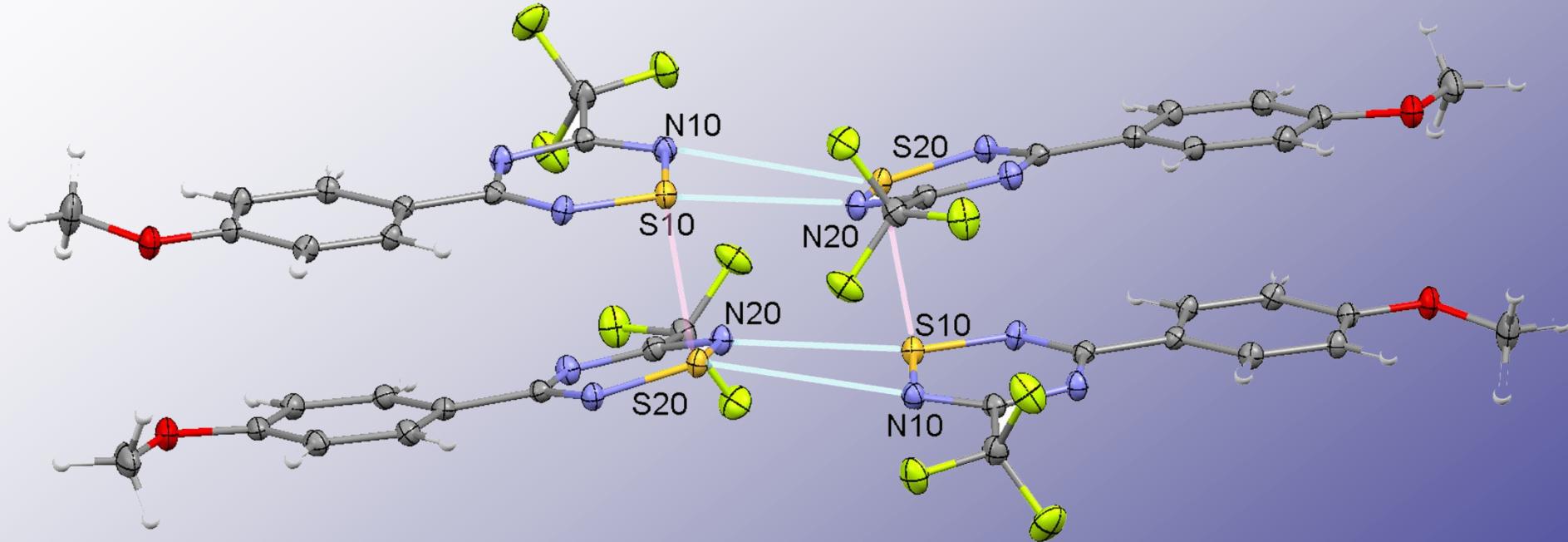


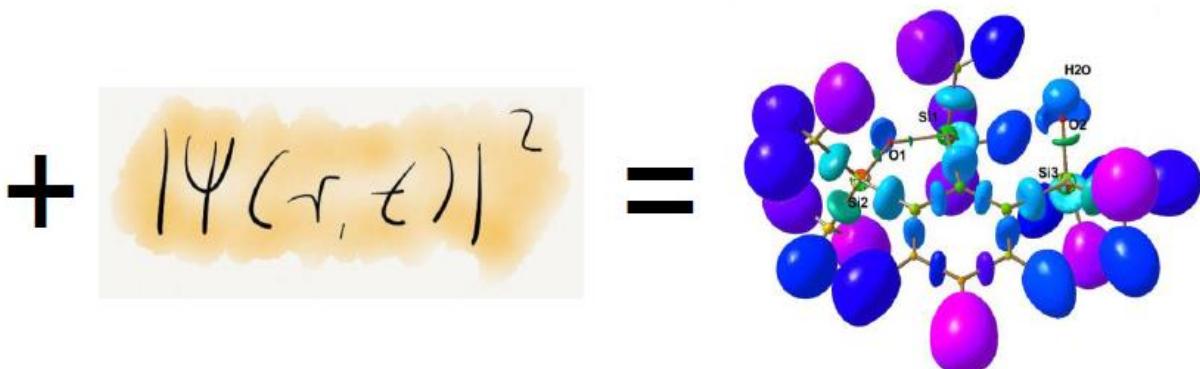
Canadian Chemical Crystallography Workshop 2022



Tutorial 7 – NoSpherA2

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.

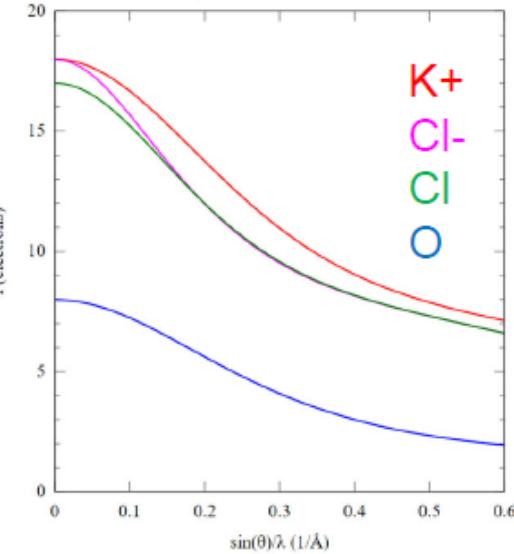
So what is this F_{obs} term?

- o Developed earlier today in the lecture on Structure Factors by Joe Ferrara
- o The mathematical theory for the construction of F_{obs}
- o Structure factor equation:

$$F_{hkl} = V \int_{x=0}^{x=1} \int_{y=0}^{y=1} \int_{z=0}^{z=1} \rho(x, y, z) e^{i\Delta\mathbf{k} \cdot (\mathbf{x}\mathbf{a} + \mathbf{y}\mathbf{b} + \mathbf{z}\mathbf{c})} dx dy dz$$

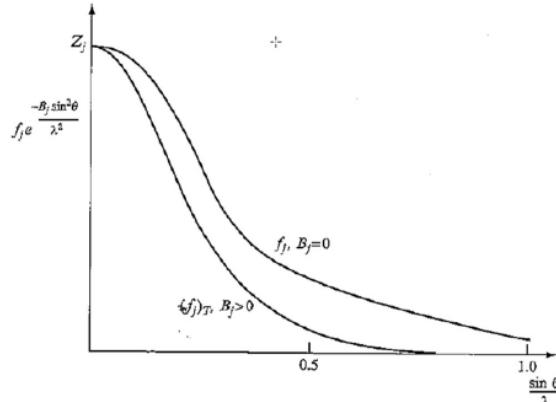
$$F_{hkl} = \sum_j f_j e^{2\pi i (hx_j + ky_j + lz_j)}$$

- o Atomic scattering (form) factor: $f_j = 4\pi \int_0^{\infty} R^2 \rho_j(R) \left(\frac{\sin\left(\frac{4\pi \sin\theta}{\lambda} R\right)}{\frac{4\pi \sin\theta}{\lambda} R} \right)$



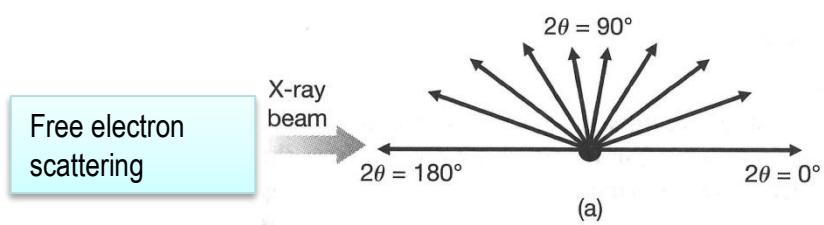
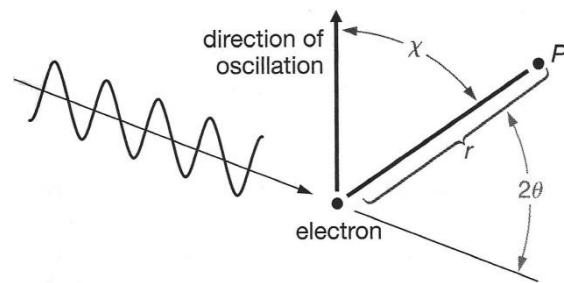
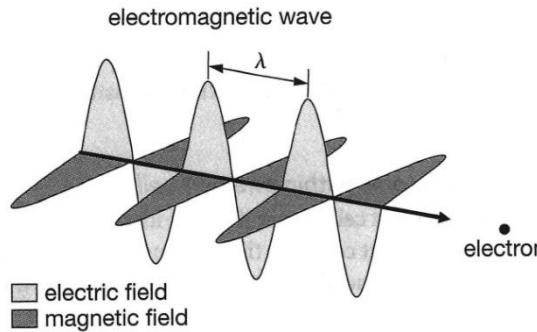
- o Debye Waller factor: motion of the atoms (vibrations) further decreases intensity with $\sin\theta/\lambda$

$$(F_{hkl})_T = \sum_j f_j e^{-B_j (2\sin\theta/\lambda)^2} e^{2\pi i (hx_j + ky_j + lz_j)}$$

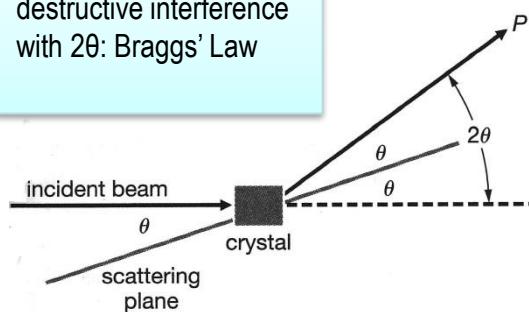


Scattering of X-rays by Matter

- o X-rays are electromagnetic radiation (\perp electric & magnetic vectors):
- o Three interactions with matter:
 1. X-rays scattered elastically (same energy)
 2. X-ray scattered inelastically (decrease in energy)
 3. X-rays absorbed
- o Scattering by electrons is the most important: intensity $\propto 1/m^2$
 - Hydrogen nucleus (1 proton) scatters X-rays 4×10^6 less than e
- o Scattering by a free e is called Thomson scattering
- o Thomson (elastic) scattering involves the X-rays causing the e to oscillate by the period of its electric field
- o The oscillating e emits X-rays of the same λ as incident X-ray, *but in all directions.*
- o Thomson scattering is ~8% intensity, but alone is responsible for **diffraction**.

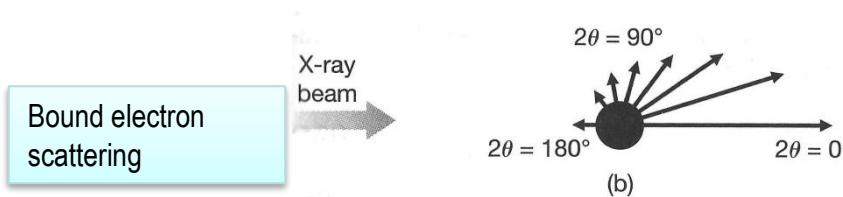


Constructive and destructive interference with 2θ : Bragg's Law

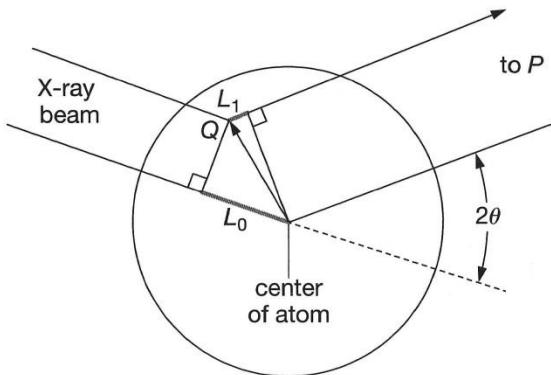


Scattering from atoms: *bound* electrons

- Electrons in atoms are *bound* to the nucleus in a spherical electrostatic field → Rayleigh scattering



- This bound condition affects how e can oscillate when interacting with X-rays.
- Due to their positions relative to the nucleus, different electrons will scatter X-rays by different amounts.

