

A Coupled Reference Interaction Site Model/Molecular Dynamics Study of the Potential of Mean Force Curve of the S_N2 $Cl^- + CH_3Cl$ Reaction in Water

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An application of the coupled reference interaction site model (RISM)/simulation methodology to the calculation of the potential of mean force (PMF) curve in aqueous solution for the identity nucleophilic substitution reaction $Cl^- + CH_3Cl$ is performed. The free energy of activation is calculated to be 27.1 kcal/mol which compares very well with the experimentally determined barrier height of 26.6 kcal/mol. Furthermore, the calculated PMF is almost superimposed with that previously calculated using the computationally rigorous Monte Carlo with importance sampling method (Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, 107, 154). Using the calculated PMF, a crude estimate of the solvated kinetic transmission coefficient also compares well with that of previous more accurate simulations. These results indicate that the coupled RISM/simulation method provides a cost-effective methodology for studying reactions in solution.

1. Introduction

The nucleophilic substitution $Cl^- + CH_3Cl$ has been used as a benchmark reaction for modeling reactive processes in solution. Solvation has a dramatic effect on its rate constant which differs by many orders of magnitude in aqueous solution from that in the gas phase. The decrease in the reaction rate constant in a polar solvent, such as water, is associated with an increased barrier height of the reaction occurring in solution compared to the one occurring in the gas phase. The underlying cause for the strong effect of a polar solvent on the barrier height of this and other charge transfer reactions is the very negative solvation free energy of small ions dissolved in polar solvents. In the case of the $Cl^- + CH_3Cl$ reaction, there is a high concentration of charge on the chloride ion in the reactants, and this highly ionic state entails a very negative free energy of solvation for the reactants. As the reaction proceeds toward the transition state, the isolated charge on the reacting chloride ion delocalizes over the entire transition state complex and, thus, results in a lesser negative solvation free energy, consequently raising the reaction barrier height. In the past, many methods, including classical MC simulations,¹ QM/MM free energy simulation,² continuum models,^{3–8} reference interaction site model (RISM),⁹ and RISM/SCF,^{10,11} have been applied to study this system.

We have recently proposed a methodology for solvation free energy based on the RISM approach, which instead uses radial distribution functions determined from a molecular dynamics or Monte Carlo simulation.^{12,13} The key advantage of this coupled RISM/simulation approach is that free energy of solvation can be determined from a single MD or MC simulation and, thus, can circumvent the computational demand of free energy simulations or technical difficulties associated with the stand alone RISM method. We have already presented a few studies demonstrating the successful performance of this coupled RISM/simulation approach.^{12,14,15} In this study, we explore its accuracy for modeling the potential of mean force of reactions

in solution. For this, we selected the reaction $Cl^- + CH_3Cl$ since it has been used as the prototype reaction for modeling reactions in solution by various methods.

Chandrasekhar et al. performed the original simulation of the $Cl^- + CH_3Cl$ reaction system.¹ In this work, a force field was first developed to describe solute–solvent interactions. The solvated potential of mean force curve was obtained by Monte Carlo simulation with importance sampling. In this method, trajectories are constrained to windows corresponding to small intervals of the reaction coordinate by weighting with an umbrella potential. The resulting PMF's can then be manually spliced together to yield the full curve, as was performed in the work being discussed, or this can be achieved by an automated process using a weighted histogram analysis method (WHAM).^{16,17} It is interesting to note that the technical difficulties associated with matching up segments of the PMF curve in umbrella sampling methods do not exist in the coupled RISM/MD method since the free energy of solvation is calculated independently for each value of the reaction coordinate.

2. Methods

Molecular Dynamics Simulations. In the work of Chandrasekhar et al.,¹ the assumption was made that the carbon atom and two chlorine atoms remain collinear throughout the reaction, and the reaction coordinate was taken to be the difference, $r_c = r_{CCl} - r_{CCL}$, between the respective distances from the leaving and substituting chlorine atoms to the carbon atom. The authors parametrized solute geometries as an analytical function of this reaction coordinate and extended this parametrization to van der Waals parameters and partial atomic charges. In our calculations, the same force field, i.e., partial charges and van der Waals parameters, is used to represent the reactive system in order to facilitate direct comparison with the results of this previous study.

