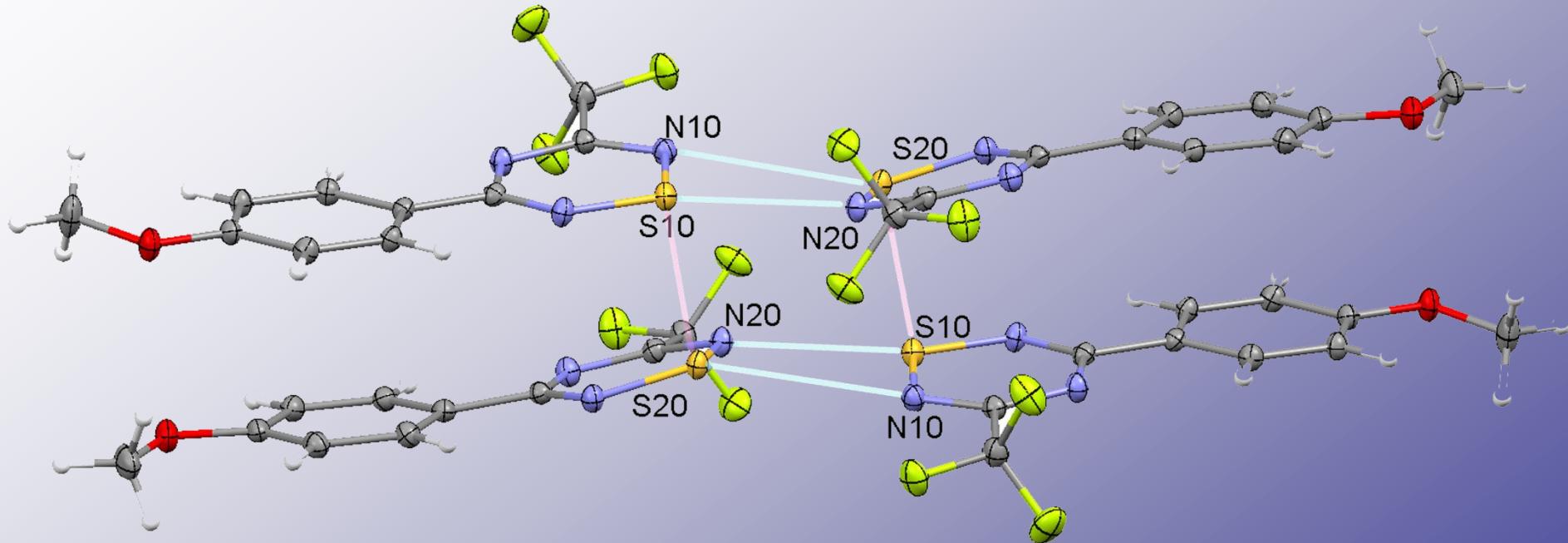


# Canadian Chemical Crystallography Workshop 2023

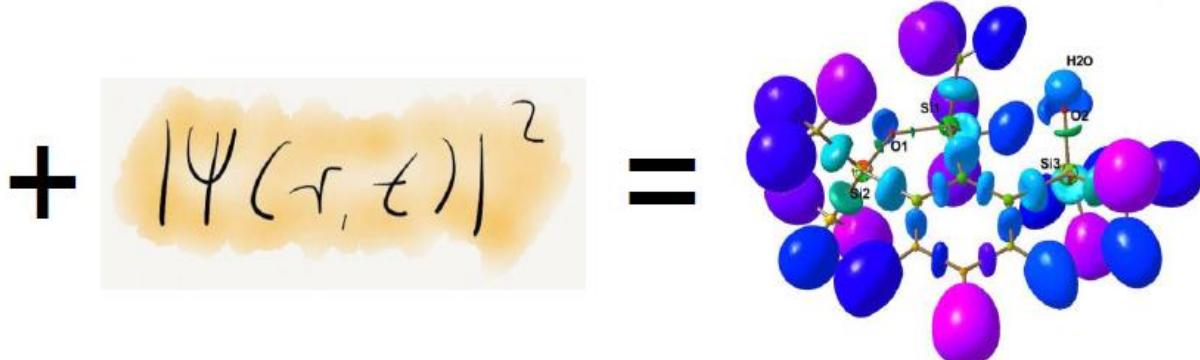


## Tutorial 5 – NoSpherA2

F. Kleemiß, et al., Chem. Sci. 2021, 12, 1675. DOI: 10.1039/d0sc05526c

# Important emerging topic in chemical crystallography

- o Implementing aspherical atom form factors (aspect of quantum crystallography)



**Measure:**  $I(hkl) \propto F_{obs}^2(hkl)$

**Model from:**  $F_{obs}(hkl)$  vs.  $F_{calc}(hkl)$

110 years of X-ray diffraction by crystals

$$R = \frac{\sum [F_{obs} - F_{calc}]}{\sum |F_{obs}|}$$

S. Grabowski, et al., Chem. Sci. **2017**, 8, 4159.

F. Kleemiss, et al., Chem. Sci. **2021**, 12, 1675.

# So what is this $F_{\text{calc}}$ term?

- Structure factor equation (a phase rule):

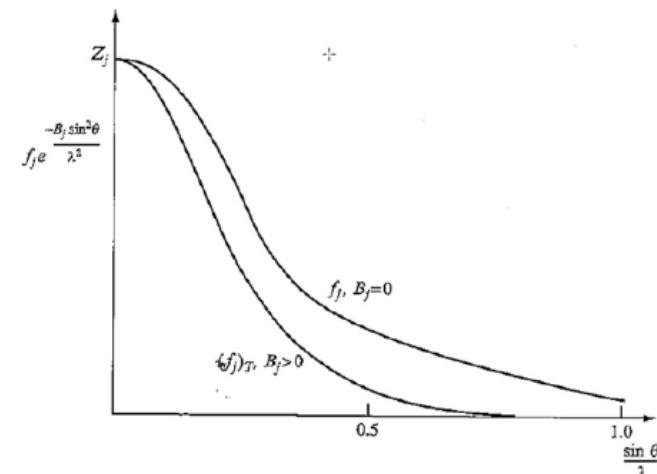
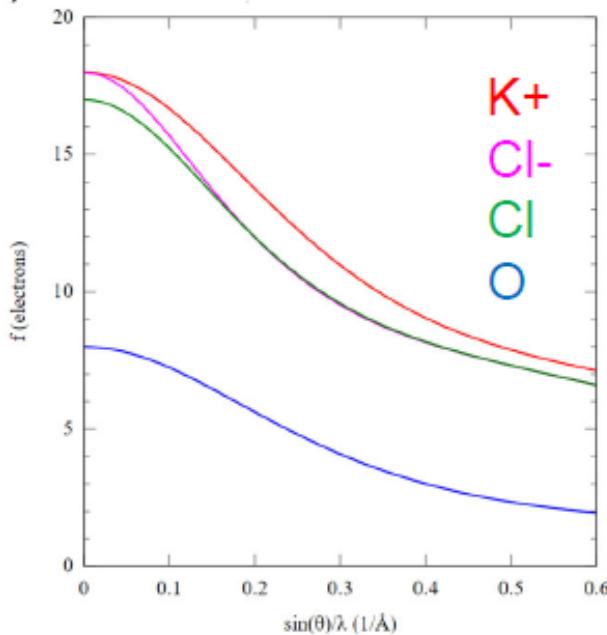
$$F_{hkl} = \sum_{j=1}^N f_j e^{[2\pi i(hx_j + ky_j + lz_j)]}$$

- Atomic scattering (form) factor  $f^0$   
for each atom  $j$ :

$$f^0 = \frac{\lambda}{\sin \theta} \int_0^\infty \rho(r) r \sin \left( \frac{4\pi \sin \theta}{\lambda} \right)^2 dr$$

- Modified by the Debye Waller factor for motion of the atoms (vibrations) that further decreases intensity with  $\sin \theta / \lambda$

$$F_{hkl} = \sum_{j=1}^N f_j e^{-B_j (2\sin \theta / \lambda)^2} e^{[2\pi i(hx_j + ky_j + lz_j)]}$$



# Sources of atomic form factors

- o At first, form factors were determined empirically, from response of standard samples to measure the decay with  $(\sin \theta)/\lambda$
- o Later replaced by self-consistent field (SCF) computation: early versions of computational chemistry based on quantum mechanics

## International Tables for Crystallography

### Intensity of diffracted intensities

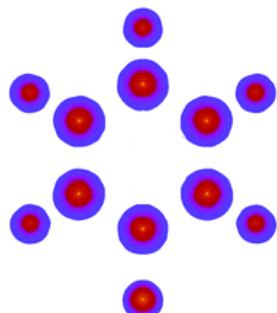
P. J. Brown, A. G. Fox, E. N. Maslen, M. A. O'Keefe and B. T. M. Willis. *International Tables for Crystallography* (2006). Vol. C, ch. 6.1, pp. 554-595  
[ doi:10.1107/97809553602060000600 ]

#### Abstract

“calculated using relativistic Hartree-Fock or Dirac-Slater wavefunctions ...”

Section 6.1.1 covers X-ray scattering from atoms and ions. Scattering is described by the Thomson formula, including coherent (Rayleigh) and incoherent (Compton) X-ray scattering. Atomic scattering factors, calculated using relativistic Hartree–Fock or Dirac–Slater wavefunctions, give the X-ray scattering from

- o Modern IAM-based Least Squares refinement programs for X-ray crystallography use tabulated forms of  $f_j$  from sources like this to model each atom type



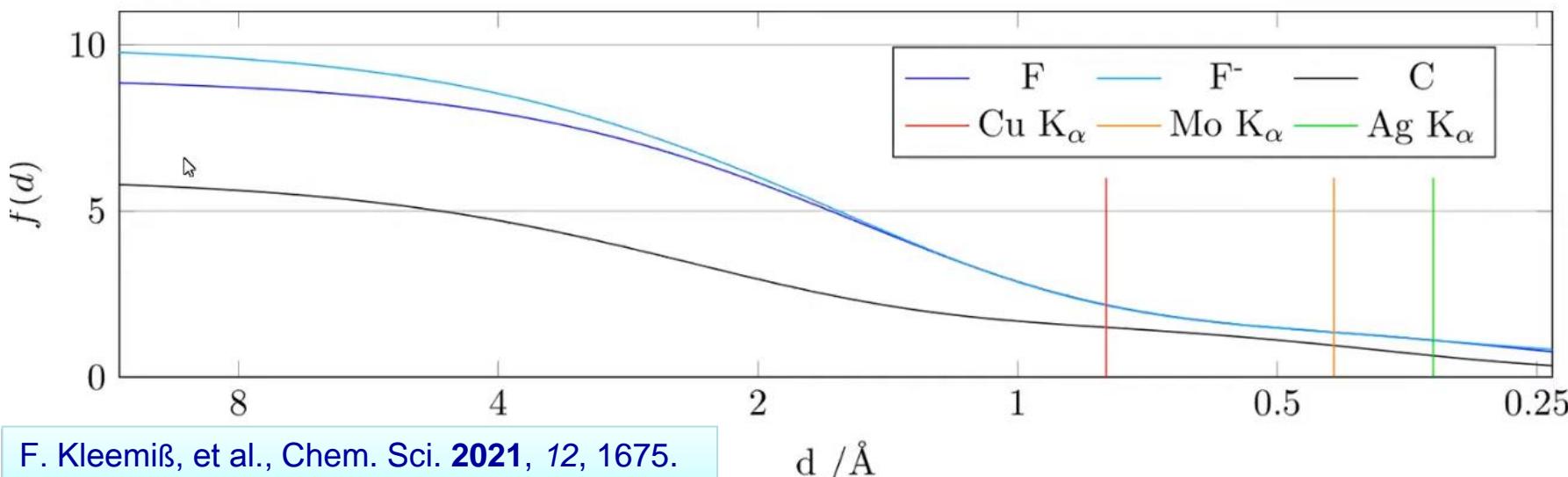
**IAM = Independent Atom Model**

- o IAM is *useful* (reasonably accurate and very effective) but it *is an approximation*

# Scattering factors w.r.t. resolution

We have fabulous hardware:

- o SuperNova dual Cu/Mo with Pilatus 200K
- o This is 100x better than the instruments of 1960's
- o Yet the *models* we build depend on the same spherical atom approximations for the form factors as used with hardware built in the 1960s!
- o Why is it important to go beyond the IAM model?
- o The 'atomic form factor'  $f_j$ : neutral F atom is not identical with the  $F^-$  form factors
- o A significant difference for the low-resolution data!



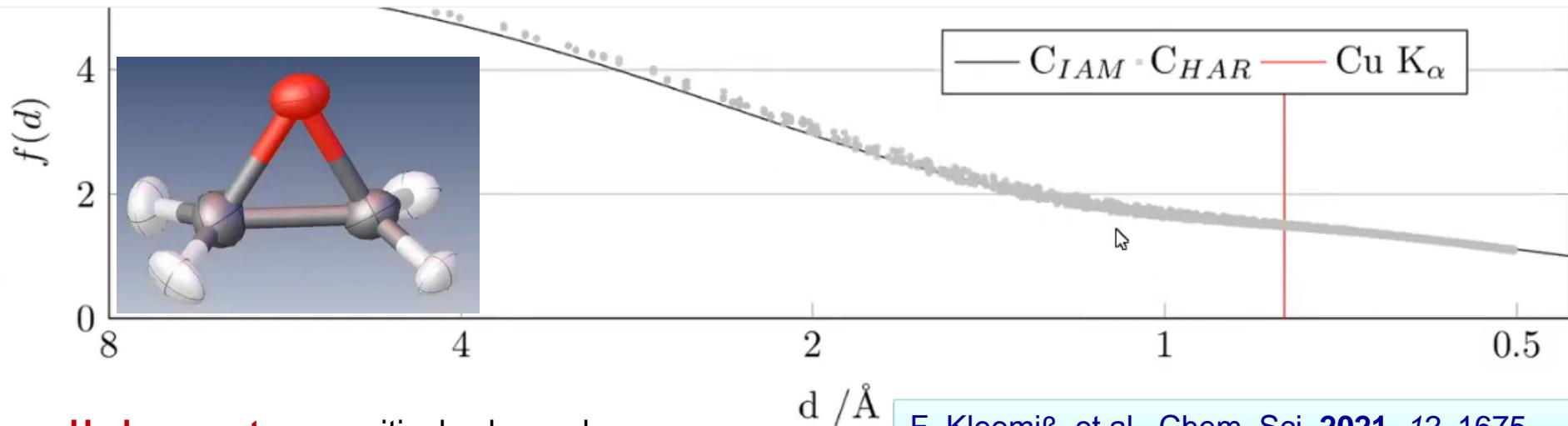
F. Kleemiss, et al., Chem. Sci. 2021, 12, 1675.



