Full Interaction Maps

2020.3 CSD Release

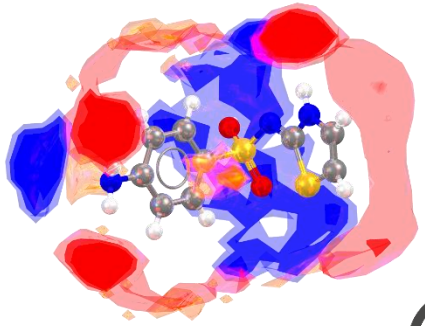

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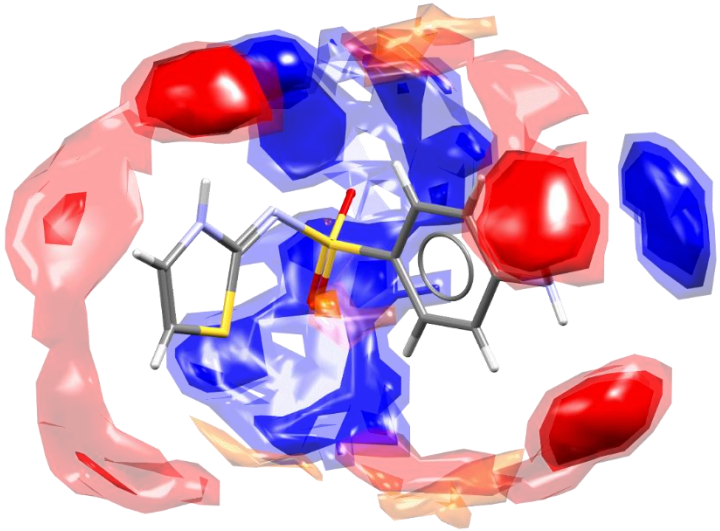
Table of Contents

Introduction

This tutorial will introduce you to the Full Interaction Maps feature included with Mercury under the CSD-Materials/CSD-Discovery toolsets.

The Full Interaction Maps tool generates a picture of the interaction landscape of your molecule from its three-dimensional coordinates. Using statistical distributions from the million 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, understanding solid form stability, and even assisting in the development of co-crystals.



Objectives

In this workshop you will:

- Learn how to produce Full Interaction Maps (FIMs) for a given molecule and how to interpret the results.
- See how the FIMs analysis can be used for co-crystal design.
- See how FIMs can be used to investigate the differences in the interaction preferences of a molecule when substitutions are made across a series.

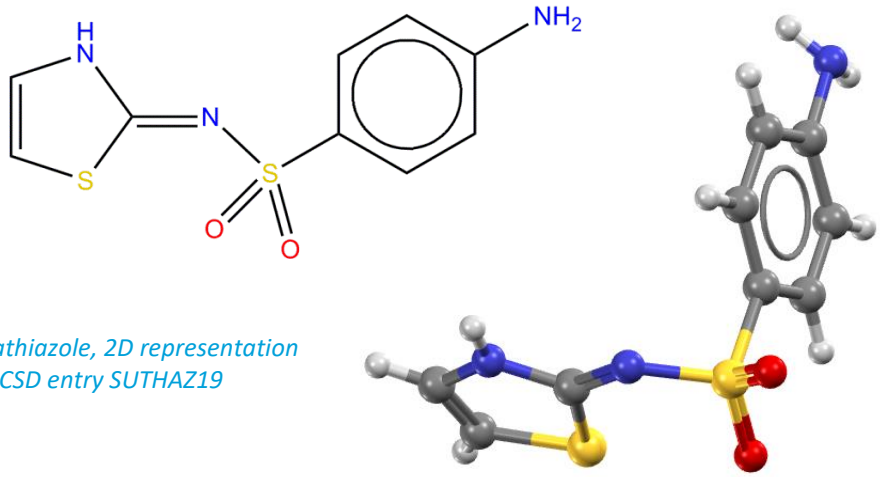
This workshop will take approximately ***30 minutes*** to be completed. If you finish early, you can try the bonus exercises, explore FIMs for other structures, or ask the tutors for more examples.

Pre-required skills

The following exercises assume you have a working knowledge of the program Mercury, namely, how to display and manipulate structures from a 3D coordinates file.

Example 1. Using Full Interaction Maps to assess polymorph stability

The stability of a given crystal structure is a balance between the intramolecular conformation and the intermolecular packing of the molecules in the crystalline state. One method for understanding the relative stability of crystal structures is to compare the observed intermolecular interactions with preferred geometries for that type of interaction.



Sulfathiazole, 2D representation and CSD entry SUTHAZ19

This example will look at two known polymorphs of sulfathiazole to answer the question: **How do the interactions in each polymorph compare with what is expected?** You will learn how to produce a Full Interaction Map for a given structure and how to interpret this map.

