Should we remediate small molecule structures? If so, who should do it?

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The Cambridge Crystallographic Data Centre
University of Southampton

ECM32 – 18th August 2019

Aston University
Birmingham

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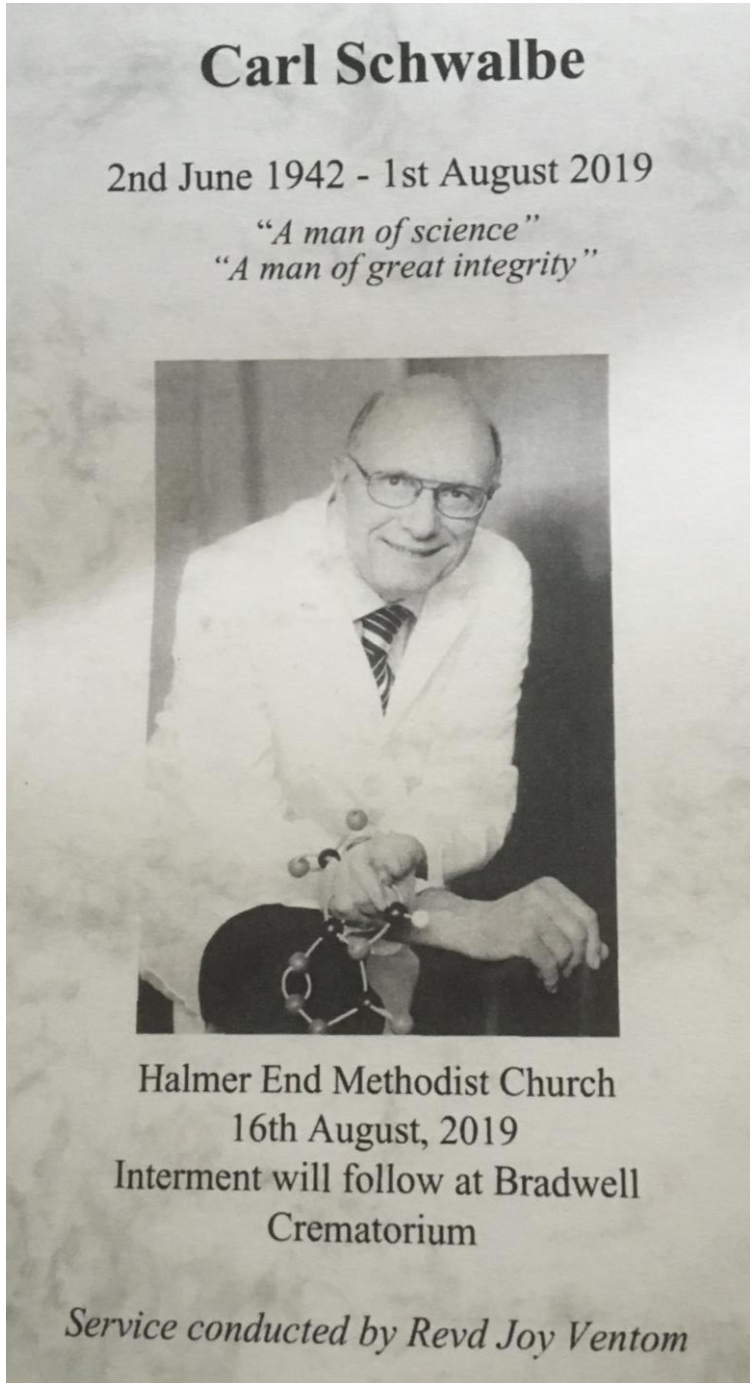
advancing structural science

Carl Schwalbe 1942-2019



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Carl Schwalbe 1942-2019

https://www.iucr.org/gallery/2009/aca-09?result_42723_result_page=24
https://www.amercrystalassn.org/assets/RefleXions/FALL2017RS.pdf
https://www2.aston.ac.uk/lhs/staff/az-index/schwalch

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A fine researcher

- The CCDC
  - 2010-2019 Emeritus Research Fellow
- Aston University
  - 2010-2019 Emeritus Professor of Medicinal Chemistry
  - 2007-2010 Professor of Medicinal Chemistry,
  - 1979-2007 Senior Lecturer in Medicinal Chemistry,
  - 1972-79 Lecturer in Medicinal Chemistry
- Max Planck Institute for Experimental Medicine
  - 1970-72 Research Fellow, (PI, Prof. W. Saenger)
- Harvard University
  - 1965-70 PhD., (PI, Prof. William N. Lipscomb)
  - 1964 AM
- Oberlin College
  - 1959-63 AB, Chemistry (summa cum laude)

https://www2.aston.ac.uk/lhs/staff/az-index/schwalch

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Member of the Medicines Research Unit

Member of research strand: 'Development of novel drugs, formulations and tissues to support healthy ageing' - Aston Research Centre for Healthy Ageing

Member of the Pharmacy and Biology Teaching Programmes

Research Interests +

- Determination of molecular structure by X-ray crystallography
- Theoretical calculation of electronic and conformational properties
- Relation of structural and electronic features to activity of drugs
- Correlation of solid-state intermolecular interactions with physico-chemical properties of drugs in solid dosage forms

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Professor Carl Schwalbe (2018)

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https://crystallography.org.uk/assets/pdf/crystallography-news/2018-03.pdf

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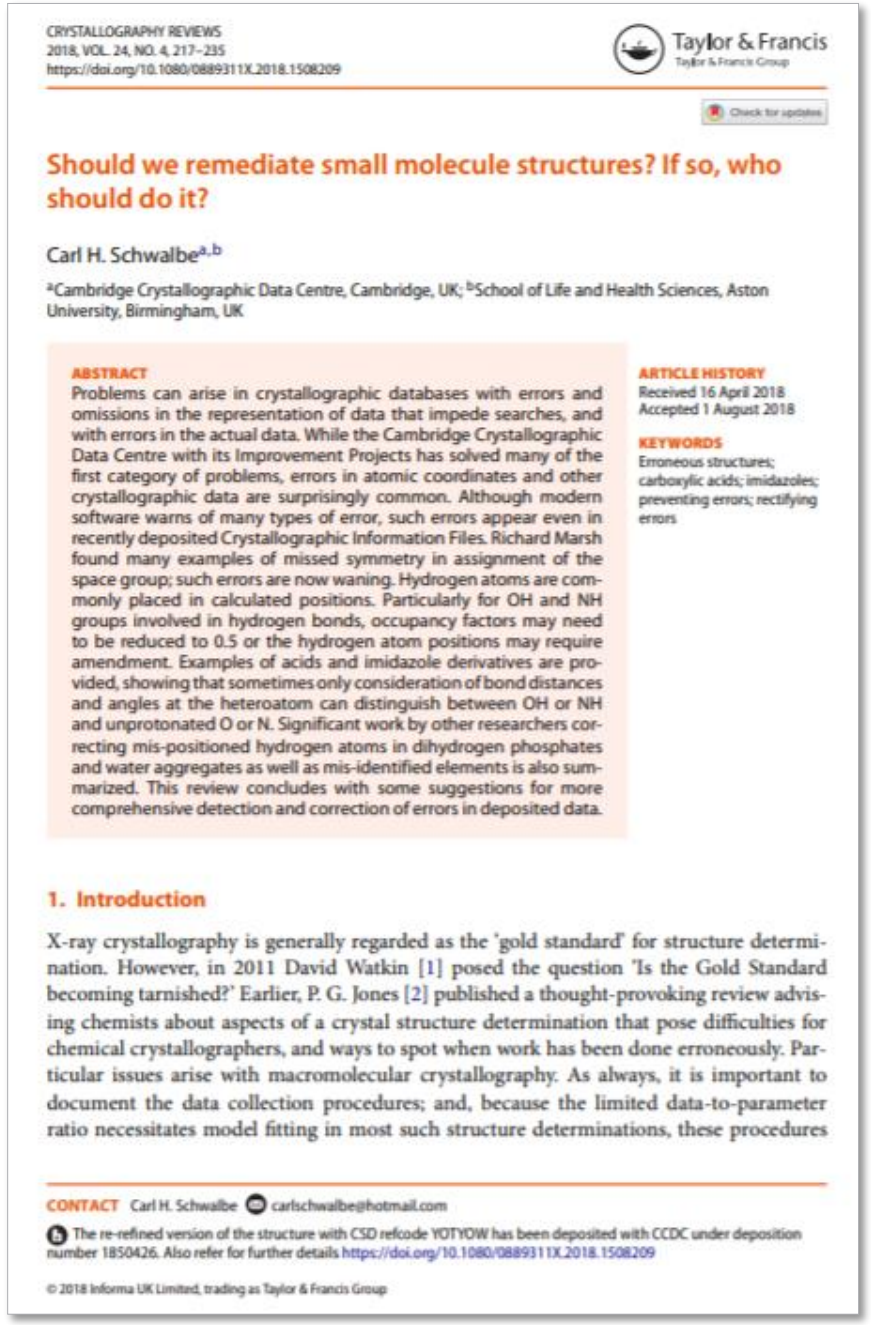

CRYSTALLOGRAPHY REVIEWS
2018, VOL. 24, NO. 4, 217–235
https://doi.org/10.1080/0889311X.2018.1508209

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Should we remediate small molecule structures? If so, who should do it?

Carl H. Schwalbe[a,b]

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ABSTRACT

Problems can arise in crystallographic databases with errors and omissions in the representation of data that impede searches, and with errors in the actual data. While the Cambridge Crystallographic Data Centre with its Improvement Projects has solved many of the first category of problems, errors in atomic coordinates and other crystallographic data are surprisingly common. Although modern software warns of many types of error, such errors appear even in recently deposited Crystallographic Information Files. Richard Marsh found many examples of missed symmetry in assignment of the space group; such errors are now waning. Hydrogen atoms are commonly placed in calculated positions. Particularly for OH and NH groups involved in hydrogen bonds, occupancy factors may need to be reduced to 0.5 or the hydrogen atom positions may require amendment. Examples of acids and imidazole derivatives are provided, showing that sometimes only consideration of bond distances and angles at the heteroatom can distinguish between OH or NH and unprotonated O or N. Significant work by other researchers correcting mis-positioned hydrogen atoms in dihydrogen phosphates and water aggregates as well as mis-identified elements is also summarized. This review concludes with some suggestions for more comprehensive detection and correction of errors in deposited data.

ARTICLE HISTORY
Received 16 April 2018
Accepted 1 August 2018

KEYWORDS
Erroneous structures; carboxylic acids; imidazoles; preventing errors; rectifying errors

1. Introduction

X-ray crystallography is generally regarded as the 'gold standard' for structure determination. However, in 2011 David Watkin [1] posed the question 'Is the Gold Standard becoming tarnished?' Earlier, P. G. Jones [2] published a thought-provoking review advising chemists about aspects of a crystal structure determination that pose difficulties for chemical crystallographers, and ways to spot when work has been done erroneously. Particular issues arise with macromolecular crystallography. As always, it is important to document the data collection procedures; and, because the limited data-to-parameter ratio necessitates model fitting in most such structure determinations, these procedures

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The re-refined version of the structure with CSD refcode YOTYOW has been deposited with CCDC under deposition number 1850426. Also refer for further details https://doi.org/10.1080/0889311X.2018.1508209

A recent article

This talk is partly based on Carl's thought-provoking article published in 2018 on the same topic:

- Should we remediate small molecule structures? If so, who should do it?
  Carl H. Schwalbe
  Crystallography Reviews
  2018, **24** 217-235
  DOI: 10.1080/0889311X.2018.1508209?

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Should we remediate small molecule structures?

