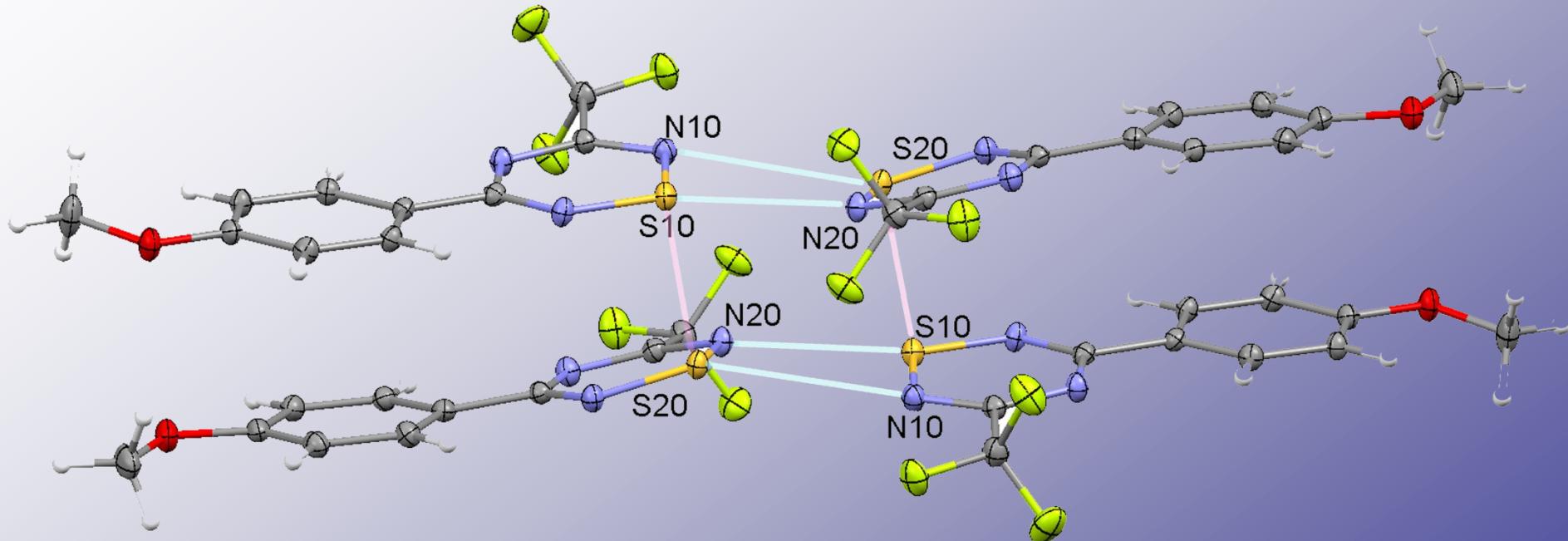


Canadian Chemical Crystallography Workshop 2022



Tutorial 2 – NoSpherA2

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

Setting the Context

- o There are *many* purposes for crystallography in research.
- o Different 'quality markers' are appropriate to these various purposes.
- o I recommend reading Amber Thompson's review for a perspective on the quality/benefit ratio of any sample that you need information on.

CRYSTALLOGRAPHY REVIEWS

2019, VOL. 25, NO. 1, 3–53

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



Taylor & Francis
Taylor & Francis Group



Chemical Crystallography: when are 'bad data' 'good data'?

Amber L. Thompson 

Chemical Crystallography, Chemistry Research Laboratory, Oxford, UK

- o So, many very weak crystals and 'crystallographically flawed' samples can be investigated.
- o Nevertheless, *many crystals* are produced with excellent crystallinity and which diffract very well.
- o Such datasets contain much more information than standard model for refinement is able to use.

Setting the Context (2)

- o Make use of *all* help – including CheckCIF!
- o Different ‘quality markers’ are appropriate to these various purposes.
- o Understand the *purpose* of the ‘validation report’ – e.g. read Ton’s paper:



Research paper

What makes a crystal structure report valid?

Anthony L. Spek

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

- o <https://checkcif.iucr.org/>
- o HTML option is helpful to get links for the meaning of the Alerts.
- o Try to fix all level ‘A’ and ‘B’ alerts.
- o If they cannot be fixed, use the Validation Response Form



A service of the
International Union of Crystallography

checkCIF reports on the consistency and integrity of c

Please upload your CIF using the form below. 

File name:

No file selected.

Select form of checkCIF report

- HTML
- PDF
- PDF email (recommended for CIFs that might take

Select validation type

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

Output Validation Response Form

- Level A alerts only
- Level A and B alerts
- Level A, B and C alerts
- None

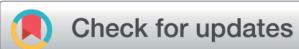
The original paper that introduced NoSpherA2

Chemical
Science



EDGE ARTICLE

[View Article Online](#)
[View Journal](#) | [View Issue](#)



Cite this: *Chem. Sci.*, 2021, 12, 1675

All publication charges for this article have been paid for by the Royal Society of Chemistry

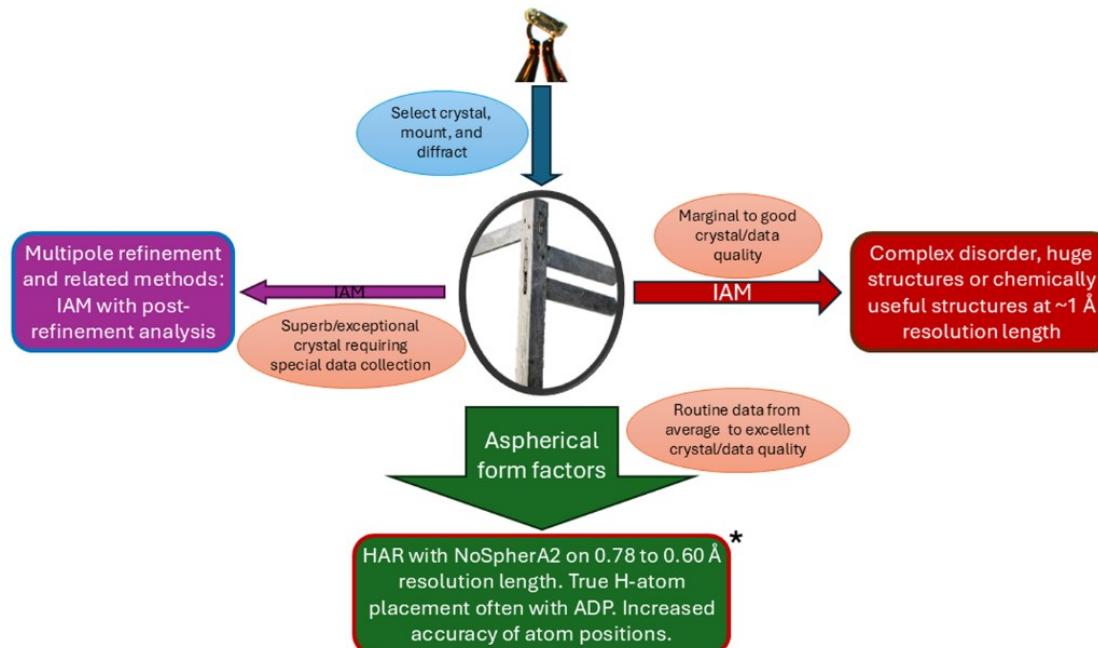
Accurate crystal structures and chemical properties from NoSpherA2†

Florian Kleemiss, ^a Oleg V. Dolomanov, ^b Michael Bodensteiner, ^c Norbert Peyerimhoff, ^d Laura Midgley, ^d Luc J. Bourhis, ^e Alessandro Genoni, ^f Lorraine A. Malaspina, ^a Dylan Jayatilaka, ^g John L. Spencer, ^h Fraser White, ⁱ Bernhard Grundkötter-Stock, ^j Simon Steinhauer, ^j Dieter Lentz, ^j Horst Puschmann ^{*b} and Simon Grabowsky ^{*a}

- Detailed 18 page article, with historical introduction to the state of the field in 2020.
- Thorough explanation of the theory for how NoSpherA2 works.
- Seven pages of applications that illustrate the ability of NoSpherA2 in very different kinds of substances: organic crystals; boron hydrides, CaF₂, osmium hydride.
- Ability to refine H-atom xyz coordinates reliably – to ‘neutron’ bond lengths.
- Possibility of anisotropic displacement ellipsoids for H-atoms (impossible in the IAM).
- Correct treatment of non-bonded ED: lone pairs, metal *d* and *f* electrons



The “crossroads” in small molecule X-ray crystallography



- ❑ Majority of modern datasets on decent-quality crystals contain more information than “independent atom model” (IAM) is able to harness.
- ❑ 110 years of misplacing H atoms in crystal structures by IAM ignoring polarization and partial charges.
- ❑ Written as a guide for ‘users’ – i.e. practical introduction for chemical crystallographers.

N.D.D. Hill and R.T. Boeré, *Chemistry–Methods*, 2025, 5, e202400052.

Why use NoSpherA2 for model refinement? (using non-spherical atom scattering factors)

What it is NOT

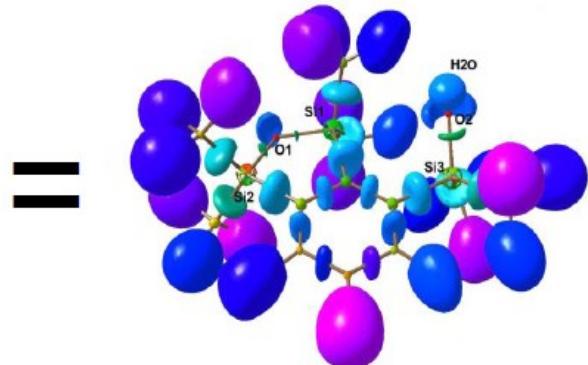
- o It is not a ‘magic fix’ for poor-quality diffraction data.
 - Identifying compounds from marginal crystals has important place (Amber Thompson article – previous slide).
 - Modern XRD instrumentation is extremely good.
 - Increased brilliance of Cu K α or RA is a real advantage here.
 - Beamlines (Canadian Light Source)
- o Low resolution experiments with 1 Å resolution – gain little from NoSpherA2!
- o It is *not* a computational structure determination!

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.

NoSpherA2 is a product of *quantum crystallography*

- Recognition that XRD *experimentally* measures electron density (ED)
- Quantum mechanics *computes* ED by the square of the wavefunction



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_{calc} term?

- Structure factor equation (a phase rule):

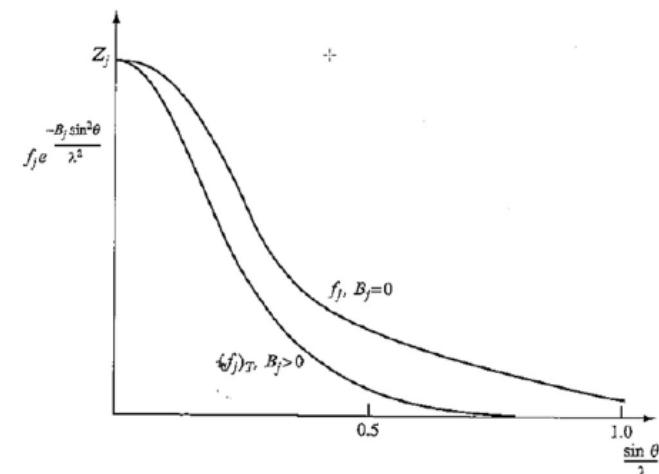
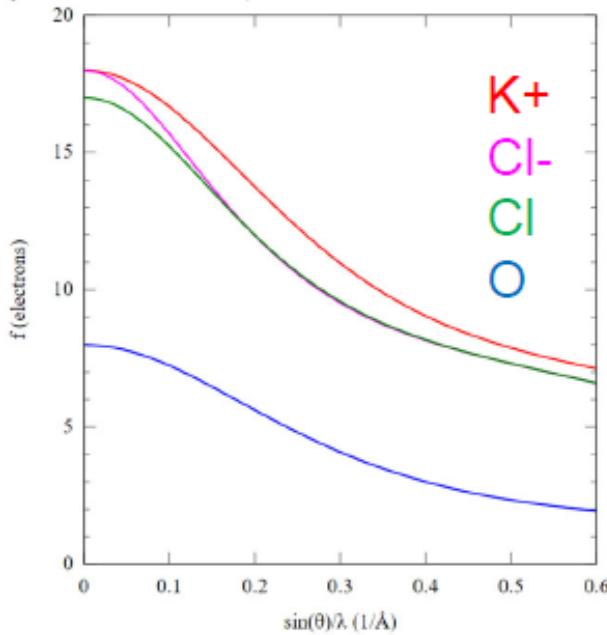
$$F_{hkl} = \sum_{j=1}^N f_j e^{[2\pi i(hx_j + ky_j + lz_j)]}$$

- 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 $\sin \theta / \lambda$

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



Where do atomic scattering (form) factors come from?

