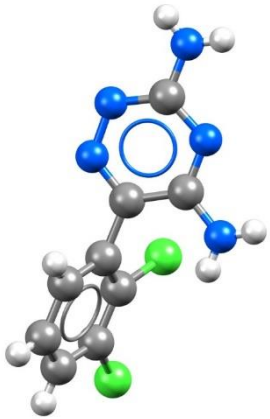
Hydrate Analyser

MAT-002

2020.3 CSD Release



advancing structural science

Table of Contents

Introduction

This tutorial will introduce you to the *Hydrate Analyser* in *CSD-Materials*.

The Hydrate Analyser tool in Mercury provides the user with the ability to quickly investigate complex hydrated structures.

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

Objectives

- Explore visualisation options and familiarise with the Hydrate Analyser dialog box.
- Investigate hydrogen bonding motifs in for water molecules in a hydrated structure.
- Explore and compare water spaces and analyse water interaction maps.
- Investigate different hydrate stoichiometries.
- Analyse hydrate polymorphs and hydrate coordinates.

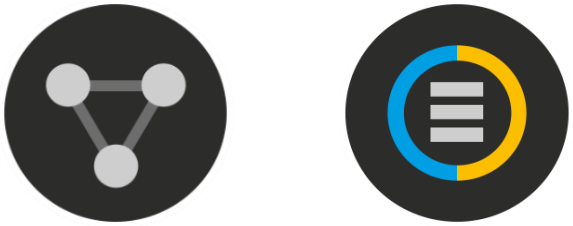
This workshop will take approximately **1** hour to be completed.

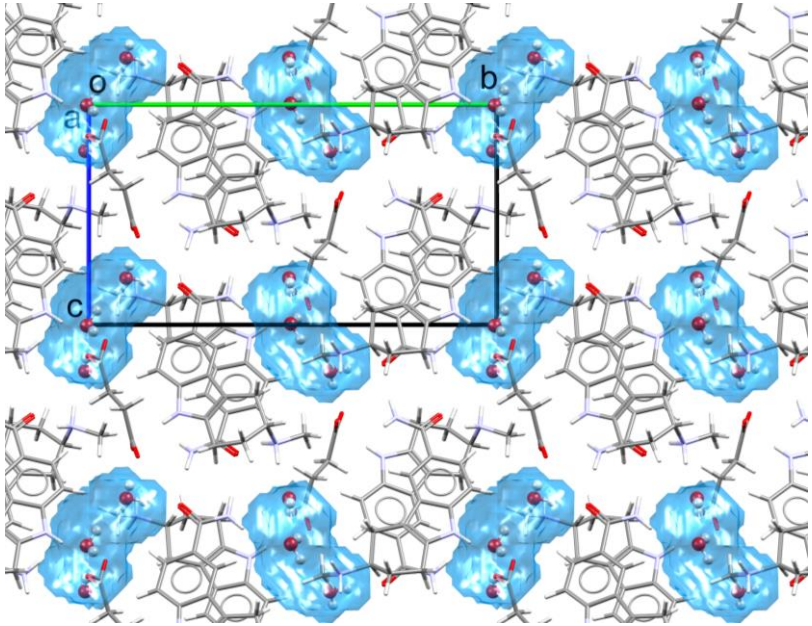
Pre-required skills

Familiarity with the Mercury interface is important; you can access the Visualization in Mercury self-guided workshop here. You can find other CSD-Materials self-guided workshops here.

Materials

There are no additional materials required for this workshop.

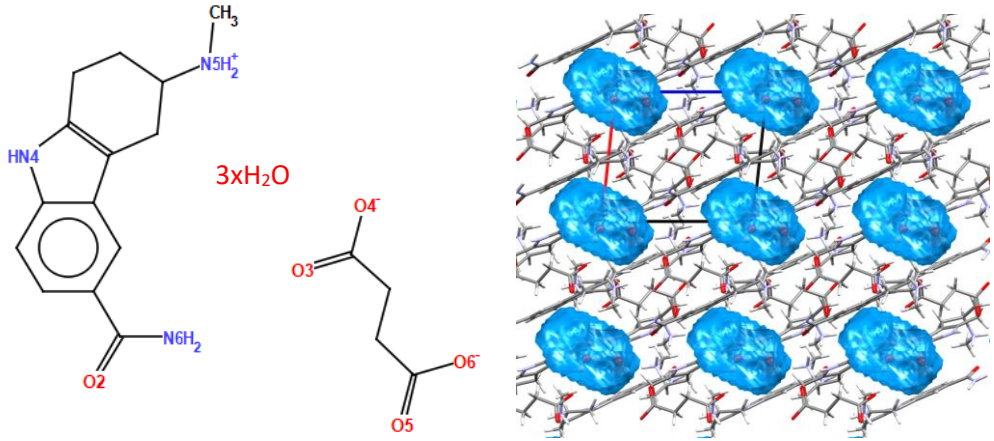




Example 1. Analysing a hydrate structure

The presence and interaction of water molecules within crystal structures has a significant influence on a solid-state material's properties. In the pharmaceutical industry this is of paramount importance as hydrate formation can occur during the manufacturing stage. This can lead to a change in the solubility of the drug with direct impact on its bioavailability. Thus, it is essential to characterise and understand hydrate behaviour in the early process of drug development.

This example shows how to analyse hydrate crystal structures using the Hydrate Analyser within CSD-Materials, illustrating how to quickly understand the environment and behaviour of water in complex hydrated structures.



Bis(frovatriptan) succinate trihydrate - CSD refcode ***MEXSEP***

Structure overview

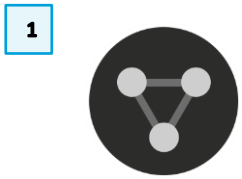
In this section, you will learn how to change display styles and add additional information items to the display in the Structure Overview of the Hydrate Analyser.