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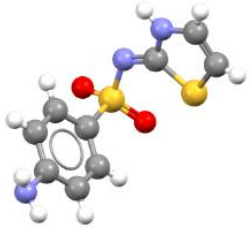
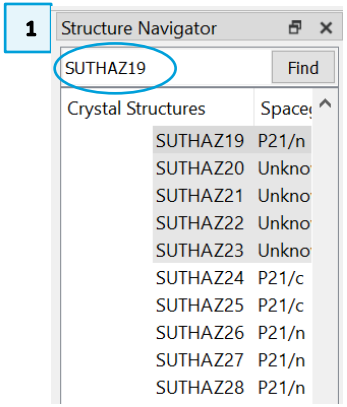
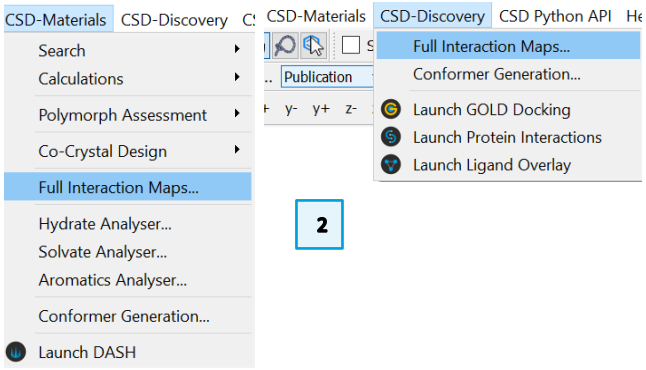
1. Launch Mercury by clicking its icon . In the Structure Navigator toolbar, type SUTHAZ19 to bring up the structure for the Form V polymorph of sulfathiazole.



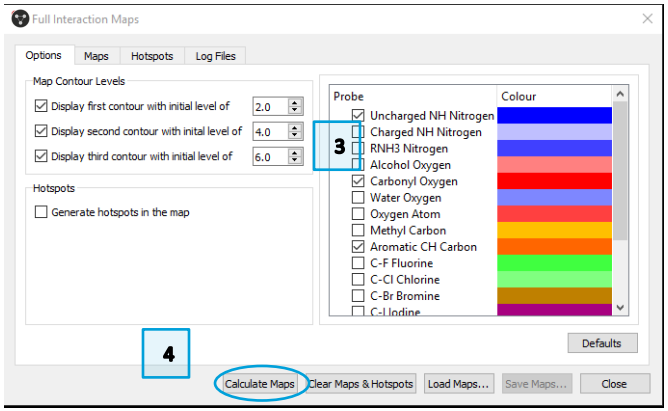


2. Click on the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps…* Note: If the CSD-Materials menu bar is inactive, click on "Help" and "Activate CSD-Materials" before proceeding further.



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 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 regions indicate hydrophobic preferences. It can be easier to view FIMS with a white background. To change the background colour, right click in an empty space on the visualiser, select “Display Options” and set the Background to a single colour of white.

6. Now we want to see how the overall packing of this polymorph 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.

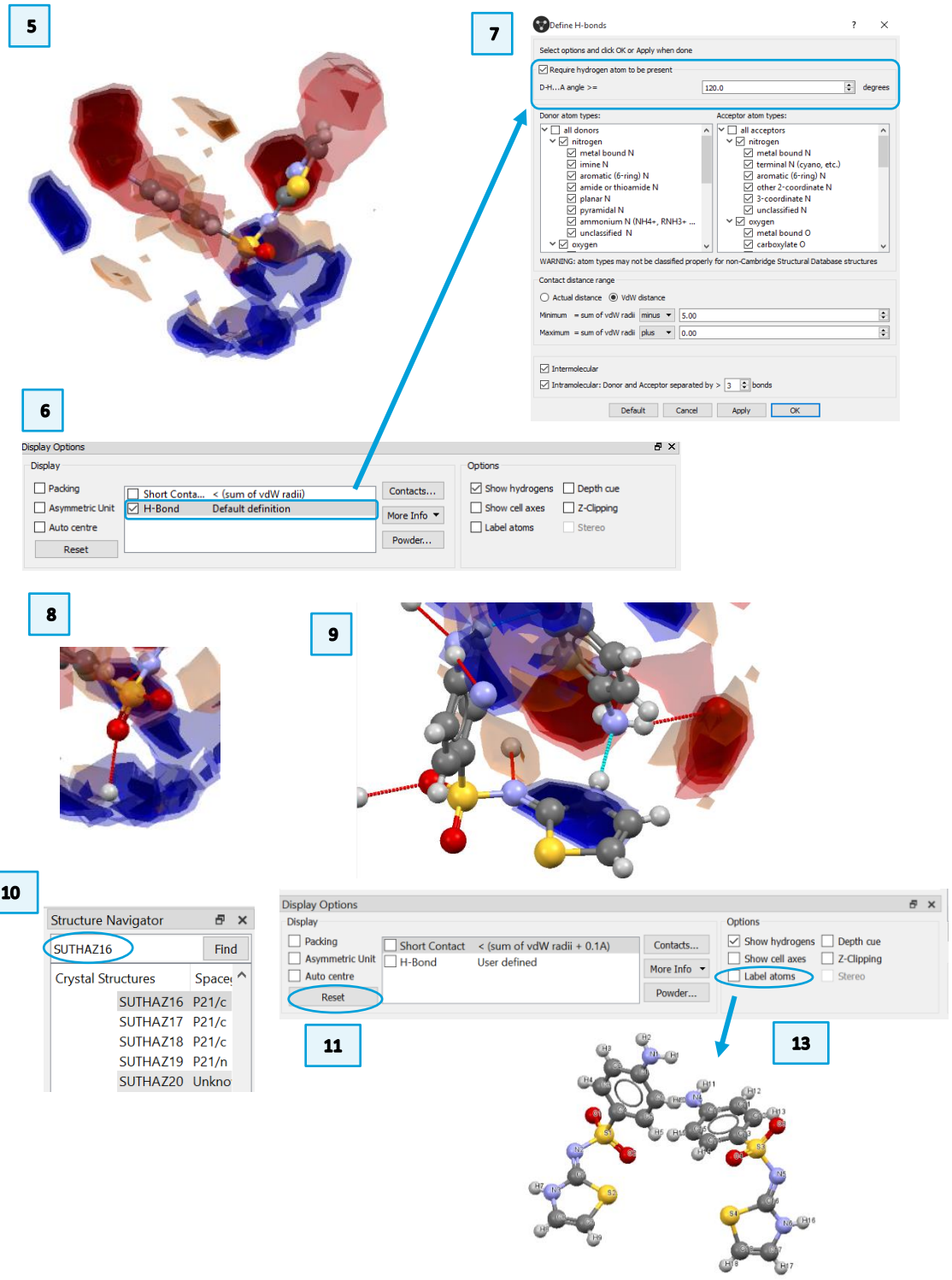
8. Now you will see dashed red lines in the Mercury window that indicate where hydrogen bonding interactions/contacts are present.