# Anisotropic form factors also important for neutral atoms

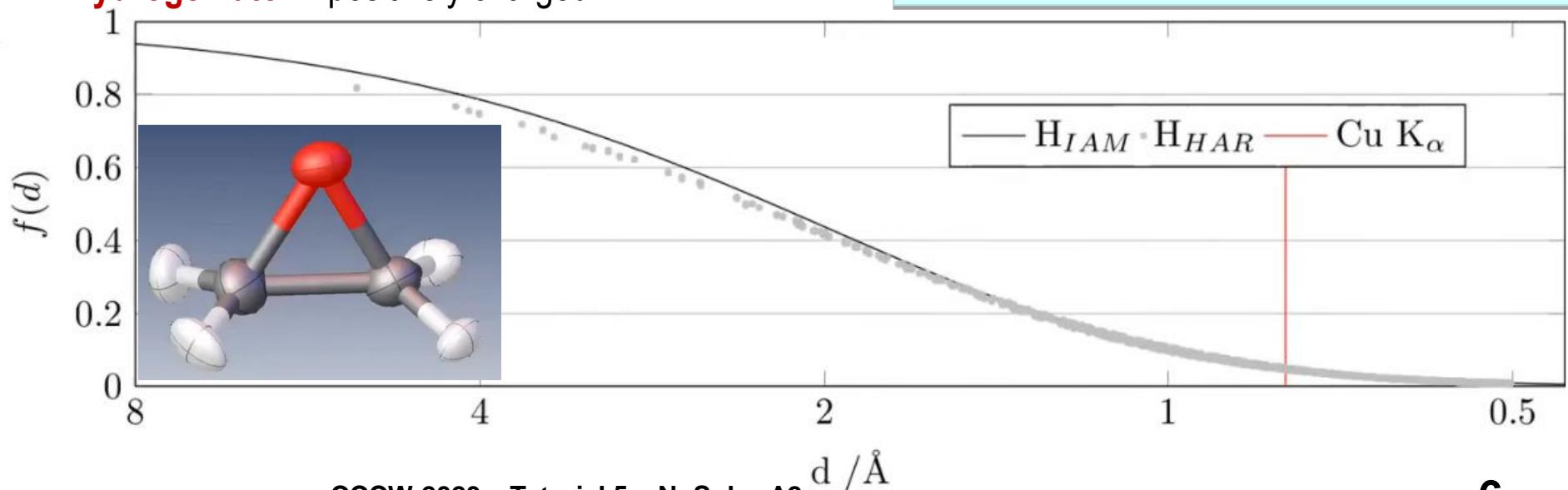
- Scattering factor curves for the IAM model (solid line) versus the corrected asphericity

**Carbon atom:** negatively charged



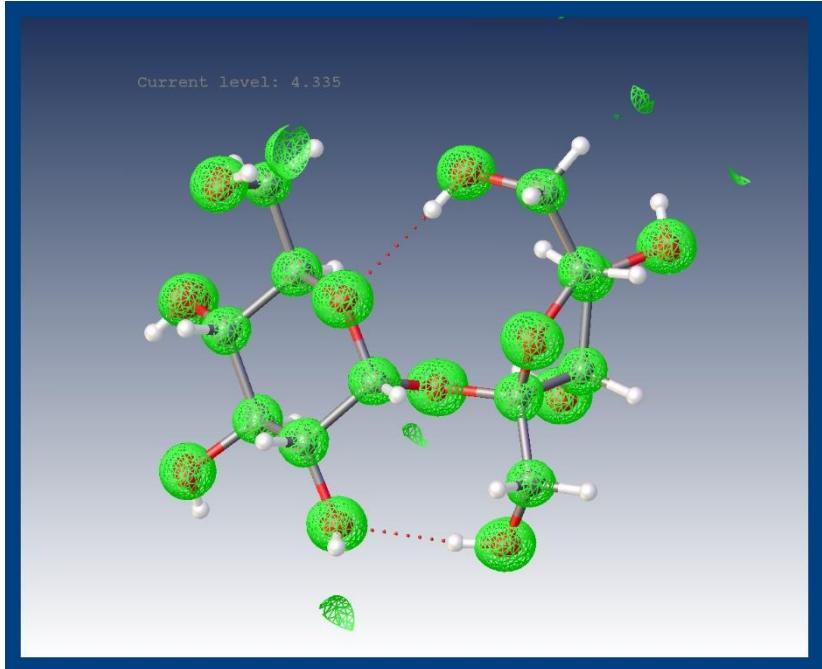
**Hydrogen atom:** positively charged

F. Kleemiss, et al., Chem. Sci. 2021, 12, 1675.

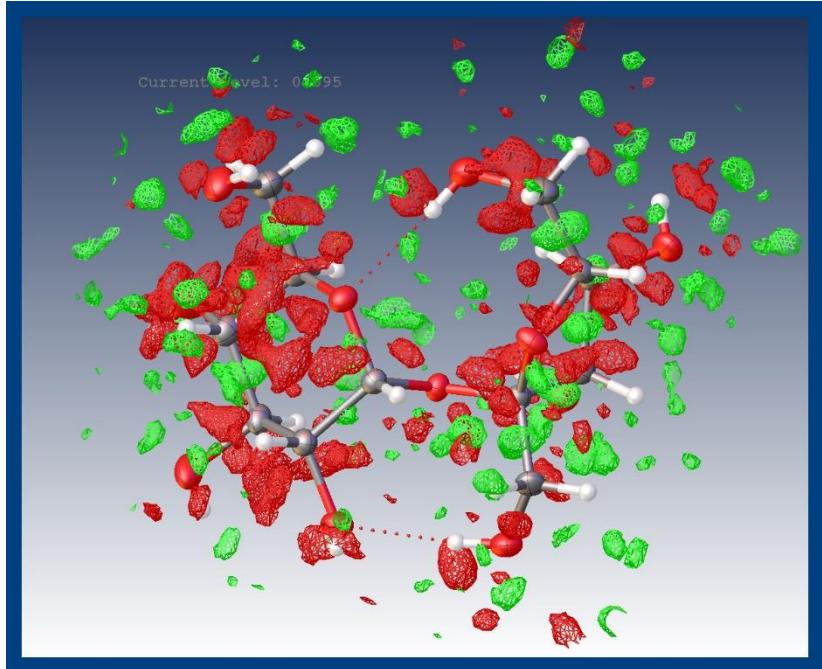


# Consequences of the IAM approximation

## 1. Residual electron density:



Sucrose: a map of  $F(\text{calc}) = \text{assigned ED}$

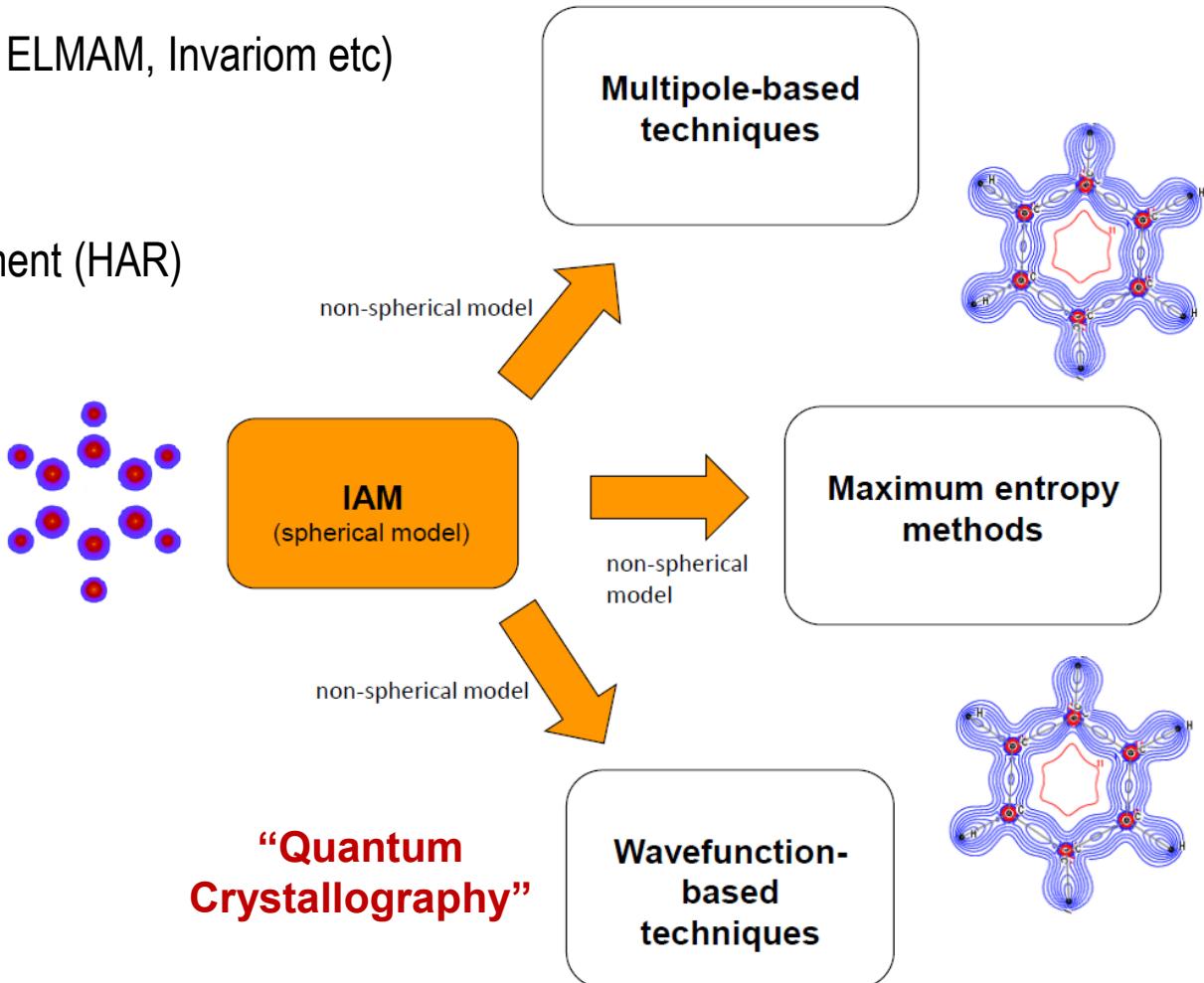


Sucrose: final difference map of  $[F(\text{obs}) - F(\text{calc})] = \text{unassigned ED}$

2. Weighting factors required in refinement
3.  $R$ -factors that cannot go to zero!  
A ‘good structure’ is one where  $R_1 < 5\%$

# Improvements on the IAM currently in use

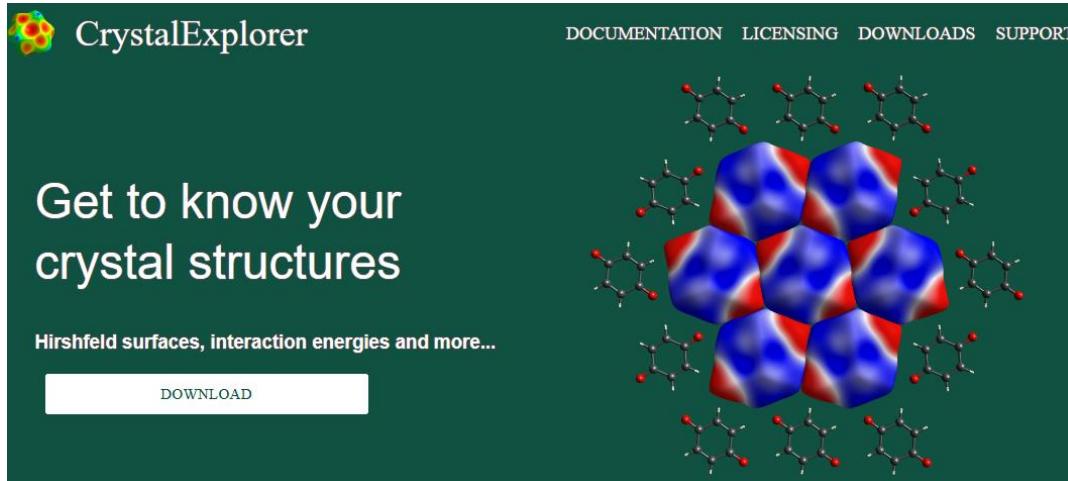
1. Multipole based techniques:
  - Refined multipoles
  - Databases (DISCAMB, ELMAM, Invariom etc)
2. Maximum Entropy methods
3. Wavefunction based
  - Hirshfeld Atom Refinement (HAR)



# Crystal Explorer and ‘Tonto’

Hirshfeld is already well known in crystallography from doing Hirshfeld Surface Analysis of charges on atoms within a crystal unit cell:

<https://crystalexplorer.scb.uwa.edu.au/>



Incorporates a low-level DFT code called Tonto (also included in NoSpherA2)  
It is the *method of charge partitioning* that comes from Hirshfeld

Theoret. Chim. Acta (Berl.) 44, 129–138 (1977)

THEORETICA CHIMICA ACTA  
© by Springer-Verlag 1977

## Bonded-Atom Fragments for Describing Molecular Charge Densities

F. L. Hirshfeld

Department of Structural Chemistry, Weizmann Institute of Science, Rehovoth, Israel

# Multipole and MEM methods

- o The Multipole concept is already quite old, and implemented in ‘charge density methods’ to recover the bonding ED
  - R. F. Stewart, *J. Chem. Phys.*, 1969, **51**, 4569-4577.
  - N. K. Hansen and P. Coppens, *Acta Cryst.*, 1978, **A34**, 909-921.
- o Similarly, the Maximum Entropy method has been around for a while:
  - a) D. M. Collins, *Nature* 1982, **298**, 49-51; b) M. Sakata and M. Sato, *Acta Cryst.*, 1990, **A46**, 263.
- o MEM has been used as an alternative method to multipole refinements, with the purpose to compute accurate electron densities that reveal the bonding electrons.
- o Charge-density crystallography has traditionally required extremely good, dedicated datasets
- o The Invariom Database approach has been developed as a practical way to refine ‘normal’ crystal structures
- o It could be fairly described as a ‘semi-empirical’ approach vs. NoSpherA2 as ‘ab-initio’

## Aspherical scattering factors for *SHELXL* – model, implementation and application

*Acta Cryst.* (2019). **A75**, 50–62

Jens Lübben,<sup>a,b</sup> Claudia M. Wandtke,<sup>a</sup> Christian B. Hübschle,<sup>c</sup> Michael Ruf,<sup>b</sup> George M. Sheldrick<sup>a</sup> and Birger Dittrich<sup>d,\*</sup>

# Why use Non-Spherical Atom Refinements?

**Standard X-ray refinement** involves data fitting to spherical atom electron distr. (IAM)

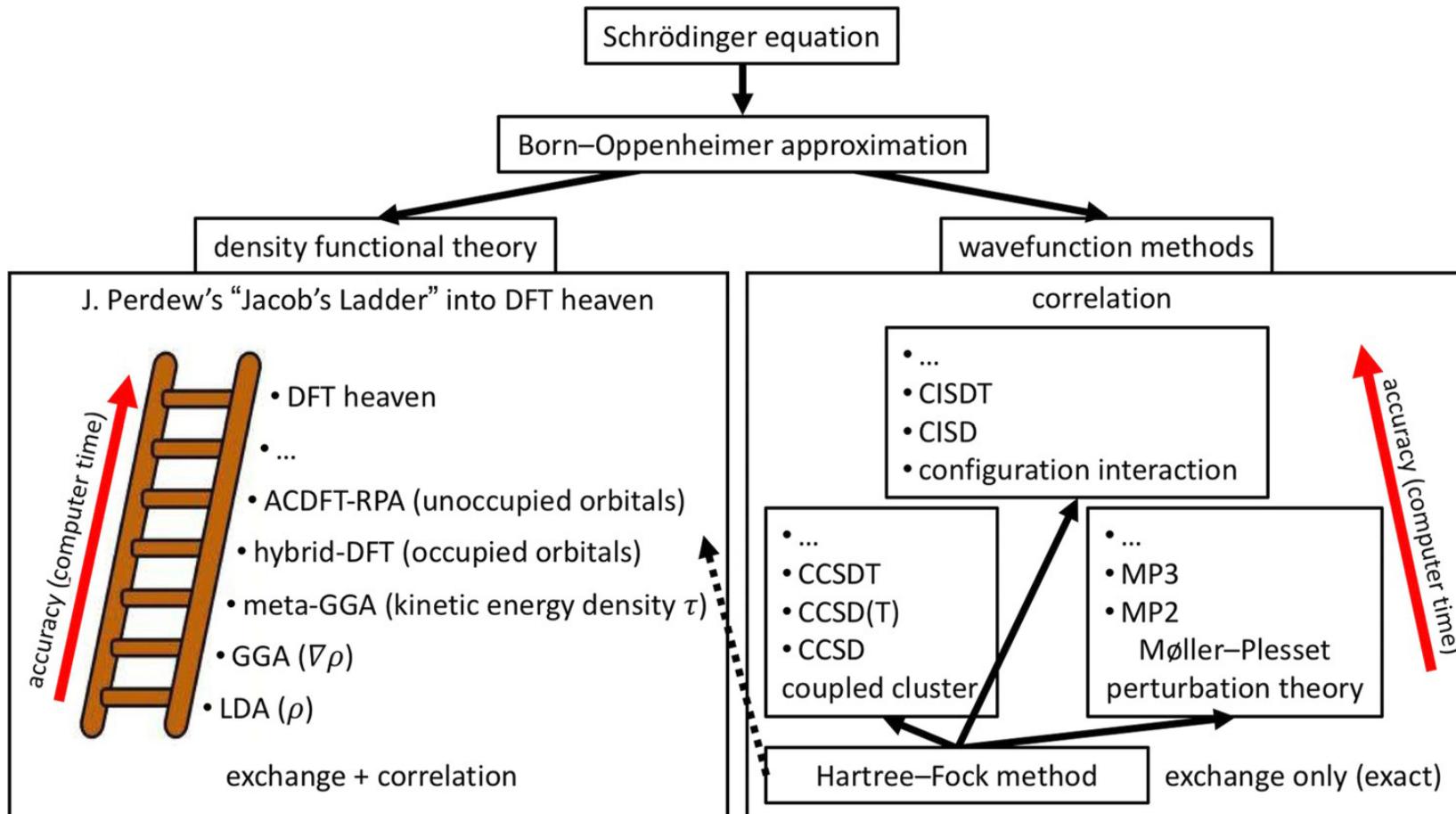
- o Assumes that the atoms are isotropic and that the atomic positions are the maxima in the ED (electron density).
- o Details of covalent interactions are missing in the model. The X-ray data carries this information. This is especially true for hydrogen atoms, which lack inner cores of electrons and have a single valence electron.

