Generating conformations using the toolpanel

Required functionality and modules: Discovery Studio Client

Required data files: Benzenesulfonamide.sd

Time: 30 minutes

Introduction

Conformation analysis of small molecules is required in many situations. Discovery Studio provides an intuitive and interactive method for exploring conformational space of a set of molecules with flexible controls for search methods, selecting rotatable bonds, and changing torsion grids. For instance, you can select a particular rotatable bond and generate a set of conformations by changing the torsion angle of that rotatable bond, and then view the conformation energy profile. You can also view all of the generated conformations in a Molecule Window to check the overall conformation coverage.

In this tutorial, you will learn how to use the Search Small Molecule Conformations tool panel to generate conformations. The following tasks are covered:

- Selecting rotatable bonds
- Searching for conformations
- Changing conformation energy threshold to a custom value
- Reviewing the conformations in the Molecule window
- Plotting a conformation energy profile and 3D conformation energy surface

Selecting rotatable bonds

From the **Files Explorer**, open **Samples | Tutorials | Conformations | Benzenesulfonamide.sd**.

This will display the benzene sulfonamide in the Molecule Window. By default, .sd files are displayed with only the Data Table View visible. To view the 3D structure, it is necessary to open the Graphics View.

With the **Molecule Window** active, press **CTRL+G** to open the Graphics View.

Tip. Clicking the top navigation button will automatically open the graphics pane.

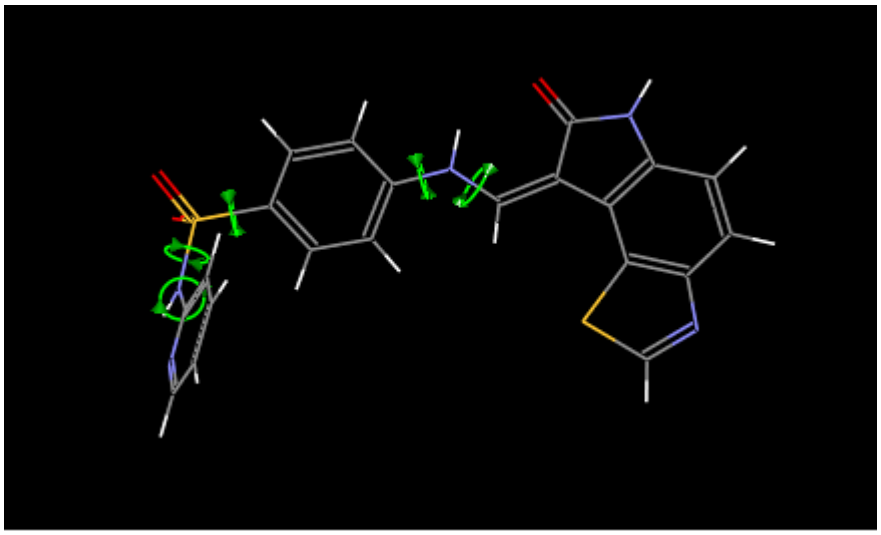
With the molecule now visible in the Graphics View, the next task will be to use the Search Small Molecule Conformations tools to analyze the ligand molecule. The first step is to specify the bonds to indicate as rotatable in the Conformation search.

From the top of the **Tools Explorer**, choose the **Conformations** layout.

Open the **Search Small Molecule Conformations** panel.

Click **Find Rotatable Bonds**.

In the Graphics View, torsion monitors are added to all rotatable bonds. Please note that you can select some of rotatable bonds and add torsion monitors to only selected bonds. Note that torsion monitors are not added to any of the selected bonds that are not rotatable.



Tip. If some torsion monitors are removed from the Molecule Window by editing, you should make sure that the *ROTBONDS* property of the modified molecules are updated. This can be done by click Find Rotatable Bonds after editing. Updating the *ROTBONDS* property is important if the selected rotatable bond information is used in Generate Conformations protocol run.

Searching for conformations

The next step is to specify the search parameters. Three conformation search methods are available: Systematic Search, Random Search, and Boltzmann Jump.