- 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

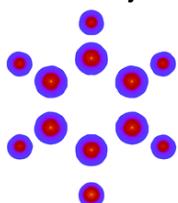
P. J. Brown, A. G. Fox, E. N. Maslen, M. A. O'Keefe and B. T. M. Willis. *International Tables for Crystallography* (2006). Vol. C, ch. 6.1, pp. 554-595
 [doi:10.1107/97809553602060000600]

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



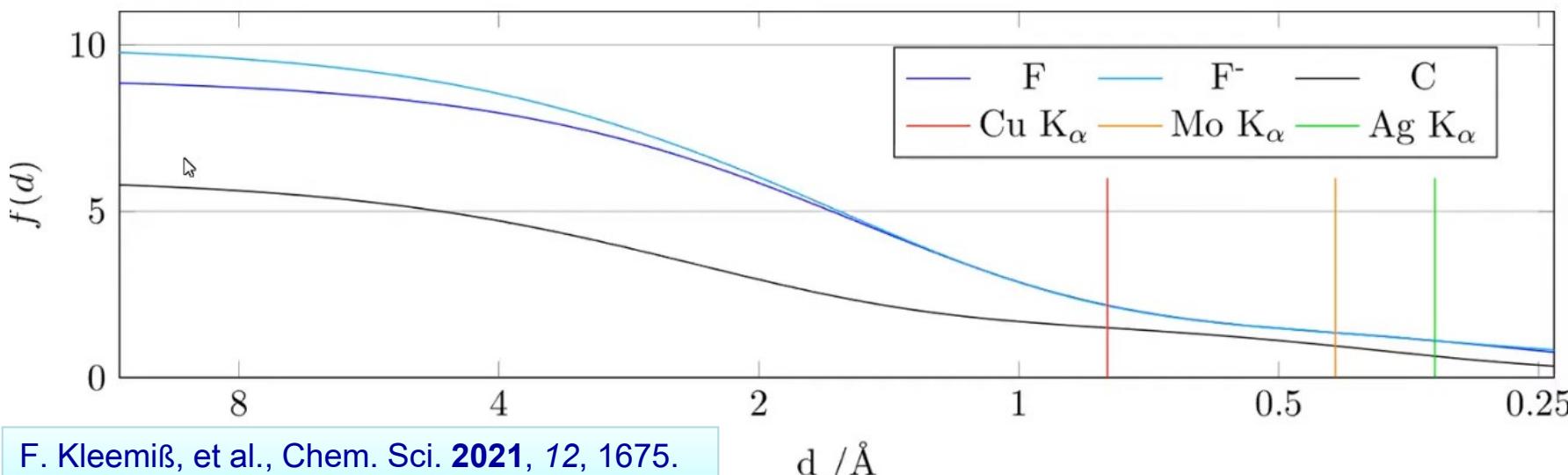
IAM = Independent Atom Model

- o **IAM is useful (reasonably accurate and very effective) but it is an approximation:**
 1. Treats each atom of a given element identically (and as a neutral atom)
 2. Ignores subtle (and gross) differences in atomic charge distributions in space
 3. (Must) treat hydrogen as if the nucleus is at the centre of the polarized ED

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!

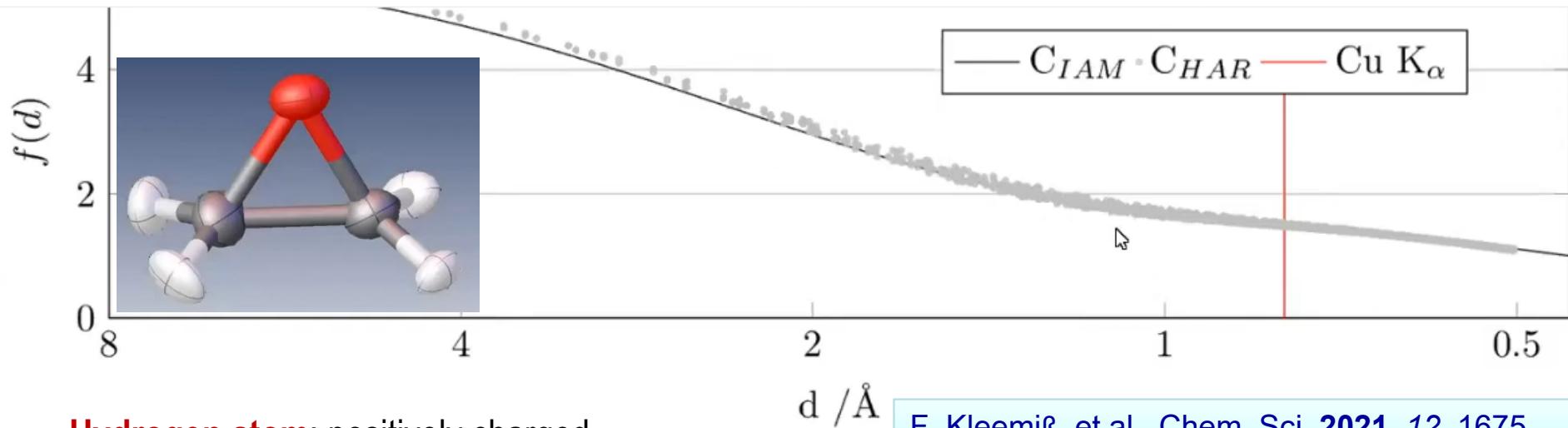


F. Kleemiss, et al., Chem. Sci. 2021, 12, 1675.

Aspherical form factors also important for neutral atoms

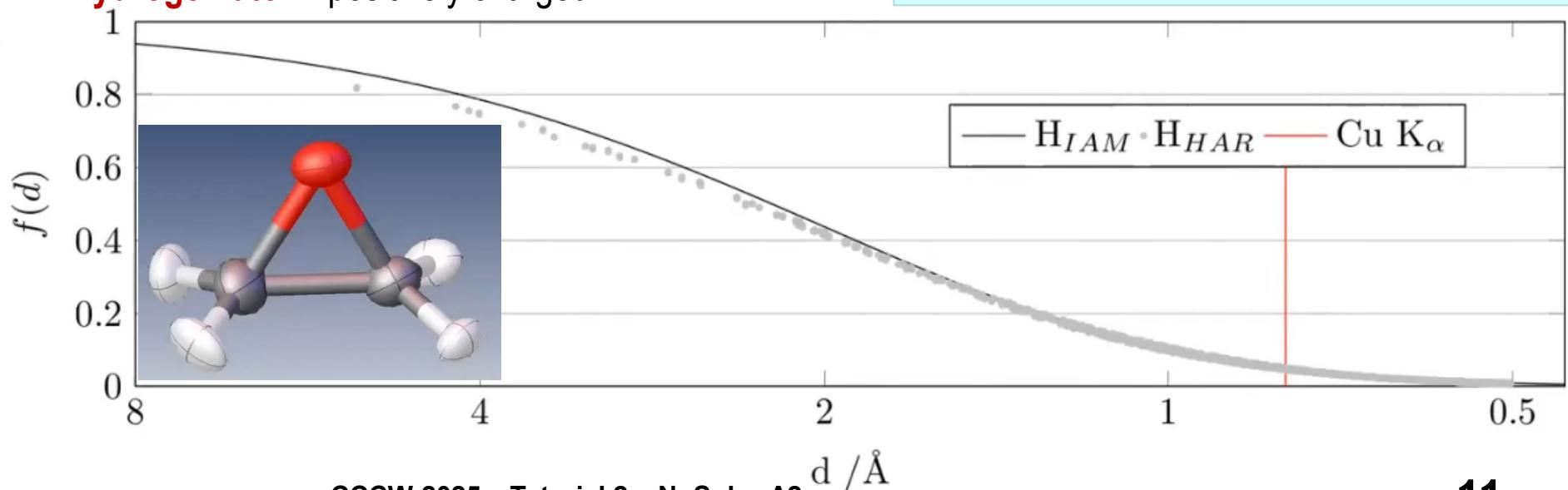
- Scattering factor curves for the IAM model (solid line) versus the corrected asphericity

