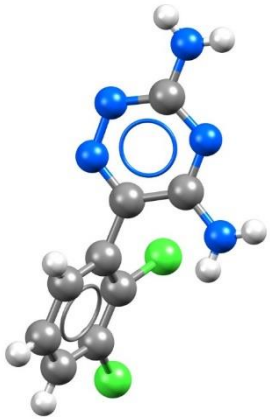
Advanced functionality for visualization and analysis of structures in Mercury – Introduction to the Conformer Generator

2024.1 CSD Release



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Introduction

The CSD Conformer Generator provides the ability to both minimise molecular conformations and generate diverse conformer subsets based on CSD data. The methodology starts from an input 3D molecular structure with all hydrogen atoms present, which is optionally minimised in the first step. Subsequently, conformations are sampled based on CSD-derived rotamer distributions and ring templates. A final diverse set of conformers, clustered according to conformer similarity, is returned. Each conformer is locally optimised in torsion space. There are three methods for generating conformers with the CSD portfolio; via the Mercury interface, the command line utility and the CSD Python API. This workshop focuses on generating conformers through the Mercury interface.

Before beginning this workshop, ensure that you have a registered copy of CSD-Materials or CSD-Discovery or CSD-Enterprise installed on your computer.

Learning Outcomes

This tutorial will guide you through the process of generating conformers in Mercury. At the end of this workshop, you will be able to:

- Sketch a structure in Mercury.
- Generate a set of conformers.
- Visualize multiple structures at once.

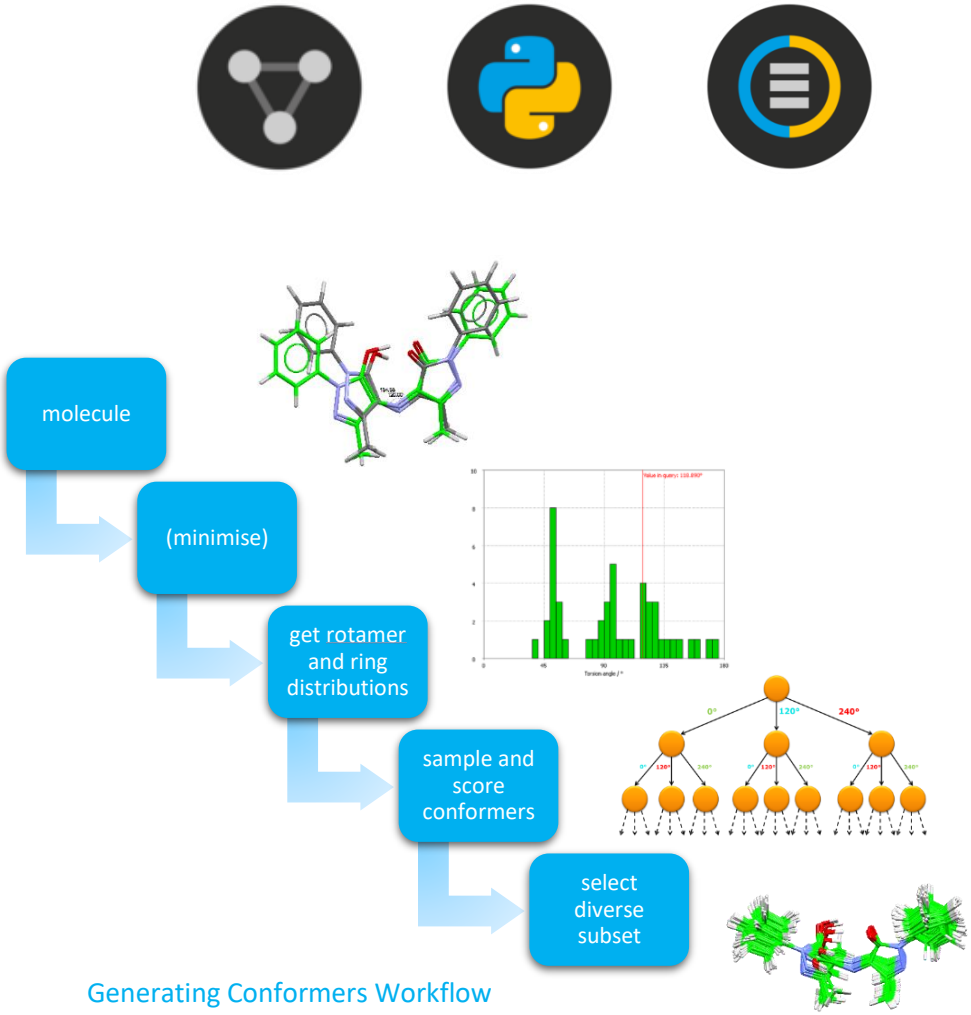
Note: This handout should take approximately **25 minutes** to be completed.

Pre-required Skills

Familiarity with the Mercury interface is important; you can access the Visualization in Mercury self-guided workshop here or review the basics of visualization in Mercury here. Knowledge of sketching a structure in ConQuest is expected, a review of sketching in ConQuest is at the end of this document.

Materials

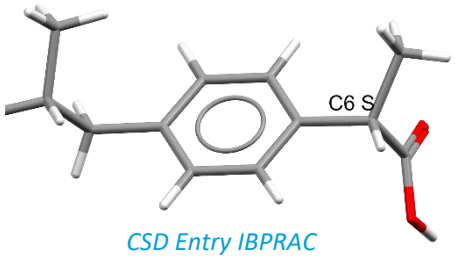
There are no additional materials for this workshop.