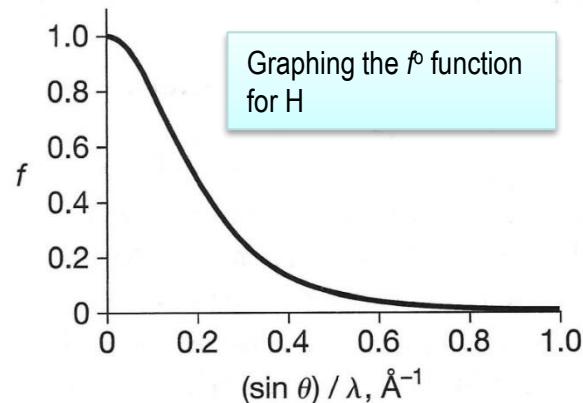


The largest loss of intensity of the scattered (diffracted) X-ray beam with the increase in $\sin\theta/\lambda$ is caused by this interference with the *other* electrons within the volume of the atoms

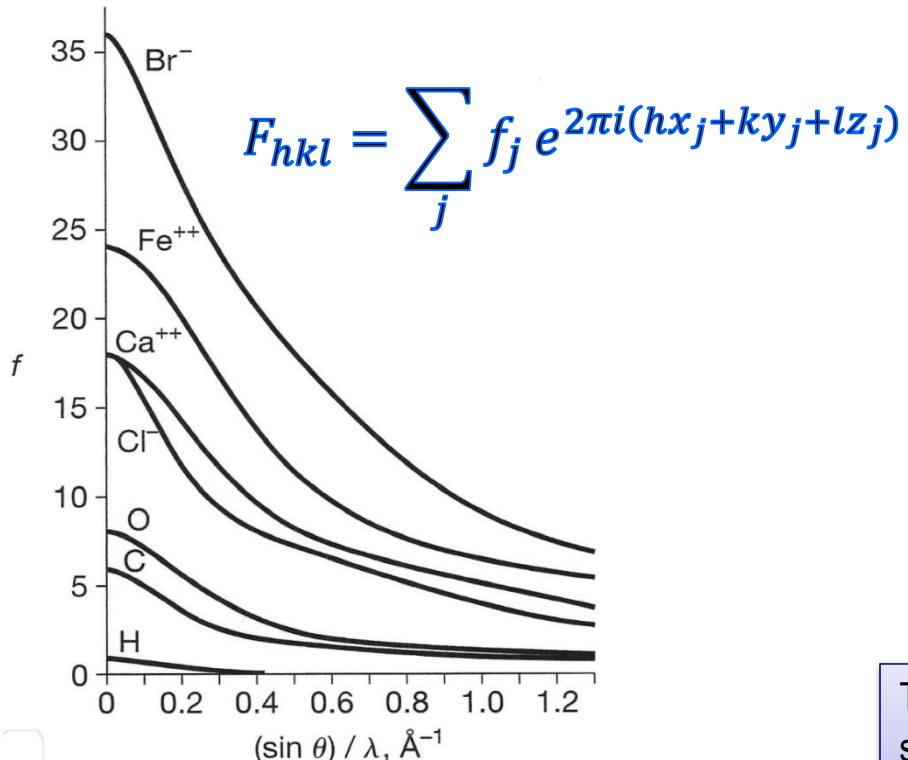
- Serious effect on structure resolution
- Serious effect on positions of light atoms – especially hydrogen

- When $2\theta = 0^\circ$, the path lengths are the same. When $2\theta > 0^\circ$, the different wavelets fall out of phase.
- The total scattered intensity from the atom becomes weaker at “higher diffraction angles” due to destructive interference.
- Dependence on angle is given by the **atomic form factor** f , better called the **atomic scattering factor**

$$f_H^0 = \left[1 + \left(\frac{2\pi a_B \sin \theta}{\lambda} \right) \right]^{-2}$$



“Atomic” form factors and effects of radiation types



Spherical *neutral* atom model is normally used for f_j . Why?

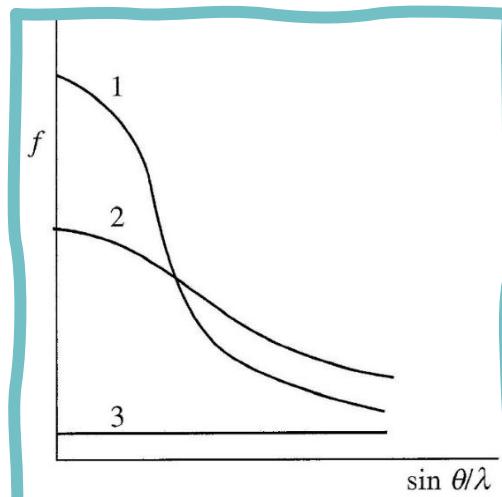
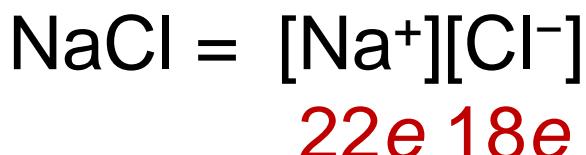


Fig. 3.B.9

Typical scattering curves for: (1) electrons; (2) X-rays; (3) neutrons.

The $\sin\theta/\lambda$ dependence of *electron* scattering is much stronger than X-rays.
 But $\sin\theta/\lambda$ dependence of *neutron* scattering is zero – neutron structures are obtained to very high resolution.

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

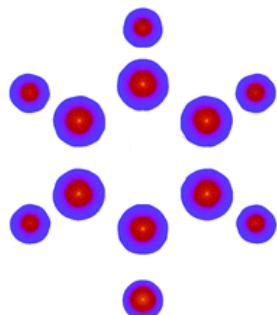
P. J. Brown, A. G. Fox, E. N. Maslen, M. A. O'Keefe and B. T. M. Willis. *International Tables for Crystallography* (2006). Vol. C, ch. 6.1, pp. 554-595
 [doi:10.1107/97809553602060000600]

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

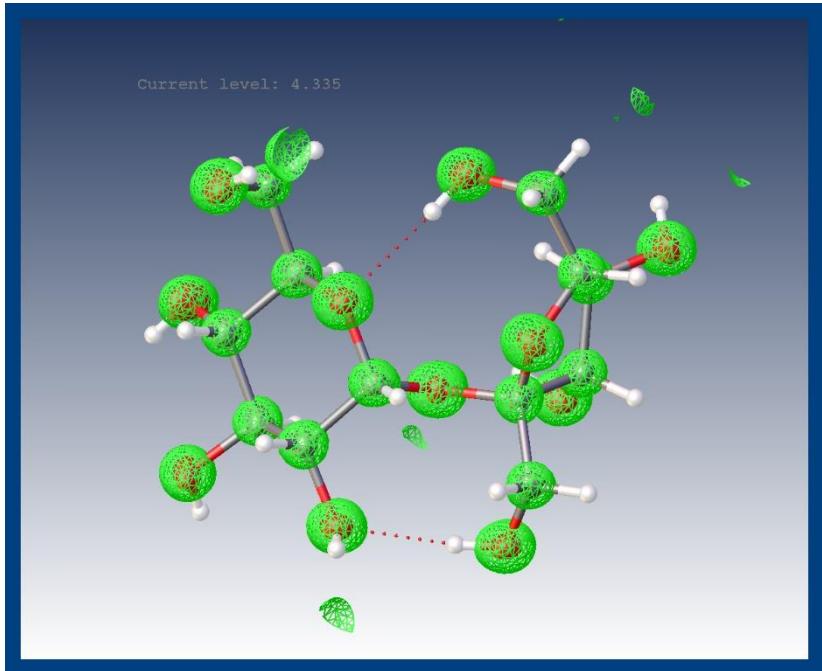


IAM = Independent Atom Model

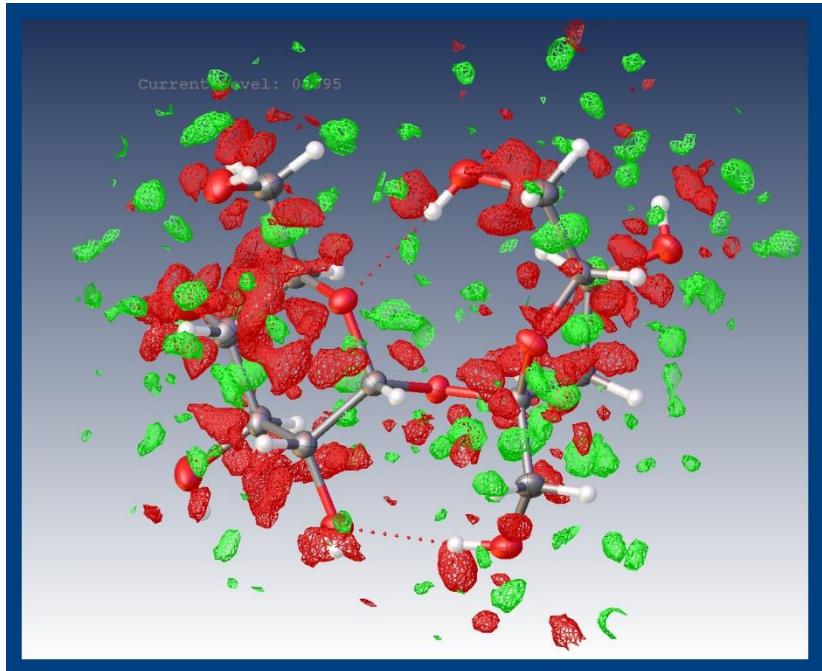
- o **IAM is a useful approximation** that is quite accurate and extremely effective – but remains an approximation!

Consequences of the IAM approximation

1. Residual electron density:



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



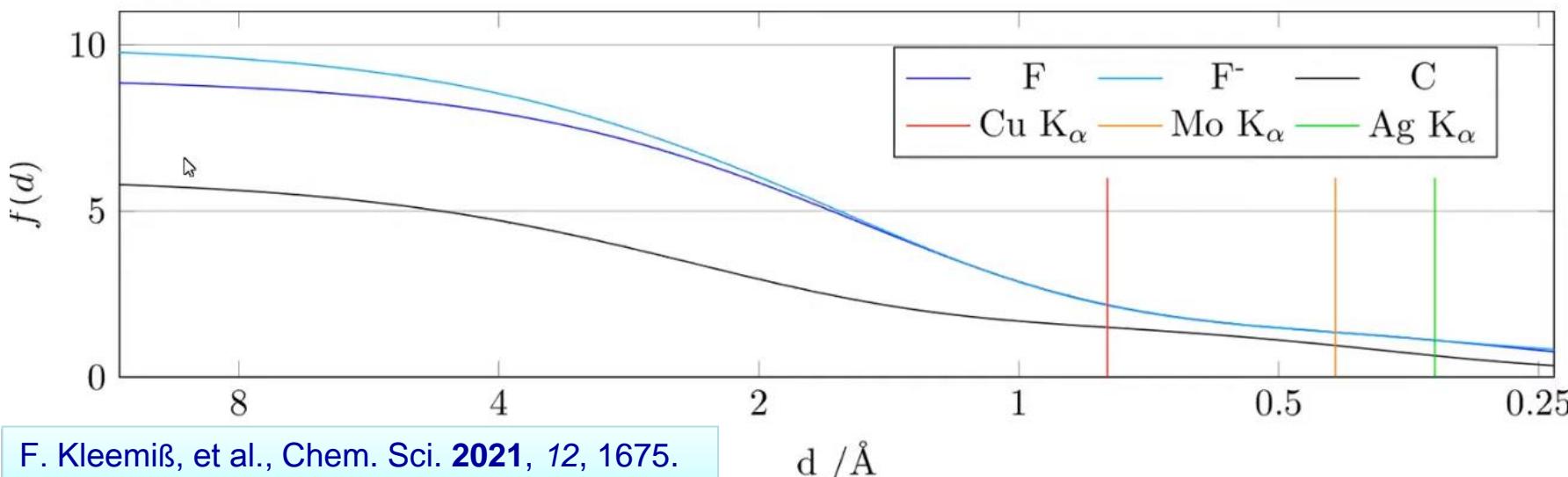
Sucrose: final difference map of $[F(\text{obs}) - F(\text{calc})] = \text{unassigned ED}$

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

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!



