Hydrogen Bonds Analysis with Hydrogen Bond Statistics in Mercury

Developed using
2022.2 CSD Release
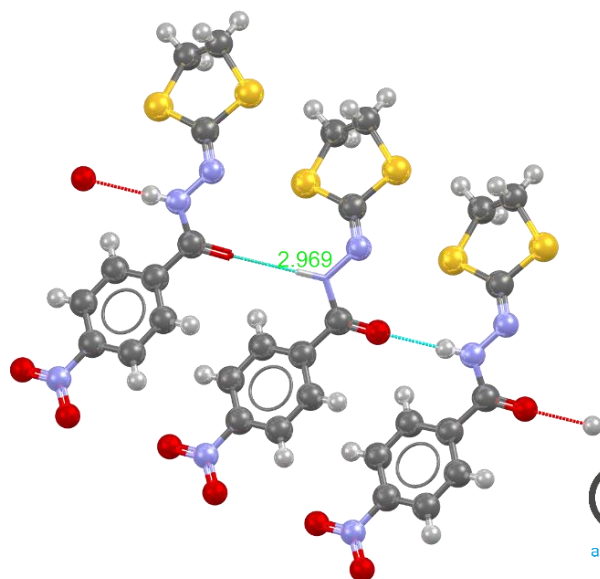
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Introduction

This workshop shows you how to use the Hydrogen Bond Statistics tool from the CSD-Materials suite. Hydrogen Bond Statistics provides automatic statistical assessment of the geometry of hydrogen bonding interactions in the context of the over 1 million highly accurate structures in the CSD. This allows you to determine whether a hydrogen bond is usual or unusual at an early stage of the functional materials development process.

Before beginning this workshop, ensure that you have a registered copy of the CSD installed on your computer. Please contact your site administrator or workshop host for further information.

Objectives

In this workshop you will learn how to perform a hydrogen bond assessment using the Hydrogen Bond Statistics tool:

- Launch the Hydrogen Bond Statistics tool from the CSD-Materials menu
- Visualize and analyse the statistics
- Interpret the results in the Hydrogen Bond Statistics table

Note: The words in *Blue Italic* in the text are reported in the Glossary at the end of this handout.

Pre-required skills

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

Materials

There are no additional materials required for this workshop.
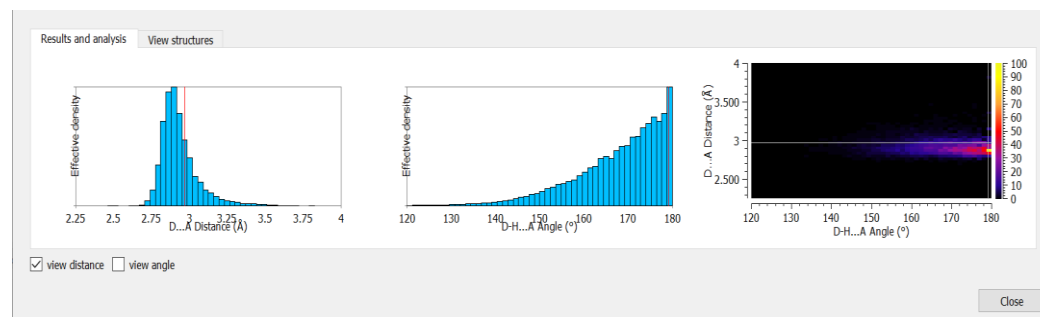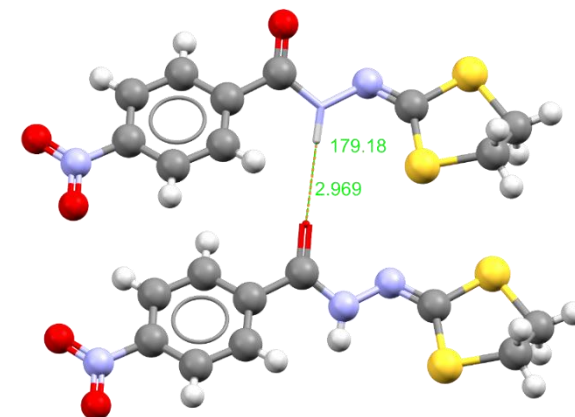
Example 1. Analysing H-bonds in polymorphs

