**Objective:** Semi-empirical AM1 and Hartree-Fock 3-21G*-SM5.4 calculations will be used to construct reaction coordinate diagrams for both the gas phase and aqueous phase S_N_2 reactions of chloride ion, bromide ion and hydroxide ion reacting with CH_3Cl.

**Background:** Nucleophilic substitution (S_N_2) is one of the most important synthetic reactions in organic chemistry. The reaction is stereospecific, with inversion at carbon, and proceeds with a large variety of nucleophiles (Nu) and Leaving groups (X).

Although most textbooks draw the reaction coordinate with a barrier, and attribute this barrier to weakened bonds in the transition state structure, the fact is that gas-phase S_N_2 reactions generally proceed with little or no energy barrier. Thus, “energy barriers” observed in solution must be related to solvent effects or solvation. It turns out that polar solvents are generally much more effective at stabilizing small, charge localized ions then at stabilizing large, delocalized ions. In a typical S_N_2 reaction, both the attacking nucleophile and the leaving group will be small, charge localized ions and the transition state for the reaction will be a large, delocalized ion. This means that the polar solvent can stabilize both the reactants and products better than the transition state. This has the net effect of creating or increasing any energy barrier for the reaction.

Quantum mechanical calculations are performed on isolated molecules (a dilute gas), whereas most chemistry is carried out in a solvent. It is therefore relevant to inquire about the role of solvent in altering gas phase structures and conformations, relative energetics, and chemical reactivity. The geometries of only a very few molecules are known with sufficient accuracy in both the gas phase and solution to judge the possible role of solvent in altering structure. It appears that solvent effects on the equilibrium geometry of neutral molecules is small, and can perhaps be safely ignored. Solvent plays a more significant role in altering the geometries of ions, but the changes still appear to be relatively small.

There is much more evidence to suggest the importance of solvent in altering the gas-phase energetics. The general rule is that the more polar the molecule, the more it will be stabilized by polar solvents. Electrostatic considerations generally discourage the buildup of charge in isolated molecules (gas-phase) and a polar solvent will, therefore, usually act to reduce gas-phase energy differences between highly polar and less polar structures. Charged molecules greatly exaggerate the situation. Solvation will be more effective for charge-localized ions than for delocalized ions. A simple example of this concerns the site of protonation of phenol. In the gas phase, the carbon-protonated phenol (structure A) is estimated to be ~15 kcal/mol more stable than the oxygen-protonated phenol (structure B). However, in water, protonation occurs predominantly at oxygen.

Computational techniques available for treatment of molecules in solution fall into two general categories. Explicit models treat the solvent as a set of distinct molecules. Operationally, the solute molecule is placed in a “box” containing several hundred to several thousand solvent molecules. The energy of the entire system is determined by averaging over all possible orientations of the individual molecules. While this is a reasonable

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1 Adapted from Hehre, W. J.; Shusterman, A. J.; Huang, W. W. *A Laboratory Book of Computational Organic Chemistry*, Wavefunction, Inc. 1998, 43-44.
approach, the need to average over a huge number of different solvent-solute configurations makes the calculation extraordinarily expensive and time consuming.

The second type of computational technique uses an entirely different approach. It treats the solvent as an electric field which interacts with the molecule. This approach is a drastic simplification of the real situation in which individual solvent molecules optimally organize themselves around the solute. Nevertheless, models have been formulated and parameterized to reproduce experimental heats of solvation. This experiment will make use of this type of solvent interaction calculation.

Solvent affects the nucleophilicity of a nucleophile in several ways. Those considered to be most significant are (1) the solvation energy of the nucleophile; (2) the strength of the bond being formed to carbon; (3) the size of the nucleophile; (4) the electronegativity of the attacking atom; and (5) the polarizability of the attacking atom. Briefly, this is how each of these factors affects nucleophilicity:

1. A high solvation energy lowers the ground-state energy relative to the transition state, in which the charge is more diffuse. This results in an increased activation energy. Viewed from another perspective, the solvation energy affects nucleophilicity because the solvation shell must be disrupted to arrive at the transition state, and this desolvation energy contributes to the activation energy.

2. A stronger bond between the nucleophilic atom and the carbon is reflected in a more stable transition state and therefore a reduced activation energy. Since the S_N2 process is concerted, the strength of the partially formed new bond is reflected in the energy of the transition state.

3. A sterically restricted nucleophile is less reactive than a more accessible one because of nonbonded repulsions which develop in the transition state. The trigonal bipyramidal geometry of the S_N2 transition state is sterically more demanding than the tetrahedral reactant, so steric congestion increases as the transition state is approached.

4. A more electronegative atom binds its electrons more tightly than a less electronegative one. Since the S_N2 process requires donation of electron density to an anti-bonding orbital (LUMO) of the reactant, high electronegativity is unfavorable.

5. Polarizability describes the ease of distortion of the electron cloud of the attacking atom of the nucleophile. Again, since the SN2 process requires bond formation by an electron pair from the nucleophile, the more easily distorted the electric field of the atom, the higher is its nucleophilicity. Polarizability increases going down and to the left in the periodic table.

