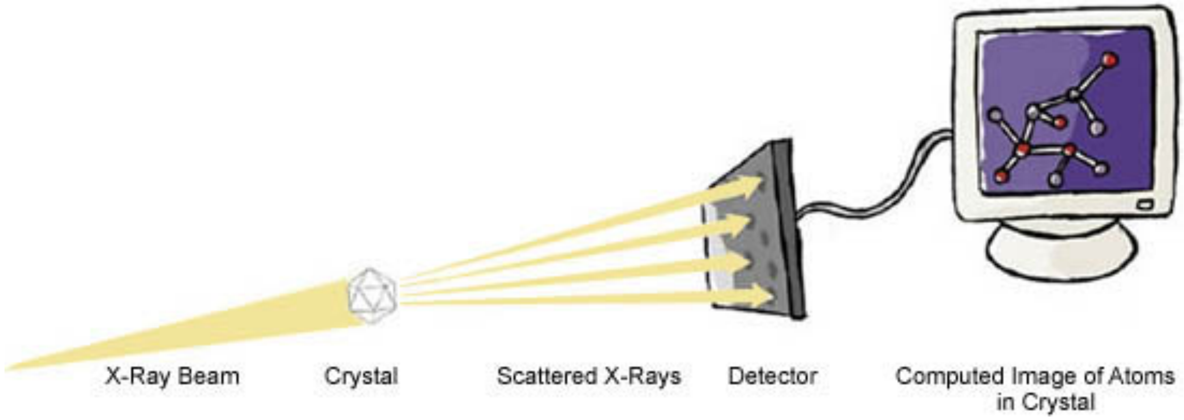
Demystifying X-ray Crystallography:
A Historical and Practical Guide for Organic Chemists



Julie L. Hofstra

Reisman Group

Literature Seminar

January 5, 2018

Motivation for the Topic

Mike

magic

Outline

1. Historical Context and Theory
    - *When was X-ray crystallography developed?*
    - *What was the historical impact on organic chemistry?*

2. Solving Structures with Modern X-ray Crystallographic Techniques
    - *What exactly goes on in that black box?*

3. Commonly Encountered Terminology for Organic Structures
    - *What is a Flack parameter?*

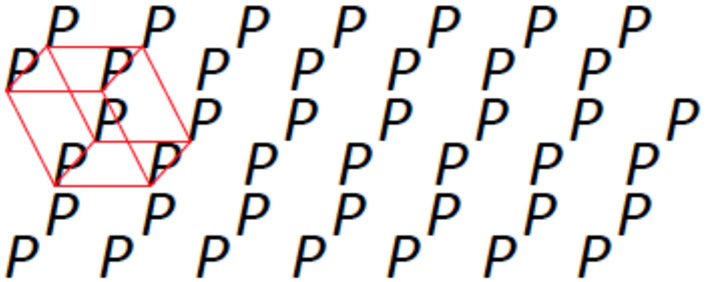
4. Resources at Caltech and Practical Crystallization Tips
    - *What instruments do we have here?*
    - *How do I grow a crystal?*
    - *What are host-guest frameworks?*

Historical Context and Theory

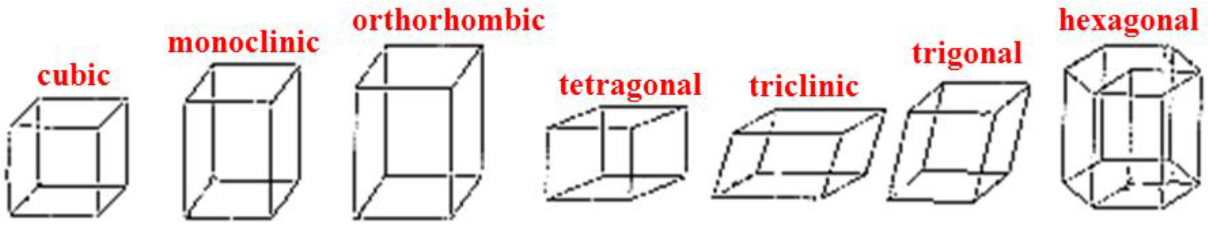
When was X-ray crystallography developed?
What was the historical impact on organic chemistry?

Basis of Crystal Structure Analysis

Definition of a crystal: a material that has atoms arranged in an ordered, repeating pattern (unit cell) which can be extended by translation in three dimensions (crystal lattice)



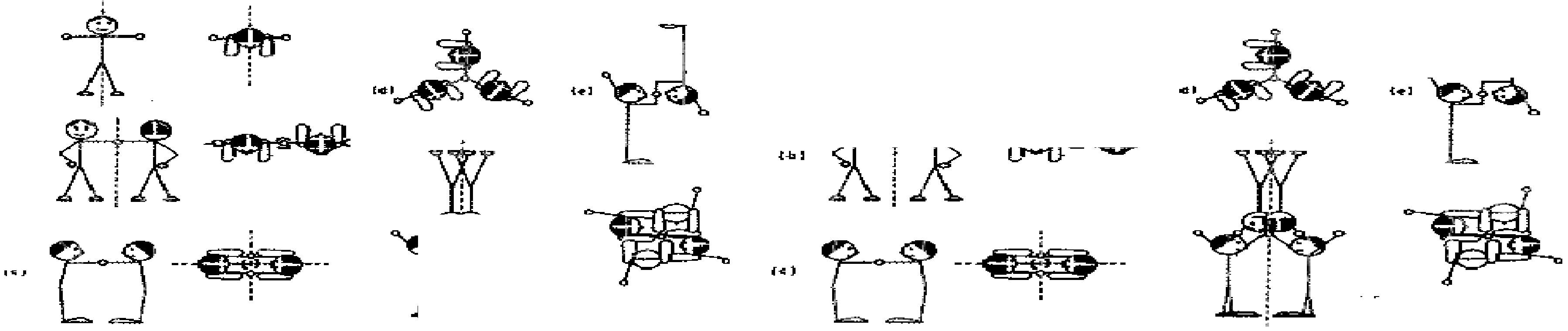
Crystal systems: seven crystal systems



Symmetry elements:

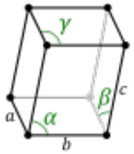
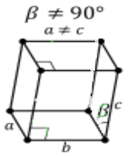
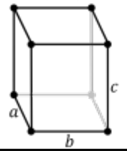
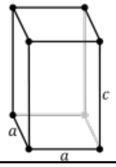
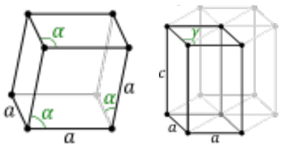
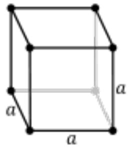
Non-translational: inversion center, reflection, rotation, and rotation-inversion

Translational: screw axis, glide plane (these cause systematic absences in X-ray diffraction)



Basis of Crystal Structure Analysis

7 crystal systems → 14 Bravais lattices → 32 point groups → 230 space groups

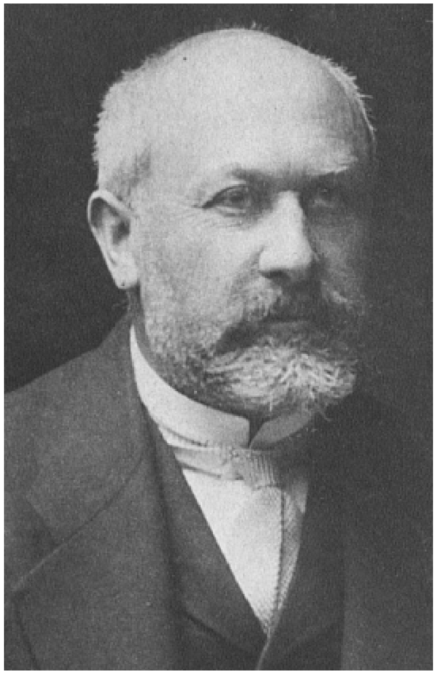
Crystal System		Symmetry Metrics	Bravais Lattice	Point Groups	
				Schönflies	**Hermann–Mauguin**
Triclinic		none $\alpha \le \beta \le \gamma$	P	C_1, C_i	$1, \bar{1}$
Monoclinic		b is unique $\alpha = \gamma = 90°$ $\beta \ge 90°$	P, C	C_2, C_s, C_{2h}	$2, m, 2/m$
Orthorhombic		$\alpha = \beta = \gamma = 90°$	P, C, I, F	D_2, C_{2v}, D_{2h}	$222, mm2, mmm$
Tetragonal		a = b, c is unique $\alpha = \beta = \gamma = 90°$	P, I	$C_4, S_4, C_{4h}, D_4, C_{4v}$, D_{2d}, D_{4h}	$4, \bar{4}, 4/m, 422$, $4mm, \bar{4}2m, 4/mmm$
Trigonal/ Hexagonal		a = b, c is unique $\alpha = \beta = 90°$ $\gamma = 120°$	P, R	$C_3, S_6\ (C_{3i}), D_3, C_{3v}$, $D_{3d}, C_6, C_{3h}, C_{6h}, D_6$, C_{6v}, D_{3h}, D_{6h}	$3, \bar{3}, 32, 3m, \bar{3}m, 6$, $\bar{6}, 6/m, 622, 6mm$, $\bar{6}m2, 6/mmm$
Cubic		a = b = c $\alpha = \beta = \gamma = 90°$	P, I, F	T, T_d, T_h, O, O_h	$23, m\bar{3}, 432, \bar{4}3m$, $m\bar{3}m$

P=primitive; C=end-centered; I=body-centered; F=face-centered; R=rhombohedral

Basis of Crystal Structure Analysis

1891

independent derivation of the
230 symmetry space groups



Artur Schöenflies

German mathematician
specialized in the study of geometry
published his book “Kristallsysteme und Kristallstruktur” in 1891

Evgraf Fedorov

Russian mathematician and crystallographer
work went under-acknowledged during lifetime as it was not translated from Russian
greatest work “Das Krystallreich” was published by students in 1920 following his death

Schöenflies, A. *Kristallsysteme und Kristallstruktur* **1891**; Federov, E. *Das Krystallreich* **1920**; Burckhardt, J. J. *Arch. Hist. Exact Sci.* **1967**, *4*, 235.

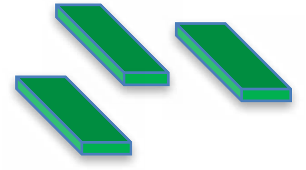
Basis of Crystal Structure Analysis

There is a difference between chirality of molecules and chirality of crystals!

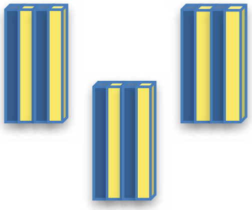
Achiral molecules:

- centrosymmetric achiral (most common)
- non-centrosymmetric achiral or chiral (*d*-quartz and *l*-quartz)

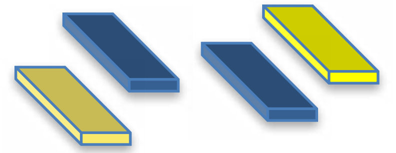
Chiral molecules (*enantiomeric mixture*):



racemic crystals
or solid state mixture



twinned crystals

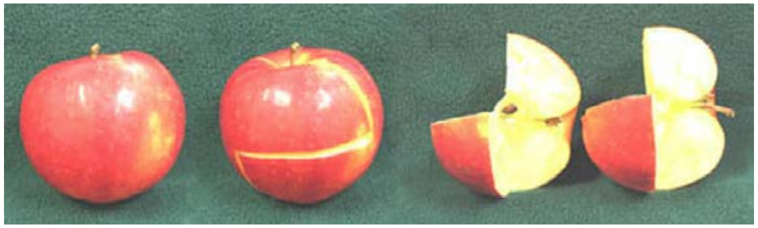


spontaneous resolution

Chiral molecules (*enantiopure*):

- ALWAYS crystallizes in a non-centrosymmetric chiral crystal (absolute configuration)
- achiral theoretically possible but has NEVER been seen in nature

La Coupe du Roi
French for "The Royal Cut"



Flack. H. D. *Helv. Chem. Acta* **2003**, *86*, 905; Thompson, A. L.; Watkins, D. J *Tetrahedron: Asymmetry* **2009**, *20*, 712.

The Development of X-ray Diffraction

1895

First detection of X-rays

Wilhelm C. Röntgen

German mechanical engineer and physicist

Refused to take patents, wanted to benefit society

First medical image he took was of his wife's hand

Awarded with the Nobel Prize in 1901

IUPAC named element 111, roentgenium, after him in 2004

The Development of X-ray Diffraction

1912

Discovery of X-ray diffraction by crystals

Max von Laue

German physicist won the Nobel Prize in 1914

Ewald studied refraction of isotropic resonators with crystal plates under Sommerfeld.

He sought out advice from Laue, who was unaware of crystal lattice, regarding some calculations.

Paul P. Ewald

Arnold Sommerfeld

Interview in 1959:

“I told him, "I can't tell you what the distance is, because the distance is very small, certainly, but we don't know whether there are atoms, or molecules in the parts of the lattice, or whether there are groups of molecules, and without knowing that we don't know what the distance is.” …He was rather distracted, and asked a few times, "What happens if you take very much shorter waves than the light waves and if they pass through the crystal?” And I said, “This can be answered very simply because the formulae I have here are strict formulae…but I want to finish my thesis, and at present I am not interested in this.” So I finished my thesis, I didn't get anything out of Laue — no help. I wrote up my thesis, and was glad to get rid of it.” –P. P. Ewald

A few months later, Laue reported the X-ray diffraction by crystals conducted by two students, Knipping and Friedrich.

Ewald, P. P. Fifty Years of X-ray Diffraction **1962**.

The Development of X-ray Diffraction

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Paul P. Ewald

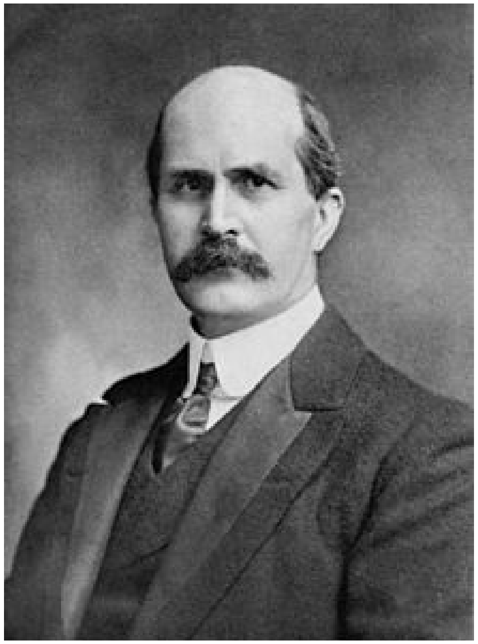
Arnold Sommerfeld

Autobiography in 1962:

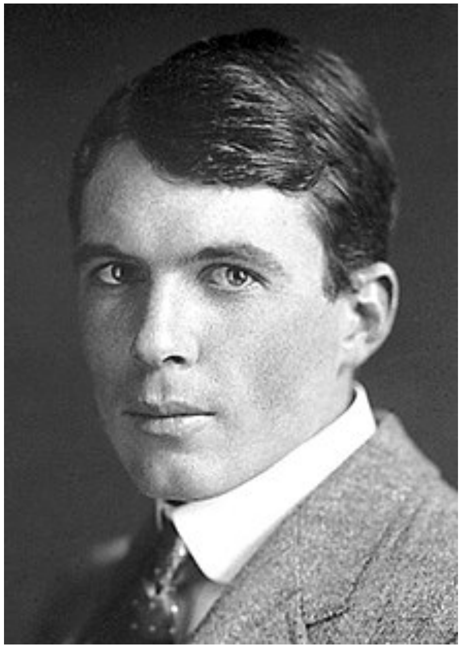
"The history of the discovery of X-ray interference illustrates beautifully the value of scientific hypothesis. Many people irradiated crystals with X-rays before Friedrich and Knipping. However, their observations were limited to the directly transmitted ray which revealed nothing remarkable beyond the weakening produced by the crystal; they missed completely the less strong diffracted rays. It was the theory of the space lattice which provoked the idea of investigating the neighborhood of the direct ray. Of course the diffracted rays would eventually have been discovered as stronger and stronger X-ray tubes were developed; some accident would have pointed them up. But it is hard to guess when this might have happened, and we can certainly say that the theory of the space lattice was absolutely essential to account for their presence." –Max von Laue

Ewald, P. P. Fifty Years of X-ray Diffraction **1962**.

The Development of X-ray Diffraction

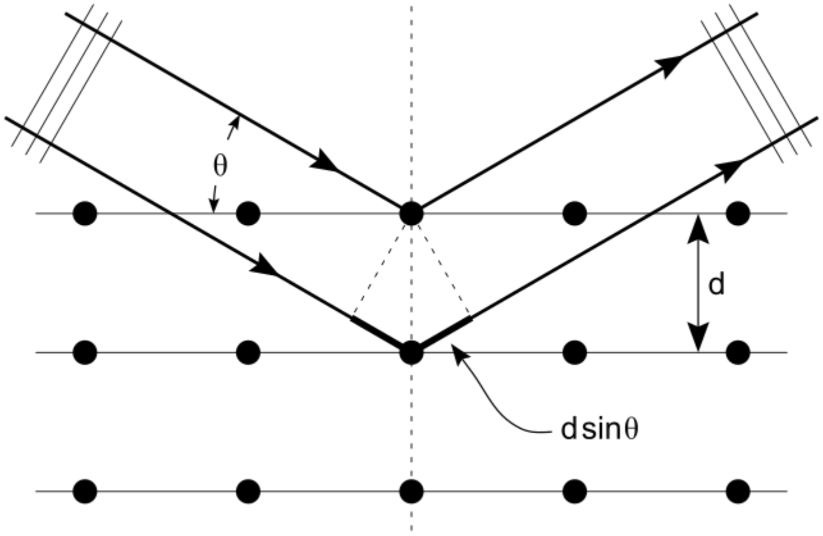


William H. Bragg
(father)



William L. Bragg
(son)

Bragg's Law: $n\lambda = 2d\sin\theta$



1913

Published Bragg's Law, which describes scattering on a crystal lattice: $n\lambda = 2d\sin\theta$

British scientists; invented the X-ray spectrometer and studied X-ray emission spectroscopy

Reported structures of NaCl, NaBr, KBr in 1913 (disproved covalent salt molecules)

Shared the receipt of the Nobel Prize in 1915

Bragg, W. H.; Bragg, W. *Proc. Royal Soc. A* **1913**, *88*, 428.

A Simplified Theory of X-ray Diffraction

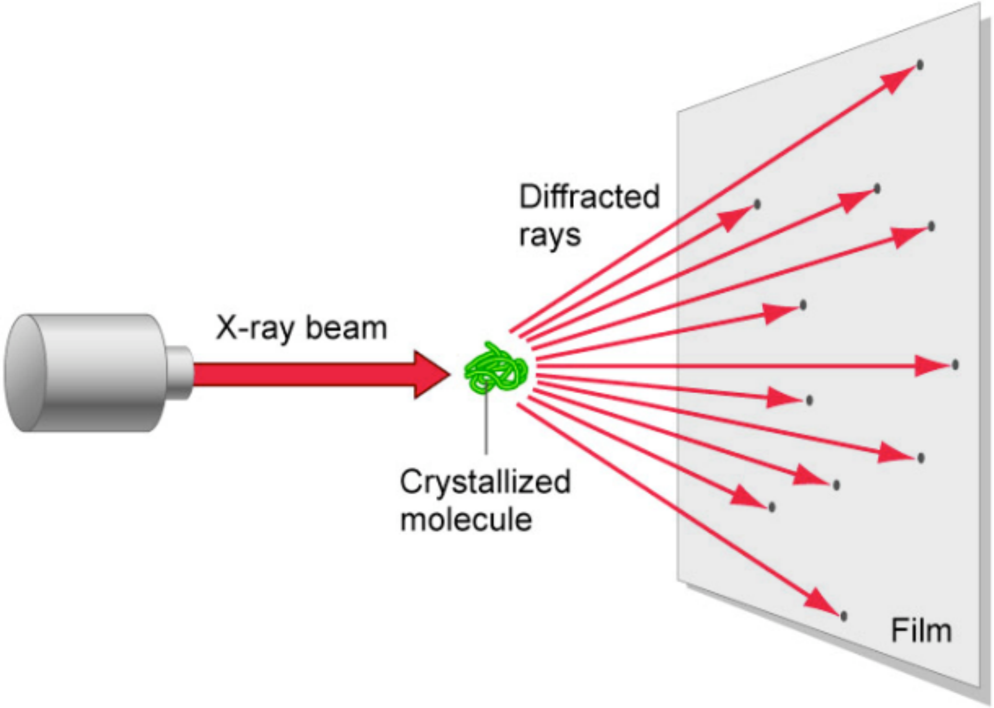
- Each crystal contains a lattice structure, this acts as a diffraction grating for the X-ray beam
- X-rays are suitable wavelength (order of magnitude as atom spacing)
- The *location* of the reflections depends on size and orientation of the unit cell
  - Reflections are labeled with indices (*h*, *k*, *l*)
  - We need to know the unit cell to use the right math
- The *intensity* of the reflections is a Fourier transform of the electron density
  - EVERY atom contributes to EVERY reflection
- To have the electron density map, we also need the *phases*
  - Phases are lost with this measurement!!
  - This is the *crystallographic phase problem*

A crystallographer considers the structure to be solved when the "lost phases" are "recovered" (i.e. appropriately estimated with a good model)

How do we figure out the phases?

Used to be solved by hand, with iterative math (2D).
Then computers were invented (3D)!
(development in 1940's and generalized late 1950's)

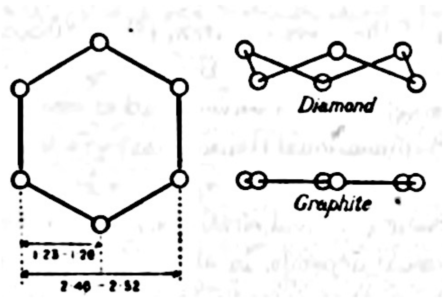
Number of developments and attempts have been made to find better ways at determining the phases:
Patterson method (**1934**)
Direct methods, XS (**1953**)
Intrinsic phasing, XT (commonly used today)

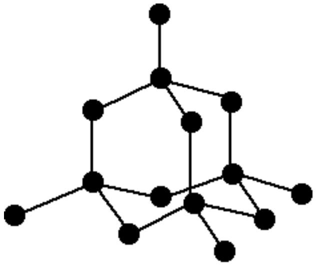


Early X-ray Crystal Structures of Organic Compounds

1913

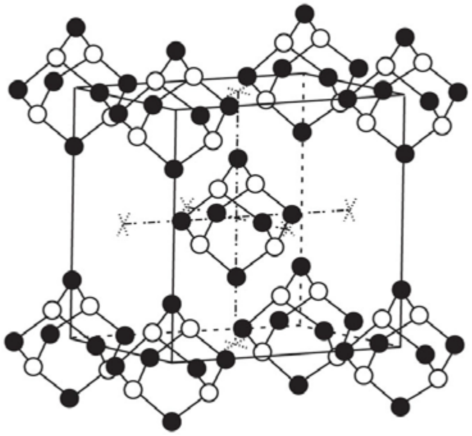
W. H. Bragg and W. L. Bragg (diamond)

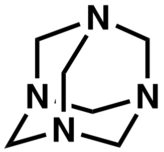




1923

R. G. Dickinson and A. L. Raymond (Caltech)
H. J. Gonell and H. Mark (Berlin-Dahlem)

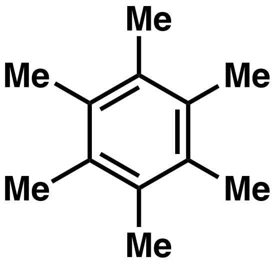




hexamethylenetetramine

1928

K. Lonsdale
structural evidence of resonance and first to use Fourier analysis



hexamethylbenzene

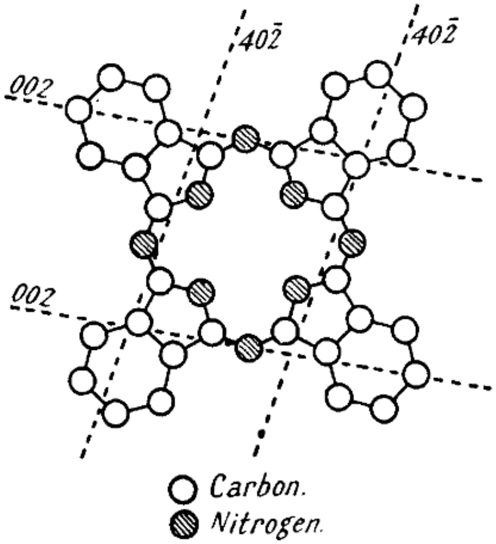
Bragg, W. H.; Bragg, W. *Nature* **1913**, *91*, 557; Dickinson, R.; Raymond, A. L. *J. Am. Chem. Soc.* **1923**, *45*, 22; Longdale, K. *Nature* **1928**, *122*, 810.

Early X-ray Crystal Structures of Organic Compounds

1935

J.M. Robertson
(phthalocyanins)

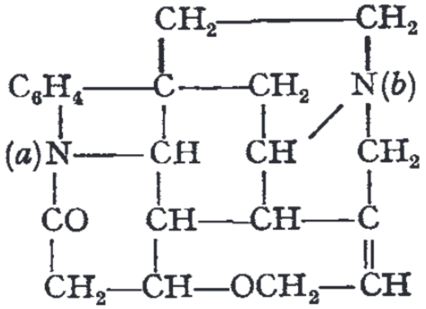
first time a complex organic molecule was solved independently by crystallography

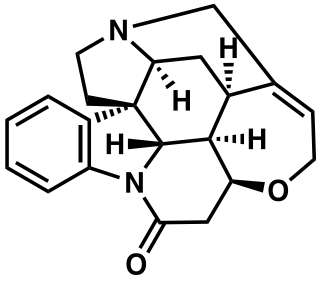


1951

J. M. Bijvoet (strychnine)

first time crystallography decided between proposed structures



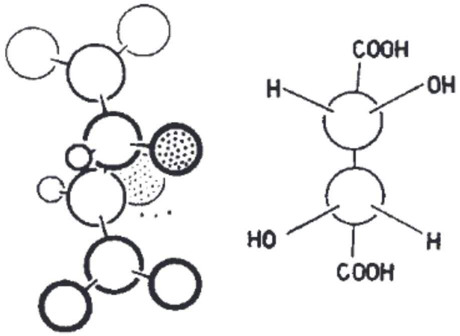


strychnine

1951

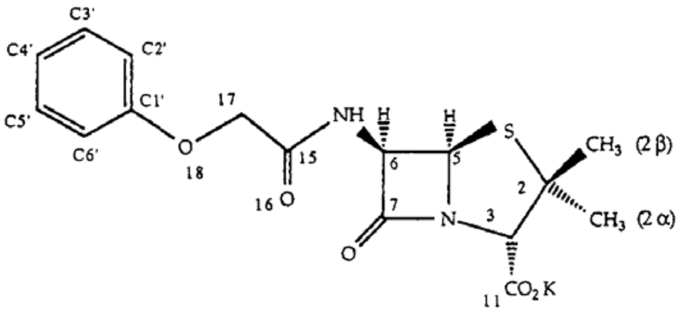
J. M. Bijvoet
(absolute configuration)

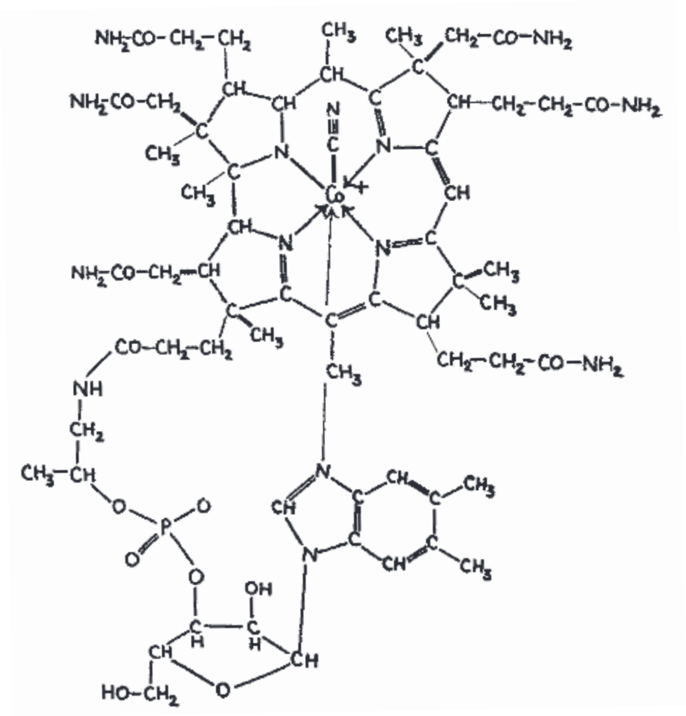
used a method called anomalous dispersion (this happens to be what we still use today)



Robertson, J. M. W. *J. Chem. Soc.* **1935**, 615; Openshaw, H. T.; Robinson, R. *Nature* **1946**, *157*, 438; Robertson, J. H.; Beevers, C. A. *Acta Cryst.* **1951**, *4*, 270; Bokhoven, C.; Schoone, J. C.; Bijvoet, J. M. *Acta Cryst.* **1951**, *4*, 275; Bijvoet, J. M.; Peerdeman, A. F; van Bommel, A. J. *Nature* **1951**, 271.

