Ab Initio Calculations of Free Energy Barriers for Chemical Reactions in Solution: Proton Transfer in $[FHF]^-$

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Abstract: This paper describes a hybrid ab initio quantum mechanical/molecular mechanics (QM/MM) method for calculating activation free energies of chemical reactions in solution, using molecular mechanics force fields for the solvent and an ab initio technique that incorporates the potential from the solvent in its Hamiltonian for the solute. The empirical valence bond (EVB) method is used as a reference potential for the ab initio free energy calculation, and drives the reaction along the proper coordinate, thus overcoming problems encountered by direct attempts to use molecular orbital methods in calculations of activation free energies. The utility of our method is illustrated by calculating the activation free energy for proton transfer between fluoride ions in the $[FHF]^-$ system, in both polar and nonpolar solution.

I. Introduction

Quantum mechanical calculations of chemical processes in solution present a major challenge to theoretical chemistry because of the enormous number of solvent atoms that interact with the reacting fragments. In order to make such calculations practical, it is necessary to divide the system into a reacting subsystem that is treated quantum mechanically and a solvent subsystem that is treated classically. Attaining reliable results with such a partitioning requires that the reacting region be described by an accurate quantum mechanical wave function, that the solvent or protein region be described by a suitable classical force field, and that the interaction potential between the two sub-regions provides a realistic description of the actual potential surface there. A further difficulty arises when experimentally measurable quantities such as the reaction rate are desired; these quantities require free energies rather than enthalpies, and the application of free energy perturbation theory to calculations of activation barriers is far from trivial. This combination of requirements presents a significant challenge to theoretical chemists studying reactions in proteins or solvents.

A promising option involves the use of hybrid molecular orbital/molecular mechanics methods, which date back to Warshel and Levitt[1] and have been extended by others.[2-9] Related techniques that treat the solvent as a dielectric continuum are also quite effective.[10-12] For some reactions one may also obtain reliable results by solvating the gas phase solute charges without allowing them to be polarized by the solvent.[13] Another powerful option is offered by the Empirical Valence Bond (EVB) method.[14-16] At present most hybrid QM/MM approaches that include the solvent in the solute Hamiltonian use semi-empirical QM techniques, and, at least in principle, ab initio approaches can be more accurate.

The present work describes a hybrid quantum mechanics/molecular mechanics method using a classical molecular dynamics description of the solvent region and an ab initio quantum mechanical description of the solute region. These calculations use free energy perturbation (FEP) theory methods along an EVB reference potential to compute the free energy curves for the reaction studied. We present results for the proton transfer in the $[FHF]^-$ model system to demonstrate the utility of our method.

II. Methods

A. Molecular Mechanics and EVB Potential Surfaces

Molecular mechanics methods[17-22] use empirical potential surfaces that represent the energetics of a molecule as a set of functions composed of bonded and non-bonded potentials. Although suitable for describing a large amount of important chemical effects, standard molecular mechanics potential surfaces are generally not capable of describing bond breaking and bond making processes. Such shortcomings may be circumvented with the EVB method,[14] which is capable of describing the breaking and reforming of chemical bonds, and, consequently, may realistically simulate chemical reactions of large molecules in solution or proteins. Other parameterized VB techniques have been developed in recent years[23] that also provide the ability to describe bond breaking and bond making processes.

The EVB method describes reacting potential surfaces using a separate potential surface to describe each of the important valence bond structures. For example, in a proton transfer reaction from molecule A to molecule B,

$$A—H \quad + \quad B^- \quad \rightarrow \quad A^- \quad + \quad H—B. \qquad (1)$$

there are three important resonance configurations:

$$\begin{aligned} \Psi_1 &= A—H \qquad B^- \\ \Psi_2 &= A^- \qquad H—B \\ \Psi_3 &= A^- \quad H^+ \quad B^- \end{aligned} \qquad (2)$$

