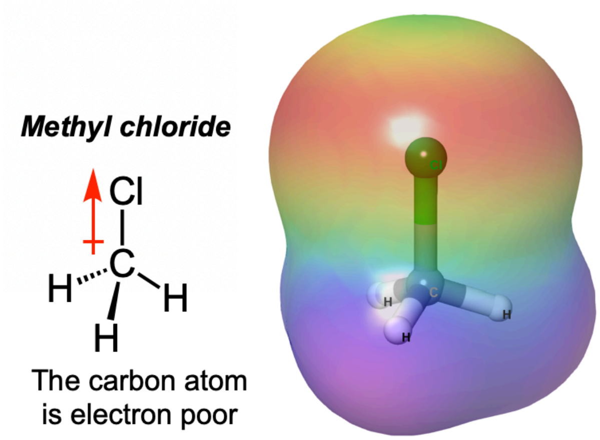
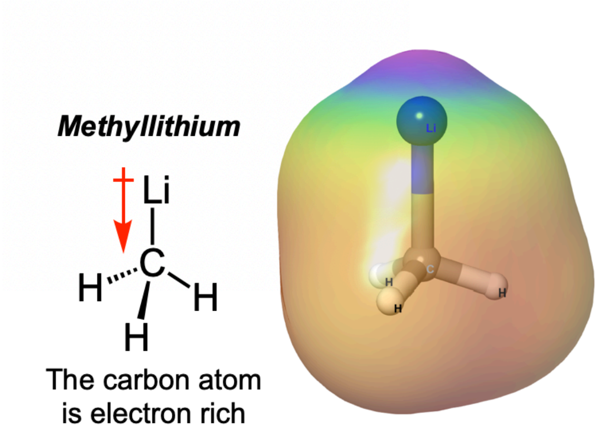
Nucleophiles & Electrophiles





Nucleophiles & Electrophiles

About this Lesson:

In this lesson plan, students will examine the behavior of nucleophiles and electrophiles. Students will learn about inductive effects and how to identify nucleophilic and electrophilic centers in a molecule. This will help with predicting where electron density can be found and where it is likely to flow during a reaction.

Using Maestro, students will create a map of electrostatic potential (ESP) of various nucleophiles and electrophiles with Jaguar and examine the electrostatic potential on the molecular surface. These renderings will help with visualizing sites of high and low electron density.

Learning Objectives:

- Differentiate between nucleophilic and electrophilic centers
- Identify electron-rich and electron-poor regions by mapping electrostatic potential surfaces onto molecules

Lesson Contents:

Standards Alignment:

- *Connections to AP*
    - Models and Representations (Skill 1)
- *IB Diploma Programme:*
    - Models of bonding and structure (Structure 2)
- *ACS Guidelines*
    - Understand molecular structure and bonding (Coursework Guidelines)
- *AAMC MCAT*
    - Nature of molecules and intermolecular interactions (5B)

Assessments for Understanding:

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

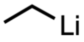
- Assessment of student understanding through discussion of warm-up questions and filling in any knowledge gaps of inductive effects
- Visual assessment of student-generated electrostatic potential surfaces of nucleophilic and electrophilic centers

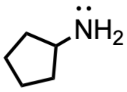
Associated Documentation Pages: Jaguar Geometry Optimization: The Basics

Warm-Up Questions:

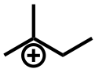
Watch the Khan Academy videos on nucleophilicity and basicity.

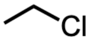
1) Identify the nucleophilic center of each molecule.





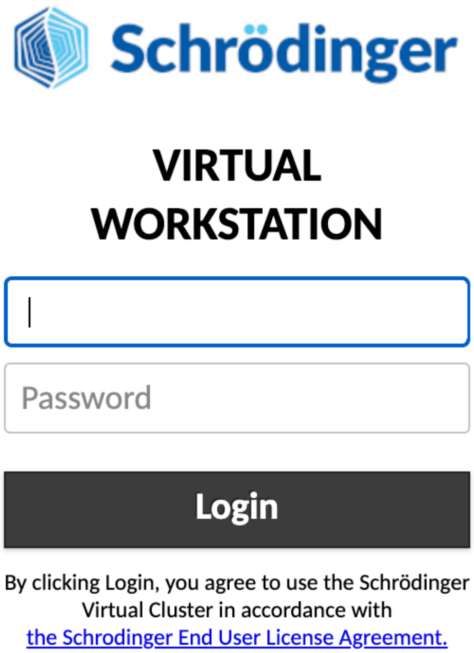
2) Identify the electrophilic center of each molecule.





1. Setting Up the Maestro Session

At the start of the Maestro session, it is essential to 1) check your mouse actions, 2) change the file path to the Working Directory for this lesson, and 3) save your project file. The working directory indicated in this section contains the files necessary to complete this lesson. If you do not set the appropriate working directory, you will be unable to run any calculations.



VIRTUAL WORKSTATION

By clicking Login, you agree to use the Schrödinger Virtual Cluster in accordance with the Schrodinger End User License Agreement.

Figure 1-1. Virtual workstation login page.

1. Launch the Virtual Cluster

Figure 1-2. Course-data folder on the desktop.

2. Double-click the **course-data** folder on the desktop

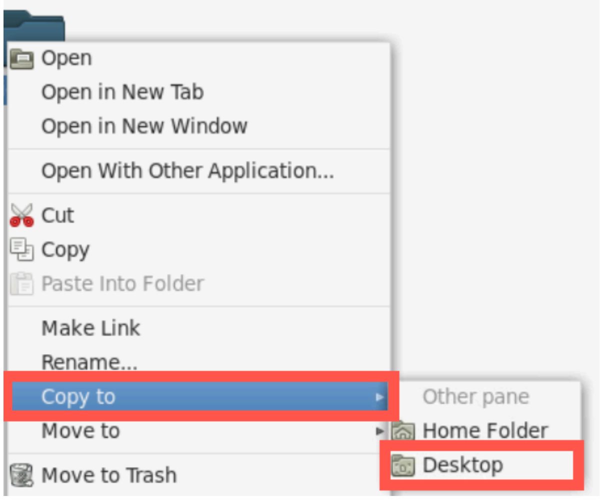
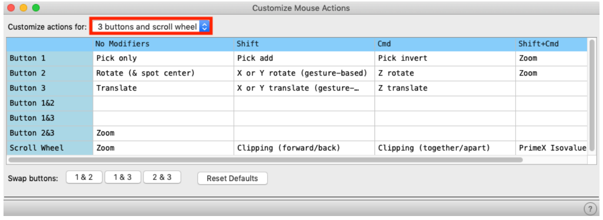


Figure 1-3. Copy the lesson folder to the Desktop.

3. Right-click the `nucleophiles` folder and select **Copy to > Desktop**

4. Double-click the Maestro icon on the desktop



	No Modifiers	Shift	Cmd	Shift+Cmd
Button 1	Pick only	Pick add	Pick invert	Zoom
Button 2	Rotate (& spot center)	X or Y rotate (gesture-based)	Z rotate	Zoom
Button 3	Translate	X or Y translate (gesture-…	Z translate	
Button 1&2				
Button 1&3				
Button 2&3	Zoom			
Scroll Wheel	Zoom	Clipping (forward/back)	Clipping (together/apart)	PrimeX Isovalue

Figure 1-4. Change the mouse actions.

5. Check your mouse actions.
    - Go to **Workspace > Customize Mouse Actions**
    - *Note:* This lesson was made with a three-button mouse with a scroll wheel, but a trackpad can still be used
    - ***Trackpad keys:***
        - **Up/Down trackpad** = Zoom In/Out
        - **Option** = Rotate
        - **Control** = Translate

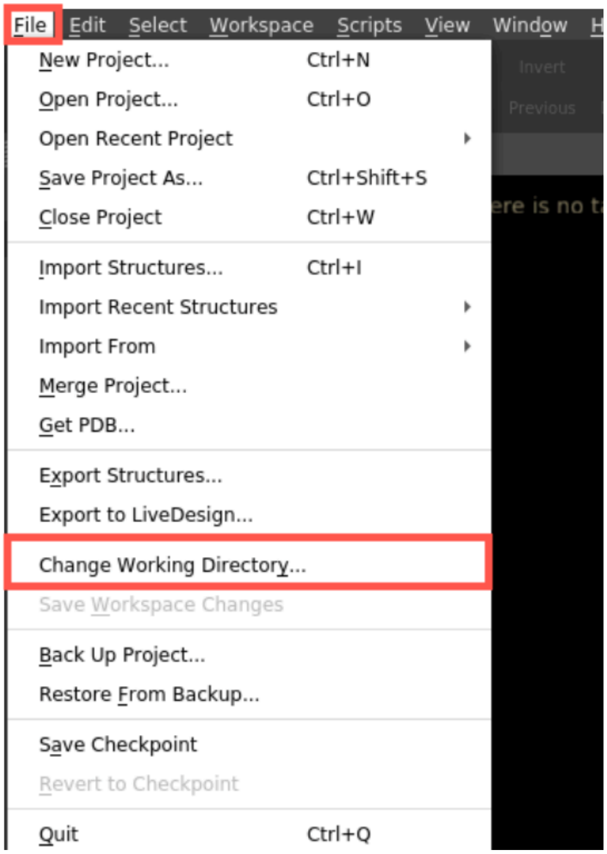
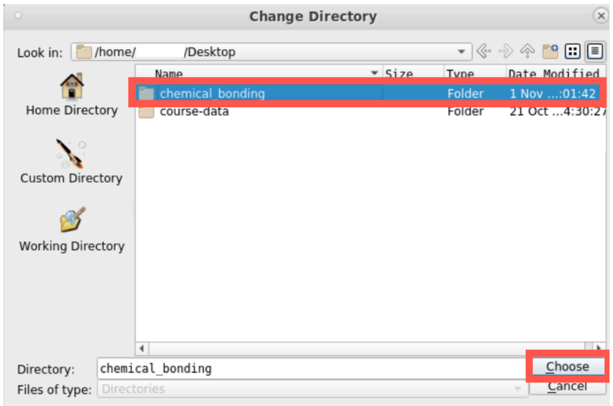


Figure 1-5. Change Working Directory option.

6. Go to File > Change Working Directory



Look in: /home/ /Desktop

Name	Size	Type	Date Modified
chemical_bonding		Folder	1 Nov ...:01:42
course-data		Folder	21 Oct ...4:30:27

Directory: chemical_bonding

Files of type: Directories

Figure 1-6. Change Working Directory panel.

