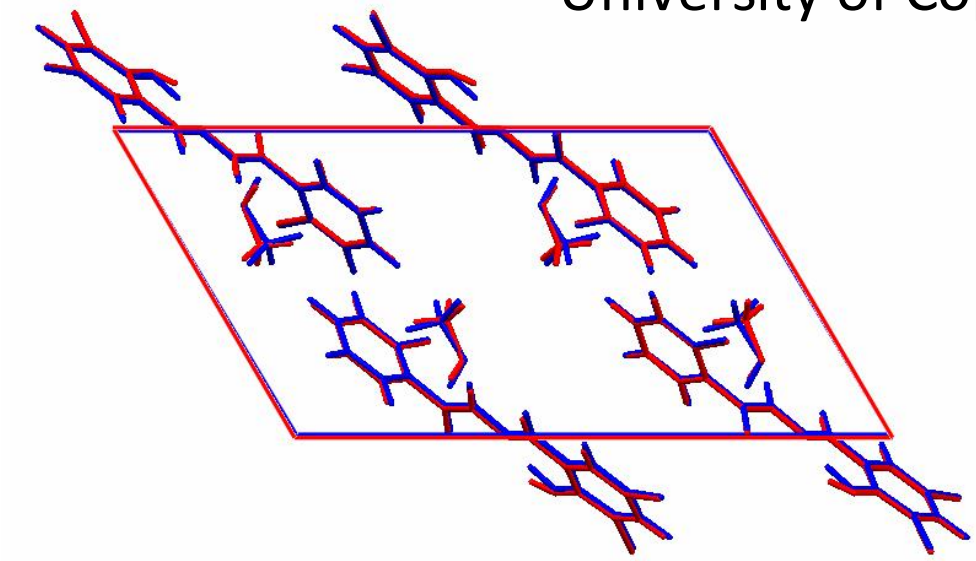
Reliable and Highly Accurate Molecular Crystal Structures from a Combination of XRPD and DFT-D

Jacco van de Streek

University of Copenhagen



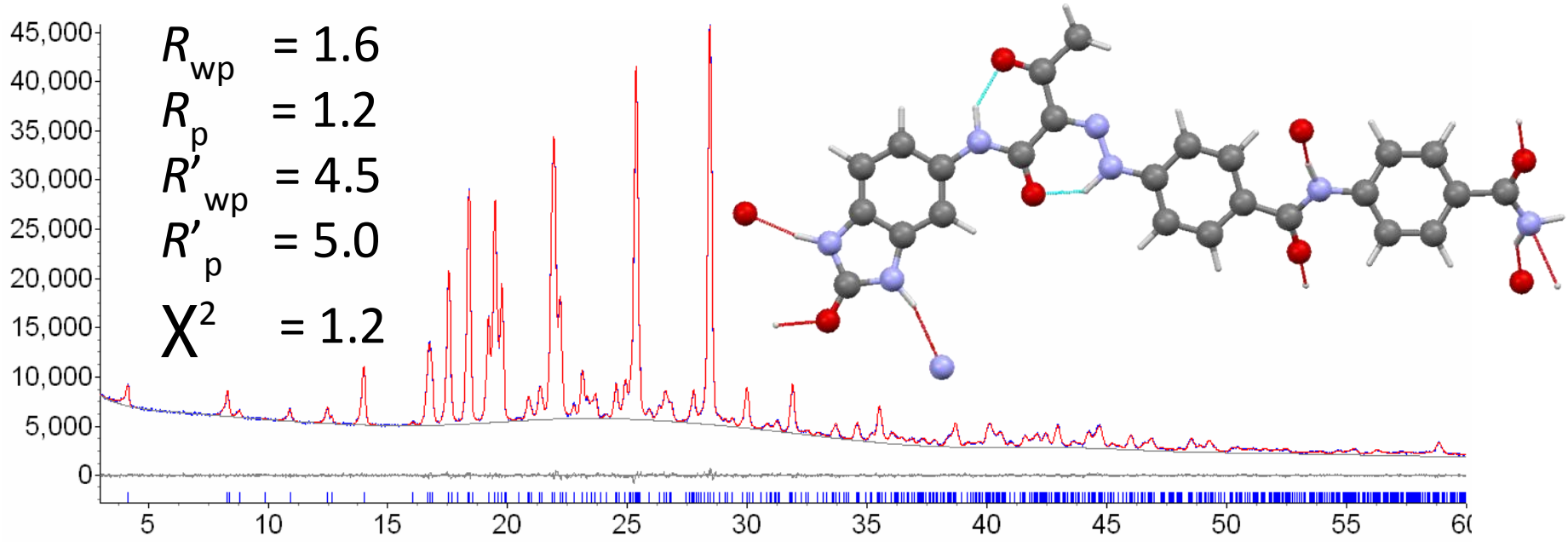
UNIVERSITY OF COPENHAGEN

Two Themes

1. Reliability: is a crystal structure from XRPD correct or not?

2. Accuracy: for a correct crystal structure from XRPD, how accurate are *e.g*. the bond lengths?

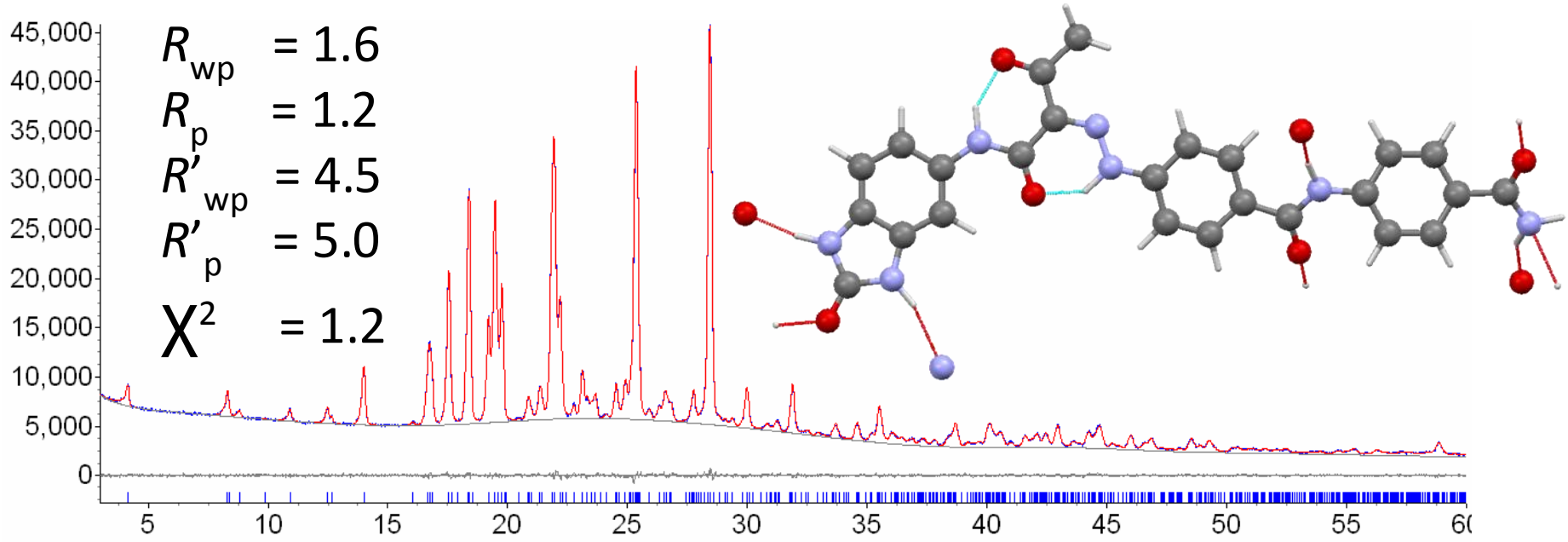
Pigment Yellow 181



Solved from powder data with *DASH*, molecular starting geometry from 6-31G** optimisation, correct chemical compound, restrained refinement with *TOPAS*, no short contacts, no voids, all bond lengths and valence angles within < 3 ESDs (*Mogul*), all torsion angles as expected, no preferred orientation, zero-point error = 0.025, B_{iso} = 2.6, all hydrogen-bond donors and accepted satisfied with perfect geometries, 1.5 Å resolution data, normal background, occupancies 1.0.

No tricks!

Pigment Yellow 181



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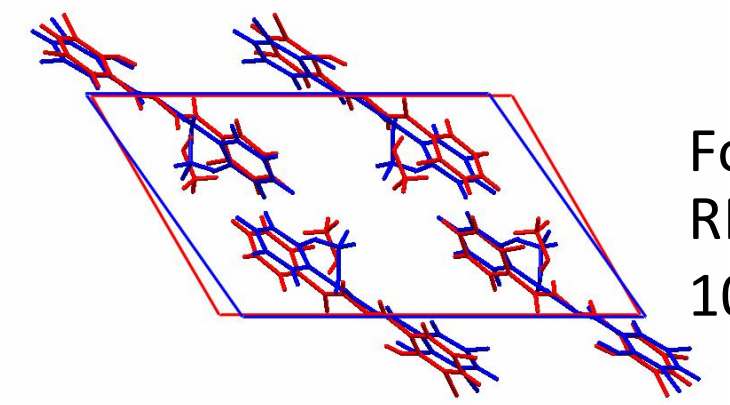
Who would suspect that this structure could possible be correct?

Dispersion-corrected DFT (DFT-D)

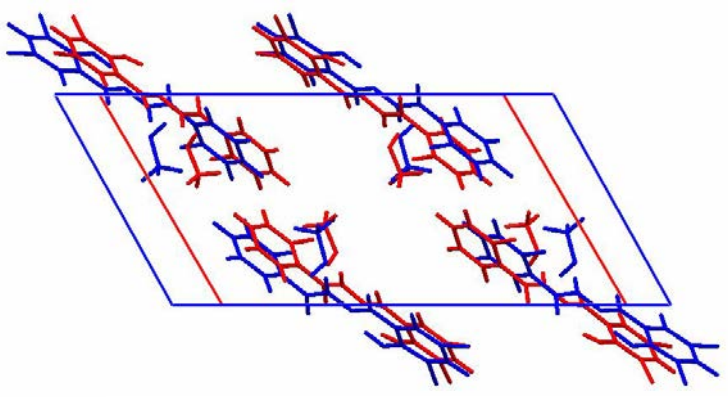


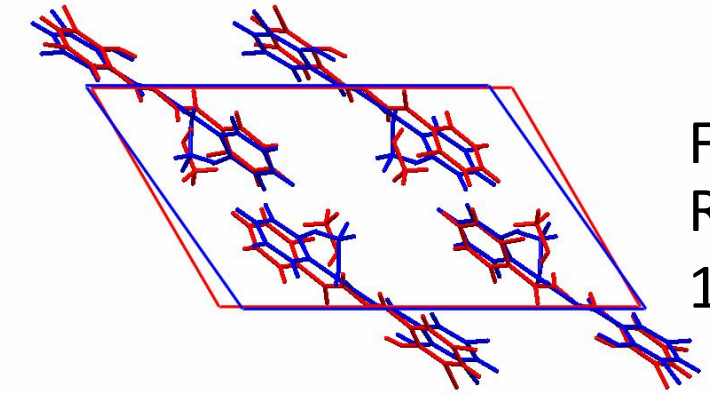
Force fields...
RMS = 0.497 Å
10 sec

Minimised
Experiment

Dispersion-corrected DFT (DFT-D)

Pure DFT...
RMS = 0.833 Å
100 hrs



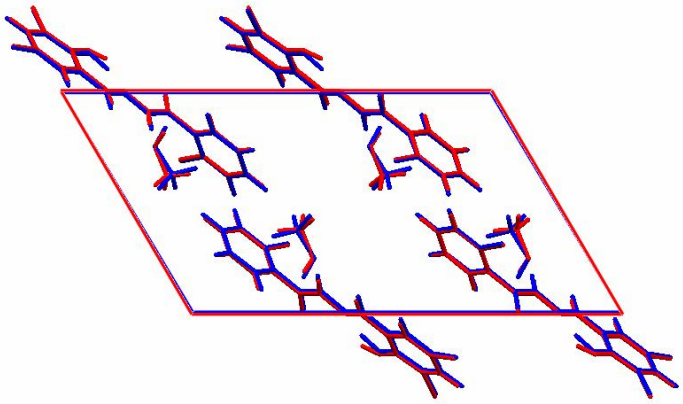


Force fields...
RMS = 0.497 Å
10 sec

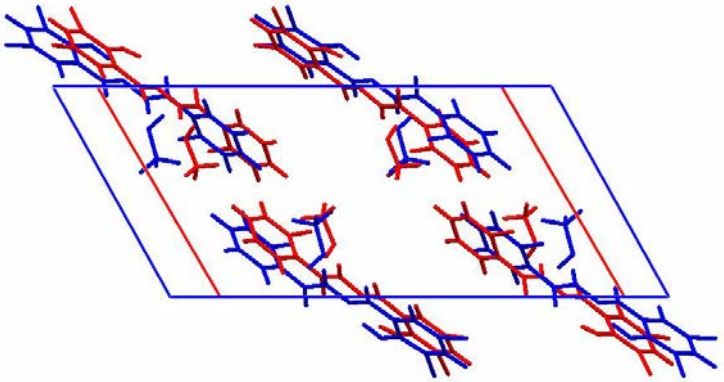
Minimised
Experiment

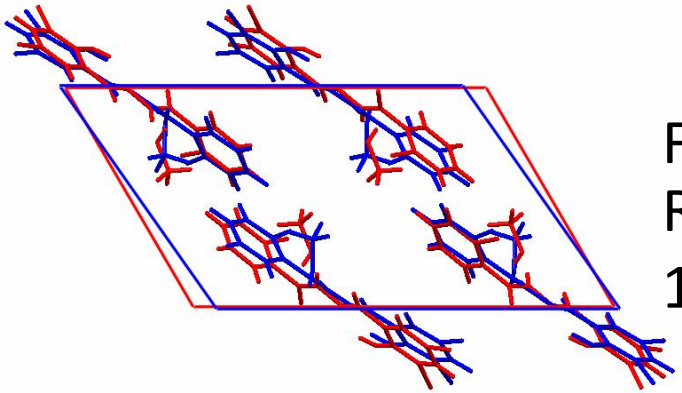
Dispersion-corrected DFT (DFT-D)

Dispersion-corrected DFT...
RMS = 0.083 Å
100 hrs



Pure DFT...
RMS = 0.833 Å
100 hrs





Force fields...
RMS = 0.497 Å
10 sec

Minimised
Experiment

Reproduction of Crystal Structures

225 “organic only” crystal structures from the August 2008 issue of *Acta Cryst*. E were downloaded (Open Access!)