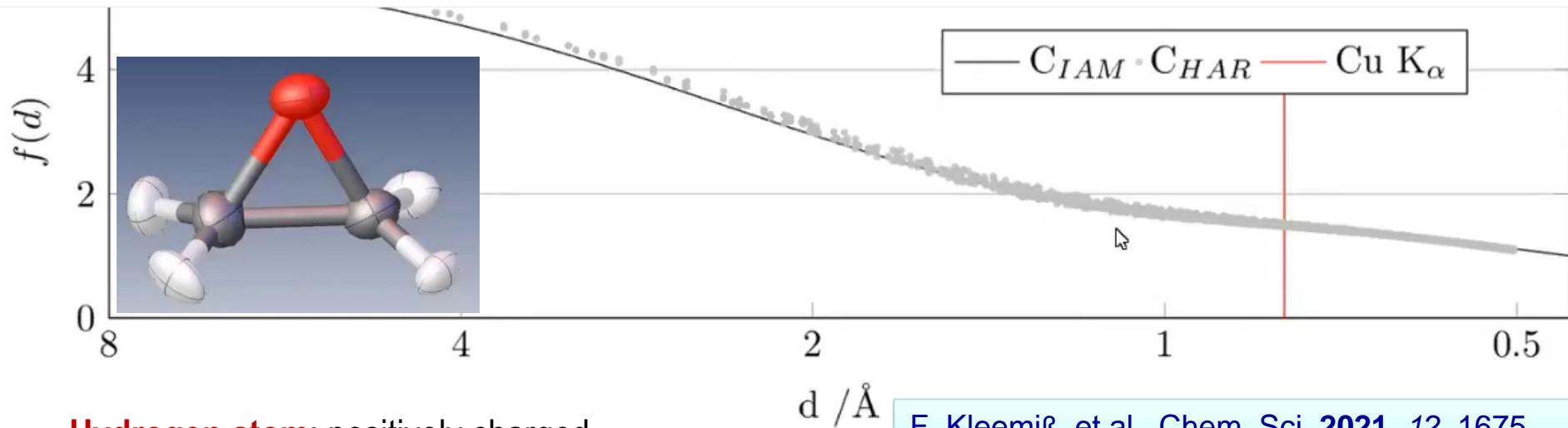
F. Kleemiss, et al., Chem. Sci. 2021, 12, 1675.



Anisotropic form factors also important for neutral atoms

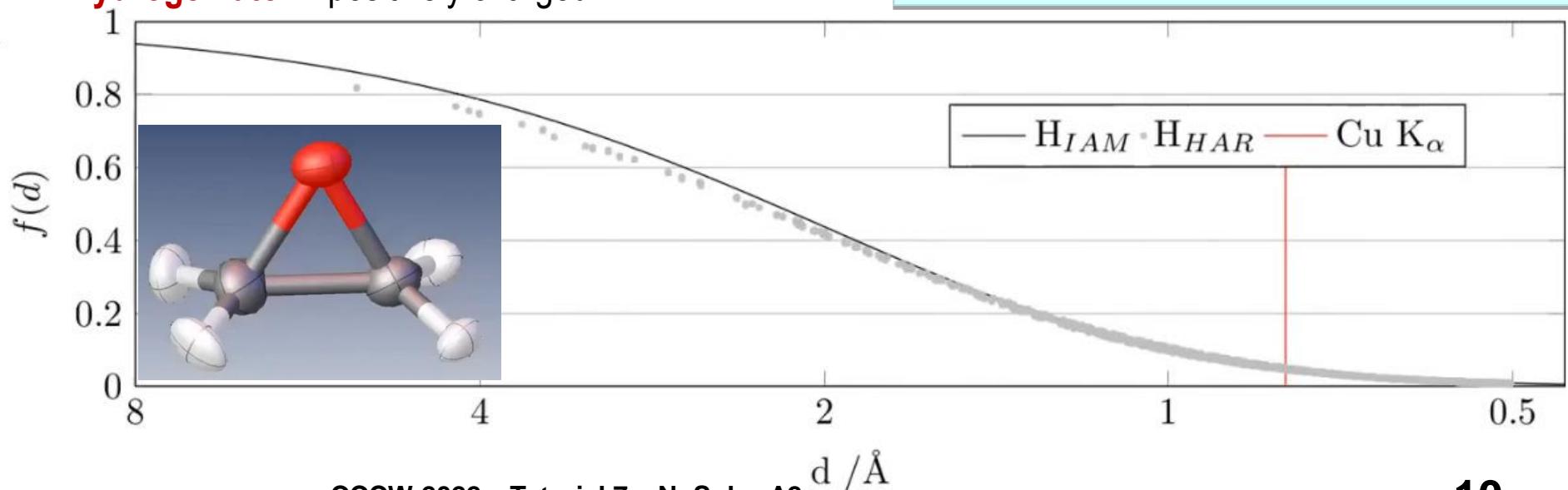
- Scattering factor curves for the IAM model (solid line) versus the corrected asphericity

Carbon atom: negatively charged



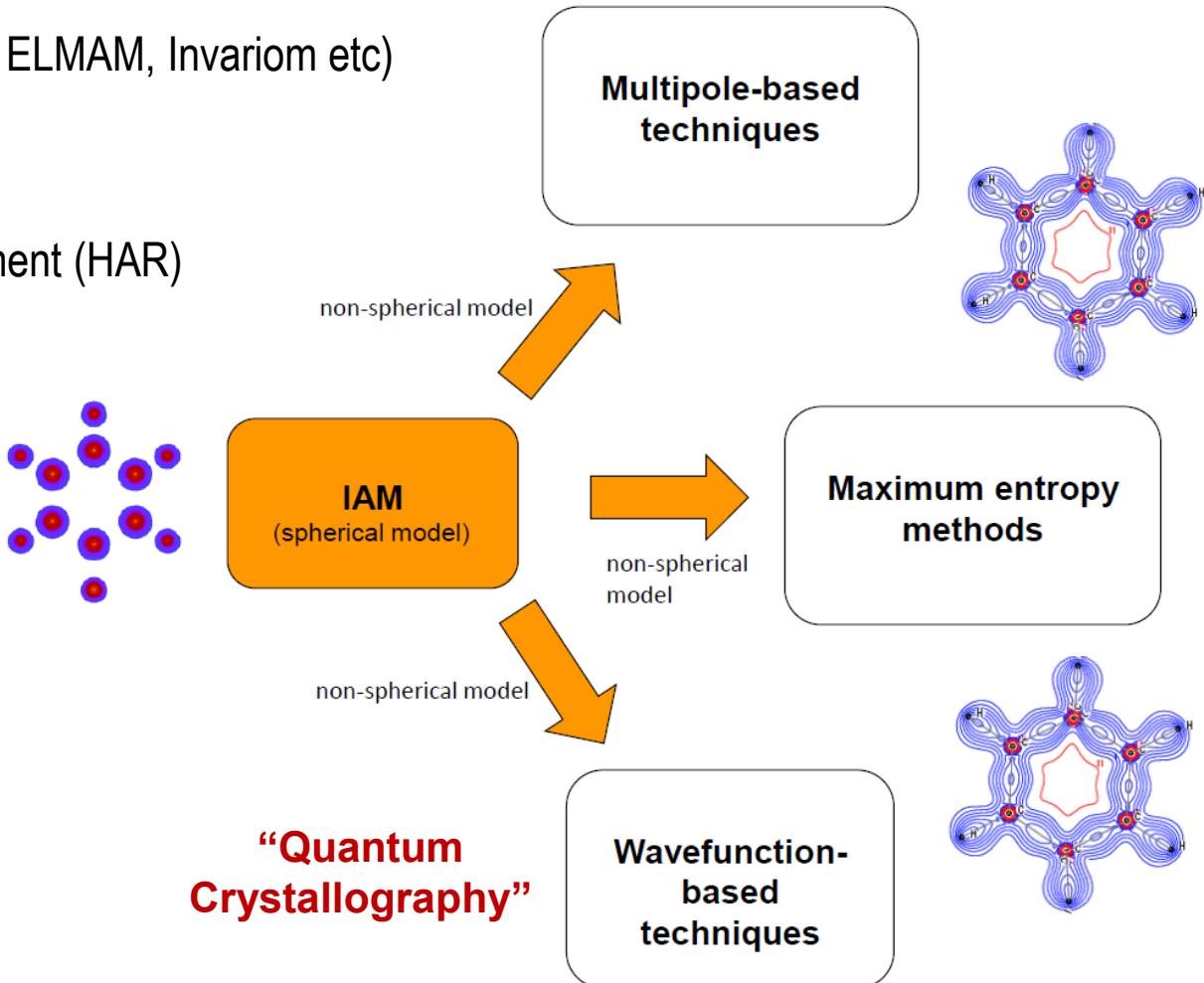
Hydrogen atom: positively charged

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



Improvements on the IAM that are in use

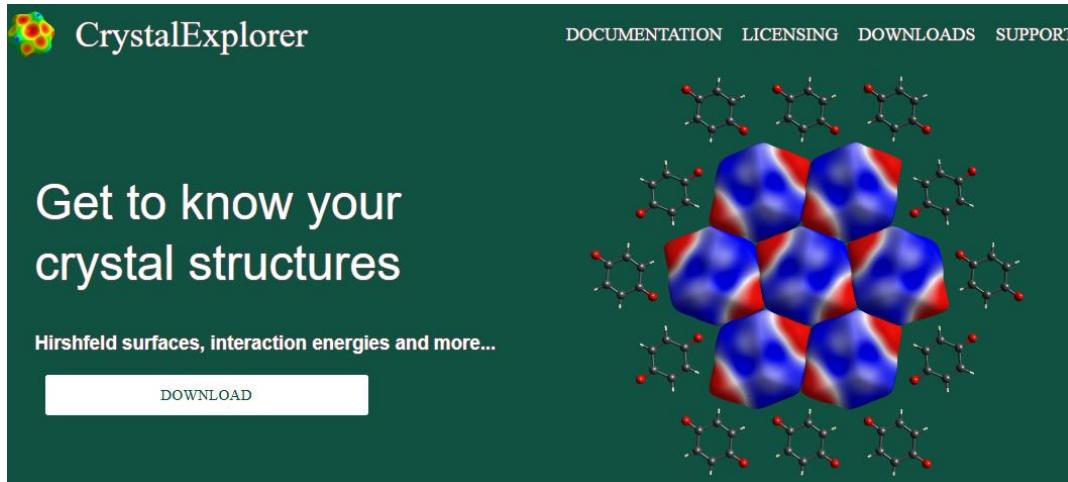
1. Multipole based techniques:
 - Refined multipoles
 - Databases (DISCAMB, ELMAM, Invariom etc)
2. Maximum Entropy methods
3. Wavefunction based
 - Hirshfeld Atom Refinement (HAR)



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 understood as an ‘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,^{a,b} Claudia M. Wandtke,^a Christian B. Hübschle,^c Michael Ruf,^b George M. Sheldrick^a and Birger Dittrich^{d,*}

Why use Non-Spherical Atom Refinements?

Standard X-ray refinement involves data fitting to spherical atom model (IAM)

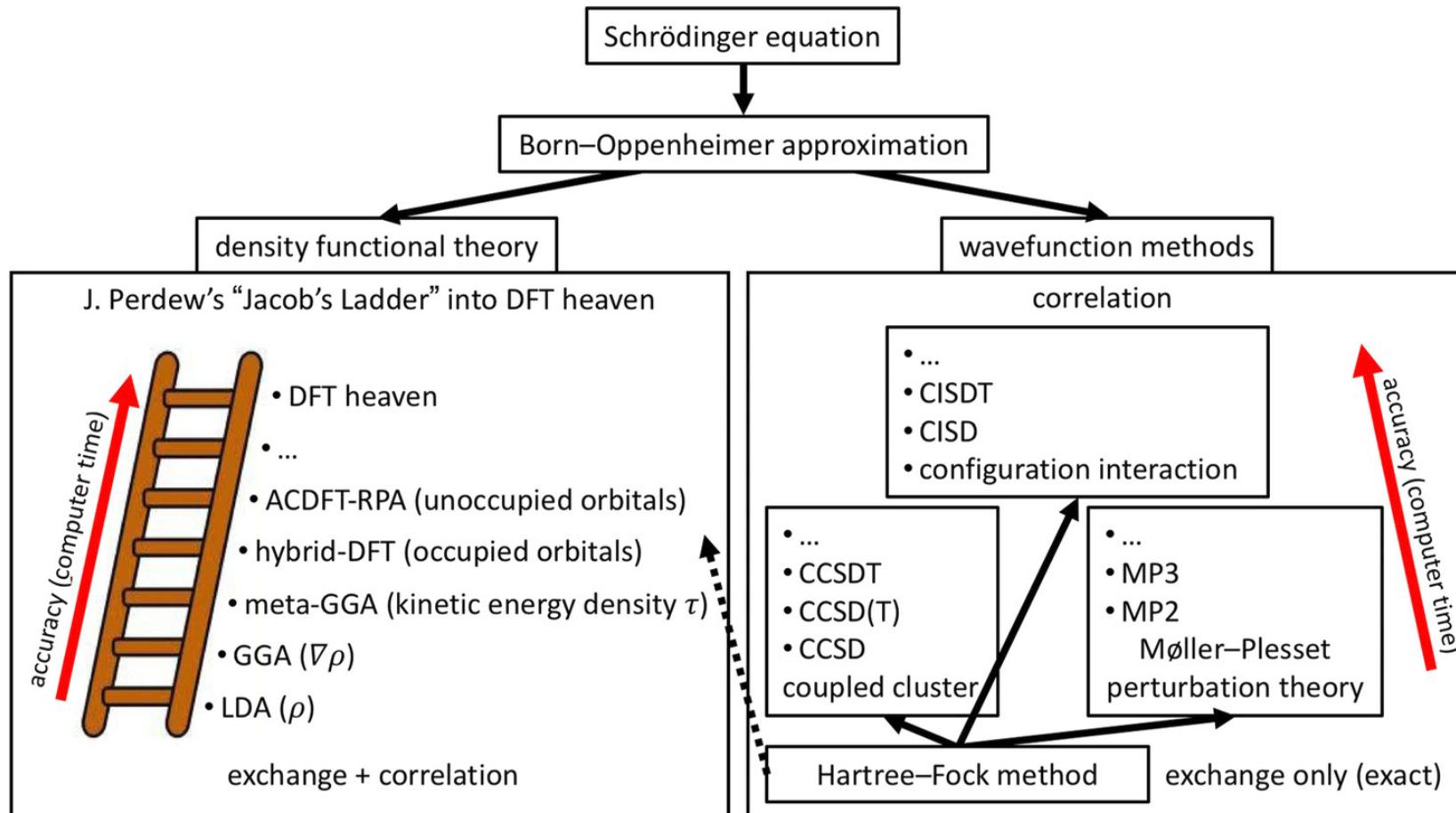
- o Assume that the atoms are isotropic and that the atomic positions are the maxima in the ED (electron density).
- o Details of covalent interactions are missing in the model. The X-ray data carries this information. This is especially true for hydrogen atoms, which lack inner cores of electrons and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

Non-Spherical Atom Refinements 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.