The AMBER¹⁸ package was used to perform the MD simulations from which the solute–solvent radial distribution

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functions were calculated. We used the structures provided by Chandrasekhar et al.,¹ which were optimized at the 6-31G(d) level, representing 8 configurations along the above user-defined reaction path from the reactants to the transition state corresponding to reaction coordinate values ranging from -5.708 to 0 Å. Systems were solvated by adding explicit TIP3P water molecules extending out to 12 Å in the x , y , or z direction from the center of any solute atom. The density of water was equal to 0.03334 Å⁻³. Water molecules were allowed to relax for 200 steps, while the solute structure was held fixed. Thermalization from an initial temperature of 10 K to the final temperature of 298 K was then carried out over 25 ps and equilibration over another 20 ps, using 1 fs time steps. The MD trajectory was then run for 2 ns, in 2 fs time steps; samples were taken every 100 configurations, or every 0.2 ps.

A full set of solute-solvent site-site radial distribution functions was obtained by averaging over the respective MD trajectory for each of the 8 configurations. Solvent-solvent radial distribution functions were taken from our previous study¹³ using the BOSS package,¹⁹ for the TIP3P water model. The calculated radial distribution functions were sampled at intervals of 0.04 Å and were gradually smoothed to zero at distances exceeding 11 Å.

The Coupled RISM/Simulation Methodology. Within the RISM integral equation theory in conjunction with the hypernetted chain (HNC) closure relation, the solvation free energy can be expressed as

$$\Delta\mu^{\text{HNC}} = \frac{\rho}{2\beta} \sum_{\alpha\gamma} \int 4\pi r^2 [-2c_{\alpha\gamma}(r) + h_{\alpha\gamma}^2(r) - h_{\alpha\gamma}(r)c_{\alpha\gamma}(r)] dr \quad (1)$$

where $h = g - 1$ is the pair correlation function and c is the direct correlation function.^{20–22} Both the pair correlation functions, h , and the direct correlation functions, c , can be determined iteratively in the standard stand alone RISM methodology from the RISM and HNC equations given by

$$\hat{\mathbf{h}}(k) = \hat{\omega}(k)\hat{\mathbf{c}}(k)\hat{\omega}(k) + \rho\hat{\omega}(k)\hat{\mathbf{c}}(k)\hat{\mathbf{h}}(k), \text{ RISM} \quad (2)$$

$$g_{\alpha\gamma}(r) = \exp(-\beta u_{\alpha\gamma}(r) + h_{\alpha\gamma}(r) - c_{\alpha\gamma}(r)), \text{ HNC} \quad (3)$$

where the carets indicate spatial Fourier transforms, the boldface denotes matrixes, $\hat{\omega}$ is the intramolecular correlation function, and u is the intermolecular pair potential. The RISM equation (eq 2) expresses the total correlation function, $h_{\alpha\gamma}$, for solvent site γ about solute site α , as the sum of a direct contribution involving only one solvent molecule and the solute, and an indirect component by which the correlation of the solvent site γ to α is mediated by a third solvent molecule, in this way defining the direct correlation function, $c_{\alpha\gamma}$.²³ Solving for the two unknown function sets, $\{h_{\alpha\gamma}\}$ and $\{c_{\alpha\gamma}\}$, simultaneously from the above two equations, RISM and HNC, has presented many technical difficulties. Furthermore, the resulting correlation functions are often not as accurate when compared to results from simulations.^{24–27} As a consequence, the free energy of solvation calculated from eq 1 is not accurate compared to that from free energy simulations.

The key idea of the coupled RISM/simulation methodology is to increase the accuracy of computed solvation free energies by using accurate pair correlation functions, h , in eq 1.^{12,13} The justification of this hypothesis can be seen from our previous study of the tautomers 2-hydroxypyridine and 2-oxypyridine which illustrates the connection between accurate pair correlation functions and accurate resulting solvation free energies.