7. Navigate to Desktop > `nucleophiles` folder and click **Choose**

Pre-generated input and results files are included for running jobs or examining output

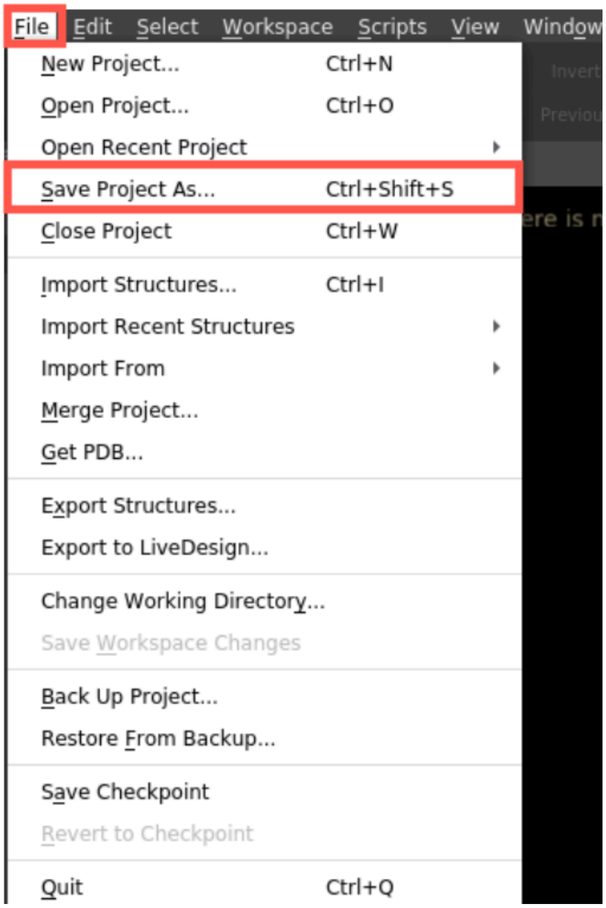
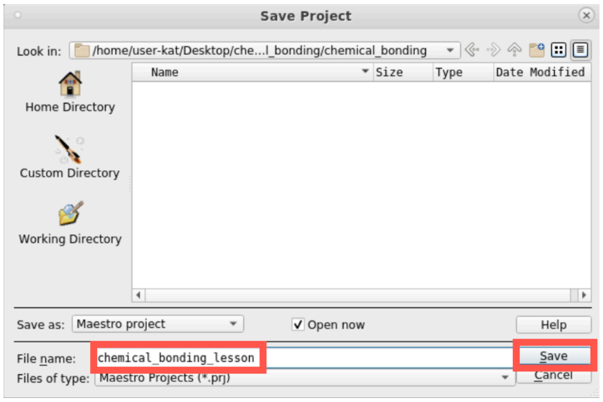


Figure 1-7. Save Project option.

8. Go to File > Save Project As



Look in: /home/user-kat/Desktop/che...l_bonding/chemical_bonding

Save as: Maestro project

☑ Open now

File name: chemical_bonding_lesson

Files of type: Maestro Projects (*.prj)

Figure 1-8. Save Project panel.

9. Change the *File name* to `nucleophiles_lesson`, click Save
    - The project is now named nucleophiles.prj

2. Polar Bonds, Induction, and Electronegativity

Bond polarity is a measure of how equally or unequally the electrons in any covalent bond are shared. A **nonpolar covalent bond** is one in which the electrons are shared equally, like in Cl_2, N_2, or H_2. In the case of Cl_2, each atom starts off with seven valence electrons, and each Cl shares one electron with each other forming one covalent bond.

Figure 2-1. Nonpolar covalent bond of Cl_2

The total number of electrons around each individual atom consists of six nonbonding electrons and two shared, bonding electrons for eight total electrons. This matches the number of valence electrons in the closest noble gas argon (Ar). Since the bonding atoms are identical, Cl_2 contains a nonpolar covalent bond.

In a **polar covalent bond**, there is an unequal distribution of electrons which is characterized by a partial positive charge on one atom and a partial negative change on the other. The atom that attracts the electrons more strongly acquires the partial negative charge and vice versa. For example, the electrons in the H–Cl bond of a hydrogen chloride atom spend more time near the more electronegative chlorine atom than near the hydrogen atom. Therefore, the chlorine atom carries a partial negative charge while the hydrogen atom has a partial positive charge. We can represent this charge distribution as:

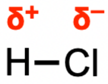
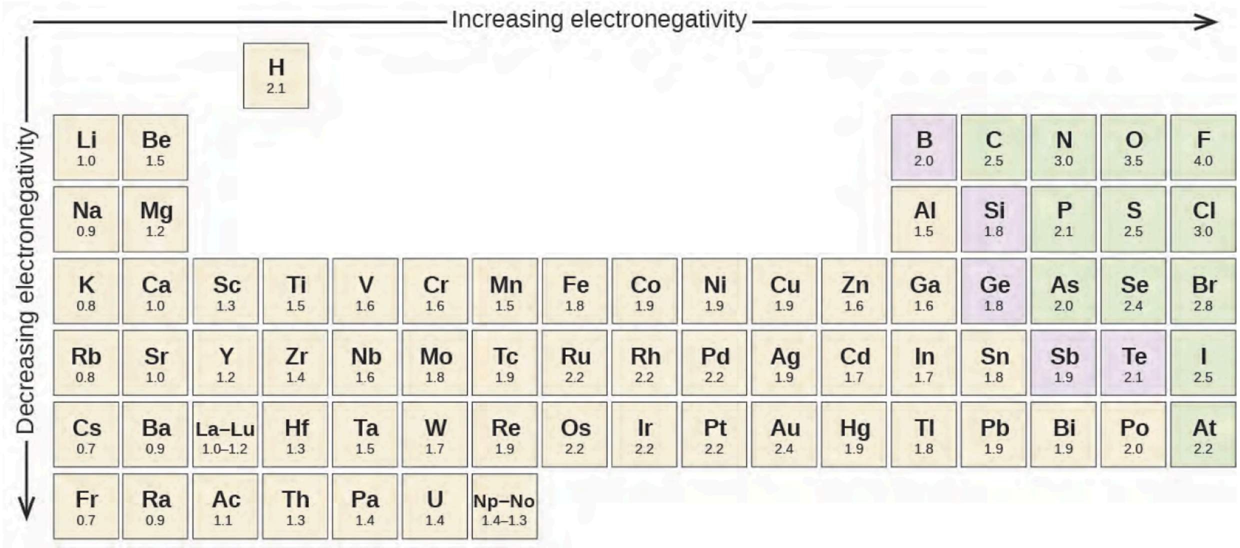


Figure 2-2. Polar covalent bond of H–Cl

The δ^+ (delta plus) and δ^- (delta minus) symbolize the partial positive and negative charges, respectively. In a polar bond, these numbers are less than a full charge of the ions.

Electronegativity is the ability of an atom in a molecule to attract electrons to itself and is used to estimate whether a given bond is nonpolar covalent, polar covalent, or ionic. The greater an atom's electronegativity, the greater its ability to attract electrons to itself. American chemist Linus Pauling developed an electronegativity scale, which is based on thermochemical data shown below.



			H 2.1													
Li 1.0	Be 1.5											B 2.0	C 2.5	N 3.0	O 3.5	F 4.0
Na 0.9	Mg 1.2											Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.9	Ni 1.9	Cu 1.9	Zn 1.6	Ga 1.6	Ge 1.8	As 2.0	Se 2.4	Br 2.8
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sb 1.9	Te 2.1	I 2.5
Cs 0.7	Ba 0.9	La–Lu 1.0–1.2	Hf 1.3	Ta 1.5	W 1.7	Re 1.9	Os 2.2	Ir 2.2	Pt 2.2	Au 2.4	Hg 1.9	Tl 1.8	Pb 1.9	Bi 1.9	Po 2.0	At 2.2
Fr 0.7	Ra 0.9	Ac 1.1	Th 1.3	Pa 1.4	U 1.4	Np–No 1.4–1.3										

Figure 2-3. Linus Pauling's Electronegativity Scale

The absolute value of the difference in electronegativity (ΔEN) of two bonded atoms provides a rough approximation of the polarity to be expected in the bond and, thus, the bond type. Note that electronegativity values have no units. When the difference is very small or zero, the bond is nonpolar covalent. When the difference is between 0.4 and 1.8, the bond is polar covalent. When the difference is above 1.8, the bond is ionic. A table summarizing electronegativity differences and bond types is shown below.

Bond Type	Electronegativity Difference
Nonpolar covalent	< 0.4
Polar covalent	0.4 – 1.8
Ionic	> 1.8

Table 2-1. Summary of bond types based on electronegativity differences

Induction (or inductive effect) is due to the difference in electronegativity of atoms bonded together. A bond between two atoms is polarized if there is a difference between their electronegativities. This **polarization** of the bond causes the appearance of partial charges (δ^+ and δ^-), which may have effects on close-by neighboring bonds. Some effects may be electron withdrawal which often occurs on atoms that are more electronegative than carbon (O, N, F, etc.), or electron repelling which often occurs on atoms that are less electronegative than carbon (Mg, Al, etc.). We will visualize inductive effects in various nucleophiles and electrophiles using calculated electrostatic potential maps later in this lesson.

3. Nucleophiles

A **nucleophile** contains an electron-rich center and comes from the Greek meaning “nucleus lover”. Nucleophiles provide the electrons to make a new bond in a substitution reaction (either S_N1 or S_N2). A nucleophilic center is characterized by its ability to react with a positive charge or partial positive charge by donating a pair of electrons. There are three different kinds of electron-rich regions:

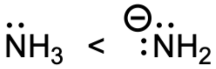
1) **nonbonding electrons** (present on oxygen, nitrogen, and negatively charged carbon atoms called carbanions) – Atoms that possess nonbonding lone pairs of electrons are nucleophilic. Note that lone pairs of electrons may not always be drawn in molecular structures so be aware of the octet rule and feel free to draw them in if they are not shown.

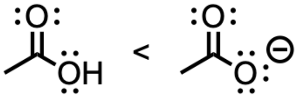
2) **a carbon atom bonded to a metal**, such as a Grignard/organomagnesium or organolithium – A carbon atom bonded to a metal has a strong negative character which can be shown through writing a resonance structure. The carbanion is considered to be a strong nucleophile.

3) **π bonds** – A π bond is also a region of high electron density. Since π bonds are not as strong as σ bonds, π electrons are more available to react in a reaction because π bonds can break more easily. Molecules containing π bonds are considered to be weak nucleophiles and can react with strong acids or electrophiles.

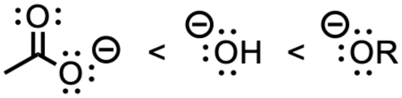
Nucleophilicity is a kinetic property measured by the rate at which a nucleophile causes a substitution reaction to occur. Certain reactions are better with strong nucleophiles while others are better with weak nucleophiles. Some factors that contribute to nucleophilicity include:

1) **Charge** – As electron density on an atom increases, so does nucleophilicity

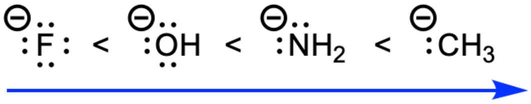




2) **Basicity** – The stronger the base, the greater the nucleophilicity

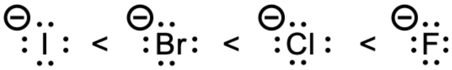


3) **Electronegativity** – For atoms in the same row of the periodic table, as electronegativity increases, nucleophilicity decreases

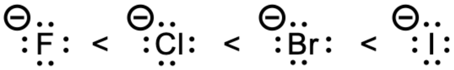


Nucleophilicity increases as electronegativity decreases

4) **Solvation effect** – Depends on whether the reaction is in polar protic or polar aprotic solvent. In polar protic solvents, nucleophilicity increases going down the periodic table. In polar aprotic solvents, nucleophilicity increases going up the periodic table

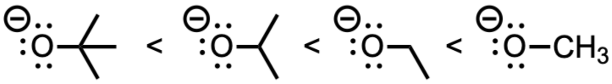


In polar protic solvent
(i.e. H_2O, MeOH, etc.)

