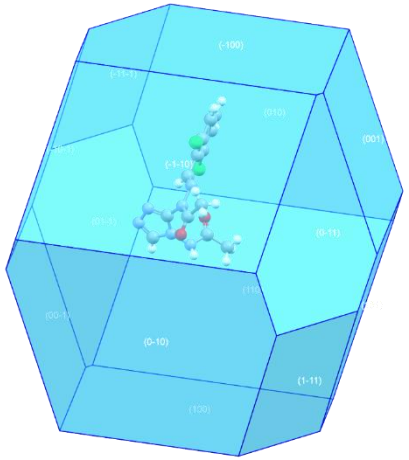
Particle Shape Calculation Using CSD-Particle (PAR-003)

Developed using
2023.1 CSD Release



advancing structural science

Table of Contents

Introduction 2
Learning Outcomes 2
Pre-required Skills 2
Materials 2
Example 1. Calculating a BFDH morphology for a structure in the CSD 3
Example 2. Calculating a morphology for a structure in the CSD using VisualHabit 5
Conclusion 7
Exercises 8
Summary 9
Next Steps 9
Feedback 9
Exercise discussion 10
Glossary 11
Basics of Mercury Visualization 13

Introduction

In this self-guided workshop, we will see the morphology calculation features included with Mercury under the CSD-Particle toolset, namely BFDH Morphology and VisualHabit.

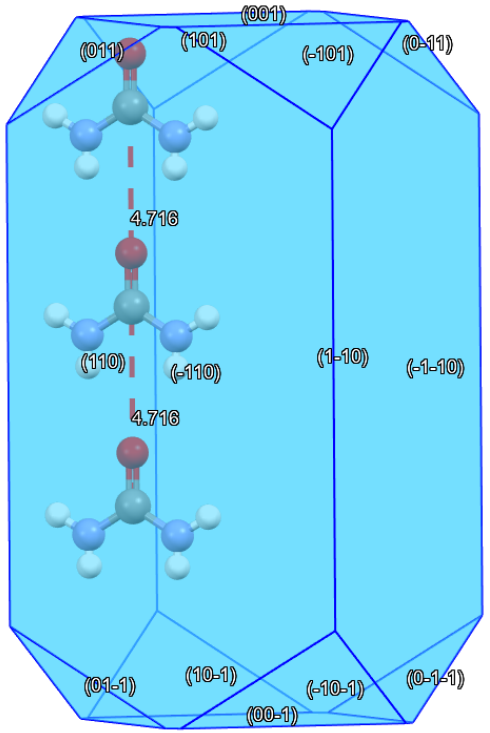
The *BFDH* morphology tool calculates approximate crystal morphology based on crystallographic geometrical consideration, including the unit cell shape and symmetry operator information. On the other hand, VisualHabit calculates morphology based on crystal structure. Using a range of forcefields, the intermolecular interactions, or synthons, in a crystal structure can be calculated; the sum of these gives the lattice energy for that system. From this lattice energy, slice energies can be calculated and, consequently, the attachment energy for each slice. Crystal growth rates are assumed to be proportional to these attachment energies[1] and can be used to predict crystal shapes. The VisualHabit tool is used to calculate and analyse these energies and to visualize the resulting morphologies, an instrumental step in enabling solid form and particle design for small molecule crystal structures.

Learning Outcomes

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

- Calculate the BFDH morphology for a crystal.
- Set up and run a VisualHabit calculation and interpret the resulting lattice energies.
- Visualize and analyse morphologies and surface energies.
- Visualize and interpret intermolecular interactions (synthons).

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



VisualHabit morphology of UREAXX with a synthon highlighted.

Pre-required Skills

For this tutorial, we recommend being familiar with the program Mercury, especially structure visualization with Mercury.

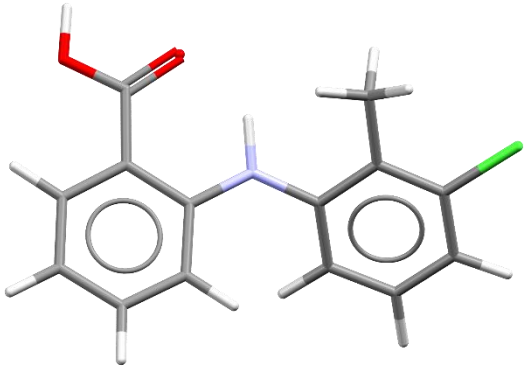
Materials

No additional materials are required to complete this self-guided workshop.

[1] P. Hartman, P. Bennema, *J. Cryst. Growth*, **1980**, 49 (1), 145-156. DOI: 10.1016/0022-0248(80)90075-5

Example 1. Calculating a BFDH morphology for a structure in the CSD.

In this example, we will employ the BFDH Morphology feature in CSD-Particle to visualise different surfaces of a 2-(3-chloro-2-methylanilino)benzoic acid crystal.



CSD Entry KAXXAI10 2-(3-chloro-2-methylanilino)benzoic acid

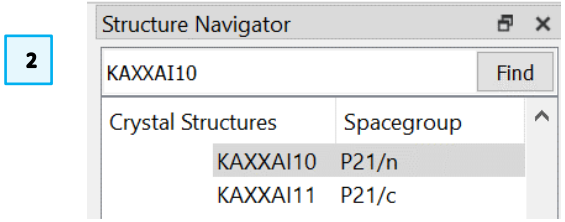
1. Open Mercury by double-clicking the Mercury icon on the desktop.

