Crystal Structure Prediction:
Synergy between Theory and Experiment

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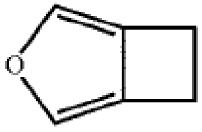
The Problem

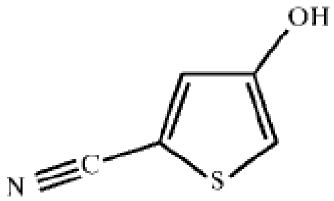
“One of the continuing scandals in the physical sciences is that it remains in general impossible to predict the structure of even the simplest crystalline solids from a knowledge of their chemical composition.”

John Maddox, “Crystals from first principles”, *Nature*, **355**, 201-201 (1988).

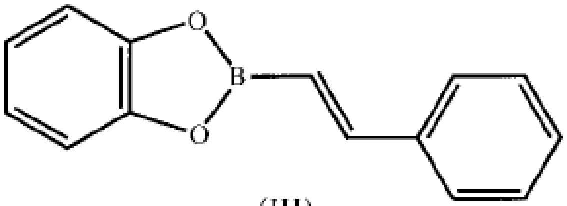
A test of crystal structure prediction of small organic molecules, *Acta Cryst. Sect. B: Structural Science*, **56**, 697-714 (2000)



(I)



(II)



(III)

Propane

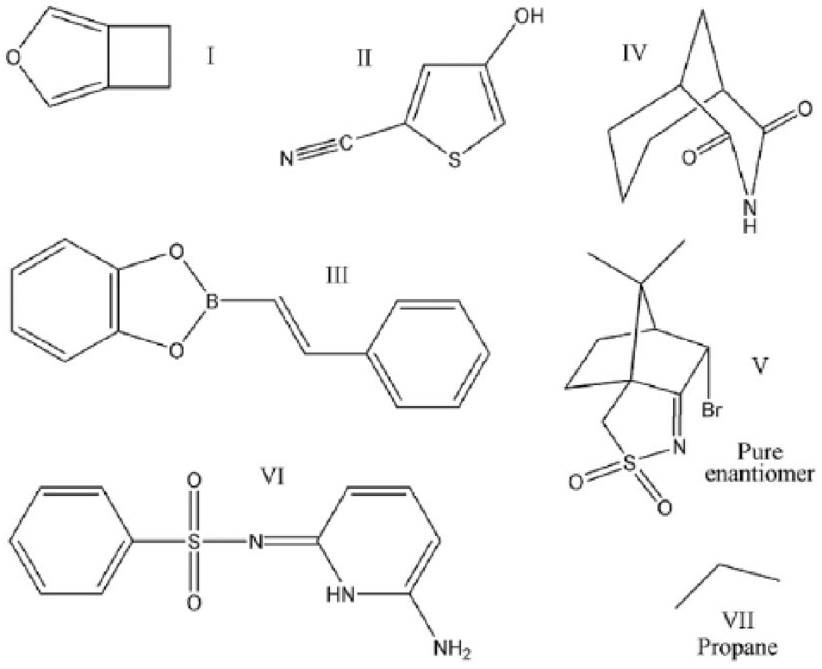
MPA

- A small rigid molecule with only C, H, N, or O atoms allowed and < 20 atoms
- A small rigid molecule with some less common elements
- A molecule with some small amount of conformational freedom
- Propane

First Blind Test (2000)

- 7 correct out of 36 predicted structures
- Compound I had two polymorphs!
- Molecules are flexible!
- “at the present stage of development, perhaps the best that can be expected from crystal structure prediction programs is to provide a list of possible candidates for experimentally observable polymorphs.”

Crystal structure prediction of small organic molecules: a second blind test, *Acta Cryst. Sect. B: Struct. Sci.*, **58**, 647-661 (2002).



- # atoms < 40
- 10 most common space groups
- Rigid molecule with only C, H, N, or O atoms, < 25 atoms
- Rigid molecule with some less common elements
- Flexible molecule with 2 degrees of acyclic torsional freedom, < 40 atoms
- Secondary test using X-ray powder data

Second Blind Test (2002)

- I: 0/4
- II: 1
- III: 1
- IV: 3/45
- V: 3/45
- VI: 0/33
- VII: 1

- There are many structures within a few kJ/mol of the global minimum
- Kinetics *vs.* thermodynamics
- Sensitivity of hydrogen bond potentials
- Z’ > 1 a problem
- Temperature: enthalpy/entropy
- CSD wasn’t big enough
- Powder data helps!

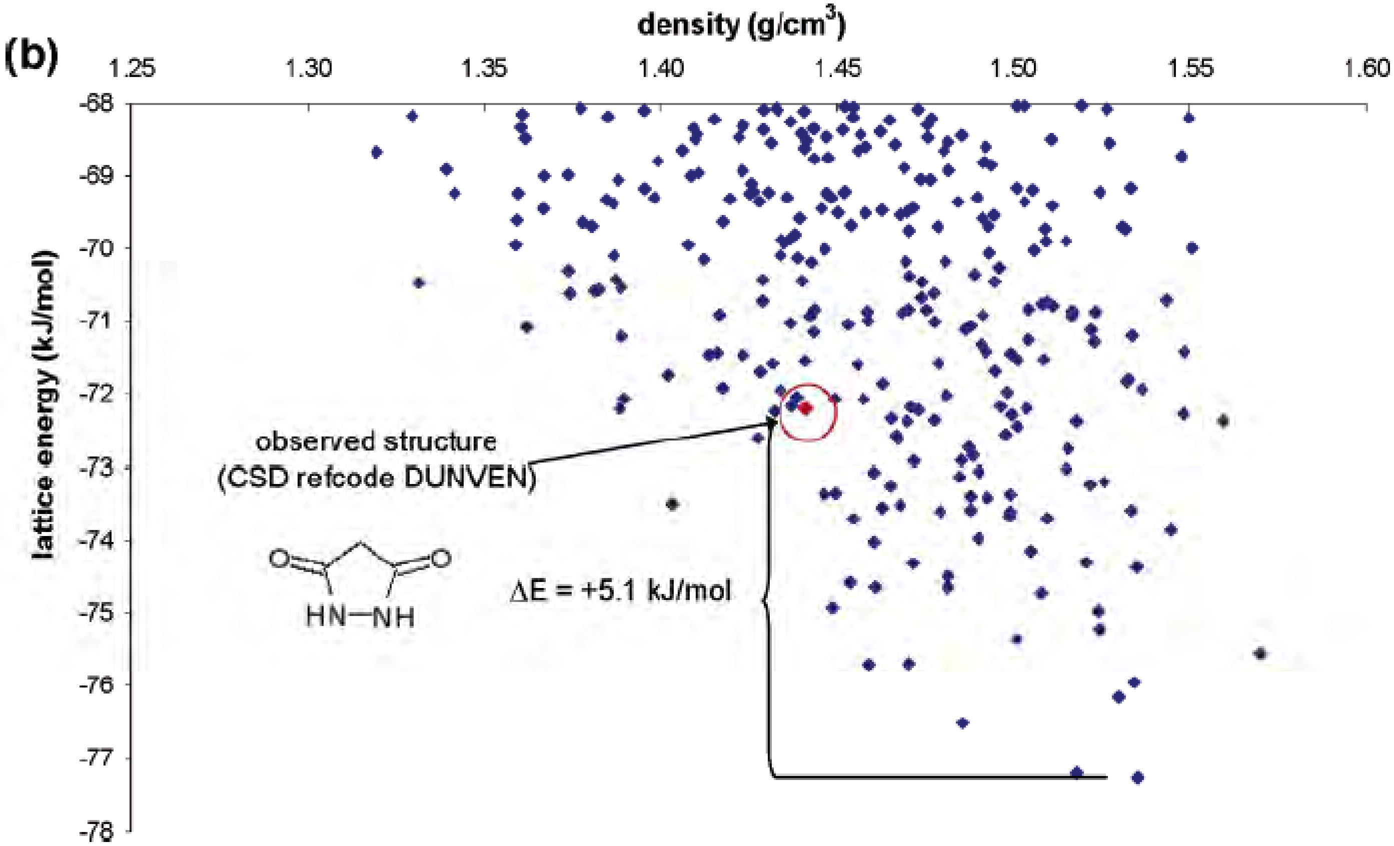
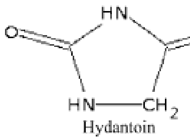


Figure 2. Predicted structures of (a) bicyclo(3.3.1)nonane-2,6-dione and (b) 3,5-pyrazolidinedione.

G. M. Day, J. Chisolm, N. Shan, W. D. S. Motherwell, and W. Jones, *Cryst. Growth Des.*, **4**, 1327-1340 (2004). (Special Issue on crystal structure prediction)

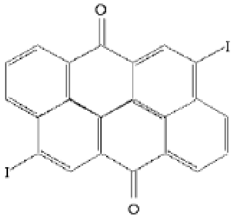
A third blind test of crystal structure prediction, *Acta Cryst. B: Struct. Sci.*, **61**, 511-527 (2005).

(VIII)



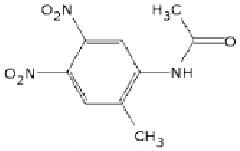
Hydantoin

(IX)



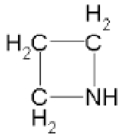
2,9-Di-iodo-anthanthrone

(X)



2-Acetamido-4,5-dinitrotoluene

(XI)



Azetidine

- Small rigid molecule containing only C, H, N, or O, < ~25 atoms
- Rigid molecule, containing "challenging" elements or functional groups, < 30-40 atoms
- Molecule with several degrees of torsional flexibility
- No restrictions of space groups
- Z' < 3

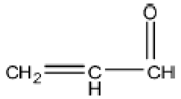
Third Blind Test (2005)

- VIII: 4+/45
- IX: 1+/45
- X: 0+/45
- XI: 0+/54 (Z’ = 2, QM)

- Z’ > 1 a problem (salts and co-crystals)
- Flexible molecules are hard
- Progress (higher success rates in whole list)
- Improved electrostatic models
- Need more than lattice energy

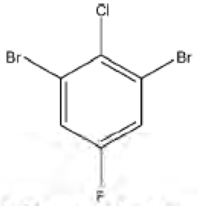
Significant progress in prediction the crystal structures of small organic molecules – a report on the fourth blind test, *Acta Cryst. B.: Struct. Sci.*, **65**, 107-125 (2009).

(XII)



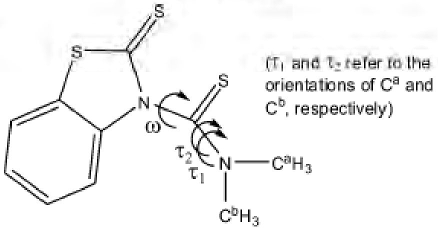
2-Propenal

(XIII)



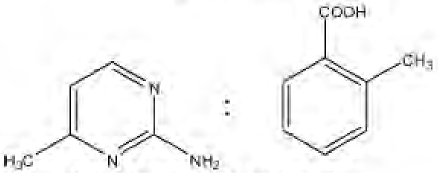
1,3-Dibromo-2-chloro-5-fluorobenzene

(XIV)



N-(Dimethylthiocarbamoyl)benzothiazole-2-thione

(XV)



2-Amino-4-methylpyrimidine: 2-methylbenzoic acid

- Open solicitation of participants
- Small rigid molecule, C, H, N, or O only, < 25 atoms
- Rigid “challenging” molecules, < 30-40 atoms
- Molecules with several degrees of conformational freedom
- Two-component crystal of rigid molecules

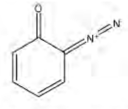
Fourth Blind Test (2009)

- XII: 4(+6)/39 (2 #1, 2 #2)
- XIII: 4(+5)/42 (all top)
- XIV: 3(+6)/36
- XV: 2(+3)/36

- COMPAK comparison, plus integral index of powder patterns
- One group 4/4 (all top)
- 7/14 groups had at least 1 success
- New ranking algorithms
- DFT optimization
- Hydrogen bonding

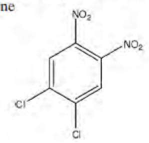
Towards crystal structure prediction of complex organic compounds – a report on the fifth blind test, *Acta Cryst. B: Struct. Sci.*, **67**, 535-551 (2011).

(XVI)



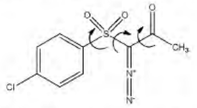
2-Diazo-3,5-cyclohexadiene-1-one

(XVII)



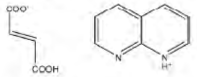
1,2-Dichloro-4,5-dinitrobenzene

(XVIII)



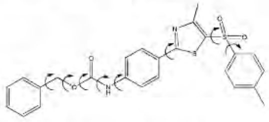
(1-((4-Chlorophenyl)sulfonyl)-2-oxopropylidene)diazenium

(XIX)



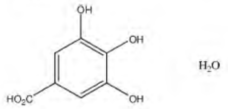
1,8-Naphthyridinium fumarate

(XX)



Benzyl-(4-(4-methyl-5-(*p*-tolylsulfonyl)-1,3-thiazol-2-yl)phenyl)carbamate

(XXI)



Gallic acid monohydrate

- Small rigid molecule, C, H, N, or O only, Z' = 1, < 25 atoms
- Rigid molecule, unusual functional groups or elements, Z' = 1, < 30 atoms
- Moderately flexible molecule, 2-4 internal degrees of freedom, Z' = 1, < 40 atoms
- Multiple independent rigid molecules, < 30 atoms
- Molecule with 4-8 internal degrees of freedom, Z' ≤ 2, 50-60 atoms
- Molecule with > 1 polymorph

Fifth Blind Test (2011)

- XVI: 2(+5)/45 (1-302, 0-5.74 kJ/mol)
- XVII: 2(+4)/39 (1-121, 0-6.39 kJ/mol)
- XVIII: 1(+3)/39 (1-29, 0-8.21 kJ/mol)
- XIX: 2(+2)/33 (2-27, 0.83-12.62 kJ/mol)
- XX: 2(+1)/30 (1-7, -0.78-1.90 kJ/mol)
- XXI: 3*(+4)/30 (1-338, -2.43-13.18 kJ/mol)

- < 200,000 CPU hours!
- Hydrogens, water
- DFT, not force fields
- Materials Module of Mercury

Revisting the Blind Tests in Crystal Structure Prediction: Accurate Energy Ranking of Molecular Crystals, A. Asmadi, M. A. Neumann, J. Kendrick, P. Girard, M.-A. Perrin, and F. J. J. Leusen, *J. Phys. Chem. B*, **113**, 16303-16313 (2009).

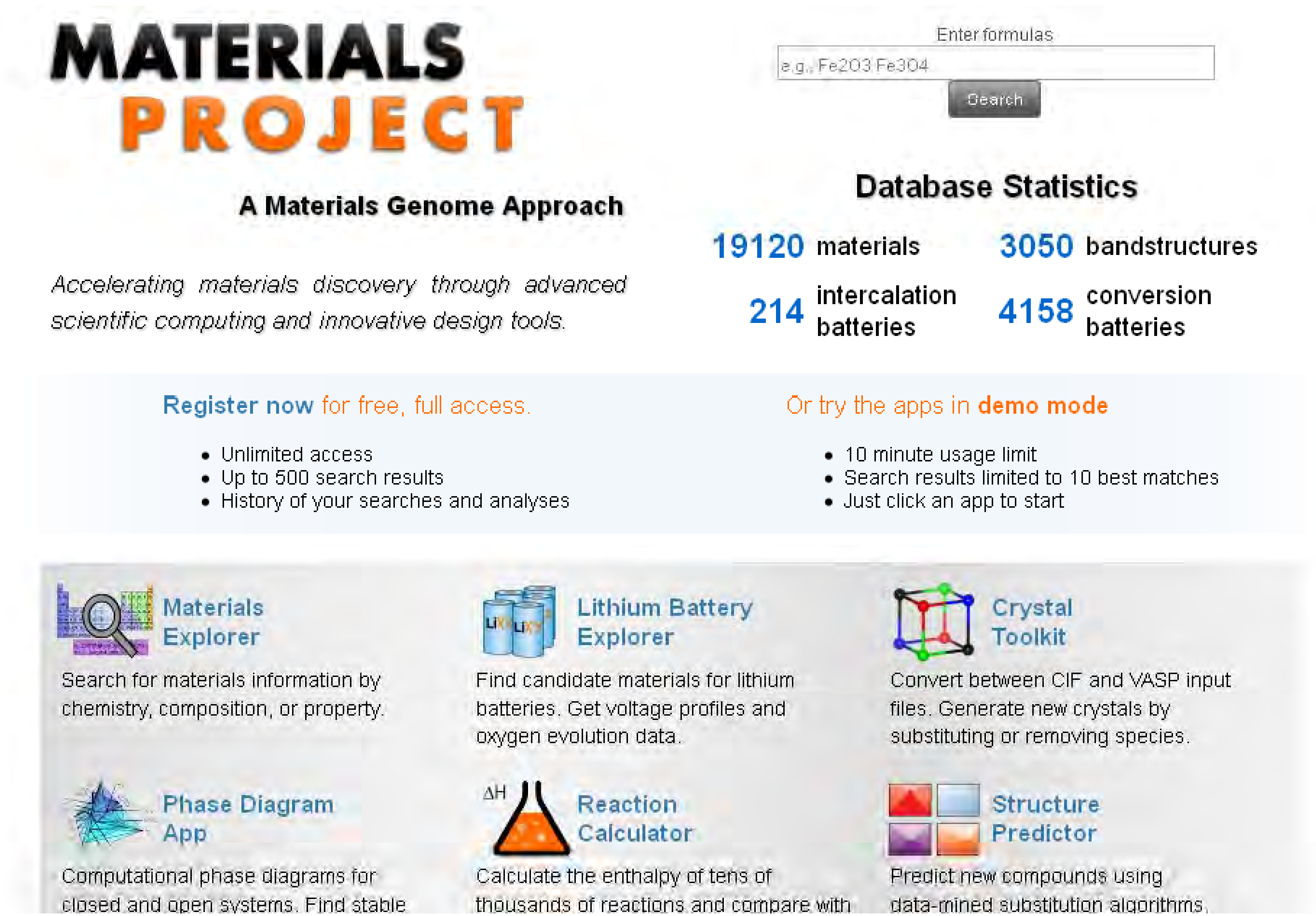
- Hybrid DFT (VASP + empirical vdW = GRACE)
- Lattice parameter errors
- 12/14 observed are lowest energy
  - Molecule II, 0.05 kJ/mol
  - Molecule V, +1.52 kJ/mol (a high-pressure form?)
- Lots of low-energy structures
  - New polymorphs of IV and VI, 0.56 and 0.92 kJ/mol

Progress in Crystal Structure Prediction, J. Kendrick, F. J. J. Leusen, M. A. Neumann, and J. van de Streek, Chem. Eur. J., 17, 10736-10744 (2011).

- Apply GRACE to molecules of the 2010/2011 blind test
- 4/6 correct predictions
- 3 of 4 have global minimum lattice energy
- All 6 were found during structure generation
- Better lattice energies and/or polymorphs

Inorganic Compounds

- How Evolutionary Crystal Structure Predictions Works – and Why, Artem R. Organov, Andriy O. Lyakhov, and Mario Valle, *Acc. Chem. Res.*, **44**(3), 227-237 (2011).
- *Modern Methods of Crystal Structure Prediction*, Artem R. Organov, ed., Wiley-VCH (2011).



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214	intercalation batteries	4158	conversion batteries

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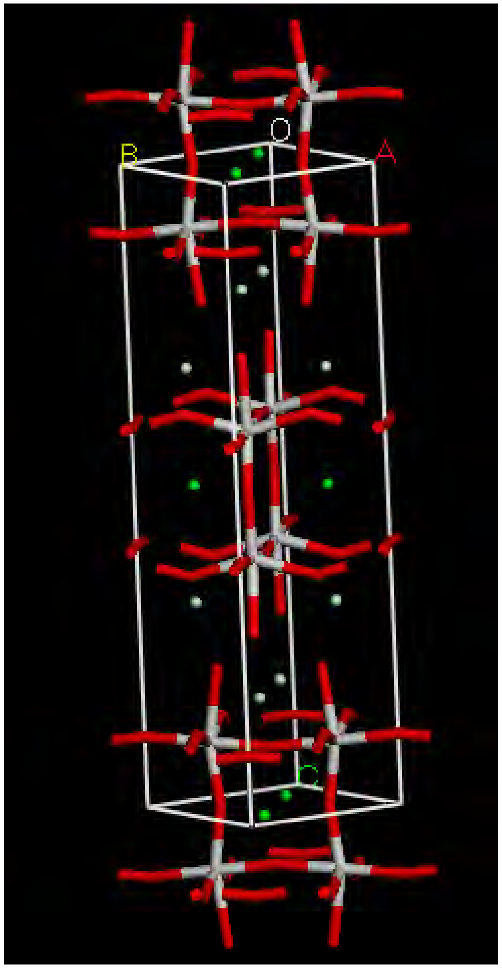
Structure Predictor

Predict new compounds using data-mined substitution algorithms.

$SrR_2Sc_2O_7$ (R = Pr, **Nd**, Sm, Eu, Gd)

- Structures reported in *Fmmm* from powder data: *Dopov. Nats. Akad. Ukr.*, 155-161 (2009)
- Nd is within 0.03 Å of *I4/mmm*, *V* = ½
- Gd (and Eu?) have primitive cell, *V* = 1

$SrR_2Sc_2O_7$ Structure Predictor

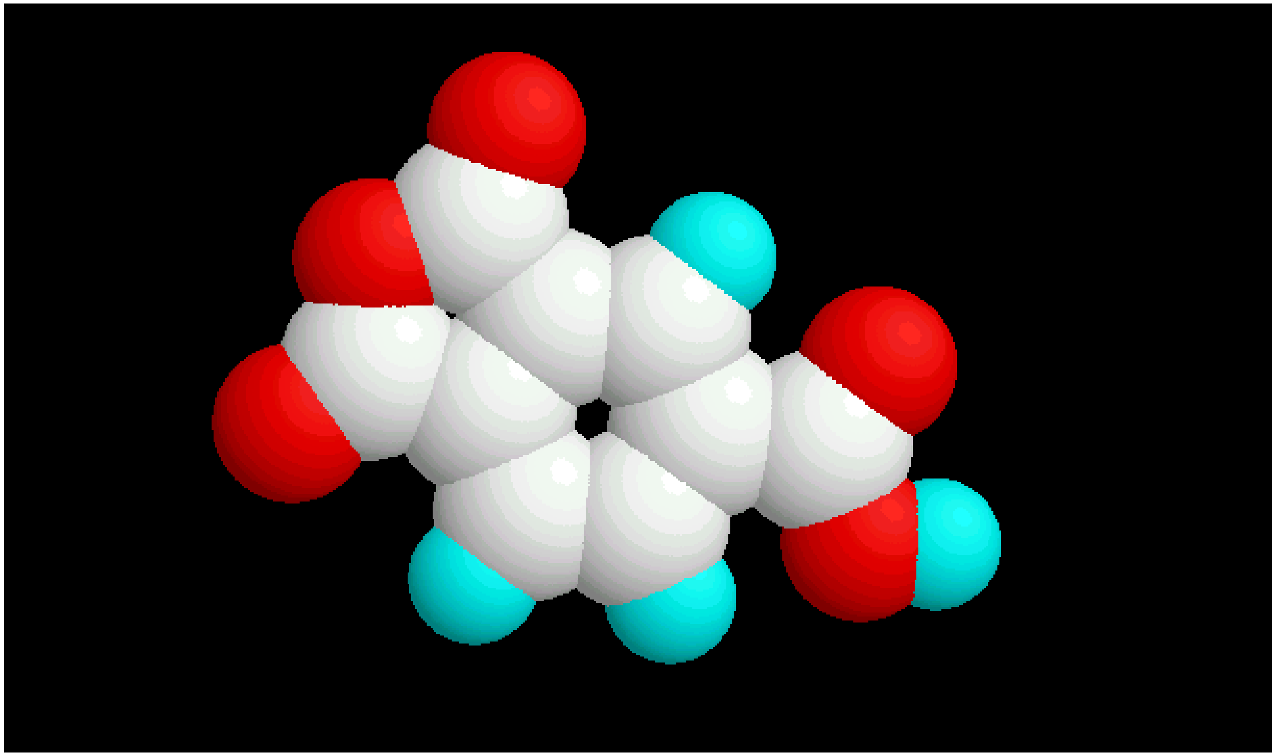


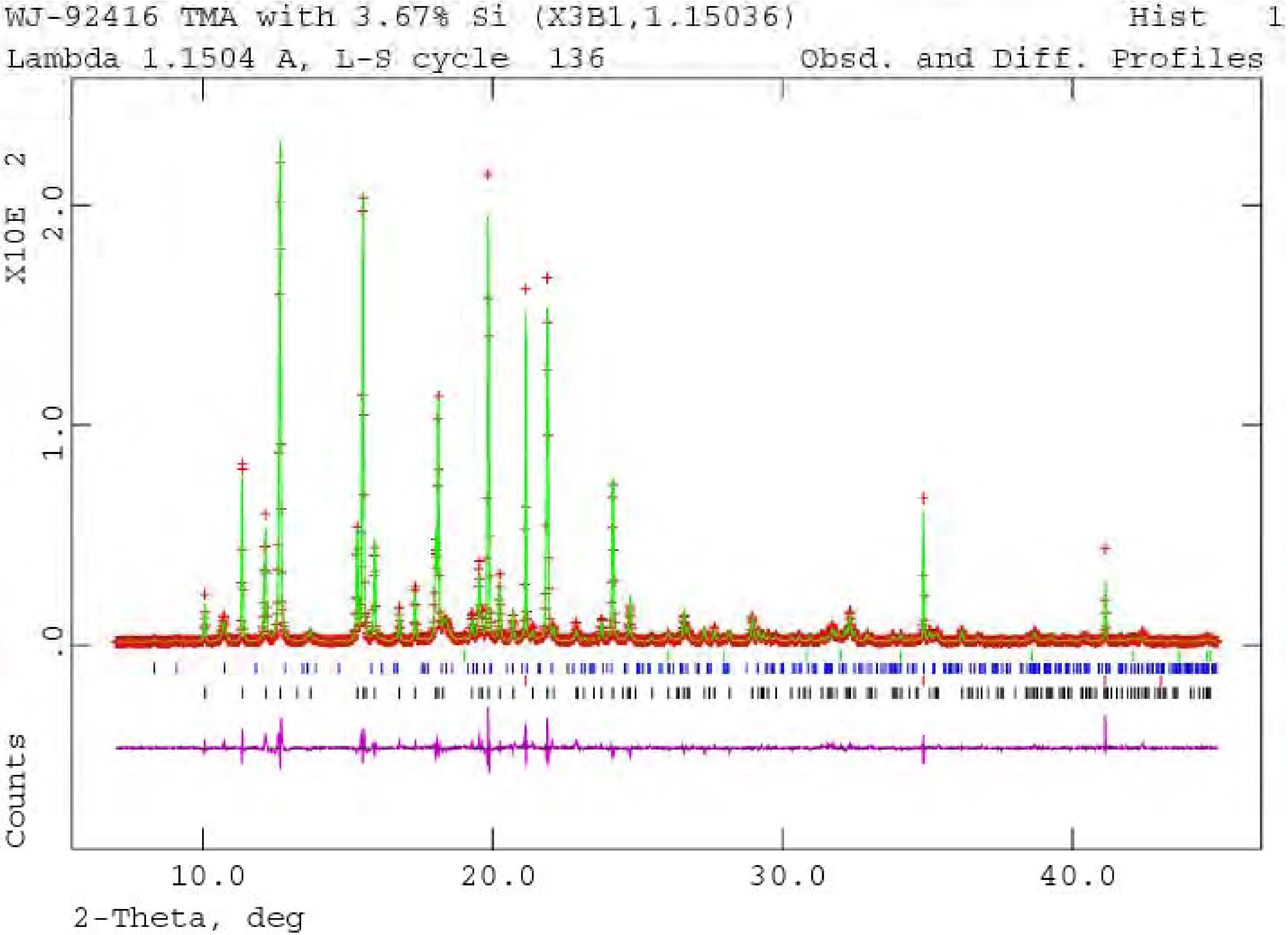
Space Group	**Log(probability)**
I4/mmm	-3.5542
P1	-4.7228
P1	-4.7450
P1	-4.8564
P1	-4.8564
I4/mmm	-4.9238

+ 23 other compositions

Trimellitic Anhydride

a versatile chemical intermediate

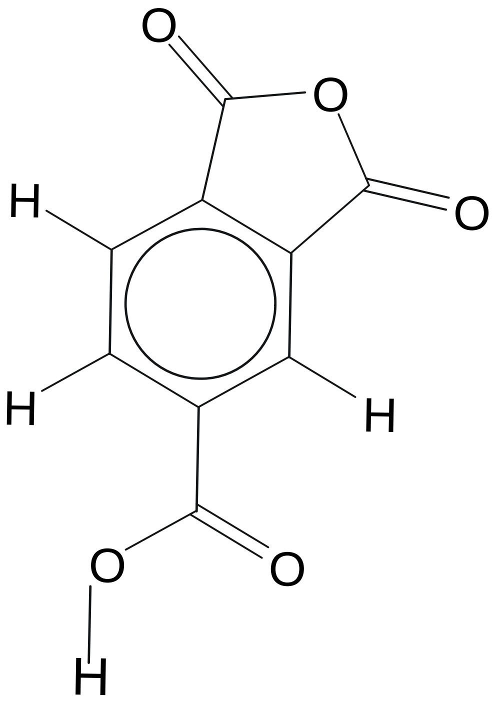



WJ-92416 TMA with 3.67% Si (X3B1,1.15036)
Hist 1
Lambda 1.1504 A, L-S cycle 136
Obsd. and Diff. Profiles
X10E 2
2.0
1.0
.0
Counts
10.0
20.0
30.0
40.0
2-Theta, deg

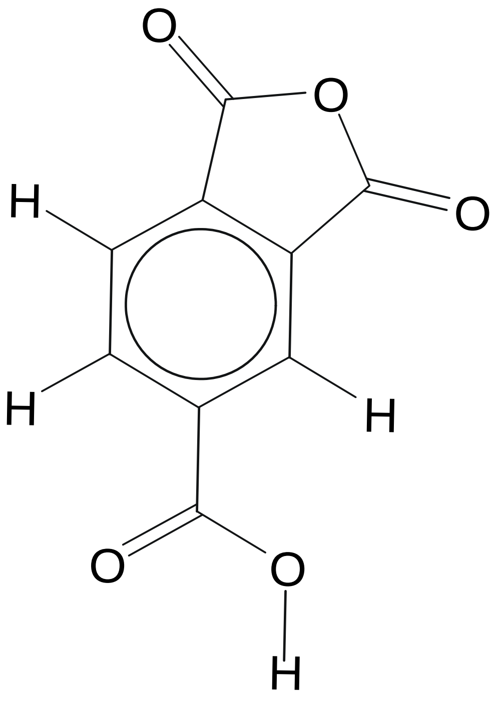
Trimellitic Anhydride

- Try to grow crystals – adducts!
- P-orthorhombic
- a = 5.3684, b = 6.8628, c = 21.6999 Å
- $P2_1xx$ – 7 possible space groups
- $P2_12_12_1$, $P2_12_12$, $Pna2_1$, $Pca2_1$ most likely
- $\rho \sim 1.6$ g/mL → Z = 4!

Two possible conformations:



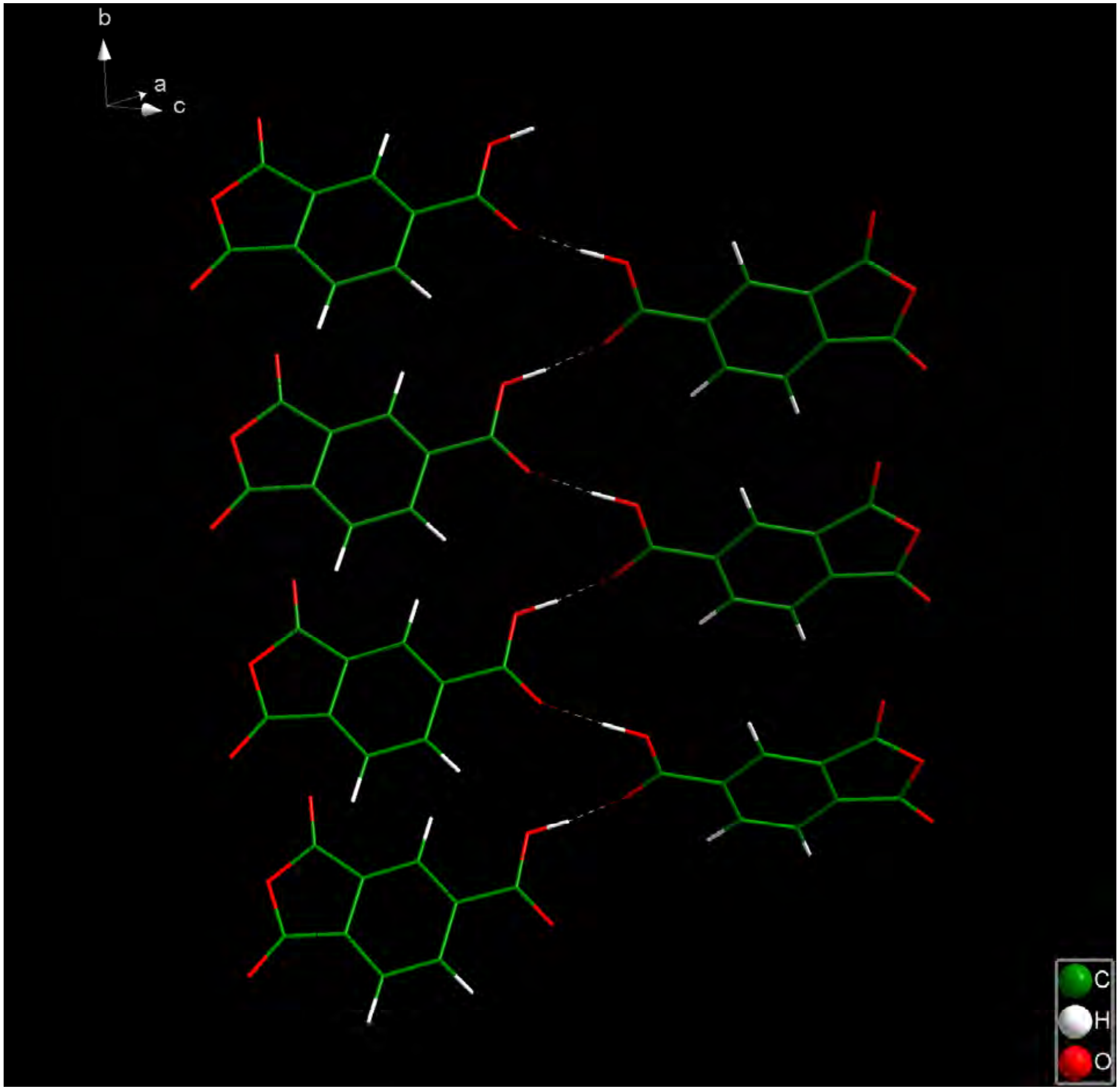
(*E*)-TMA

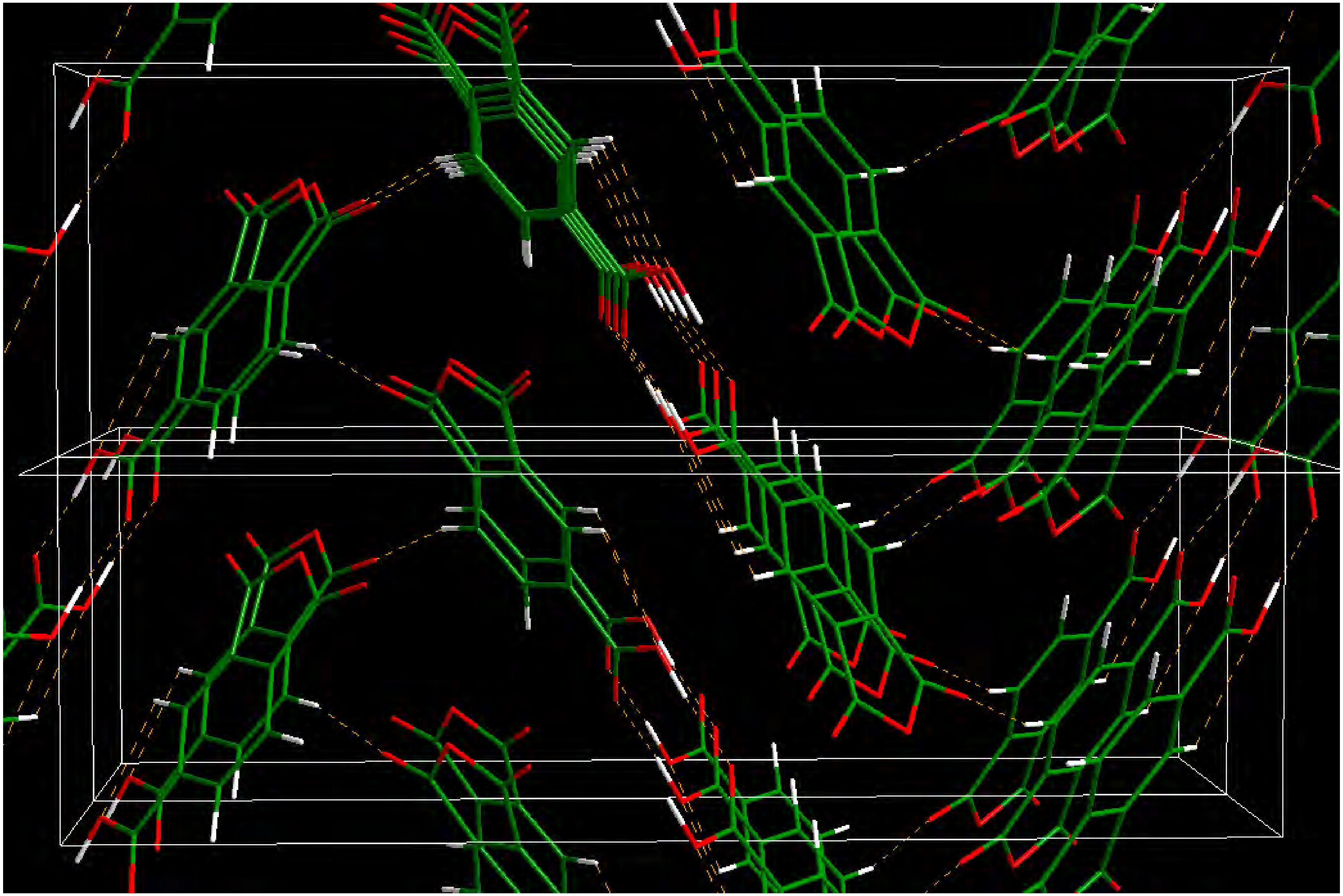


(*Z*)-TMA

Real Space Structure Solution/Prediction

- Optimize each conformation (Gaussian92)
- 2 conformations × 4 space groups
- Generate “library” of potential low-energy crystal structures
- 2nd-lowest energy in $P2_12_12_1$ had cell similar to observed
- refine


b
a
c
C
H
O



“The Crystal Structures of Trimellitic Anhydride and Two of Its Solvates”, J. A. Kaduk, J. T. Golab, and F. J. J. Leusen, *Crystal Engineering*, **1**(3/4), 277-290 (1998).