9. Click on these contacts to generate nearby molecules. You will see that in each case, the interaction falls within the contour range for the expected type. This indicates that the packing of Form V satisfies the expected interaction landscape of this conformation of sulfathiazole.

10. Now let’s look at the Form I polymorph. In the Structure Navigator toolbar, type SUTHAZ16 to load this structure.

11. Click the **Reset** button in the Display Options toolbar to remove all the hydrogen bonding interactions.

12. Note that Z’ = 2 for Form I; meaning there are two unique molecules in the asymmetric unit. We will focus on one unique molecule in the Form I structure.



13. Tick the box to Label atoms in the Display Options toolbar. Locate which molecule contains N1. This is the molecule we will focus on. Once you have located it, remember which one it is, but untick the Label atoms box to keep the display clean.

14. Right-click on the molecule that contains N1 then go to "Selection > Select Molecule". This will select the entire molecule. Alternatively, hold the Shift key and click the molecule that contains N1.

15. If the *Full Interaction Maps* dialogue is still open, simply click **Calculate Maps** again. Otherwise, follow steps 2-4 to re-open the dialogue.

16. You should now have a Full Interaction Map surrounding molecule 1.

17. Following **Steps 6-9** above, turn on the hydrogen bonding interactions and click to expand the interaction around the N1 atom.

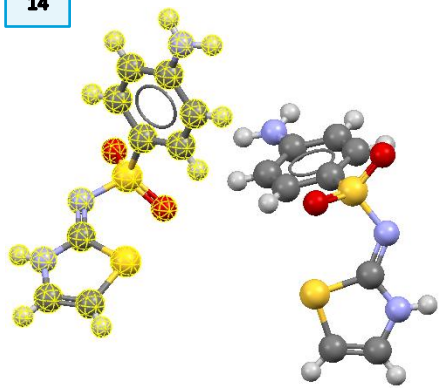
18. Notice that one of the three interactions (N1-H2…O2) falls well outside the predicted region for a hydrogen bond acceptor. This suggests that this interaction has a non-ideal geometry and is likely to be significantly less stabilising than the interactions in Form V.

Conclusions

The observed polymorphs of sulfathiazole exhibit different interactions, but also noticeably different geometries for those interactions. We can use knowledge-based approaches to compare the observed intermolecular interactions in two polymorphs with the preferred geometries for these interaction types. Full Interaction Maps indicate that Form V (known to be the most stable of the sulfathiazole polymorphs) has interactions which are near to ideal, whereas Form I (known to be metastable) has non-ideal interactions.

You should now know how to generate a Full Interaction Map of a molecule through Mercury and how to explore hydrogen bonding interactions in a crystal structure in relation to the predicted interaction landscape.

