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QM/MM Calculations for the $\text{Cl}^- + \text{CH}_3\text{Cl}$ $\text{S}_{\text{N}}2$ Reaction in Water Using CM5 Charges and Density Functional Theory

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Abstract

The prototypical $\text{S}_{\text{N}}2$ reaction of chloride ion with methyl chloride has been reinvestigated in aqueous solution using QM/MM methodology featuring MO6-2X/6-31+G(d) calculations with the TIP4P water model, and partial charges computed with the CM5 method. Though the DFT method yields excellent gas-phase energetics for the reaction, the QM/MM approach is found to yield overestimation of the activation barrier by ca. 12 kcal/mol. The discrepancy is traced to underestimation of the magnitude of the partial charges on the chlorine atoms in the transition structure. When CM1 or CM3 charges based on semiempirical wavefunctions are used instead, the agreement with experiment is much improved. The findings emphasize the sensitivity of the results of QM/MM calculations to the choice of QM method, the MM force field, and implementation of the QM/MM interface.

INTRODUCTION

The use of Quantum Mechanical/Molecular Mechanics (QM/MM) mixed calculations to study reaction mechanisms has a long history in the computational community. The first reaction to be modelled with full representation of the solvent as discrete molecules was the prototypical chloride ion plus methyl chloride $\text{S}_{\text{N}}2$ reaction in 1984.^{1,2} These calculations used Metropolis Monte Carlo (MC) statistical mechanics simulations with umbrella sampling and intermolecular potential parameters fitted to HF/6-31G(d) interaction energies. The resulting free energy profile or potential of mean force (pmf) featured an activation barrier of 26.3 ± 0.5 kcal/mol in aqueous solution, which was in close accord the experimental value (26.6 kcal/mol).³ The choice of HF/6-31G(d) for the QM was deliberate because it gave excellent gas-phase energetics for this reaction and enhanced electrostatics that represented well the solute-water interactions in the absence of explicit polarization.

There were many subsequent QM/MM studies of this reaction by other research groups in the 1980s.^{4–6} It continues to be a benchmark. For example, Higashi and Truhlar reported in 2008 the use of combined electrostatically embedded multiconfigurational molecular mechanics with the MPW1K/6-31+G(d,p) density functional theory and CM4 charges using

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Supporting Information. This information is available free of charge on the ACS Publications website at <http://pubs.acs.org>. It consists of a pdf file containing tables for the computed geometries and atomic charges from the gas-phase QM calculations, and a plot comparing the calculated pmfs in water.

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umbrella sampling and the weighted histograms analysis method (WHAM) to obtain a barrier of 25.3 kcal/mol.⁷ A general methodological study was reported by Zheng *et al.* the following year using electrostatically embedded QM/MM in a 15 Å TIP3P water cap, and molecular dynamics with umbrella sampling and WHAM; with HF/6-31G(d) chosen again for the QM component, they reported a barrier of 26.1 kcal/mol.⁸ Song *et al.* used several types of valence bond (VB) calculations incorporating the polarizable continuum method (PCM) to implicitly represent solvation effects.⁹ In particular the “breathing orbital valence bond” (BOVB-PCM) 6-31G or 6-31+G showed good agreement with the experimental barrier (26.8 and 26.1 kcal/mol, respectively). In later studies from our group, semiempirical QM methods were used for the reacting system to allow extensive sampling of solute and solvent degrees of freedom in examining substituent effects on S_N2 reactions for alkyl halides in multiple solvents.^{10,11} The latter calculations featured on-the-fly QM in which a single-point QM calculation is needed for the reacting system whenever it is modified in a Monte Carlo step. This allows location of transition structures in solution, whereas the earliest studies assumed that the reaction in solution followed the minimum-energy reaction path from the gas-phase calculations.^{1,2}

