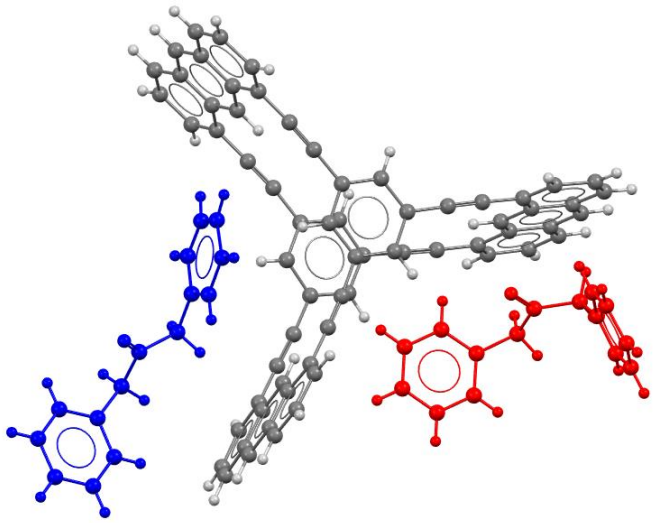
Exploring Conformation and Non-Covalent Interactions with Mogul and Aromatics Analyser (MAT-010)

Developed using CSD Software version 2025.3 and CSD release 6.01



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Contents

Introduction

This workshop demonstrates the use of Mogul to analyse the conformation of a molecule and the use of Aromatics Analyser for assessing aromatic interactions in a crystal structure.

Structural chemists can use the Mogul Geometry Check tool in Mercury to validate the three-dimensional conformation of a molecule. The data from structures in the CSD can be used to show the most likely value a particular bond, angle or torsion should adopt, as well as to assess how typical a ring conformation is. The values of these measurements can be classified as unusual or not unusual by comparison with the values stored in the Mogul Database. Unusual features could arise for several different reasons, including intermolecular interaction-driven conformational preferences.

Aromatics Analyser is a tool in Mercury which is built on a neural network, which facilitates quantitative assessment of *aromatic ring interactions*. The model is based on a geometric description of aromatic interactions involving the position of two phenyl rings relative to each other and is based on a large number of quantum mechanical calculations. The outcome of this model is a score indicating whether the aromatic interaction is weak, moderate or strong. This approach provides insight into aromatic interactions by quickly visualising them and picking out stabilising interactions.

Learning Outcomes

By the end of this workshop, you will be able to:

- Select atoms in Mercury using a SMARTS substructure.
- Use Mogul Geometry Check in Mercury to find unusual torsions.
- Use Aromatics Analyser to calculate aromatic interaction of molecules in different environments.

This workshop will take approximately ***25 minutes*** to be completed. The words in *Blue Italic* in the text are linked and reported in the Glossary at the end of this handout.

Pre-required Skills

For this tutorial, we recommend being familiar with the basic functions of Mercury. If you have not used Mercury before, we recommend studying visualization with Mercury on this page, or attempting this online module. A summary guide is also provided at the end of this handout.

Materials

No additional materials are required for this workshop.

Example: Exploring the Conformations and Interactions of Dibenzylketone in an Anthraphane Co-Crystal

α-Monosubstituted ketones are known in general to prefer a conformation in which one substituent eclipses the C=O bond. Such a conformation is optimal for *hyperconjugation*, as shown in the Figure 1 below.

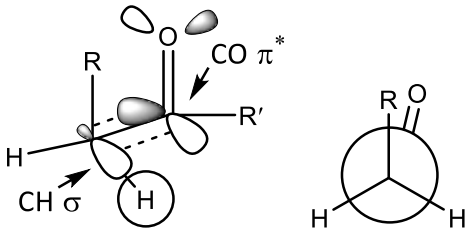


Figure 1. Hyperconjugation involving C–H bonds is generally preferred, therefore it is usual to find at least one H-C(α)-C-O torsion around 90-120° in α-monosubstituted ketones.

Dibenzylketones are of interest because they undergo *decarbonylation* reactions (sometimes in the solid state) and the ease with which this reaction occurs has been linked to intermolecular interactions[1] and conformation.[2] In the two known polymorphs of pure dibenzylketone (DBK), (refcodes: WUXDOJ and WUXDOJ02), numerous intermolecular aromatic interactions can be identified, however, the DBK molecules' conformations are considered typical (no unusual torsions for the rotatable bonds). In CSD entry EHUDAO, there are two molecules of DBK co-crystallised with one molecule of anthraphane (Figure 2, right). This presents an interesting case study for how the conformation of DBK can be influenced by interactions with a *different* molecule. In this example we will use Mogul Geometry Check and Aromatics Analyser to explore potential relationships between conformation and aromatic interactions.

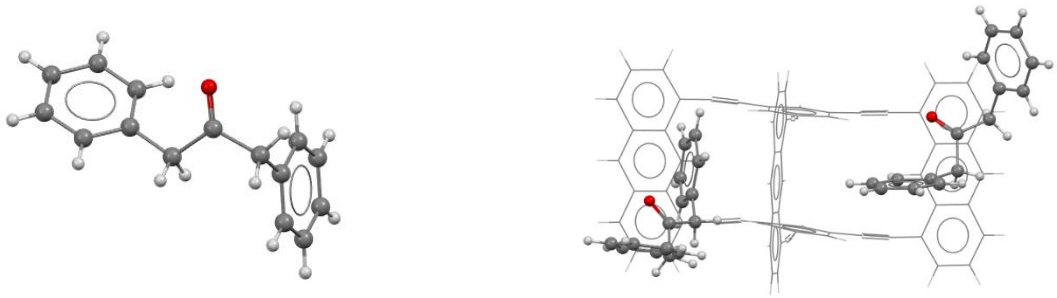
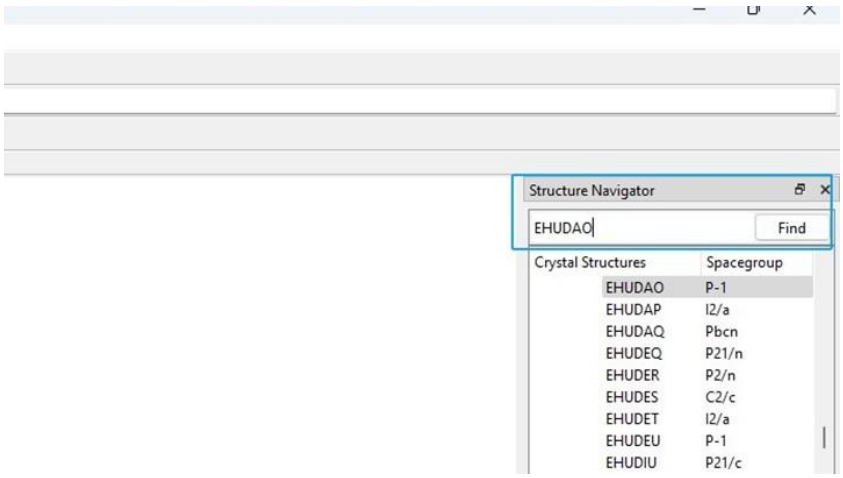


Figure 2. Left: dibenzylketone (WUXDOJ). Right: anthraphane-dibenzylketone co-crystal (EHUDAO).