Early X-ray Crystal Structures of Organic Compounds

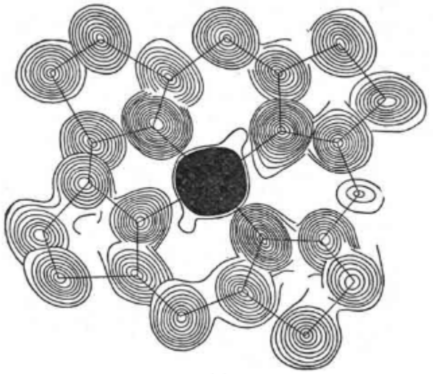


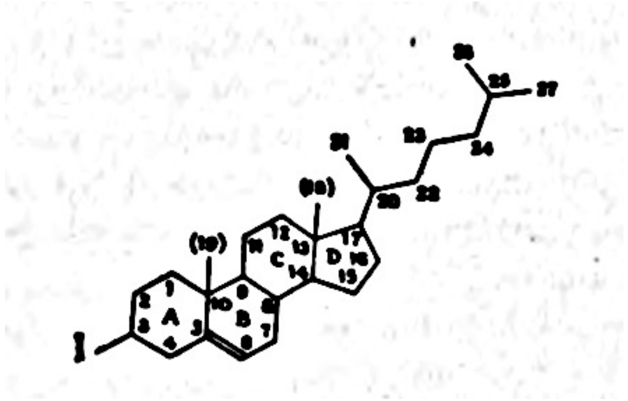


Dorothy Mary Crowfoot Hodgkin

British chemist who developed protein crystallography and won Nobel Prize in 1964

1944 – cholesteryl iodide
1949 – penicillin
1956 – vitamin B12
1971 – insulin (tertiary structure)





Carlisle, C. H.; Hodgkin, *Proc. Royal Soc. A* **1944**, *184*, 64; Crowfoot, D.; Bunn, C. W.; Rogers-Low, B. W.; Turner-Jones, A. *Princeton University Press* **1949**, *310;* D.C. Hodgkin, D. C.; Kamper, J.; Mackay, M.; Pickworth, J.; Trueblood, K. N.; White, J. G. *Nature* **1956**, *178*, 325;

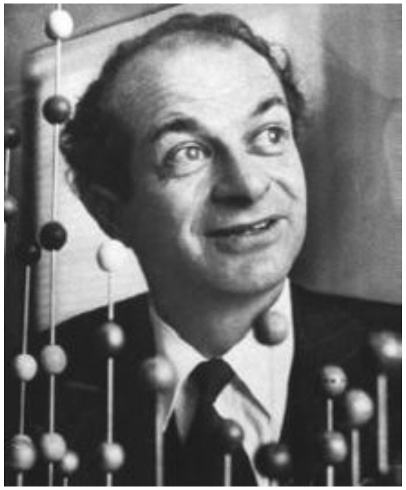
Crystallography at Caltech

Roscoe Dickinson (first person to receive Ph.D. from Caltech, 1920)
became a professor and was an advisor to Linus Pauling

Richard Bozorth (second Ph.D. from Caltech, also studied X-ray crystallography)

Linus Pauling (graduate student at Caltech and later returned as a professor) worked with Robert Corey (α-helix and β-sheet)

Numerous structures (e.g. glycine, alanine, serine, threonine, N-acetylglycine, β-glycylgycine, diketopiperazine (1939-1953)) which served as a basis for protein crystallography



1947 - IBM (Hollerith) operators at the Caltech Computing Center machine room

"Over the period of 44 years since 1917 about 350 papers on X-ray diffraction have been published from the Gates and Crellin Laboratories of Chemistry, representing the determination of the structure of about 350 crystals. Many American X-ray crystallographers received their training in the California Institute of Technology." –Linus Pauling

Nobel Prizes Awarded in X-ray Crystallography

YEAR	AREA	PEOPLE	DISCOVERY
1901	Physics	W. C. Röntgen	Discovery of X-rays
1914	Physics	M. Von Laue	X-ray diffraction
1915	Physics	W. H. Bragg and W. L. Bragg	Bragg Law and crystal structure
1917	Physics	C. G. Barkla	Characteristic radiation of elements
1937	Physics	C. J. Davisson and G. Thompson	Electron diffraction
1954	Chemistry	L. C. Pauling	Structure of complex substances
1962	Chemistry	M. Perutz and J. C. Kendrew	Structures of Hemoglobin and Myoglobin
1962	Medicine	J. D. Watson, F. H. C. Crick, and Maurice H. F. Wilkins	Structure of DNA
1964	Chemistry	D. C. Hodgkin	Structure of vitamin B12
1972	Chemistry	C. B. Anfinsen	Protein Folding
1976	Chemistry	W. N. Lipscomb	Structure of Boranes
1985	Chemistry	H.A. Hauptman and J. Karle	Direct Methods
1988	Chemistry	J. Deisenhofer, R. Huber, and H. Michel	Structure of bacteriorhodospin
1994	Physics	C. Shull and N. Brockhouse	Neutron diffraction
1996	Chemistry	R. Curl, H. Kroto, and R. Smalley	Structure of fullerene
2009	Chemistry	V. Ramakrishnan, T.A. Steitz, and A. E. Yonath	Structure and function of ribosome
2011	Chemistry	D. Shechtman	Discovery of quasicrystals

Knowledge from X-ray Crystallography

Things we possibly take for granted, learned from X-ray crystallography:

- The nature of atomic bonding
  - ionic bonding, covalent bonding, metallic bonding
  - multiple bonds vs. single bonds; bond lengths
  - resonance
  - hydrogen bonding
  - exotic bonds (e.g. 2-electron-3-center bonds, multiple metal bonds)

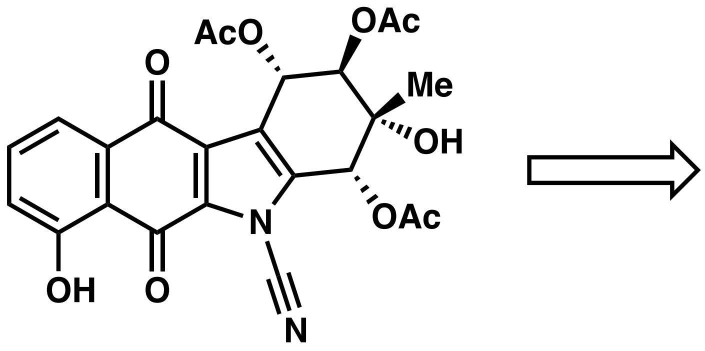
- Molecular and extended structures

- Polymorphism and implications on materials' properties
  - inorganic solids
  - drugs

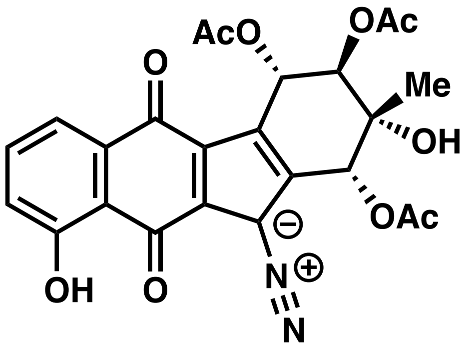
- Biological structures
  - DNA, enzymes, proteins, viruses, active sites

Natural Product Structural Revision

X-ray crystallography is not infallable!
Natural products have been misassigned by X-ray crystallography.



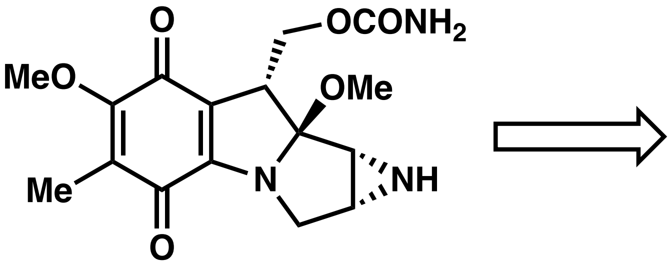
kinamycin C
(Omura et al., 1973)



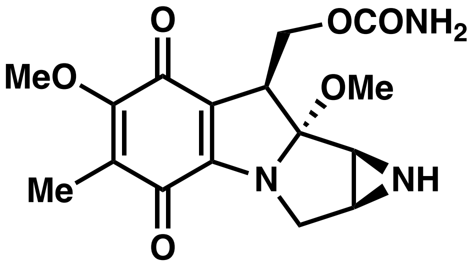
revised structure
(Gould et al., 1994 and Dmitrienko et al., 1994)

- Diazofluorene was misassigned as an *N*-cyanocarbazole
- Typical misassignments have to do with atom identity, not connectivity
- More difficult when atoms are devoid of hydrogens (organic)
- Elements confused with neighboring atom on periodic table (closest e^- density)

- Structure and absolute configuration determined by X-ray
- Crystals not the best quality
- R-factor-ratio test
- Feeding experiments indicated D-glucosamine part of biosynthesis
- Revised with new crystal



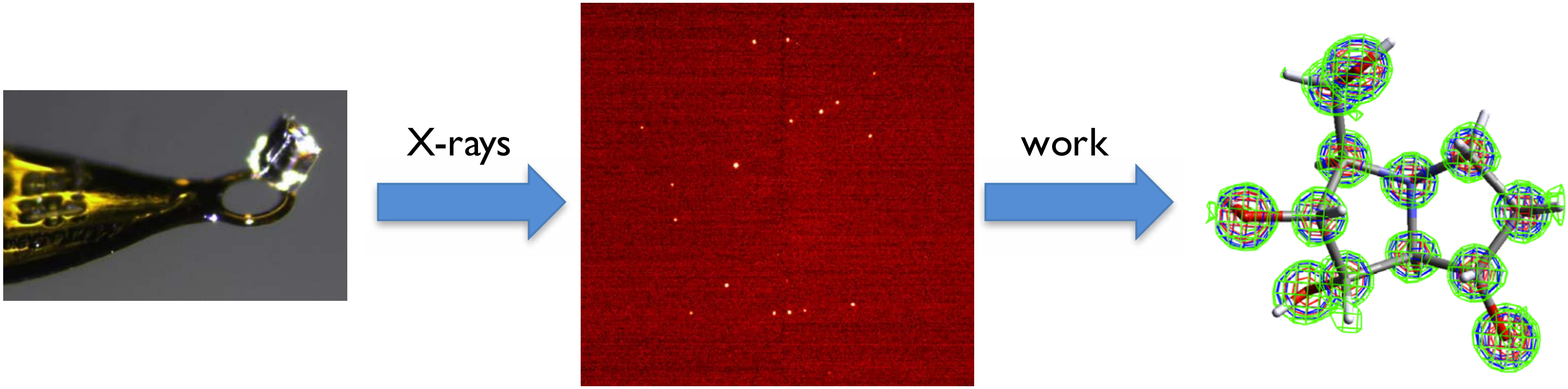
mitomycin A
(van den Hende et al., 1967)



revised structure
(Shirahata, et al., 1987)

Nicolaou, K. C.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1012.

X-ray Crystallography in One Slide



X-rays

work

location: reciprocal lattice

intensity + phases: electron density map

Solving Structures with Modern X-ray Crystallographic Techniques

What exactly goes on in that black box?

Similarities Between X-ray and NMR

NMR: a familiar friend

Running a sample and inputting collection parameters (^{1}H, ^{13}C, HSQC)	MestReNova converts FID to the spectra we know	Integrate and assign key cross-peaks to identify the compound (J values, ppm shift)	Things like baseline correct and autophase	Adding parameter tables, labeling atoms, and making it look nice for an SI

collect data → integrate data → solve data → refine data → finalize data

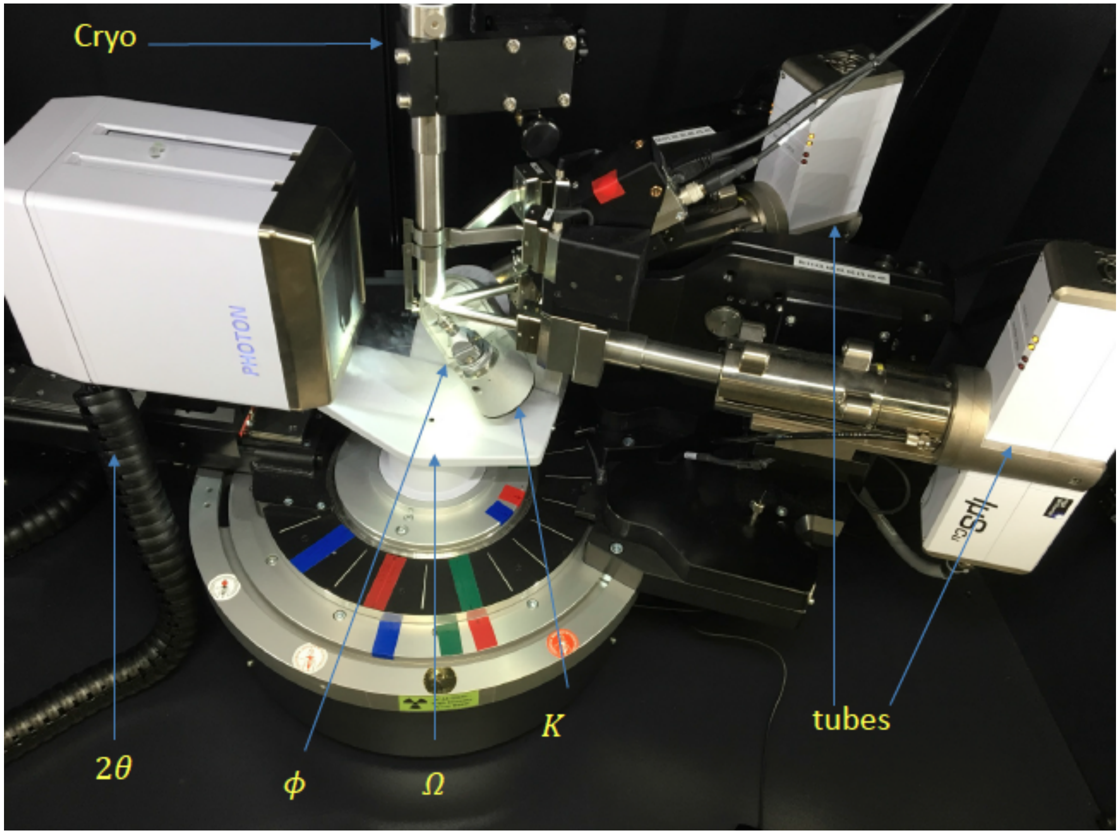
X-ray: the magic black box

Collect diffraction data, computer program determines collection parameters	Integrate and harvest the location and intensity of all reflections	Data is converted to an electron density map and program gives "best guess" solution	Modifying the solution until it matches well with the data set	Preparing CIF files for publication

Computer Programs to Solve Structures

1. Apex
   - *Collects and integrates data*
2. XPREP
   - *Space group determination*
3. XT (or XS)
   - *Structure solution program that takes a best guess at solving the data*
4. Olex (or ShelXle)
   - *Graphical interface that runs XL to to refine structures*
   - *Also used to label atoms and create final CIF file*
5. Platon
   - *Does a number of things to check refinement*
6. Mercury (or Diamond)
   - *Used to generate image of structure*
7. XCIF
   - *Used to generate the list of tables that goes in the supporting information*

Instrument Design/Setup



Detector

X-ray tube

Goniometer

Crystals are mounted on a loop in Paratone oil

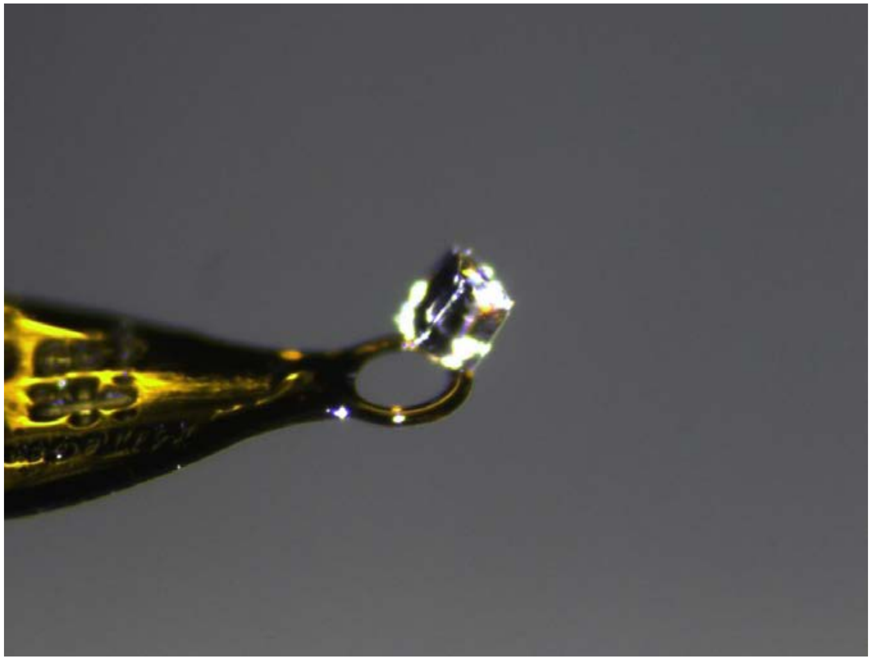
A cold stream of N_2, usually 100K, cools the sample and hardens the oil

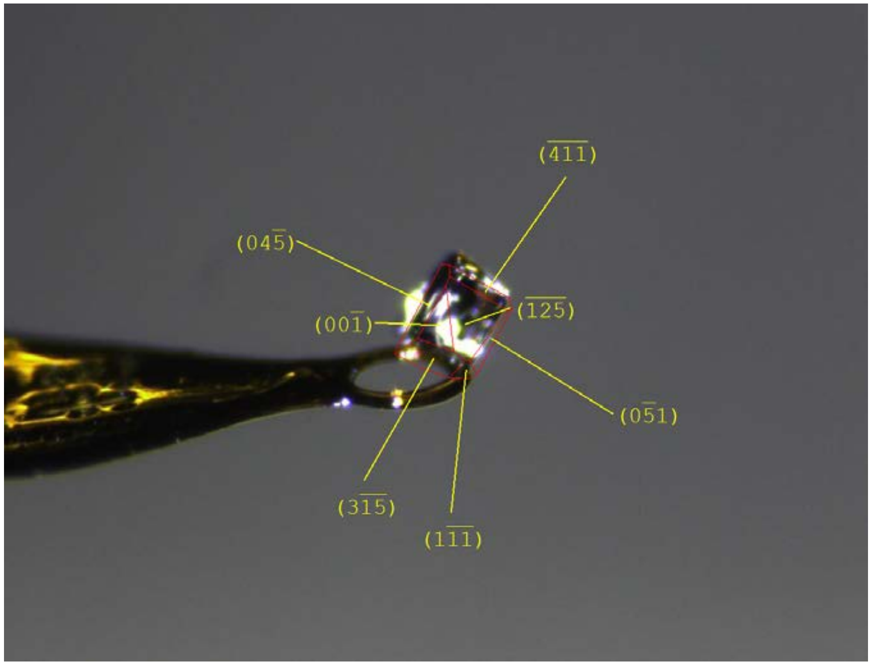
Crystal gets aligned in the center and is rotated throughout data collection

Kα wave: Cu λ = 1.54433 Å and Mo λ = 0.71354 Å

Program: Apex

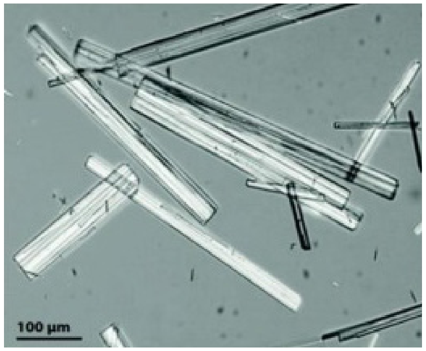
Video File and Crystal Sizing



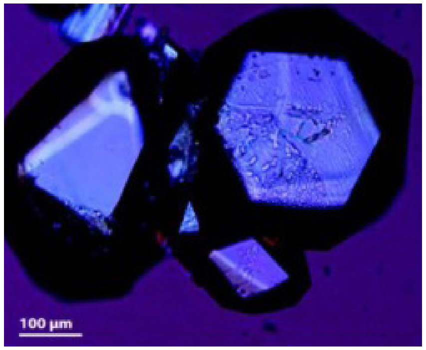


Size: 0.15 x 0.25 x 0.25 mm

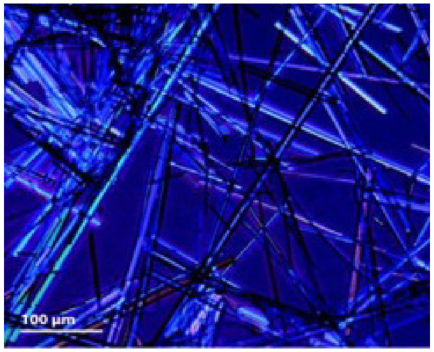
Crystal Types:



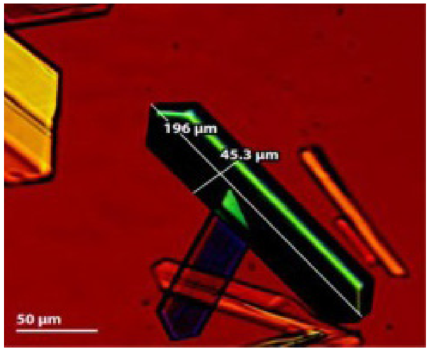
rods



blocks



needles



plates

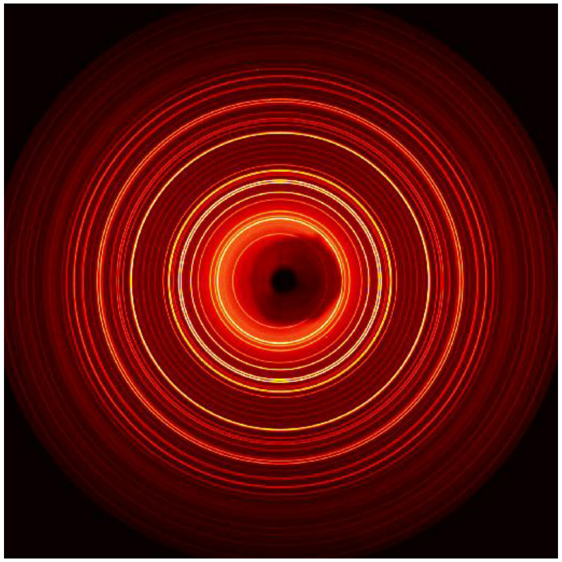
Program: Apex

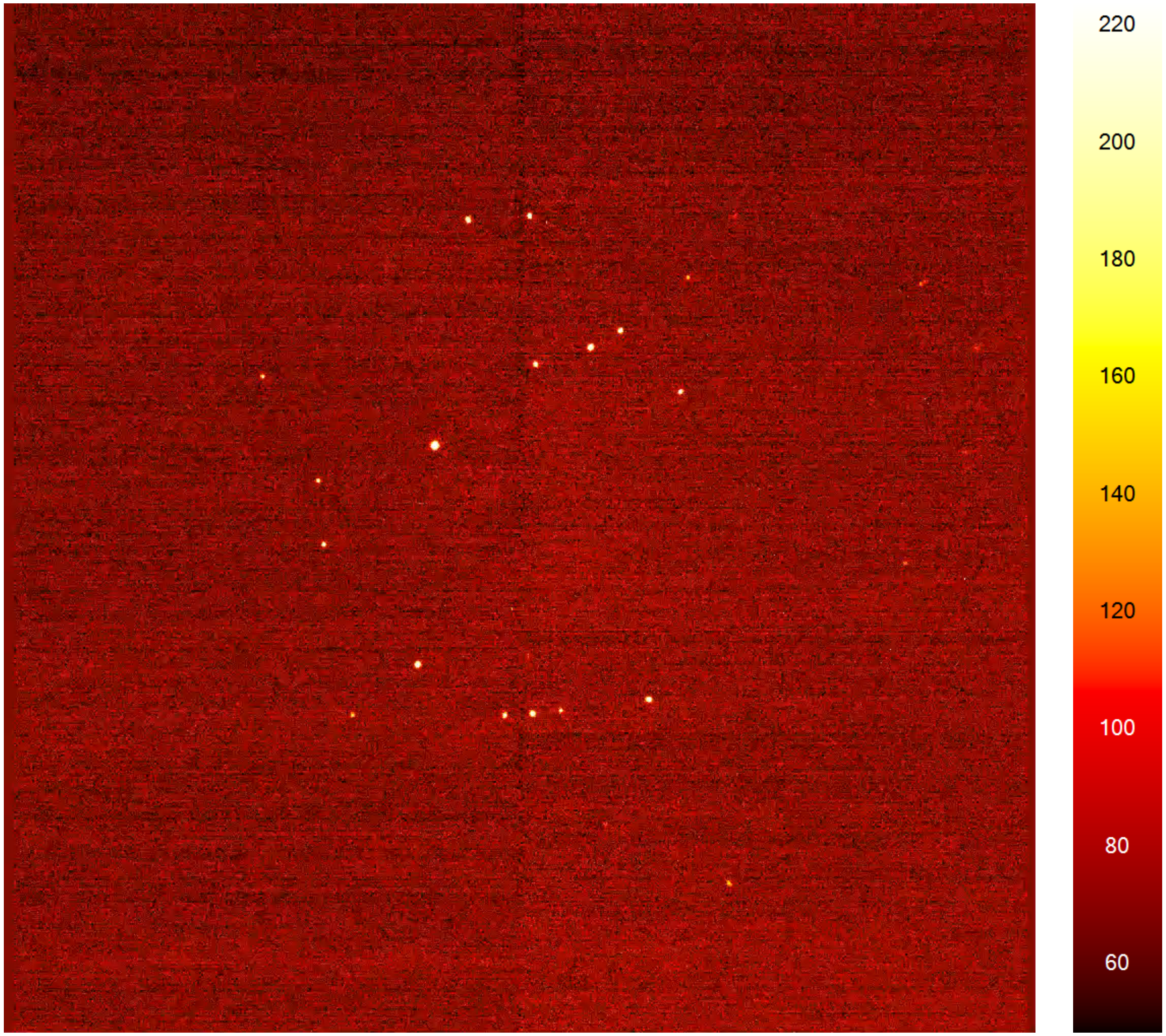
Raw Reflection Images

Reflections should appear as a random assortment of spots

No spots = no crystal

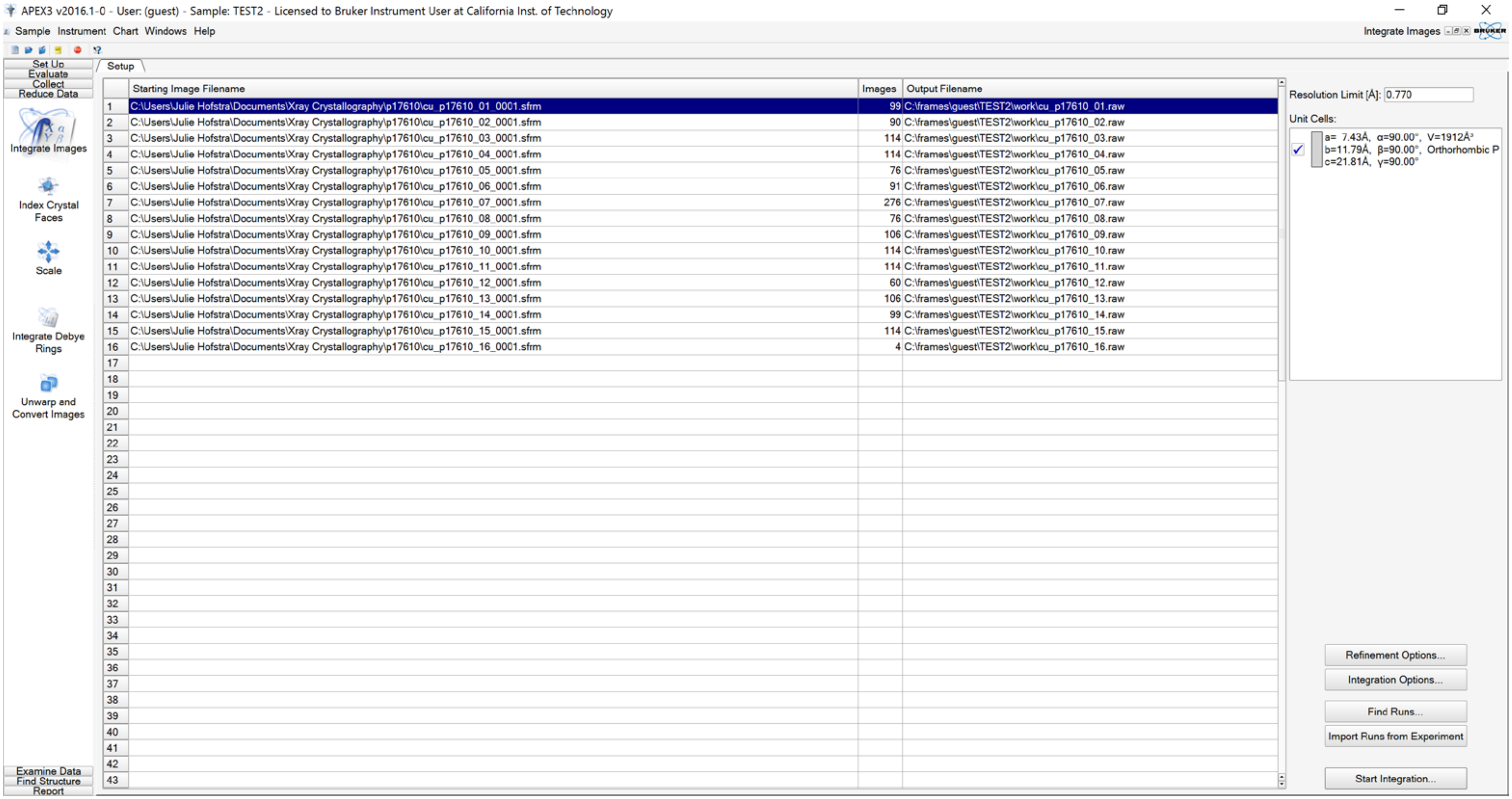
Amorphous solids will powder diffract:





Program: Apex

Data Integration



APEX3 v2016.1-0 - User: (guest) - Sample: TEST2 - Licensed to Bruker Instrument User at California Inst. of Technology

	Starting Image Filename	Images	Output Filename
1	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_01_0001.sfrm	99	C:\frames\guest\TEST2\work\cu_p17610_01.raw
2	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_02_0001.sfrm	90	C:\frames\guest\TEST2\work\cu_p17610_02.raw
3	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_03_0001.sfrm	114	C:\frames\guest\TEST2\work\cu_p17610_03.raw
4	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_04_0001.sfrm	114	C:\frames\guest\TEST2\work\cu_p17610_04.raw
5	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_05_0001.sfrm	76	C:\frames\guest\TEST2\work\cu_p17610_05.raw
6	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_06_0001.sfrm	91	C:\frames\guest\TEST2\work\cu_p17610_06.raw
7	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_07_0001.sfrm	276	C:\frames\guest\TEST2\work\cu_p17610_07.raw
8	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_08_0001.sfrm	76	C:\frames\guest\TEST2\work\cu_p17610_08.raw
9	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_09_0001.sfrm	106	C:\frames\guest\TEST2\work\cu_p17610_09.raw
10	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_10_0001.sfrm	114	C:\frames\guest\TEST2\work\cu_p17610_10.raw
11	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_11_0001.sfrm	114	C:\frames\guest\TEST2\work\cu_p17610_11.raw
12	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_12_0001.sfrm	60	C:\frames\guest\TEST2\work\cu_p17610_12.raw
13	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_13_0001.sfrm	106	C:\frames\guest\TEST2\work\cu_p17610_13.raw
14	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_14_0001.sfrm	99	C:\frames\guest\TEST2\work\cu_p17610_14.raw
15	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_15_0001.sfrm	114	C:\frames\guest\TEST2\work\cu_p17610_15.raw
16	C:\Users\Julie Hofstra\Documents\Xray Crystallography\p17610\cu_p17610_16_0001.sfrm	4	C:\frames\guest\TEST2\work\cu_p17610_16.raw
17			
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42			
43			

Resolution Limit [Å]: 0.770

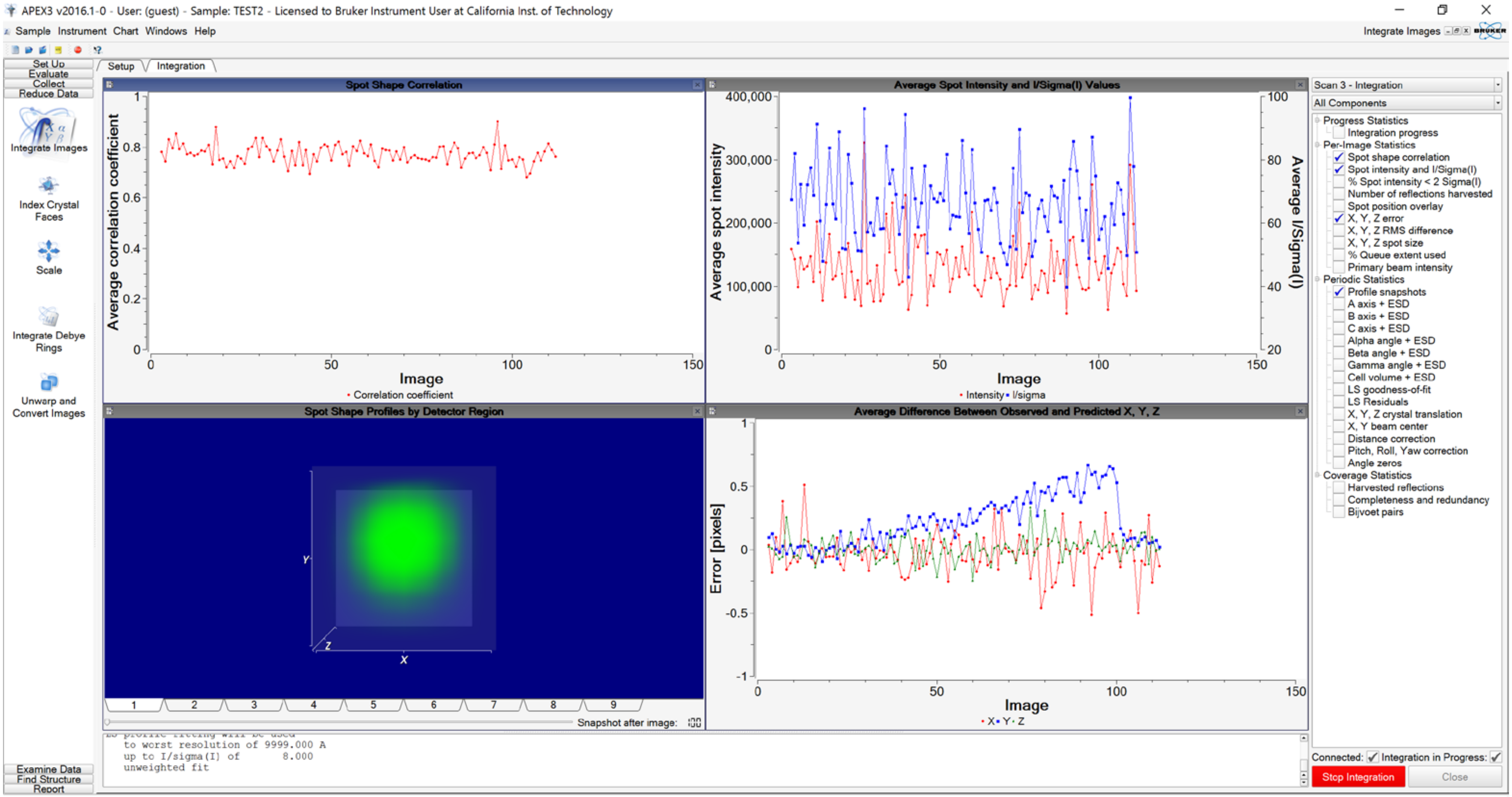
Unit Cells:

☑ a= 7.43Å, α=90.00°, V=1912Å³
b=11.79Å, β=90.00°, Orthorhombic P
c=21.81Å, γ=90.00°

Load all the frames (images) into Apex
In this case, it is 1653 images!