- All 225 were energy-optimised with unit cell free
- Nett calculation time: one month

J. van de Streek & M. A. Neumann (2010). *Acta Cryst.* B**66**, 544-558

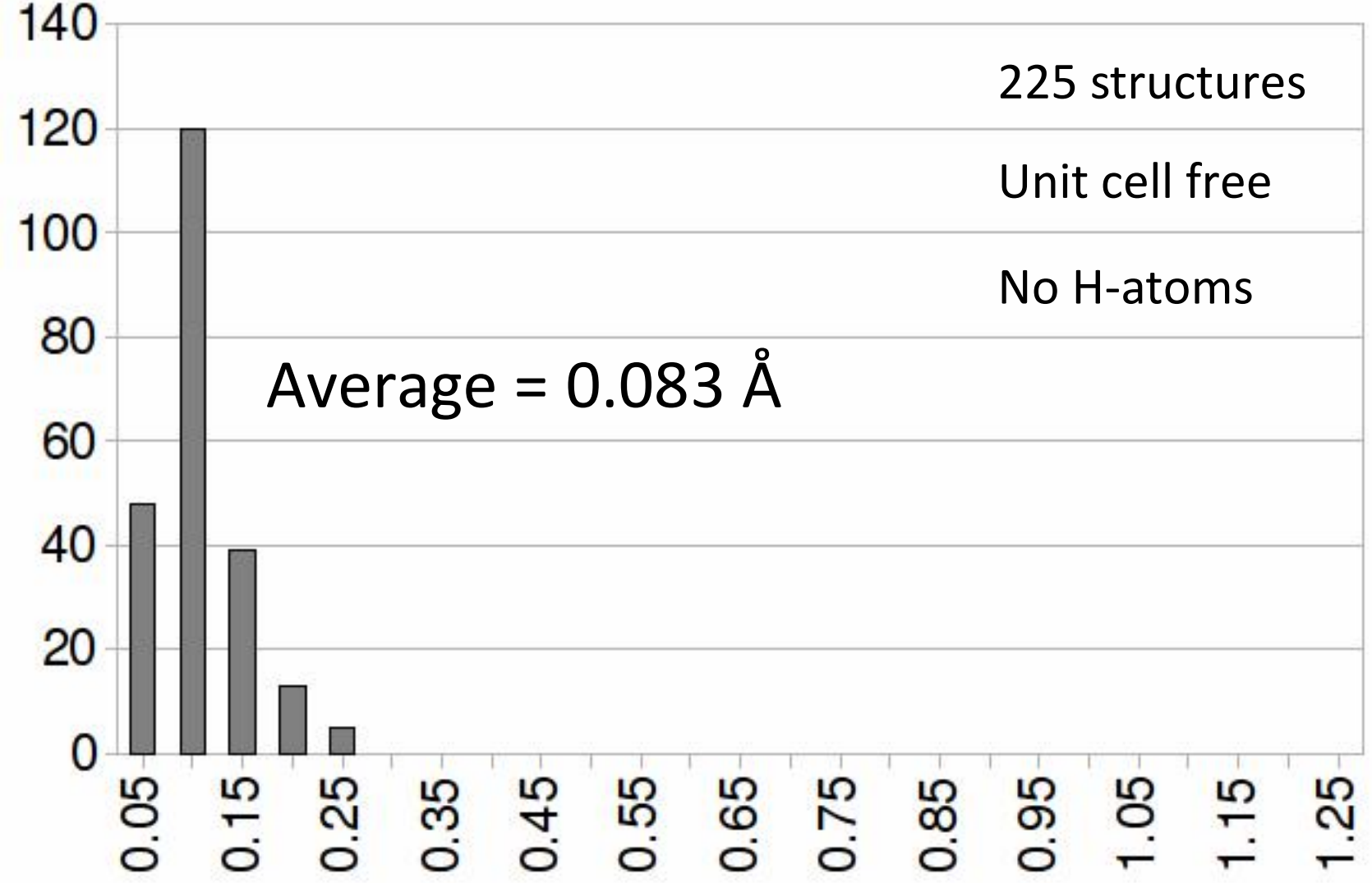
Reproduction of Crystal Structures

225 “organic only” crystal structures from the August 2008 issue of *Acta Cryst*. E were downloaded (Open Access!)
- All 225 were energy-optimised with unit cell free
- Nett calculation time: one month

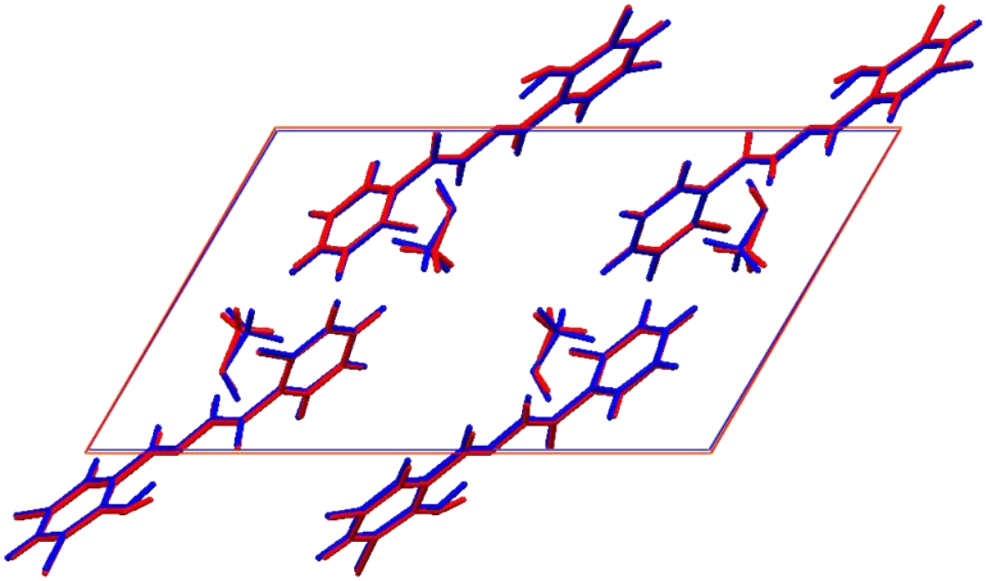
225 experimental high-quality single-crystal structures...
225 energy-minimised structures...
How well are the experimental structures reproduced?

J. van de Streek & M. A. Neumann (2010). *Acta Cryst.* B**66**, 544-558

RMS Cartesian Displacement



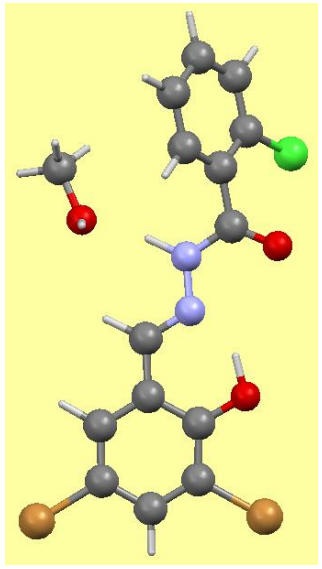
Example RMS = 0.083 Å

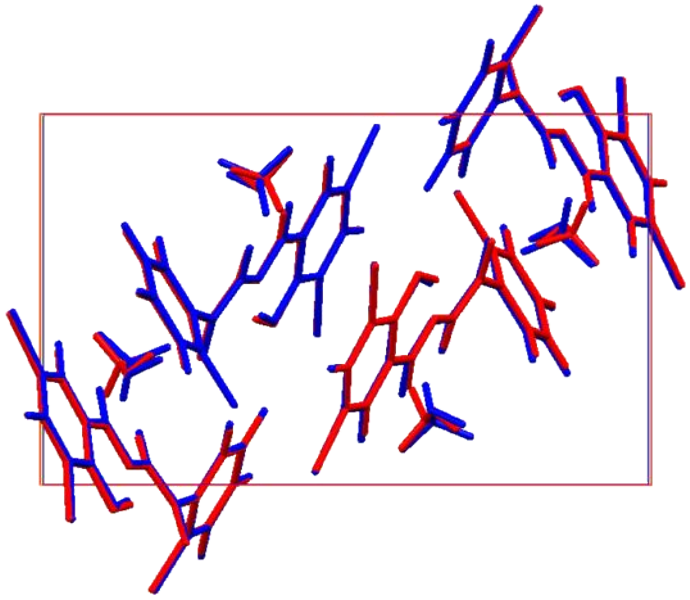


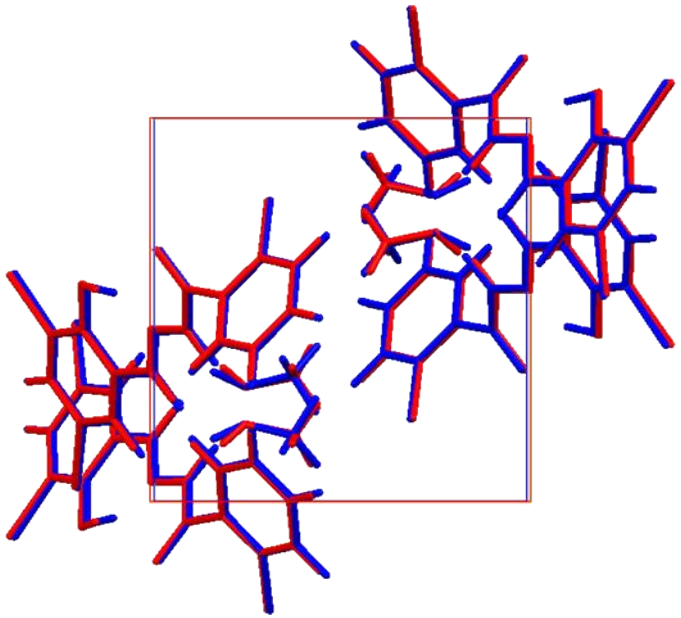
Unit cell free
ΔV = -3%

Experimental

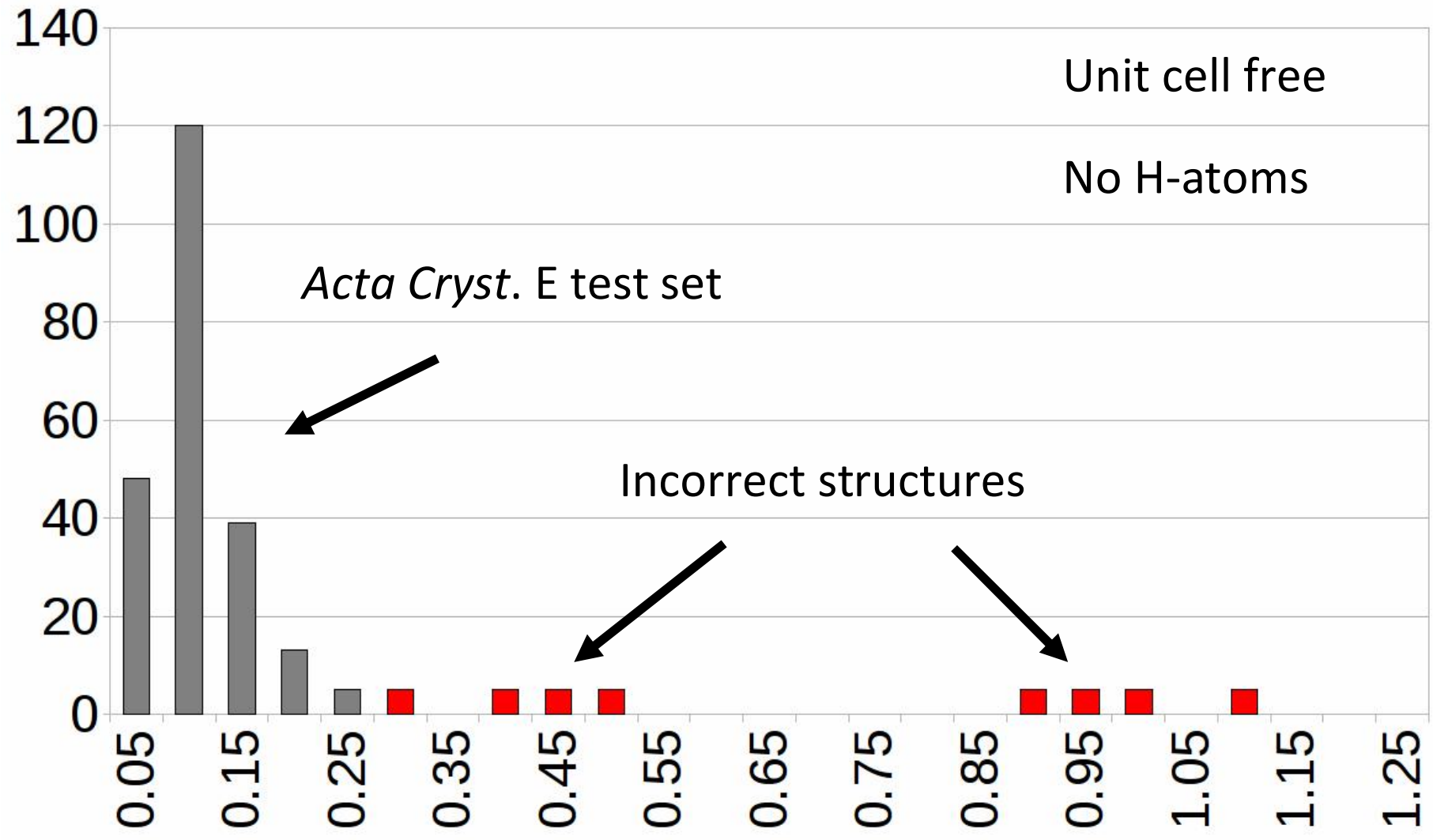
Minimised



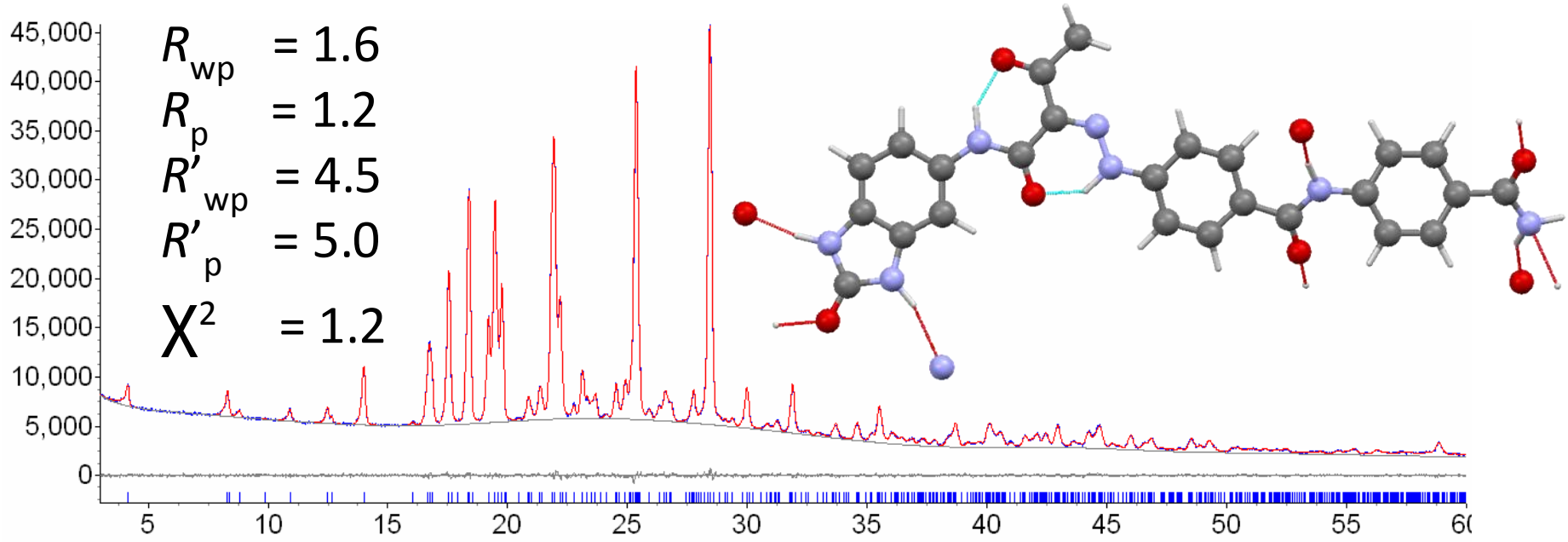




What about Wrong Structures?