14



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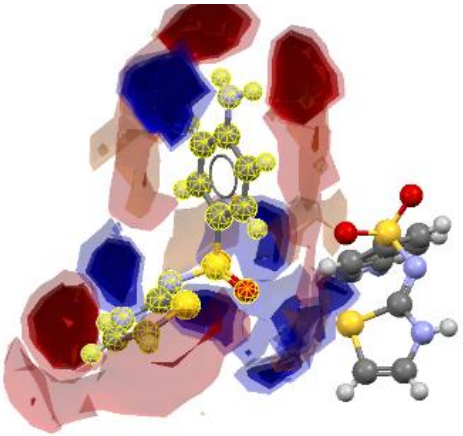

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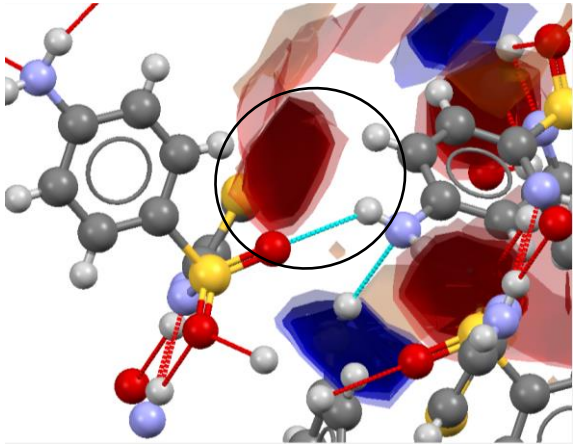
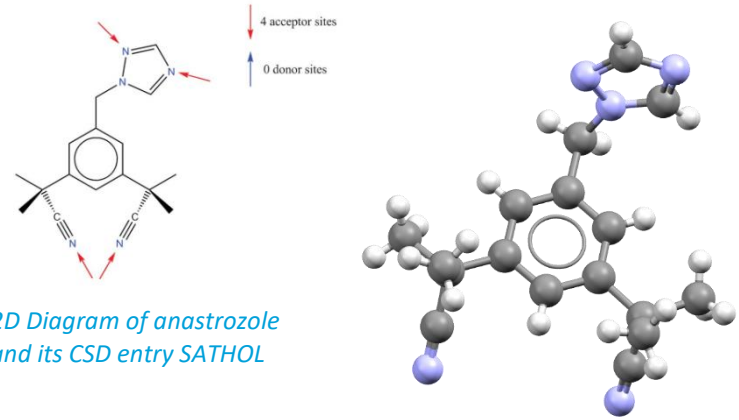


Example 2. Investigating the potential for co-crystallisation

For this tutorial, we will investigate the molecule anastrozole. This compound is a non-steroidal aromatase inhibitor used to treat breast cancer. The only published crystal structure is of the pure form. The molecule also contains no conventional hydrogen bond donors.

In this example, you will generate a Full Interaction Map for this molecule and investigate the interaction landscape. You will see how this information can be used to design a co-crystal.



2D Diagram of anastrozole and its CSD entry SATHOL

1. In the Mercury window, type SATHOL in the Structure Navigator toolbar to load the structure of anastrozole.

2. Click the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps…* from the dropdown menu.

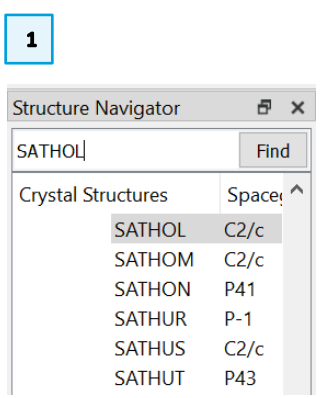
3. Keep the default settings.

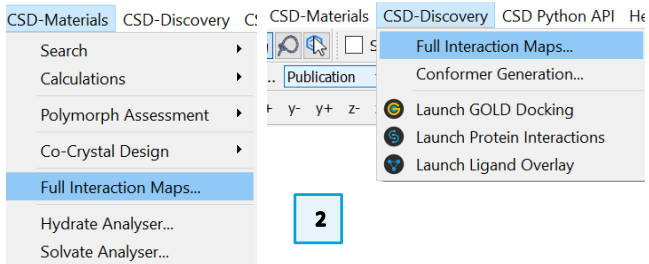
4. Click **Calculate Maps** to generate the Full Interaction Map for SATHOL.

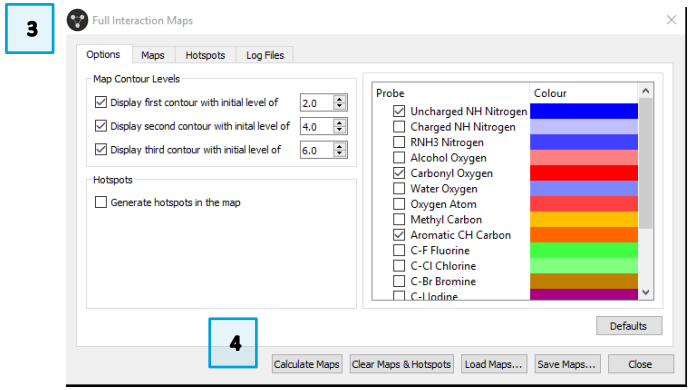
5. The resulting map shows several areas for hydrogen bond donors (blue regions); two high-probability areas near the nitrogen atoms of the triazole ring, and two slightly lower probability regions near the cyano groups.