Program: Apex

Data Integration



Scan 3 - Integration

All Components

- Progress Statistics
  - ☐ Integration progress
- Per-Image Statistics
  - ☑ Spot shape correlation
  - ☑ Spot intensity and I/Sigma(I)
  - ☐ % Spot intensity < 2 Sigma(I)
  - ☐ Number of reflections harvested
  - ☐ Spot position overlay
  - ☑ X, Y, Z error
  - ☐ X, Y, Z RMS difference
  - ☐ X, Y, Z spot size
  - ☐ % Queue extent used
  - ☐ Primary beam intensity
- Periodic Statistics
  - ☑ Profile snapshots
  - ☐ A axis + ESD
  - ☐ B axis + ESD
  - ☐ C axis + ESD
  - ☐ Alpha angle + ESD
  - ☐ Beta angle + ESD
  - ☐ Gamma angle + ESD
  - ☐ Cell volume + ESD
  - ☐ LS goodness-of-fit
  - ☐ LS Residuals
  - ☐ X, Y, Z crystal translation
  - ☐ X, Y beam center
  - ☐ Distance correction
  - ☐ Pitch, Roll, Yaw correction
  - ☐ Angle zeros
- Coverage Statistics
  - ☐ Harvested reflections
  - ☐ Completeness and redundancy
  - ☐ Bijvoet pairs

Connected: ☑ Integration in Progress: ☑

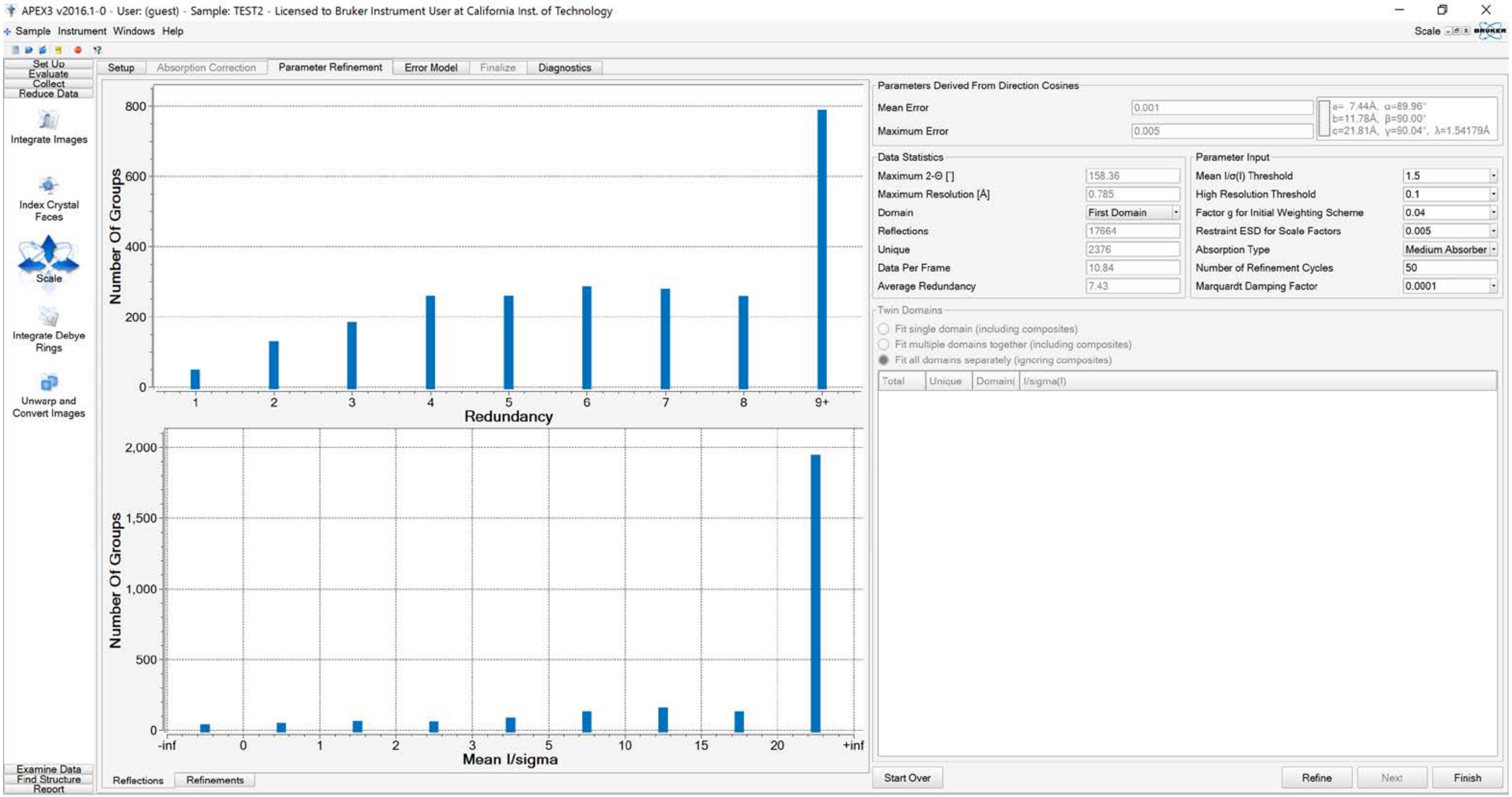
```
LS profile fitting will be used
   to worst resolution of 9999.000 A
   up to I/sigma(I) of       8.000
   unweighted fit
```

Apex integrates all the images to find location and intensity of reflections

Typically the better the "average correlation coefficient" the better the structure

Program: Apex

Absorption Correction



APEX3 v2016.1-0 - User: (guest) - Sample: TEST2 - Licensed to Bruker Instrument User at California Inst. of Technology

Parameters Derived From Direction Cosines

Mean Error	0.001
Maximum Error	0.005

a= 7.44Å, α=89.96°
b=11.78Å, β=90.00°
c=21.81Å, γ=90.04°, λ=1.54179Å

Data Statistics

Maximum 2-Θ [°]	158.36
Maximum Resolution [Å]	0.785
Domain	First Domain
Reflections	17664
Unique	2376
Data Per Frame	10.84
Average Redundancy	7.43

Parameter Input

Mean I/σ(I) Threshold	1.5
High Resolution Threshold	0.1
Factor g for Initial Weighting Scheme	0.04
Restraint ESD for Scale Factors	0.005
Absorption Type	Medium Absorber
Number of Refinement Cycles	50
Marquardt Damping Factor	0.0001

Twin Domains

○ Fit single domain (including composites)
○ Fit multiple domains together (including composites)
● Fit all domains separately (ignoring composites)

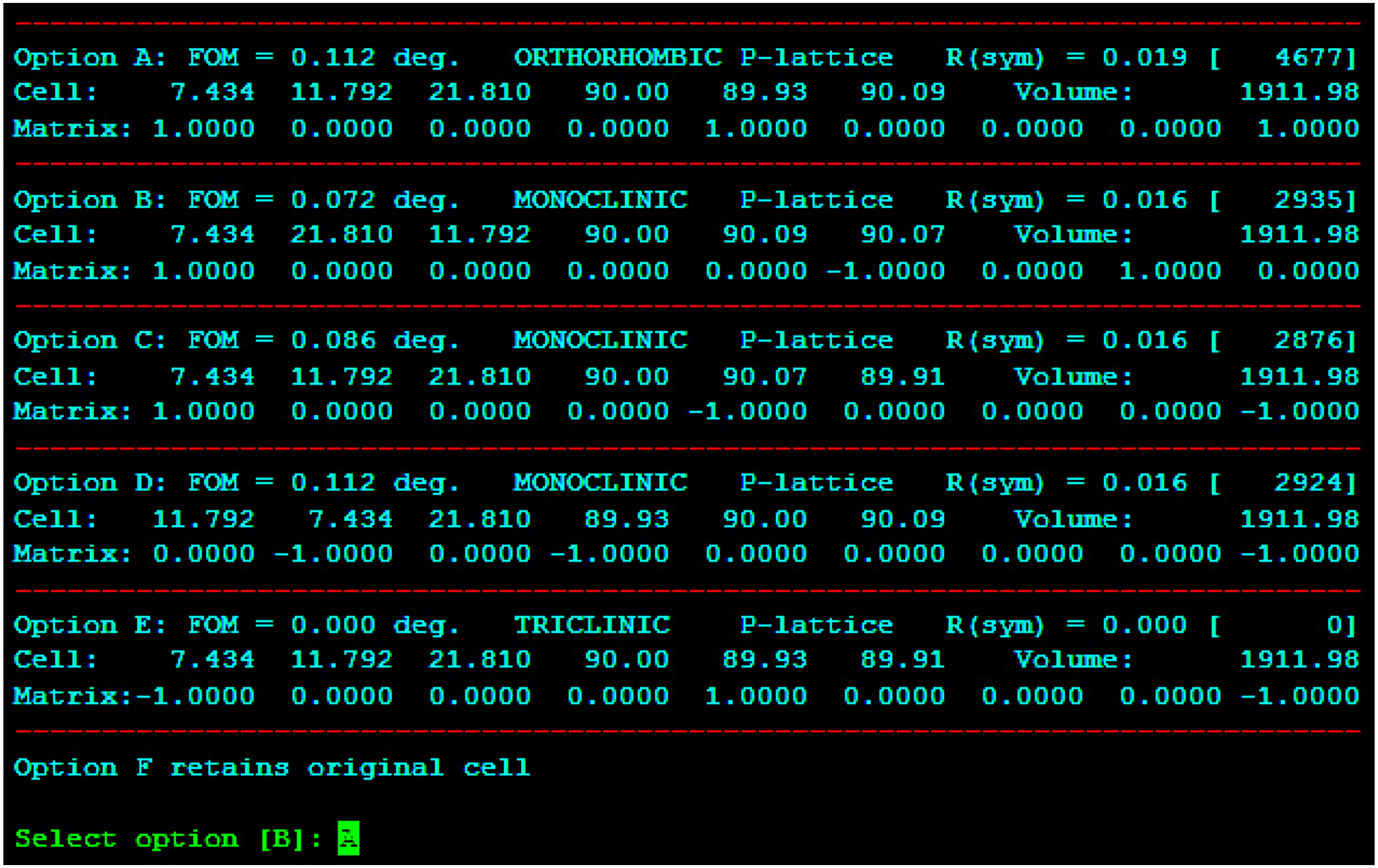
Data is scaled and refined

Corrects the intensity for the distance the X-rays have to travel through the crystal

Program: XPREP

Determine Space Group

increasing symmetry



```
-------------------------------------------------------------------------------
Option A: FOM = 0.112 deg.   ORTHORHOMBIC P-lattice   R(sym) = 0.019 [   4677]
Cell:     7.434  11.792  21.810   90.00   89.93   90.09   Volume:      1911.98
Matrix: 1.0000  0.0000  0.0000  0.0000  1.0000  0.0000  0.0000  0.0000  1.0000
-------------------------------------------------------------------------------
Option B: FOM = 0.072 deg.   MONOCLINIC   P-lattice   R(sym) = 0.016 [   2935]
Cell:     7.434  21.810  11.792   90.00   90.09   90.07   Volume:      1911.98
Matrix: 1.0000  0.0000  0.0000  0.0000  0.0000 -1.0000  0.0000  1.0000  0.0000
-------------------------------------------------------------------------------
Option C: FOM = 0.086 deg.   MONOCLINIC   P-lattice   R(sym) = 0.016 [   2876]
Cell:     7.434  11.792  21.810   90.00   90.07   89.91   Volume:      1911.98
Matrix: 1.0000  0.0000  0.0000  0.0000 -1.0000  0.0000  0.0000  0.0000 -1.0000
-------------------------------------------------------------------------------
Option D: FOM = 0.112 deg.   MONOCLINIC   P-lattice   R(sym) = 0.016 [   2924]
Cell:    11.792   7.434  21.810   89.93   90.00   90.09   Volume:      1911.98
Matrix: 0.0000 -1.0000  0.0000 -1.0000  0.0000  0.0000  0.0000  0.0000 -1.0000
-------------------------------------------------------------------------------
Option E: FOM = 0.000 deg.   TRICLINIC    P-lattice   R(sym) = 0.000 [      0]
Cell:     7.434  11.792  21.810   90.00   89.93   89.91   Volume:      1911.98
Matrix:-1.0000  0.0000  0.0000  0.0000  1.0000  0.0000  0.0000  0.0000 -1.0000
-------------------------------------------------------------------------------
Option F retains original cell

Select option [B]: A
```

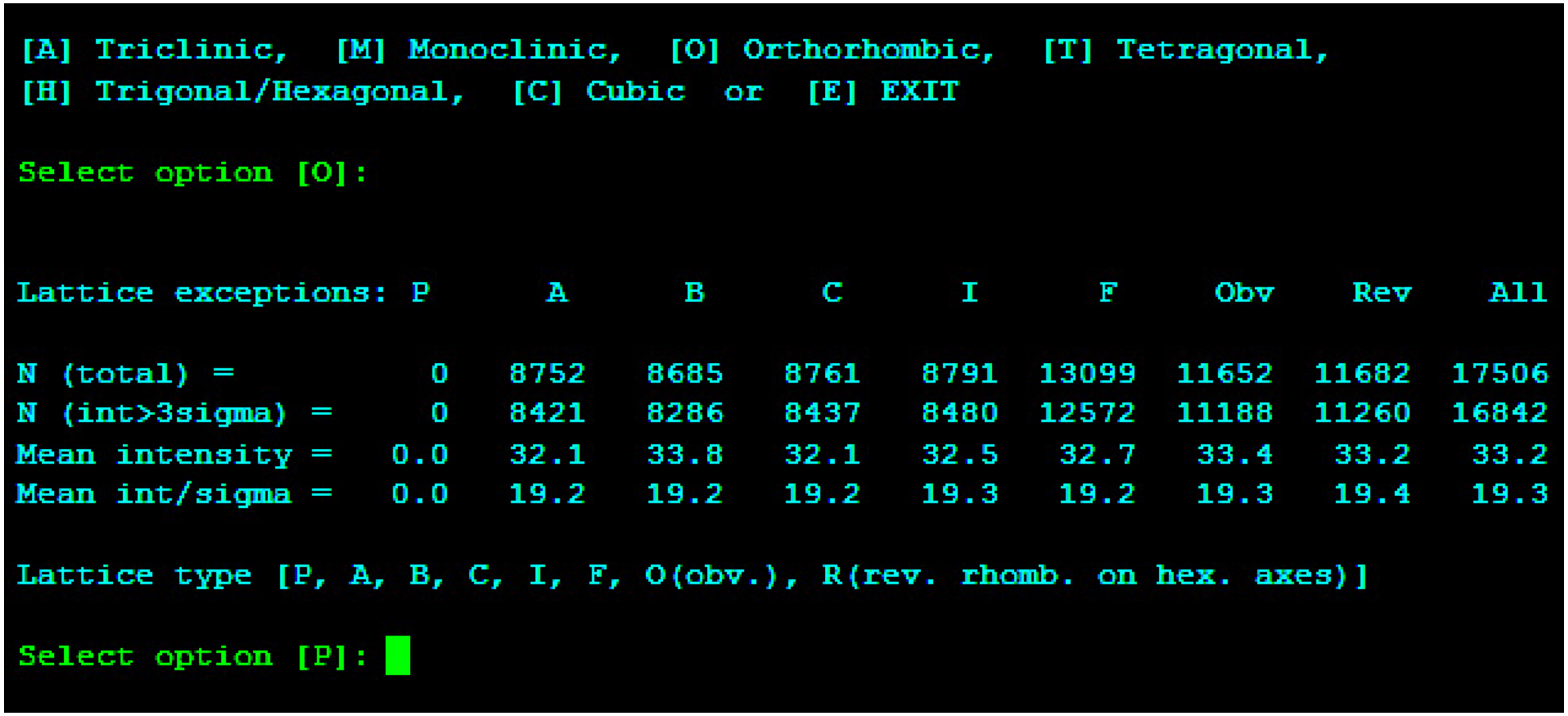
Search for higher order metric symmetry

All options have low figure of merit (FOM) and low R(sym)

XPREP picked B (lowest FOM) but better choice is A (orthorhombic)

Program: XPREP

Determine Space Group



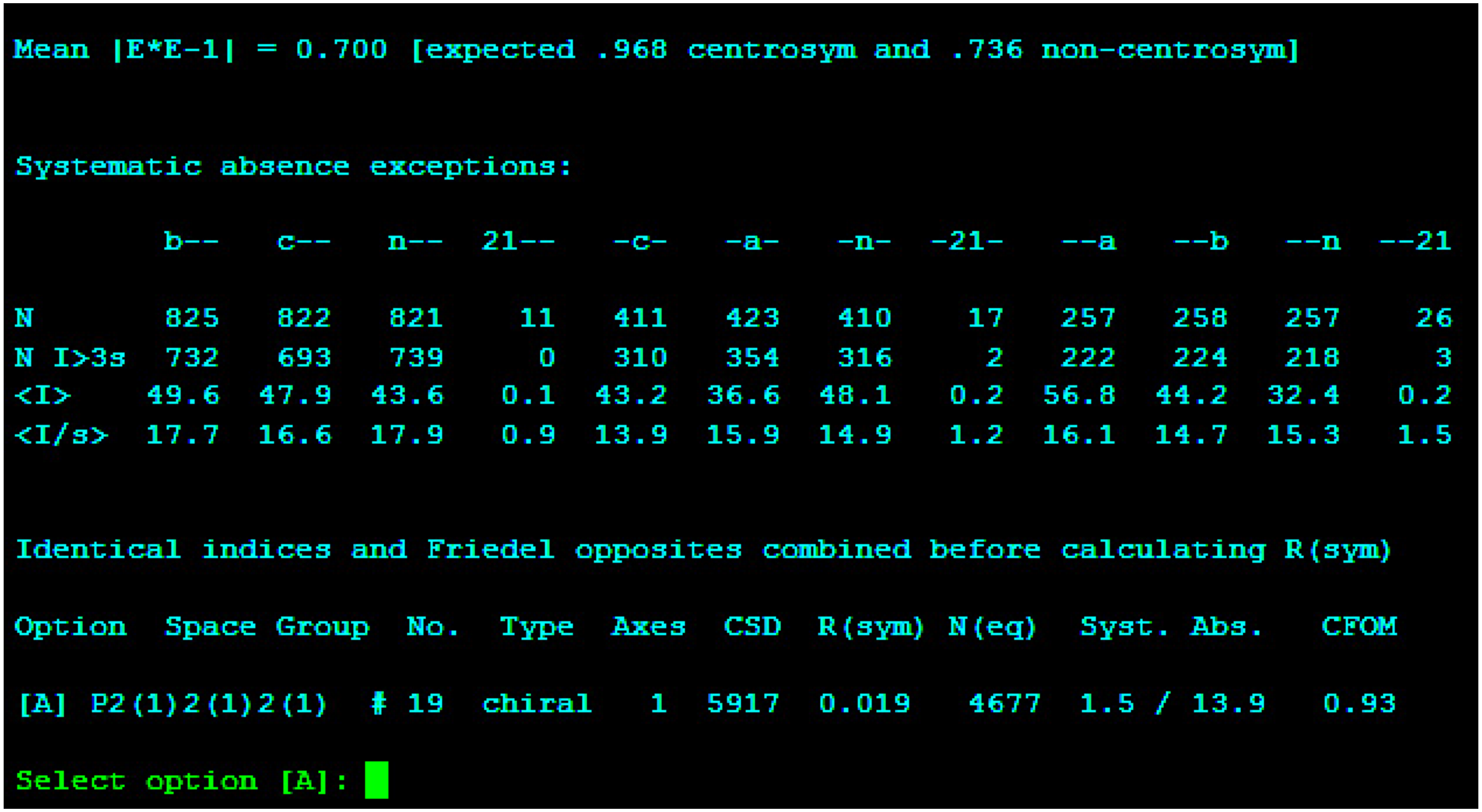
```
[A] Triclinic,  [M] Monoclinic,  [O] Orthorhombic,  [T] Tetragonal,
[H] Trigonal/Hexagonal,  [C] Cubic  or  [E] EXIT

Select option [O]:


Lattice exceptions: P      A      B      C      I      F    Obv    Rev    All

N (total) =         0   8752   8685   8761   8791  13099  11652  11682  17506
N (int>3sigma) =    0   8421   8286   8437   8480  12572  11188  11260  16842
Mean intensity =  0.0   32.1   33.8   32.1   32.5   32.7   33.4   33.2   33.2
Mean int/sigma =  0.0   19.2   19.2   19.2   19.3   19.2   19.3   19.4   19.3

Lattice type [P, A, B, C, I, F, O(obv.), R(rev. rhomb. on hex. axes)]

Select option [P]:
```

P = primitive cell; A, B, C = end-centered cells; I = body-centered cell;
F = face-centered cell; Obv = trigonal cell; Rev = hexagonal cell

Determine space group and lattice exceptions
Looking for values where mean int/sigma is close to 0, so the answer here is P (primitive)

Program: XPREP

Determine Space Group



```
Mean |E*E-1| = 0.700 [expected .968 centrosym and .736 non-centrosym]


Systematic absence exceptions:

           b--    c--    n--   21--    -c-    -a-    -n-   -21-    --a    --b    --n   --21

N          825    822    821     11    411    423    410     17    257    258    257     26
N I>3s     732    693    739      0    310    354    316      2    222    224    218      3
<I>       49.6   47.9   43.6    0.1   43.2   36.6   48.1    0.2   56.8   44.2   32.4    0.2
<I/s>     17.7   16.6   17.9    0.9   13.9   15.9   14.9    1.2   16.1   14.7   15.3    1.5


Identical indices and Friedel opposites combined before calculating R(sym)

Option  Space Group  No.  Type   Axes  CSD  R(sym) N(eq)  Syst. Abs.   CFOM

[A] P2(1)2(1)2(1)  # 19  chiral   1  5917  0.019   4677  1.5 / 13.9   0.93

Select option [A]: 
```

Look for systematic absences where <I/s> is close to 0, so here the answer is 21--, -21-, --21
Combining all this information, we choose the space group (only one option: $P2_12_12_1$)
We know the molecule is chiral, and this is a chiral space group which is a good sign

Program: XPREP

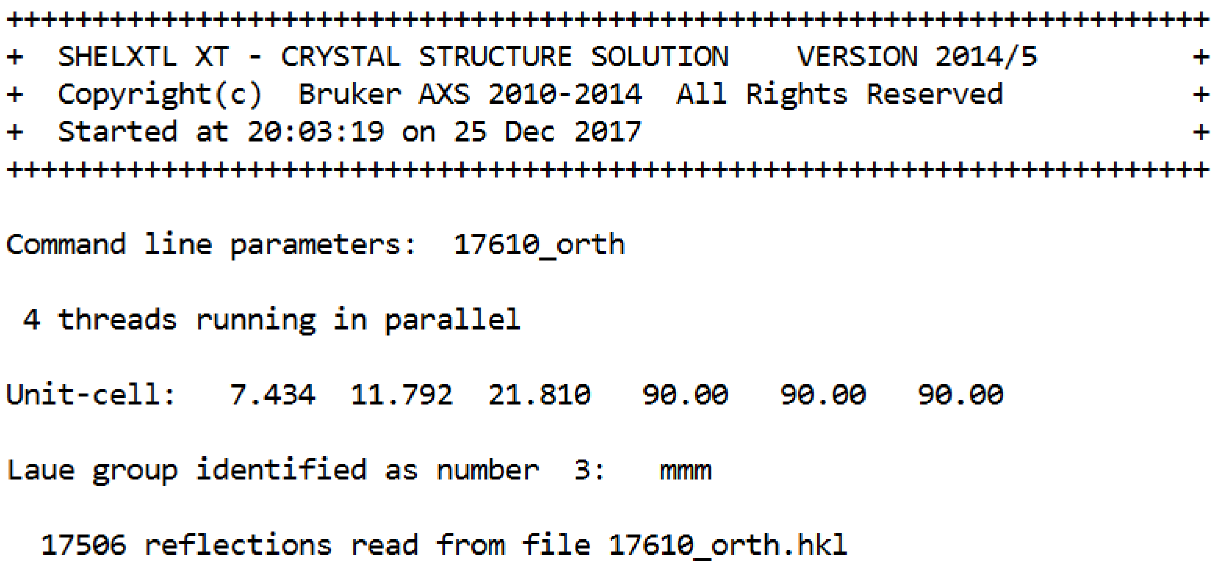
Determine Space Group

```
 Resolution    #Data #Theory %Complete Redundancy Mean I  Mean I/s Rmerge    Rsigma
 Inf - 3.63       36      37      97.3      3.32  283.41    44.55  0.0264    0.0210
3.63 - 2.30       86      87      98.9      6.18  156.55    59.11  0.0247    0.0159
2.30 - 1.80      115     115     100.0      7.03  103.78    60.37  0.0292    0.0154
1.80 - 1.54      120     120     100.0      7.14   55.68    55.08  0.0230    0.0160
1.54 - 1.39      125     125     100.0      6.88   32.71    43.03  0.0295    0.0188
1.39 - 1.28      123     123     100.0      8.31   37.74    52.24  0.0383    0.0165
1.28 - 1.20      119     119     100.0     12.87   39.70    67.99  0.0347    0.0126
1.20 - 1.14      116     116     100.0     10.69   35.23    64.95  0.0280    0.0134
1.14 - 1.09      107     107     100.0      9.00   28.56    56.40  0.0329    0.0169
1.09 - 1.04      134     134     100.0      9.87   26.43    59.73  0.0266    0.0142
1.04 - 1.00      121     121     100.0      9.48   18.69    56.79  0.0334    0.0152
1.00 - 0.97      119     119     100.0      8.87   15.75    55.15  0.0335    0.0155
0.97 - 0.94      117     117     100.0      8.56   10.29    47.06  0.0383    0.0172
0.94 - 0.91      136     136     100.0      6.88   10.90    45.64  0.0462    0.0186
0.91 - 0.89      109     109     100.0      6.72   10.14    46.75  0.0296    0.0177
0.89 - 0.87      110     110     100.0      6.64    7.97    44.94  0.0316    0.0184
0.87 - 0.85      120     120     100.0      5.78   10.57    46.15  0.0294    0.0179
0.85 - 0.83      133     133     100.0      5.61    9.60    45.67  0.0286    0.0195
0.83 - 0.81      152     154      98.7      4.38    8.42    38.48  0.0319    0.0217
0.81 - 0.80       70      75      93.3      3.48    9.43    41.08  0.0219    0.0227
0.80 - 0.79      106     123      86.2      2.13    7.29    32.57  0.0264    0.0279
```

The theoretical amount of data that could be collected for each resolution range is high
Also good redundancies and high intensities