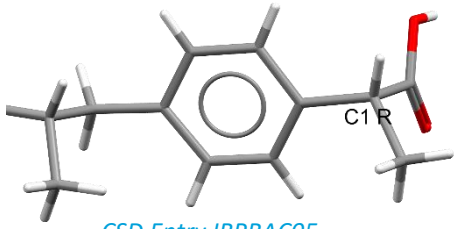
Generating Conformers Workflow

Generating Conformers in Mercury.

In this example, we will go through the steps of setting up a conformer generation run in Mercury. The CSD Conformer Generator requires as input 3D structures with all hydrogen atoms present. We will be generating conformers for both stereoisomers of 2-(4-Isobutylphenyl)propionic acid (ibuprofen).



CSD Entry IBPRAC
(*S*)2-(4-Isobutylphenyl)propionic acid



CSD Entry IBPRAC05
(*R*)2-(4-Isobutylphenyl)propionic acid

You can either sketch your structure in Mercury, import a .cif file or load one of the structures from the CSD by typing the refcode in the Structure Navigator. We will first sketch the structure of ibuprofen, but you can use one of the ibuprofen refcodes: IBPRAC or IBPRAC05.

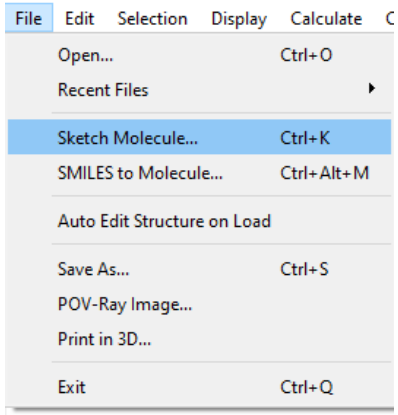
1. Start Mercury by double-clicking on the icon. Click on *File > Sketch Molecule* to bring up the sketcher.

2. The sketcher interface is the same used in ConQuest. If you need a refresher on how to sketch structures in ConQuest, check out the summary at the end of this handout. Sketch the structure of ibuprofen shown to the right.

3. Once you are done sketching the molecule, click **Done**. Your settings might add H atoms by default, making your sketched molecule look a little different. We will edit the structure later in Mercury. A pop-up window will appear asking for a name for the structure. Provide a name for the structure and click **OK**.

4. You will now return to the main Mercury window with your sketched structure displayed.

1



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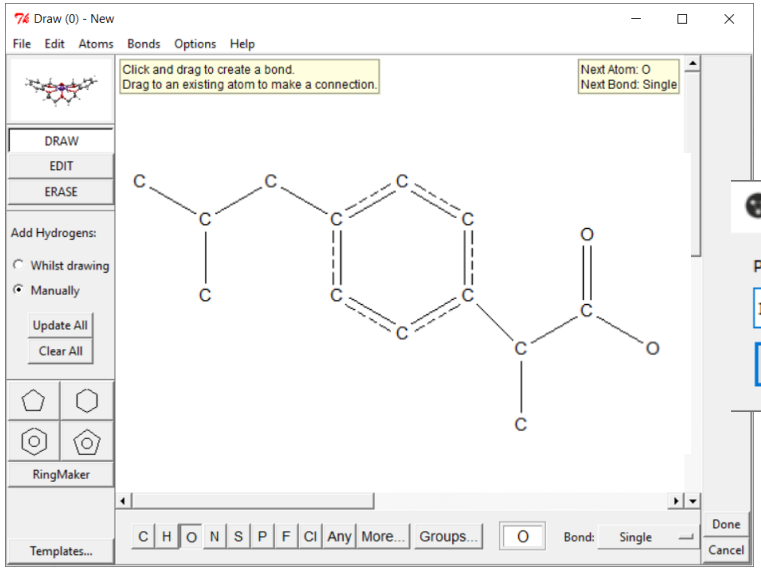

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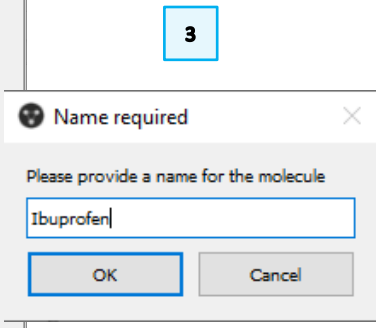