Carbon atom: negatively charged



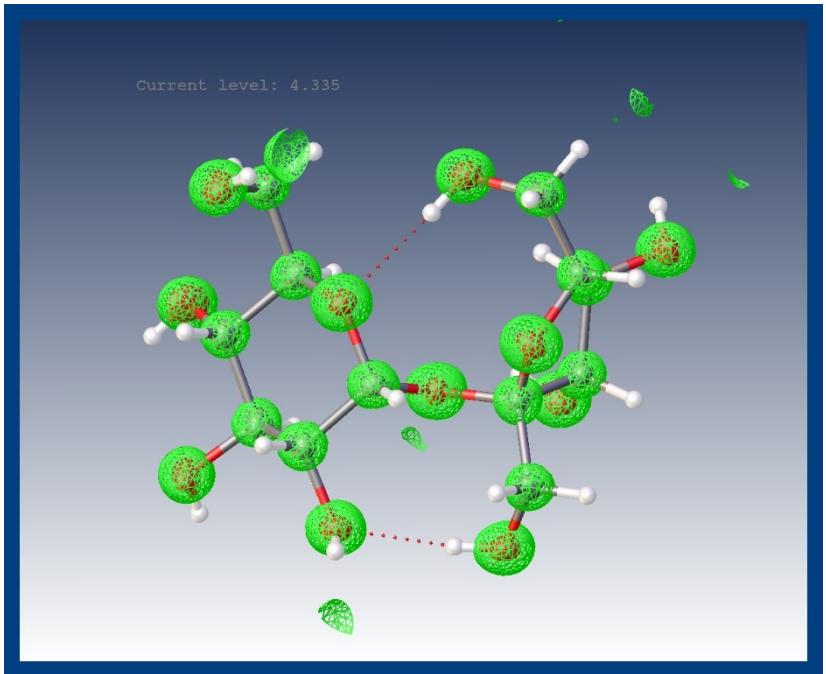
Hydrogen atom: positively charged

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

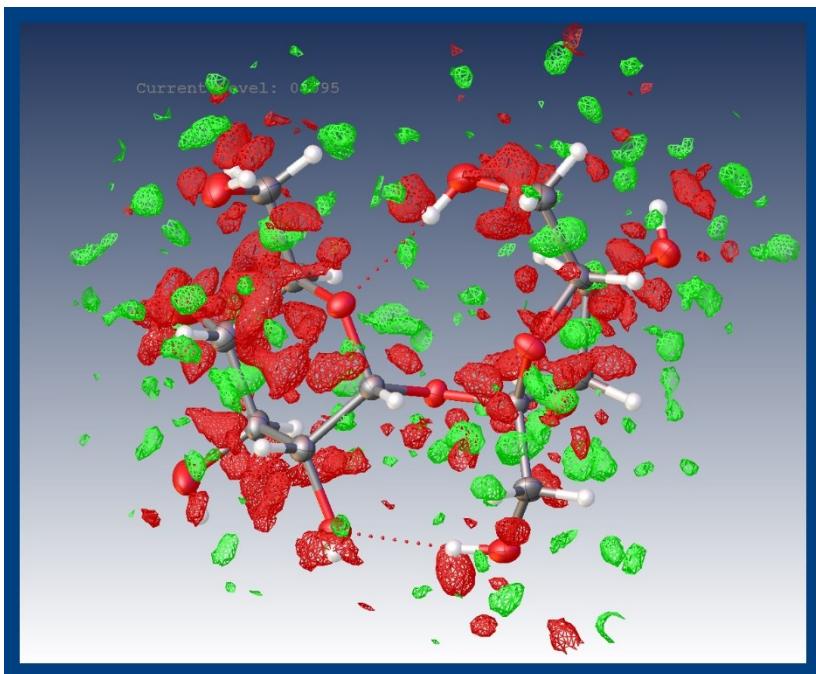


Consequences of the IAM approximation

1. Residual electron density:



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



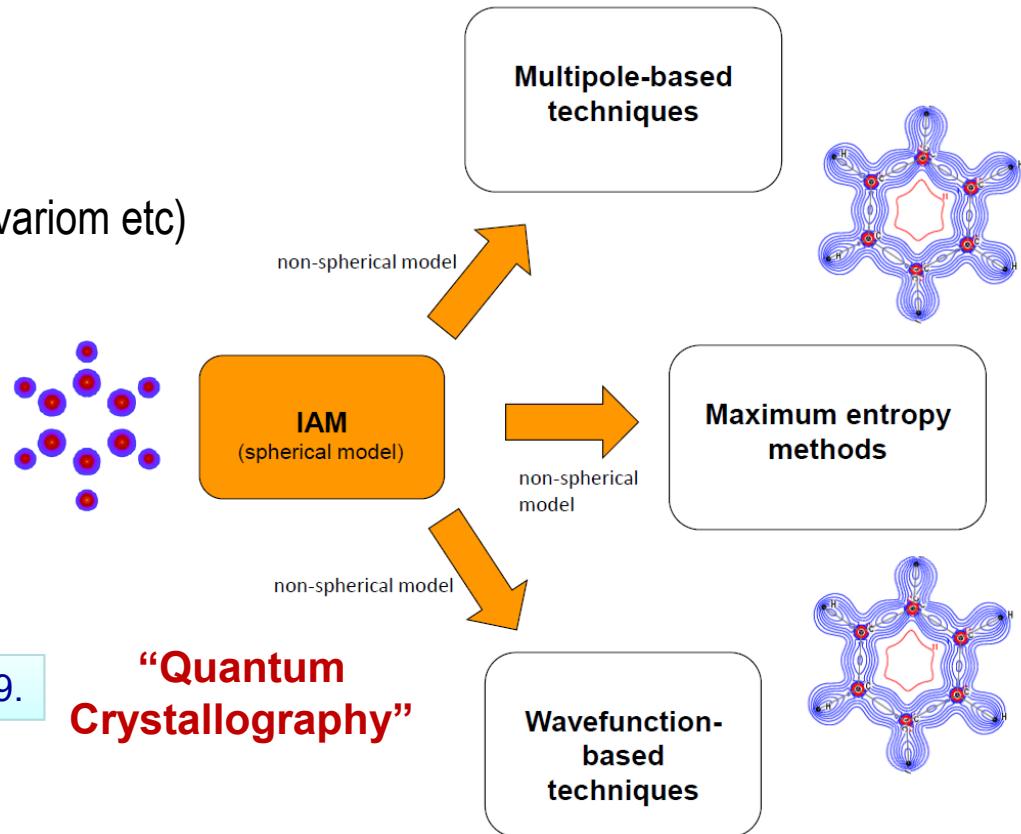
Sucrose: final difference map of $[F(\text{obs}) - F(\text{calc})] = \text{unassigned ED}$

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

4. If the data quality is good, we are losing structural information.
5. Atoms defined by low electron counts are poorly resolved – hydrogens!

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)



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

Check for updates

Chemistry—Methods

Concept
doi.org/10.1002/cmtd.202400052

 Chemistry Europe
European Chemical Societies Publishing

www.chemistrymethods.org

J-166

Small Molecule X-ray Crystal Structures at a Crossroads

Nathan D. D. Hill^[a] and René T. Boeré^{*[a]}

What does 'HAR' mean?

It is the *method of charge partitioning* which Hirshfeld proposed and called it the 'stockholder partitioning scheme'

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

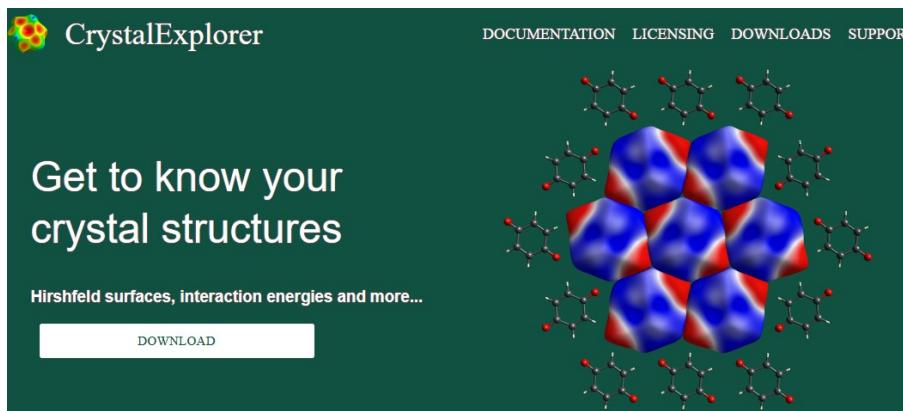
THEORETICA CHIMICA ACTA
© by Springer-Verlag 1977

Bonded-Atom Fragments for Describing Molecular Charge Densities

F. L. Hirshfeld

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

Hirshfeld terminology is also used in crystallography for Hirshfeld Surface Analysis of charges on atoms within a crystal unit cell: <https://crystalexplorer.net>



Why use Aspherical Form Factor Refinements?

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

Aspherical Form Factor 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.

Getting Started

- o Obtain Olex2 1.5: <https://www.olexsy.org/>



- o There are two versions: Olex2 1.5 (*standard version*) – I will run this only in the tutorial.
- o Olex2 1.5-alpha – a developer version that is more frequently updated with the latest tweaks

Windows

The Olex2 installer for windows is a small program which offers various installation options. You can select which [version](#) you would like to install.

You can start with the **default settings** and explore different version when you need them. For example, you may want to run the *alpha* version of Olex2 as well as the *Release* version. In any case, each major version of Olex2 will automatically update within its own series.

Welcome to Olex2

Install Olex2 here: C:\Program Files\Olex2...
 Use proxy server (URL or user:password@URL)

Olex2 repository location: C:\Users\Hrist\Downloads\plex2-win64.zip
 Always Monthly Create shortcut Create desktop shortcut
 Daily Never Exit Install

The windows installer

Installing ORCA

- o There are instructions in the Program for this (multi-hour 3 or 4 part download)
- o For help and further guidance, see: <https://www.olexsys.org/categories/nosphera2/>

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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?](#)

Scroll down...

- [ORCA: How do I install ORCA?](#)
- [Basis Set: When to use which Basis Set](#)
- [Errors during partitioning: What to do in case of errors during the partitioning \(NoSpherA2-Output\)](#)
- [Errors during the wavefunction calculation: What to do in case of errors during the wavefunction calculation](#)

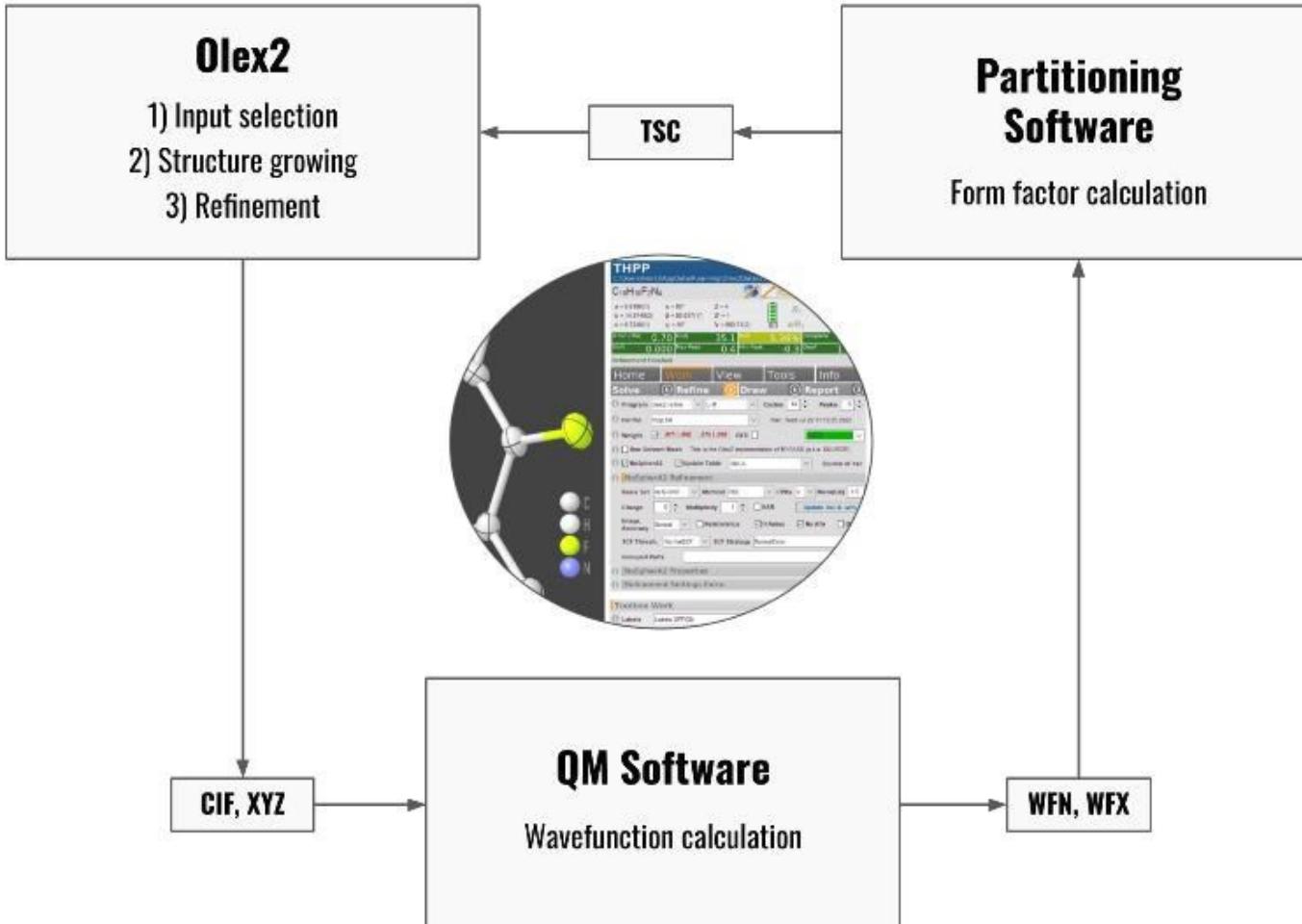
 Edit this page

 Create project issue

 Helpdesk

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

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):

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 accomodate the significant DFT and NoSphereA2 operations and store the results.

File Explorer View (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 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.

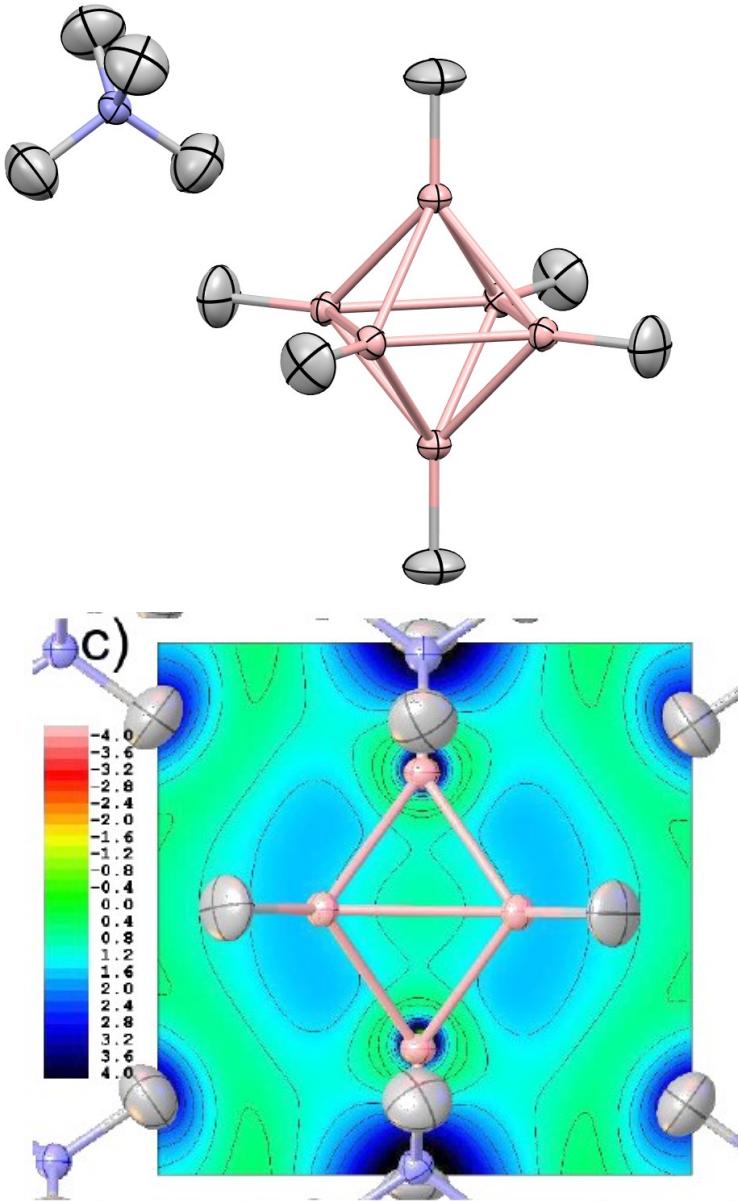
Claims for outstanding results: NoSpherA2 + olex2.refine



- 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

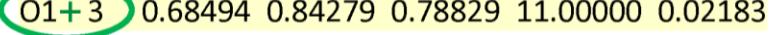
F. Kleemiß, et al., Chem. Sci. **2021**, 12, 1675.