The EVB method describes the energetics of this system with an effective Hamiltonian that represents the actual VB integrals scaled by the proper overlap matrix elements. The ground state energy may be obtained by diagonalizing the EVB Hamiltonian,[15,16]

$$H_{evb} = \begin{bmatrix} H_{11} & \delta_{12} & H_{13} \\ \delta_{12} & H_{22} & H_{23} \\ H_{31} & H_{32} & H_{33} \end{bmatrix}. \qquad (3)$$

The diagonal elements are determined by potential functions that describe the proper asymptotic behavior for that particular resonance configuration:

$$H_{ii} = \varepsilon_i = U_i^{SS} + U_i^{Ss} + U^{ss}. \qquad (4)$$

Here S and s designate the solute and solvent, respectively. U^{SS} represents the solute gas phase energy and U^{Ss} represents the electrostatic and van der Waals interaction between the solute and solvent molecules.[15,16] The off-diagonal elements are represented by analytical functions that are assumed to be independent of the solvent; that is, $H_{ij} = H_{ij}^{SS}$. The actual functions used for the diagonal and off-diagonal matrix elements are described in detail in reference 16. The most important feature of the EVB method is that it is always possible to find a set of functions that reproduce to a good approximation the ab initio energies and charges in the gas phase, and that the addition of the solvent terms in equation (4) provides a convenient way of transferring such an effective Hamiltonian to solution. The EVB Hamiltonian may also be used with umbrella sampling methods, described below, to provide a reference function for the evaluation of the activation free energy of chemical reactions in solution.

B. Hybrid Ab Initio—Molecular Mechanics Techniques

Precise investigations of chemical phenomena often require at least a certain part of the calculation to include quantum mechanical effects, and to determine the electronic wave function of the molecule by solving the time-independent Schrödinger equation.[24,25] Even the most efficient quantum mechanical methods[26-28] are still computationally intensive for large molecular systems, and, consequently, our aim is to develop methods where a small solute region is described using quantum mechanical methods, and a larger solvent region is described using the classical mechanics methods described in the previous section.

Excellent reviews of ab initio techniques exist elsewhere,[25] and so the discussion in this section will only mention the points of particular importance to the current work. We use 6-31G** basis sets with Hartree-Fock (HF) wave functions with second-order Møller-Plesset (MP2) perturbative corrections to describe the molecular electronic wave function. The GAMESS program suite[29] has been used for all of the ab initio calculations reported in this paper. With an accurate quantum mechanical method representing the solute region, our main challenge is the reliable and efficient incorporation of the surrounding solvent in the solute Hamiltonian. In implementing our hybrid QM/MM approach use the classical surface constrained all atom solvent (SCAAS) model,[30,31] as implemented in the program Enzymix,[21] to describe the solvent region. There are many ways to incorporate an external field into the Hamiltonian.[6,10] We have found that a simple and rigorous method is obtained by representing the solvent atoms as point charges, and to add the external potential field produced by the point charges to the other one-electron terms in the Hamiltonian. The only additional integrals required due to these terms in the evaluation and optimization of the quantum mechanical wave function are of the form

$$V_{ext} = \sum_{i=1}^{Norb} \sum_{k=1}^{Nch} \left\langle \phi_i \middle| \frac{Z_k}{|r - r_k|} \middle| \phi_i \right\rangle \qquad (5)$$

for a field of N_{ch} point charges with charge Z_k and location $\mathbf{r}_k$, and where ϕ_i is a molecular orbital on the solute. The integrals in equation (5) are calculated using the same techniques as nuclear attraction integrals, and are added to the other one-electron integrals (and thus automatically included in single-point electronic energy calculations, geometry optimizations, and MP2 perturbative corrections). The nonelectrostatic solute-solvent interactions are included via the standard SCAAS solute-solvent van der Waals terms.