Program: XT

Data Solution

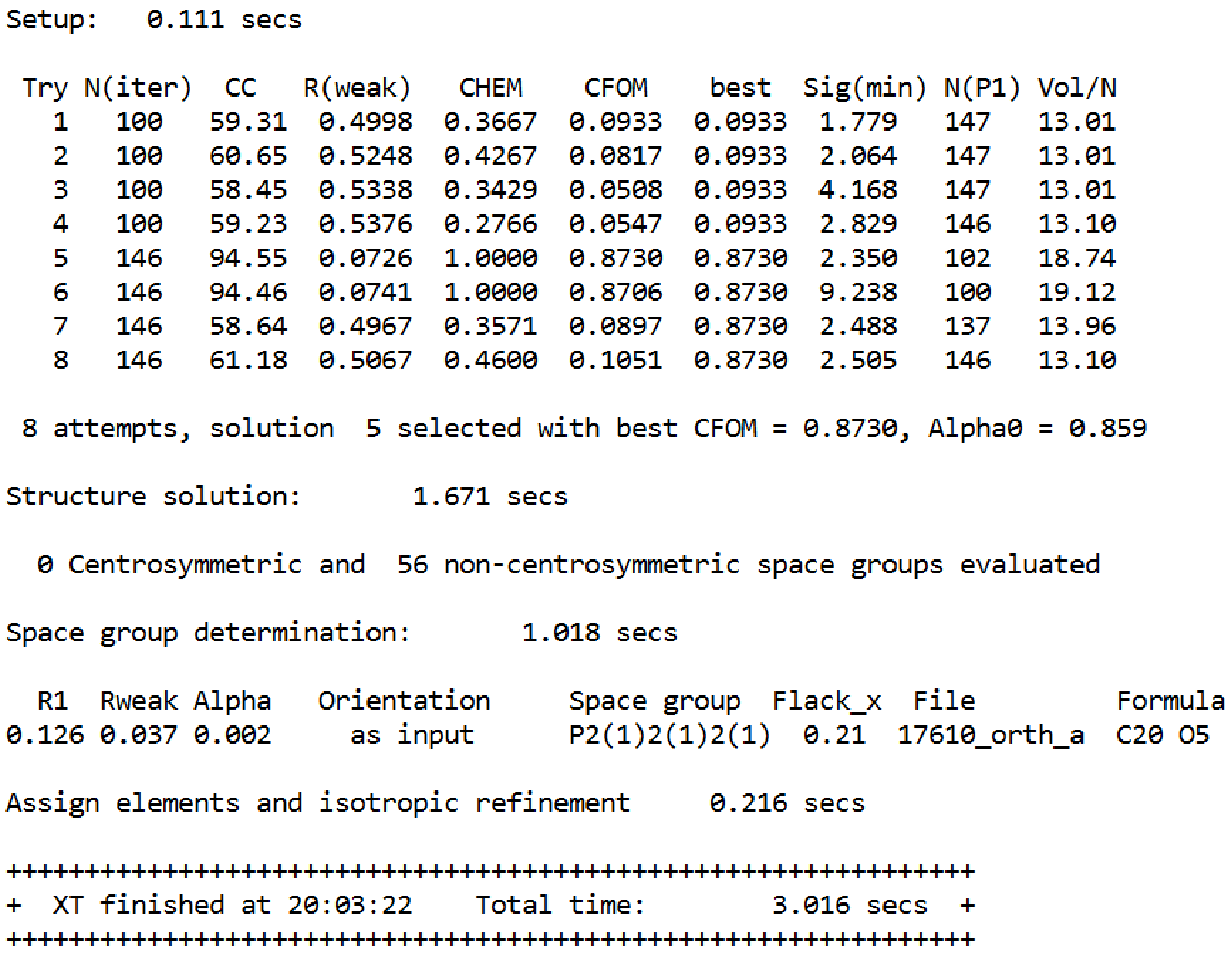


```
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  SHELXTL XT - CRYSTAL STRUCTURE SOLUTION    VERSION 2014/5        +
+  Copyright(c)  Bruker AXS 2010-2014  All Rights Reserved          +
+  Started at 20:03:19 on 25 Dec 2017                               +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++

Command line parameters:  17610_orth

 4 threads running in parallel

Unit-cell:   7.434  11.792  21.810   90.00   90.00   90.00

Laue group identified as number  3:   mmm

  17506 reflections read from file 17610_orth.hkl
```

This is where we estimate the phases
Solve data set with XT

Program: XT

Data Solution



```
Setup:    0.111 secs

 Try N(iter)  CC    R(weak)   CHEM     CFOM     best   Sig(min) N(P1) Vol/N
   1    100   59.31  0.4998  0.3667  0.0933  0.0933  1.779    147   13.01
   2    100   60.65  0.5248  0.4267  0.0817  0.0933  2.064    147   13.01
   3    100   58.45  0.5338  0.3429  0.0508  0.0933  4.168    147   13.01
   4    100   59.23  0.5376  0.2766  0.0547  0.0933  2.829    146   13.10
   5    146   94.55  0.0726  1.0000  0.8730  0.8730  2.350    102   18.74
   6    146   94.46  0.0741  1.0000  0.8706  0.8730  9.238    100   19.12
   7    146   58.64  0.4967  0.3571  0.0897  0.8730  2.488    137   13.96
   8    146   61.18  0.5067  0.4600  0.1051  0.8730  2.505    146   13.10

 8 attempts, solution  5 selected with best CFOM = 0.8730, Alpha0 = 0.859

Structure solution:       1.671 secs

  0 Centrosymmetric and  56 non-centrosymmetric space groups evaluated

Space group determination:       1.018 secs

  R1   Rweak Alpha  Orientation     Space group  Flack_x  File         Formula
0.126 0.037 0.002     as input      P2(1)2(1)2(1)  0.21  17610_orth_a  C20 O5

Assign elements and isotropic refinement      0.216 secs

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  XT finished at 20:03:22     Total time:        3.016 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

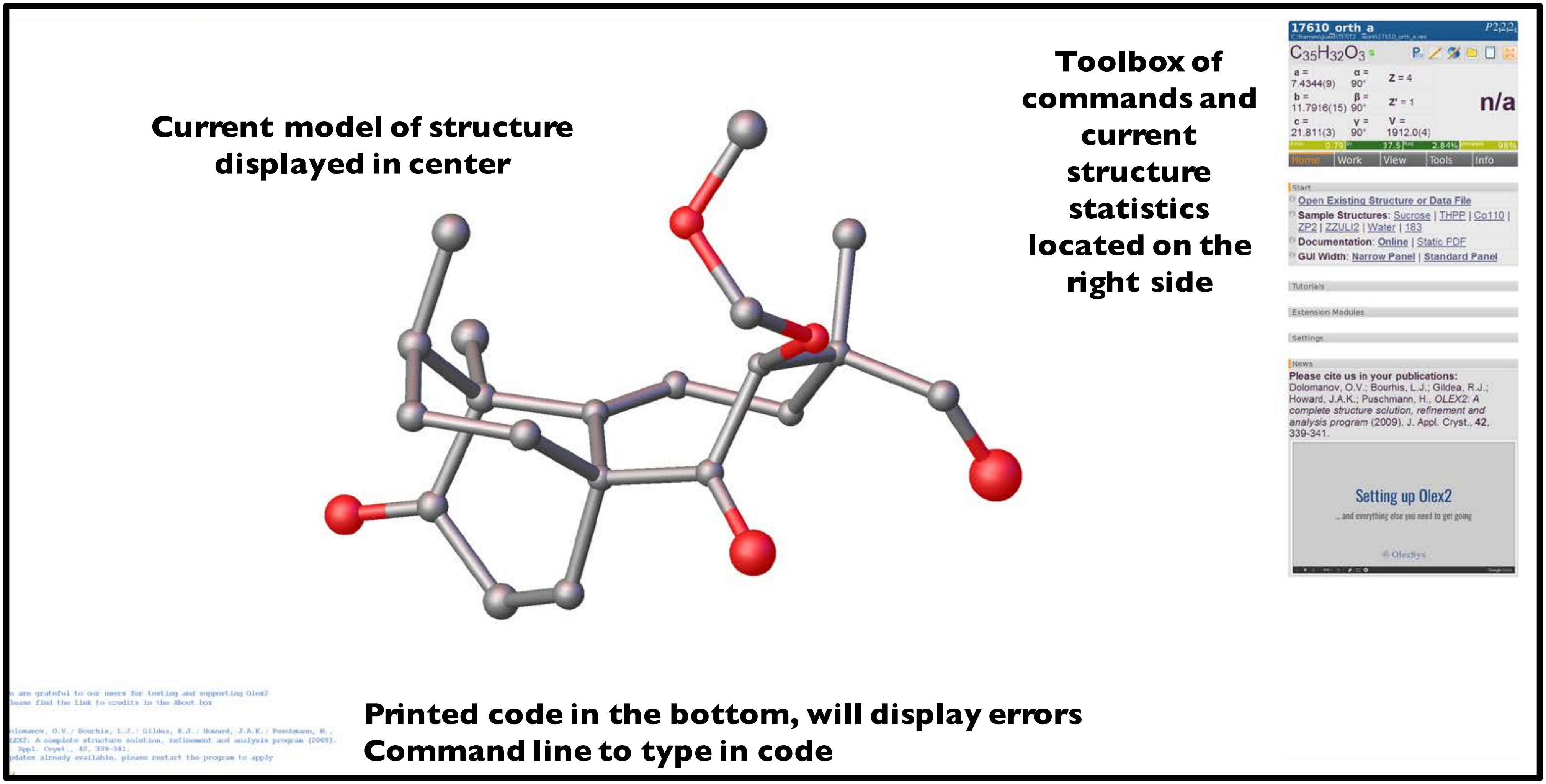
This is where we estimate the phases

Solve data set with XT

Program: Olex

Data Refinement

Recall: Olex is a graphical program to aid in data refinement



Current model of structure displayed in center

Toolbox of commands and current structure statistics located on the right side

Printed code in the bottom, will display errors
Command line to type in code

17610_orth_a $P2_12_12_1$

$C_{35}H_{32}O_3$

a = 7.4344(9)	α = 90°	Z = 4	n/a
b = 11.7916(15)	β = 90°	Z' = 1	
c = 21.811(3)	γ = 90°	V = 1912.0(4)	

Open Existing Structure or Data File

Sample Structures: Sucrose | THPP | Co110 | ZP2 | ZZULI2 | Water | 183

Documentation: Online | Static PDF

GUI Width: Narrow Panel | Standard Panel

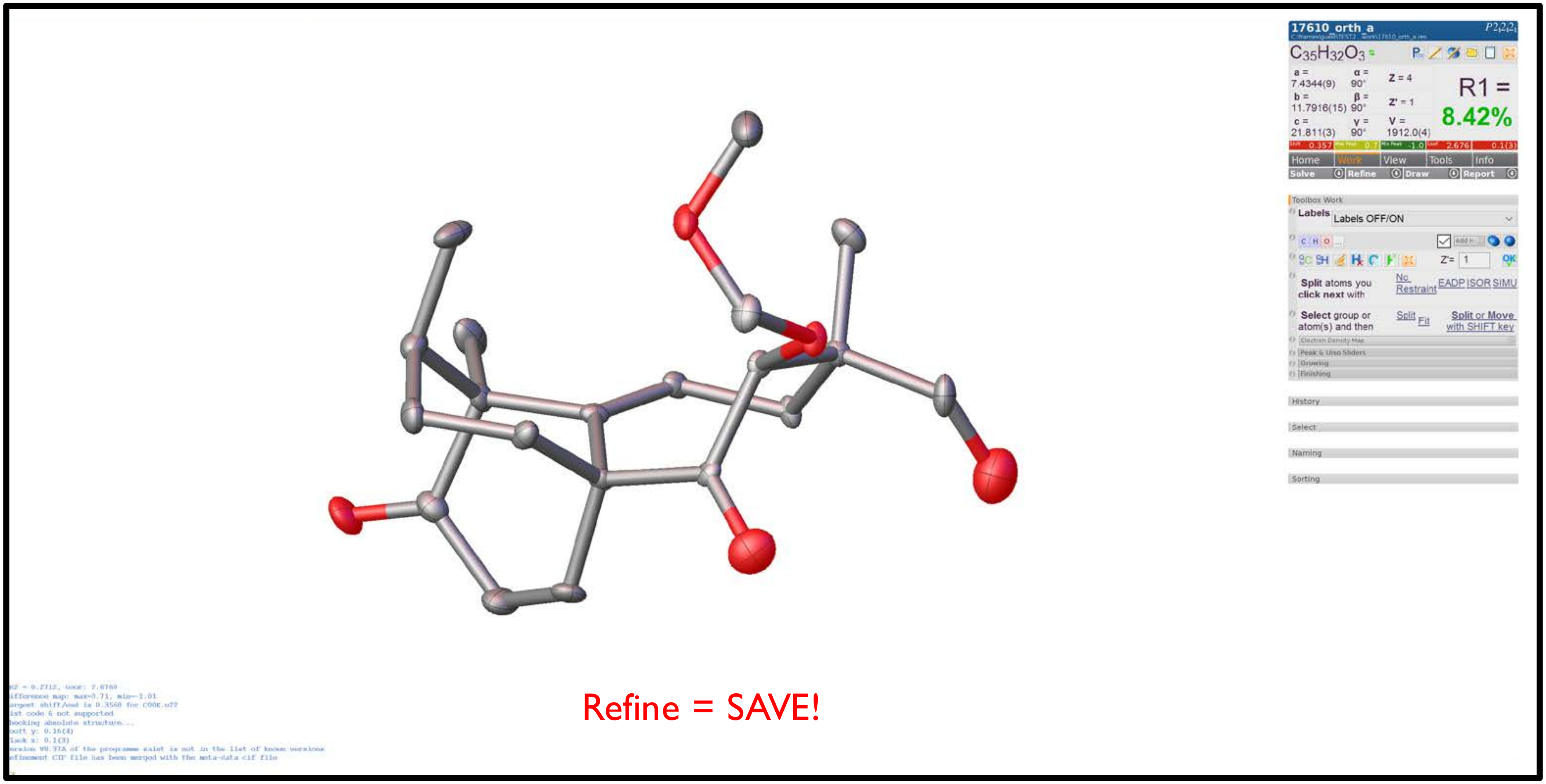
Please cite us in your publications:
Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., *OLEX2: A complete structure solution, refinement and analysis program* (2009). J. Appl. Cryst., **42**, 339-341.

```
e are grateful to our users for testing and supporting Olex2
lease find the link to credits in the About box

olomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H.,
LEX2: A complete structure solution, refinement and analysis program (2009).
. Appl. Cryst., 42, 339-341.
pdates already available, please restart the program to apply
```

Opening OLEX shows the initial guess at the developing a model for the electron density map
Atoms are shown without anisotropic displacement

Program: Olex

Data Refinement in Olex



$C_{35}H_{32}O_3$

a = 7.4344(9)
b = 11.7916(15)
c = 21.811(3)
α = 90°
β = 90°
γ = 90°
Z = 4
Z' = 1
V = 1912.0(4)

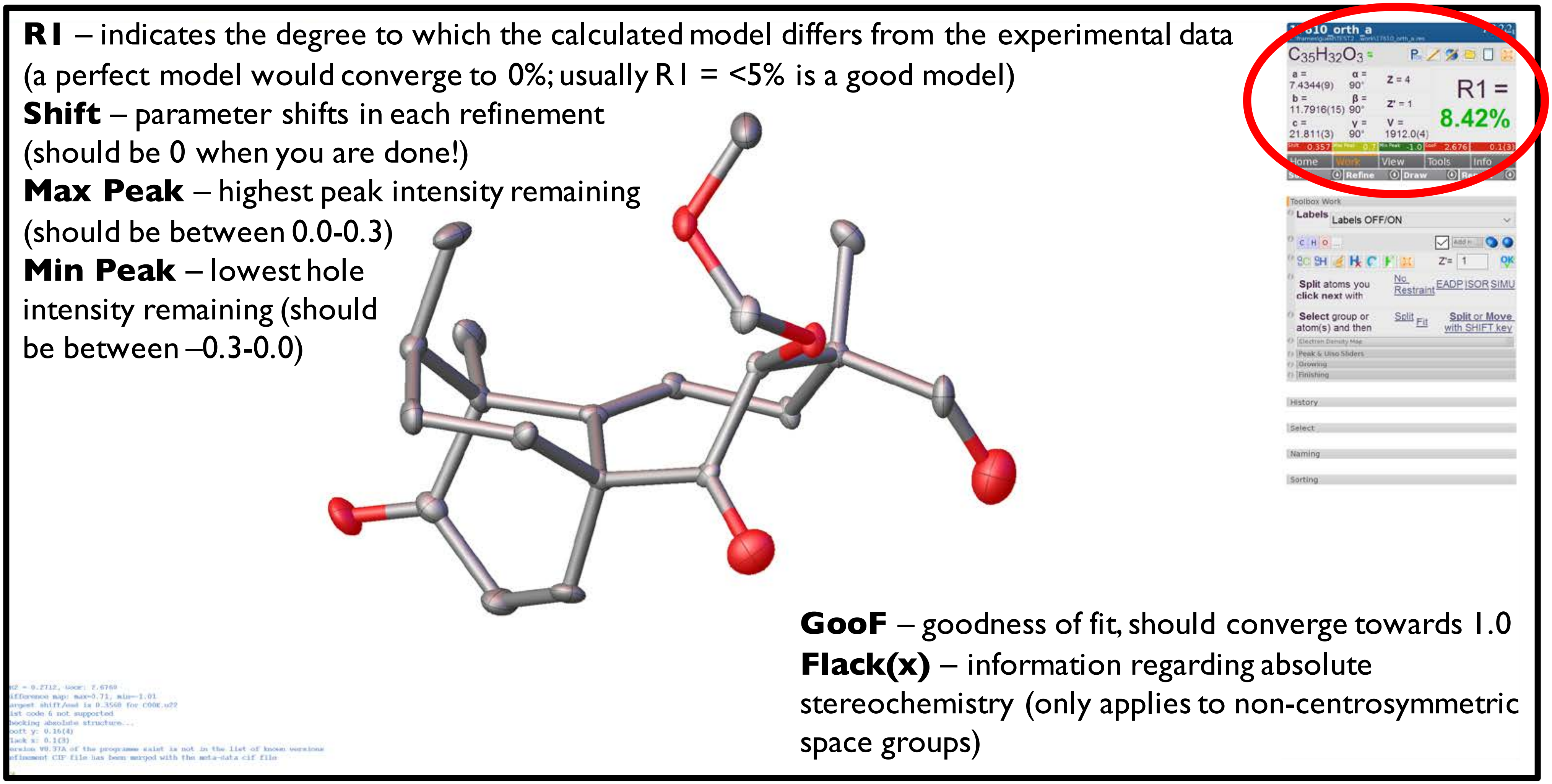
```
R2 = 0.2712, GooF: 2.6760
ifference map: max=0.71, min=-1.01
argest shift/esd is 0.3560 for C00K.u22
ist code 6 not supported
hecking absolute structure...
ooft y: 0.16(4)
lack x: 0.1(3)
ersion V8.37A of the programme saint is not in the list of known versions
efinement CIF file has been merged with the meta-data cif file
```

Refine = SAVE!

Anisotropy is added and atoms become non-spherical ellipsoids
Represents 50% probability and includes 6 parameters for placement instead of 1

Program: Olex

Data Refinement in Olex



R1 – indicates the degree to which the calculated model differs from the experimental data (a perfect model would converge to 0%; usually R1 = <5% is a good model)

Shift – parameter shifts in each refinement (should be 0 when you are done!)

Max Peak – highest peak intensity remaining (should be between 0.0-0.3)

Min Peak – lowest hole intensity remaining (should be between –0.3-0.0)

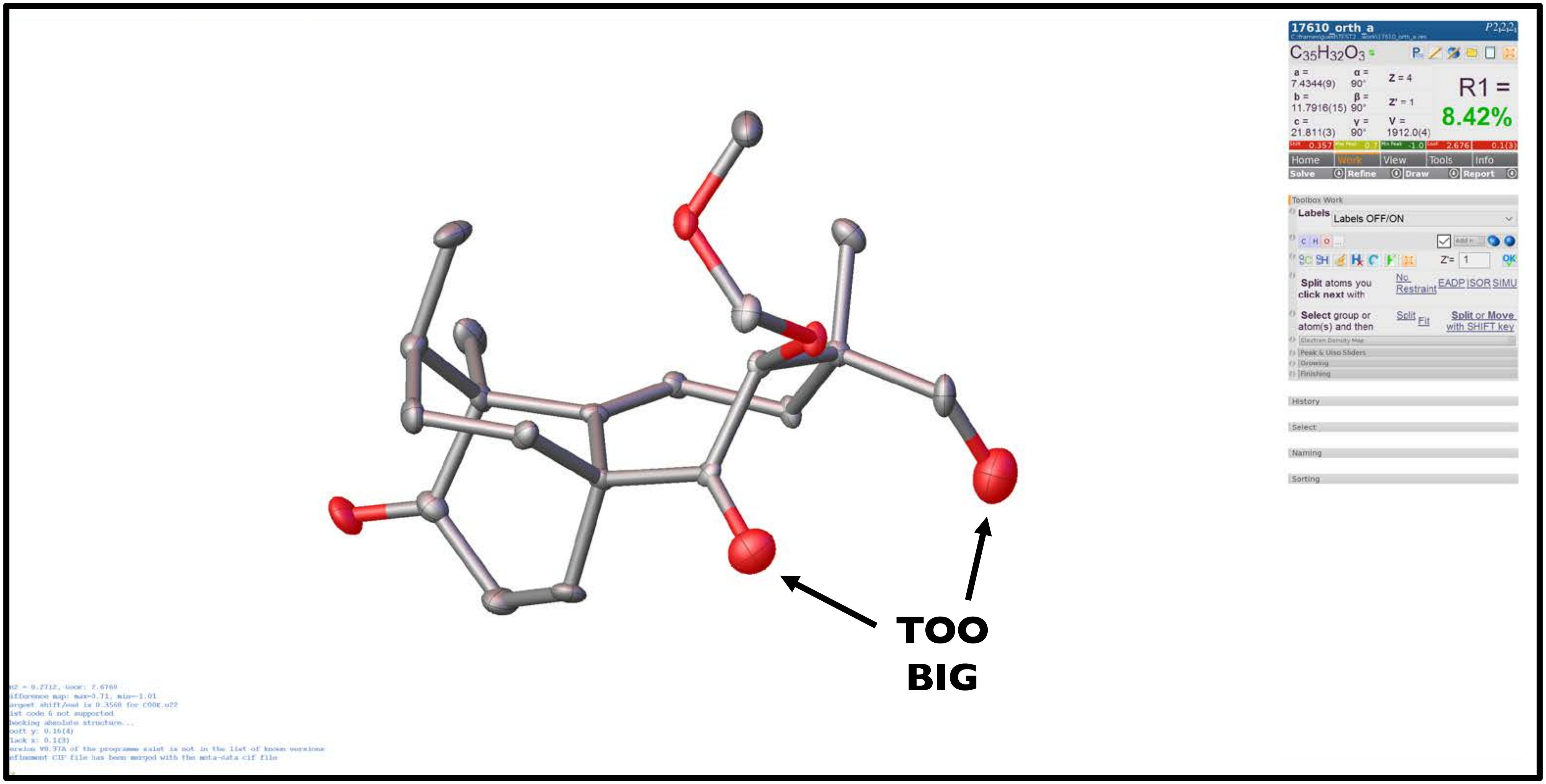
GooF – goodness of fit, should converge towards 1.0

Flack(x) – information regarding absolute stereochemistry (only applies to non-centrosymmetric space groups)

Anisotropy is added and atoms become non-spherical ellipsoids
Represents 50% probability

Program: Olex

Data Refinement in Olex



$C_{35}H_{32}O_3$

a = 7.4344(9)
b = 11.7916(15)
c = 21.811(3)
α = 90°
β = 90°
γ = 90°
Z = 4
Z' = 1
V = 1912.0(4)

R1 = 8.42%

Shift 0.357
Max Peak 0.7
Min Peak -1.0
GooF 2.676
0.1(3)

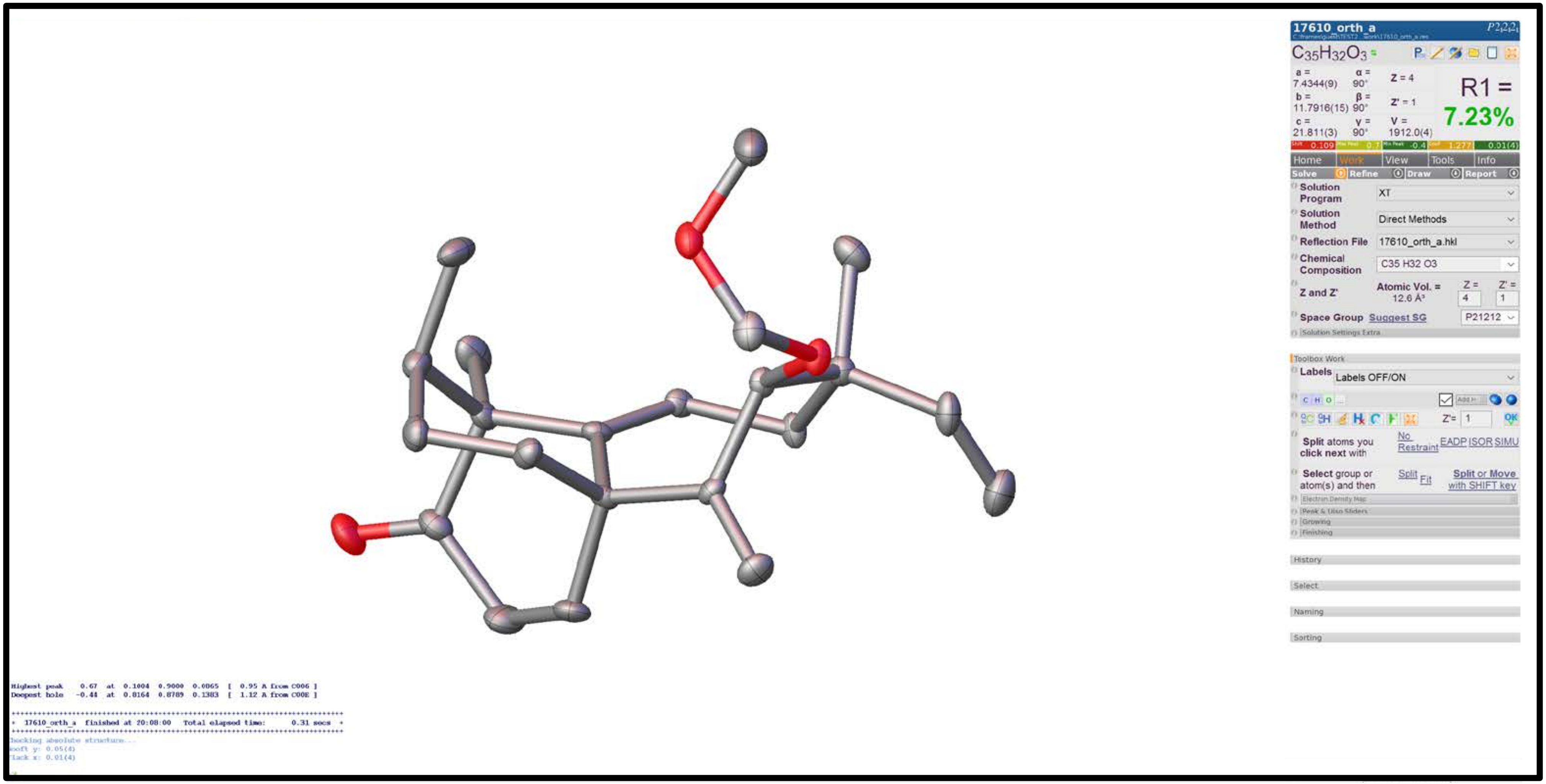
```
R2 = 0.2712, GooF: 2.6760
ifference map: max=0.71, min=-1.01
argest shift/esd is 0.3560 for C00K.u22
ist code 6 not supported
hecking absolute structure...
ooft y: 0.16(4)
lack x: 0.1(3)
ersion V8.37A of the programme saint is not in the list of known versions
efinement CIF file has been merged with the meta-data cif file
```

Atoms are appropriately assigned

Too small = not heavy enough (more e^- density); Too large = assigned too heavy

Program: Olex

Data Refinement in Olex



17610_orth_a $P2_12_12_1$

$C_{35}H_{32}O_3$

a = 7.4344(9) α = 90° Z = 4

b = 11.7916(15) β = 90° Z' = 1

c = 21.811(3) γ = 90° V = 1912.0(4)

R1 = 7.23%

Shift 0.109 | Max Peak 0.7 | Min Peak -0.4 | GooF 1.277 | 0.01(4)

Solution Program: XT

Solution Method: Direct Methods

Reflection File: 17610_orth_a.hkl

Chemical Composition: C35 H32 O3

Z and Z': Atomic Vol. = 12.6 Å³ Z = 4 Z' = 1

Space Group: Suggest SG P21212

Labels: Labels OFF/ON

Z'= 1

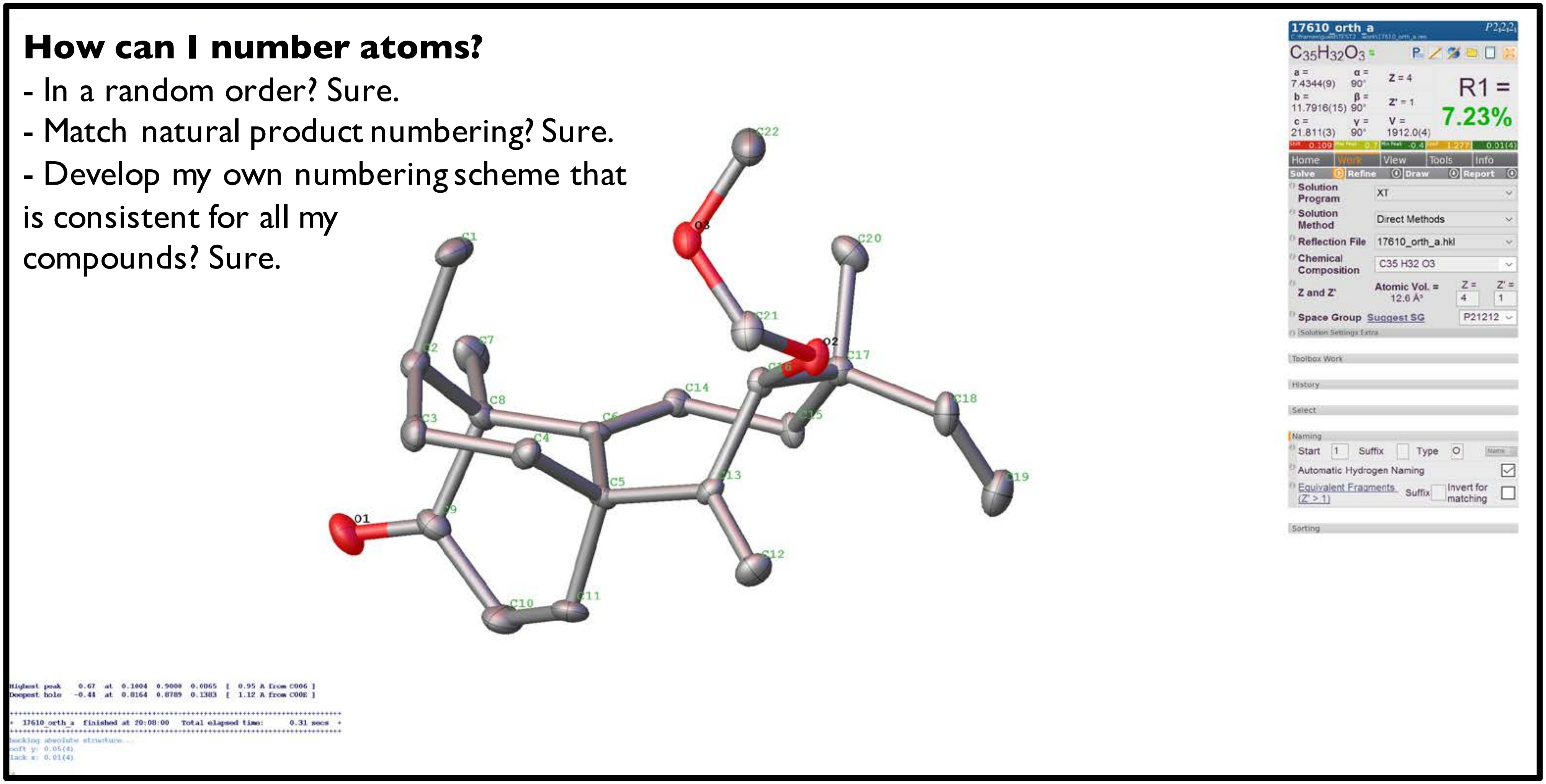
```
Highest peak    0.67  at  0.1004  0.9000  0.0065  [  0.95 A from C006 ]
Deepest hole   -0.44  at  0.8164  0.8789  0.1383  [  1.12 A from C00E ]