Pigment Yellow 181



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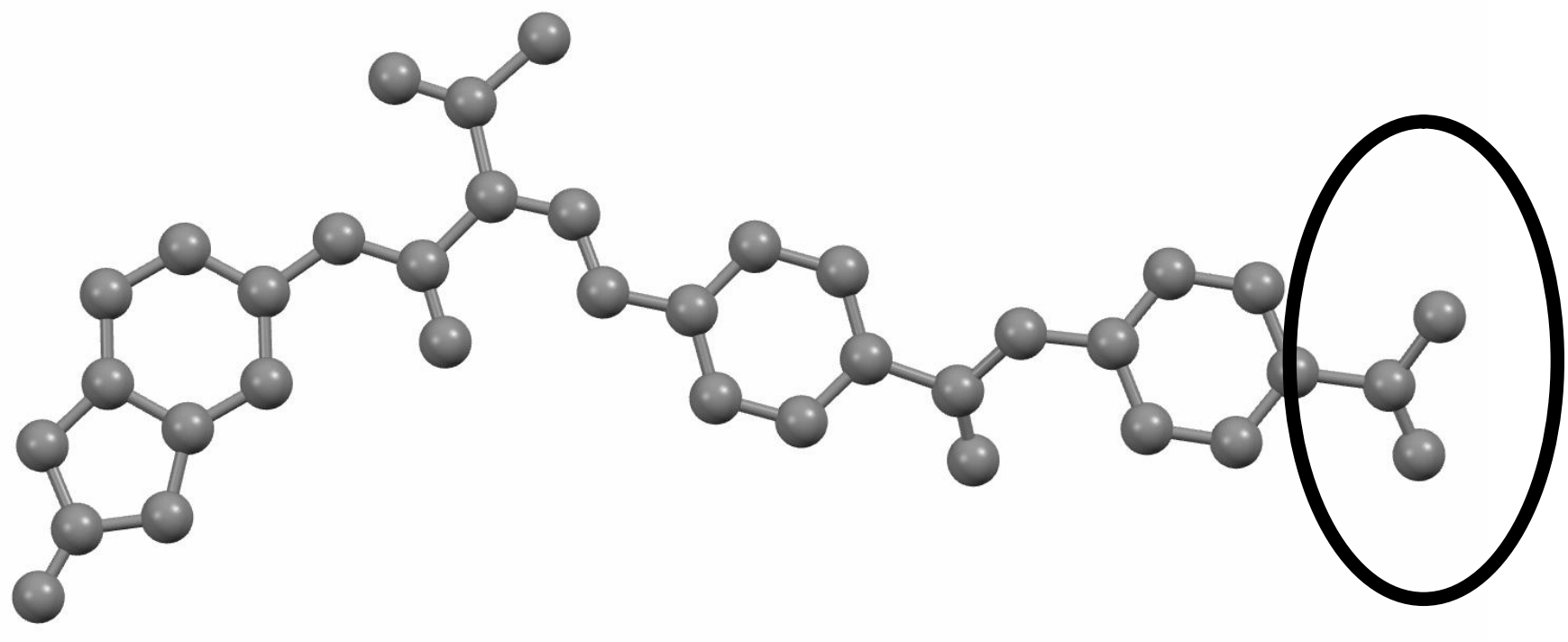
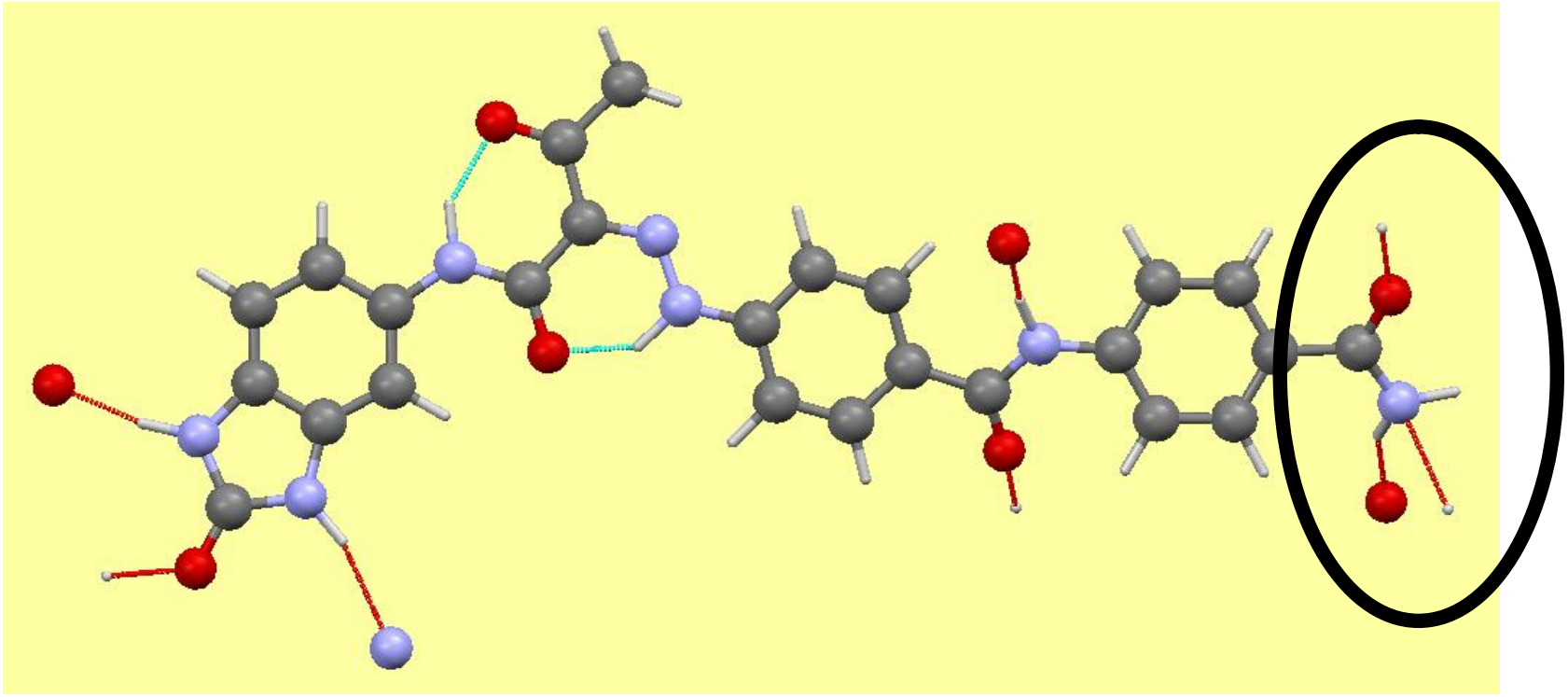
What XRPD Sees



The amide group can be turned over 180°:

- O and N (or NH_2) only 1 electron difference
- Because all hydrogen atoms are moved as well, the infinite chain of hydrogen bonds remains intact.

Chemist's Impression



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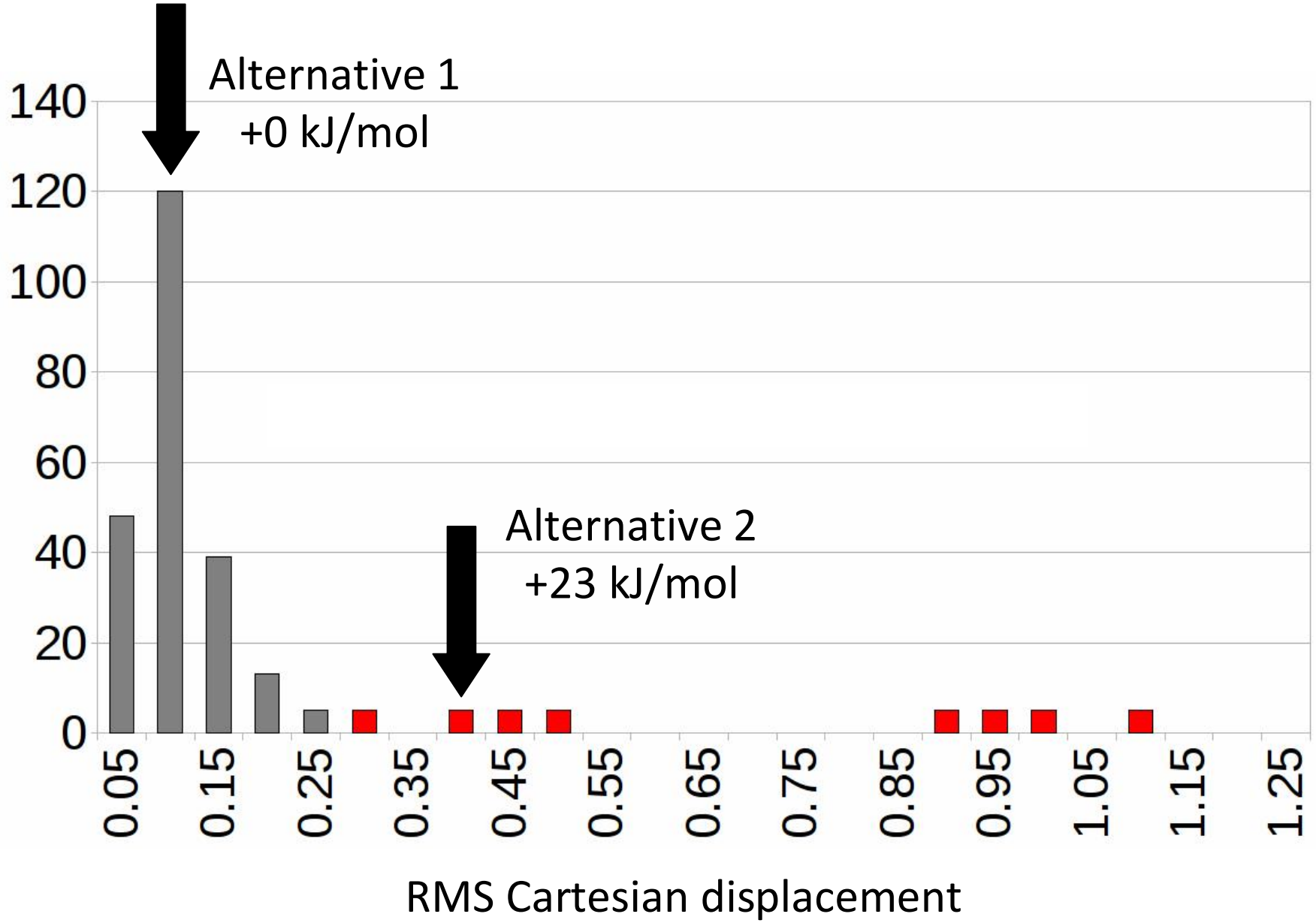
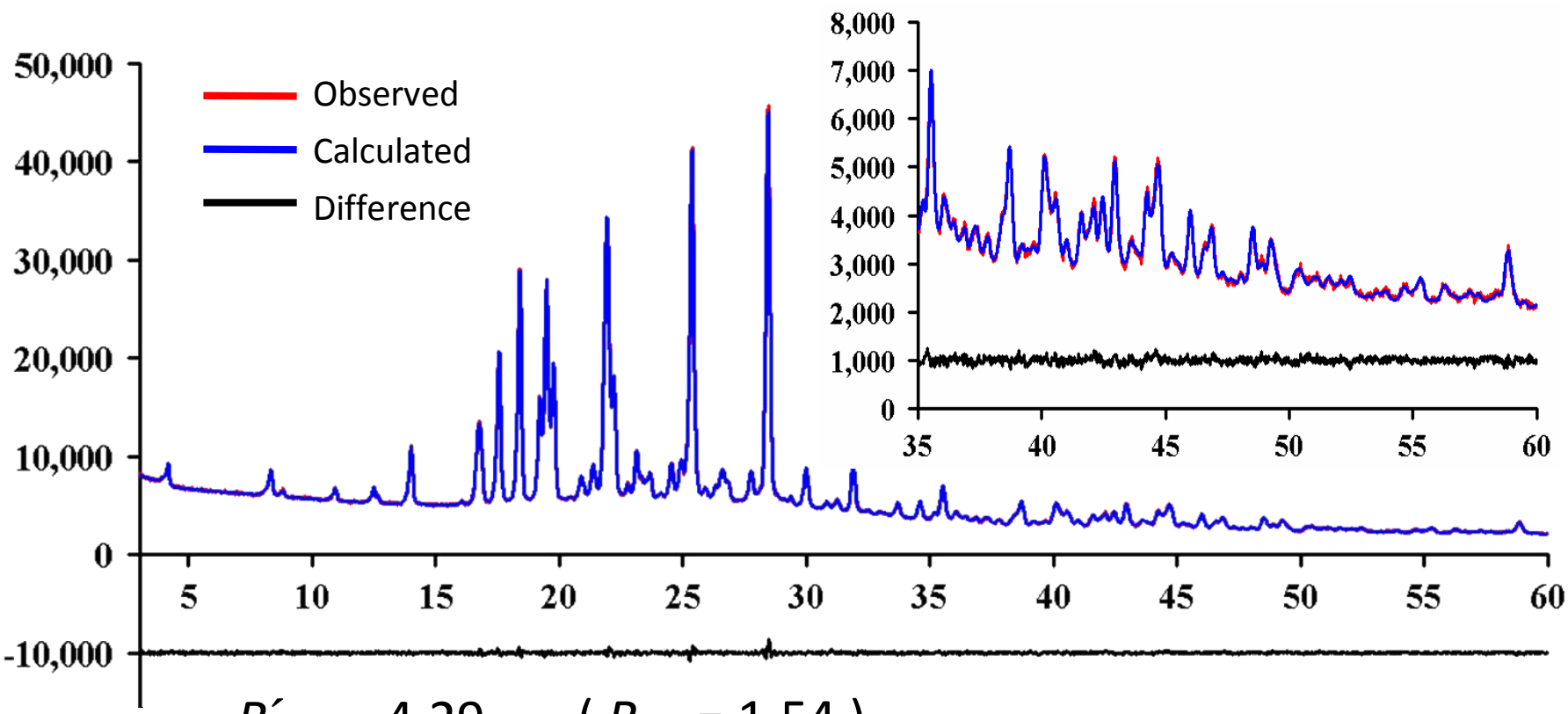
DFT-D Minimisation



