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#### Aromatics Analyser MAT-005

#### 2020.3 CSD Release





#### 2

#### Introduction

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.

You can learn more about the tool by watching the How To Aromatics Analyser video (<u>https://www.youtube.com/watch?v=mYYpggxDt-E</u>) checking the Aromatics Analyser blog: (<u>https://www.ccdc.cam.ac.uk/Community/blog/2020-</u>04-17-new-for-20201-release-aromatics-analyser-in-merc/)

#### Objectives

- Visualise Aromatic Interactions
- Assess the strength of Aromatics Interactions in a crystal structure
- Gain insight into the observed aromatic interactions by estimating their stabilising influence upon the crystal structure
- Investigating aromatic interactions for polymorphs such as:
  - o Polymorphs with different H-bonding
  - Polymorphs with the same H-boding
  - Polymorphs with no H-bonding available
  - $\circ$   $\$  Polymorphs where Aromatic Interactions are more relevant

This workshop will take approximately **2** hours to be completed.

#### Pre-required skills

For this tutorial, we recommend being familiar with the following:

- Mercury interface and basics of visualisation
- In exercise 2a and 3a, we will show graphs obtained using hydrogen Bond Propensities feature. If you want to learn more, you can read about it in the Dictionary at the end of the handout, and we suggest the <u>Hydrogen Bond Propensity Workshop</u> on our website.



7	Aromatics A	nalyser HX	ACAN				×
Sel	ect atoms in j	ust <b>one</b> mole	cule				
	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment
1	1	2	4.65	58.43	Yes	8.9	Strong
2	1	10	4.87	50.79	Yes	8	Strong
3	1	12	5.94	26.95	Yes	5.9	Moderate
4	1	7	8.93	0	Yes	0.6	Weak
5	1	8	8.6	58.43	Yes	0.6	Weak
6	1	6	9.38	0	Yes	0.4	Weak
7	1	4	9.88	50.79	Yes	0.2	Weak
	Include Intra	amolecular pa	irs 🗹 Exclu	ude symmetry e	quivalent inte	ractions	
	Calculate	Export	Atom	i info			Close

#### Definitions

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.



#### 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

Hover





#### 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*)

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





Spacegroup

Pn21a

P21/c

P21/c



#### Estrone - CSD refcode ESTRON11

3	n	CSE	-Materials	CSD-Discovery	CSD	Py
	s		Search		+	
	yle		Calculation	IS	+	F
	:		Polymorph	Assessment	•	y.
			Co-Crystal	Design	•	Γ
			Full Interac	tion Maps		
			Hydrate Ar	nalyser		
			Solvate An	alyser		
			Aromatics	Analyser	N	
			Conformer Crystal Stru	Generation ucture Prediction		
		•	Launch DA ADDoPT	SH	•	



Find

>>

5

1

2

Structure Navigator

Crystal Structures

PHYDAN01

PHYDPT

<<

PHYDAN02 Pna21 PHYDAN03 Pna21 PHYDMO

PHYDMO10 P21/c

PHYDAN01

MAT-005

- 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.
- Data can be re-ordered by left-clicking in the desired column heading (e.g. 8. 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.

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6

#### Aromatics Analyser... PHYDAN01

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

	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment	^
1	1	20	5.06	72.76	Yes	<mark>8.1</mark>	Strong	
2	2	21	5.06	72.76	Yes	<mark>8</mark> .1	Strong	
3	1	24	5.17	72.76	Yes	7.3	Strong	
4	2	25	5.17	72.76	Yes	7.3	Strong	
5	2	12	5.24	84.2	Yes	6.4	Moderate	
6	2	16	5.24	84.2	Yes	6.4	Moderate	
7	1	11	5.27	83.87	Yes	5.6	Moderate	
8	1	15	5.27	83.87	Yes	5.6	Moderate	
9	2	4	6.23	0	Yes	4.1	Moderate	
10	2	6	6.23	0	Yes	4.1	Moderate	
11	1	3	6.23	0	Yes	3	Weak	
12	1	5	6.23	0	Yes	3	Weak	
13	1	16	6.83	6.67	Yes	2.6	Weak	
14	2	11	6.83	6.67	Yes	2.6	Weak	
15	1	6	7.32	89.91	Yes	1.9	Weak	
16	2	3	7.32	89.91	Yes	1.9	Weak	~

Include Intramolecular pairs Exclude symmetry equivalent interactions Atom info

12-13

Calculate Export

11

Close

- 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 (Active Pharmaceutical Ingredient) form, using the best hydrogen bonding network from HBP (Hydrogen Bond Propensity) – 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

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#### 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.





