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Crystalline

The newsletter of The Cambridge Crystallographic Data Centre

Unique Insights Gained at Eli Lilly

to Predict Solid Form Behaviour

Dr. Susan Reutzel-Edens at Eli Lilly is applying a new powerful informatics tool, Full Interaction Mapping, to the investigation of sold state interactions. This is a new feature of Mercury's Solid Form module in the 2015 release of the Cambridge Structural Database System. Solid Form Informatics, the use of existing structural knowledge to analyse and predict solid form behaviour, is a growing area of science and software that is highly complementary to experimental and more traditional computational approaches. Here Susan explains the impact of solid form informatics in a study on tazofelone, a compound investigated in the mid-90s as a potential treatment for inflammatory bowel disease by scientists at Eli Lilly and Company [1, 2].

Tazofelone (Figure 1) was developed as a racemic mixture of two enantiomers. Two racemic polymorphs (RCI and RCII), an enantiopure structure (AR or AS) and a racemic solid solution were known. In a recent assessment of the use of crystal energy landscapes as a complement to industrial solid form screening, the solid state behavior of the compound was revisited in collaboration with Prof. Sally Price and her team at University College London [3]. Using modern methods to understand the polymorphic landscape of the compound, they discovered another polymorph (RCIII) and rationalized the difficulty of forming enantiopure crystals in terms of the intermolecular forces at play within the crystal.

Solid form informatics complemented these experimental and computational studies, providing unique insights into the solid state stability of the tazofelone crystal forms. Hydrogen Bond Propensity (HBP) methods were used to model the interaction behaviour of the two hydrogen bond donors and three acceptors in the tazofelone molecule. The HBP results showed that the more stable RC polymorphs have the highest propensity hydrogen bonds, which correlated well with the observed stability of the racemic forms relative to the enantiomorph. Extension of the HBP analysis to assess other predicted crystal structures further revealed that the single enantiomer is incapable of packing in a more stable structure with the highest propensity hydrogen bond.

Going beyond the HBP method, which assesses the likelihood of possible donor-acceptor pairings, Full Interaction Mapping can be used to assess how well donor-acceptor pairings are satisfied based on the geometry of these interactions. If the observed pairings of donors and acceptors in a crystal structure are favorable and the geometries well represented, then the polymorph may be reasonably stable. If not, other polymorphs with higher propensity hydrogen bonds and better geometries may be possible. Hence, this approach can be used to guide experimental polymorph screening studies.

Full Interaction Maps were used in the case of tazofelone to complement the HBP analysis by taking into account the geometry of the hydrogen bonding interactions. Visualisation of Full Interaction Maps for the RCII and AR structures shows the most likely positions (or hotspots) of interactions in 3D based on statistical analysis of known structures. In the RCII polymorph, two of the hotspots are satisfied, whereas the third is not. The less stable AR structure, on the other hand, has none of the hotspots satisfied by H-bond interactions. In this example, the structural informatics, CSP and experimental observations collectively suggested that crystallizing enantiopure crystals from a racemic solution will be extremely difficult.

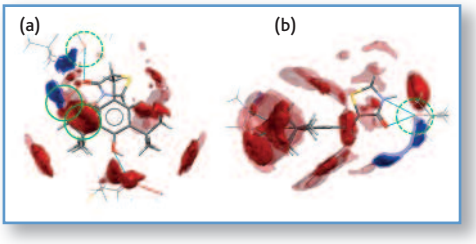

Figure 2: Full Interaction Maps visualised around the structure of tazofelone as observed in form RCII (a) and in form AR (b). The solid green circles represent hydrogen bonds that are satisfying donor or acceptor hotspots. The dashed circles highlight hydrogen bonds that are not located in hotspot regions.