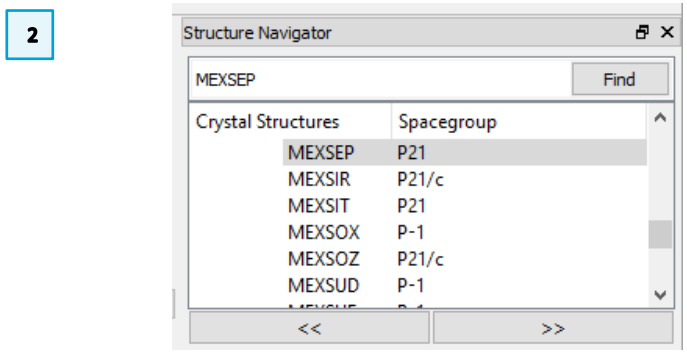
1. Open Mercury by clicking the desktop icon, or launching from the Start menu (Windows), Launchpad (macOS) or command line (Linux).

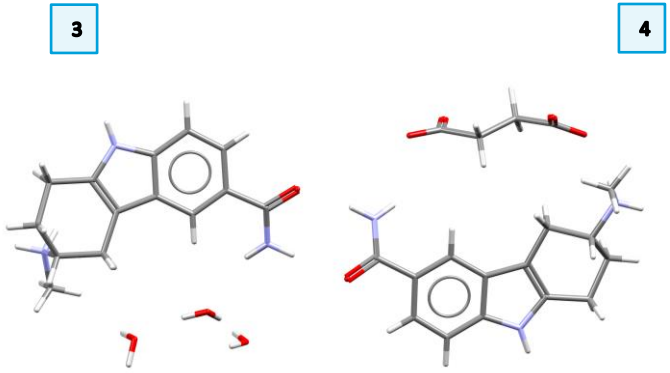
2. In the **Structure Navigator** window, type the refcode *MEXSEP*, to load the structure of bis(frovatriptan) succinate trihydrate.

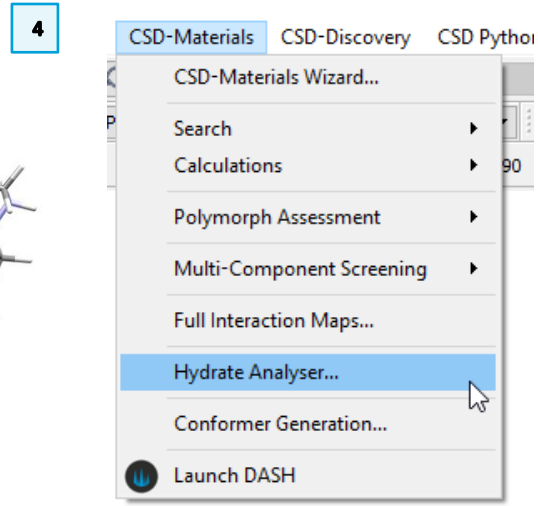
3. The structure will be displayed in the 3D visualiser.

4. From the top-level menu select **CSD-Materials > Hydrate Analyser…**







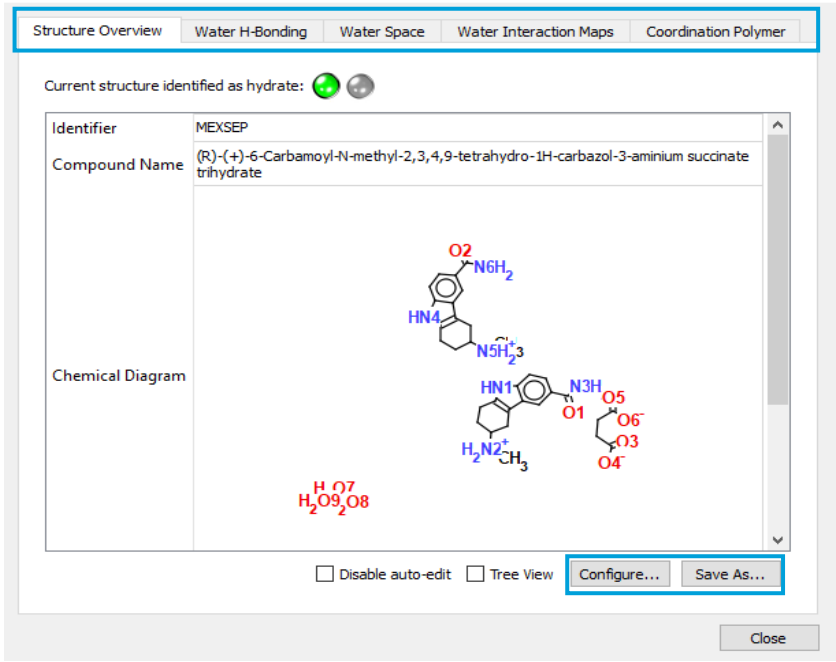


5. The *Hydrate Analyser* dialog box contains 5 tabs with different functionality options. At any point, in the *Structure Overview* tab, you can use the **Save As…** button to save a report in Word (DOCX) or HTML format.