More recently, we have interfaced the Monte Carlo program BOSS¹² with the Gaussian program¹³ to allow the QM portion of the QM/MM calculations to utilize a variety of *ab initio* and DFT methods along with various choices for computing atomic charges for solute atoms.¹⁴ The first applications included modelling two methyl transfer reactions in aqueous solution for which use of MP2/6-31G(d) calculations for the QM led to much improved agreement with the experimental barrier heights than prior QM/MM calculations with semiempirical QM.¹⁴ Access to the Gaussian program provides the possibility of obtaining highly accurate energetics for the reacting system, though there was a ca. 1000-fold increase in the computational cost for the methyl transfer reactions. In the present study, the prototypical Cl[−] + CH₃Cl S_N2 has been reinvestigated with such on-the-fly DFT calculations; key points that are addressed are the appropriate QM level and the impact of different treatments of the solute-water electrostatic interactions. In particular, the newer CM5 charge model,^{15,16} which is based on a Hirschfeld population analysis,¹⁷ has been utilized.

METHODS

Quantum Mechanical Calculations.

All gas-phase QM calculations were run using Gaussian 16, revision A.03.¹² Optimizations to minima for the isolated reactants, the encounter complex [Cl⋯CH₃Cl][−] and transition structures (TS) [Cl⋯CH₃⋯Cl][−] were carried out with the AM1 and PDDG/PM3 semiempirical methods,^{18,19} and with *ab initio* HF, MP2, CBS-QB3, and density functional theory using the B3LYP²⁰ and MO6-2X²¹ functionals and numerous basis sets. The results of optimizations to minima and transition structures were confirmed *via* frequency calculations.

Monte Carlo Simulations.

Metropolis MC simulations were carried out with the BOSS program¹¹ as modified to call Gaussian 16 upon each attempted solute move.¹⁴ Water molecules were represented by the rigid TIP4P model²² as before,^{1,2} while the $\text{Cl}\cdots\text{CH}_3\cdots\text{Cl}$ solute was represented using OPLS-AA Lennard-Jones parameters²³ and CM5 charges from Gaussian 16.¹⁵ All intermolecular interactions were truncated at 10 Å based on all non-hydrogen atom pairs, with quadratic feathering to zero over the last 0.5 Å. In view of the symmetry for this system, the transition structure has the $\text{Cl}\cdots\text{C}\cdots\text{Cl}$ fragment collinear with equal C-Cl lengths. The solute moves, which were attempted every 100 configurations, were a combination of rigid-body translations and rotations with variations in all internal degrees of freedom while keeping the $\text{Cl}\cdots\text{C}\cdots\text{Cl}$ fragment collinear. All simulations were performed in the isothermal-isobaric ensemble (NPT) at a temperature of 25 °C and pressure of 1 atm. A periodic box of 740 water molecules measuring ca. $25 \times 25 \times 37.5$ Å was used for all cases. The MM component of the simulations was run in sequential mode using a single core, while the QM was parallelized over 4 cores to increase the computational efficiency.

QM/MM Interface.

The energy evaluation on a QM/MM calculation requires the partition of the system into QM and a MM domain, each with its energy function, but also the evaluation of the energy between them. A simple method to evaluate this energy involves the assignment of Lennard-Jones parameters to each QM atom, calculating its charge by a QM procedure, and using these to calculate the energy analogously to the MM domain using eq 1.

$$E_{QM/MM} = \sum_i \epsilon^{QM} \sum_j \epsilon^{MM} \left\{ \frac{q_i q_j e^2}{r_{ij}} - 4 \epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] \right\} \quad (1)$$

This method, termed mechanical embedding, has been extensively used in our laboratory with good success to model reactions in solution.^{10,11,12,24} It is consistent with an overall MM approach, which has been dominant in modelling organic and biomolecular systems in solution. A common alternative is to use electronic embedding in which the MM charges for the solvent molecules are included in the electrostatic part of the QM calculations. Keeping in mind that the MM partial charges for solvent molecules are enhanced from gas-phase values and the electrostatics are sensitive to the choice of QM method, both approaches are imperfect. A more proper alternative is complete removal of the MM aspect of the calculations as in *ab initio* molecular dynamics, which is currently limited to moderate DFT methods, small systems, and short timescales.²⁵

Potentials of Mean Force (pmf).

