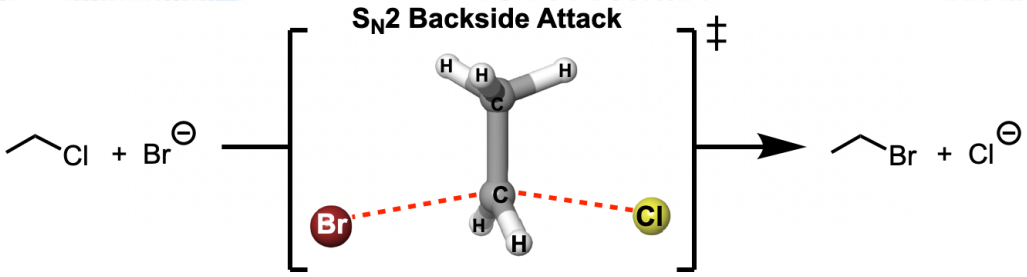
Substitution Nucleophilic (S_N2) Reactions

Created with: Release 2021-3
Prerequisites: working knowledge of Maestro
Files Supplied: SN2_reactions_worksheet
Categories: organic chemistry

About this Lesson

In this lesson plan, students will examine bimolecular substitution nucleophilic (S_N2) reactions. Transition state theory will be introduced to analyze the concerted mechanism of how a nucleophile attacks an electrophile to form a given product. Reaction energy diagrams will be investigated to determine whether a reaction is exergonic or endergonic.

Using Maestro, students will use Jaguar's AutoTS panel to perform geometry optimization calculations of the reactants and products of an S_N2 reaction, determine which bonds are breaking and forming, establish correspondence between atoms in the reactants and the products, and generate a transition state structure. Then, they will render a potential energy surface diagram to show the activation energy barrier.



Learning Objectives

- Identify transition state structures of S_N2 reaction mechanisms
- Plot reaction energy diagrams with activation energy barriers to determine their chemical reactivity characteristics (i.e. endergonic, exergonic, etc.)

Standards

- *ACS Guidelines*
  - Substitution mechanisms (Conceptual Topics)
- *ETS Chemistry GRE*
  - Organic Chemistry – Reaction Mechanisms (3.C)
- *AAMC MCAT*
  - Structure, function, and reactivity of biologically-relevant molecules (5D)

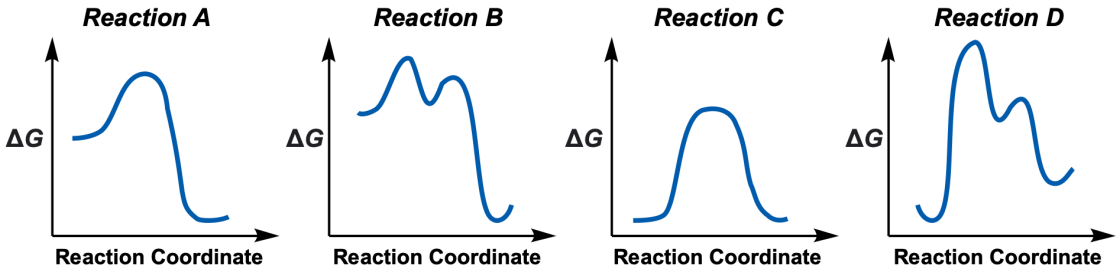
Assessments

The following types of formative assessments are embedded in this lesson:

- Assessment of student understanding through discussion of warm-up questions and filling in any knowledge gaps of chemical reactivity
- Visual assessment of student-generated transition state structures and reaction energy diagrams of S_N2 reactions

Warm-Up Questions: To be done on their own or at the beginning of class

Read the Khan Academy article on endothermic vs. exothermic reactions. Then, consider the following four reaction energy diagrams.



1) Which energy diagram(s) correspond with a two-step mechanism?
2) Which energy diagram(s) correspond with a one-step mechanism?
3) Compare energy diagrams A and C. Which has a relatively larger activation energy (E_a) barrier?
4) Compare energy diagrams A and D. Which has a positive ΔG?
5) Compare energy diagrams A and C. Which has a negative ΔG?
6) Compare all four energy diagrams. Which has the largest activation energy (E_a) barrier?