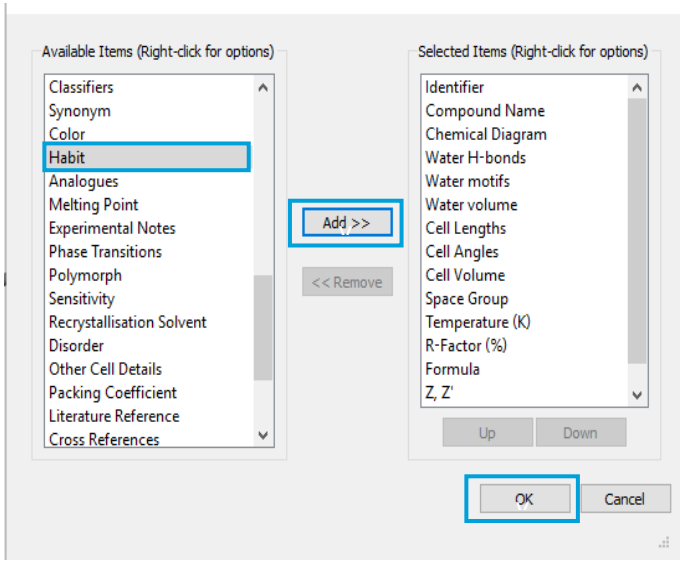
6. Click on **Configure**… to customise the information displayed in the Structure Overview tab. In the resulting dialogue box select **Habit** from the *Available Items* list, press **Add >>** and then **OK**.

7. If you scroll down in the structure overview section, the habit will be now listed as plate.

5



6



7

Water volume	Use Water Space tab to calculate.
Cell Lengths	**a** 8.7239(11) **b** 18.662(2) **c** 10.1270(13)
Cell Angles	**α** 90 **β** 96.098(2) **γ** 90
Cell Volume	1639.4
Space Group	P 2_1 (4)
Temperature (K)	Room Temp. (283-303)
R-Factor (%)	4.1
Formula	$2(C_{14}H_{18}N_3O^+),C_4H_4O_4^{2-},3(H_2O)$
Z, Z'	**Z**: 2 **Z'**: 1
Density (CCDC)	1.334
Habit	plate

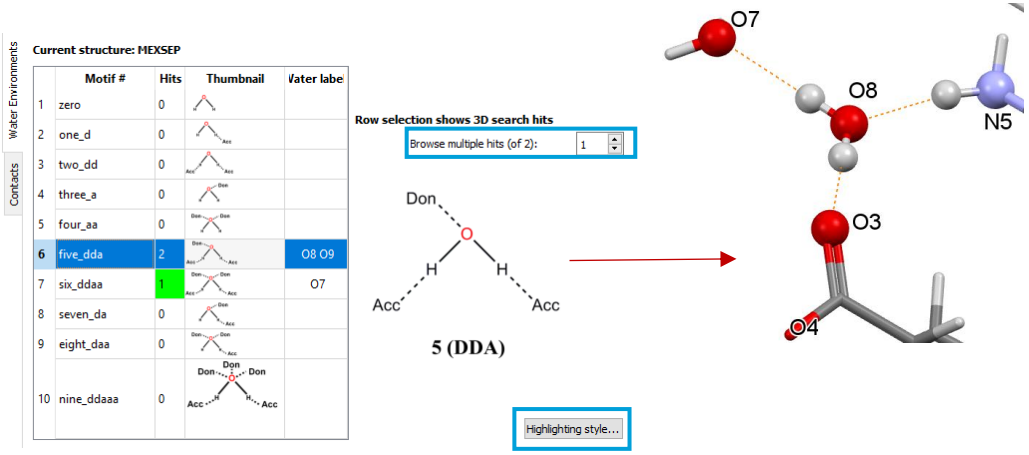
Investigating H-bonding

In this section, you will learn how to generate a quick view of the water H-bonding motifs.

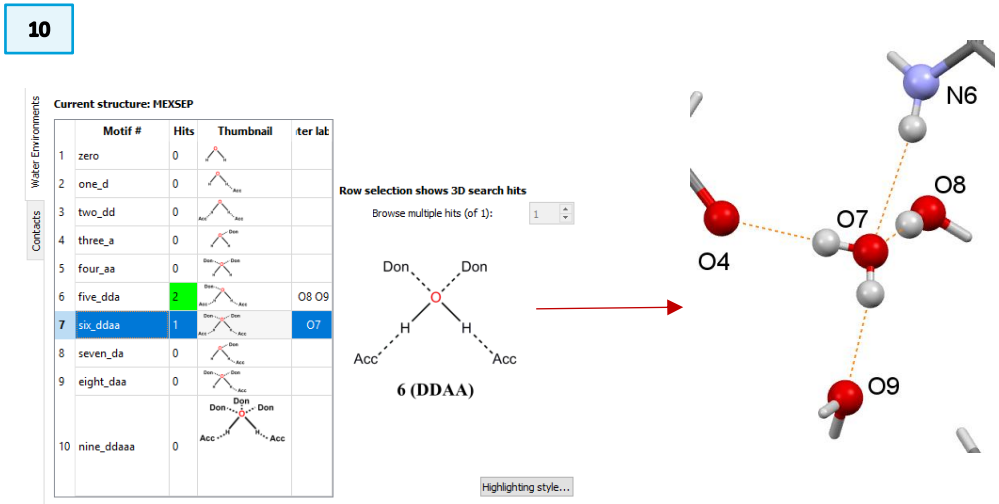
8. Click on the **Water H-Bonding** tab. This shows an automated analysis of the H-bonding environments of the water molecules. This is a quick way to investigate the H-bonding in complex hydrates. The two water molecules containing atoms O8 and O9 exhibit the same H-bonding environment – "five (DDA)". This environment consists of the water molecule donating twice (DD) and accepting once (A) - this is the environment most commonly observed in the CSD. See Gillon et al., Cryst. Growth Des., 2003, 3, 663-673 for details of the environments observed in the CSD including five (DDA).
9. The table is interactive, if you click on a row in the table, the H-bonding environment will be displayed next to the table as 2D sketch and the atoms involved in the environment will be highlighted in the 3D visualiser. If there is more than one matching environment, you can browse them using the dial box on the right-hand side of the tab labelled *Browse multiple hits*. There are two donations and one acceptance each for O8 and O9. You can change the style of the H-bond interactions displayed in the 3D viewer by using the **Highlighting style…** button in the lower right-hand side corner.
10. Note that O7 has a different H-bonding environment. Click on it to display the H-bond contacts. In this case there are two donations and two acceptances.