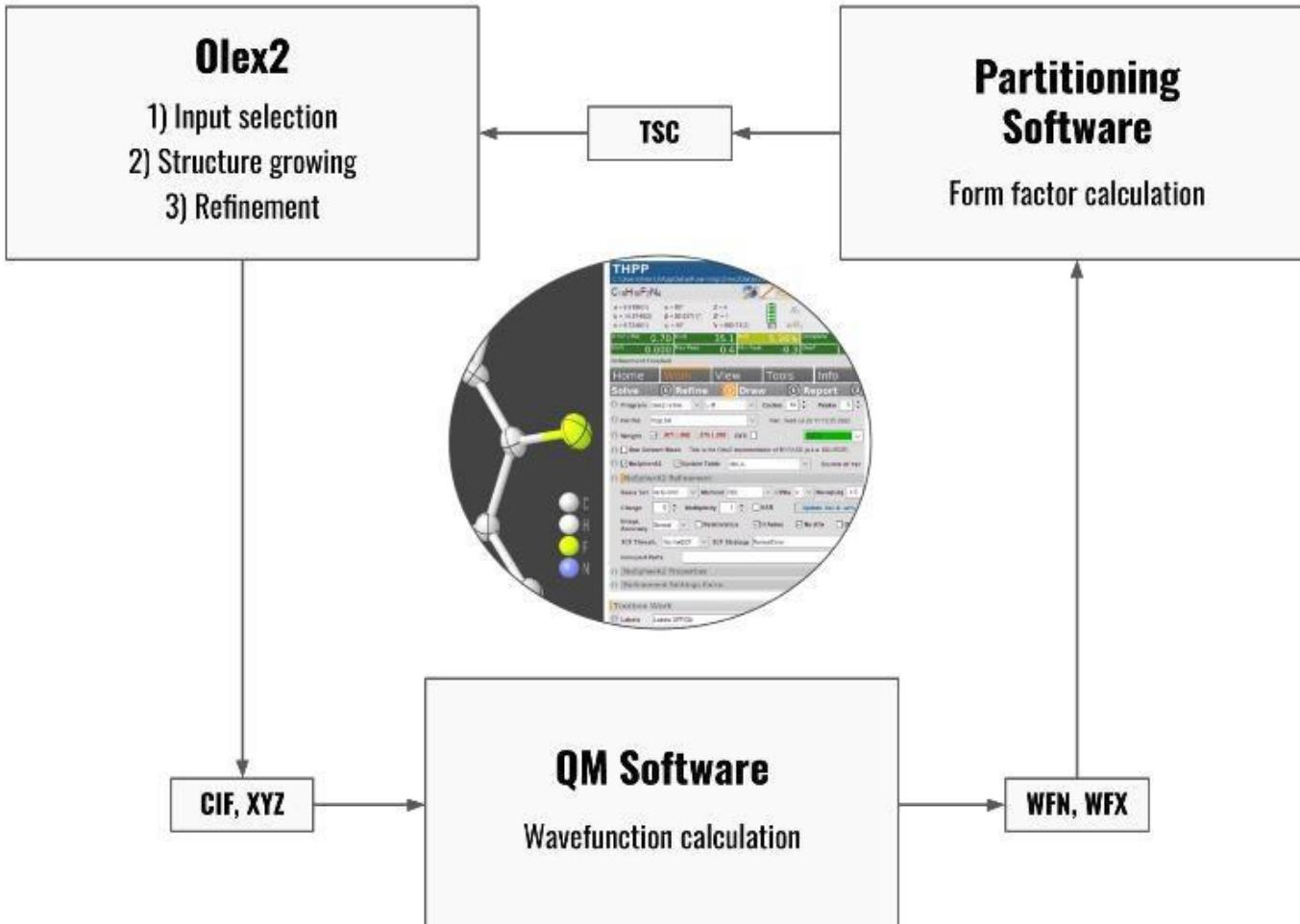
Why use Density Functional Theory (DFT)?

- 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



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 olex2refine full-featured model refinement method
- o Full QM analysis of the outputs can be visualized within the Olex2 GUI

The File Structure in NoSphereA2

The three key files are added to the main structure folder

File Explorer view showing the file structure:

- Root: Olex1.5-samples > sucrose-b-nsa
- Left pane (Folders):
 - fc5002sup2.zip
 - jz9b02646_si_002.zip
 - Olex1.5-samples
 - 183
 - Co110
 - malbac
 - Periodic Table
 - sucrose
 - sucrose-b
 - sucrose-b-nsa** (selected)
 - movie
 - olex2
 - NoSphereA2_history
 - originals
 - temp
 - Wfn_job
 - sucrose-c
 - THPP
- Right pane (Files):
 - 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
 - sucrose.res**
 - sucrose.tsc**
 - sucrose.wfn**
 - sucrose.wfx**
 - sucrose_tables.html**

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

File Explorer view showing the contents of the sucrose-b-nsa > olex2 folder:

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 code to be added
- 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.

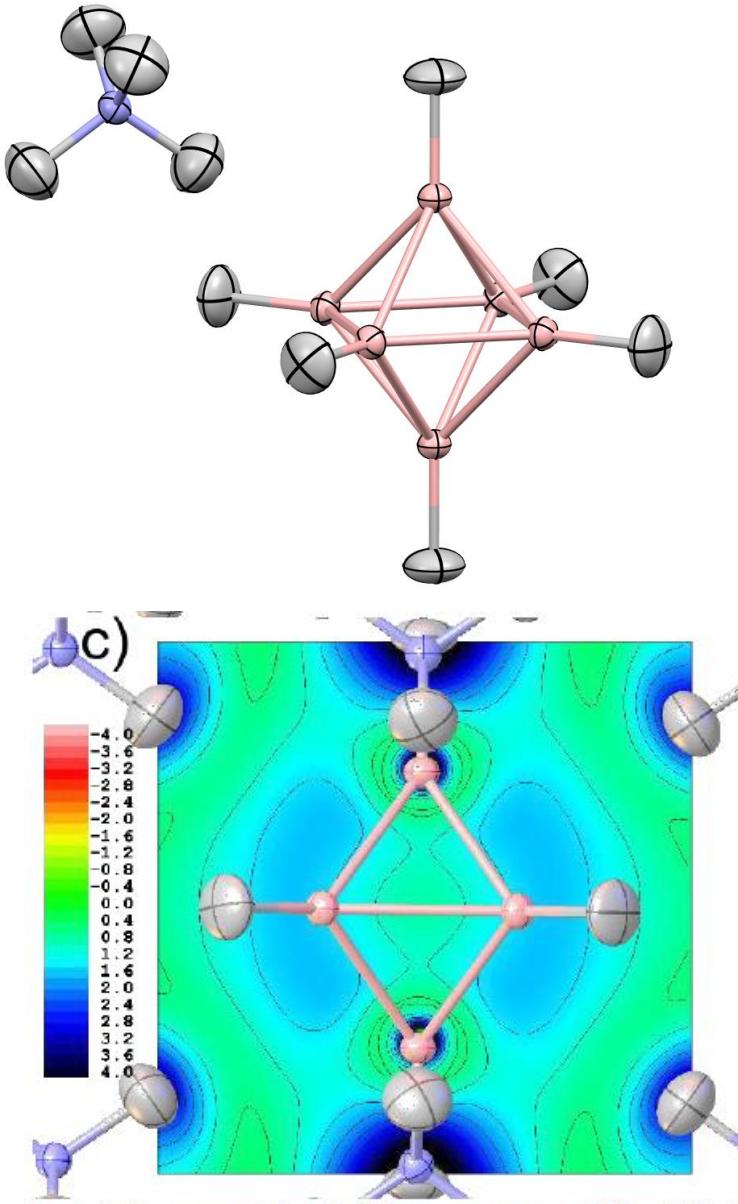
Claims for outstanding results: NoSpherA2 + olex2.refine



- 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

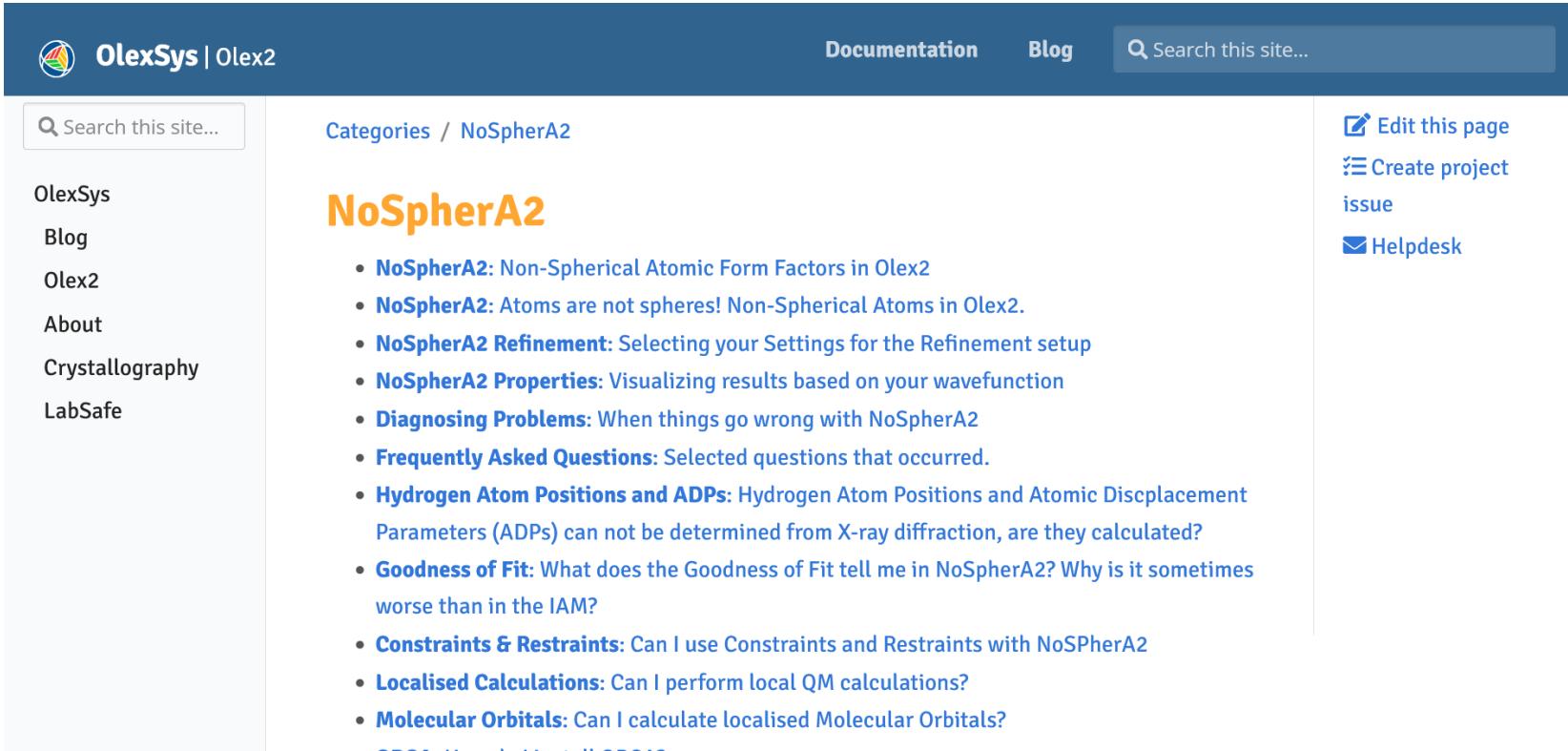
F. Kleemiß, et al., Chem. Sci. **2021**, 12, 1675.