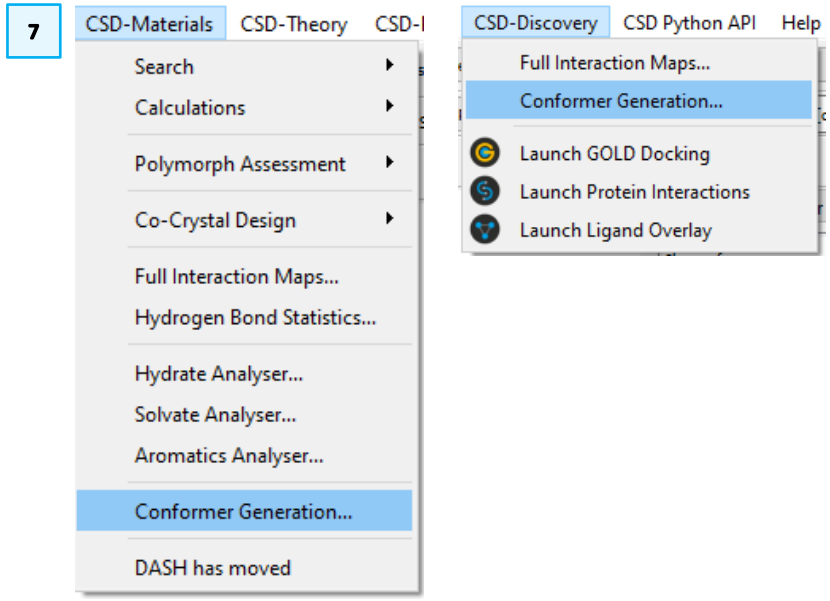
5. We first need to make sure that all bond types in our structure are correct. We can do so by using the Edit Structure option. Click *Edit > Auto Edit Structure*. Leave the default options ticked and click **Apply**. If there are any changes made, it will be shown in the pop-up.

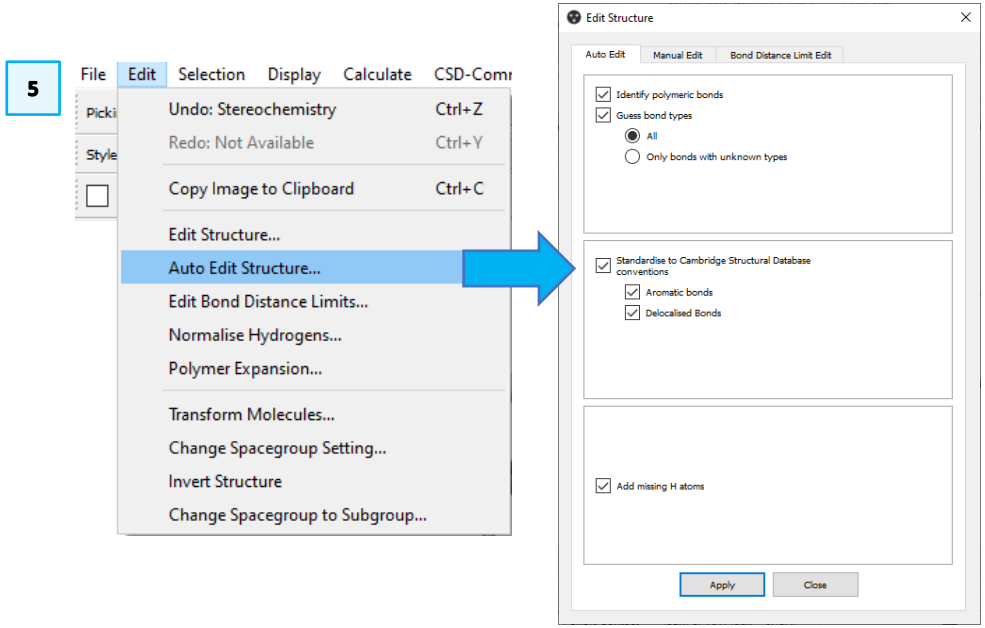
6. 2-(4-Isobutylphenyl)propionic has a chiral centre, however we were unable to specify chirality when we sketched the structure. We can view the stereocentre that our structure has. Tick the **Show Labels for** box, select *Stereocentres* with *Stereochemistry*. The structure shown here is the *R* enantiomer but yours could be different.

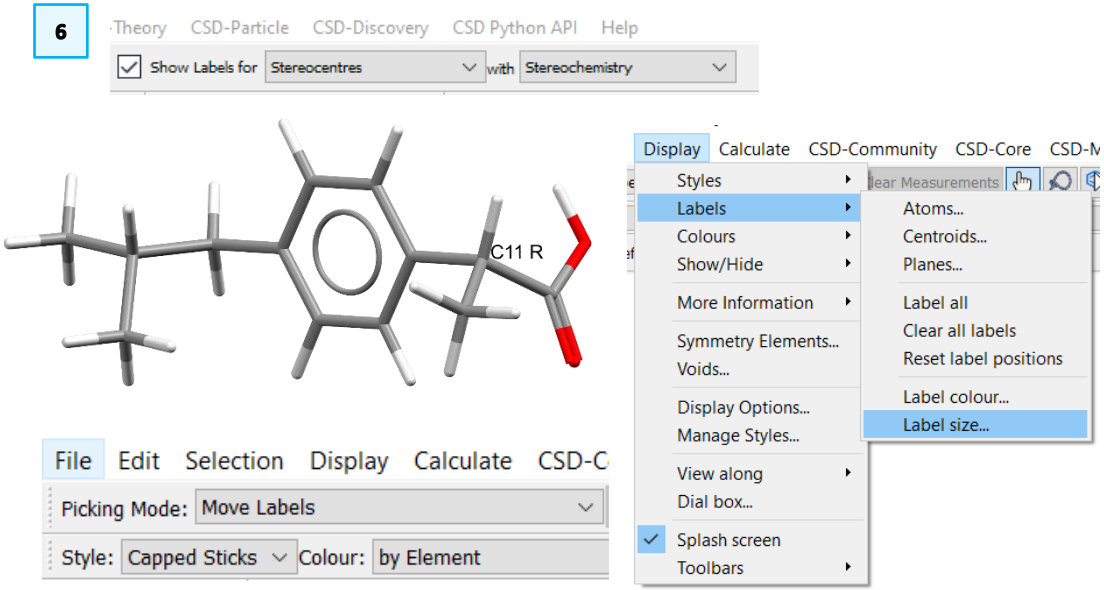
   Tip: You can change the label size from the Display menu; *Display > Labels > Label size*. Change the *Picking Mode* to *Move Labels*.