+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:08:00   Total elapsed time:      0.31 secs  +
+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
ooft y: 0.05(4)
lack x: 0.01(4)
```

Atoms are appropriately assigned

Too small = not heavy enough (more e$^-$ density); Too large = assigned too heavy

Program: Olex

Data Refinement in Olex



How can I number atoms?

- In a random order? Sure.
- Match natural product numbering? Sure.
- Develop my own numbering scheme that is consistent for all my compounds? Sure.

a = 7.4344(9)
b = 11.7916(15)
c = 21.811(3)
α = 90°
β = 90°
γ = 90°
Z = 4
Z' = 1
V = 1912.0(4)
R1 = 7.23%
Shift 0.109
Max Peak 0.7
Min Peak -0.4
GooF 1.277
0.01(4)

Solution Program: XT
Solution Method: Direct Methods
Reflection File: 17610_orth_a.hkl
Chemical Composition: C35 H32 O3
Z and Z': Atomic Vol. = 12.6 Å³ Z = 4 Z' = 1
Space Group: Suggest SG P21212
Solution Settings Extra

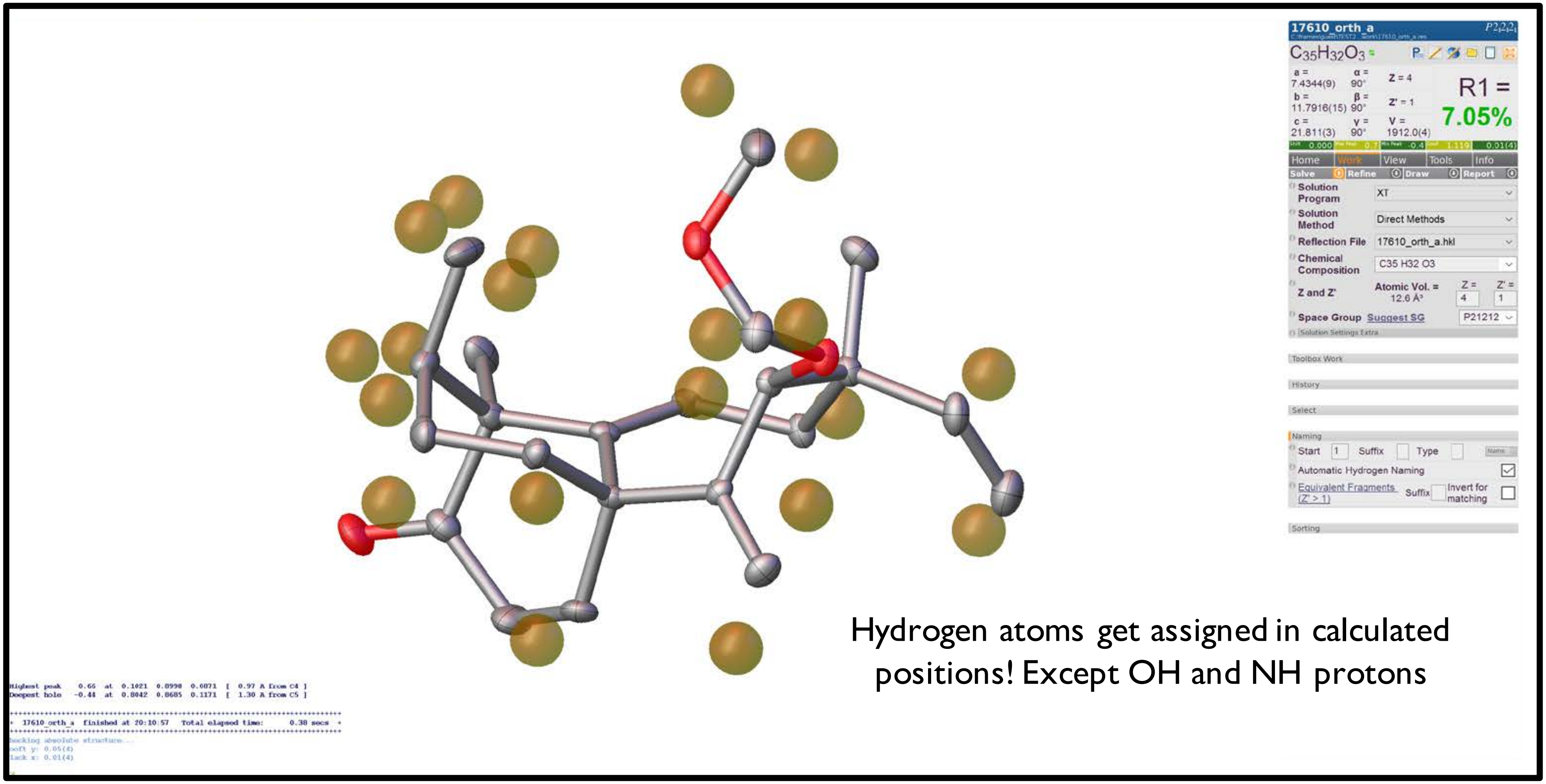
Start 1 Suffix Type O
Automatic Hydrogen Naming ☑
Equivalent Fragments (Z' > 1) Suffix Invert for matching ☐

```
Highest peak    0.67  at  0.1004  0.9000  0.0065  [  0.95 A from C006 ]
Deepest hole   -0.44  at  0.8164  0.8789  0.1383  [  1.12 A from C00E ]

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:08:00   Total elapsed time:      0.31 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
oft y: 0.05(4)
lack x: 0.01(4)
```

Renumber the heavy atoms before adding in hydrogens
Hydrogen atoms are named based on the carbon numbering

Program: Olex

Data Refinement in Olex



17610_orth_a

$P2_12_12_1$

$C_{35}H_{32}O_3$

a = 7.4344(9)
b = 11.7916(15)
c = 21.811(3)
α = 90°
β = 90°
γ = 90°
Z = 4
Z' = 1
V = 1912.0(4)

R1 = 7.05%

Shift 0.000 Max Peak 0.7 Min Peak -0.4 GooF 1.119 0.01(4)

Solution Program: XT
Solution Method: Direct Methods
Reflection File: 17610_orth_a.hkl
Chemical Composition: C35 H32 O3
Z and Z': Atomic Vol. = 12.6 Å³ Z = 4 Z' = 1
Space Group: P21212

Start 1
Automatic Hydrogen Naming ☑
Equivalent Fragments (Z' > 1) Suffix Invert for matching ☐

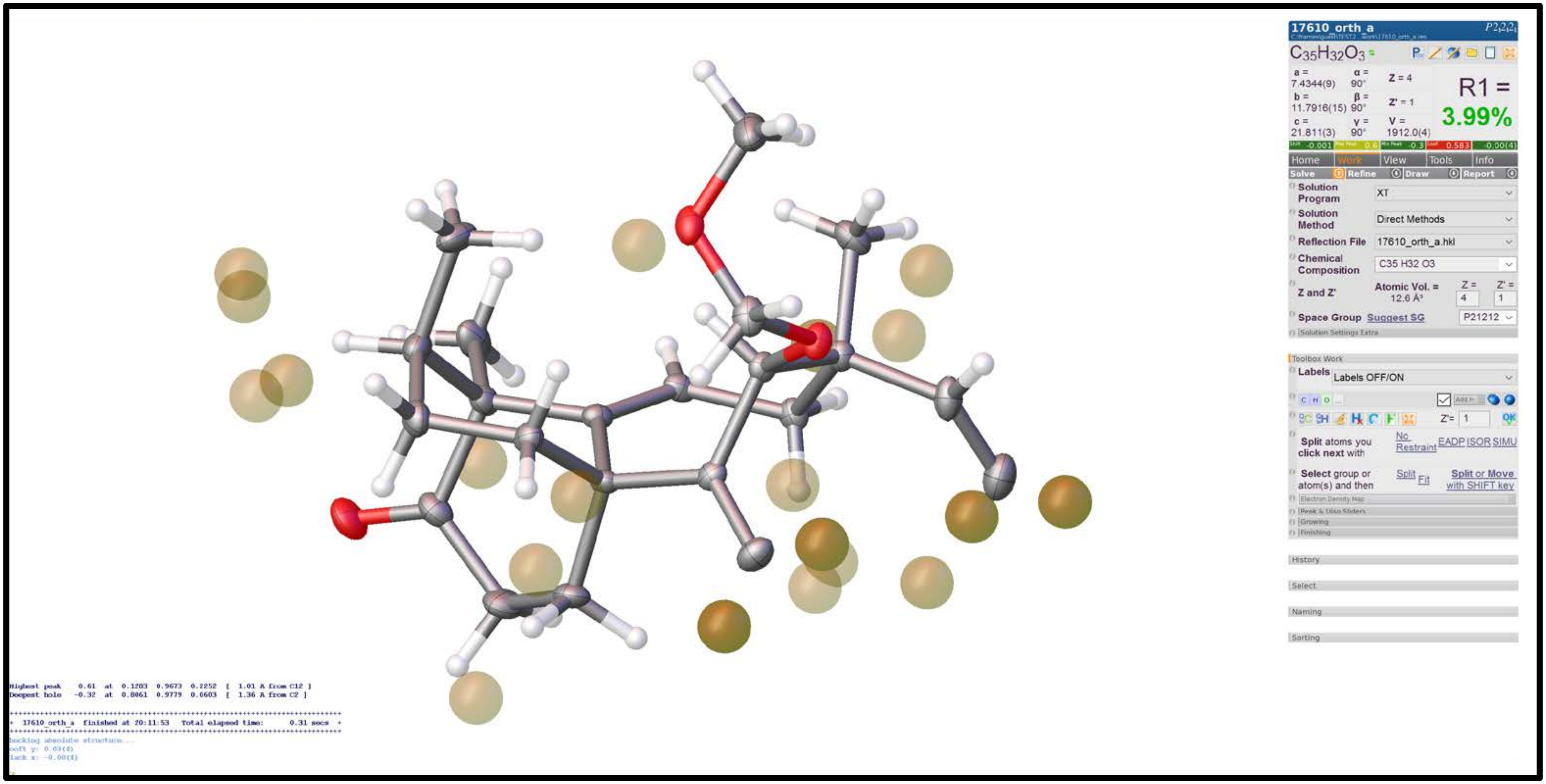
```
Highest peak    0.66  at  0.1021  0.0998  0.0071  [  0.97 A from C4 ]
Deepest hole   -0.44  at  0.8042  0.8685  0.1171  [  1.30 A from C5 ]

+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:10:57   Total elapsed time:     0.38 secs  +
+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
ooft y: 0.05(4)
lack x: 0.01(4)
```

Hydrogen atoms get assigned in calculated positions! Except OH and NH protons

Refine again and look at the Q peaks (indicates next level of missing electron density)
Most of the Q peaks fall in hydrogen positions

Program: Olex

Data Refinement in Olex



```
Highest peak    0.61  at  0.1203  0.9673  0.2252  [  1.01 A from C12 ]
Deepest hole   -0.32  at  0.8061  0.9779  0.0603  [  1.36 A from C2 ]

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:11:53   Total elapsed time:      0.31 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
ooft y: 0.03(4)
lack x: -0.00(4)
```

17610_orth_a $P2_12_12_1$

$C_{35}H_{32}O_3$

a = 7.4344(9) α = 90° Z = 4

b = 11.7916(15) β = 90° Z' = 1

c = 21.811(3) γ = 90° V = 1912.0(4)

R1 = 3.99%

Shift -0.001 | Max Peak 0.6 | Min Peak -0.3 | GooF 0.583 | -0.00(4)

Solution Program: XT

Solution Method: Direct Methods

Reflection File: 17610_orth_a.hkl

Chemical Composition: C35 H32 O3

Z and Z': Atomic Vol. = 12.6 Å³ Z = 4 Z' = 1

Space Group: P21212

Labels: Labels OFF/ON

Z'= 1

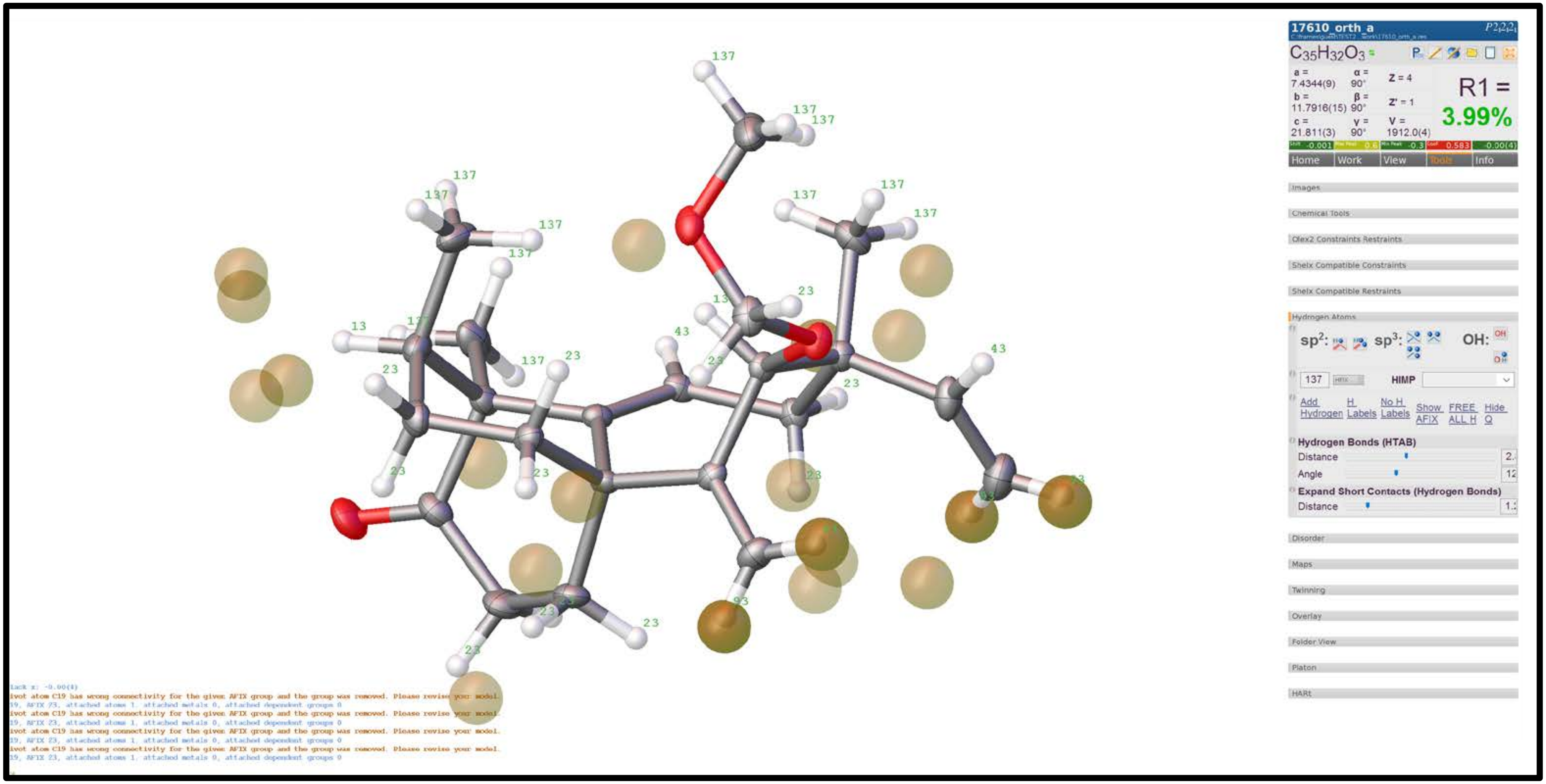
Split atoms you click next with

Select group or atom(s) and then

Add H atoms and refine again

Program: Olex

Data Refinement in Olex



17610_orth_a $P2_12_12_1$

$C_{35}H_{32}O_3$

a = 7.4344(9) α = 90° Z = 4

b = 11.7916(15) β = 90° Z' = 1

c = 21.811(3) γ = 90° V = 1912.0(4)

R1 = 3.99%

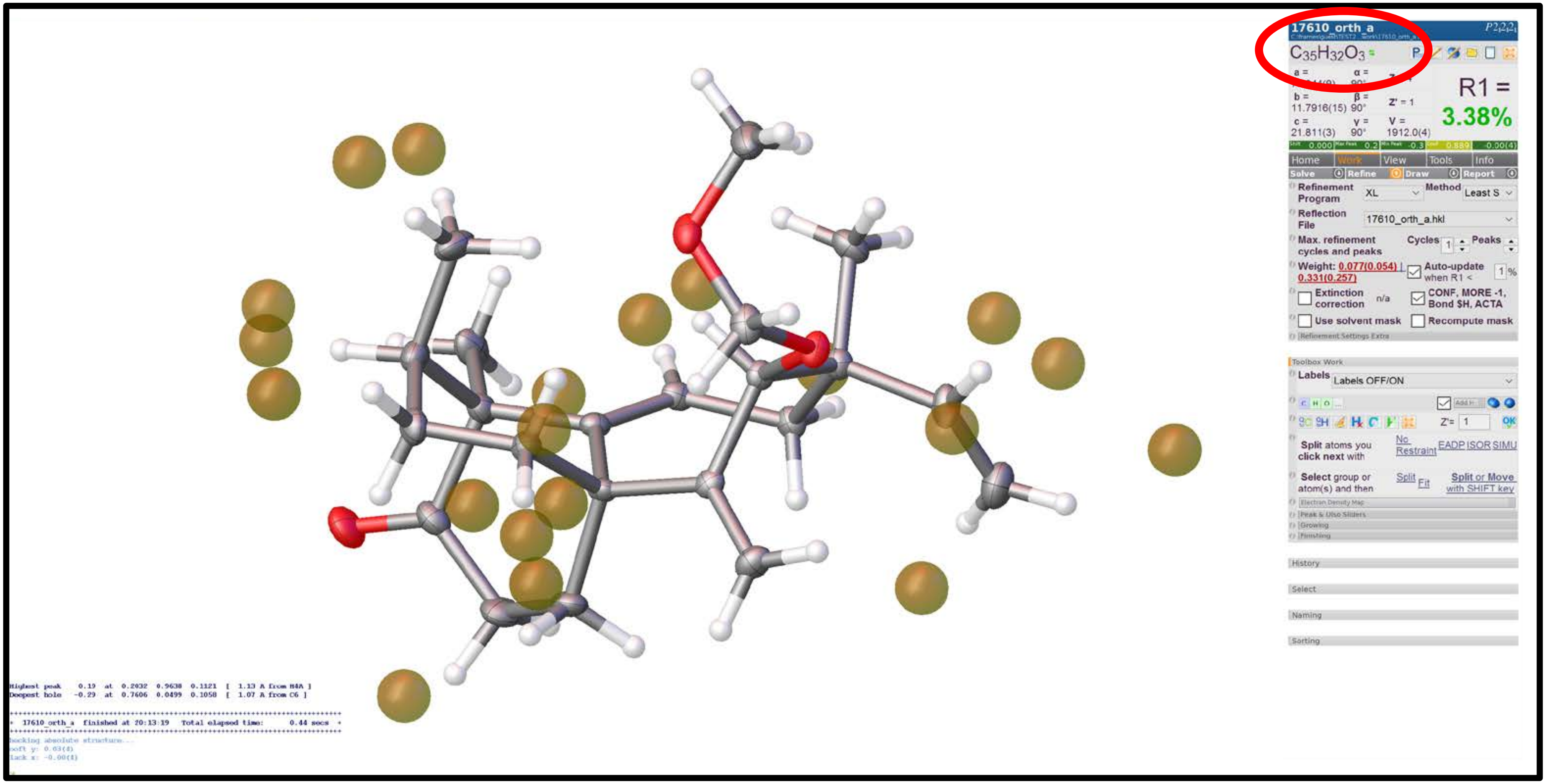
Shift -0.001 Max Peak 0.6 Min Peak -0.3 GooF 0.583 -0.00(4)

```
lack x: -0.00(4)
ivot atom C19 has wrong connectivity for the given AFIX group and the group was removed. Please revise your model.
19, AFIX 23, attached atoms 1, attached metals 0, attached dependent groups 0
ivot atom C19 has wrong connectivity for the given AFIX group and the group was removed. Please revise your model.
19, AFIX 23, attached atoms 1, attached metals 0, attached dependent groups 0
ivot atom C19 has wrong connectivity for the given AFIX group and the group was removed. Please revise your model.
19, AFIX 23, attached atoms 1, attached metals 0, attached dependent groups 0
ivot atom C19 has wrong connectivity for the given AFIX group and the group was removed. Please revise your model.
19, AFIX 23, attached atoms 1, attached metals 0, attached dependent groups 0
```

Add the H atoms the general "ADD Hs" tool couldn't figure out (here, alkenes)

Program: Olex

Data Refinement in Olex



17610_orth_a

$P2_12_12_1$

$C_{35}H_{32}O_3$

b = 11.7916(15) β = 90° Z' = 1

c = 21.811(3) γ = 90° V = 1912.0(4)

R1 = 3.38%

Shift 0.000 Max Peak 0.2 Min Peak -0.3 GooF 0.889 -0.00(4)

Refinement Program: XL Method: Least S

Reflection File: 17610_orth_a.hkl

Max. refinement cycles and peaks: Cycles 1

Weight: 0.077(0.054) | 0.331(0.257) ☑ Auto-update when R1 < 1 %

☐ Extinction correction n/a ☑ CONF, MORE -1, Bond $H, ACTA

☐ Use solvent mask ☐ Recompute mask

Labels: Labels OFF/ON

Split atoms you click next with: No Restraint EADP ISOR SIMU

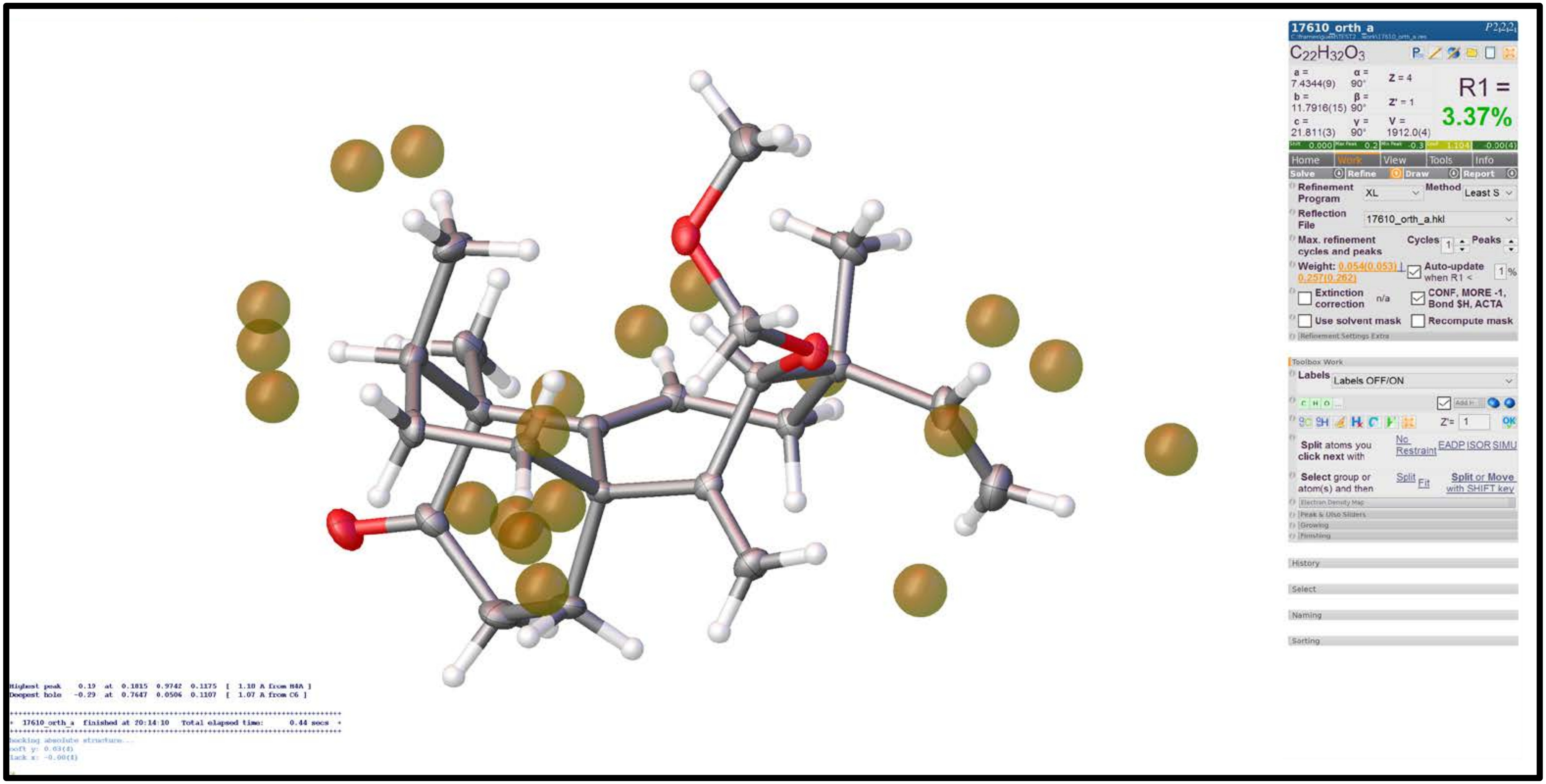
Select group or atom(s) and then: Split Fit Split or Move with SHIFT key

```
Highest peak    0.19  at  0.2032  0.9638  0.1121  [  1.13 A from H4A ]
Deepest hole   -0.29  at  0.7606  0.0499  0.1058  [  1.07 A from C6 ]

+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:13:19   Total elapsed time:      0.44 secs  +
+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
oft y: 0.03(4)
lack x: -0.00(4)
```

Refine structure and update molecular formula

Program: Olex

Data Refinement in Olex



17610_orth_a $P2_12_12_1$

$C_{22}H_{32}O_3$

a = 7.4344(9) α = 90°
b = 11.7916(15) β = 90°
c = 21.811(3) γ = 90°
Z = 4
Z' = 1
V = 1912.0(4)

R1 = 3.37%

Shift 0.000 Max Peak 0.2 Min Peak -0.3 GooF 1.104 -0.00(4)

Refinement Program: XL Method: Least S
Reflection File: 17610_orth_a.hkl
Max. refinement cycles and peaks: Cycles 1 Peaks
Weight: 0.054(0.053) | 0.257(0.262) ☑ Auto-update when R1 < 1 %
☐ Extinction correction n/a ☑ CONF, MORE -1, Bond $H, ACTA
☐ Use solvent mask ☐ Recompute mask

Labels: Labels OFF/ON

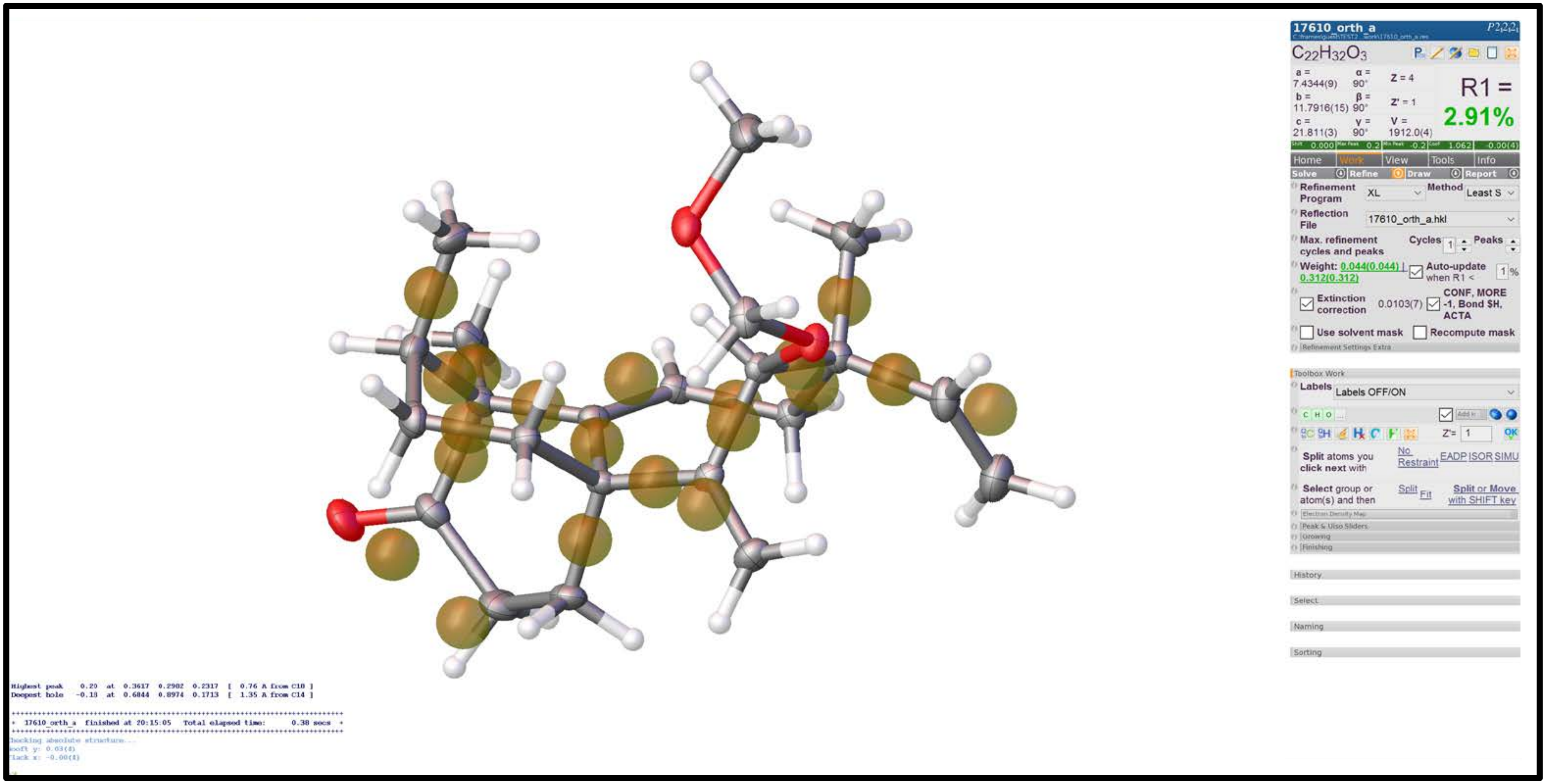
```
Highest peak    0.19  at  0.1815  0.9742  0.1175  [  1.10 A from H4A ]
Deepest hole   -0.29  at  0.7647  0.0506  0.1107  [  1.07 A from C6 ]