In the **Tools Explorer**, locate **Conformation Method** button, and select the **Systematic** search method from the pull-down list.

Now you can specify the conformation energy threshold. Four threshold values are available: 5, 10, 15, and 20 kcal/mol.

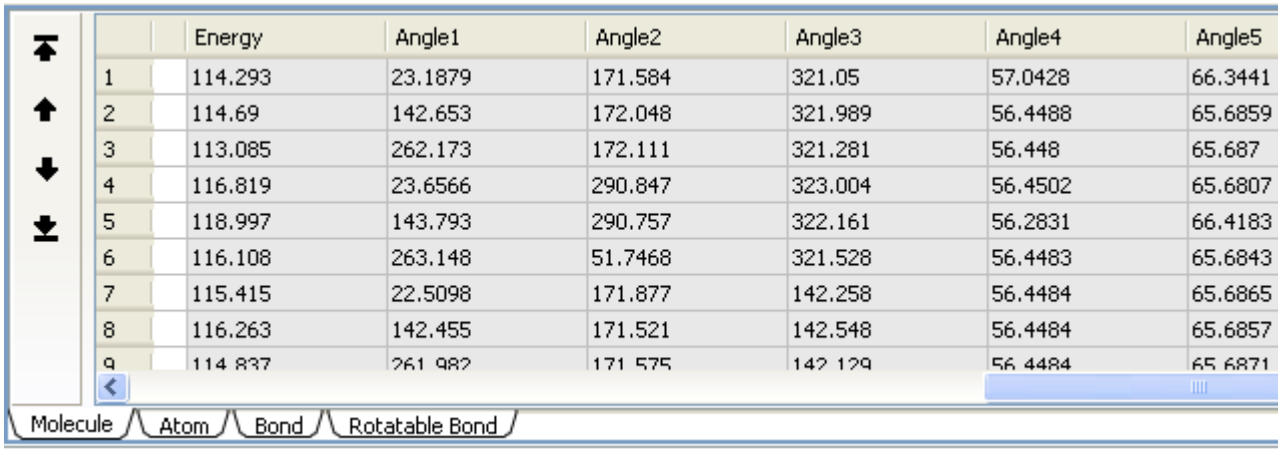
For **Energy Threshold**, keep the default value of 20kcal/mol.

Click **Conformation Generation**.

This begins the conformation search. During the search, you can monitor progress from the Progress bar in the bottom-right corner of the main application window. If a job is running too long (e.g., if you have selected multiple molecules), you can cancel the running job by clicking the check box in the Progress bar.

Tip. The search methods in the Conformation Generation tool panel are designed for quick and interactive conformation searches of a small number of molecules. If it is necessary to generate conformations for large numbers of molecules, we recommend that you use the Generate Conformations protocol, which is specifically designed for performing high throughput analyses.

When the search is complete, the generated conformations are automatically added to the Molecules tab of the Data Table View:



	Energy	Angle1	Angle2	Angle3	Angle4	Angle5
1	114.293	23.1879	171.584	321.05	57.0428	66.3441
2	114.69	142.653	172.048	321.989	56.4488	65.6859
3	113.085	262.173	172.111	321.281	56.448	65.687
4	116.819	23.6566	290.847	323.004	56.4502	65.6807
5	118.997	143.793	290.757	322.161	56.2831	66.4183
6	116.108	263.148	51.7468	321.528	56.4483	65.6843
7	115.415	22.5098	171.877	142.258	56.4484	65.6865
8	116.263	142.455	171.521	142.548	56.4484	65.6857
9	114.837	261.982	171.575	142.129	56.4484	65.6871

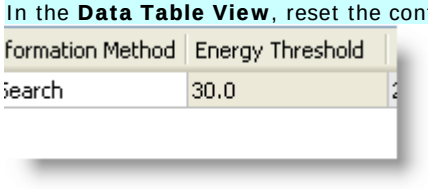
Molecule | Atom | Bond | Rotatable Bond

Changing conformation energy threshold to a custom value

The toolpanel controls only offers four values: 5, 10, 15, and 20 kcal/mol. If you want to use a different value for a particular molecule, you can modify the *Energy Threshold* molecule property from the Data Table View.