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



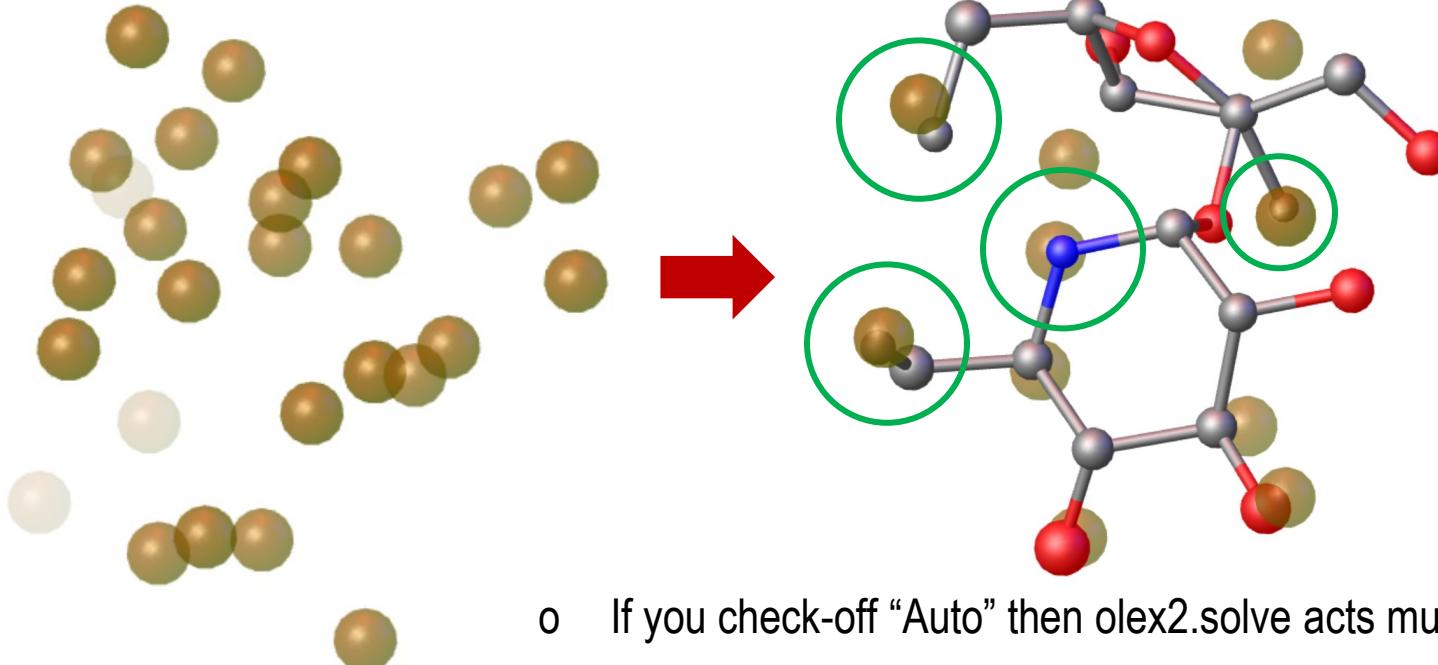
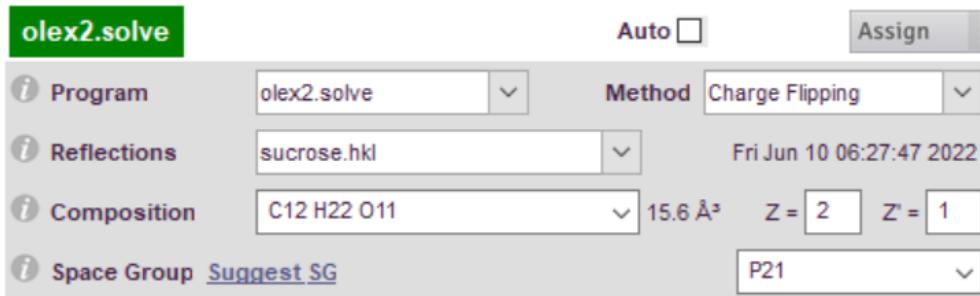


University of Lethbridge NoSpherA2 Workflow

1. Completed best possible structure model in the IAM, including disorder (90-98% accurate, compact, reliable, familiar).
2. Refine using olex2.refine (G-N level) with **spherical form factors** and save the file for future use.
Ensure atoms are all named correctly (**atom labels used in DFT to define the .tscb, so do not rely only on SFAC code!**)
 In .ins file, “3” identifies this atom as O and label is arbitrary.
3. **Implement NoSpherA2 in a copy of the original folder.**
Easily done in Olex2 or in FileExplorer; ability to move rapidly between IAM and HAR models.
4. Relax the E-H distances in AFIX (> NeutronHDist, followed by 1 cycle of L.S.)
5. Select NoSpherA2 and choose the computational software and level of theory (see step 7).
Maintain AFIX; maintain isotropic displacements of H-atoms.
6. Obey the laws of quantum mechanics: no half bonds(!); correct spin multiplicity!!!!
DFT calculation always *works on what's on the screen* so use GROW to define a computationally compatible molecule
DFT can even calculate aggregates – H-bonded dimers
7. Step through the three 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
After successful .tscb calculation, refine to XRD convergence.
Relax desired AFIX by selection followed by > AFIX 0 at command line and refine again
(usually all E-H; however, refrain for minor disorder components and/or poorly-defined hydrocarbon portions).
Relax selected H atoms to anisotropic displacement ellipsoids (select, then > ANIS -h) and refine.
Examine model carefully (badly-behaved H atoms benefit from RIGU for E-H combo's and/or ISOR restraints).
Final: iterative (10x) for final polishing of the model.
8. Validate model by careful examination of final model, submitting to IUCr CheckCIF, etc.

Demonstrate with Sucrose

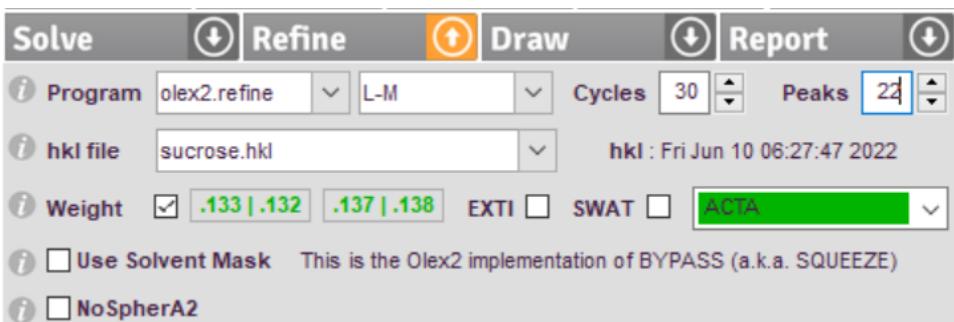
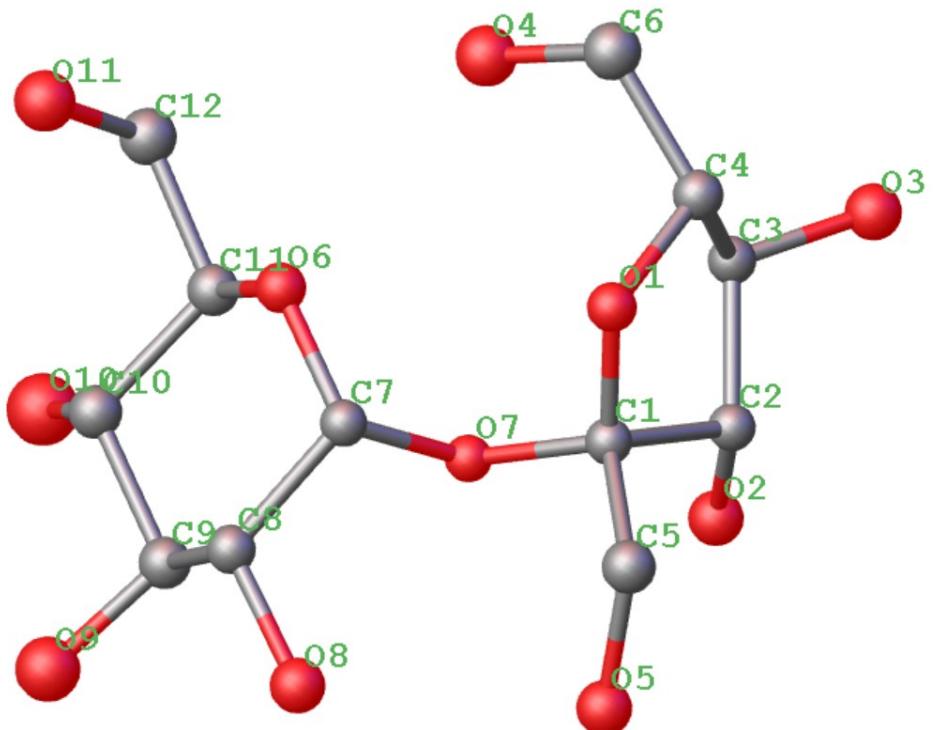
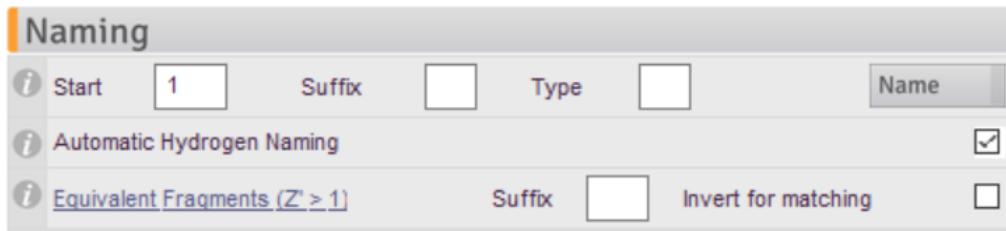
- o Copy the sucrose folder from C:\Program Files\Olex2-1.5-alpha\sample_data\sucrose> to a working area on your computer
- o Open the .res file on Olex2-1.5alpha
- o Use Model/Reset to revert to the raw data + ins file
- o Solve with shelXT or olex2.solve



- 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

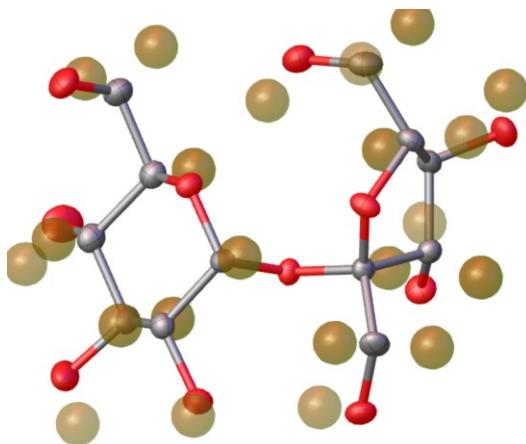
Label atoms in a defined way (no change later!)

