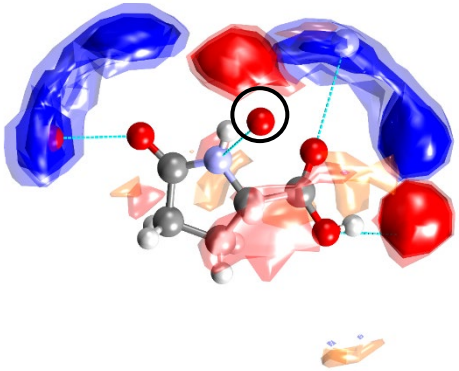
Introduction to Full Interaction Maps (MER-002)

2023.2 CSD Release



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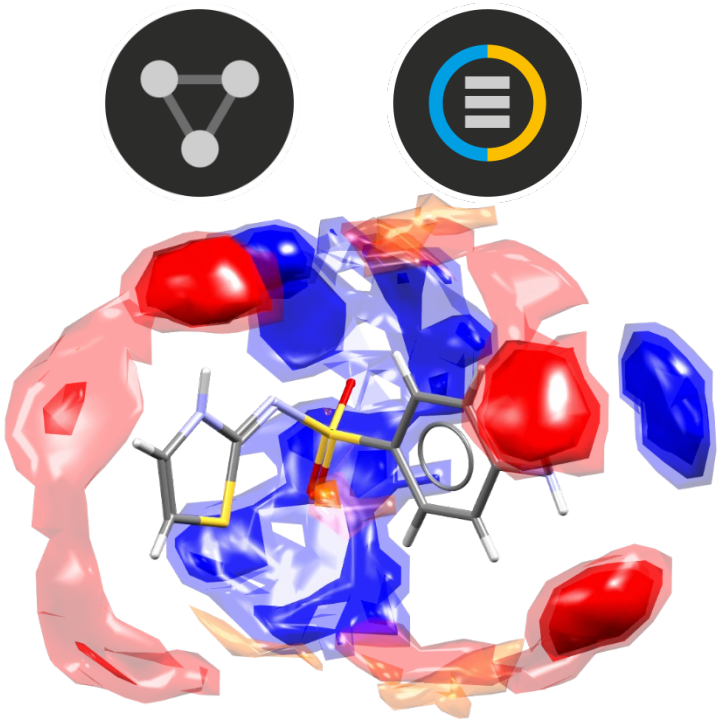
Introduction

The Full Interaction Maps tool will generate a picture of the interaction landscape of your molecule from its three-dimensional coordinates. Using statistical distributions from the hundreds of thousands of structures included in the CSD, we can predict the most likely locations for a variety of functional groups. By comparing this distribution against a 3D packing diagram, we can determine whether a crystal structure fulfills the desired interactions of a particular conformation of a particular molecule. The Full Interaction Maps tool is instrumental in highlighting the potential for polymorphism of a given compound, assisting in the development of co-crystals, and understanding solid form stability.

Before beginning this workshop, ensure that you have installed Mercury, CSD Main Data and CSD IsoStar Data. Full Interactions Maps module can be accessed from both the CSD-Materials and CSD-Discovery menu in Mercury.



Learning Outcomes

In this workshop you will learn about the Full Interaction Maps (FIMs) feature in Mercury, specifically you will learn:

- How to produce Full Interaction Maps (FIMs) and Hotspots
- How to interpret FIMs, particularly to assess hydrogen bonding.
- How FIMs can be used to investigate the differences in the interaction preferences of a molecule when substitutions are made across a series.

This workshop will take approximately 30 minutes to be completed. The Glossary at the end of this handout contains useful terminology for the exercises.

Pre-required Skills

To complete this workshop, you would need to be comfortable with basics of Mercury visualization, including navigating the Mercury interface and interacting with structures. If you are not, we recommend the Structure Visualization Workshop (MER-001), available on this page.

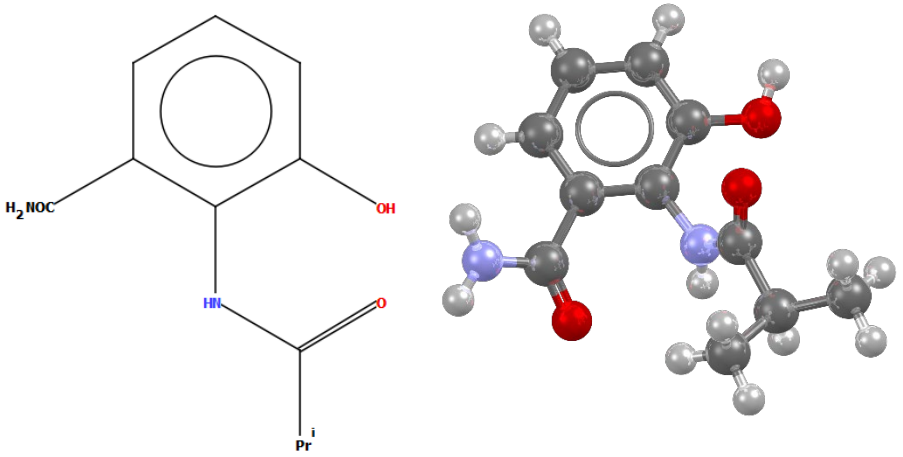
Materials

There are no additional materials required for this workshop.

Example 1. Using Full Interaction Maps to explore crystal structures.

Crystallisation is a process that occurs when a set of molecules comes together to form a condensed array with regular repeating interactions. A fundamental understanding of these interactions is therefore crucial in the analysis, evaluation and prediction of crystal forms. One method for trying to understand molecular interactions is to make use of the contacts observed within experimentally determined crystal structures.[1] This can be achieved using Full Interaction Maps.

