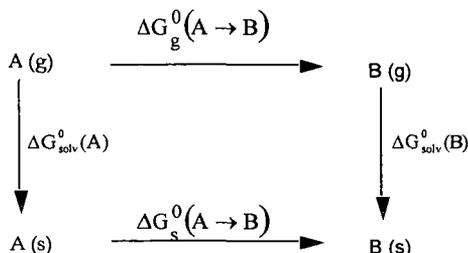


## QUANTUM MOLECULAR MODELING OF REACTIONS IN WATER: A DIELECTRIC CONTINUUM APPROACH

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The dielectric continuum solvation approach provides a simple methodology for inclusion of solvent effects directly into the matrix elements of the solute Hamiltonian. This allows that computational procedures for studying reactions in the gas phase such as optimizing transition state structure and determining reaction path, etc. can also be used for reaction in solution. However, direct application of such procedures is not correct. From a thermodynamic cycle, we proposed a rigorous methodology for modeling free energy profiles of reactions in solution within the frame work of the dielectric continuum solvation approach.<sup>1</sup> Let us consider an A → B reaction. The standard free energies of reaction in the gas phase and in solution are denoted as  $\Delta G_g^0$  and  $\Delta G_s^0$ , respectively. Associating with the reactant A and product B are free energies of solvation denoted as  $\Delta G_{\text{solv}}^0$ . From the thermodynamic cycle given below



the standard free energy of the reaction in solution can be written as

$$\Delta G_s^0 = \Delta G_g^0 + \left\{ \Delta G_{\text{solv}}^0(\text{B}) - \Delta G_{\text{solv}}^0(\text{A}) \right\}, \quad (1)$$

where the gas-phase free energy is given by

$$\Delta G_g^0 = \Delta E - RT \ln \left( \frac{Q^{\text{B}}}{Q^{\text{A}}} \right). \quad (2)$$

Here  $\Delta E$  is the reaction energy;  $R$  is the Boltzmann constant;  $T$  is the temperature;  $Q^{\text{A}}$  and  $Q^{\text{B}}$  are the total partition functions evaluated with the zero of energy set at the bottom of each respective potential well.

This expression can be generalized for the free energy profile of reaction in solution. In particular, the standard free energy at a point  $\mathbf{R}(s)$  along the reaction coordinate  $s$  relative to that of the reactant A is expressed as

$$\Delta G_s^0(s) = \Delta G_s^0(\text{A} \rightarrow \mathbf{R}(s)) = V_{\text{MEP}}(s) - RT \ln \left( \frac{Q(\mathbf{R}(s))}{Q^{\text{A}}} \right) + \Delta G_{\text{solv}}^0(\mathbf{R}(s)) - \Delta G_{\text{solv}}^0(\text{A}) \quad (3)$$

where  $V_{\text{MEP}}(s)$  is the gas-phase potential energy along the reaction coordinate  $s$  with the zero of energy set at the reactant. Eq. (3) indicates that *in order to obtain accurate free energy profile for reaction in solution, one requires to have not only accurate free energy of solvation but also*

*accurate gas-phase free energy profile.* In calculations of free energies of activation of many reactions in solution, previous studies have focused mostly on the solvation free energy contributions and often overlooked errors in the calculated gas-phase free energy profile.

The central issue here is how to define the reaction coordinate  $s$ . Adopting the reaction path Hamiltonian formalism, the reaction coordinate  $s$  for reactions in solution is defined as the distance along the minimum free energy path on the free energy surface. However, following the reaction path on the solution-phase free energy surface, as defined in Eq. (3), is almost an impossible task. The major difficulty arises from the necessity to perform normal mode analysis at every point on the gas-phase potential surface in order to calculate vibrational partition functions. To circumvent this problem, an assumption is made that the gas-phase Born-Oppenheimer potential energy surface  $E(\mathbf{R})$  has similar topology to the gas-phase free energy surface along the reaction coordinate. In this case, a pseudo-free energy surface  $G^*(\mathbf{R})$  in the solute nuclear coordinates  $\mathbf{R}$  is related to  $E(\mathbf{R})$  by the following expression

$$G^*(\mathbf{R}) = E(\mathbf{R}) + \Delta C_{\text{solv}}(\mathbf{R}). \quad (4)$$

The pseudo-free energy surface defined above allows one to utilize advanced computational methods that have been well developed for following reaction paths in the gas phase. Analogous to the gas phase, the reaction coordinate  $s$  in solution is defined as the distance along the minimum free energy path (MFEP) which is the steepest descent path from the transition state toward both the reactant(s) and product(s) on the pseudo-free energy surface  $G^*(\mathbf{R})$ . To obtain free energy profile of reaction in solution the gas-phase  $-RT \ln \left( \frac{Q(s)}{Q^A} \right)$  term is added to the pseudo-free energy profile  $\Delta G^*(s)$ . In summary, the procedure for calculating free energy profiles of reaction in solution involves three steps: 1) select the appropriate level of theory and basis set that can give accurate gas-phase free energy surface; 2) Determine the transition state and calculate the minimum free energy path on the pseudo-free energy surface defined above; 3) Add contributions from the gas-phase solute internal degrees of freedom along this MFEP. These contributions were mistakenly omitted in previous dielectric continuum calculations of free energies of activation including our own first study of solvent effects on reaction profile of the  $\text{S}_{\text{N}}2 \text{ Cl}^- + \text{CH}_3\text{Cl}$  reaction.<sup>2</sup>

We will discuss advantages and disadvantages of the above methodology in details through applications to several important organic reactions.<sup>1,3,4</sup>

#### References

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