- 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

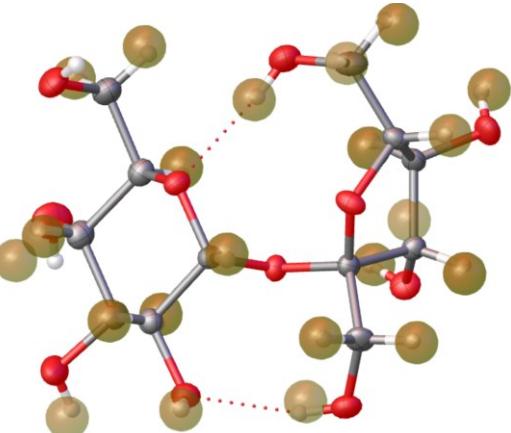


- o Check (once, carefully) names; then turn off
- o Type 'anis' at the command line
- o Type 'rigu' to apply RIGU 0.004 as a default to the non-H atoms
- o Type ^R to initiate refinement
- o Review the results (next slide)

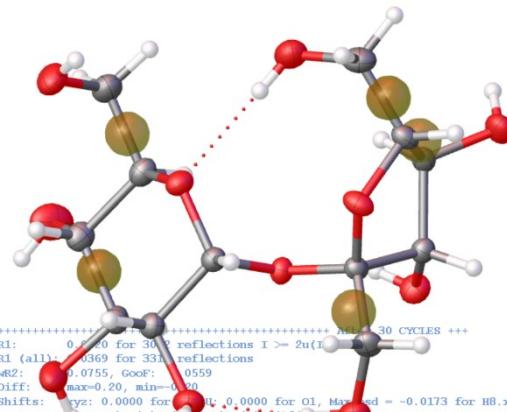
Adding H atoms and completing the IAM model



Difference map with 22 peaks

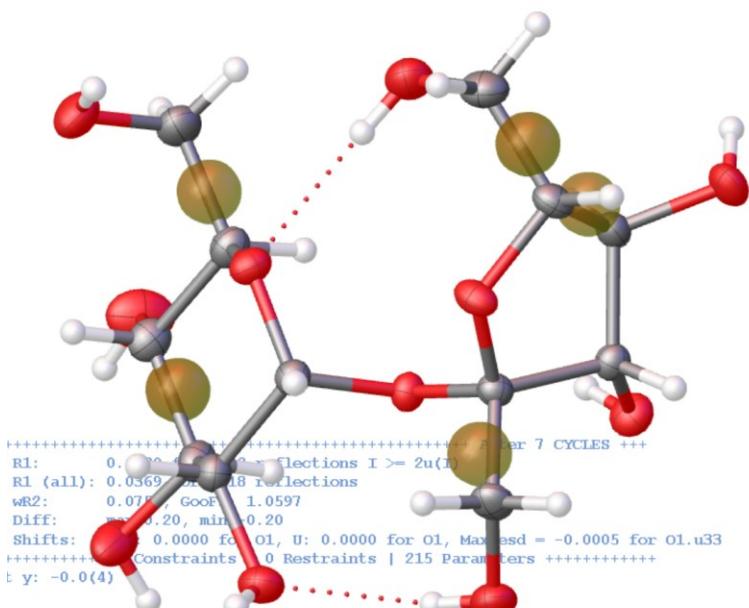


"hadd" command – insert into Qs



```
RL: 0.000 for 303 reflections I >= 2u(I)
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 H8.x
t: v: -0.0(4)
```

Refined with 5 highest Q peaks.



Sucrose

C:\Datafiles\CCCW22\Session17-NoSpherA2\Olex1.5-samples\sucrose-c\sucrose.res

P2₁

C₁₂H₂₂O₁₁

a = 7.7727(9) α = 90° Z = 2
 b = 8.7216(11) β = 102.983(11)° Z' = 1
 c = 10.8637(11) γ = 90° V = 717.63(15)

R₁ 3.20 % wR₂ 7.54 %

d min (Mo) 0.73 I/σ(I) 32.7 Rint 3.39% Full 50.5° 99.7%

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 <input checked="" type="checkbox"/> .035 .035	.087 .087	EXTL	SWAT	<input checked="" type="checkbox"/> SQUEEZE					
<input type="checkbox"/> Use Solvent Mask This is the Olex2 implementation of BYPASS (a.k.a. SQUEEZE)									
<input type="checkbox"/> NoSpherA2									
Refinement Settings Extra									

Toolbox Work

Labels Labels OFF/ON

C H O ... Add H

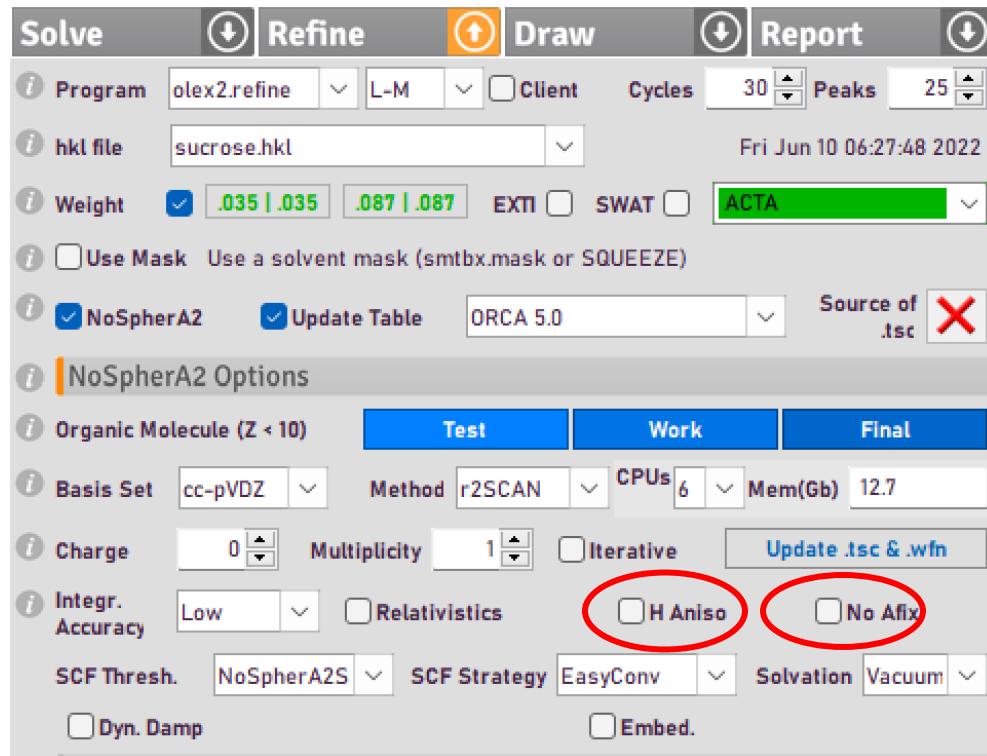
QC to CH H C F X Z=1 OK

MAP Diff Show Map Map Settings

- o All the steps learned in previous tutorial 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 ***H-Aniso & No Afix are unchecked***
- o Then, press on **Test** and refine.
- o It takes about 8 s 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 (20 s), 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. Also worth testing Solvation: *use water!*

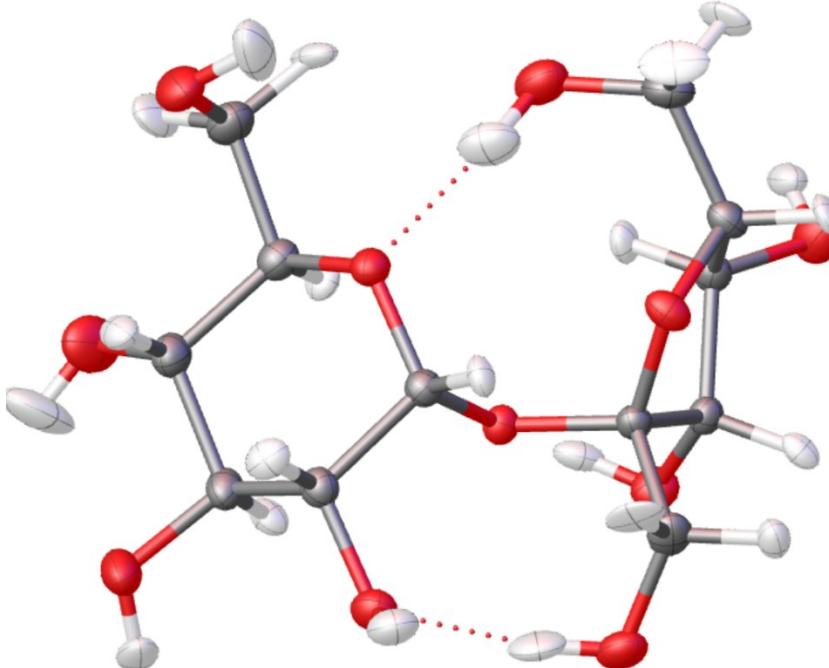


Finalizing HAR refinement model

- o O–H are mostly a bit less than 1.0 Å, and the C–H are around 1.1 Å
- o Since there are expected to be H-bonds, also do command: “HTAB”; 7 are found