In the **Hierarchy View**, remove all conformations and keep only the first molecule.

In the **Data Table View**, reset the conformation Energy Threshold to 30 by directly changing the value in the cell:



formation Method	Energy Threshold
Search	30.0

In the **Tools Explorer**, click **Conformation Generation**.

Tip. If you reset the *Energy Threshold* in the Data Table View, do not click the *Energy Threshold button* in the toolpanel, otherwise the threshold will be changed to the selected value in the toolpanel.

Reviewing the conformations in the Molecule Window

To visually check the overall conformation distribution of a molecule, it is convenient to use the *Molecule tab* of the Data Table View. For example, you can review the conformations using the navigation controls to compare the different variants with the original ligand.

In the **Data Table View**, locate the row for the original molecule and check the **Visibility Locked** checkbox to make sure it remains visible.

Use the **Previous** and **Next**.

The *Previous* and *Next* buttons display each conformation individually while the original molecule remains visible. This way you can compare the conformations.

Plotting a conformation energy profile and 3D conformation energy surface

From the **Files** menu, open a new copy of **Benzenesulfonamide.sd**.

Press **CTRL+H** and **CTRL+G** to display the Hierarchy and Graphics Views.

In the **Hierarchy View**, expand **Benzenesulfonamide.sd**.

Select the rotatable bond between the sulfonamide and the benzene ring:

In the Hierarchy View, right-click and choose **Display Bonds**.

Choose bond **C19-S22**.

In the **Tools Explorer**, click **Find Rotatable Bonds**.

In the **Data Table View**, click the **Rotatable Bond** tab.

Change the **Torsion Increments** property from the default value of 120 to 5.

In **Molecule** tab, change Energy Threshold to 50.

In the **Tools Explorer**, click **Conformation Generation**.

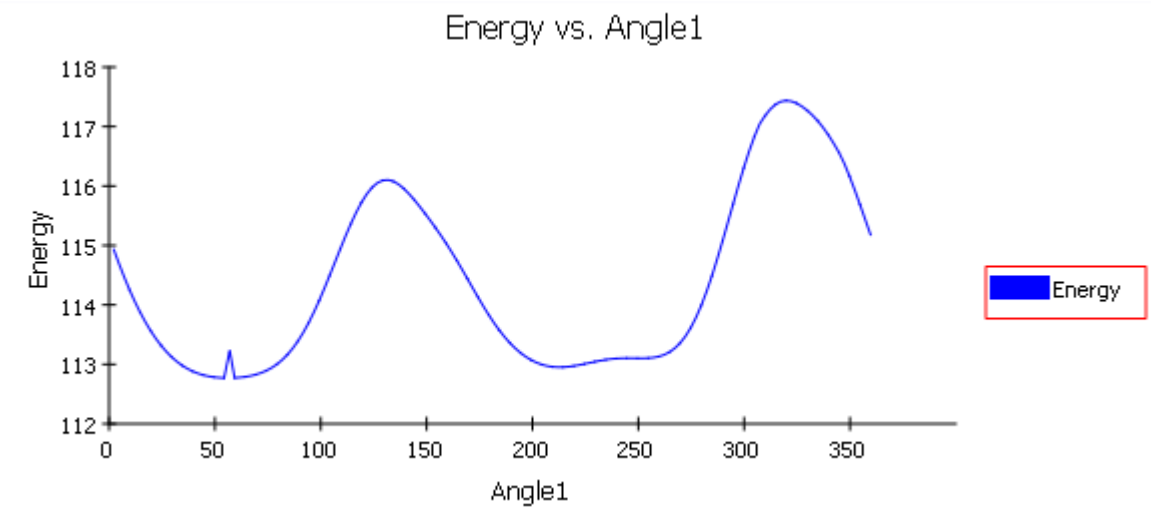
In the **Data Table View** click the **Molecule** tab.

From the menu bar, choose **Chart | Line Plot**.