**Non-Spherical Atom Refinement** involves quantum-mechanical determination of electron density from wave function-based calculations. The electron density is the square of the absolute value of the wave function. The interpretation of X-ray data is then carried out in terms of Hirshfeld scattering factors from the Quantum-mechanical model.

- o Drastically improves the refined models (e.g.  $R_1 = 3\%$  for IAM,  $0.7\%$  for NoSpherA2).
- o For accurate charge densities it allows separating harmonic and anharmonic thermal motion effects from density deformations due to bonding.
- o Precise location and refinement of hydrogen atoms without neutron radiation.
- o Allows refining positions of hydrogen atoms bound to transition or heavy elements.
- o Often featureless residual density (i.e. all the information that is in the X-ray data has been extracted).
- o The *weights* used in refinement become negligible as the model is now so good.

# Why use Density Functional Theory (DFT)?

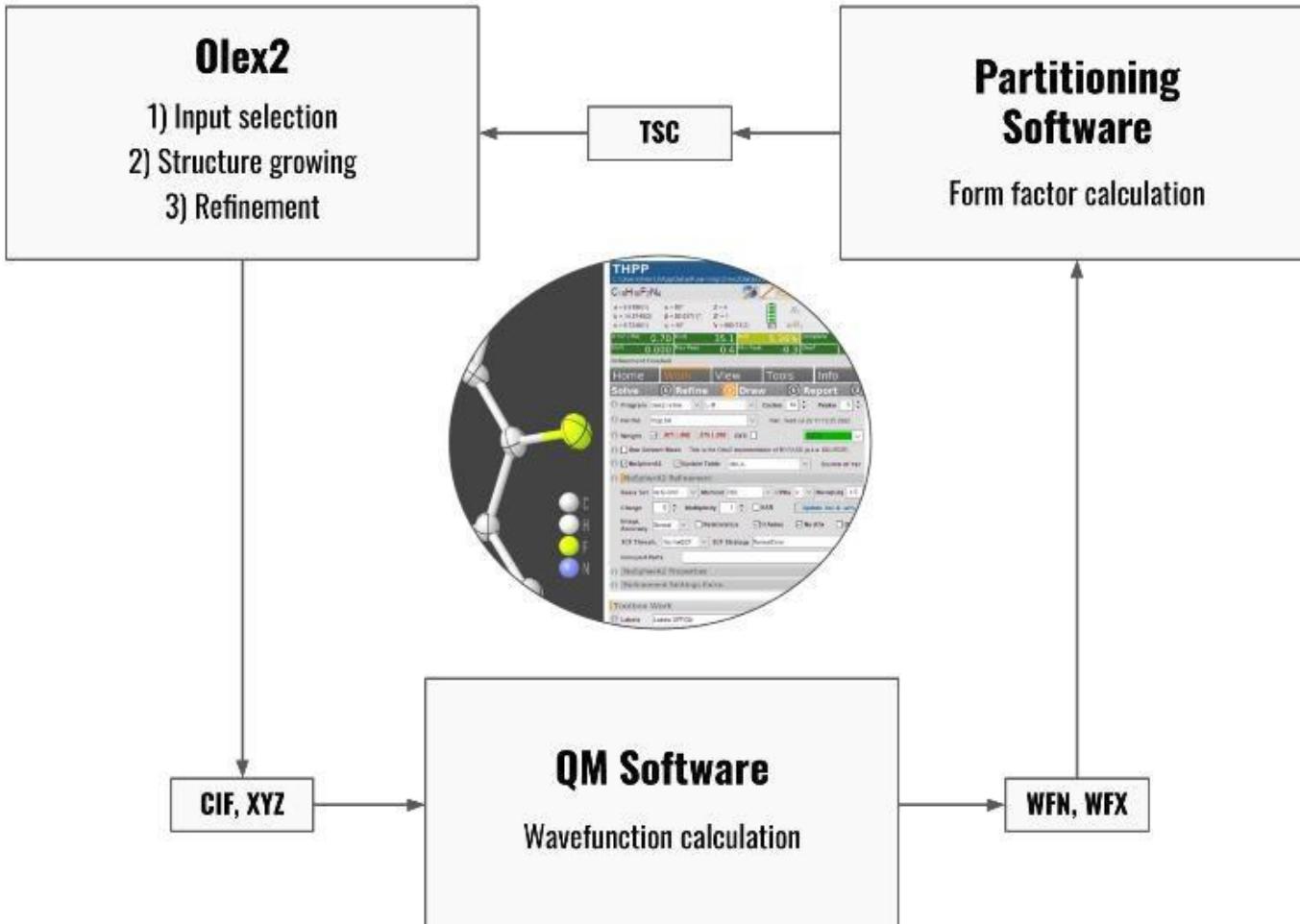
- Quantum mechanics *applied to chemistry* is about the theoretical/computational determination of electronic structure, using only first-principles of physics.
- X-ray diffraction measures electron density distributions in crystalline solids



S. Grabowski, et al., Chem. Sci. **2017**, 8, 4159.

# NoSpherA2 in Olex2

- Flowchart of the process behind HAR controlled by NoSpherA2 and a visual representation of the GUI for NoSpherA2 inside Olex2.



- Florian Kleemis *NoSpherA2: Novel Charge Density Tools in Olex2*
- Watch: <https://www.rigaku.com/webinars/single-crystal/no-sphera2-in-olex-2>

florian@olexsy.org



# Features of NoSpherA2

- o It works with ‘ordinary’ – albeit good quality – crystallographic datasets
- o It works with disorder models – kiss of death for multipole methods!
- o It works with open-shell wavefunctions and e spin multiplicity
- o It handles heavy elements very well – including relativistic wavefunctions where required
- o It works for *any element* and does not use ‘empirical’ atom definitions as in the Invariom method
- o Best of all, it is *fully supported* within Olex2 and *completely controlled by the GUI*
- o It is implemented with TONTO, Gaussian for Windows and ORCA – works best with ORCA
- o *All the methods for standard crystallographic refinements* are fully supported and enabled
  - Isotropic and anisotropic atom refinements
  - Interatomic interactions – short contacts and hydrogen bonding
  - Full support for symmetry, including atoms on ‘special positions’
  - Use of constraints and restraints in refinement
  - RIGU is particularly helpful for anisotropic H-atom refinement
  - Use of PART commands and partial occupancies that can be refined
  - Use of solvent masks (BYPASS or ‘squeeze’)
- o Based on rapid DFT methods easily implemented on a desktop PC!
- o It is implemented in the excellent olex2.refine full-featured model refinement method
- o Full QM analysis of the outputs can be visualized within the Olex2 GUI

# What does NoSpherA2 achieve? (using non-spherical atom scattering factors)

## What it is NOT

- o It is not a ‘magic fix’ for poor-quality diffraction data.
  - Identifying compounds from marginal crystals has its place.
  - Increased brilliance of Cu K $\alpha$  or RA is a real advantage here.
- o Low resolution experiments with 1 Å resolution – gain little from NoSpherA2!
- o It is *not* a computational structure determination!
- o The DFT calculation *only* calculates what the true atom scattering factors are.

## What it IS

- o We use DFT methods to calculate the *actual* atom scattering factors, for each atom, in its environment.
- o Uses relatively undemanding calculations on static geometries.
- o Uses *ordinary crystals*, with good *quality* datasets, to get *more accurate* crystal structure models.
- o *Fully uses* the electron density determined at high resolution from superb diffractometers.
- o Places H-nuclei accurately.
- o Often allows for refinement of full anisotropic H-atom displacements.

# Get a handle on your data quality early!

Two very helpful advice articles are highly recommended, especially for new crystallographers

## CRYSTALLOGRAPHY REVIEWS

2019, VOL. 25, NO. 1, 3–53

<https://doi.org/10.1080/0889311X.2019.1569643>



Taylor & Francis  
Taylor & Francis Group

 Check for updates

## Chemical Crystallography: when are ‘bad data’ ‘good data’?

Amber L. Thompson 

Chemical Crystallography, Chemistry Research Laboratory, Oxford, UK



Contents lists available at [ScienceDirect](#)

## Inorganica Chimica Acta

journal homepage: [www.elsevier.com/locate/ica](http://www.elsevier.com/locate/ica)

Research paper

What makes a crystal structure report valid?

Author of “CheckCIF”!

Anthony L. Spek

*Crystal and Structural Chemistry, Bijvoet Centre for Biomolecular Research, Utrecht University, Padualaan 8, 3584CH Utrecht, The Netherlands*

# The File Structure in NoSphereA2

The three key files are added to the main structure folder

File Explorer View:

- fc5002sup2.zip
- jz9b02646\_si\_002.zip
- Olex1.5-samples
- 183
- Co110
- malbac
- Periodic Table
- sucrose
- sucrose-b
- sucrose-b-nsa**
- movie
- olex2
- NoSphereA2\_history
- originals
- temp
- Wfn\_job
- sucrose-c
- THPP

Details View (sucrose-b-nsa folder contents):

Name
movie
olex2
kpts.dat
NoSphereA2.log
NoSphereA2.log_org
screenshot.png
sucrose.cif
sucrose.cif_od
sucrose.fcf
sucrose.hkl
sucrose.ins
sucrose.log
sucrose.lxt
sucrose.NoSphereA2
<b>sucrose.res</b>
<b>sucrose.tsc</b>
<b>sucrose.wfn</b>
<b>sucrose.wfx</b>
<b>sucrose_tables.html</b>

The olex2 ‘support folder’ grows in size significantly to accomodate the significant DFT and NoSphereA2 operations and store the results.

File Explorer View (olex2 folder contents):

Name
NoSphereA2_history
originals
temp
Wfn_job
sucrose.hist5
sucrose.metacif
sucrose.odb
sucrose.phil

# Why must I use olex2.refine?

- o Olex2.refine is written in C++ and Python code – not Fortran77
- o It has an open structure that allows alternative data sources to be added seamlessly
- o The definition files for the form factors easily allow for substitution by alternates

**TITLE:** optional title of the structure  
**SYMM:** 'expanded' or list of symmetries  
**SCATTERERS:** space-separated list of all atoms  
**[ ANYTHING ]:** colon must be present  
**DATA:** (denotes the end of the header)

$h$	$k$	$l$	$A_1$	$A_2$	...	$A_n$
$h_1$	$k_2$	$l_1$	$f_1(h_1, k_1, l_1)$	$f_2(h_1, k_1, l_1)$	...	$f_n(h_1, k_1, l_1)$
$h_2$	$k_2$	$l_2$	$f_1(h_2, k_2, l_2)$	$f_2(h_2, k_2, l_2)$	...	$f_n(h_2, k_2, l_2)$
⋮	⋮	⋮	⋮	⋮	⋮	⋮
$h_n$	$k_n$	$l_n$	$f_1(h_n, k_n, l_n)$	$f_2(h_n, k_n, l_n)$	...	$f_n(h_n, k_n, l_n)$

"olex2.refine,a powerful code that is comparable to, and compatible with, the trusted, reliable ShelXL method but implemented in modern programming languages in an open-source, extensible environment"

M.A. Ibrahim & R.T. Boéré,  
New J. Chem. 2022, 46, 5479.

Midgley, L., Bourhis, L. J., Dolomanov, O., Peyerimhoff, N., Puschmann, H. Crystallographic Refinement using Non-Spherical Form Factors in Olex2. refine. arXiv preprint arXiv:1911.08847, 2019.

```
TITLE: epoxide.cif
SYMM: 1 0 0 0 1 0 0 0 1;-1 0 0 0 1 0 0 0 -1
SCATTERERS: O1 C2 H2a H2b C3 H3a H3b
DATA:
-9 0 1 1.42558118e+00,-7.39703734e-03 1.11903575e+00,3.00122359e-04 8.72665
-9 0 3 1.43530211e+00,-5.21987789e-03 1.12718348e+00,-5.18793337e-03 9.9320
-9 0 5 1.41414548e+00,-3.00424795e-03 1.09412822e+00,-7.48879988e-03 7.7967
-9 1 0 1.40928713e+00,-6.79622200e-03 1.10384187e+00,5.07665937e-04 7.54873
-9 1 1 1.42383652e+00,-6.48364645e-03 1.12085059e+00,-1.00041152e-03 8.8466
-9 1 2 1.43161099e+00,-5.11468321e-03 1.12489786e+00,-6.33712547e-03 9.3681
-9 1 3 1.43149427e+00,-5.11255049e-03 1.12050436e+00,-4.70365583e-03 9.4510
-9 1 4 1.42485345e+00,-4.75333257e-03 1.10994897e+00,-4.53835622e-03 8.6950
```

Midgley, L., Bourhis, L. J., Dolomanov, O., Peyerimhoff, N., Puschmann, H. Crystallographic Refinement using Non-Spherical Form Factors in Olex2. refine. arXiv preprint arXiv:1911.08847, 2019.