In this example, you will learn how to produce a Full Interaction Map for 3-hydroxyl-2-*N*-iso-butyryl-anthranilamide (CSD entry UVEKAI), a compound isolated from mangrove actinomycetes *Streptomyces* sp.,[2] to see how well the predicted interactions for the molecule are fulfilled in the crystal structure.

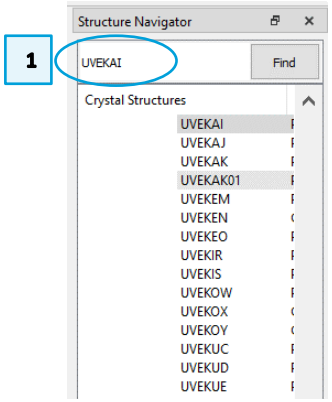


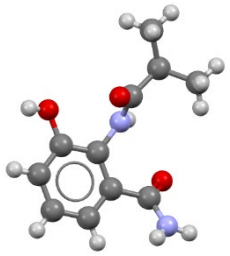
Chemical diagram and molecular structure of 3-hydroxyl-2-N-iso-butyryl-anthranilamide (CSD entry UVEKAI).

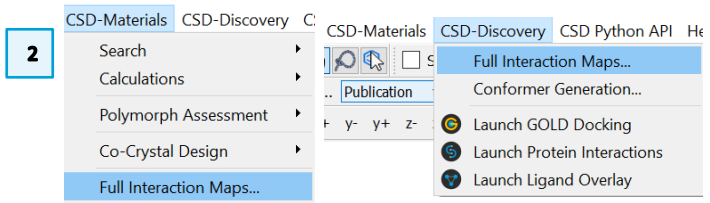
1. Launch Mercury by clicking its icon . In the Structure Navigator toolbar, type "UVEKAI" to bring up the structure of 3-hydroxyl-2-*N*-iso-butyryl-anthranilamide.

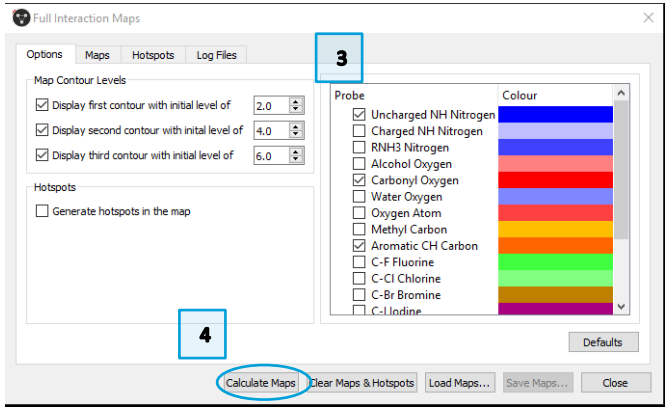
2. Click on the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps…* Note: if the CSD-Materials menu bar is inactive or there is a key icon next to the FIMs feature, you will need to activate the software with a license key that includes the use of CSD-Materials suite.

3. In the *Full Interaction Maps* dialogue box, you will see several options. On the left you will find options to change the display *contour levels*. On the right, you will see a list of functional groups to be used as probes. For the purposes of this tutorial, we will keep the default options. These typically work well for most situations, but if you know you are looking for a specific functional









[1] P. A. Wood, T. D. G. Olsson, J. C. Cole, S. J. Cottrell, N. Feeder, P. T. A. Galek, C. R. Groom and E. Pidcock, *CrystEngComm*, 2012, **15**, 65 –72.

[2] G. Chen, H. Gao, J. Tang, Y. Huang, Y. Chen, Y. Wang, H. Zhao, H. Lin, Q. Xie, K. Hong, J. Li and X. Yao, *Chem. Pharm. Bull.*, 2011, 59, 447 – 451.

group, or if you want to change the look of the map, you will want to change these settings.

4. Click the **Calculate Maps** button to start.

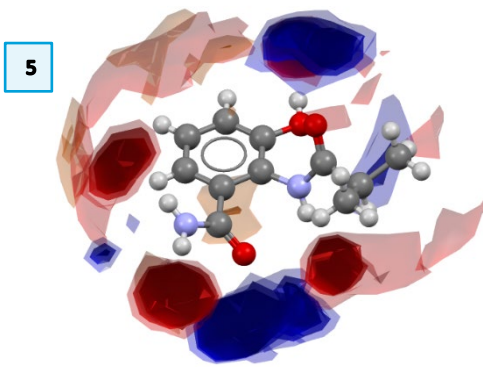
5. The generated map will now be displayed in the main Mercury window. Notice the three different colours in the map. Red regions of the map denote areas in which there is a high probability of locating a *hydrogen bond* acceptor. Blue regions denote hydrogen bond donors, and brown areas indicate hydrophobic regions.

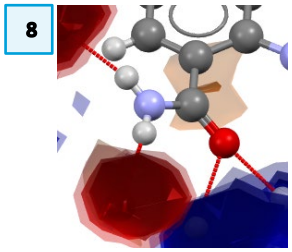
6. Now we want to see how the overall packing of this structure fits with the Full Interaction Map we have generated. Tick the box for **H-Bond** in the Display Options toolbar.

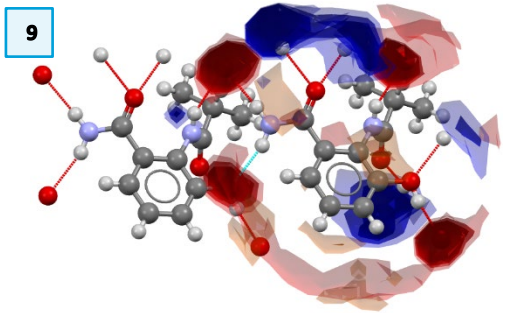
7. Double click the *H-Bond* line to launch the *Define H-bonds* dialogue. In this dialogue, tick the box for **Require hydrogen atom to be present**. Click **OK** to apply the change.