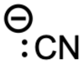


In polar aprotic solvent
(i.e. DMSO, THF, etc.)

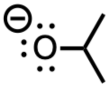
5) **Steric hindrance** (or bulkiness) – The less bulky, the better the nucleophile since it is easier for the nucleophile to backside attack



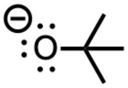
Example #1: Rank the following compounds in order of increasing nucleophilicity.



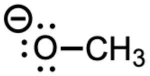
A



B



C



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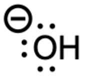


E

Computational Exercise #1: Generating Electrostatic Potential (ESP) Maps on the Molecular Surface

Now we will calculate the electrostatic potential surfaces of ethanol and ethoxide to visually identify which nucleophile is strong and which is weak. ESP maps will show the electron-density distribution on the surface of the molecules. This exercise involves three parts:

6) Build the molecules and minimize their geometries
7) Generate surfaces of the molecules
8) Map the electrostatic potentials to the molecular surfaces

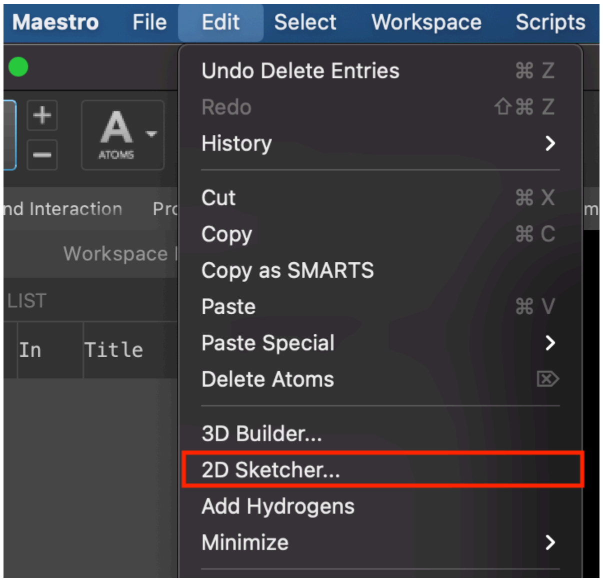


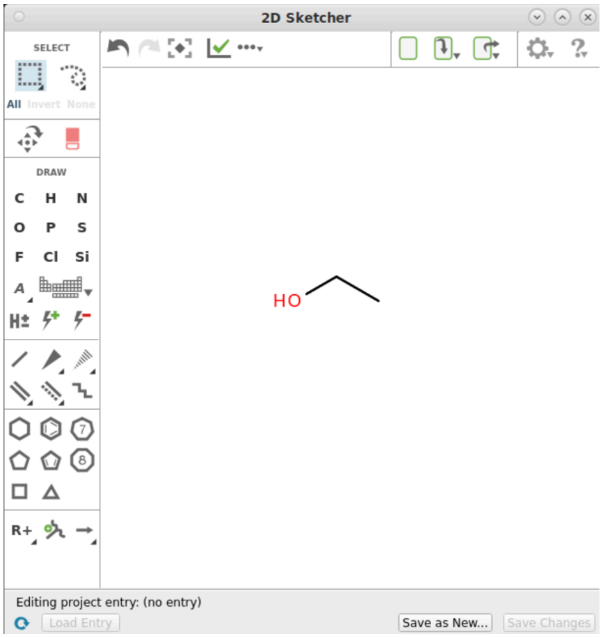
Figure 3-1. Open 2D Sketcher.

Part 1. Build the molecules and minimize their geometries

Before generating any surfaces, build and minimize the structures for ethanol and ethoxide

1. Go to **Edit** > **2D Sketcher**

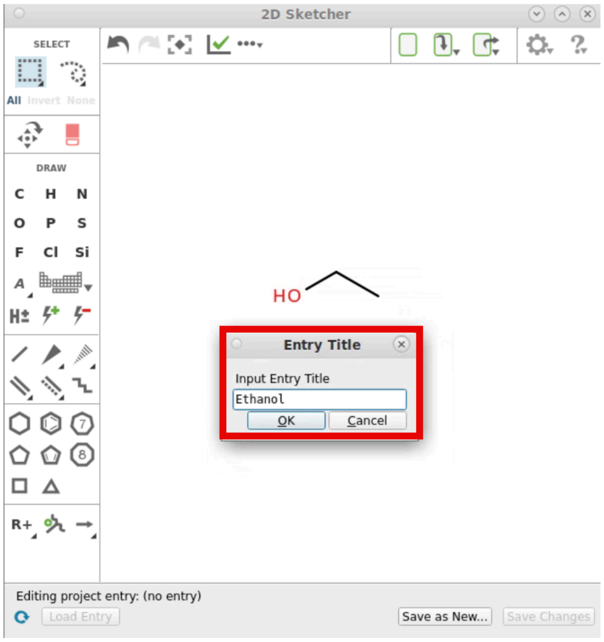
The 2D sketcher functions like many standard 2D molecular drawing tools. For a complete overview of using the sketcher panel, see the 2D Sketcher Panel documentation.



Editing project entry: (no entry)

Figure 3-2. Drawing ethanol.

2. **Draw** ethanol
    - Go to the selection bar on the left
    - Choose the single bond button
    - Click and drag in the workspace to form ethane
    - Click and drag again from one of the carbon atoms to form propane (linear 3-carbon chain)
    - Click “O” in the selection bar and click the end of the single bond to change a carbon to OH at the end

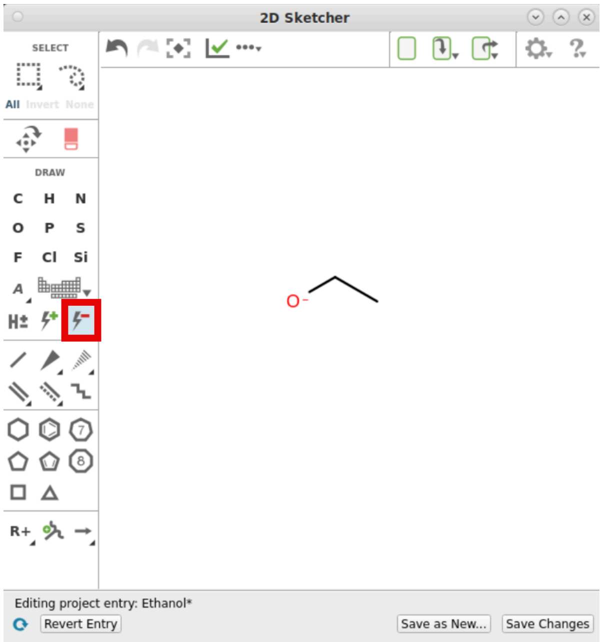


Input Entry Title: Ethanol

Editing project entry: (no entry)

Figure 3-3. Saving Ethanol.

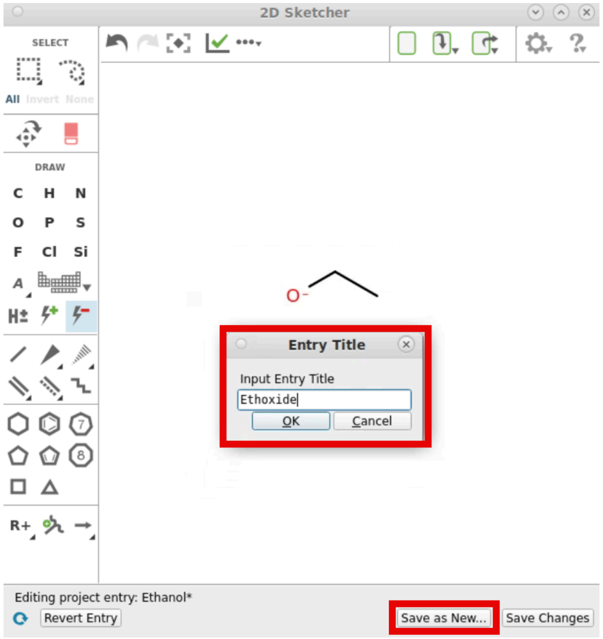
3. Click on **Save as New** and for *Input Entry Title* write **Ethanol**. Click **OK**.



Editing project entry: Ethanol*

Figure 3-4. Drawing Ethoxide.

4. **Draw** ethoxide
    - Go to the selection bar on the left
    - Choose the single bond button
    - Click and drag in the workspace to form ethane
    - Click and drag again from one of the carbon atoms to form propane (linear 3-carbon chain)
    - Click “O” in the selection bar and click the end of the single bond to change a carbon to OH at the end
    - Click the lightning bolt Decrease Charge button then click the Oxygen atom in your molecule. This removes the H from OH and adds a negative charge to O.

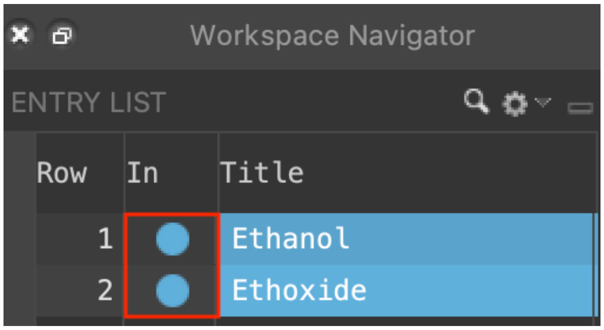


Ethoxide

Editing project entry: Ethanol*

Figure 3-5. Saving Ethoxide.

5. Click on **Save as New** and for *Input Entry Title* write **Ethoxide**. Click **OK**.



Row	In	Title
1	●	Ethanol
2	●	Ethoxide

Figure 3-6. Including both molecules.

Viewing multiple molecules at the same time can be important for comparing and contrasting them. We will show ethanol and ethoxide side by side so we can easily see how they differ.