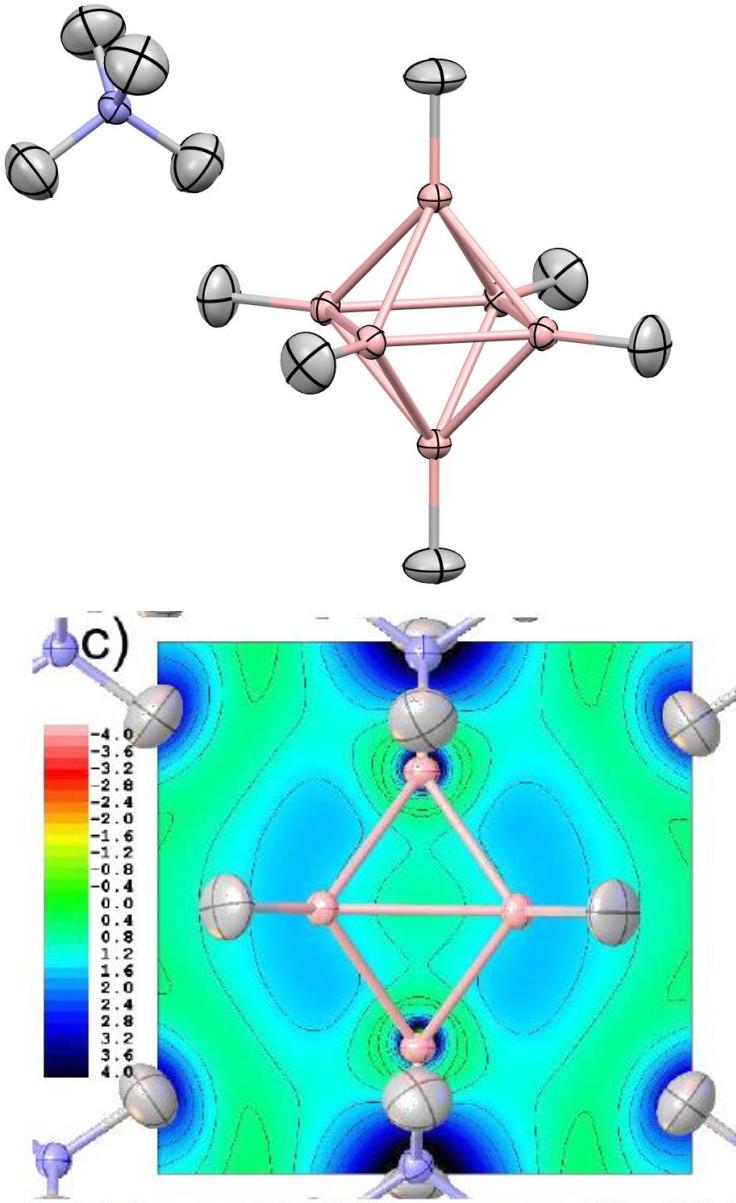
# Claims for outstanding results: NoSpherA2 + olex2.refine



- o Full anisotropic Debye-Waller displacement ellipsoids of all atoms, including hydrogens!
- o Shown at right with 50% probability DEs
- o Hydrogen is critical to the chemistry of the boranes, with important applications to H-storage for the ‘hydrogen economy’
- o Note just how much the hydrogen atoms are displaced from the equilibrium positions
- o Effectively, the H atoms are ‘large’ albeit diffuse.
- o Electron localizability indicator contours can be determined and show evidence for 3D-aromaticity in the polyhedral borane

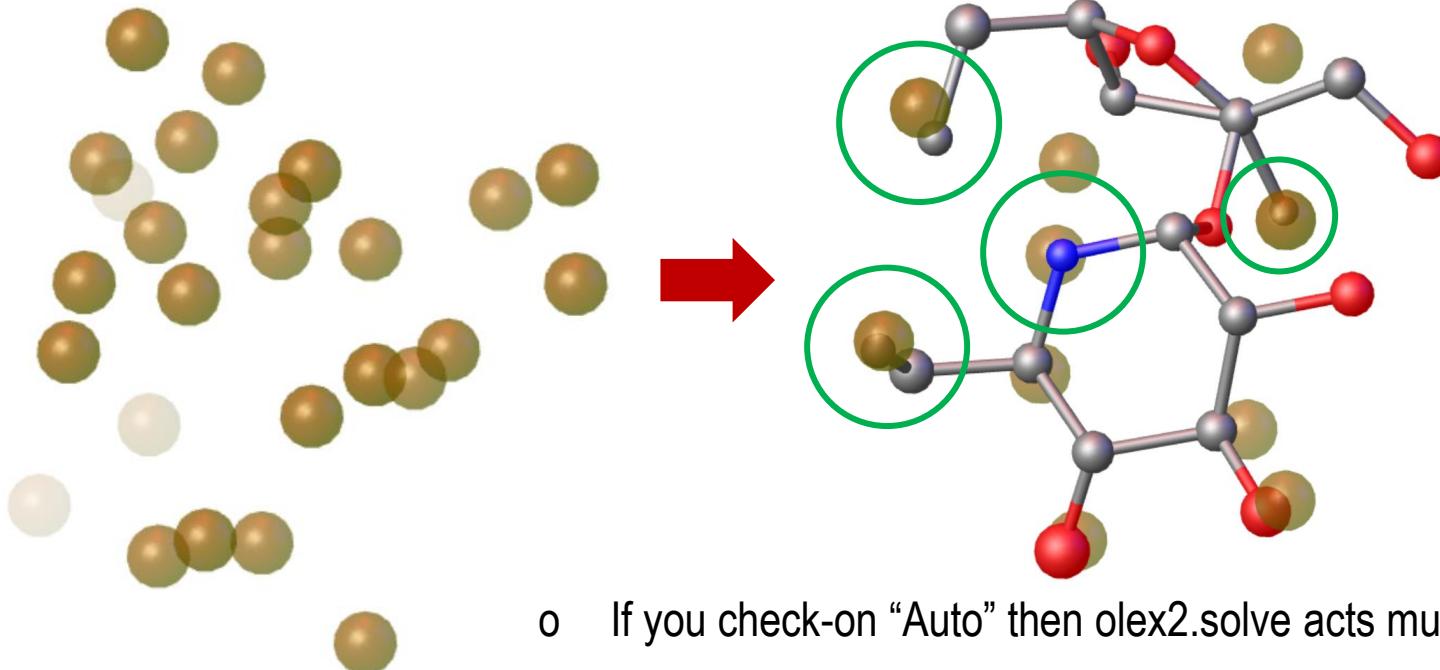
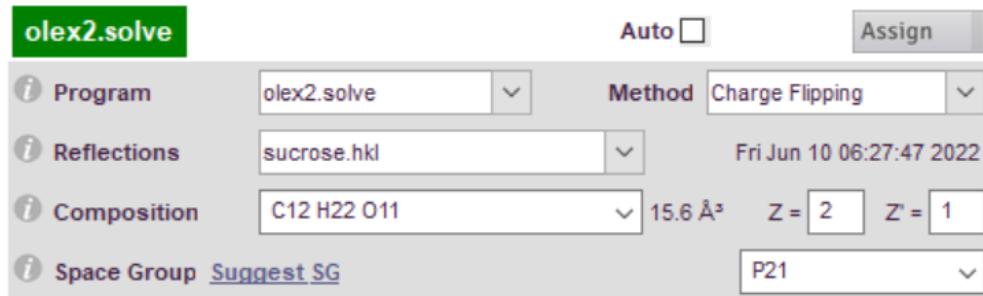
F. Kleemiß, et al., Chem. Sci. **2021**, 12, 1675.

So, now let's work through a demo stepwise.



# Demonstrate with Sucrose

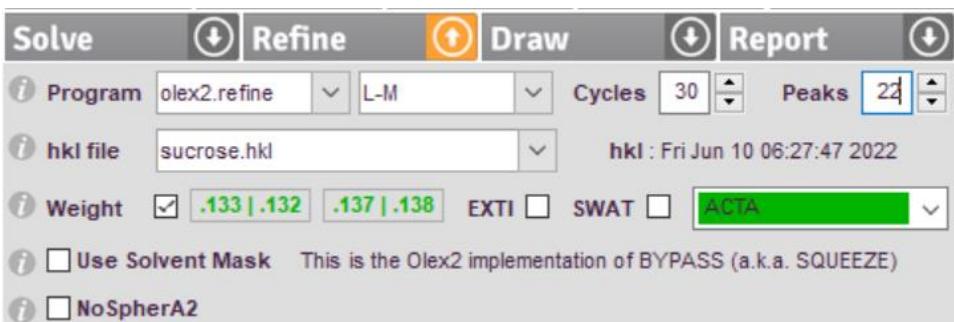
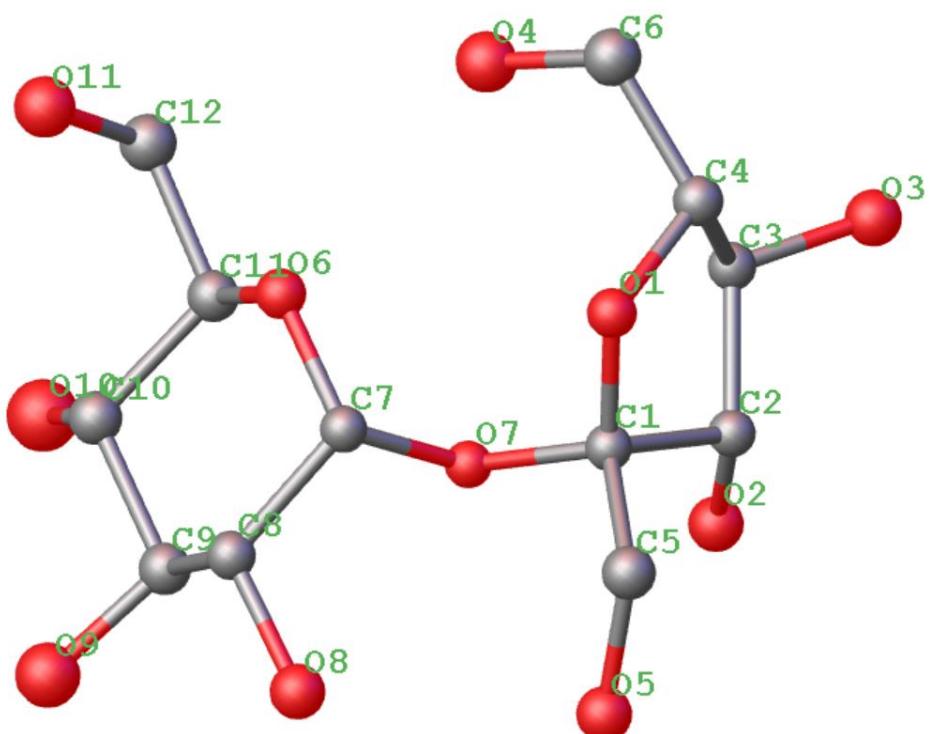
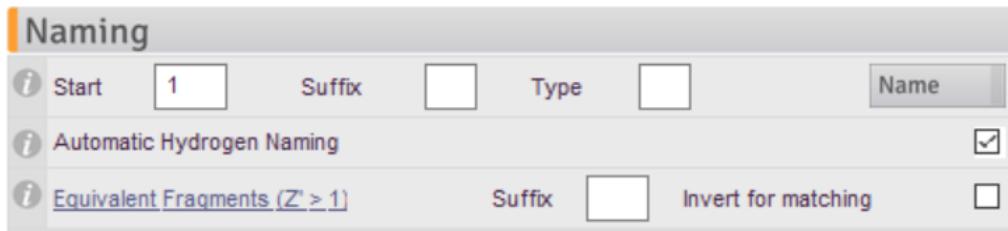
- o Copy the sucrose folder from C:\Program Files\Olex2-1.5-alpha\sample\_data\sucrose> to a working area on your computer
- o Open the .res file on Olex2-1.5alpha
- o Use Model/Reset to revert to the raw data + ins file
- o Solve with shelXT or olex2.solve



- o If you check-on “Auto” then olex2.solve acts much like shelXT
- o The assignments are slightly less accurate than my XT sol’n
- o The circled atoms have incident Q peaks → i.e. are O atoms

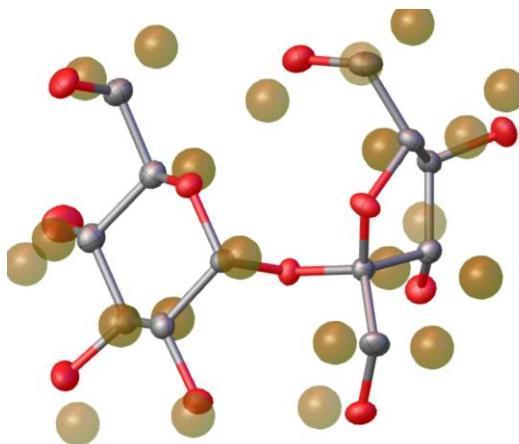
# Label atoms in a defined way (no change later!)

- o Use the GUI labeling system
- o (Note: olex2.solve gives better names than shelXT – but not my preference – so *rename*.)
- o Name C atoms in my desired pattern from 1 → 12, followed by O atoms 1 → 11.
- o Sort the list, and refine with olex2.refine

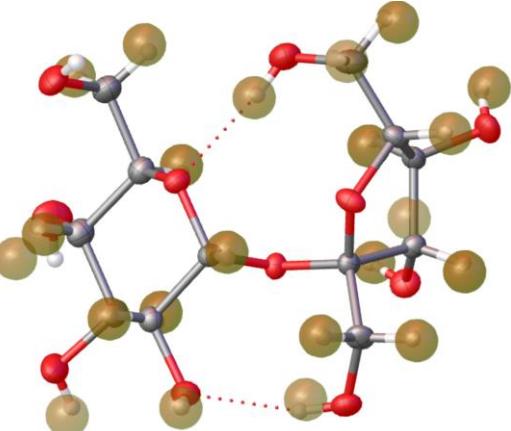


- o Check (once, carefully) names; then turn off
- o Type 'anis' at the command line
- o Type ^R to initiate refinement
- o Review the results (next slide)

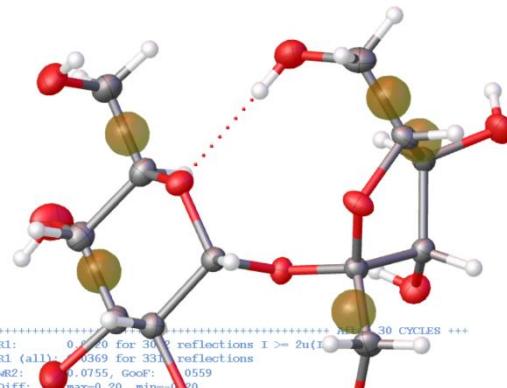
# Adding H atoms and completing the IAM model



Difference map with 22 peaks

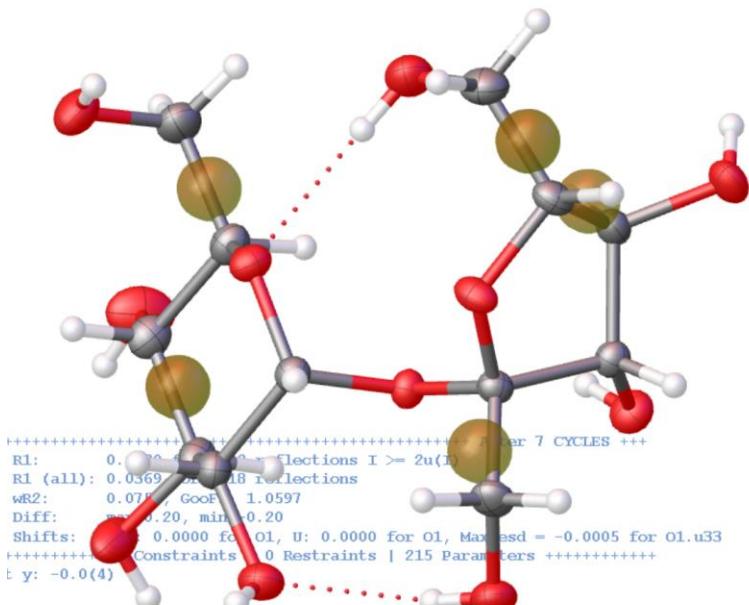


"hadd" command – insert into Qs



```
RL: 0.000 for 303 reflections I >= 2u(I)
RL (all): 0.0369 for 331 reflections
wR2: 0.0755, GoOF: 0.0559
Diff: max=0.20, min=-0.20
Shifts: x: 0.0000 for O1, U: 0.0000 for O1, Max esd = -0.0173 for R8.x
t: v: -0.0(4)
```

Refined with 5 highest Q peaks.