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:14:10   Total elapsed time:      0.44 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
ooft y: 0.03(4)
lack x: -0.00(4)
```

Molecular formula is fixed

Most would consider this structure good enough for publication

Program: Olex

Data Refinement in Olex



17610_orth_a $P2_12_12_1$

$C_{22}H_{32}O_3$

a = 7.4344(9) α = 90°
b = 11.7916(15) β = 90°
c = 21.811(3) γ = 90°
Z = 4
Z' = 1
V = 1912.0(4)

R1 = 2.91%

Shift 0.000 | Max Peak 0.2 | Min Peak -0.2 | GooF 1.062 | -0.00(4)

Refinement Program: XL
Method: Least S
Reflection File: 17610_orth_a.hkl
Max. refinement cycles and peaks: Cycles 1
Weight: 0.044(0.044) | 0.312(0.312)
☑ Auto-update when R1 < 1 %
☑ Extinction correction 0.0103(7)
☑ CONF, MORE -1, Bond $H, ACTA
☐ Use solvent mask
☐ Recompute mask

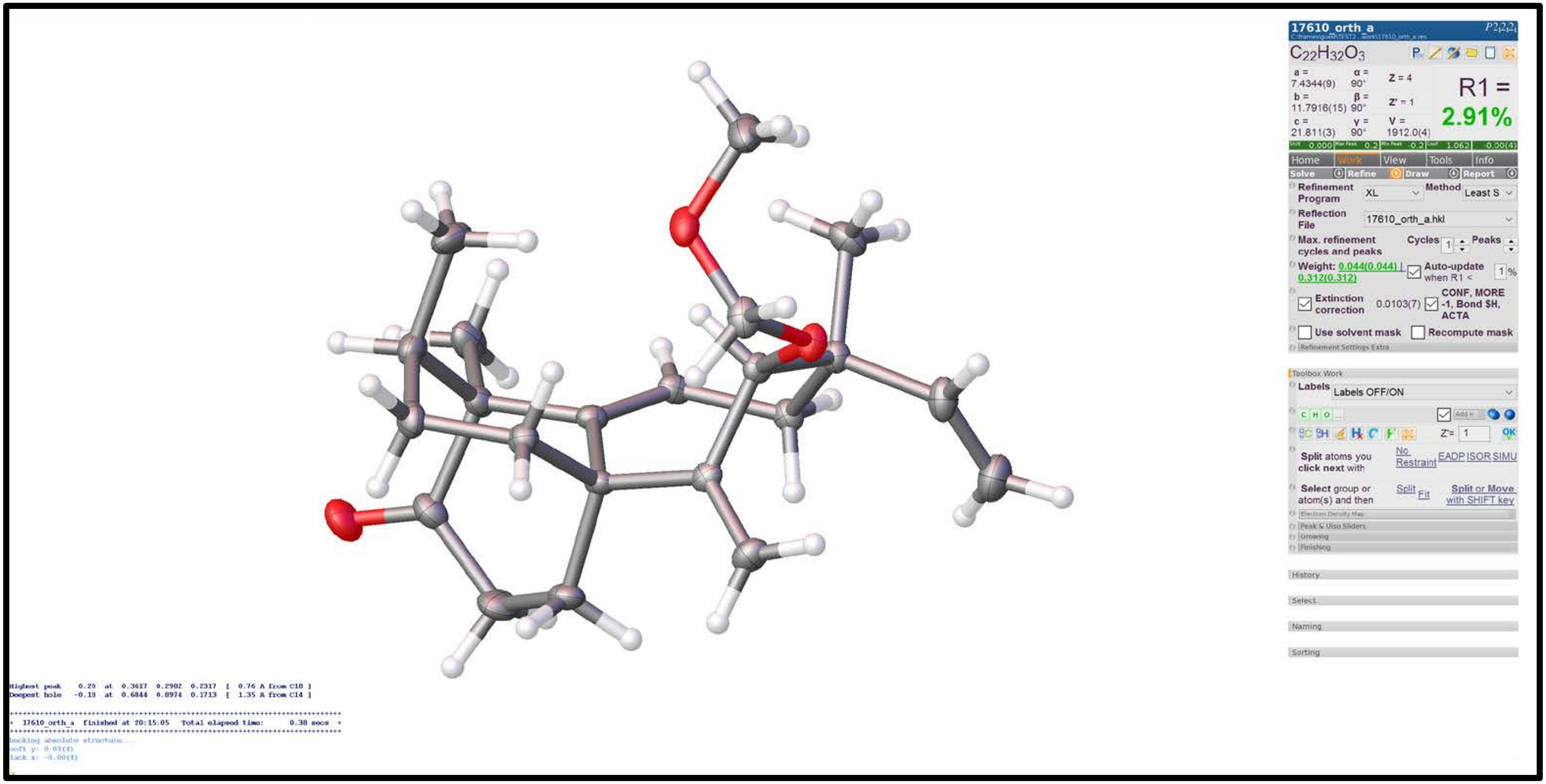
Labels: Labels OFF/ON

```
Highest peak    0.20  at  0.3617  0.2902  0.2317  [  0.76 A from C10 ]
Deepest hole   -0.18  at  0.6044  0.8974  0.1713  [  1.35 A from C14 ]

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:15:05   Total elapsed time:      0.38 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
Checking absolute structure...
Hooft y: 0.03(4)
Flack x: -0.00(4)
```

Organic crystal structures typically benefit from including an extinction coefficient
All the remaining Q peaks move from empty space to the C–C bonds

Program: Olex

Data Refinement in Olex



17610_orth_a
$P2_12_12_1$
$C_{22}H_{32}O_3$
a = 7.4344(9)
α = 90°
Z = 4
b = 11.7916(15)
β = 90°
Z' = 1
c = 21.811(3)
γ = 90°
V = 1912.0(4)
R1 = 2.91%
Shift 0.000
Max Peak 0.2
Min Peak -0.2
GooF 1.062
-0.00(4)
Refinement Program: XL
Method: Least S
Reflection File: 17610_orth_a.hkl
Max. refinement cycles and peaks: Cycles 1
Weight: 0.044(0.044) | 0.312(0.312)
☑ Auto-update when R1 < 1 %
☑ Extinction correction 0.0103(7)
☑ CONF, MORE -1, Bond $H, ACTA
☐ Use solvent mask
☐ Recompute mask
Labels: Labels OFF/ON
Z'= 1

```
Highest peak    0.20  at  0.3617  0.2902  0.2317  [  0.76 A from C10 ]
Deepest hole   -0.18  at  0.6844  0.8974  0.1713  [  1.35 A from C14 ]

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
+  17610_orth_a  finished at 20:15:05   Total elapsed time:      0.38 secs  +
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
hecking absolute structure...
ooft y: 0.03(4)
lack x: -0.00(4)
```

Assign absolute determination: typically AD (anomalous dispersion)
Generate final CIF file, then DONE! R1 = 2.91% (very good structure)

CheckCIF

International Union of Crystallography (IUCR) sponsors an online website that checks and validates CIF files: **https://checkcif.iucr.org/**

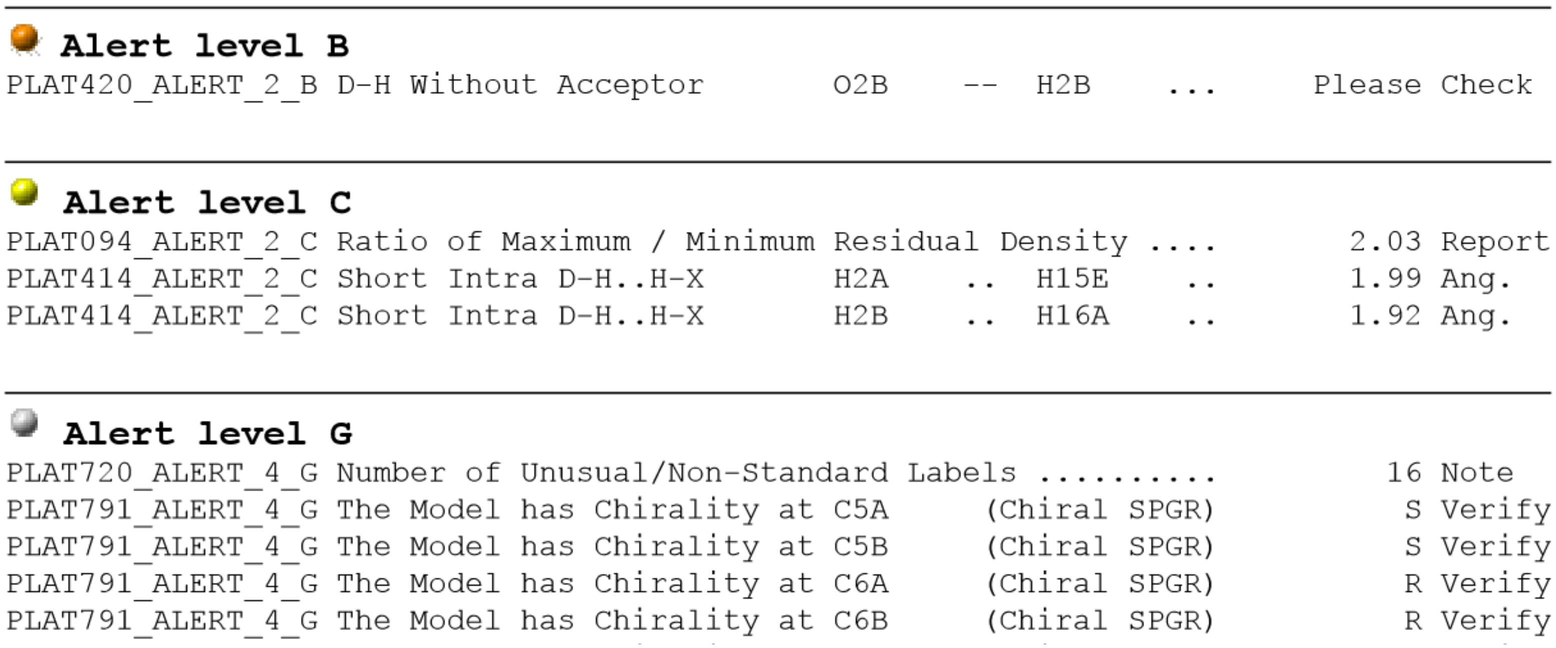
Alert levels:

A – Most likely a serious problem, resolve or explain

B – A potentially serious problem, consider carefully

C – Check, ensure it is not caused by an omission or oversight

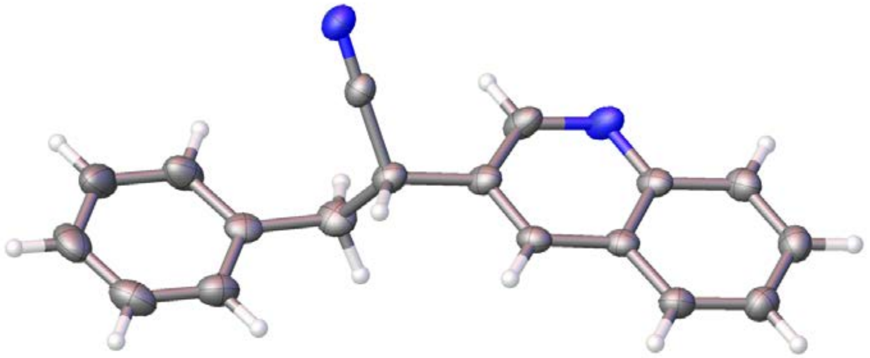
G – General information/check it is not something unexpected



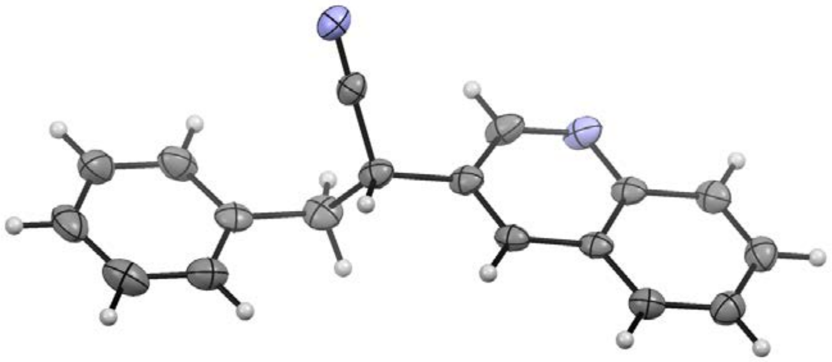
```
● Alert level B
PLAT420_ALERT_2_B D-H Without Acceptor       O2B     --  H2B     ...      Please Check

● Alert level C
PLAT094_ALERT_2_C Ratio of Maximum / Minimum Residual Density ....        2.03 Report
PLAT414_ALERT_2_C Short Intra D-H..H-X       H2A     ..  H15E     ..      1.99 Ang.
PLAT414_ALERT_2_C Short Intra D-H..H-X       H2B     ..  H16A     ..      1.92 Ang.