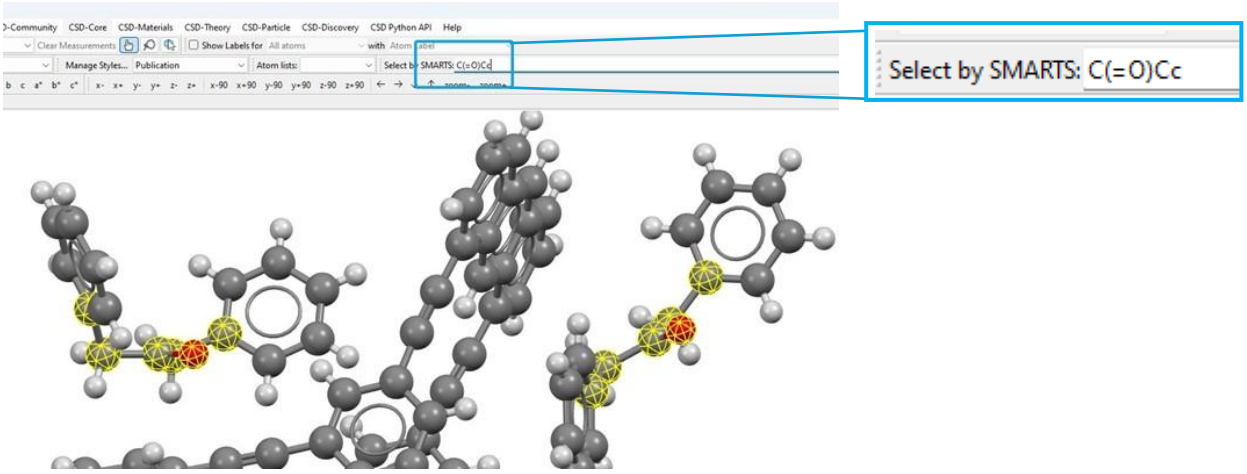
[1] J. Zhang, M. Gembicky, M. Messerschmidt and P. Coppens, Chem. Commun, 2007, 2399-2401 DOI: 10.1039/B700073A

[2] M. J. E. Resendiz and M. A. Garcia-Garibay, Org. Lett., 2025, 7, 371-374 DOI: 10.1021/j100087a005

1. Open Mercury by double clicking on the Mercury icon. In the Structure Navigator, type "EHUDAO".[3]

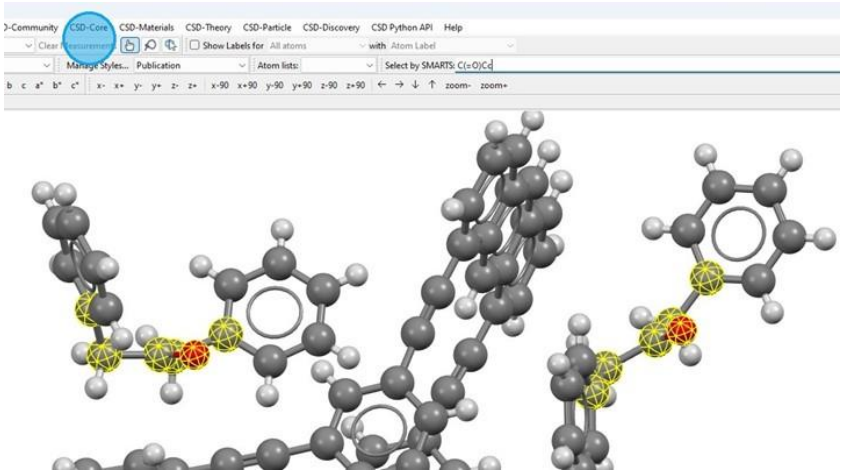


2. In the Select by *SMARTS* box, delete [c] and type "C(=O)Cc" and press enter. This is the SMARTS substructure pattern for the part of the molecule we are interested in analysing with Mogul. The selected atoms will be highlighted in yellow.

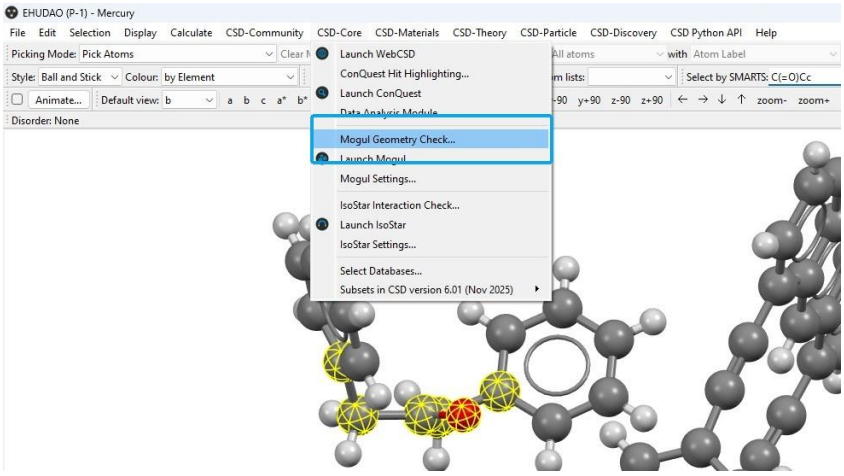


[3] Please follow the instruction in the Materials section if you are using a workshop license or have not downloaded the CSD.

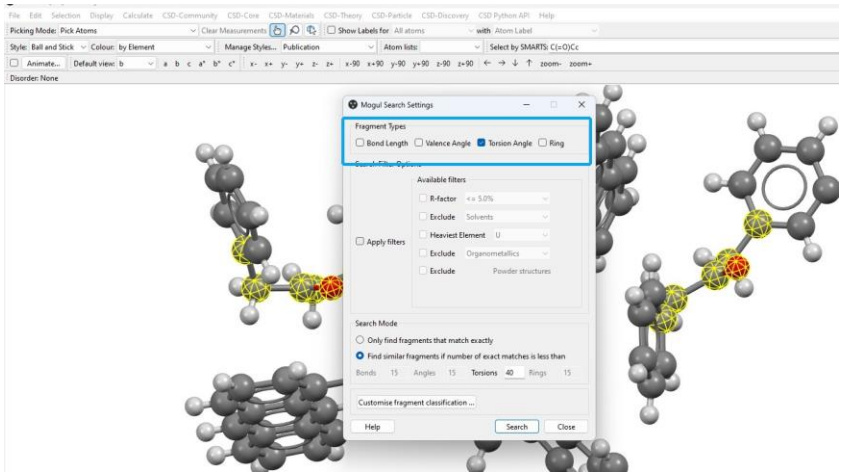
3. From the top menus, click **CSD-Core**.



