A Priori Computation of a Solvent-Enhanced S_N2 Reaction Profile in Water: The Menshutkin Reaction

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The profound solvent effects on chemical reactions have been recognized for over a century and continue to attract both experimental and theoretical attention.[1] During the past 5 years, there has been a new surge of theoretical investigation of organic reactions in solution.[2-7] This was led and pioneered by the first ab initio calculation of the reaction profile for an S_N2 reaction involving chloride and methyl chloride in aqueous and DMF solution.[2] The striking solvent effects were demonstrated by an increase of ca. 15 kcal/mol in activation energy over its intrinsic barrier.[2,8] Further, for the symmetrical S_N2 reaction of Cl^- + CH_3Cl, the position and structure of the transition state (TS) in solution were predicted to be invariant from those in the gas phase owing to the balanced solvation on both sides of the TS.[2c] However, switching to a system consisting of a neutral nucleophile and an anionic leaving group, where charge separation occurs during the reaction, should yield an uneven solvation effect accompanying a reduction of the reaction barrier and an increase in exothermicity in aqueous solution.[9] This could also lead to a TS shift according to the Hammond postulate.[10] Consequently, we chose to determine the reaction profile for the S_N2 Menshutkin reaction of H_3N + CH_3Cl in water. This, together with the chloride exchange reaction,[2-8] provides a set of examples demonstrating the importance and influence of medium effects on S_N2 reactions.[1,10] The expectations on the reaction surface were confirmed as presented here.

As usual, the computation followed three major steps:[2,3] (1) determination of gas-phase minimum energy path (MEP), (2) development of intermolecular potential functions for solute–solvent interactions, and (3) condensed-phase simulations of the reaction using statistical perturbation theory (SPT).[11] The reaction coordinate (RC) was defined as $RC = r_{CCl} - r_{CN} - R_{ts}$, where R_{ts} is the difference between C–Cl and C–N bond lengths at TS. The MEP was determined at the Hartree–Fock level with the 6-31+G(d) basis set,[12,13] at fixed values of RC with C_{3v}

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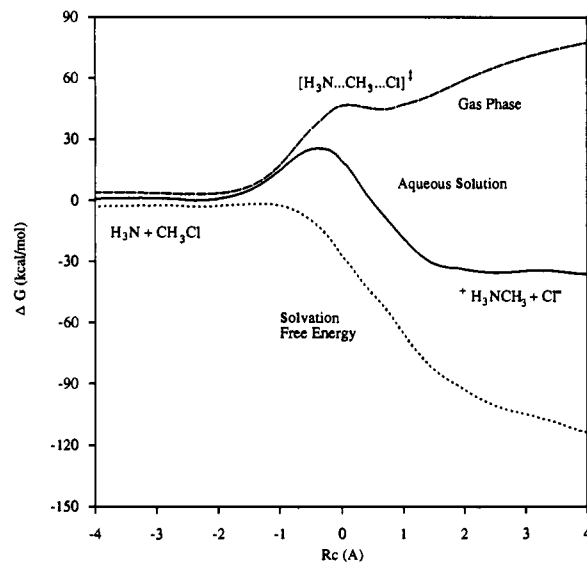
Figure 1. Calculated free energy profile in the gas phase (dashed curve), solvation free energy (dotted curve), and the potential of mean force in aqueous solution (solid curve) for the Menshutkin reaction [H_3N + CH_3Cl] as a function of the reaction coordinate.

symmetry. This was then followed by single-point energy computations at the MP4SDTQ/6-31+G(d) level for all structures considered. Finally, the gas-phase free energy profile (Figure 1) was constructed using standard procedures by including zero-point energy and entropic contributions obtained from the 6-31+G(d) vibrational frequencies.[13-15] The calculated free energy of reaction (119 kcal/mol) was in excellent agreement with the experimental value (110 ± 5 kcal/mol).[16]

To describe intermolecular interactions between the reactants and solvent, the familiar pair-wise Coulomb plus Lennard-Jones functions were used. The OPLS potential function and TIP4P model were adopted for water,[17a] Cl^-,[17b,c] and $CH_3NH_3^+$,[18] while potentials for CH_3Cl and ammonia were derived.[19] These parameters were shown to yield excellent structural and energetic results as demonstrated by good agreements between the computed and experimental free energies of hydration and radial distribution functions.[17-20] The critical step, however, is to provide a set of parameters for the reacting system along the entire RC. This was accomplished by consideration of 6-31+G(d) bimolecular complexes between H_3NCH_3Cl and H_2O spanning the whole reaction

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coordinate. The resultant parameters were fitted to a cubic spline function of RC[3,21] and are provided as supplementary material.