Pigment Yellow 181



R'_{wp} = 4.29 (R_{wp} = 1.54)

R'_{p} = 4.76 (R_{p} = 1.19)

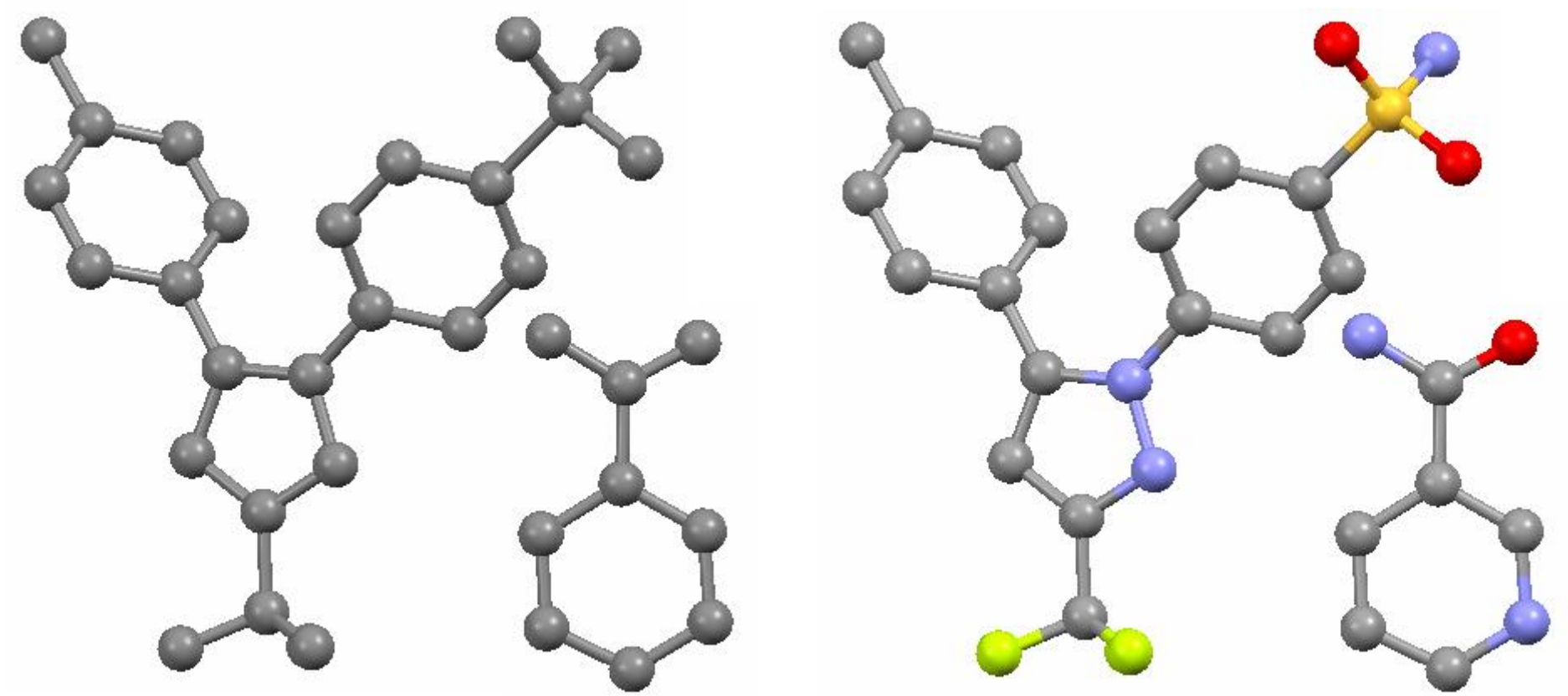
χ^2 = 1.19

E. Pidcock, J. van de Streek & M. U. Schmidt (2007) *Z. Krist.* **222**, 713-717

J. van de Streek, J. Brüning, S. N. Ivashevskaya, M. Ermrich, E. F. Paulus, M. Bolte & M. U. Schmidt (2009) *Acta Cryst.* B**65**, 200-211

Example: Celecoxib Nicotinamide

3 x 2 x 2 = 12 different possibilities
mentioned in paper



Remenar, Peterson, Stephens, Zhang *et al*. (2007). *Mol. Pharmaceutics* **4**, 386-400
Chan, Kendrick, Neumann, Leusen (2013). *CrystEngComm* **15**, 3799-3807

Accuracy

In this talk, we only look at the atomic *x*,*y*,*z* coordinates of molecular crystal structures.

No disorder.

Hydrogen atoms: ?

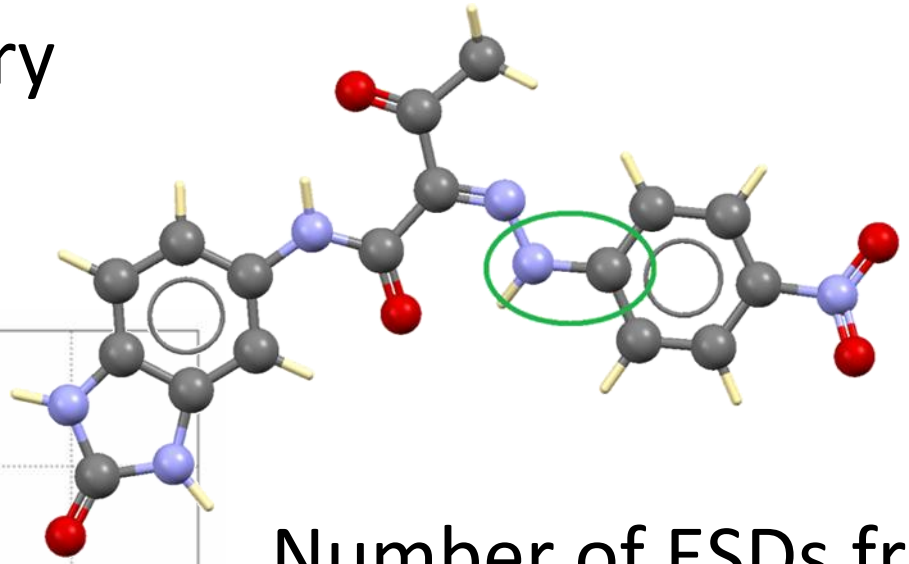
Peak shape, background *etc*. are “nuisance parameters”.

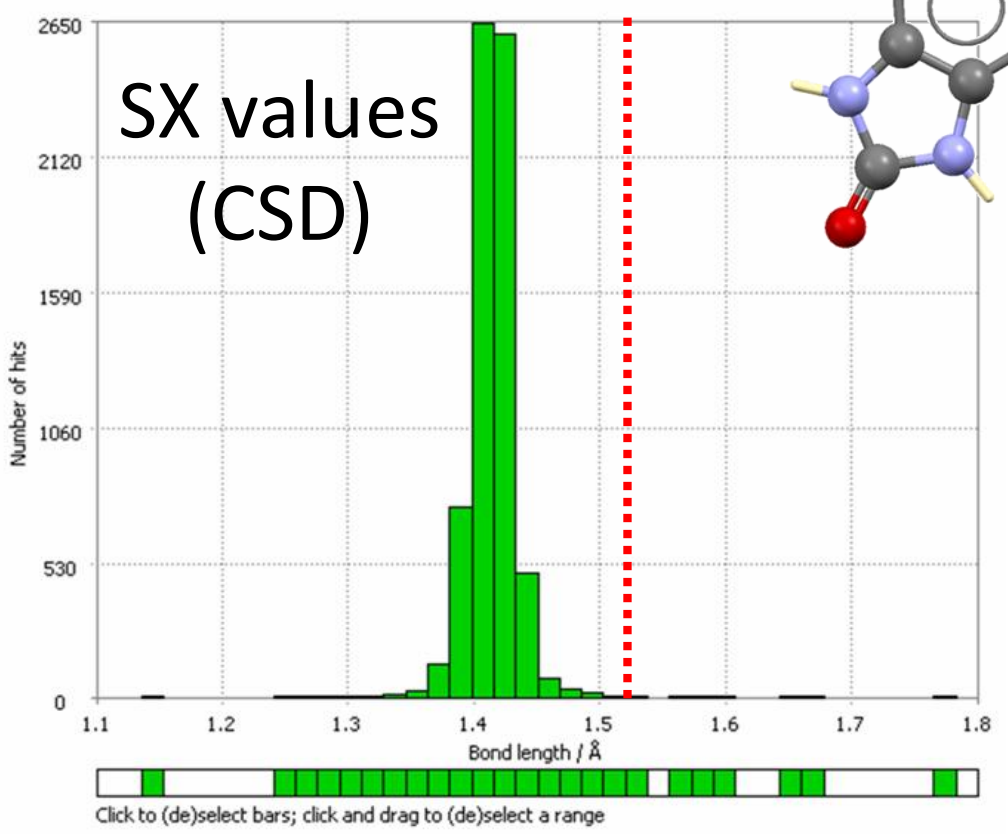
Common excuse: “it is only XRPD data, so the fit is not so good”. It is the opposite way round!

Accuracy: single crystal as gold standard, we also use RMS Cartesian displacement with DFT-D

Mogul *z*-scores

= value in query





Number of ESDs from mean = *z*-score

Each bond has a *z*-score

Each angle has a *z*-score

Accuracy with DFT-D

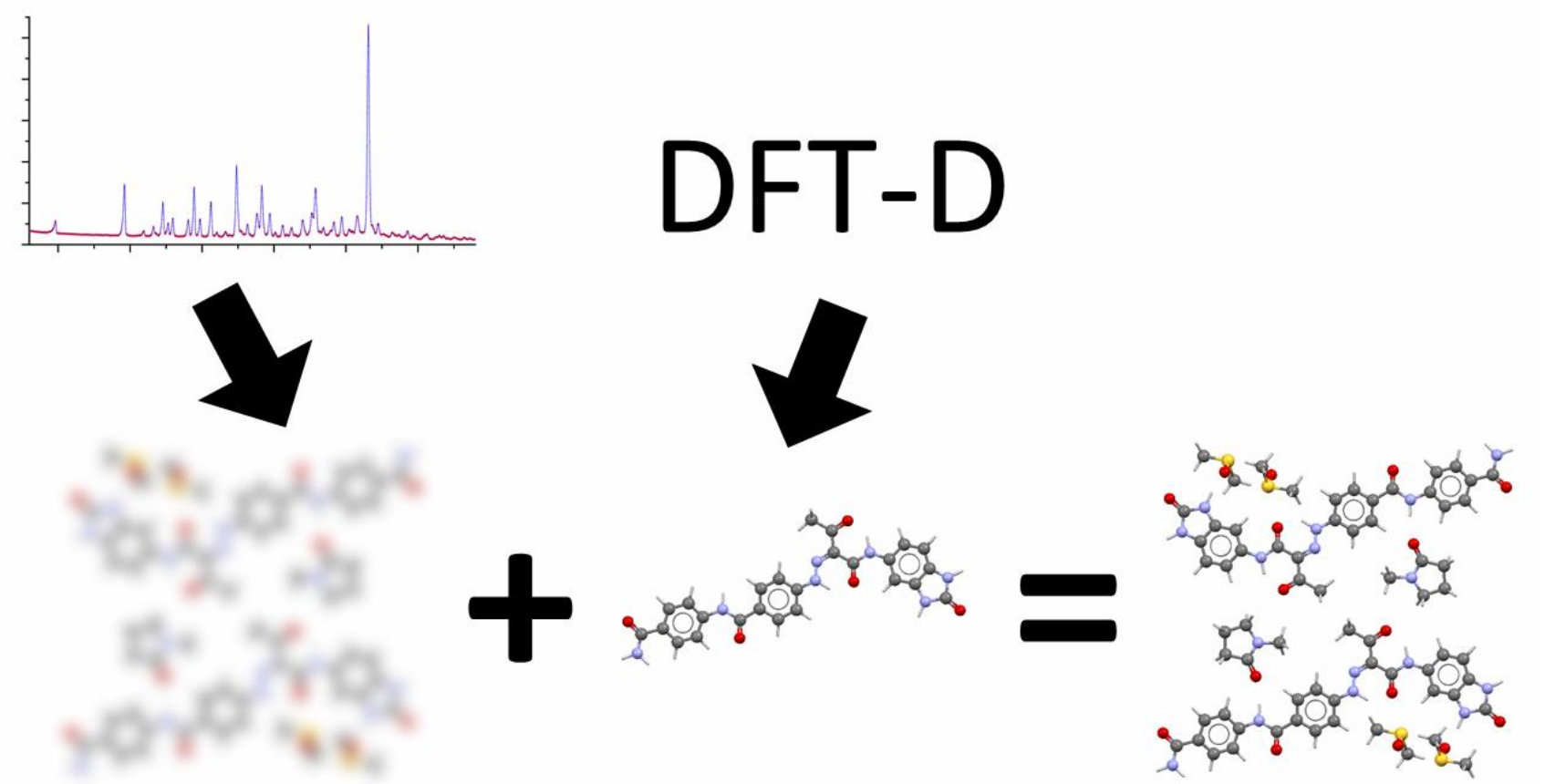
Validating the crystal structure is done *after* the Rietveld refinement: it does not influence the Rietveld process.

This is a pity: the DFT-D contains a lot of independent information, can this information be used *as part of* the Rietveld refinement?

I.e. can the independent information from the DFT-D be merged into the Rietveld refinement to *complement* the experimental data to make the final result more accurate?