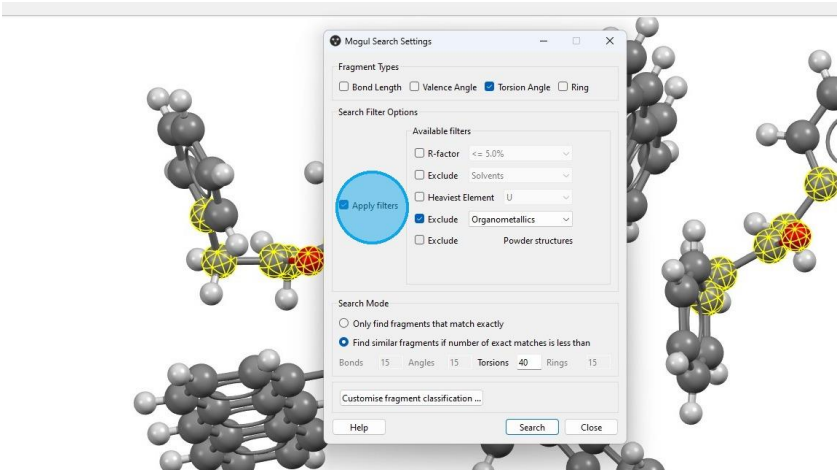
4. Click **Mogul Geometry Check...**



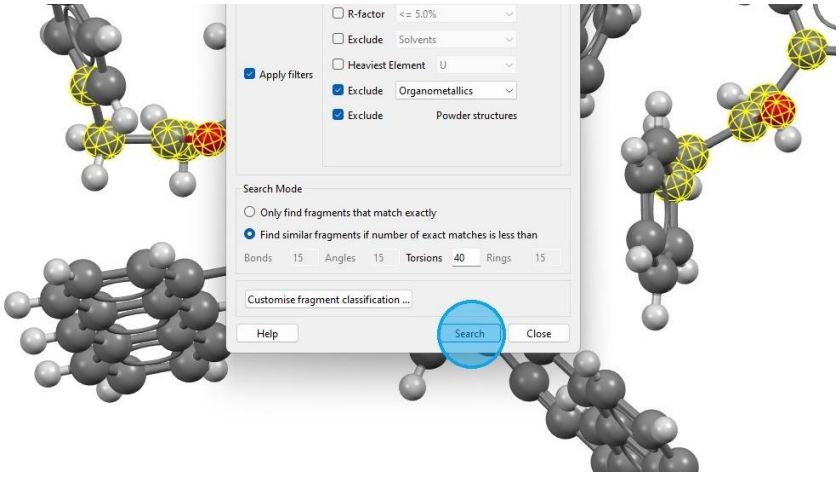
5. Untick **Bond Length**, **Valence Angle** and **Ring** from the Fragment Types area.



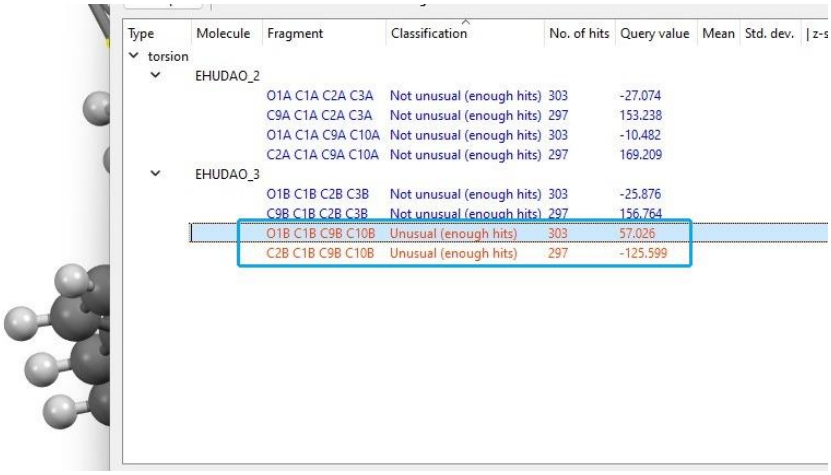
6. Tick **Apply filters**, and tick **Exclude Organometallics** and **Exclude Powder Structures**.



7. Click **Search**.

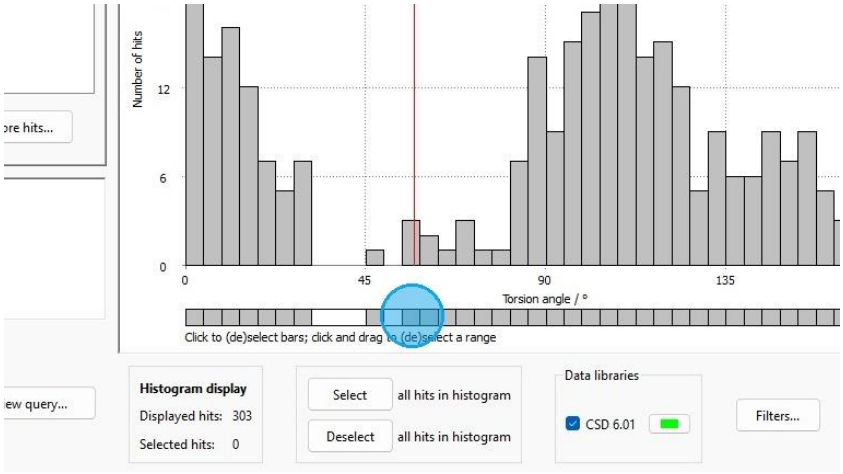


8. The Mogul Results Viewer will appear when the analysis is finished. The unusual torsion angles are highlighted in red. Double-click on a row to view the underlying histograms of data used for comparison of a query value. In this instance, we will look at O1B C1B C9B C10B, so double-click on that row.

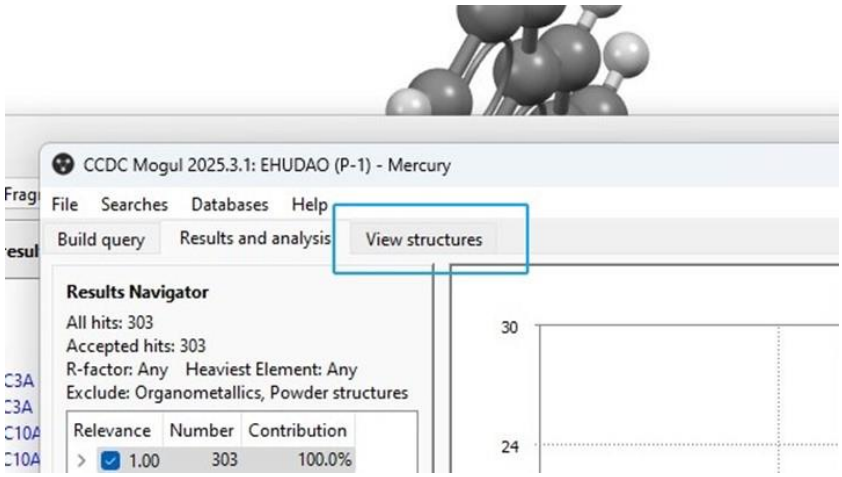


9. The Mogul histogram relevant to the O1B C1B C9B C10B torsion will appear. The value measured in the query (the molecule from EHUDAO that was selected) will be marked as a red line. In this case we can see it lies in a relatively unpopulated region of the histogram. Why would you expect this region of the histogram to have relatively few measurements in it? See the introduction for some hints. To see the structures that have torsions most like the query, first click Deselect at the bottom of the window.