**Sucrose**

C<sub>12</sub>H<sub>22</sub>O<sub>11</sub>

P2<sub>1</sub>

a = 7.7727(9)	$\alpha = 90^\circ$	Z = 2	R <sub>1</sub> 3.20 %	
b = 8.7216(11)	$\beta = 102.983(11)^\circ$	Z' = 1	wR <sub>2</sub> 7.54 %	
c = 10.8637(11)	$\gamma = 90^\circ$	V = 717.63(15)		
d min (Mo)	0.73	I/σ(I)	32.7 Rint	3.39% Full 50.5°
2θ=58.4°				99.7 96% to 58.4°
Shift	-0.001	Max Peak	0.2	Min Peak -0.2 GoOF 1.060 Hooft -0.0(4)

Refinement Finished

Home Work View Tools Info

Solve Refine Draw Report

Program: olex2.refine L-M Cycles: 30 Peaks: 5

hkl file: sucrose.hkl hkl: Fri Jun 10 06:27:47 2022

Weight: .035 | .035 | .087 | .087 EXT1 SWAT OK

Use Solvent Mask This is the Olex2 implementation of BYPASS (a.k.a. SQUEEZE)

NoSpherA2

Refinement Settings Extra

Toolbox Work

Labels Labels OFF/ON

C H O ... Add H

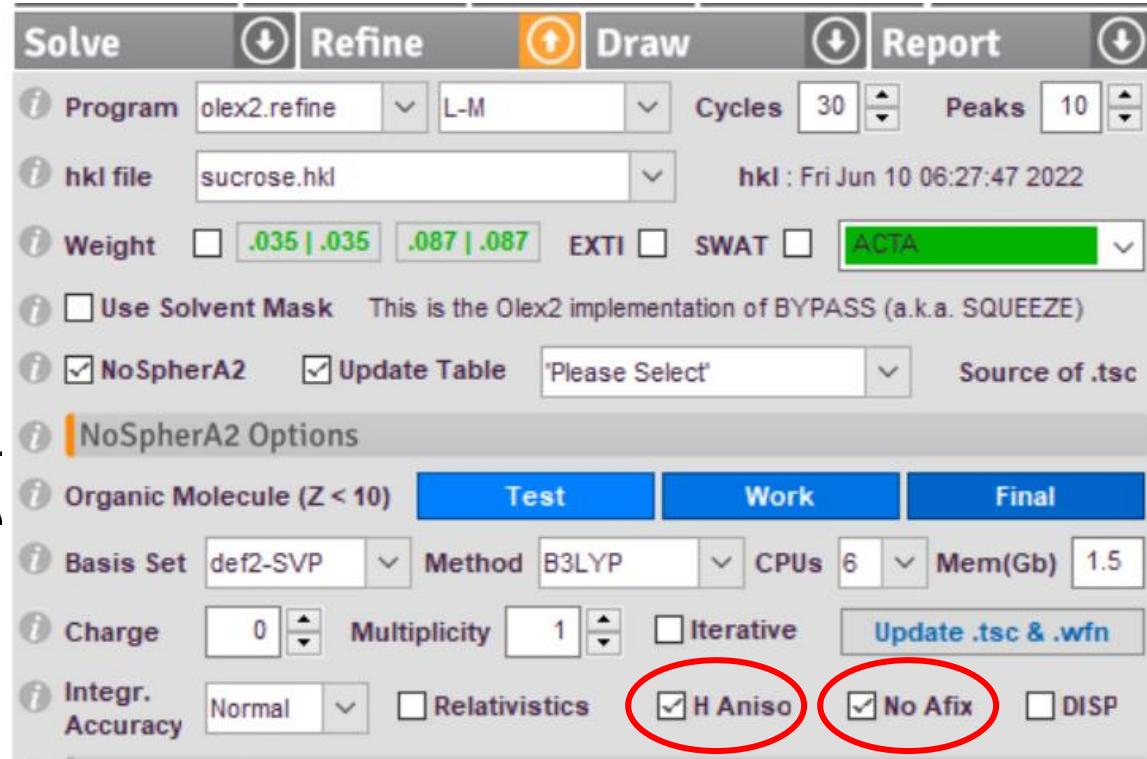
QC to CH H C F X Z= 1 OK

MAP Diff Show Map Map Settings

- o All the steps learned in previous tutorials are completed and the result is reviewed.
- o CheckCIF report is generated and carefully reviewed.
- o **I.e. – the best IAM model possible before implementing HAR.**

# Implementing HAR with NoSpherA2

- o My preference: copy to a new directory called “sucrose-nsa” (short for NoSpherA2)
- o Open in Olex2 1.5alpha, and check the NoSpherA2 box and the NoSpherA2 Options
- o Use “please select” to pick the DFT method: Tonto, ORCA, get pySCF. I will use ORCA5
- o ***Uncheck H-Aniso & No Afix***
- o Then, press on **Test** and refine.
- o It takes about 30s to run ORCA to generate the WFN and WFX files, and NoSpherA2 to calc. the TSC file. The  $R_1$  reduces slightly to 3.10%.
- o The main point of Test is to see that the system is set up right, so move to **Work**.
- o This takes a bit longer but still < 1 min, but does not change  $R_1$ . Note that HFIX are still in place!
- o Repeat the Update Table, check the “No Afix” option, and Refine.  $R_1$  drops to 2.75, and the bond lengths are significantly elongated on average.
- o O–H are mostly a bit less than 1.0 Å, and the C–H are around 1.1 Å.

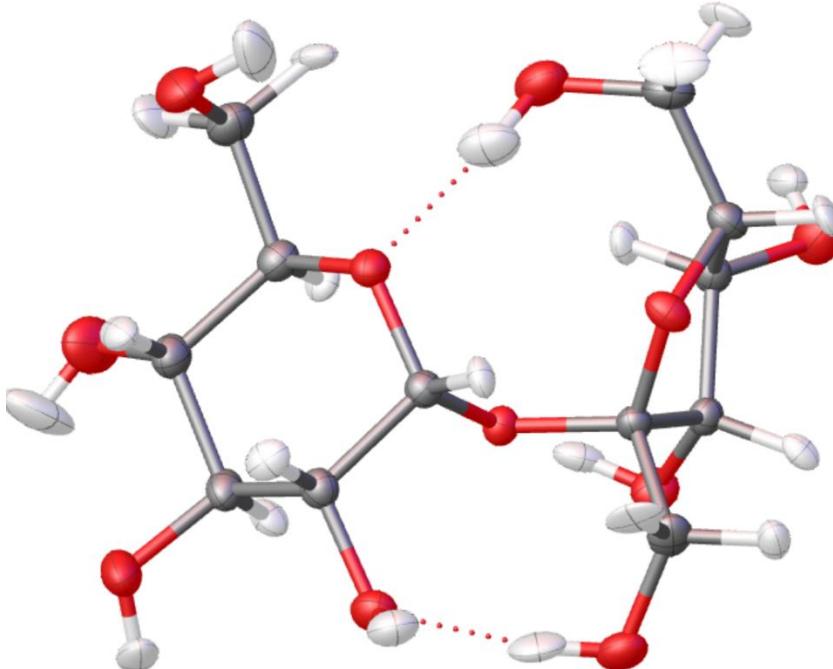


# Finalizing HAR refinement model

- o Command: anis -H
- o Since there are expected to be H-bonds, also do command: "HTAB"; 7 are found

Processing HTAB with max D-A distance 2.9A and minimum angle 120

```
HTAB O2 O3 $1 d=2.876
HTAB O3 O5 $2 d=2.72
HTAB O4 O6 d=2.855
HTAB O5 O8 d=2.784
HTAB O8 O4 $3 d=2.864
HTAB O9 O2 $4 d=2.865
HTAB O11 O9 $5 d=2.848
```

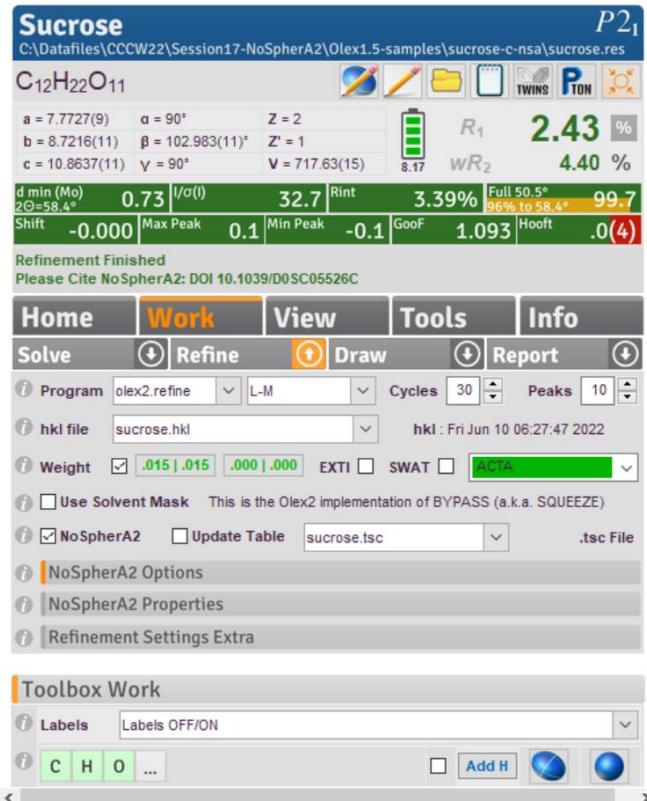
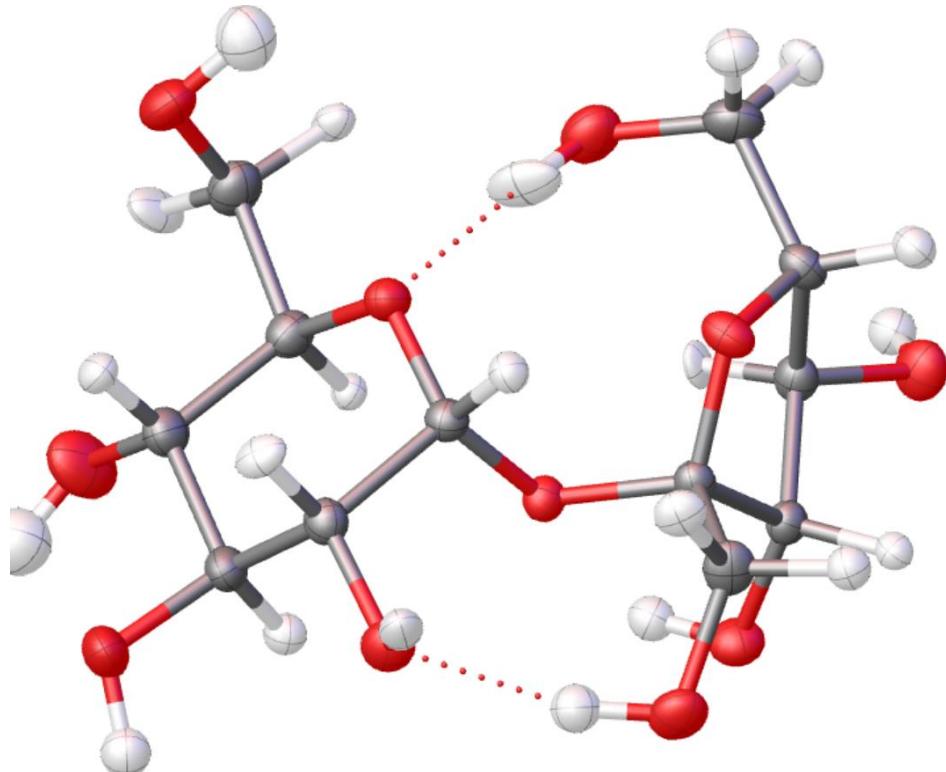


- o Now Refine this model →
- o Further cycles of olex2.refine are used till all fields are green.
- o Do a thorough check that everything looks good.
- o For poorly shaped H atoms, first try RIGU for the O-H or C-H bond pairs, as needed.
- o Then you will be ready for the **Final** model refinement, higher level of DFT and 10 repetitions. This takes about 6 minutes to run.
- o Final polishing can be done such as further restraining H atoms using ISOR restraints.
- o Assess and validate the final model in the usual way (CheckCIF; review the derived params).



# Validation and evaluation of the model

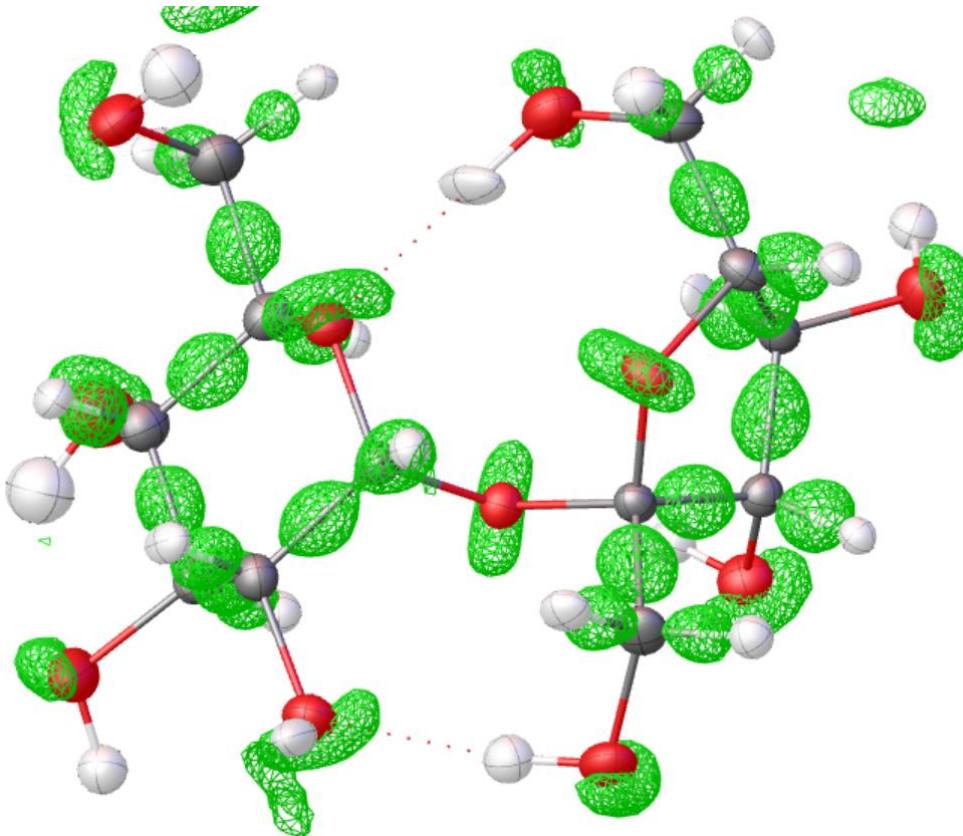
- The final  $R_1$  has lowered from 3.20 to 2.43%
- Max and min peaks are reduced from 0.2 to -0.1 e/Å<sup>3</sup>



- CheckCIF is passable – an ALERT B for the data/parameter ratio
- Another for one outlier in the C–H bond length of 1.17 Å
- The average bond precision: C–C = 0.0017 Å has gone down 15% from 0.0020 Å

# Uses of the NoSpherA2 accurate models for $F_{\text{obs}}(hkl)$

- Olex2 provides a Map option that is reserved for HAR refinement:  $F_o$  and Deformation ( $F_c$ - $F_{mc}$ )



- Thus, a difference between the spherical Atom model and the current model.
- Note that all this ED is either around the covalent bonds or at the u.p.e. sites in molecule or at atom lone pairs of electrons

# What has HAR refinement with NoSpherA2 achieved?

- Numerical data – let's consider only the hydrogen bonds

**Table 6 Hydrogen Bonds for sucrose.**

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O3 <sup>1</sup>	0.913(19)	1.97(2)	2.8750(15)	170.5(15)
O3	H3	O5 <sup>2</sup>	0.944(16)	1.791(16)	2.7201(13)	167.4(15)
O4	H4	O6	1.039(19)	1.84(2)	2.8525(14)	163(2)
O5	H5	O8	0.94(2)	1.877(19)	2.7814(15)	159.5(17)
O8	H8	O4 <sup>3</sup>	0.97(2)	1.90(2)	2.8639(16)	171.2(16)
O9	H9	O2 <sup>4</sup>	0.941(17)	1.931(17)	2.8653(13)	171.7(16)
O11	H11	O9 <sup>5</sup>	1.06(3)	1.82(3)	2.8463(17)	164(2)

<sup>1</sup>-X,-1/2+Y,-Z; <sup>2</sup>-1+X,+Y,+Z; <sup>3</sup>1+X,+Y,+Z; <sup>4</sup>1-X,-1/2+Y,-Z; <sup>5</sup>1-X,1/2+Y,1-Z

- The average O-H bond distance is 0.97 (5) Å
- The ‘gold standard’ for OH bond distances comes from neutron data: 0.99 (3) Å.