In this example we will focus on the polymorphs of N'-(1,3-dithiolan-2-ylidene)-4-nitrobenzohydrazide, i.e., the refcode family DEDMUX, DEDMUX01, DEDMUX02. In particular, we will investigate the two hydrogen bonds network using the *Hydrogen Bond Statistics* tool from CSD-Materials to identify whether they are Unusual and which ones Not Unusual. By observing the results, we can try to identify in which of the two structures the H-bond formed is more optimal.
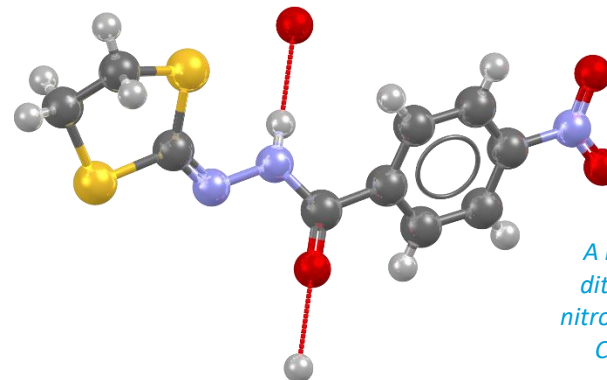
A molecule of N'-(1,3-dithiolan-2-ylidene)-4-nitrobenzohydrazide from CSD Entry DEDMUX

1. Open Mercury by double-clicking the Mercury icon on the desktop.

2. In the *Structure Navigator* on the right-hand side of the Mercury interface type the refcode DEDMUX to bring up the polymorphic family of N'-(1,3-dithiolan-2-ylidene)-4-nitrobenzohydrazide, namely refcodes DEDMUX, DEDMUX01, DEDMUX02.

3. First, we will investigate the *hydrogen bonds* for each of the three *polymorphs*. Visualize the hydrogen bonds by ticking **H-Bond** in the *Display Options* box at the bottom of the Mercury interface. Double click **H-bond** in *Display Options* and tick **Require hydrogen atom to be present** in the *Define H-bonds* pop-up window then click **Apply**. To change polymorphic structure, click on the refcode of each of the polymorphs in the *Structure Navigator*.

4. **Observe**: how many different hydrogen bond *motifs* do you recognise among these 3 structures? Which polymorphs have the same motif?

2

Structure Navigator

DEDMUX | Find

Crystal Structures	Spacegroup
DEDMUX	P21/c
DEDMUX01	P-1
DEDMUX02	P21/c
DEDNAB	P21/a

3

Display Options

Display

☐ Packing   ☐ Short Contact
☐ Asymmetric Unit   ☑ H-Bond
☐ Auto centre

Reset

Define H-bonds ×

Select options and click OK or Apply when done

☑ Require hydrogen atom to be present

D-H...A angle >=   120.0   degrees

Donor atom types:
☐ all donors
 ☑ nitrogen
  ☑ metal bound N
  ☑ imine N
  ☑ aromatic (6-ring) N
  ☑ amide or thioamide N
  ☑ planar N
  ☑ pyramidal N
  ☑ ammonium N (NH4+, RNH3+ ...
  ☑ unclassified N
 ☑ oxygen

Acceptor atom types:
☐ all acceptors
 ☑ nitrogen
  ☑ metal bound N
  ☑ terminal N (cyano, etc.)
  ☑ aromatic (6-ring) N
  ☑ other 2-coordinate N
  ☑ 3-coordinate N
  ☑ unclassified N
 ☑ oxygen
  ☑ metal bound O
  ☑ carboxylate O

WARNING: atom types may not be classified properly for non-Cambridge Structural Database structures

Contact distance range
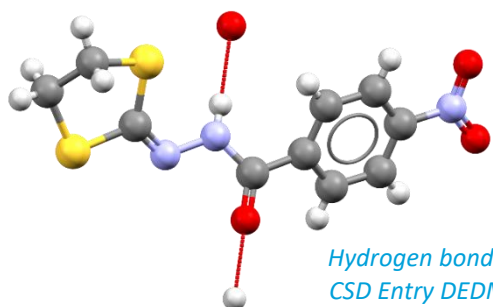○ Actual distance   ● VdW distance