Set the **X axis** to *Angle1*, and the **Y axis** to *Energy*.

Click **OK**.

This creates a plot of energy profile versus torsion angle:



The plot shows which torsion angle regions have rotation bumps.

The 3D shape of conformation energy of two adjacent torsions, such as Ramachandran plot, can provide important information about biopolymer structures. The conformation toolbar in Discovery Studio provides a convenient way for generating a 3D Ramachandran plot to view conformation energy.

Sketch a simple alcohol molecule c4h9oh.

Add two rotatable bond monitors.

Set the **Torsion Increments** to 10 for both rotatable bonds.

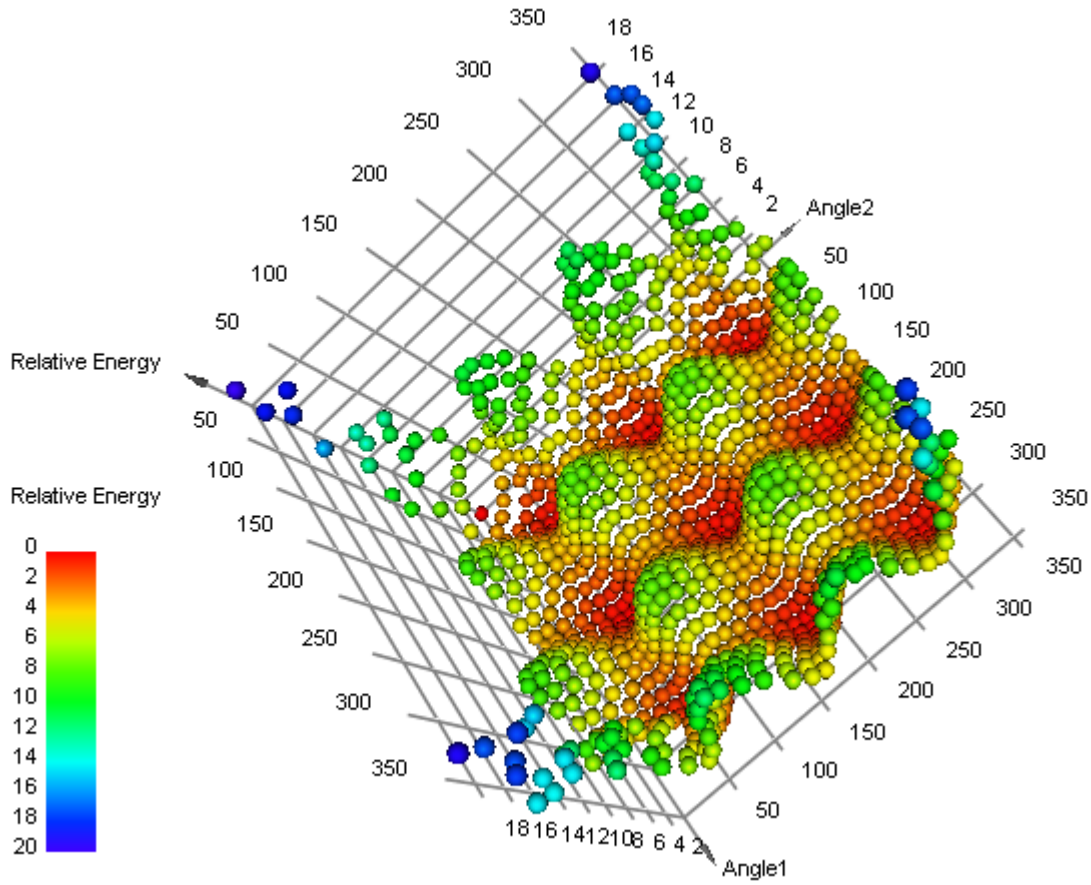
Run **Conformation Generation**.

From the menu bar, choose **Chart | 3D Point Plot**

Set the **X axis** to Angle1, **Y axis** to Angle2, and the **Z axis** (color code) to Relative Energy.

Click **OK**.

This creates the following 3D energy surface:



Further information

Conformations