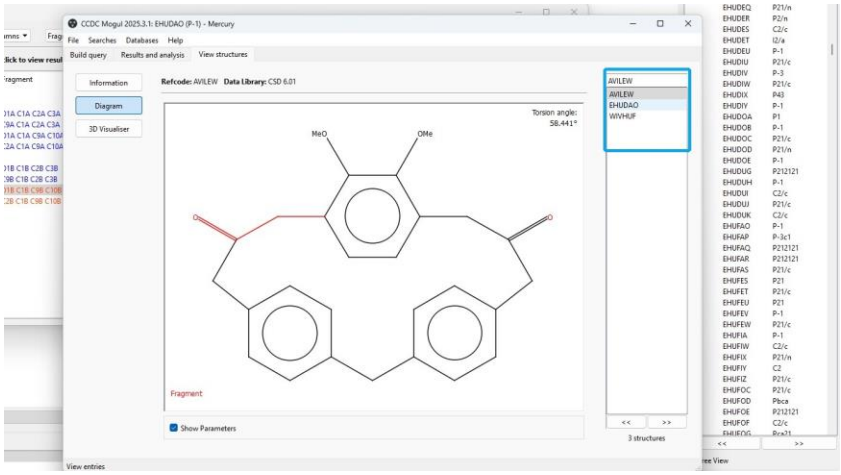
10. Click on the small grey box directly underneath the relevant bar of the histogram.



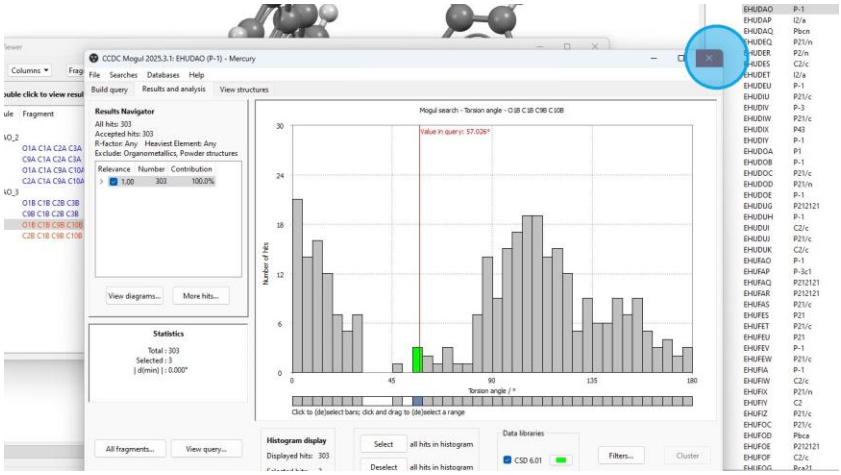
11. Click the **View structures** tab.



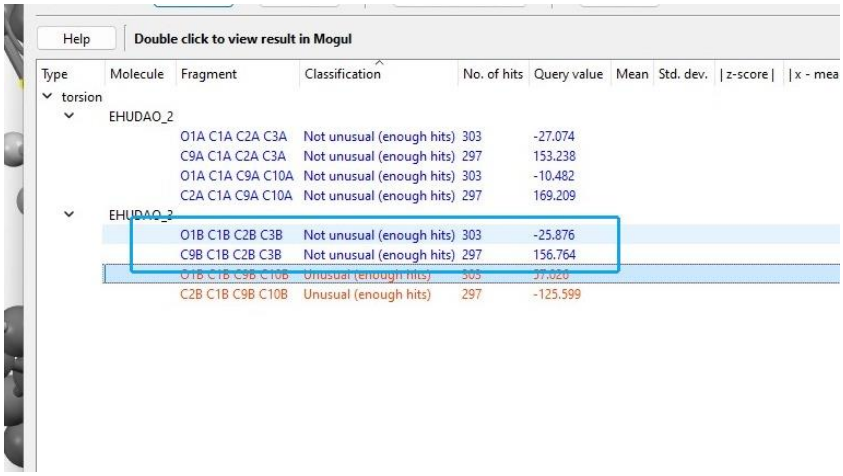
12. By default, the Diagram panel will be displayed. Here you can see the structures which are in the selected histogram bin. The fragment where the measurement originates from is highlighted in red. Click through the structures to view them.



13. When you are finished, click the close button.

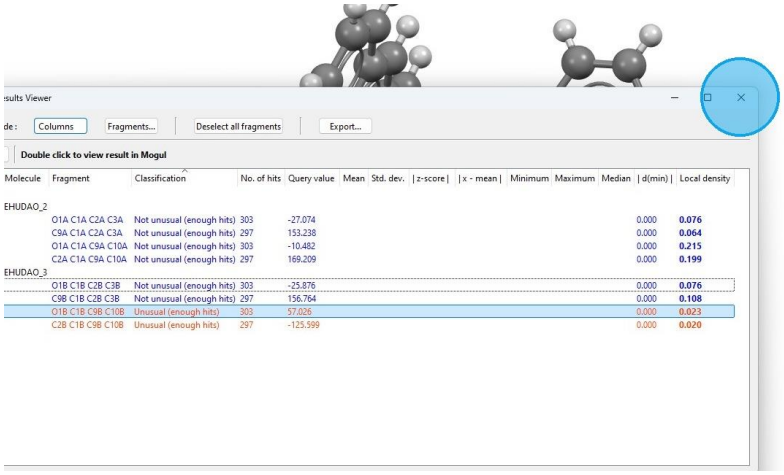


14. For comparison, look at a "Not unusual hit", such as O1B C1B C2B C3B.

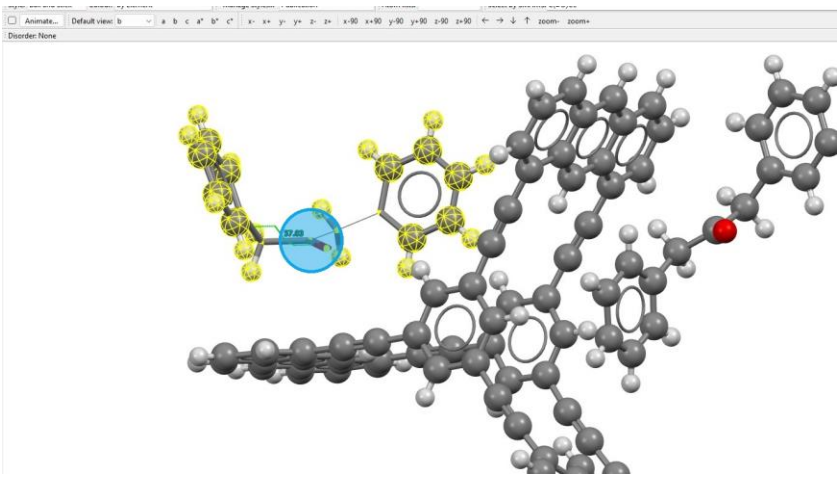


15. You will see that it lies in a well-populated region of the histogram, albeit towards the edge of that region. When you have finished examining the histogram, click the close button.