8

9



10

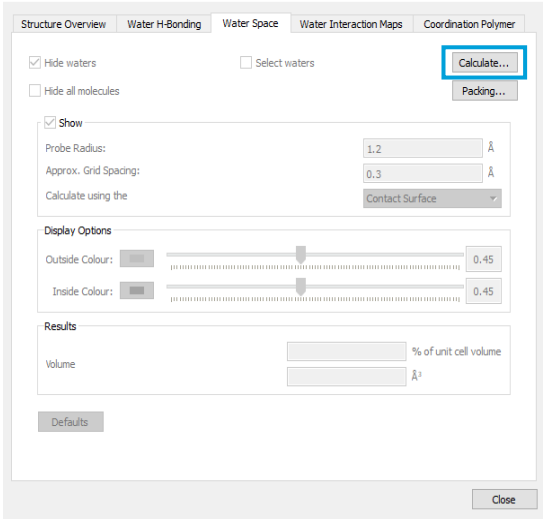


Exploring water space

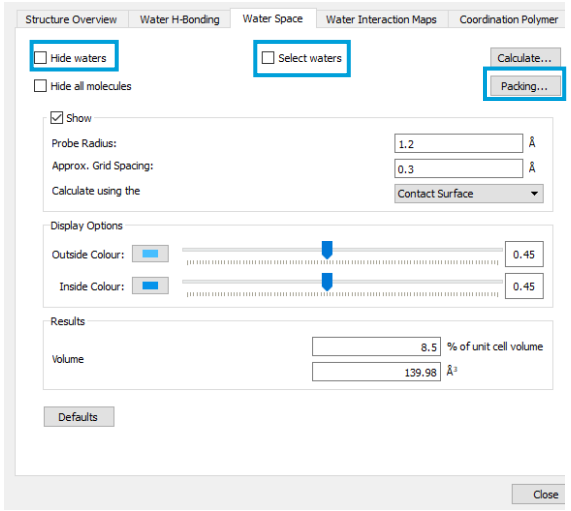
In this section, you will learn how to generate and visualise water space in hydrated structures.

11. Select **Water Space** from the top-level tabs. Note that most of the options are initially unavailable until the water space has been calculated. Click **Calculate…** to generate the water space. This will automatically create a 1x1x1 packing diagram and display the space occupied by water or structural voids.
12. By default, the water molecules are hidden from the visualiser. Uncheck the **Hide waters** box to display the water molecules. You can make the water molecules easier to see by clicking on the **Select waters** checkbox and changing the *Style* to **Ball and Stick** from the top-level Mercury toolbar.
13. To further explore the location of the water space, click the **Packing…** button. Enter -0.5 to 1.0 for the *a* axis, -0.5 to 2.0 for the *b* axis and -0.5 to 2.5 for the *c* axis to obtain a more complete picture of the voids. Click **OK** and then **Calculate**…. Click *a* axis from the top level toolbar to view along it. Note that the water molecules are found in isolated pockets within the crystal lattice. There is no clear escape route for the molecules, so along with the H-bonding it looks likely that removal of the waters would result in structural collapse.