F. H. Allen and I. J. Bruno, Acta Cryst. 2010, B66, 380.

- Pretty good agreement – on a ‘normal’ data set collected a long time ago with no intention of obtaining a high resolution structure model.

# Experience based rules for using NoSpherA2

1. First develop an accurate structure model in the IAM  
IAM is 90-95% accurate, compact, reliable, familiar – so use it and use it well!
2. First refine using olex2.refine with **spherical form factors**  
Recommended if another IAM program (shelXL, etc) was initially used for IAM model
3. Ensure atoms are all named correctly  
DFT program and the NoSpherA2 form factor tables identify atoms through their labels as well as types  

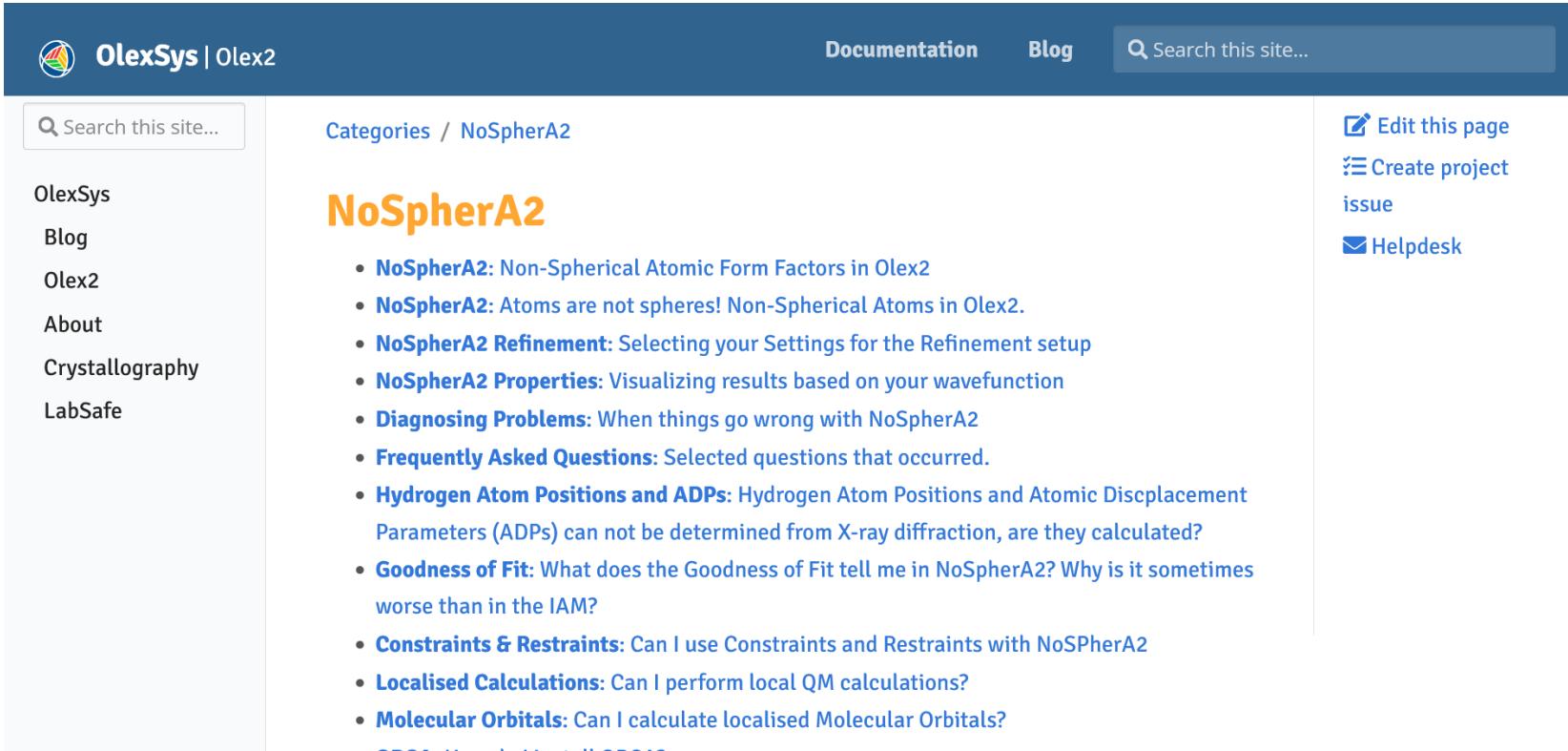
O1	3	0.68494	0.84279	0.78829	11.00000	0.02183
----	---	---------	---------	---------	----------	---------

O1 3 0.68494 0.84279 0.78829 11.00000 0.02183

In Shelx suite, “3” identifies this atom as O  
The label is quite arbitrary, any 4 ASCII
4. Implement NoSpherA2 in a copy of the original folder
5. Obey the laws of quantum mechanics: no half bonds(!); correct spin multiplicity(!!!)  
DFT calculations *works on what's on the screen* so use GROW first!  
DFT can even calculate aggregates – H-bonded dimers
6. Step through the 3 Levels in NoSpherA2 refinement: Test – Work – Final  
**Test:** purpose is to check for glitches (naming errors, correct spin state, etc)  
**Work:** here the HAR model is fully developed
  - Default levels of theory usually OK
  - Leave HFIX and anis-H unchecked at first
  - Apply RIGU (0.004, 0.002 or 0.001) to E-H bonds (pairs of atoms) when H are poorly shaped**Final:** iterative (10x) for final polishing of the model

# Resources and support

- o First and foremost, the [www.olexsy.org](https://www.olexsy.org) support pages



The screenshot shows the OlexSys website interface. At the top, there is a navigation bar with links for Documentation, Blog, and a search bar labeled "Search this site...". On the left, a sidebar menu includes links for OlexSys, Blog, Olex2, About, Crystallography, and LabSafe. The main content area has a search bar and a breadcrumb trail "Categories / NoSpherA2". The title "NoSpherA2" is prominently displayed in orange. Below the title is a list of 14 bullet points, each linking to a specific page about NoSpherA2's features and applications.

**NoSpherA2**

- [NoSpherA2: Non-Spherical Atomic Form Factors in Olex2](#)
- [NoSpherA2: Atoms are not spheres! Non-Spherical Atoms in Olex2.](#)
- [NoSpherA2 Refinement: Selecting your Settings for the Refinement setup](#)
- [NoSpherA2 Properties: Visualizing results based on your wavefunction](#)
- [Diagnosing Problems: When things go wrong with NoSpherA2](#)
- [Frequently Asked Questions: Selected questions that occurred.](#)
- [Hydrogen Atom Positions and ADPs: Hydrogen Atom Positions and Atomic Displacement Parameters \(ADPs\) can not be determined from X-ray diffraction, are they calculated?](#)
- [Goodness of Fit: What does the Goodness of Fit tell me in NoSpherA2? Why is it sometimes worse than in the IAM?](#)
- [Constraints & Restraints: Can I use Constraints and Restraints with NoSpherA2](#)
- [Localised Calculations: Can I perform local QM calculations?](#)
- [Molecular Orbitals: Can I calculate localised Molecular Orbitals?](#)

- o Web docs and video links: <https://www.olexsy.org/olex2/docs/nosphera2/>

- o Olex2 has its own YouTube channel!

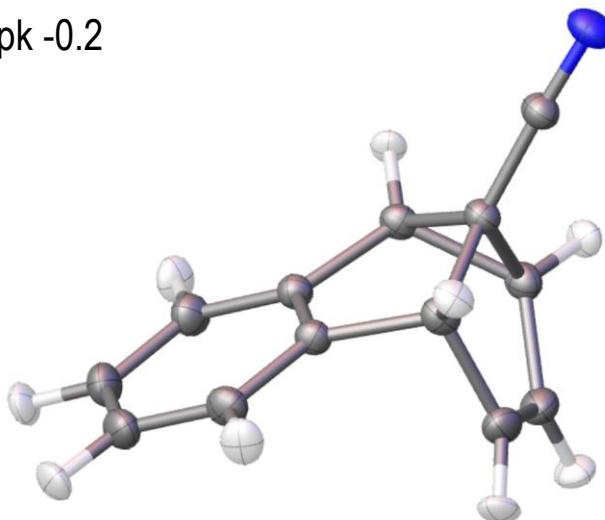
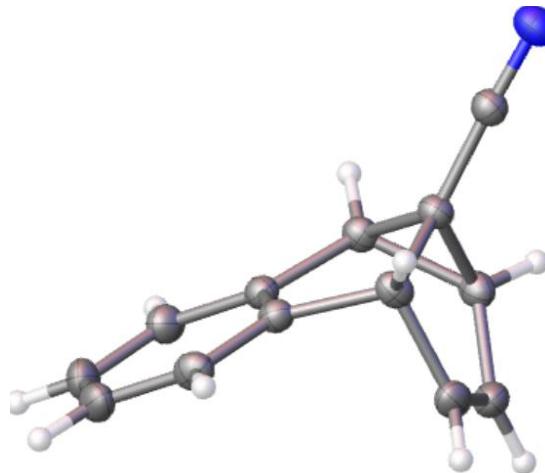
"If you use NoSpherA2 you agree to cite the following literature in your main manuscript:"

Kleemiss et al., Chem. Sci., 2021, <https://pubs.rsc.org/en/content/articlepdf/2021/sc/d0sc05526c>

So, now it is time to try it on a live model – follow along if you wish!

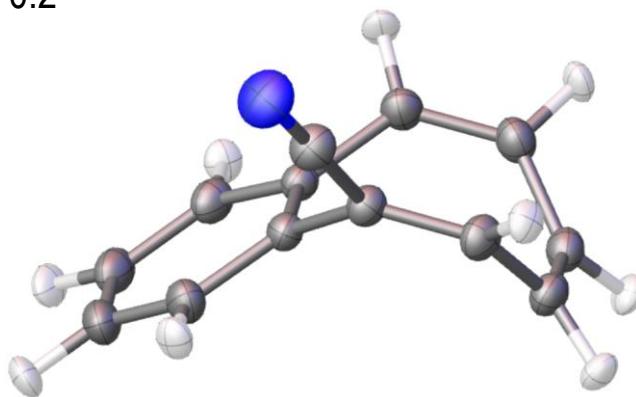
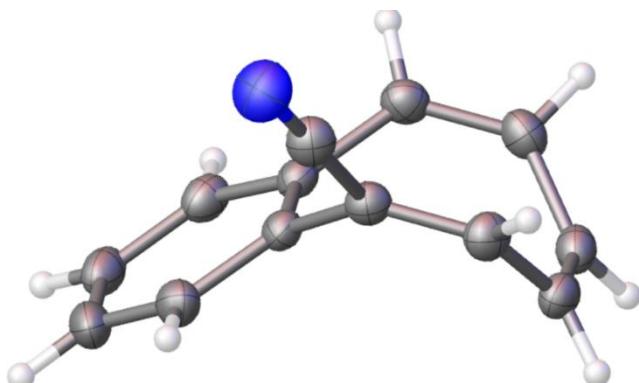
## More examples from our laboratory

- o RB13013 – C<sub>7</sub>H<sub>9</sub>N IAM:  $R_1 = 3.33$ ; Max pk 0.2; min pk -0.2



NoSpherA2:  $R_1 = 0.93$ ; Max pk 0.1; min pk -0.1

- o RB13009 – C<sub>7</sub>H<sub>9</sub>N IAM:  $R_1 = 3.68$ ; Max pk 0.2; min pk -0.2



NoSpherA2:  $R_1 = 1.25$ ; Max pk 0.1; min pk -0.1

# Now have a collection of 14 similar structures

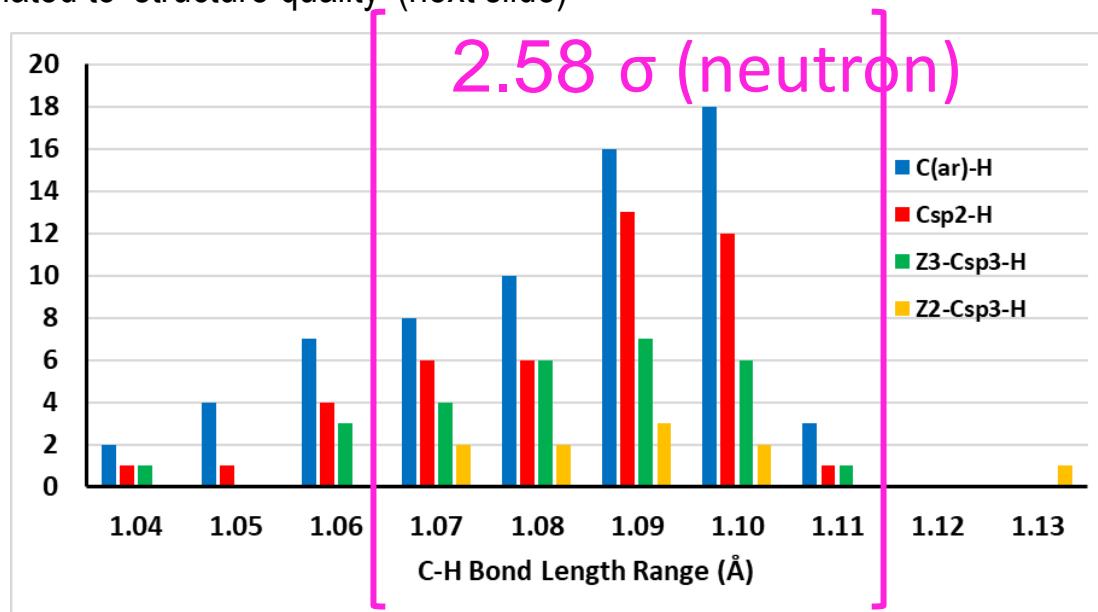
- What are the structural features of note?

Comparison of C-H bond lengths from this work with values from neutron diffraction

C-H bond type	IAM standard values (AFIX @ 100 K)/ Å	1 – 14, this work		Neutron Data 60 ≤ T ≤ 140 K	
		d /Å	n	d /Å	n
Z <sub>3</sub> -Csp <sup>3</sup> -H	1.00	1.083 (18)	28	1.099 (7)	66
Z <sub>2</sub> -Csp <sup>3</sup> -H <sub>2</sub>	0.99	1.090 (17)	10	1.097 (6)	136
Csp <sup>2</sup> or C(ar)-H	0.95	1.082 (17)	112	1.085 (9)	184

Neutron data from: Allen, F. H., Bruno, I. J.; *Acta Crystallogr B*, **2010**, 66 (Pt 3), 380-6

- Close to C-H bond lengths determined by neutron diffraction
- Possible trend noted of NoSpherA2 to slightly underestimate C-H bond lengths
- Not correlated to 'structure quality' (next slide)



# Structure precision improvement

- o How good are the results?