   We are now ready to set up the Conformer Generator. The CSD Conformer Generator can be accessed through the **CSD-Materials** and **CSD-Discovery** menus within Mercury.

7. From the CSD-Materials or CSD-Discovery menu, click on *Conformer Generation…* to open the Conformer Generation window.







8. In the **Conformer Generation** window in the *Source molecule* section, you can specify a CSD entry, an in-house database entry, or another structure as the input molecule for conformer generation. The default selected molecule is the present molecule in the main display window. Alternatively, you can select a file on the disk as the input by selecting **From file:** option and clicking on the **Browse** button.

9. The working directory can be selected under *Working Directory* section of the **Conformer Generation** window. You can stick with the default here or Click the **Browse** button and navigate to the folder you want the results saved to A folder will be created in this directory named after the identifier of the input molecule used. Both a copy of the input molecule and the generated conformers will be written to the output folder.

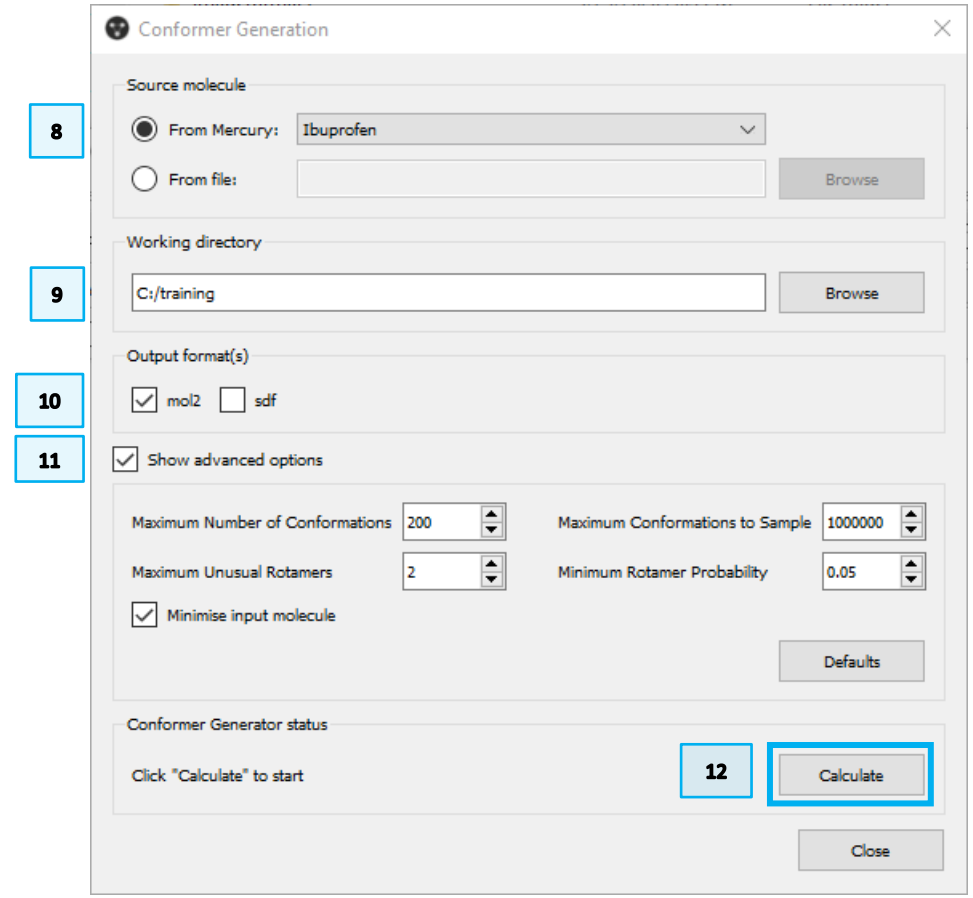
10. Conformers may be generated in *.mol2* or *.sdf* format by choosing the relevant checkboxes under *Output format(s)*. The default *.mol2* format will be used in this tutorial.

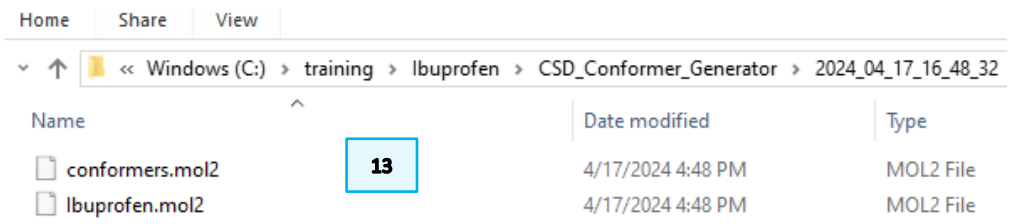
11. Tick the **Show advanced options** to view the defaults. You can change the values here if necessary but we will stick with the defaults.