- New reports of small molecule crystal structures should be error-free
  - Most reputable journals require validation of crystallographic data with CheckCIF
  - CheckCIF integrated into the CCDC deposition procedure
- Not all errors pointed out
  - Some journals appear to ignore or not use crystallographic referees
- What if authors are unable or unwilling to make corrections when required?
  - Should an otherwise correct structure be rejected because a hydrogen atom has been incorrectly placed?
  - Or disorder of a terminal methyl group has not been entered into the model?
- Should such a structure be published or deposited with a warning message, or should a corrected version be created?
- These questions have particular force with regard to already published structures that have errors

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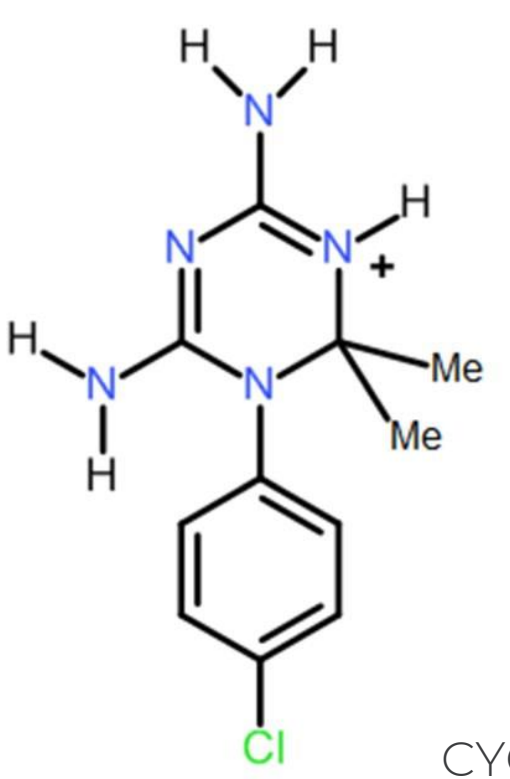
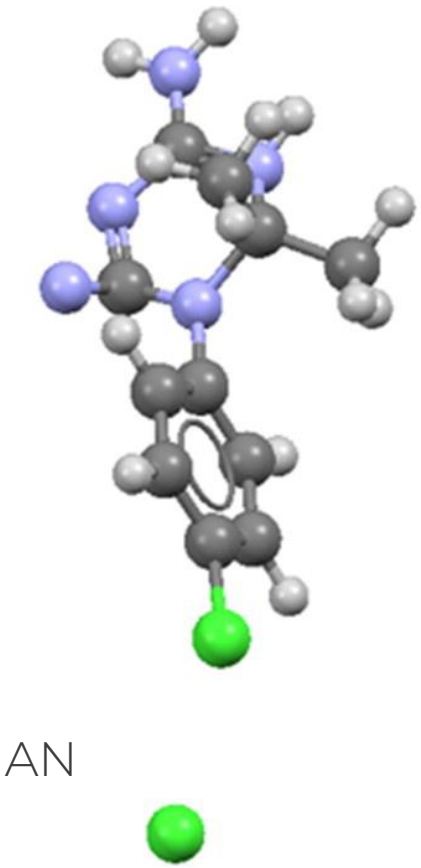
When remediation goes wrong





CYGUAN

- Coordinates hand-typed & transcribed at CCDC
- CCDC checks to identify and correct typing errors
- Impossible bond distances corrected by:
  - Adding or deleting a minus sign
  - Transposing a pair of digits
  - Including a clear statement of what had been altered.
- CYGUAN and the unintended effect
  - The x-coordinate of amino N5 missing a minus sign
  - Change in N5 to C atom too small to be noticed
  - N5 to H's distances were too long and it was assumed the H atoms were wrong and they were deleted
- Saved by neutron diffraction - CYGUAN01 and Carl

Carl.H. Schwalbe, W.E.Hunt, Chemical Communications, 1978, 188, DOI: 10.1039/C39780000188
Carl H. Schwalbe, *Crystallography Reviews* , 2018, 24 217-235 DOI: 10.1080/0889311X.2018.1508209

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Crystallographic “vigilantes”

- Space group symmetry
  - R E. Marsh (2009), Acta Cryst. B65, 782-783
- Misplaced hydrogen atoms
  - I. Bernal & S. F. Watkins (2013), Acta Cryst. C69, 808-810.
  - C. H. Schwalbe (2016) Abstract 01.11.01.12, 66th ACA Annual Meeting, Denver. Acta Cryst. (2017). A73, a133 Should we remediate small molecule structures? If so, who should do it? Carl Schwalbe United Kingdom Aston University
- Misidentified atoms, misplaced H atoms, etc.
  - F. Fronczek, (2019) ACA Abstract. How to Remedy Incorrect Duplicates in the CSD?

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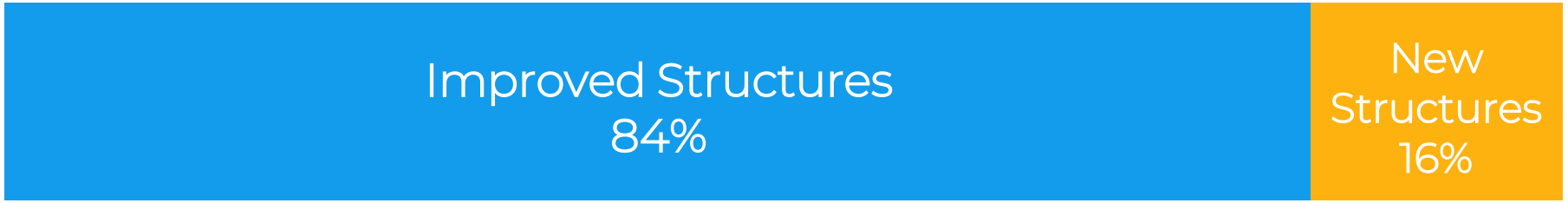
Space Group Symmetry – “Marshed”

- >1,350 structures



- Issues spotted predominantly were:
  - Missing inversion centres in a non-centrosymmetric structures
  - Other missing symmetry elements
- Leading to assignment of and refinement in the wrong space group
- Spotting and correcting these was non-trivial as
  - Data often only available from the printed supplementary pages
  - Data entered by hand
  - Structure re-refined in corrected space group

Data integrity checks

checkCIF

A service of the
International Union of Crystallography

checkCIF reports on the consistency and integrity of crystal structure determinations reported in CIF format.

Please upload your CIF using the form below.

File name:
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Select form of checkCIF report
- (•) HTML
- ( ) PDF
- ( ) PDF (recommended for CIFs that might take a long time to check)

Select validation type
- (•) Full validation of CIF and structure factors
- ( ) Full IUCr publication validation of CIF and structure factors
- ( ) Validation of CIF only (no structure factors)

Output Validation Response Form
- ( ) Level A alerts only
- ( ) Level A and B alerts
- ( ) Level A, B and C alerts
- (•) None

Send CIF for checking

Information about this version of checkCIF ...

Useful links
Prepublication check for submissions to IUCr journals
Details of checkCIF/PLATON tests
CIF dictionary
Download CIF editor (publCIF) from the IUCr
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Acta Cryst. (2009). D**65**, 148-155
https://doi.org/10.1107/S090744490804362X
Cited by 11515

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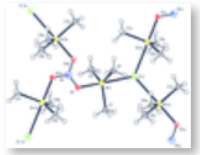

Structure validation in chemical crystallography

A. L. Spek

Automated structure validation was introduced in chemical crystallography about 12 years ago as a tool to assist practitioners with the exponential growth in crystal structure analyses. Validation has since evolved into an easy-to-use *checkCIF*/*PLATON* web-based IUCr service. The result of a crystal structure determination has to be supplied as a CIF-formatted computer-readable file. The checking software tests the data in

My Crystallographic History- R.E.Marsh 2013
http://www.amercrystalassn.org/h-marsh

Fortunately, in the past few years they have decreased in number, thanks to computer programs such as CheckCIF and to slowly-successful pleas to journal editors to insure that authors make use of these programs. My recent surveys have suggested that the "wrong structure" disease may be getting close to extinction.

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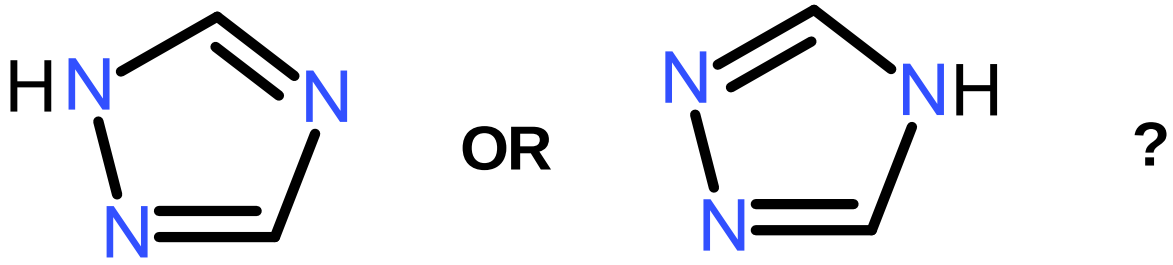
Published data case study 1
Tautomerism in triazoles



- Ab-initio calculations show 1*H* 6.25 kcal mol^{-1} more stable
- CSD shows 203 1*H* vs 7 4*H* tautomer hits
- Do the 7 4H tautomers actually exist?!

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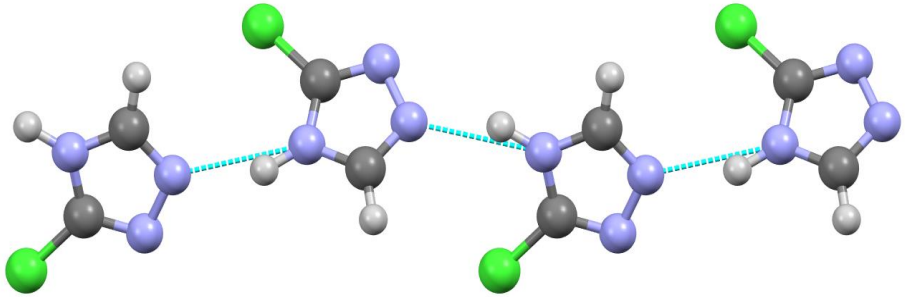
Redetermination…



- Two 4H tautomers redetermined as 1H (CLTRZL & JUGYOB)
- These two pairs of structures enable evaluation of descriptors to establish tautomeric form
  - Electron density and H-bonding poor (1- and 4- positions link with each other into chains, so unclear which N is protonated)
  - Bond distances to N poor as similar distances for formally ‘single’ and ‘double’ bonds wrongly suggests N’s are identical
  - Endocyclic bond angles good as VSEPR ‘squeezes’ angles at unprotonated N atoms, revealing identity

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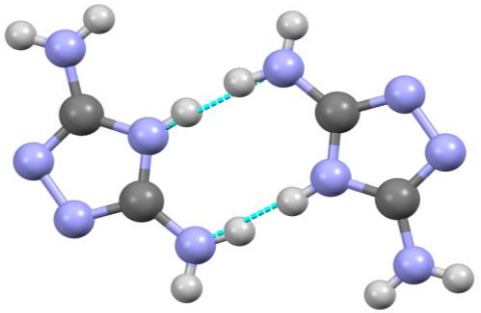
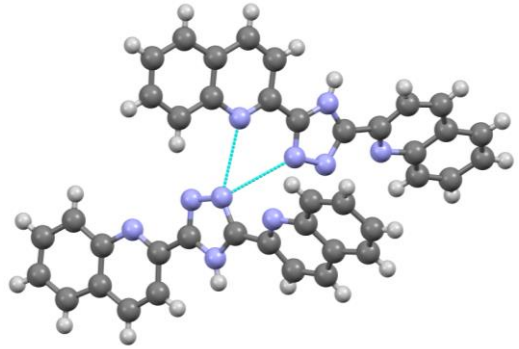
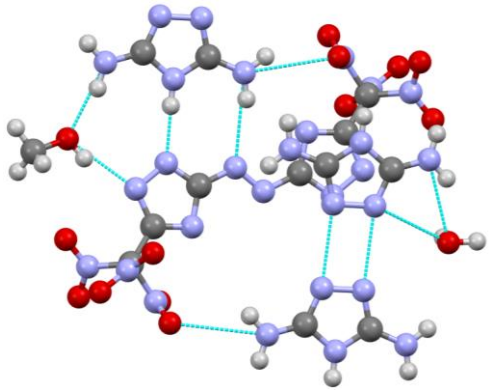
Reinvestigation required