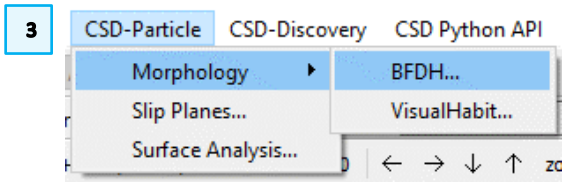
2. In the **Structure Navigator** toolbar type the refcode “KAXXAI10”.

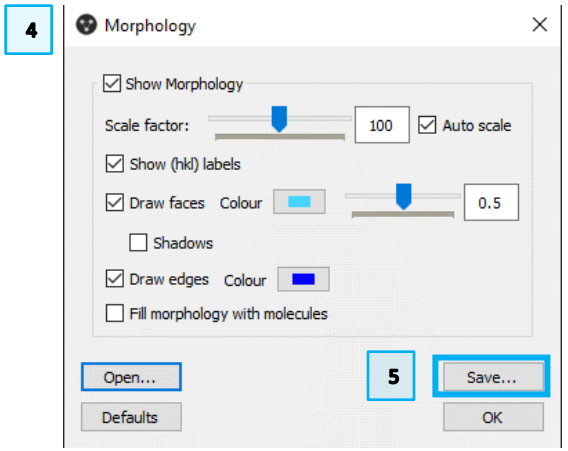
3. We want to identify facets of interest in this morphology. We will first create the morphology using the *BFDH morphology* feature. From the top-level menu select *CSD-Particle* > *Morphology* > *BFDH…* to generate the morphology. BFDH morphology uses the unit cell to create the morphology you see, therefore it does not account for the chemistry of the structure.

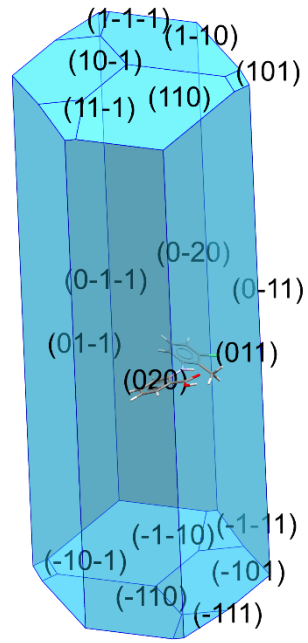
4. Rotate the structure to view the various facets that have been generated. If you wish, explore options in the **Morphology** window.

5. The morphology can be modified, for example if you want to represent a crystal observed from growth experiments. In the **Morphology** window, click **Save…** and place the .cif file in a folder where you have permissions.