12. Click the **Calculate** button to generate conformers.

13. The calculation should take less than a minute. You can navigate to the folder you selected in step 9, the conformers you have generated are placed in \path\to\structure\CSD_Conformer_Generator\YYYY_MM_DD_hh_mm_ss\ conformers.mol2.

Replace \path\to\ with the actual path to the folder selected in step 9. Please note that YYYY_MM_DD_hh_mm_ss is the date and time when the calculation was run. You will have a different folder name corresponding to your own calculation date and time.



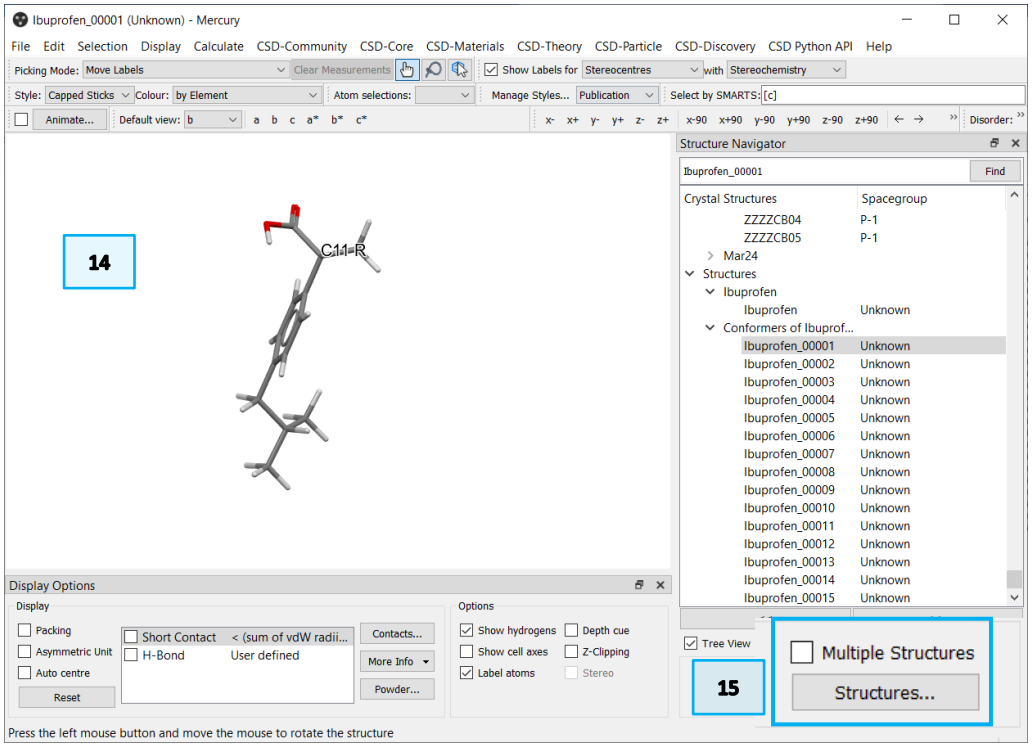


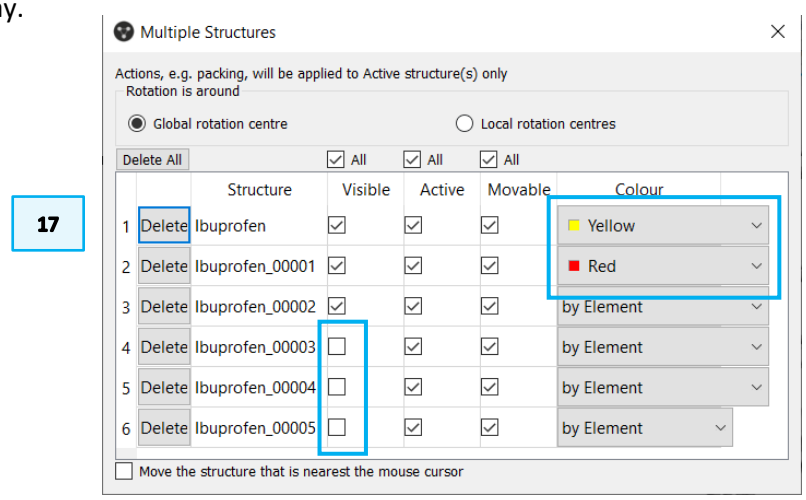
14. The conformers are also populated in the **Structure Navigator** as new entries. Note that the first conformer generated is now shown in the Mercury window. You can scroll through the conformers by clicking on each entry or the down arrow on your keyboard. A couple of things to note here are *a*. the stereochemistry is conserved in all conformers and *b.* it is not easy to see the differences between the conformers if viewing one by one. We will load multiple conformers at once and superimpose them.