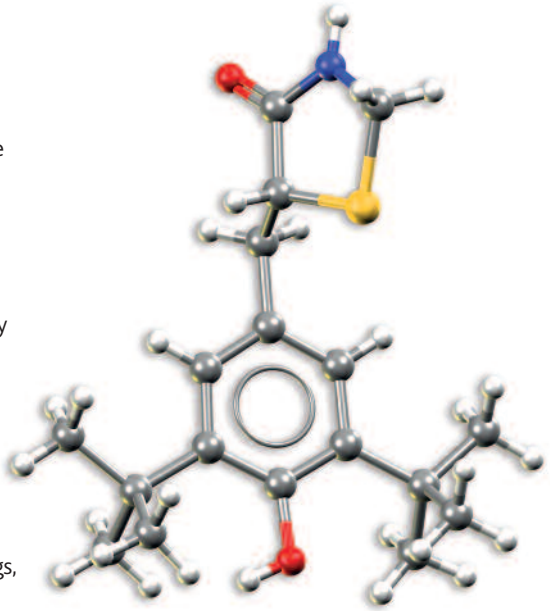

Figure 1: Molecular structure of tazofelone

Susan Reutzel-Edens (Eli Lilly) and Shyam Vyas (CCDC). Susan Reutzel-Edens is Senior Research Advisor of Small Molecule Design & Development at Ely Lilly & Company and has more than 20 years of experience working in the pharmaceutical industry. After studying for her PhD under the supervision of the late Professor Margaret C. Etter, Susan joined Eli Lilly & Company in 1991 where she developed and now leads the comprehensive solid form screening effort. She is a Topic Editor for Crystal Growth and Design and serves on the Editorial Advisory Board of the Journal of Pharmaceutical Sciences.

For more details on Full Interaction Mapping, see the companion article in this Newsletter entitled "Intermolecular Interaction Preferences in Context".

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[1] 4-Thiazolidinones, Potent Antioxidants, as Antiinflammatory Agents
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[3] A molecular picture of the problems in ensuring structural purity of tazofelone
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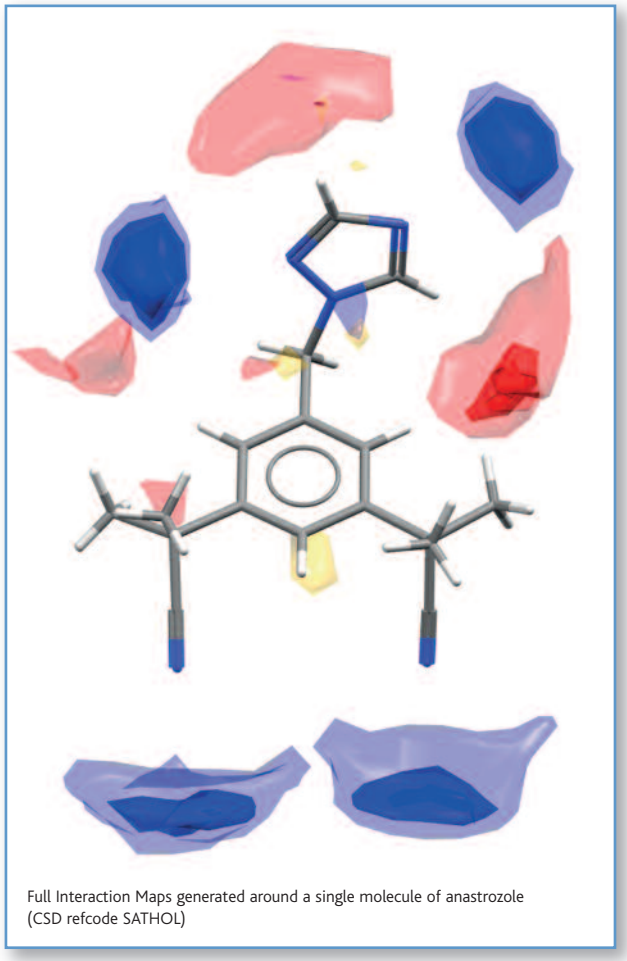
Intermolecular Interaction Preferences in Context

Crystallographers and solid state research scientists frequently find themselves studying a small molecule crystal structure and wondering how the nature and geometry of the observed intermolecular interactions compare to what would be expected for that compound. This can be particularly important when critically assessing a newly determined crystal structure for publication, or when reviewing the relative stability of a given crystal form. Such a review of intermolecular interactions in a structure is somewhat akin to enCIFer's check on CIF syntax, PLATON/checkCIF's report on consistency and integrity of structure determinations and Mogul's assessment of intramolecular geometry. Tables of geometric criteria can be generated for hydrogen-bonding, halogen-bonding and stacking contacts observed in the structure, but this is not very visual and misses the connection to what should be expected for the compound based on known chemically related structures.