- DAMTRZ21 isostructural unit cell with 3 other 1*H* structures
  - CheckCIF Level A Alert about a D-H…H-D clash of 1.29 Å
  - Endocyclic angles clearly show that H atom should be on N1
- MAJSOH has no comparison, but…
  - CheckCIF Level C Alert that N4-H lacks an acceptor
  - Moving the H atom from N4 to N1 would make a bifurcated HB
- FALDAZ has 3 triazoles (two identical with missing H and third 4H)
  - Endocyclic angles suggest 1H tautomers throughout
  - A credible HB scheme can be created by reversing N4-H…N







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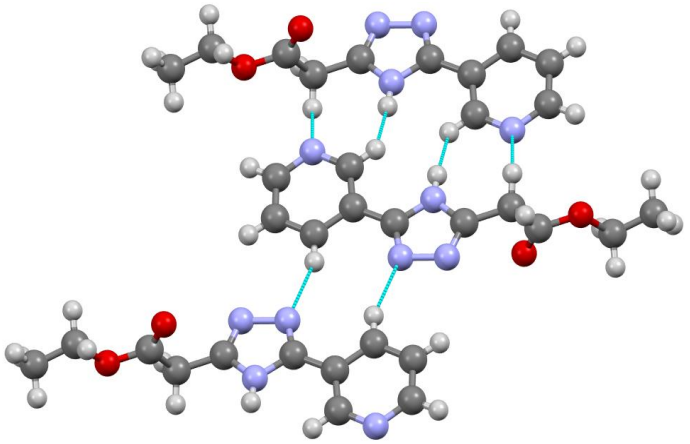
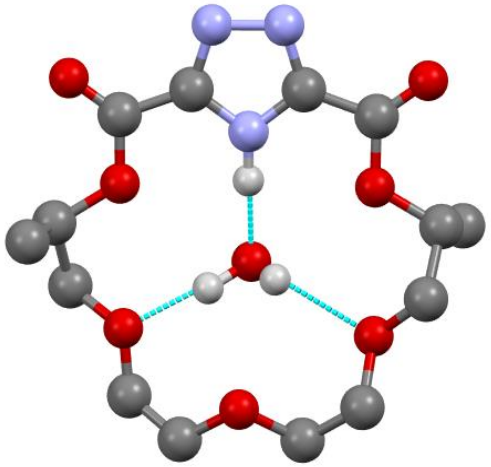
Triazole structures continued…

- FUZPOH devoid of actual or potential N-H…N hydrogen bond
  - Bond angles give a fairly weak indication of a 1*H* tautomer
  - Moving the H atom to N1 allows N2 and N4 to accept C-H…N HBs



- DEGNIM triazole incorporated into a crown ether
  - Water molecule that can interact with triazole N and ether O atoms
  - Endocyclic angles seem to contradict a 4*H* tautomer but may be affected by attachment to the macrocycle
  - The water molecule is significant
  - With the 4*H* tautomer as reported it can make three HBs
  - A different tautomer would only allow it two HBs



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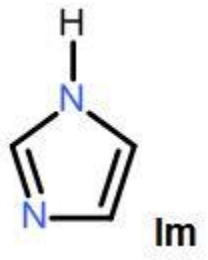
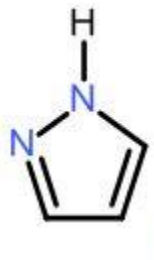
Conclusions (triazole)

- Reported *4H* structures are rare and, with one exception, likely to be incorrect
- CheckCIF Alerts about N-H donors without acceptors or clashing N-H…H-X or N…N but otherwise silent about correct tautomer
- Bond distances for C-NH and C=N can be misleadingly similar
- Endocyclic bond angles, affected by VSEPR are useful to distinguish C-N(H)-X from C=N-X
- Need to evaluate trends in related structures to understand which descriptors to use for disambiguation

Published data case study 2
Misplaced H atoms and undetected disorder



Im



Pyzl

- The imidazole ring of histidine can participate in proton relays
- Protonation sites may be obscure due to similarity of electron density between H-bonded NH…:N and N:…HN
- Geometrical criteria can be more reliable

- Differences in Im C-NH and C=N bond length and C-NH-C and C=N-C bond angle are most significant (Malinska *et al.*, 2015)
- Neutron diffraction on Im at 103 K shows 1.347, 1.322 Å and 107.1, 105.1°
- In Z’ = 2 Pyzl exhibits some charge transfer between rings and NH/N disorder
- At 100 K Pyzl C-NH and C=N distances are 1.338, 1.334 and 1.347, 1.330 Å; C-NH-N and C=N-NH angles are 112.2, 104.2 and 112.2, 104.5°

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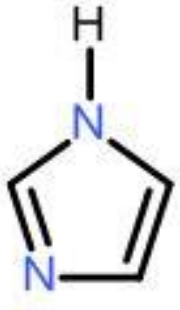
Studying the CSD



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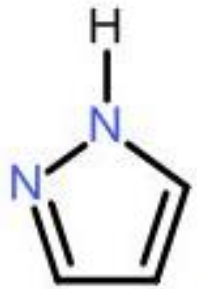


Pyzl

CSD2018
R <= 10%
Organic
No disorder

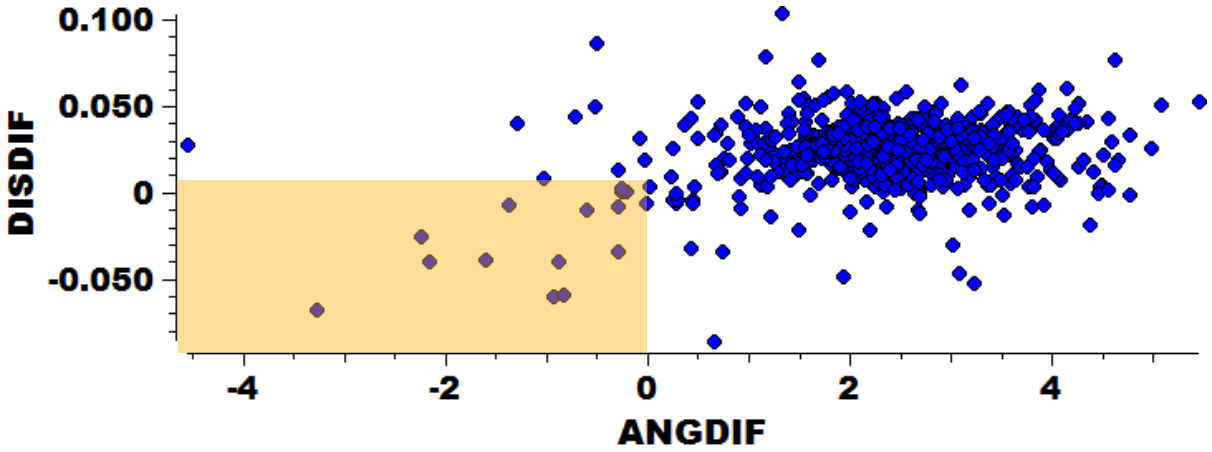
547 hits

723 hits

Imidazoles

DISDIF - difference between C-NH and C=N bond distances
ANGDIF – difference between angles

Mean DISDIF = 0.024(12) Å
Mean ANGDIF =2.3(8)°.



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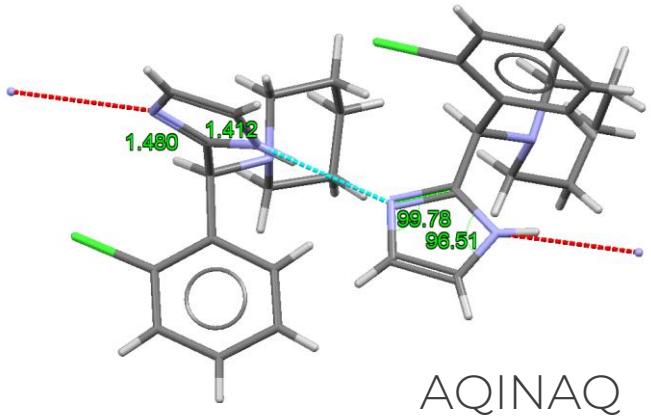
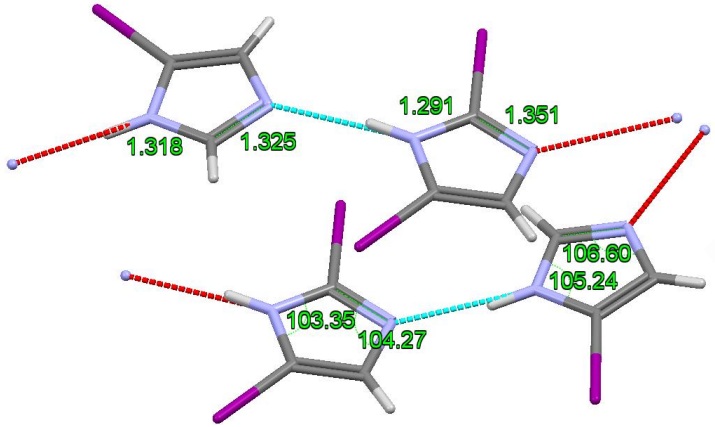
Misplaced hydrogens

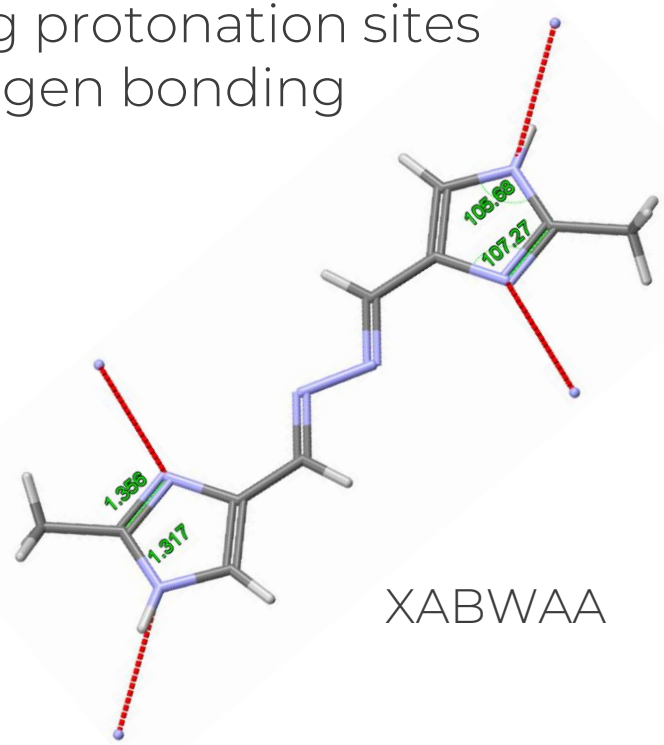
- 5 structures with large negative difference
  - In 3 with intermolecular NH...N interactions, exchanging protonation sites makes the differences positive and preserves the hydrogen bonding scheme