Minimum = sum of vdW radii minus   5.00
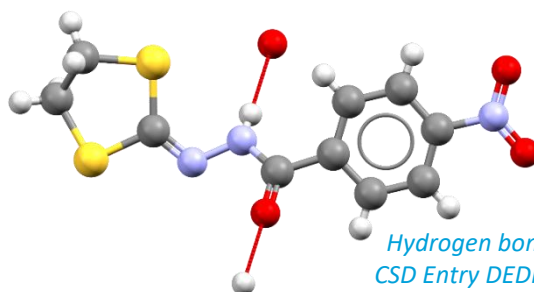Maximum = sum of vdW radii plus   0.00

☑ Intermolecular
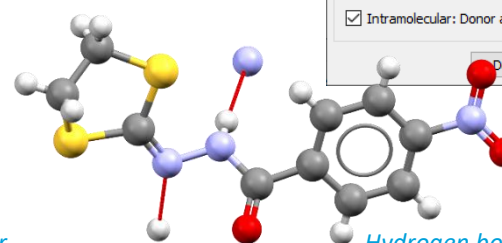☑ Intramolecular: Donor and Acceptor separated by >   3   bonds

Default | Cancel | Apply | OK

Hydrogen bonds for CSD Entry DEDMUX

Hydrogen bonds for CSD Entry DEDMUX01

Hydrogen bonds for CSD Entry DEDMUX02

5. We observe that the first two polymorphs considered, namely refcodes DEDMUX and DEDMUX01 have the same H-bond *motif*, involving the NH group donating to oxygen of the C=O group; on the other hand, DEDMUX02 presents a hydrogen bond *motif* that involves the NH group donating to the C=N nitrogen atom. For this example, we will compare the two different *motifs* by considering the two structures DEDMUX and DEDMUX02.

6. Turn off the H-bonds for the next step, by unticking the box that resulted ticked at **Step 3**.

7. Make sure that in the *Structure Navigator* you have selected the refcode DEDMUX.

8. To run Hydrogen Bond Statistics tool, go to **CSD-Materials > Hydrogen Bond Statistics**. The *Hydrogen Bond Statistics* dialog will open.

9. For this example, keep the values at the default, then click **Search**. A progress window will appear, informing on the progress of the search.

10. Once the search is run, the results are shown in a table in the *Hydrogen Bond Statistics* dialog. In this case there is only one hydrogen bond pair formed, so only one row was populated. You will see the following fields: donor and acceptor atoms; the observed distance, its classification (Not Unusual / Unusual) and the statistics from the CSD for comparison; the observed angle, its classification (Not Unusual / Unusual) and the statistics from the CSD for comparison. To export the results as a .csv file, click **Export**.

11. Now click on the entry to visualise the results in plots. The first histogram represents the distribution of D-A (Donor-Acceptor) distances, with the distance measured in the H-bond under analysis highlighted by a red line. In this case, we read from the table that the distance measured (2.97 Å) is Not Unusual, and we see that reflected in the histogram.

8 CSD-Materials CSD-Theory CSD-

- Search ▶
- Calculations ▶
- Polymorph Assessment ▶
- Co-Crystal Design ▶
- Full Interaction Maps...
- Hydrogen Bond Statistics...
- Hydrate Analyser...
- Solvate Analyser...
- Aromatics Analyser...
- Conformer Generation...
- DASH has moved

Hydrogen Bond Statistics ... DEDMUX

Hydrogen Bond Definition   [Edit]

Quantile settings

Classify as unusual if:

Distance < [0.05] or distance > [0.95] quantiles

Angle < [0.05] or angle > [0.95] quantiles

[Reset]

**9** [Search] [Cancel]

Progress

Collecting Hydrogen Bond Statistics

[████   ] 19%

[Cancel]

10

Hydrogen Bond Statistics ... DEDMUX

|	Donor	Acceptor	Distance D-A	Distance classification	Distance threshold	Distance hits	Distance mean	Distance std. dev.	Distance min.	Distance max.	Angle D-H...A	Angle classification	Angle threshold	Angle hits	Angle mean	Angle std. dev.	Angle min.	Angle max.
1	N2 (acyclic_amide)	O1 (acyclic_amide)	2.97	Not Unusual	(2.79, 3.19)	12121	2.93	0.12	2.46	3.79	179.18	Not Unusual	(147.63, 179.35)	12121	167.78	10.11	120.19	179.98

[Export...]