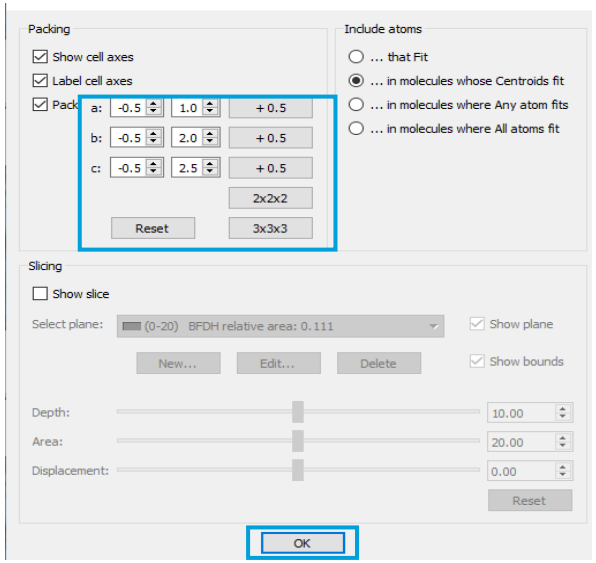
11

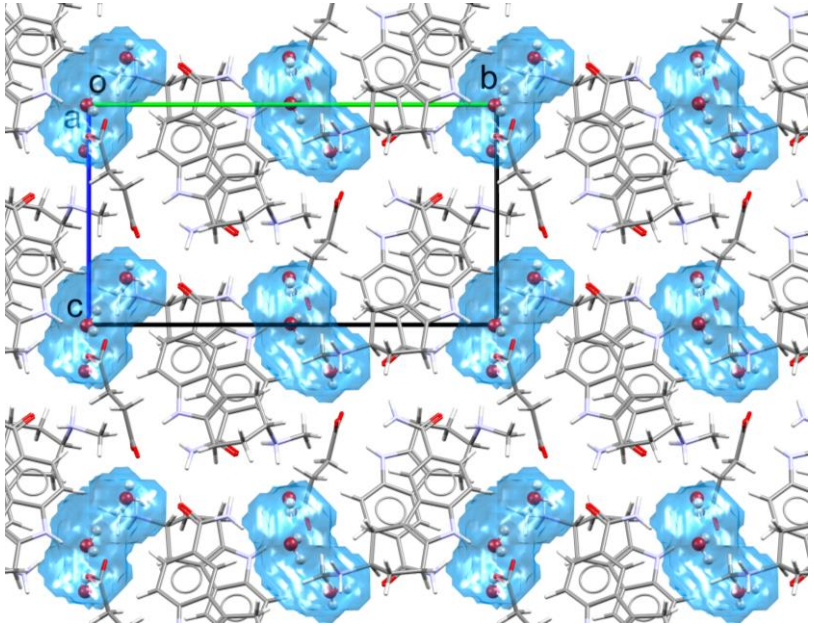


12



13



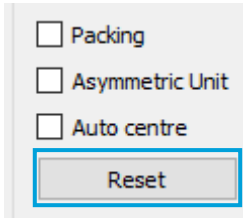


Analysing interaction maps

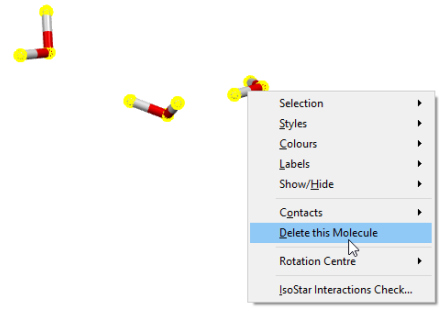
In this section, you will learn how to asses if the water molecules are occupying expected locations based on interaction maps.

14. To go back to the initial view click **Reset** in the *Display Options* area of the Mercury interface.
15. Select all the water molecules using the **Lasso selection mode** from the top-level toolbar or hold shift and click on the molecules, then right click on each molecule and select **Delete this Molecule**.
16. Select the API molecule and the counter-ion.
17. Click on the **Water Interaction Maps** tab in the Hydrate Analyser and click the **Calculate…** button. Interaction maps will be generated around just the molecules that are selected.
18. Toggle on the **H-Bond** checkbox in the *Display Options* area of the Mercury interface to display the H-bond interactions.
19. Note that all the hanging contacts of the water molecules are within the expected water locations based on CSD data (blue peaks in the interaction maps). Therefore, all the waters form H-bond interactions with optimal geometries based on interaction maps.

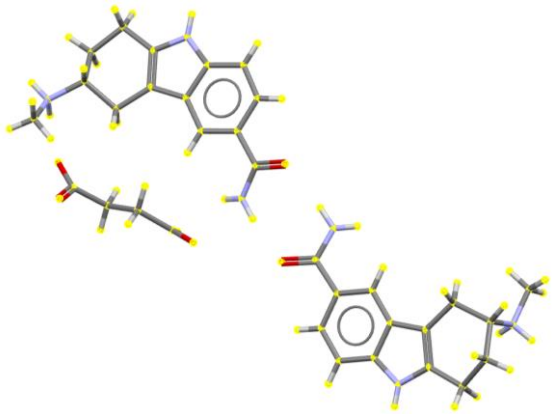
14



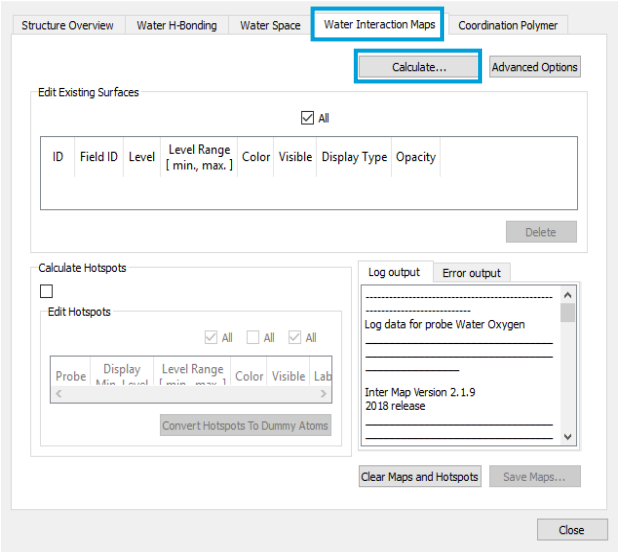
15



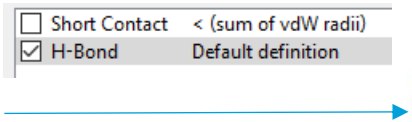
16



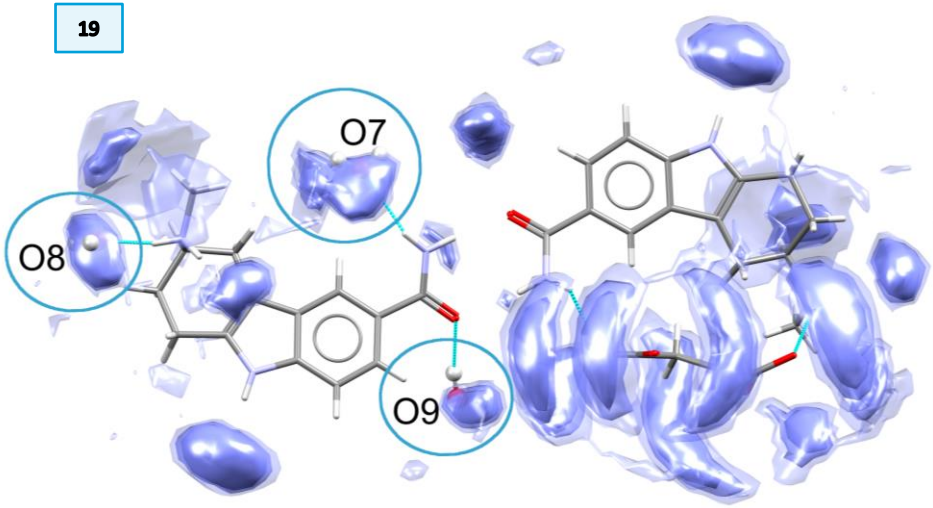
17



18



19



Analysing different stoichiometries

We will now investigate the water behaviour in a different stoichiometry hydrate form of this compound, the monohydrate, and compare it with the trihydrate structure. Follow steps 2 through 4 to load the structure of frovatriptan succinate monohydrate using the *MEXSIT* refcode and open the **Hydrate Analyser**.