8. Now you will see dashed red lines in the Mercury window that indicate where hydrogen bonding interactions/contacts are present.

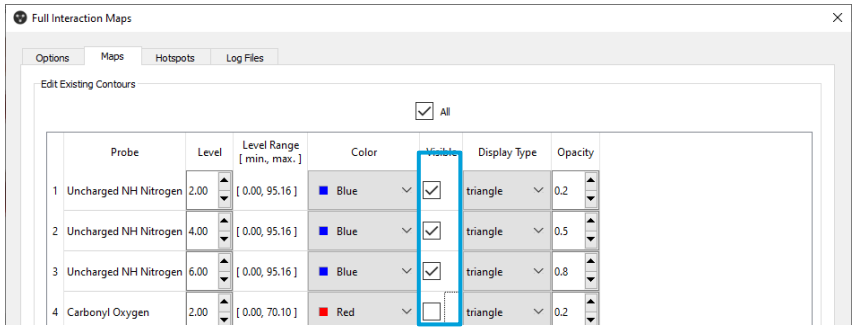
9. Click on these contacts to generate nearby molecules. You will see that the interactions generally fall within the contour range for the expected type. Note: for the N-H nitrogen probe, it is the nitrogen atom that should fall within the blue region. It is often found that the blue regions are less well satisifed than the red regions, in general.



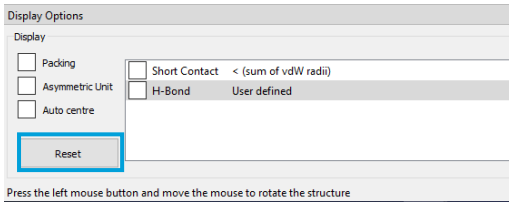


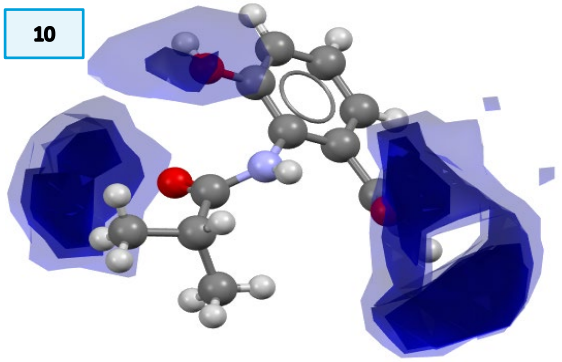


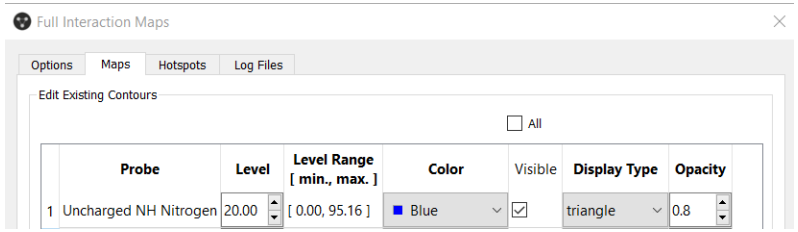
10. You can customise the display to show interaction types individually. First, click **Reset** in **Display Options**. Then, click the **Maps** tab of the Full Interaction Maps window. Next to each probe you will see various display options. In the *Visible* column, untick all except the three in the *Uncharged NH Nitrogen* rows (rows 1-3)

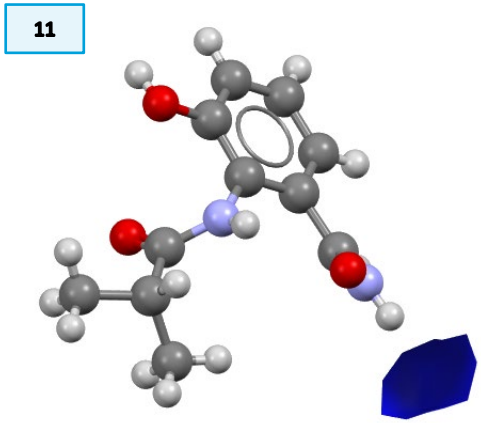


11. Untick all except row *1* in the *Visible* column of the Maps table. You should see the dense blue regions disappear. The *Levels Range [min., max.]* indicates the range of values for the probability of an interaction above random; the *Level* controls the probability value of the surface plotted. Change the *Level* to 20 and the *Opacity* to 0.8. Notice how the surface only encloses a small region, next to one carbonyl oxygen.









Calculate Hotspots

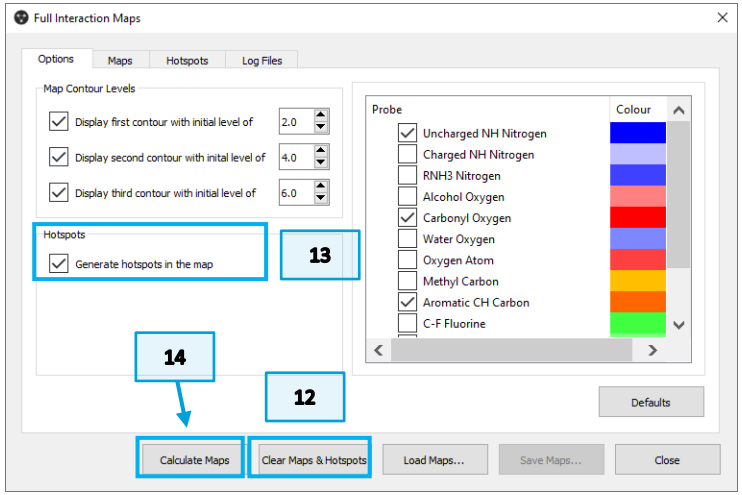
Hotspots indicate the points of highest local interaction density found for each contour surface and can be calculated together with Full Interaction Maps concurrently.

