Reaction Mechanisms and Transition States

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Description:
In this lab we will consider the S_N1 and S_N2 reaction mechanism for nucleophilic substitution. By considering transition structures, intermediates and solvation effects we will determine which pathway is favored for the reactions involving CN^- attack of bromomethane and t-butyl bromide.

Suggested level: Graduate/advanced undergraduate.

Learning objectives: Learn how compute stable structures, reaction intermediates, and transition states; review concepts of enthalpy, entropy, and Gibbs free energy; learn how to incorporate solvent in calculations.

I. BACKGROUND

Nucleophilic substitution is a class of reactions where an electron-rich nucleophile attacks an electron-deficient electrophilic center causing the departure of the leaving group. For saturated carbon centers, two key reaction mechanisms have been proposed: S_N1 and S_N2. The 1 and 2 in these names indicate that the rate-determining step is either uni-molecular (first-order reaction) or bi-molecular (second-order reaction), respectively.
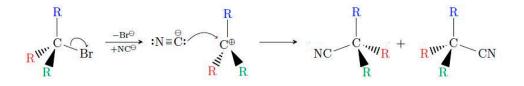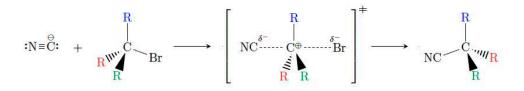

FIG. 1: S_N1 mechanism

FIG. 2: S_N2 mechanism

The preferred mechanism for a given reaction depends on many factors including the strength of the nucleophile, the nature of the leaving group, the stability of intermediates, solvent effects and the steric environment around the electrophilic center. For a primary alkyl, S_N1 is unfavored as the intermediate radical is unstable, whereas S_N2 kinetics are good, unless hindered by the nucleophile. For a tertiary alkyl the opposite is true: S_N1 kinetics are good because the tertiary radical is relatively stable, whereas steric factors hinder S_N2.
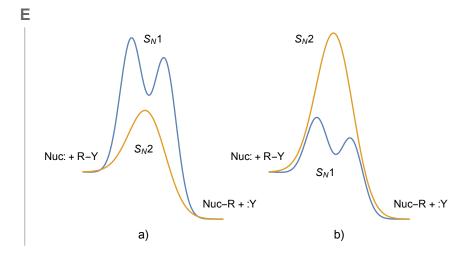

FIG. 3: Reaction profiles for S_N1 and S_N2 showing a) S_N2 favored and b) S_N1 favored.

II.   METHOD

In this lab we are going to calculate energy profiles for the following reactions:

$$CH_3Br + CN^{\ominus} \longrightarrow CH_3CN + Br^{\ominus}$$
$$C(CH_3)_3Br + CN^{\ominus} \longrightarrow C(CH_3)_3CN + Br^{\ominus}$$

Identify the species involved in these reactions for each of the mechanisms (S_N1 and S_N2) and make a list of these. You should have 10 systems in total, including 8 equilibrium structures and 2 transition structures.

All Q-Chem calculations should be at the HF/6-31G* level of theory.

Equilibrium Structures:

1. Build each of your 8 equilibrium structures in IQMOL ensuring the geometries are minimized and symmetrized. Do not worry about setting the charge on the system in this step as we just want an initial structure for the geometry optimizations in the next step.

2. Use Q-CHEM to optimize the geometries of your 8 structures using the HF/6-31G* level of theory. Make sure the charge and multiplicity of each system is correct before submitting the job (note that all species are singlets):
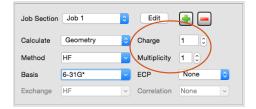
FIG. 4: Setting the charge and multiplicity in the QUI

Transition Structures:

Transition structure are more difficult to find and often require a careful navigation of the potential energy surface. To find the geometries of your transition structures, use the following approach:

1. Set up constraints on the Br-C and C-CN bond lengths using the given in the following table and clean up your structures in IQMOL.

Bond	$Br-C^{\oplus}$	$C^{\oplus}-CN$
$[Br\text{-}CH_3\text{---}CN]^{\ominus}$	2.3 Å	2.4 Å
$[CN\text{--}t\text{-Butyl--}Br]^{\ominus}$	3.1 Å	2.8 Å

2. Submit a Q-CHEM geometry optimization using HF/6-31G*, ensuring the constraints are copied across to the input file (this is done automatically). This allows the geometry to relax in the presence of the constraints.

3. Submit a Q-CHEM frequency job using your optimized geometry. You could combine this step with the previous one using two job sections and the @@@ construct.

4. Note how many imaginary frequencies you have and determine which one vibrates along the reaction coordinate (this will most likely be the first mode).

5. Submit a combined frequency calculation, followed by a transition structure search. Use Mode Following and read in the Hessian in the TS job to give the optimizer a good idea of what the PES looks like.