6. Simultaneously **include** (control + click or command + click) all molecules

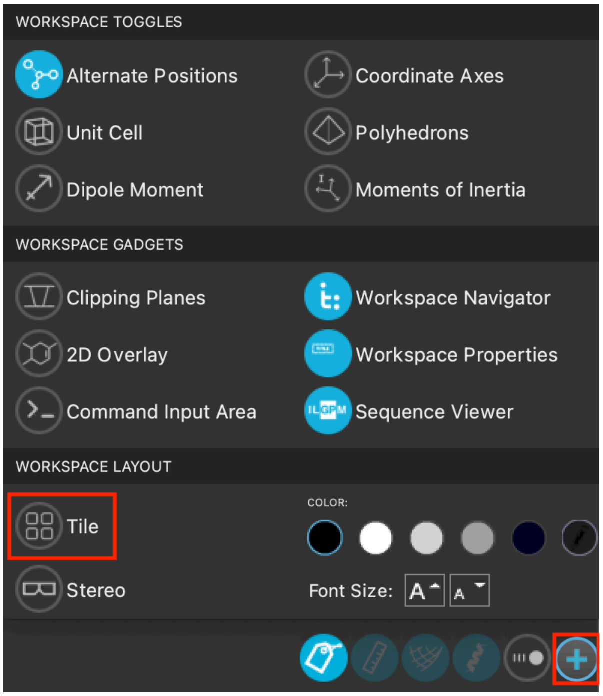
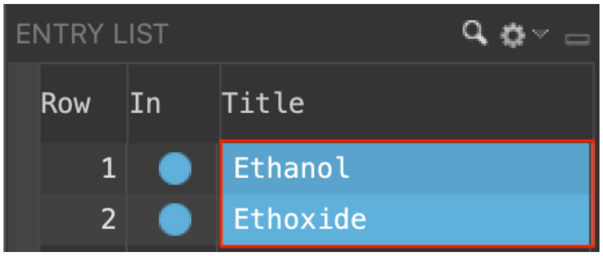


Figure 3-7. Tiling both molecules.

7. **Show** workspace configuration panel by clicking the Plus symbol at the bottom right corner
8. Click **Workspace Layout > Tile**



Row	In	Title
1	●	Ethanol
2	●	Ethoxide

Figure 3-8. Selecting both entries.

9. Simultaneously **select** (control + click or command + click) all molecules
10. Change their representations to ball-and-stick by clicking on the **Style** menu and choosing **Apply ball-and-stick representation**
11. Include atom labels if you'd like by clicking **Apply Labels > Custom Label**

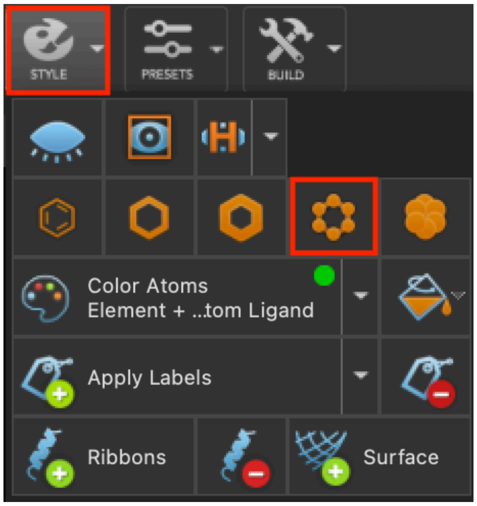


Figure 3-9. Applying ball-and-stick style to all entries.

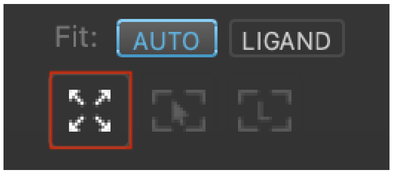


Figure 3-10. Centering the views of all three entries.

12. To center all the molecules within their respective areas, click **Fit view to all visible objects**

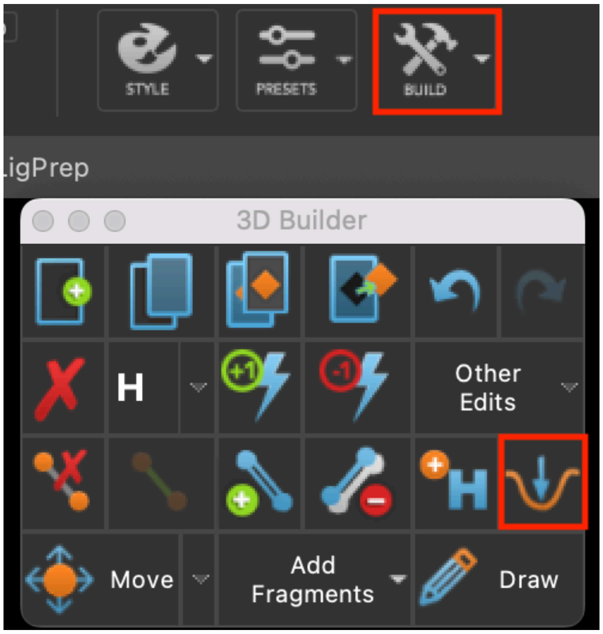


Figure 3-11. Performing force field minimization on all entries

13. **Select** all three molecules in the workspace (there are many approaches to do so: Main Menu, Select > All; Toolbar, Quick Select, All, Shift + Click + Drag and more)
14. In the **Build** dropdown from the toolbar (3D Builder panel), select **Minimize selected atoms**
    - The molecule is minimized, and the parameters adjust slightly

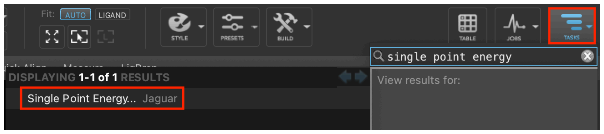
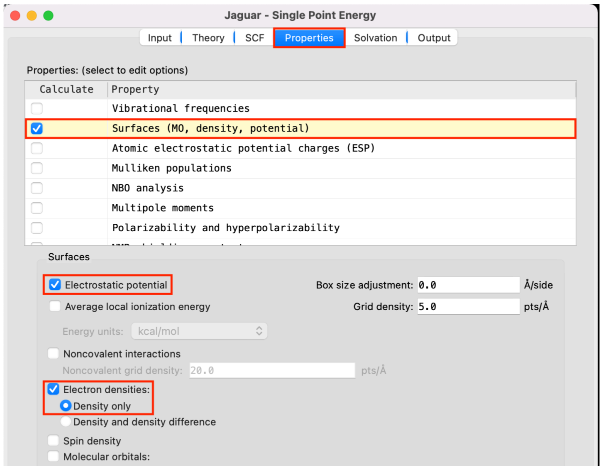


Figure 3-12. Open the Jaguar - Single Point Energy Panel.

Part 2. Generate surfaces for the molecules

1. **Select** all three molecules – we will be running the next calculations in parallel
2. Open the **Jaguar - Single Point Energy** panel from the *Task* button
    - Click **Browse > Jaguar > Single Point Energy**
    - Or, type **Single Point Energy** in the search bar



Properties: (select to edit options)

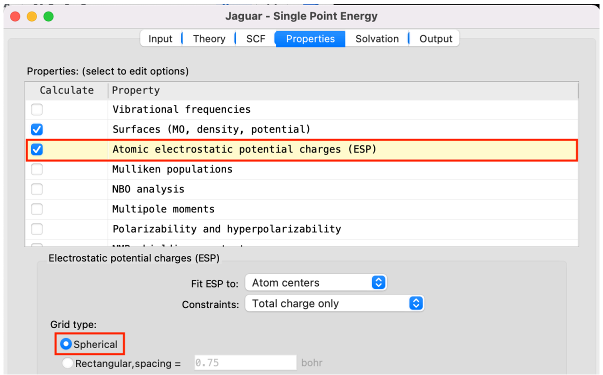
Calculate	Property
☐	Vibrational frequencies
☑	Surfaces (MO, density, potential)
☐	Atomic electrostatic potential charges (ESP)
☐	Mulliken populations
☐	NBO analysis
☐	Multipole moments
☐	Polarizability and hyperpolarizability

Surfaces

☑ Electrostatic potential
Box size adjustment: 0.0 Å/side
☐ Average local ionization energy
Grid density: 5.0 pts/Å
Energy units: kcal/mol
☐ Noncovalent interactions
Noncovalent grid density: 20.0 pts/Å
☑ Electron densities:
● Density only
○ Density and density difference
☐ Spin density
☐ Molecular orbitals:

Figure 3-13. Choosing the surface controls under the Properties tab.

3. In the **Properties** tab, select the row for **Surfaces** and click the check box
    - The **Surfaces** controls are displayed
4. In the **Surfaces** section, select **Electrostatic potential** and **Electron densities**, and ensure that no other surface types are selected
5. Ensure that **Density** only is selected under **Electron densities**



Properties: (select to edit options)

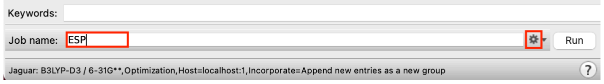
Calculate	Property
☐	Vibrational frequencies
☑	Surfaces (MO, density, potential)
☑	Atomic electrostatic potential charges (ESP)
☐	Mulliken populations
☐	NBO analysis
☐	Multipole moments
☐	Polarizability and hyperpolarizability

Electrostatic potential charges (ESP)

Fit ESP to: Atom centers
Constraints: Total charge only
Grid type:
● Spherical
○ Rectangular,spacing = 0.75 bohr

Figure 3-14. Choosing atomic electrostatic potential charges under the Properties tab.

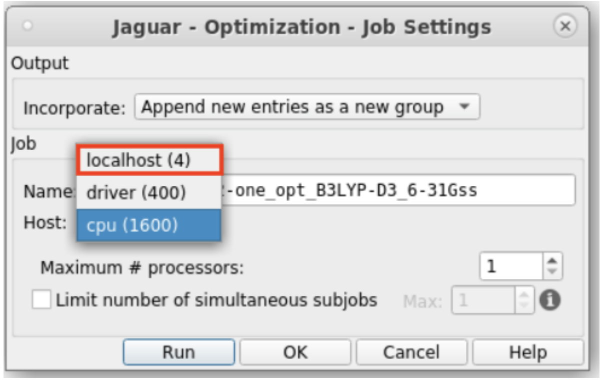
6. Check the box for **Atomic electrostatic potential charges (ESP)** in the **Properties** table



Keywords:
Job name: ESP
Jaguar: B3LYP-D3 / 6-31G**,Optimization,Host=localhost:1,Incorporate=Append new entries as a new group

Figure 3-15. Running the ESP jobs in parallel.