There, we compared accurate radial distribution functions obtained by MD simulation with two sets of radial distribution functions calculated by separate stand alone RISM studies using two different parameter sets. Of these two studies, we observed that the one for which parametrization yielded a close match to radial distribution functions from our MD simulations was far more successful in correctly predicting relative solvation free energies for the two tautomers.¹⁵

In the coupled RISM/simulation approach, a single equation should suffice to solve for the second variable set, $\{c_{\alpha\gamma}\}$, because one of these variable sets, namely, $\{h_{\alpha\gamma}\}$, has been predetermined by simulation. Thus, there are two apparent routes to the direct correlation function, c . One of these identifies the direct correlation function, c^{HNC} , which satisfies the HNC equation; a second form of the direct correlation function, c^{RISM} , can be solved for in reciprocal space from the RISM equation.^{12,13}

The question is how one or both of these sets of direct correlation functions should enter the RISM solvation free energy expression (eq 1). To address this issue, we took advantage of the invariance principle for the solvation free energy expression at the solution c to the RISM and HNC equations shown by Singer and Chandler.¹² This allows the use of both sets of c , namely, c^{HNC} and c^{RISM} , in the RISM solvation free energy expression in such a way that contributions from errors in either c may be minimal. Consequently, the free energy of solvation expression shown in eq 1 has the form

$$\Delta\mu^{\text{HNC}} = \frac{\rho}{2\beta} \sum_{\alpha\gamma} \int 4\pi r^2 [-2c_{\alpha\gamma}^{\text{HNC}}(r)(1 + h_{\alpha\gamma}(r)) + [h_{\alpha\gamma}(r)]^2 + h_{\alpha\gamma}(r)c_{\alpha\gamma}^{\text{RISM}}(r)] dr \quad (4)$$

Within the RISM theory, there are two other variations on the solvation free energy expression in addition to the original HNC expression given above, namely, the partial wave (PW) and the Gaussian fluctuation (GF) expressions. The PW expression of Tenno et al. represents an improvement over the HNC expression, being derived in a manner similar to that of the HNC expression but somewhat more rigorously.^{28,29} It has the form given by

$$\Delta\mu^{\text{PW}} = \frac{\rho}{2\beta} \sum_{\alpha\gamma} \int 4\pi r^2 [-2c_{\alpha\gamma}^{\text{HNC}}(r)(1 + h_{\alpha\gamma}(r)) + h_{\alpha\gamma}(r)h_{\alpha\gamma}^{\text{PW}}(r) + h_{\alpha\gamma}(r)c_{\alpha\gamma}^{\text{RISM}}(r)] dr$$

where

$$\hat{h}_{\text{sv}}^{\text{PW}} = [\hat{\omega}_{\text{s}}]^{-1}[\hat{h}_{\text{sv}}][\hat{\omega}_{\text{v}}]^{-1} \quad (5)$$

On the other hand, the GF expression has employed different approximations in the derivation and has the form³⁰

$$\Delta\mu^{\text{GF}} = \frac{\rho}{2\beta} \sum_{\alpha\gamma} \int 4\pi r^2 [-2c_{\alpha\gamma}^{\text{HNC}}(r)(1 + h_{\alpha\gamma}(r)) + h_{\alpha\gamma}(r)c_{\alpha\gamma}^{\text{RISM}}(r)] dr \quad (6)$$

Our previous studies indicated that the PW expression produces the best results for neutral molecules when compared to those from the other two expressions.^{12–15} To test which of the expressions performs most suitably for the ionic species being considered here, we calculated PMF curves using each of the three expressions.

Computational Details. One source of error in the coupled RISM/simulation approach arises from the discrepancy $c^{\text{RISM}} - c^{\text{HNC}}$ between the two direct correlation functions being calculated, also known as the bridge function, which is assumed to equal zero within the HNC approximation. In our previous work,¹² we were able to improve absolute solvation free energies calculated in the coupled RISM/simulation approach by incorporating a term correcting for this bridge function relying upon empirical bridge functions previously determined for Lennard-Jones spheres.^{31–33} In the present application involving charged solutes, we found that the use of this bridge correction made very little difference in calculated solvation free energies, being inadequate to treat the error caused by the inequality between \hat{c}^{RISM} and \hat{c}^{HNC} at very low k where the condition numbers of the matrices used to calculate \hat{c}^{RISM} are divergent. We, thus, employed a method suggested in our earlier work, whereby we level off \hat{c}^{RISM} at low k values for which the matrices occurring in the RISM equation are extremely ill-conditioned.^{12,13}

