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Introduction & Definitions

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

The Aromatics Analyser tool in Mercury provides the user with the ability to quickly and easily visualise and identify aromatic interactions within a crystal structure, including their distance and relative orientation.

The tool allows insight into the observed aromatic interactions by estimating their stabilising influence upon the crystal structure.

This uses a neural network model* to provide a score between 0 and 10 based on how stabilising an aromatic ring interaction is expected to be, and assessment into ‘strong’, ‘moderate’ and ‘weak’ interactions.

* The model is based on a geometric description of aromatic interactions involving the position of two benzene rings relative to each other, in order to estimate the associated energy with an aromatic interaction, presented as a ‘score’. The influence of non-H substituents are not explicitly accounted for (model based on phenyl...phenyl aromatic interactions). The tool can be applied for aromatic rings that incorporate non-carbon atoms, but in such cases the interpretation should be approached with more care, because all the atoms will be treated as carbon (since the model is based on benzene rings), and the results can be less relevant.

### Aromatics Analyser score

- **Strong (10 → 7):** Likely to be significantly stabilising and potentially structure-directing
- **Moderate (7 → 3):** Likely to be noticeably stabilising, but less optimal geometries
- **Weak (3 → 0):** Likely to have a low contribution to lattice stabilisation

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### Packing shell:
van der Waals radii +0.5 Å

### Distance:
centroid-centroid distance (Å)

### Relative orientation:
angle between ring normals (*)
Summary of Aromatics Analyser interface

The Aromatics Analyser is interactive with the 3D visualiser in Mercury, and is simple to use (select a molecule and click Calculate).

Overview of dialogue box & associated actions

- Save a .csv file
- More info for atoms involved in interaction
- Tailor which interactions are specified
- Structure analysed
- Centroid-centroid distance (Å)
- Angle between ring normals (°)
- Scale of 0 (weak) to 10 (strong)
- Hover for info, click to re-order
- Bond types may be edited using Edit Structure... from the main window

Structure analysed:

- Centroid-centroid distance (Å)
- Angle between ring normals (°)
- Scale of 0 (weak) to 10 (strong)
- Hover for info, click to re-order

Tailor which interactions are specified:

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- Bond types may be edited using Edit Structure... from the main window
- Structure analysed

More info for atoms involved in interaction:

- Save a .csv file
- Centroid-centroid distance (Å)
- Angle between ring normals (°)
- Scale of 0 (weak) to 10 (strong)
- Hover for info, click to re-order
1. Visualising aromatic interactions

The presence and types of different aromatic interactions within crystal structures can be difficult to visualise and understand.

The two examples in this section illustrate how to quickly and easily visualise aromatic interactions and associated parameters using the Aromatics Analyser within CSD-Materials, and introduces the use of the tool to analyse and assess the nature of the resulting aromatic interactions.

1a. Example of favourable aromatic interactions (PHYDAN01)

1. Open Mercury by double-clicking mercury.exe from within the Mercury 4.1.1 folder (provided to CFC members).

2. In the Structure Navigator window, type the refcode PHYDAN01, to load the structure of phenytoin (Dilantin), an anti-seizure medication.

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

4. From the top-level menu select CSD-Materials > Aromatics Analyser to launch the Aromatics Analyser dialog box.

5. Select one molecule in the 3D visualiser by Shift+Left-click, then click on Calculate in the Aromatics Analyser dialog box to generate the aromatic interactions of the selected molecule and its neighbours. A packing shell is generated using a default value of van der Waals radii +0.5 Å.
6. A table of data relating to the aromatic interactions found in *PHYDAN01* will now be displayed in the *Aromatics Analyser* dialog box. The refcode of the structure being analysed is displayed at the top of the dialogue box.

7. The table is interactive: if you click within a row in the table, the aromatic rings involved in that interaction will be highlighted in the 3D visualiser. This allows a quick route to easily viewing the aromatic interactions present in the crystal structure and their associated geometric parameters.