7. Name the job ESP
8. Adjust the settings by clicking the gear icon
9. Choose localhost (4) as the Job Host
10. Click Run
    - When the jobs finish, the structures are imported and the electron density surfaces may be displayed



Incorporate: Append new entries as a new group

Name: ...-one_opt_B3LYP-D3_6-31Gss

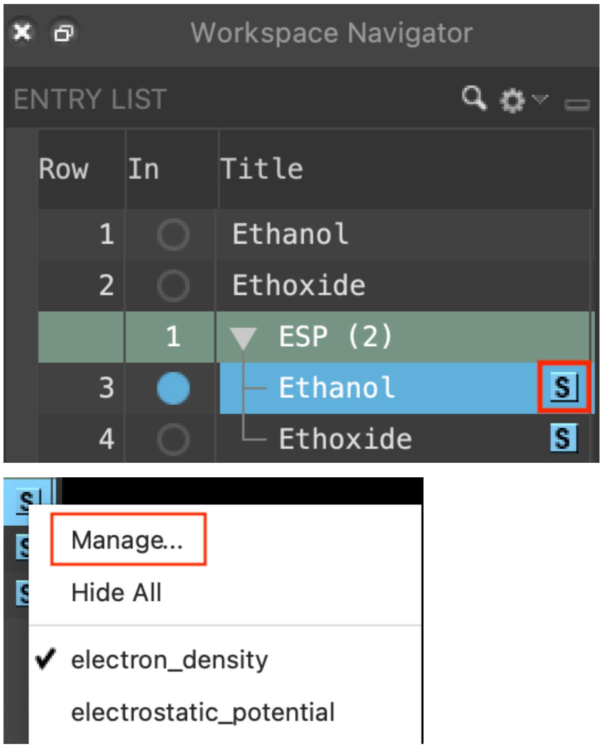
Maximum # processors: 1

Figure 3-16. Adjusting the job settings.

- ○ The incorporated jobs will be shown in a separate Entry Group in the Entry List

Part 3. Map the electrostatic potential to the molecular surfaces

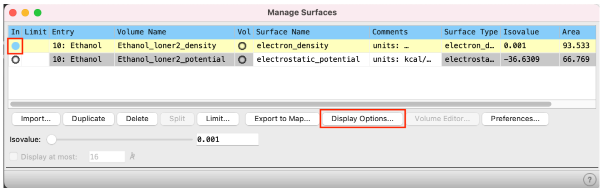
1. Click the **S** button in the **Entry List** for **Ethanol** and choose **Manage**
    - ○ The Manage Surfaces panel opens



Row	In	Title
1	○	Ethanol
2	○	Ethoxide
	1	ESP (2)
3	●	Ethanol
4	○	Ethoxide

Figure 3-17. Clicking the S button in the Entry List and choosing Manage.

2. Click the **In** column for the electron density surface to include it in the Workspace
3. Click **Display Options**

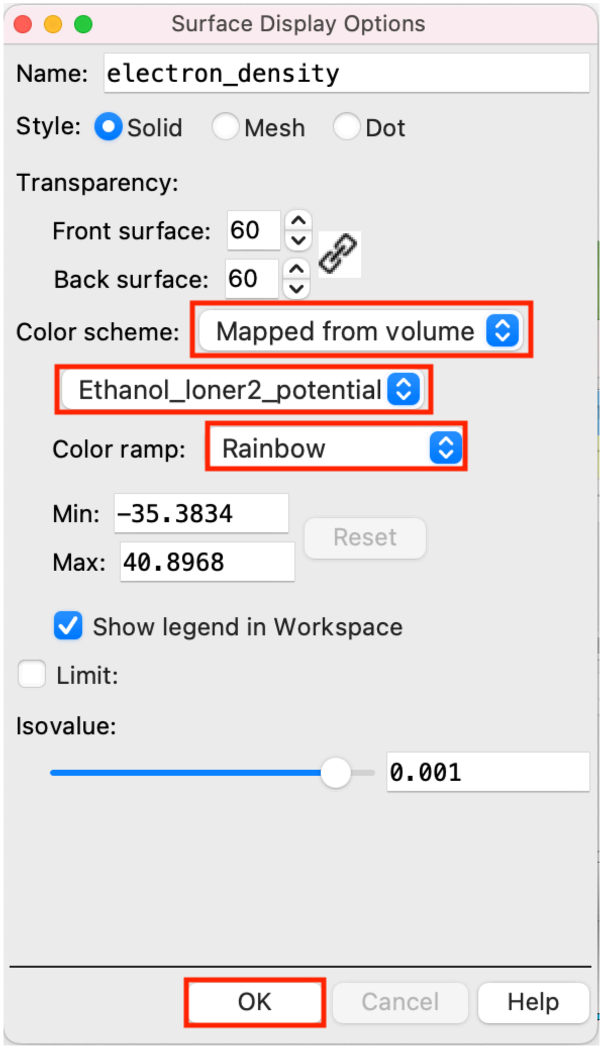


In	Limit	Entry	Volume Name	Vol	Surface Name	Comments	Surface Type	Isovalue	Area
●		10: Ethanol	Ethanol_loner2_density	○	electron_density	units: …	electron_d…	0.001	93.533
○		10: Ethanol	Ethanol_loner2_potential	○	electrostatic_potential	units: kcal/…	electrosta…	-36.6309	66.769

Isovalue: 0.001

Figure 3-18. Choosing settings in the Manage

- The **Surface Display Options** panel opens



Surface Display Options

Name: electron_density

Style: ● Solid ○ Mesh ○ Dot

Transparency:

Front surface: 60

Back surface: 60

Color scheme: Mapped from volume

Ethanol_loner2_potential

Color ramp: Rainbow

Min: -35.3834

Max: 40.8968

☑ Show legend in Workspace

☐ Limit:

Isovalue: 0.001

Figure 3-19. Choosing settings in the Surface Display Options panel

4. For **Color scheme**, select **Mapped from volume**
5. Select **Ethanol_loner2_potential** from the volume data list
6. From the **Color ramp** option menu, choose **Rainbow**
7. Click **OK**
8. Repeat steps 25-31 for Ethoxide.

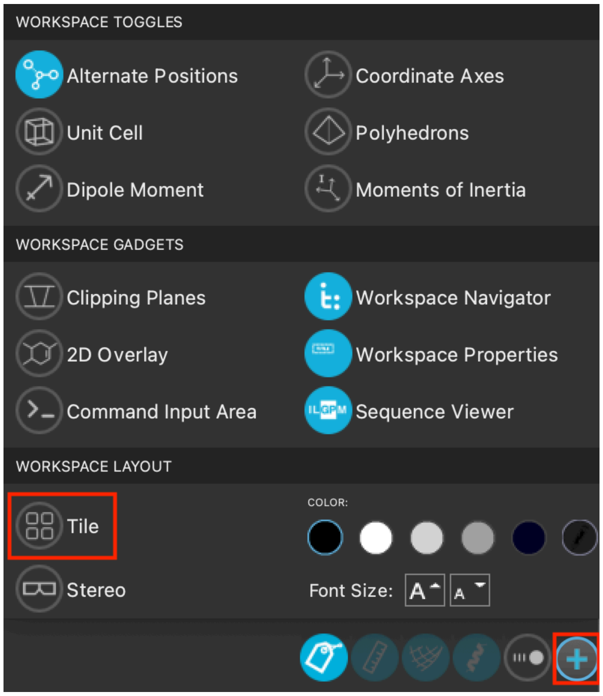
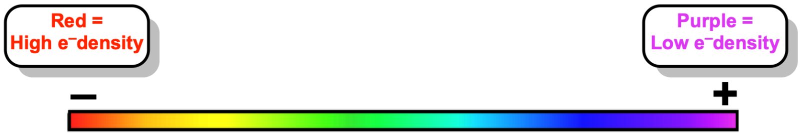


Figure 3-20. Tile both electrostatic potential surfaces.

9. Once you have displayed both electrostatic potential surfaces, tile the molecules so we can compare them
    - Click **Workspace Layout > Tile**
10. Feel free to play around with them and notice any similarities or differences between each molecule

When analyzing electrostatic potential surfaces, red represents regions of high electron density while purple represents regions of low electron density. See the range shown below:



Take a screenshot of the two electrostatic potential maps of ethanol and ethoxide and put it into your worksheet. In a few sentences, analyze any differences you see between the two surfaces. Determine which regions of each nucleophile dictate its strength, or lack thereof, towards attack of an electrophile.

Both ethanol and ethoxide contain oxygen atoms with lone pairs, so both molecules can act as nucleophiles. The ethoxide ion contains a negative charge on the oxygen atom making it a stronger nucleophile than the neutral ethanol molecule. This is indicative in their electrostatic potential maps – the red, more electron dense region is larger in ethoxide whereas the red region in ethanol is more localized to only the oxygen atom. Ethanol is a weak nucleophile because it is overall neutral whereas ethoxide is a strong nucleophile because it is negatively charged.

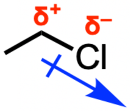
The strength of ethoxide is affected by **polarizability**. Polarizability is the ability of an atom to distribute its electron density unevenly in response to external influences. For example, HS^- is a particularly strong nucleophile because sulfur is a large atom with many electrons distant from the nucleus. Sulfur's polarizability causes its electron density to be unevenly distributed as it attacks an electrophile.

This example represents a standalone comparison of these two nucleophiles; it is important to note that the solvent in which these two nucleophiles may react may change its nucleophilicity towards a given substrate.

4. Electrophiles

An **electrophile** is an "electron loving" species that is typically either positively charged or has a partial positive charge (δ^+). An electrophilic center is an electron-deficient atom that is capable of accepting a pair of electrons, similar to that of a Lewis acid. Two examples of electrophiles are:

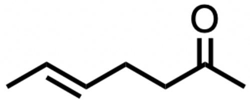
1) An electrophilic carbon atom from inductive effects of a halide



2) A carbocation which is a positively charged carbon atom – a carbocation has an empty *p* orbital that functions as a site that can accept a pair of electrons.

Electrophiles may have electron-withdrawing groups which is a group containing electronegative elements pulling the electron density towards them. Furthermore, electrophiles may also have polarizable π-bonds such as C=O or C=N bonds where partial charges can be drawn in.

<u>Example #2:</u> Predict where the nucleophilic and electrophilic centers are in the following molecule (*E*)-hept-5-en-2-one. Draw in any partial charges if applicable.