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#### S Aromatics Analyser... ESTRON11

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

	/ / -		•		1		
	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment
1	1	3	7.46	0	Yes	1.8	Weak
2	1	4	7.46	0	Yes	1.8	Weak
3	1	7	7.52	11.06	Yes	1.5	Weak
4	1	9	7.52	11.06	Yes	1.5	Weak
5	1	6	7.83	11.06	Yes	1.3	Weak
6	1	8	7.83	11.06	Yes	1.3	Weak
7	1	12	7.35	40.19	Yes	1	Weak
8	1	13	7.35	40.19	Yes	1	Weak
9	1	2	12.19	0	Yes	0	Weak
10	1	5	12.19	0	Yes	0	Weak
11	1	10	16.88	40.19	Yes	0	Weak
12	1	11	16.88	40.19	Yes	0	Weak
] ]	Include Intra	nolecular pairs	Exclue	de symmetry equ	uivalent intera	ictions	
C	Calculate	Export	Atom	info			Close

#### 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 Analyser*, both visually and quantitatively, and how these may align with other aspects.

Examples include those with different and the same type of hydrogen bonding.





Bicalutamide - CSD refcodes JAYCES (Form I) JAYCES02 (Form II) Paracetamol - CSD refcodes HXACAN01 (Form I) HXACAN (Form II)

#### 2a. Bicalutamide Forms I and II (JAYCES and JAYCES02)

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?



	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment
1	2	20	4.39	0	Yes	8.6	Strong
2	1	17	4.68	0	Yes	7.5	Strong
3	1	14	5.13	25.81	Yes	6.7	Moderate
4	2	11	5.13	25.81	Yes	6.7	Moderate
5	2	12	6.26	64.29	Yes	3.2	Moderate
6	2	14	6.26	64.29	Yes	3.2	Moderate
7	2	22	6.88	0	Yes	3.1	Moderate
8	2	26	6.63	64.29	Yes	2.8	Weak
9	2	28	6.63	64.29	Yes	2.8	Weak
10	1	29	6.82	14.92	Yes	2.2	Weak
11	1	31	6.82	14.92	Yes	2.2	Weak
12	1	7	8.06	14.92	Yes	1	Weak

- 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. JACES02 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.
- 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 (JAYCESO2) overall, and lower number of aromatic interactions identified.
- 9. The Aromatics Analyser thus indicates that Form I (JAYCES) is more favourable than Form II (JAYCESO2) 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 (Learn more about HBP in the *Dictionary* section),, compared to both Form II (*JAYCESO2*) 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.

\* D. R. Vega, G. Polla, A. Martinez, E. Mendioroz, M. Reinoso, *Int. J. Pharm.*, **2007**, 328 (2), 112-118.

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

	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment	^
1	1	4	3.89	13.3	Yes	7.6	Strong	
2	2	13	3.89	13.3	Yes	7.6	Strong	
3	2	24	5.19	0	Yes	5.7	Moderate	
4	2	28	7.28	0	Yes	2.2	Weak	
5	1	17	7.24	0	Yes	2.1	Weak	
6	1	15	7.46	0	Yes	1.9	Weak	
7	1	24	7.46	13.3	Yes	1.7	Weak	
8	2	23	7.46	13.3	Yes	1.7	Weak	
9	1	18	8.15	13.3	Yes	1	Weak	
10	1	20	8.14	13.3	Yes	1	Weak	
11	2	17	8.15	13.3	Yes	1	Weak	
12	2	19	8.14	13.3	Yes	1	Weak	~
	Include Intrar	nolecular pairs	Exclud	le symmetry equ	uivalent intera	ctions		
C	Calculate	Export	Atom i	info			Close	



#### 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.

\* G. L. Perlovich, T. V. Volkova, A. Bauer-Brandl, J. Them. Anal. Cal., 2007, 89 (3), 767-774

\*\* B3LYP-D3/6-311G\*\* calculations on benzene dimers extracted from the crystal structures  $\rightarrow$  estimated energy (kJ mol<sup>-1</sup>) for the top 3 ranked aromatic interactions.