The potential of mean force (pmf) for the Menshutkin reaction in water was obtained through Monte Carlo statistical perturbation calculations.[11] Precise evaluation of the free energy difference at different values of RC was achieved using $\Delta G(RC_1) - \Delta G(RC_0)$ $= -RT \ln \langle \exp(-[H(RC_1) - H(RC_0)]/kT)\rangle_{H(0)}$, where $\langle \rangle_{H(0)}$ represents an ensemble average corresponding to the Hamiltonian $H(RC_0)$, while $H(RC_1)$ is the Hamiltonian for the perturbed system. The simulation was carried out by moving the RC forward and backward at intervals of ±0.1 Å when |RC| ≤ 1.0 Å and of ±0.15 Å for other regions. Thus, a total of 30 simulations was executed to cover the whole reaction. All calculations were performed for the reactants plus 750 water molecules in a rectangular box at 25 °C and 1 atm using the NPT ensemble. As in previous studies, periodic boundary and preferential sampling techniques were employed to enhance the solute–solvent statistics.[18] An equilibration period of 1 × 10⁶ configurations was followed by 1.5 × 10⁶ configurations for averaging for each run. The standard deviations (±σ) were computed from fluctuations of separate averages for blocks of 1 × 10⁵ configurations. All computations were performed on a SUN SPARCstation 2 and a STARDENT 3030 computer in our laboratory; the Monte Carlo simulations required ca. 15 days.

In Figure 1, the computed free energy profile, or pmf, for the Menshutkin reaction of $H_3N + CH_3Cl$ in water was compared with that in the gas phase. The solution-phase curve was anchored to the computed total free energy of hydration of the reactant molecules.[20] Therefore, Figure 1 represents an absolute free energy scale. Clearly, solvation leads to a tremendous stabilization of the products and a large decrease of barrier height. The most striking finding in the present study is that there is a shift of 0.4 Å on the transition state toward the reactants, in accord with empirical expectations.[9,10] It should be noted, however, that the observed TS shift is entirely due to the solvent effects since solute geometries were kept fixed during the Monte Carlo simulations. Inclusion of internal degrees of freedom may result in additional changes of the TS in solution. The charge separation at the TS was ca. 70% as predicted from Mulliken population analysis using various basis sets, which is consistent with previous estimates.[22] The computed free energy of reaction in water, −37 ± 2 kcal/mol from the pmf or −32 ± 2 kcal/mol from the hydration free energies,[20] may be compared with the experimental data (−34 ± 10 kcal/mol).[23] This represents a decrease of ca. 155 kcal/mol due to solvation. The agreement emphasizes the validity of the potential functions used in the present study and supports the computational procedure.

The computed activation free energy of 25.6 ± 1 kcal/mol is a reduction of 21 kcal/mol relative to the gas-phase process. Experimental data do not appear to be available for this particular reaction; however, comparison can be made to an activation *energy* of 23.5 kcal/mol for the reaction of $H_3N + CH_3I$ in water.[24] Interestingly, a unimodal reaction profile in water was also obtained for the Menshutkin reaction, a result similar to that found in the previous chloride exchange reaction.[2a,25] Further analysis of the present Menshutkin reaction in water will be presented later.[26]

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Structure of Dilithiobenzenide: An ab Initio Study

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In a recent communication, Sakurai et al.[1] reported a determination of the crystal structure of bis[(tetrahydrofuran)lithium(I)] hexakis(trimethylsilyl)benzenide (**1**). They found the six-membered ring to be significantly folded, forming a boat, with the lithium cations located on the same side of the ring (syn-facial) in surprisingly short distance from one other (2.722 Å). Because of the serious steric hindrance expected in **1**, a question arises as to whether the crystal structure data may serve as an appropriate

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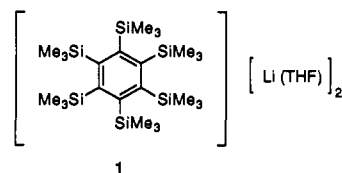
model for dilithiobenzenide itself. The latter compound is of great theoretical interest, although not observed experimentally. Herein we report the results of the first ab initio calculations on monomeric, unsolvated dilithiobenzenide that resolve the above question.

Preliminary MNDO[2] calculations provided two minima, **2** and **3**: one with syn- and the other with anti-facial arrangement of the lithium cations. MNDO predicts **3** to be more stable by

2 (C₂ᵥ)   2 (rear view)

3 (C₂ₕ)
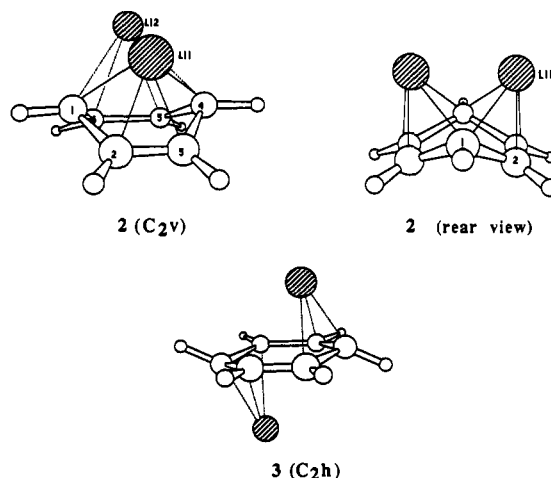
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