<u>Computational Exercise #2:</u> Optimizing the Geometry and Generating an Electrostatic Potential (ESP) Map on the Molecular Surface on (*E*)-hept-5-en-2-one

Now we will optimize the geometry of (*E*)-hept-5-en-2-one and calculate the electrostatic potential surfaces to visually show the electron-density distribution on the surface of the molecule. This exercise involves four parts:

1) Build the molecule and minimize its geometry
2) Optimize the geometry using quantum mechanical DFT
3) Generate surface of the molecule
4) Map the electrostatic potentials to the molecular surfaces

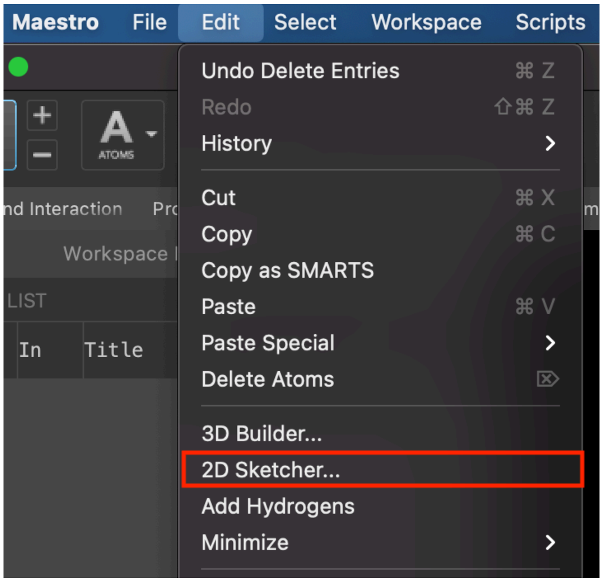
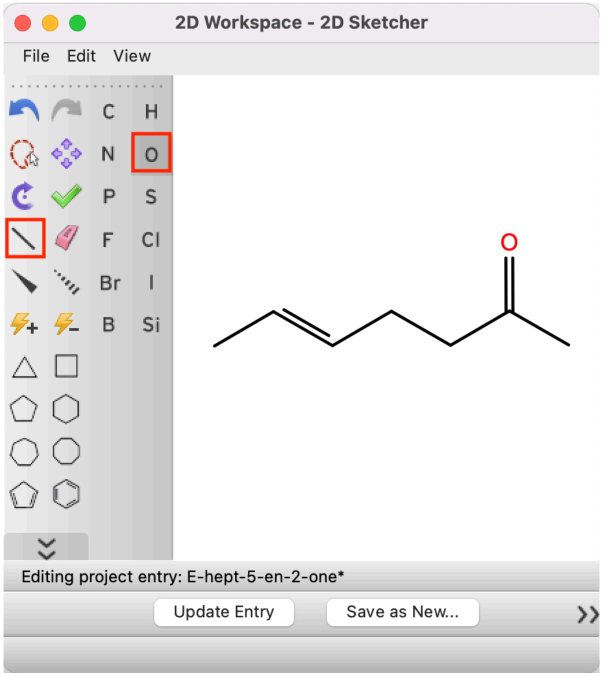


Figure 4-1. Open 2D Sketcher.

Part 1. Build (E)-hept-5-en-2-one using 2D Sketcher

Before optimizing any molecular geometry, you will need a starting molecule in your workspace. Let's draw the structure of (E)-hept-5-en-2-one using the 2D sketcher.

1. Go to **Edit > 2D Sketcher**



Editing project entry: E-hept-5-en-2-one*

Figure 4-2. Draw (E)-hept-5-en-2-one

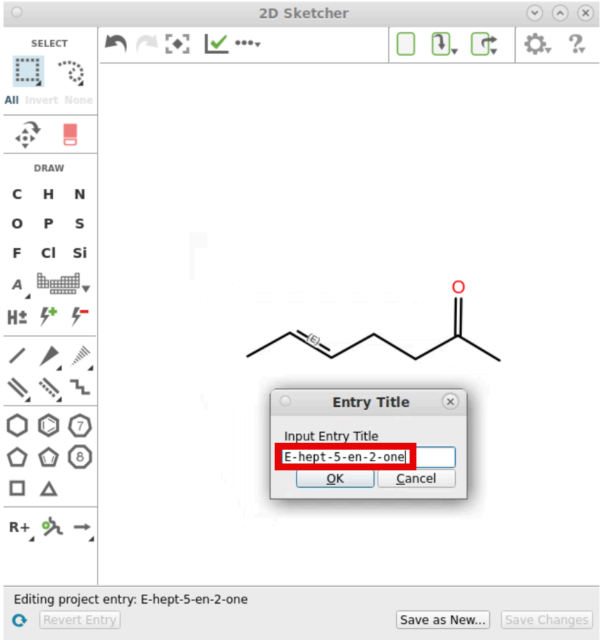
2. **Draw** the structure of (E)-hept-5-en-2-one. You do not need to draw in any lone pair of electrons; only show the bonds.
    - Go to the selection bar on the left
    - Choose the single bond button
    - Click and drag in your workspace to form ethane
    - Continue to click and drag until you form heptane (7-carbon linear chain)
    - Click and drag at the C2 position from the right to draw a methyl group
    - Click the center of this bond to form an alkene

- Click the Oxygen atom to add an O to the end of the alkene you just made; this makes a carbonyl
- Choose the single bond button again and click the center of the C5–C6 bond to form a double bond

Note: You could also use **O** on your keyboard for atom assignments.

The 2D sketcher functions like many standard 2D molecular drawing tools. For a complete overview of using the sketcher panel, see the 2D Sketcher Panel documentation.

3. Click on **Save as New**
4. For *Input Entry Title*, write **E-hept-5-en-2-one**. Click **OK**.



Input Entry Title: E-hept-5-en-2-one

Editing project entry: E-hept-5-en-2-one

Figure 4-4. Include and select the entry.

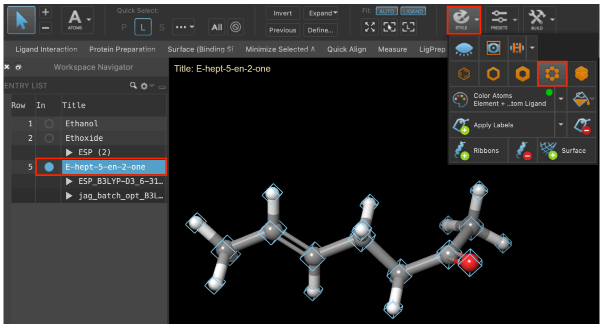


Figure 4-4. Viewing and styling (E)-hept-5-en-2-one

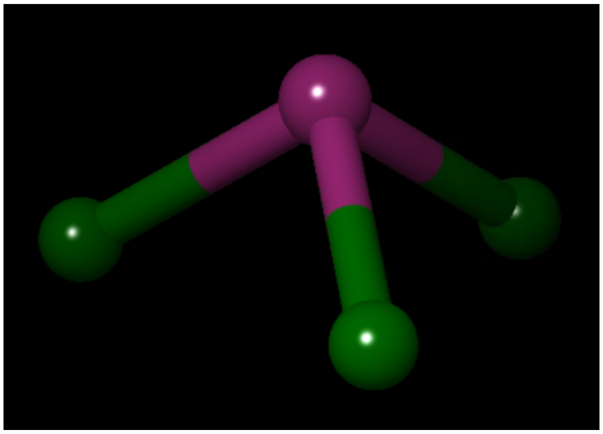


Figure 4-6. Styling PCl3 as ball-and-stick.

5. Close the 2D Sketcher panel
6. The (E)-hept-5-en-2-one molecule is <u>selected</u> in the entry list and <u>included</u> in the <u>workspace</u>
7. Change the representation to ball-and-stick by clicking on the **Style** menu and choosing **Apply ball-and-stick representation**
8. Change the color of the atoms by clicking on the **Style > Color Atoms > Element + Custom Ligand**

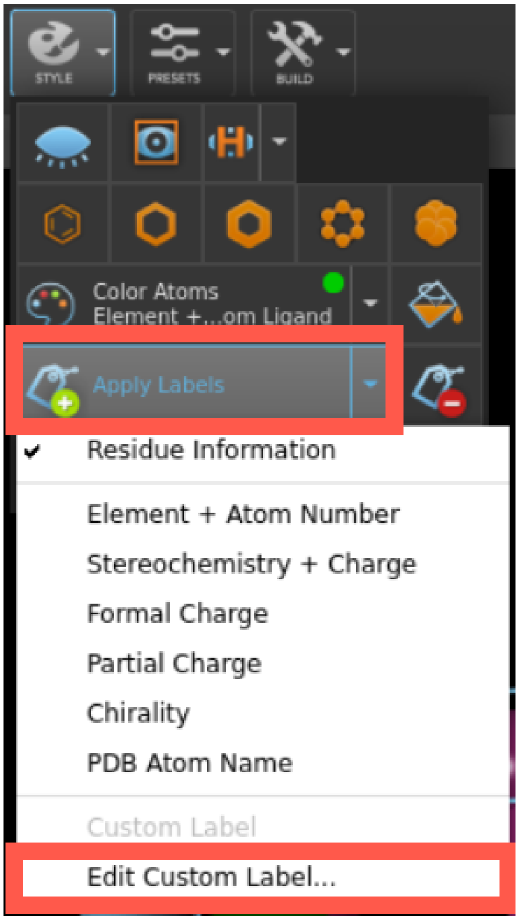
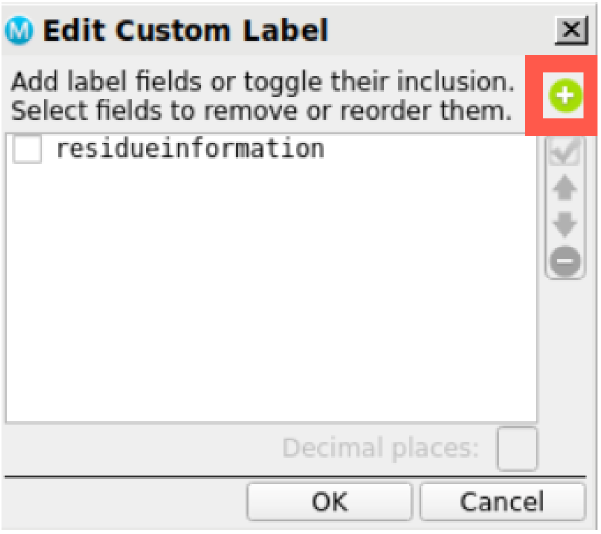


Figure 4-7. Labeling atoms.

9. To display atom labels, click **Style > Apply Labels** then click the drop down arrow on the right side
10. Click **Edit Custom Labeling**



Add label fields or toggle their inclusion. Select fields to remove or reorder them.

☐ residueinformation

11. The **Edit Custom Label** window will open
12. Click the green **plus** button

Figure 4-8. Editing custom labels.

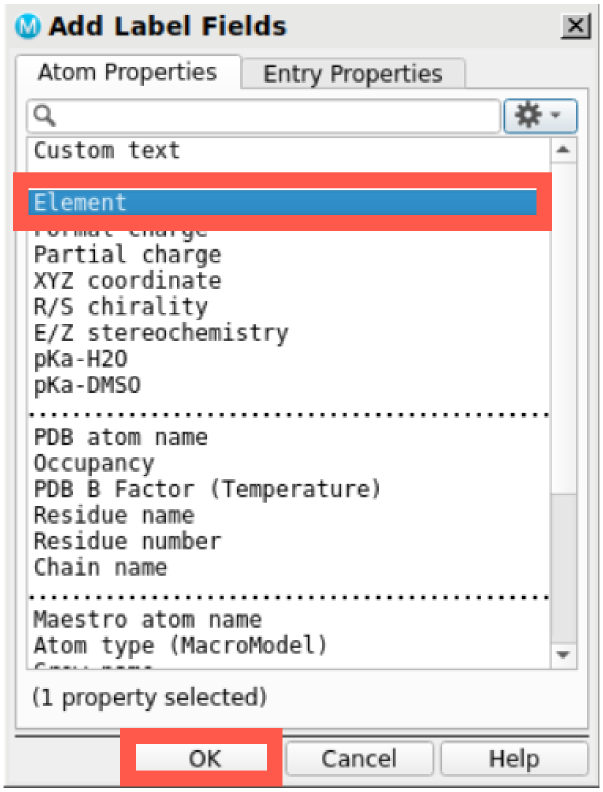


Figure 4-9. Adding label fields.