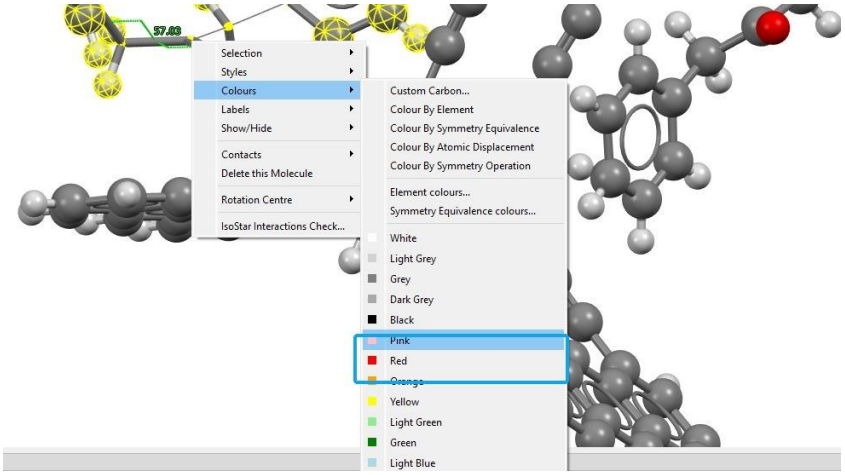
16. Make sure that one row with an unusual value is selected and deselect the others before closing the Mogul Results Viewer. The selected torsion will remain marked on the molecule so you can identify it easily. This is important because we will analyse the aromatic interactions of each unique DBK molecule separately in the next section.



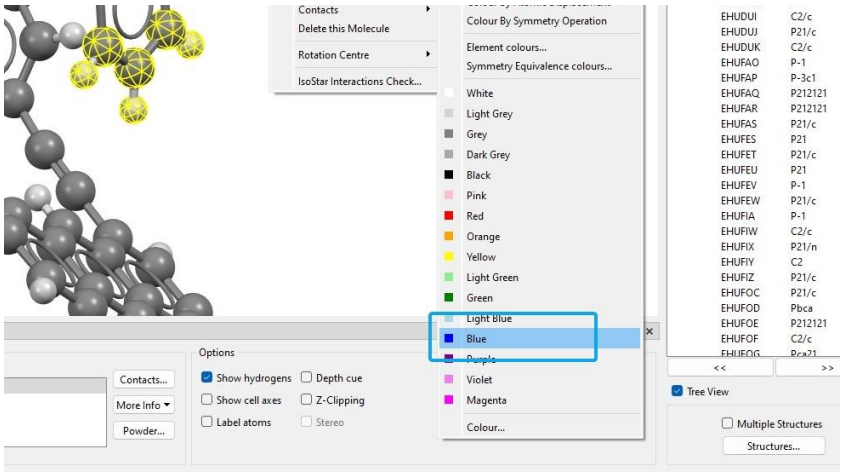
17. Locate the DBK molecule with the unusual torsion. Ensure that no atoms in the other molecules are selected by clicking in any empty region of the visualiser, then hold down Shift and left-click on the DBK molecule to select all atoms in it.



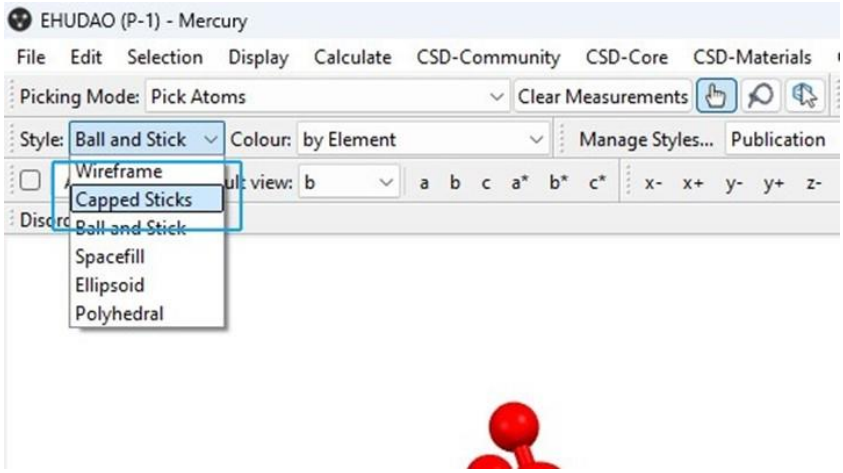
18. Right-click near to the molecule in the visualiser area and from the drop-down menu that appears, select **Colours > Red** (or whichever colour you prefer).



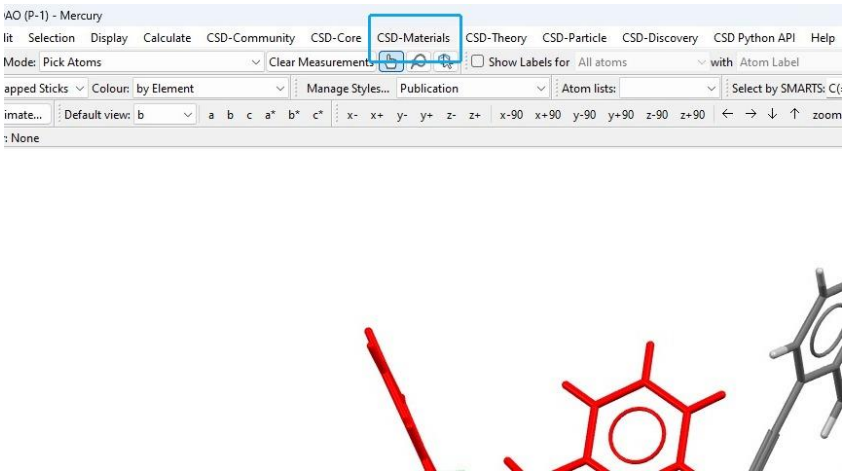
19. Repeat this process for the other DBK molecule but chose a different colour, such as blue.



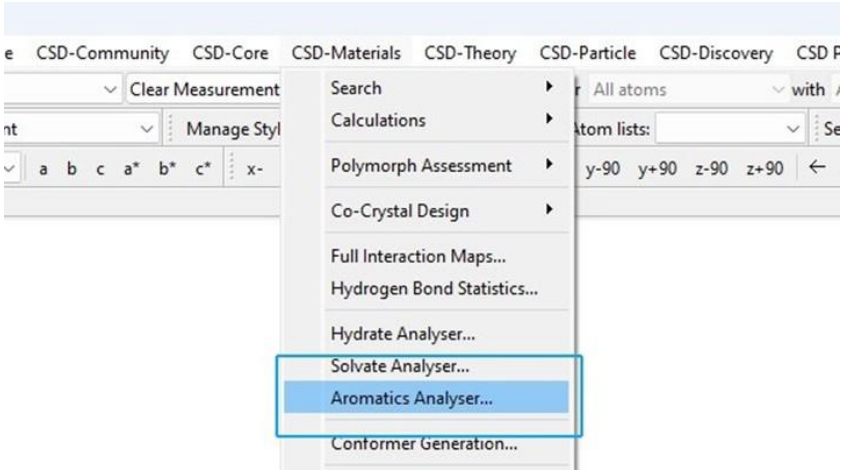
20. To make it easier to view the molecules in the next steps, change the style by clicking on the **Style** drop-down menu and choosing **Capped Sticks**.