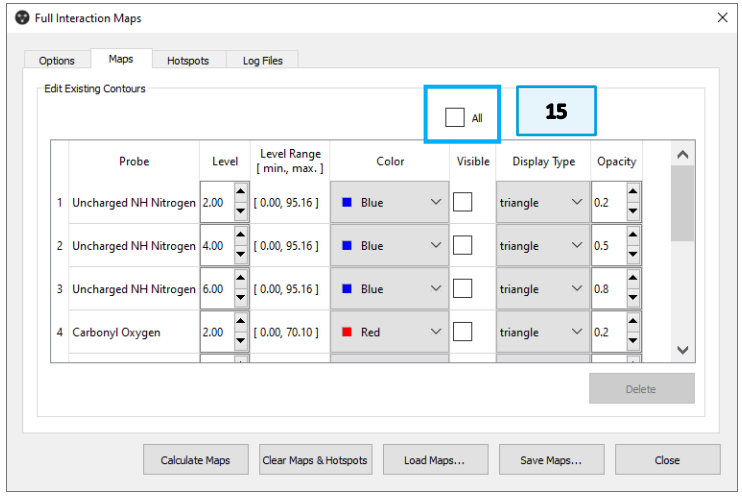
12. Click **Clear Maps & Hotspots** in the **Options** tab of the **Full Interaction Maps** window.

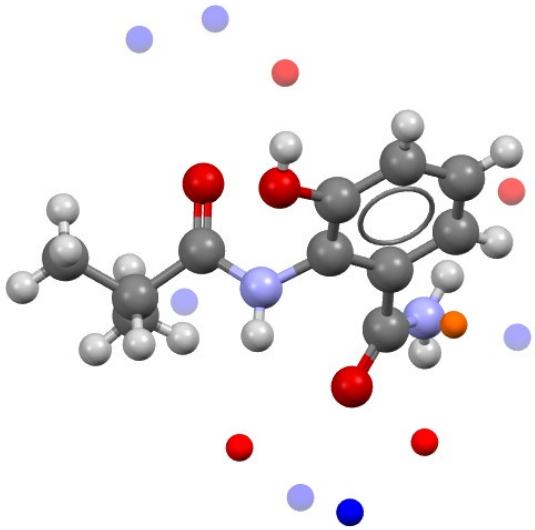
13. In the Options tab, tick **Generate hotspots in the map**.

14. Click **Calculate Maps**.

15. The result should look very similar to the previously generated maps. To see the hotspots, click on the **Maps** tab and untick the **All** box above the *Visible* column of the table. The result should look as shown below. The opacity relates to the propensity; less opaque means a smaller local propensity maximum. If you wish, you can customise the display from the **Hotspots** tab, however, we will keep the default settings.







16. Tick **H-bond** in **Display Options** and expand the contacts to see how well satisfied the predicted interactions are.

17. Press **Reset** in **Display options** and in the **Hotpots** tab of the **Full Interaction Maps window**, click **Convert Hotspots To Dummy Atoms**. This will convert the hotspots into objects that can be used in calculation and measurements in Mercury.

18. In the top toolbar, tick **Show Labels** for *All atoms* with *Atom Label*. The hotpots, together with the probe type and propensity value are given in the labels.

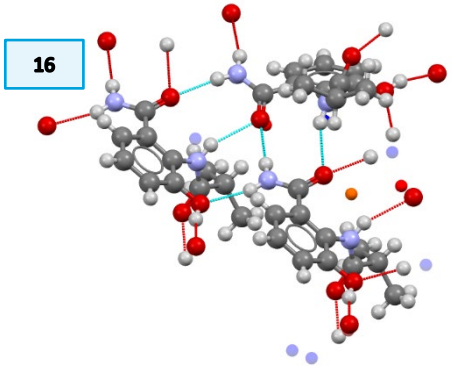
Conclusions

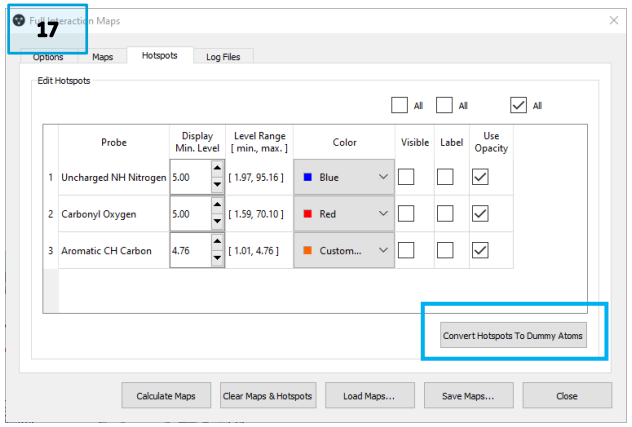
In this example we have studied the Full Interaction Maps for a benzamide crystal structure. The results have shown that all predicted hydrogen bonding interactions are fulfilled to a good degree in this structure, suggesting a favourable crystal packing arrangement. We have also seen how Hotpots can produce a simplified picture and be used to generate object for further analysis.