Crystal Structures of Group 1 and Group 2 Citrate Salts

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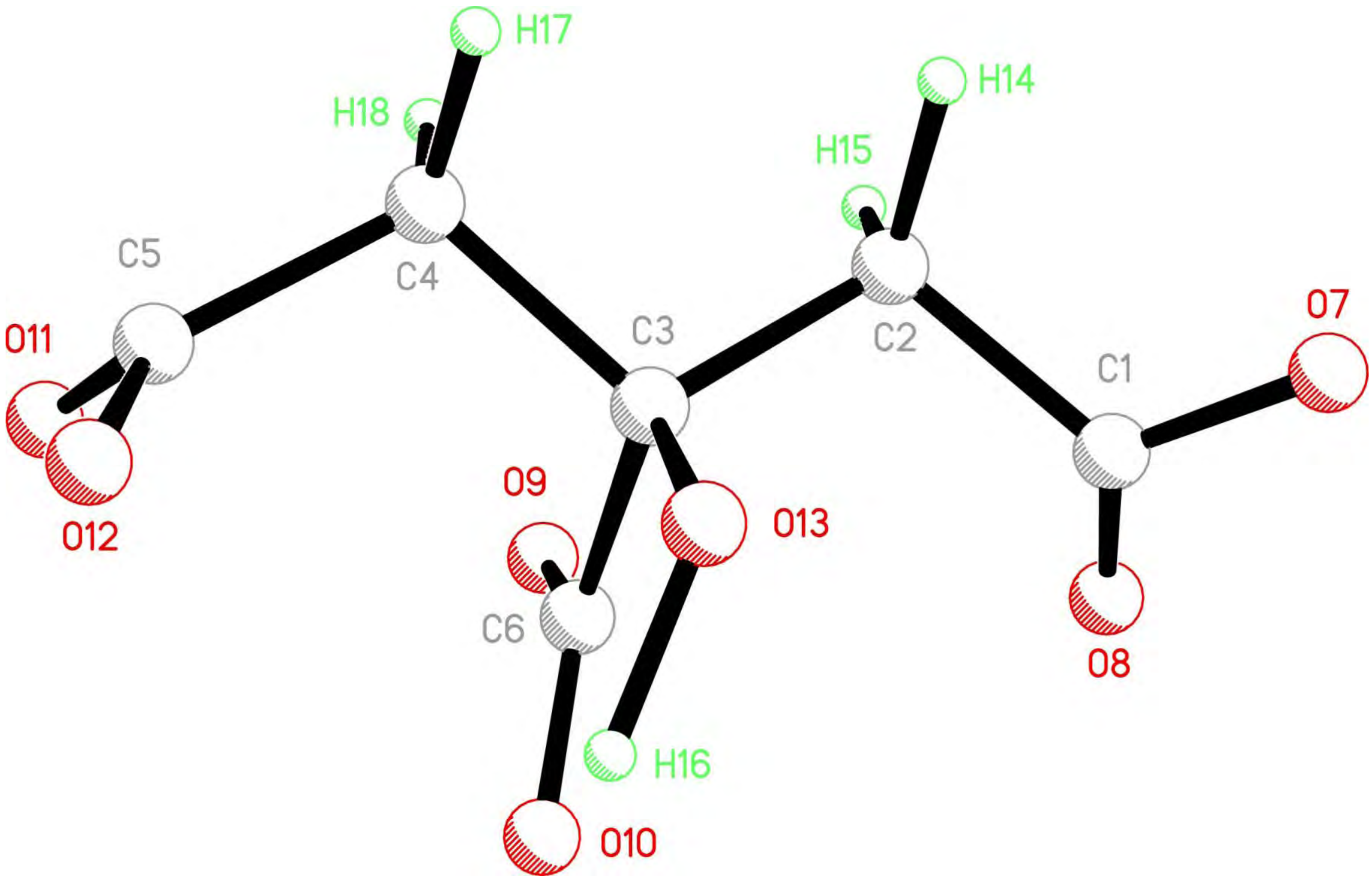
Al Rammohan,
Atlantic International University

Citrate Trianion

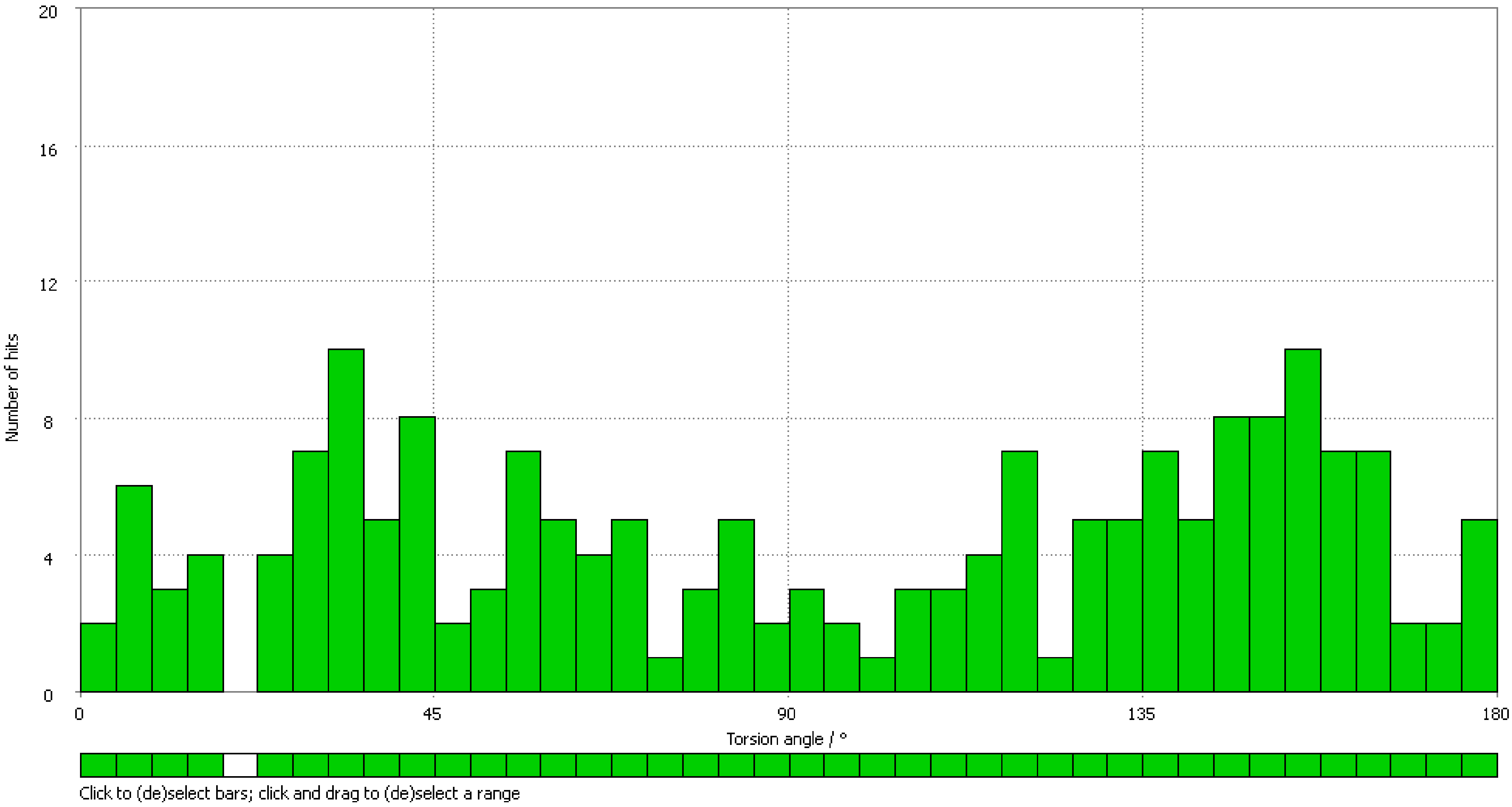


Citrate Geometry (Mogul)

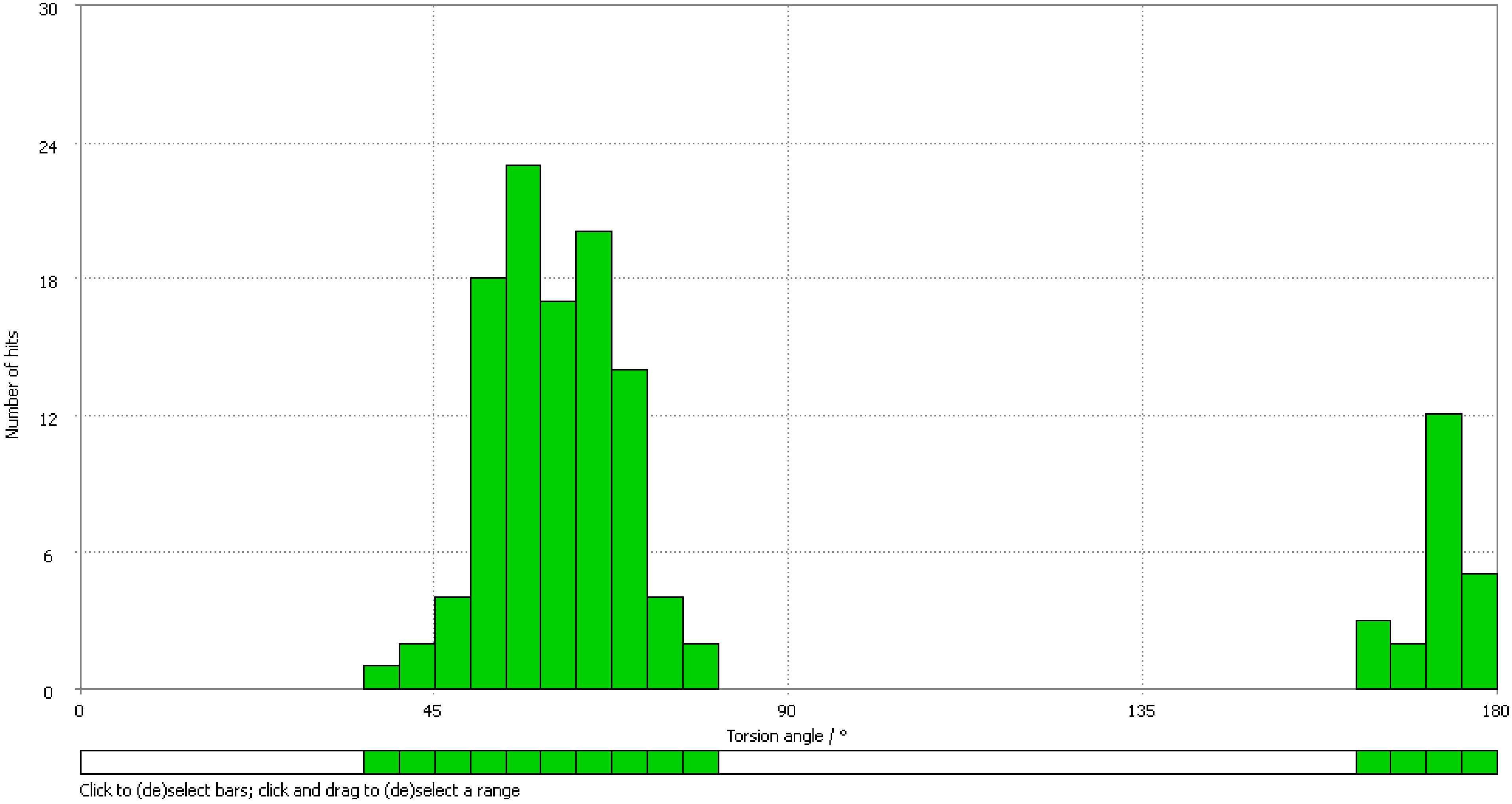
Bond	Distance, Å
C1-C2 C4-C5	1.52(2)
C2-C3 C3-C4	1.53(1)
C3-C6	1.54(1)
C1-O7 C1-O8 C5-O11 C5-O12	1.25(3)
C6-O9 C6-O10	1.24(4)
C3-O13	1.43(2)

Angle	Value, °
C1-C2-C3 C3-C4-C5	115(2)
C2-C3-C4	109(2)
C2/4-C3-C6	110(2)
C7-C1-O8 C11-C5-C12	124(2)
O9-C6-O10	127(4)
O7/8-C1-C2 O11/12-C5-C4	118(4)
O9/10-C6-C3	117(2)
O13-C3-C3/4	109(2)
O13-C3-C6	109(2)