Processing HTAB with max D–A distance 2.9Å 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
```

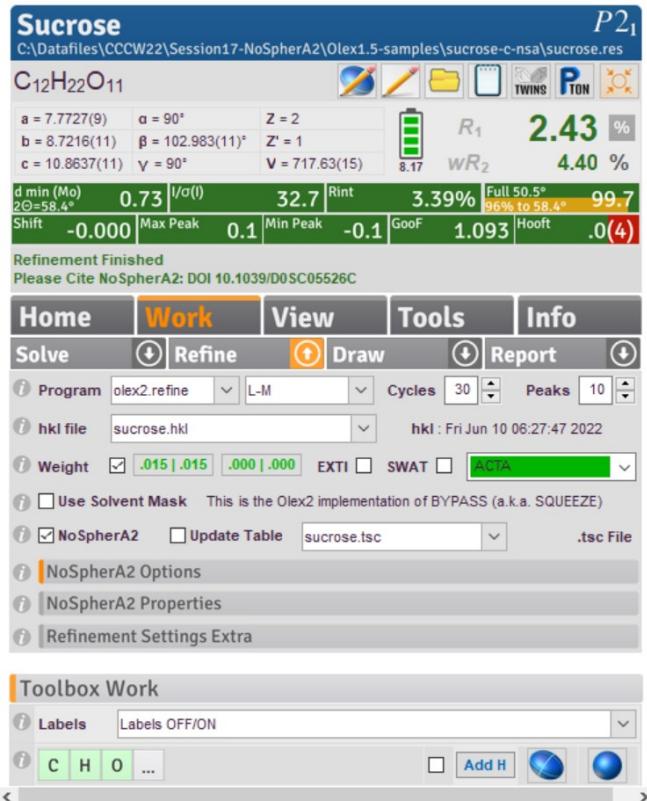
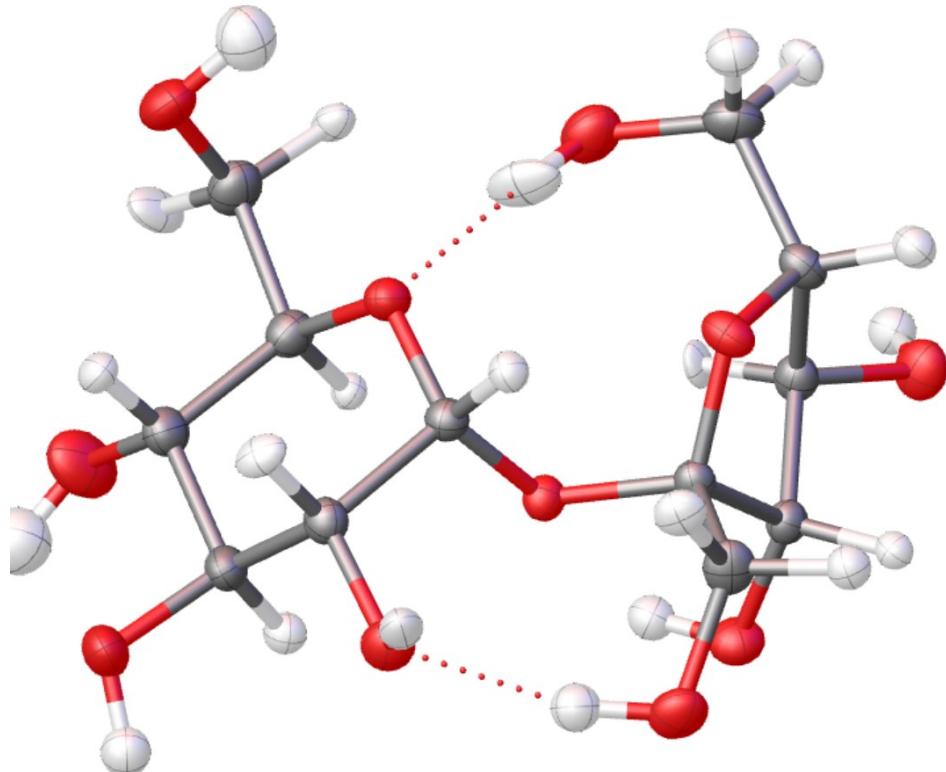


- o Now Refine this model →
- o Further cycles of olex2.refine are used till all fields are green.
- o Do a thorough check that everything looks good.
- o Then you will be ready for the **Final** model refinement, higher level of DFT and 10 repetitions. Suggestion Water solvation to improve ED calculation. This takes about 4 minutes to run.
- o Final polishing can be done such by constraining H atoms using ISOR restraints and/or restrain E–H bonds using the RIGU command (individually per bond pair).
- o Assess and validate the final model in the usual way (CheckCIF; review final derived values).



Validation and evaluation of the model

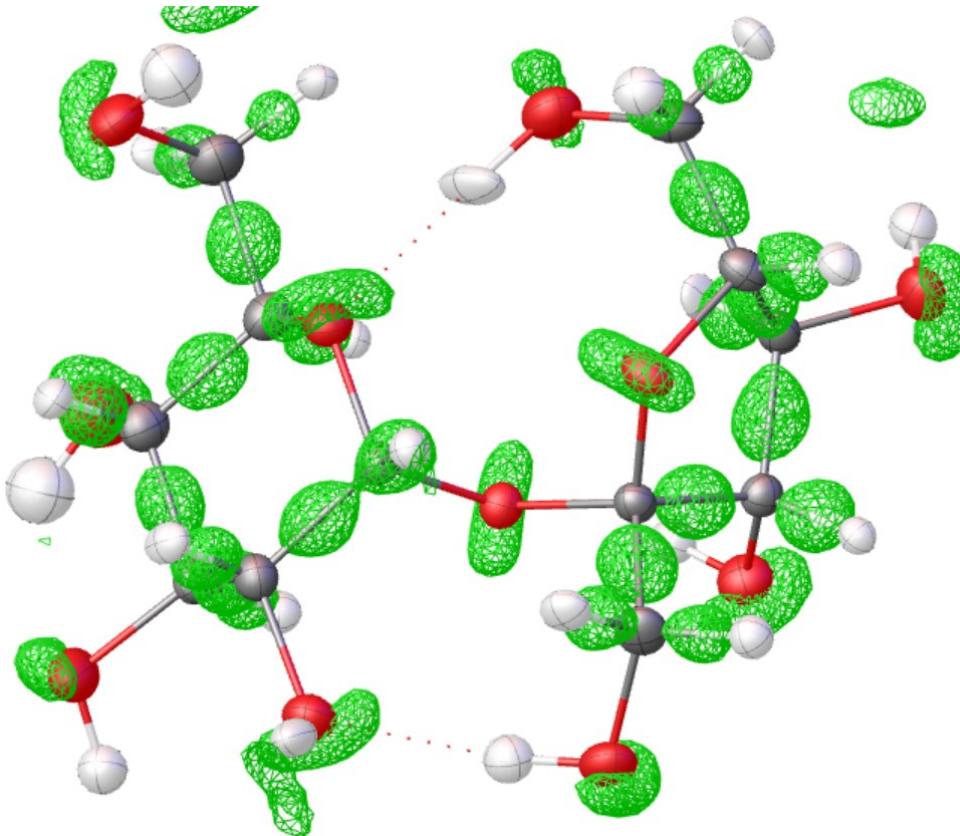
- o The final R_1 has lowered from 3.20 to 2.43%
- o Max and min peaks are reduced from 0.2 to -0.1 e/Å³



- 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?

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

H-bonds in NoSpherA2

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)
O11H11O9 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

H-bonds in IAM

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	O4 ¹	0.8200	2.049(2)	2.851(2)	165.55(17)
O4	H4	O9 ²	0.8200	2.046(2)	2.8654(16)	177(2)
O5	H5	O7 ³	0.8200	2.0479(19)	2.8585(19)	169.73(18)
O7	H7	O1	0.8200	2.049(3)	2.8576(17)	168.8(15)
O8	H8	O10 ⁴	0.8200	1.914(3)	2.7243(17)	169.7(14)
O9	H9	O8 ⁵	0.8200	2.067(3)	2.8777(19)	169.5(15)
O10H10O5			0.8200	2.011(5)	2.7826(18)	156.5(12)

¹-X,1/2+Y,2-Z; ²-X,-1/2+Y,1-Z; ³1+X,+Y,+Z; ⁴-1+X,+Y,+Z; ⁵-1-X,-1/2+Y,1-Z

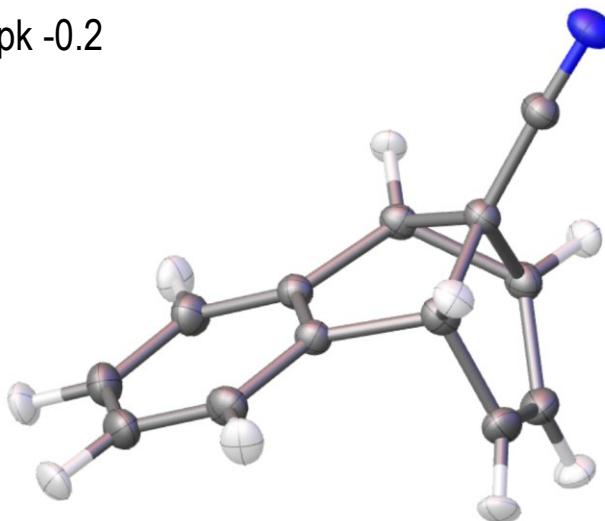
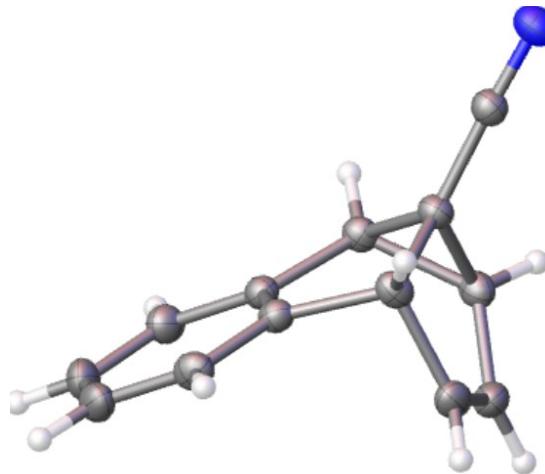
- The average O-H bond distance is 0.97 ± 0.05 Å
- The ‘gold standard’ for OH bond distances comes from neutron data: 0.99 ± 0.03 Å.

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.

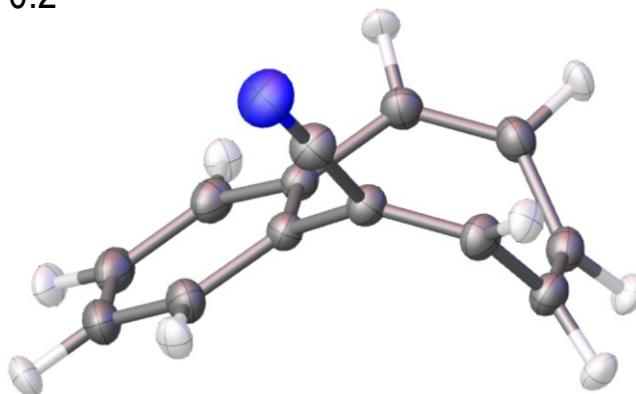
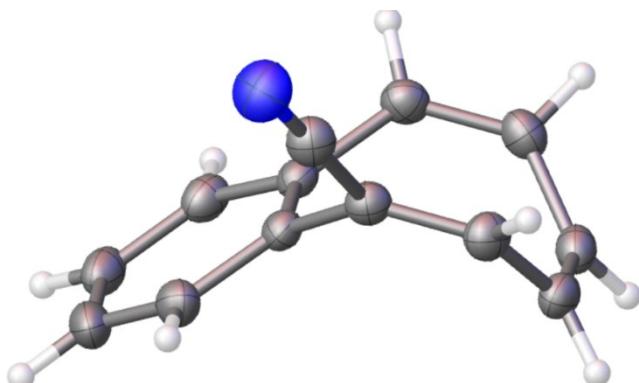
More examples from our laboratory

- o RB13013 – C₇H₉N 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 – 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

Now have a collection of 14 similar structures

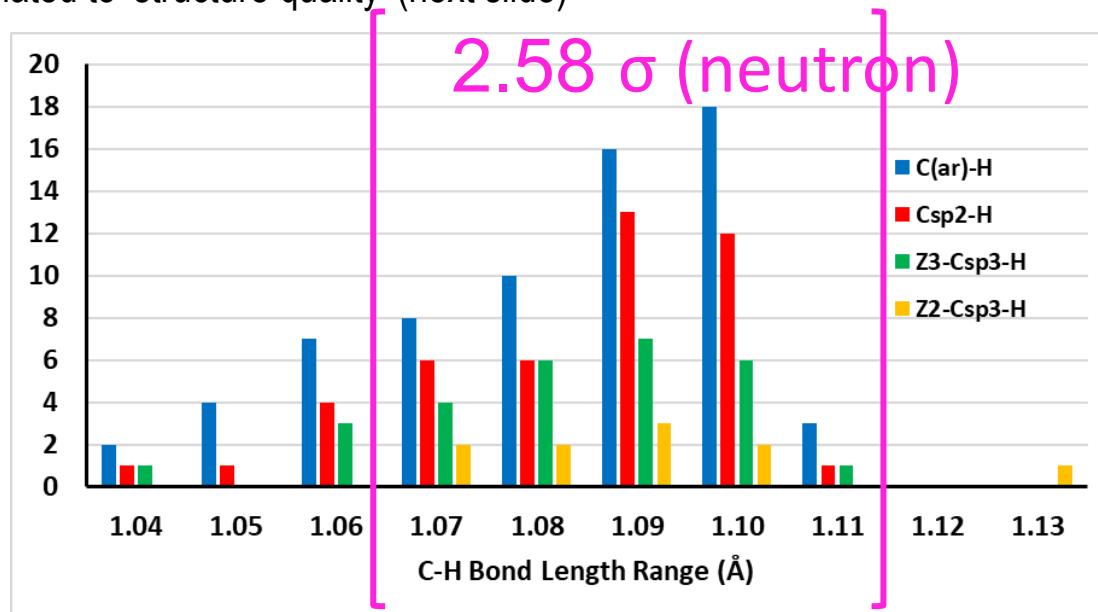
- What are the structural features of note?

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 ₃ -Csp ³ -H	1.00	1.083 (18)	28	1.099 (7)	66
Z ₂ -Csp ³ -H ₂	0.99	1.090 (17)	10	1.097 (6)	136