● Alert level G
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels ..........          16 Note
PLAT791_ALERT_4_G The Model has Chirality at C5A     (Chiral SPGR)           S Verify
PLAT791_ALERT_4_G The Model has Chirality at C5B     (Chiral SPGR)           S Verify
PLAT791_ALERT_4_G The Model has Chirality at C6A     (Chiral SPGR)           R Verify
PLAT791_ALERT_4_G The Model has Chirality at C6B     (Chiral SPGR)           R Verify
```

Generating Images

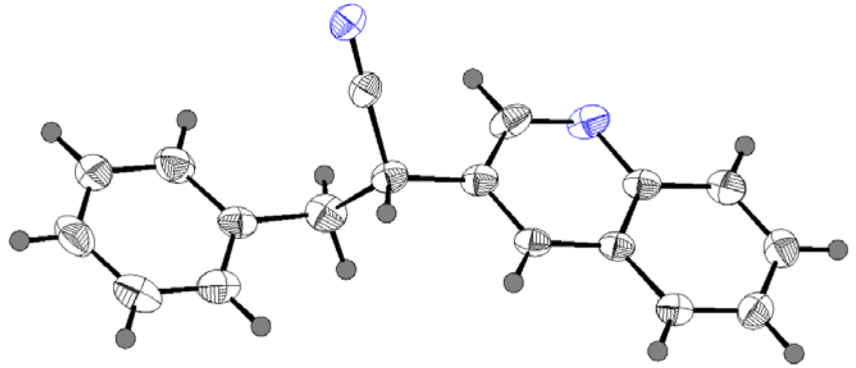
Olex: simplest image to obtain



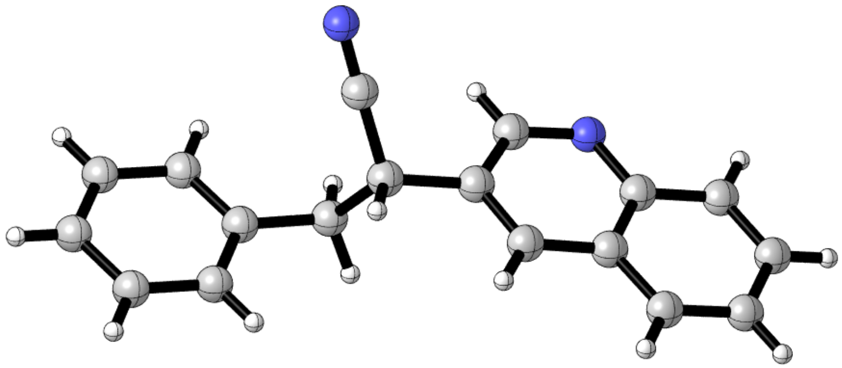
Mercury: easy to use, can use depth cue



Diamond: favored by inorganic chemists, more complicated software



CYL View: designed for computational chemistry, removes aniostropic displacement



Public Structural Databases

Nine major systems:

1. Bilbao Crystallographic Server (**BCS**)
2. Biological Macromolecule Crystallization Database (**BMCD**)
3. CRYSTMET
4. Cambridge Structural Database (**CSD**)
5. Inorganic Crystal Structure Database (**ICSD**)
6. Nucleic Acid Database (**NDB**)
7. The Pauling File
8. Protein Data Bank (**PDB**)
9. Powder Diffraction File (**PDF**)

The Cambridge Crystallographic
Data Centre

The Cambridge Structural Database is *"the world's most comprehensive and up-to-date database of crystal structures with over 900,000 curated entries" obtained by both X-ray and neutron diffraction*

Cambridge Crystallographic Data Centre (**CCDC**) is an organization that compiles and maintains the CSD.

Public Structural Databases

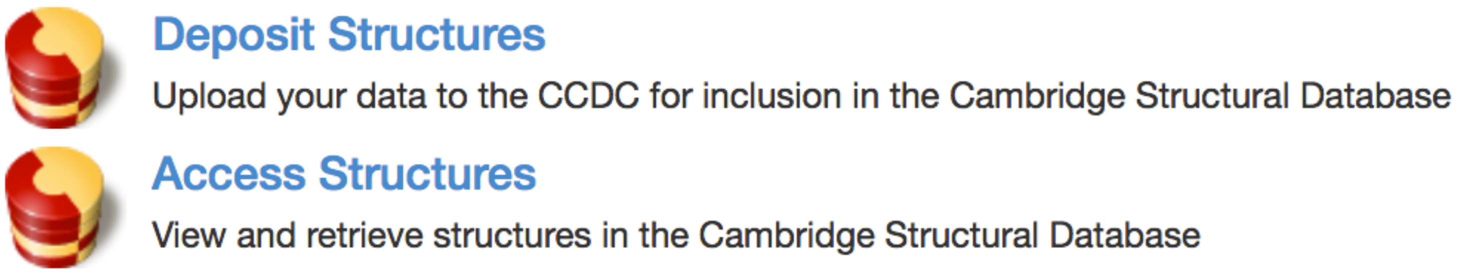
Submit your structures to the Cambridge Crystallographic Data Centre (**CCDC**)!

CIF files are easily deposited on the website, authors provide:

- CIF file
- Author names
- Email addresses
- Other info RE journal, etc. is not necessary (it will be inputted for you later)

Structures not referenced in publications 1 year after deposition will be made available to the public! Depositing structures should be the last thing you do before paper submission.

Structures will be assigned deposition numbers (basically an ID code), which is received by email, usually fairly quickly (approx. 10 min) with the new updated system.



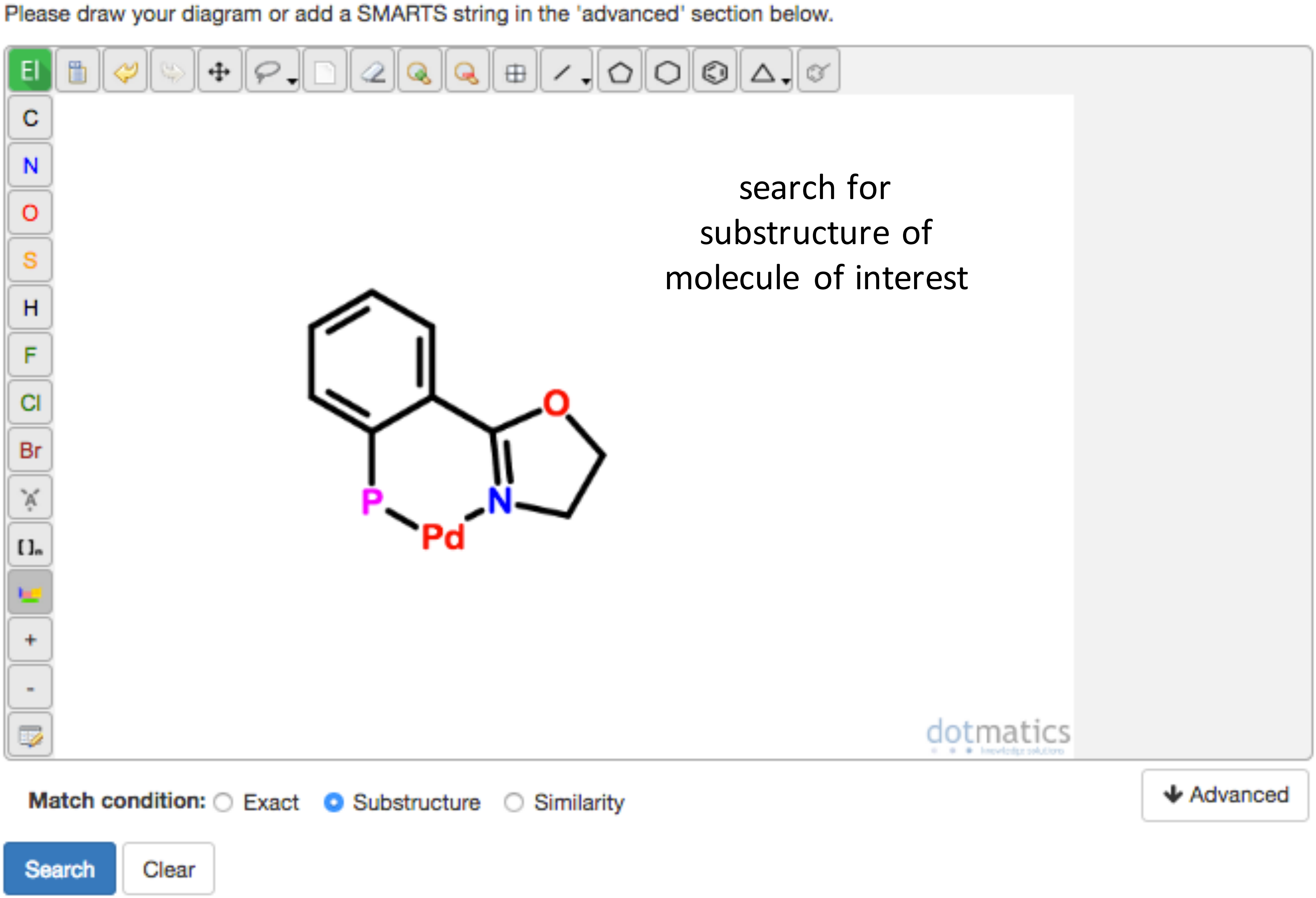
Deposit Structures

Upload your data to the CCDC for inclusion in the Cambridge Structural Database

Access Structures

View and retrieve structures in the Cambridge Structural Database

Public Structural Databases

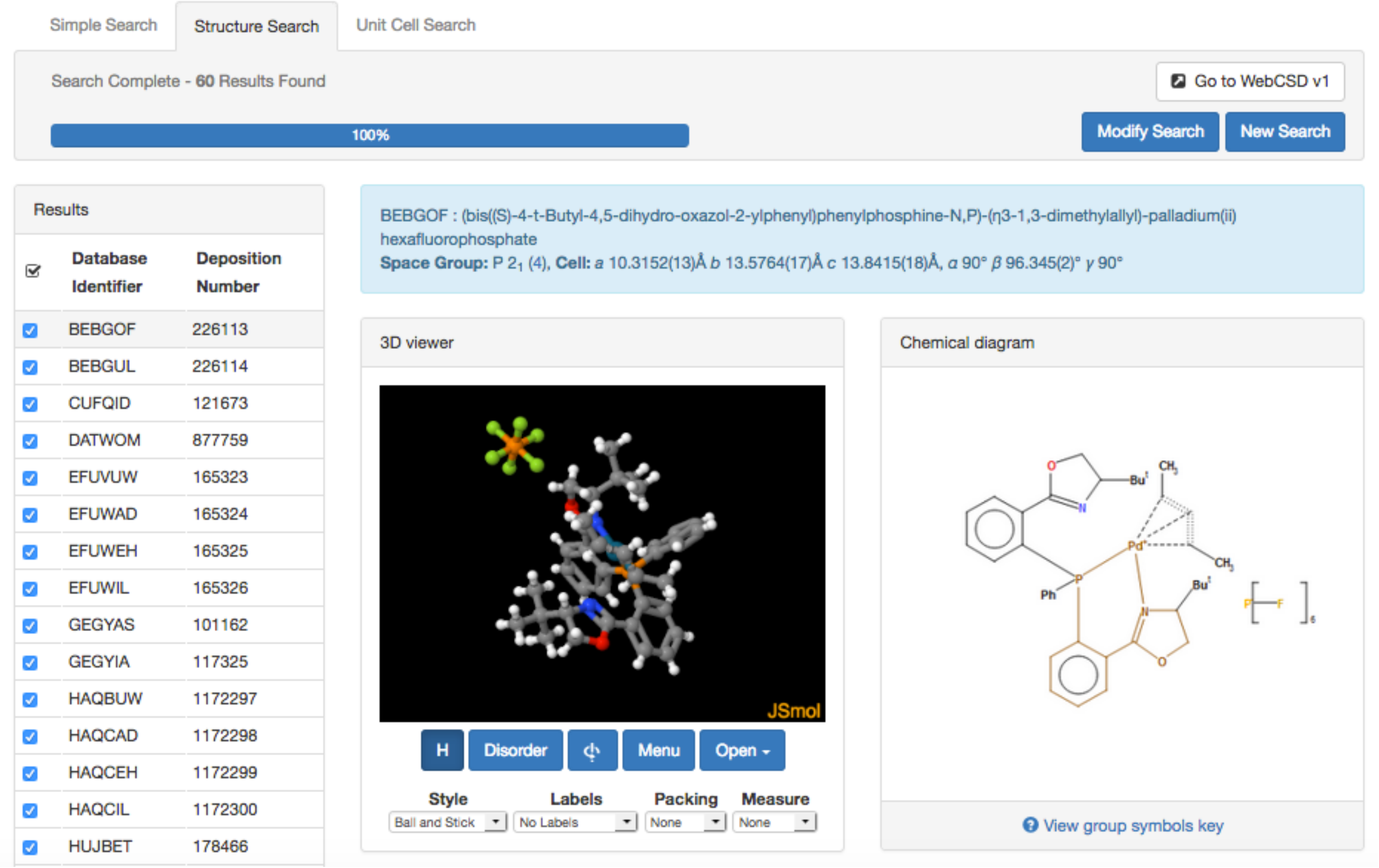


Please draw your diagram or add a SMARTS string in the 'advanced' section below.

Match condition: ○ Exact ● Substructure ○ Similarity

search for substructure of molecule of interest

Public Structural Databases



Search Complete - **60** Results Found

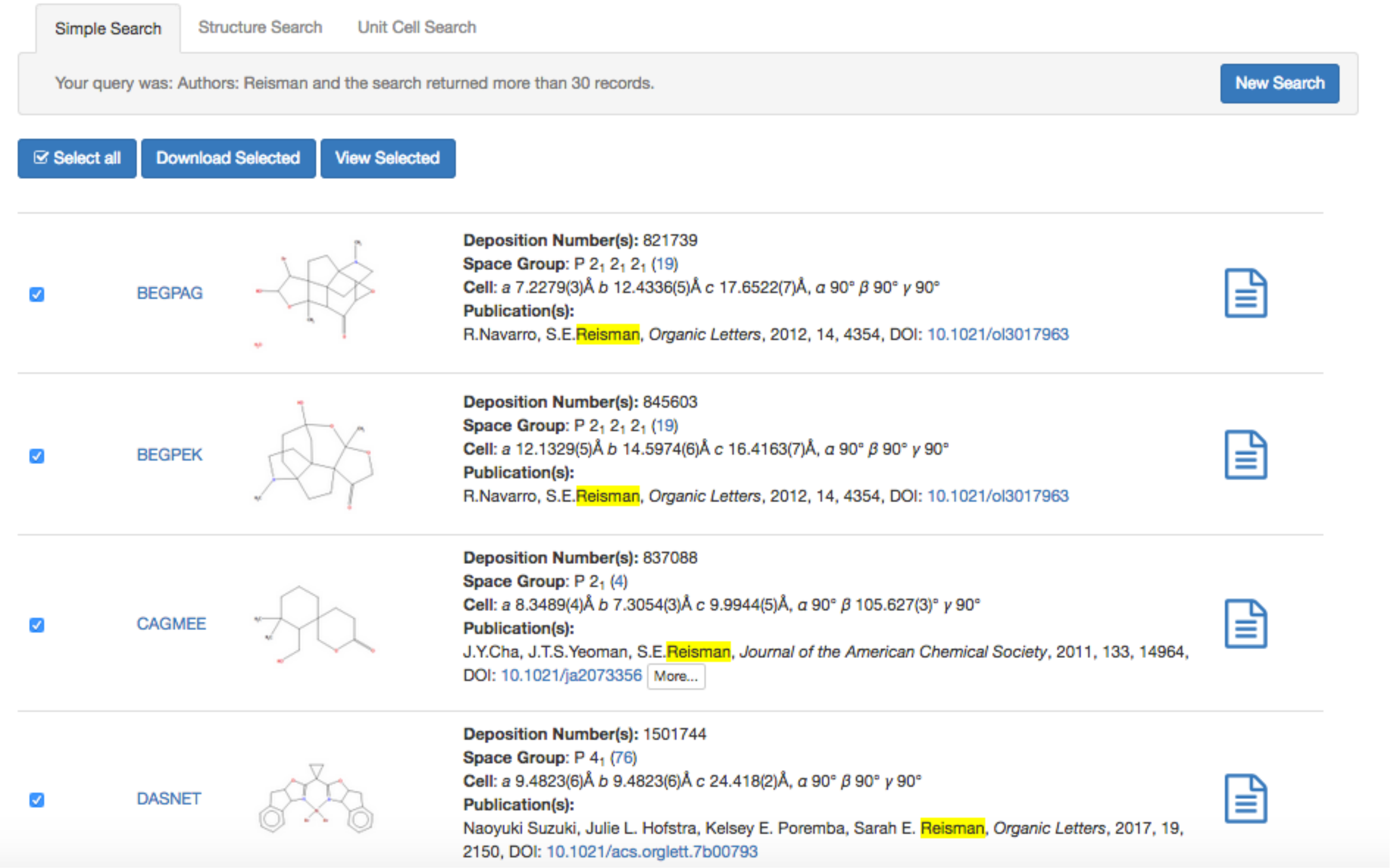
☑	Database Identifier	Deposition Number
☑	BEBGOF	226113
☑	BEBGUL	226114
☑	CUFQID	121673
☑	DATWOM	877759
☑	EFUVUW	165323
☑	EFUWAD	165324
☑	EFUWEH	165325
☑	EFUWIL	165326
☑	GEGYAS	101162
☑	GEGYIA	117325
☑	HAQBUW	1172297
☑	HAQCAD	1172298
☑	HAQCEH	1172299
☑	HAQCIL	1172300
☑	HUJBET	178466

BEBGOF : (bis((S)-4-t-Butyl-4,5-dihydro-oxazol-2-ylphenyl)phenylphosphine-N,P)-(η3-1,3-dimethylallyl)-palladium(ii) hexafluorophosphate

Space Group: P 2_1 (4), **Cell:** *a* 10.3152(13)Å *b* 13.5764(17)Å *c* 13.8415(18)Å, *α* 90° *β* 96.345(2)° *γ* 90°

Style	Labels	Packing	Measure
Ball and Stick	No Labels	None	None

Public Structural Databases



Your query was: Authors: Reisman and the search returned more than 30 records.

☑ BEGPAG

Deposition Number(s): 821739
Space Group: P 2_1 2_1 2_1 (19)
Cell: a 7.2279(3)Å b 12.4336(5)Å c 17.6522(7)Å, α 90° β 90° γ 90°
Publication(s):
R.Navarro, S.E.Reisman, *Organic Letters*, 2012, 14, 4354, DOI: 10.1021/ol3017963

☑ BEGPEK

Deposition Number(s): 845603
Space Group: P 2_1 2_1 2_1 (19)
Cell: a 12.1329(5)Å b 14.5974(6)Å c 16.4163(7)Å, α 90° β 90° γ 90°
Publication(s):
R.Navarro, S.E.Reisman, *Organic Letters*, 2012, 14, 4354, DOI: 10.1021/ol3017963

☑ CAGMEE

Deposition Number(s): 837088
Space Group: P 2_1 (4)
Cell: a 8.3489(4)Å b 7.3054(3)Å c 9.9944(5)Å, α 90° β 105.627(3)° γ 90°
Publication(s):
J.Y.Cha, J.T.S.Yeoman, S.E.Reisman, *Journal of the American Chemical Society*, 2011, 133, 14964, DOI: 10.1021/ja2073356

☑ DASNET

Deposition Number(s): 1501744
Space Group: P 4_1 (76)
Cell: a 9.4823(6)Å b 9.4823(6)Å c 24.418(2)Å, α 90° β 90° γ 90°
Publication(s):
Naoyuki Suzuki, Julie L. Hofstra, Kelsey E. Poremba, Sarah E. Reisman, *Organic Letters*, 2017, 19, 2150, DOI: 10.1021/acs.orglett.7b00793

Commonly Encountered Terminology for Organic Structures

What is a Flack parameter?

Commonly Used Terminology

Flack parameter: a factor used to determine absolute structure

"Absolute structure leads to absolute configuration. Absolute structure is a crystallographer's term and applies to non-centrosymmetric crystal structures. Absolute configuration is a chemist's term and refers to chiral molecules"

Number is:

Close to 0.0 – structure is correctly depicted in the displayed enantiomeric series

Close to 0.5 – structure is likely racemic or twinned

Close to 1.0 – structure is displayed in the opposite enantiomeric series

Examples: usually if $\mu<0.10$, it is a reasonable value

x(μ)	**x**	**μ**	**good?**
0.12(5)	0.12	0.05	yes
0.23(12)	0.23	0.12	no → Flack value is high but due to refinement issues
0.05(3)	0.05	0.03	yes
0.05(7)	0.05	0.07	yes
0.017(2)	0.017	0.002	yes
0.0162(19)	0.0162	0.0019	yes
–0.15(8)	–0.15	0.08	yes
–0.04(4)	–0.04	0.04	yes

Commonly Used Terminology

Bijvoet-Pair analysis: an analysis of the Bijvoet (Friedel) pairs for the determination of absolute structure

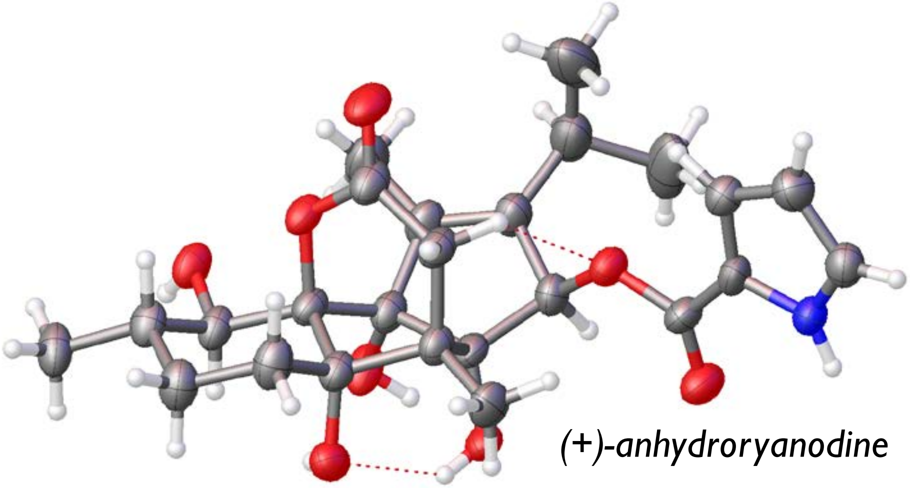
Take away message: this is a different analysis than the Flack parameter which can be used when the certainty of the Flack parameter is not good enough to assign absolute structure

PLATON

A Multipurpose Crystallographic Tool

(C) 1980-2012 A.L.Spek - 100M-Version: 210512

Data is analyzed in the program Platon

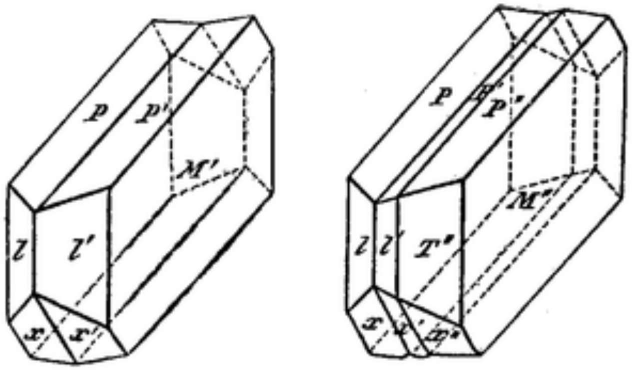


(+)-anhydroryanodine

Bayesian Statistics:	Flack = 0.23(12)
P3(true) – likelihood the absolute structure is correct	P3(true) = 0.977
P3(rac-twin) – likelihood the structure is a 50:50 inversion twin	P3(rac-twin) = 0.023
P3(false) – likelihood the structure should be inverted	P3(false) = 0.2×10^{-13}

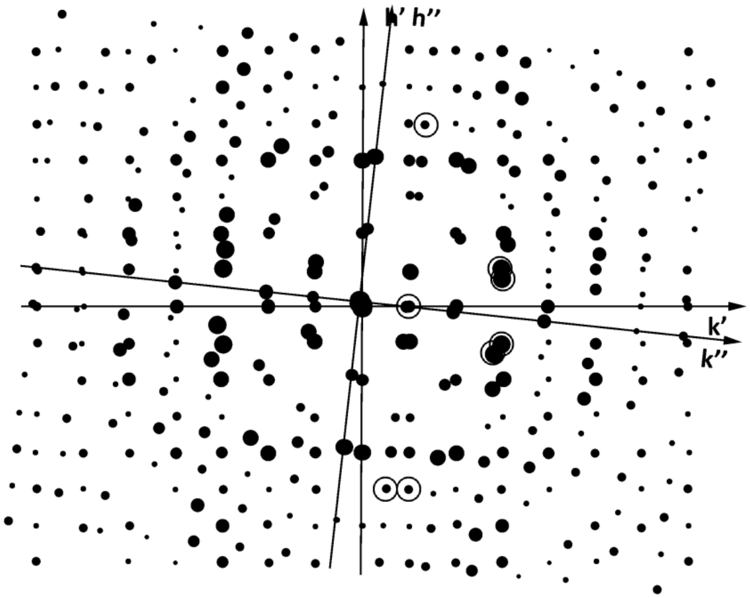
Commonly Used Terminology

Crystal twinning: two (or more) separate crystals share some of the same crystal lattice points (i.e. you do not have a single crystal)



There are different types of twins:

- merohedral twins (hard to identify, appears to be a single crystal from diffraction data; can accidentally be solved in incorrect higher space group)
- non-merohedral twins (easier to identify)

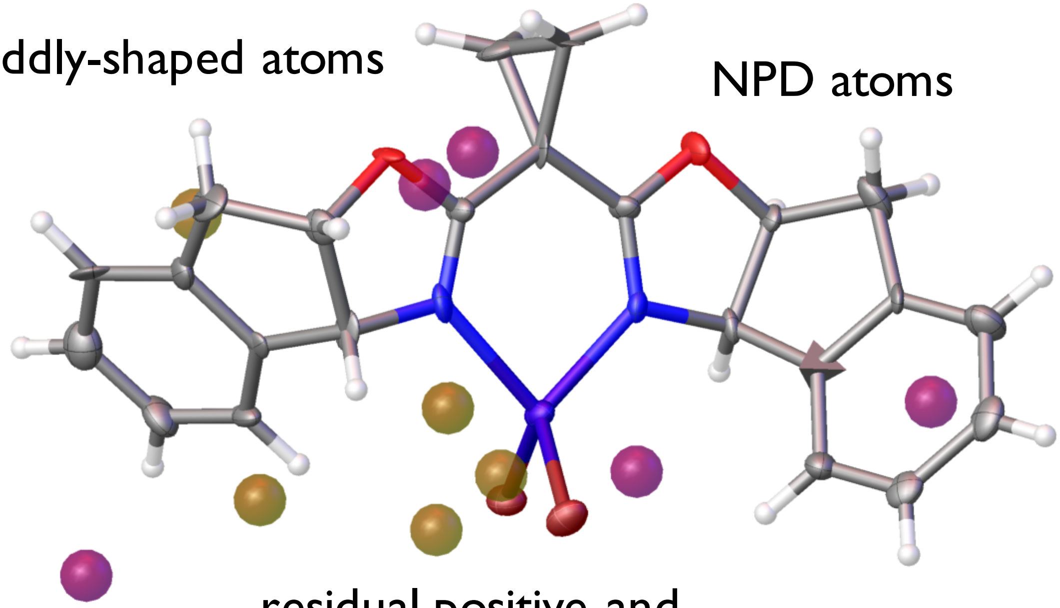


A twinned crystal does not produce a simple diffraction pattern and can often be recognized by observing the raw diffraction data.

Commonly Used Terminology

Crystal twinning: two (or more) separate crystals share some of the same crystal lattice points (i.e. you do not have a single crystal)

How do we fix this? Search for and apply twin laws.



oddly-shaped atoms

NPD atoms

residual positive and negative density in space

a15178_0m_a

C:\Users\Julie Hofstra\Documents\Xra...(LNiBr2)\work - Copy\a15178_0m_a.res

$C_{23}H_{20}Br_2N_2NiO_2$

a = 9.4823(6)

b = 9.4823(6)

c = 24.418(2)

α = 90°

β = 90°

γ = 90°

Z = 4

Z' = 1

V = 2195.5(3)

R1 = 23.00%

Shift 0.000

Max Peak 5.0

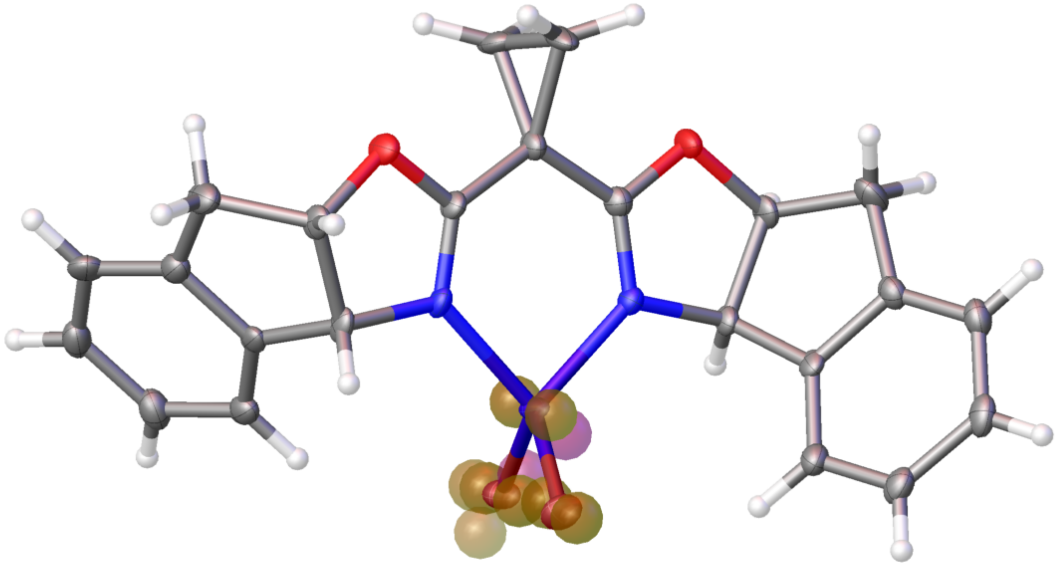
Min Peak -7.5

Goof 3.117

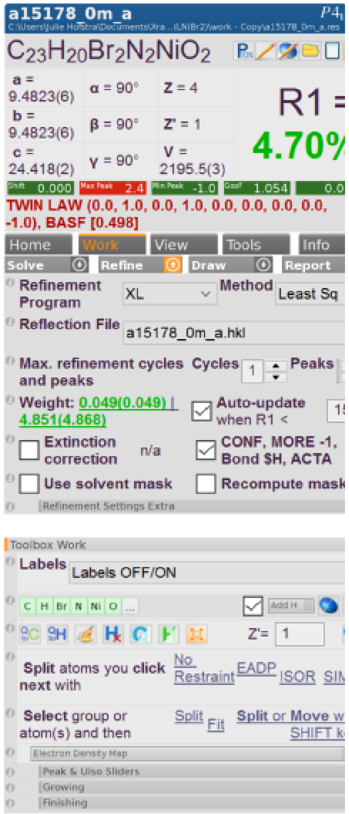
Commonly Used Terminology

Crystal twinning: two (or more) separate crystals share some of the same crystal lattice points (i.e. you do not have a single crystal)

How do we fix this? Search for and apply twin laws.



residual positive and negative density lies next to $NiBr_2$ atoms (suggests atoms are "wiggling" but were not further disordered)



a15178_0m_a

C:\Users\Julie Hofstra\Documents\Xra...(LNiBr2)\work - Copy\a15178_0m_a.res

$C_{23}H_{20}Br_2N_2NiO_2$

a = 9.4823(6)	α = 90°	Z = 4
b = 9.4823(6)	β = 90°	Z' = 1
c = 24.418(2)	γ = 90°	V = 2195.5(3)

R1 = 4.70%

Shift 0.000 Max Peak 2.4 Min Peak -1.0 GooF 1.054 0.0

TWIN LAW (0.0, 1.0, 0.0, 1.0, 0.0, 0.0, 0.0, 0.0, -1.0), BASF [0.498]

Refinement Program: XL

Method: Least Sq

Reflection File: a15178_0m_a.hkl

Max. refinement cycles and peaks: Cycles 1 Peaks

Weight: 0.049(0.049) | 4.851(4.868)

☑ Auto-update when R1 <

☐ Extinction correction n/a

☑ CONF, MORE -1, Bond $H, ACTA

☐ Use solvent mask

☐ Recompute mask

Labels: Labels OFF/ON

Z'= 1

Split atoms you click next with: No Restraint EADP ISOR

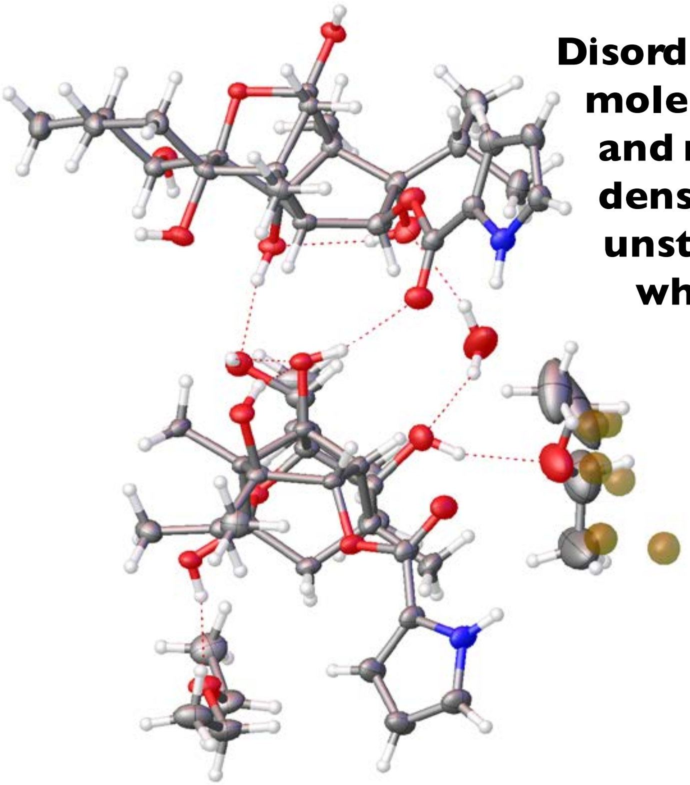
Select group or atom(s) and then: Split Fit Split or Move w SHIFT k

Commonly Used Terminology

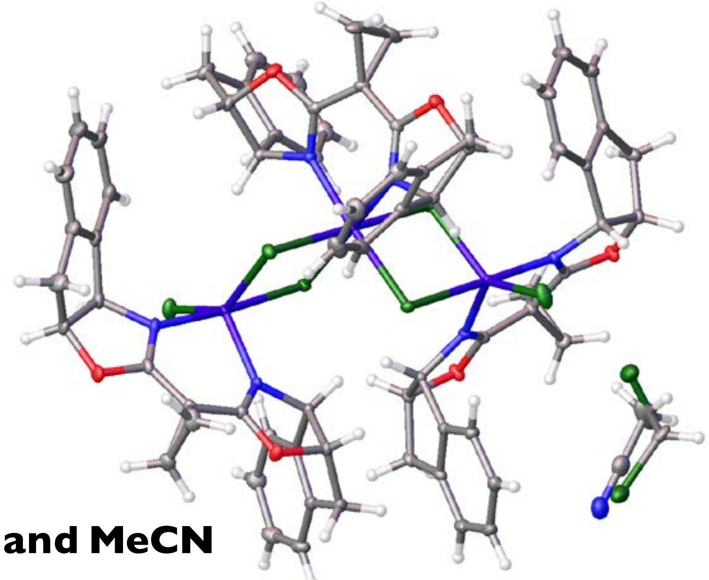
Disorder: occurs when atoms in the unit cell adopt different orientations

Types: Positional disorder (same atoms occupy different sites) or substitutional disorder (different atoms occupy the same site)

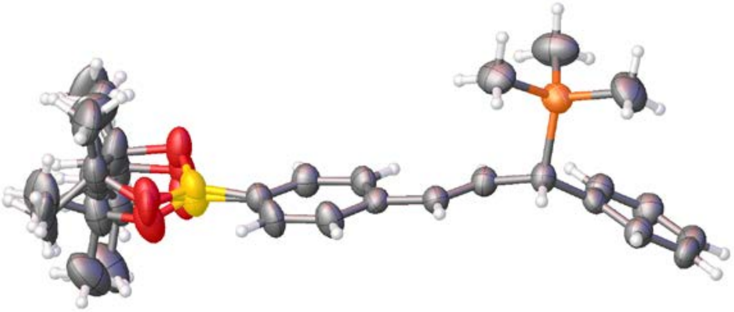
Remember, data is averaged over SPACE and TIME. Small disorder can be left represented by atom size, larger differences should be split into parts



Disordered ether solvent molecule (large atoms and residual electron density). In this case, unstable refinement when disordered.



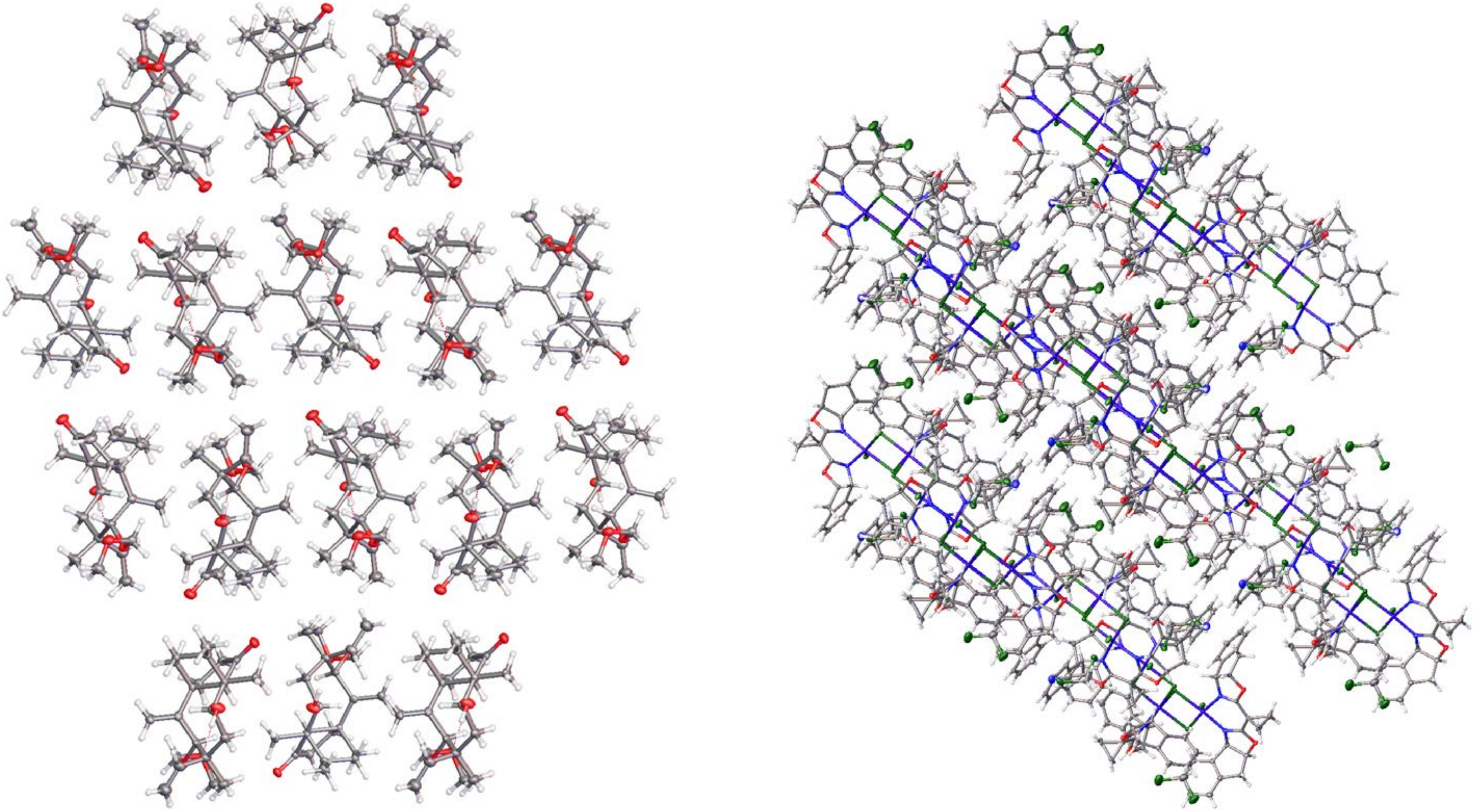
DCM and MeCN occupy same space in the lattice.



Boronate group exists in three conformations (47%, 34%, 19%). Bond restraints were applied. Notice TMS group has slight rotational disorder.

Commonly Used Terminology

Grow function: command in Olex to view packing arrangement
Useful to view void spaces and hydrogen bonding between molecules



Resources at Caltech and Practical Crystallization Tips

What instruments do we have here?
How do I grow a crystal?
What are host-guest frameworks?

Caltech X-ray Crystallographic Facility (XRCF)

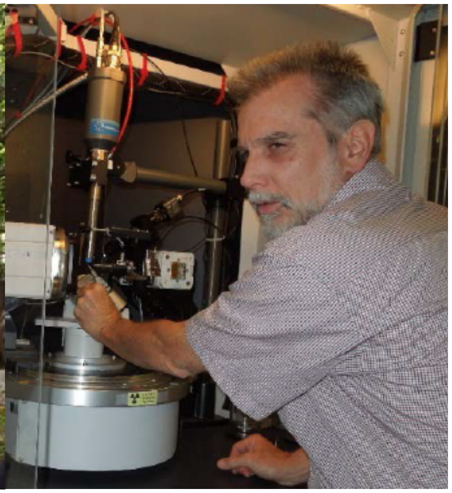
X-ray Laboratory, BI 110, x2741

Two instruments primarily used:

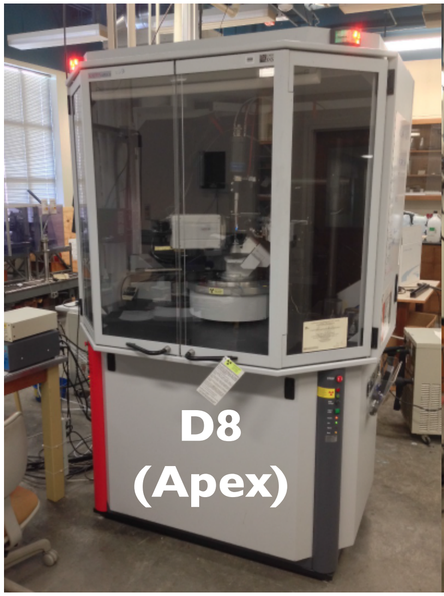
1. D8 KAPPA APEX II
    - Mo radiation
    - good for large crystals (>0.15 mm)
    - can get absolute stereochemistry if there is a heavy atom
    - collection time 12-24 hr
2. D8 VENTURE Photon100 Dual IμS
    - Dual Mo and Cu radiation
    - good for smaller crystals
        - <0.15 mm for Mo
        - <0.10 mm for Cu
    - can get absolute stereochemistry without heavy atoms using Cu
    - collection time <12 hr

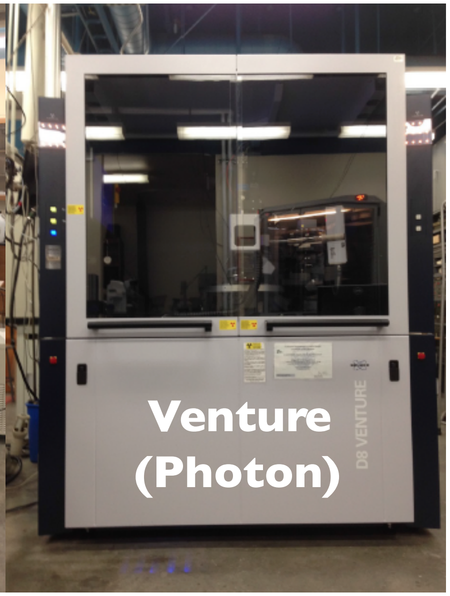
Prior to 2018, files labeled A or P (e.g. P13544)
Since 2018, new CPAD detectors, files labeled V or D

Dr. Mike Takase
BI 116, x2734



Mr. Larry Henling
BI 128, x2735





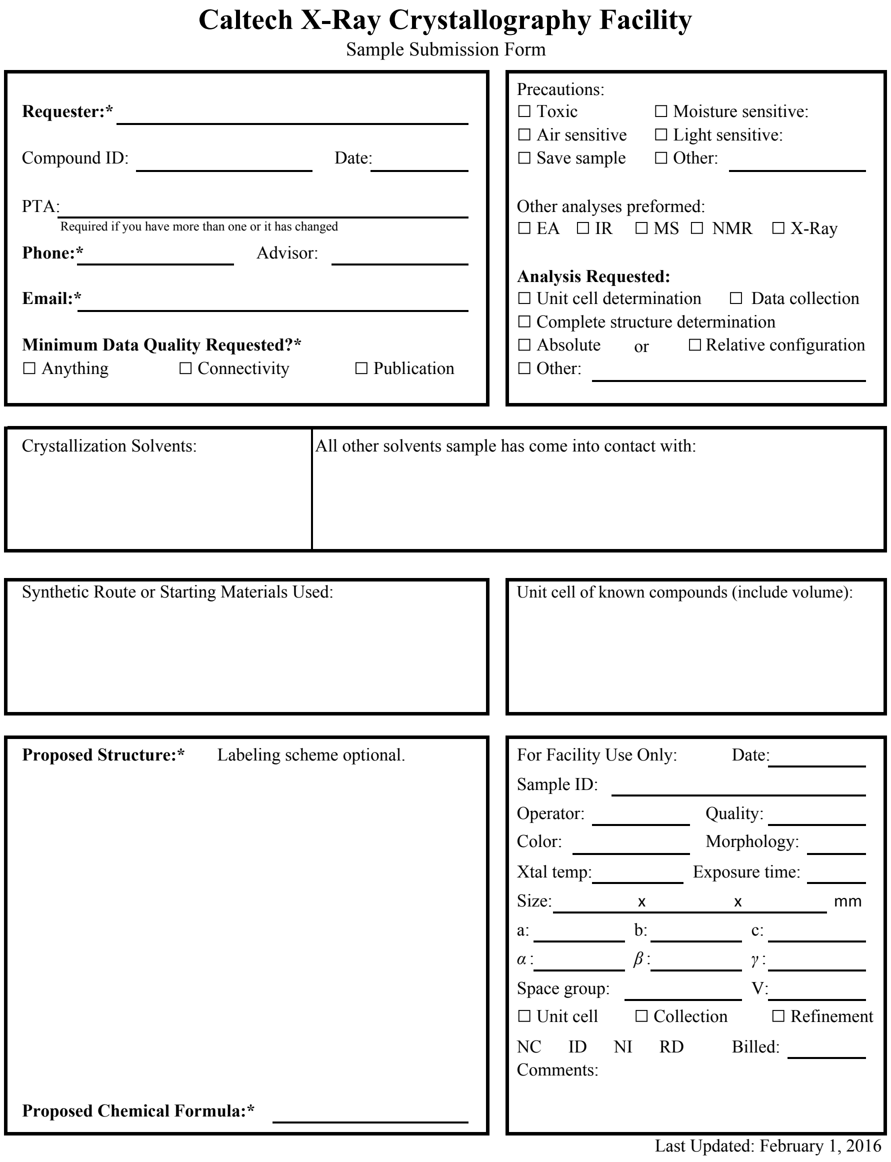
Caltech X-ray Crystallographic Facility (XRCF)

Website: http://www.its.caltech.edu/~xray/

1) Login to the website and add your name to the X-ray Queue
    - Each group gets one user per cycle (inorganic uses instruments most, so any organic submissions usually get priority to run next)
2) Print and fill out submission form
    - Make sure to note absolute or relative configuration
    - Check "data collection" if your group solves their own structures ($250) or "complete structure solution" if your group needs full solution ($500)
    - Truncated data collection for examination/connectivity/ID is $150
3) Bring sample and form to BI 110

Are my crystals good enough? Just ask!

High powered microscope + polarimeter



Caltech X-Ray Crystallography Facility

Sample Submission Form

Requester:* ____________

Compound ID: ____________ Date: ________

PTA: ____________

Required if you have more than one or it has changed

Phone:* ________ Advisor: ________

Email:* ____________

Minimum Data Quality Requested?*

☐ Anything ☐ Connectivity ☐ Publication

Precautions:

☐ Toxic ☐ Moisture sensitive:

☐ Air sensitive ☐ Light sensitive:

☐ Save sample ☐ Other: ________

Other analyses preformed:

☐ EA ☐ IR ☐ MS ☐ NMR ☐ X-Ray

Analysis Requested:

☐ Unit cell determination ☐ Data collection

☐ Complete structure determination

☐ Absolute or ☐ Relative configuration

☐ Other: ________

Crystallization Solvents:

All other solvents sample has come into contact with:

Synthetic Route or Starting Materials Used:

Unit cell of known compounds (include volume):

Proposed Structure:* Labeling scheme optional.

Proposed Chemical Formula:* ________

For Facility Use Only: Date: ________

Sample ID: ________

Operator: ________ Quality: ________

Color: ________ Morphology: ________

Xtal temp: ________ Exposure time: ________

Size: ____ x ____ x ____ mm

a: ________ b: ________ c: ________

α: ________ β: ________ γ: ________

Space group: ________ V: ________

☐ Unit cell ☐ Collection ☐ Refinement

NC ID NI RD Billed: ________

Comments:

Last Updated: February 1, 2016

Crystallization Techniques

Crystallization occurs when the concentration of a compound in solution is higher than its solubility