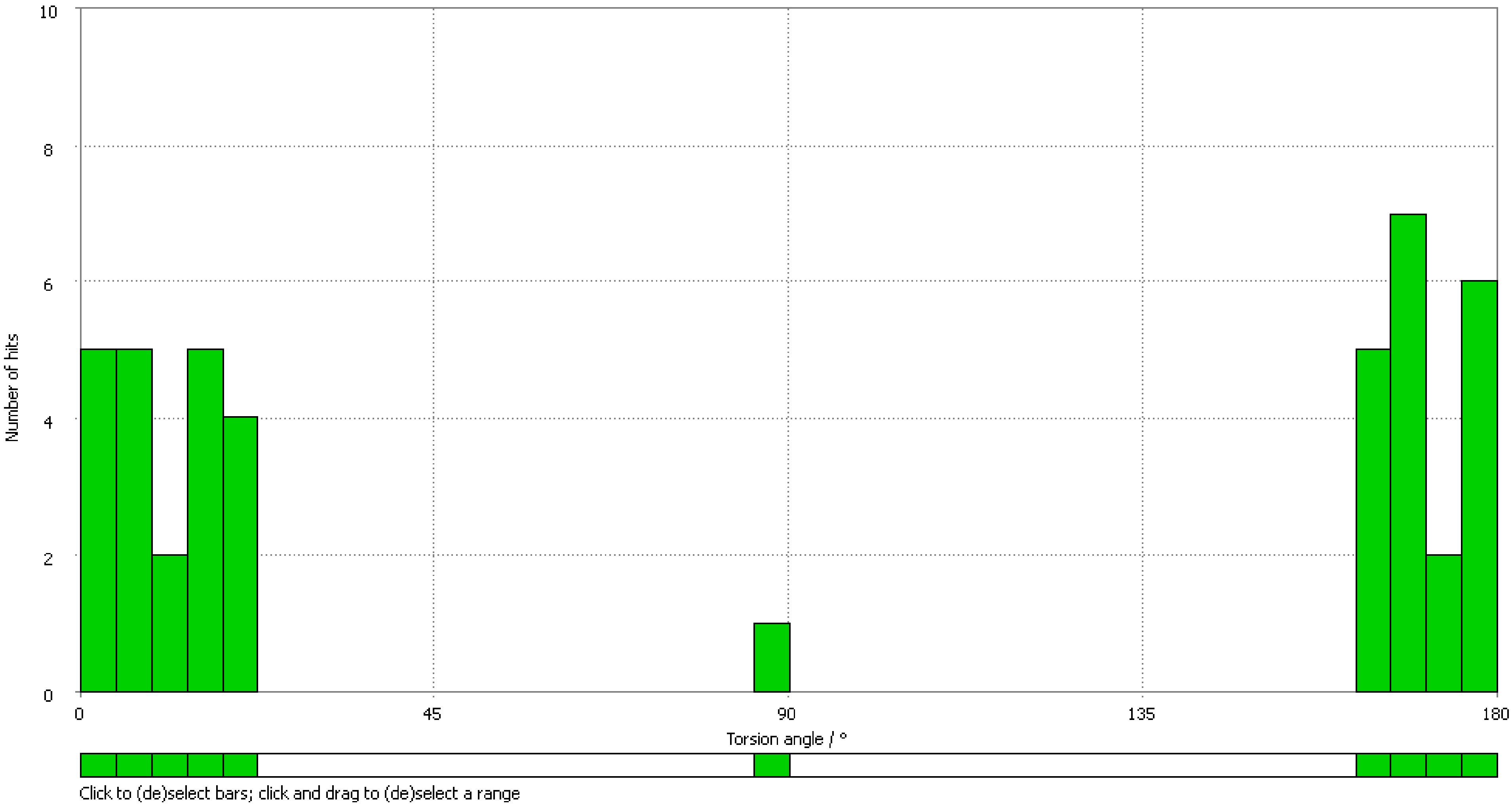
O7/8/11/12-C1/5-C2/4-C3 Torsions



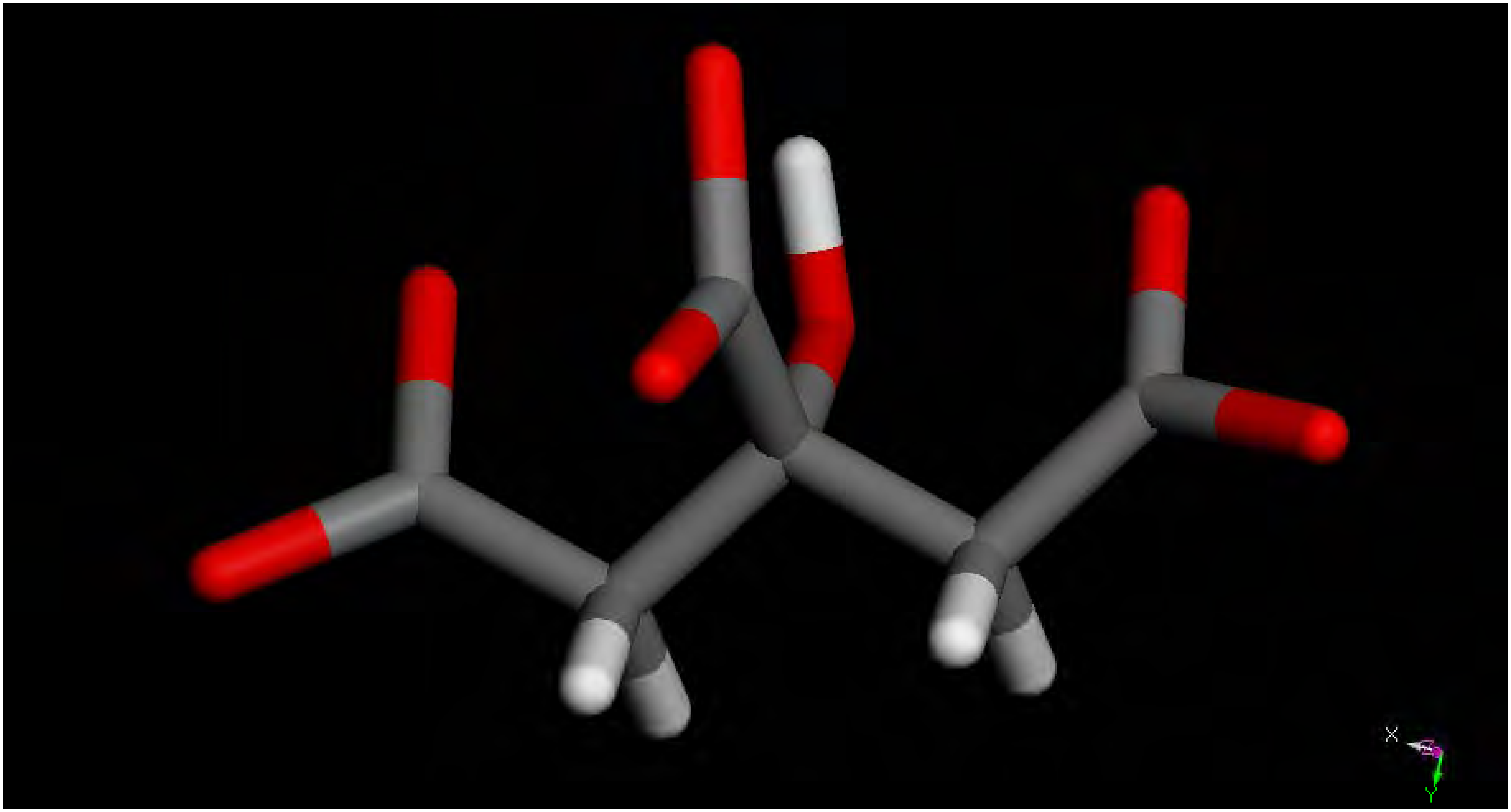
C1/5-C2/4-C3-C6 Torsions



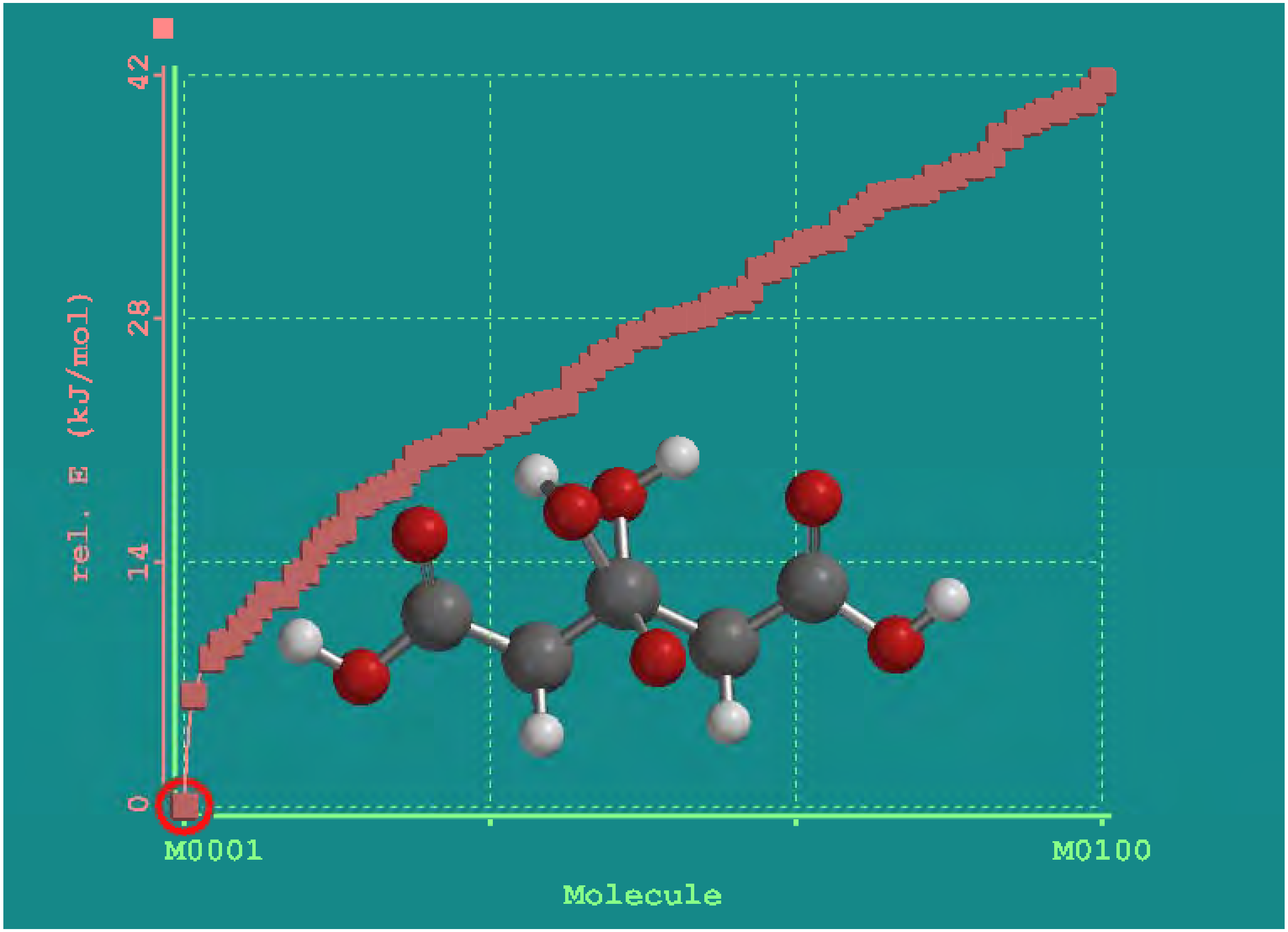
O13-C3-C6-O9/10 Torsions



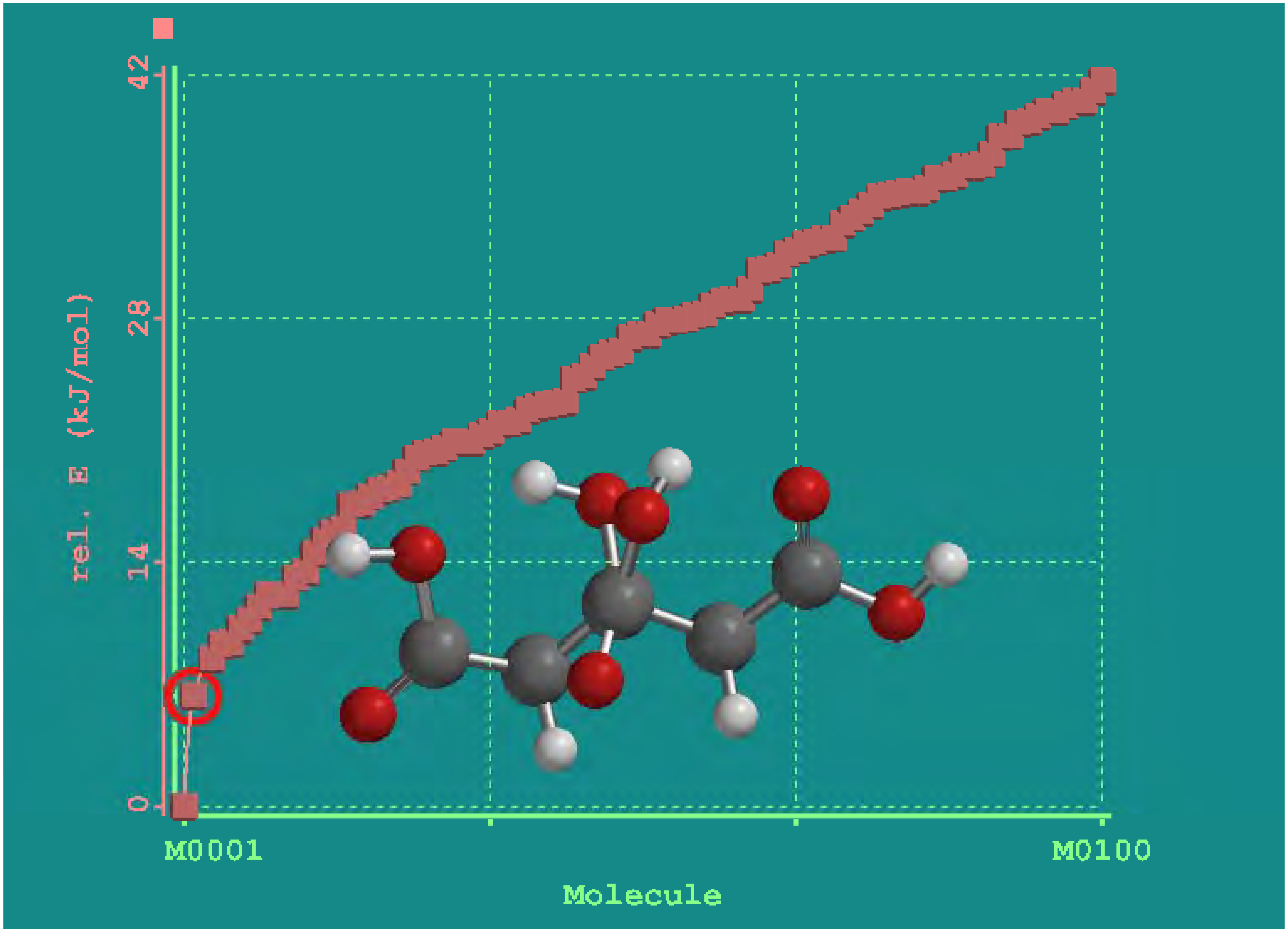
An “Average” Citrate



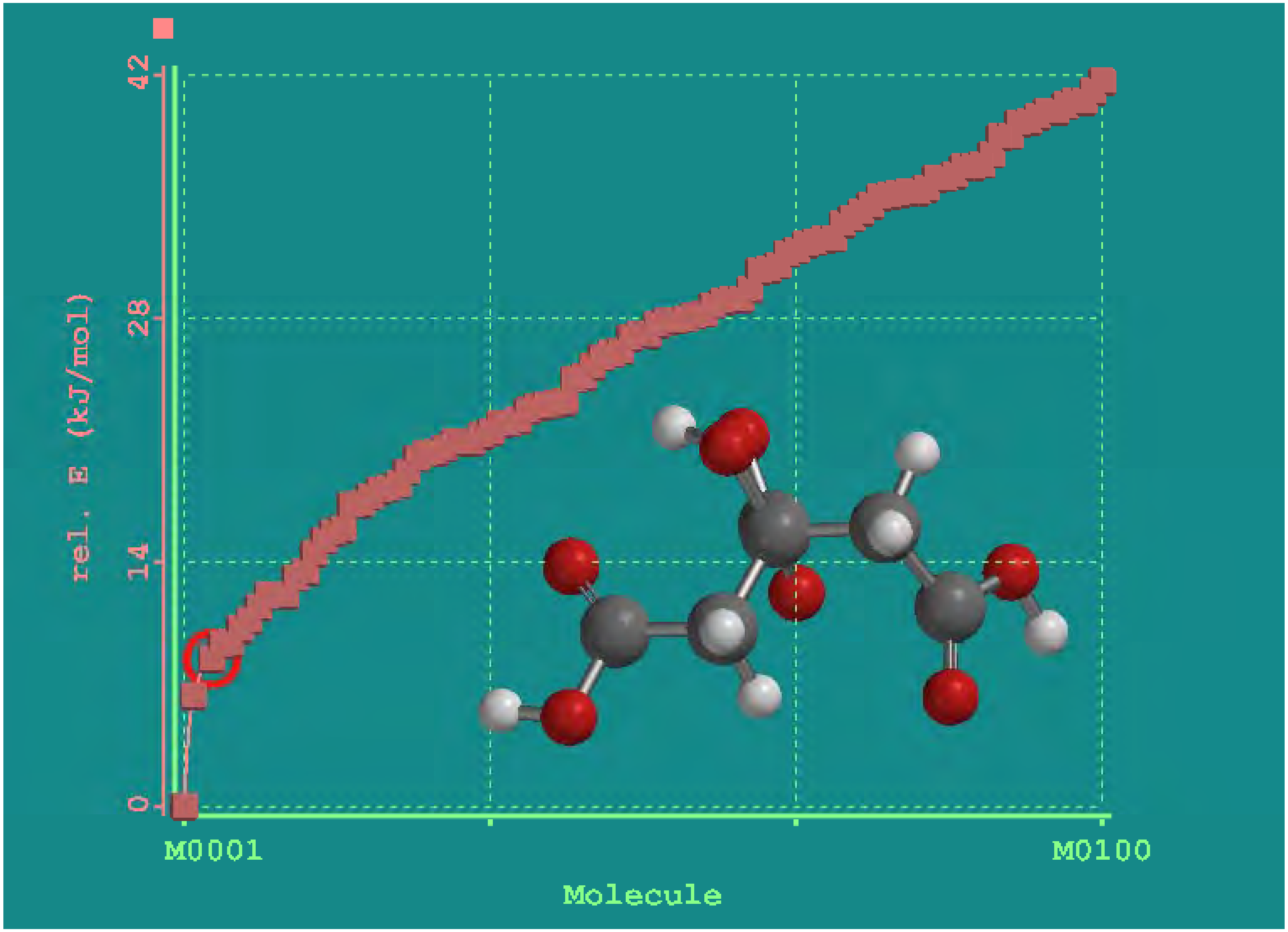
Minimum Energy Conformation



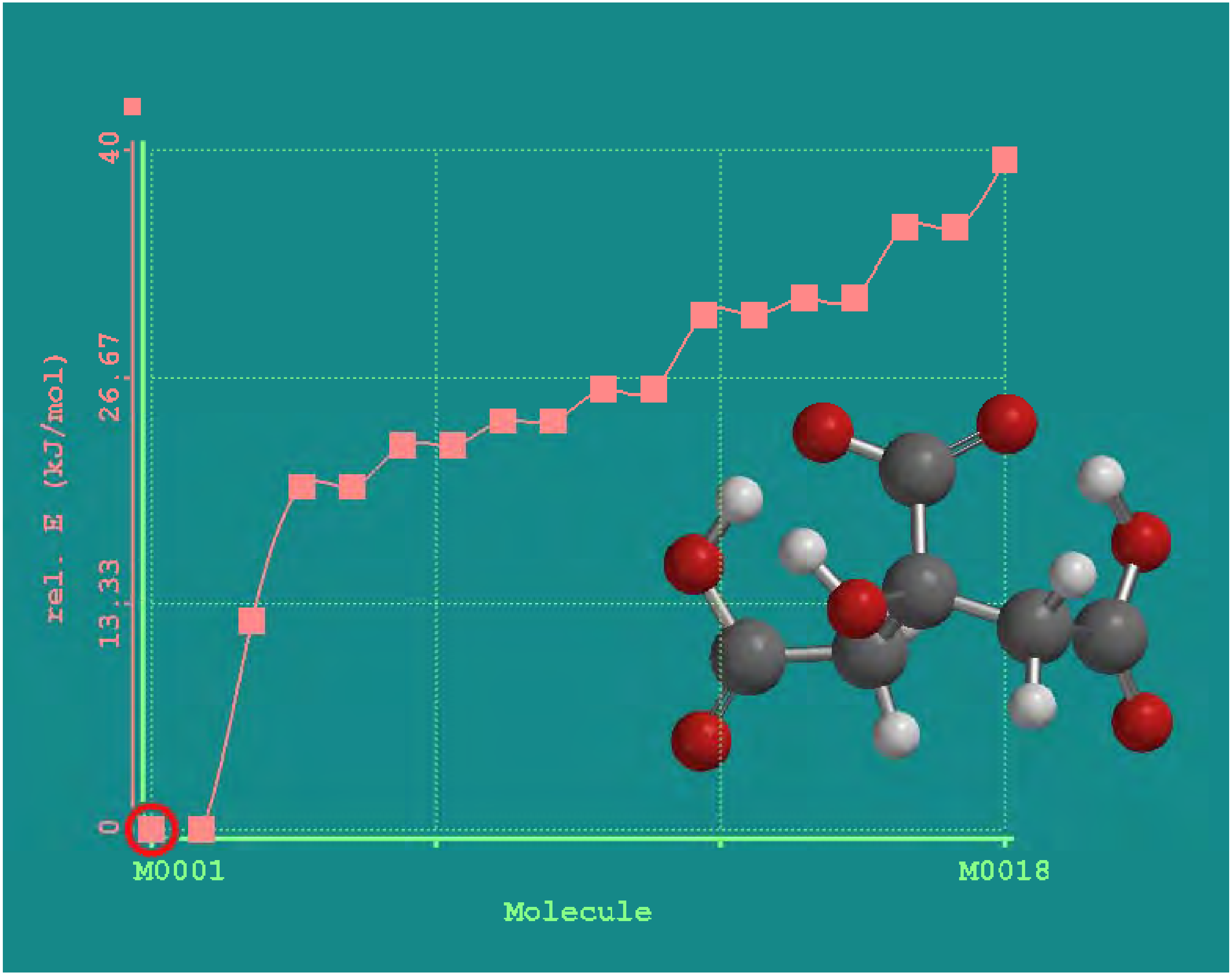
+6.33 kJ/mol



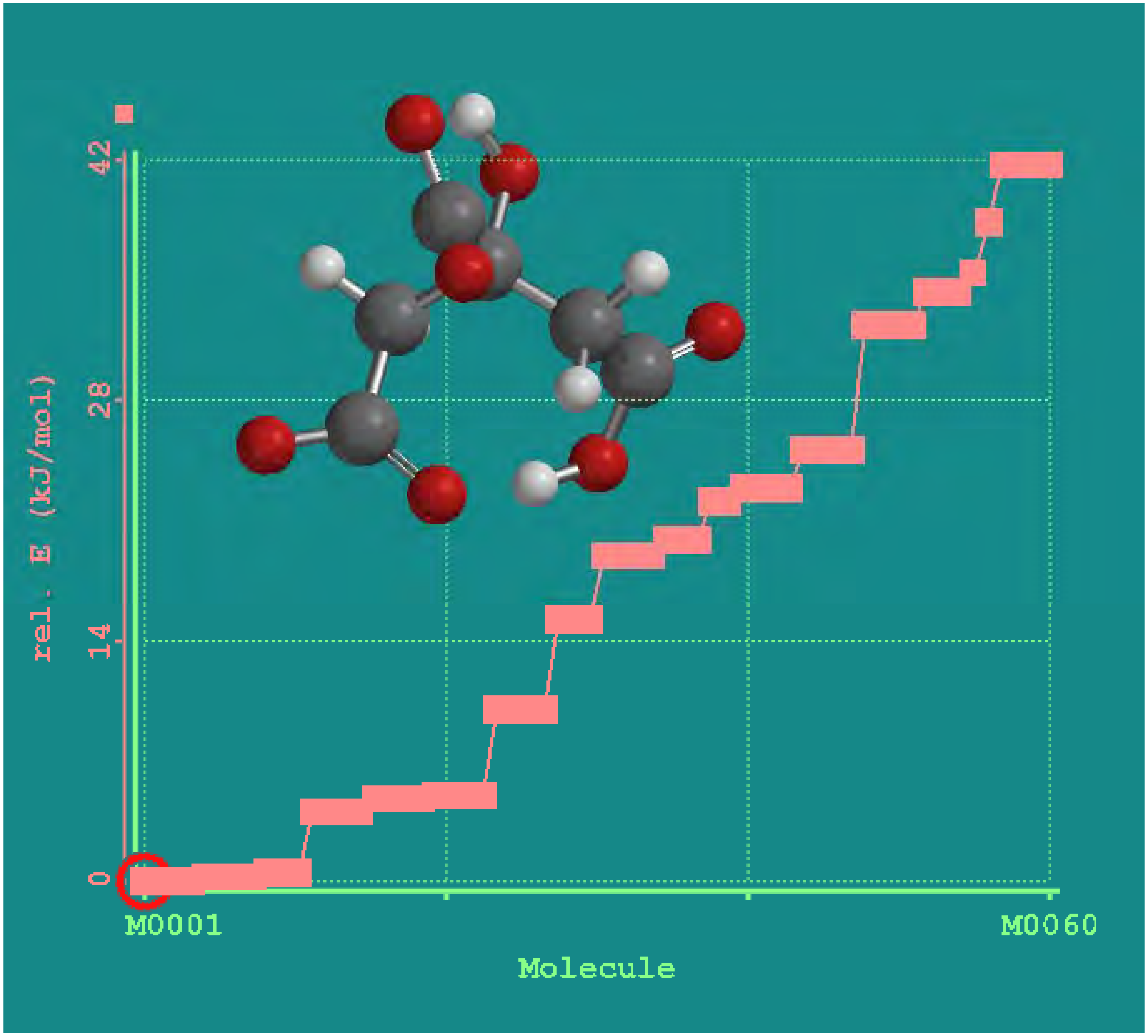
+8.47 kJ/mol

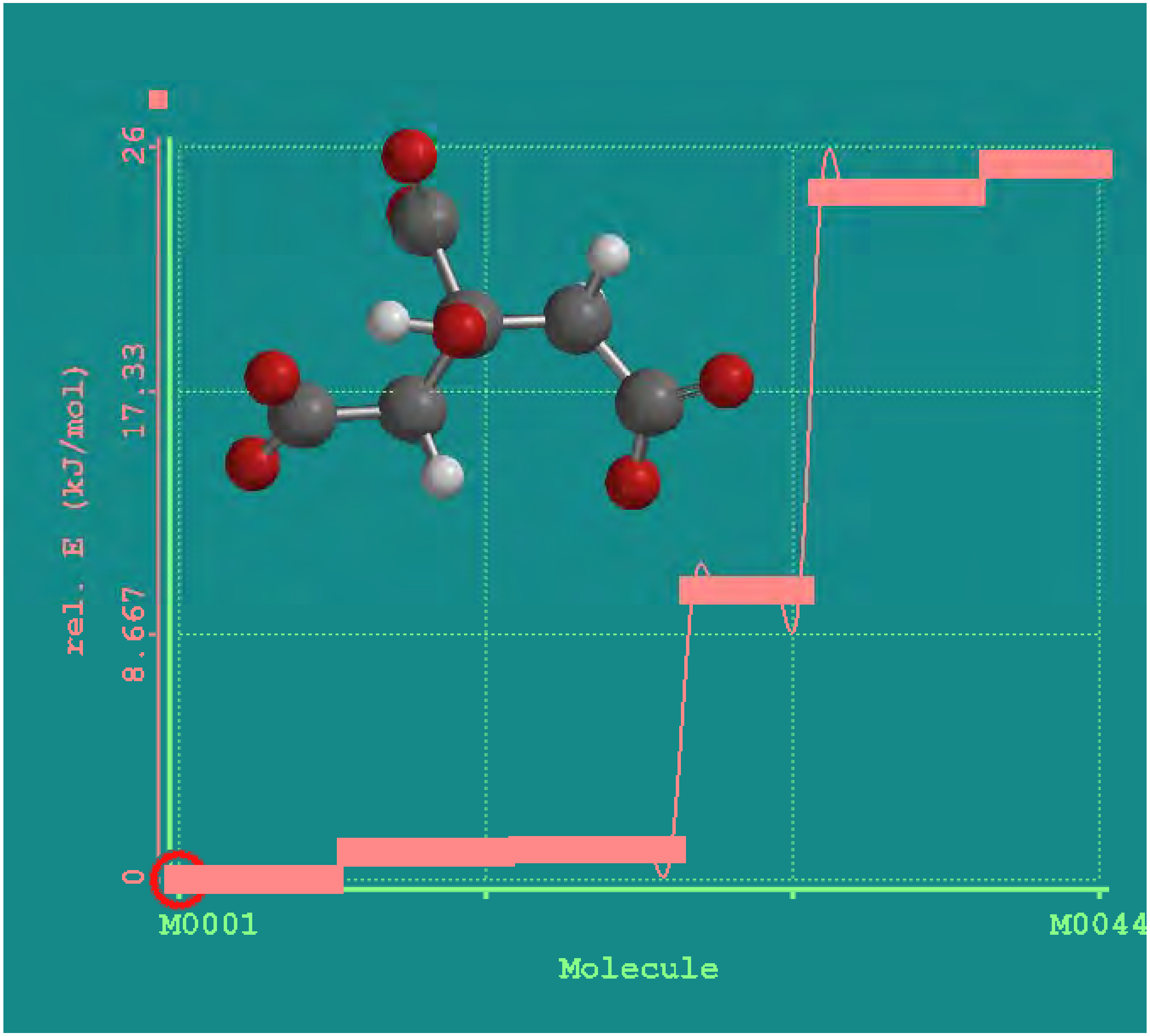


But things change (in the gas phase) on ionization



rel. E (kJ/mol)
40
26.67
13.33
0
M0001
M0018
Molecule

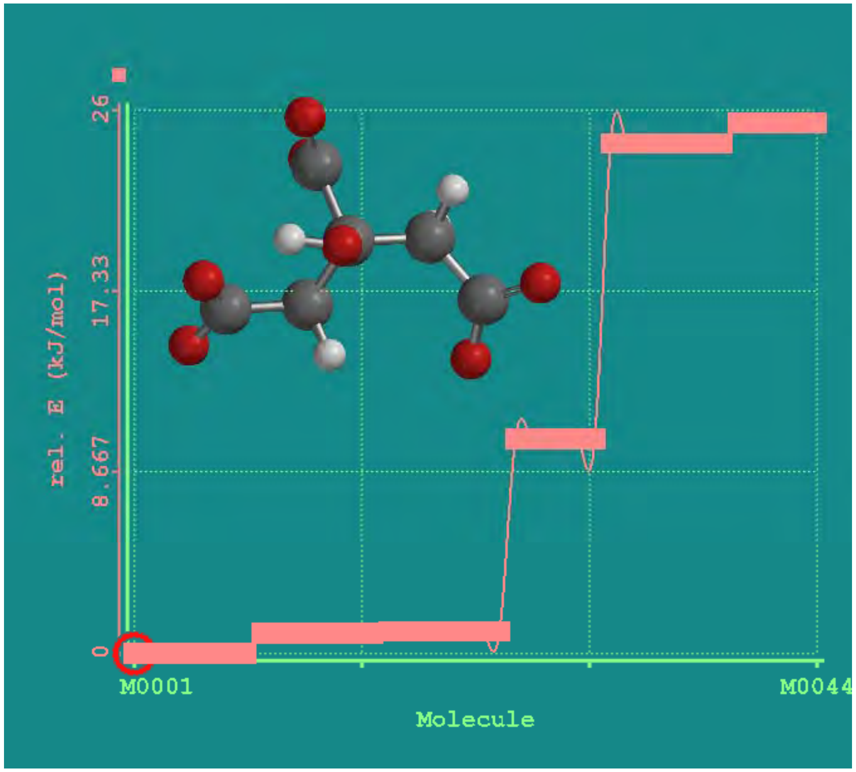

42
28
14
0
rel. E (kJ/mol)
M0001
M0060
Molecule


26
17.33
8.667
0
rel. E (kJ/mol)
M0001
M0044
Molecule

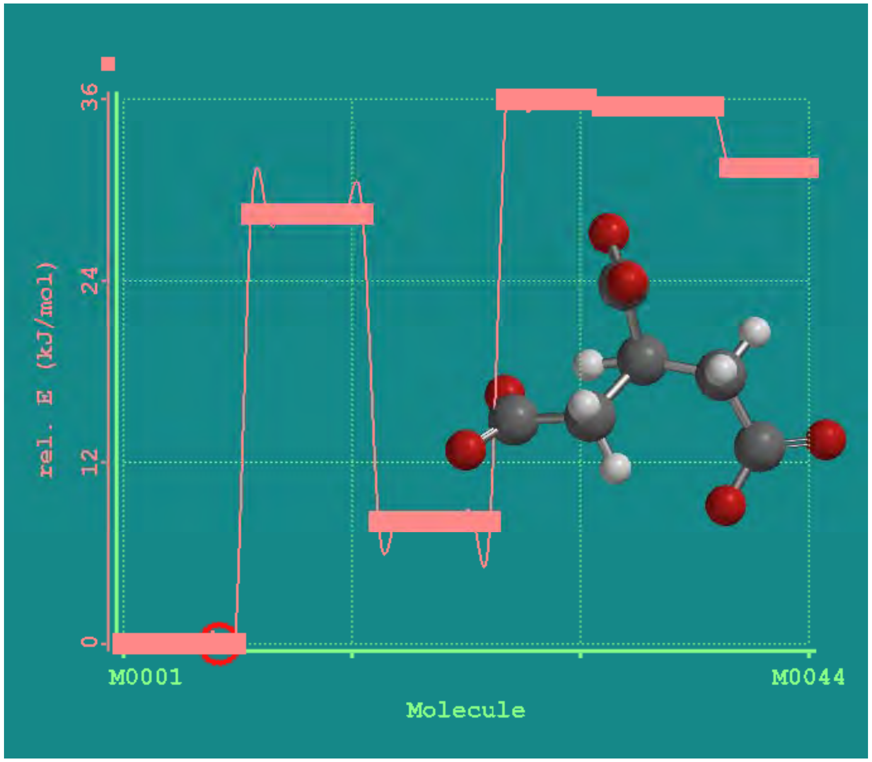
and in water

$C_6H_5O_7^{3-}$

Vacuum

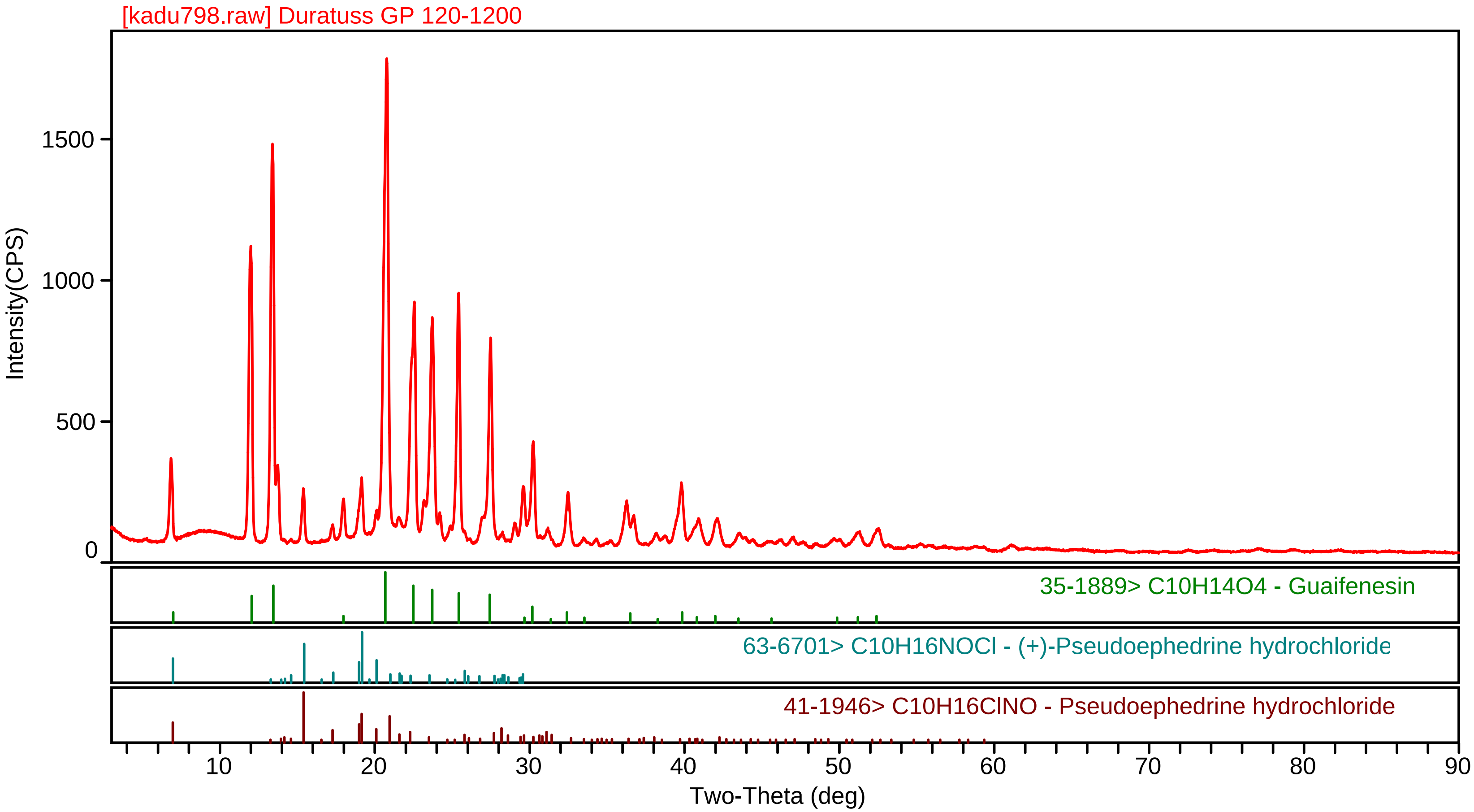


Water

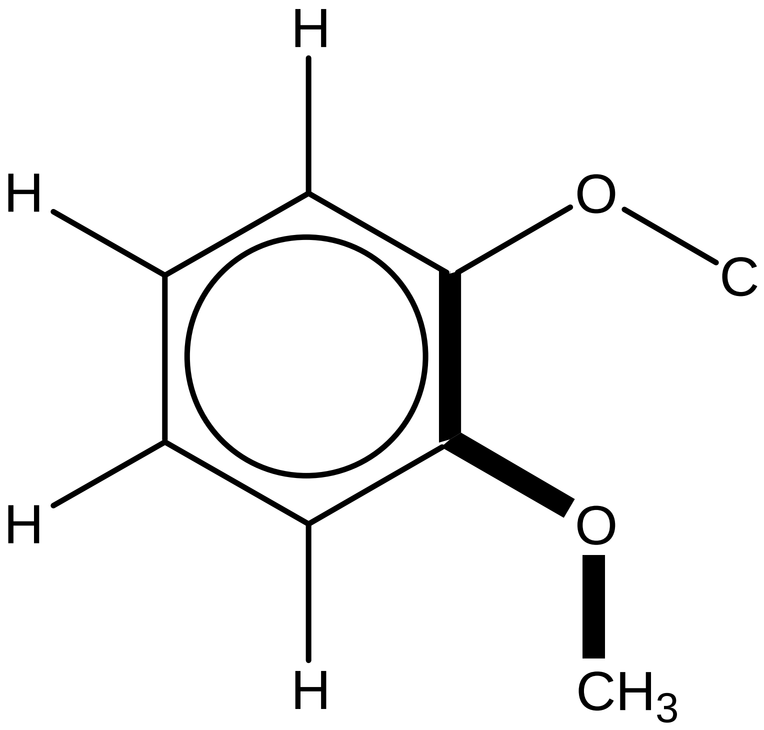


The Crystal Structure of Guaifenesin, 3-(2-methoxyphenoxy)-1,2-propanediol

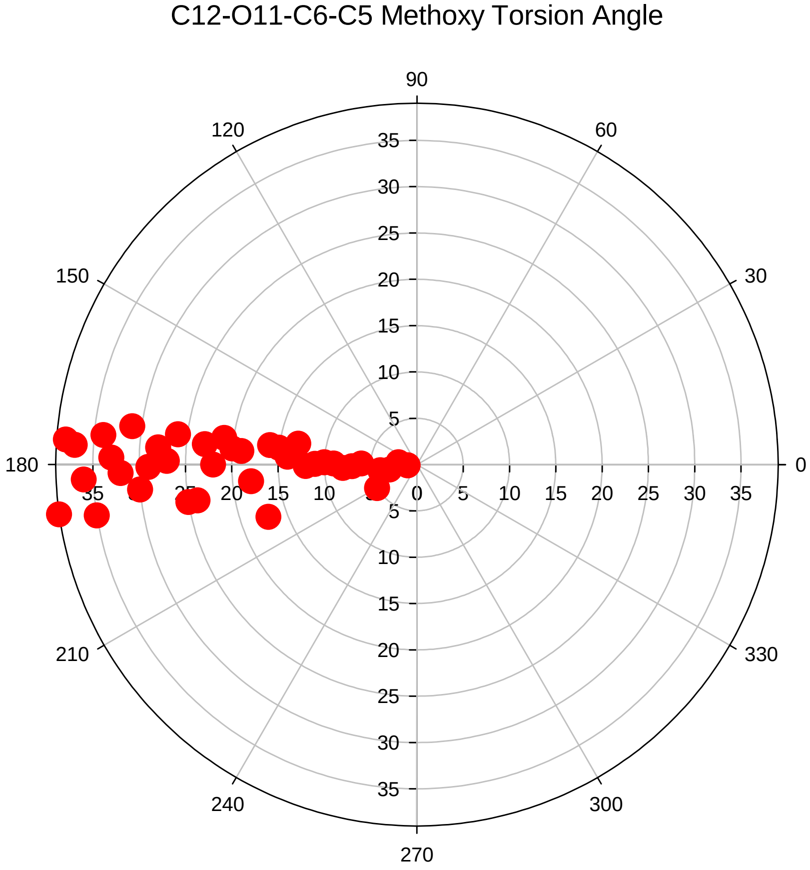
Duratuss GP 120-1200



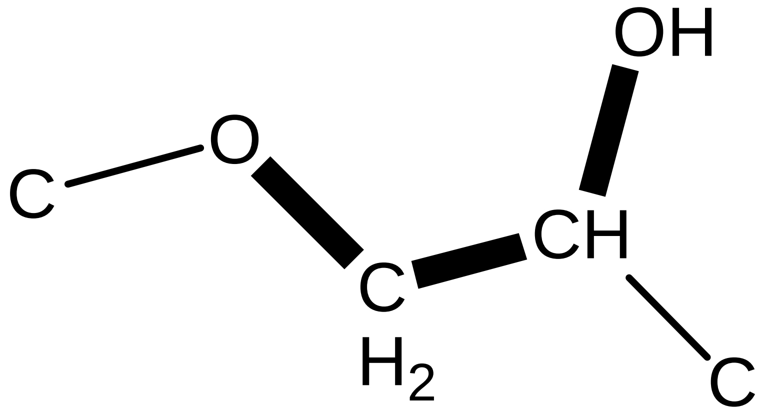
The methoxy torsion

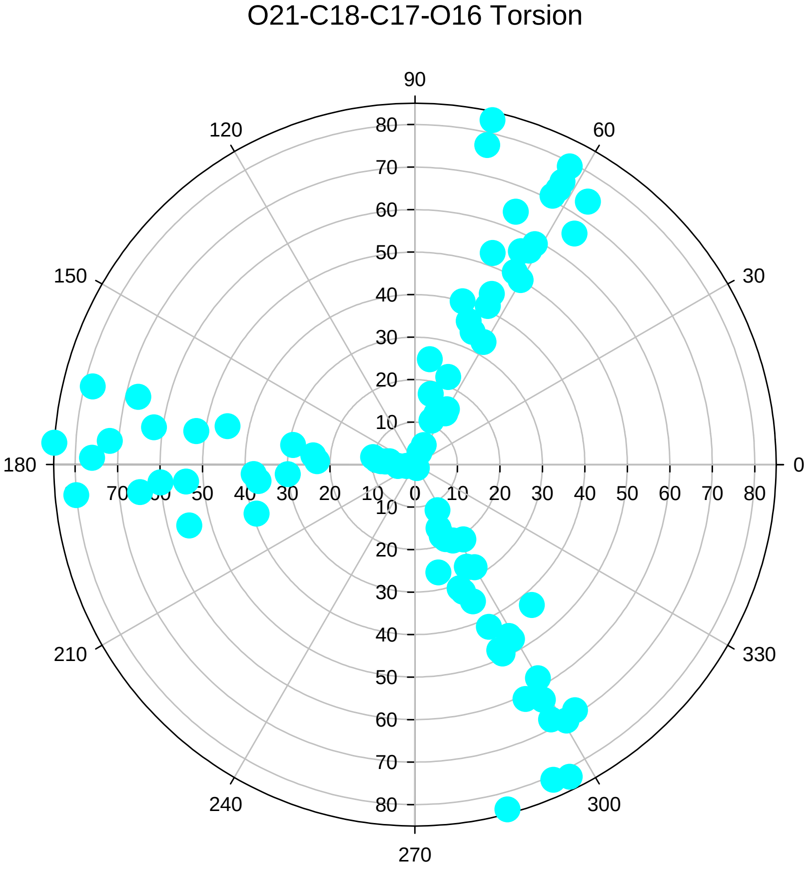


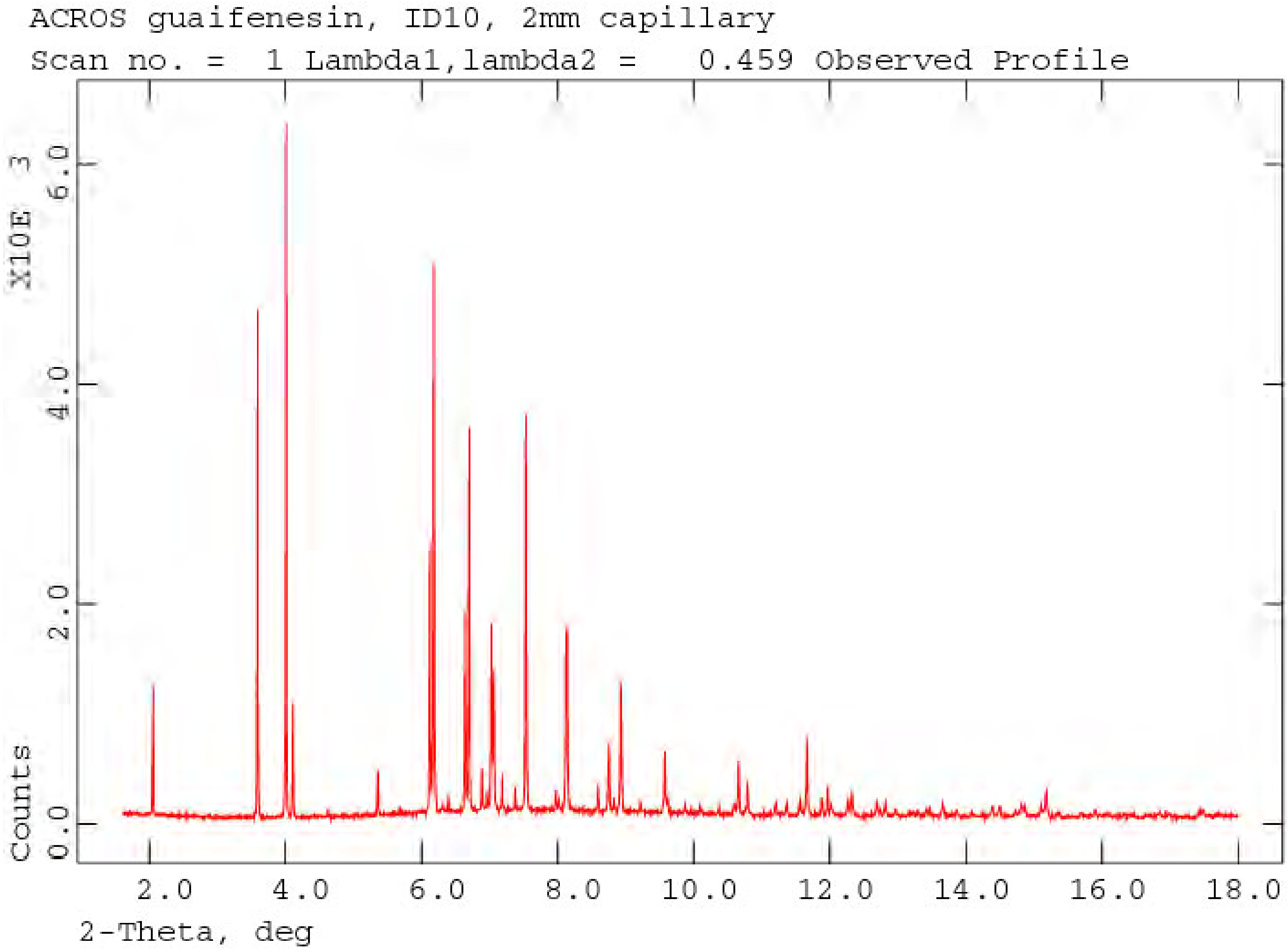
181(8)°



Propyl Torsions (2)




O21-C18-C17-O16 Torsion



ACROS guaifenesin, ID10, 2mm capillary

Scan no. = 1 Lambda1,lambda2 = 0.459 Observed Profile

Index the patterns

- Laboratory (NIST 640b Si internal std.)

  ITO: P-orthorhombic, FOM = 63.6, 16/20

  a = 7.661, b = 25.693, c = 4.981 Å

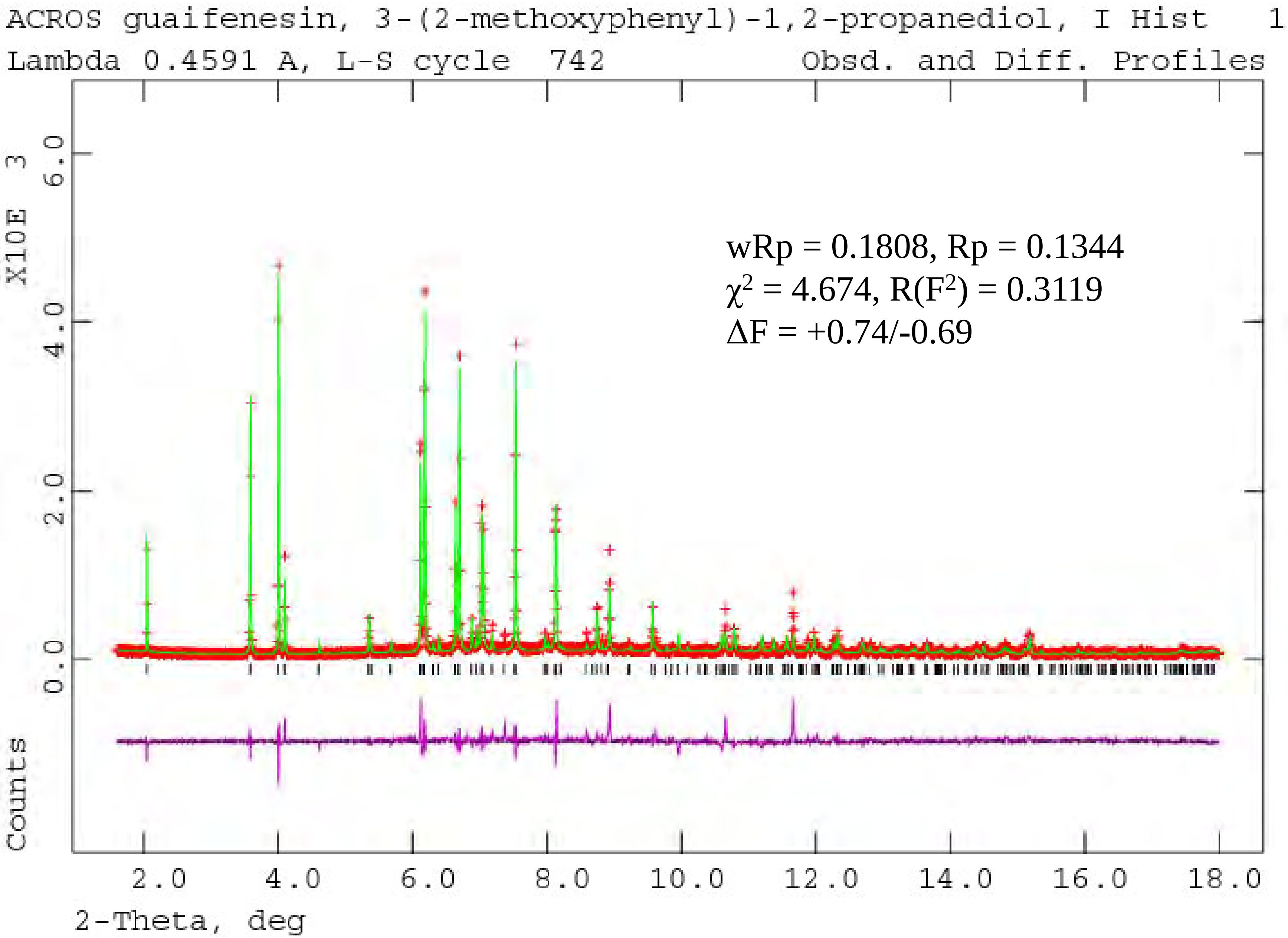
- Synchrotron (MR-CAT ID10, λ = 0.459141 Å)

  DICVOL91: P-orthorhombic

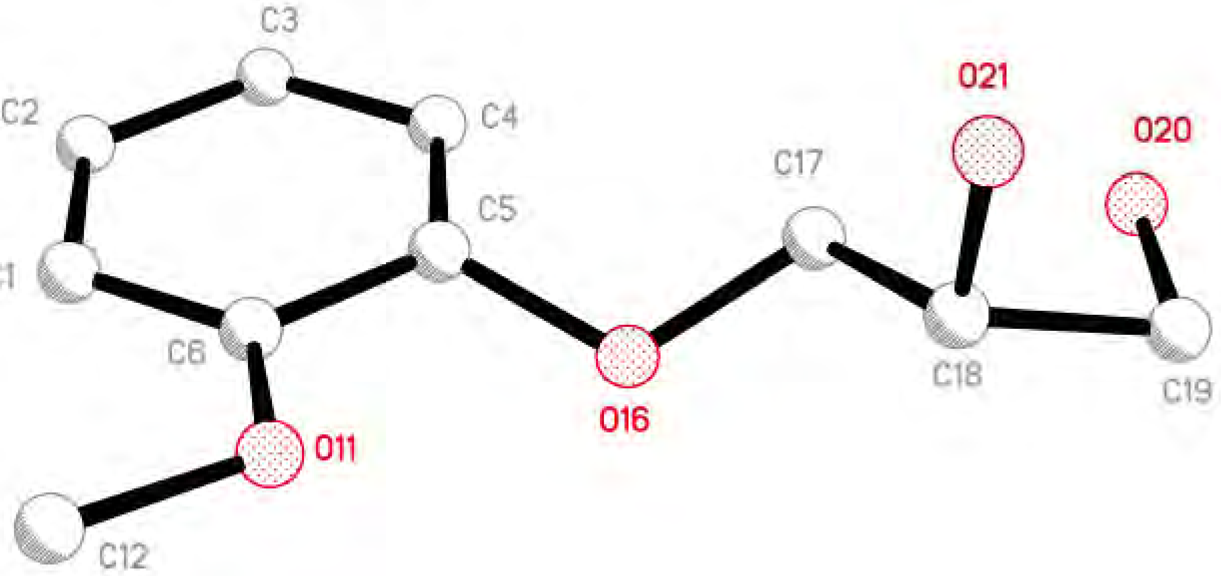
  a = 25.6388, b = 7.6480, c = 4.9733 Å, V = 975.2 $Å^3$

  M(24) = 135.7, F(24) = 1074.0(0.0007,33)

  Space group $P2_12_12_1$ (#19)

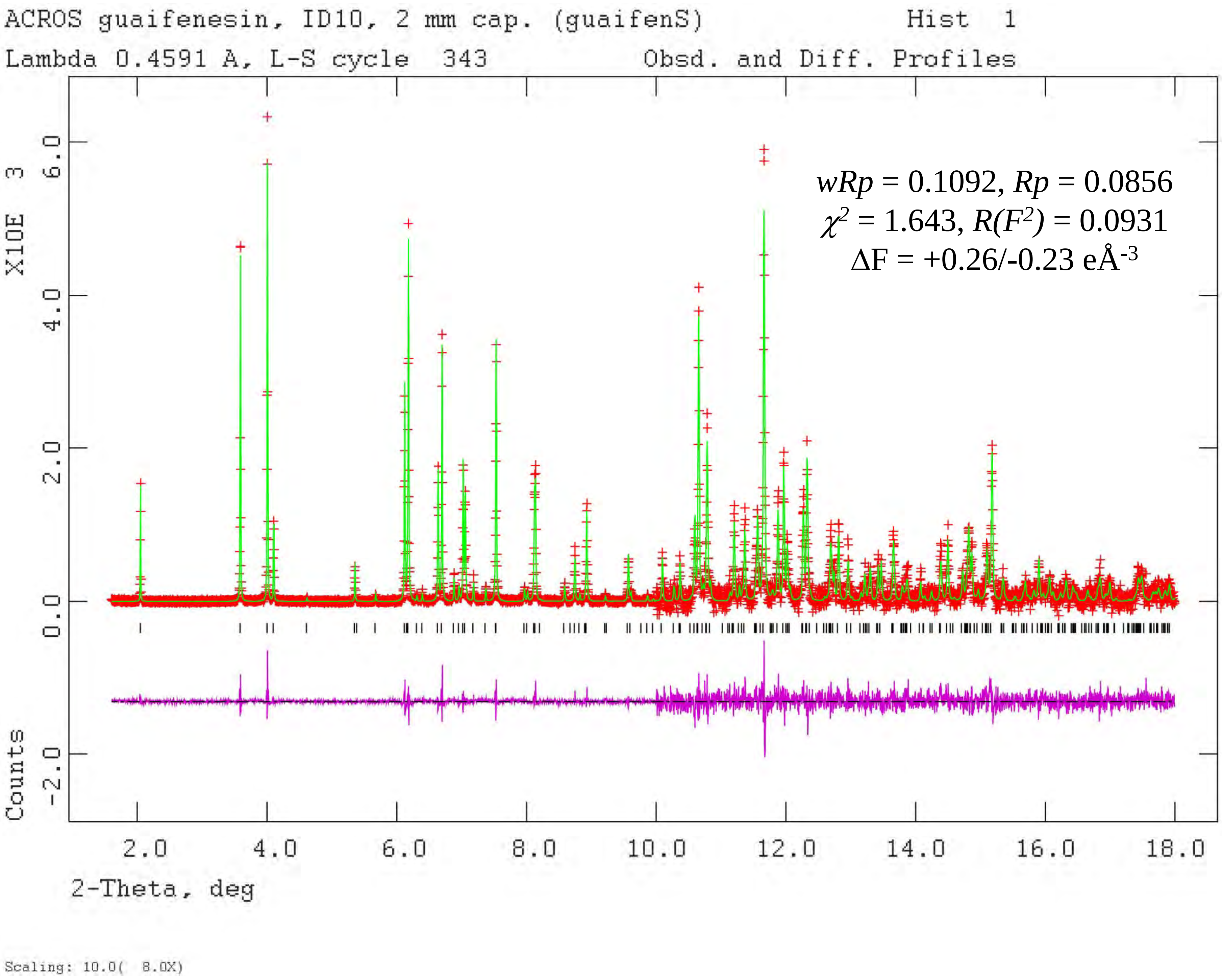


wRp = 0.1808, Rp = 0.1344
$\chi^2 = 4.674$, $R(F^2) = 0.3119$
$\Delta F = +0.74/-0.69$


C3
C2
C4
O21
O20
C17
C5
C1
C18
C19
C6
O16
O11
C12

Guaifenesin Torsions

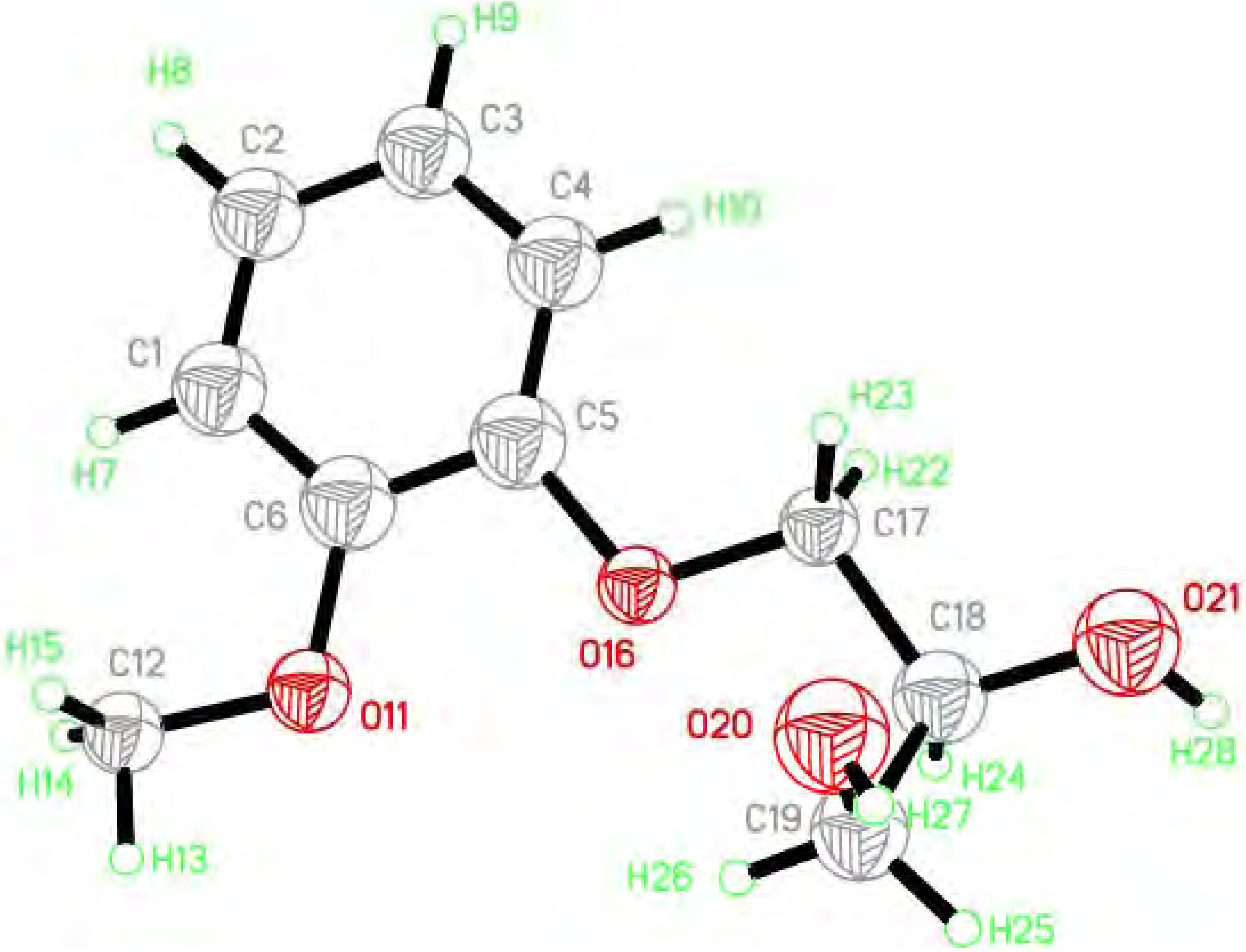
Torsion	Expected (CSD)	Refined
C12-O11-C6-C5	180	173.3
C17-O16-C5-C6	180	209.7
C18-C17-O16-C5	180	222.8
C19-C18-C17-O16	180, ±60	138.2
O21-C18-C17-O16	180, ±60	-108.9
C17-C18-C19-O20	180, ±60	18.6
O21-C18-C19-O20	180, ±60	-101.4