The Fourier transformations for the RISM calculations were carried out on a linear grid of 537 points, with zero-aliasing to twice this range, meaning that an additional 537 points were zero-filled.³⁴ This gave a total interval length of 43 Å which was used to calculate values of k . $\hat{c}^{\text{RISMsr}}(k)$ is leveled off for all $k \leq 10\Delta k$.^{12,13}

In carrying out the numerical integration for the solvation free energy, we cut off the radial distribution functions at 11 Å. All energies were calculated at 298 K. An adjustment was made to the solvation free energy expression on the basis of differences between coordination numbers of solvent O and H atoms, with respect to each solute site. Further computational details have been described in our previous work.¹²

3. Results and Discussion

Potential of mean force curves were calculated as

$$W(r_c) = \Delta\mu^S(r_c) + U_0(r_c) \quad (7)$$

where $\Delta\mu^S$ represents the solvation free energy contribution and $U_0(r_c)$ is the gas-phase potential energy function.¹ In Figure 1, we show results for the PMF curves calculated using each of the HNC, PW, and GF solvation free energy expressions, along with the gas-phase potential energy $U_0(r_c)$. The solution-phase values shown in Figure 1 are relative to values at the most separated reactant configuration used here, corresponding to $r_c = 5.708$ Å.

The calculated free energies of activation for this reaction in water are 30.6, 27.1, and 29.9 kcal/mol using the HNC, PW, and GF free energy of solvation expressions, respectively. In the Monte Carlo with importance sampling study from which the force field used in the present study was adopted, this barrier height was determined to be 26.3 kcal/mol¹ which is close to the experimental value of 26.6 kcal/mol.^{1,35–37} Thus, application of the coupled RISM/MD approach using the PW solvation free energy formulation gives excellent agreement with both the previous simulation result and the experimental one. This is consistent with our past observations that the PW expression for solvation free energies works best when compared with the two other expressions.^{12–15}

We have also included the stand alone RISM results of Huston et al.⁹ in Figure 1. The same force field that we used here was modified slightly for this study. These results were computed using the HNC solvation free energy expression and are in good agreement with our results using the same solvation free energy expression in the transition state region, although

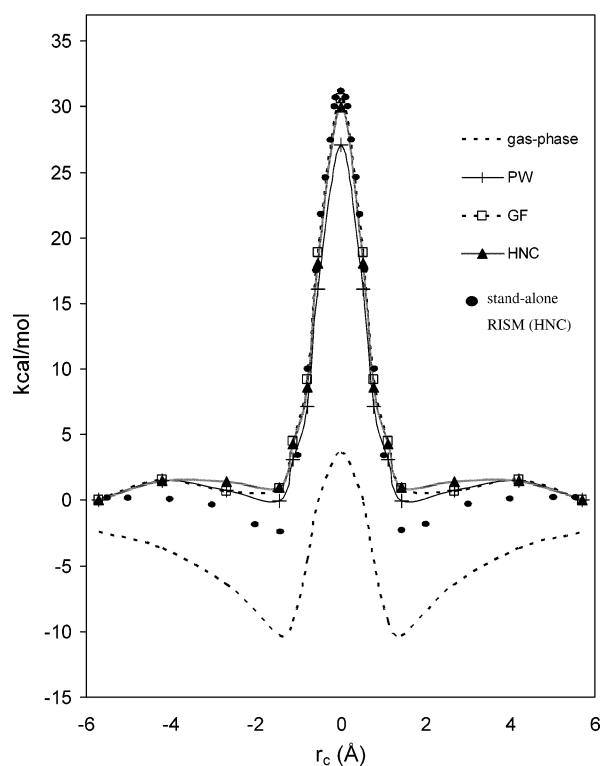


Figure 1. Potential of mean force curves for the $\text{S}_{\text{N}}2$ reaction $\text{Cl}^- + \text{CH}_3\text{Cl}$ in aqueous solution. Gas-phase conformational energies (dashed line) were summed to solvation free energies calculated by coupled RISM/MD using the PW, GF, or HNC solvation free energy expression. We also show, for comparison, the stand alone RISM/HNC results of Huston et al.,⁹ calculated by the HNC solvation free energy expression.