8. Data can be re-ordered by left-clicking in the desired column heading (e.g. high to low relative orientation).

9. The data in the table includes the distance between aromatic ring centroids (Å), relative orientation (°), as well as a score (0-10) assessing the strength of that interaction. Further information can be obtained by hovering the mouse over the column heading (e.g. definitions of parameters, units, how the score is classed for the ‘Assessment’) or over the coloured assessment result (for the meaning of ‘strong’, ‘moderate’ and ‘weak’).

10. The numbering of aromatic rings in the *Centroid1* and *Centroid2* columns corresponds with those visible in the 3D visualiser. The *Centroid1* column contains only aromatic ring(s) from within the originally selected molecule. For *PHYDAN01*, there are 2 aromatic rings in the structure, labelled as 1 and 2 in the *Centroid1* column.

11. You can include Intramolecular pairs or exclude symmetry equivalent interactions from the table by toggling on the checkboxes at the bottom of the *Aromatics Analyser* dialog. By default, intramolecular pairs are excluded and symmetry inequivalent interactions are included. For example, excluding symmetry equivalent interactions in *PHYDAN01* halves the number of rows.

12. The Export button allows you to generate a summary of the main table content in CSV format, to facilitate further investigations of the numerical data.
13. By clicking the **Atom info** button, you can gain additional information about the atoms involved in the aromatic interaction highlighted in the main table, together with their distance, van der Waals adjusted distance and van der Waals overlap. Clicking on either of the atoms in a row will display the distance between that pair of atoms in the 3D visualiser.

14. **Examine the aromatic interactions and data for PHYDAN01.** There are a total of 48 aromatic interactions over a range of angles and centroid-centroid distances for the two, symmetry-related rings. These include (i) the strongest interactions approaching T-shape and (ii) parallel displaced interactions at slightly longer distances.

15. Of the aromatic interactions in *PHYDAN01*, 4 are assessed as ‘strong’ with higher scores – these are likely to be significantly stabilising in the structure. These are accompanied by a good range of moderately stabilising interactions, and several weaker interactions.

16. **PHYDAN01 is an example of a structure that appears to be quite favourable in terms of aromatic interactions.** It is the developed API form, using the best hydrogen bonding network from HBP – the packing satisfies both hydrogen bonding and aromatic interactions particularly well.

**Further Exercises**

- Look at the hydrogen bonding and aromatic interactions for *PHYDAN01* together to see how they complement one another
1b. Example of less favourable aromatic interactions (ESTRON11)

17. To look at a different structure, it must be selected in the 3D visualiser and the table updated by clicking Calculate.

18. Examine the aromatic interactions for Estrone, an estrogen derivative. Type the refcode ESTRON11 into the Structure Navigator window, select the molecule by Shift+Left-click and then click Calculate to view the aromatic interactions. Note the refcode identifier at the top of the Aromatics Analyser has now changed to ESTRON11.

19. There are only 12 aromatic interactions for ESTRON11 (6 symmetry equivalent interactions). None of these are classed as strongly or moderately stabilising – there are no close centroid-centroid distances and no ‘high’ or ‘moderate’ scores.

20. ESTRON is an example of a structure with less favourable aromatic interactions. The stabilising impact of aromatic interactions on this structure is expected to be minimal, and certainly none of these would be supposed to be structure-directing.

21. The Close button can be used to close the Aromatics Analyser dialog box.
2. Investigating aromatic interactions for polymorphs

This section looks at comparing the nature and influence of aromatic interactions across different polymorphic forms using the Aromatics Analysers, both visually and quantitatively, and how these may align with other aspects. Examples include those with different and the same type of hydrogen bonding.

2a. Bicalutamide Forms I and II (JAYCES and JAYCE502)

Bicalutamide (Casodex) is an antiandrogen medication primarily used to treat prostate cancer. Bicalutamide contains 2 different aromatic rings, and there are 2 reported forms in the CSD.