C. Calculations of Ab Initio Free Energy Surfaces

1. General Considerations of Free Energy Surfaces

In general one may define a free energy function $\Delta g_a(X)$ that expresses the probability of finding the system at a specified value, X_n, of a given reaction coordinate, X, for a potential surface E_a, as

$$\exp\{-\beta\Delta g_a(X_n)\} = \frac{z_a(X_n)}{Z_a} \tag{6}$$

where β=1/k_BT and k_B is the Boltzmann constant. The partition functions z_a and Z_a are defined as

$$\begin{aligned} z_a(X_n) &= \int \exp\{-\beta E_a(X_n)\} d\gamma_n \\ Z_a &= \int z_a(X) dX \end{aligned} \tag{7}$$

where γ_n represents the coordinates perpendicular to X at X_n. It is useful to write $z_a(X_n)$ as

$$z_a(X_n) = \int \delta(X - X_n) \exp\{-\beta E_a(X)\} d\Gamma \tag{8}$$

where dΓ = dγdX. The probability $z_a(X_n)/Z_a$ may in principle be determined by running very long trajectories and evaluating the ratio between the time the system is at X_n to the total time. Such an approach is very inefficient when X_n corresponds to a high energy region of the potential surface, and it is advantageous to rewrite equation (6) as (see reference 31)

$$\begin{aligned} \exp\{-\beta\Delta g_a(X_n)\} &= \left(\frac{Z_m}{Z_a}\right)\left(\frac{z_a(X_n)}{Z_m}\right) \\ &= \left(\frac{\int \exp\{-\beta(E_m - E_a) - \beta E_a\} d\Gamma}{\int \exp\{-\beta E_a\} d\Gamma}\right)\left(\frac{z_a(X_n)}{Z_m}\right) \\ &= \left\langle \exp\{-\beta(E_m - E_a)\}\right\rangle_{E_a}\left(\frac{z_a(X_n)}{Z_m}\right) \end{aligned} \tag{9}$$

where $\langle\ \rangle_{E_a}$ denotes a MD average over the potential surface E_a, using the standard approach[32] of replacing a configuration integral by an average over a trajectory. We may further rewrite this expression using (see also reference 31)

$$\exp\{-\beta\Delta g_a(X_n)\} = \langle\exp\{-\beta(E_m - E_a)\}\rangle_{E_a} \times\left(\frac{\int\delta(X - X_n)\exp\{-\beta(E_a - E_m + E_m)\}d\Gamma}{\int\exp\{-\beta E_m\}d\Gamma}\right) \tag{10}$$

to finally obtain

$$\begin{aligned}\exp\{-\beta\Delta g_a(X_n)\} &= \langle\exp\{-\beta(E_m - E_a)\}\rangle_{E_a} \\ &\quad\times\langle\delta(X - X_n)\exp\{-\beta(E_a - E_m)\}\rangle_{E_m} \\ &= \exp\{-\beta\Delta G_{a\to m}\} \\ &\quad\times\langle\delta(X - X_n)\exp\{-\beta(E_a - E_m)\}\rangle_{E_m}\end{aligned}. \tag{11}$$

This expression[33] is particularly effective when E_m is chosen as the potential that forces X to spend most of its time at X_n. The $\langle\ \rangle_{E_a}$ average is evaluated by standard free energy perturbation approaches using a series of mapping potentials (see below).

The proper coordinate X should reflect both solute and solvent reaction coordinates. X may be obtained from the difference in energy (ε_1-ε_2) between the two valence bond states (Ψ_1) and (Ψ_2) in equation (2). This energy difference is negative when the system is in state (Ψ_1), goes through zero at the transition state, and is positive when the system is in state (Ψ_2), and, consequently, the progress of the reaction in equation (1) may be monitored via the energy difference (ε_1-ε_2). What is most significant about the definition X=(ε_1-ε_2) is that it not only incorporates the solute contribution to the reaction coordinate, but it also includes contributions from the solvent reaction path, as the electrostatic part of X is a function of the interaction between the reaction field from the solvent and the solute dipole moment.[15] Because solvent fluctuations, and the corresponding changes of X, play a major role in chemical processes in solution, it is crucial to be able to sample these fluctuations. Unfortunately, the solvent component of the reaction coordinate involves a concerted motion of many coordinates and one cannot simply force all water molecules to rotate in a given direction in the same way that a single bond in a gas phase calculation is forced to stretch. Thus it is important to use an effective mapping procedure that will use some parametric representation of the change in the solute charges during the reaction to map the solvent coordinates. Such a mapping approach is conveniently provided by the EVB mapping approach as described below.