AQINAQ



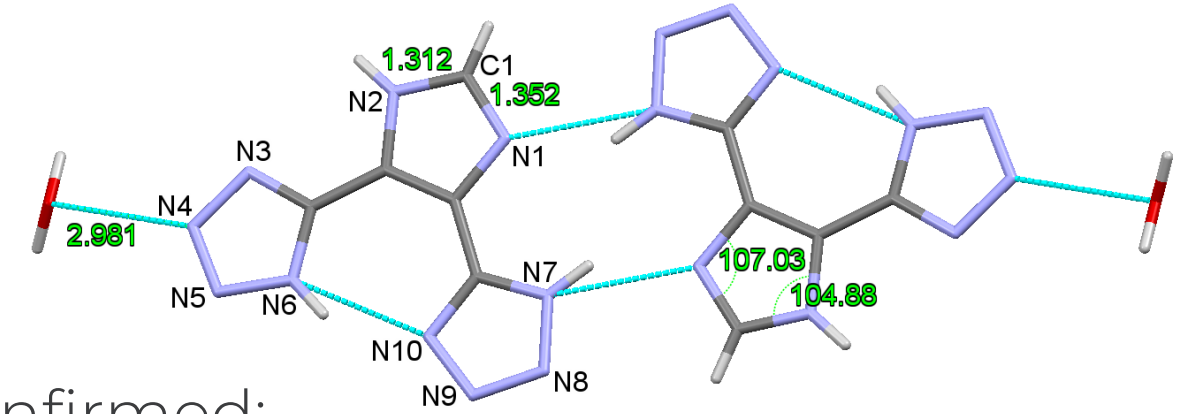
BOWSAJ



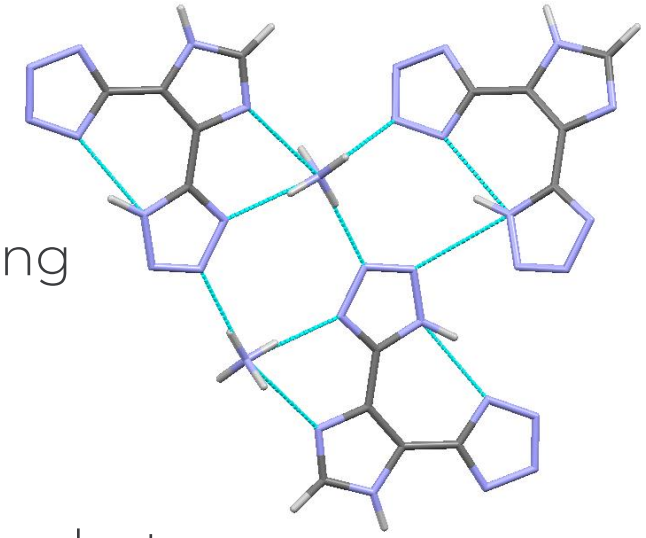
XABWAA

A trickier structure

- Interchanging N and NH creates problems elsewhere
- Structure factors deposited
- Difference electron density map confirmed:
  - H atoms on tetrazole N6, Im C1 and Im N1
  - No H atom on N2
- Surprises!
  - No H atom appeared on N7 or elsewhere on tetrazole ring
  - Four H atoms surrounded the “water oxygen atom”
- An ammonium salt!
  - Chemical analysis required for unequivocal confirmation, but NH_4Cl was a reagent in the synthesis



YOTYOW



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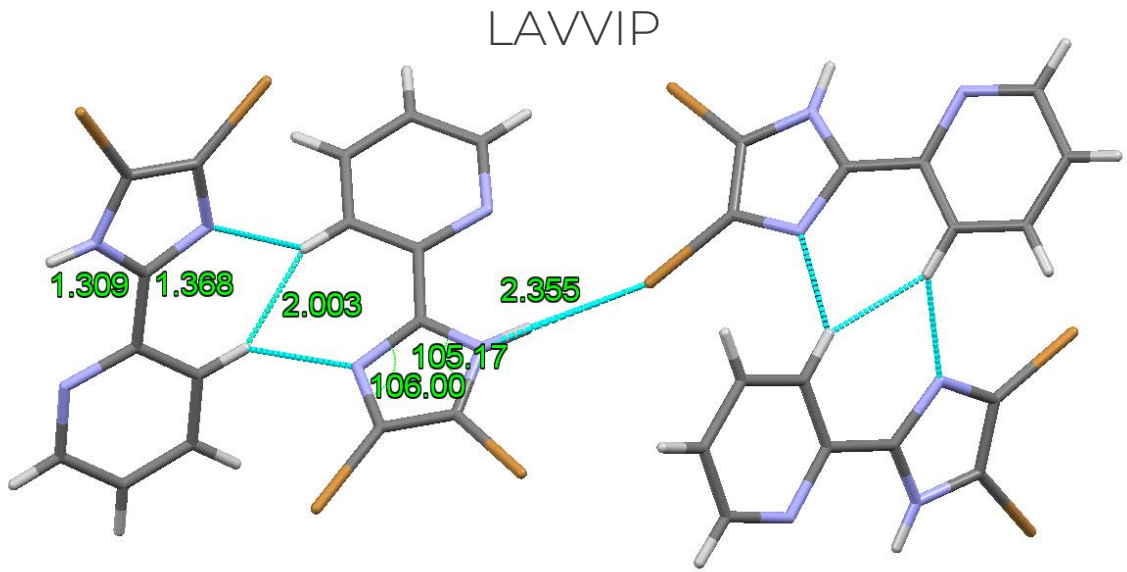
The last misplaced H structure

- Differences of -0.059 Å and -0.83° suggest protonation of the “wrong” imidazole N atom
  - Disconcertingly close contacts
  - Swapping N and NH on the imidazole ring worsens the log-jam of H atoms



- Rotating the pyridine ring by 180° about its link to imidazole appears to work
  - The new H atoms appear too close, but some relaxation might take place

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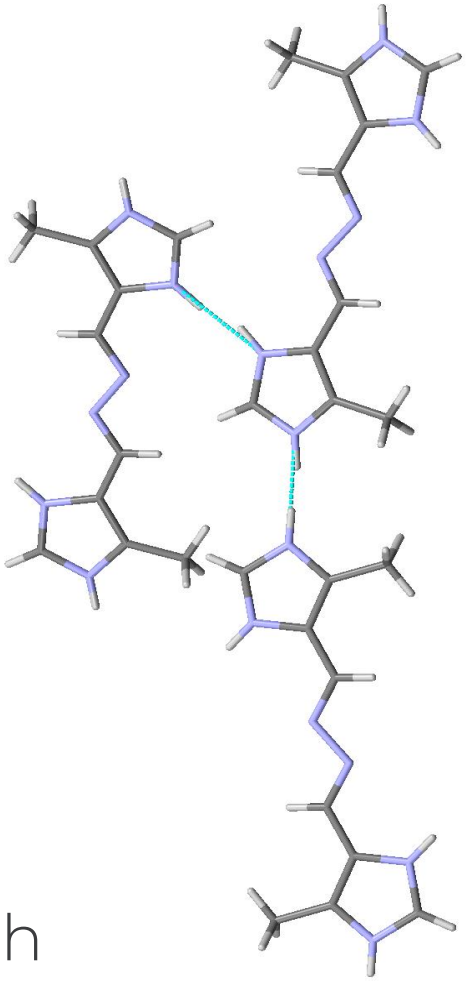
Rotational disorder of imidazole rings

- DISDIF / ANGDIF plot shows points near origin with absolute values of differences much < 0.021 Å and 2.4°
- Likely explanation is disorder, some rings having been rotated so as to interchange N and NH within the ring
- Known phenomenon - Drew *et al.* carefully compared possible tautomers of an imidazole structure with reference both to crystal structure and DFT calculations
- Packing requires 50:50 occupancy
- They cited 3 other structures which had been refined with 50:50 disorder of tautomers



Drew MGB, Das D, De S, Naskar JP, Datta D. (2008) *J. Chem. Cryst.* 38: 507-512

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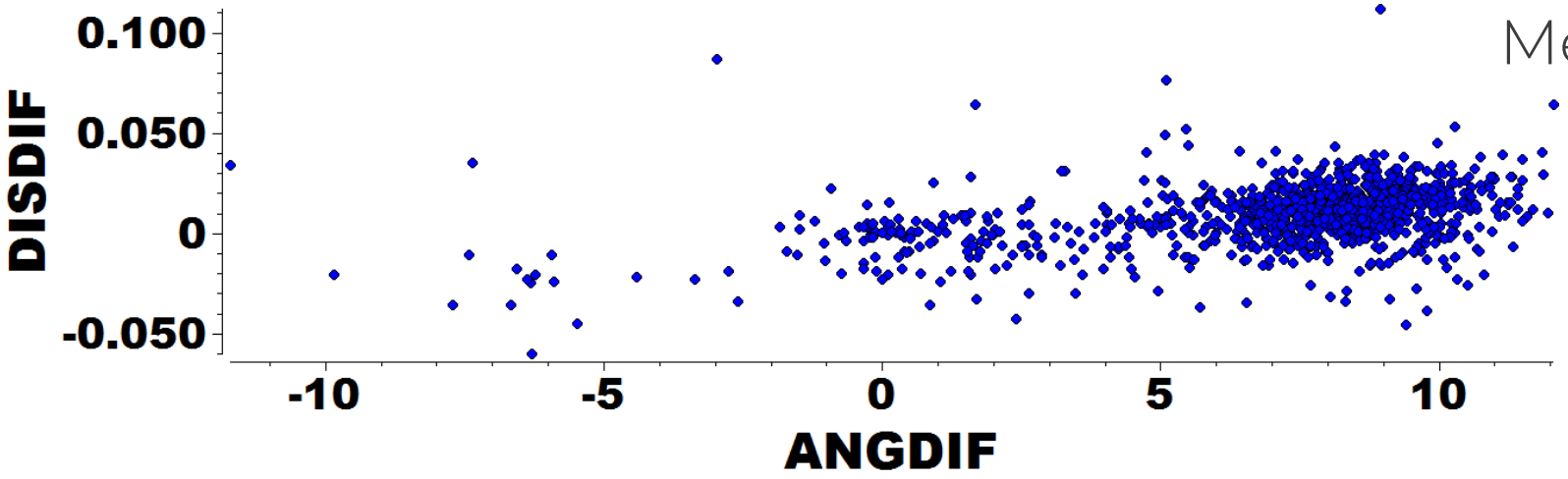
Pyrazoles

- DISDIF difference between C-NH and C=N bond distances
- ANGDIF difference between C-NH-N and C=N-NH angles
- While most Pyzl structures have large positive ANGDIF, the long “tail” towards zero suggests that N/NH disorder is common
- Negative ANGDIF values suggest errors

Mean DISDIF = 0.009(11) Å,
Mean ANGDIF = 7(2)°



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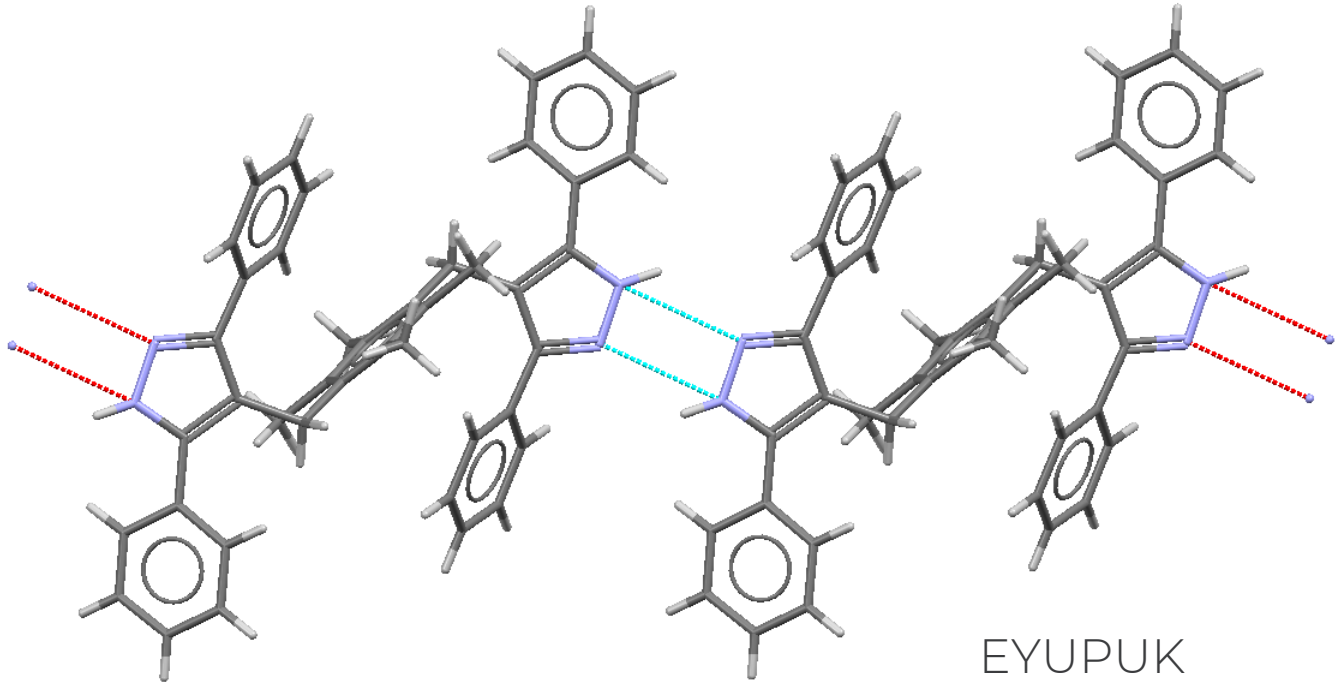
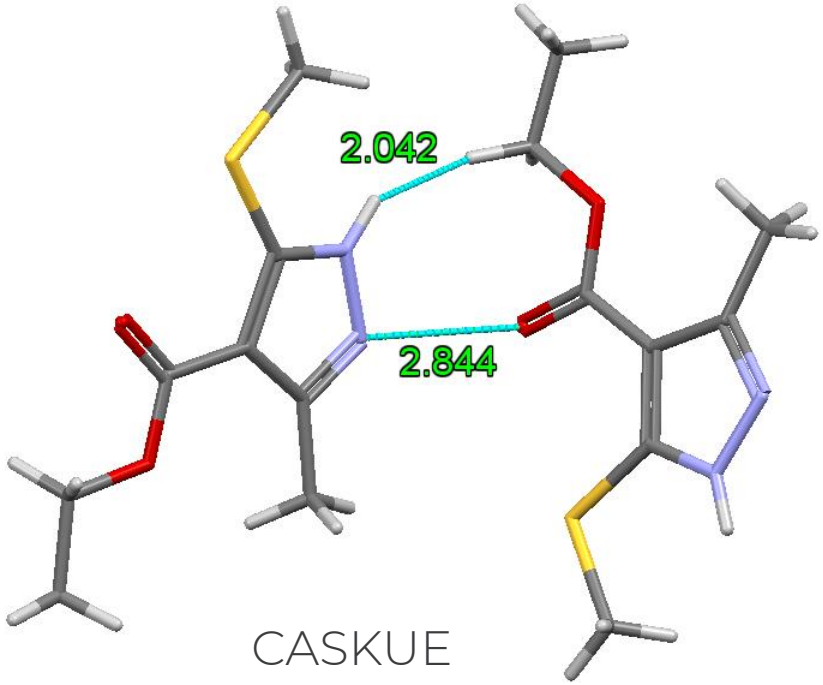
6 representative examples