1. **Load Form I of bicalutamide, JAYCES.** Open Mercury, select the JAYCES molecule, and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. **Examine the interactions and data for JAYCES (Form I)** in the 3D visualiser and resulting table. The identified aromatic interactions cover a range of different distances and relative orientations from parallel to tilted.

3. **Assessment indicates** there are many stabilising aromatic interactions for both ring #1 and ring #2 (see Centroid1 column), of which several are classed as ‘strong’ and ‘moderate’.

4. **JAYCES therefore looks quite favourable in terms of aromatic interactions.** How does this compare with the second polymorph of bicalutamide?
5. **Look at Form II of bicalutamide, JAYCES02.** Select the JAYCES02 molecule in Mercury, and click Calculate in the Aromatics Analyser to update the table.

6. **Examine the interactions and data for JAYCES02 (Form II) in the resulting table.** The identified aromatic interactions cover a range of different distances, although in this case all the relative orientations are near-parallel.

7. **JAYCES02 has two aromatic interactions with a high score (one per ring) that are likely to be significantly stabilising (‘strong’), and one moderate interaction for ring #2.** All the remaining interactions are relatively weak, and not likely to offer much in terms of lattice stabilisation. There are thus a few very good aromatic interactions in JAYCES02, although not that many.

8. **Comparison with Form I (JAYCES) shows the aromatic interactions are less favourable in both quality and quantity – lower scores for the aromatic interactions in Form II (JAYCES02) overall, and lower number of aromatic interactions identified.**

9. The Aromatics Analyser thus indicates that Form I (JAYCES) is more favourable than Form II (JAYCES02) in terms of aromatic interactions. It also highlights the differences in relative orientations of the aromatic rings within the two crystal structures.

10. **Form I and II of bicalutamide exhibit different hydrogen bonding.** Form I (JAYCES) is the best in HBP, compared to both Form II (JAYCES02) and all other networks.

11. **Form I (JAYCES) is the most thermodynamically stable Form.**

12. **This example has shown an instance of aromatic interactions aligning with other evidence about the stability of Form I over Form II of bicalutamide.**

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2b. Paracetamol Forms I and II (HXACAN01 and HXACAN)

1. **Load Form I of paracetamol, HXACAN01.** Select the HXACAN01 molecule in Mercury and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. **Examine the interactions and data for HXACAN01 (Form I) in the resulting table.** The identified aromatic interactions cover a range of different distances in parallel and T-shape orientations. Assessment indicates there is one stronger aromatic interaction, accompanied by some moderately stabilising interactions and a range of weaker interactions.

3. **Load Form II of paracetamol, HXACAN.** Select the HXACAN molecule in the 3D visualiser, and click Calculate to update the table.

4. **Examine the interactions and data for HXACAN (Form II) in the resulting table.** The identified aromatic interactions cover a range of different distances and orientations. Assessment indicates there are four stronger aromatic interactions, accompanied by a few moderately stabilising interactions and a range of weaker interactions.

5. **Compare and contrast the data on the aromatic interactions for Form I (HXACAN01) and Form II (HXACAN) of paracetamol.** Both have a similar top-ranked interaction (similar score and distance). There are a larger number of high scores for HXACAN (strong interactions over close distances), although there is a larger quantity of aromatic interactions overall for HXACAN01.

6. **Form I (HXACAN01) is the more thermodynamically stable Form.** In this case, both forms exhibit the same type of hydrogen bonding. Analysis using the Aromatics Analyser reveals the additional stabilisation for Form I does not appear to originate from better individual aromatic interactions. This is reinforced by comparison with DFT calculations,** which show the aromatic interactions in Form II (HXACAN) are associated with slightly better energies.

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** B3LYP-D3/6-311G** calculations on benzene dimers extracted from the crystal structures → estimated energy (kJ mol⁻¹) for the top 3 ranked aromatic interactions.
3. Investigating cases where aromatic interactions may be more relevant

This section looks at comparing the nature and influence of aromatic interactions for solid forms where aromatic interactions may be considered particularly pertinent to assessing structure stability.

Examples include cases where with no hydrogen bonding, or where there is limited or unfavourable information from other areas.