	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment	^	Energy*
1	1	10	4.74	0	Yes	8.1	Strong		-12.5
2	1	8	5.26	0	Yes	6.9	Moderate		-10.9
3	1	12	6.47	89.92	Yes	4.4	Moderate		-6.9
4	1	13	6.47	89.92	Yes	<mark>4.</mark> 4	Moderate		-6.9
5	1	9	7.18	0	Yes	2.1	Weak		-2.3
6	1	6	7	89.92	Yes	2	Weak		
7	1	7	7	89.92	Yes	2	Weak		L 1
8	1	11	7.22	89.92	Yes	1	Weak		$\langle \cdot \rangle$
9	1	14	7.22	89.92	Yes	1	Weak		
10	1	2	8.58	89.92	Yes	0.6	Weak	~	

X

6

DFT

(kJ mol<sup>-1</sup>)

atics Ar	alyser HXA	CAN					$\times$		
oms in ju	st <b>one</b> molec	Distance	Relative	Inter-	Score	Assessment	^	Energy*	ן
	2	4.65	Orientation 58.43	molecular Yes	8.9	Strong		-15.3	6
	3	4.65	58.43	Yes	8.9	Strong		-15.3	
	10	4.87	50.79	Yes	8	Strong		-13.5	DFT (kl mol <sup>-1</sup> )
	11	4.87	50.79	Yes	8	Strong		-13.5	
	12	5.94	26.95	Yes	5.9	Moderate		-9.2	
	13	5.94	26.95	Yes	5.9	Moderate		-9.2	
	7	8.93	0	Yes	0.6	Weak			
	8	8.6	58.43	Yes	0.6	Weak		•	Tor
	9	8.6	58.43	Yes	0.6	Weak			Y
	6	9.38	0	Yes	0.4	Weak			

Close

2

4

Arom

Select at

3 1

4 1

5 1

6 1

9 1

10 1

Calculate

Export

Atom info

Ce

S Aromatics Analyser... HXACAN01

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

#### 3a. Tesaglitazar (MATXUD)

Tesaglitazar is PPAR $\alpha/\gamma$  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.

2	🔊 A Sele	vromatics An	alyser MAT st <b>one</b> molecu	XUD	0=	Ri H₃C ■S	ing #1	Tes	Ring #2 Eto
		Centroid1	Centroid2	Distance	Relative Orientation	O Inter- iolecula	Score	Assessment	
	1	1	15	5.16	58.54	Yes	6.5	Moderate	
	2	1	19	5.16	58.54	Yes	6.5	Moderate	
	3	1	3	5.76	0	Yes	6.3	Moderate	
	4	1	5	5.76	0	Yes	6.3	Moderate	
	5	1	16	5.78	82.59	Yes	5.1	Moderate	
	6	2	19	5.78	82.59	Yes	5.1	Moderate	
	7	2	4	5.76	0	Yes	5	Moderate	
	8	2	6	5.76	0	Yes	5	Moderate	
	9	2	28	7.34	28.22	Yes	2	Weak	
	10	2	30	7.34	28.22	Yes	2	Weak	



#### 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 1<sup>st</sup> molecule of *WASTEP01* in the resulting table.
- 5. Examine the interactions and data for the 2<sup>nd</sup> 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).



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- 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
- \* D. Mealey, M.Svärd, Å. C. Rasmuson, Fluid Phase Equilibr., 2014, 375, 73-79