- $R_{\text{int}}$  from 0.6 to 8.4 %
- Final HAR  $R_1$  from 0.84 to 4.63 %



So a range of crystal/data quality

Structure	$R_1$	$R_{\text{int}}$	Bond precision <sup>c</sup> : C-C in Å, impr. %	Data/par. ratio
1	0.0184	0.0273	0.0018 – 0.0038, 52.6%	12.0
2	0.0309	Twin	0.0025 – 0.0034, 26.5%	11.4
3	0.0179	0.0270	0.0007 – 0.0015, 53.3%	8.3
4	0.0087	0.0180	0.0004 – 0.0015, 73.3%	10.0
5	0.0102	0.0159	0.0009 – 0.0015, 60.0%	11.6
6	0.0137	0.0060	0.0004 – 0.0015, 73.3%	11.3
7	0.0154	0.0169	0.0006 – 0.0015, 60.0%	10.5
8	0.0131	0.0186	0.0005 – 0.0016, 68.8%	10.2
9	0.0224	0.0240	0.0013 – 0.0021, 38.1%	8.7
10	0.0287	0.0436	0.0013 – 0.0020, 35.0%	10.8
11	0.0313	0.0841	0.0014 – 0.0021, 33.3%	10.6
12	0.0242	0.0237	0.0010 – 0.0019, 47.4%	9.2
13	0.0192	0.0304	0.0009 – 0.0019, 52.6%	8.3
14	0.0463	0.1102	0.0030 – 0.0046, 34.8%	9.8
Average			0.0012 – 0.0022, 49.2%	

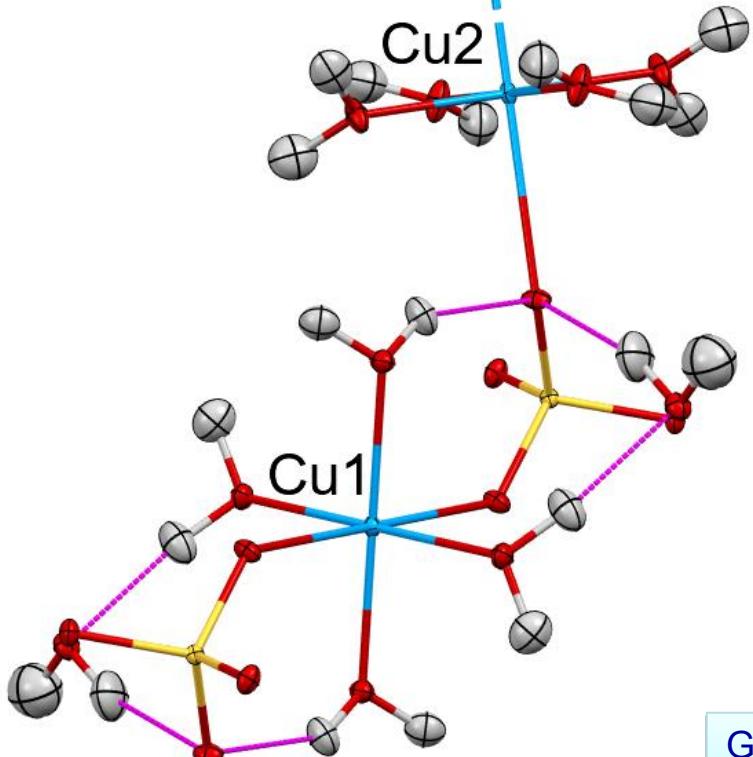
- Ave. C–C bond precision *improvement* from IAM to HAR/NoSpherA2 of 49% (min 26, max 73%)
- No structure was *reduced* in precision with HAR/NoSpherA2 refinement

# More examples from our laboratory: hydrated TM salts

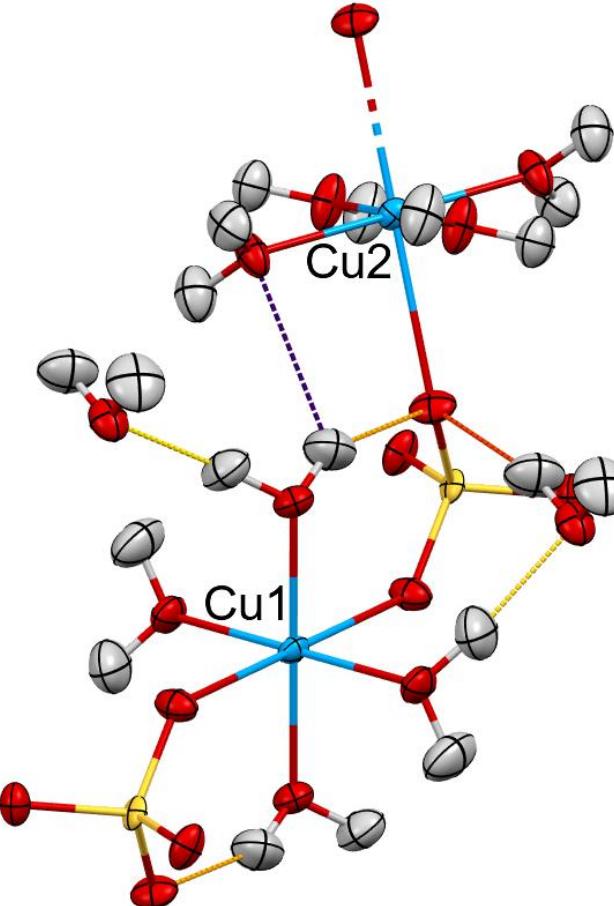
- o  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  NoSpherA2:  $R_1 = 2.59$ ; Max pk 0.6; min pk -0.6 (100 K)



M.A. Ibrahim & R.T. Boeré,  
New J. Chem. **2022**, *46*, 5479.



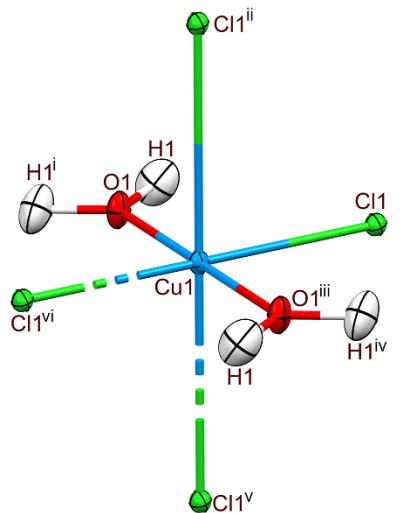
Combined neutron diffraction on  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  at RT:  $R_1 = 3.7\%$  min pk -0.1 (RT)



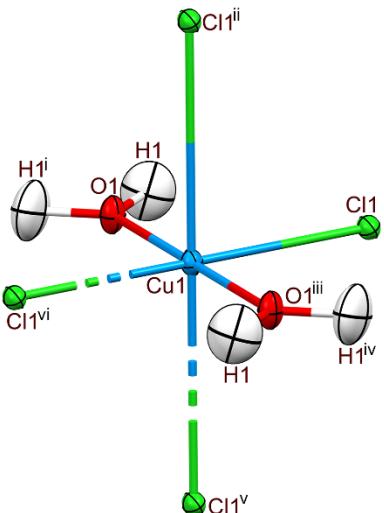
G. E. Bacon and D. H. Titterton, Z. Cryst. **1975**, *141*, 330.

# More examples from our laboratory

o  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$

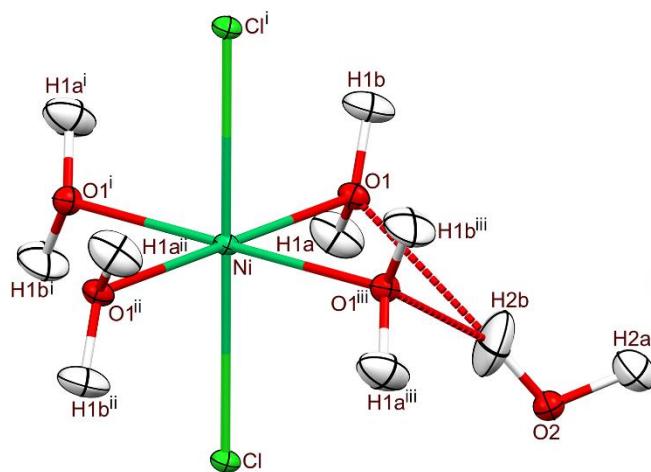


Mo K $\alpha$  (NoSpherA2):  $R_1 = 1.20\%$ ; Max pk 0.6; min pk -0.4 (173 K)

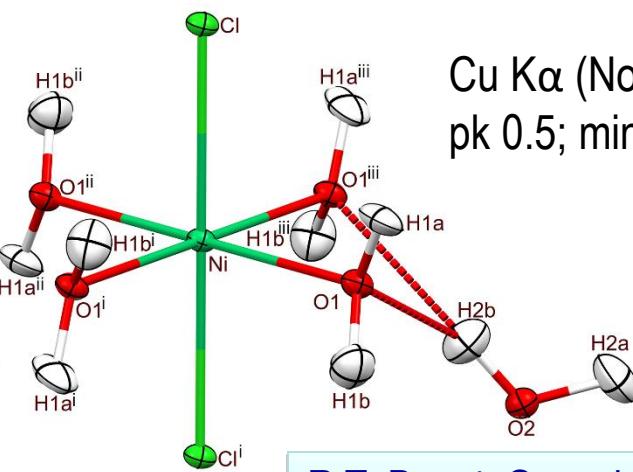


Cu K $\alpha$  (NoSpherA2):  $R_1 = 1.33\%$ ; Max pk 0.3; min pk -0.2 (173 K)

o  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$



Mo K $\alpha$  (NoSpherA2):  $R_1 = 1.75$ ; Max pk 0.4; min pk -0.5 (173 K)

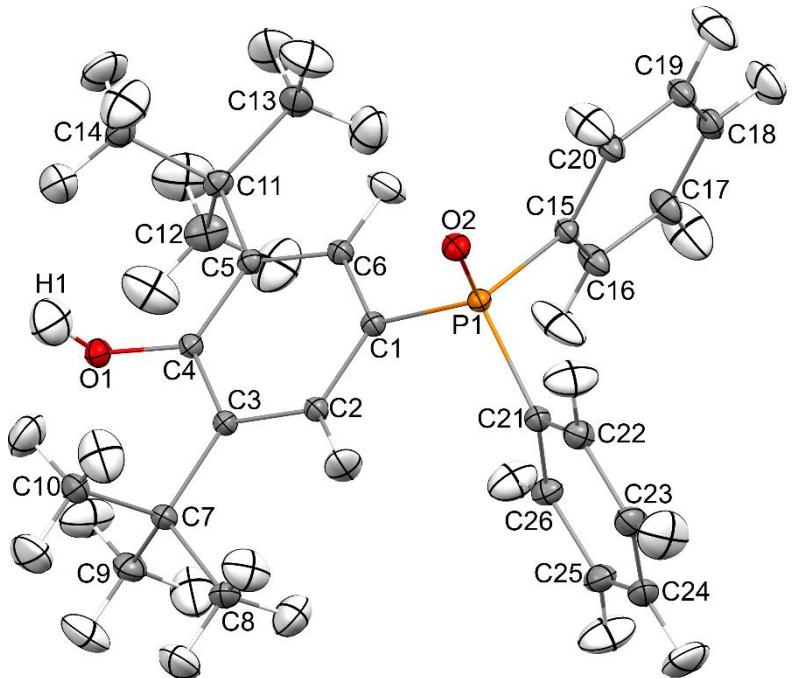


Cu K $\alpha$  (NoSpherA2):  $R_1 = 2.95\%$ ; Max pk 0.5; min pk -0.5 (173 K)

R.T. Boeré, Crystals. 2023, 13, 293:1-12.

# Another example: Ph<sub>2</sub>-3,5ditBuOHP=O practice

- o C<sub>21</sub>H<sub>31</sub>O<sub>2</sub>P      NoSphereA2:  $R_1 = 1.04$ ; Max pk 0.2; min pk -0.2
- o Improvement in mean C–C bond precision from 0.0016 to 0.0005 Å – 69% improvement.



**Table 6. Mean Element Bond Lengths (Å) from NoSphereA2 X-ray Refinement and Neutron Diffraction**

bond type (100 K)	mean (s.u.) in this work	mean (s.u.) in Allen <sup>a</sup>
tertbutyl C–sp <sup>3</sup> –H	1.089(3)	1.084(13)
TMS C–sp <sup>3</sup> –H	1.090(22)	1.084(13)
phenyl C(ar)–H	1.079(3)	1.085(9)
2,6-aryl C(ar)–H	1.081(15)	1.085(9)
C–O–H	0.95(5)	0.99(3)

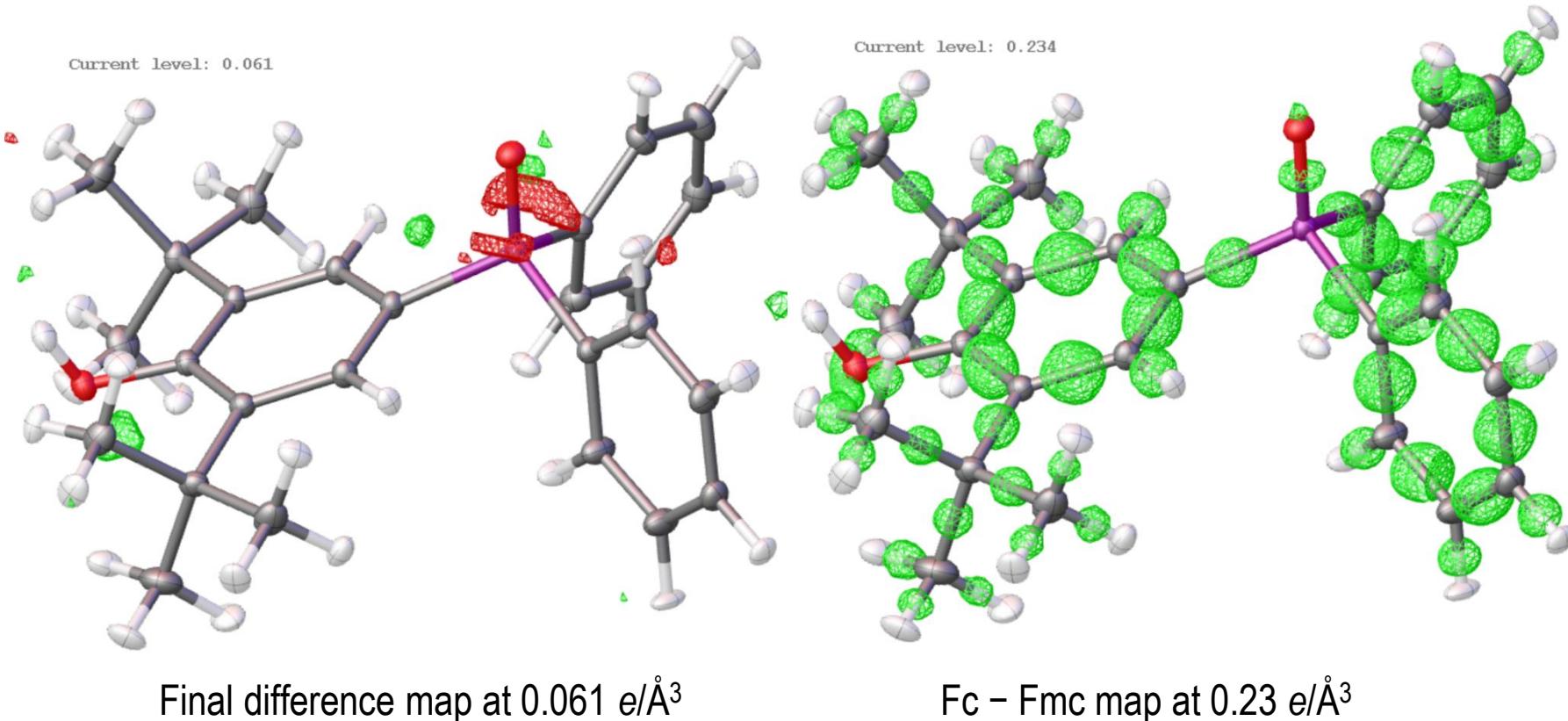
<sup>a</sup>Neutron data from a critical review of the literature for experiments taken at  $60 \leq T \leq 140$  K. Allen, et al. (2010).<sup>52</sup>

- o Improvements in bond precision observed for all 17 structure, including those that are worse behaved.
- o Mean element-H bond lengths are in good agreement with neutron diffraction data.