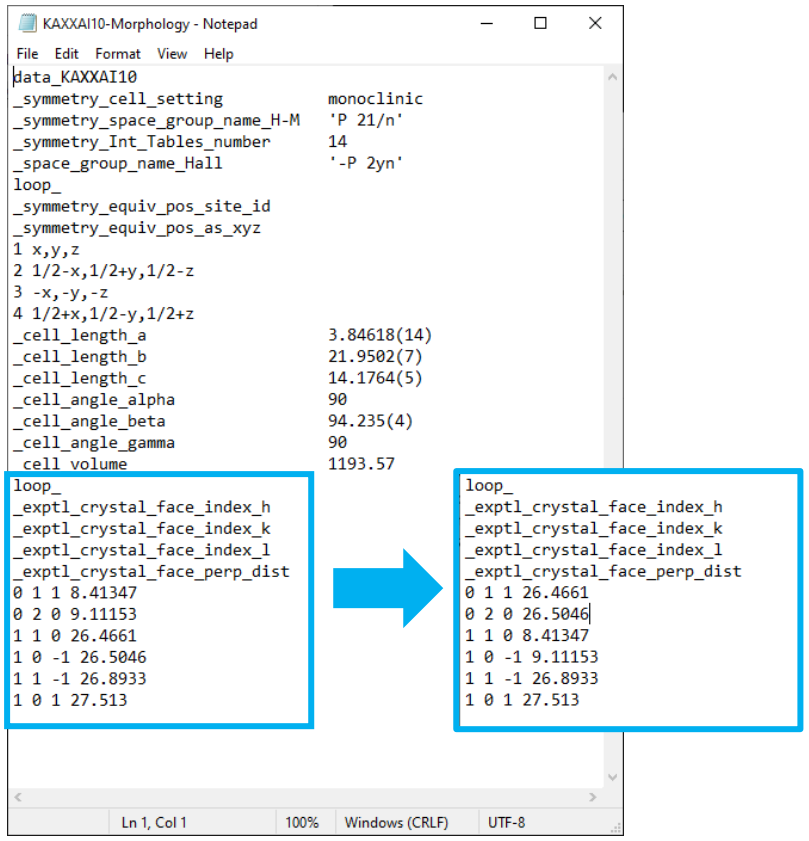




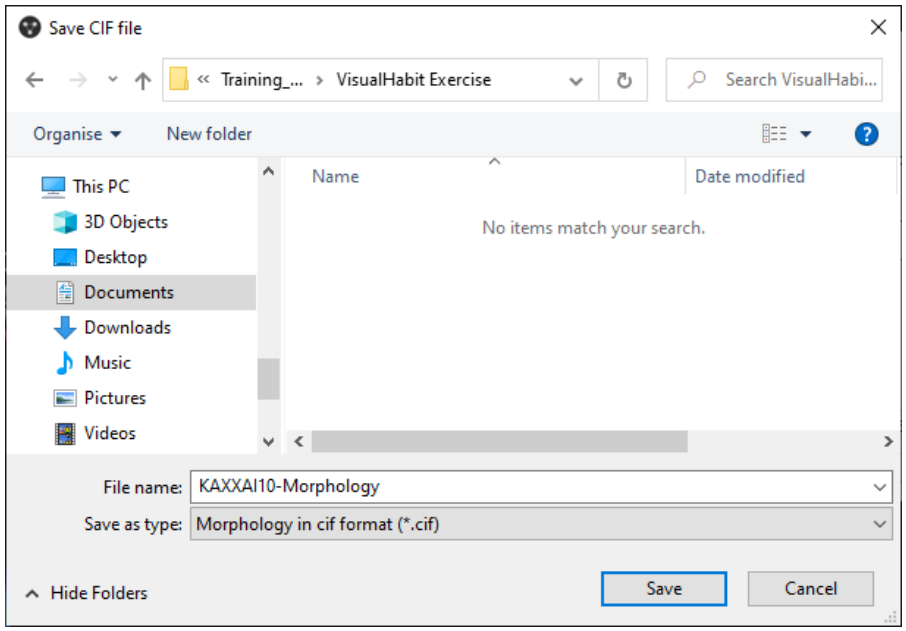


6. Using a text editor of your choice open the morphology CIF file. You will see the data that correspond to the *hkl* indices and perpendicular distances. You can modify these values to change the morphology. For the purposes of this example, we will simply switch the values of some of the perendicular distances. Note that these changes are not based on experimental observation.

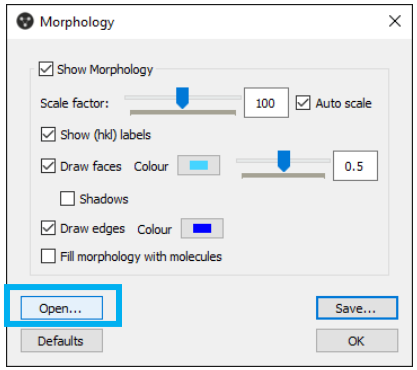
6



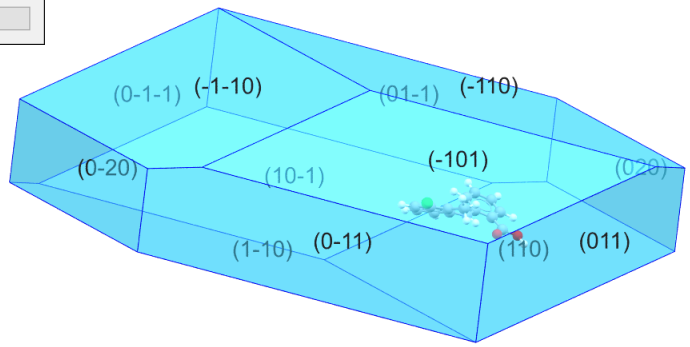
5



7



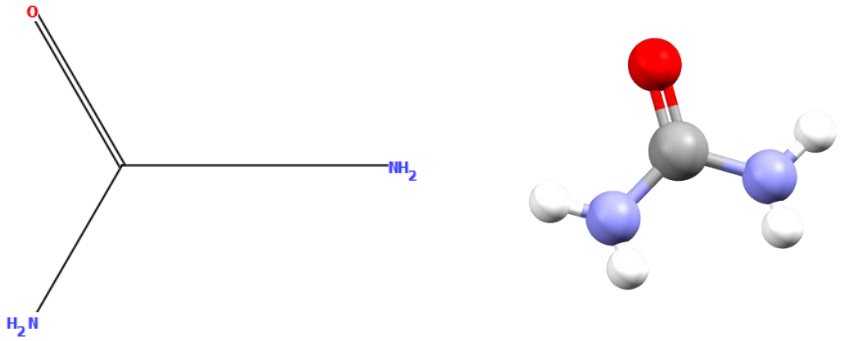
7. Back in Mercury, In the **Morphology** window click **Open…** and select your modified CIF file to visualize the new morphology.



Example 2. Calculating a morphology for a structure in the CSD using VisualHabit

The shape of a crystal results from the relative growth rates in different directions. Strong intermolecular interactions, or *synthons*, in one direction can result in the formation of elongated crystal shapes like needles. Needle-shaped crystals are common in pharmaceuticals and are undesirable due to their poor processing characteristics. Being able to predict needle formation from a crystal structure is helpful to understand potential manufacturing challenges.

Urea is known to exhibit a variety of habits, the most widely known being the prismoidal needle shape obtained from aqueous solution.[2] This example will look at the crystal structure of urea to answer the question: *How do elongated morphologies result from the directionality of intermolecular interactions?* You will learn how to calculate a morphology using *VisualHabit* for a structure in the CSD and how to analyse the output of the calculation.

