11.0 | −9.6 | −17.8 | −18.8 | −17.7 |
| CHELPG of H(O) | +0.391 | +0.369 | +0.441 | +0.445 | +0.426 |
| CHELPG of O | −0.371 | −0.336 | −0.414 | −0.418 | −0.380 |
| CHELPG of $^{\bullet}CH_2$ | −0.020 | −0.033 | −0.027 | −0.027 | −0.046 |

predict higher solvation (albeit to within 1 kJ mol$^{-1}$) for the radical relative to the parent. These results are contrary to the present discrete solvent model results and experiment. Furthermore, the present results suggest a general *decrease* in the magnitude of the free energy of solvation of the radical with increasing size or substitution at the $^{\alpha}$C center, while the solvation of the parent is essentially constant (in this small sample). As the interaction of the solvent with the solute, whether radical or parent, is primarily electrostatic in nature, and the electrostatic potential of each is described approximately as an atom-centered monopole expansion via the CHELPG, one may compare the CHELPG of the two solutes for insight into the reason for the lower solvation of the radical. CHELPG of OH and methyl/methylene groups of the methanol radical and parent in both the gas phase and solution (SCRF) are representative of the series and are listed in columns 2 and 5 of Table 3. The principal difference between radical and parent in either phase is the considerably greater charge separation across the C−O bond in the case of the parent compared to the radical. This is shown graphically in Figure 4. The lower bond polarity of the radical reflects the delocalization of the oxygen lone pair of electrons into the half-empty 2p orbital of the $^{\alpha}$C atom. As anticipated, the presence of the reaction field leads to increased charge separation compared to the gas phase in each case, but the change is smaller in the case of the radical and the lower electrostatic potential around the O of the radical remains. In the parent, the C−O bond becomes more polar, making the oxygen more basic, and the polarity change increases as the $^{\alpha}$C center goes from primary to secondary to tertiary (not shown). The associated increase in H-bonding from the water must compensate for the hydrocarbon part of the parent, resulting in approximately constant solvation free energy over the series. On the other hand, the reaction field induces a smaller change in the radical, and the oxygen remains a poorer H-bond acceptor. The inability to account for such important solute−solvent interactions as H-bonding is an inherent limitation of all continuum models.

**Is SCRF Necessary?** The differences between $\Delta G_{\text{soln}}{}^{\text{SCRF}}$ and $\Delta G_{\text{soln}}$(expt) (Table 2) represent agreement with the raw BOSS results without correction for the gas phase distortion of the solute. The average deviation is 1.4 kJ mol$^{-1}$, with the largest being 2.7 kJ mol$^{-1}$ for the ethanol radical. There is no significance between this result and the average deviation of 1.2 kJ mol$^{-1}$ for the most appropriate comparison discussed above. At least for the small molecules being considered here, the effects of the reaction field on the geometry (geometry optimization with SCRF−SCIPCM) are very small, and this is reflected in the negligible change in $\Delta H^{\text{SCRF}}$(A), the first term in eq 7. The major part of $\Delta G^{\text{SCRF}}$ (column 2 of Table 2) arises in the change in the entropy as calculated using the gas phase and solution (i.e., vibrational frequencies with SCRF−SCIPCM) phases. As the magnitude of $\Delta G^{\text{SCRF}}$ is less than the expected experimental error, and its contribution does not significantly improve agreement with experiment, it appears that one may avoid both the geometry optimization and the vibrational frequency analysis in the presence of the reaction field. The latter process is especially tedious, as it must be carried out numerically.