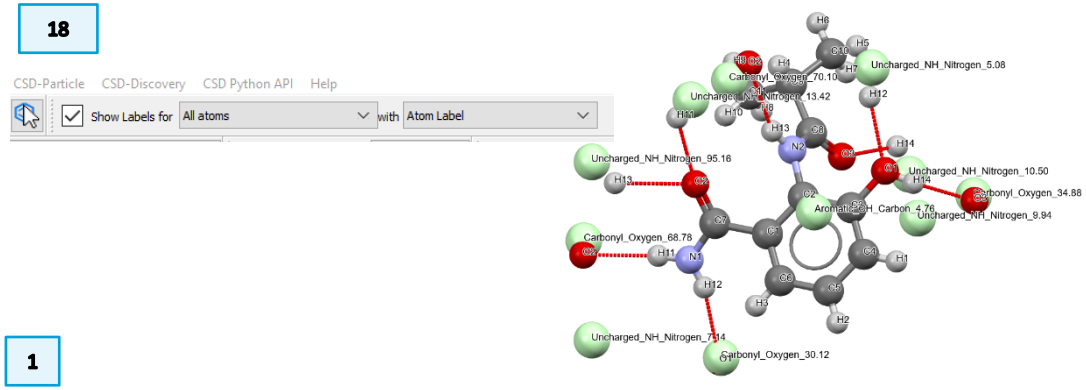
Exercises

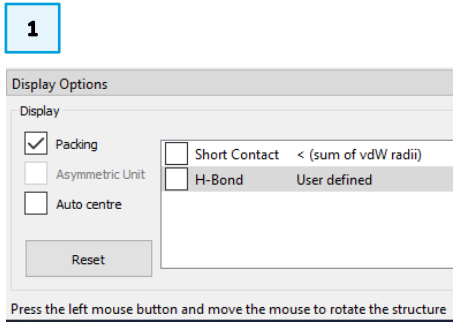
1. Customise the FIMs, as in steps 10 – 11, but this time explore the contours for the aromatic C-H probe. Are potential hydrophobic interactions fulfilled? **Hint: you will need to turn on Packing in the Display Options toolbar.**

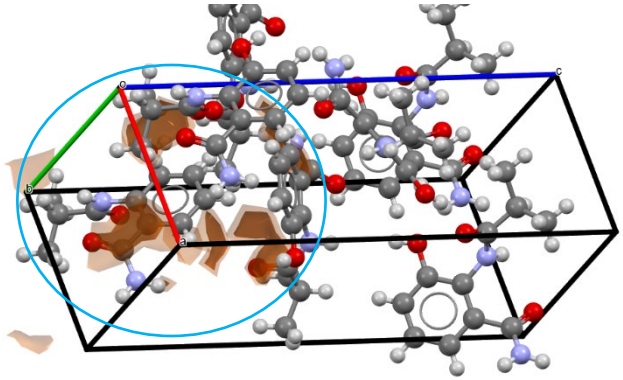
2. Following on from steps 17 – 18, turn on H-bonds and measure the distance H11···Carbonyl_Oxygen_68.78. How does the predicted distance compare with the actual distance observed in the crystal structure?

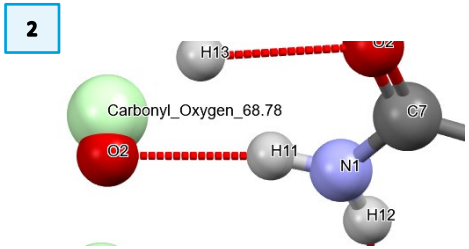






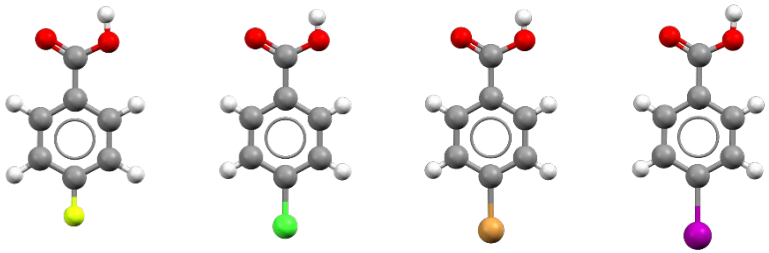






Example 2. Investigating a series of halogenated molecules.

When designing molecules to fit a specific purpose, chemists will often make subtle changes to a single functional group; for example, replacing fluorine with chlorine, bromine or iodine. We can use Full Interaction Maps to investigate the differences in the interaction preferences of a molecule when these substitutions are made across a series.



A series of halogenated benzoic acids

This example will look at the series of halogenated benzoic acids to compare what differences there are across the series.