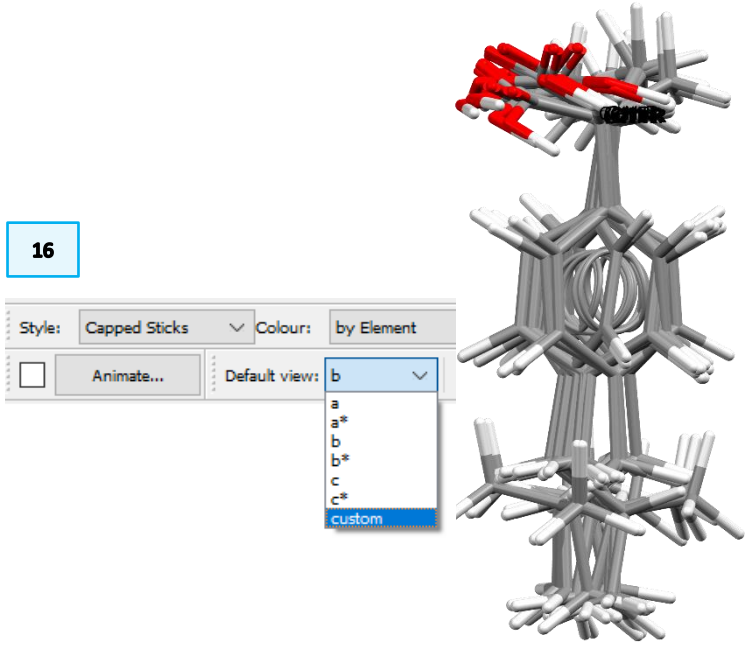
15. Tick the **Multiple Structures** box in the lower right corner of the Mercury window. Click on however many conformers you want and the input molecule to view them at once. For some users, the structures might be superimposed but if they are not, you can use the view options to change that.

16. From the *Default view:* menu, select *Custom*. You may need to untick and tick again the Multiple Structures box. Now when you click on multiple structures, they should be superimposed along the same axis.

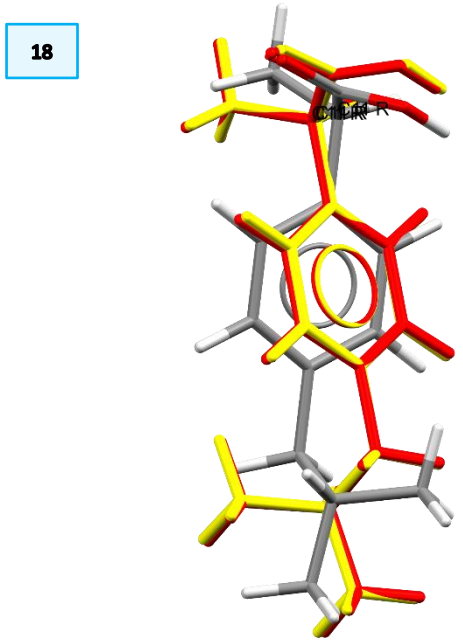
17. You can change the colour of each conformer displayed to make the differences more visible. Click on **Structures…** in the lower right corner to bring up the *Multiple Structures* menu. Change the colour by clicking **on by Element** box and choose a colour. You can also hide some of the entries from the display.







18. The colour of the entries should change in the display window.



In this example, we started with a sketched structure. As mentioned, it is possible to generate conformers from structures already in the CSD. If you have completed this section and you have more time left, you can generate conformers for the other enantiomer using either refcode IBPRAC for an *S* enantiomer or IBPRAC05 for an *R* enantiomer.

Conclusion

We have used the conformer generator feature in Mercury to generate conformers of ibuprofen. After this workshop you should now be able to:

- Sketch a structure in Mercury.
- Generate conformers for a given structure.
- Use different display options for viewing multiple structures.

Summary

In this example, we have generated conformers for a single molecule. If this is your first step in performing ligand-based virtual screening, you can use the conformers generated here as your starting point. You are also able to generate conformers from a file with multiple ligands.

Next Steps

The CSD Conformer Generator User Guide can be found here or from the Documentation and Resources section of our website. There are two other methods for generating conformers: via the CSD Python API and the command line. If you are interested in exploring those, instructions can be found in the Ligand-based Virtual Screening handout on this page.

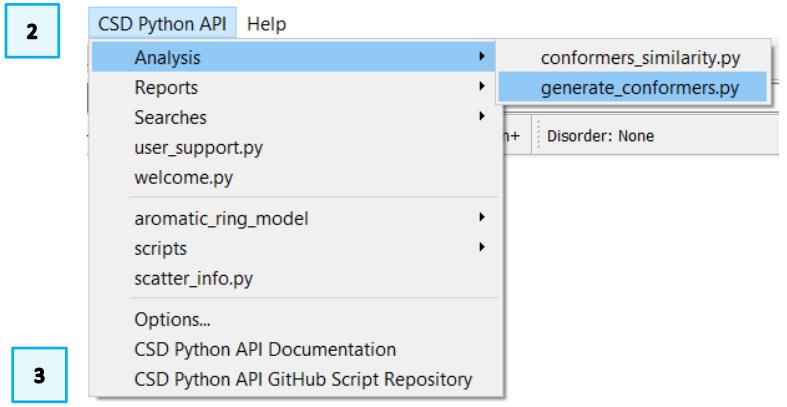
https://www.ccdc.cam.ac.uk/community/training-and-learning/workshop-materials/csd-discovery-workshops/