F. Marszaukowski et al., Cryst. Growth Des. 2022, 22, 2512.

# More on Ph2-3,5ditBuOHP=O NoSpherA2 refinement

- o  $\text{C}_{21}\text{H}_{31}\text{O}_2\text{P}$  NoSphereA2:  $R_1 = 1.07$ ; Max pk 0.1; min pk -0.1
- o Improvement in mean C–C bond precision from 0.0016 to 0.0005 Å – 69% improvement.



- o An excellent crystal collected under our normal target of 5-fold redundancy and 0.70 Å resolution on Cu gives, with maybe 1 H of work in refinement, gives an accurate depiction of bonding electron density.

F. Marszaukowski et al., Cryst. Growth Des. 2022, 22, 2512.

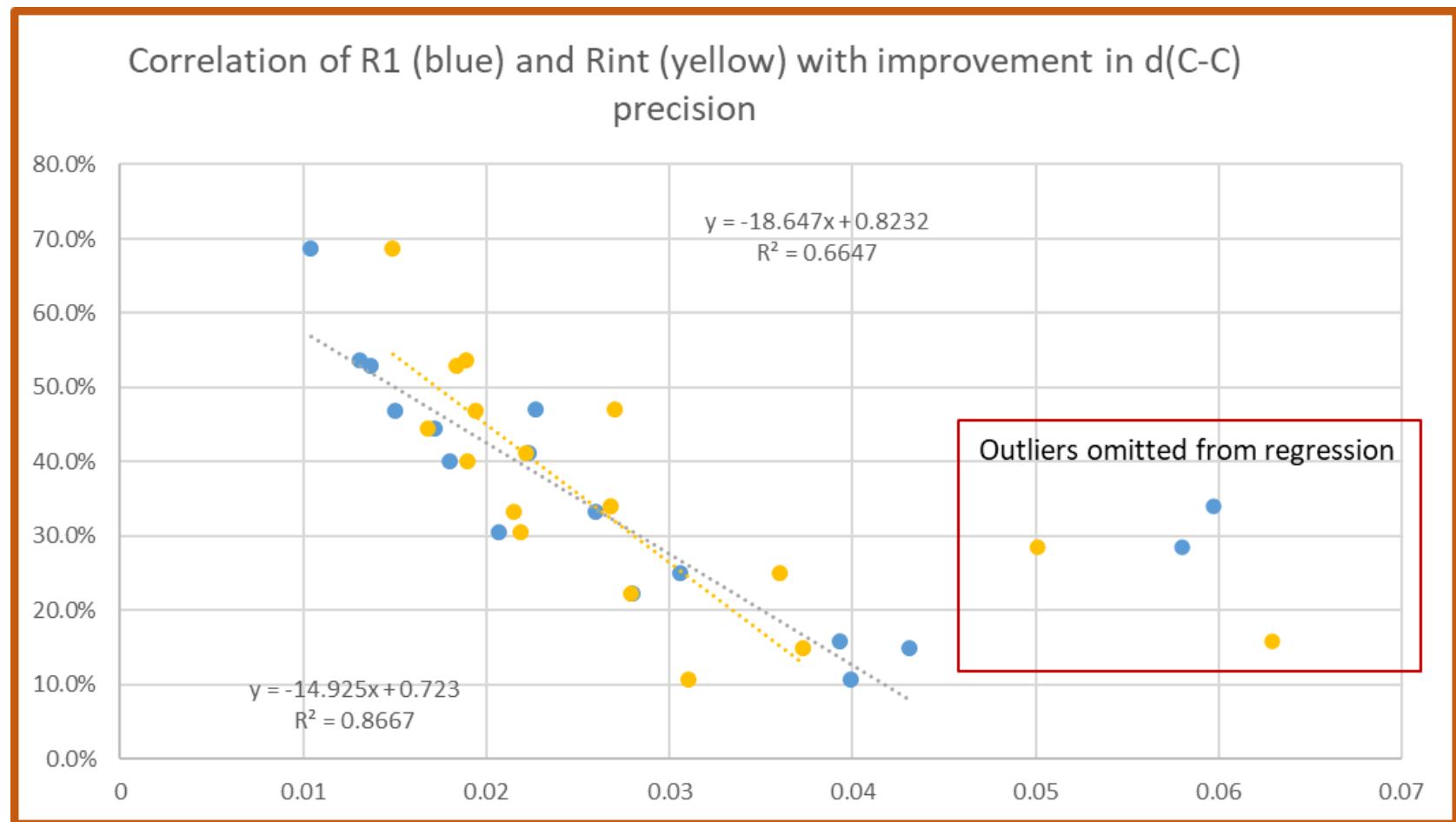
# Assessing structure quality

- Improvement in mean C–C bond precision for 17 structures as calculated by PLATON

Structure	$R_1$	$R_{\text{int}}$	Bond precision <sup>c</sup> : C–C in Å, impr. %	Data/par. ratio
1	0.0137	0.0184	0.0008 – 0.0017 52.9%	8.2
2	0.0260	0.0215	0.0012 – 0.0018 33.3%	8.5
2a	0.0172	0.0168	0.0010 – 0.0018 44.4%	8.5
2a'	0.0180	0.019	0.0009 – 0.0015 40.0%	10.3
2b	0.0207	0.0219	0.0016 – 0.0023 30.4%	8.6
2c	0.0104	0.0149	0.0005 – 0.0016 68.8%	8.4
2c'	0.0597	0.0268	0.0031 – 0.0047 34.0%	19
3	0.0399	0.031	0.0025 – 0.0028 10.7%	14.9
3a	0.0131	0.0189	0.0013 – 0.0028 53.6%	10.4
3b	0.0150	0.0194	0.0017 – 0.0032 46.9%	11.0
4	0.0227	0.027	0.0009 – 0.0017 47.1%	8.0
4a	0.0306	0.036	0.0015 – 0.0020 25.0%	8.0
4a'	0.0280	0.0279	0.0014 – 0.0018 22.2%	13.6
4b	0.0580	0.0501	0.0020 – 0.0028 28.6%	16.2
4c	0.0223	0.0222	0.0010 – 0.0017 41.2%	11.1
4c'	0.0393	0.0629	0.0019 – 0.0016 15.8%	14.1
4c''	0.0431	0.0373	0.0023 – 0.0027 14.8%	12.9
Average			0.0015 – 0.0023, 34.9%	

- Good structures improved more than poorer ones (10.7 to 68.9 % improvement).
- All structure improved in average precision with HAR refinement!

# Correlation diagram for the improvement in refinement precision and R-factors



# Accuracy of H-atom placement: import. to H-bonds

- o X-ray diffraction with the IAM places H-nuclei incorrectly – well known!
- o NoSpherA2 refinement achieved near-neutron accuracy in the placement of H in 17 structures

**Table 6. Mean Element Bond Lengths ( $\text{\AA}$ ) from NoSpherA2 X-ray Refinement and Neutron Diffraction**

bond type (100 K)	mean (s.u.) in this work	mean (s.u.) in Allen <sup>a</sup>
tertbutyl C- $sp^3$ -H	1.089(3)	1.084(13)
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phenyl C(ar)-H	1.079(3)	1.085(9)
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C-O-H	0.95(5)	0.99(3)

<sup>a</sup>Neutron data from a critical review of the literature for experiments taken at  $60 \leq T \leq 140$  K. Allen, et al. (2010).<sup>52</sup>

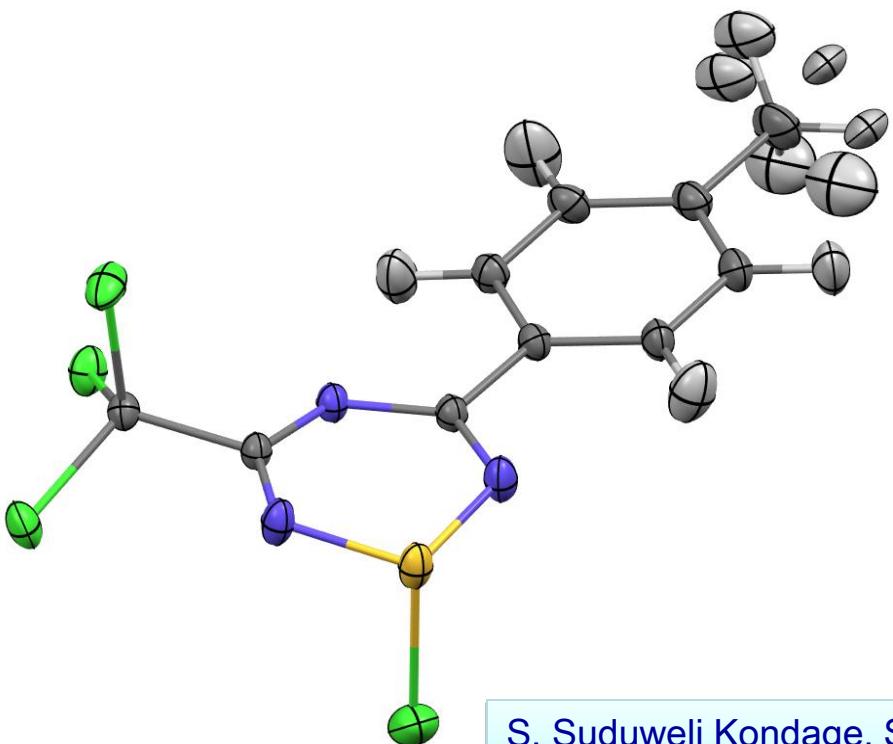
F. Marszałkowski et al., Cryst. Growth Des. 2022, 22, 2512.

- o Accurate work on H-bonding with IAM models has always required an adjustment in E-H distance from that determined from the X-ray diffraction experiment (*normalization*).
- o This is no longer necessary in our experience with using olex2.refine/NoSpherA2.

T. Steiner, Angew. Chem. Int. Ed. 2002, 41, 48.

# Modelling H-atom disorder with NoSpherA2

- o HAR on a series of 1-chloro-3-aryl-5-trihalotrihalomethyl-1 $\lambda^4$ ,2,4,6-thiatriazines
- o Where the aryl substituent was the 4-tolyl group, HAR detected insufficient ED for the CH<sub>3</sub> H atoms and the displacement parameters became oversized (initial isotropic refinement).
- o A disorder model was therefore developed and refined to 50:50 occupancy for the two rotamers of the methyl group
- o Completing HAR in NoSpherA2 on the disorder model is very successful, as shown: R<sub>1</sub> = 2.05% with a smooth final difference Fourier



How does NoSpherA2 handle such a two-part disorder model for HAR?

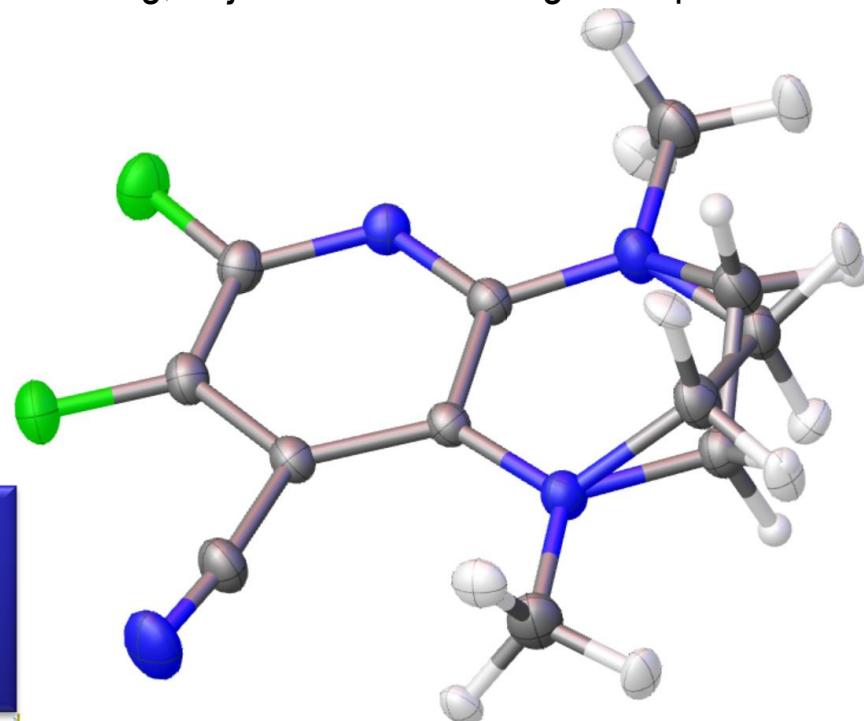
- Two full models are computed in DFT, one after the other
- One where the CH<sub>3</sub> is in first conformation.
- A second with CH<sub>3</sub> in second conformation
- The two are overlaid in the refinement ratio
- Custom form factors are available for the two sets of 'half' H atoms

S. Suduweli Kondage, *SynLett.* **2023**, *Early View*. DOI: 10.1055/a-2071-4235

# A two-part disorder model you can try on Olex2 THPP

**THPP:** substituted tetrahydropyrido[2,3-b]pyrazine – like sucrose, an Olex2 provided dataset

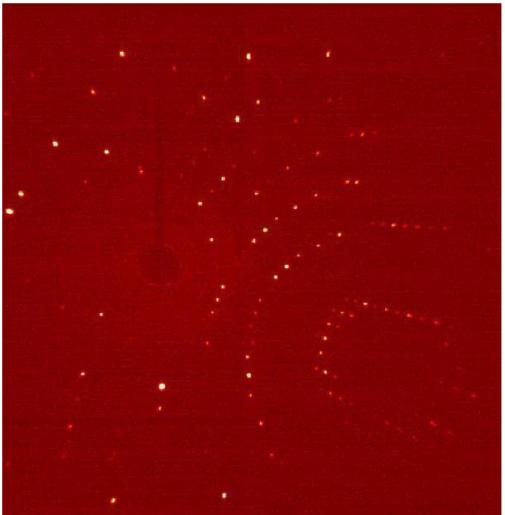
- o There is a conformational disorder in the  $-\text{CH}_2\text{CH}_2-$  component of the hydrated pyrazine
- o Minor component is 11.8% and the major 88.2%
- o Even with this disorder the major and minor components can be anisotropically refined for non-hydrogen atoms, and for the H atoms of the major component.
- o The low occupancy second component H atoms are isotropically refined *and retained in HFIX*.
- o The HFIX C–H distance is, in the final tweaking, adjusted to an average NoSpherA2 length:  
**AFIX 23 1.09**
- o IAM:  $R_1 = 3.93$ ; NOTE:  $R_{\text{int}} = 5.36\%$   
Max pk 0.3; min pk -0.3  
 $\text{C-C} = 0.0012 \text{ \AA}$
- o NoSphereA2:  $R_1 = 2.19$ ;  
Max pk 0.2; min pk -0.2  
 $\text{C-C} = 0.0007 \text{ \AA}$



So even with a marginal  $R_{\text{int}} > 5\%$  we obtain about 42% improvement in mean precision.  
HAR with NoSpherA2 yields more accurate crystal structures!

# Summary

**Model from:  $F_{obs}(hkl)$  vs.  $F_{calc}(hkl)$**



$$R = \frac{\sum [ |F_{obs}| - |F_{calc}| ]}{|F_{obs}|}$$

$$F'_{calc}(hkl) = \sum_j^{N_{atoms}} f_{hkl,j} \cdot e^{2\pi i \vec{h} \cdot \vec{r}_j} \cdot T_j(\vec{h})$$

$f_{hkl,j}^{aniso}$  = **Non-spherical f.f.**

$T_j(\vec{h})$  = **Debye-Waller factor**

## Assessment and prediction

- o NoSpheraA2 lives up to the claims made for it by the developers
- o It is straightforward and manageable to implement
- o It uses the knowledge base of modern chemists who are familiar with DFT methods
- o HAR refinement with NoSpheraA2 has the potential to significantly improve structure determinations from X-ray crystallography
- o Approaches the accuracy of neutron diffraction for H-atom placement in structures