Procedure:

Build anionic complexes of nucleophile + CH\textsubscript{3}Cl and calculate the energy at several different distances between the incoming nucleophile and the electrophilic carbon. To build the anionic complex, open Spartan Pro and click on the new model icon in the toolbar. Click on the expert model kit tab at the right side of the screen. Select C from the periodic table and five-coordinate trigonal bipyramidal from among the atomic hybrids. Click anywhere in the builder area and you will see a penta-coordinate carbon atom (5 open yellow valencies). Select Cl from the periodic table and one-coordinate from the atomic hybridizations and then click on one of the axial free valencies of the five-coordinate carbon. There will be three valencies in the same plane about 120° from each other and two valencies perpendicular to them. These two perpendicular valencies are the axial valencies. The two axial valencies are 180° apart. Select the appropriate atom for the nucleophile you will be using. Start with chlorine. Make sure the selected hybridization is one-coordinate and then click on the remaining axial free valence. (NOTE: when you build the complex with the hydroxide ion as the nucleophile, you will need to select the bent divalent hybridization option for the oxygen atom.) Click on the constrain distance icon (or select constrain distance from the geometry menu) and then click on the nucleophilic atom and then the carbon. An open padlock icon will appear in the lower right corner of the screen. Click on this. The padlock should close and the distance between the two clicked atoms appears in the adjacent box. Change this value to 6.0 and hit enter. This sets the distance at 6.000 angstroms and the complex has been made. Click on the minimize energy icon and you should see the constrained distance become large relative to the unconstrained C-Cl distance.

To setup the energy calculation, select calculation from the setup menu. Calculate an equilibrium geometry with a semi-empirical AM1 algorithm. Set the total charge to anion (keep the multiplicity at singlet) and click the subject to constraints box. Click OK and then submit the calculation by selecting submit from the setup menu. You will

\[\text{Streitwieser, Jr., A. Solvolytic Displacement Retwo clicked atoms actions, McGraw-Hill, New York, 1962.}\]
be prompted to name and save your structure. Be sure to name it Cl6 and save to your personal folder. Once
the calculation is complete, you need to set up a second calculation to determine both the gas-phase and
aqueous energies for this complex. Select calculations from the setup menu and change the calculation to single
point energy, Hartree-Fock, 3-21G*. Make sure the total charge is set to anion and then click the box next to E.
Solvation in the compute options and subject to constraints. Click OK and then submit the calculation. When the
calculation is complete, select properties from the display menu. A small window will appear with both the gas-
phase energy (in a.u.) and an aqueous energy labeled energy + SM5.4/A. Record both of these energies. Atomic units (a.u.) can be converted into kcal/mole with the conversion factor 1 a.u. = 627.5 kcal/mol.

Click on the constrain distance icon and then click on the constrained bond. The distance appears in the lower
right corner of the screen. Change this value to the next shorter distance (6.0, 5.0, 4.0, 3.0, 2.5, 2.0, 1.5) and hit
enter. Save this file as Cl5 and redo the calculations as described above and record the appropriate energies.
Complete the table below for all of the complexes.

<table>
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<tr>
<th>Nu-C Distance (Angstroms)</th>
<th>Cl-CH₃-Cl</th>
<th>Br-CH₃-Cl</th>
<th>HO-CH₃-Cl</th>
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<td></td>
<td>Gas-Phase</td>
<td>Aqueous</td>
<td>Gas-Phase</td>
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<tr>
<td></td>
<td>3-21G*</td>
<td>SM5.4/A</td>
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1. Construct a reaction energy diagram by plotting Nu-C distance (x-axis) vs energy (y-axis) for both gas phase
and aqueous energies for each nucleophilic substitution. Do not plot the energies in a.u. because the
differences are so small. Instead, subtract the calculated energy at the 6.0 angstrom distance from each of the
other energies in the column. This sets the calculated energy at 6.0 anstroms as the zero point energy. Now
convert these energy differences into units of kcal/mol. Use Excel to make these plots look nice.

2. Estimate the activation energy for each of the reactions in both the gas phase and in aqueous conditions.
(Your Excel graph will probably be plotted in what looks like a backwards direction. Be sure to view the graph
so you are looking at the energy as the distance between the nucleophile and electrophilic carbon decreases.
As the nucleophile approaches there may be some initial stabilization then the energy should increase as the
transition state is neared.)

3. For each nucleophile, summarize whether the estimated activation energy increased, decreased or remained
essentially the same when comparing gas phase to aqueous conditions.

4. Choose the structure which is closest to the transition state for each reaction. Use bond lengths and angles
to justify the assumption that the structure resembles the transition state for an Sn2 reaction.

5. Look at the structure for hydroxide ion attacking at both 6.0 and 5.0 angstroms. Is there a 180° angle
between the hydroxide hydrogen, oxygen and carbon? What is that angle? Is this what you would expect? Explain.

6. Which reaction appears to have no energy barrier in the gas phase? Does this reaction have an energy
barrier in the aqueous phase? WHY?

7. Can you estimate, from your graphs, whether the reaction should be exothermic or endothermic?