So, let's try it and see how good it can be in practice



Resources and support

- o First and foremost, the www.olexsy.org support pages



The screenshot shows the OlexSys | Olex2 website with a dark blue header. The header includes a search bar, the site name, and links for Documentation, Blog, and a search bar labeled "Search this site...". On the left, a sidebar lists navigation links: OlexSys, Blog, Olex2, About, Crystallography, and LabSafe. The main content area shows the "Categories / NoSpherA2" page for "NoSpherA2". The page title is "NoSpherA2" in orange. Below it is a list of 14 blue links related to NoSpherA2, including topics like Non-Spherical Atomic Form Factors, Refinement, Properties, Diagnosing Problems, Frequently Asked Questions, Hydrogen Atom Positions and ADPs, Goodness of Fit, Constraints & Restraints, Localised Calculations, and Molecular Orbitals. To the right of the content area is a sidebar with links for "Edit this page", "Create project issue", and "Helpdesk".

- 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>

Experience based rules for using NoSpherA2

1. First develop an accurate structure model in the IAM

IAM is 95-99% accurate, compact, reliable, familial – so use it and use it well!

2. 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

In Shelx suite, “3” identifies this atom as O
The label is an arbitrary label, only.

3. Implement NoSpherA2 in a copy of the original folder

4. First refine using olex2.refine with **spherical form factors**

Recommended if another IAM program (shelXL, etc) used for IAM model

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 full developed

Default levels of theory usually OK

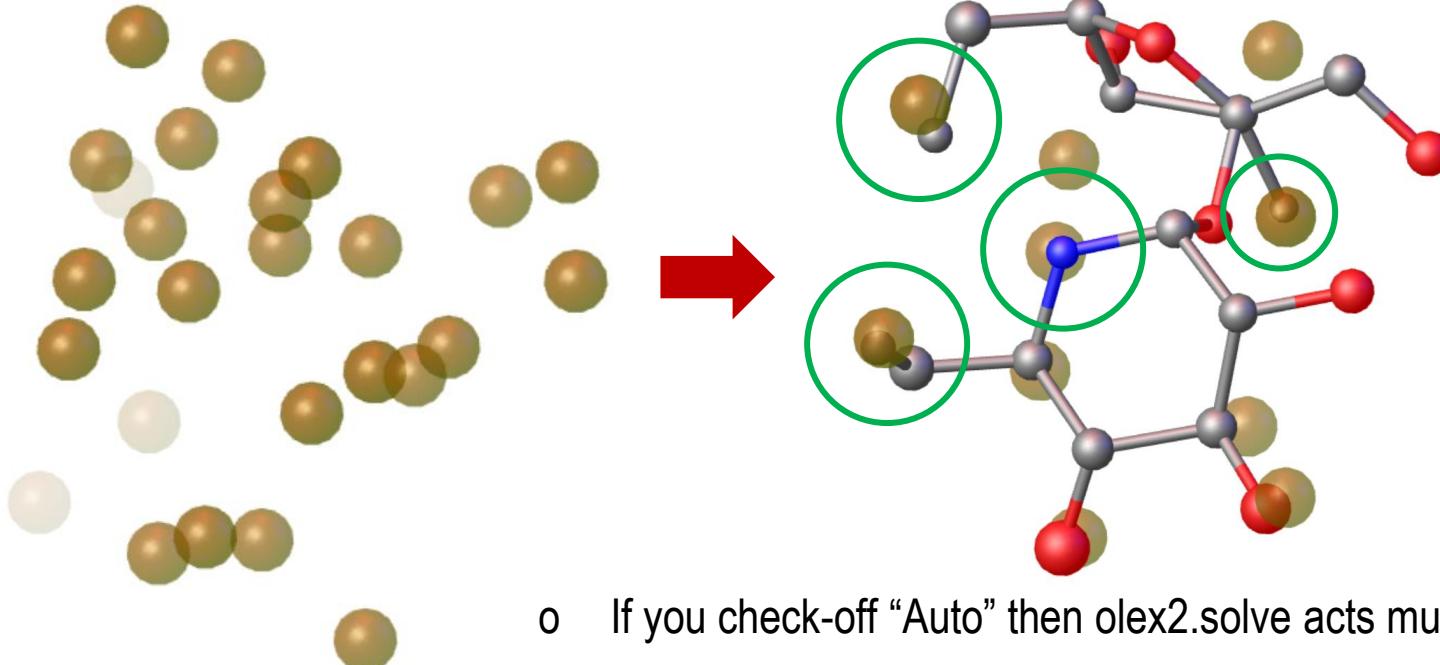
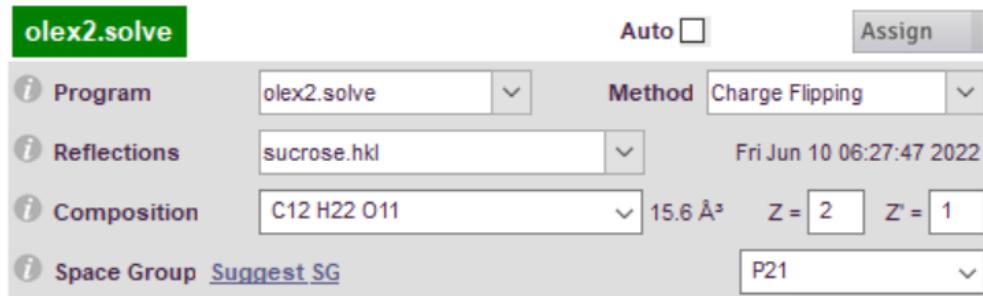
Leave HFIX and anis-H unchecked at first

Apply RIGU (0.004, 0.002 or 0.001) to H before refining

Final: iterative (10x) for final polishing of the model

Demonstrate with Sucrose

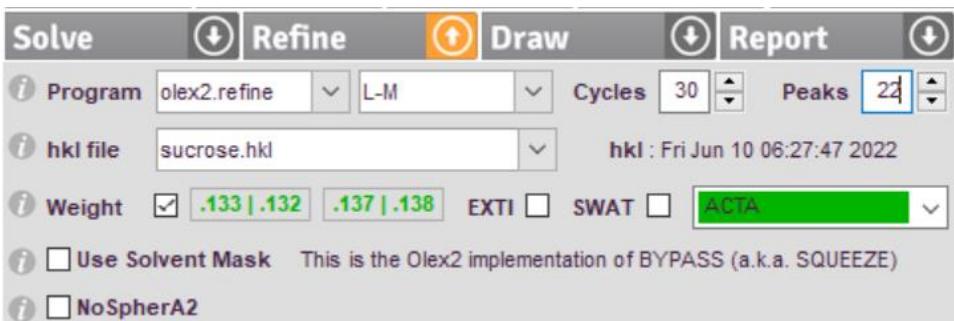
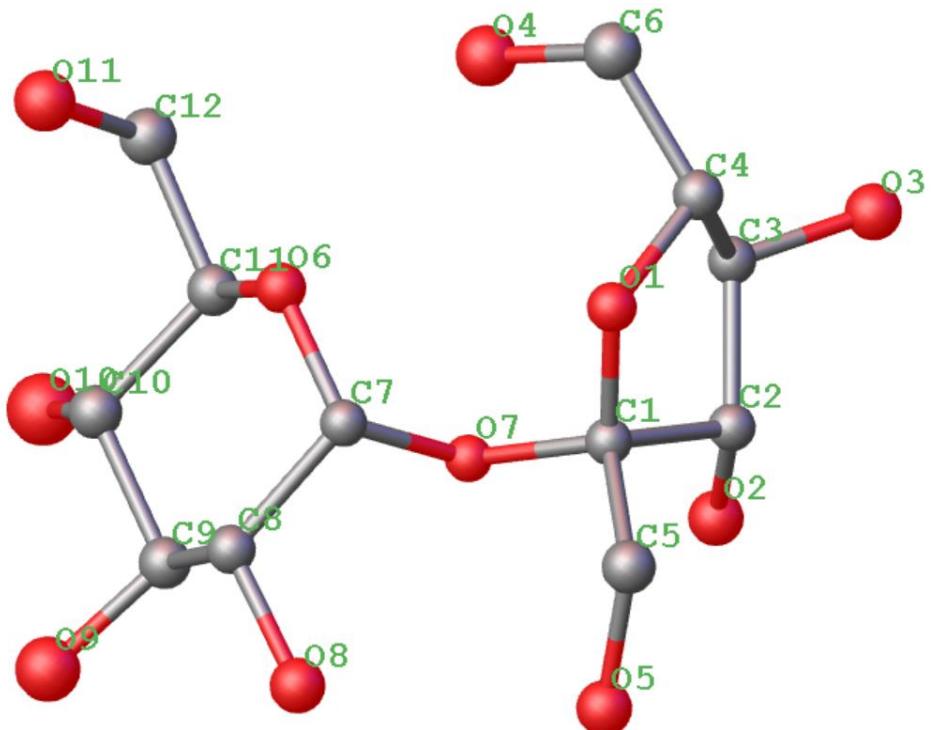
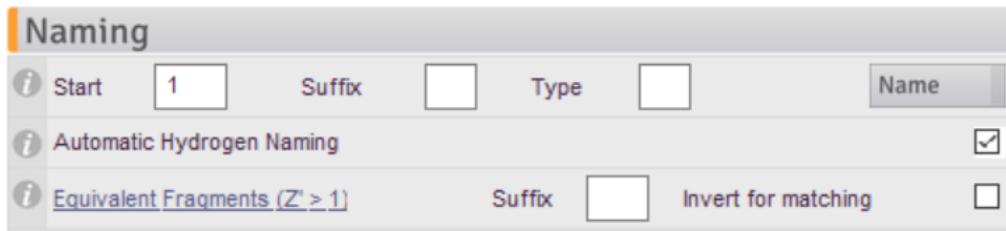
- o Copy the sucrose folder from C:\Program Files\Olex2-1.5-alpha\sample_data\sucrose> to a working area on your computer
- o Open the .res file on Olex2-1.5alpha
- o Use Model/Reset to revert to the raw data + ins file
- o Solve with shelXT or olex2.solve



- o If you check-off “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

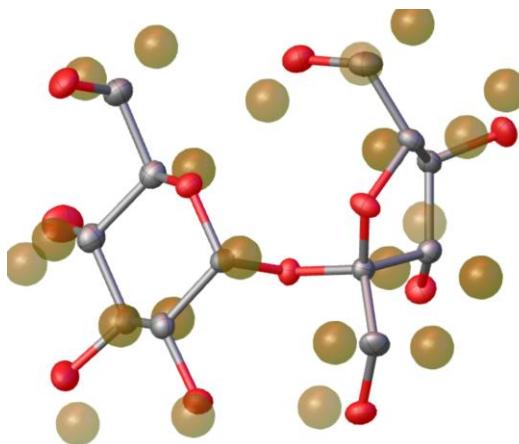
Label atoms in a defined way (no change later!)