Accuracy with DFT-D

XRPD provides the packing… …DFT-D provides the details



Accuracy with DFT-D

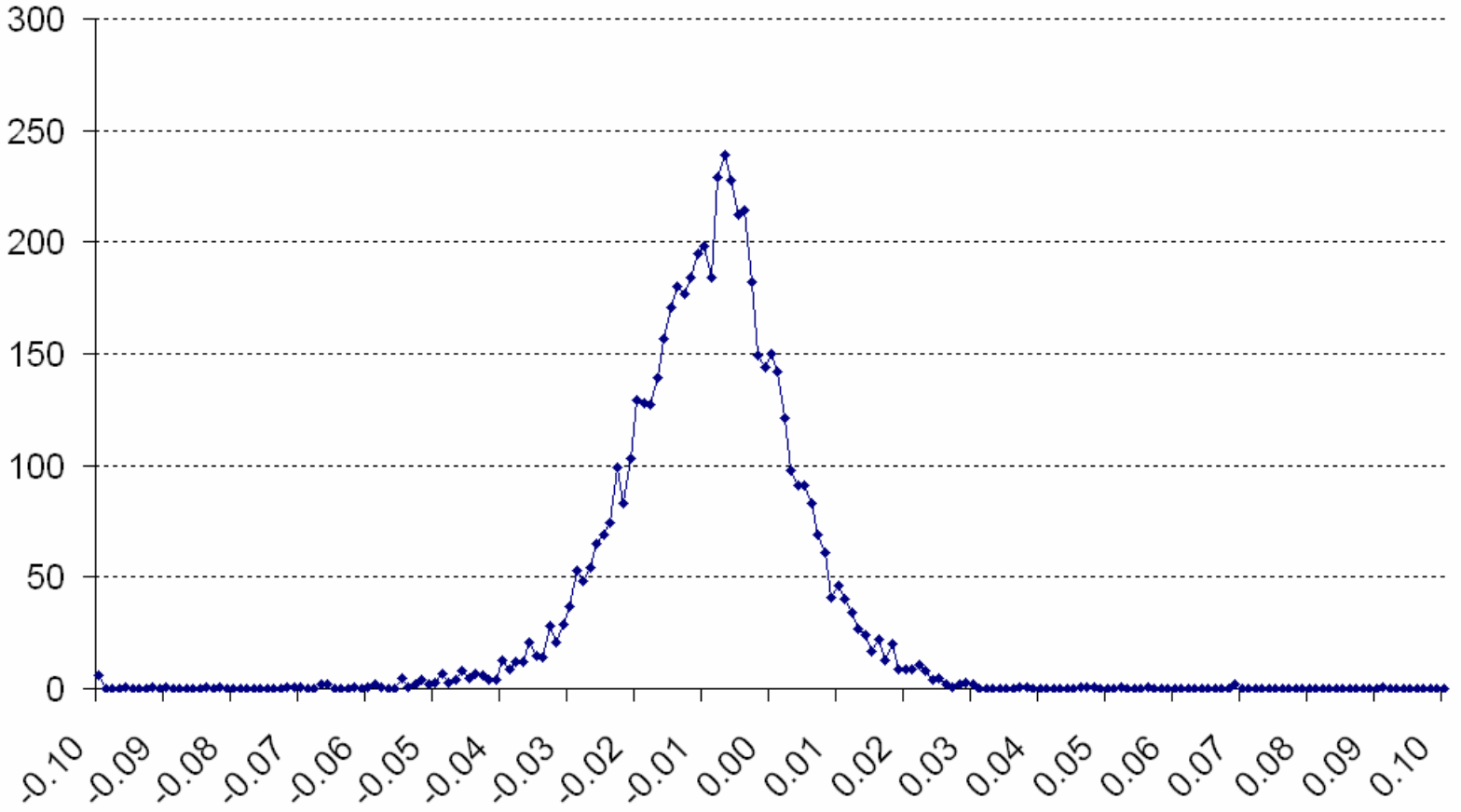
Even better than restraints from a single molecule in vacuum: use the bond lengths and bond angles from the DFT-D minimised crystal structure as restraints.

“Polymorph-dependent restraints”.

Only *after* the structure has been validated as being correct, otherwise you are biasing your refinement.

Accuracy with DFT-D

Average absolute difference over 5,778 bonds from *Acta* E test set: 0.013 Å (non-hydrogen atoms only)



Bond length deviations: SX – DFT-D [Å]

Accuracy with DFT-D

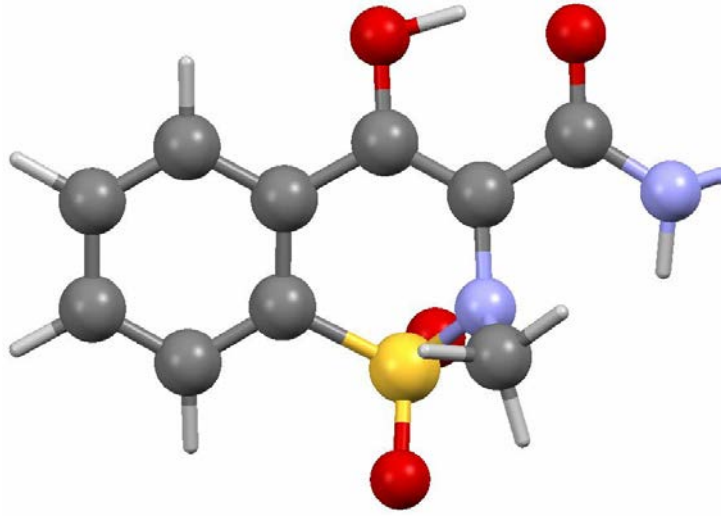
Polymorph-dependent restraints in *TOPAS*:

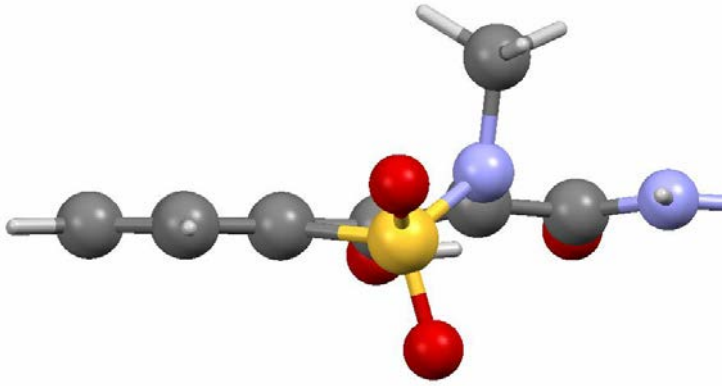
```
Distance_Restrain( N1   C2,  1.47872, 1.47998`_0.00610, 0, 10000 )
Distance_Restrain( N1   C3,  1.47894, 1.48956`_0.00690, 0, 10000 )
Distance_Restrain( N1   C4,  1.48941, 1.48492`_0.00524, 0, 10000 )
Distance_Restrain( C2   C5,  1.50425, 1.47233`_0.00715, 0, 10000 )
Distance_Restrain( C2   H6,  0.95,      0.96054`_0.01471, 0, 10000 )
Distance_Restrain( C2   H7,  0.95,      0.94072`_0.01347, 0, 10000 )
Distance_Restrain( C3   C8,  1.50403, 1.49550`_0.00524, 0, 10000 )
Distance_Restrain( C3   H9,  0.95,      0.95970`_0.01483, 0, 10000 )
…
Angle_Restrain( C2   N1   C3, 111.15614, 115.12083`_0.35599, 1, 1 )
Angle_Restrain( C2   N1   C4, 112.79224, 112.04806`_0.36718, 1, 1 )
Angle_Restrain( C3   N1   C4, 114.20513, 113.81510`_0.39248, 1, 1 )
Angle_Restrain( N1   C2   C5, 112.35920, 113.55737`_0.35977, 1, 1 )
Angle_Restrain( N1   C2   H6, 111.80674, 113.25174`_1.01145, 1, 1 )
…
```

Planarity Restraints

The DFT-D tells you which atoms are in the same plane, so the planarity restraints are also based directly on the DFT-D calculations

Flatten(C5 C15 H27 C26 O40 C38 H47, , 4.17658429`_5.92244831, 0, 100000)





Hydrogen Atoms

For the hydrogen atoms, restraints are not always sufficient.

Better solution: energy-minimise hydrogen positions with non-hydrogens and unit cell kept fixed.

Example: Piroxicam III

Max. *Mogul* *z*-scores:

Bonds: 2.3

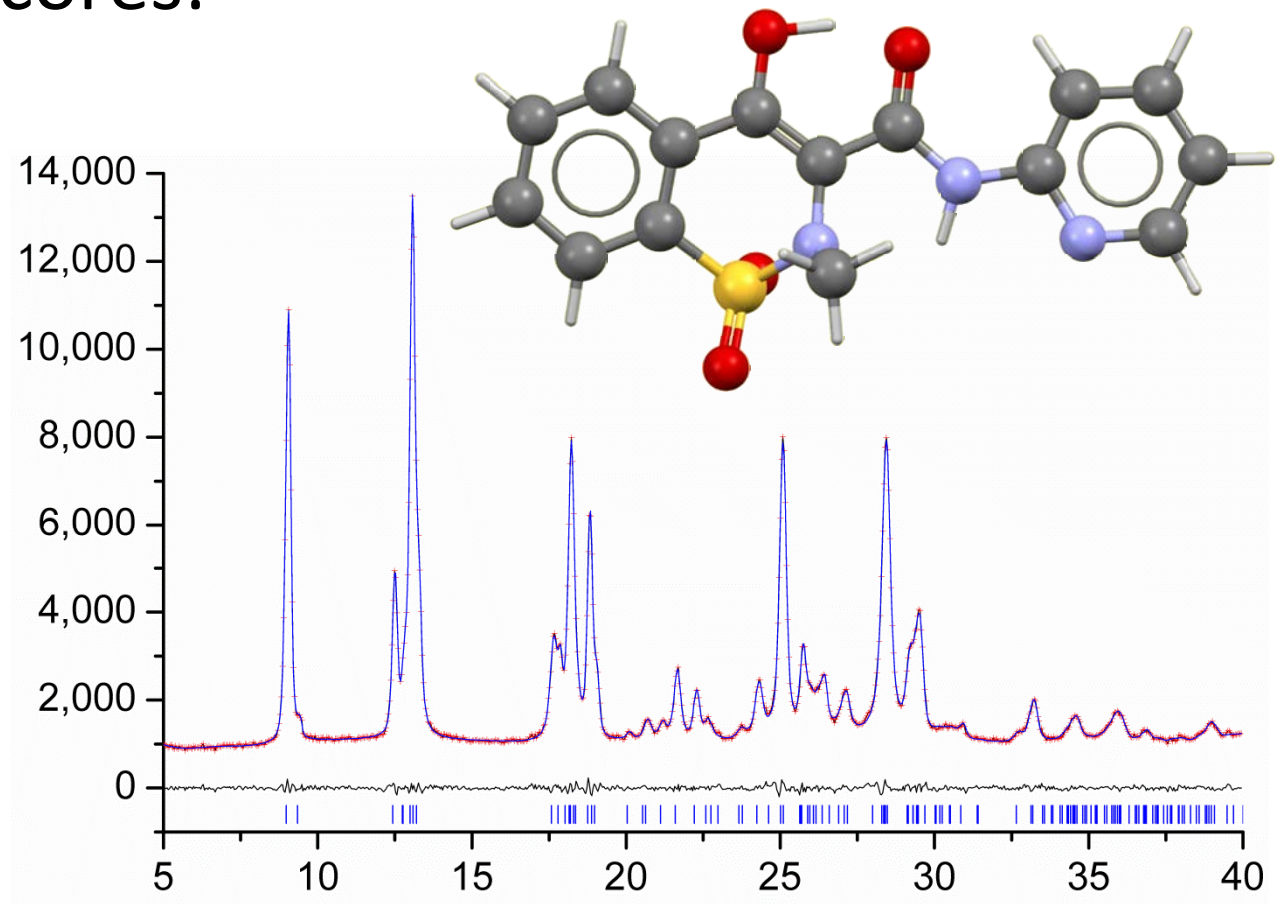
Angles: 3.7

RMSCD: 0.10 Å

χ^2 = 1.30

Lab data

No PO



K. Naelapää, J. van de Streek, J. Rantanen, A. D. Bond (2012). *J. Pharm. Sci.* **101**, 4214-4219

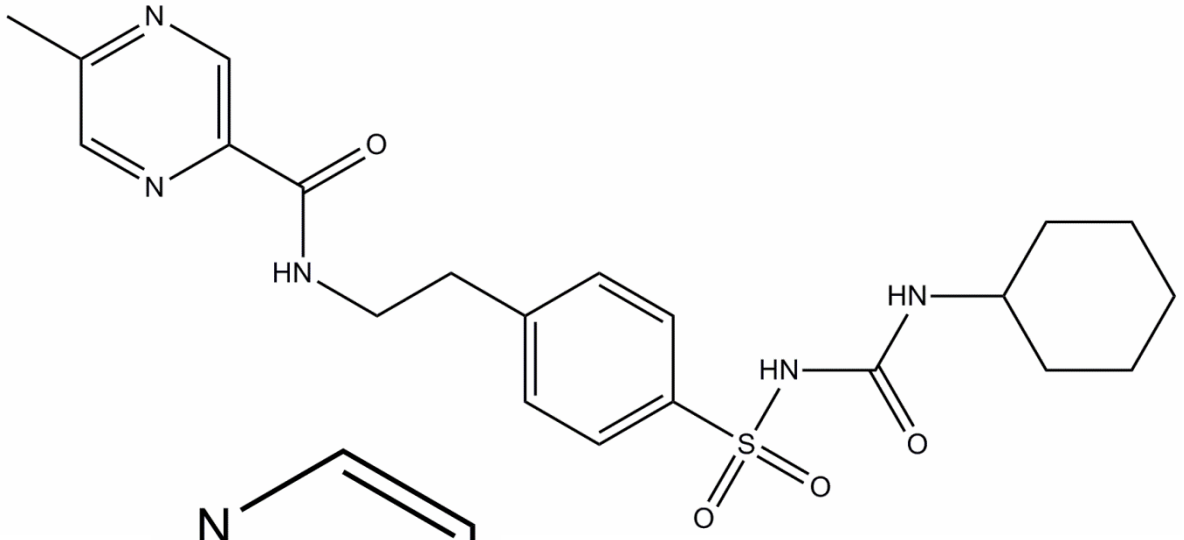
Reliable *and* Accurate

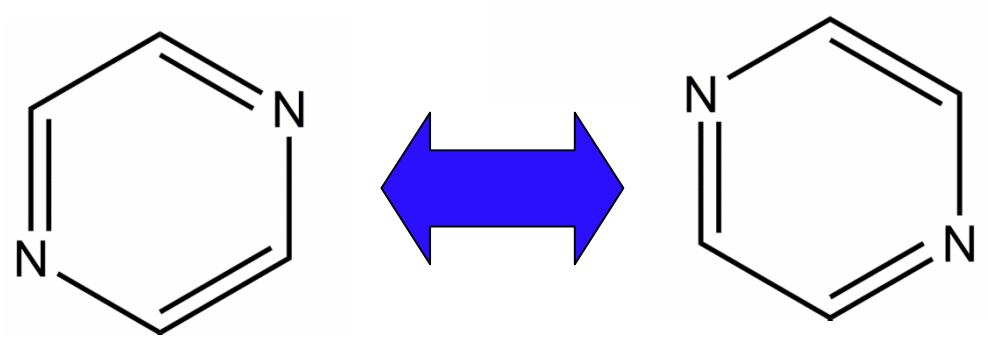
Some example of crystal structures from the literature that can be corrected with DFT-D

and

for which DFT-D provides the polymorph-dependent restraints for the Rietveld refinement