EYUPUK

NH…N linkages between rings may be swapped

- EYUPUK -0.021, -6.22
- DICQUD -0.025, -6.30
- GINZIN -0.011, -5.94



CASKUE

H…H clashes and missing hydrogen bonds

- CASKUE -0.036, -7.70
- NABVUK -0.036, -6.67
- VOJZEB -0.045, -5.47

CCDC

Conclusions (Im and Pyzl)

- Some reported crystal structures of neutral Im and Pyzl derivatives appear to have NH mistaken for N, or disordered swapping.
- CheckCIF often doesn't pick these kind of issues up
- Ring geometry (in combination with sensible H-bonding network and chemistry) provides a useful means to distinguish N from NH
- These are essentially 'human' checks right now
- Difficult to see these issues when looking at individual structures – need to see trends in related structures

What tools are available for new structures?

checkCIF

A service of the
International Union of Crystallography

checkCIF reports on the consistency and integrity of crystal structure determinations reported in CIF format.

Please upload your CIF using the form below.

File name:
Choose File | No file chosen

Select form of checkCIF report
- (•) HTML
- ( ) PDF
- ( ) PDF (recommended for CIFs that might take a long time to check)

Select validation type
- (•) Full validation of CIF and structure factors
- ( ) Full IUCr publication validation of CIF and structure factors
- ( ) Validation of CIF only (no structure factors)

Output Validation Response Form
- ( ) Level A alerts only
- ( ) Level A and B alerts
- ( ) Level A, B and C alerts
- (•) None

Send CIF for checking

Information about this version of checkCIF ...

Useful links
Prepublication check for submissions to IUCr journals
Details of checkCIF/PLATON tests
CIF dictionary
Download CIF editor (publCIF) from the IUCr
Download CIF editor (enCIFer) from the CCDC

checkCIF is sponsored by

IUCr Journals
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ELSEVIER
WILEY
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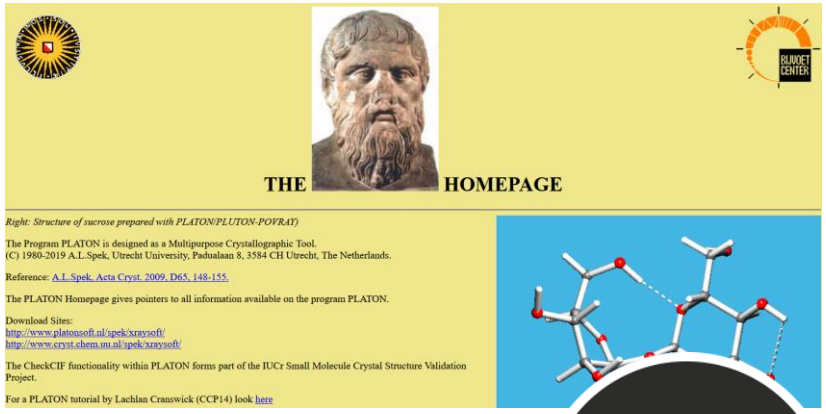
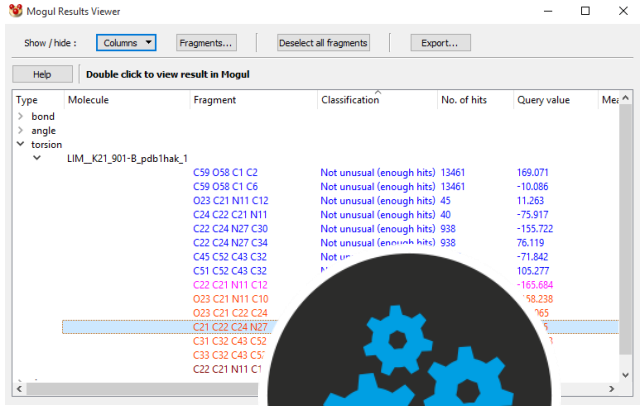
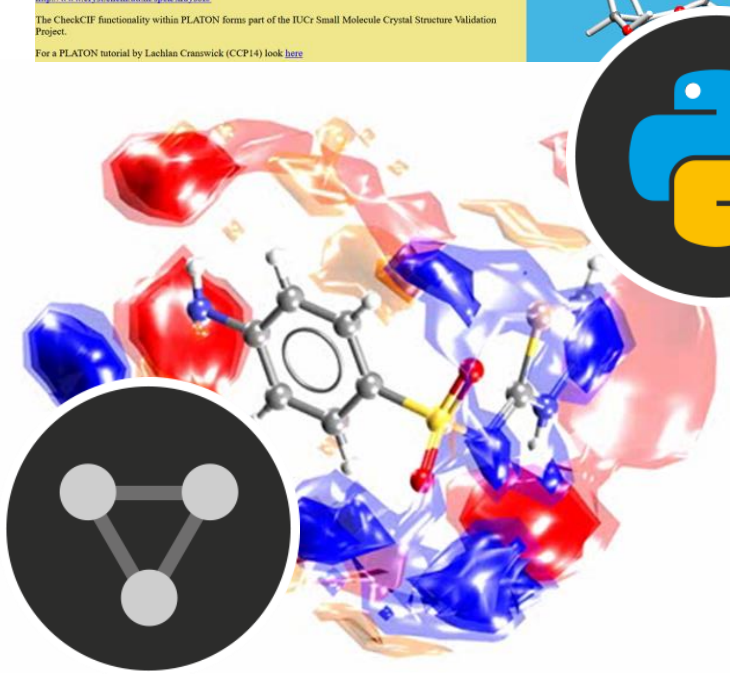
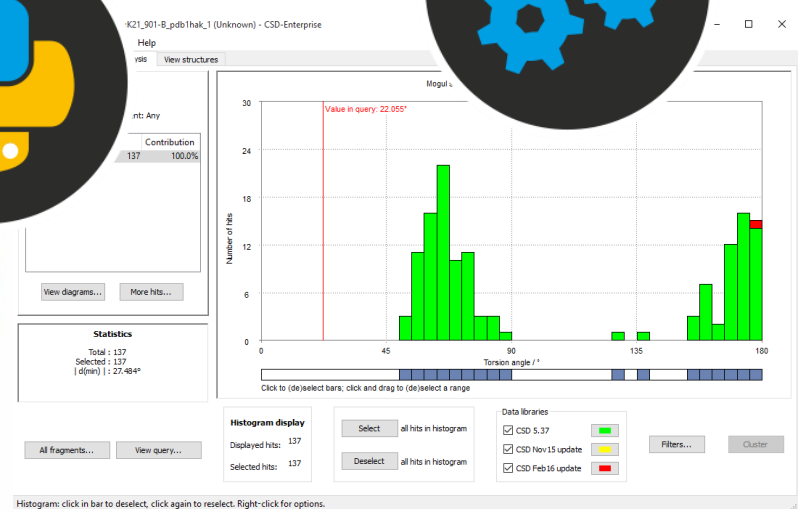
ROYAL SOCIETY OF CHEMISTRY
THE CHEMICAL SOCIETY OF JAPAN NIPPON KAGAKUKAI
crystals an open access journal by MDPI









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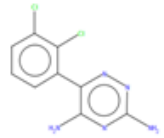
Additional validation for new structures?

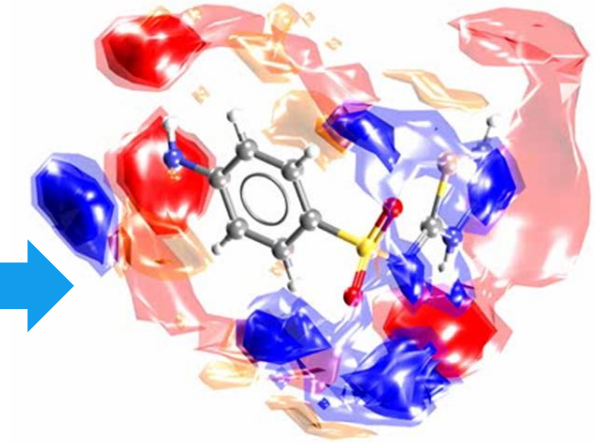
CCDC 1234567

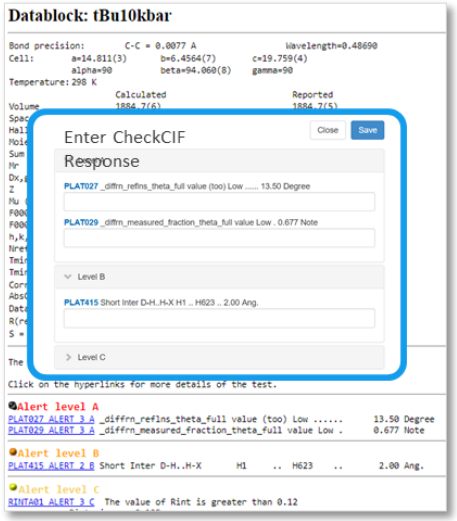


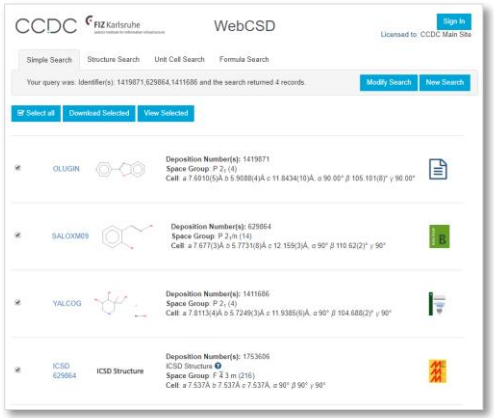
0 syntax issues
1 crystallographic issue
2 chemical issues
0 space group issues

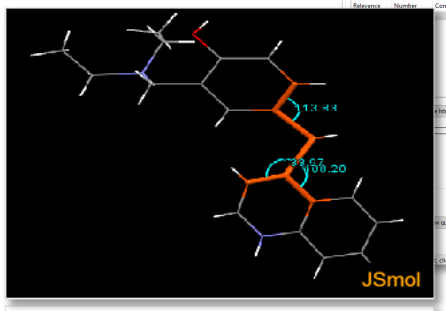
Level A	Most likely a serious problem - resolve or explain
Level B	A potentially serious problem, consider carefully
Level C	Check. Ensure it is not caused by an omission or oversight
Level G	General information/check it is not something unexpected