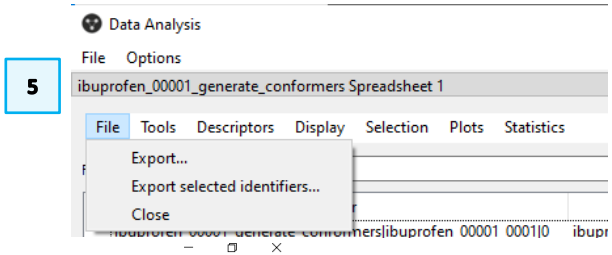
Bonus Exercise

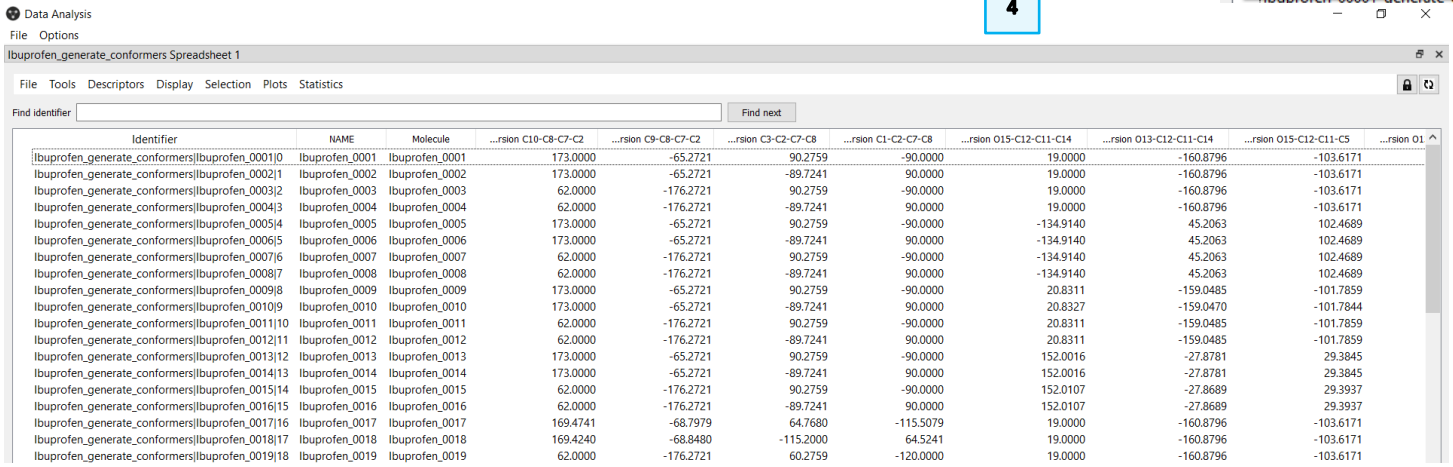
You can also use the conformer generator script in the CSD Python API menu in Mercury. This bonus exercise covers the steps for that.

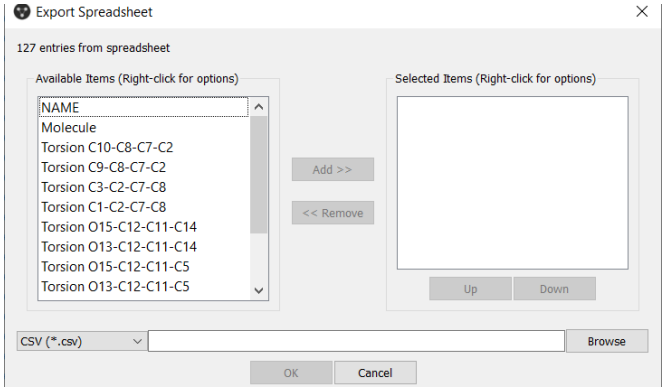
Generating conformers via the CSD Python API script in Mercury.

1. Load the Ibuprofen structure in Mercury or select the entry from the Structure Navigator.
2. From the CSD Python API menu select *Analysis > generate_conformers.py*
3. There will be a window showing the progress, the script should take less than 30 seconds to be completed. The output folder where the files are written is displayed in this window.
4. Once the script is done running, a **Data Analysis** window will open with the conformers generated and torsion angles in each molecule. Clicking on each entry will place the conformer in the Mercury display window. You can choose to plot some of the angles or export the parameters.
5. To export the entries into a .csv, click on *File > Export* in the **Data Analysis** window. This will open the **Export Spreadsheet** window where you can select items you want saved to the spreadsheet.
6. If you have experience editing python scripts and want to view this script, it is in path\to\CCDC\ccdc-software\mercury\scripts\Analysis replacing path\to\ with your actual install location.