With great enthusiasm, we are expanding Mercury's Solid Form module for the 2015 release of the Cambridge Structural Database System (CSDS) to include a Full Interaction Mapping tool [1] which is built on top of the current IsoStar [2] interaction knowledge-based technology already in the CSDS. Full Interaction Mapping provides the ability to visualise a molecule's interaction preferences at the click of a button and in the context of the observed crystal structure. This means the molecule's preferred interactions can be viewed in 3D and any experimentally known packing can be evaluated quickly and easily, whilst also generating appealing visuals for inclusion in reports or publications.

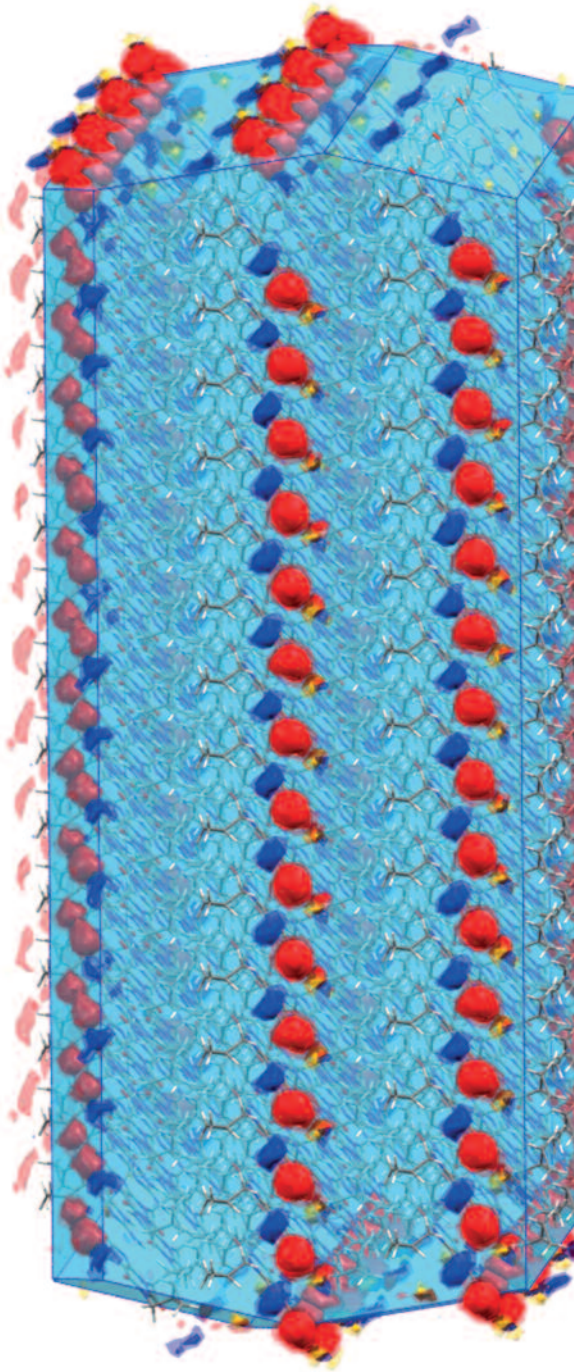
For an observed crystal form, the default settings of the Full Interaction Mapping tool provide a view in 3D of how hydrogen bond donors (blue), hydrogen bond acceptors (red) and hydrophobic groups (yellow) most commonly interact with the target molecule. This allows assessment of the relative strengths of each intermolecular interaction preference as well as comparison of the preferred geometry compared to the observed geometry.



Full Interaction Maps generated around a single molecule of anastrozole (CSD refcode SATHOL)

Going beyond the assessment of interactions for individual molecules, Full Interaction Mapping is also able to assess the interaction preferences of arrays of molecules from pairs of molecules all the way up to simulated particles. In industrial applications, the particle shape of a crystalline sample can have a profound effect on how the material behaves including tableting, flow, dispersion and filtering properties. **Using Mercury's morphology prediction and visualisation tools it is easy to predict particle shape based on a known crystal structure and assess the interaction preferences of the whole particle.**

This means that growth directions can be rationalised and strategies for design of surface inhibitors can even be developed based on the observed interaction patterns.



Full Interaction Maps generated around a simulated particle of cipamfylline (CSD refcode MOVYEC)

The new Full Interaction Mapping tool is a really powerful addition to Mercury's Solid Form module capabilities and we encourage all CSDS users to assess their own crystal structures with it.