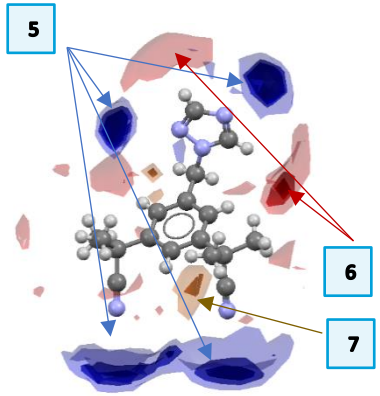
6. While there are no true hydrogen bond donors in this structure, the C-H groups in the triazole ring could interact with possible hydrogen bond acceptors (red regions).

7. There is also a small brown region indicating the possibility for a hydrophobic or π—π interaction.









8. As there are no conventional hydrogen-bond donors in this structure, there will be nothing to display by ticking the H-Bond box in the Display Options toolbar. Instead, tick the Short Contact box.

9. Double click this bar to open the *Define Short Contacts* dialogue box. Change this so that we find contacts shorter than the sum of the vdW radii **plus** 0.15Å. Click **OK** to save your changes.

10. Let's first look at the region around the triazole ring. We can see that there are two C-H donors that will satisfy the interaction preferences of the two N acceptors in the triazole ring. Click on the two contacts (dashed red lines) to generate the neighbouring molecules.

11. Looking at the region around the cyano groups, there are some short contacts available for interactions, but these are not directed toward the high-probability areas.

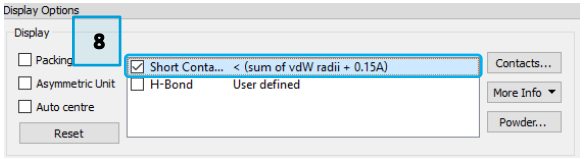
12. From the acceptor probe maps (red contours), we can see that the main region of acceptor preference is only weakly satisfied by the cyano group from one molecule and the triazole ring from another. Click the contacts to expand nearby molecules. The other acceptor regions are not satisfied at all.

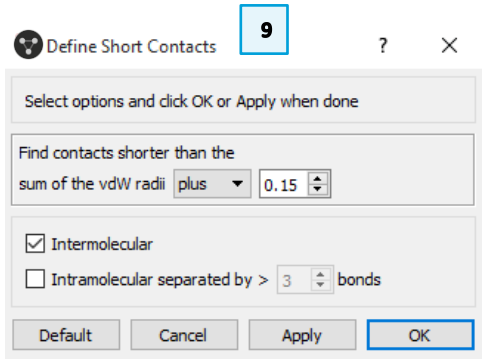
13. Finally, there is a weak π—π interaction between the two phenyl rings that matches with one of the hydrophobic regions.

Conclusions

The Full Interaction Maps for SATHOL show that the highest probability regions for interactions, the donor regions for the triazole N atoms, are quite nicely satisfied. However, this comes at the cost of satisfying the interactions that would fulfill the acceptor sites. Since anastrozole has no classical H-bond donors of its own to fulfill those interactions, a molecule with one or more H-bond donors would be a good choice for a potential co-crystallisation agent.

There are no co-crystals or solvates of anastrozole yet found in the CSD.





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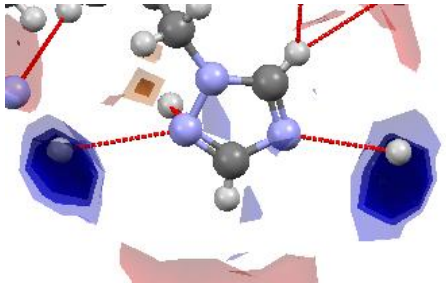

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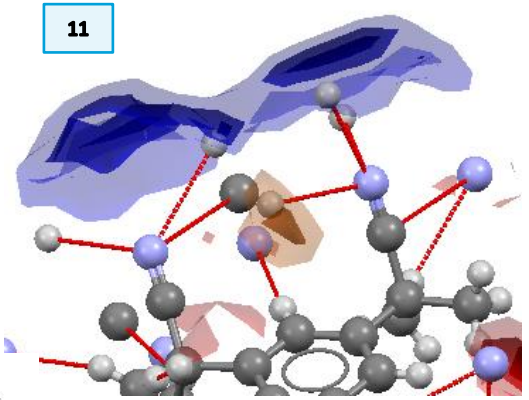

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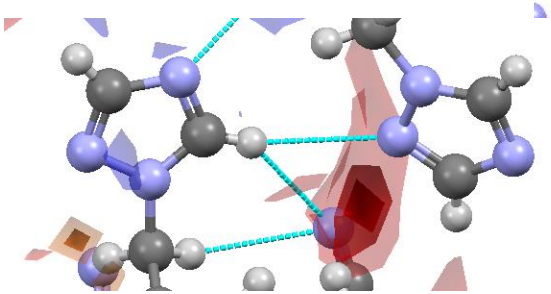