# WASTEP01, Molecule #1

1			Orientation	molecular	Score	Assessment	
	10	6.87	14.58	Yes	1.8	Weak	
1	2	6.97	14.58	Yes	1.1	Weak	
1	5	7.66	0	Yes	1	Weak	
1	3	9.94	0	Yes	0.2	Weak	
1	4	9.94	0	Yes	0.2	Weak	
1	6	18.24	0	Yes	0	Weak	
1	7	15.6	0	Yes	0	Weak	
1	8	26.12	0	Yes	0	Weak	
1	9	18.58	14.58	Yes	0	Weak	
1	11	19.68	14.58	Yes	0	Weak	
1 nclude Intram	11 nolecular pairs	19.68	14.58 le symmetry equ	Yes iivalent intera	0 Inctions	Weak	
	1 1 1 1 1 1 1 1 1 1	1 2   1 5   1 3   1 4   1 6   1 7   1 8   1 9   1 11   nclude Intramolecular pairs	1 2 6.97   1 5 7.66   1 3 9.94   1 4 9.94   1 6 18.24   1 6 18.24   1 7 15.6   1 8 26.12   1 9 18.58   1 11 19.68   uclude Intramolecular pairs Exclude Intramolecular pairs	1   2   0.97   14.36     1   5   7.66   0     1   3   9.94   0     1   4   9.94   0     1   6   18.24   0     1   7   15.6   0     1   8   26.12   0     1   9   18.58   14.58     1   11   19.68   14.58	1   2   0.97   14.36   Yes     1   5   7.66   0   Yes     1   3   9.94   0   Yes     1   4   9.94   0   Yes     1   6   18.24   0   Yes     1   7   15.6   0   Yes     1   8   26.12   0   Yes     1   9   18.58   14.58   Yes     1   11   19.68   14.58   Yes	1   2   0.97   14.38   Tes   1.1     1   5   7.66   0   Yes   1     1   3   9.94   0   Yes   0.2     1   4   9.94   0   Yes   0.2     1   6   18.24   0   Yes   0.2     1   7   15.6   0   Yes   0     1   8   26.12   0   Yes   0     1   9   18.58   14.58   Yes   0     1   11   19.68   14.58   Yes   0	1   2   0.97   14.56   1es   1.1   Weak     1   5   7.66   0   Yes   1   Weak     1   3   9.94   0   Yes   0.2   Weak     1   4   9.94   0   Yes   0.2   Weak     1   6   18.24   0   Yes   0.2   Weak     1   6   18.24   0   Yes   0.2   Weak     1   7   15.6   0   Yes   0   Weak     1   8   26.12   0   Yes   0   Weak     1   9   18.58   14.58   Yes   0   Weak     1   19.68   14.58   Yes   0   Weak     1   19.68   14.58   Yes   0   Weak

#### **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?
- 5 WASTEP01, Molecule #2

The Aromatics Analyser... WASTEP01



×

#### Bond types may be edited using Edit | Edit Structure... from the main window

	Centroid1	Centroid2	Distance	Relative Orientation	Inter- molecular	Score	Assessment	Ì
1	1	12	5.97	0	Yes	3.9	Moderate	
2	1	4	6.87	14.58	Yes	1.8	Weak	
3	1	2	6.97	14.58	Yes	1.1	Weak	
4	1	10	9.94	0	Yes	0.2	Weak	
5	1	11	9.94	0	Yes	0.2	Weak	
6	1	3	19.68	14.58	Yes	0	Weak	
7	1	5	18.58	14.58	Yes	0	Weak	
8	1	6	15.03	14.58	Yes	0	Weak	
9	1	7	14.74	14.58	Yes	0	Weak	
10	1	8	21.8	14.58	Yes	0	Weak	
	Include Intrar	molecular pairs	s 🗌 Exclud	le symmetry equ	uivalent intera	ictions		
C	Calculate	Export	Atom i	info			Close	

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#### Conclusions

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?

#### Feedback

We hope this workshop improved your understanding of the *Aromatics Analyser* and you found it useful for your work. As we aim at continuously improve our training materials, we would love to hear your feedback. Click on <u>this link</u> 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-005. Thank you!



#### Dictionary

#### Hydrogen Bond Propensity (HBP)

- The HBP tool in Mercury>CSD-Materials evaluates the relative likelihoods of possible H-bonding networks in any observed polymorphs of a target system.
- Probabilities for hydrogen bond pairings to form in the target system are calculated from a statistical model built from relevant structures in the CSD. The model encapsulates information regarding the environment of the functional groups, which ensures the prediction is specific to the target molecule.
- Combining probabilities of hydrogen bond formation with a statistical model that captures information regarding how often a functional group participates allows the generation of chemically sensible alternative structures.
- The view of the solid-state landscape of an active ingredient afforded through the combination of propensity and coordination addresses questions such as how likely polymorphism is and whether there is the possibility of a more stable form. Specifically, you can:
  - $\circ$   $\;$   $\;$  Predict likely hydrogen bonds for a given molecule.
  - Assess crystal forms e.g. by identifying sub-optimal hydrogen bonding.
  - Calculate hydrogen bond propensities for individual donor and acceptor groups.
  - Perform a comprehensive analysis of hydrogen bonding on a set of structures.

#### The Chart:

- plots Mean H-bond Propensity vs the Mean H-Bond Co-ordination
- target structure is represented as a magenta circle
- the most likely H-bonding network is displayed in the lower-right corner, the outcome should be read along the diagonal
- QIJZOY refcode has the most likely H-bonding network for sulfasalazine listed first in the lower right-hand corner





Eg.: Sulfasalazine exhibits 3 potential donors and 6 acceptors that might compete in forming H-bond interactions. HBP can be used to evaluate which of these potential interactions are more likely to form.