Lesson Outline

1. What you will need for this lesson

	1. Go to the 'Data' folder and open your Class Folder found on the virtual cluster's desktop. 2. Right-click on the folder called "SN2_Reactions" and copy folder to Desktop ● Here, you will find the lesson plan, worksheet, and any additional resources
	3. Open **Maestro** a. See Starting Maestro if you need help

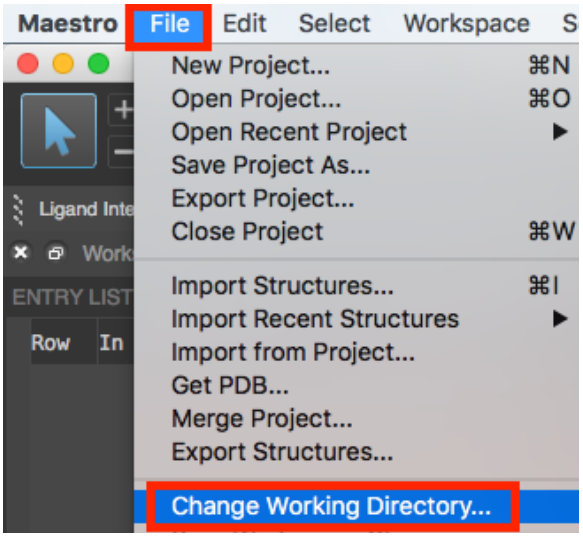


Figure 1-1. Change Working Directory option.

4. Go to **File > Change Working Directory**
5. Find your "SN2_Reactions" folder that you duplicated to your Desktop, and click **Choose**

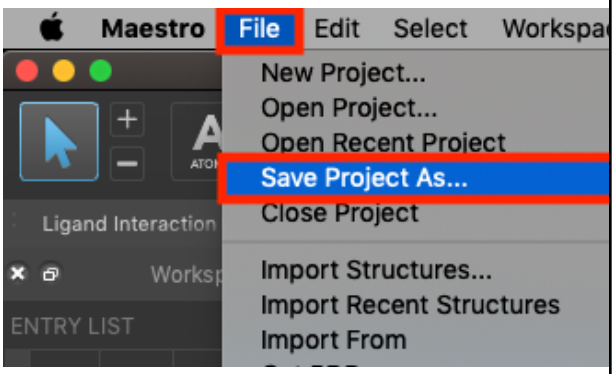


Figure 1-2. Save Project panel.

6. Next, go to **File > Save Project As**
7. Type "**SN2_tutorial**" and click **Save**
    a. The project will be titled **SN2_tutorial.prj**

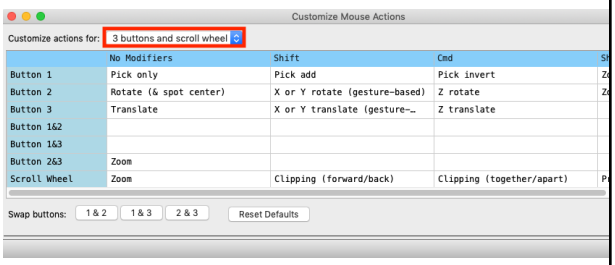


Figure 1-3. Choose the best mouse option for your set up.

8. Finally, check your **Mouse Actions**
    a. PC : **Edit > Customize Mouse Actions**
    b. Mac : **Workspace > Customize Mouse Actions**
9. Make sure you have **the best option chosen for your set up**. This lesson was written with a three-button mouse with a scroll wheel, meaning the scroll wheel is a button as well as a wheel. If you do not have a mouse, choose **Trackpad**.

2. Introduction to S_N2 Reactions

Substitution reactions are common reactions in organic chemistry. Its importance can be attributed to the fact that it can be used to introduce many functional groups from alkyl halide precursors. For example, substitution reactions are vital in the synthesis of alcohols, ethers, thiols, sulfides, nitriles, azides, halides, esters, and acetylenes.

There are two types of substitution reactions: S_N1 and S_N2 reactions. For this lesson, we will be focusing on the characteristics and mechanism of S_N2 reactions. S_N2 reactions are based on a concerted (one-step) mechanism where a nucleophile substitutes the place of a leaving group in an electrophile. See the figure below for the different components of an S_N2 reaction.