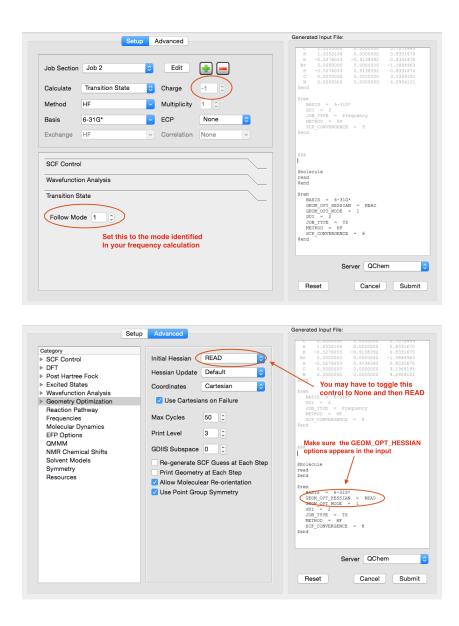If you are having trouble locating the TS, email to the instructor.

FIG. 5: Setting up mode following and reading in the Hessian for the TS calculations

Free Energies:

For each of your optimized structures run a frequency calculation to get the enthalpy and entropy corrections to the energy. Look in the output file for the following section after the vibrational frequencies are reported:

```
The Molecule is a Symmetric Top
Translational Enthalpy:      0.889 kcal/mol
Rotational Enthalpy:         0.889 kcal/mol
Vibrational Enthalpy:       21.166 kcal/mol
gas constant (RT):           0.592 kcal/mol
Translational Entropy:      34.068  cal/mol.K
Rotational Entropy:         11.784  cal/mol.K
Vibrational Entropy:         0.031  cal/mol.K

Total Enthalpy:             23.536 kcal/mol
Total Entropy:              45.882  cal/mol.K
```

The last two lines are the ones that you are after. Note that the values are given in kcal/mol and cal/mol.K, respectively.

Save the output files from these calculations for your report.

To compute the effects of solvent on each of the structures, set up a ChemSol calculation by computing the single point energy with Chemsol set to true. This is done in the Advanced panel in the QUI:
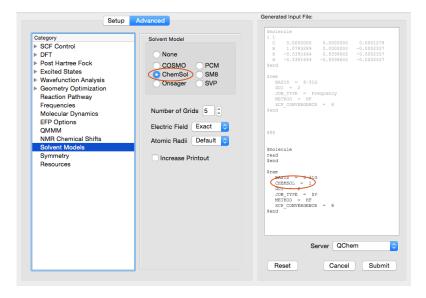

FIG. 6: Setup for a ChemSol energy calculation in the QIU

Leave all the other ChemSol options at their default values. The contribution to the free energy from the solvent (water) is printed in the output file:

```
Iterative Langevin Dipoles (ILD) Results (kcal/mol):
----------------------------------------------------
LD Electrostatic energy                 -75.47
Hydrophobic energy                        0.26
van der Waals energy (VdW)               -1.59
Bulk correction                         -10.13
Solvation free energy dG(ILD)           -86.94
```

Record the Solvation free energy dG(ILD) from the last line.

III. EXERCISES

1. Identify the intermediates and transition structures involved in each mechanism (S_N1 and S_N2) for the two reactions.

2. Compute the reaction barriers use the following equations to compute your reaction

free energies:

$$\Delta E = \sum_{\text{intermediates}} E - \sum_{\text{reactants}} E \tag{1}$$

$$\Delta H = \sum_{\text{intermediates}} H - \sum_{\text{reactants}} H \tag{2}$$

$$\Delta S = \sum_{\text{intermediates}} S - \sum_{\text{reactants}} S \tag{3}$$

$$\Delta G_{\text{sol}} = \sum_{\text{intermediates}} dG_{\text{ILD}} - \sum_{\text{reactants}} dG_{\text{ILD}} \tag{4}$$

$$\Delta G_{\text{gas}} = \Delta E + \Delta H - T\Delta S \tag{5}$$

$$\Delta G = \Delta G_{\text{sol}} + \Delta G_{\text{gas}} \tag{6}$$

E values come from your converged HF calculations, H and S values from your final frequency calculations, and dG_{ILD} values from the ChemSol calculations. Use $T = 298$ for the temperature. Note that for S_N1 reactions we do not compute the true barrier height (which would require optimizing on the free energy surface), just the barrier to the intermediates.

3. Which mechanism is favored for each of the two reactions?

4. Compute the free energies for the total reactions using the above equations, but where you now consider the products rather than the intermediates.

5. Why is it important to consider solvation effects for these reactions?

6. You calculated barrier heights should give qualitative correct predictions, but will not be comparable to experiment. Give two ways the calculations could be improved, and why you think your changes would have an effect.

You report should consist of a zip file containing the frequency calculations for each structure used to determine the free energy barriers, along with your calculations for the free energy barrier heights and reaction energies, and answers to the above questions. You may submit your energy calculations in a spreadsheet but, if you do, make sure it contains appropriate labels and comments so that it is clear what you are calculating. Always report the units (kcal/mol and kJ/mol are used for energy differences, hartrees are used for total energies).