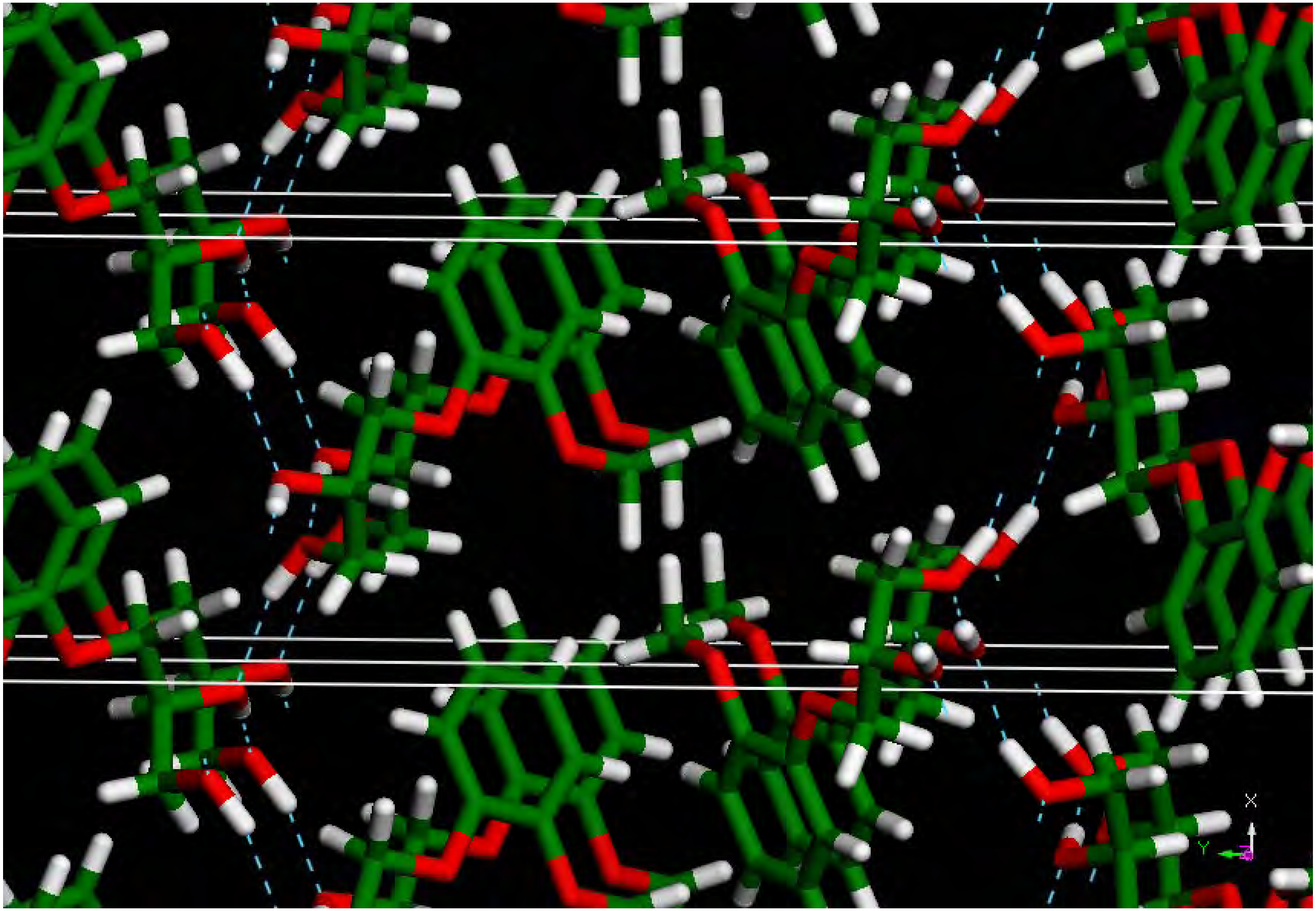


$wRp = 0.1092$, $Rp = 0.0856$

$\chi^2 = 1.643$, $R(F^2) = 0.0931$

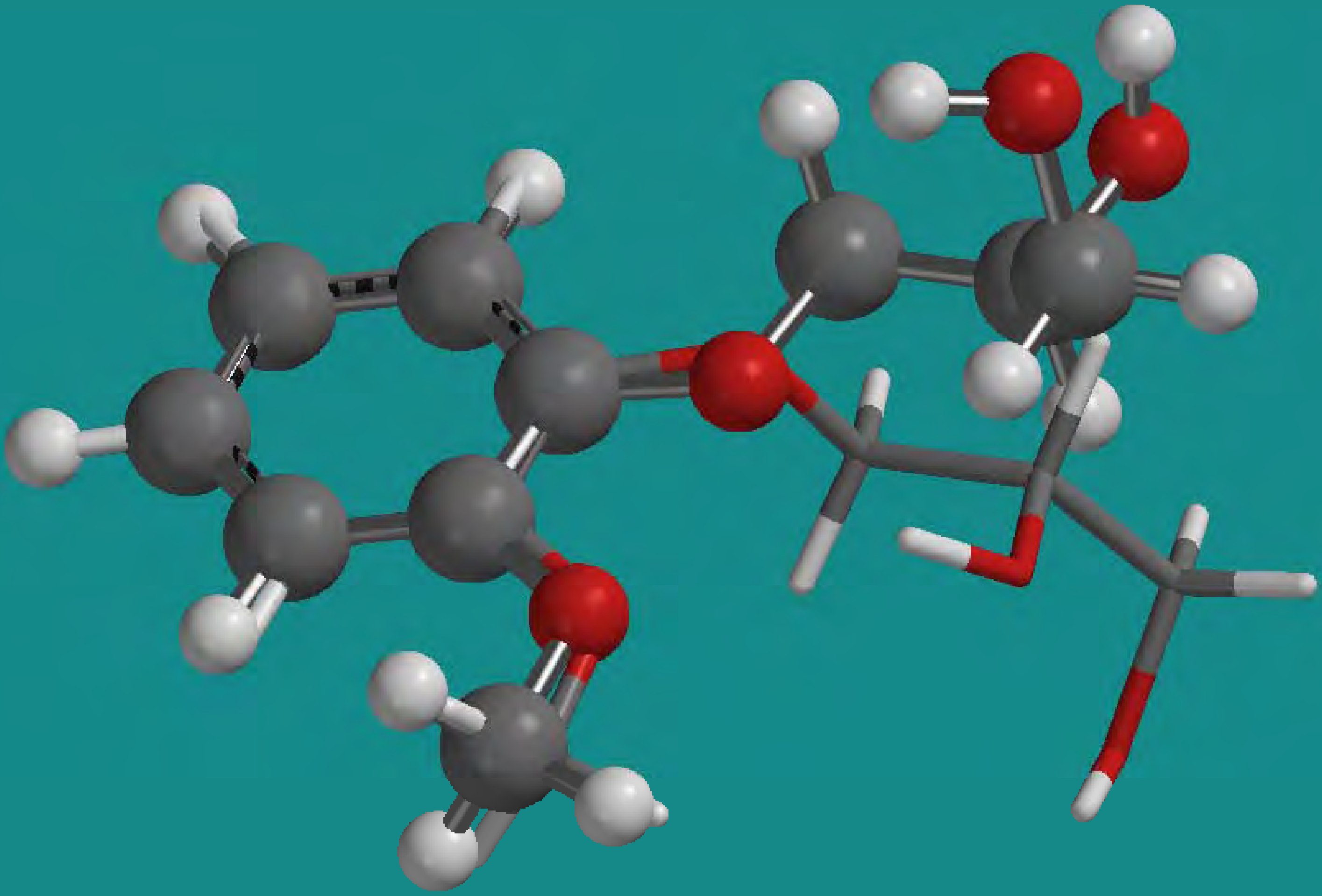
$\Delta F = +0.26/-0.23\ e\text{Å}^{-3}$


H9
H8
C3
C2
C4
H10
C1
H23
C5
H22
H7
C6
C17
O21
C18
O16
H15
C12
O20
O11
H24
H28
H14
H27
C19
H13
H26
H25


X
Y

Hydrogen Bonds in Guaifenesin

Bond	O20-H27···O21	O21-H28···O20
O-H, Å	1.000	1.002
H···O, Å	1.682	1.696
O···O, Å	2.787	2.715
O-H···O, °	160.2	169.3
Overlap, *e*	0.13	0.13
E, kcal/mole	49.9	49.9

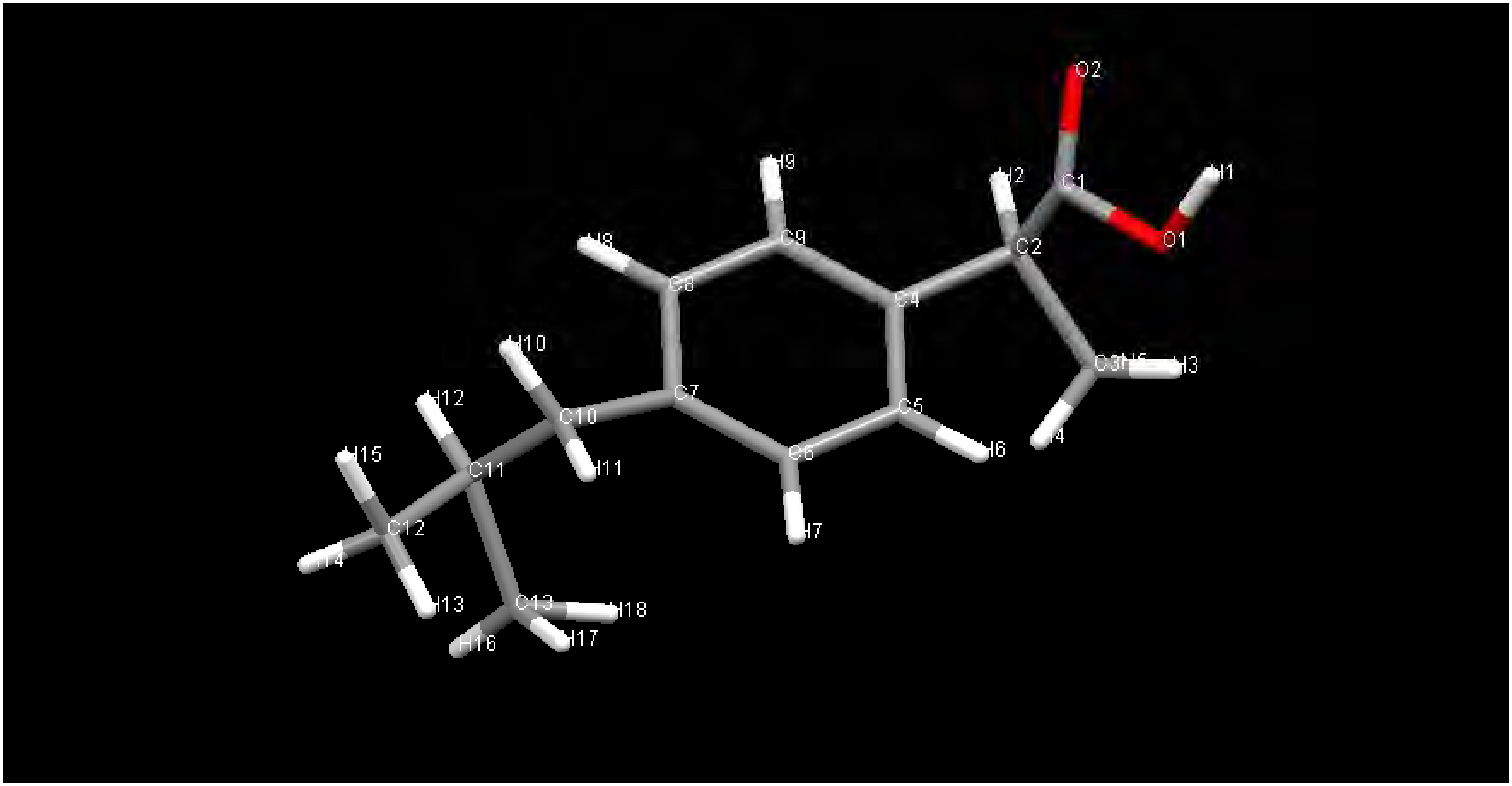


observed – minimum = +3.79 Kcal/mole

Ab initio structure determination of Phase II of racemic ibuprofen by X-ray powder diffraction

Patrick Derollez, Emeline Dudognon,
Frederic Affouard, Florence Danede, Natalia
T. Correia, and Marc Descamps, *Acta Cryst.*
B: Struct. Sci., **66**, 76-80 (2010)

Ibuprofen Form II



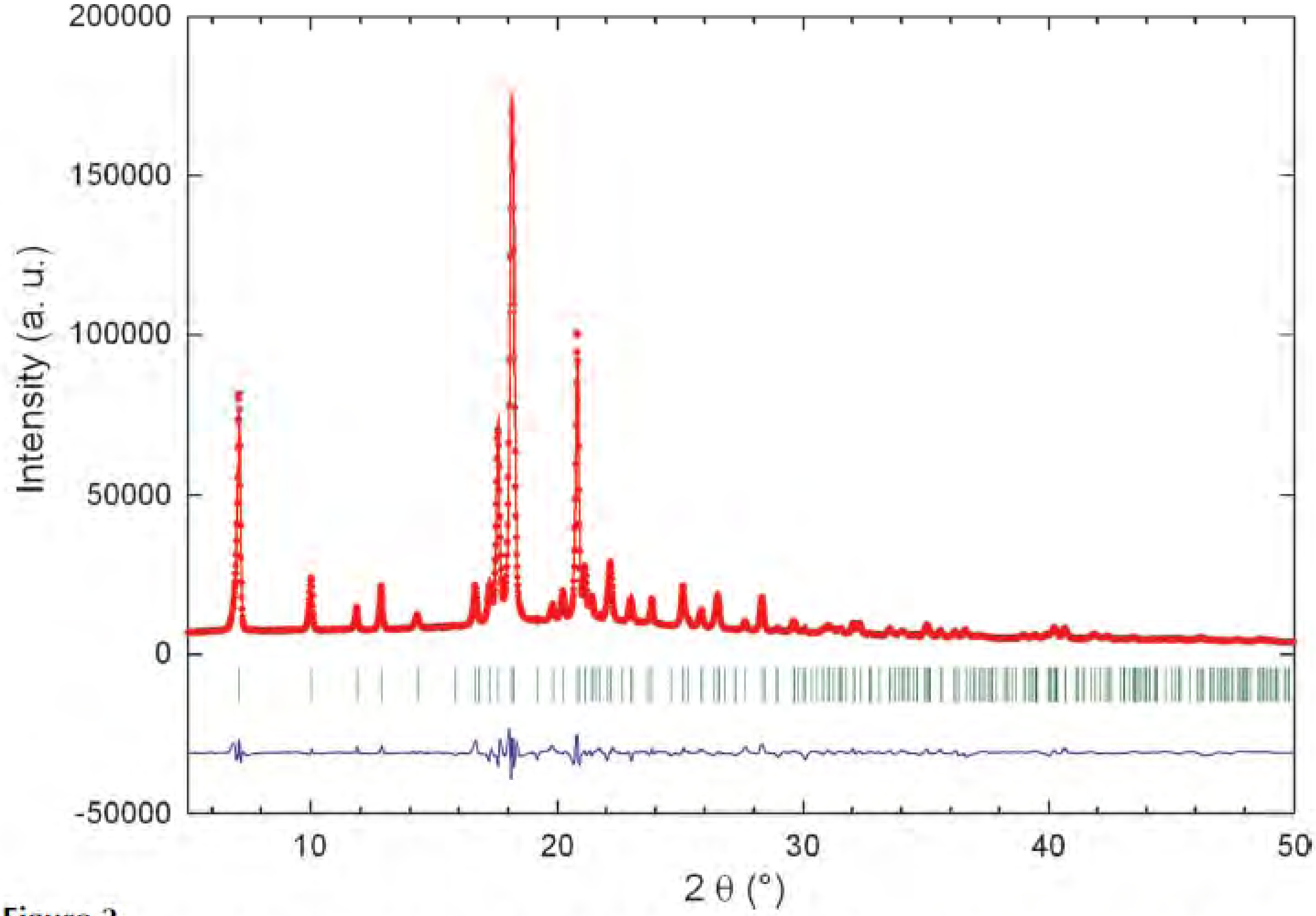
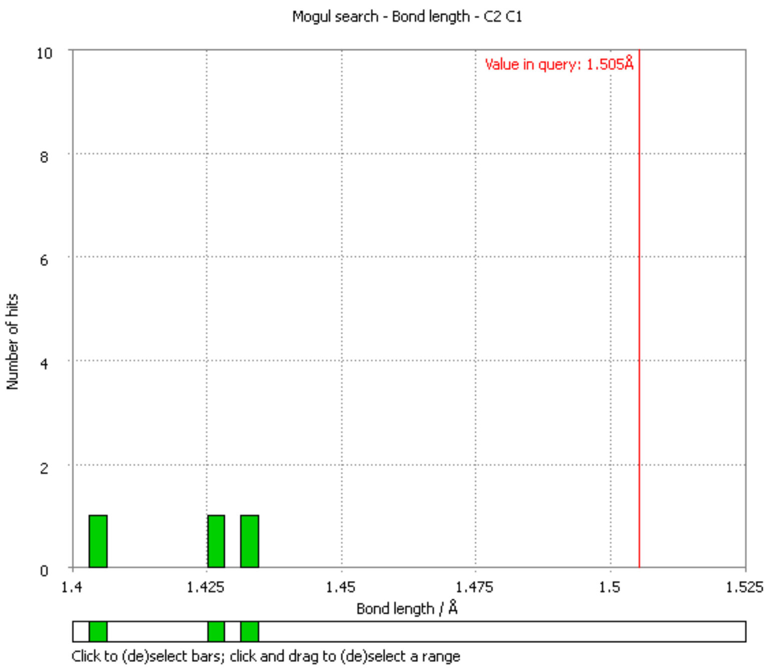
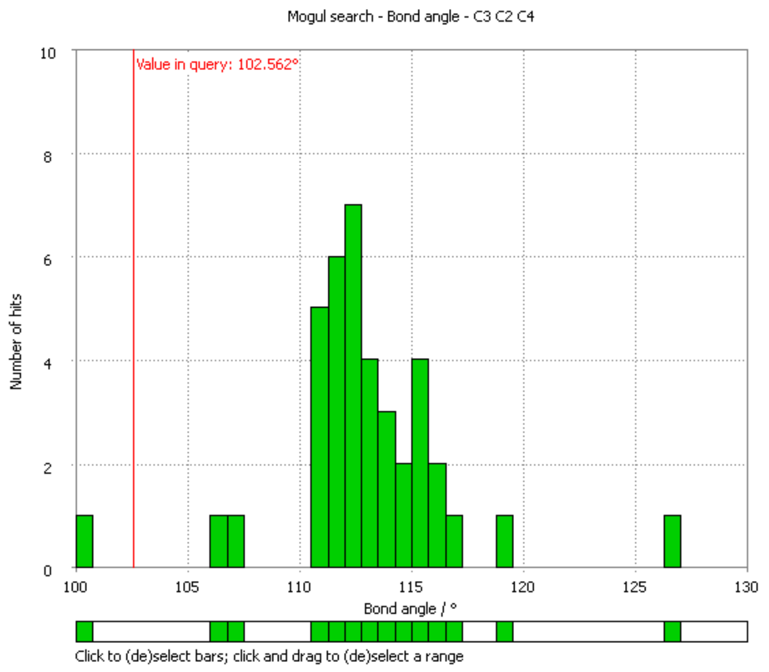
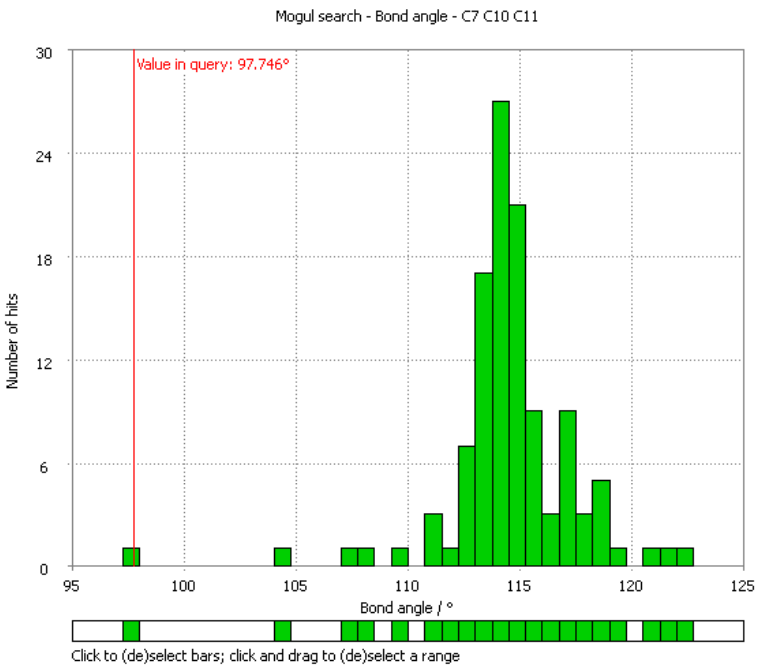


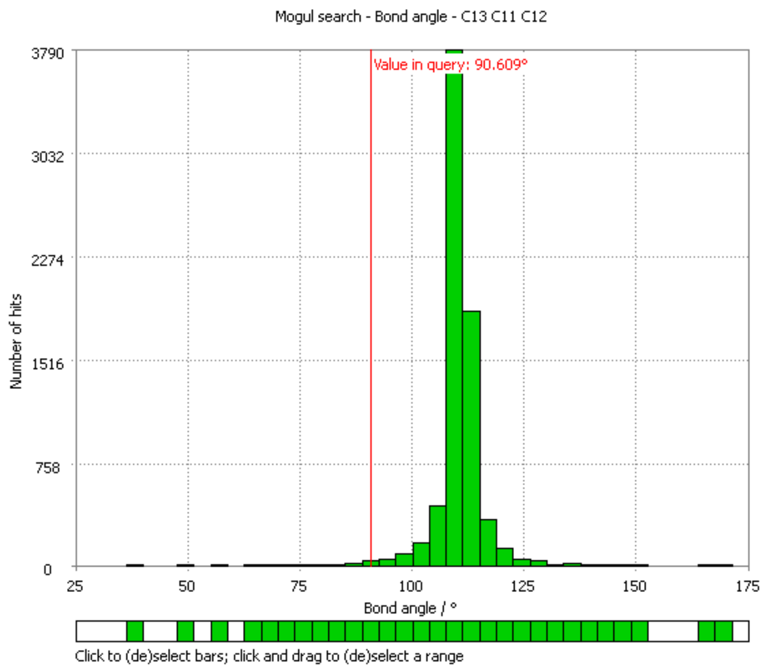
Figure 2

Final Rietveld plot of phase II of ibuprofen at 258 K, between 5 and 50° 2θ for clarity. Observed intensities are indicated by dots, the best-fit profile (upper trace) and the difference pattern (lower trace) are solid lines. The vertical bars correspond to the positions of the Bragg peaks.


Mogul search - Bond length - C2 C1
Value in query: 1.505Å
Number of hits
0
2
4
6
8
10
1.4
1.425
1.45
1.475
1.5
1.525
Bond length / Å
Click to (de)select bars; click and drag to (de)select a range


Mogul search - Bond angle - C3 C2 C4
Value in query: 102.562°
Number of hits
0
2
4
6
8
10
100
105
110
115
120
125
130
Bond angle / °
Click to (de)select bars; click and drag to (de)select a range


Mogul search - Bond angle - C7 C10 C11
Value in query: 97.746°
Number of hits
0
6
12
18
24
30
95
100
105
110
115
120
125
Bond angle / °
Click to (de)select bars; click and drag to (de)select a range


Mogul search - Bond angle - C13 C11 C12
Value in query: 90.609°
Number of hits
0
758
1516
2274
3032
3790
25
50
75
100
125
150
175
Bond angle / °
Click to (de)select bars; click and drag to (de)select a range

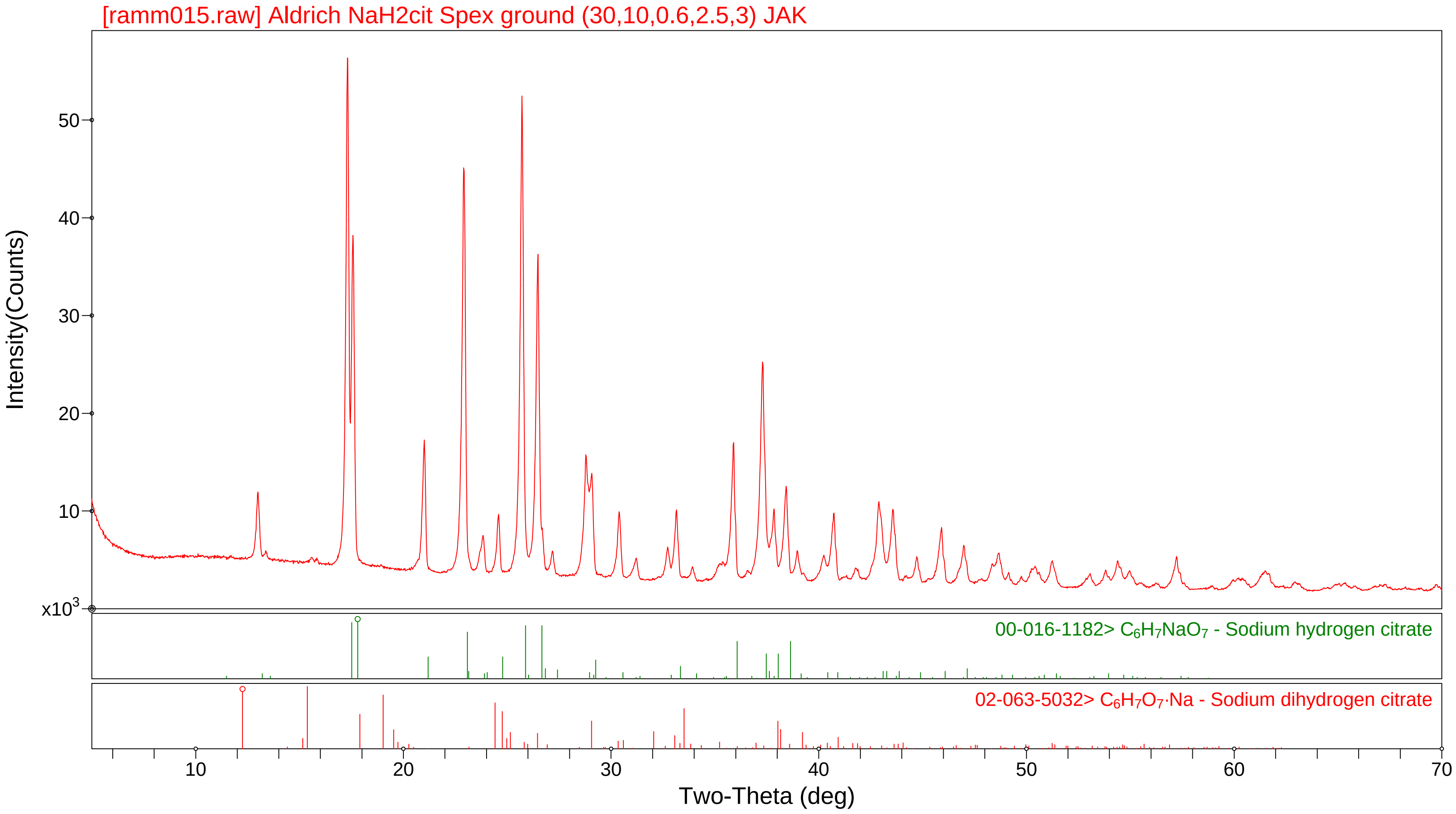
Known Group 1 Citrates

Li_1H_2	02-063-2391/LIHCIT	$(H_2O)_1$	02-082-5699/PIGPUQ
Li_2H_1	ionic liquid/glass		
Li_3		$(H_2O)_4$ $(H_2O)_5$	02-076-0249/FUQFUS 02-060-8758/CADJIA
Na_1H_2	00-016-1182 02-063-5032/NAHCIT	$(H_2O)_1$	00-016-1181
Na_2H_1		$(H_2O)_{1.5}$	00-016-1180
Na_3	00-043-1525,6	$(H_2O)_1$ $(H_2O)_2$ $(H_2O)_{5.5}$	00-043-1524 02-085-6148/UMOGAE 02-062-4497/FATTID
K_1H_2	00-020-1687	$(H_2O)_2$	
K_2H_1	02-073-8659/ZZZQRO01	$(H_2O)_3$	00-021-1645
K_3		$(H_2O)_1$	02-064-1651,2/ZZZHVI01
Rb_1H_2	02-082-8054/RBHCIT03+		
Rb_2H_1			
Rb_3		$(H_2O)_1$	
Cs_1H_2			
Cs_2H_1			
Cs_3		$(H_2O)_1$	

Known Group 2 Citrates

$Mg(H_2cit)_2$			
$Mg(Hcit)$		$(H_2O)_2$	
$Mg_3(cit)_2$		$(H_2O)_{10}$ $(H_2O)_{14?}$	02-063-3628/MGCITD 00-001-0186
$Ca(H_2cit)_2$		$(H_2O)_2$	
$Ca(Hcit)$		$(H_2O)_3$ $(H_2O)_?$	02-060-8946/CAHCIT
$Ca_3(cit)_2$		$(H_2O)_4$	00-028-2003, earlandite
$Sr(H_2cit)_2$			
$Sr(Hcit)$			
$Sr_3(cit)_2$		$(H_2O)_5$	02-067-4890/LATRAZ
$Ba(H_2cit)_2$			
$Ba(Hcit)$			
$Ba_3(cit)_2$		$(H_2O)_7$	00-01-0009

$NaH_2C_6H_5O_7$


[ramm015.raw] Aldrich NaH2cit Spex ground (30,10,0.6,2.5,3) JAK
Intensity(Counts)
50
40
30
20
10
x10^3
00-016-1182> $C_6H_7NaO_7$ - Sodium hydrogen citrate
02-063-5032> $C_6H_7O_7{\cdot}Na$ - Sodium dihydrogen citrate
10
20
30
40
50
60
70
Two-Theta (deg)

$NaH_2C_6H_5O_7$ Crystal Data

New Form

$P2_12_12_1$, $Z = 4$

$a = 7.4527(3)$

$b = 7.7032(3)$

$c = 13.4551(4)$

$V = 772.45(5)$ (13.8 Å^3/non-H)

$\rho = 1.841$

This Work

P. de Wolff, *ICDD Grant-in-Aid* (1966).

NAHCIT

$P2_1/a$, $Z = 4$

$a = 9.668(12)$

$b = 11.682(15)$

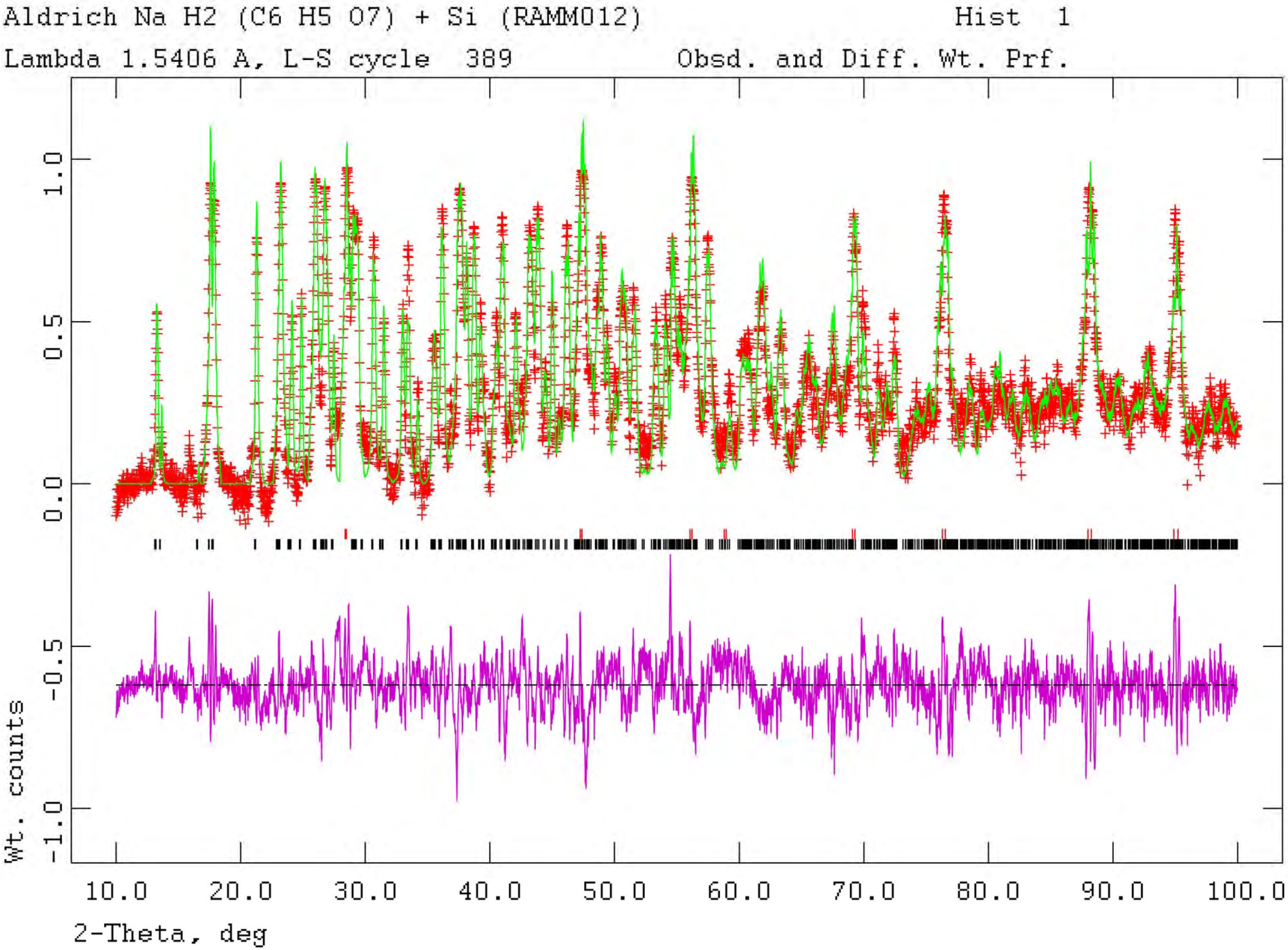
$c = 7.484(10)$

$\beta = 105.33(10)$

$V = 815.141$ (14.6 Å^3/non-H)

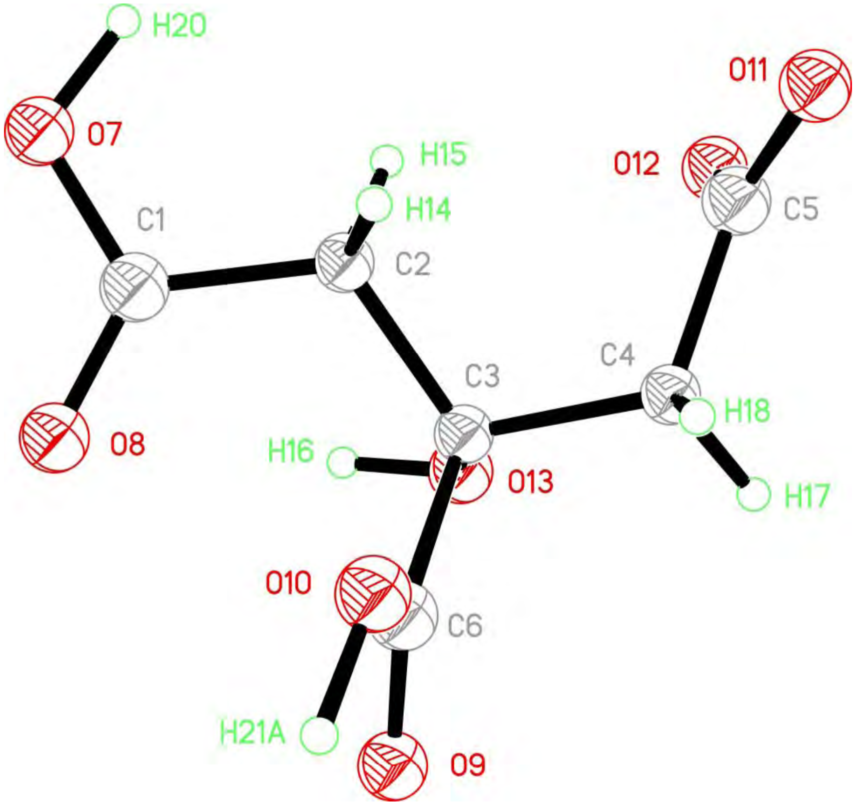
$\rho = 1.744$

J. P. Glusker, D. van der Helm, W. E. Love, M. L. Dornberg, J. A. Minkin, C. K. Johnson, and A. L. Patterson, *Acta Cryst.*, **19**, 561-572 (1965).