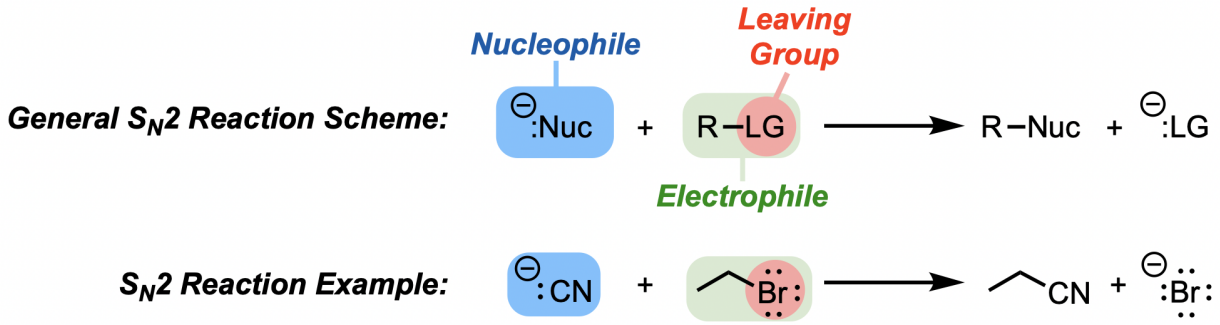


Figure 2.1. The components of a general S_N2 reaction.

Nucleophiles are chemical species that are electron donors while electrophiles are electron acceptors. See the lesson on Nucleophiles (link this) for a deeper dive on their chemical properties. In an S_N2 mechanism, the nucleophile attacks the α-carbon, which is the carbon atom that the leaving group is attached to. Simultaneously, the carbon-leaving group bond breaks. An S_N2 reaction progresses by going from reactants to transition state structure to products, but we will touch more on transition states in section 4 of this lesson. See the figure below for a general arrow-pushing mechanism of an S_N2 reaction.

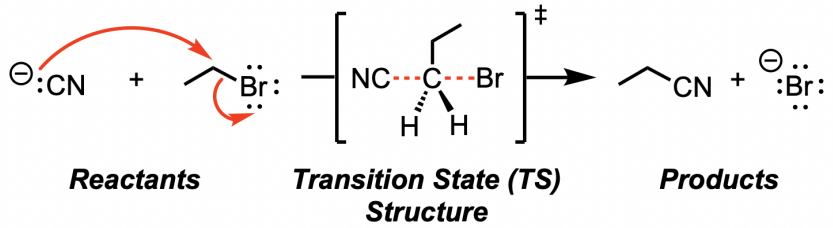
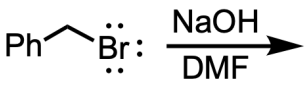


Figure 2.2. Arrow-pushing mechanism of an S_N2 reaction.

Example #1. Predict the product and arrow-pushing mechanism of the following S_N2 reaction



3. Locating Transition States with AutoTS

In this lesson, we are going to analyze the S_N2 reaction between chloroethane and a bromide ion by determining the energetics of the reactants, transition state structure, and products. To do this, we will be using Maestro, Schrödinger's molecular modeling software.

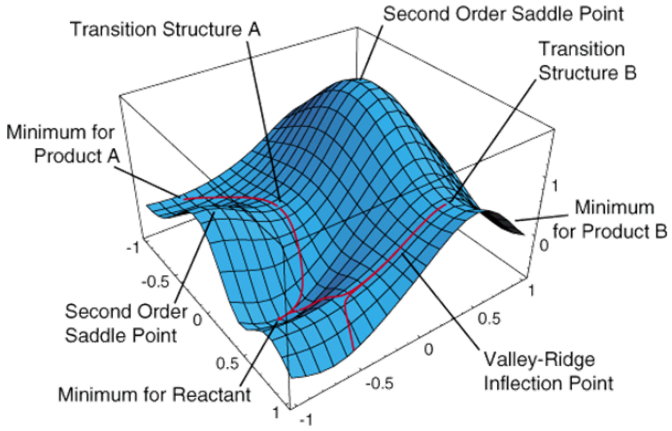


Figure 3.1. General potential energy surface.

Used with permission. Created by Professor H. Bernhard Schlegel, Wayne State University, Detroit, MI.

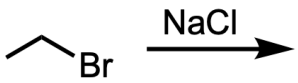
Locating a transition state is essential for computing the activation energy of a reaction, and thereby the reaction rate. As a result, finding transition states is useful in many applications: predicting reactivity, understanding reaction mechanisms, catalyst design and optimization, predicting outcomes of various competing reactions and more. Besides, locating a transition state is unique to computation -- meaning the transition state cannot be 'found' in the lab. Read more about Schrödinger's work in the space of Catalysis and Chemical Reactivity.