The BOSS free energies of solution, $\Delta G_{\text{soln}}{}^{\text{SCRF}}$, in Table 2 were generated with B3LYP/6-31G(D) geometries evaluated with SCRF−SCIPCM. Table 3 lists the results of a number of tests in which this "state" of $CH_3OH$ and $^{\bullet}CH_2OH$ (column 5) is transmuted by FEP calculations into others that differ in wave function (gas phase or SCRF) with small (6-31G(D)) or large (6-311+G(3DF,2P)) basis set and geometry (gas phase or SCRF). $\Delta\Delta G_{\text{soln}}$ describes the direct result of the FEP, and $\Delta G_{\text{soln}}{}^{\text{SCRF}}$ is the corresponding absolute free energy of solution (relative to NOTHING). The $\Delta G_{\text{soln}}{}^{\text{SCRF}}$ values may be directly compared with the experimental $\Delta G_{\text{soln}}$ values from Table 2: $CH_3OH$ −21.3 kJ mol$^{-1}$; $^{\bullet}CH_2OH$ −17.3 kJ mol$^{-1}$. It is immediately apparent that all three SCRF wave function entries (columns 4−6) are in good agreement with experiment while the two entries where the gas phase wave function was used to derive the CHELPG (columns 2 and 3) show too low free energies of solution for both the parent and radical. These results are independent of whether a small or large basis set was used. Comparison of columns 4 and 5 confirms that essentially the same results are obtained with either gas phase- or SCRF-optimized geometries, provided the SCRF wave function (from a single point calculation in the first case) is used. The larger difference occurs in the case of the radical for which the free energy of solution is calculated to be lower by 1.0 kJ mol$^{-1}$ with the gas phase geometry compared to the SCRF-optimized geometry.

**Sensitivity to Choice of Lennard-Jones Parameters.** Because calculations on free radicals by BOSS have not previously been reported, one further test was carried out, namely the consequences of the choice of Lennard-Jones parameters for the tricoordinated radical center. The geometry at this carbon atom is intermediate between planar (sp$^2$ hybridized) and one with tetrahedral angles (sp$^3$ hybridized). All of the results hitherto discussed used the same parameters as internally defined for an sp$^2$ hybridized carbon atom. An FEP calculation on methanol was carried out in which the standard state (column 5 of Table 3) was changed to one with sp$^3$ hybridized carbon parameters. The result (not shown) was a $\Delta\Delta G_{\text{soln}}$ value of −0.04 kJ mol$^{-1}$. Thus, either choice would produce equivalent results.

## Conclusions

**Methodology.** The BOSS Monte Carlo discrete solution simulation package, combined with quantum mechanical (QM+BOSS) calculations, is capable of yielding accurate free energies of aqueous solution for $^{\alpha}$C-centered free radicals derived from alcohols, and for the parent alcohols themselves. The results are not sensitive to the choice of Lennard-Jones parameters for the radical center. The recommended procedure involves geometry optimization and frequencies by QM methods (B3LYP/6-31G(D)) in the gas phase, followed by a single point SCRF−SCIPCM calculation to obtain CHELPG. The SCRF-derived CHELPG model the electrostatic potential of the substance as it exists in solution and is seen by the solvent water molecules. They are not sensitive to the size of the basis set. Omission of the SCRF step yields free energies of solution that are too low compared to experiment.

**Gas-Phase Free Energies of Formation of $^{\alpha}$C-Centered Free Radicals.** The gas phase free energies of formation of the $^{\alpha}$C-centered radicals from the lower alcohols were derived from a combination of experimental data and theoretical procedures. Enthalpies of formation were taken from experiment (methanol radical and ethanol radical) or derived from $\Delta_f H^{\circ}{}_{(g)}$ of the parent alcohols and calculated BDEs (radicals of 1- and 2-propanol). Entropies were obtained from the rigid rotator−harmonic oscillator approximation, taking account of the conformational mix of the free radicals. The derived quantities are listed in Table 1.

**Solvation of $^{\alpha}$C-Centered Free Radicals.** The absolute free energies of solution, $\Delta G_{\text{soln}}$, of the $^{\alpha}$C-centered radicals from the lower alcohols in water are quantitatively described by QM+BOSS calculations: methanol radical, expt $-17.3$ kJ mol$^{-1}$, calc $-16.2$ kJ mol$^{-1}$; ethanol radical, expt $-11.8$ kJ mol$^{-1}$, calc $-12.3$ kJ mol$^{-1}$; 2-propanol radical, expt $-12.3$ kJ mol$^{-1}$, calc $-13.3$ kJ mol$^{-1}$. A value is predicted for the 1-propanol radical, $\Delta G_{\text{soln}} = -15.4$ kJ mol$^{-1}$. The radicals are less solvated than the parent alcohols. Examination of the CHELPG suggests that the reason lies in the lower polarity of the C−O bond and lower H-bond acceptor ability of the oxygen atom. The latter factor is not modeled by continuum models. The SCRF−SCIPCM procedure actually yields a slightly higher solvation energy for the radicals in contradiction with the experimental and the present QM+BOSS results.

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