the stand alone RISM result predicts a slightly larger barrier height. However, some differences between results from the stand alone RISM and present coupled RISM/MD methods using the same HNC free energy expression can be observed up until the point in the reaction corresponding to the gas-phase stabilized ion–dipole intermediate. At this point, the stand alone RISM graph indicates a slightly stabilized ion–dipole complex in solution.

In Figure 2, we make a direct comparison between the PMF curves in the present study using the PW free energy of solvation expression and that from the previous MC simulations with importance sampling of Chandrasekhar et al.¹ The two plots give excellent overlap, showing similar barrier widths and heights. In addition, both show only very slight dips at the gas-phase stabilized intermediates, indicating that in water there is no stable ion–dipole reaction intermediate since the attraction of the ion–dipole complex is offset by the cost of desolvating both the ion and polar molecule. This feature signifies the unimodal character of the reaction in water, in contrast to its bimodal mechanism in the gas phase.¹

We also performed error analysis on the convergence of the input radial distribution functions used in our calculation at the completion of the 2 ns simulation trajectories. To do this, we calculated solvation free energies for reactants and transition states using radial distribution functions computed after somewhat smaller time intervals, testing for stabilization in the final computed values from 2.0 ns simulations. By averaging solvation barrier height contributions over values calculated from trajectories of lengths 1.6, 1.7, 1.8, 1.9, and 2.0 ns, we found that the nonbiased standard deviation from the average is 0.11

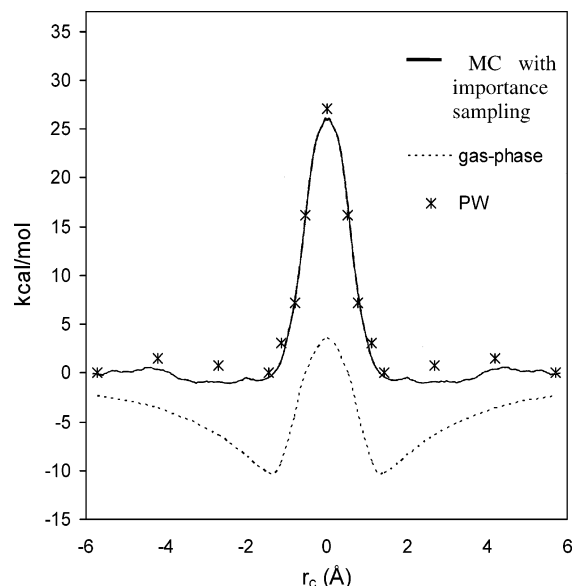


Figure 2. Comparison of the potential of mean force profile calculated in the present work by coupled RISM/MD using the PW solvation free energy expression and the MC with importance sampling result of Chandrasekhar et al.¹

kcal/mol. The small error range confirms that the radial distribution functions are converged by the end of the 2.0 ns simulations.

4. Solvated Kinetic Transmission Coefficient

Although the main objective of this work is to show the applicability of coupled RISM/MD to the determination of the PMF curve of a reaction in solution, the simple formulation suggested by Huston et al.⁹ for the solvated kinetic transmission coefficient motivated us to also calculate this kinetic quantity. The connection between the solvent contribution to the potential of mean force for a reaction and the reaction's rate constant is given by the expression

$$k = \kappa k_g^{\text{TST}} \exp(-\beta \Delta G^S) \quad (8)$$

where the transmission coefficient, κ , represents the factor by which the rate constant differs from the transition state theory result, k_g^{TST} is the gas-phase transition state theory rate constant, and ΔG^S is the solvation component of the activation free energy.³⁸ Hynes and co-workers^{17,39–42} have shown how this factor may be obtained in the frozen solvent limit, and later, Huston et al.⁹ performed a similar calculation facilitated by the RISM approach. However, in general, a significant coupling may be expected between solute and solvent dynamics, i.e., the frozen solvent assumption that there is no time for the solvent to respond to the motion of the solute along the reaction coordinate in the short time required for reaction may be invalid; these situations would require much further work, including the identification of relevant memory functions, so that the generalized Langevin equation (GLE) might be solved for the transmission coefficient, κ , to give the effect of nonadiabatic solvation.³⁸ However, previous studies have demonstrated that the frozen solvent approximation is justified for the S_N2 reaction being studied here.⁴³ We evaluated the transmission coefficient using the expression formulated by Huston et al.