Searching for a transition state is typically a relatively difficult task in molecular modeling. Unlike an optimization to a minimum (see: Introduction to Geometry Optimizations, Functionals and Basis Sets), the search for a transition state highly depends on the quality of the initial guess, the initial Hessian and the search direction. Search for transition states is sometimes described as an 'art'. Experience and practice are key, as well as maintaining a thorough understanding of the available tools.

There are several alternative approaches to searching for a transition state with Jaguar (Schrödinger's Quantum Mechanics Engine). For this lesson, we will be using the AutoTS panel which is an automated workflow in which reactants and products are input and interpolation is used to search for the transition state with minimal user intervention. AutoTS is an automated way of finding transition states, particularly for elementary reactions. Its workflow requires only the structures of the reactants and the products as input, and then automates the rest of the process: it optimizes reactants and products, determines which bonds are breaking and forming, establishes correspondence between atoms in the reactants and the products, generates a transition state guess (either from a template or using an interpolated reaction path), launches a transition state search with the DFT engine Jaguar, verifies if the located transition state is trustworthy, runs frequency calculations, connects the transition state with the reactants and the products using an intrinsic reaction coordinate (IRC) algorithm and finally prints the potential energy surface diagram showing the transition state barrier. AutoTS works best on reactions that have only one transition state between the reactants and the products, such as the S_N2 reaction.

We will be using the AutoTS panel for the S_N2 reaction between bromoethane and a chloride ion. Before we get started, answer the following question:

Example #2. Predict the product and arrow-pushing mechanism of the following S_N2 reaction. Include the transition state structure of the reaction.



Computational Exercise #1: Generating a Transition State, Geometries of Reactants and Products, and an Energy Diagram using AutoTS

Let's employ the AutoTS panel for the S_N2 reaction between bromoethane and a chloride ion. When an AutoTS job is submitted, it produces the following results:

1) Optimized geometries of the reactants and products
2) A transition state structure with an animation to show bonds breaking and forming
3) A potential energy surface diagram that includes a transition state barrier

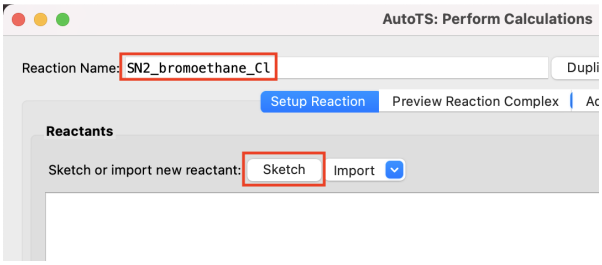


Figure 3-1. Opening the AutoTS panel.

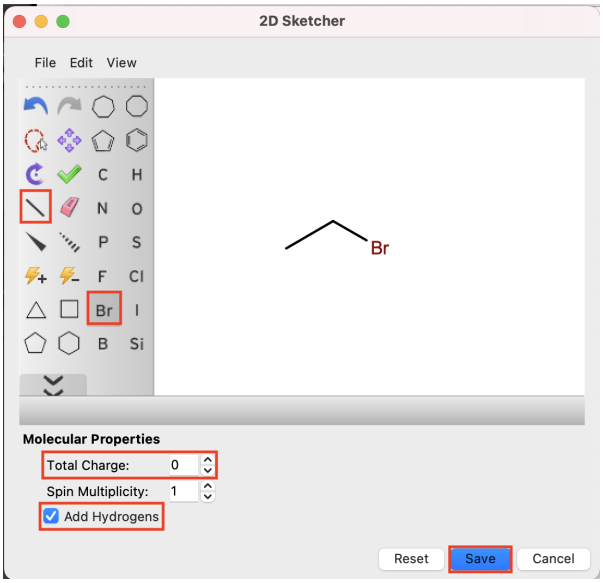


Figure 3-2. Sketching the EtBr reactant in the AutoTS panel.

We will first perform an AutoTS calculation on a simple S_N2 reaction between chloroethane and a bromide ion to learn the mechanics of the panel.

1. Go to **Tasks** and type **AutoTS**. Click **AutoTS… Other Applications** (under the AutoTS category)
    - The AutoTS: Perform Calculations panel opens
2. Change the Reaction Name to **SN2_bromoethane_Cl**
3. Under *Reactants*, click **Sketch** and **draw bromoethane**. In the 2D Sketcher, select the carbon single bond, then click and drag to form a C–C single bond. Then click **Br** to place a bromine at the end of the 2-carbon chain. Under Molecular Properties, ensure the Total Charge is 0, Spin Multiplicity is 1, and the box to Add Hydrogens is checked. Click **Save**.