[Close]

The second histogram represents the distribution of D-H...A (Donor-Hydrogen...Acceptor) angles with the angle measured in the H-bond under analysis highlighted in red. In this case, we read from the table that the angle measured (179.18°) is marked as Not Unusual, and this is observed in the histogram. The third plot is a 2D representation of the distance and angle distribution, with a colour scale from black to yellow based on the occurrence of distance-angle points. The point where the white lines cross represents the combination of distance and angle observed in the structure.
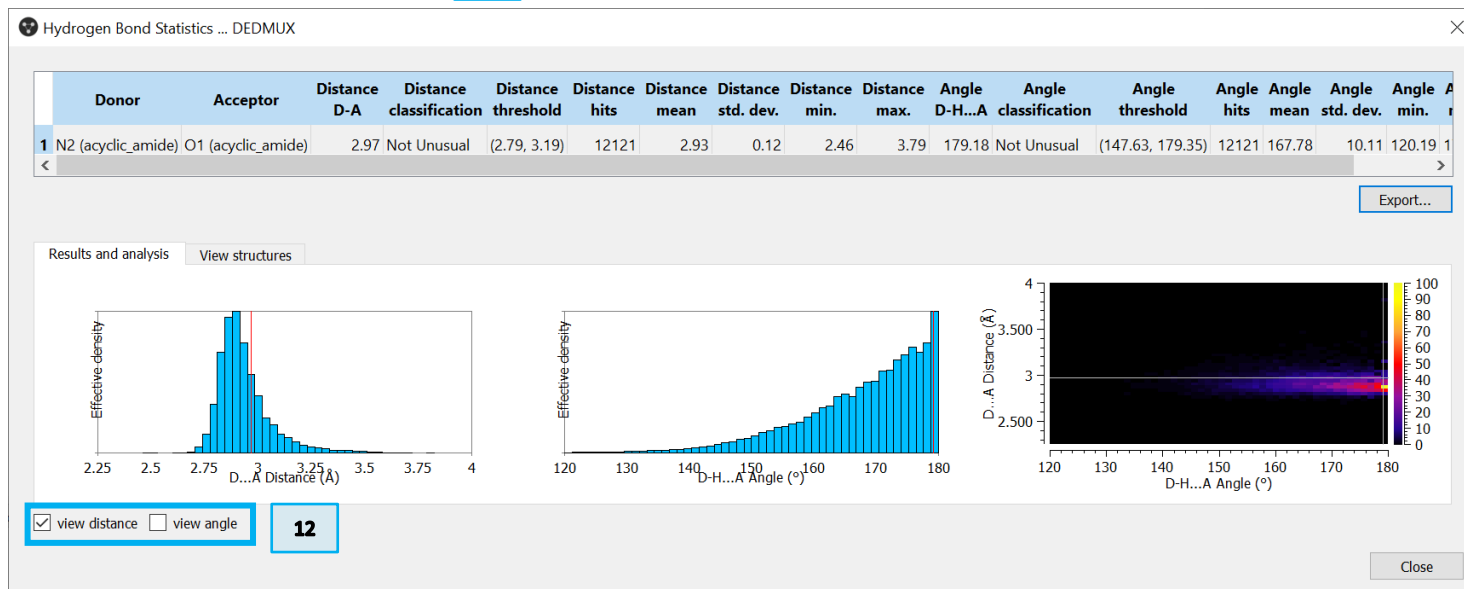
12. You will also notice that the hydrogen bond is displayed in the Mercury visualiser, with the value of the distance shown in a label. You may also tick the view angle option in the *Hydrogen Bond Statistics* window to display the angle value as well.