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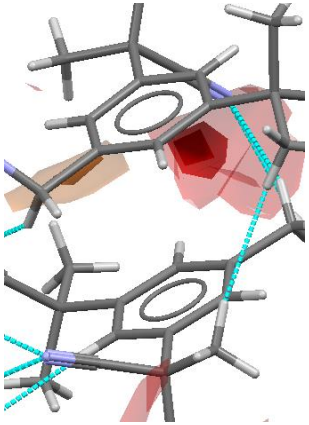
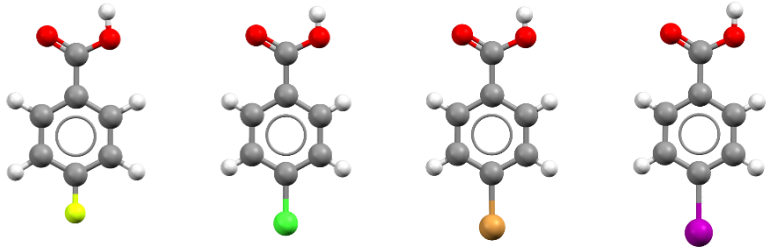


Example 3. Investigating a series of halogenated molecules

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.

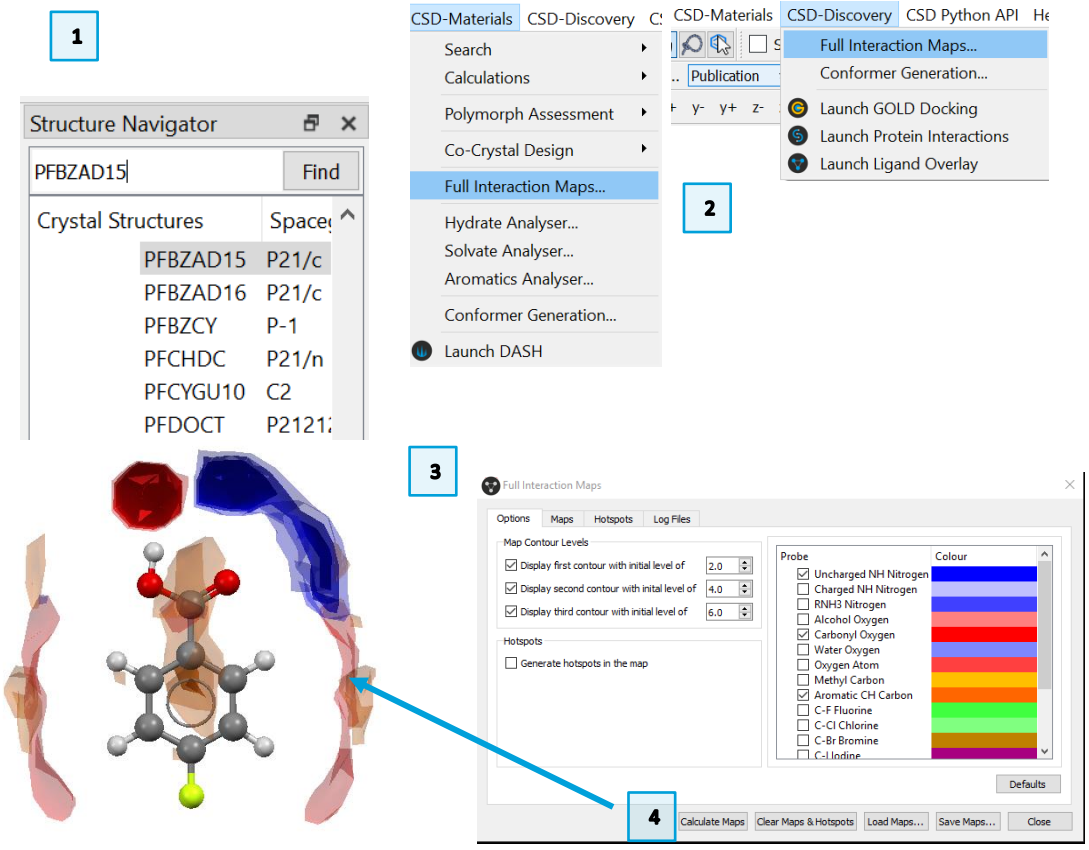
2. Click the *CSD-Materials* menu or *CSD-Discovery* menu and choose *Full Interaction Maps…* from the drop-down menu.

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/CSD_2020/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.