Glipizide (2005)

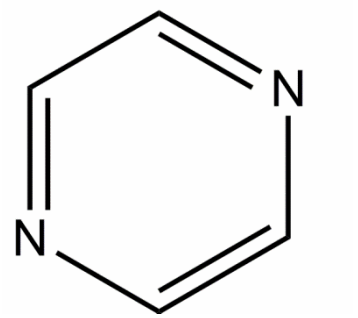




The pyrazyl ring can be turned over 180°:
N and C (or CH) only 1 electron difference
Ambiguity mentioned in paper

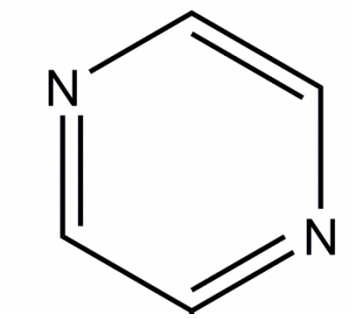
J. C. Burley (2005). *Acta Cryst.* B**61**, 710-716

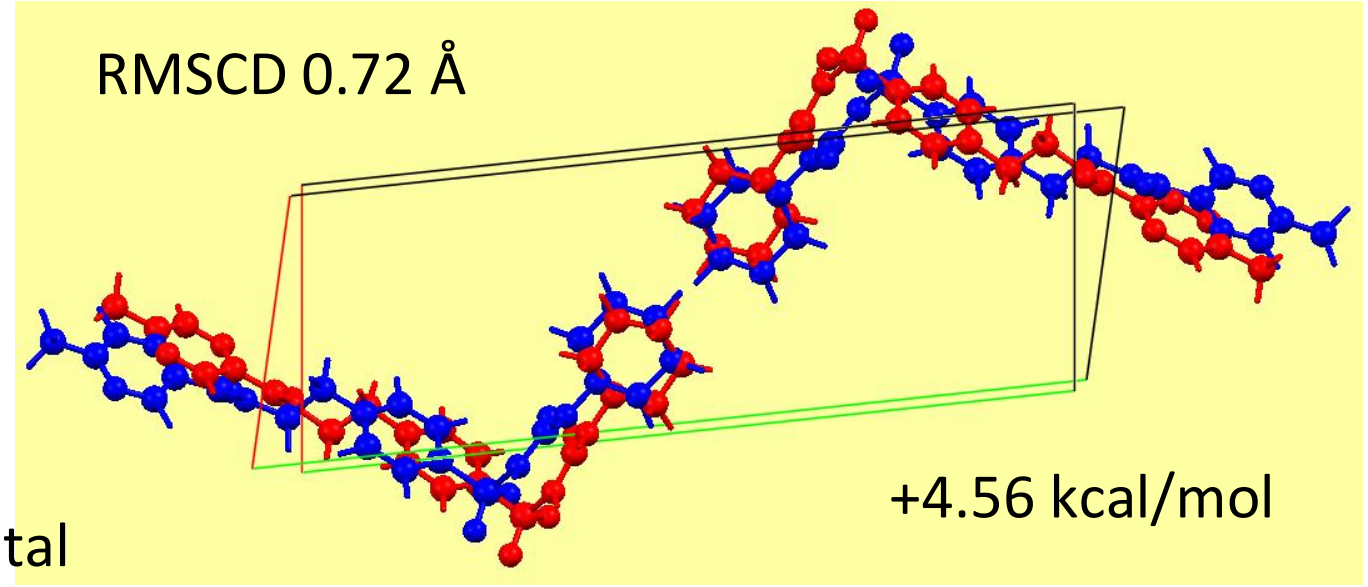
Glipizide (2005)

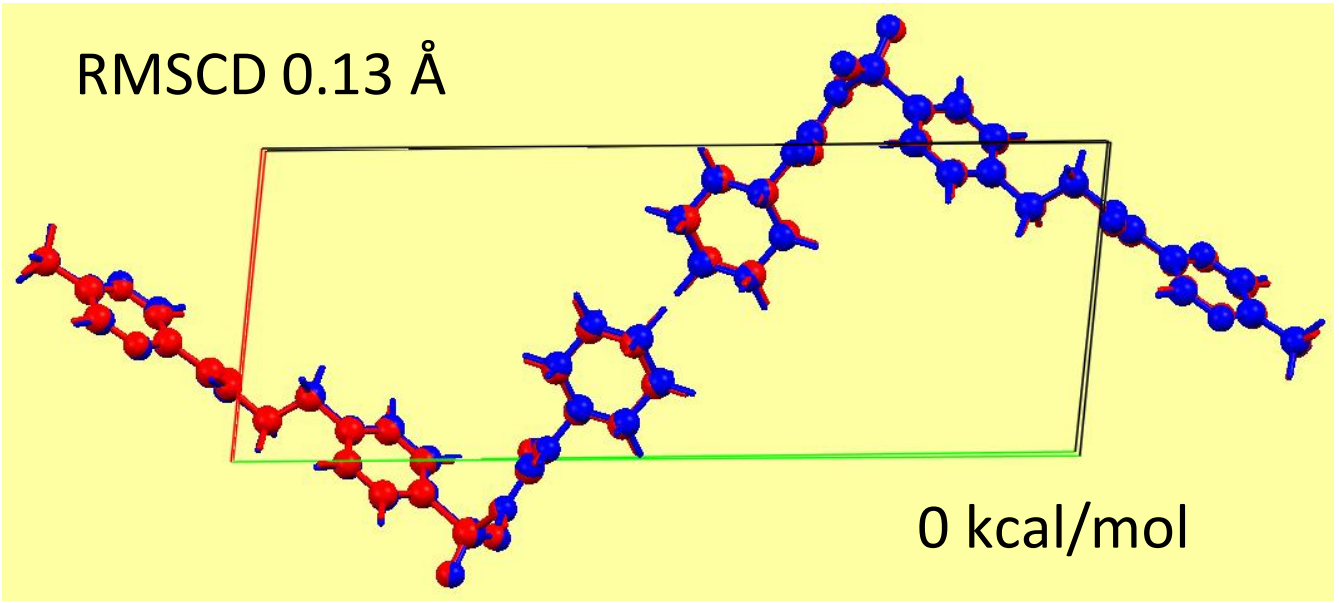


Experimental

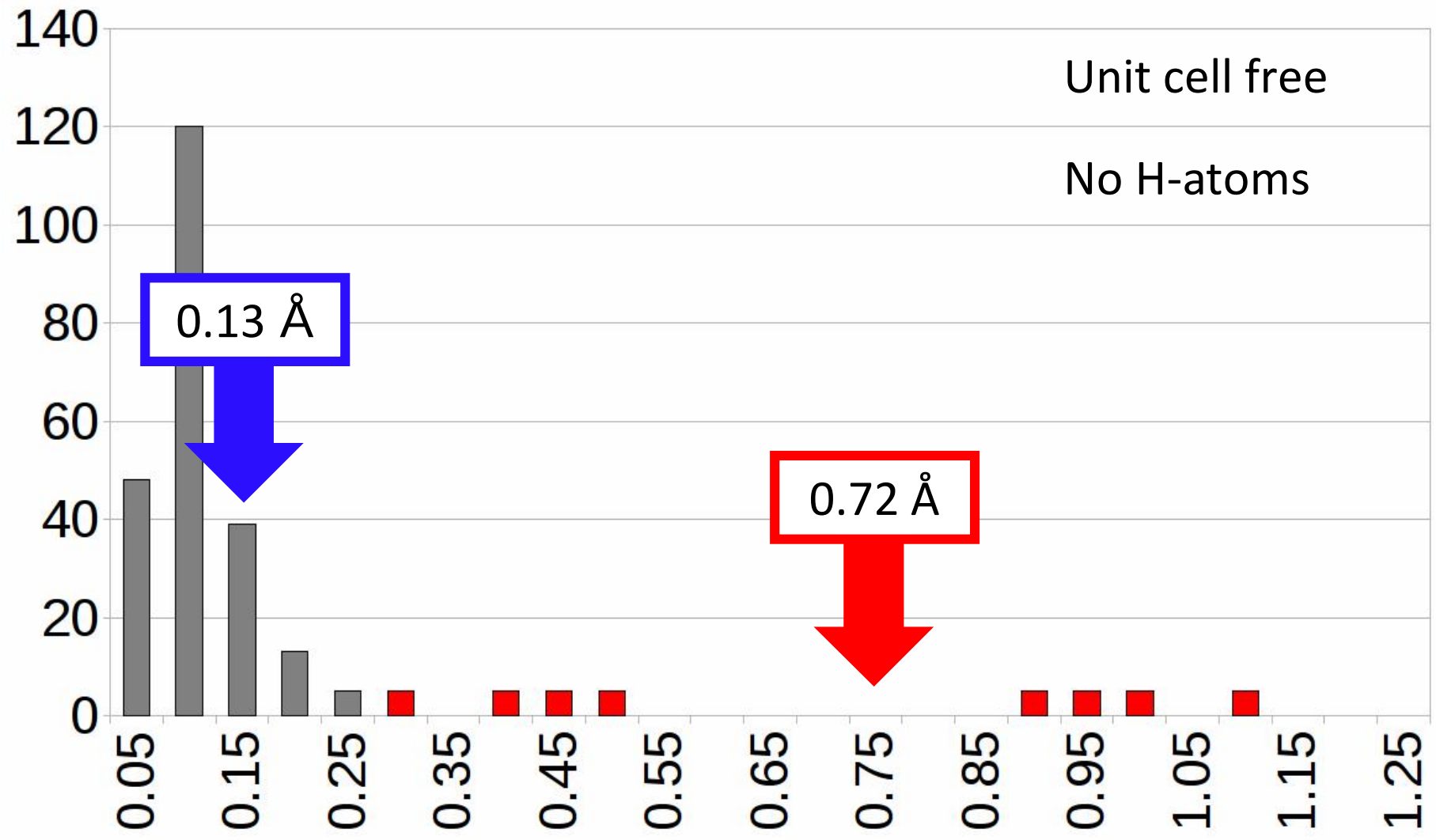
Minimised







RMS Cartesian Displacement



Glipizide Corrected

Max. *Mogul z*-scores:

Bonds: 2.1

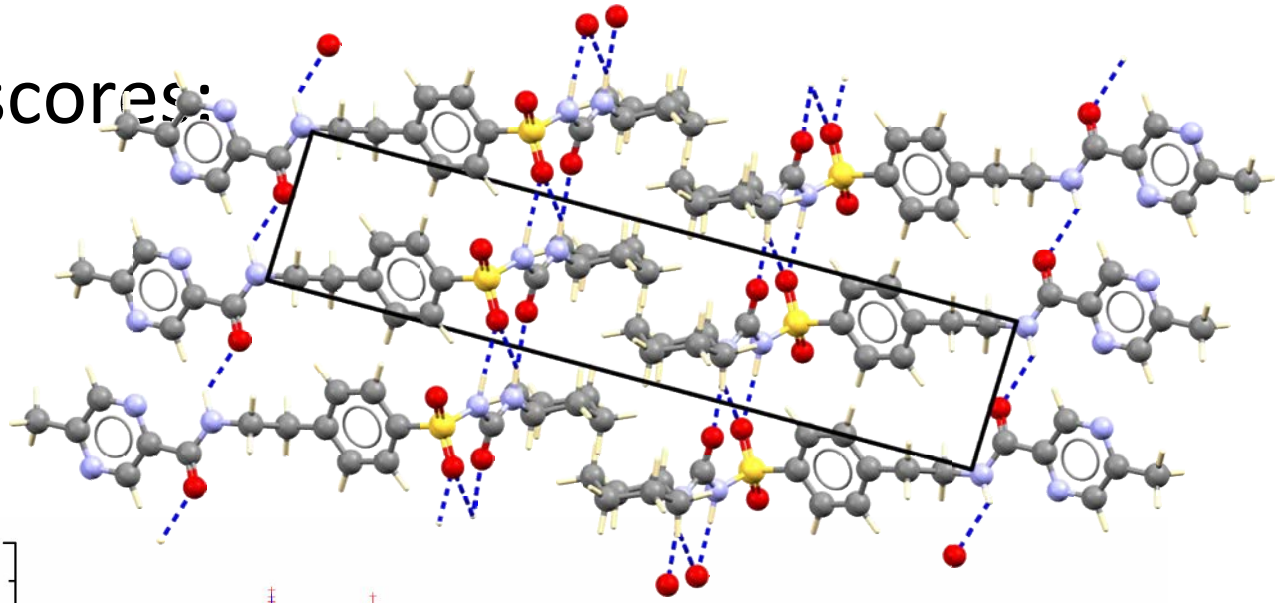
Angles: 1.9

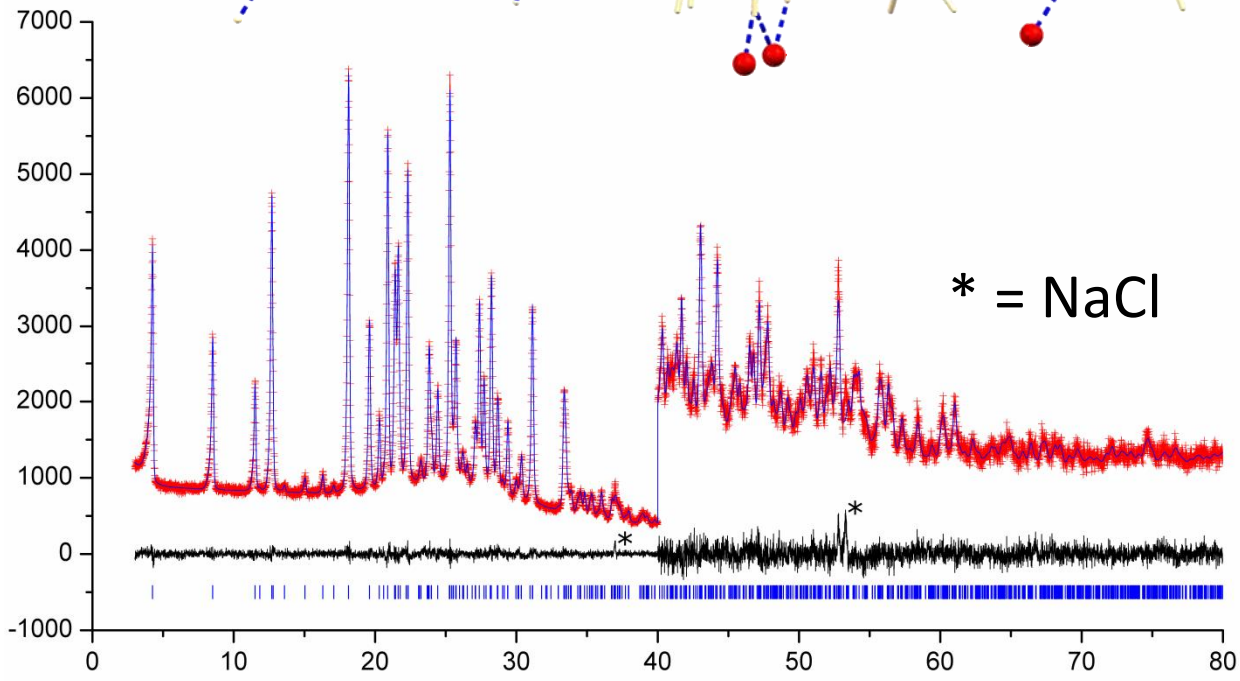
RMSCD: 0.13 Å

χ^2 = 1.11

Lab data

No PO





Clarithromycin Monohydrate (2012)