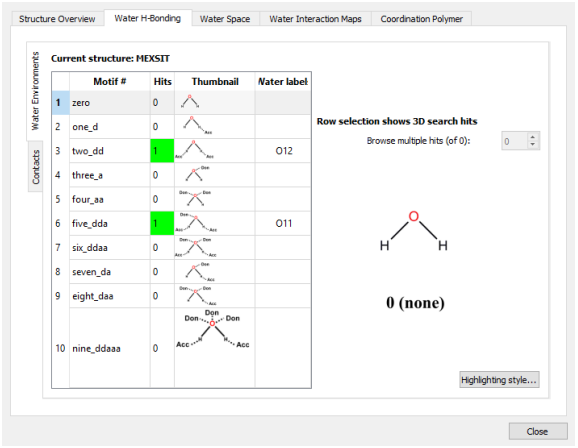
20. This structure is a monohydrate by formula, but it is Z'=2, so there are two unique water molecules. How do the two water molecules interact with the API and counter-ion? Follow steps 8 to 10 above to investigate the Water H-bonding

21. Explore the water space and packing, following steps 11 and 12 and resetting the packing to 1x1x1.
    How does it compare with the bis(frovatriptan) succinate trihydrate? How many water molecules sit in the pockets?

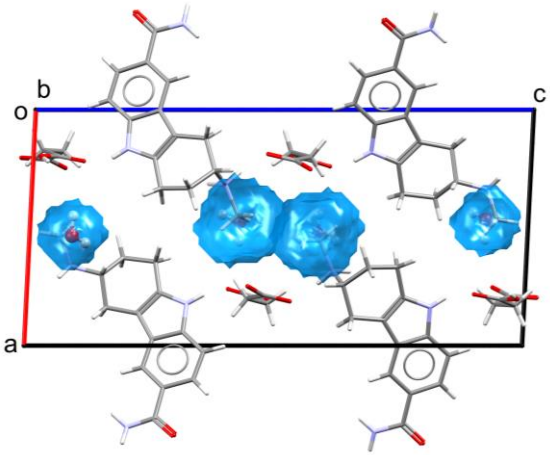
22. Select the frovatriptan and succinate molecules in the 3D visualiser and under the **Water Interaction Maps** tab click **Calculate**. Note that the water molecules are located outside of the expected areas.

Based on these analyses, the trihydrate structure looks like a more structurally stable system than the monohydrate.