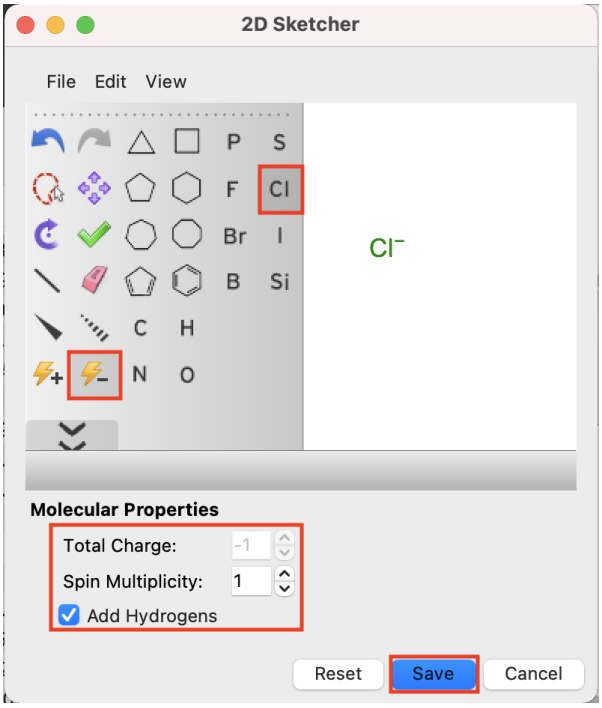


Figure 3-3. Sketching the Cl⁻ reactant in the AutoTS panel.

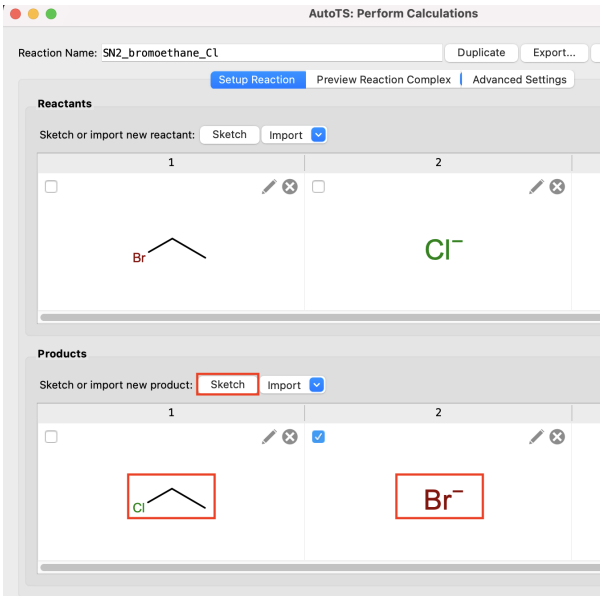


Figure 3-4. Sketching the products in the AutoTS panel.

4. Under *Reactants*, click **Sketch** and **draw a chloride ion.** Select **Cl** and place one atom in the workspace. Notice that HCl was placed rather than a single Cl atom. Click the **lightning bolt minus** symbol. This will decrease the charge to Cl– so you are left with a chloride ion. Under Molecular Properties, ensure the Total Charge is -1 since this is an anion, Spin Multiplicity is 1, and the box to Add Hydrogens is checked. Click **Save**.
5. Under *Products*, repeat the process and draw the products of the S_N2 reaction.
    - Your inputs should match the *Figure 3-4.*

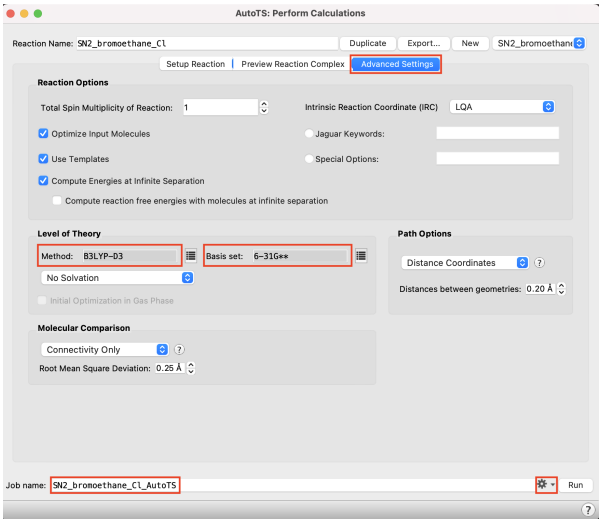


Figure 3-5. Advanced settings and naming the job.