All pmf calculations were run using the BOSS program to determine the free energies differences between two states A and B using free energy perturbation (FEP) theory, which is based in the Zwanzig equation²⁶ (eq 2). In this case the states A and B represent different values of the changing C-Cl distances. Since good convergence would be difficult to obtain for large changes of this distance, the transformations are subdivided into a number of steps

as controlled by a coupling parameter λ_i (eq 3) which scales linearly the distance between the initial and final states.²⁷

$$\Delta G(A \rightarrow B) = G_B - G_A = -k_b T \ln \langle \exp[-(E_B - E_A)/k_b T] \rangle_A \quad (2)$$

$$\chi_i = \lambda_i \chi_B + (1 - \lambda_i) \chi_A \quad (3)$$

The simulations comprising the pmf were run using the same parameters as described above, and each window featured an equilibration length of 2.5×10^6 MC configurations, where no perturbation was made, and an averaging length of 5.0×10^6 configurations using double-wide sampling²⁷ with increments in the C-Cl bond length of ± 0.05 Å, thus covering a total change of 0.1 Å. The full change from 60 windows thus covered a distance of 6 Å. The reaction coordinate was defined as the difference in lengths between the two C-Cl bonds, $R_c = R_{(C^1-Cl)} - R_{(C-Cl^2)}$. During each of the 60 windows a total of 17.5×10^6 Gaussian 16 calls were done, for a total of 1.05×10^9 QM single-point calculations. The total computing time was ca. 84,000 CPU-hours.

Charge Perturbation.

An additional FEP calculation was run to estimate the effect of changing the partial atomic charges for the transition structure (TS) on the activation energy. The geometry of the TS was fixed, while the charges on the chlorine atoms were converted from -0.75 to -0.45 e to cover the entire range found from the gas-phase QM calculations; the overall charge of -1 e was maintained by adjusting the charge on the carbon atom. Only the change in the solute-solvent energy was considered in the FEP calculations, so the results correspond to the change in free energy of hydration, G_{hyd} . The FEP calculation covered 10 windows, each with 5×10^6 and 10×10^6 configurations for equilibration and averaging, respectively.

RESULTS AND DISCUSSION

Gas Phase Calculations.

In order to find the best level of QM theory to pair with the Monte Carlo simulations, results from different methods were obtained for comparison with the best known relative energies of the ion-dipole complex and TS of the reaction. These are given in Table 1, where it can be seen that the calculations using the MO6-2X functional with the /6-31+G(d) basis set match the results of the highest level known, CCSD(T)/TZ2Pf+diff,²⁸ at far less computational cost. PDDG-PM3 also does well for S_N2 reactions of alkyl halides, as known.¹⁰ The Cl $\cdots$ C and C-Cl distances and charges were also compared, as listed in Tables S1 and S2 in the Supplementary Information. The results for the C $\cdots$ Cl distance for the TS are 2.314 and 2.302 Å from the MO6-2X and CCSD(T) calculations, respectively. As discussed more below, the partial charges on the chlorines in the TS from the CM5 method with Gaussian 16 using various basis sets and HF, MP2 or DFT methods range from -0.57 to -0.68 e , while the charges are more negative, near -0.75 e with the semiempirical methods.

Monte Carlo QM/MM Simulations in Water.

The Monte Carlo simulations were run in two stages, first the transition state was located by running a pmf for varying both Cl $\cdots$ C $\cdots$ Cl distances together at 0.050 Å intervals. The minimum with MO6-2X/6-31+G(d) was found at 2.315 Å, showing negligible difference between the gas-phase and aqueous solution.²⁹ The TS thus found was used to start the QM/MM pmf in which one of the Cl-C bonds was stretched in 60 windows covering 0.1 Å each. The results, shown in Figure 1, feature a shallow minimum for the ion-dipole complex [Cl $\cdots$ CH₃-Cl]⁻ at $R_C = -4.2$ Å with a $G = -1.6 \pm 0.4$ kcal/mol and a TS with a $G^\ddagger = 38.3 \pm 0.4$ kcal/mol. This value is significantly higher than the experimental value of 26.6 kcal/mol, or those calculated typically by other methods.³⁻¹¹ Analysis of the radial distribution functions and energy distributions show results qualitatively similar to previous studies, but looking closer at the charge distributions in Table S2 reveals a significant range for the partial atomic charges calculated for the Cl atoms in the TS. At $-0.57 e$, these are 0.1-0.2 e less negative for both DFT methods (B3LYP and MO6-2X) than from the other methods tested, namely, $-0.68 e$ for HF/6-31G(d) and $-0.75 e$ for the semiempirical methods CM1/AM1 and CM3/PDDG-PM3.^{30,31} Thus, stabilization of the TS by hydrogen-bonding to water molecules is expected to be diminished with the CM5/MO6-2X/6-31+G(d) combination.