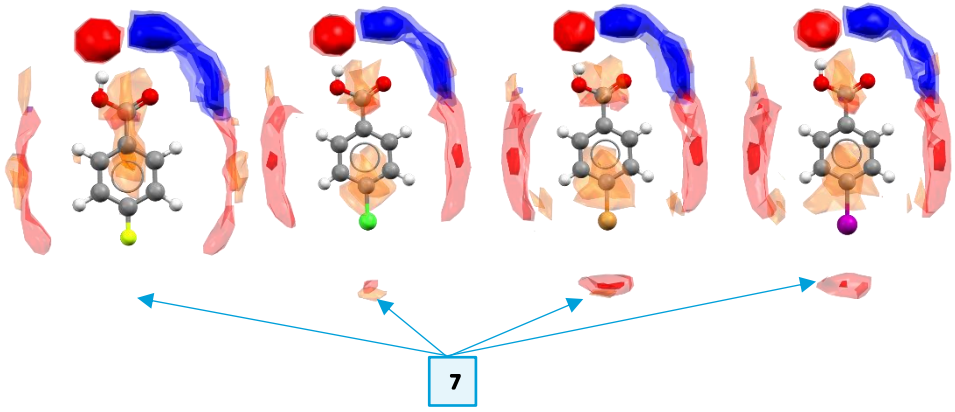
7. Look at the maps generated across the series. You should notice that as the size of the halogen increases across the series, there is an increased likelihood of finding an acceptor interacting with the halogen. This interaction is non-existent for the fluoro species, but well-defined for the bromo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

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

9. Start with the iodo analogue (BENMOW07). 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.



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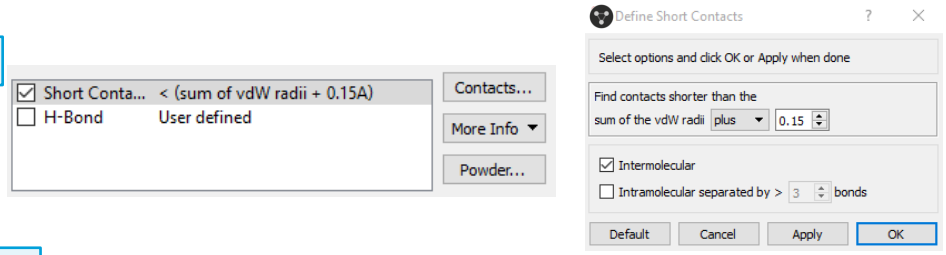

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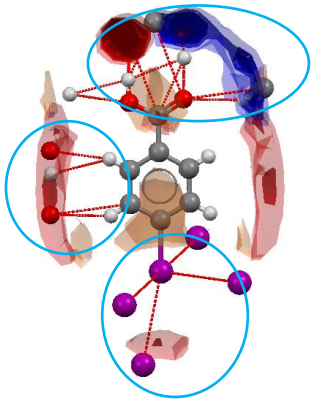

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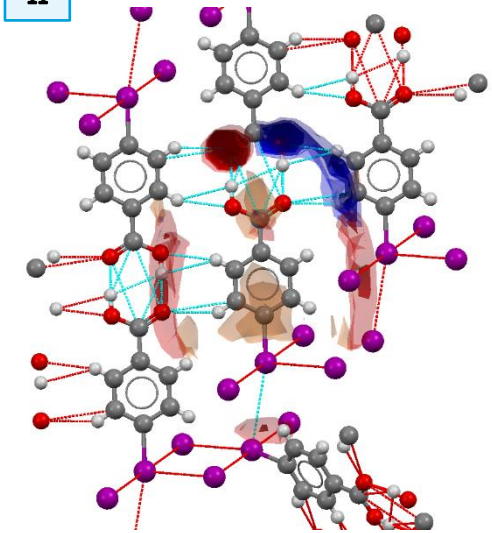


12. Repeat **Steps 9-11** for the Br and Cl analogues. What similarities and differences do you see across the series so far? What do you expect to see for the fluoro analogue?

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.

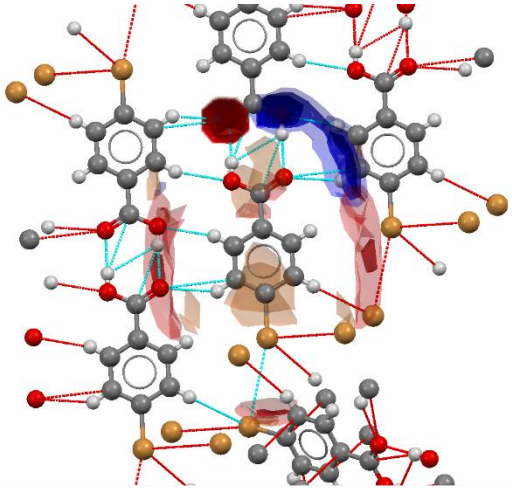
Conclusions

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.

Bonus 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.
- Advanced: Try designing a ConQuest search to return just the molecules we used for this example. How close can you get? *Tips: You may want to try using the* ***Formula*** *and* ***Author/Journal*** *query types, too.*

12



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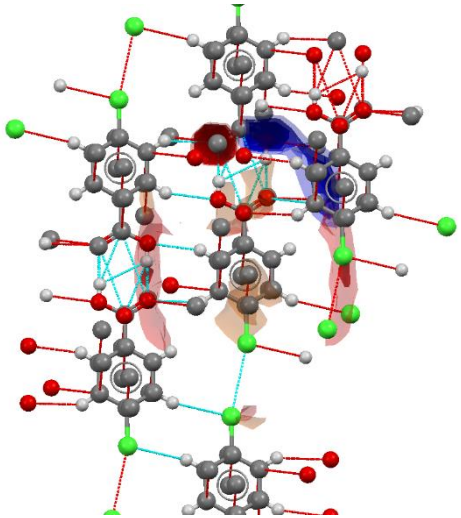