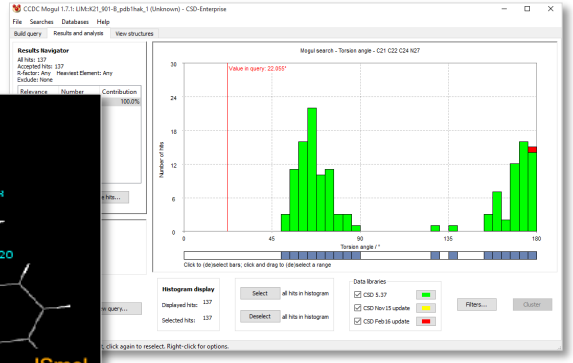
Structure	Summary	checkCIF	Duplicates	Geometry check	Interaction check
Select all / Download Selected / View Selected					
1234567	View Report	View Report	0 duplicates	View Report	View Report
1234568	View Report	View Report	View 1	View Report	View Report
1234569	View Report	View Report	View 2	View Report	View Report











Fragment	Labels	Value	Mean	Z-score	Classification
angle	C1 C14 N43	108.195	119.352	13.008	Unusual (enough hits)
angle	C15 N43 C14	105.5	126.772	9.135	Unusual (enough hits)
angle	C12 C14 N43	133.97	122.923	3.579	Unusual (enough hits)
angle	C22 C15 N43	113.828	120.673	2.136	Unusual (enough hits)

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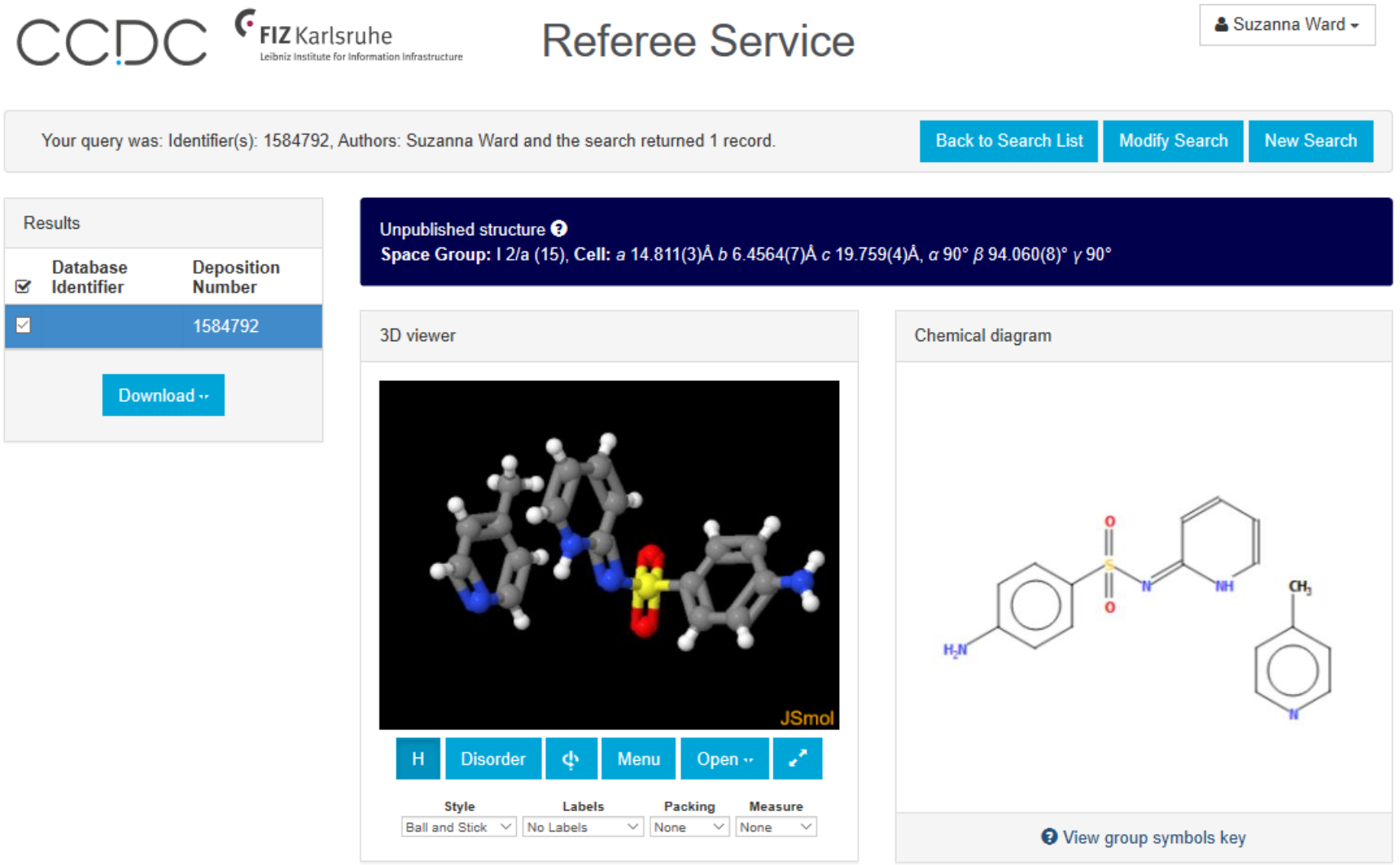
Additional information provided to referees?



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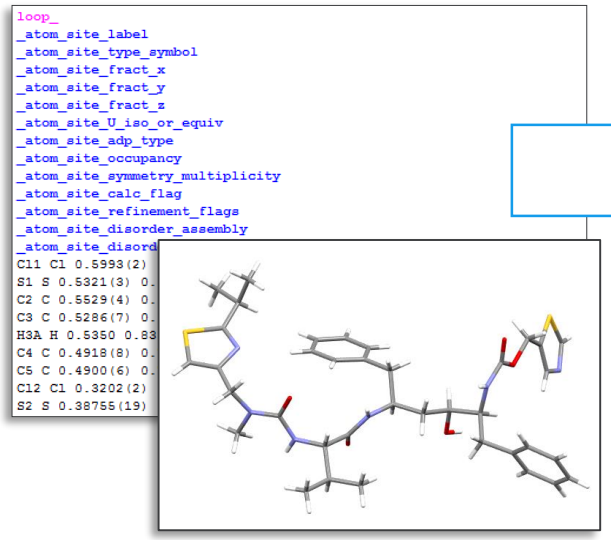
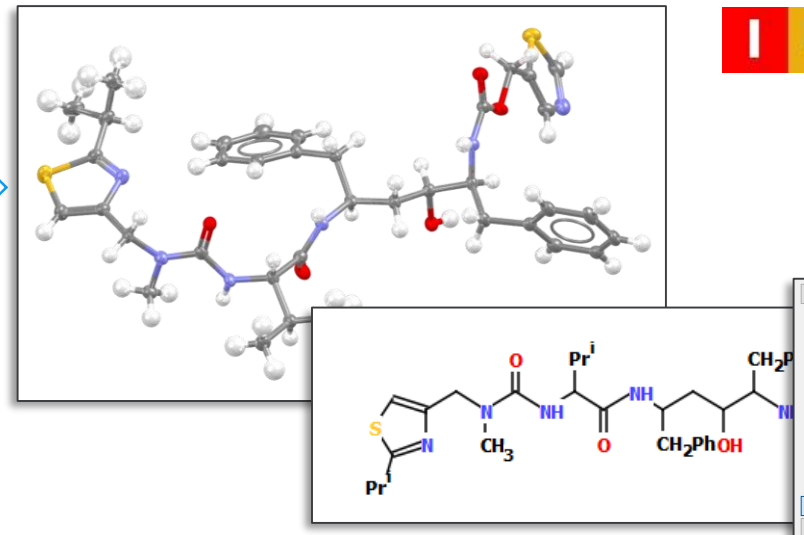
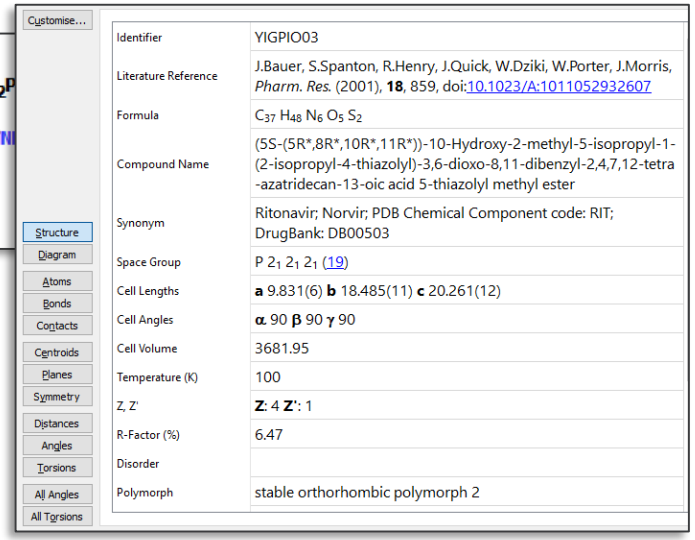
Structures in the CSD

Deposited CIF

CSD Entry







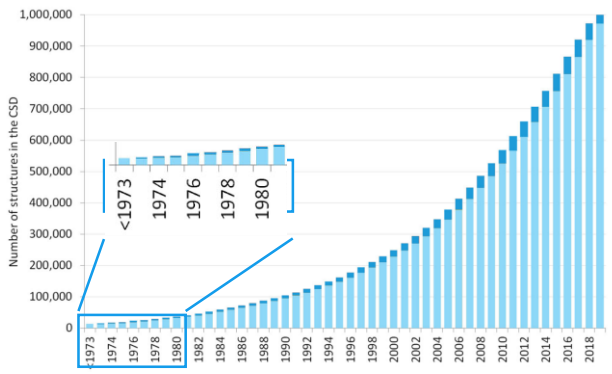
- Assignment of a chemically meaningful representation is determined using data in the CSD and manual curation.
- Important for data discovery, re-use, mining, analysis and interoperability

Bruno *et al*, *Acta Crystallogr. Sect. B Struct. Sci.* 67, 333–349 (2011)

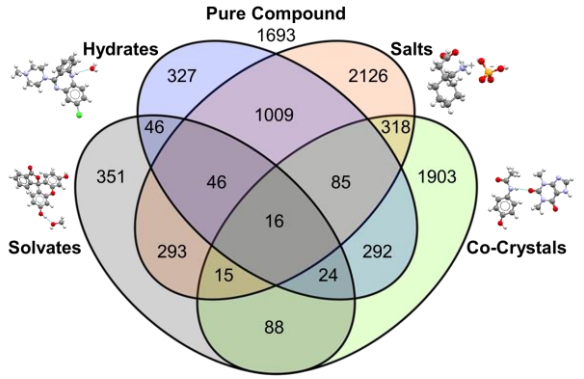
Revisiting CSD entries

Targeted improvements allow improved integrity, consistency, discoverability and value of data

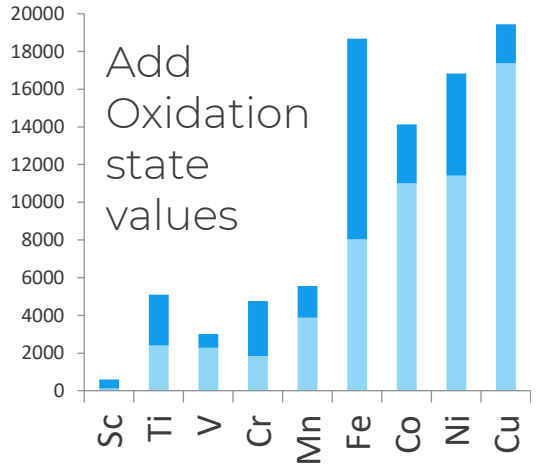
Ensure standardisation of early CSD entries