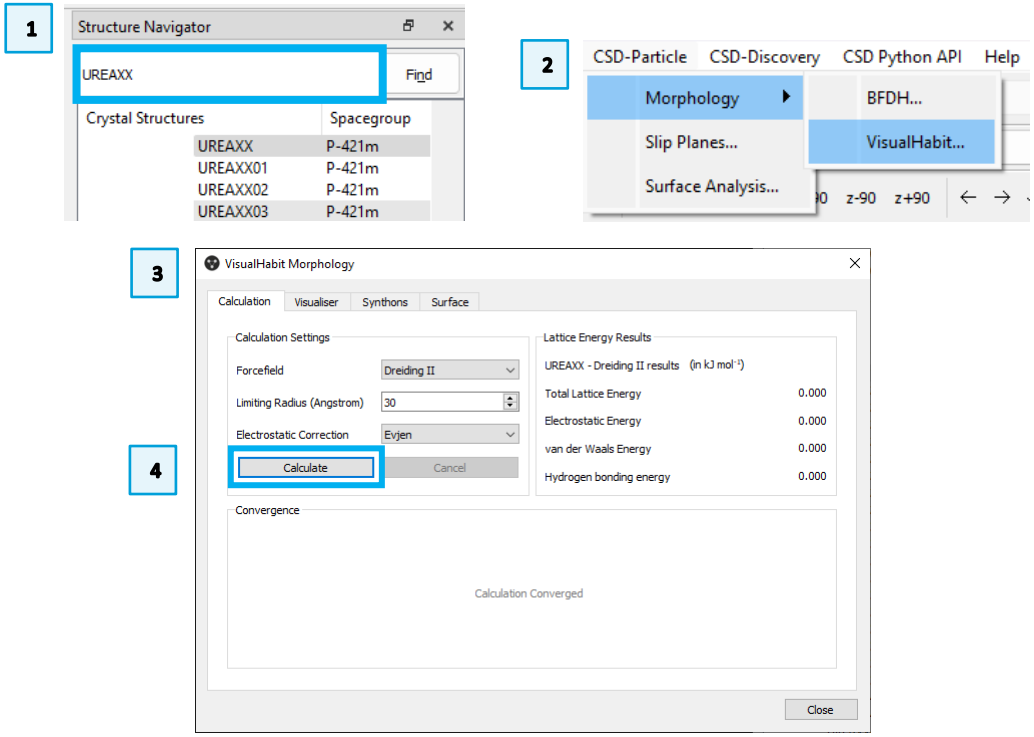


Urea, 2D representation and CSD entry UREAXX.

1. Launch Mercury by clicking its icon . In the **Structure Navigator** toolbar, type “UREAXX” to bring up the structure for urea.

2. Click on the **CSD-Particle** menu, select *Morphology > VisualHabit…*

3. In the **VisualHabit Morphology** window, you will see several options. On the left you will find options to change the calculations settings, such as which *forcefield* is used and the limiting radius for the calculation. You can also choose whether to add an electrostatic correction or not. On the right you will see where the lattice energy results will appear once the calculation is complete. 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 at specific chemistry or a charged system, you may want to change these settings.



[2] M. Salvalaglio, T. Vetter, M. Mazzotti and M. Parrinello, *Angew. Chem. Int. Ed.*, **2013**, 52, 13369 – 13372 DOI: 10.1002/anie.201304562

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

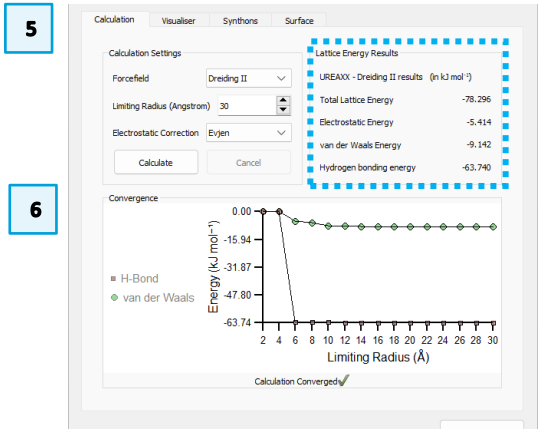
5. The window will now update to show the results of the VisualHabit calculation. The lattice energy results are shown in the section on the right in kJ mol^{-1}. From here, you can see the total lattice energy as well as the contributions from the electrostatic, *van der Waals*, and *hydrogen bonding* energy terms. It is clear from these results that the lattice energy for urea is dominated by the hydrogen bonding energy in the crystal structure.

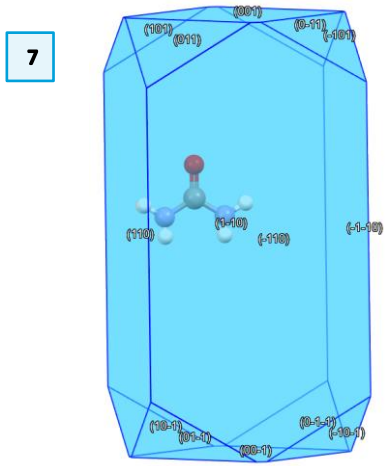
6. The convergence chart shows how the lattice energy changes over the course of the calculation out to the limiting radius and gives an indication of whether the calculation has converged successfully (indicated by the green tick at the bottom of the chart). This chart tells us that the lattice energy comes close to its final value in a small distance for this structure. Urea is a small molecule, so this is what we would expect to see.