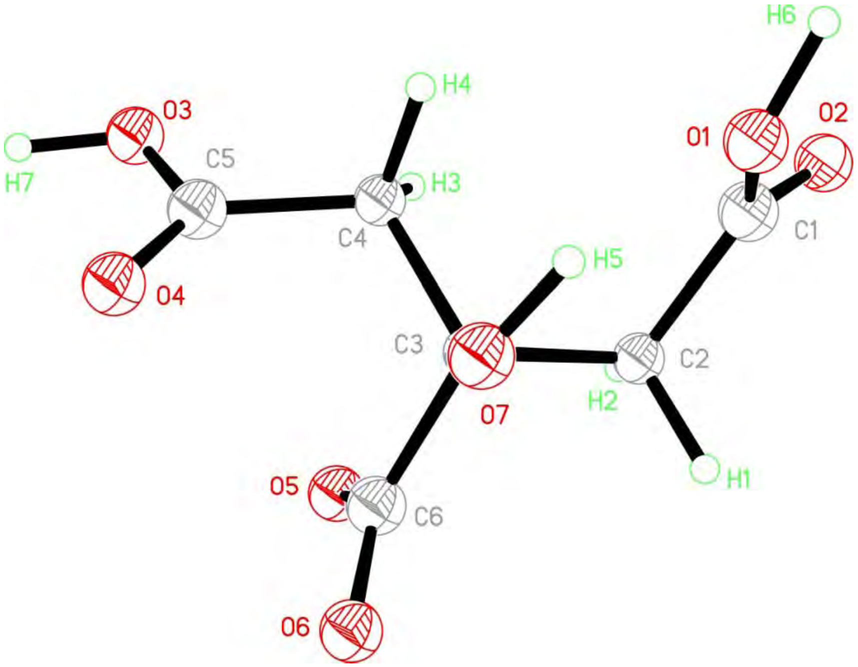

Aldrich Na H2 (C6 H5 O7) + Si (RAMM012)
Hist 1
Lambda 1.5406 A, L-S cycle 389
Obsd. and Diff. Wt. Prf.
1.0
0.5
0.0
-0.5
-1.0
Wt. counts
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
2-Theta, deg

$NaH_2C_6H_5O_7$ Citrate Anions

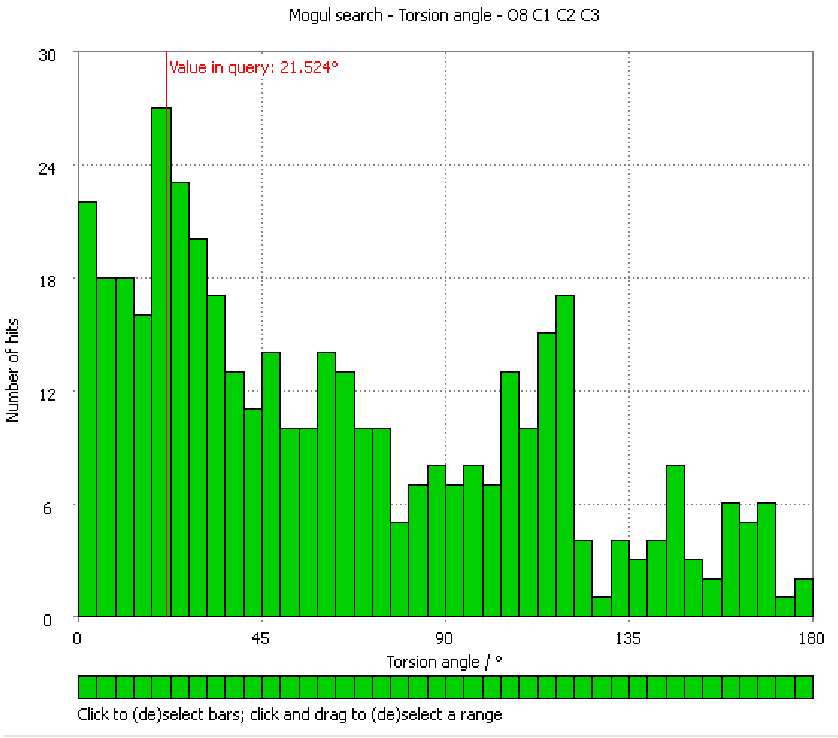
New Form

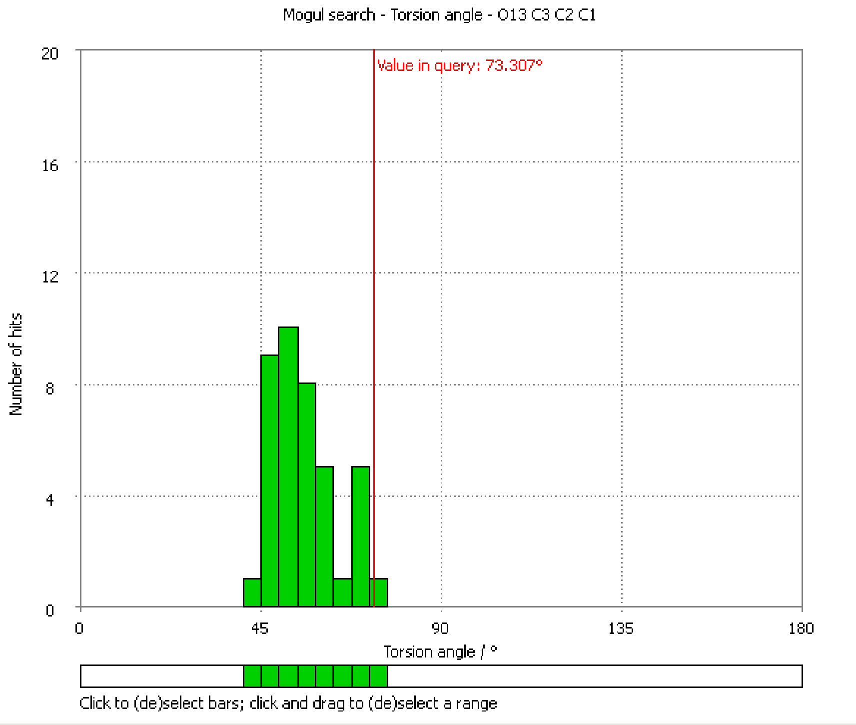


NAHCIT



The citrate is fairly typical





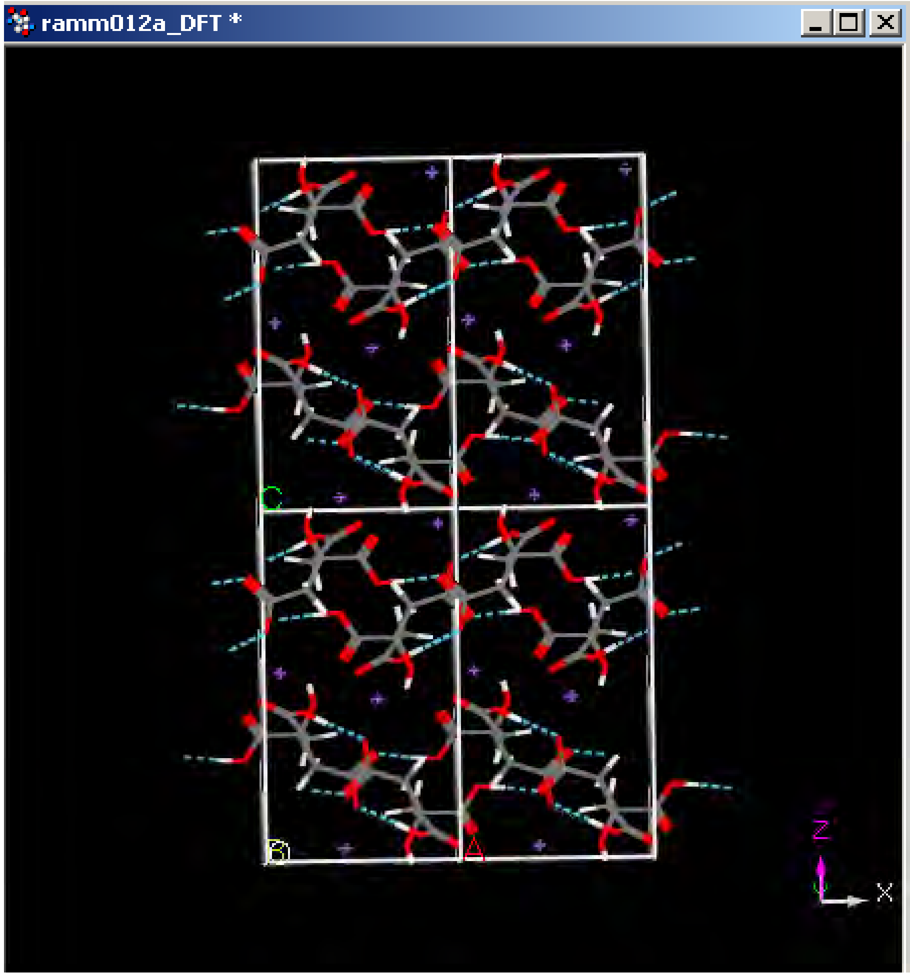
Energies of (fixed) citrate conformations (Spartan)

Conformation in new form is

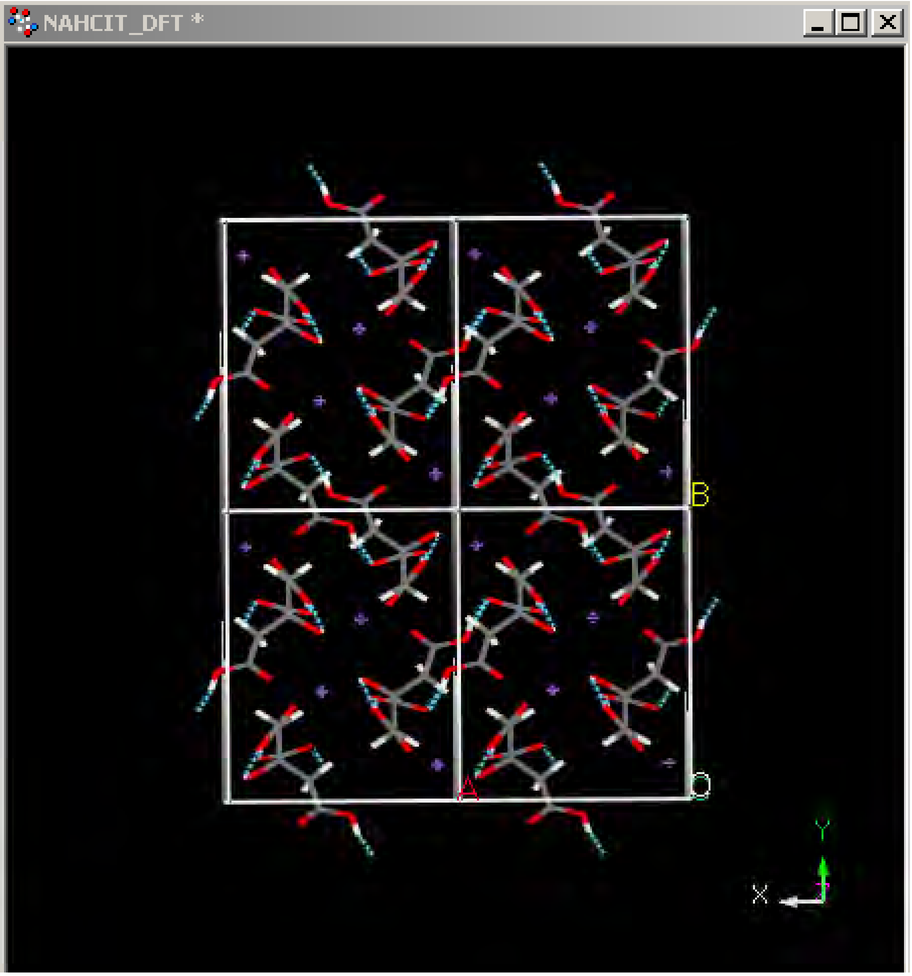
64.46 kcal/mole higher in energy

(in vacuum)

$NaH_2C_6H_5O_7$ Crystal Structures

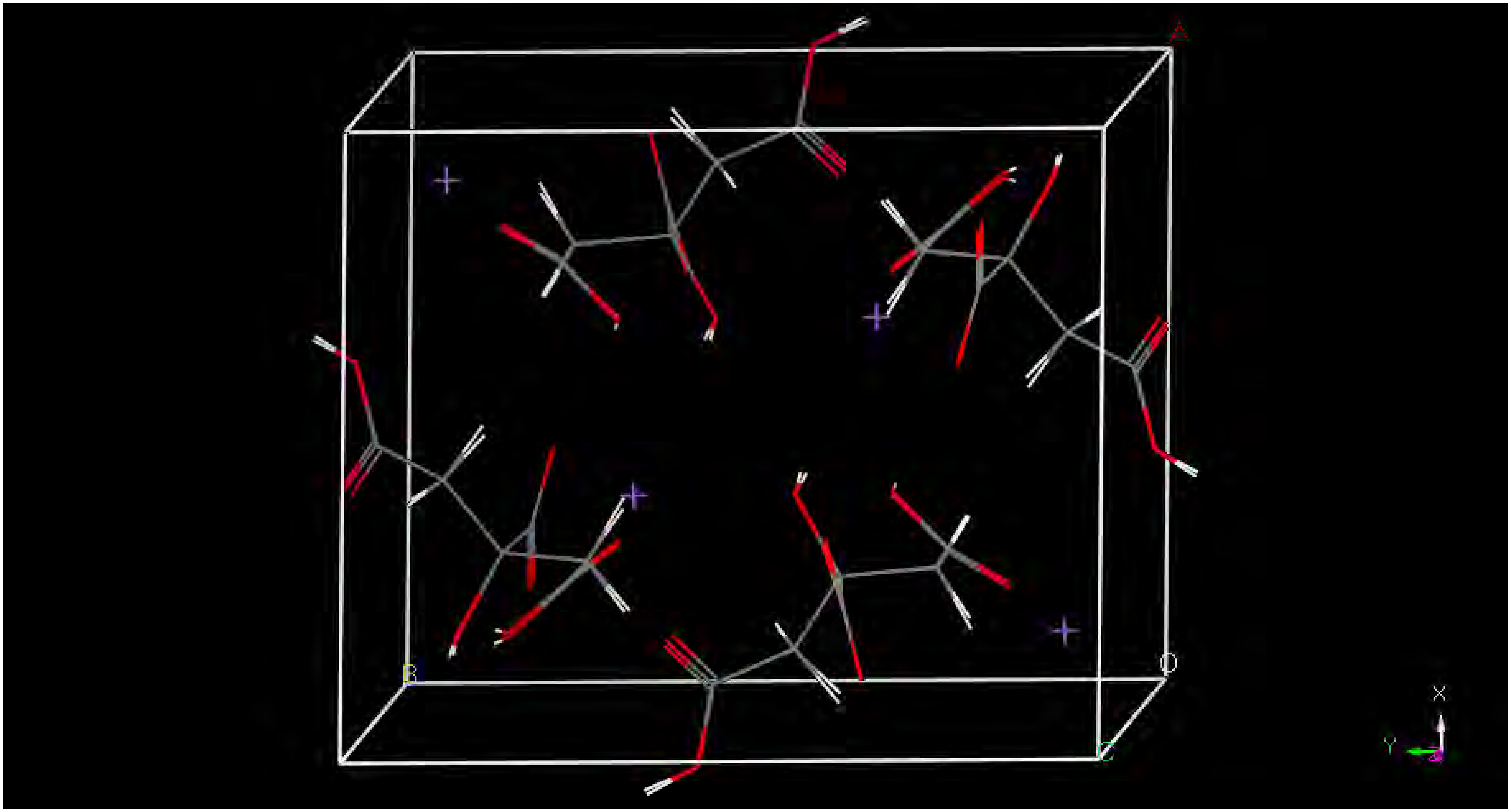


E = +3.24 kcal/mole

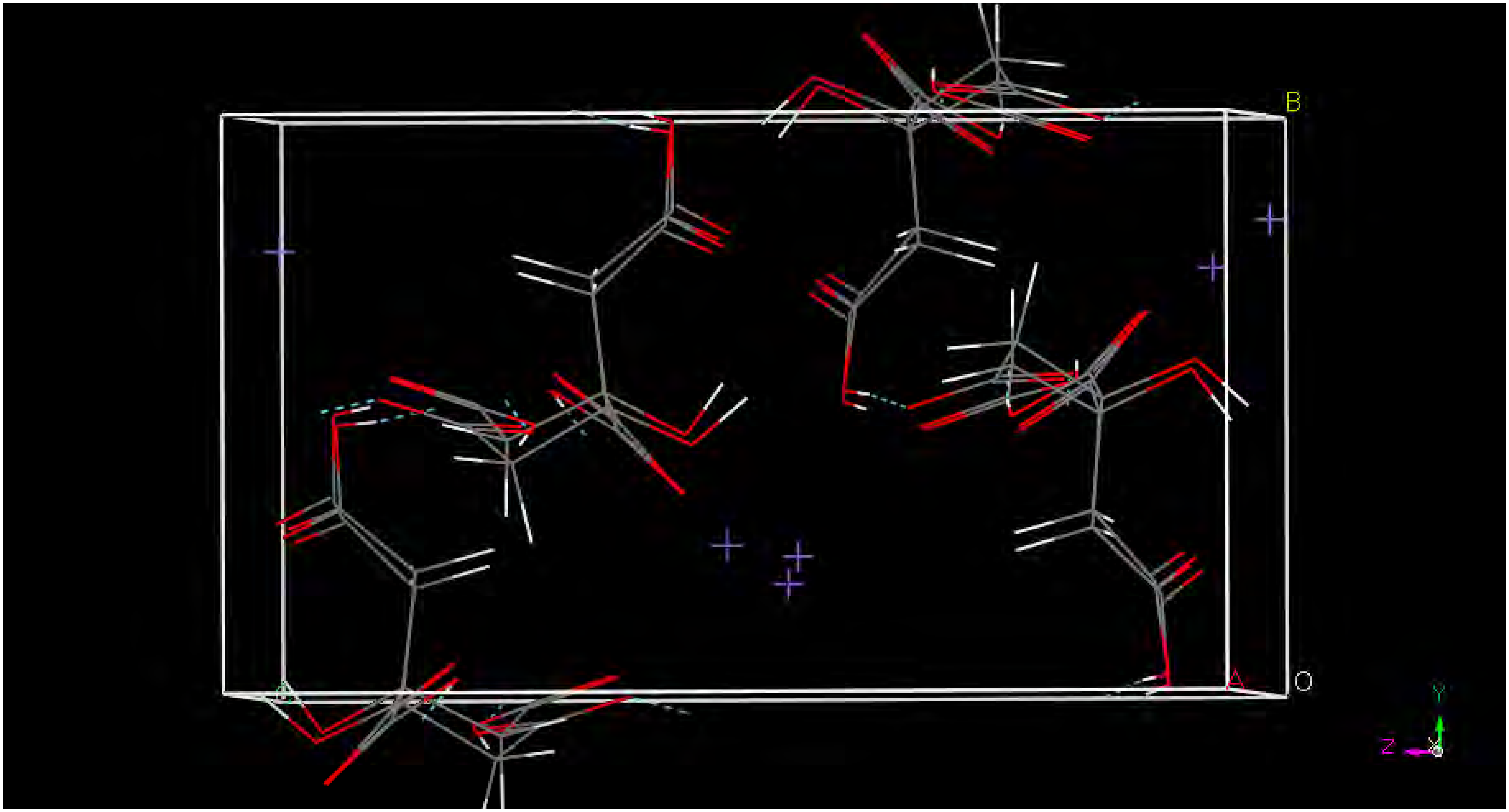


E = 0.00

NAHCIT SC and DFT



New $NaH_2C_6H_5O_7$ Rietveld and DFT

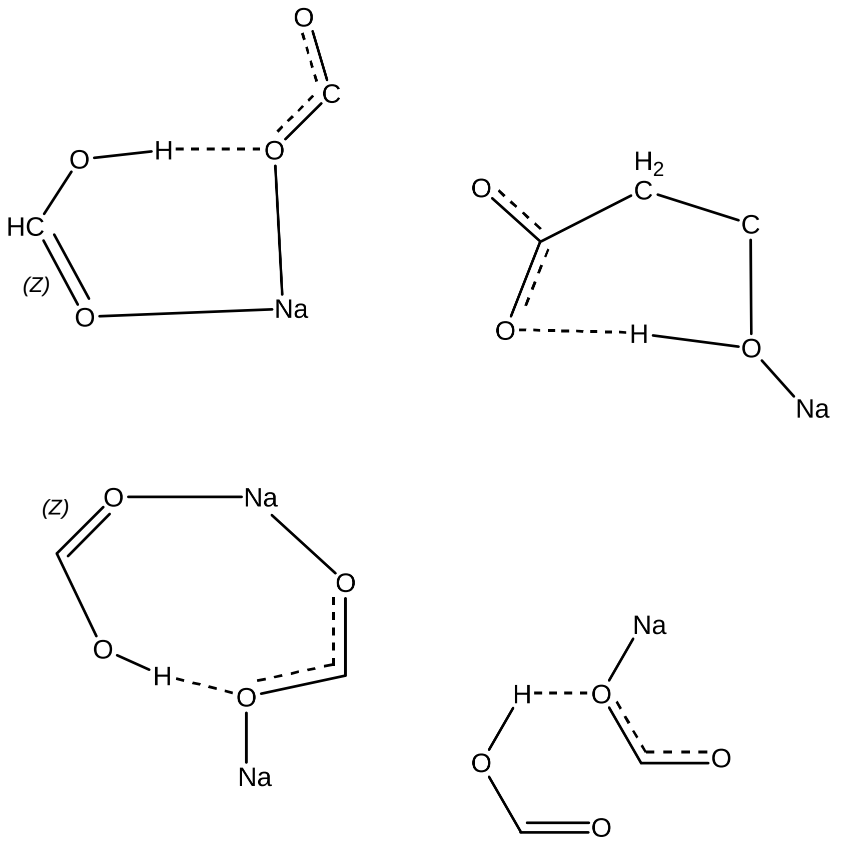


$NaH_2C_6H_5O_7$ Hydrogen Bonds

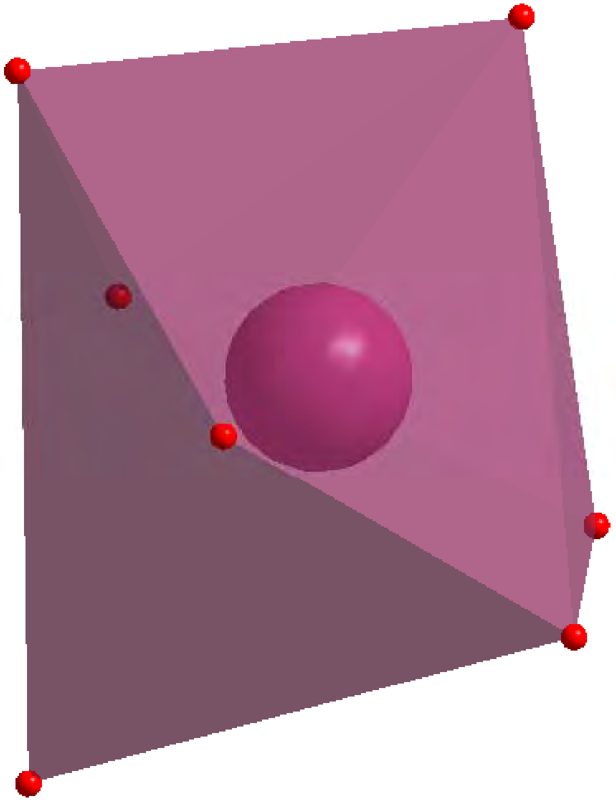
	D-H, Å	**H···A, Å**	**D··A, Å**	**D-H··A, °**	**Overlap, *e***
RAMM012A					
O7-H20··O11	1.014	1.614	2.627	176.1	0.078
O10-H21··O12	1.040	1.461	2.498	174.6	0.090
O13-H16··O8	0.974	2.503	3.033	114.0	0.011
C2-H15··O8	1.090	2.498	3.166	118.5	0.011
NAHCIT					
O7-H5··O1	0.972	1.933	2.737	138.3	0.036
O1-H6··O6	1.038	1.521	2.551	171.1	0.089
O3-H7··O5	1.006	1.635	2.623	166.1	0.069

Graph Sets of Hydrogen Bonds

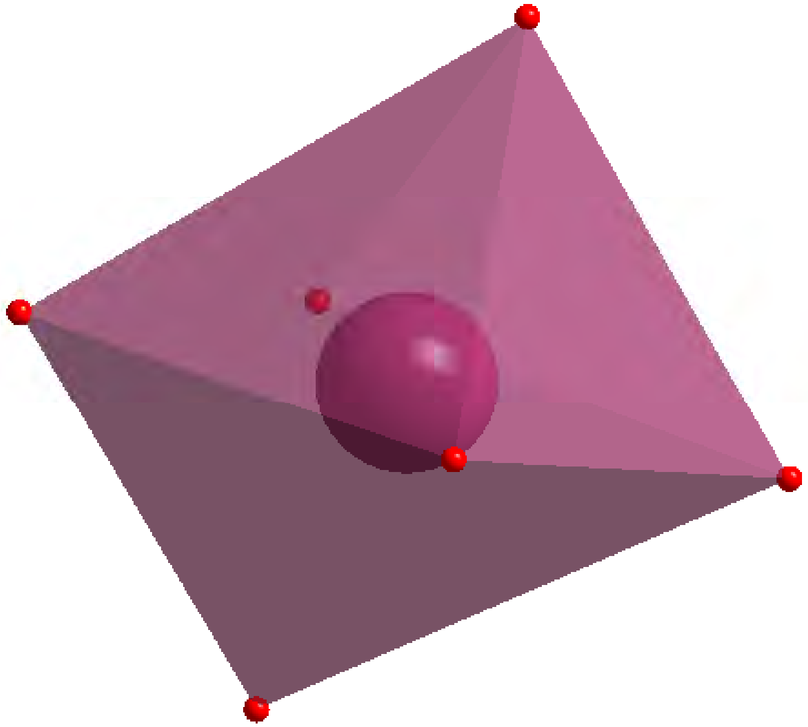
RAMM012a	
O10-H21···O12	R1,1(7)
O7-H20···O11	R2,2(16)
Both	C2,2(11) C2,2(15) R3,3(24) R4,4(26) R4,4(28)
NAHCIT	
O7-H5···O1	S1,1(6)
O1-H6···O6	R1,1(7)
O3-H7···O5	R2,2(14)
Both	R2,2(20) R2,2(24)



$NaH_2C_6H_5O_7$ Na Coordination



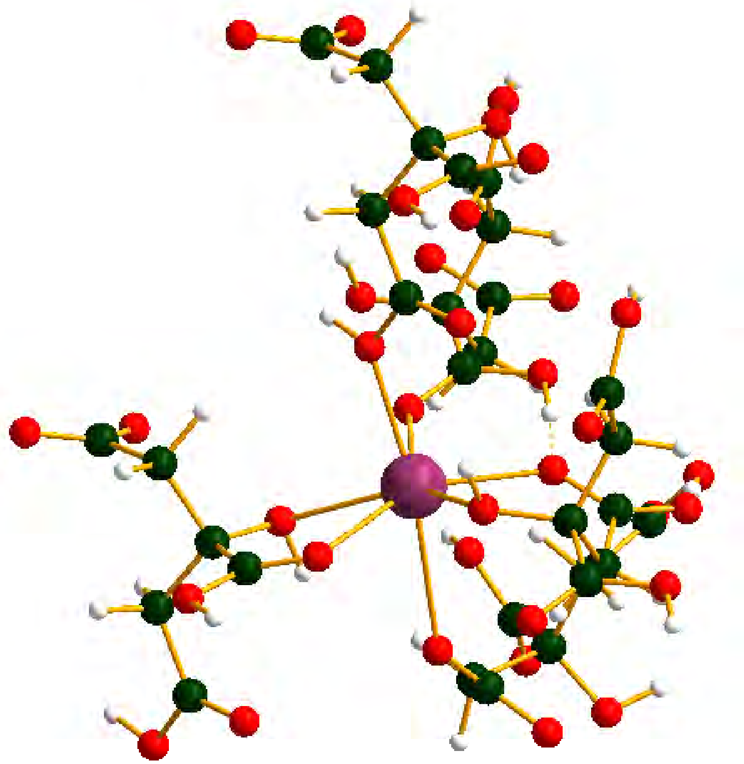
BVS = 1.12



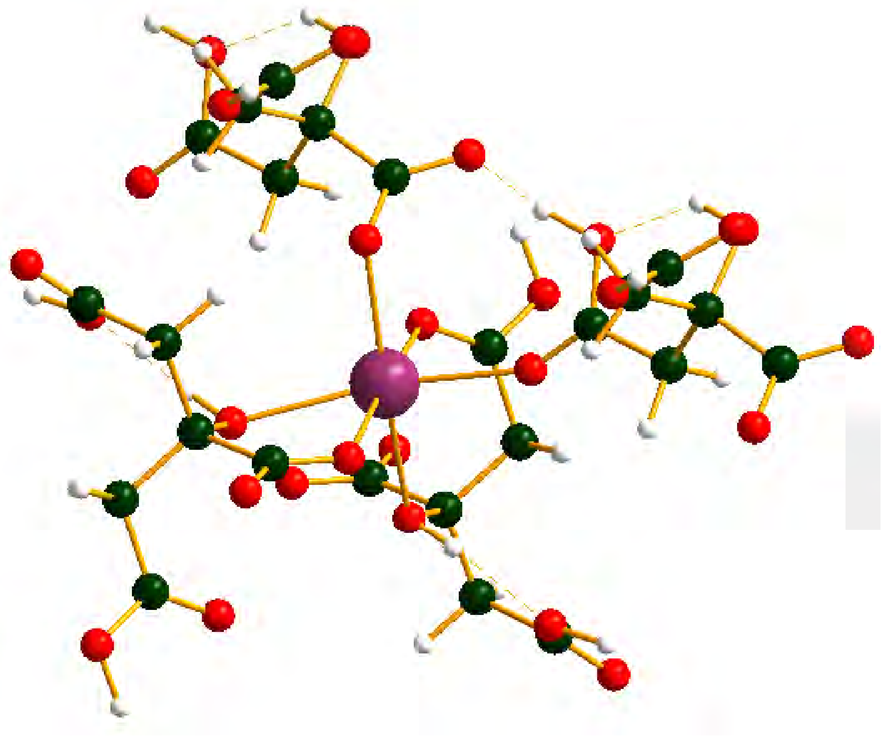
BVS = 1.33

$NaH_2C_6H_5O_7$ Na Coordination

RAMM012a

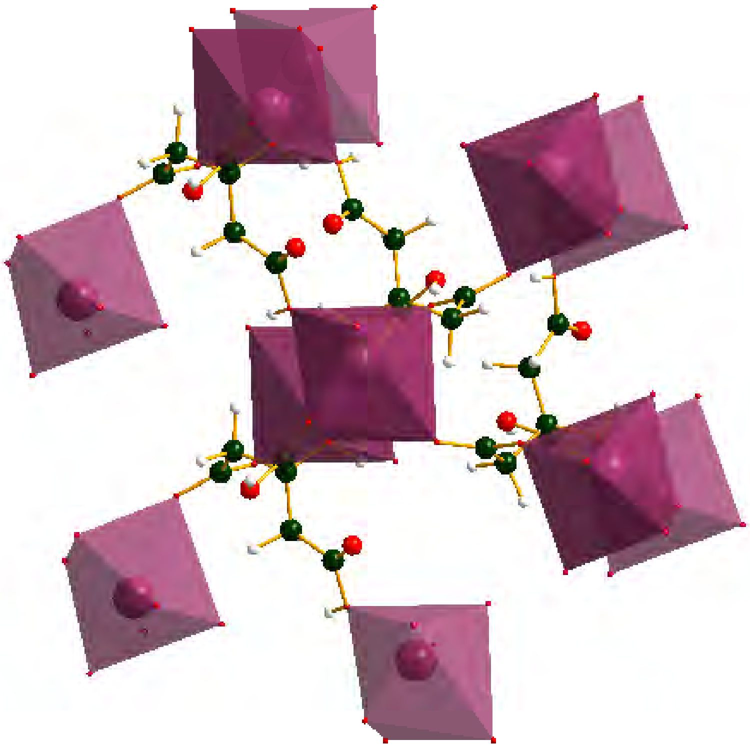


NAHCIT



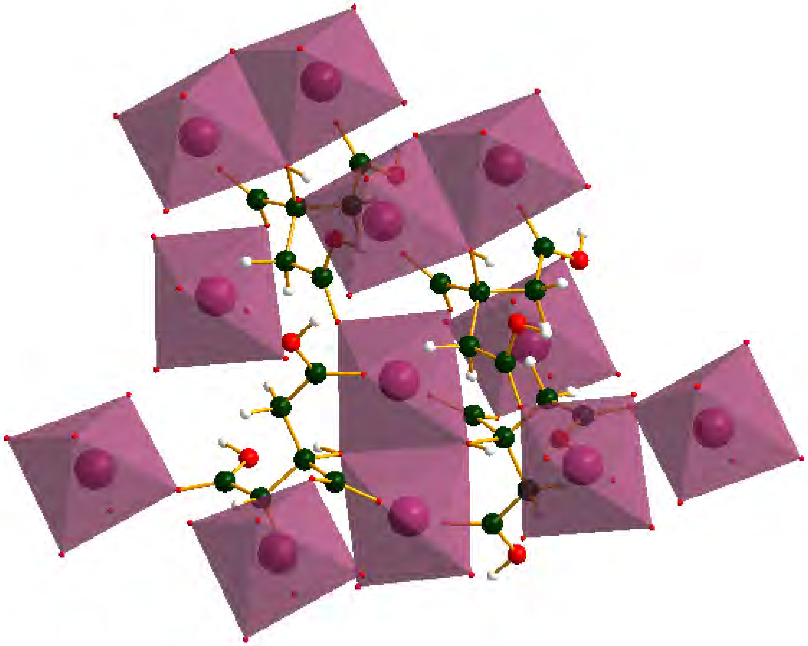
$NaH_2C_6H_5O_7$ Na Coordination

Ramm012a



Edge-sharing chains down *a*

NAHCIT



Pairs bridged by 2 OH

Na-O Bonding

- RAMM012a, Na +0.883

Bond	D, Å	Overlap	O
O7	2.398	0.009	-0.561
O9	2.348	0.014	-0.564
O12	2.326	0.014	-0.630
O13	2.536	0.010	-0.622
O11	2.855		-0.606
O9	2.561		-0.564
O13	2.550		-0.622

- NAHCIT, Na +0.877

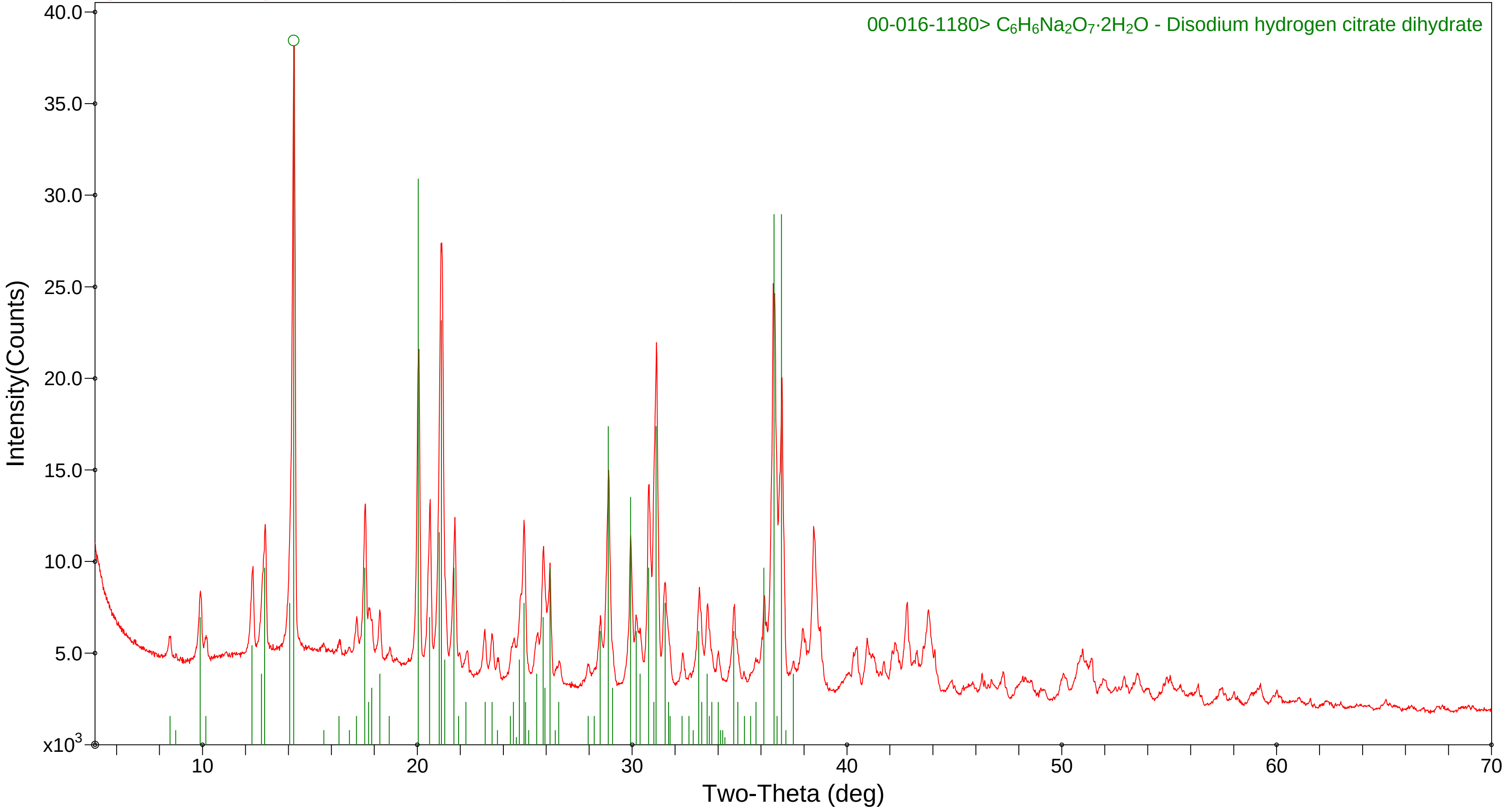
Bond	d, Å	Overlap	O
O16	2.319	0.011	-0.549
O18	2.328	0.013	-0.516
O19	2.338	0.012	-0.642
O20	2.308	0.014	-0.620
O21	2.431	0.011	-0.646
O21	2.450		-0.646