- 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

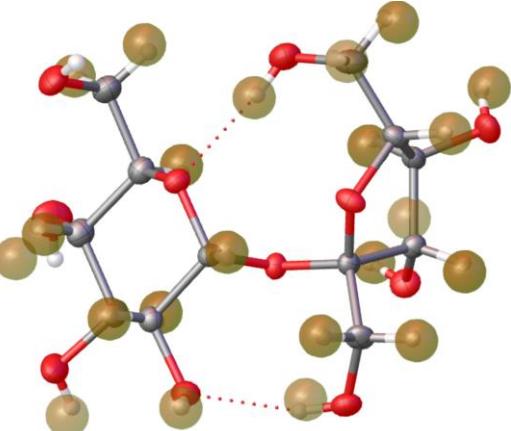


- o Check (once, carefully) names; then turn off
- o Type 'anis' at the command line
- o Type 'rigu' to apply RIGU 0.004 as a default to the non-H atoms
- o Type ^R to initiate refinement
- o Review the results (next slide)

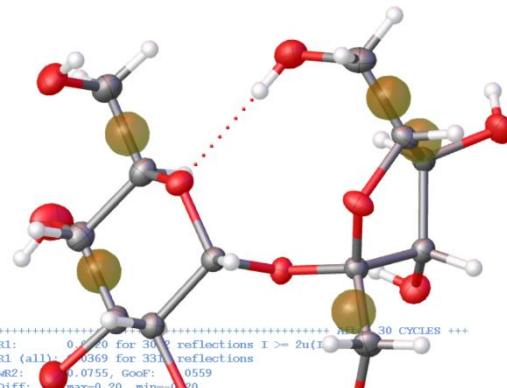
Adding H atoms and completing the IAM model



Difference map with 22 peaks

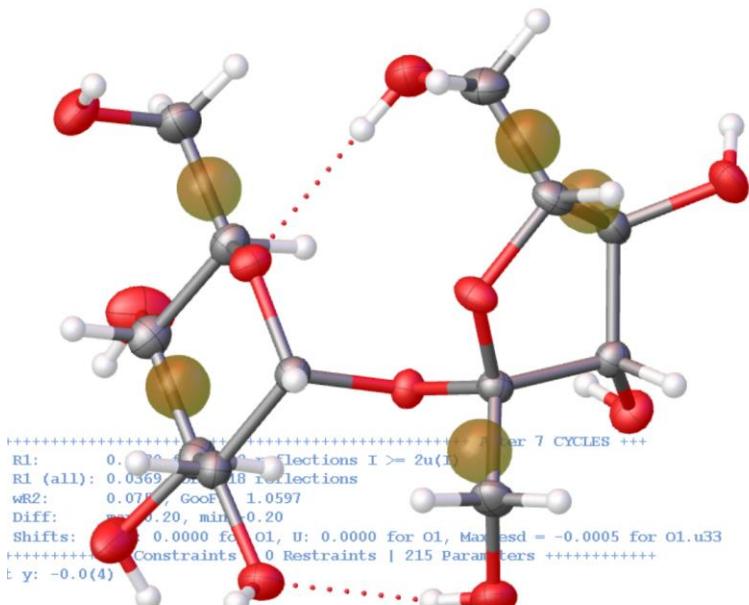


"hadd" command – insert into Qs



```
RL: 0.000 for 303 reflections I >= 2u(I)
R1 (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.



```
RL: 0.000 for 303 reflections I >= 2u(I)
R1 (all): 0.0369 for 331 reflections
wR2: 0.0755, GoOF: 1.0597
Diff: max=0.20, min=-0.20
Shifts: x: 0.0000 for O1, U: 0.0000 for O1, Max esd = -0.0005 for O1.u33
Constraints: 0 Restraints | 215 Parameters
t: v: -0.0(4)
```

Sucrose

C₁₂H₂₂O₁₁

P2₁

a = 7.7727(9)	$\alpha = 90^\circ$	Z = 2	R ₁ 3.20 %	
b = 8.7216(11)	$\beta = 102.983(11)^\circ$	Z' = 1	wR ₂ 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

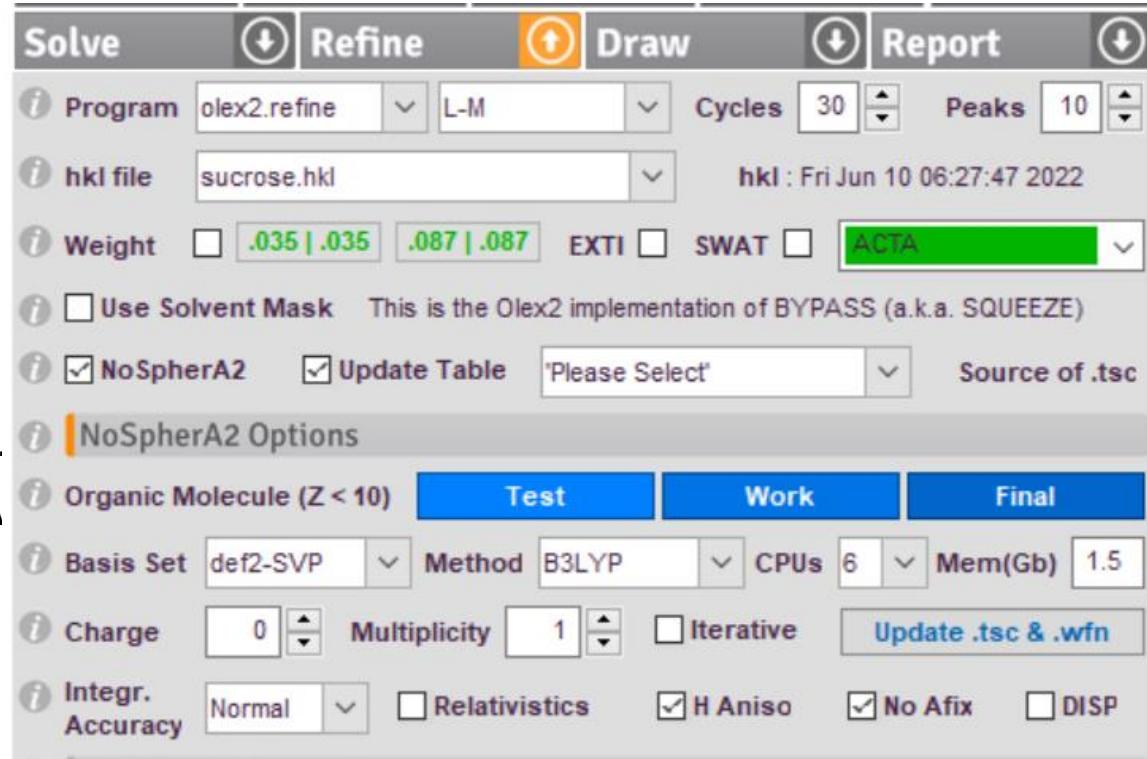
QC to CH H C F X Z= 1 OK

MAP Diff Show Map Map Settings

- All the steps learned in previous tutorial are completed and the result is reviewed.
- CheckCIF report is generated and carefully reviewed.
- 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.

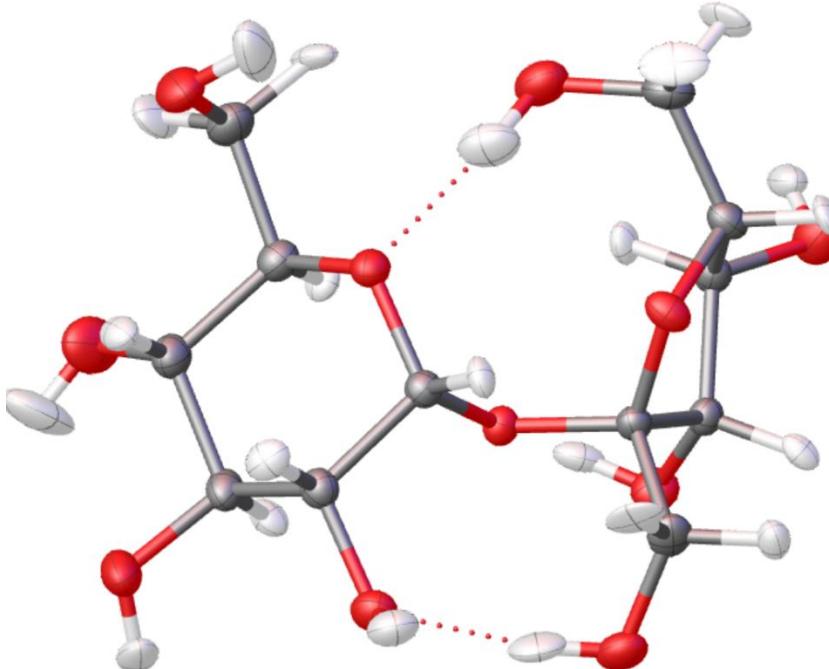


Finalizing HAR refinement model

- o Command: "sel \$H"; Command: anis-H; Command: "sel \$H"; command RIGU 0.002
- 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
```

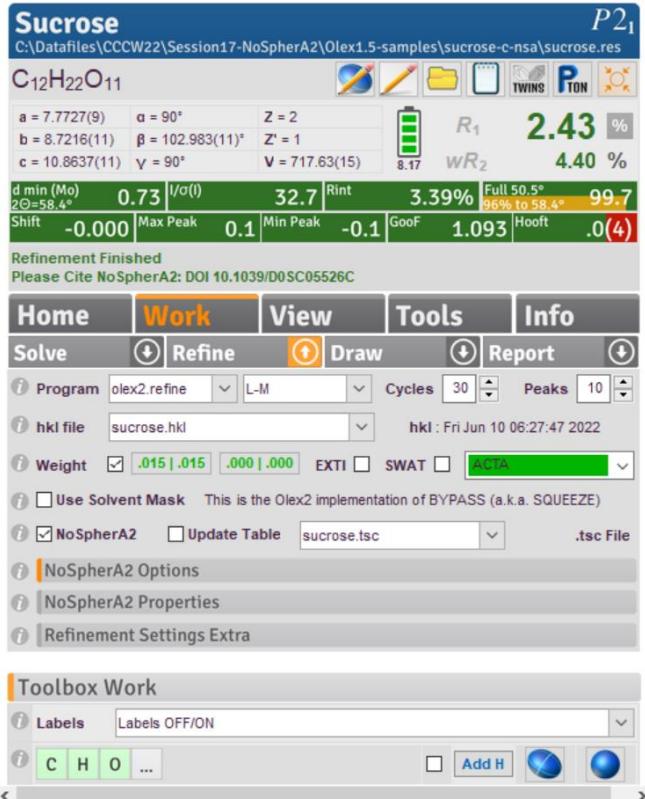
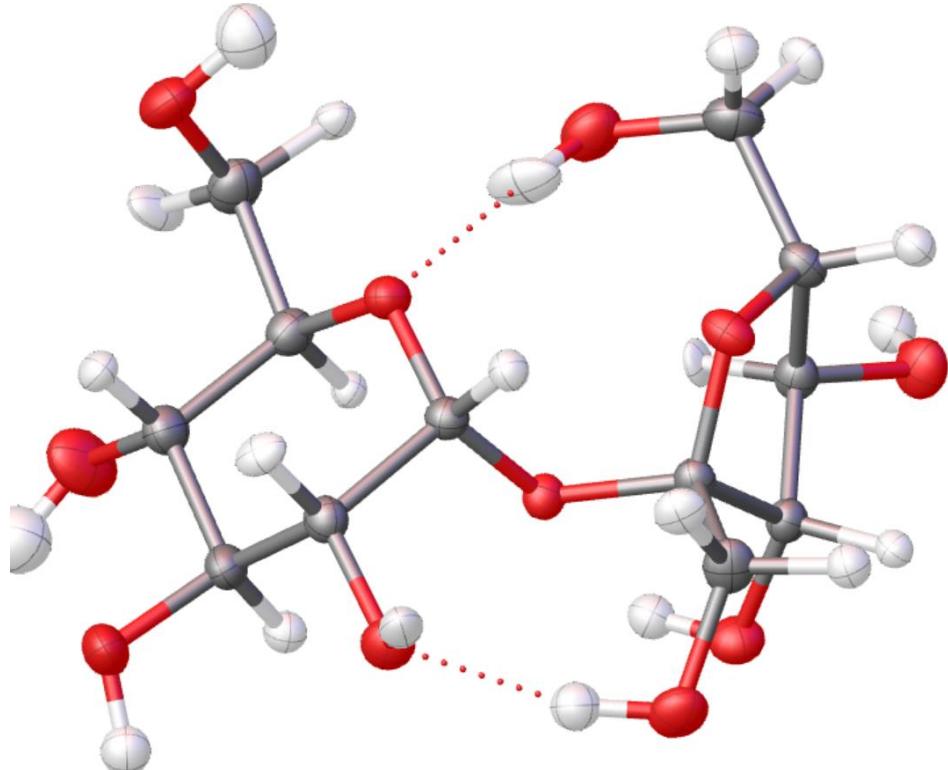


- o Now Refine this model →
- o Further cycles of olex2.refine are used till all fields are green.
- o Do a thorough check that everything looks good.
- o Then you will be ready for the **Final** model refinement, higher level of DFT and 10 repetitions. This takes about 6 minutes to run.
- o Final polishing can be done such by constraining H atoms using ISOR restraints.
- o Assess and validate the final model in the usual way (CheckCIF; review the final derived parameter).