Maximum *Mogul* *z*-scores:

Bonds: 7.4

Angles: 3.2

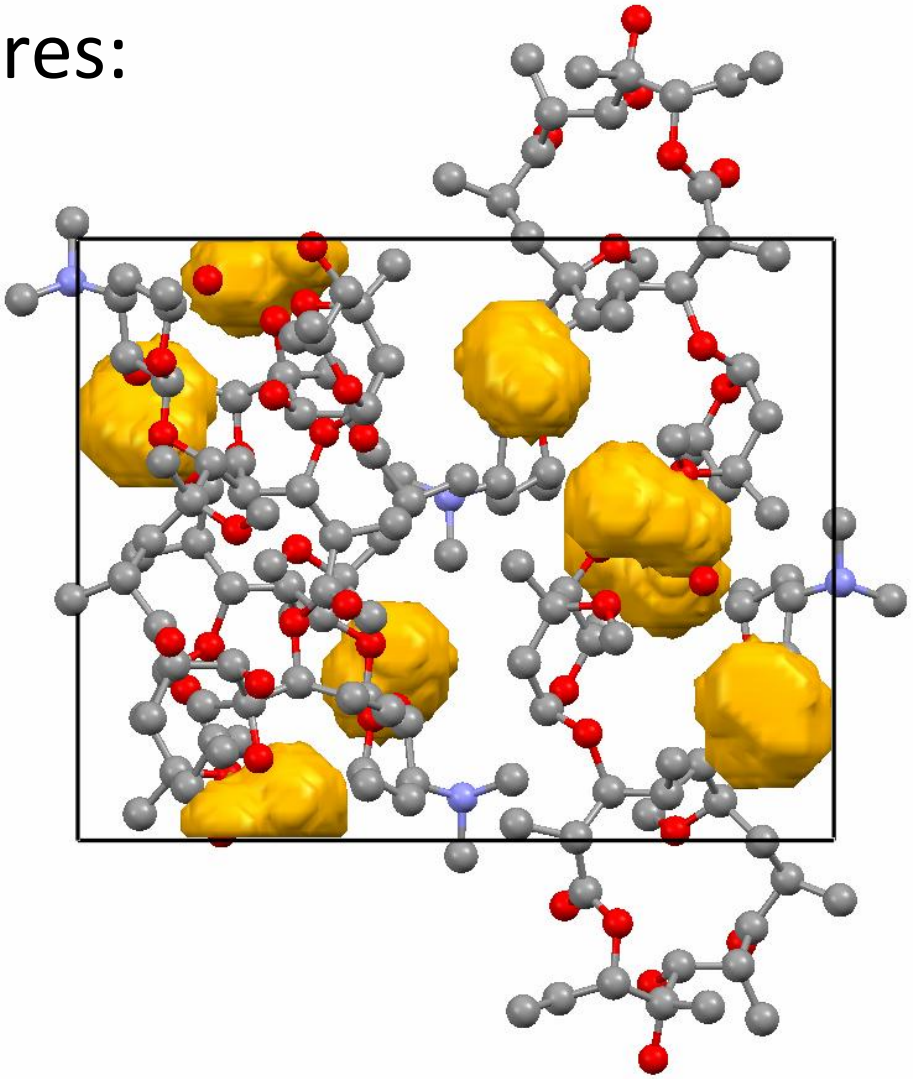
Voids/*Z* (H_2O = 21 $Å^3$)

Mercury: 40 $Å^3$

Hofmann: 55 $Å^3$

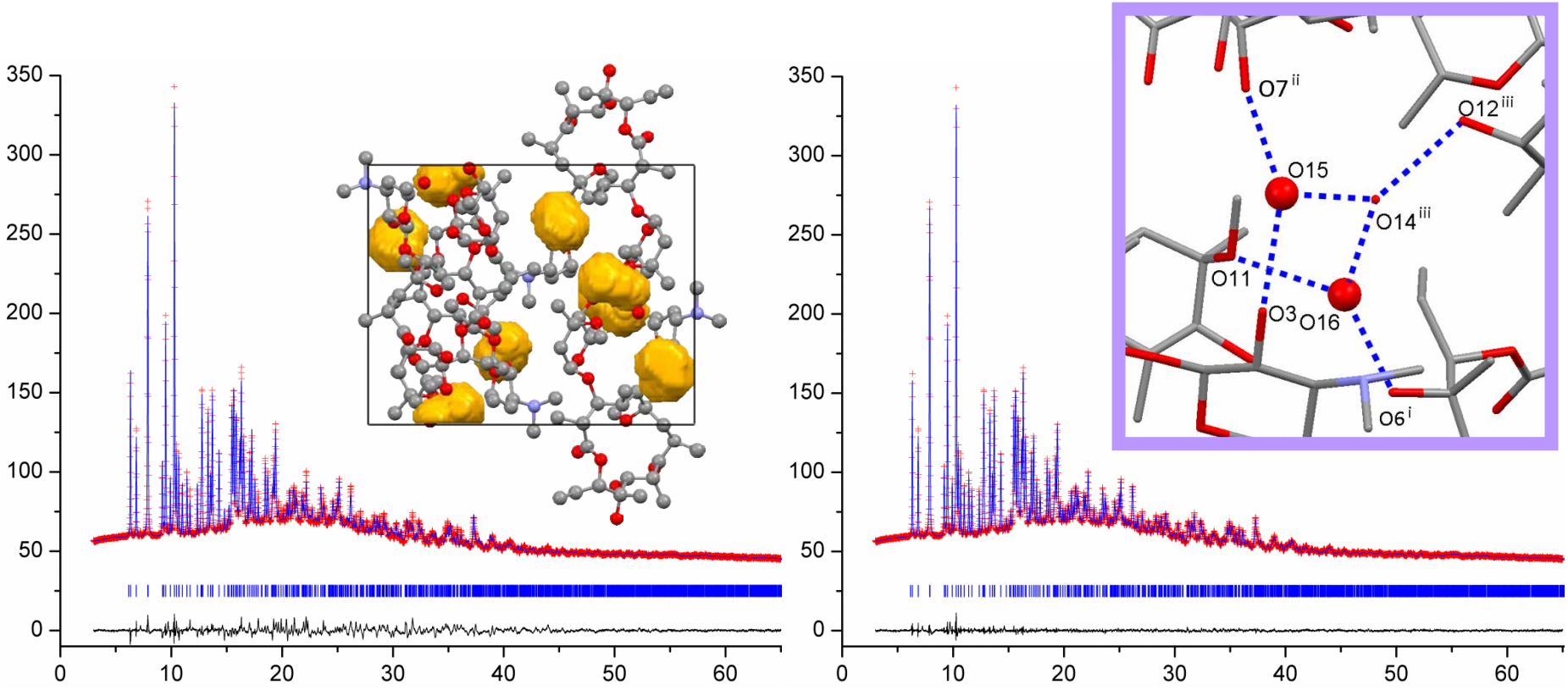
RMSCD: ?

Synchrotron



Noguchi, Fujiki, Iwao, Miura & Itai (2012). *Acta Cryst*. E**68**, o667-o668

Clarithromycin *Tri*hydrate Corrected



Clarithromycin
"monohydrate"

Clarithromycin
*tri*hydrate

Synchrotron data, *y*-axis: $\sqrt{I}$

Clarithromycin Trihydrate

Maximum *Mogul* *z*-scores:

Bonds: 5

Angles: 8

Synchrotron

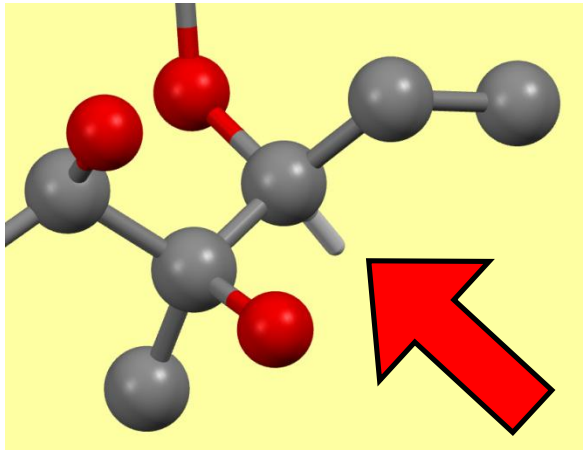
“Clarithromycin” Trihydrate

Maximum *Mogul* *z*-scores:

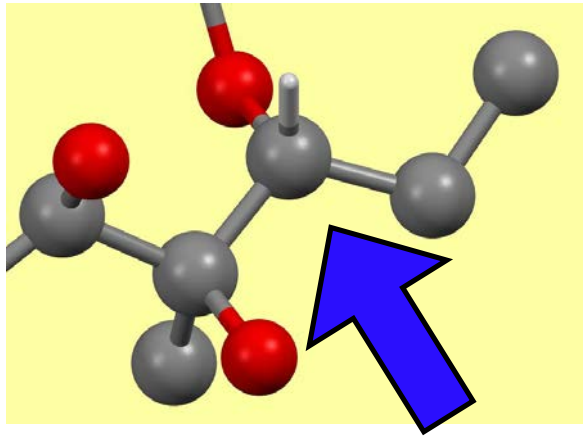
Bonds: 5

Angles: 8

Synchrotron



One of the stereo-centres is wrong: this is not Clarithromycin



Clarithromycin Trihydrate Corrected

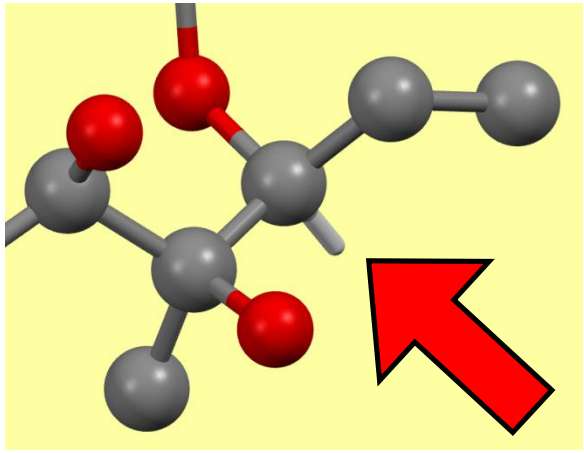
Maximum *Mogul z*-scores:

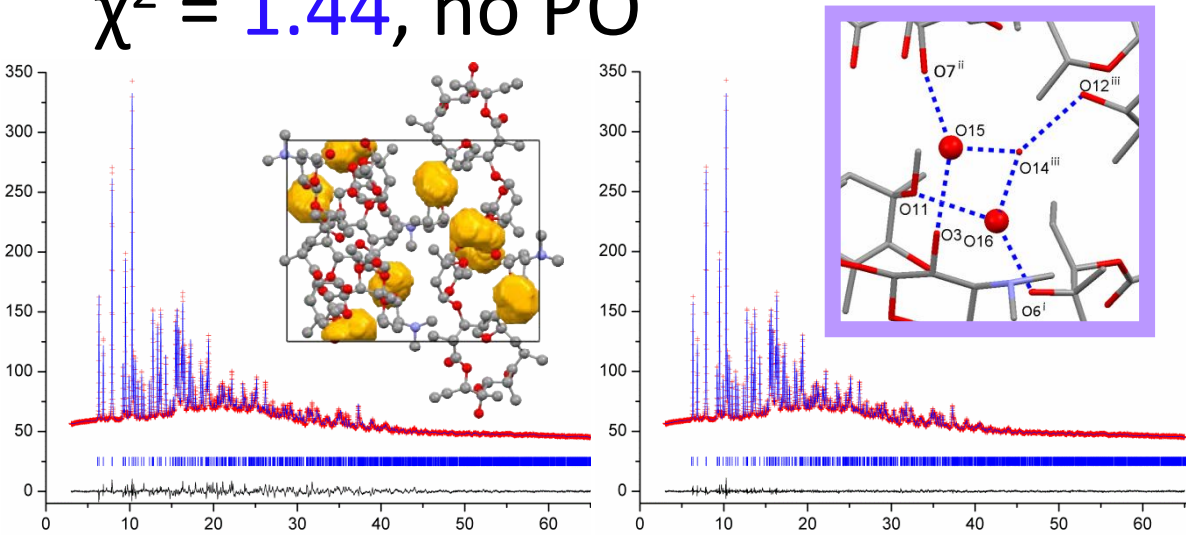
Bonds: 1.4, Angles: 3.4

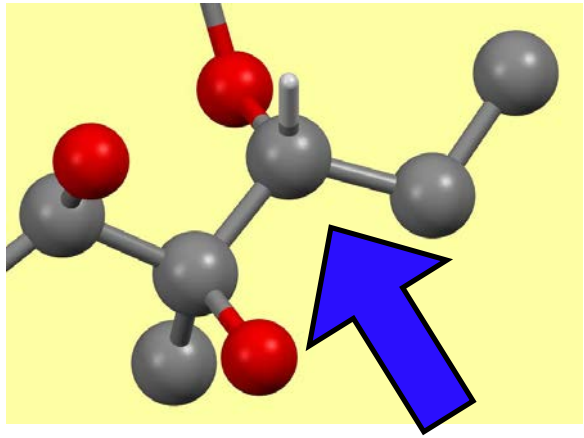
RMSCD: 0.14 Å

Synchrotron

χ^2 = 1.44, no PO







J. van de Streek (2012). *Acta Cryst.* C**68**, o369-o372

Where does DFT-D Enter the Process?

1. To give a better starting molecular geometry
2. Validate the crystal structure
3. Feed back the energy-minimised crystal structure as polymorph-dependent restraints
4. Energy-minimise the hydrogen atoms, keeping the unit-cell parameters and the positions of the non-hydrogen atoms fixed

DFT-D

Which functional? Which dispersion correction?

For *energies*, these questions are critical.