$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$

Amy Sarjeant

Northwestern

[ramm009.raw] Aldrich Na2Hcit(H2O)1.5 (30,10,0.6,2.5,3) JAK

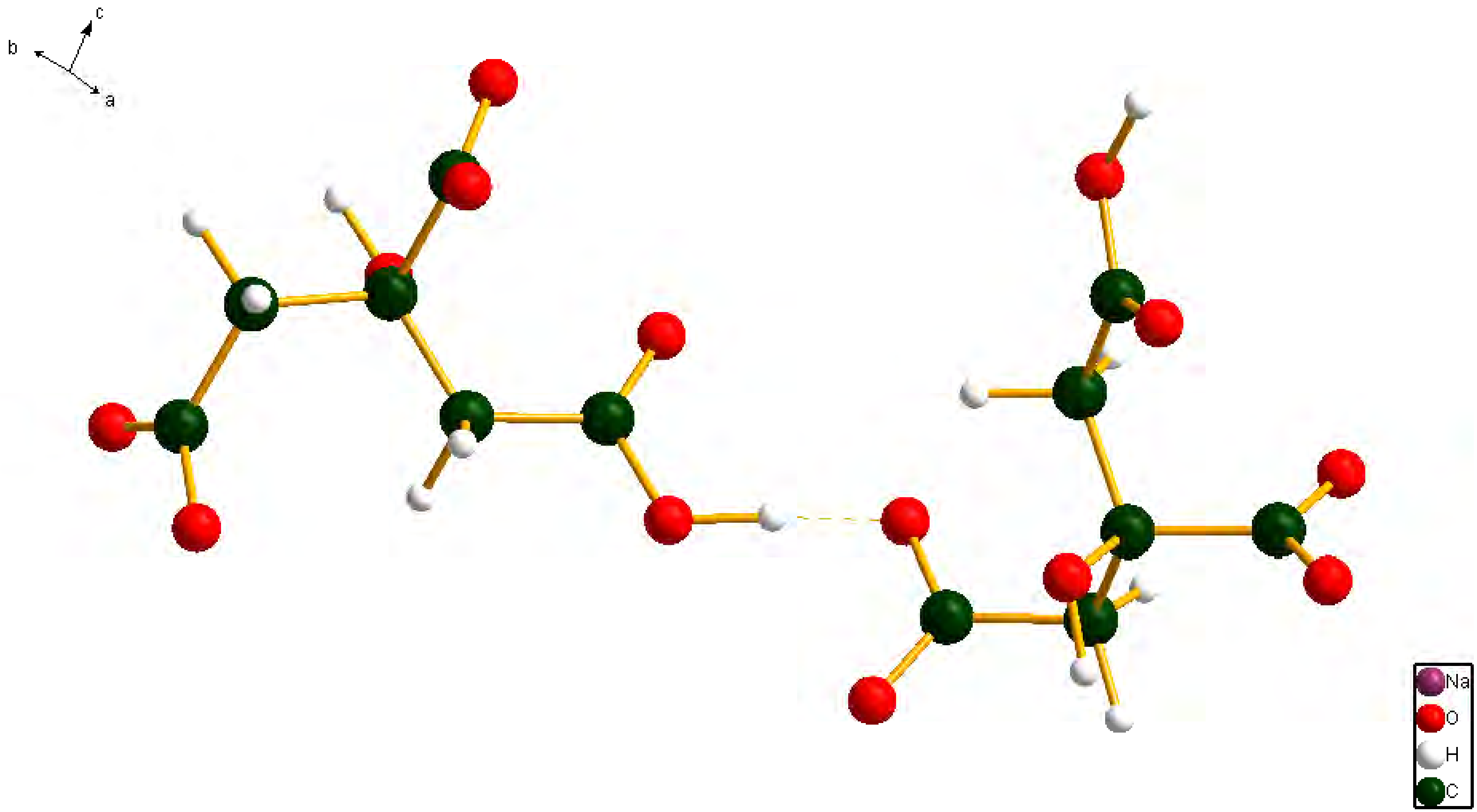


$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$ Crystal Data

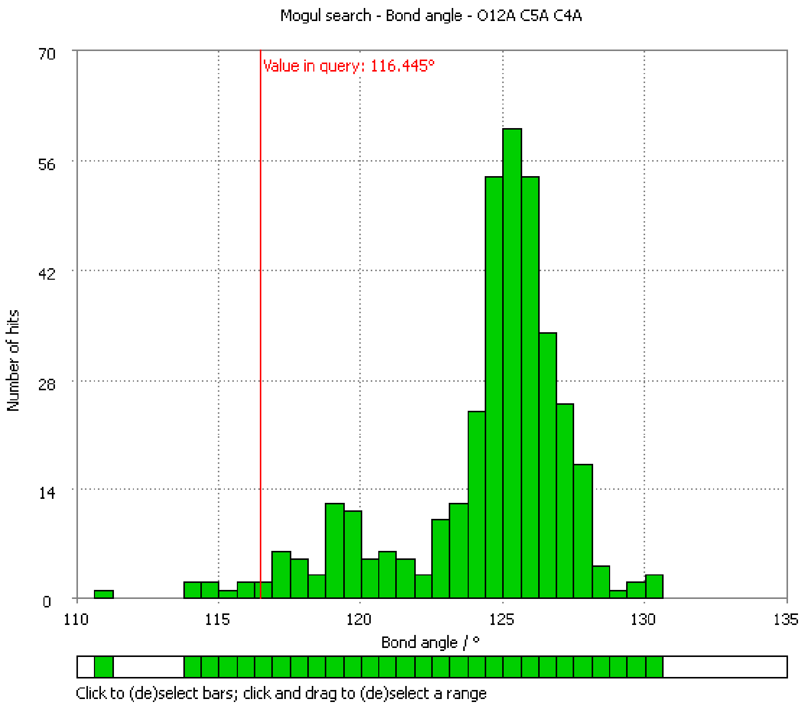
- 100K (single crystal)
- $P\bar{1}$, $Z = 4$
- $a = 8.6713(4)$
- $b = 10.6475(4)$
- $c = 10.9961(4)$
- $\alpha = 68.461(1)$
- $\beta = 79.617(2)$
- $\gamma = 81.799(2)$
- $V = 925.633$

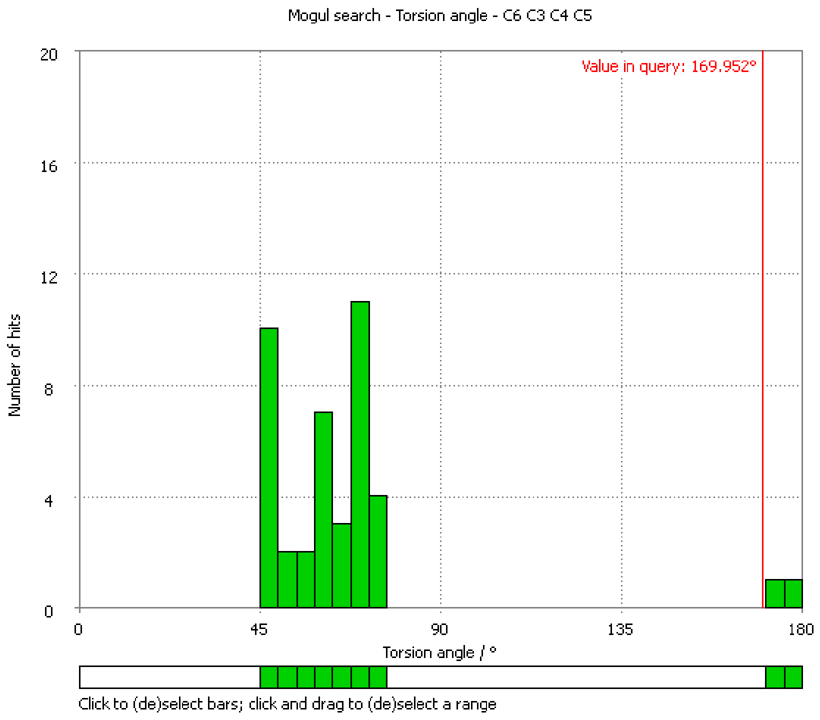
- Ambient (powder)
- $P\bar{1}$, $Z = 4$
- $a = 8.7578(6)$
- $b = 10.6697(10)$
- $c = 11.0964(10)$
- $\alpha = 68.890(4)$
- $\beta = 79.414(6)$
- $\gamma = 81.726(6)$
- $V = 947.41(16)(102.3\%)$
- (14.3 Å^3/non-H)

$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$ Citrates

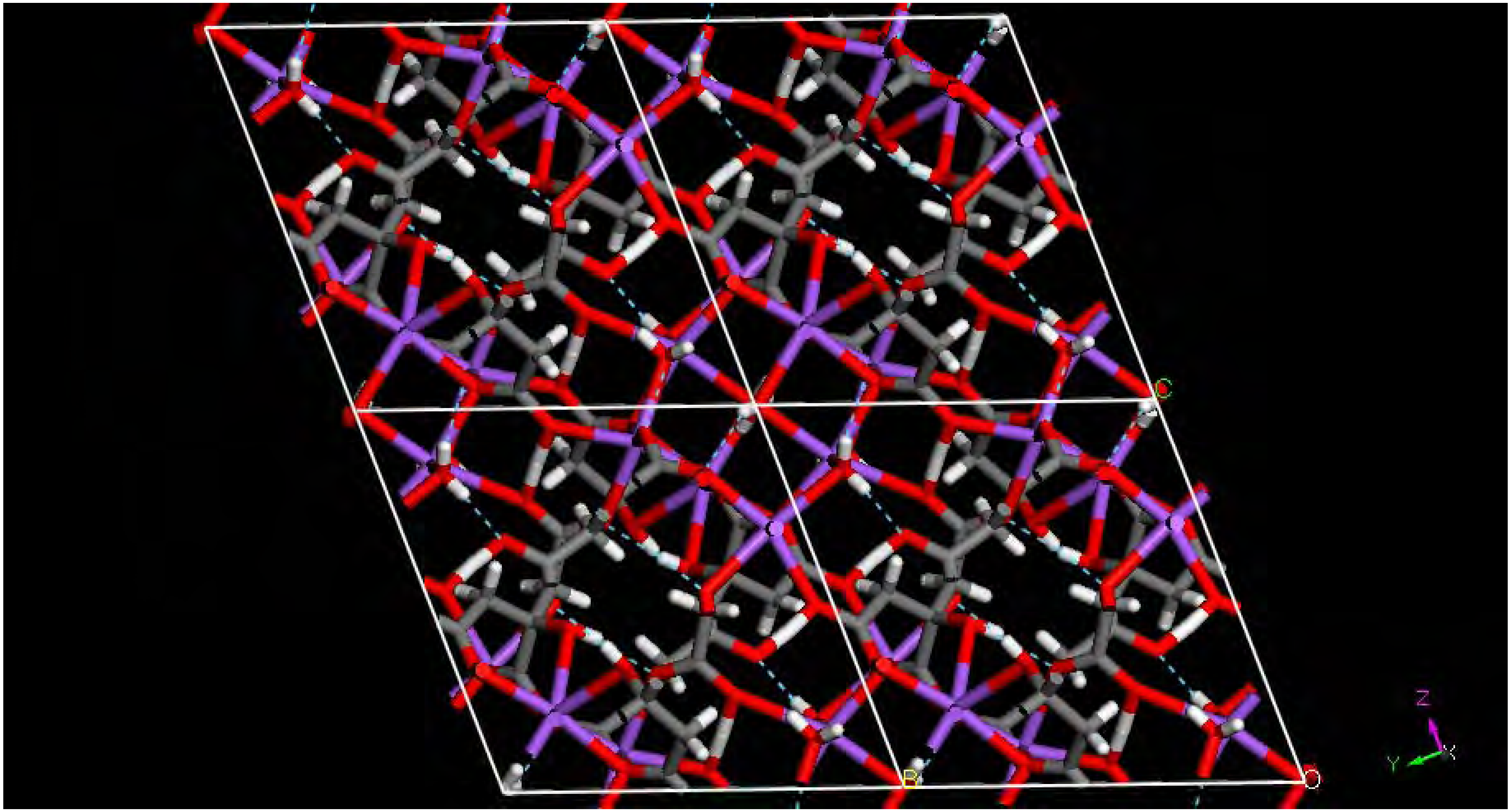


$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$ Mogul

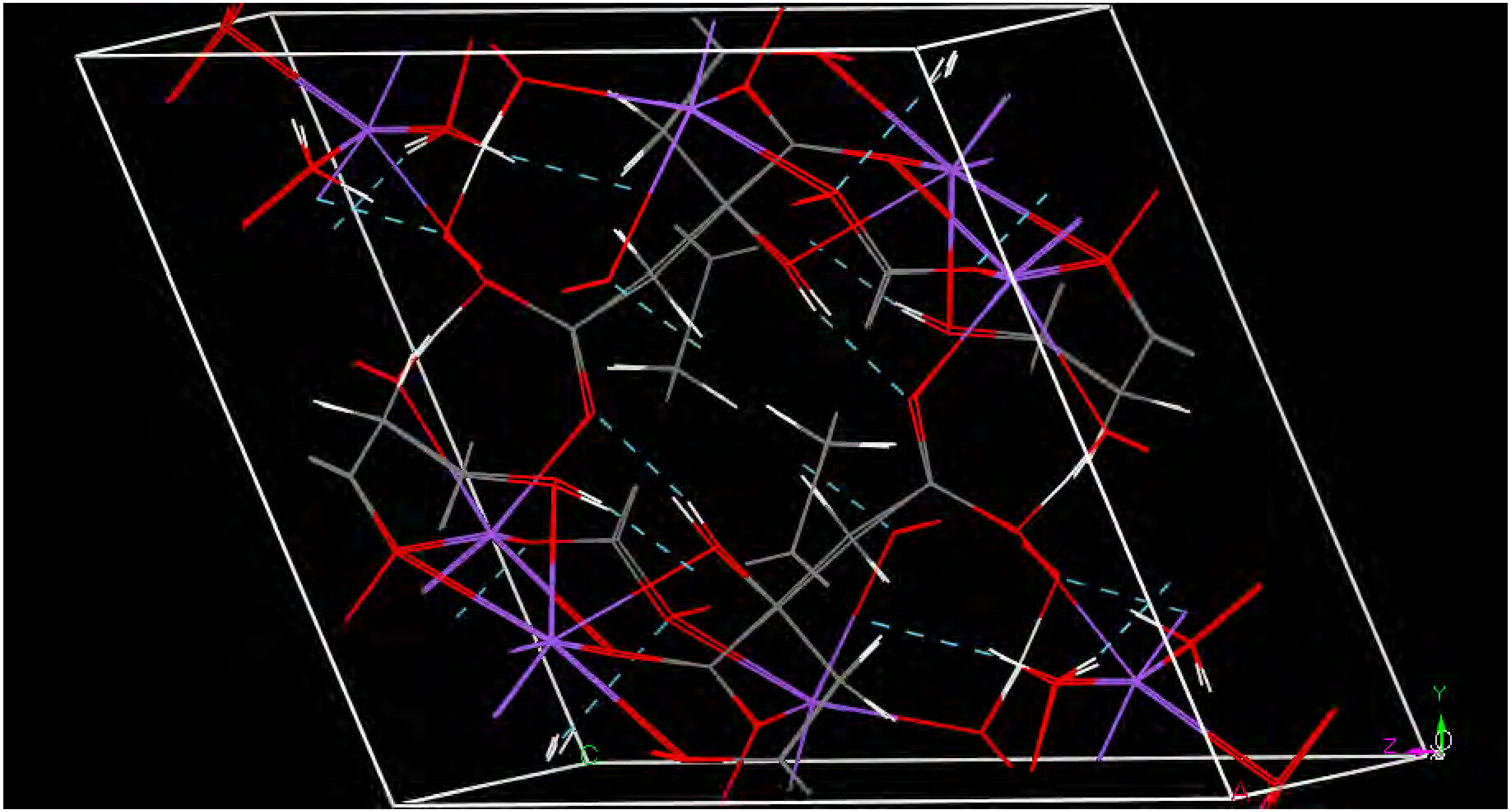




$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$



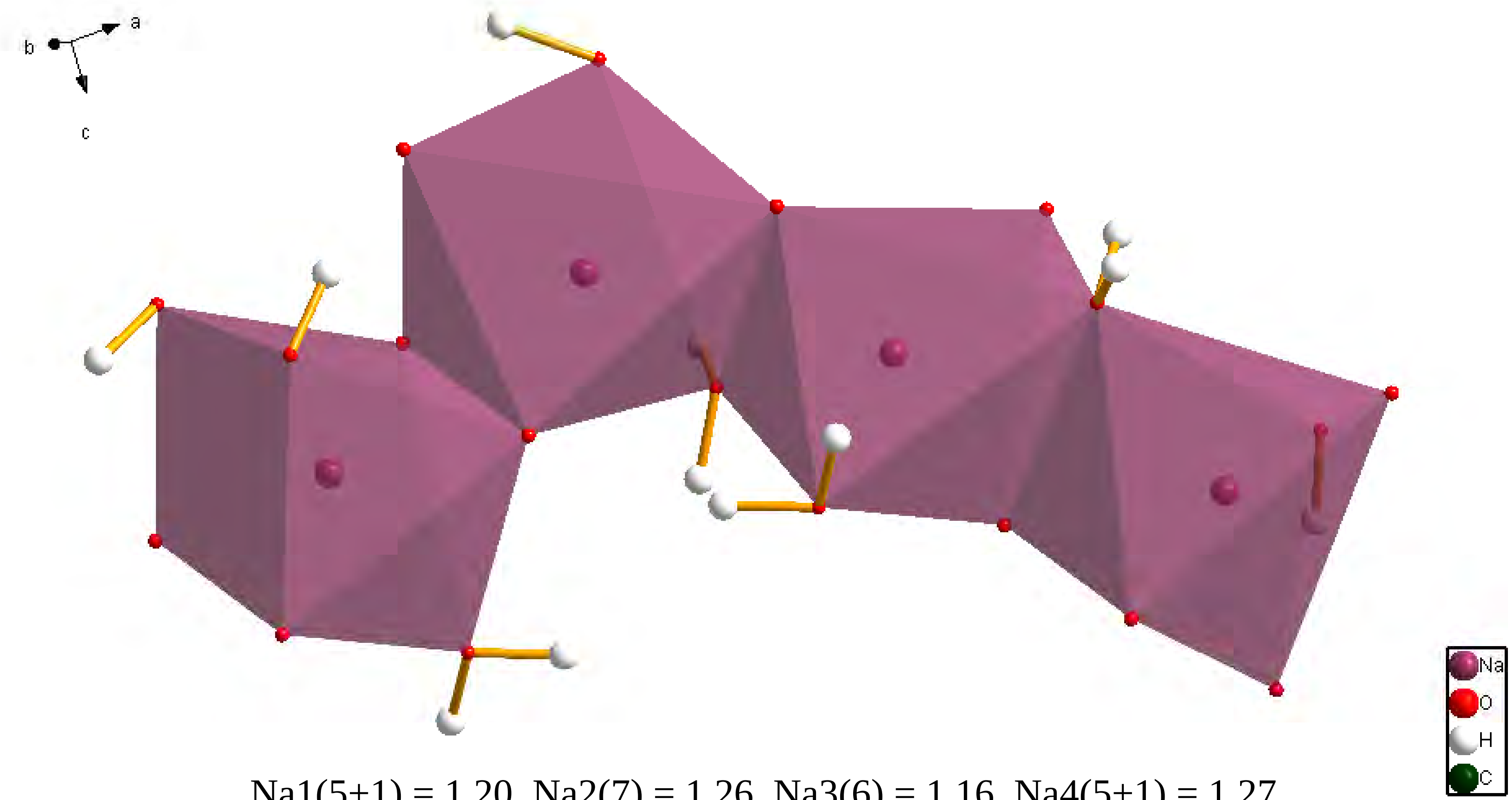
$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$ Expt & DFT



$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$ H-Bonds

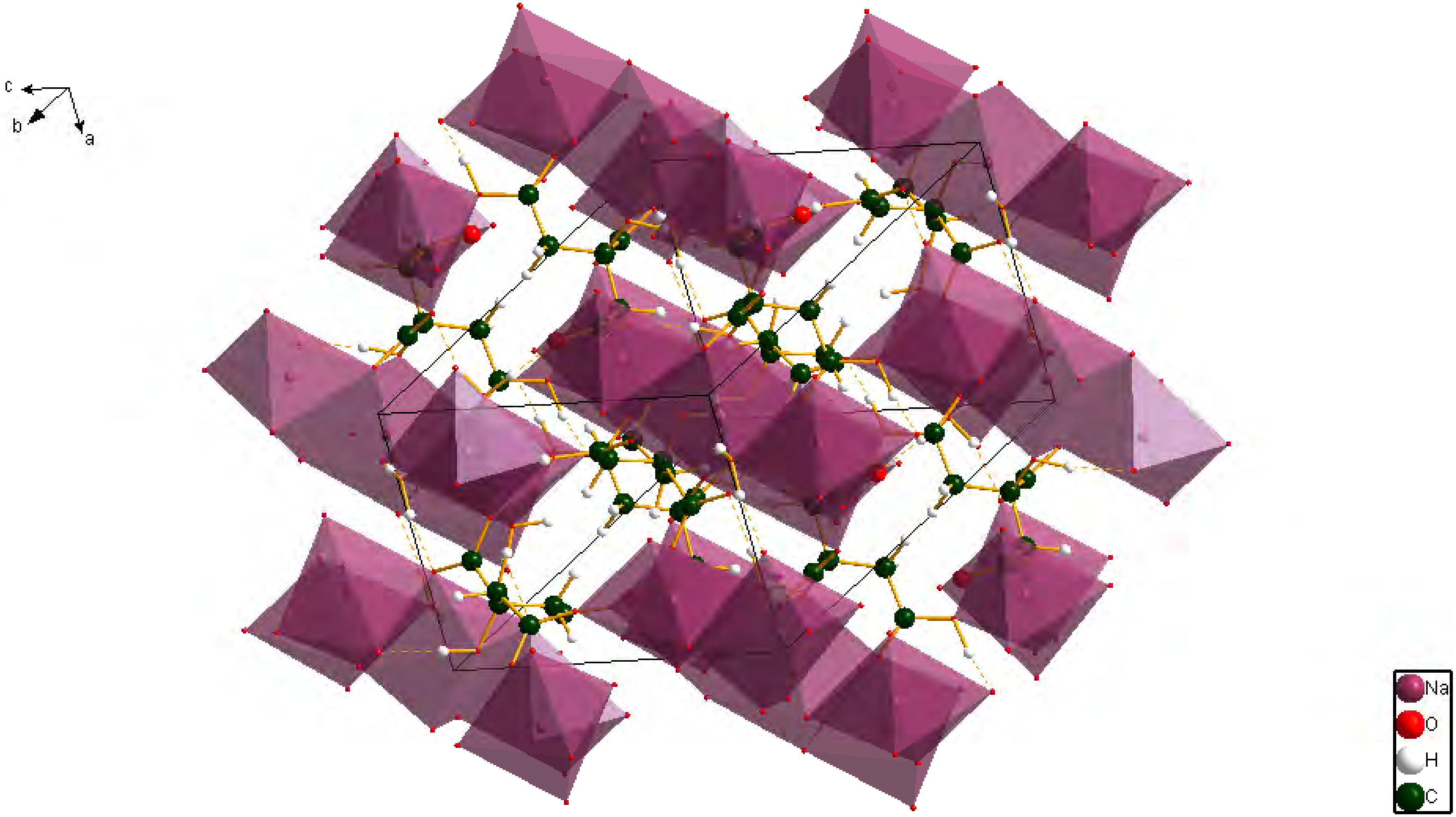
	D-H, Å	**H···A, Å**	**D··A, Å**	**D-H··A, °**	**Overlap, *e***
O1W-H1W···O10	0.988	1.806	2.772	165.0	0.063
O1W-H2W···O10A	0.980	2.122	3.067	161.4	0.039
O2W-H3W···O8	0.972	2.146	2.946	138.6	0.022
O2W-H4W···O12	0.971	2.171	2.877	128.4	0.023
O3W-H5W···O12A	0.981	1.751	2.714	165.9	0.054
O3W-H6W···O9A	0.979	1.945	2.881	159.0	0.043
O13-H16···O11	0.987	1.760	2.743	173.4	0.061
O13A-H16A···O11A	0.986	1.725	2.698	168.3	0.062
O7-H19···O12A	1.079	1.382	2.456	172.5	0.105
O7A-H19A···O12	1.079	1.393	2.465	171.1	0.111

$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$ Na Coord.

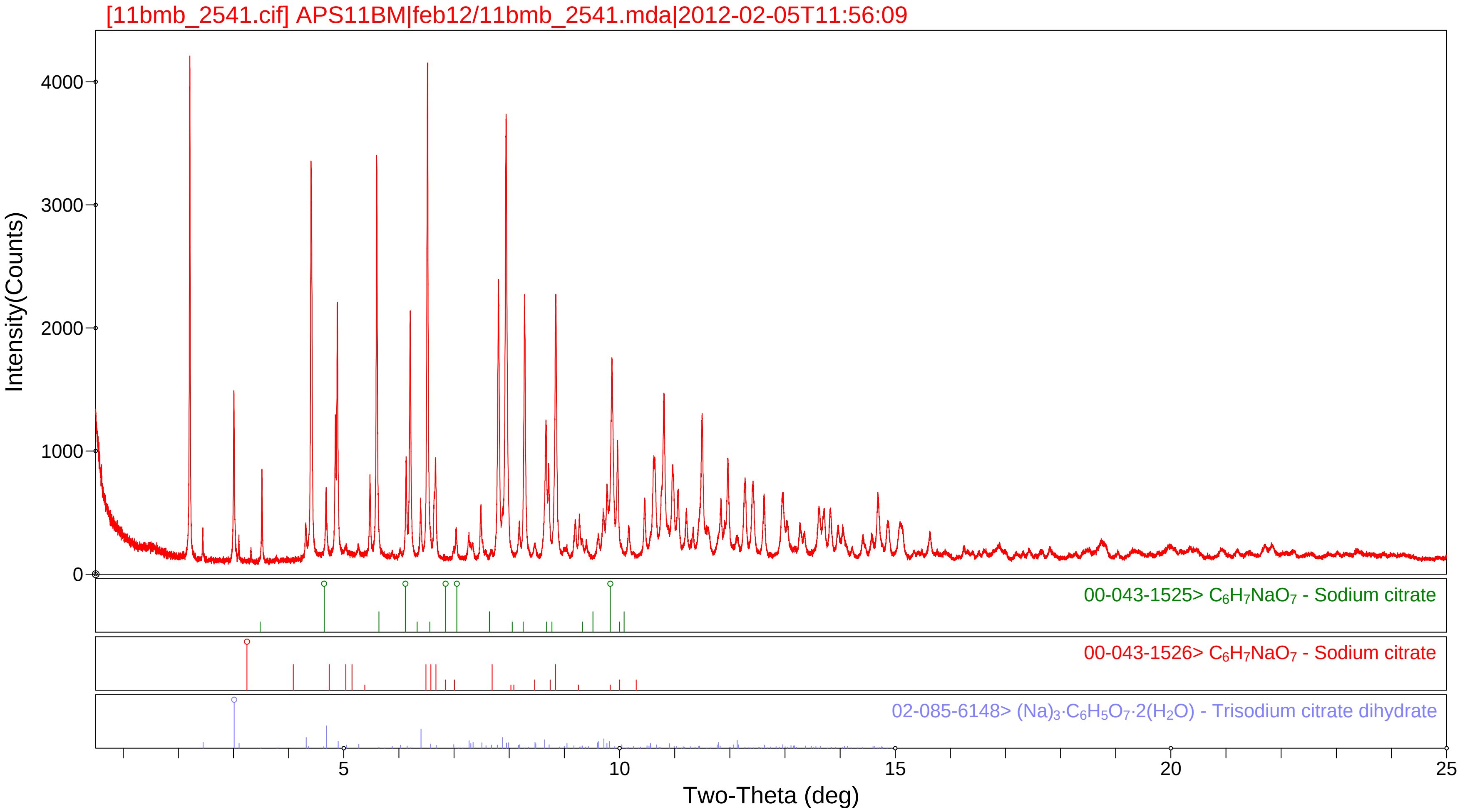


Na1(5+1) = 1.20, Na2(7) = 1.26, Na3(6) = 1.16, Na4(5+1) = 1.27

$Na_2(HC_6H_5O_7)(H_2O)_{1.5}$



$Na_3C_6H_5O_7$


[11bmb_2541.cif] APS11BM|feb12/11bmb_2541.mda|2012-02-05T11:56:09
Intensity(Counts)
4000
3000
2000
1000
0
00-043-1525> $C_6H_7NaO_7$ - Sodium citrate
00-043-1526> $C_6H_7NaO_7$ - Sodium citrate
02-085-6148> $(Na)_3 \cdot C_6H_5O_7 \cdot 2(H_2O)$ - Trisodium citrate dihydrate
5
10
15
20
25
Two-Theta (deg)

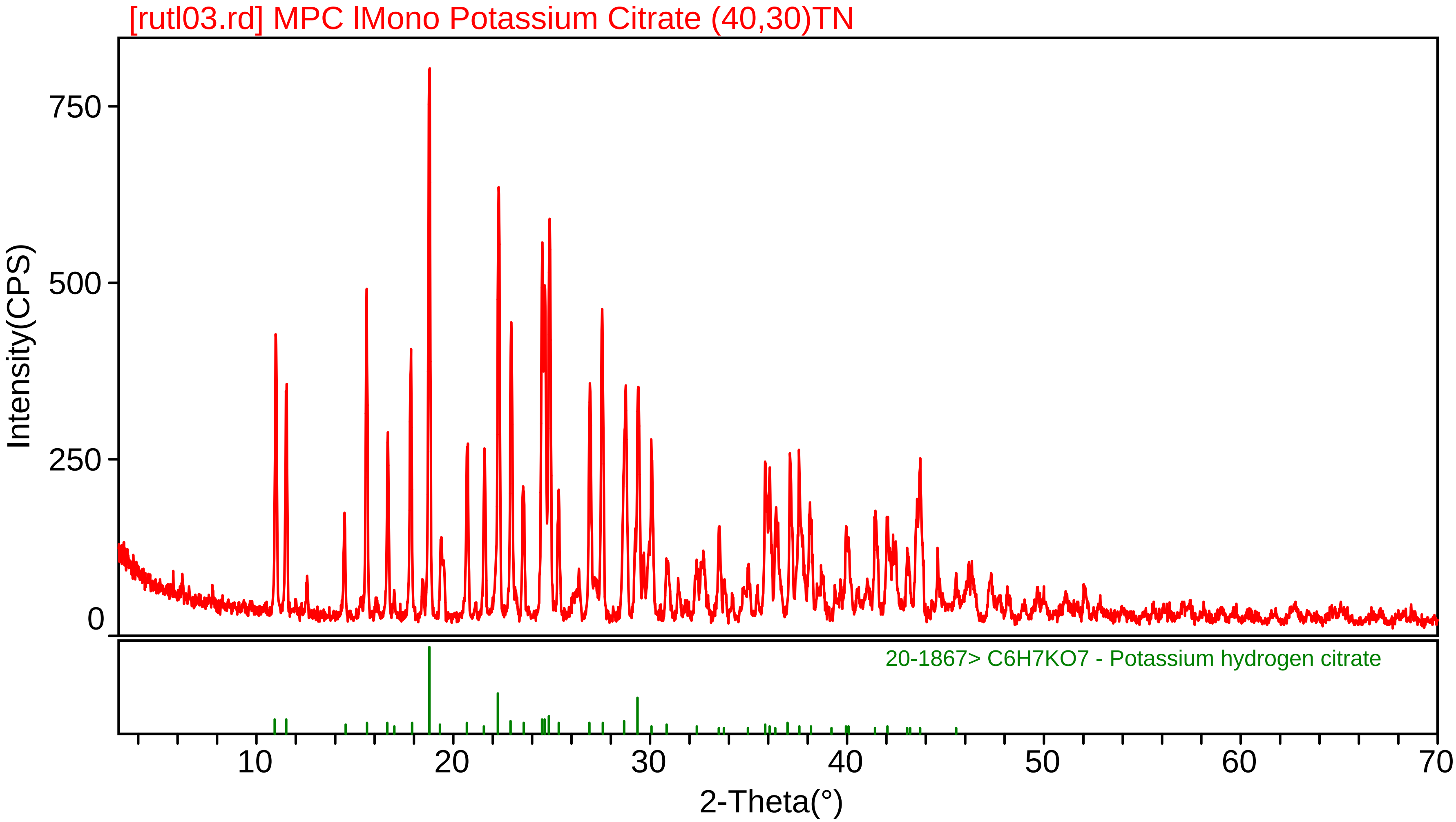
$Na_3C_6H_5O_7$ Crystal Data

- $P2_1$?, $Z = 2$
- $a = 7.73403(5)$
- $b = 5.43450(4)$
- $c = 11.03451(7)$
- $\beta = 103.885(1)$
- $V = 427.706(3)$ (13.4 $Å^3$/non-H)

$KH_2C_6H_5O_7$

Charlotte Stern

Northwestern



[rutl03.rd] MPC lMono Potassium Citrate (40,30)TN
Intensity(CPS)
750
500
250
0
20-1867> C6H7KO7 - Potassium hydrogen citrate
10
20
30
40
50
60
70
2-Theta(°)

Blend with NIST 640b Si internal standard, and try to index…

- ITO figure of merit = 79
- a = 6.5039(2), b = 8.8328(3), c = 8.9398(3) Å,

α = 64.640(2), β = 75.356(2), γ = 71.130(2)°,
V = 430.94 Å^3 (15.4 Å^3/non-H)

- only indexes 15 of the first 20 lines (strong ones among the five)!
- but there has to be some truth in this (“some of these zones are probably correct”)…

Search the NIST Crystal Data Identification File for supercells $\leq 4\ V$

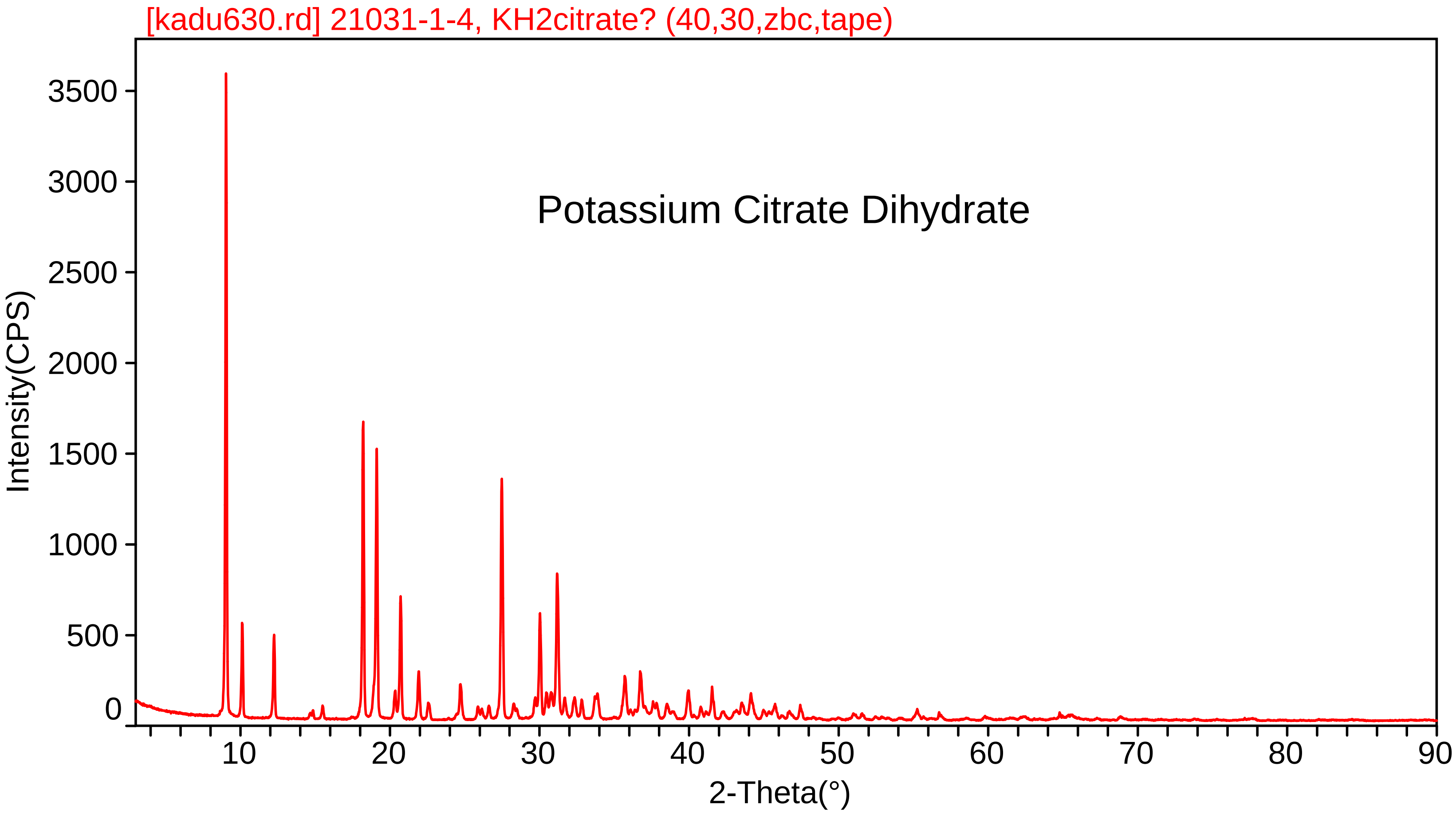
Among the hits was $K^+C_6H_7O_7^-$!