2. Using the EVB Method as a Reference Potential

It is essential to force the system to spend significant time at the transition state to obtain reasonable convergence of free energy calculations. An ideal way to bring the system to the transition state is to use a mapping potential that can polarize the solvent to the desired configuration, such as a valence bond mapping potential[15,34]

$$\varepsilon_{ref}^{m} = (1-\lambda_m)\varepsilon_1 + \lambda_m \varepsilon_2 \qquad (12)$$

where λ_m is a variable that changes from 0 to 1 to control the progress of the reaction from state ε_1 to state ε_2. Unlike the ground state EVB potential, obtained by diagonalizing H_{evb} in equation (3), the EVB mapping potential evaluates the energy using a fixed ratio of the two valence bond resonance structures, ε_1 and ε_2. The potential surface of these valence bond states is represented as

$$\varepsilon_i = U_i^{SS}(R) + U_i^{Ss}(R, Q_i^0(R)) + U^{ss} \qquad (13)$$

where R denotes the solute geometrical coordinates, $Q_i^0(R)$ is the solute gas phase charge distribution in the ith resonance structure, and S and s again designate the solute and solvent respectively. Substituting equation (13) for E_m in equation (11) we obtain[15]

$$\begin{aligned} \exp\{-\beta\Delta g(X_n)\} = {} & \exp\{-\beta\Delta G_{ref}(\lambda_0 \to \lambda_m)\} \times \\ & \left\langle \delta(X - X_n)\exp\left\{-\beta\left(E_q - \varepsilon_{ref}^{m}\right)\right\}\right\rangle_{\varepsilon_{ref}^{m}} \end{aligned} \qquad (14)$$

where ε_{ref}^{m} is the mapping potential from equation (12), λ_m is the value of λ that keeps the system closest to X_n, and E_q is the given quantum mechanical potential surface (either the ab initio surface or the ground state EVB surface obtained by solving equation (3)). The free energy $\Delta G_{ref}(\lambda_0 \to \lambda_m)$ is obtained using standard free energy perturbation (FEP) approaches with a gradual change of λ in m discrete steps:[15,32,35,36]

$$\exp\left\{-\beta\Delta G_{ref}(\lambda_0 \to \lambda_m)\right\} = \sum_{n=0}^{m}\left\langle \exp\left\{-\beta\left(\varepsilon_{ref}^{n+1} - \varepsilon_{ref}^{n}\right)\right\}\right\rangle_{\varepsilon_{ref}^{n}} . \qquad (15)$$

The reaction coordinate X is usually taken as the energy difference between ε_1 and ε_2.

III. Results and Discussion

In order to demonstrate and examine our approaches we select as a model problem proton transfer in the $[FHF]^-$ system (Figure 1) in aqueous and nonpolar solution.

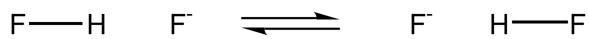

Figure 1: Proton transfer reaction studied in the present work.

As a first step in our procedure we examine the gas phase ab initio potential and calibrate the corresponding EVB potential surface. The gas phase minimum energy structure at the HF/6-31G** level is symmetric and linear with R_{FH}=1.122 Å. Because a polar solvent may interact more strongly with localized charges than with delocalized charges, we expect solvation to destabilize this symmetric geometry, where the negative charge is spread over the two oxygen atoms, in favor of an asymmetric geometry, where the negative charge is concentrated on only one of the oxygen atoms.

Values for the EVB parameters must be found so that the ground state energy obtained by diagonalizing H_{evb} reproduces the results from ab initio quantum mechanics. Figure 2 shows gas-phase potentials using ab initio (GAMESS with MP2/6-31G**) and EVB techniques. The curves in this picture show that it is possible to obtain excellent reproduction of ab initio results with judicious choice of the EVB parameters.