13. **Extra tip**: You can change the size of the labels by going to **Display > Labels > Label size**. To move the labels, change **Picking Mode** to *Move Labels.*
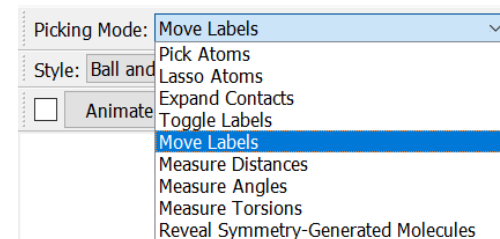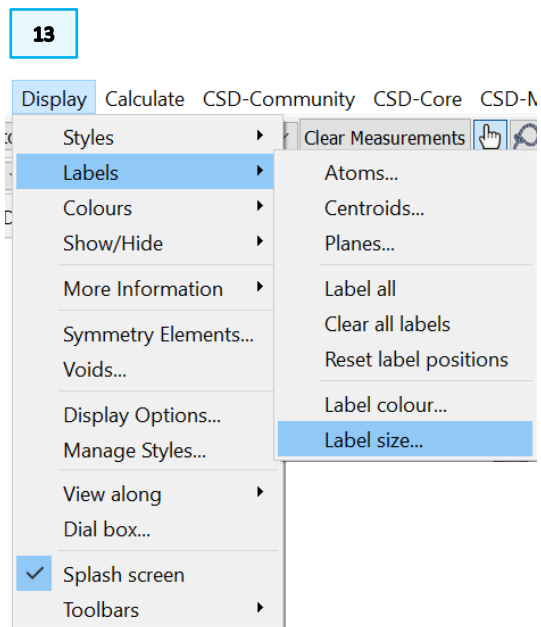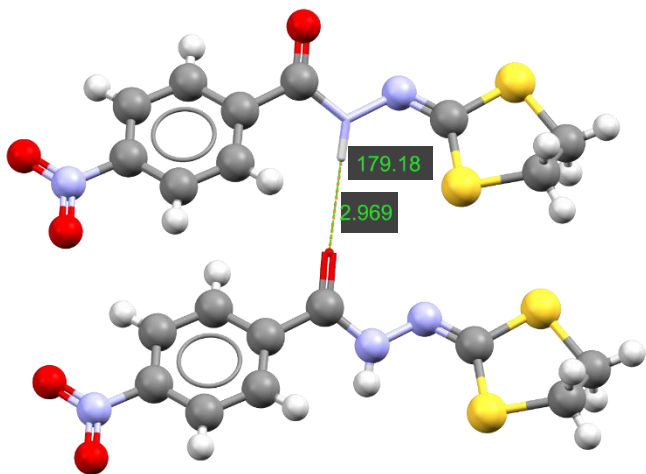
14. You can visualize and analyse the structures contributing to the statistics by clicking on the *View structures* tab in the *Hydrogen Bond Statistics* window.

15. In this tab you can observe the list of refcode hits on the right-hand side, and click on each one to move between them. On the left, you can switch between the *3D Visualiser*, the *Diagram*, and *Information*. If you tick or untick *view distance* and *view angle*, these will be shown or not on the structure currently displayed in the *3D Visualiser*. Right-clicking in the *3D Visualiser* will show a menu with a number of options. You may explore any of these.

16. In the *Diagram* we can observe the fragment contributing to the statistics highlighted in red.
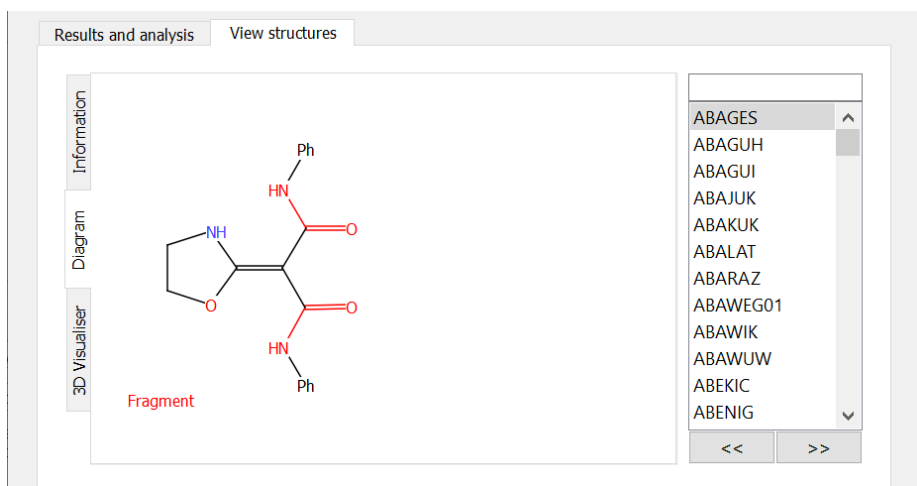
17. Let's repeat this analysis for CSD Entry DEDMUX02. Close *Hydrogen Bond Statistics* window, then select DEDMUX02 in the *Structure Navigator*.