W. E. Love and A. L. Patterson, *Acta Cryst.*, **13**, 426-428 (1960).

a = 9.44, b = 12.98, c = 14.97 Å, α = 110.00, β = 91.60, γ = 93.35°,
V = 1719 Å^3 (15.3 Å^3/non-H),

P1 or *P-1*, Z = 8!

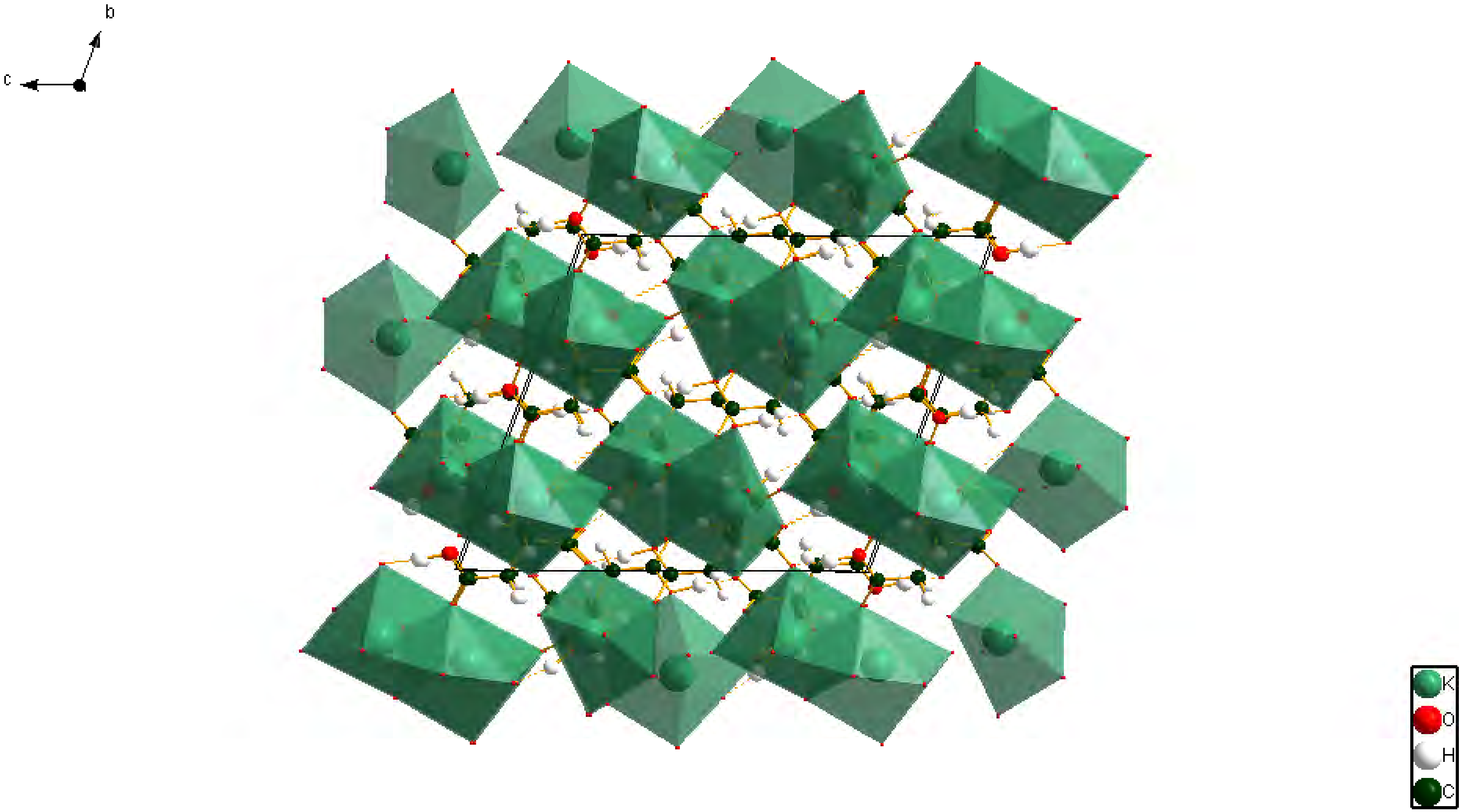
This would represent a 68- or 136-parameter *ab initio* structure solution problem, so try to grow crystals…


[kadu630.rd] 21031-1-4, KH2citrate? (40,30,zbc,tape)
Potassium Citrate Dihydrate
Intensity(CPS)
3500
3000
2500
2000
1500
1000
500
0
10
20
30
40
50
60
70
80
90
2-Theta(°)

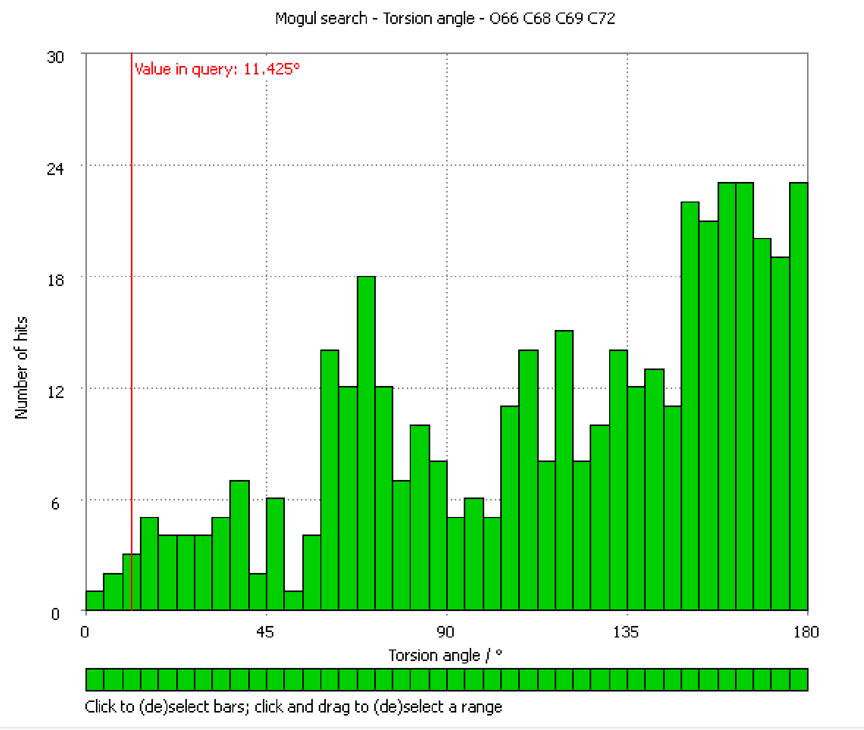
Not much happens with T:

	$KH_2C_6H_5O_7$			$KH_2C_6H_5O_7(H_2O)_2$		
	-110°	20°C	Δ, %	-110°	20°C	Δ, %
a, Å	9.4121(33)	9.4537(2)	0.44	6.1274(5)	6.1572(3)	0.49
b, Å	13.000(4)	13.0068(2)	0.52	8.8094(7)	8.8430(2)	0.38
c, Å	14.932(5)	14.9400(3)	0.5	10.0538(8)	10.1249(3)	0.71
α, °	110.32(2)	109.882(1)		100.822(1)	100.614(1)	
β, °	91.72(5)	91.555(2)		101.867(1)	102.254(2)	
γ, °	93.65(3)	93.394(2)		90.203(1)	90.148(3)	
V, $Å^3$	1707.3	1722.34(6)	0.88	521.1	529.00(3)	1.54
ρ, g/cm^3	1.791	1.776		1.697	1.671	

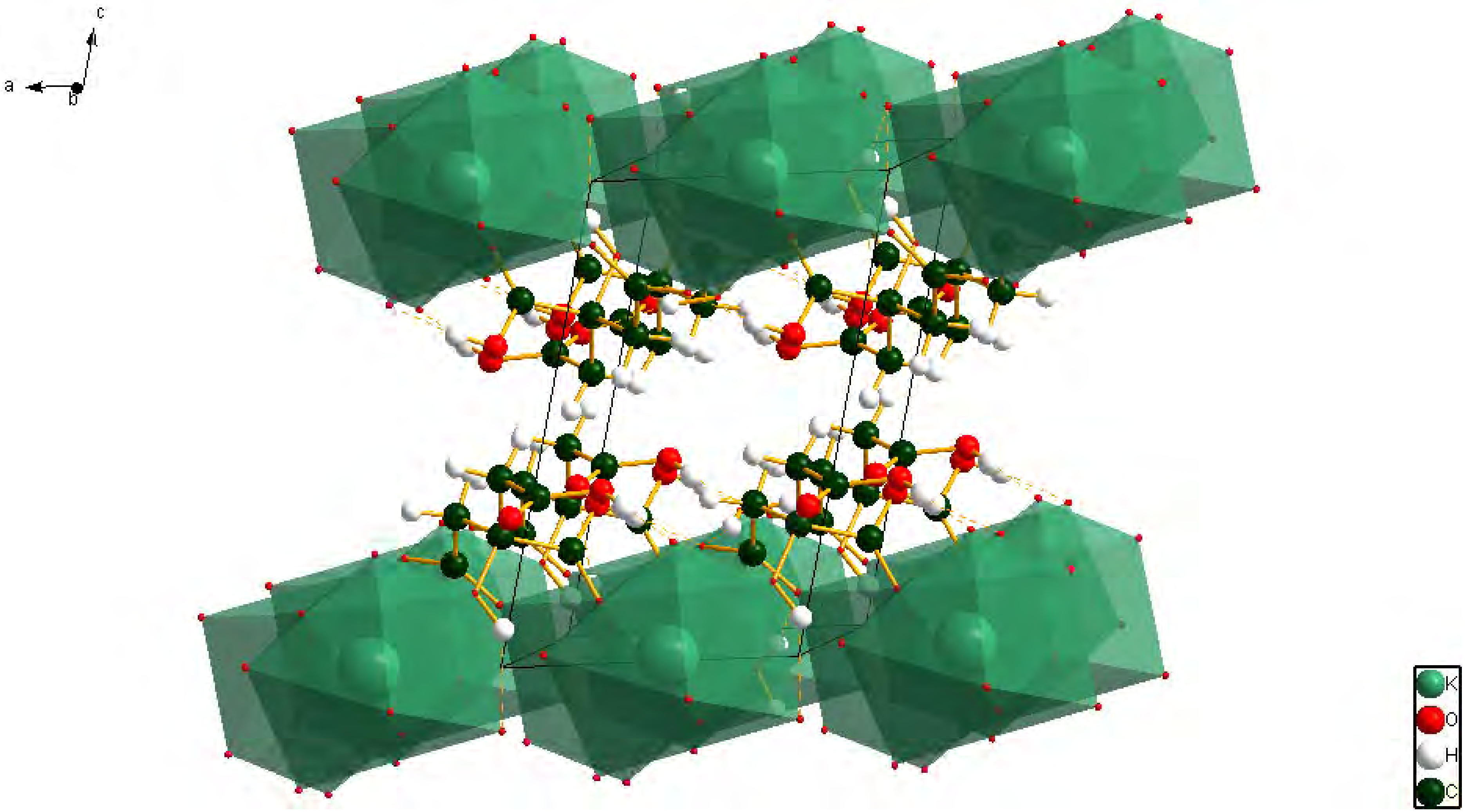
$KH_2C_6H_5O_7$



3 typical, one unusual citrate



$KH_2C_6H_5O_7(H_2O)_2$



Why?

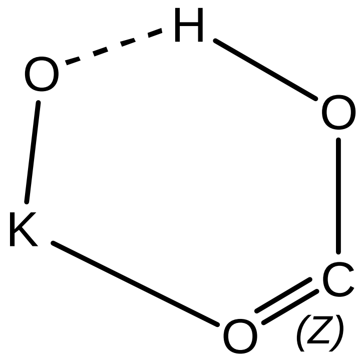
Conformational Energy
Isolated Citrates (vacuum)

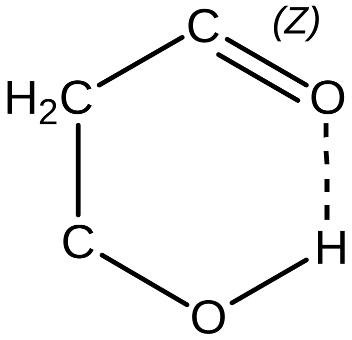
	eV	ΔeV	Δkcal/mol	ΔkJ/mole
1	-8232.4128337	0.0190519	0.44	1.97
2	-8232.3175319	0.1233537	2.84	11.88
3	-8232.3870740	0.0538116	1.24	5.19
4	-8232.4408856	0	0	0

$(H_2O)_2$	-8230.7682782	1.6726074	38.57	161.39

$KH_2C_6H_5O_7$ Graph Sets (1)

H-Bond	**Graph Set**
O23-H24···O77	S1,1(6)
O26-H27···O56	S1,1(6)
O33-H34···O25	S1,1(6)*
O46-H47···O76	S1,1(6)





Energetics of $KH_2C_6H_5O_7$

- Conformational
- Hydrogen Bonds
- K-O coordination
- van der Waals

- +38.08 kJ/mole/cell
- -2739.32 kJ/mole/cell

- ρ = 1.791, *vs.* expected 1.56(33)

-342.4 kJ/citrate

Energetics of $KH_2C_6H_5O_7(H_2O)_2$

- Conformational
- Hydrogen Bonds
- K-O coordination
- van der Waals

- +161.4 kJ/mole/cell
- -1192.9 kJ/mole/cell

- $\rho = 1.697$

-435.1 kJ/citrate

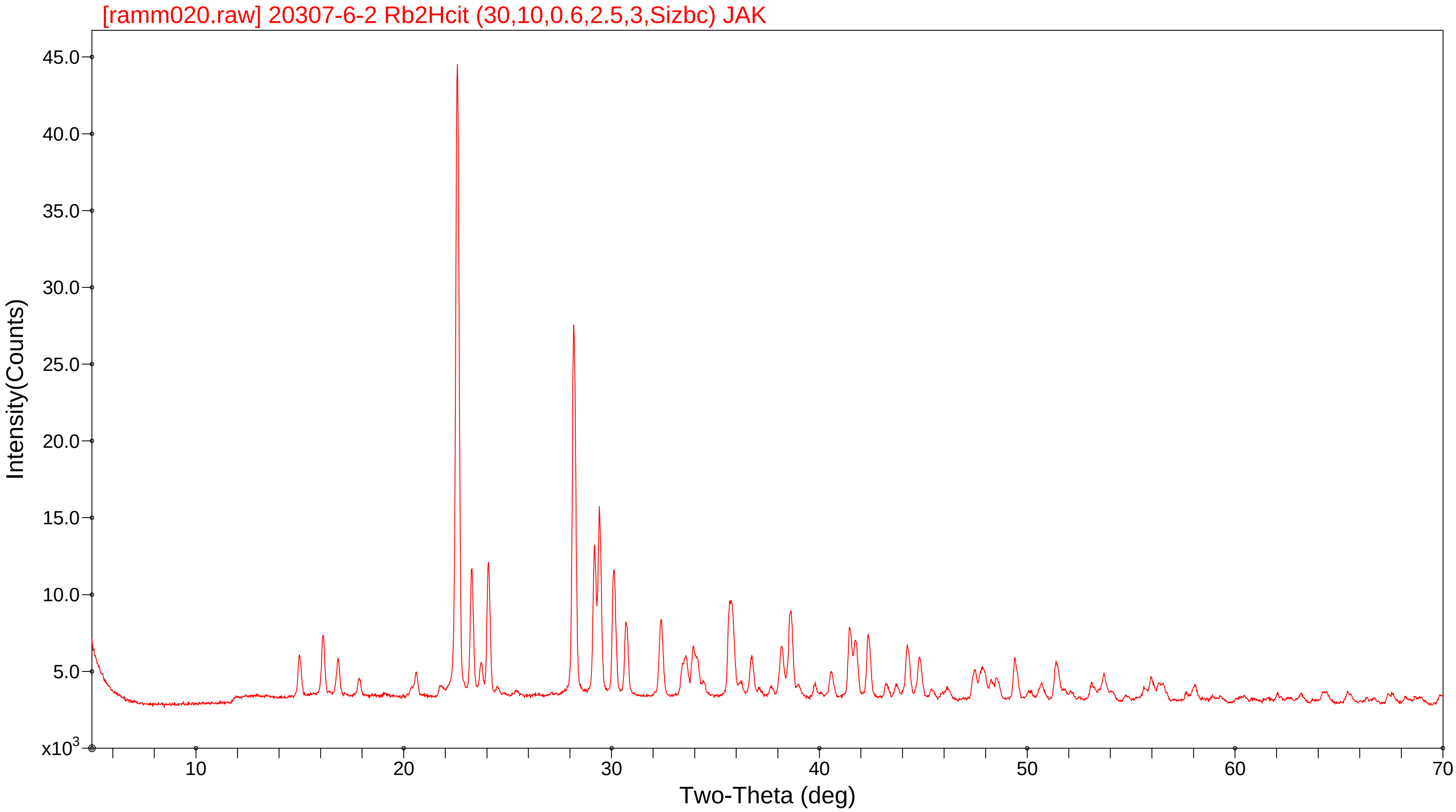
CASTEP Energy Differences

	$KH_2C_6H_5O_7(H_2O)_2$	$KH_2C_6H_5O_7+2H_2O$
Integrated charge density	98.0000	98.0000
Electronic kinetic energy	2298.7467	2297.1764
Local potential energy	**-4780.7431**	**-4839.6635**
Non-local pot. Energy	1654.1133	1652.5601
Hartree energy correction	**-2512.0526**	**-2988.6137**
Ex-corr energy correction	413.5081	412.9943
Ewald energy	**-3003.6098**	**-2683.1359**
Pseudopot. Core energy	85.3054	77.2213
Electron entropy	0	0
Sum	-5844.7319	-5843.3571
Δ	-1.3748 eV	
	-31.71 kcal/mole	
	-132.72 kJ/mole	

Summary

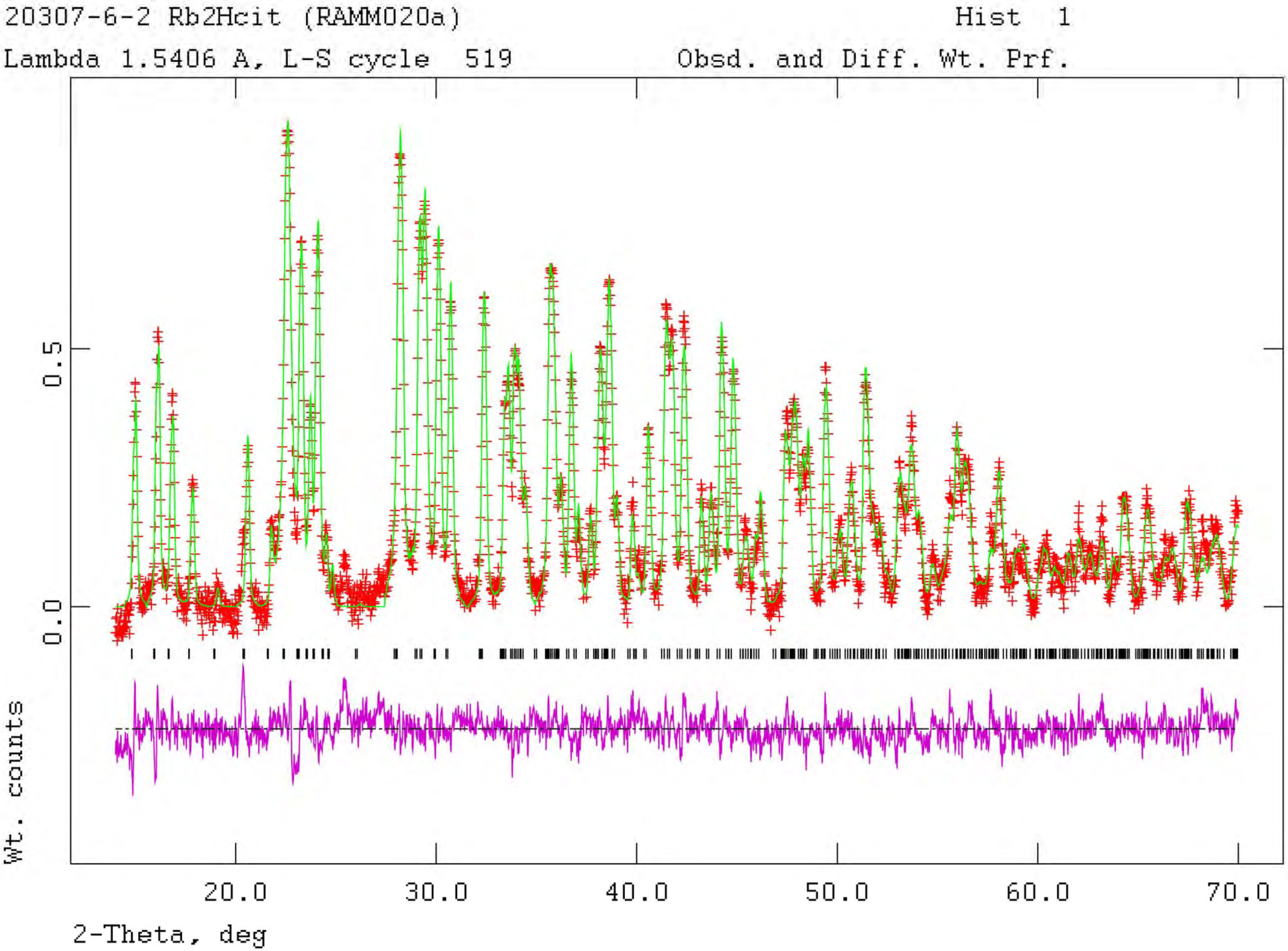
- The dihydrate is lower energy (low T)
- The dihydrate is less-dense because of the formation of stronger hydrogen bonds (ice/water)
- Water is a better ligand than COOH, and COO^- is better than COOH
- $\Delta G = \Delta H - T\Delta S$

$Rb_2H_1C_6H_5O_7$

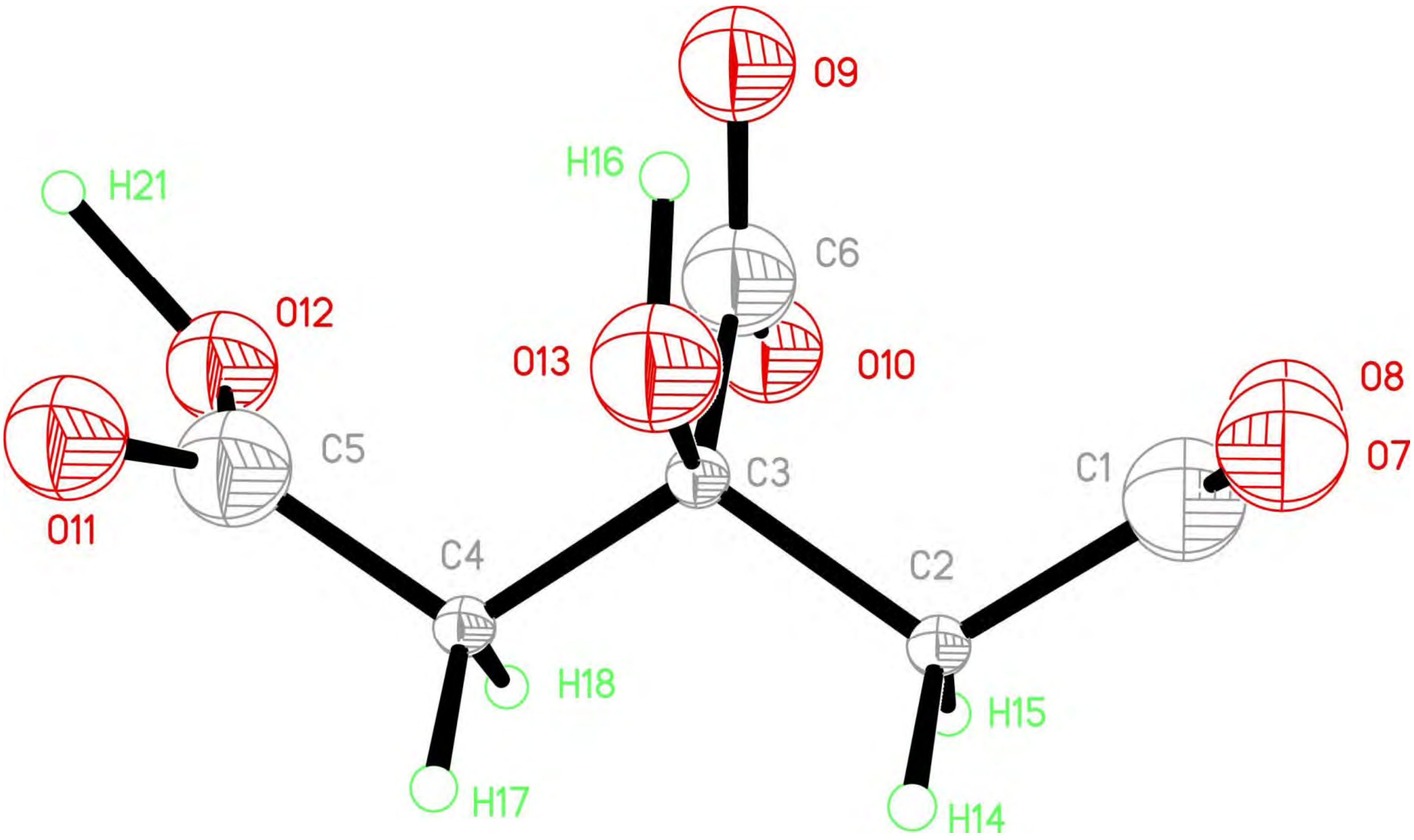

[ramm020.raw] 20307-6-2 Rb2Hcit (30,10,0.6,2.5,3,Sizbc) JAK
Intensity(Counts)
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
x10^3
10
20
30
40
50
60
70
Two-Theta (deg)

$Rb_2H_1C_6H_5O_7$ Crystal Data

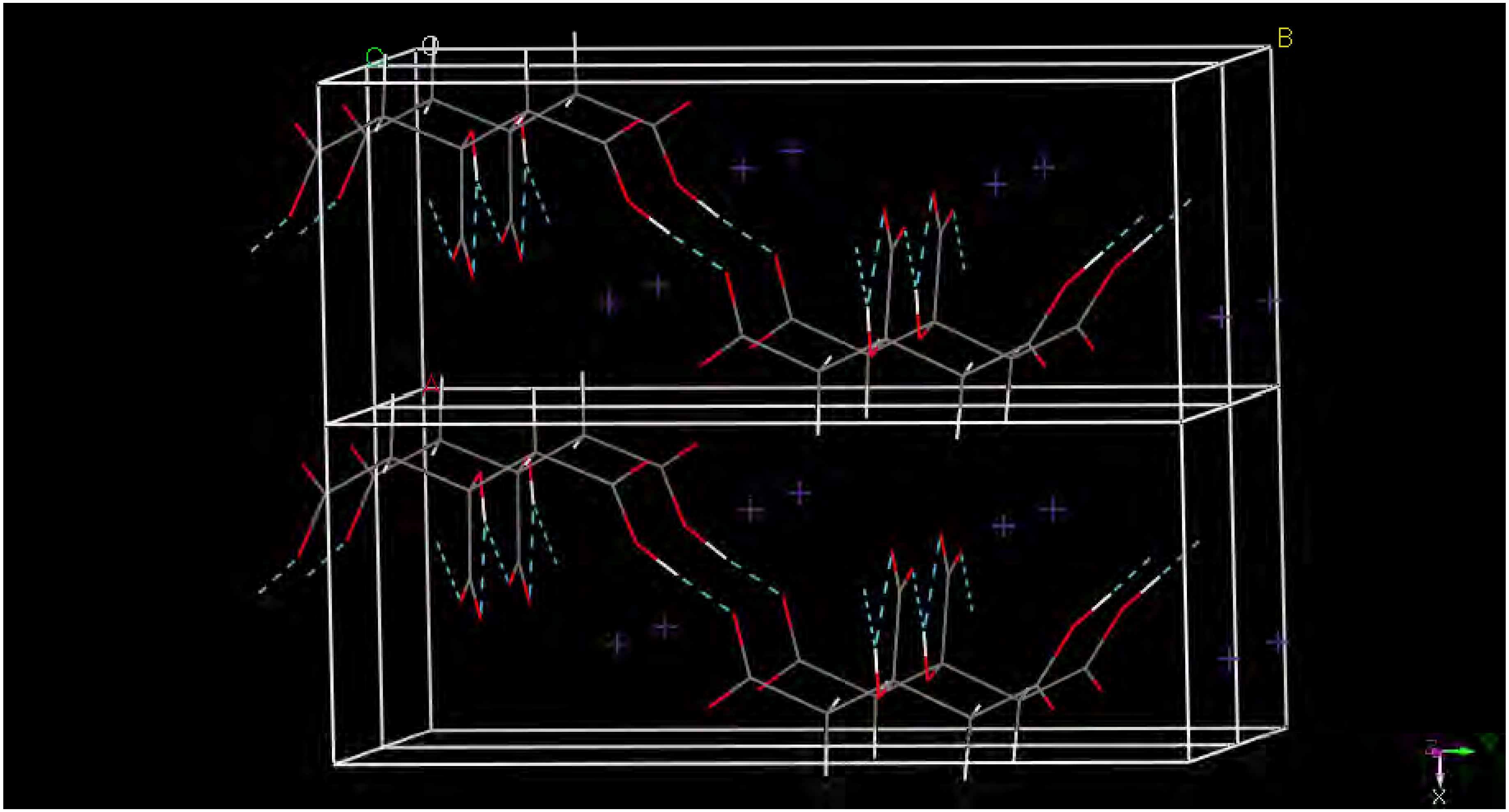
- $P2_1$, $Z = 2$
- $a = 5.9780(2)$
- $b = 15.0961(5)$
- $c = 5.3207(2)$
- $\beta = 93.935(1)$
- $V = 479.04(3)$ (16.0 $Å^3$/non-H)


20307-6-2 Rb2Hcit (RAMM020a)
Hist 1
Lambda 1.5406 A, L-S cycle 519
Obsd. and Diff. Wt. Prf.
0.5
0.0
Wt. counts
20.0
30.0
40.0
50.0
60.0
70.0
2-Theta, deg

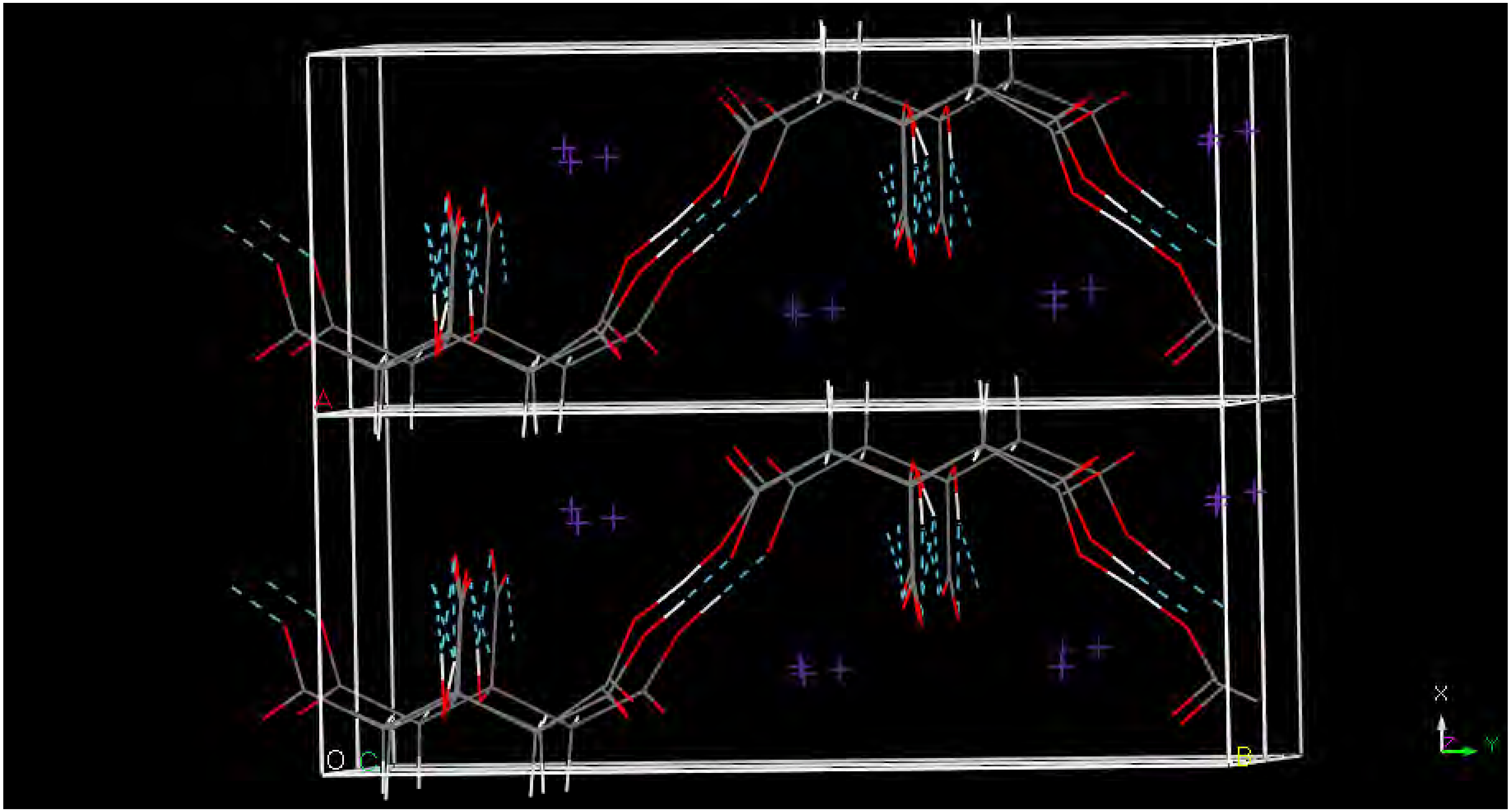
$Rb_2H_1C_6H_5O_7$ Citrate Anion



$Rb_2H_1C_6H_5O_7$ Crystal Structure

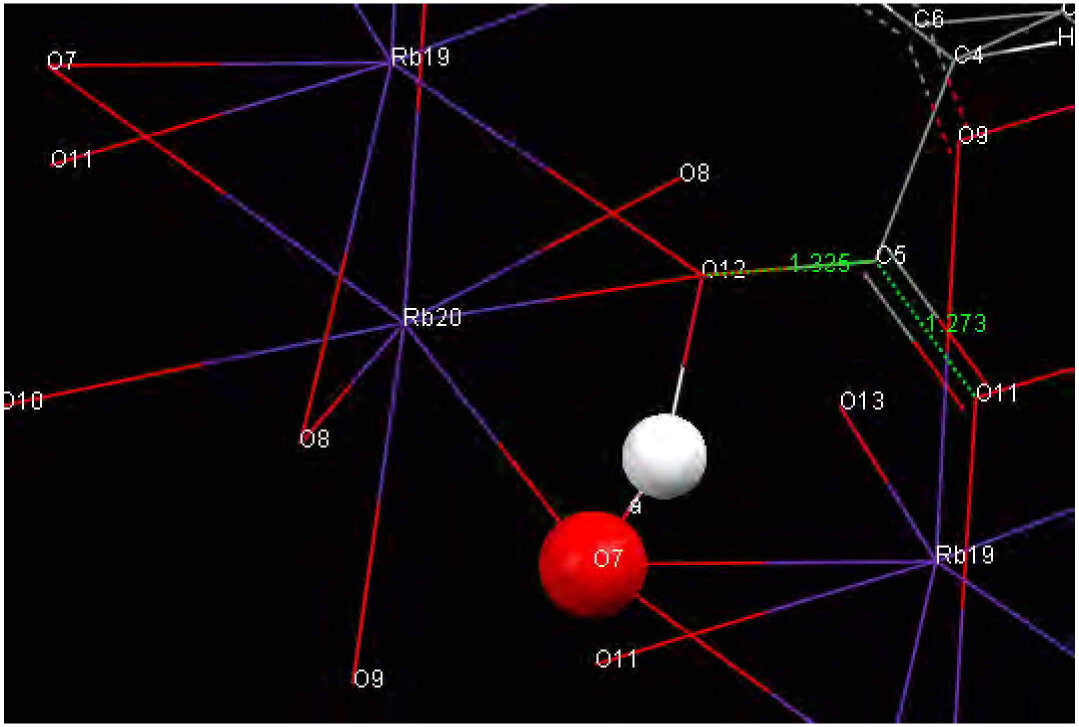


$Rb_2H_1C_6H_5O_7$ Rietveld and DFT



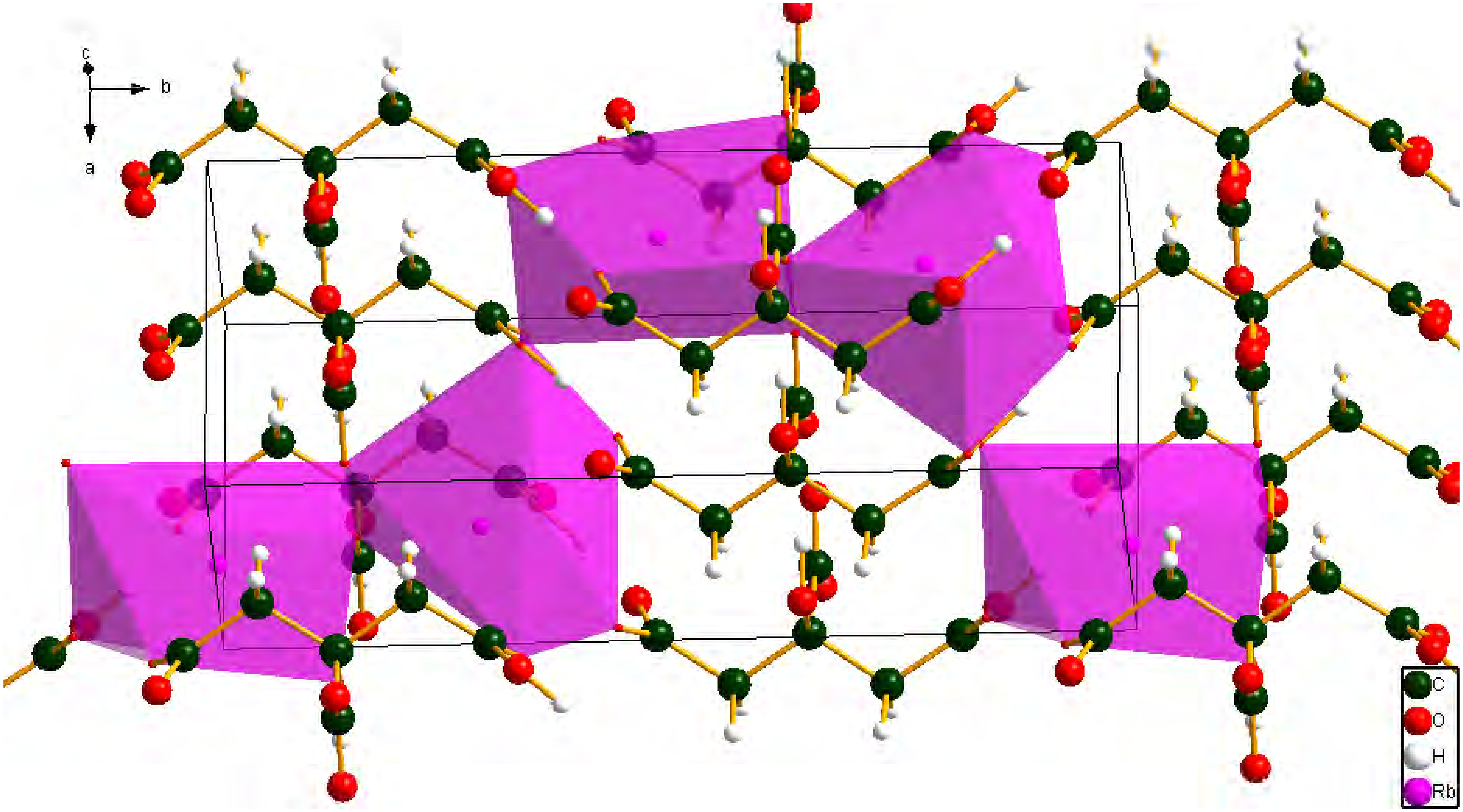
$Rb_2H_1C_6H_5O_7$ Hydrogen Bonds

RAMM020a	**D-H, Å**	**H···A, Å**	**D··A, Å**	**D-H··A, °**	**Overlap, *e***
O7-H21···O12	1.093	1.362	2.222	158.4	0.114
O13-H16··O9	0.978	2.001	2.677	119.9	0.046
O13-H16··O10	0.978	2.304	3.067	145.1	0.027