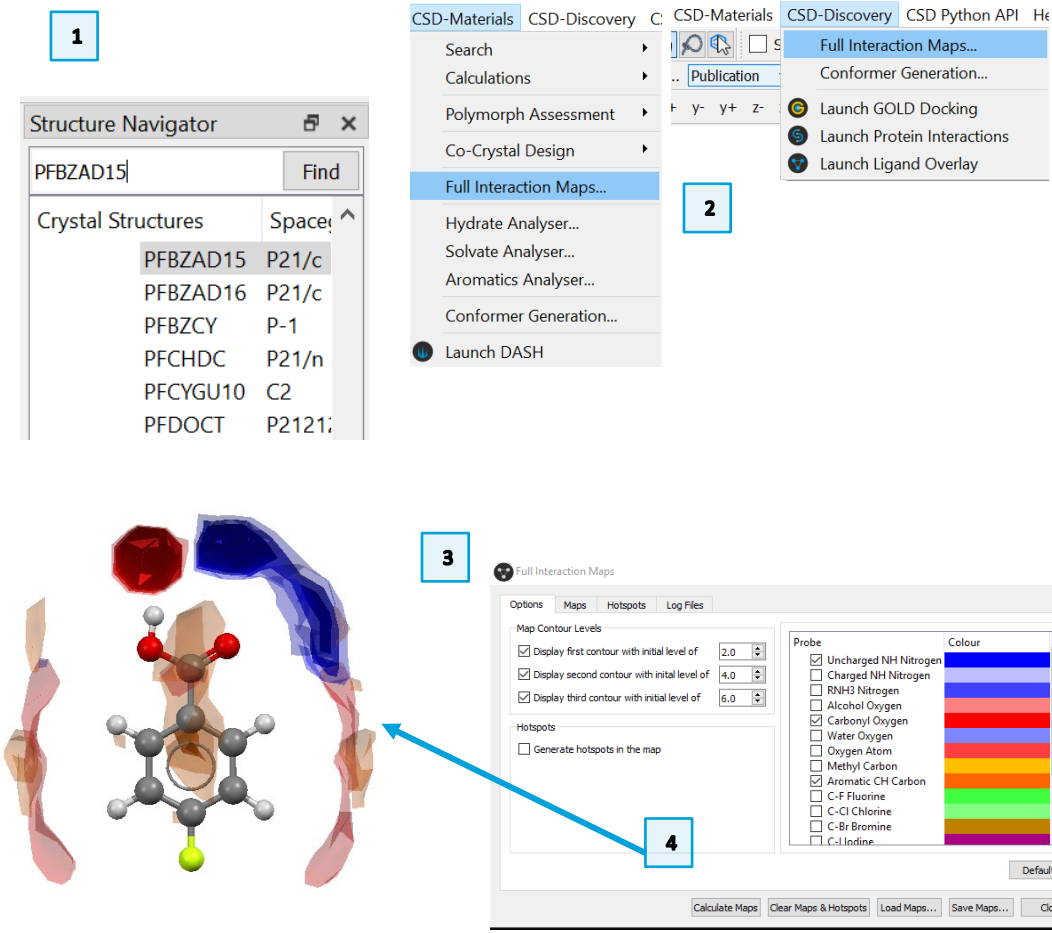
1. Launch Mercury and type PFBZAD15 in the Structure Navigator tool bar to bring up one of the parafluorobenzoic acid entries.

2. Click the *CSD-Materials* menu or *CSD-Discovery* menu and choose *Full Interaction Maps…* from the drop-down menu.

3. We will again use the default settings.

4. Click **Calculate Maps** to generate the Full Interaction Map for parafluorobenzoic acid.

5. Repeat steps 1-4 for the other molecules in this series. Open a new instance of Mercury each time so you can easily compare the results. Use refcodes CLBZAP10 for the Cl analogue, BRBZAP01 for the Br analogue, and BENMOW07 for the I analogue. These particular entries were chosen because they are relatively recent crystal structure determinations at low temperatures. To open multiple Mercury windows on a Mac, open a terminal window and run this command:
   open -n -a "/Applications/CCDC/ccdc-software/mercury/mercury.app"
   This command tells the system to open a new instance (the "`-n`" flag) of an application (the "`-a`" flag) that is the given name in quotes.



6. Now let's compare the maps for each molecule in the series.

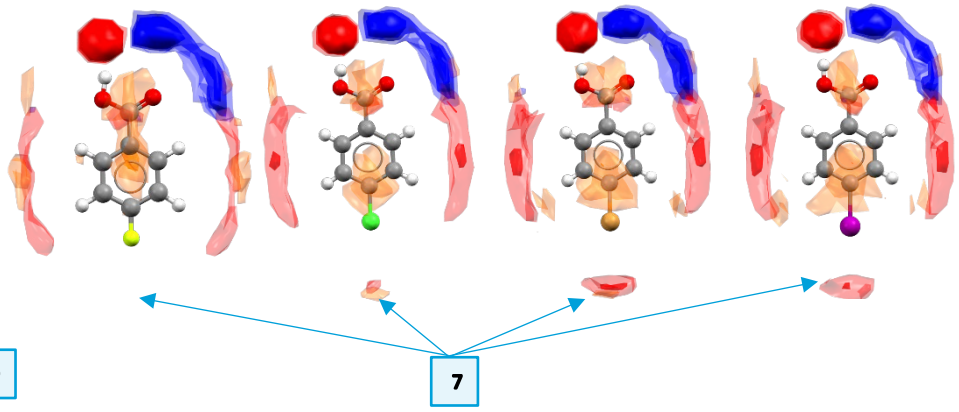
7. Look at the maps generated across the series. You should notice that as the size of the halogen increases across the series, there is an increased likelihood of finding an acceptor interacting with the halogen. This interaction is non-existent for the fluoro species, but fairly well-defined for the bromo and iodo analogues.

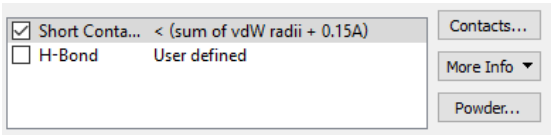
8. Now we will investigate how this affects the packing in each crystal structure.

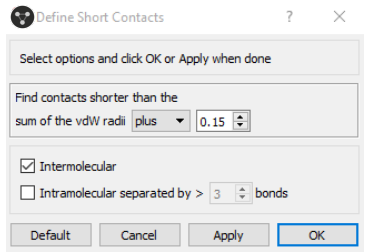
9. Start with the iodo analogue (BENWOM07). In the Display Options make sure the Short Contact settings are for "sum of vdW radii **plus** 0.15Å". If not, double click that line to open the Define Short Contacts dialog and change the settings. Click **OK** to accept these changes. Then tick the box to display Short Contacts.