Creation and maintenance of subsets



Enrichment of data



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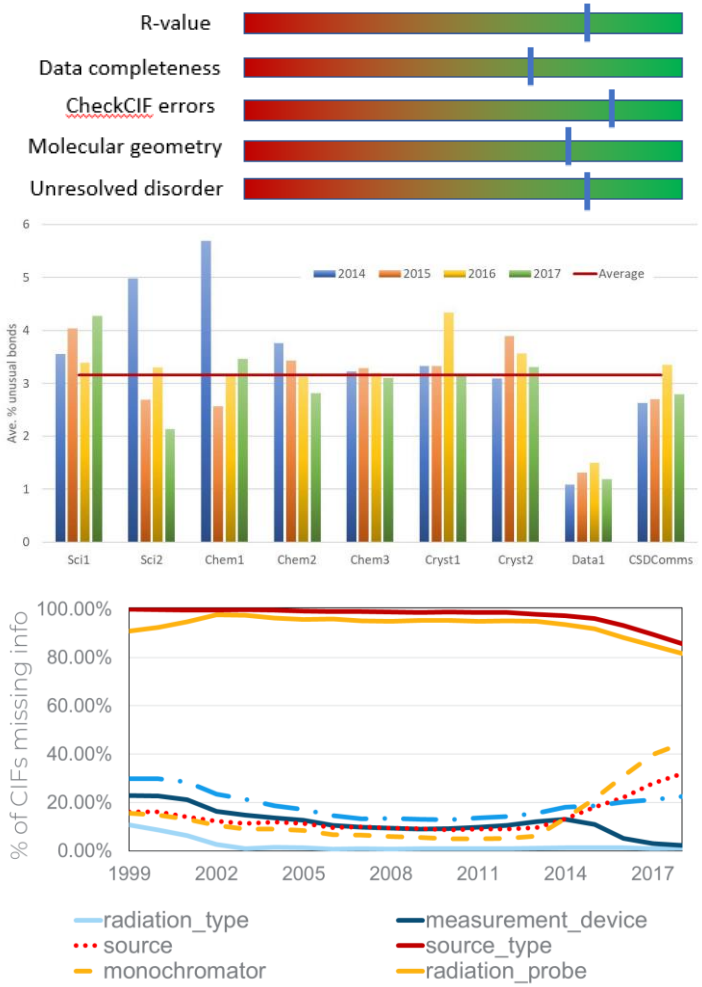
Maintaining data integrity in the CSD

- **Integrity** – Completeness, consistency and trustworthiness
- **Data completeness** – trends in reporting of metadata
  - Interactive CSD Deposit checks
  - New filters to select fit for purpose data
- **Consistency** – looking at experimental metadata to identify trends in information supplied
- **Trustworthiness** – Establishing automatic identification of potential cases of misconduct – including fraudulent and plagiarised data



Research integrity is much more than misconduct. *Nature*, 2019, 570, 5-5. DOI:10.1038/d41586-019-01727-0

Underlying issues in the CSD

- Underlying CIFs match published datasets
- Issues can be reported to CCDC – data_edits@ccdc.cam.ac.uk
- CCDC will:
  - Investigate issue and either correct CCDC representation or:
    - Contact authors and/or publisher
    - Add a comment to CSD entry
    - If appropriate suggest correction to be published and deposited
    - Accept re-refinements of existing structures and link datasets
    - Re-refinements can be *CSD Communications* or published structures

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Identifying issues in existing structures

- Faults in structures have been corrected by “vigilantes” in their particular area of interest
- But such coverage is inevitably limited
- Can and should the crystallographic community organize a systematic validation and correction effort?
- Can and should the CCDC do more to identify issues?
- When a corrected version of a structure is found how should the CCDC/CSD handle these new models?

Remembering Carl

Organic 92%

Metal-Organic 8%

Disordered 15%

No modelled disorder 80%

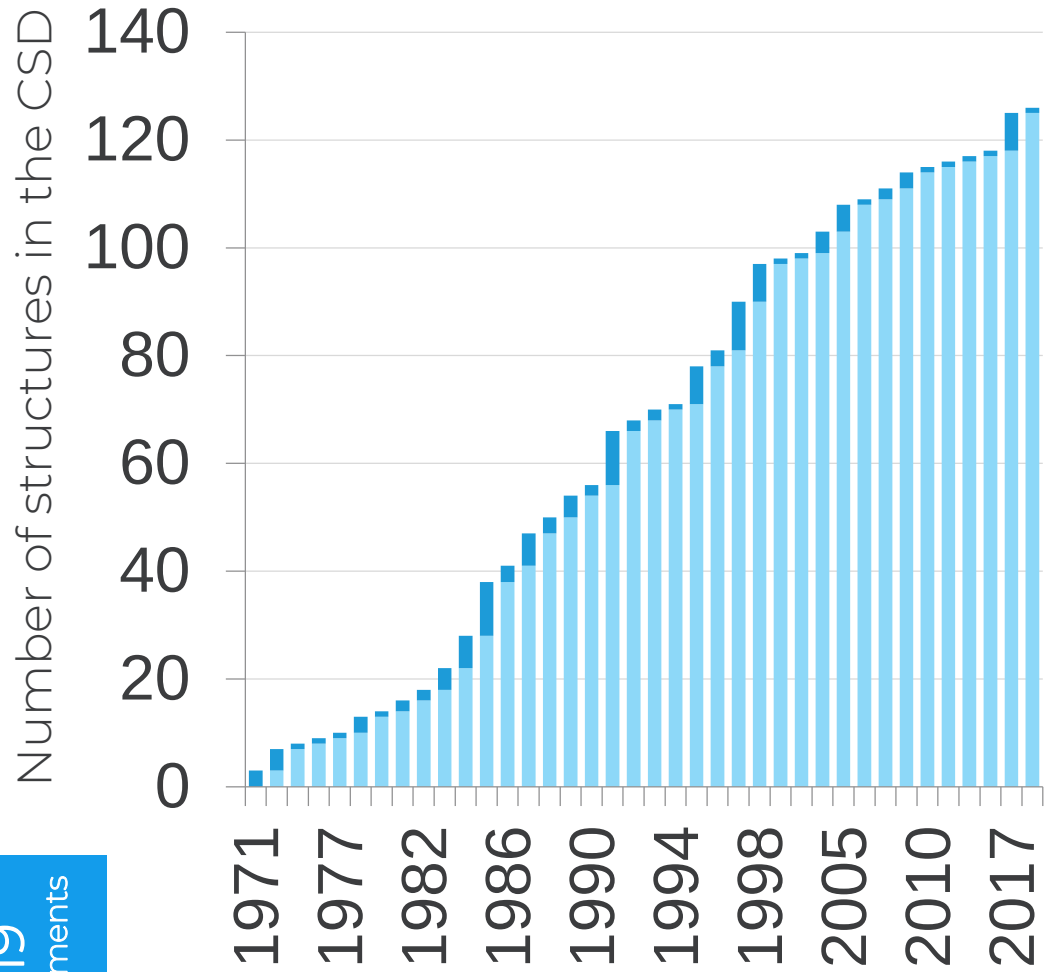
Non IUCr Publications 65%

IUCr publications 35%

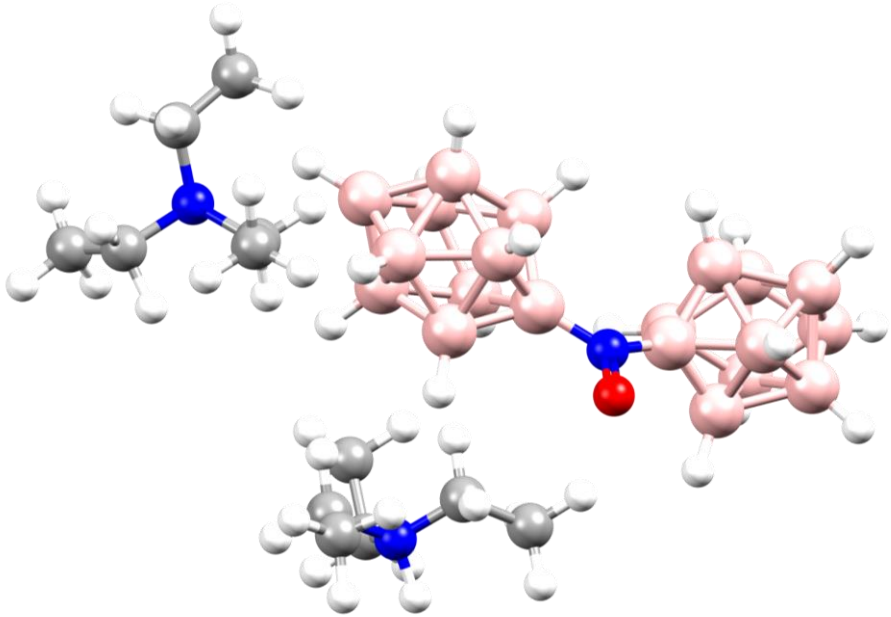
126 Structures

184 co-authors

19 elements



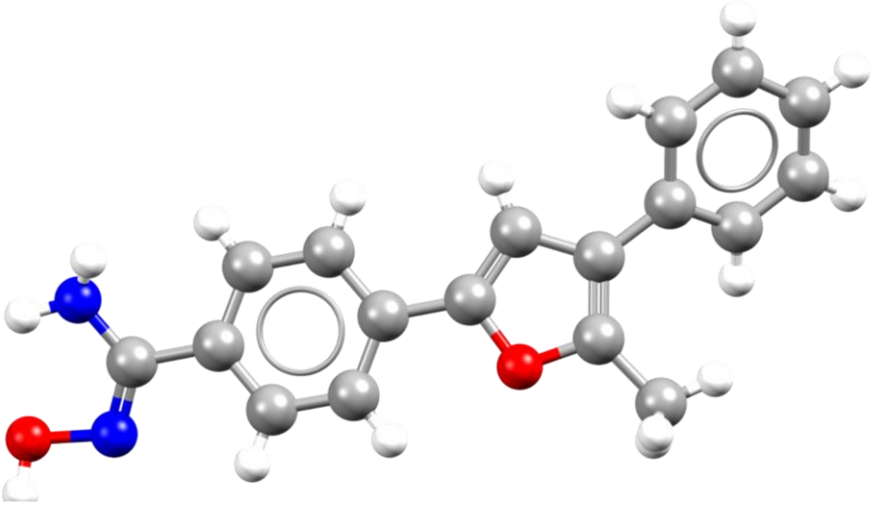
CCDC

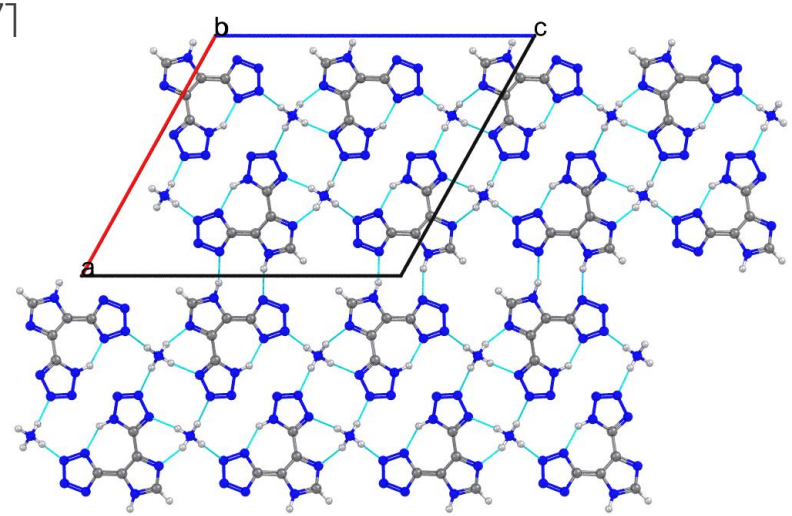


EAMBNO10
First published - January 1st 1971

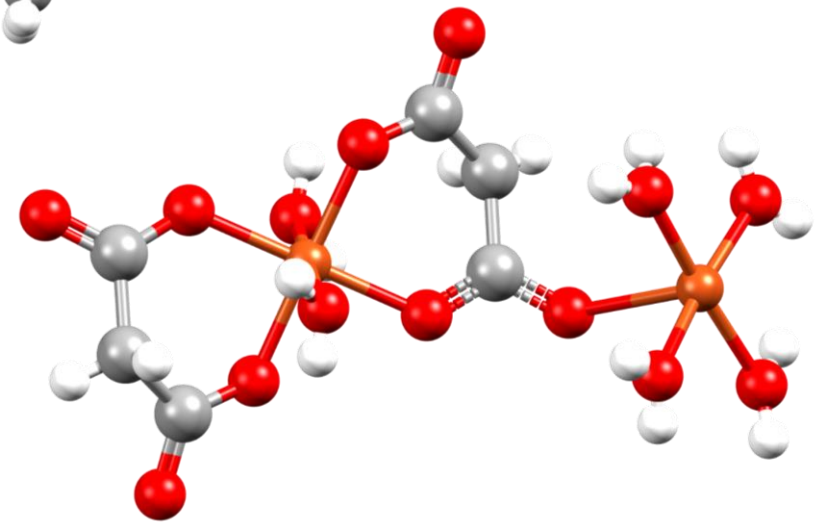
YOTYOW → YOTYOW01
Latest corrected structure

XEZFIU
Most recent – published 12/03/2018





PECMIT
Most cited article



EAMBNO10 – DOI: 10.1021/ic50095a031, XEZFIU - DOI: 10.1016/j.bmcl.2018.03.025
YOTYOW01 - DOI: 10.1080/0889311X.2018.1508209 , PECMIT – DOI: 10.1039/DT9930000913

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Summary and workshop questions

- Not all structures are perfect, and a variety of approaches need to be taken to identify and resolve issues….
- How can we identify errors more automatically/systematically?
- When systematic errors are found experts may need to look at different approaches to fixing them
  - Re-determinations
  - Re-refinements
  - Generation of CSP/DFT/cleaned structures
  - Extensive annotation
- How are we going to do it at a whole-community level?
- What would be the incentives for individuals to engage?
- How should different versions of structures be stored?