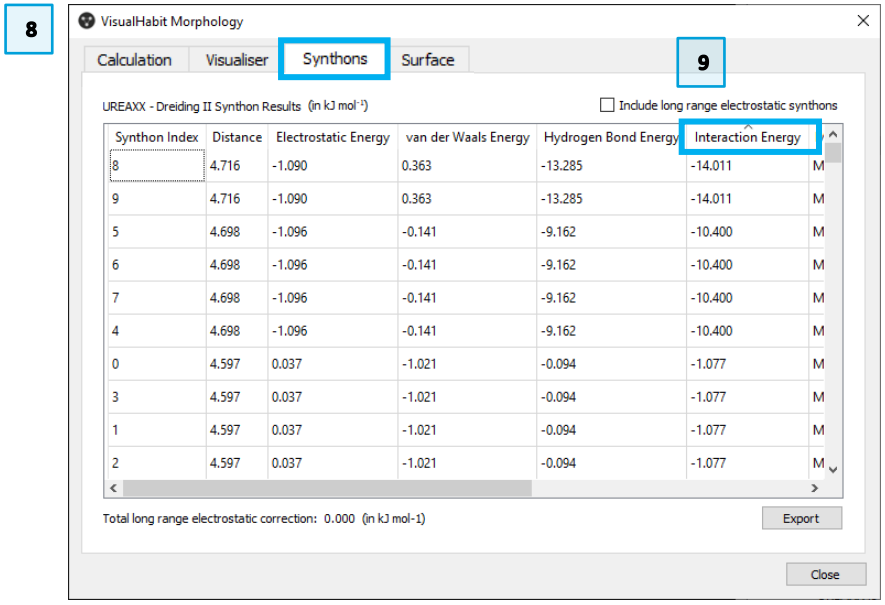
7. If we look at the Mercury visualizer, we will see that the calculated morphology for urea is now shown. VisualHabit calculates an elongated morphology for urea where the long axis is aligned to the polar axis of the urea molecule.

8. We will now explore the reasons for this elongated shape by examining the nature of the intermolecular interactions, or *synthons*, in more detail. Click on the **Synthons** tab in the to change the information that is shown.

9. The synthons that contribute to the lattice energy, along with the centroid-centroid distance and component energy terms, are now shown. Click on the *Interaction Energy* header (you may need to scroll along to see it) to sort this column from the strongest interaction to the weakest. Once again, you will see that the lattice energy for urea is dominated by a small number of strong hydrogen bonding interactions.







10. Now let us look at the two most important interactions. Click on one of the rows in the table to highlight that interaction and show the synthon in the Mercury visualizer. You can select multiple rows by holding down Ctrl and clicking on the rows of interest. Holding down Shift and clicking will let you select multiple rows at once. Select the top two interactions for UREAXX (synthons 8 and 9).

11. You will see in the Mercury visualizer that two other urea molecules have appeared above and below the central molecule. The red dashed lines between the molecules highlight the synthon, and the value beside the line shows the interaction energy. You can clearly see that the strongest interaction in urea aligns with the fastest growth direction.

12. Click the **Visualiser** tab in the **VisualHabit Morphology** window. From this tab you can change the way that the morphology is displayed in Mercury, such as changing the colour of the faces and the edges. You can also change how synthons are displayed.

13. Click the radio dial in the *Synthons* section to display *Distance* rather than *Energy.* The Mercury visualizer will update to show the centroid-centroid distance of the synthons in Å. These short, strong types of hydrogen bonds in the crystal structure of urea are key to understanding its growth and the shape of its crystals.

Conclusion

Crystal shape is governed by the relative growth rates in different directions. Strong intermolecular interactions, or *synthons*, in one direction can result in elongated morphologies. The crystal structure of urea is dominated by strong hydrogen bonding interactions that occur in tapes that propagate along the crystallographic *c*-axis. This results in an elongated morphology for urea.