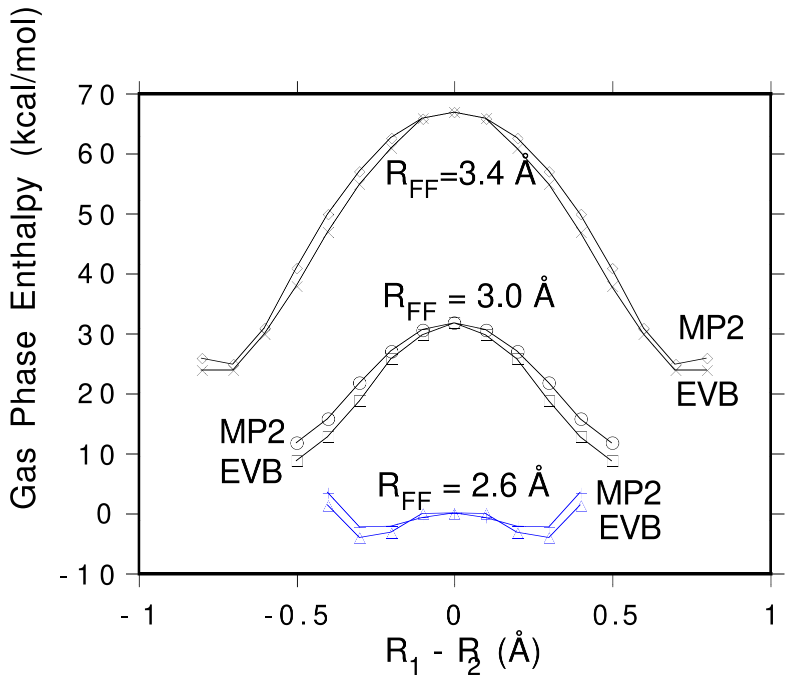

Figure 2: Gas phase potential surfaces for proton transfer in the $[FHF]^-$ ion, using both ab initio MP2/6-31G** and EVB methods. Results are presented at R_{FF}=2.6, 3.0 and 3.4 Å, with energies relative to the symmetric geometry at R_{FF}=2.6 Å.

With the EVB Hamiltonian for the $[FHF]^-$ system and the EVB mapping procedure it is possible to obtain the ab initio free energy curves for the reaction in nonpolar and aqueous solution. Figure 3 presents results using EVB mapping to compute the ab initio (AI) and the EVB activation free energy curves in nonpolar solution. These curves are obtained from 6 mapping steps of 1000 time step trajectories at 200°K with step size 0.5 fs. The F-F distance in these simulations in constrained to 3.4 Å. The free energies of activation obtained from these two methods agree very well, 40 and 35 kcal/mol, respectively. This agreement is not surprising given the agreement of the gas phase potentials reported in Figure 2.