Validation and evaluation of the model

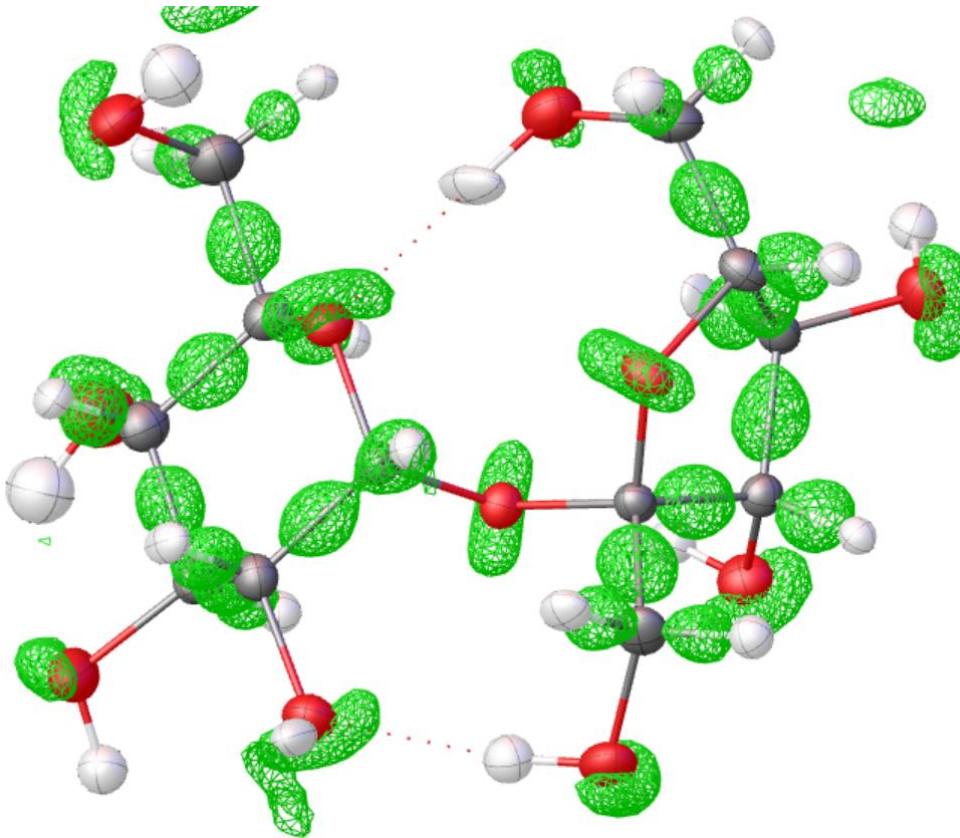
- o The final R_1 has lowered from 3.20 to 2.43%
- o Max and min peaks are reduced from 0.2 to -0.1 e/Å³



- o CheckCIF is passable – an ALERT B for the data/parameter ratio
- o Another for one outlier in the C–H bond length of 1.17 Å
- o 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?

- o 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 ¹	0.913(19)	1.97(2)	2.8750(15)	170.5(15)
O3	H3	O5 ²	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 ³	0.97(2)	1.90(2)	2.8639(16)	171.2(16)
O9	H9	O2 ⁴	0.941(17)	1.931(17)	2.8653(13)	171.7(16)
O11	H11	O9 ⁵	1.06(3)	1.82(3)	2.8463(17)	164(2)

¹-X,-1/2+Y,-Z; ²-1+X,+Y,+Z; ³1+X,+Y,+Z; ⁴1-X,-1/2+Y,-Z; ⁵1-X,1/2+Y,1-Z

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

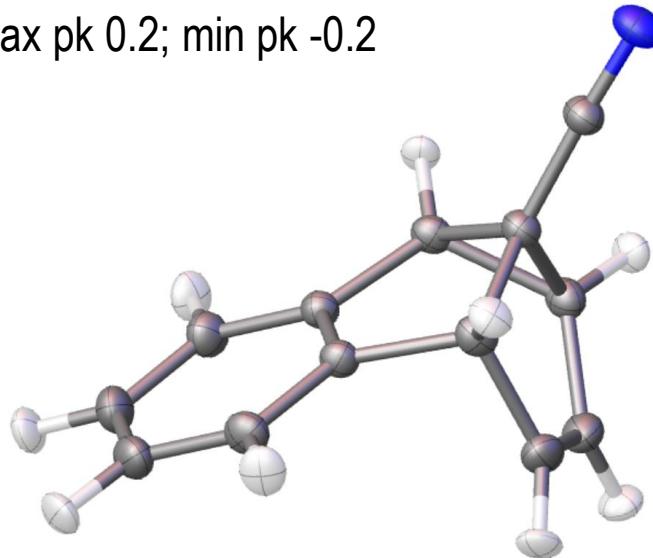
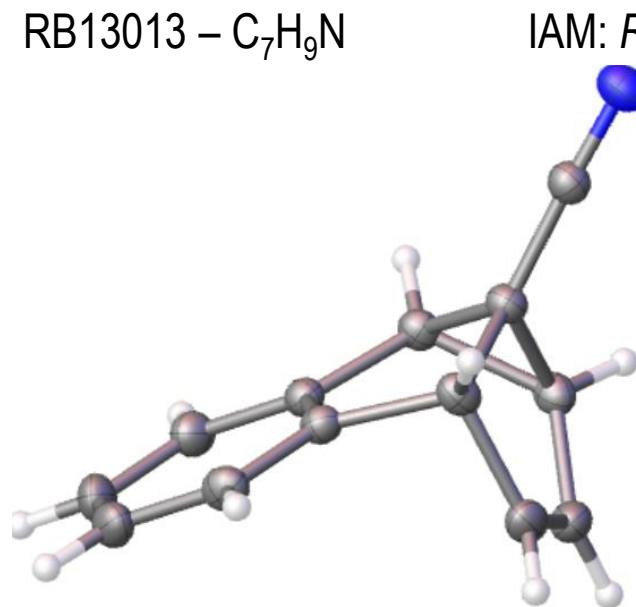
F. H. Allen and I. J. Bruno, Acta Cryst. 2010, B66, 380.

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

More examples from our laboratory

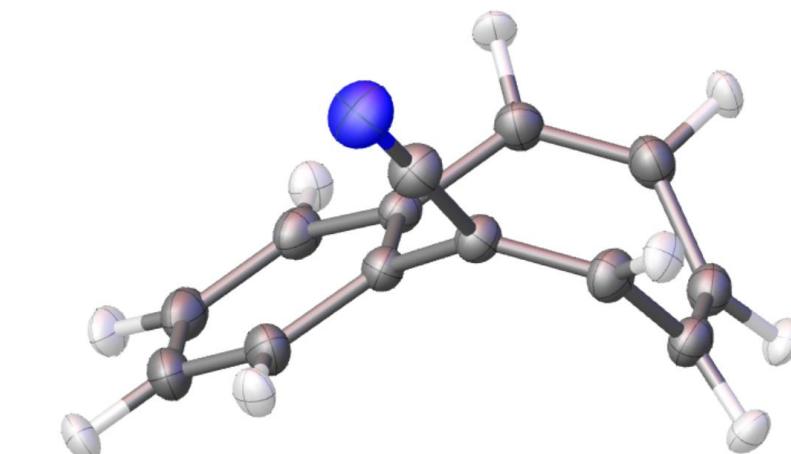
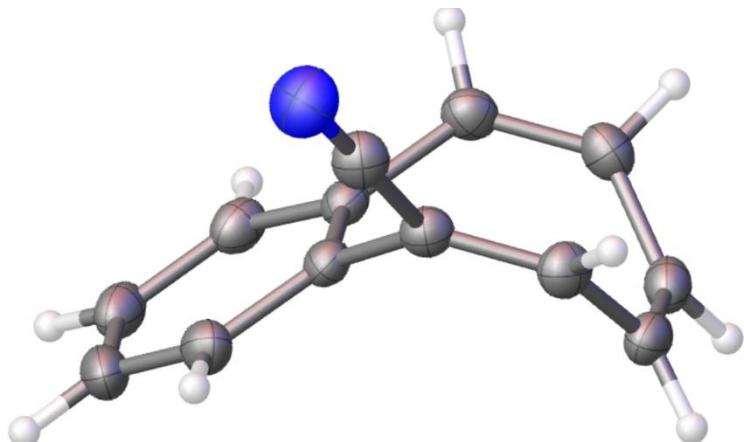
o RB13013 – C₇H₉N

IAM: $R_1 = 3.33$; Max pk 0.2; min pk -0.2



o RB13009 – C₇H₉N

IAM: $R_1 = 3.68$; Max pk 0.2; min pk -0.2



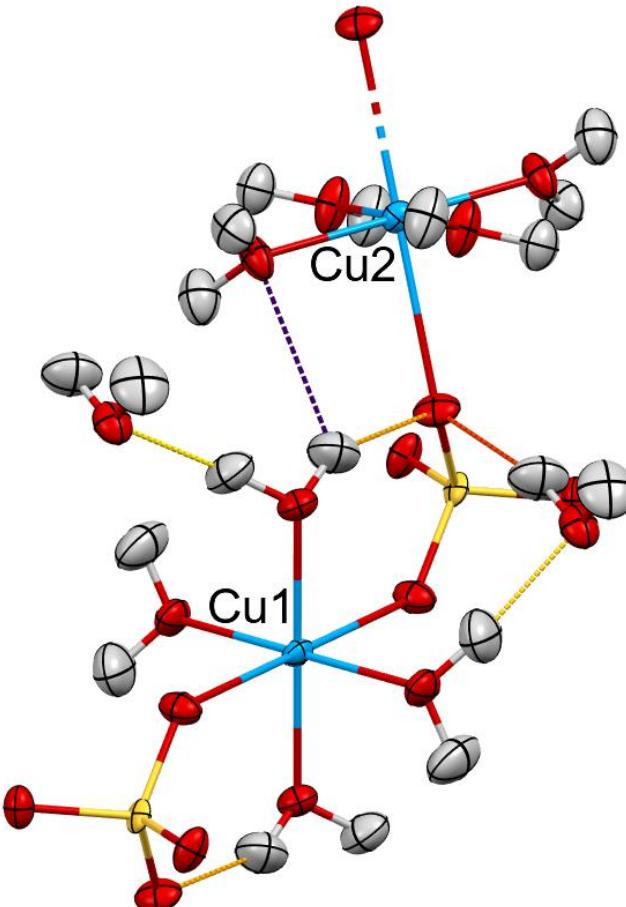
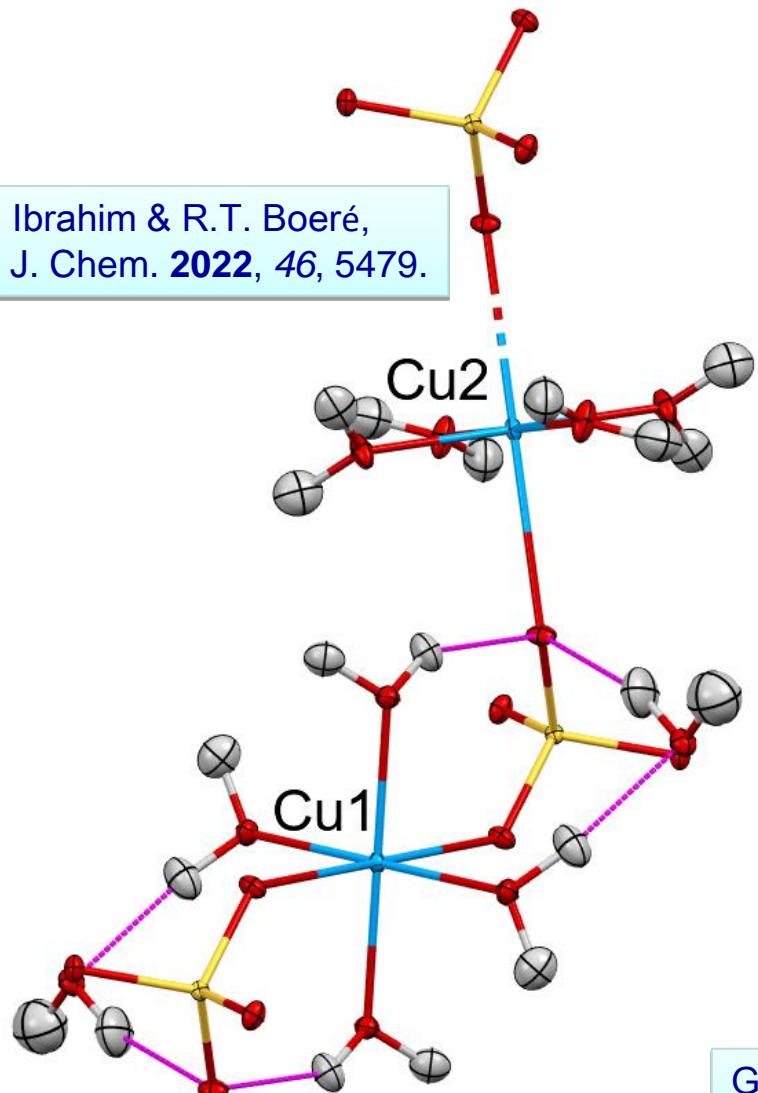
NoSpherA2: $R_1 = 1.25$; Max pk 0.1; min pk -0.1

More examples from our laboratory

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)

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: $R_1 = 3.7\%$ -0.1 (RT)

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



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

Another example: Ph2-3,5ditBuOHP=O practice

- o $\text{C}_{21}\text{H}_{31}\text{O}_2\text{P}$ 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.