Exercises

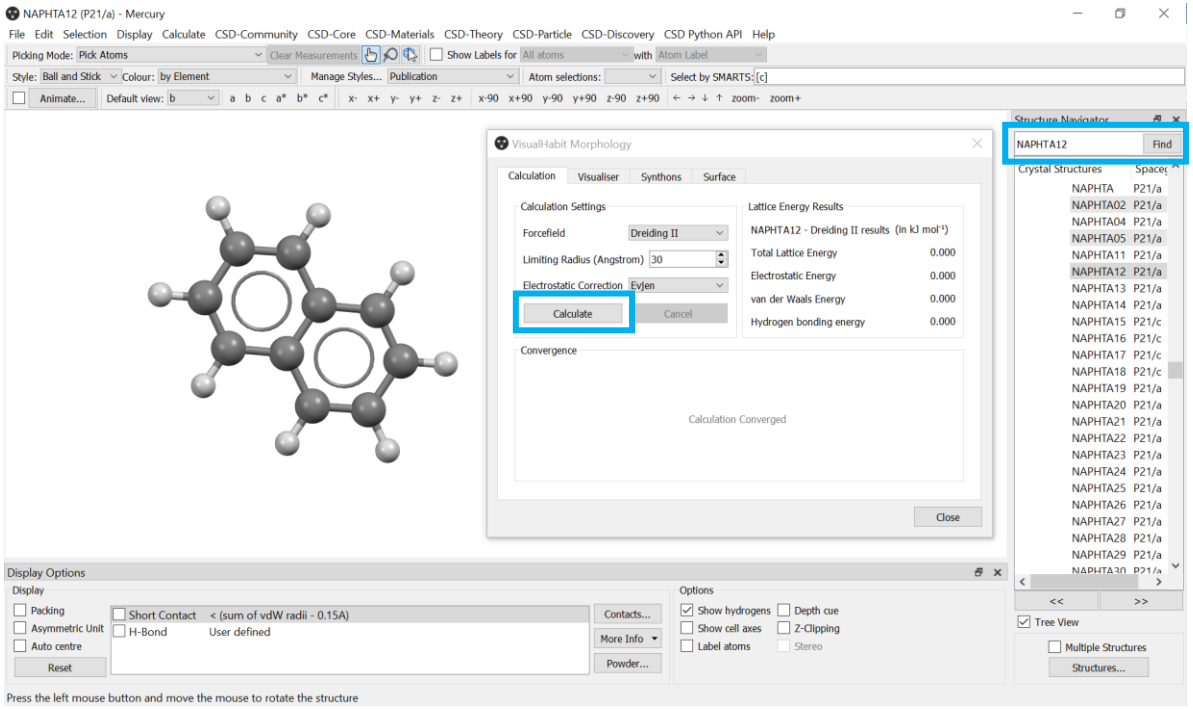
Locate the structure NAPHTA12 from the **Structure Navigator** and calculate its morphology with VisualHabit using the method in the example and answer the following questions:

1. What is the dominant term in the lattice energy?

2. Examine the *van der Waals Energy* in the **Synthons** tab. What can you deduce about the types of intermolecular interaction from the synthons with the lowest (most negative) van der Waals energy?

3. Look at the calculated morphology in the visualizer area, what are the dominant *forms* and what does this tell you about the relative growth rate of the faces?

4. In the **Surface** tab, locate the {001} form and compare the *Percentage Facet Area(%)* and *van der Waals Energy* values to some of the other forms in the table – how does this relate to molecular orientation?



Summary

In this self-guided workshop, you have learned how to perform a VisualHabit morphology calculation for a crystal structure and have explored features and options for this functionality. You should now be able to:

- Perform a VisualHabit calculation on a crystal structure.
- Visualize the predicted crystal morphology.
- Retrieve information about intermolecular interaction energies and structural features from VisualHabit.

For your reference, you can find further information on VisualHabit in the Mercury user manual which can be accessed from this page.

Next Steps

If you enjoyed this workshop you may like to review other CSD-Particle self-guided workshops available here. You can also complete our free on-demand training module "Surface Analysis with CSD-Particle" to receive a certificate.

Feedback

We hope this workshop improved your understanding of *VisualHabit* and particle shape calculation and you found it useful for your work. As we aim to continuously improve our training materials, we would love to hear your feedback. Follow the link on the workshop homepage and insert the workshop code, which for this self-guided workshop is *PAR-003*. It will only take 5 minutes and your feedback is anonymous. Thank you!

Exercise discussion

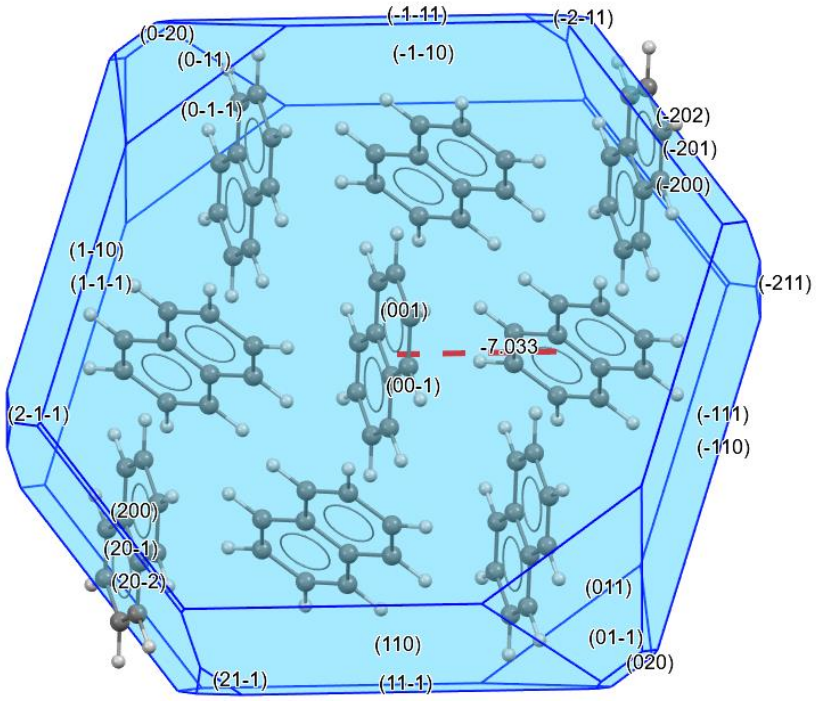
This exercise looks at a crystal in which the dominant intermolecular interactions are aromatic in nature and there is no hydrogen bonding. In contrast to the example with urea, the crystal is predicted to be lozenge-shaped.