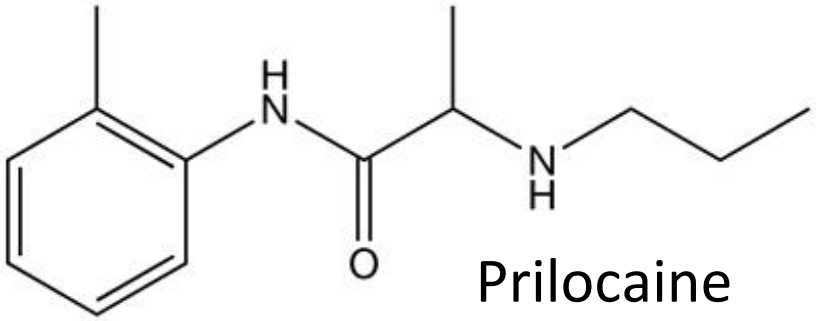
For *structures* (coordinates / unit-cell parameters): it does not matter.

PBE, PW91, BLYP, B3LYP, Neumann & Perrin, Grimme 2006, Grimme 2010 give very similar results.

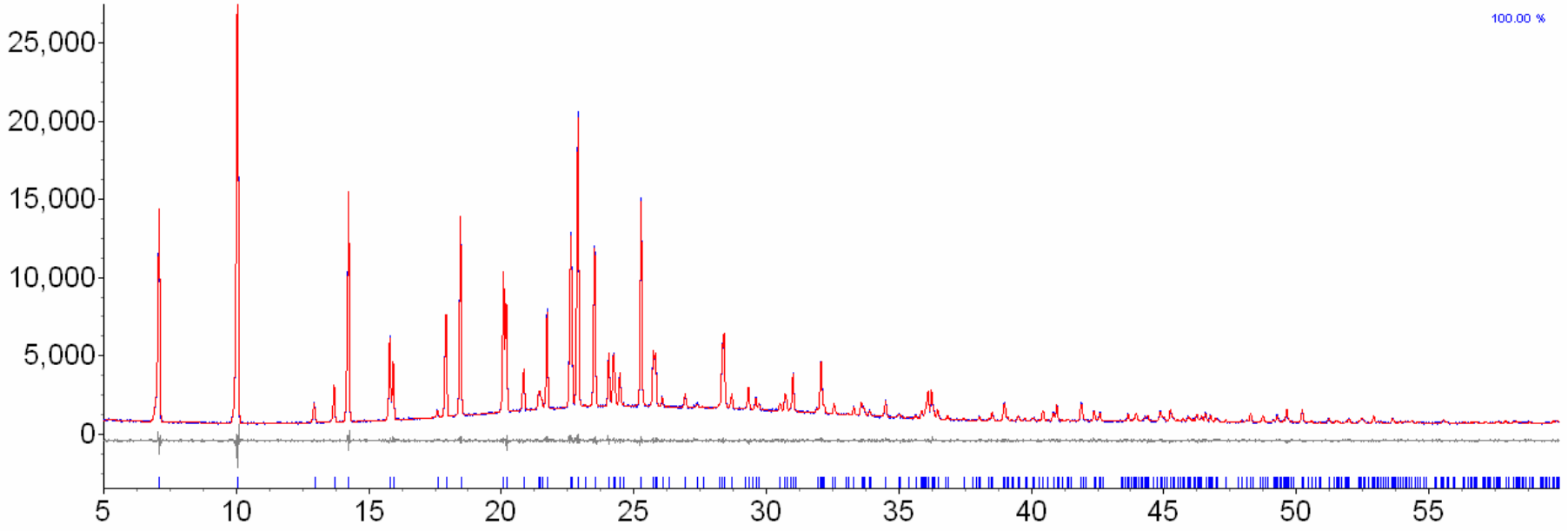
Limitations…

Temperature effects
Metals
Disorder
Hydrogen atoms (salt *versus* co-crystal)

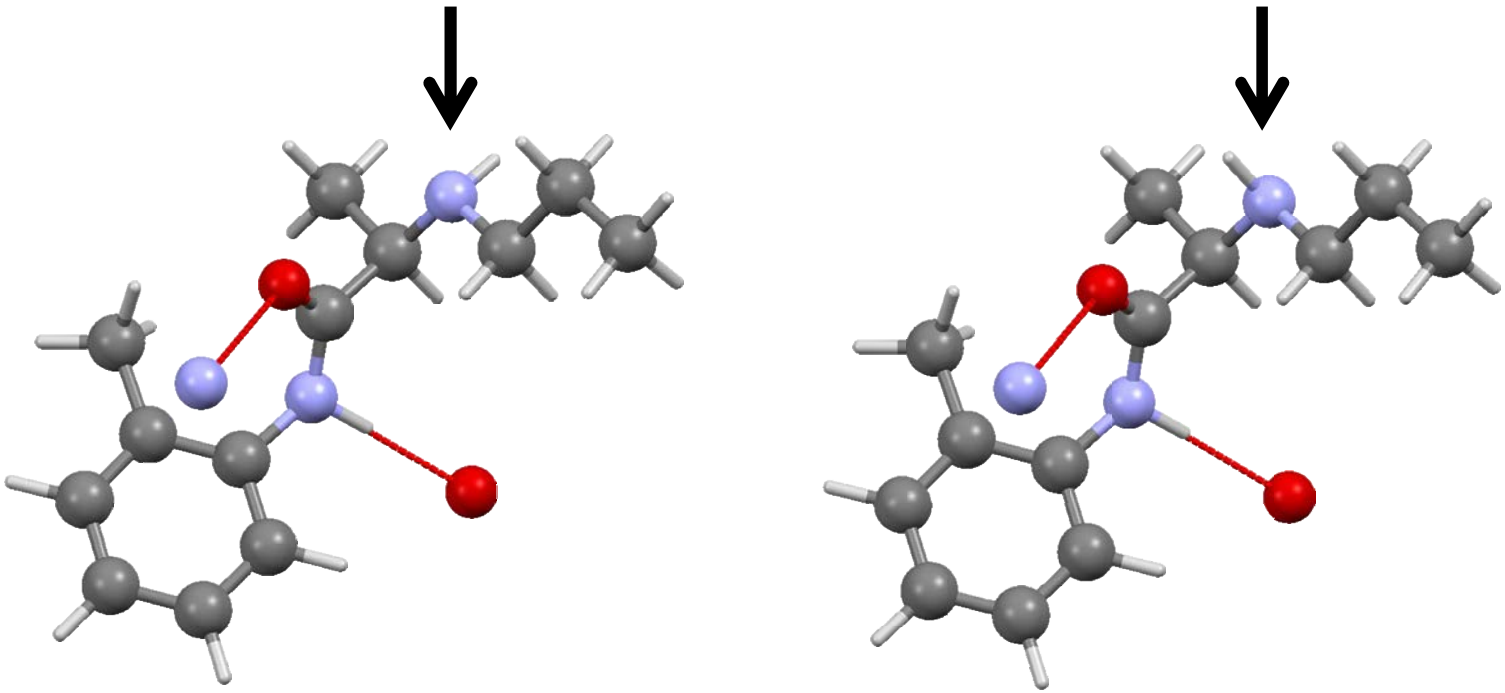
Hydrogen Atoms



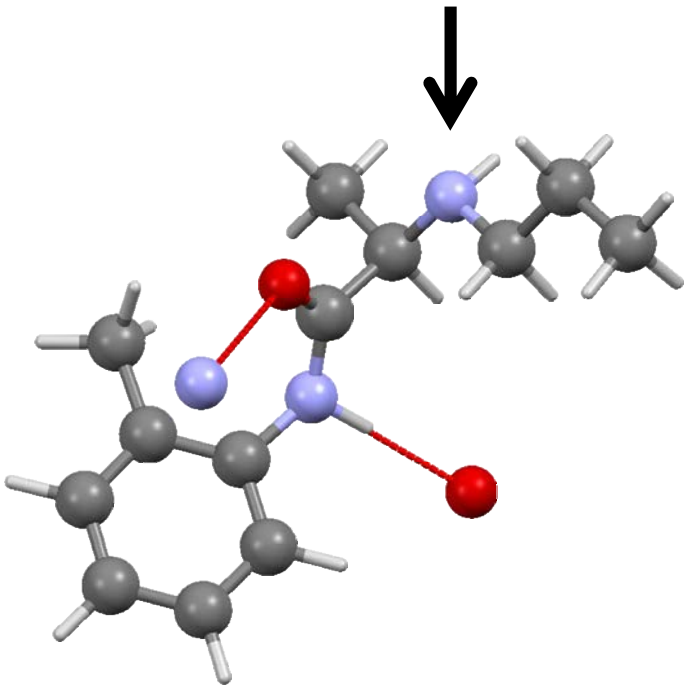
Prilocaine



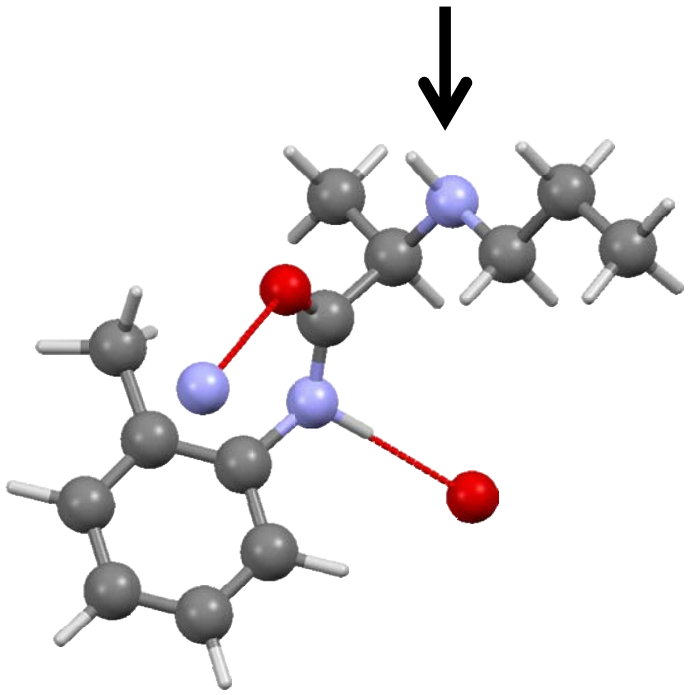
Hydrogen Atoms



Hydrogen Atoms

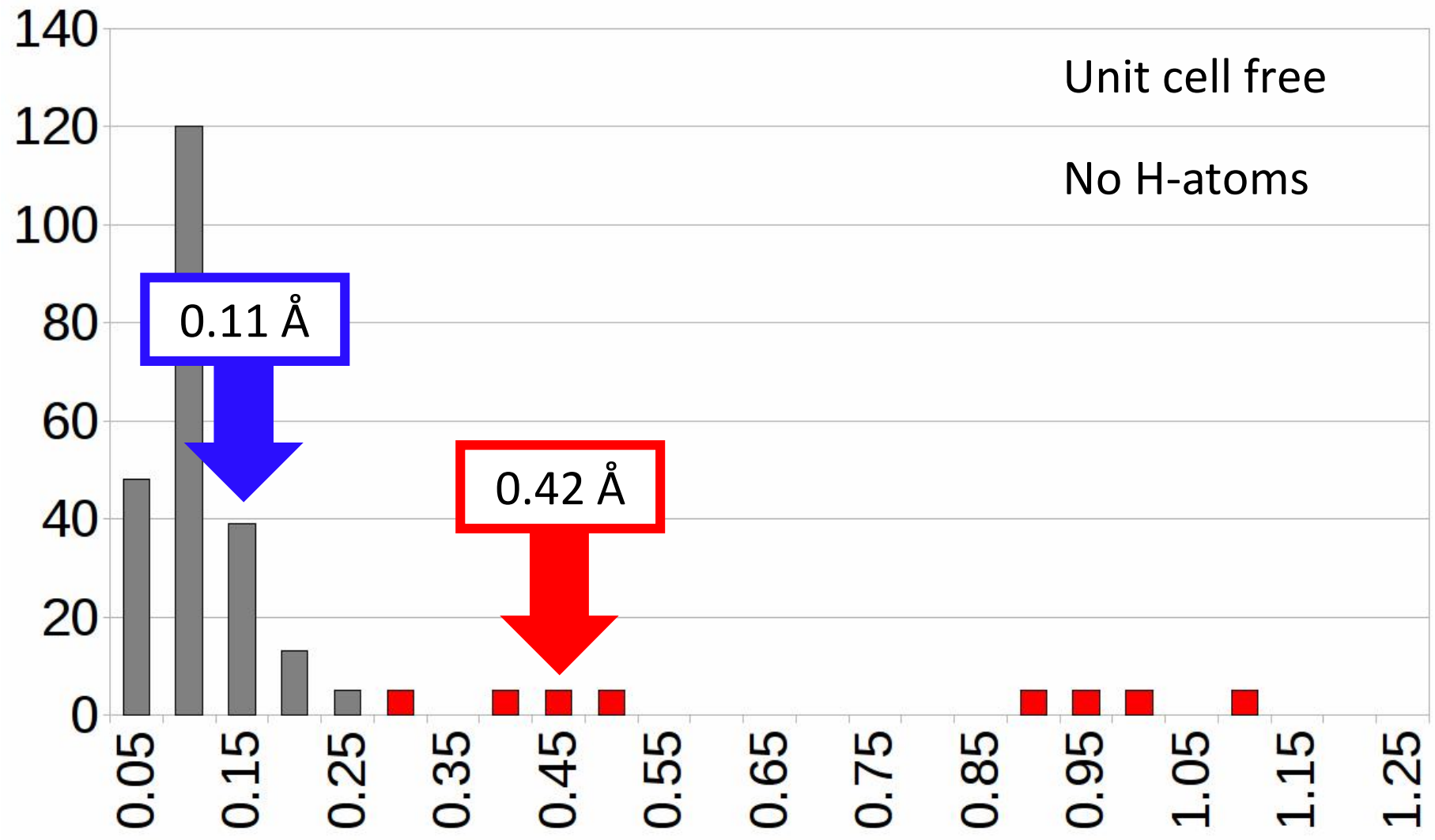


RMS = 0.42 Å
+4.8 kcal/mol



RMS = 0.11 Å
0.0 kcal/mol

RMS Cartesian Displacement



Virtual Beamline Pilot

Funding from Villum Foundation for hardware / software

Permission from Avant-garde Materials Simulation and the University of Vienna

Molecular XRPD structures in IUCr journals only

Your crystal structures are energy-minimised with DFT-D free of charge as part of the review process

Conclusions

- DFT-D calculations can *validate* crystal structures determined from XRPD data.
- DFT-D calculations can provide polymorph-dependent *restraints* for crystal structures determined from XRPD data.
- DFT-D calculations can accurately position the *hydrogen atoms* in crystal structures determined from XRPD data.
- Limitations: *T* effects, metals, disorder, H atoms

Acknowledgements

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