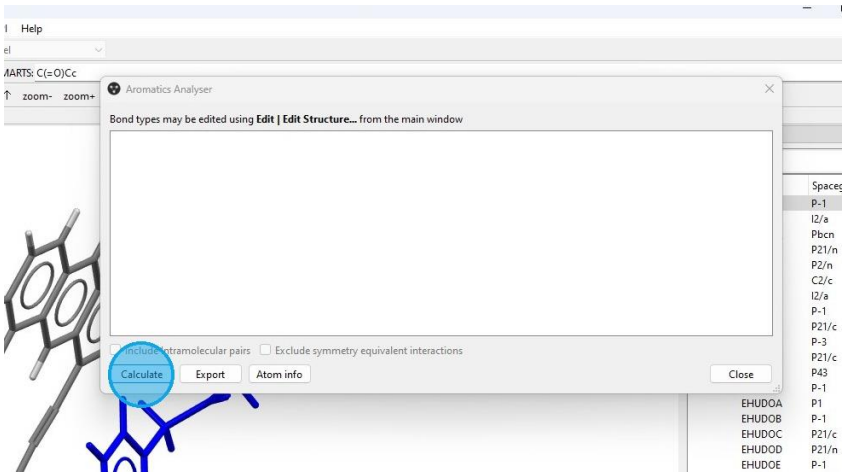
21. We will now use Aromatics Analyser to analyse aromatic interactions involving the DBK molecules. From the top menus, click **CSD-Materials**.



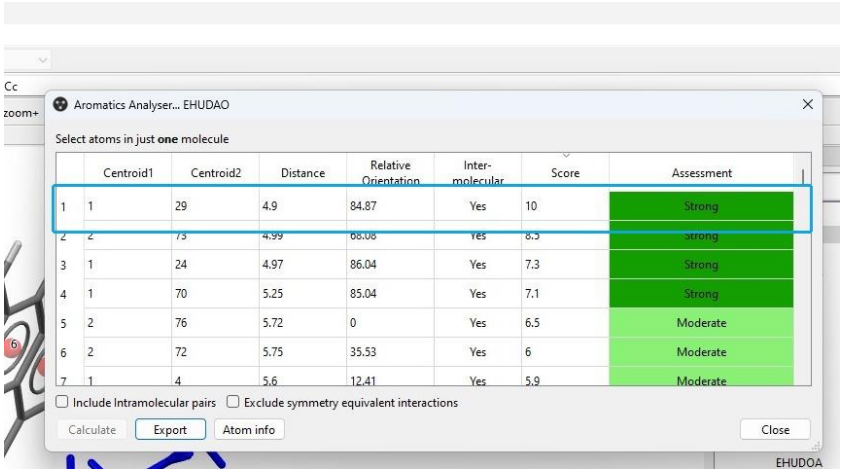
22. Click **Aromatics Analyser...**



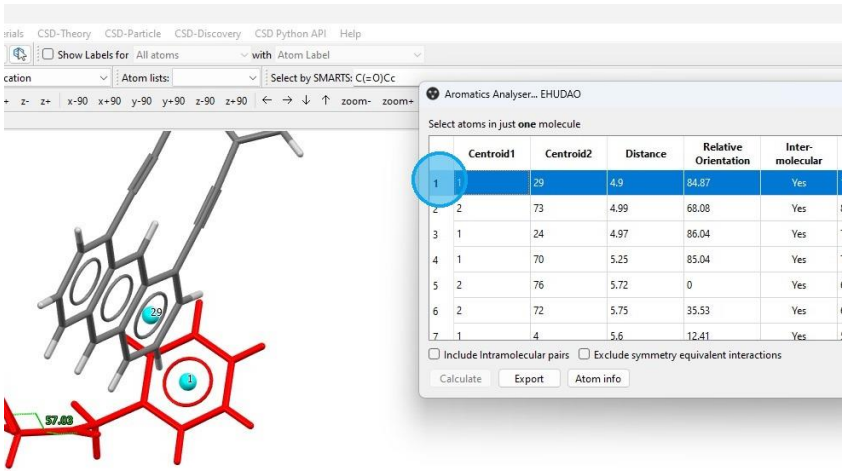
23. Hold down Shift and left-click on the red molecule to select it. Then click **Calculate** in the Aromatics Analyser window to start the analysis.



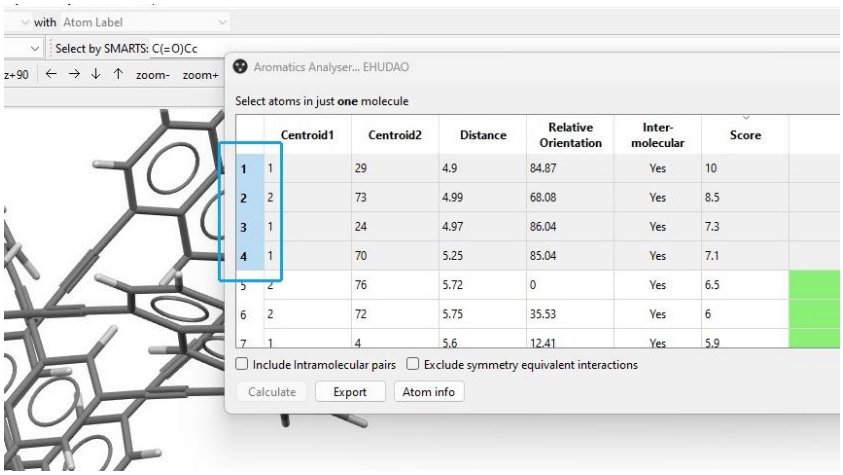
24. Aromatics Analyser typically takes 1-2 minutes to run. When the calculation is complete, you will see the table is populated with likely aromatic interactions, identified by the two centroids of the interacting rings. Click on a row in the table to display an interaction in the visualiser.
    - The orientation and distance help to identify the type of aromatic interaction. For example, a relative orientation of 0° (parallel planes) indicates a stack, 90° indicates an edge-to-face interaction and so on.
    - The interaction strengths are scored on a 1-10 scale, with 7-10 being strong, 3-7 being medium strength and 0-3 being weak interactions.



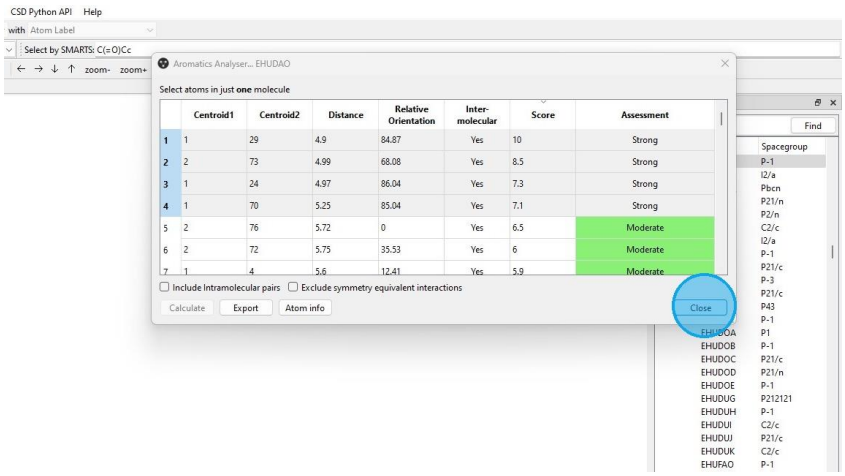
25. Click rows individually to explore specific interactions.