Dr Pete Wood, Senior Research & Applications Scientist.

References:

[1] Evaluation of molecular crystal structures using Full Interaction Maps P. A. Wood *et al*, *CrystEngComm* (2013) 15, 65-72. 10.1039/C2CE25849H

[2] IsoStar: A library of information about nonbonded interactions I. J. Bruno *et al*, *J. Comput. -Aided. Mol. Des.* (1997) 11, 525-537. 10.1023/A:1007934413448

Exciting Developments in the Creation of the CSD

It is an exciting time in crystal structure data management! With approximately 60,000 structures being added to the CSD this year and over 9,000 entries added to the CSD in a single month in 2014 we needed to radically develop our systems to allow us to keep up with all your crystal structures. It isn't just the number of structures in the CSD that are going up, but the number of transactions and interactions that go on behind the scenes is also on the rise as we work with publishers and reviewers during the peer review process.

As a consequence the Scientific Editors and the Deposition Coordinators now use a new highly sophisticated system to manage your data depositions and process entries into the CSD. This new system was launched last year and any of you who have deposited structures or searched for data in the CSD should already have seen some changes. In June 2014 we launched a new web-deposition process to make it even easier for you to deposit your data into the CSD. We are delighted to report that more of you than ever are now depositing your data via the web and on top of that we have seen an increase in the number of depositions we are receiving, an increase in the number of unpublished structures added to the CSD as Private Communications and a rise in the number of structure factors added to our system. This is great news, as it means more of your data are being shared and that reviewers have access to structure factor data during the peer review process. Many of you will have also already noticed how quickly we now assign CCDC numbers and how quickly we are able to add published articles including 'Just Accepted' articles to WebCSD.

There are still many challenges ahead and we will be working hard to further ensure that the data are as accessible and discoverable as possible. Assigning Digital Object Identifiers (DOIs) to data in the CSD was the first step on this journey but expect to hear about many more developments in this area on our social media pages in the coming months.

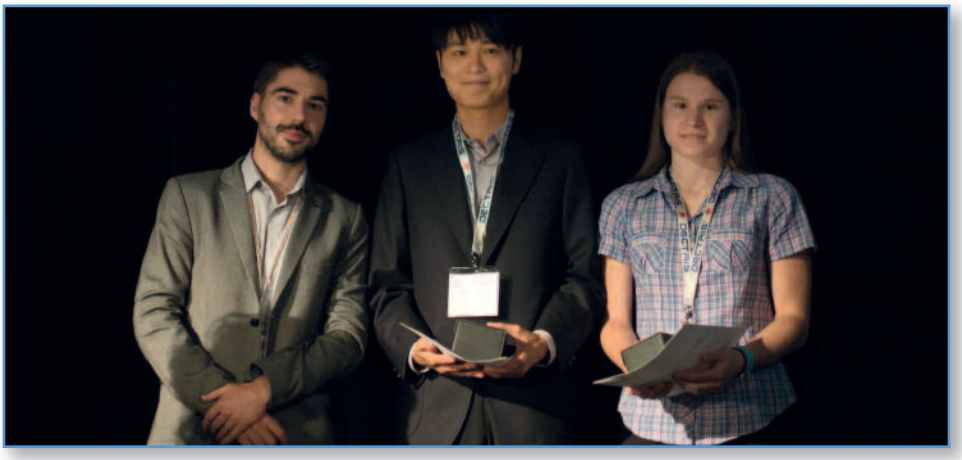
Lastly, as the recently appointed Manager of the CSD, I wanted to say what a pleasure it has been to meet so many of you at conferences during 2014. It has been a privilege to show you how we have developed over the last few years. Equally it has been invaluable to hear how you would like to see us develop and what matters to you. Your opinions will be paramount in helping define the future direction of the CSD. I look forward to sharing new developments with you and hearing how you would like to see us develop and evolve through our social media pages and in person at conferences in 2015!