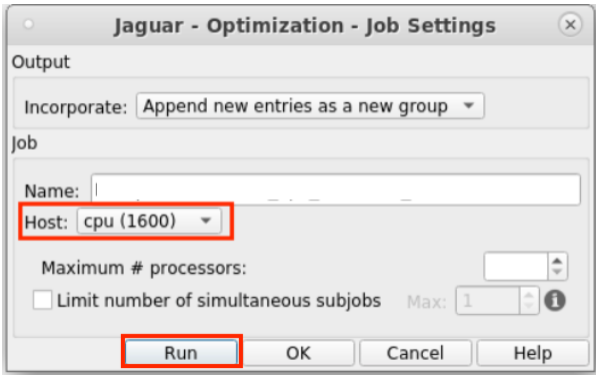


Figure 3-6. Adjusting job settings from the gear icon and running the job.

6. Go to the **Advanced Settings** tab
    - We will keep the settings as default in this case
    - Level of theory:
        i. Method: B3LYP-D3
        ii. Basis Set: 6-31G**
7. Change the *Job name* to **SN2_bromoethane_Cl_AutoTS**
8. Adjust the job settings () as needed
    - Change host from local host to **CPU host**.
    - Change the **Maximum # of Processors to 12**. The job can be completed in about 5 minutes on a 12 CPU host
9. If you would like to run the job yourself, click **Run**. Otherwise, we can import pre-generated outputs in the analysis stages
10. **Close** the AutoTS panel

Note: The *Preview Reaction Complex* tab can be used to generate reactant and product complexes (merged structures) and to see a guess at the reaction path. Adjustments can be made as needed

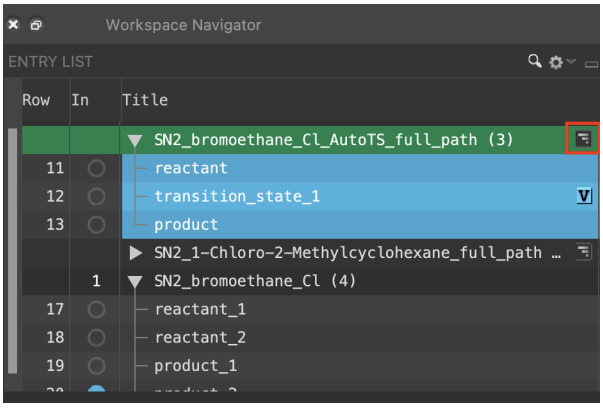


Figure 3-7. Importing the results of the AutoTS calculation.

When the job is complete, we can view the results in the AutoTS: View Results panel. The AutoTS calculation assesses various paths without any additional user input

11. Go to **File > Import Structures**
12. Select the `SN2_bromoethane_Cl_AutoTS_full_path.mae` file and click **Open**
    - If you did not perform the calculation yourself and wish to open the pre-generated results, select the `Ethyl_Br_SN2_full_path.mae` file and click **Open**
    - An entry group including the reactant, transition state and product structures is added to the entry list
13. Use the Workflow Action Menu (WAM) button ( ) to access the Results panel

Alternatively, go to **Tasks** and type **AutoTS Results** and load the full_`path.mae` file via the **Import** button

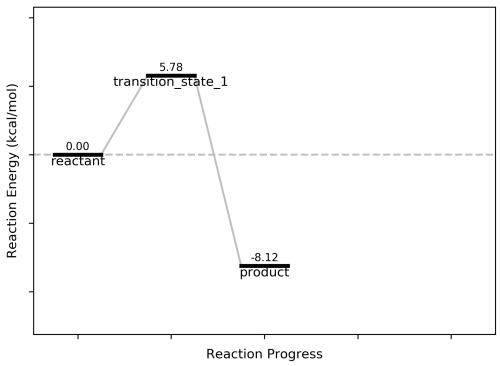


Figure 3-8. AutoTS results.