18. Run Hydrogen Bond Statistics tool, as done in **Steps 8 and 9**.

19. Observe the results obtained in the table.

	Donor	Acceptor	Distance D-A	Distance classification	Distance threshold	Distance hits	Distance mean	Distance std. dev.	Distance min.	Distance max.	Angle D-H...A	Angle classification	Angle threshold	Angle hits	Angle mean	Angle std. dev.	Angle min.	Angle max.
1	N2 (acyclic_amide)	N1 (acyclic_nhn)	2.98	Unusual	(3.09, 3.53)	132	3.31	0.14	2.98	3.60	174.98	Not Unusual	(124.81, 176.86)	132	146.80	16.66	120.39	176.86

20. You will notice that there is one hydrogen bond formed again, so only one row was populated. However, the entry is in red which means at least one of the parameters resulted Unusual. Indeed, the distance is classified as Unusual, while the angle is classified as Not Unusual. Notice that the type of hydrogen bond acceptor is different to DEDMUX.

21. Let us take a closer look at the distance distribution. Click on the entry to visualise the results in plots. The first histogram has a broad distribution, ranging from 2.98 Å (the value from our structure) to 3.60 Å (exact values can be seen in the table under Distance min. and Distance max.). The value from our structure, highlighted in red, is indeed at the very tail of the distribution, hence classifying as unusual.

22. Continue the investigation by observing the angle histogram and the distance-angle heat map. Based on your observations, **which of the two hydrogen bond networks shown in these polymorphs seem to be the most optimal?**

23. **Extra tip**: right click on the plots to bring up a menu to edit their appearance and the areas plotted.
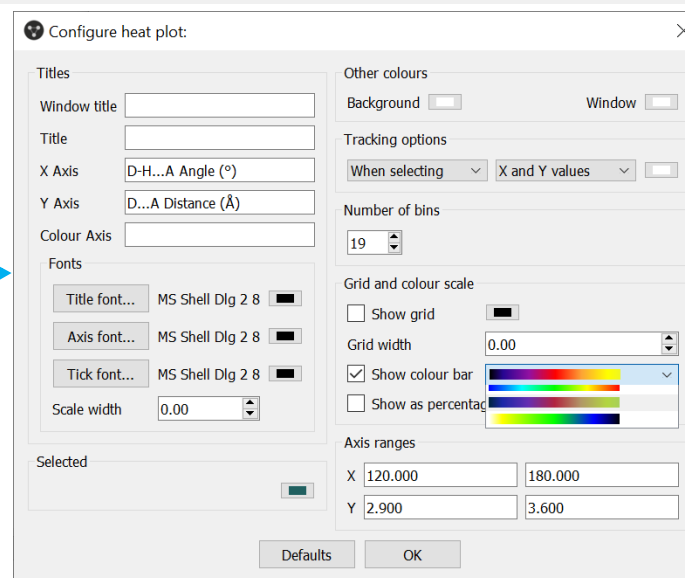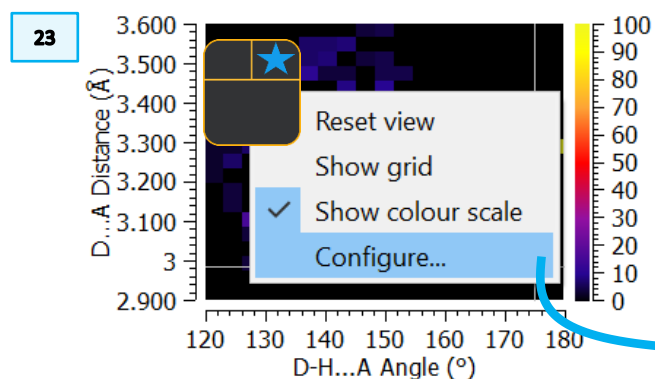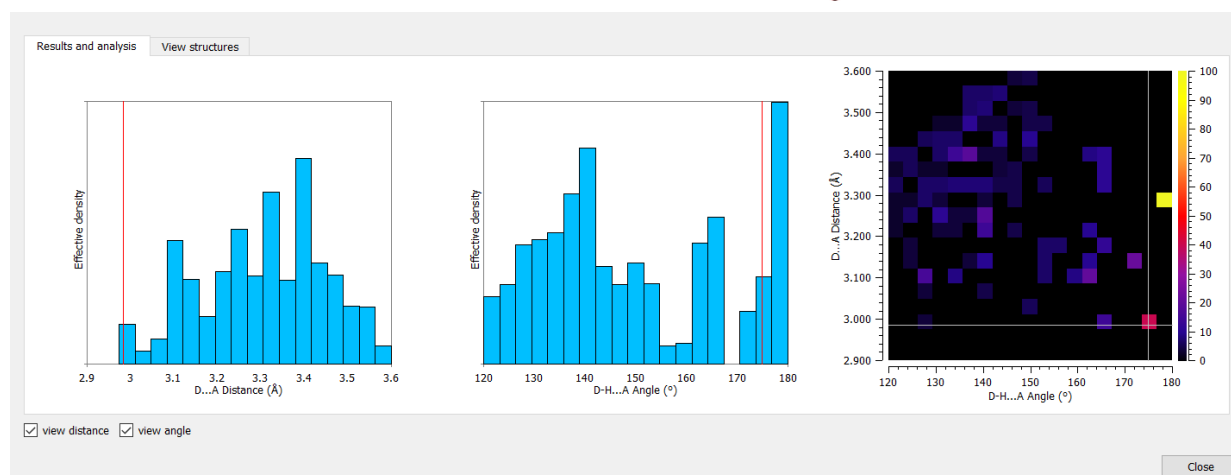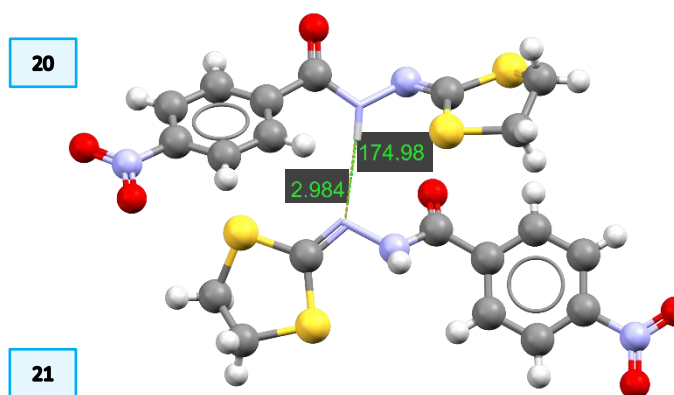
Conclusion