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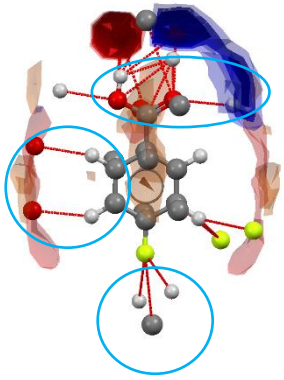

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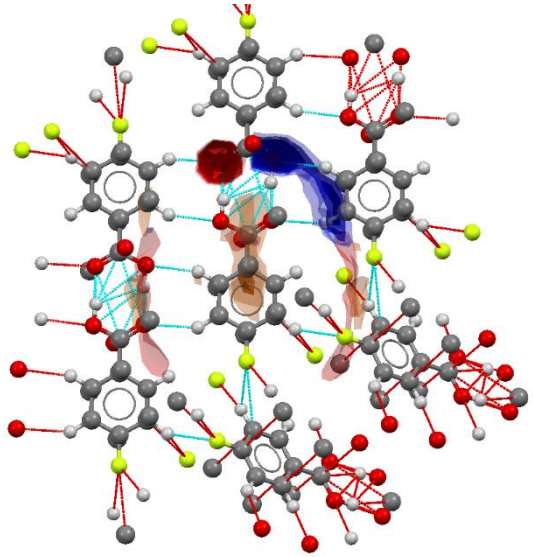
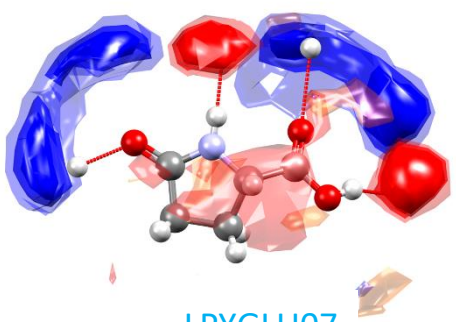


Conclusions

After this workshop you will:

- Know how to produce Full Interaction Maps (FIMs) for a given molecule and how to interpret the results.
- Have experience in exploring and assessing the hydrogen bonding interactions in a crystal structure in relation to the interaction landscape predicted by FIMs.
- Be familiar with how the FIMs analysis can be used for co-crystal design.
- Be familiar with how FIMs can be used to investigate the differences in the interaction preferences of a molecule when substitutions are made across a series.



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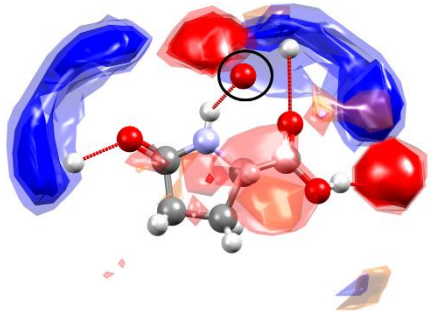


LPYGLU08

Next steps

After this workshop, you can explore more exercises in the self-guided workshops available from the CSD-Materials workshops area. 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/

Glossary

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

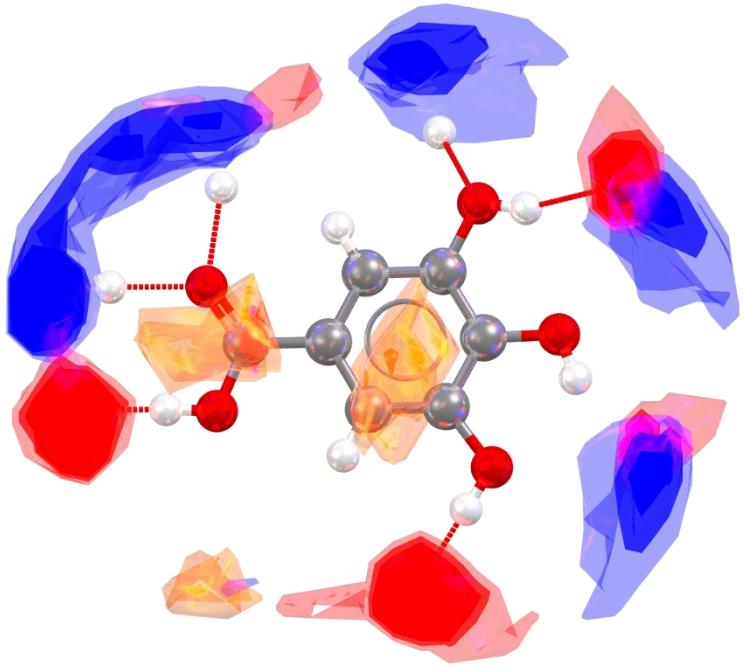
Hotspots
Hotspots represent the positions of highest local density for each contour Surface.

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**