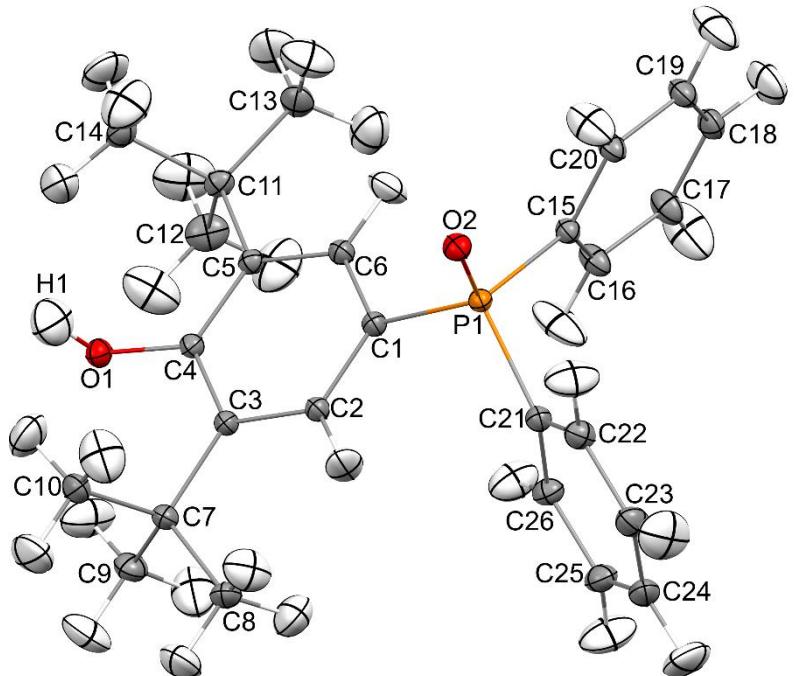


Table 6. Mean Element Bond Lengths (Å) from NoSphereA2 X-ray Refinement and Neutron Diffraction

bond type (100 K)	mean (s.u.) in this work	mean (s.u.) in Allen ^a
tertbutyl C– sp^3 -H	1.089(3)	1.084(13)
TMS C– sp^3 -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)

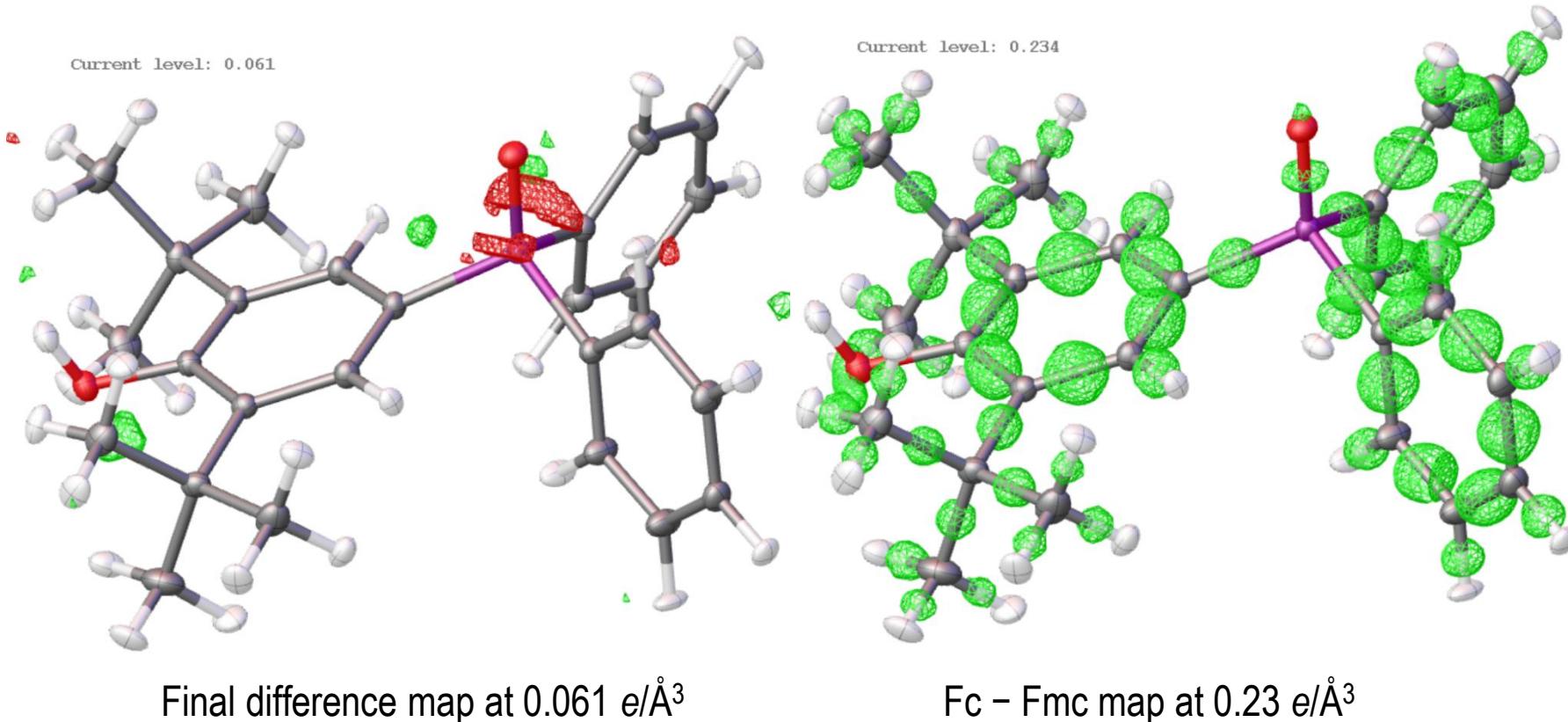
^aNeutron data from a critical review of the literature for experiments taken at $60 \leq T \leq 140$ K. Allen, et al. (2010).⁵²

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

- 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.

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.



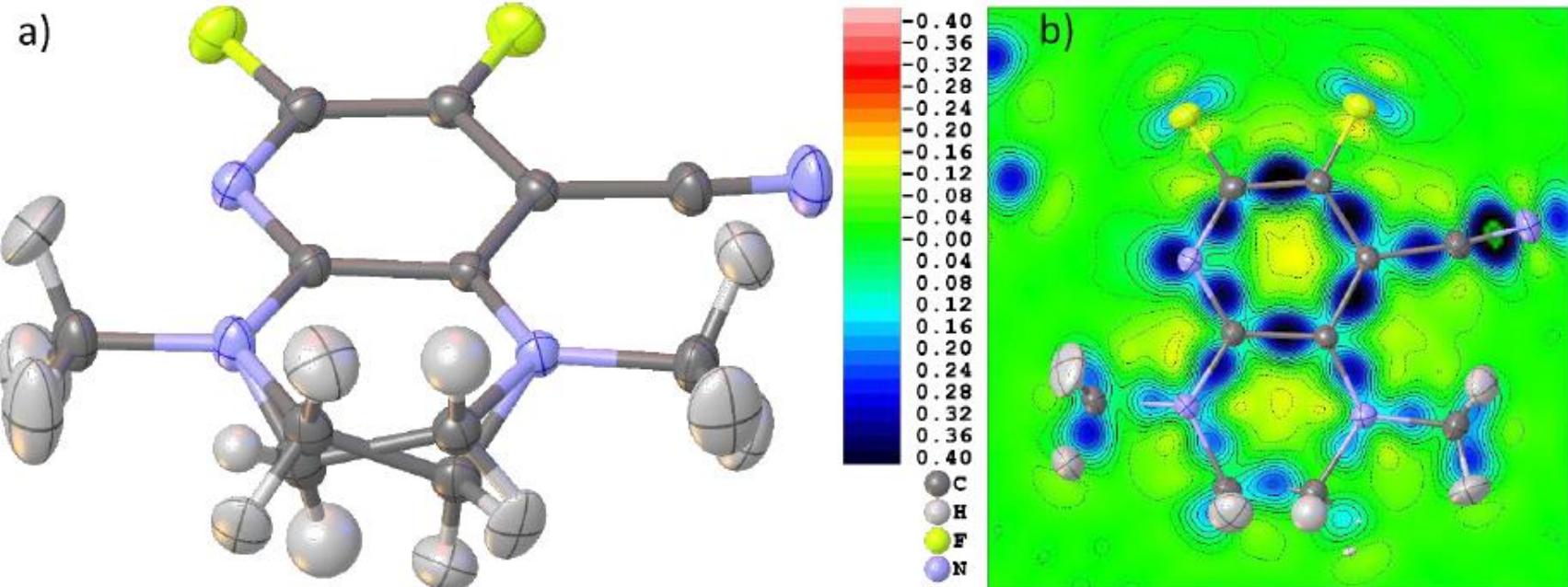
- o An excellent crystal collected under our normal target of 5-fold redundancy and 0.70 Å resolution on Cu gives, with maybe 1 H of work in refinement, gives an accurate depiction of bonding electron density.

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

This is another data test set from Olex2

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

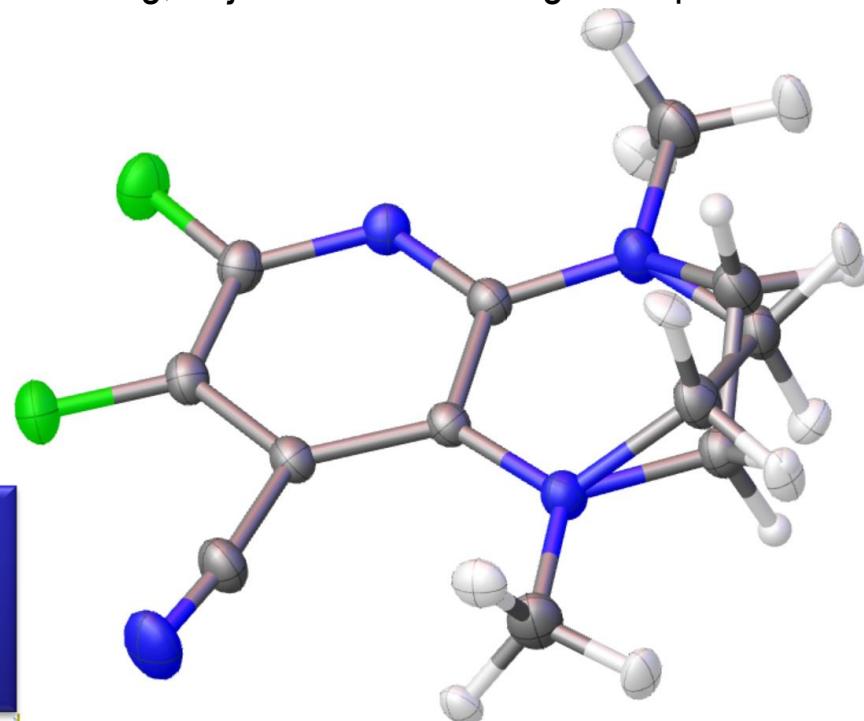
- o There is a conformational disorder in the -CH₂CH₂- component of the hydrated pyrazine
- o Minor component is 11.8% and the major 88.2%
- o Even with this disorder the major component can be anisotropically refined
- o The low occupancy second component is isotropically refined
- o The dynamic deformation density distribution in the main molecular plane of the molecule is also shown, i.e. the difference electron density of the HAR and the IAM including the effect of refined atomic displacement parameters.



This one you can also try yourself

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!