In this example we investigated the hydrogen bonds in two different polymorphs of N'-(1,3-dithiolan-2-ylidene)-4-nitrobenzohydrazide. Using the Hydrogen Bond

Statistics tool, it was possible to assess the distance and angles of H-bonds formed by comparison with data in the CSD.

Conclusions

After this workshop you will be able to:

- Run Hydrogen Bond Statistics from CSD-Materials in Mercury
- View the statistics results in the table and the visualiser
- Compare observed values against hits
- Change the appearance of the plots
- Analyse and interpret Hydrogen Bond Statistics results

Next steps

If you have completed this workshop, you can try Hydrogen Bond Statistics on your structures or ask the tutors for more examples!

Glossary

Graph Sets

Graph set analysis of hydrogen bonding describes the pattern of the hydrogen bond chains or motif and includes the numbers of donors and acceptors.

A graph-set descriptor is written as $G^a_d(n)$, in which **G** represents the type of pattern, **a** is the number of hydrogen bond acceptors involved in that pattern, **d** is the number of donors and **n** the number of atoms in the pattern. The pattern type, G, can be one of four different options: C for an infinite chain, S for an intramolecular hydrogen bonding pattern, R for an intermolecular ring and D for a discrete, finite hydrogen-bonding pattern.

Relevant bibliographic references:
• M. C. Etter, *Acc. Chem. Res.*, 23, 120, 1990
• J. Bernstein, R. E. Davis, L. Shimoni, and N.-L. Chang, *Angew. Chem. Int. Ed.*, 34, 1555, 1995
• W. D. S. Motherwell, G. P. Shields, and F. H. Allen, *Acta. Cryst.*, B56, 466, 2000
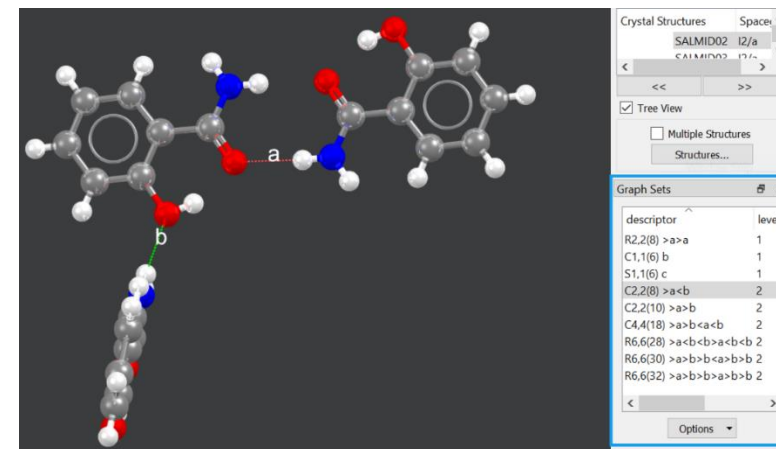
Hydrogen Bonds

Hydrogen bonding is a primarily electrostatic interaction between an electronegative donor attached to a hydrogen atom and an electronegative acceptor with a lone pair of electrons. Hydrogen bonds can be intermolecular (between molecules), or intramolecular involving donor and acceptor atoms within the molecule (typically separated by at least 3 covalent bonds).

Relevant bibliographic references:
• Definition of the hydrogen bond (IUPAC Recommendations 2011), *Pure Appl. Chem.*, 83, 8, 1637–1641, 2011
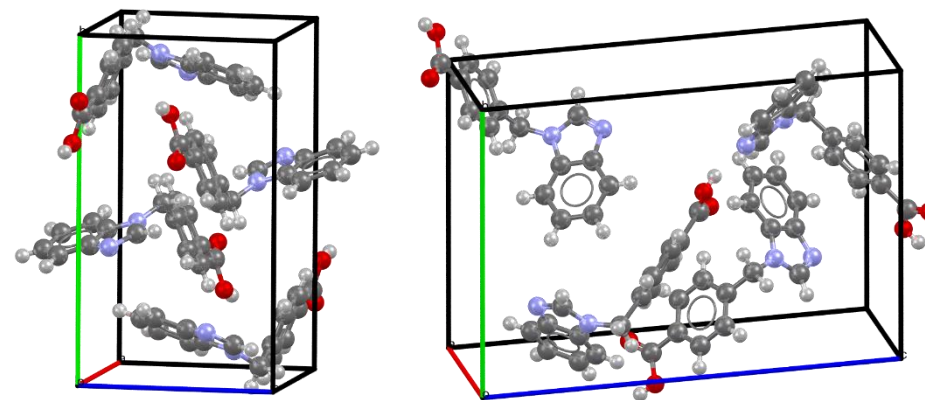
Polymorph

Polymorphism is the occurrence of two or more crystalline forms of the same substance. Where available, polymorph information can be displayed for Cambridge Structural Database (CSD) structures. Structures known to be polymorphic contain comments which include the word polymorph (when reported by the author), e.g., non-triboluminescent polymorph. There is also a CSD subset of polymorphic structures (**CSD-Core > Subsets** in **Mercury**, or **View Databases > Subsets** in **ConQuest**).

Example of Graph Sets display for structure SALMID01
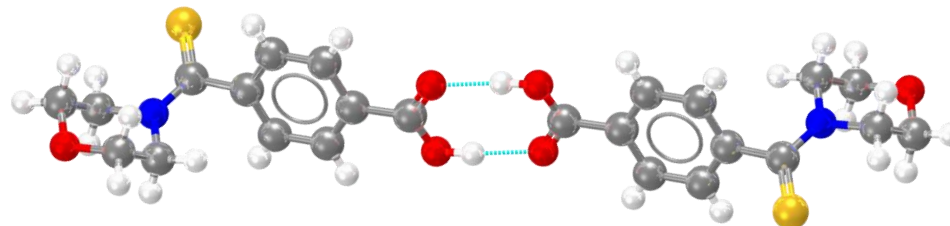
In light blue, example of hydrogen bonds for refcode MULWIC.

Example of polymorphic structures of 4-(1H-Benzimidazol-1-ylmethyl)benzoic acid: the monoclinic polymorph (CSD Entry ABADIS) on the left, and the orthorhombic polymorph (CSD Entry ABADIS01) on the right.