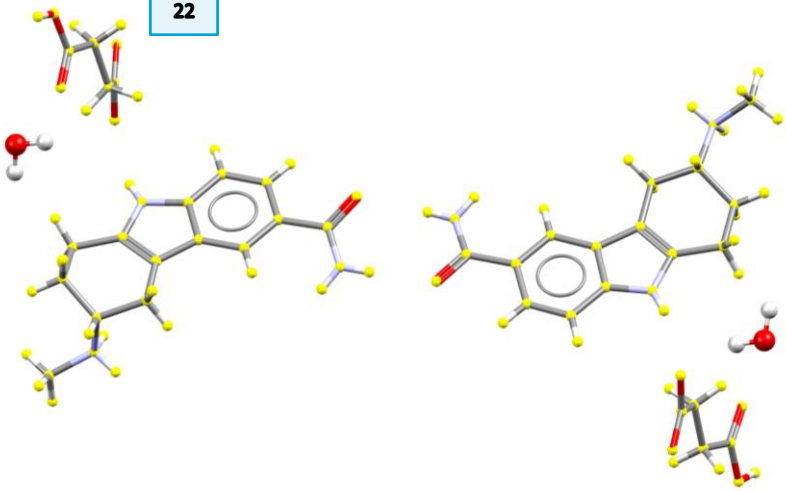
20

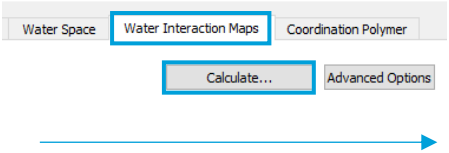


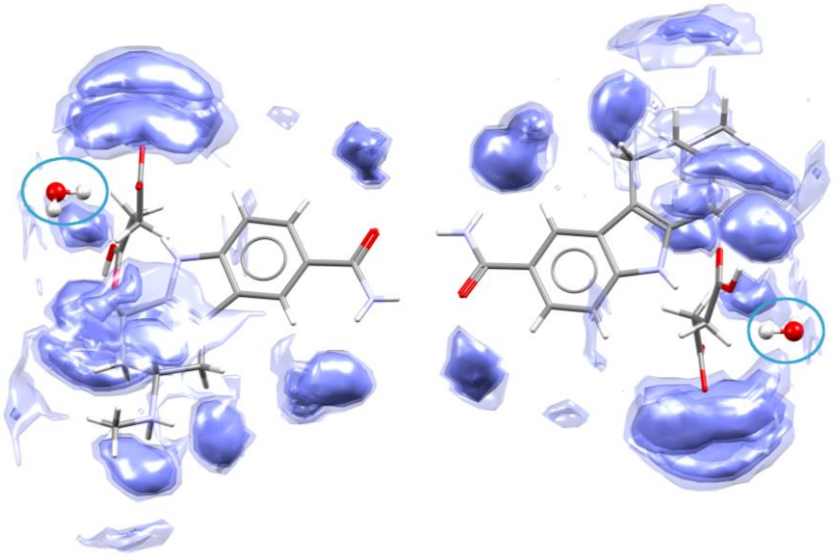
21



22

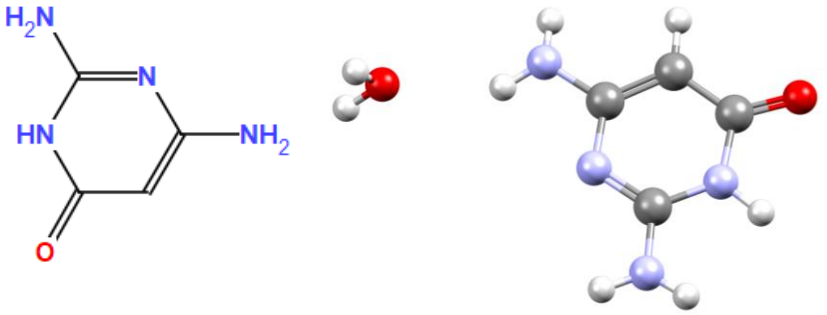






Example 2. Analysing hydrate polymorphs

As was shown in the previous example, water molecules can occupy isolated sites (or pockets) surrounded by the host molecule, such water molecules are typically difficult to remove, especially when they also form strong hydrogen bonds. Hydrates can also form channels within a crystal lattice and the dehydration process will depend on the extent of hydrogen network and the channel size. Hydrated crystalline systems can exhibit polymorphism with different water environments and water space, e.g. pockets or channels. One example is 2,6-diaminopyrimidin-4(3H)-one. The monohydrate of this compound exhibits two known polymorphs, CSD refcodes: *SEYDIJ* and *SEYDIJ01*.

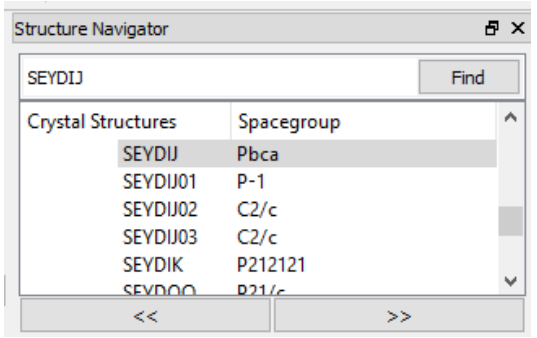


2,6-diaminopyrimidin-4(3H)-one monohydrate ***SEYDIJ***

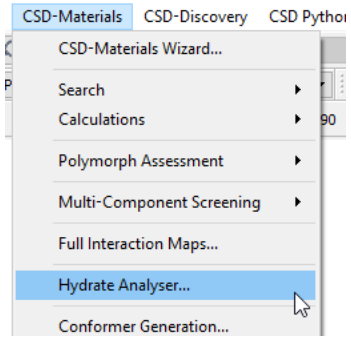
1. Open Mercury by clicking the desktop icon, or launching from the Start menu, Launchpad (MacOS) or command line (Linux).
2. In the **Structure Navigator** window, type the refcode *SEYDIJ*, to bring up the structure of the monohydrate in its orthorhombic form.
3. From the top-level menu select **CSD-Materials > Hydrate Analyser**….
4. Select the **Water Space** tab in the Hydrate Analyser and click **Calculate…** to generate the water space.
5. Examine the packing of the orthorhombic polymorph. The channels are formed along the crystallographic *b* axis and a double column of water molecules is filling the channel space.
6. Explore the water space in the triclinic polymorph *SEYDIJ01*, following the steps above. The default settings for water space (and general void analysis) use a probe radius of 1.2 Å - this corresponds to the expected van der Waals volume of water. For strongly H-bonded waters you might have to lower the probe radius to see the water space – for this example, change the probe radius to 0.9 Å. How does the water space compare with the orthorhombic polymorph?

1

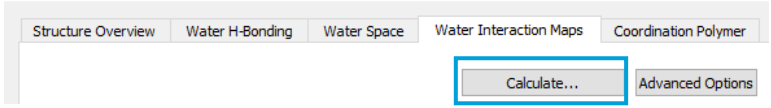
2



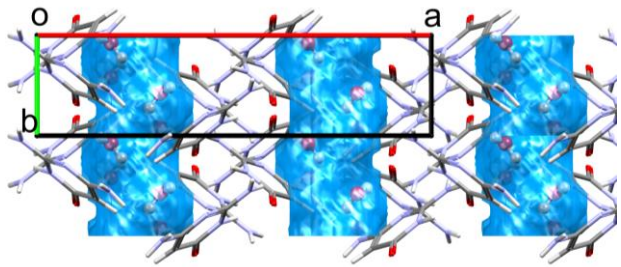
3

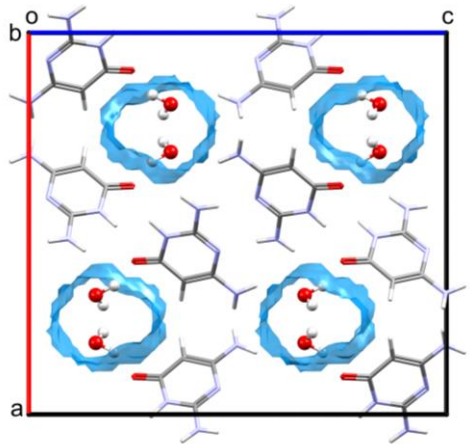


4



5





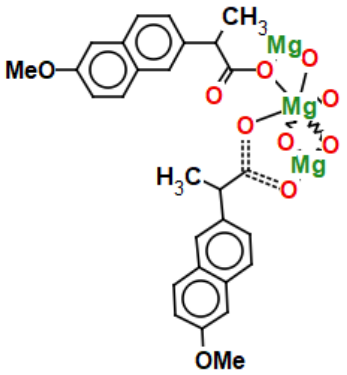
Example 3. Analysing coordinated hydrates