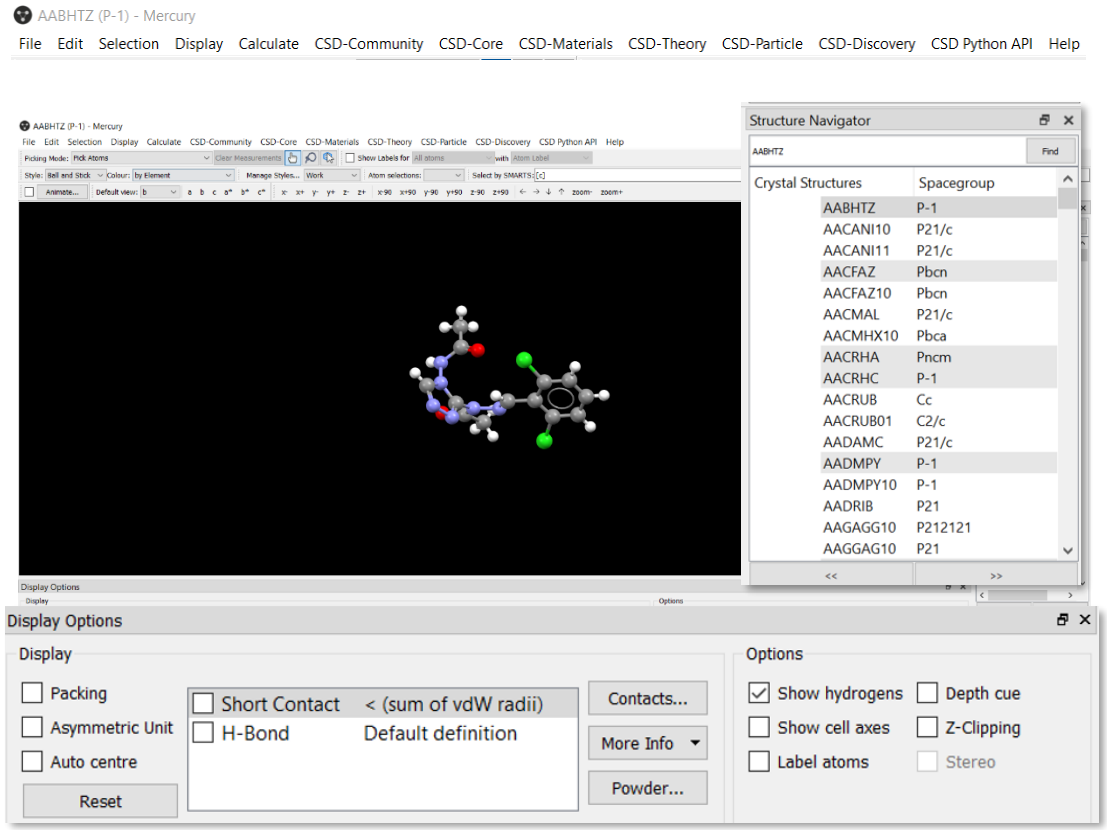
Basics of Mercury Visualization

Mercury is the CCDC's visualization software to view 3D structures of small molecules, generate images, and animations of molecules.

In the following we will see some of the basics of navigation and visualization in Mercury that you will find helpful to support your analysis.

In the **Mercury interface** we find:

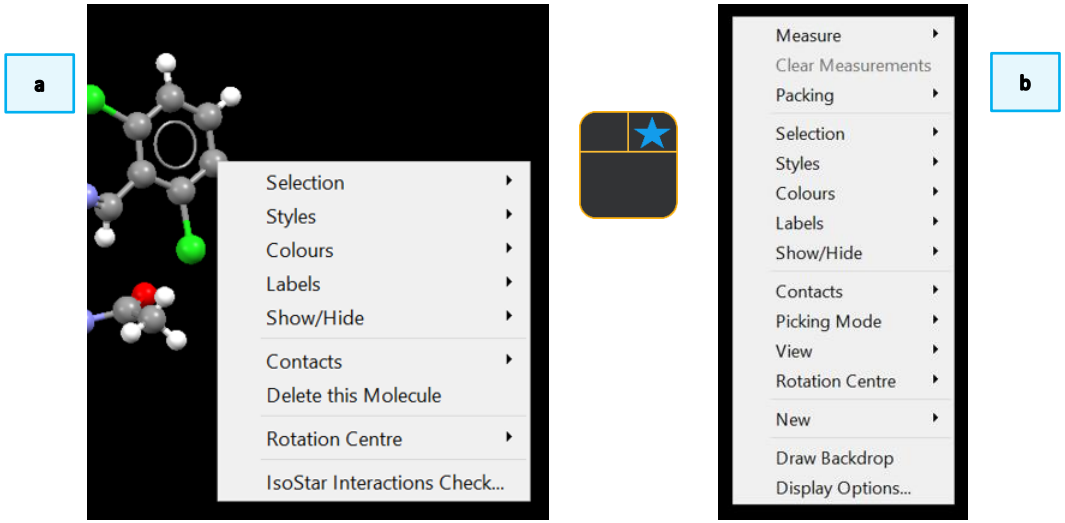
- **At the top**: list of menus from which we can access visualization and analysis options, and other CSD components such as CSD-Materials.
- **On the right-hand side**: the **Structure Navigator**, with the database loaded (depending on your licence). The Structure Navigator allows you to select a refcode to visualize in the main Mercury window.
- Beneath the main display window: Display options toolbar. You can quickly view a packing diagram, display Hydrogen bonding and detailed information about the molecule using the More Info option.



Using the **mouse to enhance visualization**:

- Left mouse button and move – rotate molecules.
- Middle Mouse wheel – move molecules up and down.
- Right mouse button and move up and down – zoom in and out of molecules.
- Shift + Left mouse button and move - rotate in the plane molecules.
- Ctrl + Left mouse button and move - translate molecules.

Right click:
a) Near a molecule and b) Away from a molecule



Review. Draw Window

All drawing takes place in the central white area of the *Draw* window. In addition to creating 2D chemical structure sketches, the *Draw* window allows for the inclusion of 3D parameters for searching or for filtering.

ConQuest sketching conventions

- Left click in the sketcher to insert the selected atom type
- Left click and drag to sketch two bonded atoms
- Use the **Edit** button to modify properties of or delete atoms, bonds or entire substructures
- Right-click on atoms or bonds to modify their properties
- Use the **Templates…** button to pick from a list of CSD editor devised and drawn substructures
- Use the **More…** button to find less frequently used element types, or generic atom type groups (e.g. halogens), or define custom element combinations (e.g. C or N or O).