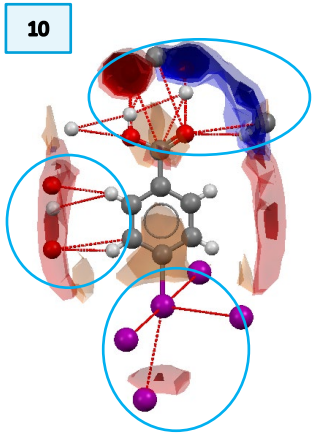
10. With the short contacts displayed, you should see that most of the interactions are satisfied. The two high-probability donor and acceptor sites near the carboxylic acid group are satisfied, as are the weaker acceptor sites near the aromatic hydrogen atoms on the phenyl ring. The iodine from a neighbouring molecule serves as the acceptor for a halogen-halogen interaction.

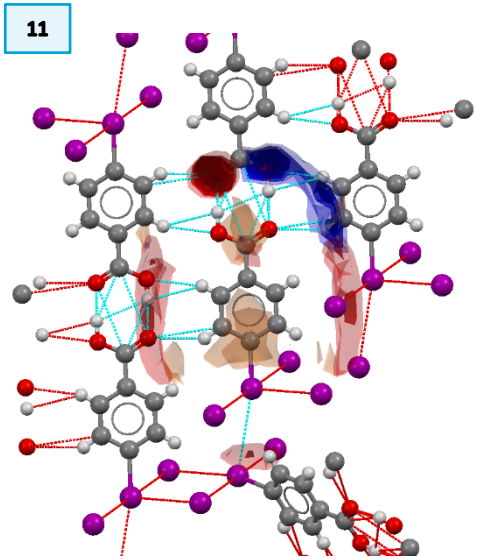
11. Click the interactions highlighted in Figure 10 to expand these neighbouring molecules. You will notice that while the acceptor (red) contours on either side of the phenyl ring are roughly equivalent, only one region is satisfied well by an interaction. Iodine atoms from neighboring molecules fill this region on the opposite side.











12. Repeat steps 9-11 for the Br (BRBZAP01) and Cl (CLBZAP10) analogues. What similarities and differences do you see across the series so far? What do you expect to see for the fluoro analogue?

13. For the fluoro analogue, follow step 9 to generate the short contacts.

14. You will see that the interactions for the carboxylic acid group and for the two weak C-H donors on the phenyl ring are satisfied. However, there is no probability of an acceptor for the fluorine, and consequently there is only C and H in this region.

15. Click these contacts to expand the neighbouring molecules. Now you can see that there is no halogen-halogen interaction involving the fluorine.

Conclusions

It is well understood that iodine forms halogen-halogen interactions more so than the other halogen atoms. Using Full Interaction Maps, we can clearly see how the probability of these interactions affects the overall packing in a crystal structure.

Exercises

- Try calculating Full Interaction Maps using only the C-F and C-Cl probes. Do the results match your expectations?
- Investigate the hydrophobic interactions among the halogenated benzoic acid molecules in this series.
- Try looking at ortho- or meta- substituted halogenated benzoic acid species. Do your results match your expectations?
- Use Full interaction maps for a crystal that exhibits jumping properties, L-pyroglutamic acid, before (LPYGLU07) and after a phase transition (LPYGLU08). What do you observe for the phase transition structure?
- Run a Full Interaction Maps calculation on your own molecules.

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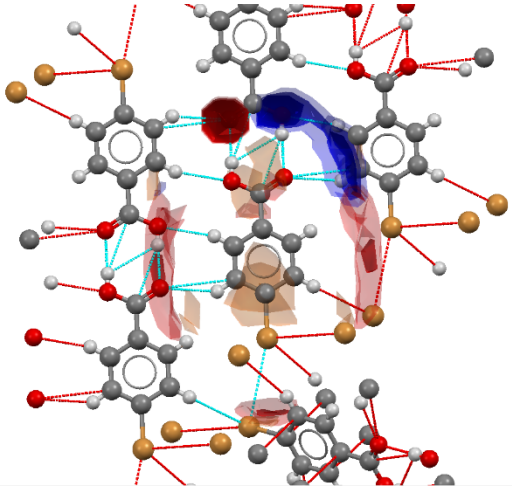

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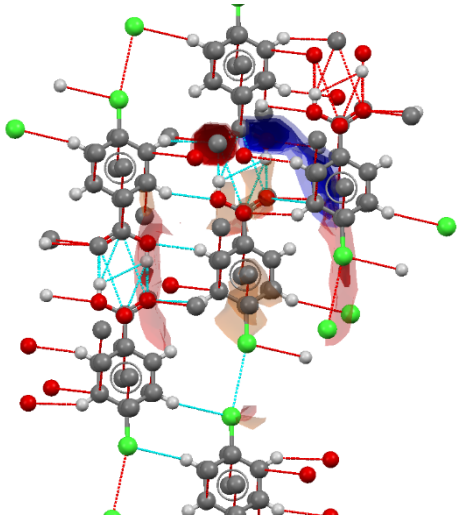

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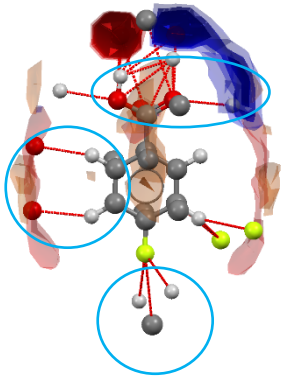