Drugs are often used in combination with metal ions to enhance their physicochemical properties. Such compounds often incorporate water in their crystal lattice and may be displayed in Mercury as coordinated networks rather than disconnected units. The **Coordination Polymer** tab in *Hydrate Analyser* dialogue box can help identifying and exploring these types of structures.

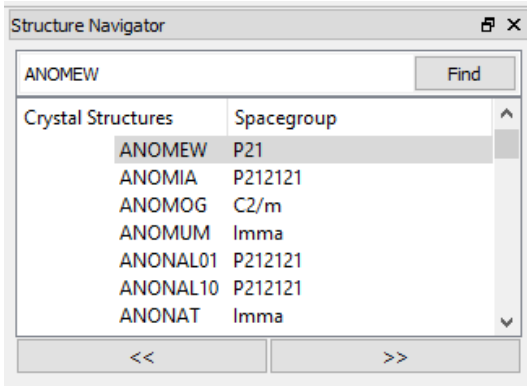
You can investigate metal-coordinated hydrates using this tool. This allows you to expand the polymers by clicking on *Po* labels next to each polymeric bond.

1. Open Mercury by clicking the desktop icon, or launching from the Start menu (Windows), Launchpad (macOS) or command line (Linux).
2. In the **Structure Navigator** window, type the refcode *ANOMEW*, to bring up the structure of magnesium naproxen hydrate. The structure will be displayed in the 3D visualiser.
3. From the top-level menu select **CSD-Materials > Hydrate Analyser**….
4. Click on **Coordination Polymer** tab. The green traffic light icon at the top of the tab is shown confirming that the current structure is identified as a polymer. The hanging polymeric bonds are labelled as **Po** in the 3D visualiser. Expand the polymeric bonds by clicking on the **Po** labels.
   In conclusion here, this feature is designed to identify and expand hydrated polymeric structures.

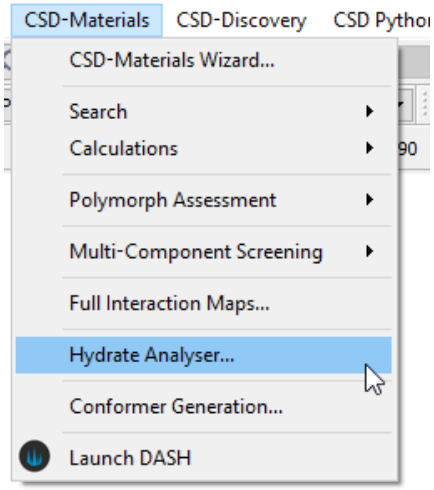
1



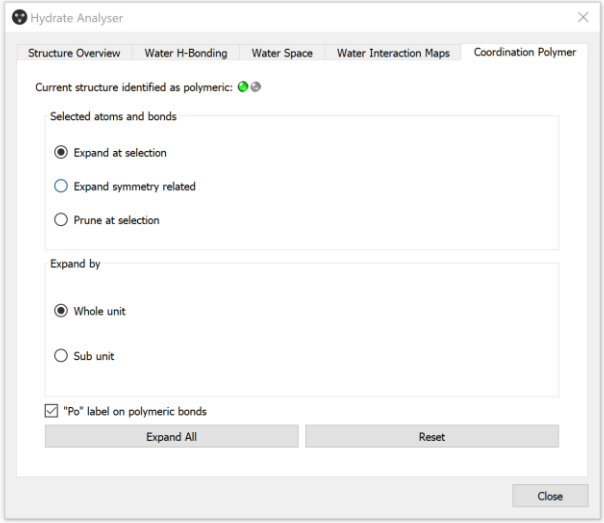
2



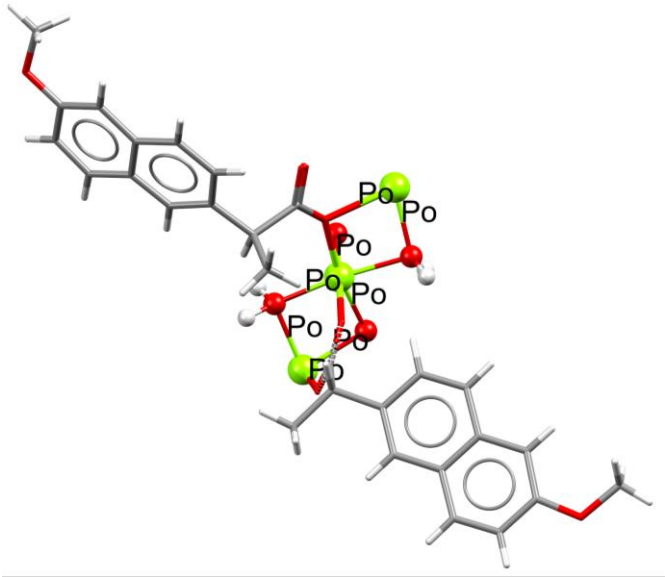
3



4



5



Feedback

We hope this workshop improved your understanding of the *Hydrate Analyser* and you found it useful for your work. As we aim at continuously improving 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 MAT-002. Thank you!