13. The **Add Label Fields** window will open
14. Select **Element** and press **OK**
15. In the **Edit Custom Label** window, press **OK**

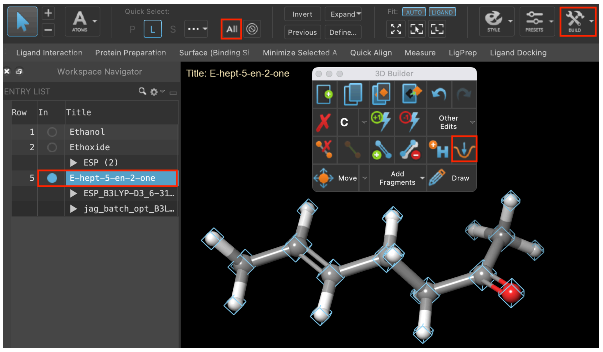


Figure 4-8. Force field minimization.

Part 2. Force Field Minimization

We can improve upon this starting structure by using a force field minimization. The molecule will still not be optimized by quantum mechanics (QM), but it will improve the starting geometry.

1. **Select** all atoms in the workspace (there are many approaches to do so: Main Menu, Select > All; Toolbar, Quick Select, All, Shift + Click + Drag and more)
2. In the **Build** dropdown from the toolbar (3D Builder panel), select **Minimize selected atoms**

    - The molecule is minimized, and the parameters adjust slightly

Note: Force fields are usually good at generating structures of molecules with common functional groups and elements. When it comes to more exotic atomic arrangements and less frequent elements (such as transition metals) or simply large molecules, force fields can yield structures with inaccurate or even unphysical geometries, and in those cases, quantum mechanical geometry optimizations become absolutely indispensable.

Part 3. Optimize the Geometry using Quantum Mechanic DFT

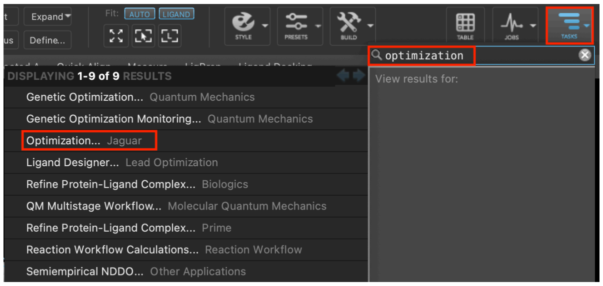
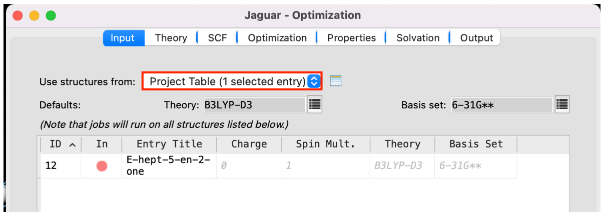


Figure 4-9. Opening the Jaguar Optimization panel.

Now let's optimize the molecule at the quantum mechanical level.

1. With the (E)-hept-5-en-2-one entry selected and included, go to **Tasks > Optimization** using Jaguar
    - Type optimization in the Tasks search bar
    - The Jaguar Optimization panel opens



Use structures from: Project Table (1 selected entry)

Defaults: Theory: B3LYP-D3 Basis set: 6-31G**

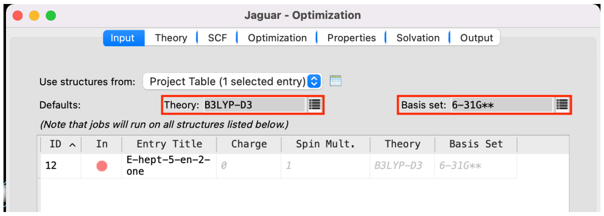
(Note that jobs will run on all structures listed below.)

ID	In	Entry Title	Charge	Spin Mult.	Theory	Basis Set
12	●	E-hept-5-en-2-one	0	1	B3LYP-D3	6-31G**

Figure 4-10. Setting the Jaguar Optimization panel to optimization.

2. Use structures from **Project Table (1 selected entry)**

Note: We are optimizing one molecule, (E)-hept-5-en-2-one. By selecting many molecules in the entry list, we can optimize as many molecules as we would like concurrently with the same QM settings.



Use structures from: Project Table (1 selected entry)

Defaults: Theory: B3LYP-D3 Basis set: 6-31G**

(Note that jobs will run on all structures listed below.)

ID	In	Entry Title	Charge	Spin Mult.	Theory	Basis Set
12	●	E-hept-5-en-2-one	0	1	B3LYP-D3	6-31G**

Figure 4-11. Setting the QM parameters for optimization.

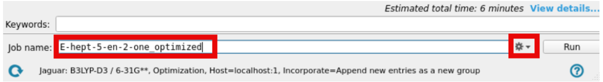
Various settings can be altered depending on the specific use case. We will only adjust the Input tab for this example.

For Theory, select **B3LYP-D3**

For Basis set, select **6-31G****

A few additional comments about preparing for an optimization calculation:

- If you hover the mouse over the basis set in the table, you can see the number of basis functions associated with the basis set. This is useful to know since the quality of the basis set usually improves as the number of functions increases, noting again the trade-off between quality and computational expense
- Always make sure the charge and the spin multiplicity are correct (in this case, PCl_3 is a neutral, singlet, so charge = 0 and spin multiplicity = 1). Multiplicity is defined as 2S + 1, where S is the total orbital spin of the molecule. For instance, a system with one unpaired electron is a doublet (multiplicity = 2), since the total orbital spin S = ½.
- Use the *Atom-Level Settings* button to define per-atom basis sets
- Constraints can be defined on the Optimization tab
- Properties, such as atomic charges, vibrational frequencies, surfaces and more can be requested on the Properties tab
- Solvent can be defined via several implicit solvation models on the Solvation tab. Note that this example is a gas-phase geometry optimization
- Read more about geometry optimization with Jaguar here and learn more about using the QM Multistage Workflow panel in the Introduction to Multistage Quantum Mechanical Workflows tutorial



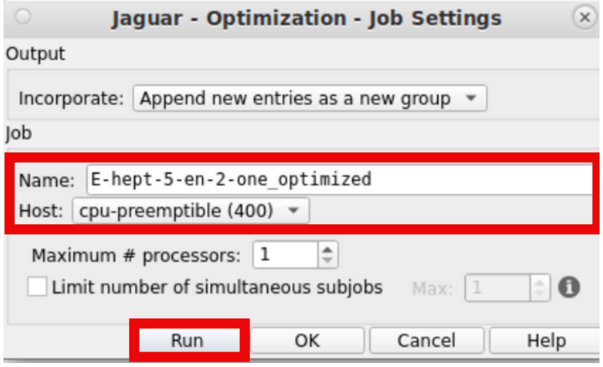
Estimated total time: 6 minutes View details...

Keywords:

Job name: E-hept-5-en-2-one_optimized

Jaguar: B3LYP-D3 / 6-31G**, Optimization, Host=localhost:1, Incorporate=Append new entries as a new group

3. Change the *Job name* to **E-hept-5-en-2-one_optimized**



Output

Incorporate: Append new entries as a new group

Job

Name: E-hept-5-en-2-one_optimized

Host: cpu-preemptible (400)

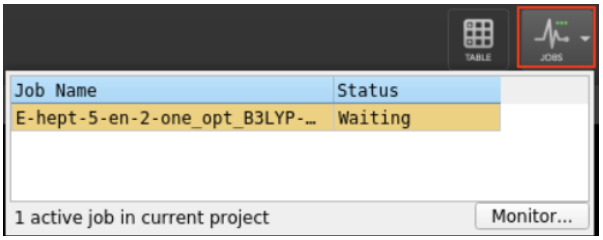
Maximum # processors: 1

☐ Limit number of simultaneous subjobs Max: 1

Figure 4-12. Naming and running the job.

4. Adjust the job settings and change the Host to **cpu-preemptible (400)**
    - ○ This job requires a CPU host and should complete in under 5 minutes
5. Click **Run**

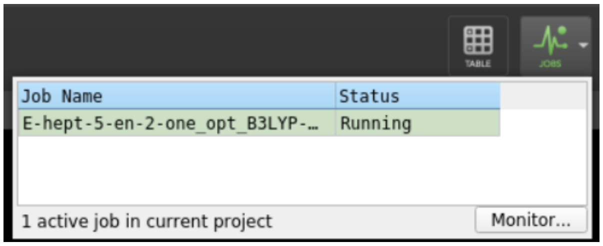
Note: It is advised to also add in a *Vibrational frequencies* calculation (from the *Properties* tab). This involves a bit more computational expense, but is a useful way to be sure that your output is a minimum (as opposed to a maximum) on the Potential Energy Surface (PES). For more detail, see the Locating Transition States tutorial.



Job Name	Status
E-hept-5-en-2-one_opt_B3LYP-…	Waiting

1 active job in current project

Figure 4-13. Status when a job is in the queue.



Job Name	Status
E-hept-5-en-2-one_opt_B3LYP-…	Running

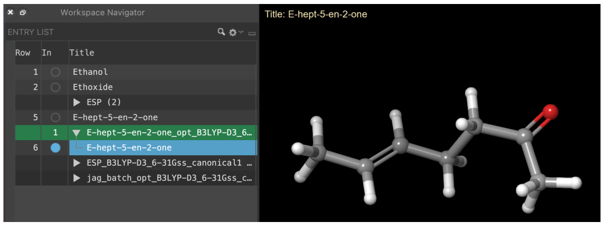
1 active job in current project

Figure 4-14. Status when a job is running.

When a job is submitted to the queue, you can check its status by clicking the Jobs button in the upper right-hand corner

- If the job is in the queue, it will say 'Waiting'
- If the job is in progress, it will say 'Running'

When the job finishes, a banner will appear indicating that the result has been incorporated. At this time, the molecule with the optimized geometry is now shown in the workspace



Row	In	Title
1	○	Ethanol
2	○	Ethoxide
		▶ ESP (2)
5	○	E-hept-5-en-2-one
	1	▼ E-hept-5-en-2-one_opt_B3LYP-D3_6…
6	●	E-hept-5-en-2-one
		▶ ESP_B3LYP-D3_6-31Gss_canonical1 …
		▶ jag_batch_opt_B3LYP-D3_6-31Gss_c…

Title: E-hept-5-en-2-one

Figure 4-15. The output molecule.

6. A new entry group is added to the entry list titled E-hept-5-en-2-one_optimized.01. This is your optimized structure.

Your structure may look a bit different because you may have built a different conformer. This is okay and you can still proceed to the next step as it will not change your ESP results.