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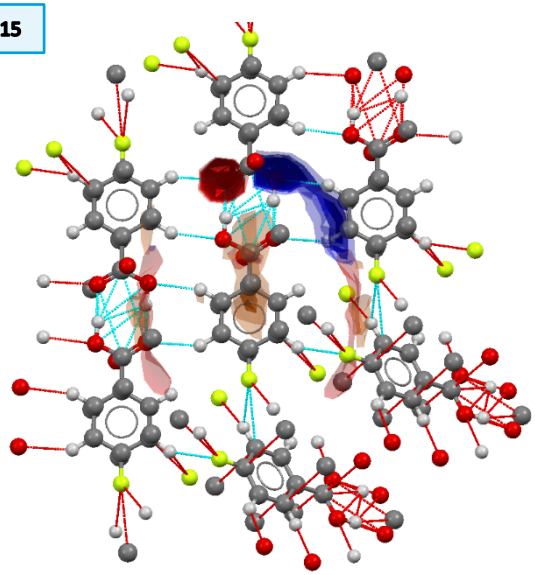


Summary

After this workshop you should now be able to:

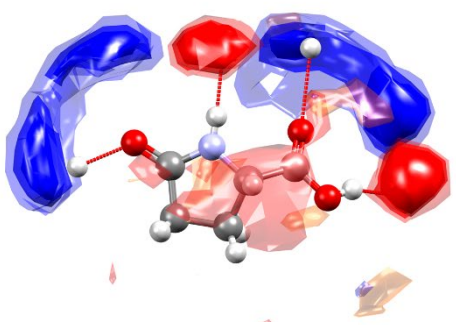
- Produce Full Interaction Maps (FIMs) for a given molecule and interpret the results.
- Explore and assess the hydrogen bonding interactions in a crystal structure in relation to the interaction landscape predicted by FIMs.
- Generate interaction hotspots and dummy atoms to complement FIMs.
- Use FIMs to investigate the differences in the interaction preferences of a molecule when substitutions are made across a series.

Next Steps

After this workshop, you can explore more exercises in the self-guided workshops available from the CSD-Materials workshops area and the CSD-Discovery workshops area on our website. If you are interested in CSD-Materials, we suggest trying the Hydrogen Bond Propensity workshop, which presents complementary tools to the Full Interaction Maps in assessing solid forms.
https://www.ccdc.cam.ac.uk/Community/educationalresources/workshop-materials/

Feedback

We hope this workshop improved your understanding of *Full Interaction Maps* and you found it useful for your work. As we aim to continuously improve our training materials, we would love to hear your feedback. Click on this link to a survey (link also available from workshops webpage), it will take less than 5 minutes to complete. The feedback is anonymous. You will be asked to insert the workshop code, which for this self-guided workshop is MER-002. Thank you!



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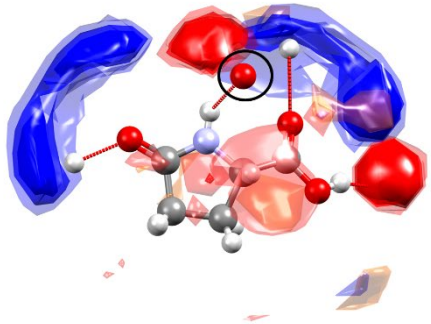

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Glossary

Contour level
The number of times more than random an interaction is likely to occur in a specific region of space.

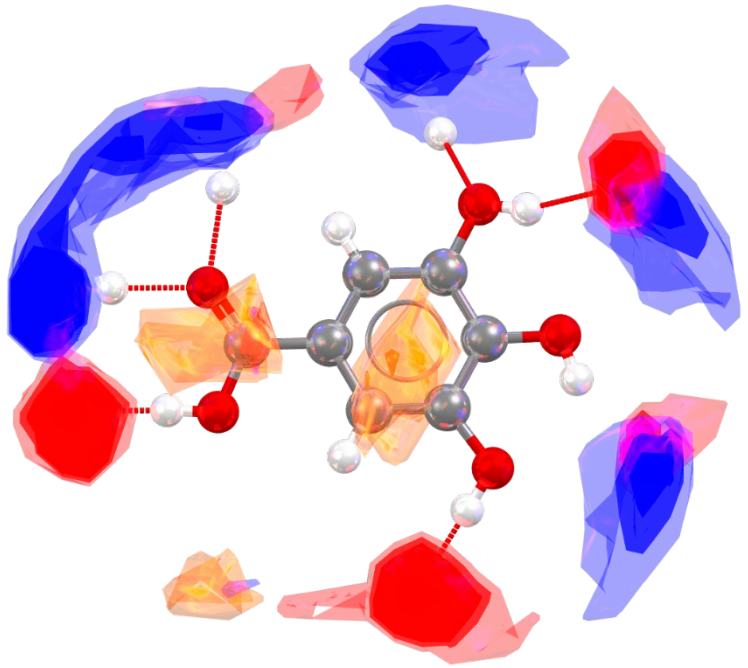
Hotspots
Hotspots represent the positions of highest local density for each contour Surface.

Van der Waals, Aromatic and Hydrogen Bond Interactions

Van der Waals forces are formed between atoms or molecules that are in each other's close proximity and are driven by induced electrical interaction. They are the weakest of all type of intermolecular attractions between molecules. However, with a lot of Van der Waals forces interacting between two molecules, the interaction can be very strong.

Aromatic Interactions are noncovalent interactions formed between aromatic rings. These interactions are important in material science since they will contribute to the overall crystal structure stability. The orientation of the aromatic ring can vary from parallel to T-shape, and we found during our DFT calculations that the T-shape interactions are very close in strength to the parallel displaced ones. Their strength is found between 0 and 16 kJ/mol based on DFT calculations.

Hydrogen Bonding occurs between donor-acceptor interactions precisely involving hydrogen atoms. The H-bonds interactions are classified as: strong (mostly covalent), moderate (mostly electrostatic) and weak (electrostatic).
Their strength is observed to be between 12 and 30 kJ/mol.



Interaction type	*Strength (kJ/mol)*
Van der Waals	**0.4-4.0**
Aromatics	**0-16**
Hydrogen Bonds	**12-30**