3a. Tesaglitazar (MATXUD)

Tesaglitazar is PPARα/γ agonist proposed for the management of type 2 diabetes. The structure investigated here is the commercially developed solid form, yet it exhibits some less than favourable aspects including HBP outcome and morphology.

1. **Load the structure of tesaglitazar (MATXUD).** Select the MATXUD molecule in Mercury and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. **Examine the interactions and data for MATXUD** in the resulting table. There are a decent number of good stabilising aromatic interactions (scores between 5 and 6.5) across both of the aromatic rings (#1 and #2). The structure appears reasonably favourable in terms of aromatic interactions, and would be expected to be quite supportive in terms of lattice energy stabilisation.

3. The hydrogen bonding in MATXUD involves donation from the carboxylic acid OH to one of the ether C-O groups. This results in the worst outcome in HBP (best arises from sulfonyl S=O accepting). Morphology for MATXUD is also sub-optimal, resulting in needles.

4. The aromatic interactions look quite reasonable for MATXUD, aligning with it being chosen as the solid form for development despite other caveats.
3b. Risperidone Forms I and II (WASTEP and WASTEP01)

Risperidone (*Risperdal*) is used as an antipsychotic. It exists as two polymorphs, one of which has $Z' = 2$. There are no donor protons in the structure, so the solid forms cannot be assessed via hydrogen bonding.

1. Load the structure of Form I of risperidone (*WASTEP*). Select the *WASTEP* molecule in Mercury and calculate the aromatic interactions (steps 1-5 for Example 1a).

2. Examine the interactions and data for *WASTEP* in the resulting table.

3. Load the structure of Form II of risperidone (*WASTEP01*). Select the *WASTEP01* molecule in the 3D visualiser. This form has $Z' = 2$, so we will need to select which molecule to analyse first. Toggle on ‘show labels’ for the non-CH atoms at the top of Mercury, and select the molecule containing O1, then click Calculate to update the table in the Aromatics Analyser dialogue box.

4. Examine the interactions and data for the 1st molecule of *WASTEP01* in the resulting table.

5. Examine the interactions and data for the 2nd molecule of *WASTEP01*. Repeat the same process, but this time selecting the molecule containing O3 for *WASTEP01*: click the ‘Reset’ button below the 3D visualiser, then select the required molecule and update the results by clicking ‘Calculate’ in the Aromatics Analyser dialogue box.

6. Compare and contrast the results for Form I (*WASTEP*) and Form II (*WASTEP01*). There is one ‘strong’ interaction in *WASTEP* (score of 9.0), accompanied by many aromatic interactions that would only be considered to weakly contribute to lattice stability at best. The situation is substantially less favourable for *WASTEP01*, however, where molecule #1 has no strong or moderately stabilising interactions and molecule #2 only has one interaction towards the bottom of the ‘moderate’ range (score of 3.9).
7. Form I (WASTEP) looks significantly more favourable than Form II (WASTEP01) from aromatic interactions, although distinguishing between the forms effectively comes down to a single aromatic interaction.

8. Assessment from the Aromatics Analyser agrees with the thermodynamic stability* – Form I (WASTEP) is more favourable


Further Exercises
- Investigate the overlap of phenyl and heterocycle rings between molecules for the two forms.
- How differently do the symmetrically inequivalent molecules in WASTEP01 behave in terms of aromatic interactions?
4. Summary

We have applied the *Aromatics Analyser* tool for several structures, including systems with no hydrogen bonding and polymorphic forms.

This has facilitated (1) easy visualisation and identification of aromatic interactions, and (2) a measure of quantitative assessment of their strength.

Further Exercises

- Analyse a structure of interest to you – what can you learn?
- Pick one of the examples and probe the aromatic interactions further in conjunction with another aspect (e.g. packing, hydrogen bonding, overlap of rings between molecules). What does it reveal?
- What would you consider bad / concerning / not well satisfied in terms of aromatic interactions?
- Is *quality* of aromatic interactions always more important than *quantity*?