The AutoTS: View Results panel contains the energy diagram associated with the reaction. If you are interested in viewing the vibration associated with the transition state, use the vibration viewer (V) in the entry list and animate in the workspace

Example #3. Using the AutoTS results, let's analyze the S_N2 reaction further. Answer the following questions:

a) Take screenshots of the optimized geometries for the reactants, transition state structure, and products.
b) List the bond distances of each molecule using the Measure button in units of ångstroms.

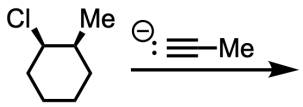
Reactants	Transition State Structure	Products
Screenshot:	Screenshot:	Screenshot:
C–C bond distance: C–Br bond distance:	C–C bond distance: C–Br bond distance: C–Cl bond distance:	C–C bond distance: C–Cl bond distance:

c) Now let's analyze the transition state structure. Look at the animation of its vibration. What is the geometry of the central carbon atom at the transition state? How does this differ from the electrophile's starting geometry as a reactant?

d) Take a screenshot of the reaction energy diagram. Is the reaction exergonic or endergonic? What is the activation energy barrier in units of kcal/mol? Would the reaction speed up or slow down if the nucleophile was iodide instead? Why?

4. Individual Exercise

Answer the following questions based on the following S_N2 reaction:



a) Predict the product and arrow-pushing mechanism of the S_N2 reaction. Include the transition state structure of the reaction. Take note of any stereochemical inversions as well.

b) Look at the AutoTS results of this reaction. Go to **Tasks** and type **AutoTS Results**. Then import `SN2_1-Chloro-2-Methylcyclohexane_full_path.mae`. Recall that cyclohexane is not planar but is in a chair conformation. Redraw your S_N2 mechanism in chair conformation and take note of the substituent positions – are they in axial or equatorial positions? (Note: The carbon with chloride is C1 and the carbon with methyl is C2; the numbering of the ring is going clockwise).

c) Take screenshots of the optimized geometries for the reactants, transition state structure, and products. Try your best to capture the chair conformations by rotating the molecule. Also, list the bond distances of each molecule using the Measure button in units of ångstroms.

Reactants	Transition State Structure	Products
Screenshot:	Screenshot:	Screenshot:
C–Cl bond distance:	C(chair)–C(alkyne) bond distance: C–Cl bond distance:	C(chair)–C(alkyne) bond distance:

d) Take a screenshot of the reaction energy diagram. Is the reaction exergonic or endergonic? What is the activation energy barrier in units of kcal/mol?

5. Summary, Additional Resources, and References

Using Maestro, students learned how to use Jaguar's AutoTS panel to perform geometry optimization calculations of the reactants and products of an SN2 reaction, determine which bonds are breaking and forming, establish correspondence between atoms in the reactants and the products, and generate a transition state structure. Lastly, they learned how to render a potential energy surface diagram to show the activation energy barrier.

For further learning:

For some related practice, proceed to explore other relevant tutorials:

- Introduction to Geometry Optimizations, Functionals, and Basis Sets
- Locating Transition States

For further reading:

- Exploring potential energy surface for chemical reactions: An overview of some practical methods. DOI:10.1002/jcc.10231
- Introduction to Computational Chemistry, 3rd Edition
- Essentials of Computational Chemistry: Theories and Models, 2nd Edition
- Molecular Modelling: Principles and Applications, 2nd Edition
- See the Jaguar help documentation

Glossary of Terms:

Entry List - a simplified view of the Project Table that allows you to perform basic operations such as selection and inclusion

Included - the entry is represented in the Workspace, the circle in the In column is blue

Project Table - displays the contents of a project and is also an interface for performing operations on selected entries, viewing properties, and organizing structures and data

Recent actions - This is a list of your recent actions, which you can use to reopen a panel, displayed below the Browse row. (Right-click to delete.)

Scratch Project - a temporary project in which work is not saved. Closing a scratch project removes all current work and begins a new scratch project

Selected - (1) the atoms are chosen in the Workspace. These atoms are referred to as "the selection" or "the atom selection". Workspace operations are performed on the selected atoms. (2) The entry is chosen in the Entry List (and Project Table) and the row for the entry is highlighted. Project operations are performed on all selected entries

Working Directory - the location that files are saved

Workspace - the 3D display area in the center of the main window, where molecular structures are displayed

2D Workspace - the 2D panel that opens from the “edit” dropdown that allows for the construction of molecules using a 2D sketcher

Tile - if multiple entries are included, included entries are displayed side by side in individual boxes rather than being overlaid in the same space