1. The lattice energy is dominated by the van der Waals energy term (as expected there is no hydrogen bonding energy term), which is –62.555 kJ mol^{-1}.

2. The synthons with the most negative van der Waals energy (–6.736 kJ mol^{-1} each) are associated with edge-to-face (T-shaped) aromatic interactions, which are commonly observed for non-polar aromatics.[3]

3. The {001} form dominates this crystal. These facets are strongly inclined with respect to the plane of the aromatic rings, where there are minimal possibilities for aromatic interactions. Attachment of naphthalene molecules to these facets is predicted to be less favourable (so they would grow slowly).

4. The van der Waals energy associated with the (001) form in the **Surface** tab is –19.633 kJ mol^{-1}, the least negative of any in the table consistent with the interpretation in point (3).



VisualHabit morphology of NAPHTA12 with molecules inside the bounding facets. A very favourable synthon is highlighted by the red dashed line and joins molecules arranged in an edge-to-face stacking motif.

[3] C. A. Hunter, K. R. Lawson, J. Perkins and C. J. Urch, *J. Chem. Soc., Perkin Trans. 2*, **2001**, 651 – 669 DOI: 10.1039/b008495f

Glossary

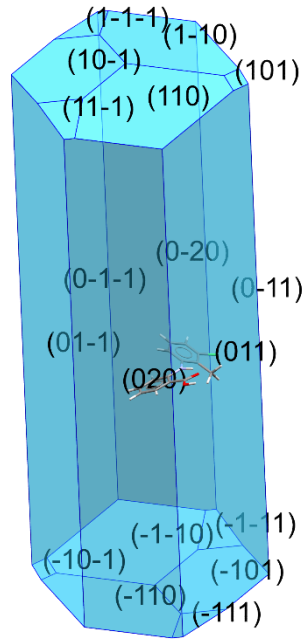
BFDH Morphology
Simulation of morphology using the Bravais Friedel Donnay Harker (BFDH) method. BFDH crystal morphology is an approximation based on crystallographic geometrical considerations. For a given structure, the BFDH algorithm will predict the habit or shape of a crystal using the corresponding unit cell and symmetry operator information.

Forcefield
In computational chemistry, the forcefield includes all the parameters employed to calculate the energy of a system.
In VisualHabit, three forcefields are available, namely Dreiding II, Momany, and Gavezzotti. More details and references are available in the Mercury User Guide: https://www.ccdc.cam.ac.uk/media/mercury.pdf .

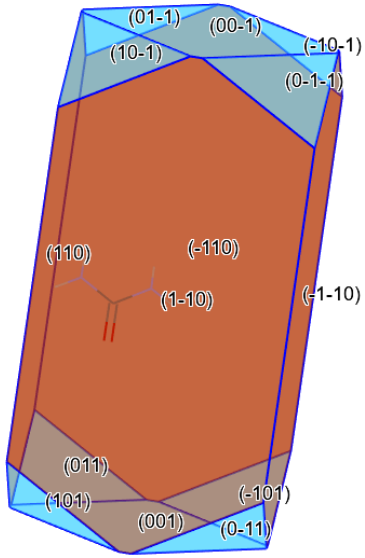
Form
A crystal form is a set of faces that are related to each other by symmetry. Crystal forms are designated by Miller Index notation with the indices enclosed in curly braces. For example, in CSD Entry UREAXX, (110), $(\bar{1}\bar{1}0)$, $(\bar{1}10)$ and $(1\bar{1}0)$ are related by fourfold symmetry and are written as {110}.

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).

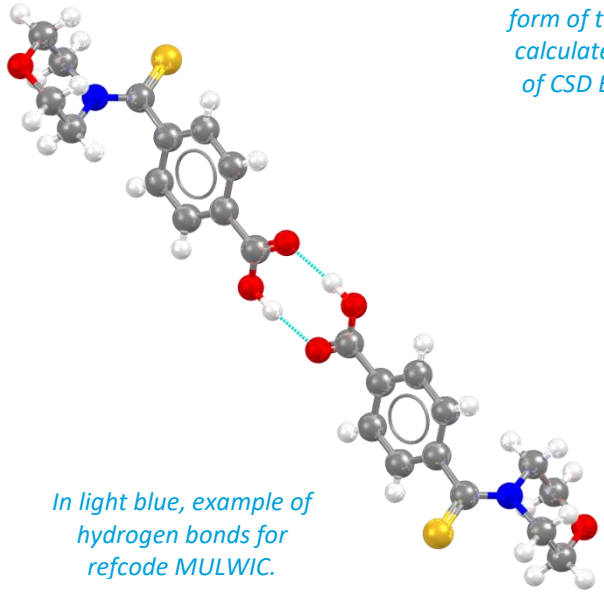
Relevant bibliographic references:
• Definition of the hydrogen bond (IUPAC Recommendations 2011), *Pure Appl. Chem.*, 83, 8, 1637–1641, 2011



Example of BFDH Morphology for CSD Entry KAXXAI10.



In orange, the {110} form of the VisualHabit-calculated morphology of CSD Entry UREAXX.



In light blue, example of hydrogen bonds for refcode MULWIC.