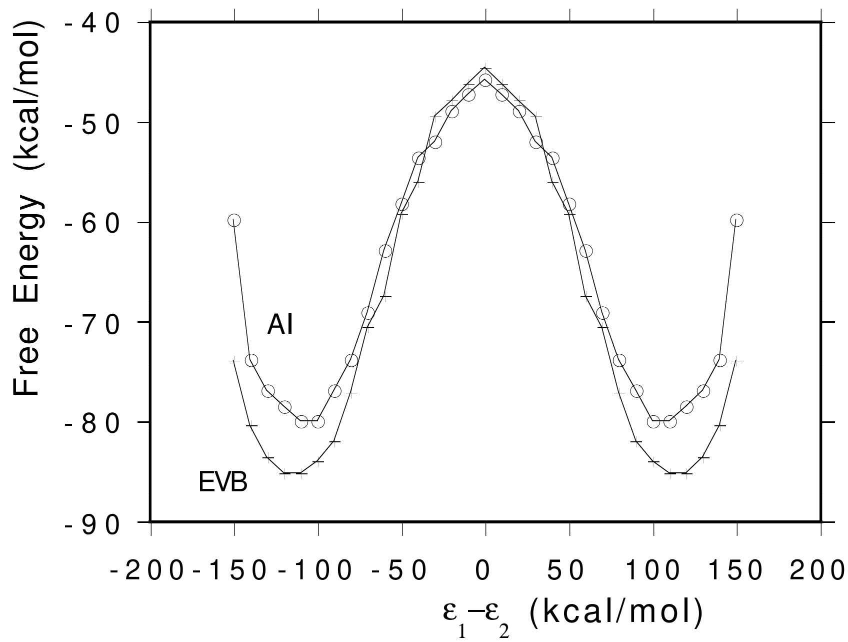

Figure 3: Ab initio (AI) and EVB free energies curves, in kcal/mol, using EVB mapping techniques, for proton transfer in $[FHF]^-$ model system in nonpolar solution with fixed R_{FF} value of 3.4 Å.

Figure 4 presents data for simulations in aqueous solution. These results are again obtained from 6 mapping steps of 1000 time step trajectories at 200°K with step size 0.5 fs on the $[FHF]^-$ model system described earlier, and again the F-F distance is constrained to 3.4 Å. As expected, the barrier height with both the EVB and ab initio Hamiltonians increases in solution, due to the destabilization of the charge delocalized transition state upon solvation. The effect is notably more strong with the ab initio free energy surface, which increases from 35 kcal/mol in the nonpolar solution to 68 kcal/mol in aqueous solution. A smaller effect is seen with the EVB free energy curve, which increases from 40 to 58 kcal/mol when moving from nonpolar to aqueous solution.

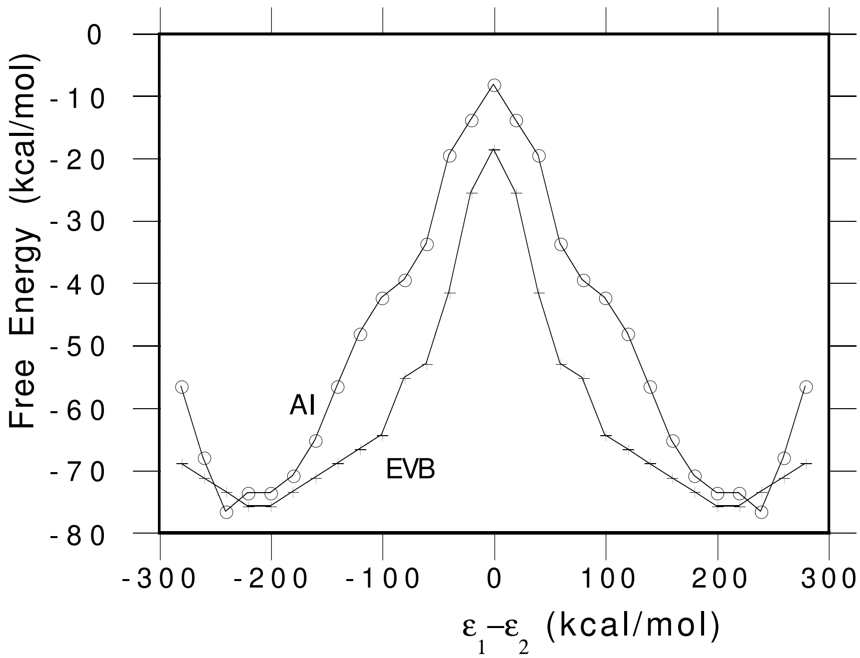

Figure 4: Ab initio (AI) and EVB free energies curves, in kcal/mol, using EVB mapping techniques, for proton transfer in $[FHF]^-$ model system in nonpolar solution with fixed R_{FF} value of 3.4 Å.

The discrepancy between the EVB and ab initio curves shown in Figure 4 does not present a serious problem in our study since the EVB potential is used only as a tool for effective mapping of the ab initio potential surface. If a more accurate EVB surface is required (e.g. for a series of studies of the present reaction in different catalytic environments) it could have been obtained quite easily. For example, the larger ab initio barrier indicates that the EVB Hamiltonian is polarized by the solvent less than the ab initio Hamiltonian. A larger polarization of the EVB results could be achieved by further adjustment of the charges of the EVB resonance structures, or by scaling the off-diagonal matrix elements. A more systematic fitting procedure would require us to reproduce the response of the $[FHF]^-$ system to external charges in the system. The current paper, however, does not attempt to refine the best EVB parameters for this system, but, rather, only uses them as a reference potential. In order to obtain optimal EVB parameters we usually consider experimental data since the ab initio calculations may not be sufficiently accurate. However, the present paper only considers the solvated $[FHF]^-$ as a tool for illustrating our method.