The solvated structures sampled during the simulations have hydrogen-bonding patterns qualitatively similar to those from other simulations as seen in Figure 2.^{1,2} Integration of solute-solvent energy pair distributions shows that there are on average 6.8 hydrogen-bonded water molecules with an average interaction energy of -15.7 kcal/mol for the ion-dipole complex compared with 7.4 water molecules with an average interaction energy of -8.1 kcal/mol in the TS. These numbers are consistent with the standard picture of a more charge-delocalized, and therefore more weakly stabilized transition structure.

In order to address if the differences in the atomic charges is sufficient to explain the discrepancy in the activation barrier, the quantitative effect of the charge change was examined by FEP. The results are shown in Figure 3, where the red marker indicates the charge on chlorine for the TS with CM5/MO6-2X/6-31+G(d). As the charge on chlorine becomes more negative, the free energy of hydration for the TS becomes increasingly favorable. The predicted change in free energy of hydration (-10.5 kcal/mol) in progressing to charges similar to those from the semiempirical calculations ($-0.75 e$) is indeed sufficient to bring the free energy of activation down to a very reasonable 27.8 kcal/mol.

For confirmation, the pmf calculations were repeated using the semiempirical methods CM3/PDDG-PM3 and CM1/AM1 in the same manner as for the CM5/MO6-2X calculations described above. The results, ($G^\ddagger = 26.8 \pm 0.4$ and 21.8 ± 0.4 kcal/mol, respectively) are compared to other results in Table 2. The corresponding plots of the activation profile are provided in Figure S1. The CM3/PDDG-PM3 results show much better agreement with both the experimental result and the earliest calculations,^{1,2} while the CM1/AM1 combination underestimates the barrier by 5 kcal/mol. This discrepancy can be mostly attributed to the lower gas-phase barrier predicted with AM1, as shown in Table 1. It should also be noted that neither of the semiempirical calculations yield a free-energy minimum for the ion-dipole

complex in water. And, the calculations for the entire *pmf* with these methods took just under 8 cpu-hours.

Methodologically, the CM1³⁰ and CM3³¹ charge models are based on Mulliken or Löwdin charges modified through empirical functions and parameters designed to reproduce experimental dipole moments and ESP-based *ab initio* charges, while the CM5 model evolved from a similar approach, but is based on Hirshfeld charges.¹⁵ The latter method assigns charge to each atom in the same proportion as the spherically averaged atom contributes charge to a reference distribution.³² It is not clear if this procedure can assign the electron density correctly to unconventionally bonded species such as the transition structure of the S_N2 reaction. A comparison of the computed charges between CM5/MO6-2X with all the other methods in Table S2 shows the biggest differences are for the Cl atoms in the TS. The CM5 charge for the Cl atoms with MO6-2X/6-31+G(d) is $-0.570 e$, which is essentially the same the underlying Hirshfeld charge, $-0.563 e$. Analysis of the same wavefunction to give Mulliken and ChelpG³³ charges yields -0.627 and $-0.737 e$, respectively. The semiempirical CM3/PDDG and CM1/AM1 calculations give values for the chlorine charges of -0.767 and $-0.734 e$, respectively, very similar to the ChelpG results. Clearly, the results for solvation of molecules in equilibrium geometries or transition structures are very sensitive to the choice of partial atomic charges in force-field-like calculations. In the present case, partial charges derived from *ab initio* or semiempirical wavefunctions yield better results for the activation barrier in aqueous solution than ones based on DFT calculations.