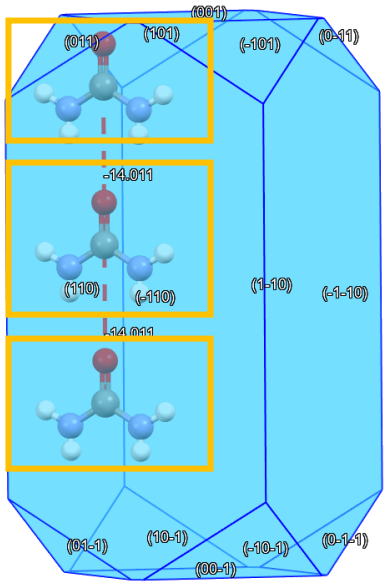
Synthon
A structural unit within a molecule which is related to a synthetic operation, such as calculating individual intermolecular interactions that make up the lattice energy in the VisualHabit Morphology component.

Teaching Subset
The Teaching Subset is a collection of the structural data for over 750+ chemical structures, freely available for education. Find out more here: https://www.ccdc.cam.ac.uk/community/education-and-outreach/education/teaching-subset/ .

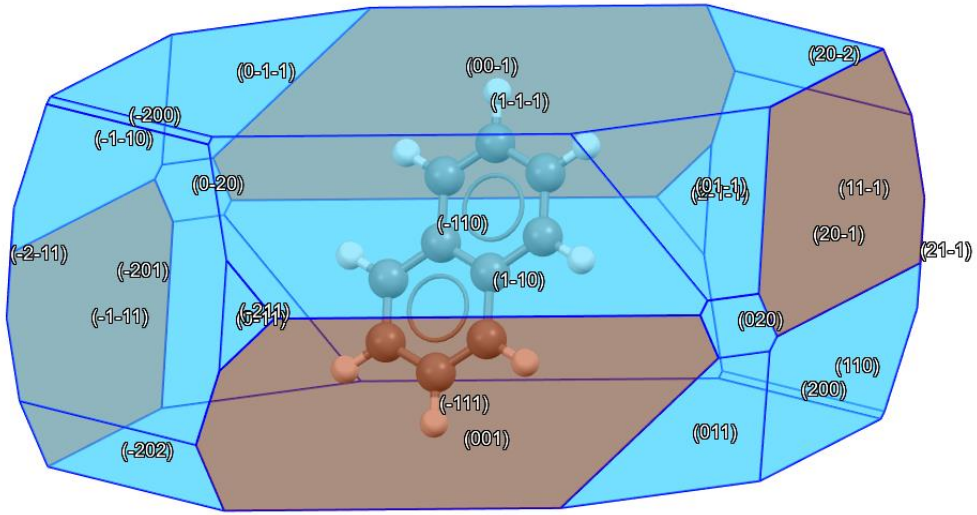
Van der Waals
Van der Waals forces are formed between atoms or molecules that are in each other's close proximity and are driven by induced electrical interaction. They are the weakest of all type of intermolecular interactions between molecules. However, with a lot of Van der Waals forces interacting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

VisualHabit
The VisualHabit Morphology component is an implementation of HABIT developed alongside collaborators at the University of Leeds. It can be used to calculate and visualise an attachment energy morphology, visualise individual intermolecular interaction energies (synthons), and provide information about the surface energies of the predicted morphology. Please refer to the following references for more details of the underlying method:

- G. Clydesdale, R. Docherty, K. J. Roberts, Comput. Phys. Commun. 1991, 64 (2), 311–328. DOI: https://doi.org/10.1016/0010-4655(91)90040-R
- G. Clydesdale, K.J. Roberts, R. Docherty, J Cryst. Growth, 1996, 166, 78-83. DOI: https://doi.org/10.1016/0022-0248(96)00056-5
- K. Roberts, R. Hammond, V. Ramachandran, and R. Docherty. Synthonic engineering. In Y. A. Abramov, editor, Computational Pharmaceutical Solid State Chemistry, 8, 87-116. John Wiley and Sons, Hoboken, 2016. ISBN: 978-1-118-70074-7



In the yellow boxes, example of synthons employed to calculate the lattice energy in VisualHabit for CSD Entry UREAXX.



Example of morphology calculated with VisualHabit with symmetry equivalent faces highlighted for CSD Entry NAPTHA12.

Basics of Mercury Visualization

Mercury is the CCDC's visualization software to view 3D structures of small molecules, generate images, and animations of molecules.

In the following we will see some of the basics of navigation and visualization in Mercury that you will find helpful to support your analysis.

In the **Mercury interface** we find:

- **At the top**: list of menus from which we can access visualization and analysis options, and other CSD components such as CSD-Materials.
- **On the right-hand side**: the **Structure Navigator**, with the database loaded (depending on your licence). The Structure Navigator allows you to select a refcode to visualize in the main Mercury window.
- Beneath the main display window: Display options toolbar. You can quickly view a packing diagram, display Hydrogen bonding and detailed information about the molecule using the More Info option.

Using the **mouse to enhance visualization**:

- Left mouse button and move – rotate molecules.
- Middle Mouse wheel – move molecules up and down.
- Right mouse button and move up and down – zoom in and out of molecules.
- Shift + Left mouse button and move - rotate in the plane molecules.
- Ctrl + Left mouse button and move - translate molecules.

Right click:
a) Near a molecule and
b) Away from a molecule