CCDC

Thank You Carl

and...

Simon Coles

Natalie Johnson

Stephen Holgate

Clare Tovee

Seth Wiggin

Aston University
Birmingham

CCDC

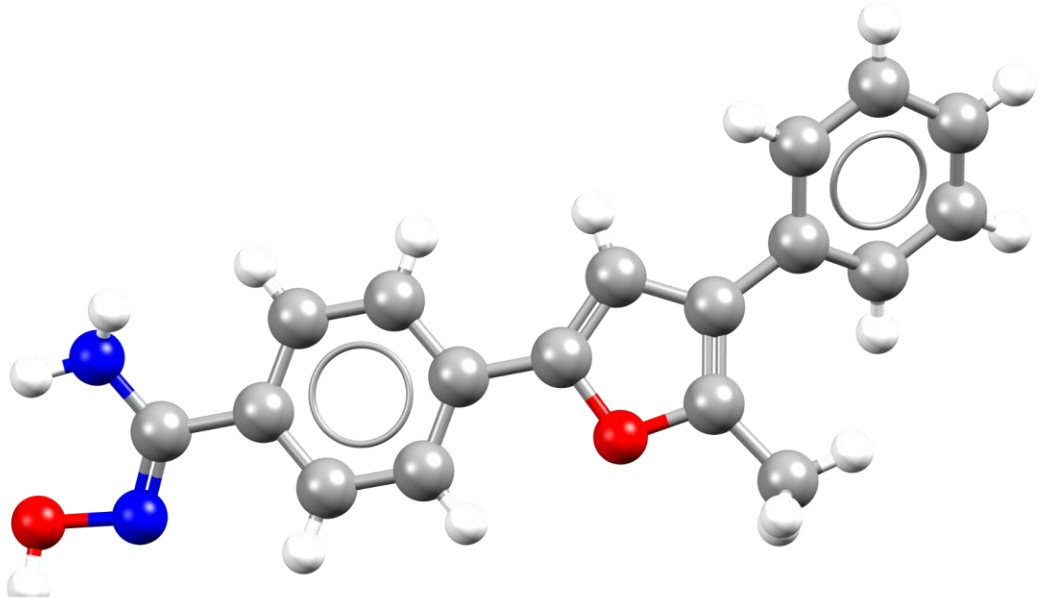
Should we remediate small molecule structures?

If so, who should do it?

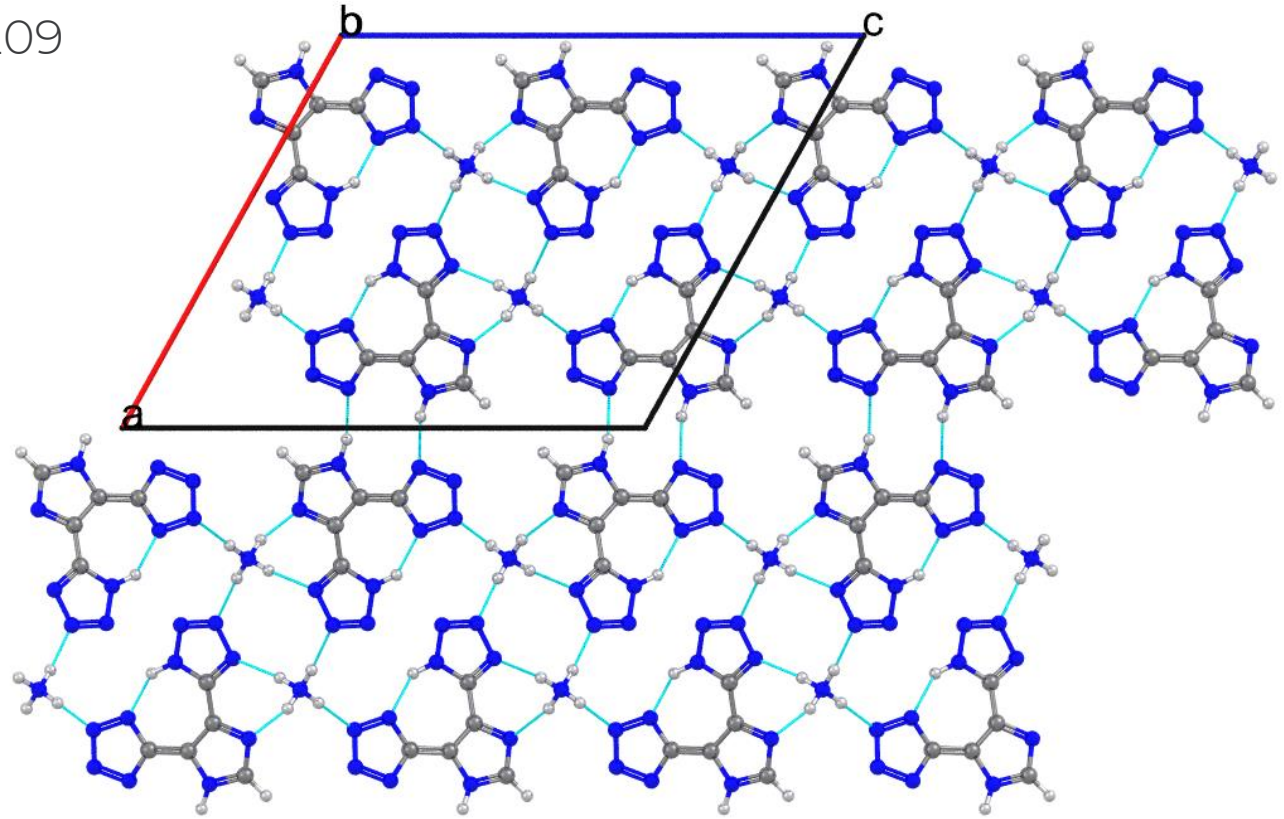
In principle, new reports of small molecule crystal structures should be error-free since most reputable journals require validation of crystallographic data with CheckCIF and this software is integrated into the CCDC deposition procedure. However, because some chemical journals appear to ignore or not even to use crystallographic referees, errors may not be pointed out. Furthermore, what should happen if authors are unable or unwilling to make corrections when required? Should an otherwise correct structure be rejected because a hydrogen atom has been incorrectly placed or disorder of a terminal methyl group has not been entered into the model? Should such a structure be published or deposited with a warning message, or should a corrected version be created by an external referee? These questions have particular force with regard to already published structures that have errors. An example from the author's early work shows that well-intentioned remediation can sometimes go wrong. Faults in structures have been corrected by "vigilantes" in their particular area of interest, such as space group symmetry [1] and misplaced hydrogen atoms [2,3]; but such coverage is inevitably limited. Can and should the crystallographic community organize a systematic validation and correction effort?

[1] R. E. Marsh (2009), Acta Cryst. B65, 782-783.
[2] I. Bernal & S. F. Watkins (2013), Acta Cryst. C69, 808-810.
[3] C. H. Schwalbe (2016) Abstract 01.11.01.12, 66th ACA Annual Meeting, Denver. Acta Cryst. (2017). A73, a133 Should we remediate small molecule structures? If so, who should do it? Carl Schwalbe United Kingdom Aston University

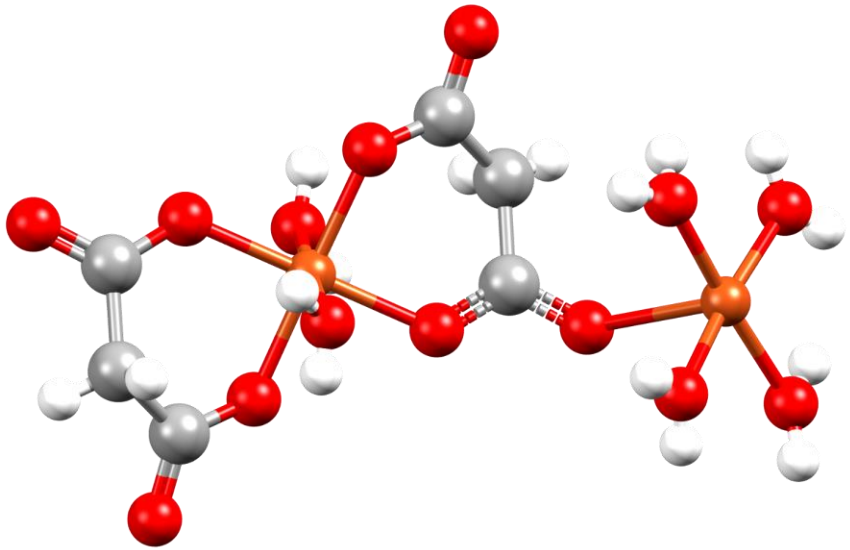
Last published
XEZFIU – published 12/03/2018
10.1016/j.bmcl.2018.03.025

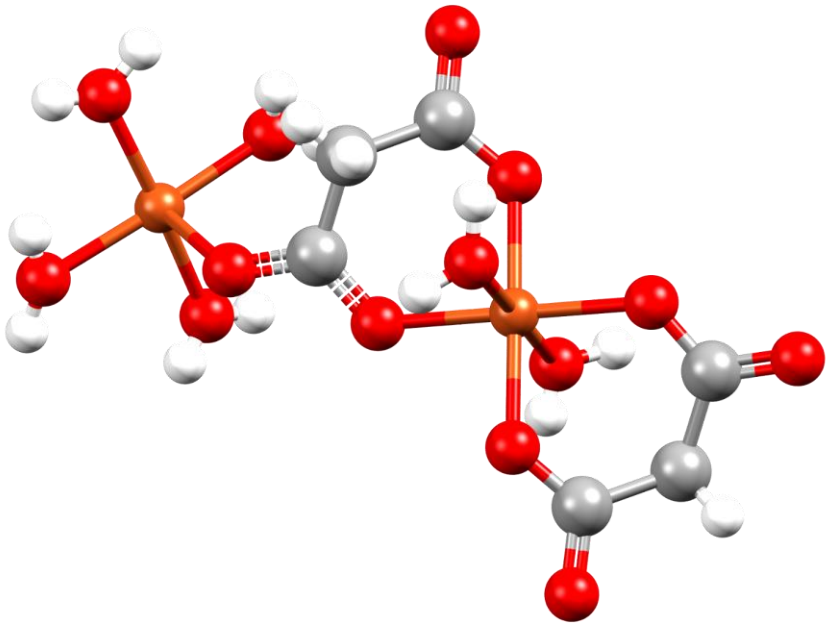


Latest corrected structure
YOTYOW → YOTYOW01
10.1080/0889311X.2018.1508209



Most cited: PECMIT
Cited by: 72
DOI: 10.1039/DT9930000913





Scopus; as of 12/08/2019

CCDC