Suzanna Ward – Manager, Cambridge Structural Database

Events

Date	Conference, meeting or event	Venue	Location	Activity
2 Nov 2014	PSDI, Protein Structure Determination in Industry	Hotel Miragem	Cascais, Portugal	Exhibition
2 Nov 2014	AAPS, American Association of Pharmaceutical Scientists Annual Meeting and Exposition	San Diego Convention Center	San Diego, CA, USA	Scientific Poster
12 Nov 2014	BCA, British Crystallographic Association - Industrial Group Autumn Meeting	Royal Institution of Great Britain	London, UK	Scientific Talk
12 Nov 2014	Material Science and Engineering in Drug Development	DECHEMA-House	Frankfurt, am Main, Germany	Scientific Talk
19 Nov 2014	BCA, British Crystallographic Association - Chemical Crystallography Group Autumn Meeting	RSC Chemistry Centre, Burlington House	London, UK	Scientific Talk
22 Mar 2015	ACS, American Chemical Society National Meeting & Exposition	Colorado Convention Center	Denver, Colorado, USA	Scientific Talk, Exhibition
30 Mar 2015	BCA, British Crystallographic Association - Spring Meeting	University of York	York, UK	Scientific Talk, Exhibition
16 Apr 2015	SCI Young Chemists Panel Crystallisation Conference		Cambridge, UK	Scientific Talk

Over the coming months, CCDC staff and researchers will attend important meetings and events around the world. We look forward to meeting you there.



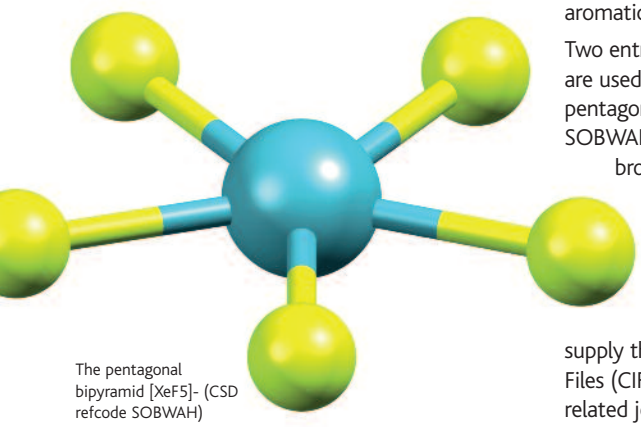
Dr Pete Wood (left) pictured during the IUCr Congress, Montreal, Aug 2014, with the recipients of the CCDC poster prizes: Chiaki Tsuboi, University of Kyoto, Japan (middle) and Doris Braun, University of Innsbruck, Austria (right). The third winner Filipe Almeida Paz, University of Aveiro, Portugal is not pictured. (Photograph: Daniel Wilson)

Crystallography in Chemical Education

Dr. Daron E. Janzen is an Associate Professor of Chemistry and currently the Endowed Chair in the Sciences at St. Catherine University http://minerva.stkate.edu/people.nsf/homepages/dejanzen. **Daron teaches undergraduate general chemistry and inorganic chemistry courses. He founded a crystallography consortium of Primarily Undergraduate Institutions (PUIs) in Minnesota (funded through the NSF-MRI award #1125975) to support the work of chemistry faculty involved in undergraduate research.**

When introduced, as a chemistry undergraduate student, to Valence Shell Electron Pair Repulsion theory (VSEPR) I was captivated by the idea that such a simple scheme could be used to predict molecular geometry with fair accuracy. Later, I became involved in research where crystallography was key to understanding the solid-state properties of our systems. Only then I realized how important crystallography was to verify those predictions of VSEPR. As a result, I now extensively use the free teaching subset of the Cambridge Structural Database when I teach undergraduate inorganic chemistry.

Early in my course, I have students complete a VSEPR exercise developed by the CCDC for use with the teaching subset (freely available from http://webcsd.ccdc.cam.ac.uk/teaching_database_demo.php).

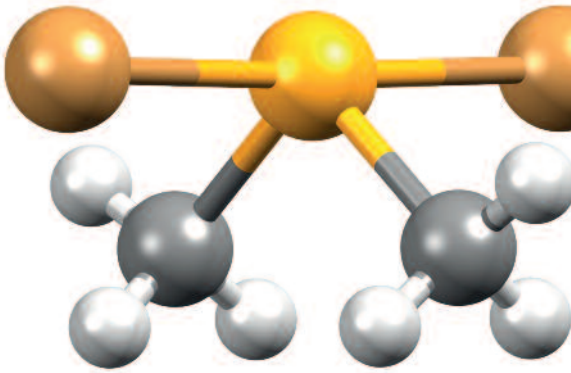


The pentagonal bipyramid [XeF5]- (CSD refcode SOBWAH)