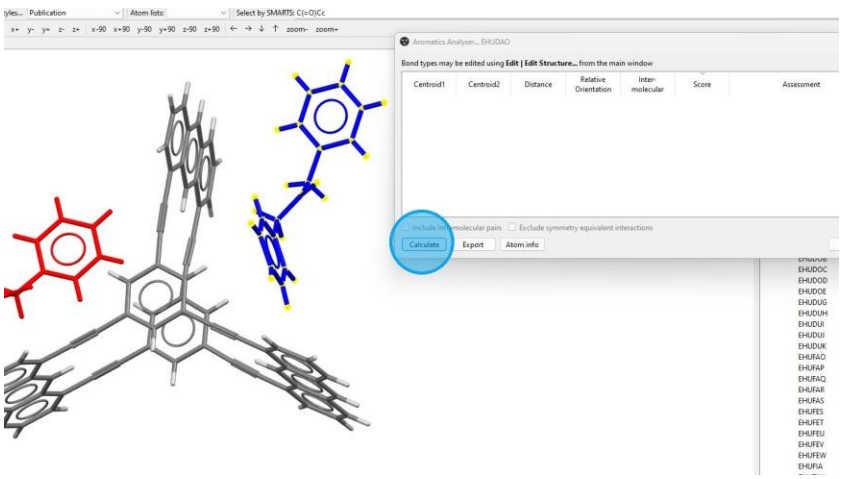
26. Click and drag with the mouse over the Strong rows (so that all the relevant interactions are visible at once). Explore these in the visualiser. What type of aromatic interactions are present?



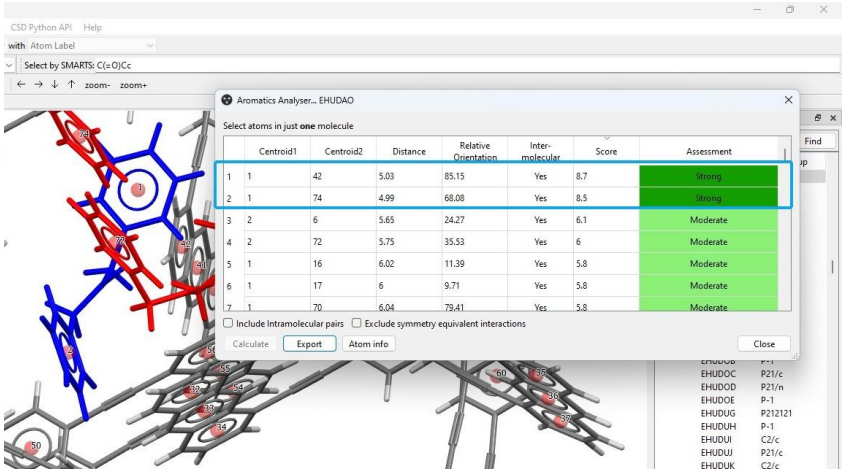
27. When you have finished exploring, click **Close**. Then click **Reset**.



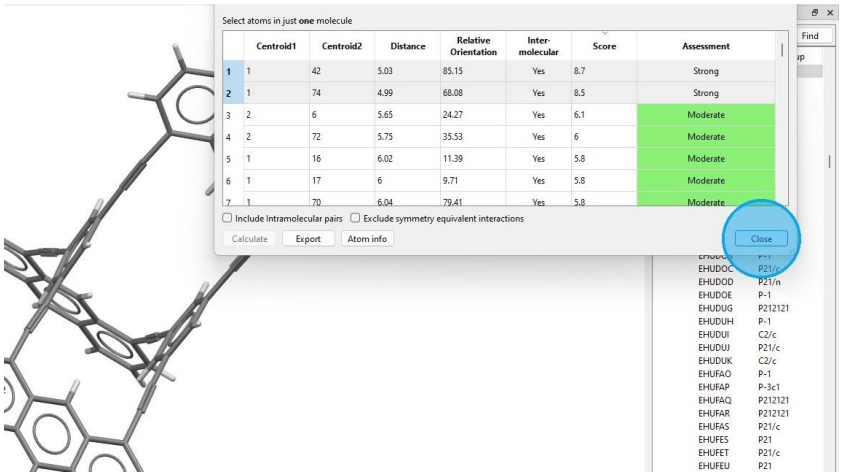
28. Select the other DBK molecule (the blue one shown below) and run Aromatics Analyser, following steps 21-23.



29. Notice that two strong interactions have been identified for this molecule compared to four in the previous instance. Click on them to explore. Are any of these interactions also identified in the analysis for the other (red) molecule?



30. When you are finished, click **Close** in the Aromatics Analyser window.



31. Click **Reset** in the Display options toolbar.

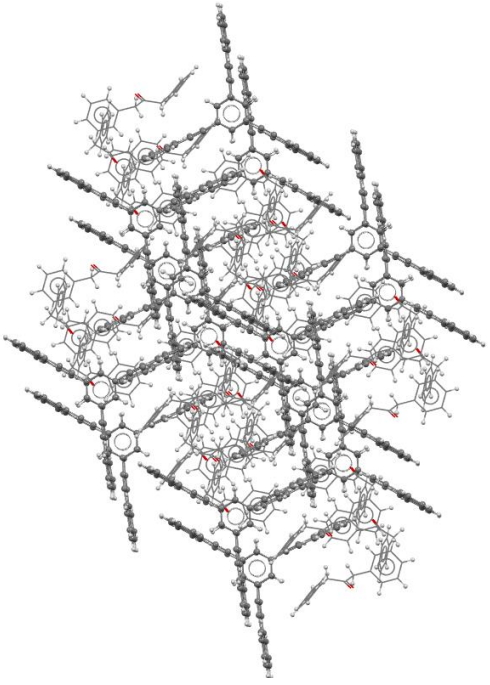
Conclusions

In this example, we have seen that a co-crystal of anthraphane and DBK exhibits numerous aromatic interactions. However, one of the two unique DBK molecules forms a larger number of strong aromatic interactions; this molecule is associated with a non-ideal conformation, showing a single unusual torsion.

Exercises

In the example, you have examined aromatic interactions involving the DBK molecules.

- Use Aromatics Analyser to explore interactions between the anthraphane molecules. Can you suggest a reason for the offset stacking of the anthraphane molecules in the crystal?
- Examine other structures from this paper: M. Servalli, N. Trapp, M. Wörle and F.-G. Klärner, *J. Org. Chem.*, **81**, 2016, 2572-2580 DOI: 10.1021/acs.joc.6b00209. Do any of them show similar interactions and packing?



Tip: you can search a DOI in Access Structures to find the refcodes associated with a publication.

Summary

In this workshop we have used tools available in Mercury, namely Mogul Geometry Check and Aromatics Analyser, to explore potential relationships between conformation and non-covalent interactions and have uncovered a likely case of such a relationship in a co-crystal of anthraphane and dibenzylketone. You should now be confident to:

- Select substructures using a SMARTS pattern in Mercury.
- Conduct a Mogul Geometry Check on a substructure of a molecule in Mercury.
- Run Aromatics Analyser on aromatic molecules and assess the importance of aromatic interactions in a structure.