Csp ² 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_{int} from 0.6 to 8.4 %
- Final HAR R_1 from 0.84 to 4.63 %



So a range of crystal/data quality

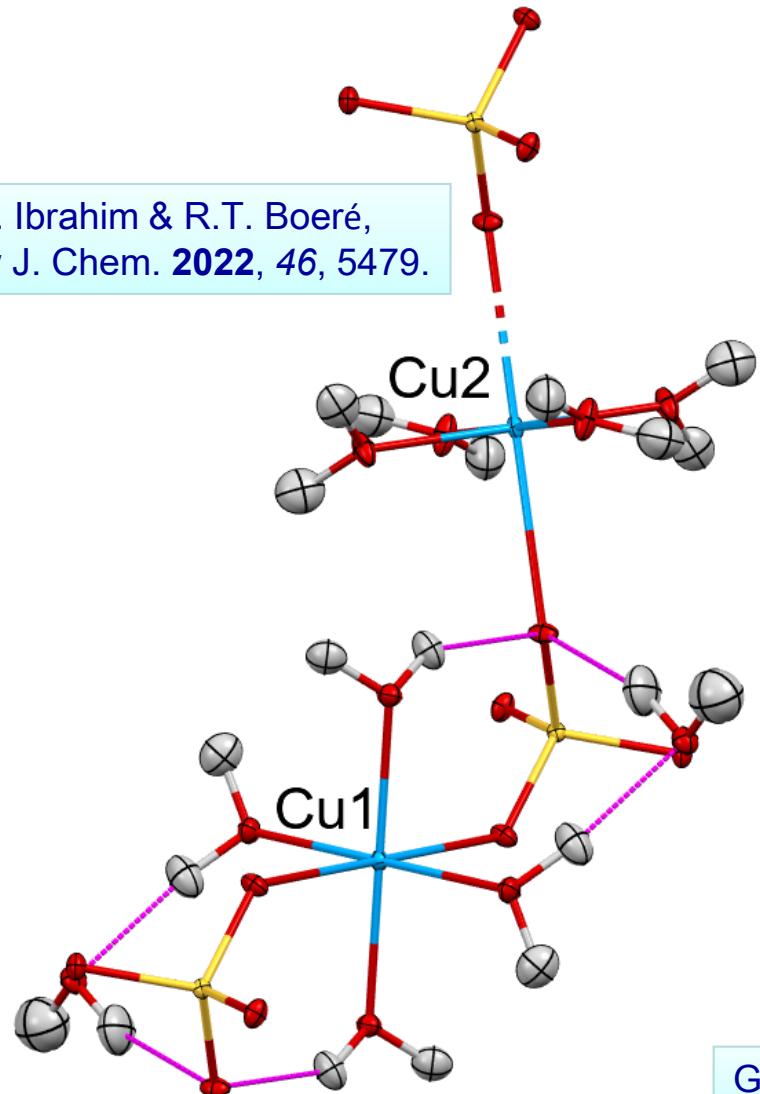
Structure	R_1	R_{int}	Bond precision ^c : C-C in Å, impr. %	Data/par. ratio
1	0.0184	0.0273	0.0018 – 0.0038, 52.6%	12.0
2	0.0309	Twin	0.0025 – 0.0034, 26.5%	11.4
3	0.0179	0.0270	0.0007 – 0.0015, 53.3%	8.3
4	0.0087	0.0180	0.0004 – 0.0015, 73.3%	10.0
5	0.0102	0.0159	0.0009 – 0.0015, 60.0%	11.6
6	0.0137	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

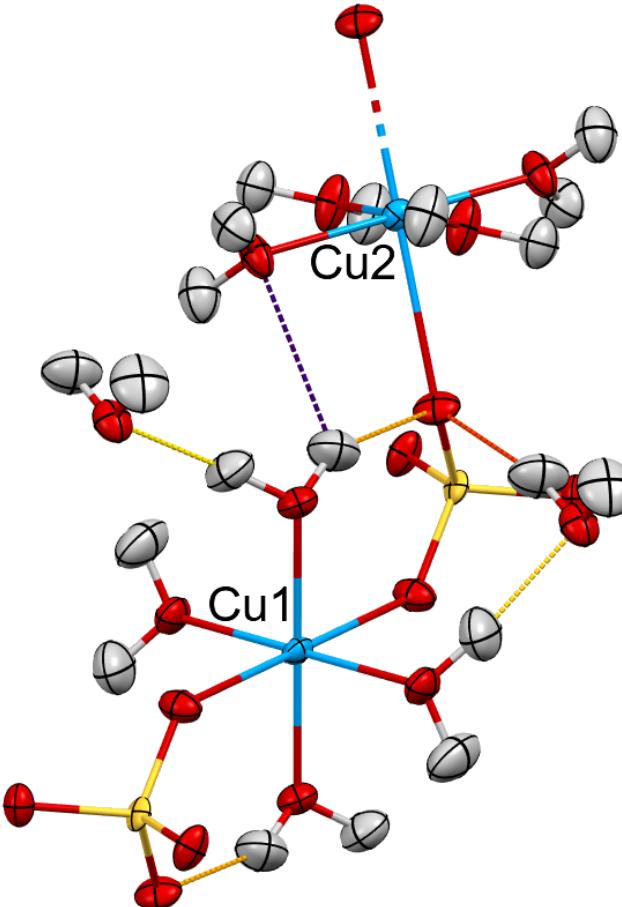
More examples from our laboratory: hydrated TM salts

- 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. Boéré,
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.

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.

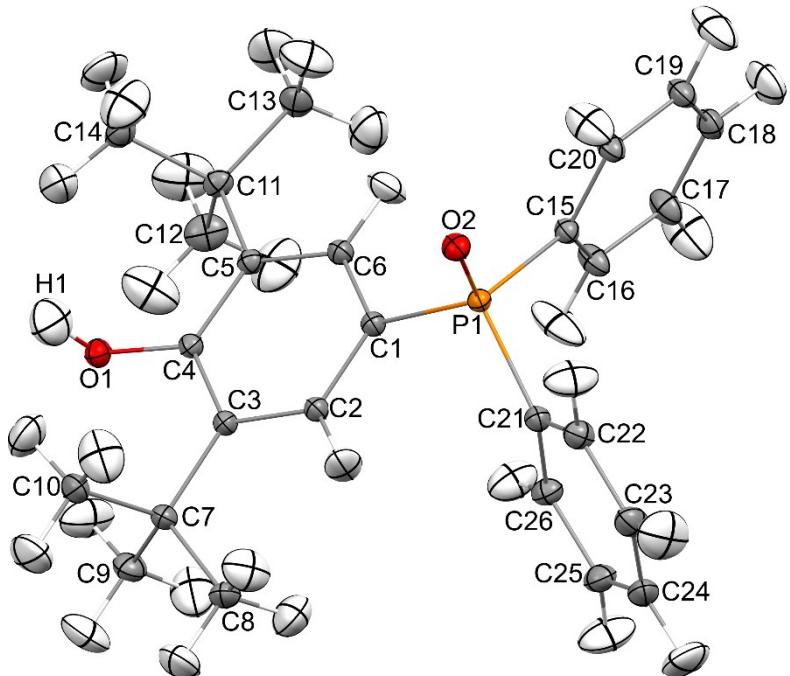


Table 6. Mean Element Bond Lengths (Å) from NoSpherA2 X-ray Refinement and Neutron Diffraction

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

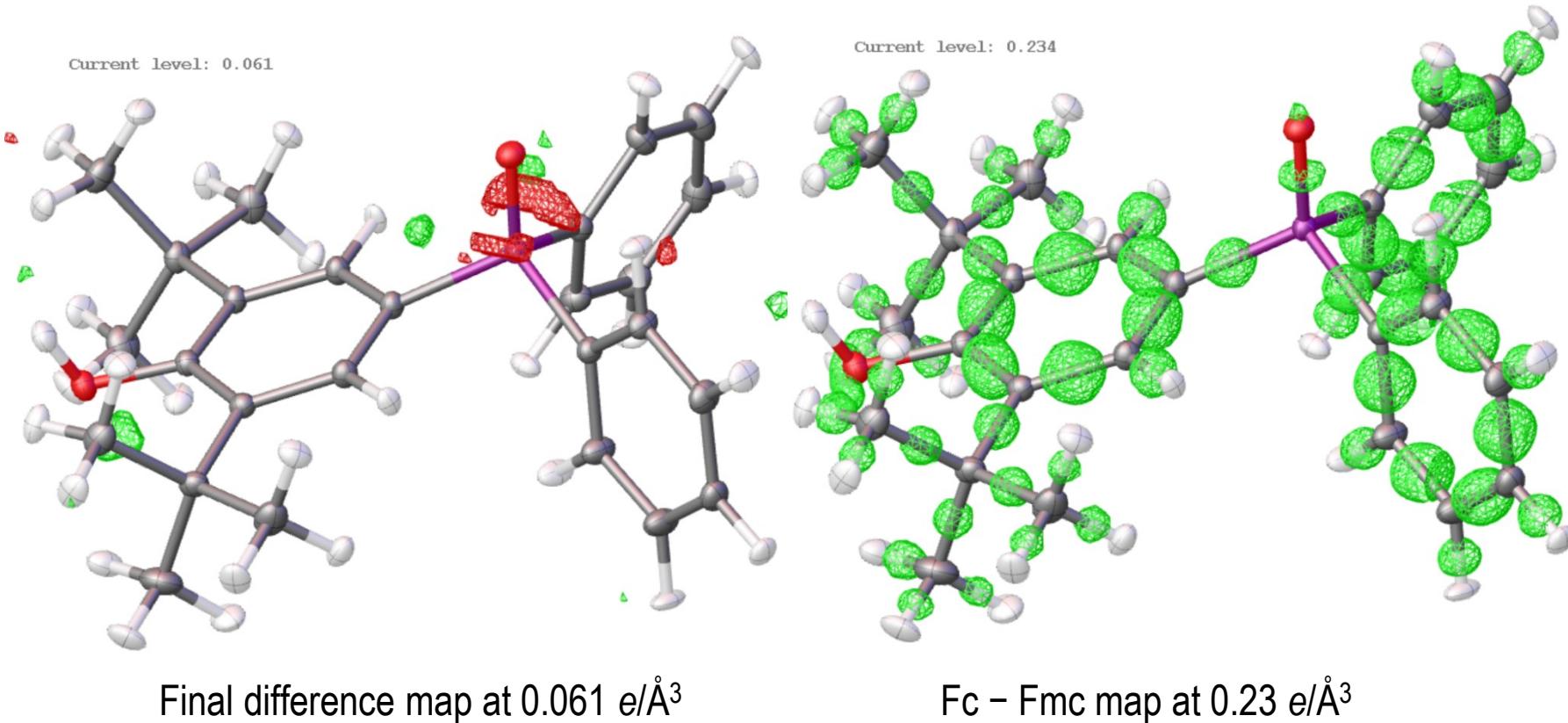
- Accurate work on H-bonding with IAM models has always required an adjustment in E–H distance from that determined from the X-ray diffraction experiment (*normalization*).
T. Steiner, Angew. Chem. Int. Ed. 2002, 41, 48.
- This is no longer necessary in our experience with using olex2.refine/NoSpherA2.

- 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. Marszałkowski 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.

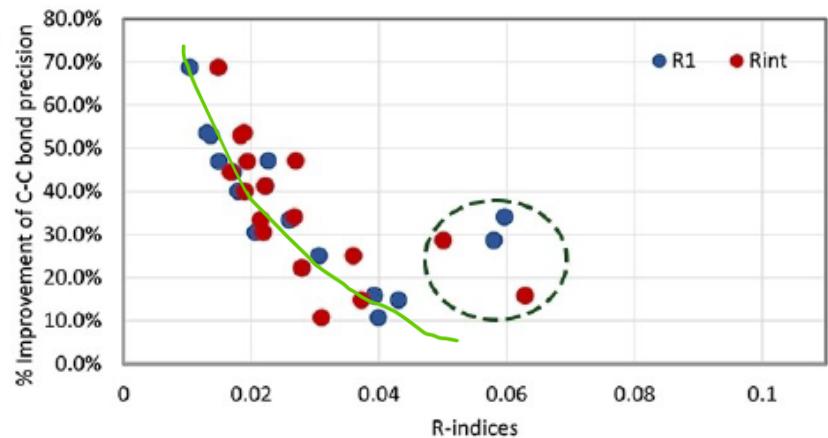


- o An excellent crystal collected under our normal target of 5-fold redundancy and 0.70 Å resolution on Cu gives, with maybe 1 H of work in refinement, gives an accurate depiction of bonding electron density.

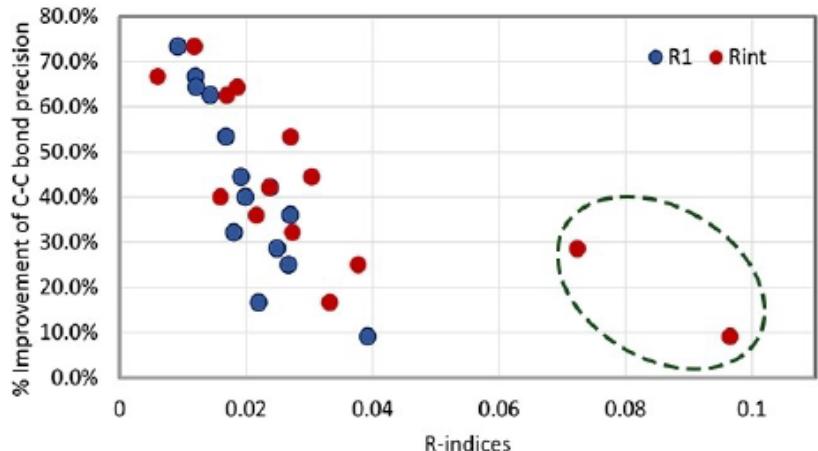
F. Marszakowski et al., Cryst. Growth Des. 2022, 22, 2512.

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

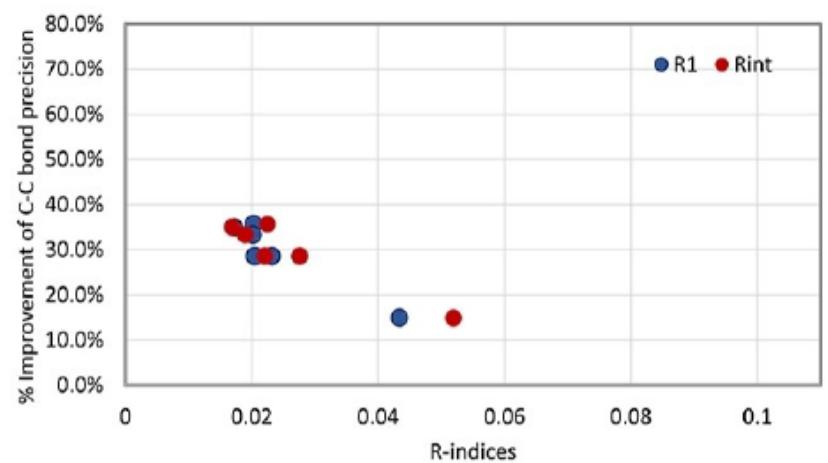
A



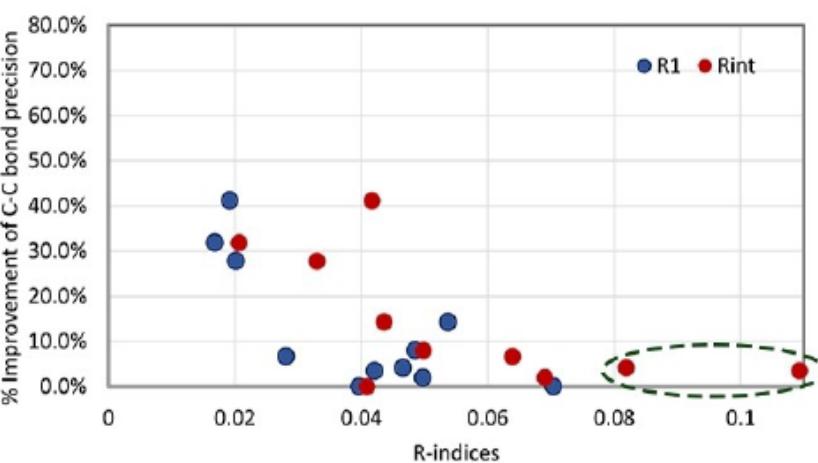
B



C

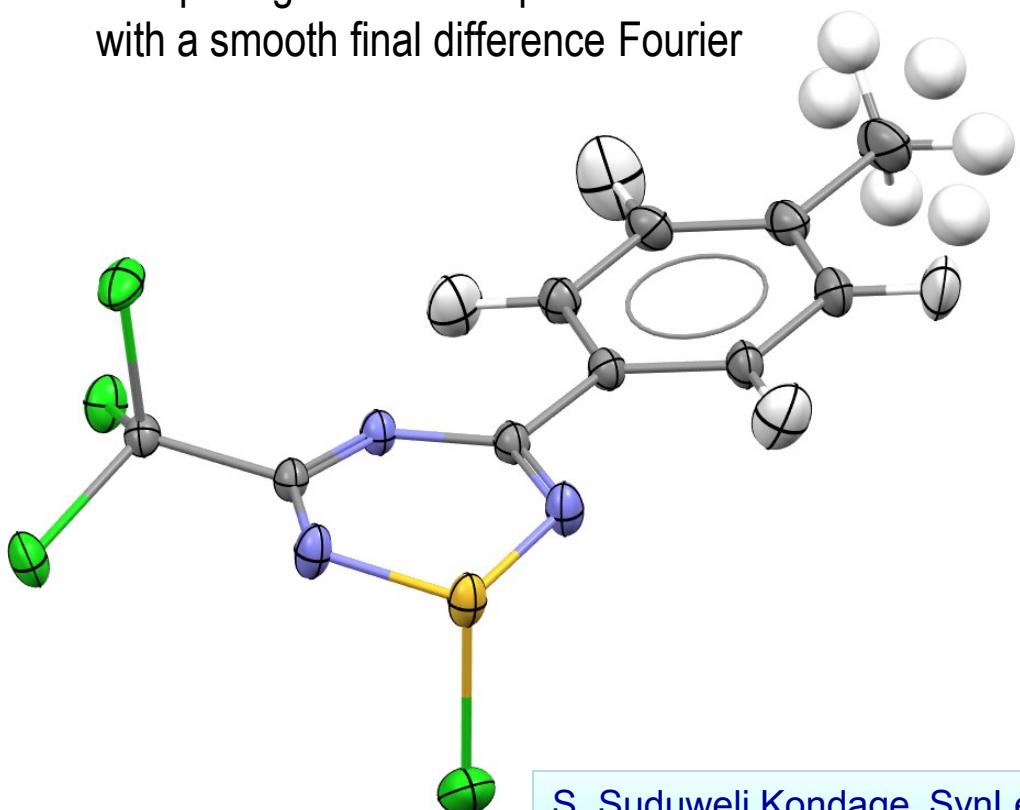


D



Modelling H-atom disorder with NoSpherA2

- o HAR on a series of 1-chloro-3-aryl-5-trihalotrihalomethyl-1 λ^4 ,2,4,6-thiatriazines
- o Where the aryl substituent was the 4-tolyl group, HAR detected insufficient ED for the CH₃ 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: R₁ = 2.05% with a smooth final difference Fourier



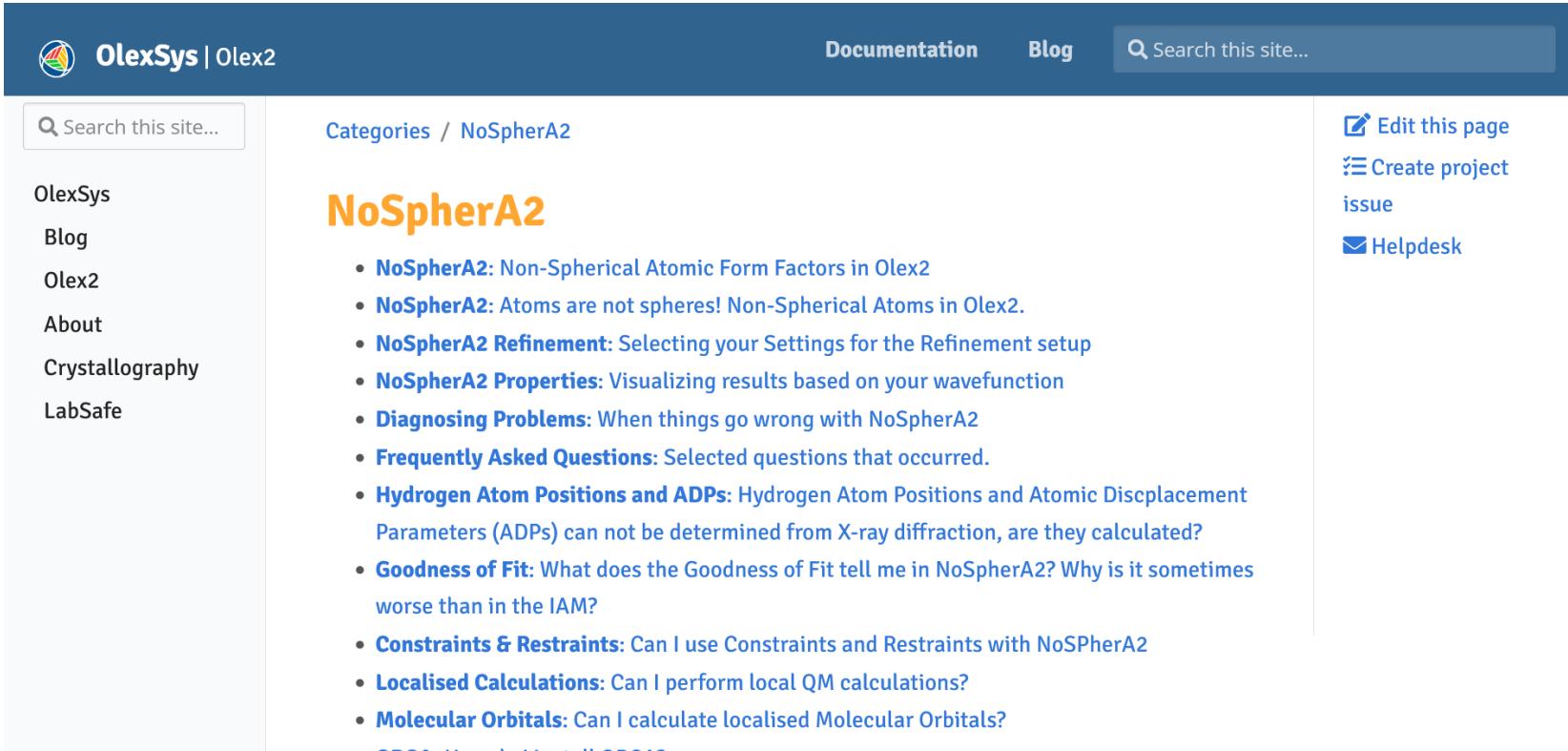
How does NoSpherA2 handle such a two-part disorder model for HAR?