This exercise, while largely a review of VSEPR for these students, exposes them to interaction with the CSD. As well as the free web-based interface to the teaching subset, we make use of the CCDC's 3D visualizer Mercury (available under licence as part of the CSD System, or as a free download from the CCDC website: http://www.ccdc.cam.ac.uk/Solutions/FreeSoftware/Pages/FreeMercury.aspx) to view entries in the teaching subset, giving them the opportunity to interact with the structures more and carry out tasks such as measuring bond lengths and angles. For many students, this is one of their first experiences with small-molecule crystallographic data. I find this exercise is a very important tool in helping students understand the difference between structural data and theorized or calculated molecular structures they are more familiar with. This exercise requires students to predict molecular structures based on Lewis structure drawings followed by comparison with relevant database structures in the teaching subset. Careful manipulation of the crystallographic data using Mercury is needed to measure and describe structural parameters and overall geometry of the example structures. Structural examples that do not follow VSPER predictions are even included, showing students all theories have limitations and weaknesses. Other tutorials on concepts including hapticity, ring conformations, stereochemistry, and aromaticity are also available.

Two entries in the free teaching subset and that are used in the VSEPR teaching exercise. The pentagonal bipyramid [XeF5]- (CSD refcode SOBWAH) and the "see-saw" shape of di-bromodimethylselenium (CSD refcode RIZMIW).

I also have students use Mercury on a regular basis throughout my inorganic course to analyze structures as a part of weekly homework problems. I may supply the needed Crystallographic Information Files (CIFs), have students retrieve .CIFs from related journal websites, or require the students



The see-saw" shape of di-bromodimethylselenium (CSD refcode RIZMIW).

to use WebCSD to find the structural data. These teaching exercises include concepts such as effects of intra- and intermolecular interactions including hydrogen-bonding, comparison of bond length predictions with data to make inferences about bond strengths or relative importance of resonance structure contributions, rationalizing isomers based on symmetry of spectroscopic evidence from NMR, and Jahn-Teller distortions, to name a few.

Through repeated use of the CSD and Mercury through my course, students gain an appreciation for the power of crystallographic data and of the CSD. They begin to see how detailed structural data can reveal features of chemical systems otherwise difficult to obtain or simply inaccessible by other techniques. With the ever increasing role of crystallography in all areas of chemistry as well as material science and other disciplines, training of undergraduate students in using crystallographic information is even more crucial in preparing crystallographically literate scientists of the future.

The free teaching set and some exercises can be found on the CCDC's website: http://www.ccdc.cam.ac.uk/Community/Initiatives/Pages/TeachingInitiatives.aspx. For queries concerning the full Cambridge Structural Database System please contact admin@ccdc.cam.ac.uk.

CCDC Publications *May 2014 to Sept 2014*

The CCDC team frequently publish results of their research, which is often the work of collaboration with industrial or academic scientists.
You can find the full list of our publications at www.ccdc.cam.ac.uk/publications. Here are our most recent titles, published since 1st May 2014.

The cloud and other new computational methods to improve molecular modelling
O. Korb, P. W. Finn, G. Jones, *Expert Opin. Drug Discov.*, 2014, 9, 1121-1131 10.1517/17460441.2014.941800

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C. H. Schwalbe, *Cryst. Rev.*, 2014, 20, 295-306
10.1080/0889311X.2014.943202

Sixth blind test of organic crystal-structure prediction methods
C. R. Groom, A. M. Reilly, *Acta Cryst.*, 2014, B70, 776-777
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Which intermolecular interactions have a significant influence on crystal packing?
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Knowledge-Based Approaches to Co-Crystal Design
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Kernel Density Estimation Applied to Bond Length, Bond Angle and Torsion Angle Distributions
P. McCabe, O. Korb, J. C. Cole, *J. Chem. Inf. Model.*, 2014, 54, 1284-1288 10.1021/ci500156d

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Lars Vegard: key communicator and pioneer crystallographer
C. H. Schwalbe, *Cryst. Rev.*, 2014, 20, 9-24
10.1080/0889311X.2013.838674

Partial-wave analysis of particular peaks in total scattering cross sections caused by a single partial wave
K.-E. Thylwe, P. McCabe, *Eur. Phys. J. D* (2014) 68, 323. 2014
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