$$\kappa = (1 - \{(k_{\text{eq}} + \langle d^2 U_{\text{uv}} / dr_c^2 \rangle_{r_c=0}) / (k_{\text{eq}} + k_b)\})^{1/2} \quad (9)$$

where k_b and k_{eq} are harmonic force constants for the gas-phase

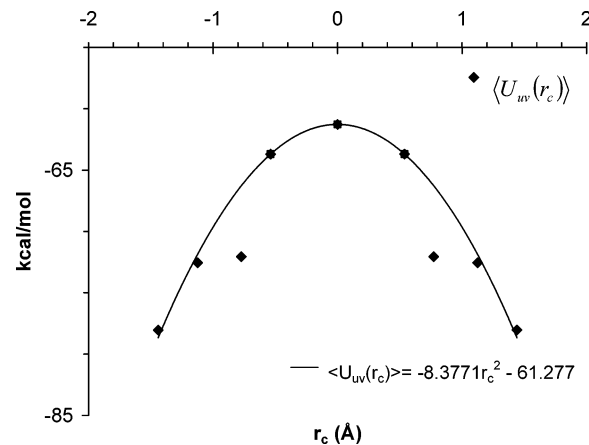


Figure 3. Solute-solvent potential energy function averaged over solvent coordinates as a function of the reaction coordinate, fit to a quadratic curve at the transition state.

reaction and the solvation free energy contribution to the solvent-equilibrated reaction, respectively, and U_{uv} is the solute-solvent potential energy.⁹

Huston et al. determined the second derivative in eq 9 analytically before averaging over solvent coordinates.⁹ However, as pointed out in their study, the parameter set of Chandrasekhar et al. results in a Lennard-Jones potential that is nondifferentiable at the transition state. Therefore, we first determined averages over solvent configurations $\langle U_{\text{uv}}(r_c) \rangle$ for r_c values in the transition state region. Then, we plotted these numbers using a harmonic fit to determine the second derivative; it was found to be $16.8 \text{ kcal mol}^{-1} \text{Å}^{-2}$ (see Figure 3). Using the value $k_{\text{eq}} = 48.51 \text{ kcal mol}^{-1} \text{Å}^{-2}$ calculated from our solvated PMF curve and the gas-phase frequency, $\omega_b = 461.2 \text{ cm}^{-1}$,⁴² corresponding to a force constant of $k_b = 55.1 \text{ kcal mol}^{-1} \text{Å}^{-2}$ (calculated with $\mu = 18.214 \text{ amu}^{9,44}$), we calculated the value of κ to be 0.61 for the transmission coefficient which corresponds well with the value of 0.55 from a more reliable simulation.⁴²

5. Conclusion

In conclusion, we have applied the coupled RISM/MD approach to finding the PMF curve for the S_N2 $\text{Cl}^- + \text{CH}_3\text{Cl}$ reaction in aqueous solution. We found a PMF that is very close to that obtained by the Monte Carlo simulation with umbrella sampling using the same potential force field. This indicates the prospective advantage of applying the coupled RISM/simulation methodology to the determination of solution phase PMF curves or simply free energies of activation of reactions in solution over more computationally demanding and laborious free energy simulation approaches.

We have tested the simple expression derived by Huston et al. for the nonequilibrium solvation transmission coefficient as a correction to the transition state theory for reaction rates in solution and found that the result compared well with that from a more reliable simulation. This further suggests that it is possible to use the coupled RISM/MD method in conjunction with dynamical methods, such as the generalized Langevin equation, to study kinetics of reactions in solution.

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