IV. Conclusion

The results presented in this paper demonstrate that it is possible to calculate free energy barriers using hybrid QM/MM methods, which are shown to be particularly effective when one uses the EVB Hamiltonian as a reference potential for the ab initio free energy calculations. The use of EVB reference potentials provides several major advantages: (1) The EVB reference potential allows one to consistently evaluate the solvent contribution to the free energy barrier, thus overcoming fundamental problems in approaches that use the ab initio potential for evaluating ab initio free energies. (2) MD simulations on the reference potential do not require evaluation of the ab initio forces. (3) Although not used in the current paper, the use of an EVB reference potential allows one to dramatically reduce the computation time when computing activation barrier heights by the use of a thermodynamic cycle. In such a cycle the mapping from the EVB reference potential to the ab initio potential surface is only performed at the ground and transition states, and the ab initio free energy of activation is obtained by summing the free energy along the reference potential surface $\Delta G_{ref}(\lambda_0 \rightarrow \lambda^\dagger)$ with the difference at the ground and transition states in the free energy changes between the reference and ab initio potential surfaces.

Obtaining fast convergence requires the reference potential to be similar to the corresponding ab initio potential. Fortunately, and as demonstrated in this work, it is quite simple to approximate the ab initio results by an EVB Hamiltonian. That is, as Figure 2 shows, the EVB and ab initio surfaces are quite similar and can be made more similar by further refinement (although it might be better to use in the final refinement of the EVB potential experiments in solution rather than the corresponding ab initio results). Our experience indicates that both the energy and the charge distribution of large ab initio calculations may be reproduced with a few physically relevant parameters using EVB techniques.

EVB Hamiltonians provide a convenient framework whereby ab initio potentials may be transferred into solution. The simplest (zero-order) option for solvating ab initio potentials would be to evaluate the ab initio charges at different points along the gas phase reaction path[13,38] and then to add the corresponding solvation energies to the gas phase energies. Such an approach, however, does not reflect the polarization of the solute by the solvent and can lead to quite incorrect results in studies of charge separation processes.[15] The EVB method offers a simple method of capturing the physics of the polarization of the solvent due to an external solvation field. As shown here, one may easily obtain an EVB Hamiltonian that is calibrated to reproduce the gas phase energy surface and charge distribution. Solvating the gas phase EVB charges will reproduce the zero order results, and solvating the diabatic states in equation (4) and then diagonalizing H_{evb} will provide a model that clearly accounts for the main features of solvent-induced solute polarization, where stabilization of ionic states increases their contribution to the ground state charge distribution. Such a model can reproduce the exact results at the asymptotic regions (where the molecule is broken to ionic fragments), which is not necessarily the case for the zero-order model. In the non-asymptotic region the model can be further refined by calibrating it to reproduce the response of the gas phase charges to external fields. Reproducing the ab initio gas phase solute polarizability guarantees that the solute polarization by the solvent field is approximated in a reasonable way.

Although the EVB method provides a practical way of obtaining free energy surfaces for reactions in solution it is important to be able to obtain such surfaces from a more rigorous, ab initio approach. The evaluation of such surfaces provides a major challenge that could not be addressed by the available methods until recently. In particular, the fluctuations of the solvent lead to corresponding fluctuations in the solute-solvent potential surface and averaging over these fluctuations is extremely time consuming. Thus one of the main points of this work is in providing a practical way of obtaining free energy barriers for models that include the solvent in the solute Hamiltonian. Since our approach is significantly more efficient than alternative approaches it can be used not only for reactions in solutions but also for reactions in proteins and such a study will be reported in a subsequent work.

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