- Two full models are computed in DFT, once after the other
- One where the CH₃ is in first conformation.
- A second with CH₃ 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

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, navigation links for Documentation and Blog, and a search bar for the site. On the right side of the header are links for "Edit this page", "Create project", "issue", and "Helpdesk". The main content area shows the "Categories / NoSpherA2" page. The title "NoSpherA2" is in orange. Below it is a list of 14 items, each with a blue link. The items are:

- [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!

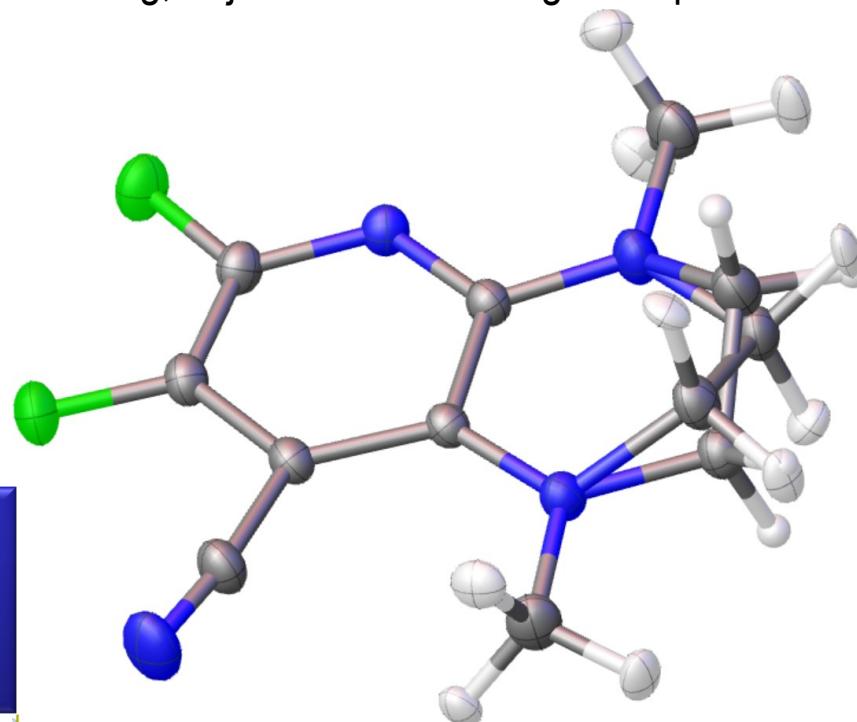
"If you use NoSpherA2 you agree to cite the following literature in your main manuscript:"

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

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

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

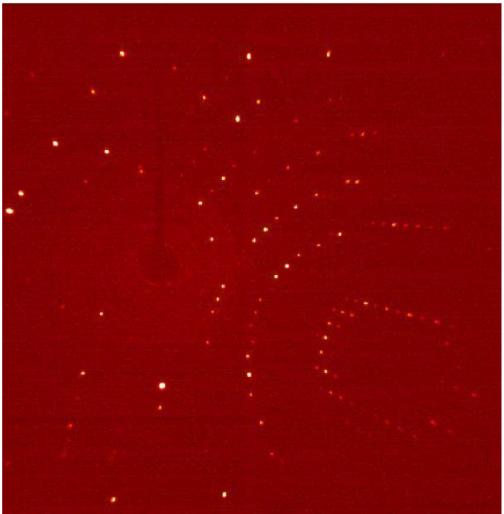
- o There is a conformational disorder in the $-\text{CH}_2\text{CH}_2-$ component of the hydrated pyrazine
- o Minor component is 11.8% and the major 88.2%
- o Even with this disorder the major and minor components can be anisotropically refined for non-hydrogen atoms, and for the H atoms of the major 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 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
- o Large importance for supramolecular chemistry involving non-bonded contacts of all types

Further information

1. Capelli, S. C.; Burgi, H. B.; Dittrich, B.; Grabowsky, S.; Jayatilaka, D., **Hirshfeld atom refinement**. *IUCrJ* **2014**, 1 (Pt 5), 361-379.
2. Woińska, M.; Grabowsky, S.; Dominiak, P. M.; Woźniak, K.; Jayatilaka, D., **Hydrogen atoms can be located accurately and precisely by x-ray crystallography**. *Science Advances* **2016**, 2 (5), e1600192.
3. F. Kleemiss et al. **Accurate crystal structures and chemical properties from NoSpherA2**, *Chem. Sci.* (2021), **12**, 1675–1692.
4. S. Grabowsky, A. Genoni and H-B. Bürgi, **Quantum Crystallography**, *Chem. Sci.* (2017), **8**, 4159.
5. F. H. Allen, I. J. Bruno, **Bond lengths in organic and metal-organic compounds revisited: X-H bond lengths from neutron diffraction data**. *Acta. Crystallogr.* (2010) **B66**, 380-6.

Prof R.T.Boeré

NoSpherA2 for Routine Chemical
Crystallographic Refinement

Personal Experiences and Recommendations by

1h:15'



<https://www.youtube.com/watch?v=fidBw8sl1Wk>

End of CCCW-2025 Tutorial 2