For your reference, you can find the Mercury user manual at this link.

Next Steps

If you have enjoyed this workshop, you might like to explore other workshops on Mogul which you can find in the CSD-Core self-guided workshops page or explore further examples of Aromatics Analyser, which can be found from the CSD-Materials self-guided workshops page. If you would like to learn more about selecting by SMARTS, you can watch this YouTube video.

How to Cite this Tool

Mercury: C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Cryst.*, **53**, 226-235, 2020 DOI: 10.1107/S1600576719014092

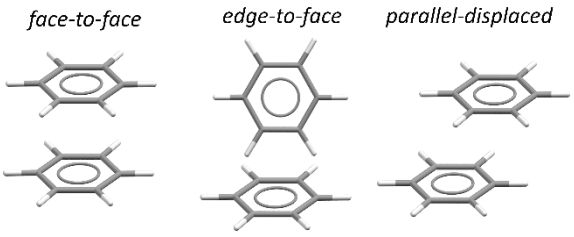
Feedback

We hope this workshop improved your understanding of *[tool name and activity]* and you found it useful for your work. As we aim to continuously improve our training materials, we would love to hear your feedback. Follow the link on the workshop homepage and insert the workshop code, which for this self-guided workshop is *MAT-010*. It will only take 5 minutes and your feedback is anonymous. Thank you!

Glossary

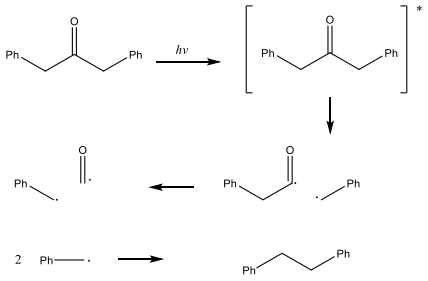
Aromatic interactions

Aromatic interactions are non-covalent forces involving aromatic systems such as benzene. Contributing factors to aromatic interactions include electrostatics, dispersion, induction and charge transfer. Common geometries for aromatic interactions include face-to-face, edge-to-face and parallel-displaced. Face-to-face and parallel-displaced are subsets of the stacking geometry.



Decarbonylation

Decarbonylation is a reaction in which loss of CO occurs. In the case of dibenzylketone, a Norrish Type I α-cleavage of the triplet state can occur, which generates a benzyl and a phenacetyl radical; the phenacetyl radical can subsequently decarbonylate. 1,2-diphenyethane is the major product of this reaction.



Hyperconjugation

Hyperconjugation is the stabilizing interaction that occurs when electrons in a σ (sigma) bond—usually C–H or C–C—delocalize into an adjacent empty or partially filled p-orbital or π-system. In the case of ketones, a C–H or C–C bond from the α-carbon acts as the filled orbital, and the π* orbital of the carbonyl group acts as the vacant orbital.

SMARTS

Smiles ARbitary Target Specification (SMARTS) is a line notation used for describing substructure patterns in molecules. It is an extension of the SMILES notation with logical rules and operations.

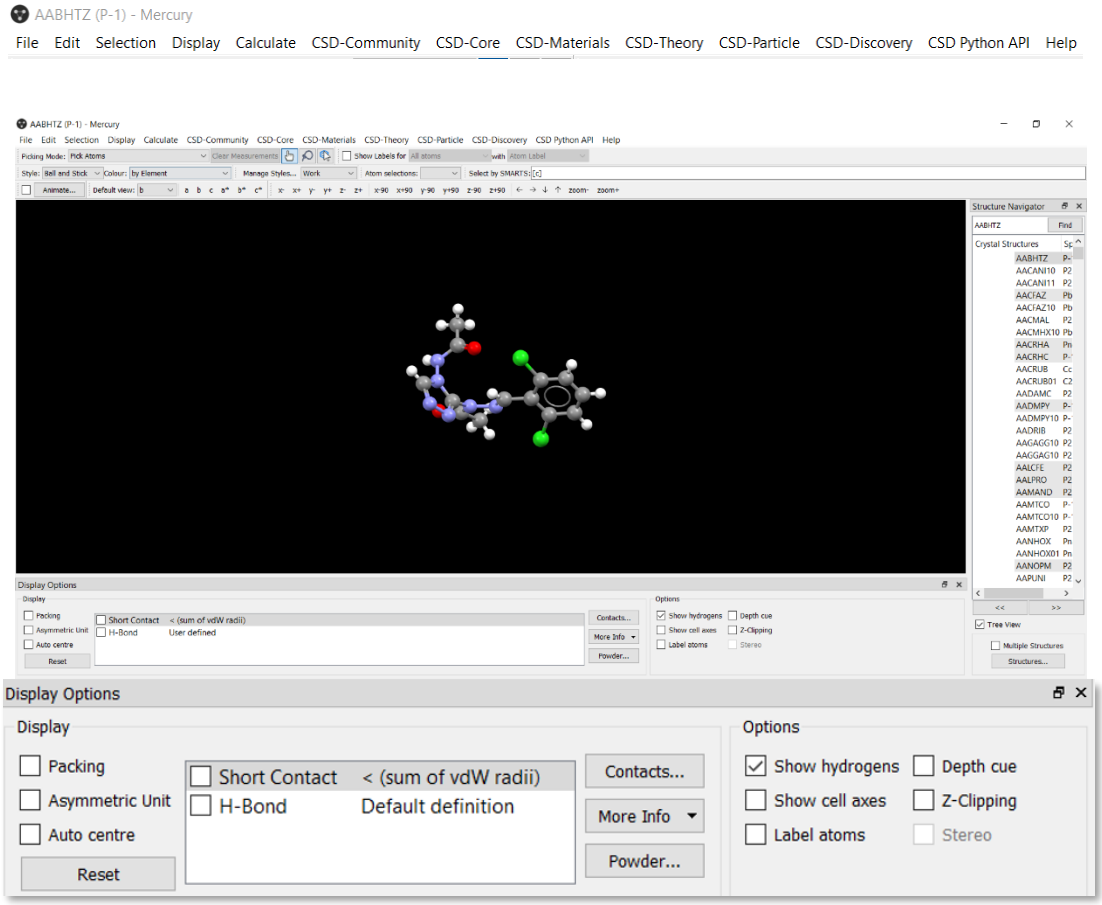
Basics of Mercury Visualization

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. You can also find an extensive range of video resources here.

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.



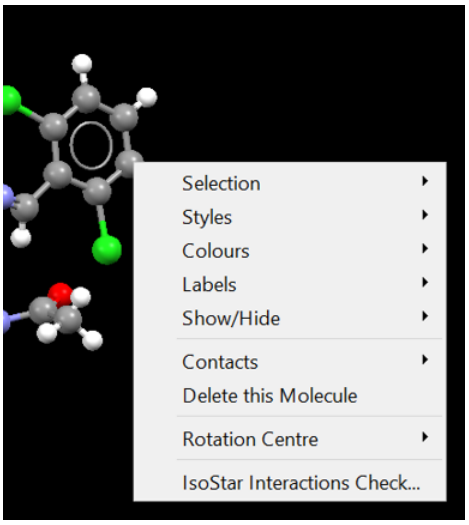
Using the **mouse to enhance visualization**:

- 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

a



b