In principle, different ways of treating the QM/MM partition that would include some of the surrounding water molecules in the QM calculation could be explored, although they can cause imbalance in the energetics and forces of the otherwise identical molecules that are treated differently. Of particular interest would be methods that correct for these problems, such as the flexible boundary³⁴ and the adaptive QM/MM³⁵ algorithms. However the scaling of most exchange-containing DFT methods such as MO6-2X is of $O(N^4)$. This means that adding a simple first layer of solvating water molecules, approximately 20 at the TS, would increase the CPU time by a rather prohibitive factor of ca. 3,000.

CONCLUSION

Statistical mechanics simulations using Metropolis Monte Carlo and QM/MM methods have been used to calculate the free energy profile of the prototypical S_N2 reaction between chloride anion and methyl chloride. When using the CM5 charge model and the density functional method MO6-2X/6-31+G(d) the calculated free energy barrier, 38.3 ± 0.4 kcal/mol, exceeds the experimental value of 26.6 kcal/mol. The same calculations using the semiempirical PDDG-PM3 method and CM3 charges or the AM1 method with CM1 charges give results much closer to the experimental value. The difference seems to be predominantly due to the methods for calculating partial atomic charges that are used in evaluating solute-solvent interactions. This expectation was confirmed by evaluating the change in free energy of hydration upon transforming the charges from the CM5 value of $-0.57 e$ for the chlorine atoms in the transition structure to a value closer to that from the CM1/AM1 and CM3/PDDG-PM3 methods, $-0.75 e$. The resulting G_{hyd} of -10.5

kcal/mol would bring the free energy barrier much closer to the observed value (27.8 vs. 26.6 kcal/mol). The results emphasize the sensitivity of QM/MM results for activation barriers to the choices of QM method, MM force field, and implementation of the QM/MM interface. Improving any one component does not guarantee better performance in comparison to experimental data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Potential of mean force for the $\text{Cl}^- + \text{CH}_3\text{Cl} \rightarrow \text{ClCH}_3 + \text{Cl}^-$ reaction. The reaction coordinate, R_c , is expressed as the difference between the two C-Cl distances.

Figure 2.
Representative snapshots of the ion-dipole complex (left) and transition structure (right).

Figure 3. Results of FEP calculations for changing the charges on the Cl atoms in the TS, $[Cl \cdots CH_3 \cdots Cl]^-$. The red marker corresponds to the CM5/MO6-2X value for the charge.

Table 1.

Gas-Phase Relative Energies (kcal/mol) of the Complex and TS.

Method	Complex	TS
HF/6-31G(d)	-10.26	3.57
MP2/6-31G(d)	-10.89	4.54
MP2/6-31G+(d)	-9.59	7.66
MP2/6-31++G(d,p)	-9.66	7.64
MP2/ <i>aug</i> -cc-PVTZ	-10.98	3.00
B3LYP/6-31+G(d)	-9.54	-0.84
B3LYP/6-311G(2d,d,p)	-10.78	-3.02
B3LYP-D3/6-31+G(d)	-11.10	-2.54
MO6-2X/6-31+G(d)	-11.20	2.06
CBS-QB3	-10.07	2.09
AM1	-8.56	0.49
PDDG-PM3	-12.36	3.30
CCSD(T)/TZ2Pf+diff ^a	-10.57	2.07

^aRef. 28.

Table 2.

QM/MM Calculated Free Energies (kcal/mol) for the Complex and TS.

QM Method	Charges	$G(\text{complex})$	$G(\text{TS})$
HF/6-31G(d) ^a	-	not found	26.3 ± 0.5
MO6-2X/6-31+G(d)	CM5	-1.6 ± 0.4	38.3 ± 0.4
AM1	CM1	not found	21.8 ± 0.4
PDDG-PM3	CM3	not found	26.8 ± 0.4
Experimental ^b	-	-	26.6

^aRef. 1.^bRef. 3.