Often supersaturation must be reached in order to obtain crystals

Two steps: *nucleation* and *growth*

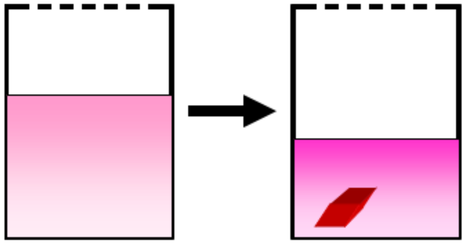
Nucleation can occur from dust particles or imperfections the glass. The less nucleation sites and the slower the crystal growth, the bigger the crystals will be.

Important things to remember:

- Growing crystals is an art form.
- Luck often plays an important role.
- The quality of the crystal structure is impacted by the quality of the crystal.
- Good crystals take time to grow! (expect 2-7 days so put them in a place where you can monitor them without disturbing the container)
- Size should be around 0.1-0.3 mm in each dimension.
- Once you have crystals, never remove them from the solvent
    - Solvent can incorporate into crystal lattice

Crystallization Techniques

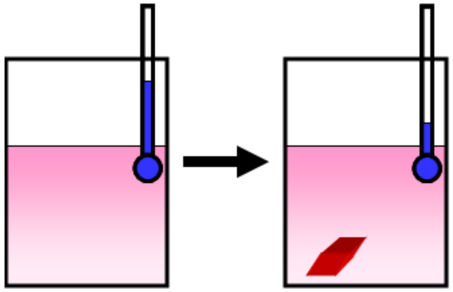
1. Slow evaporation



As simple as it sounds. Dissolve your compound almost to saturation, transfer to clean container (filter solution through Kimwipe plug to remove particles), and cover (e.g. foil with holes, septa with a needle). Sometimes you can let it slowly evaporate in the NMR tube.

Advantage: easy
Disadvantage: often requires a lot of material; better for polar compounds that are not extremely soluble or else can concentrate to an oil; crystals get stuck to walls of the container

2. Slow cooling

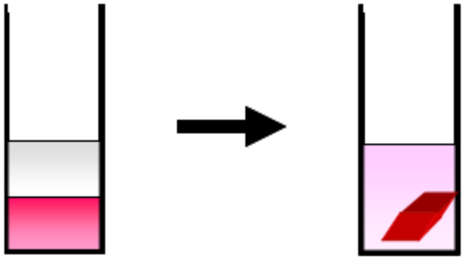


Standard recrystallization method. *Does not dissolve at r.t.?* Heat it up until dissolved and let it slowly cool down. *Does dissolve at r.t.?* Put it in the freezer to try and obtain crystals.

Advantage: easy
Disadvantage: often requires a lot of material; finding appropriate solvent conditions; if crystals are grown at cold temperature, indicate this on the sign-up form so they can remain in freezer until ready to be analyzed

Crystallization Techniques

3. Layer diffusion

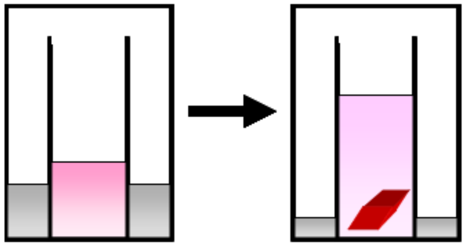


Choose a binary solvent system that includes two solvents which mix well. The compound of interest should dissolve in one solvent (called the solvent) but not in the other (called the precipitant). Prepare a concentrated solution and have the precipitant solvent on hand. In a vial, add the liquid with the higher specific density on the bottom and layer the liquid with the lower specific density on top. Over time, the layers will mix and crystals should form. The bottom layer can also be frozen before the top layer is added.

Advantage: works well for small amounts of material; can be easy to control variables
Disadvantage: this method is slightly complicated and perfectly layering the two liquids can be difficult

Crystallization Techniques

4. Vapor diffusion



Choose a binary solvent system for two solvents that mix well. Prepare a concentrated solution of the compound and place inside an inner vial. The inner vial is placed in a larger vial with the precipitant solvent and the system is sealed. Over time, the solvents will mix via vapor diffusion.

Advantage: works well for small amounts of material; very successful setup
Disadvantage: finding two solvents can be difficult

Lower number solvent will diffuse into the higher number solvent

Solvent		**Solvent**		**Solvent**	
Diethyl ether	34.6	Methanol	64.1	Acetonitrile	81.8
Pentane	36.1	Hexane	68.7	Heptane	98.4
Dichloromethane	40.7	Ethyl Acetate	77.1	Toluene	110
Acetone	56.5	Ethanol	78.4	Octane	125
Chloroform	61.3	Benzene	80.1		

Crystallization Techniques

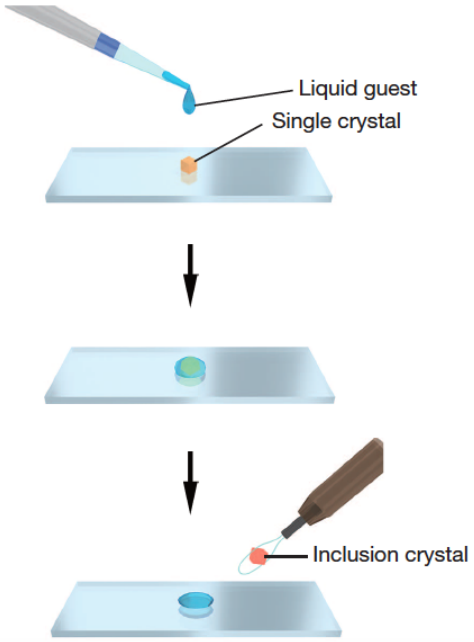
What if my compound isn't crystalline?

Chemical derivatization

- Protect alcohols or amines
    - ex. *para*-nitro benzoate groups or *para*-bromo benzoate groups
- Convert into an ion and form a salt
    - ex. deprotonate or protonate

Use co-crystals

- Numerous examples of co-crystals
- See review: *Cryst. Growth Des*. **2009**, *9*, 4212.
- Typically more useful for aromatic compounds
- Triphenylphosphine oxide can be a useful co-crystallant for proton donors

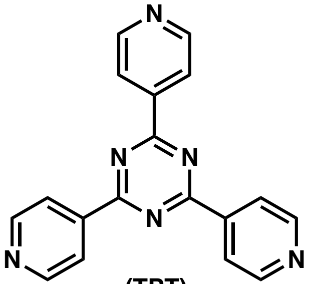


Clathrates (i.e. crystalline sponge)

- Pioneered by Makoto Fujita within the last decade
- Soak up non-crystalline material into an existing crystal lattice
- Can be successful on as little as 80 ng of material

Etter, M. C.; Baures, P. W. *J. Am. Chem.* Soc. **1988**, 110, 639; Stahly, G. P. *Cryst. Crowth Des*. **2009**, 9, 4212

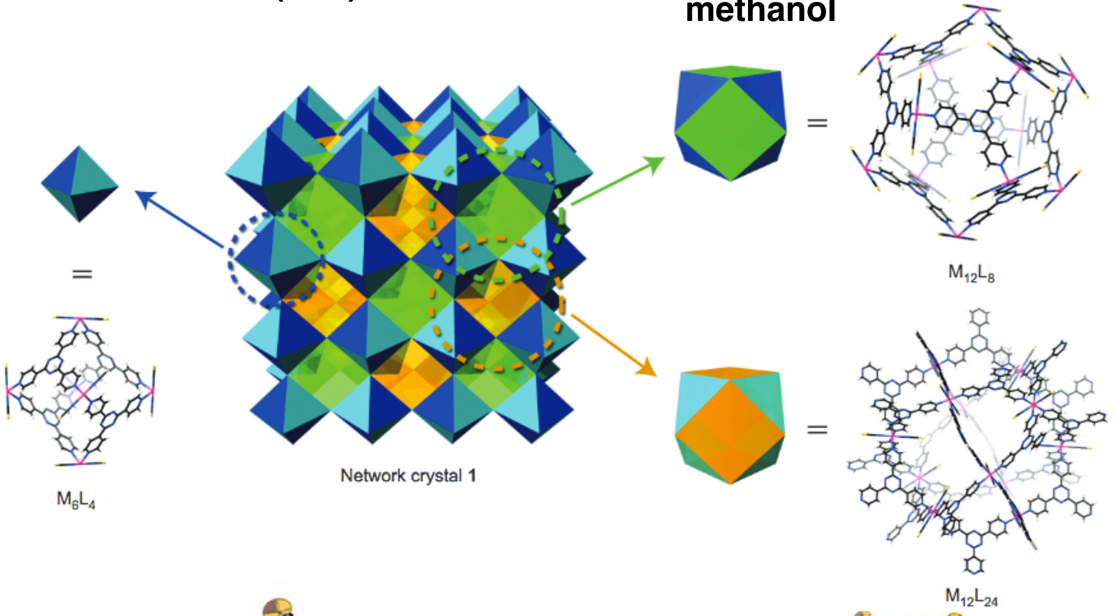
Crystalline Sponge Method



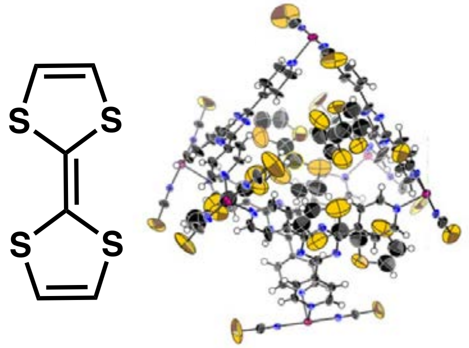
(TPT)

Fujita, *Nature Chemistry* **2010**: the beginnings of host/guest crystallography

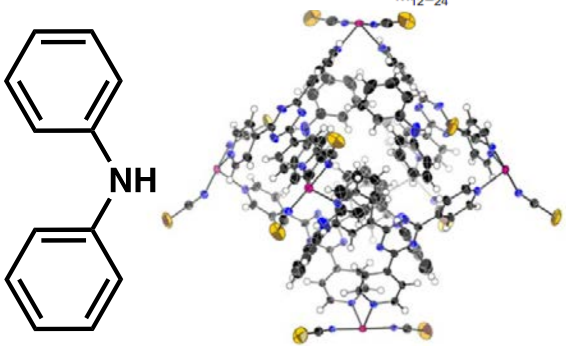
$$\text{2,4,6-tris(4-pyridyl)-1,3,5-triazine (TPT)} \xrightarrow[\textit{o}\text{-dichlorobenzene, methanol}]{\text{Co(NCS)}_2} ([(\text{Co(NCS)}_2)_3(\text{TPT})_4]\cdot 25(\textit{o}\text{-dichlorobenzene})\cdot 5(\text{MeOH}))_n$$



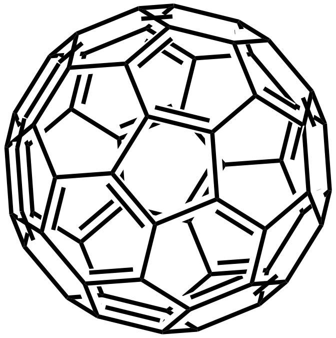
- Fujita reported Co and Pd network crystals formed with TPT
- Metal-organic frameworks
- Octahedral M_6L_4 cage motifs with $M_{12}L_8$ and $M_{12}L_{24}$ interstitial vioids
- Solvent included as “guests”
- Guests were exchanged for tetrathiafulvalene, diphenylamine, or fullerene
- Other solvents (e.g. toluene, water) remain in “host”.

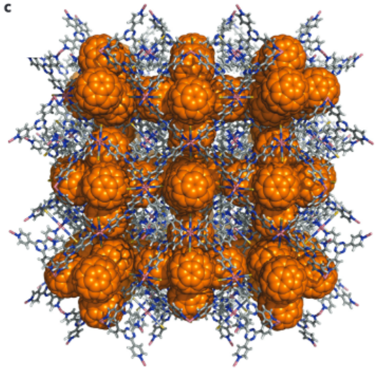


tetrathiafulvalene



diphenylamine



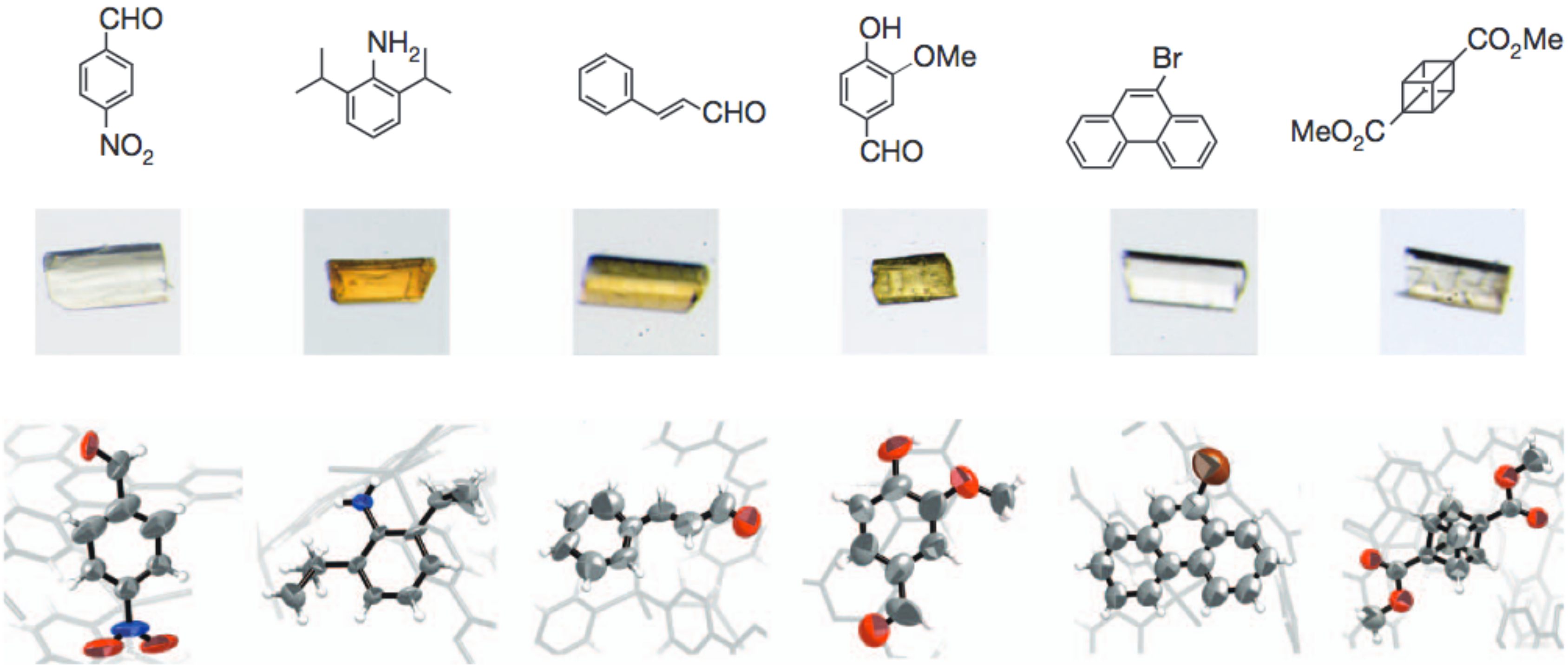


space fill of fullerene

Inokuma, Y.; Arai, T.; Fujita, M. *Nature Chemistry* **2010**, 2, 780.

Crystalline Sponge Method

Fujita, *Nature* **2013**: use of similar ZnI_2 framework to solve organic structures



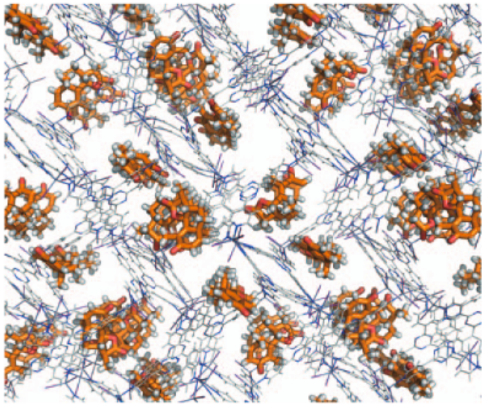
"Six appropriate samples were selected and one of us (S.Y.) performed the trace-amount crystallography with only ~5 μg of each sample and without any knowledge of the structures. In this blind test, three structures were fully determined from only the diffraction data (Fig. 3). The other three were initially flawed because of atom misassignment, symmetry problems and guest disorder, which are common problems in crystallographic analysis. However, the incorrect structures could be easily corrected using only the mass spectrometric data (molecular weight information)."

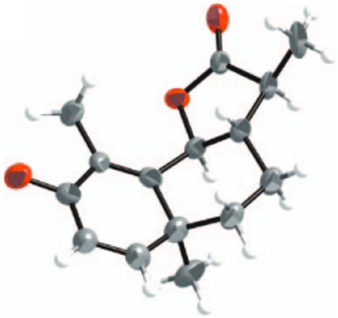
Inokuma, Y.; Yoshioka, S.; Ariyoshi, J.; Arai, T.; Hitora, Y.; Takada, K.; Matsunaga, S.; Rissanen, K.; Fujita, M. *Nature* **2013**, 495, 461.

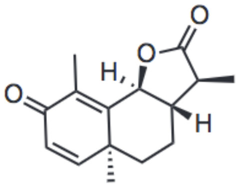
Crystalline Sponge Method

Fujita, *Nature* **2013**: use of similar ZnI_2 framework to solve organic structures

What about non-aromatic compounds?







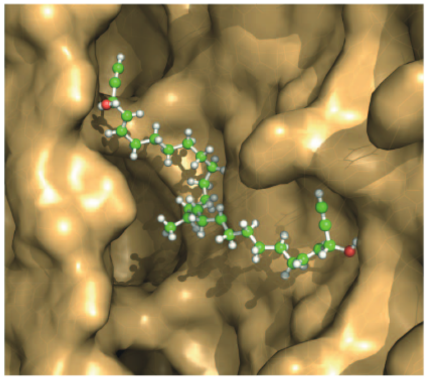
santonin

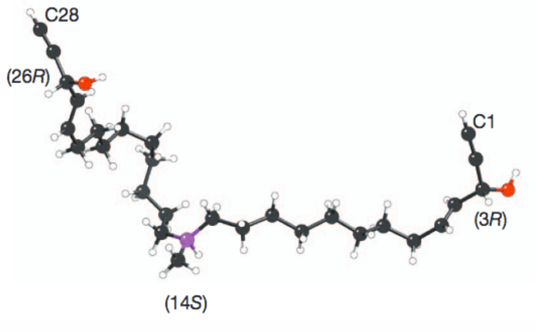
- Structure of sanotonin, an anhelminthic drug
- Good enough for absolute stereochemistry
- Heavy atoms exist in host cell
- Original C2/*c* achiral space group
- Enclathrated crystal became $P2_1$ chiral space group
- Flack(x) = 0.092(18)

- Miyakosyne A marine natural product
- C3 and C26 stereochemistry was already known
- Spectroscopic methods unable to determine C14 stereochemistry
- Structure 50% solved occupancy (remaining was disordered or solvent)
- Data only converged on 14S form, not the 14R form (later corrected)

12

miyakosyne A

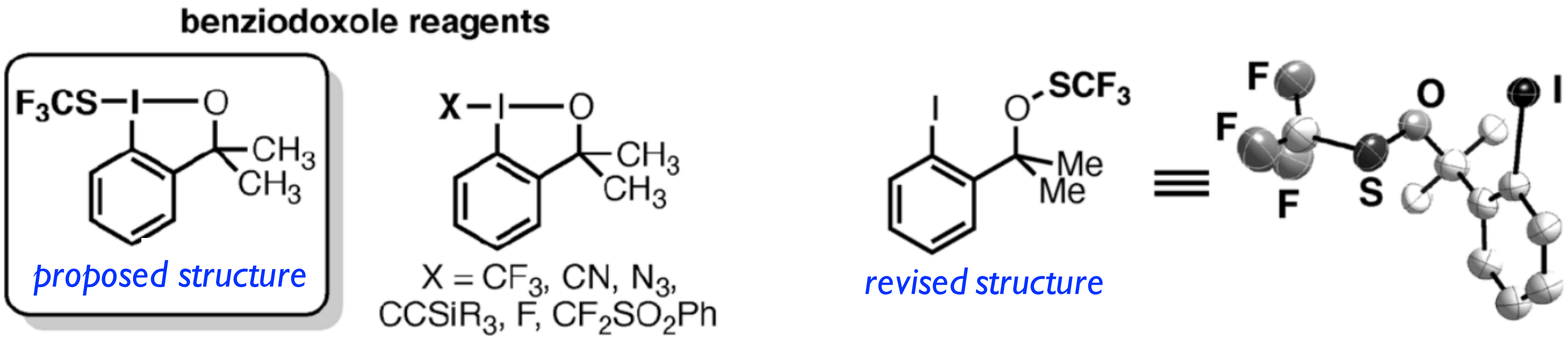




Inokuma, Y.; Yoshioka, S.; Ariyoshi, J.; Arai, T.; Hitora, Y.; Takada, K.; Matsunaga, S.; Rissanen, K.; Fujita, M. *Nature* **2013**, 495, 461.
Correction: *Nature* **2013**, *501*, 262.

Crystalline Sponge Method

Buchwald, *Angew. Chem. Int. Ed.* **2014**: reassigned reagent structure



- Structural reassignment of benziodoxole reagent used in electrophilic trifluorothiomethylation reactions

Baran/Blackmond, *Angew. Chem. Int. Ed.* **2014**: obtained structures of reaction products

- Reported electrochemical C-H trifluoromethylation
- Possible constitutional isomers determined by X-ray analysis
- Crystalline sponge method used for amorphous solids, volatile solids, and oils
- Less than 2 mg needed for each structure

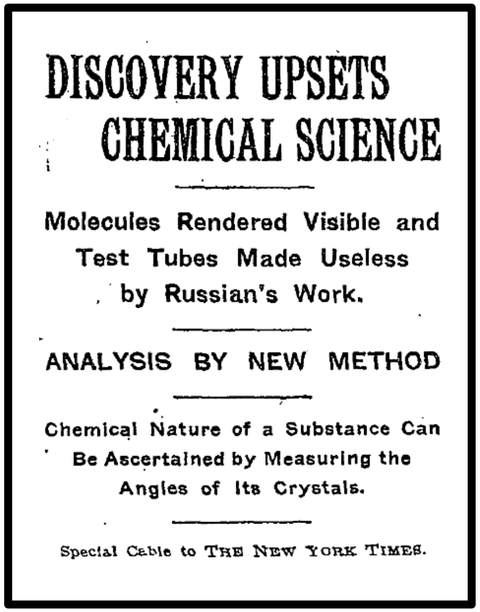
Vinogradova, E.V.; Müller, P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2014**, 53, 3125; O'Brien, A.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 11868.

Concluding Thoughts

Where has X-ray crystallography taken organic chemistry?

"In the case of those complex structures on the edge of the ever growing field of chemistry, we can now state with some confidence that we know how to use the X-ray method to solve unknown structures containing up to 100 atoms or more in the molecule. This can often be done more quickly and always far more precisely than by the classical methods of organic chemistry. This accomplishment, however, now raises a very serious problem for the immediate future. In the past many of the great discoveries of organic chemistry have been made in the course of the long and patient investigations that are required in the elucidation of natural product structures. While solving a structure the chemist does far more than merely find the relative positions of the atoms in space. He makes many discoveries and learns a lot of chemistry, which can often be utilized, for example, in effecting a total synthesis of the compound out of its elements…Perhaps we solve some problems only to create others. In the long run, however, it is quite certain that a tremendous advance has now been made, and that in another ten years' time organic chemistry will be a very different subject from what it is today."

– John Monteath Robertson (1962)



DISCOVERY UPSETS
CHEMICAL SCIENCE

Molecules Rendered Visible and
Test Tubes Made Useless
by Russian's Work.

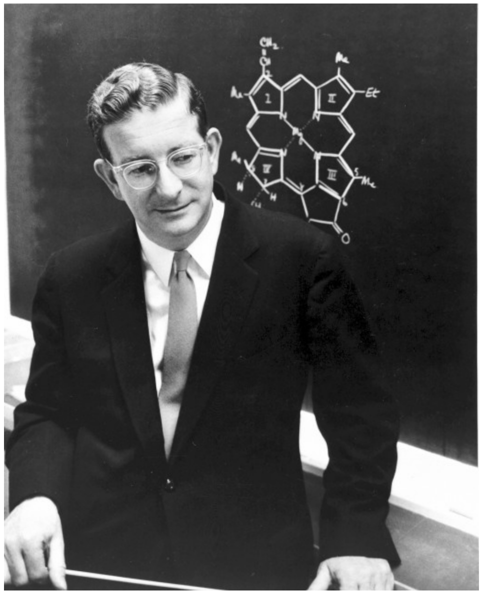
ANALYSIS BY NEW METHOD

Chemical Nature of a Substance Can
Be Ascertained by Measuring the
Angles of Its Crystals.

Special Cable to THE NEW YORK TIMES.

New York Times (1912)

Concluding Thoughts



"But it is worth while to point out here that the establishment of the structure of strychnine was accompanied by no surcease of interesting chemical developments…This short history should give pause to those whose talent for despair is lavished upon an organic chemistry ornamented and supplemented–or as they fancy, burdened–by magnificent new tools which permit the establishment in days or weeks of enlightenments which once would have required months or years. While it is undeniable that organic chemistry will be deprived of one special and highly satisfying kind of opportunity for the exercise of intellectual *élan* and experimental skill when the tradition of purely chemical structure elucidation declines, it is true too that the not infrequent dross of such investigation will also be shed; nor is there any reason to suppose that the challenge for the hand and intellect must be less, or the fruits less tantalizing, when chemistry *begins* at the advanced vantage point of an established structure. Of course, men make much use of excuses for activities which lead to discovery, and the lure of unknown structures has in the past yielded a huge dividend of unsought fact, which has been of major importance in building organic chemistry as a science. Should a surrogate now be needed, we do not hesitate to advocate for the case of synthesis."

– R. B. Woodward (1963)

Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Dafniker, H. U.; Schenker, K. *Tetrahedron* **1963**, 19, 247.

Additional Resources

Ooi, L. *Principles of X-ray Crystallography* 2010.
(textbook for undergraduates, very understandable to read)

Thompson, A. L.; Watkins, D. J. X-ray crystallography and chirality: understanding the limitations *Tetrahedron: Asymmetry* 2009, *20*, 712.

Online step-by-step resources on structure solution:

http://scs.illinois.edu/x-ray/software2/xshellguide.pdf
http://xray.chem.wisc.edu/Resources/Manuals/Ilia_Guzei_notes_on_OLEX2.pdf
http://imserc.northwestern.edu/crystallography-resources.html

Shelxl website: http://shelx.uni-goettingen.de/

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Structure contributions: Sean Feng, Elliot Farney, Arthur Han, Nathaniel Kadunce, Chen Xu
And others: Jorden Beck, Lauren Chapman, Kangway Chuang, Kelsey Poremba, Alice Wong

Additional Website Resources

http://oldwww.iucr.org/iucr-top/comm/cteach/pamphlets/13/node1.html

https://www.acs.org/content/dam/acsorg/events/popular-chemsitry/Slides/2014-05-15-crystallography.pdf

https://www.aip.org/history-programs/niels-bohr-library/oral-histories/4595

https://decor.cst.temple.edu/FS05.pdf

http://www.cdifx.univ-rennes1.fr/RECIPROCS/ANF2014/pdf/Bruker_SC-XRD_FISDIV_Space_Group_Determination_Structure_Solution.pdf

https://www.iucr.org/gallery/1947/caltech

http://www.chem.ucla.edu/~harding/ec_tutorials/tutorial73.pdf

https://www.acs.org/content/dam/acsorg/membership/acs/benefits/extra-insights/crystallography.pdf

http://www.cryst.chem.uu.nl/spek/platon/pl000606.html

http://shelx.uni-ac.gwdg.de/~athorn/2011.html

https://www2.chemistry.msu.edu/facilities/crystallography/xtalgrow.pdf