Part 4. Generate the ESP surface for the molecule

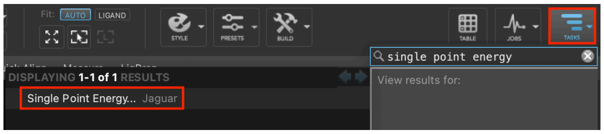
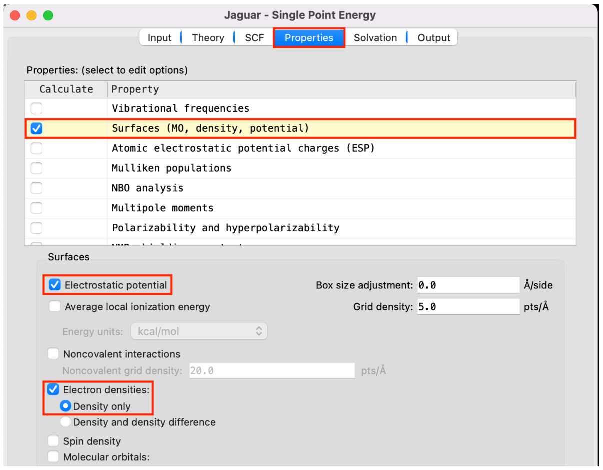


Figure 4-16. Open the Jaguar - Single Point Energy Panel.

1. **Select** the optimized molecule
2. Open the **Jaguar - Single Point Energy** panel from the **Task** button
3. Click **Browse > Jaguar > Single Point Energy**
4. Or, type **Single Point Energy** in the search bar



Properties: (select to edit options)

Calculate	Property
☐	Vibrational frequencies
☑	Surfaces (MO, density, potential)
☐	Atomic electrostatic potential charges (ESP)
☐	Mulliken populations
☐	NBO analysis
☐	Multipole moments
☐	Polarizability and hyperpolarizability

Surfaces

☑ Electrostatic potential

Box size adjustment: 0.0 Å/side

☐ Average local ionization energy

Grid density: 5.0 pts/Å

Energy units: kcal/mol

☐ Noncovalent interactions

Noncovalent grid density: 20.0 pts/Å

☑ Electron densities:

● Density only

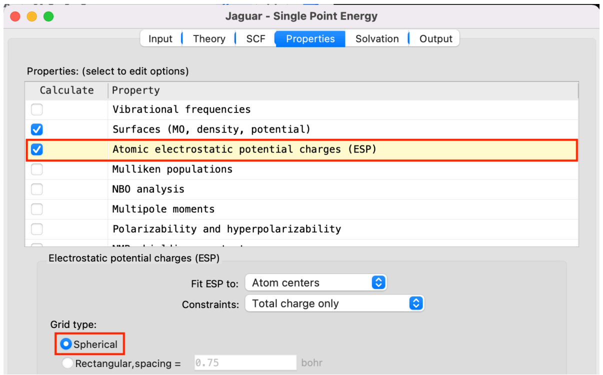
○ Density and density difference

☐ Spin density

☐ Molecular orbitals:

Figure 4-17. Choosing the surface controls under the Properties tab.

5. In the **Properties** tab, select the row for **Surfaces** and click the check box
6. The **Surfaces** controls are displayed
7. In the **Surfaces** section, select **Electrostatic potential** and **Electron densities**, and ensure that no other surface types are selected
8. Ensure that **Density only** is selected under **Electron densities**



Properties: (select to edit options)

Calculate	Property
☐	Vibrational frequencies
☑	Surfaces (MO, density, potential)
☑	Atomic electrostatic potential charges (ESP)
☐	Mulliken populations
☐	NBO analysis
☐	Multipole moments
☐	Polarizability and hyperpolarizability

Electrostatic potential charges (ESP)

Fit ESP to: Atom centers

Constraints: Total charge only

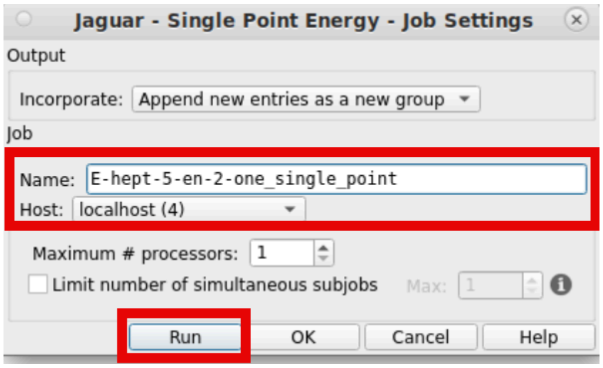
Grid type:

● Spherical

○ Rectangular,spacing = 0.75 bohr

Figure 4-18. Choosing atomic electrostatic potential charges under the Properties tab.

9. Check the box for **Atomic electrostatic potential charges (ESP)** in the **Properties** table



Incorporate: Append new entries as a new group

Name: E-hept-5-en-2-one_single_point

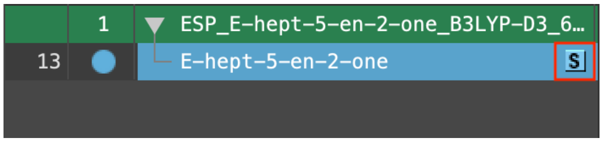
Host: localhost (4)

Maximum # processors: 1

☐ Limit number of simultaneous subjobs Max: 1

Figure 4-20. Adjusting the job settings.

10. Name the job ESP_E-hept-5-en-2-one_B3LYP-D3_6-31Gss
11. Adjust the settings by clicking the **gear icon**
12. Choose **localhost (4)** as the Job Host
13. Click **Run**
    - When the jobs finish, the structures are imported and the electron density surfaces may be displayed
    - The incorporated jobs will be shown in a separate Entry Group in the Entry List



Part 5. Map the electrostatic potential to the molecular surfaces

1. Click the **S** button in the **Entry List** for Ethanol and choose **Manage**

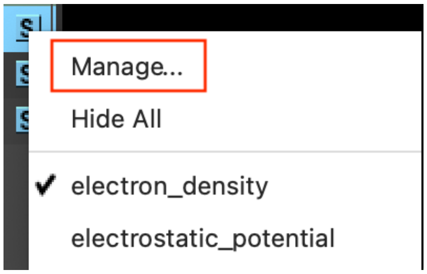
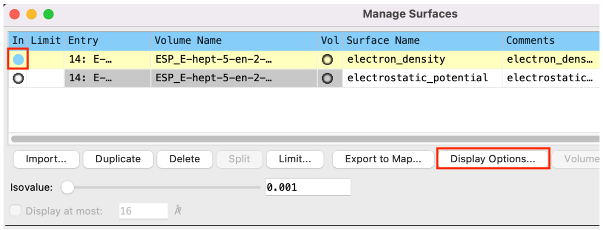


Figure 4-21. Clicking the S button in the Entry List and choosing Manage.

- ○ The **Manage Surfaces** panel opens



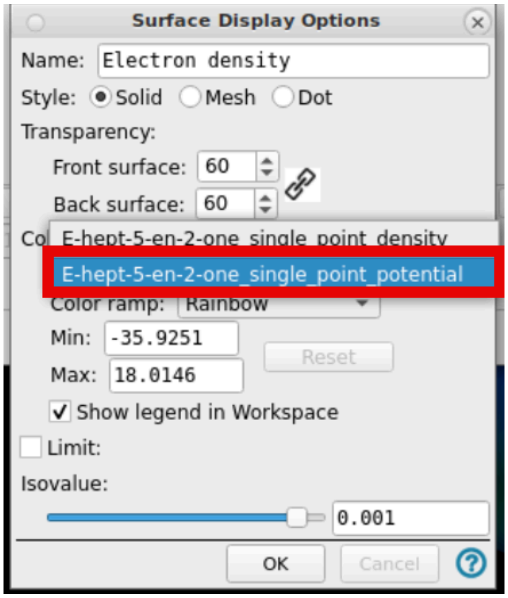
In	Limit	Entry	Volume Name	Vol	Surface Name	Comments
●		14: E-…	ESP_E-hept-5-en-2-…	○	electron_density	electron_dens…
○		14: E-…	ESP_E-hept-5-en-2-…	○	electrostatic_potential	electrostatic…

Isovalue: 0.001

☐ Display at most: 16

Figure 4-22. Choosing settings in the Manage Surfaces panel.

2. Click the **In** column for the electron density surface to include it in the Workspace
3. Click **Display Options**
    - ○ The **Surface Display Options** panel opens



Name: Electron density

Style: ● Solid ○ Mesh ○ Dot

Transparency:

Front surface: 60

Back surface: 60

E-hept-5-en-2-one_single_point_density

E-hept-5-en-2-one_single_point_potential

Color ramp: Rainbow

Min: -35.9251

Max: 18.0146

☑ Show legend in Workspace

☐ Limit:

Isovalue: 0.001

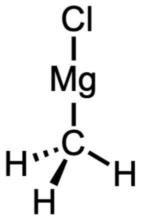
Figure 4-23. Choosing settings in the Surface Display Options panel

4. For Color scheme, select **Mapped from volume**
5. Select **E-hept-5-en-2-one_single_point_potential** from the volume data list
6. From the **Color ramp** option menu, choose **Rainbow**
7. Click **OK**

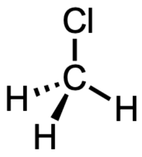
Take a screenshot of your electrostatic potential map and analyze the nucleophilic and electrophilic regions of (E)-hept-5-en-2-one.

5. Individual Exercise

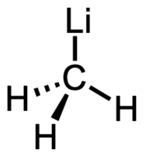
All three molecules below contain carbon atoms but some act as a nucleophile while some act as an electrophile.



A



B



C

For each of the molecules:

a) Build the molecules in Maestro using the 2D sketcher and minimize the structures.

b) Optimize their geometries using Jaguar. Take screenshots of your optimized structures with a ball-and-stick representation (from the Style toolbar).
  - Theory: B3LYP-D3, Basis set: 6-31gss
  - Use local host to run the jobs

c) Run single point calculations using Jaguar to generate electrostatic potential maps. Take screenshots of each ESP map.
  - Theory: B3LYP-D3, Basis set: 6-31gss
  - Use local host to run the jobs

d) Determine whether the carbon atoms are nucleophilic and electrophilic centers.

6. Summary, Additional Resources, and References

In this lesson, you learned about nucleophiles and electrophiles. A nucleophile is a reactant that provides a pair of electrons to form a new covalent bond whereas an electrophile is a reactant that accepts a pair of electrons. You learned about inductive effects and how to identify nucleophilic and electrophilic centers in a molecule. Understanding how electrons flow from electron-rich regions to electron-poor regions is essential in learning organic chemical reactions.

Using Maestro, a simple geometry optimization using Jaguar can be performed to show a molecule's structure. Electrostatic potential surfaces can also be generated to visualize electron-poor and electron-rich regions in both nucleophiles and electrophiles.

For further learning:

- 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
- See the Jaguar help documentation

7. 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