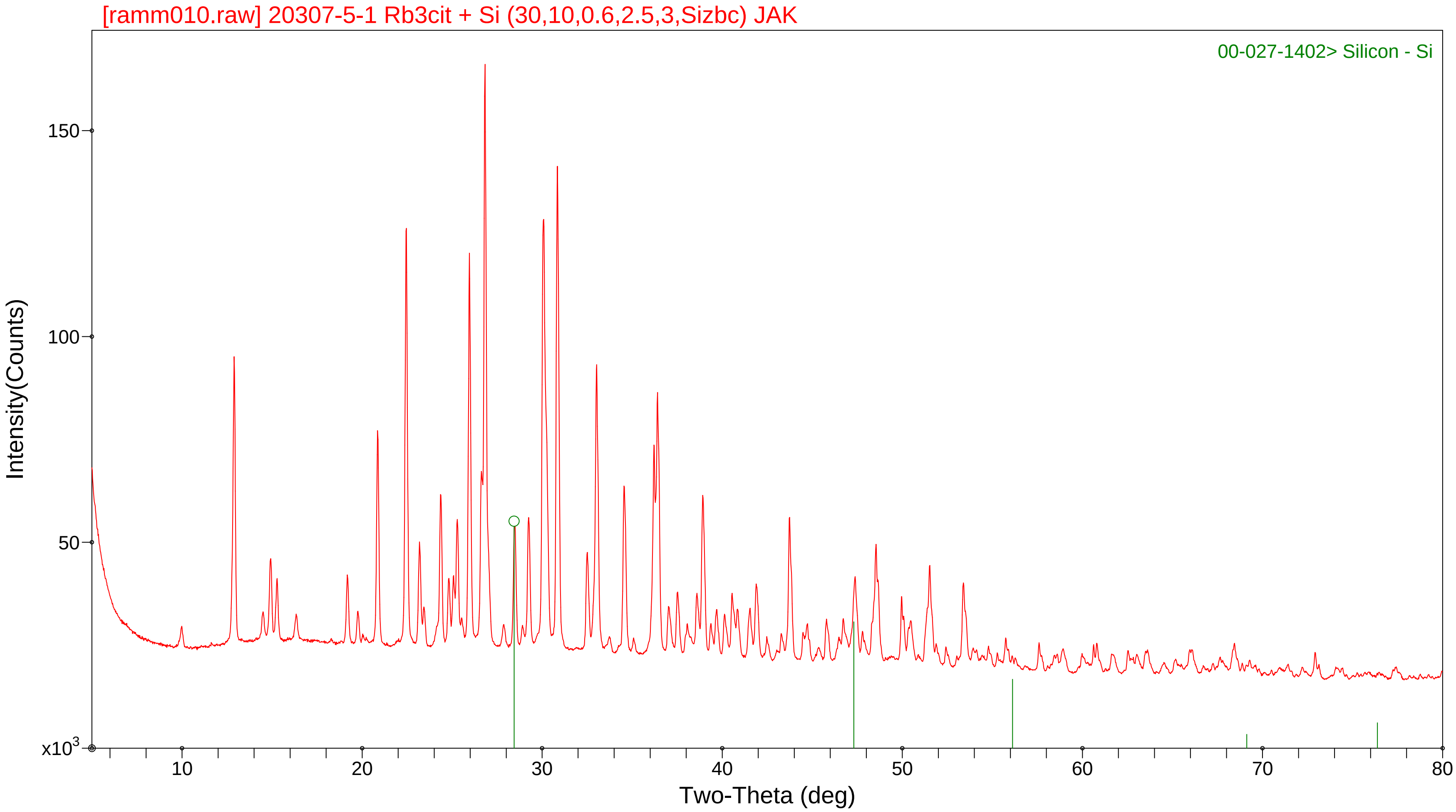
R1,1(4)

$Rb_2H_1C_6H_5O_7$ Rb Coordination



Rb19(7) BVS = 1.02, Rb20(8) BVS = 1.16

$Rb_3(C_6H_5O_7)(H_2O)$

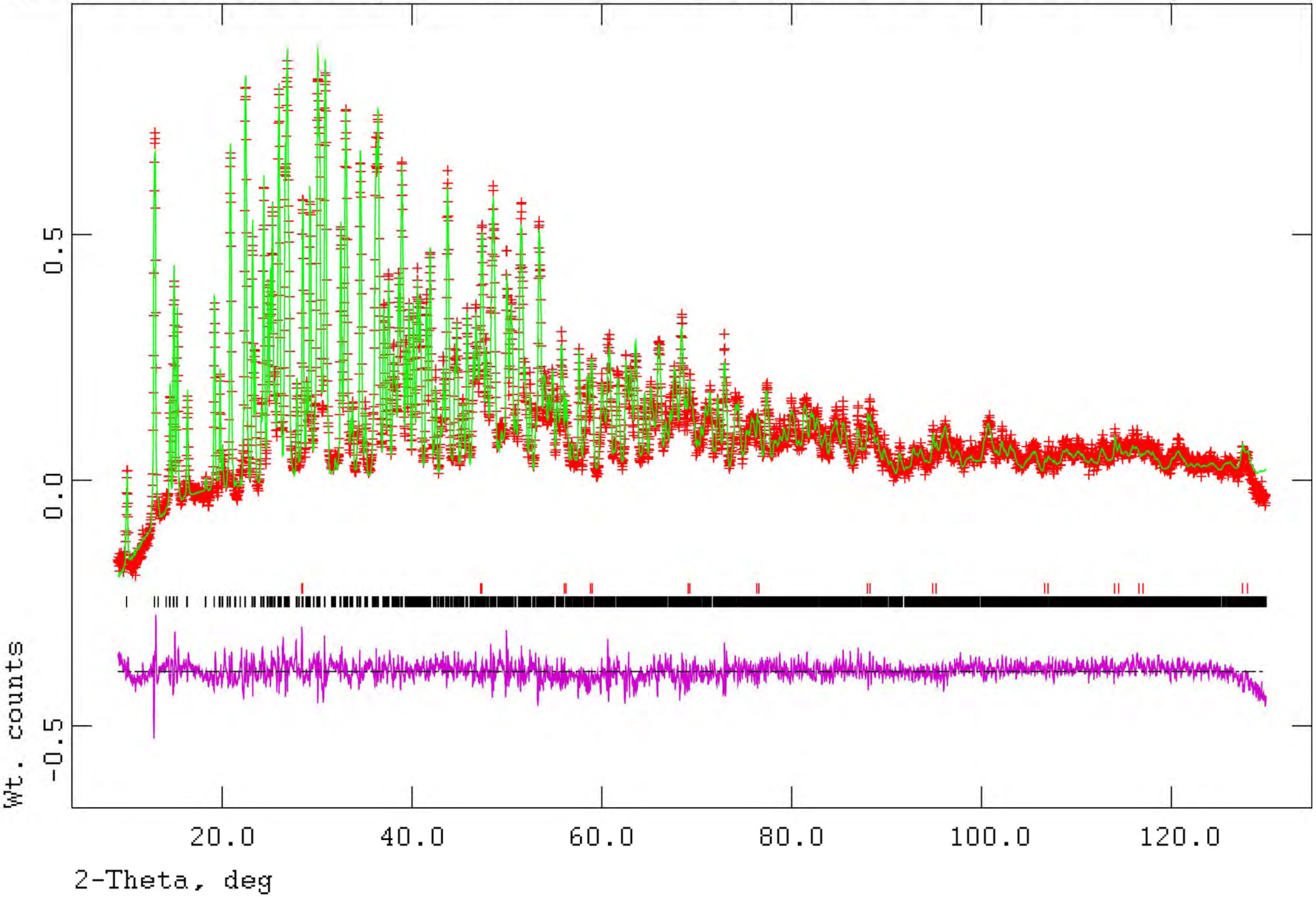

[ramm010.raw] 20307-5-1 Rb3cit + Si (30,10,0.6,2.5,3,Sizbc) JAK
00-027-1402> Silicon - Si
Intensity(Counts)
150
100
50
$x10^3$
10
20
30
40
50
60
70
80
Two-Theta (deg)

$Rb_3(C_6H_5O_7)(H_2O)$ Crystal Data

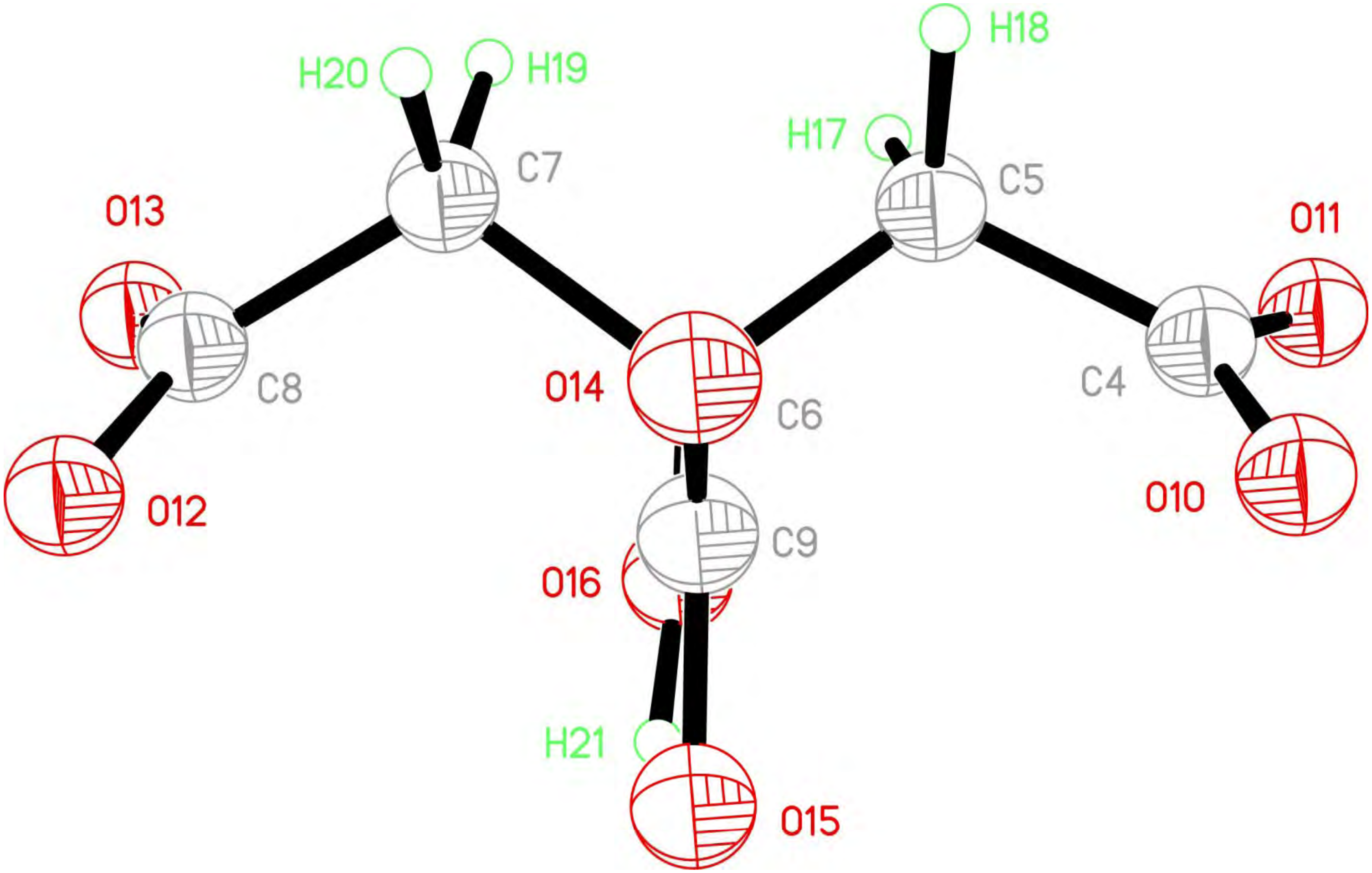
- $P2_1/n$, $Z = 4$
- $a = 7.44769(10)$
- $b = 11.87554(16)$
- $c = 13.41675(18)$
- $\beta = 97.8820(9)$
- $V = 1175.44(3)$ (17.3 Å^3/non-H)

20307-5-1, Rb3 (C6 H5 O7) (H2 O) (RAMM010)   Hist   1

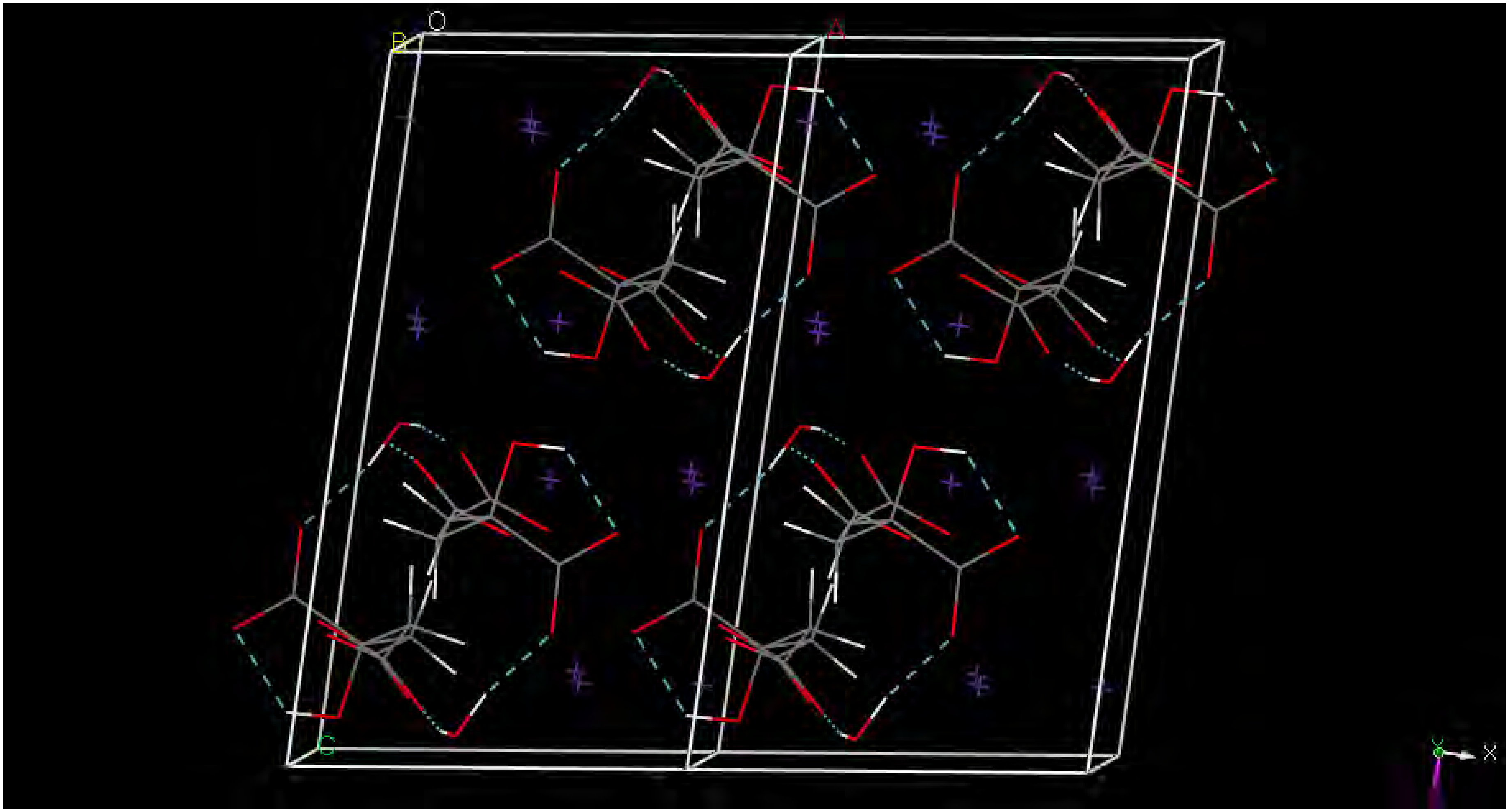
Lambda 1.5406 A, L-S cycle 492   Obsd. and Diff. Wt. Prf.



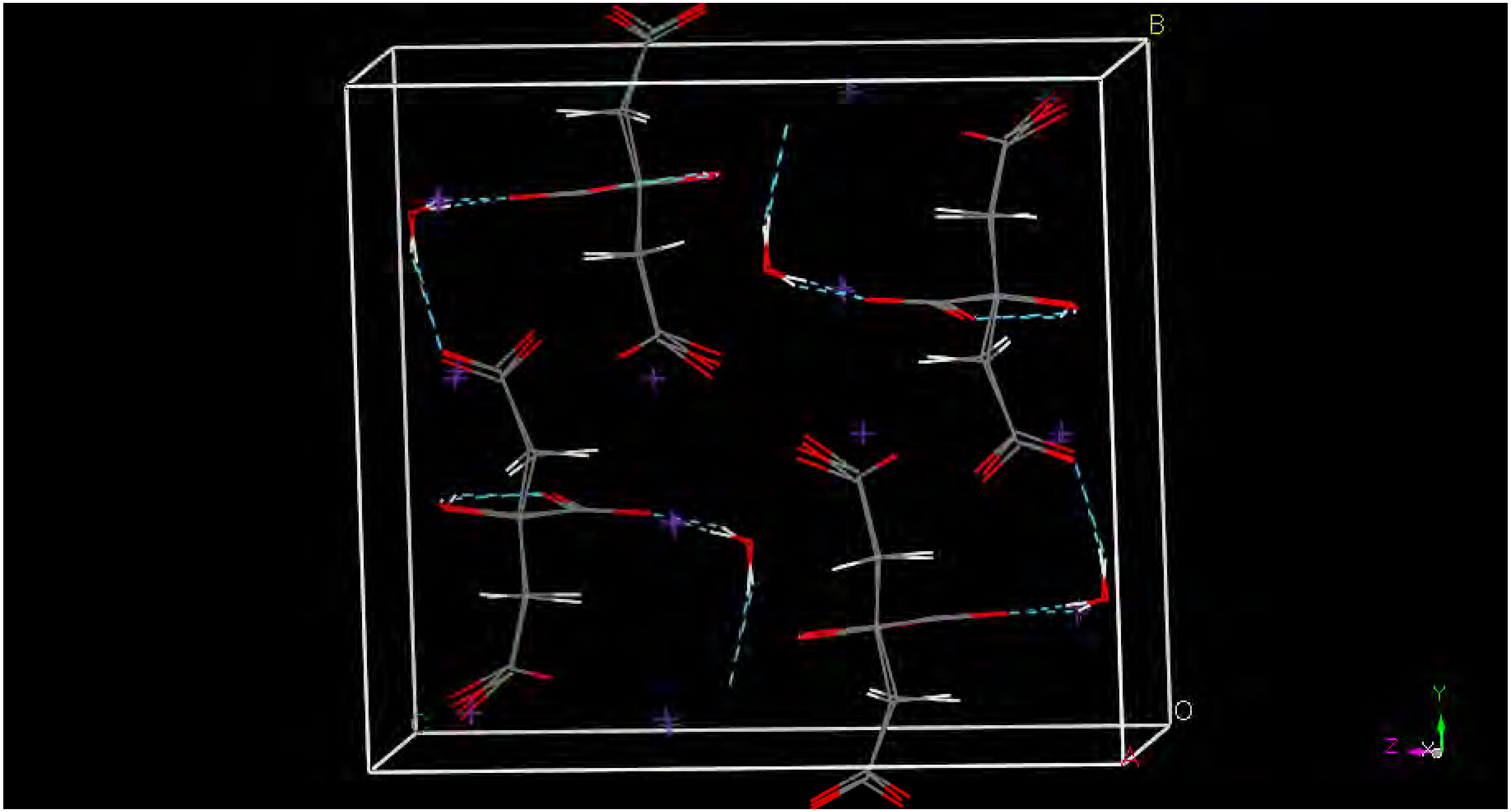
$Rb_3(C_6H_5O_7)(H_2O)$ Citrate Anion



$Rb_3(C_6H_5O_7)(H_2O)$ Crystal Structure



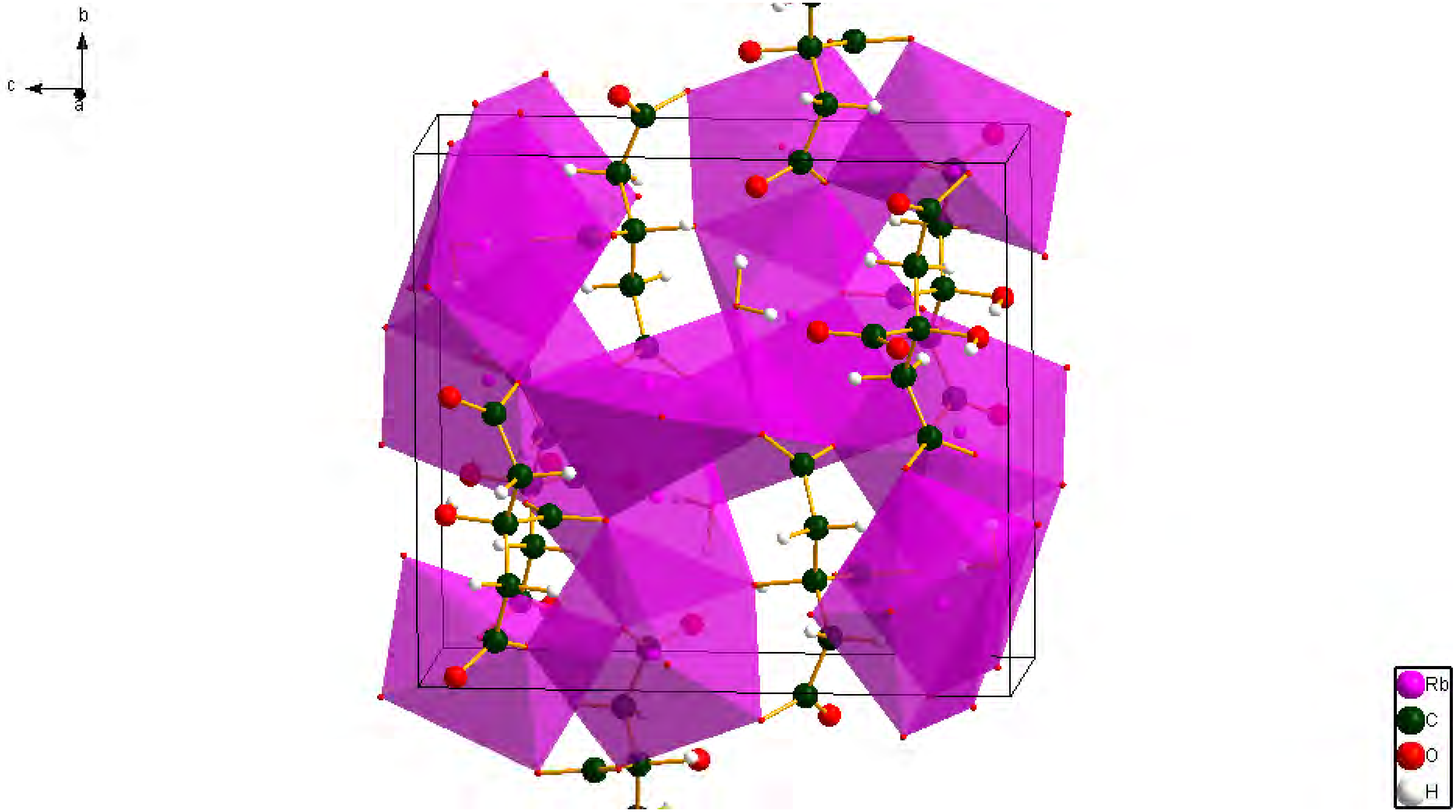
$Rb_3(C_6H_5O_7)(H_2O)$ Rietveld and DFT



$Rb_3(C_6H_5O_7)(H_2O)$ Hydrogen Bonds

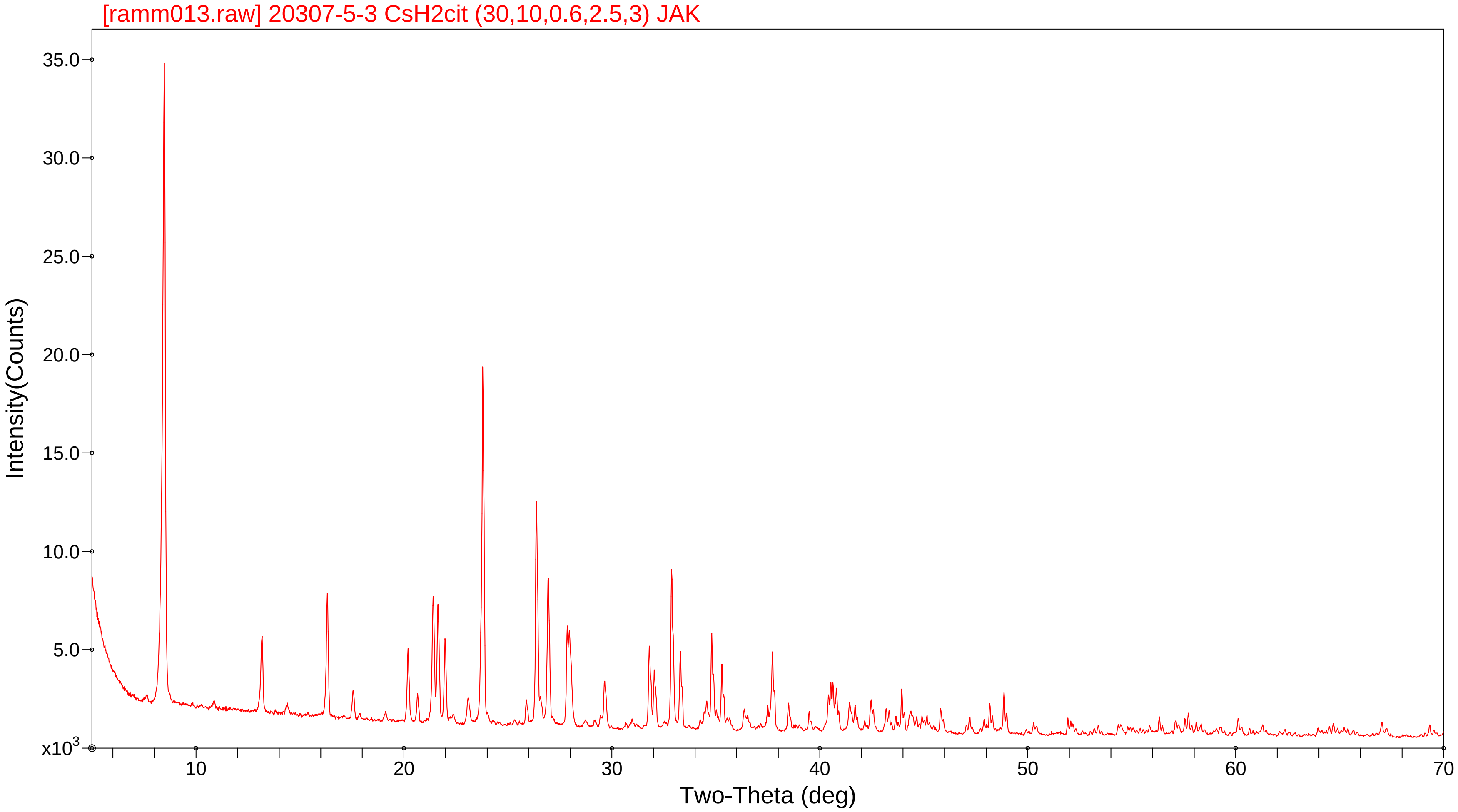
RAMM010	**D-H, Å**	**H···A, Å**	**D··A, Å**	**D-H··A, °**	**Overlap, *e***
O16-H21··O15	0.984	1.838	2.552	126.9	0.064
O22-H23··O14	0.983	1.704	2.672	168.7	0.066
O22-H24··O13	0.984	1.707	2.683	170.8	0.064
C5-H17··O22	1.093	2.674	3.749	167.4	0.023

$Rb_3(C_6H_5O_7)(H_2O)$ Rb Coordination



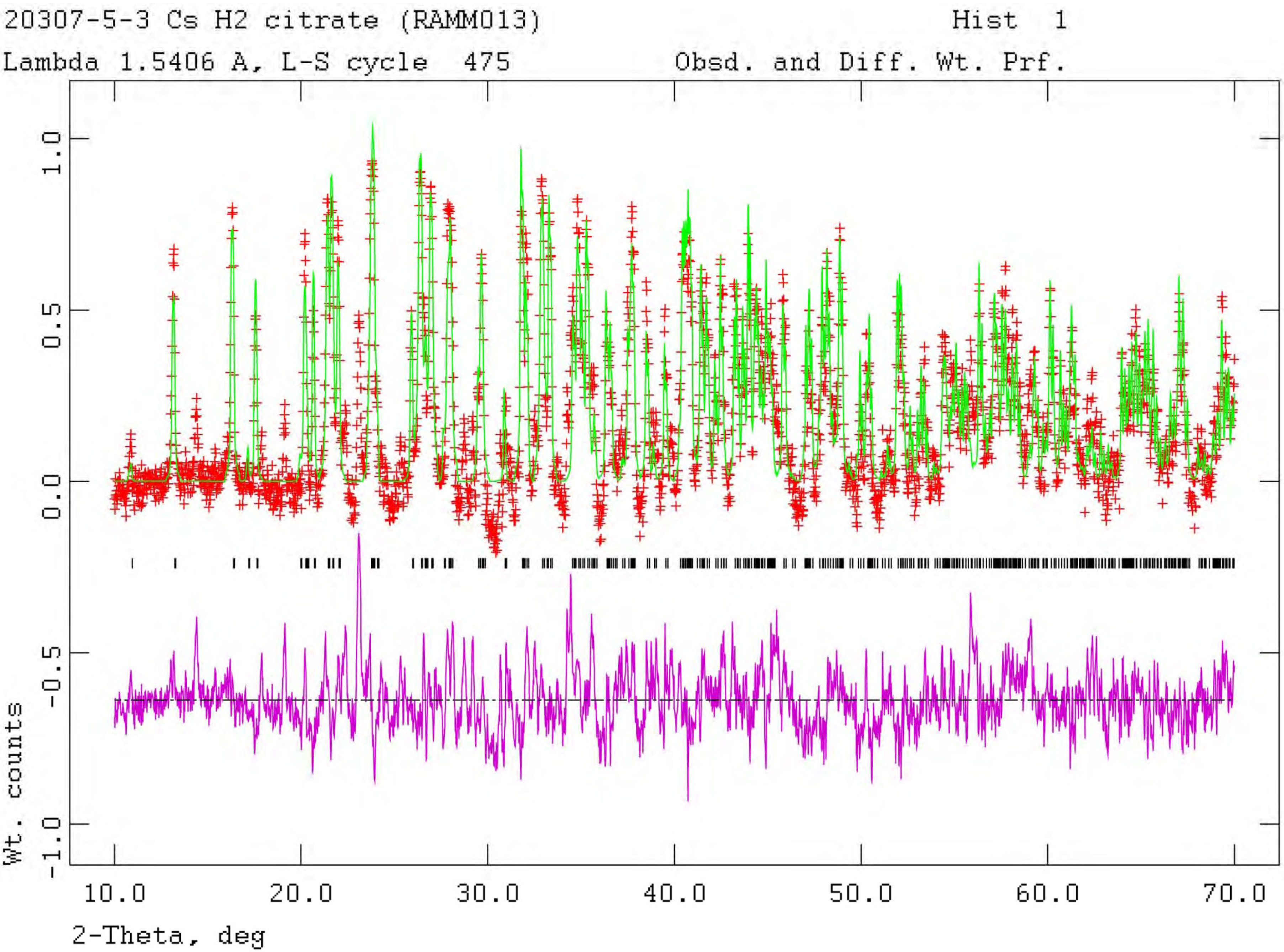
Rb1(7) BVS = 0.84, Rb2(6) BVS = 1.02, Rb3(7) BVS = 1.11

$Cs_1H_2C_6H_5O_7$

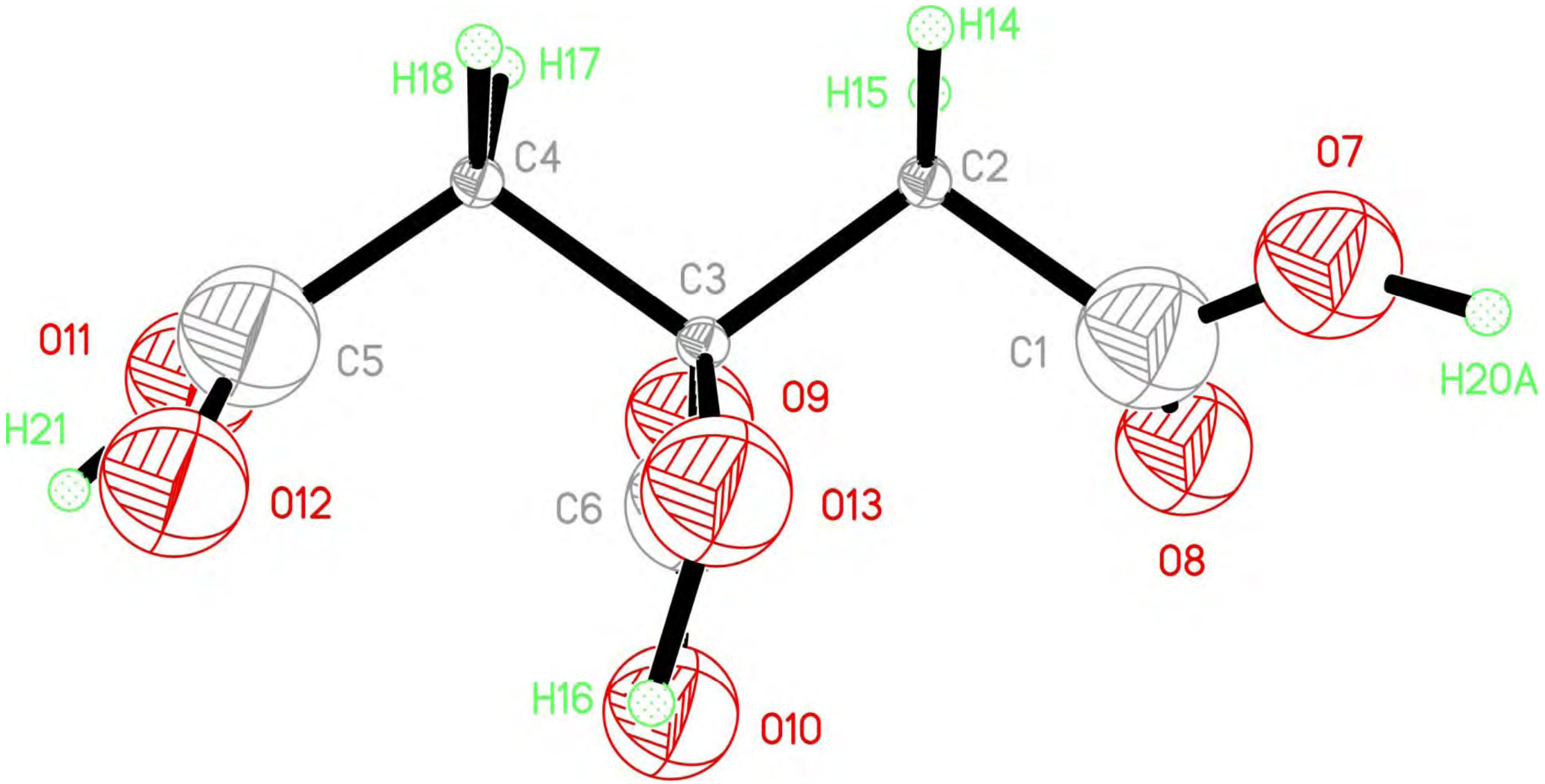

[ramm013.raw] 20307-5-3 CsH2cit (30,10,0.6,2.5,3) JAK
Intensity(Counts)
35.0
30.0
25.0
20.0
15.0
10.0
5.0
x10^3
10
20
30
40
50
60
70
Two-Theta (deg)

$Cs_1H_2C_6H_5O_7$ Crystal Data

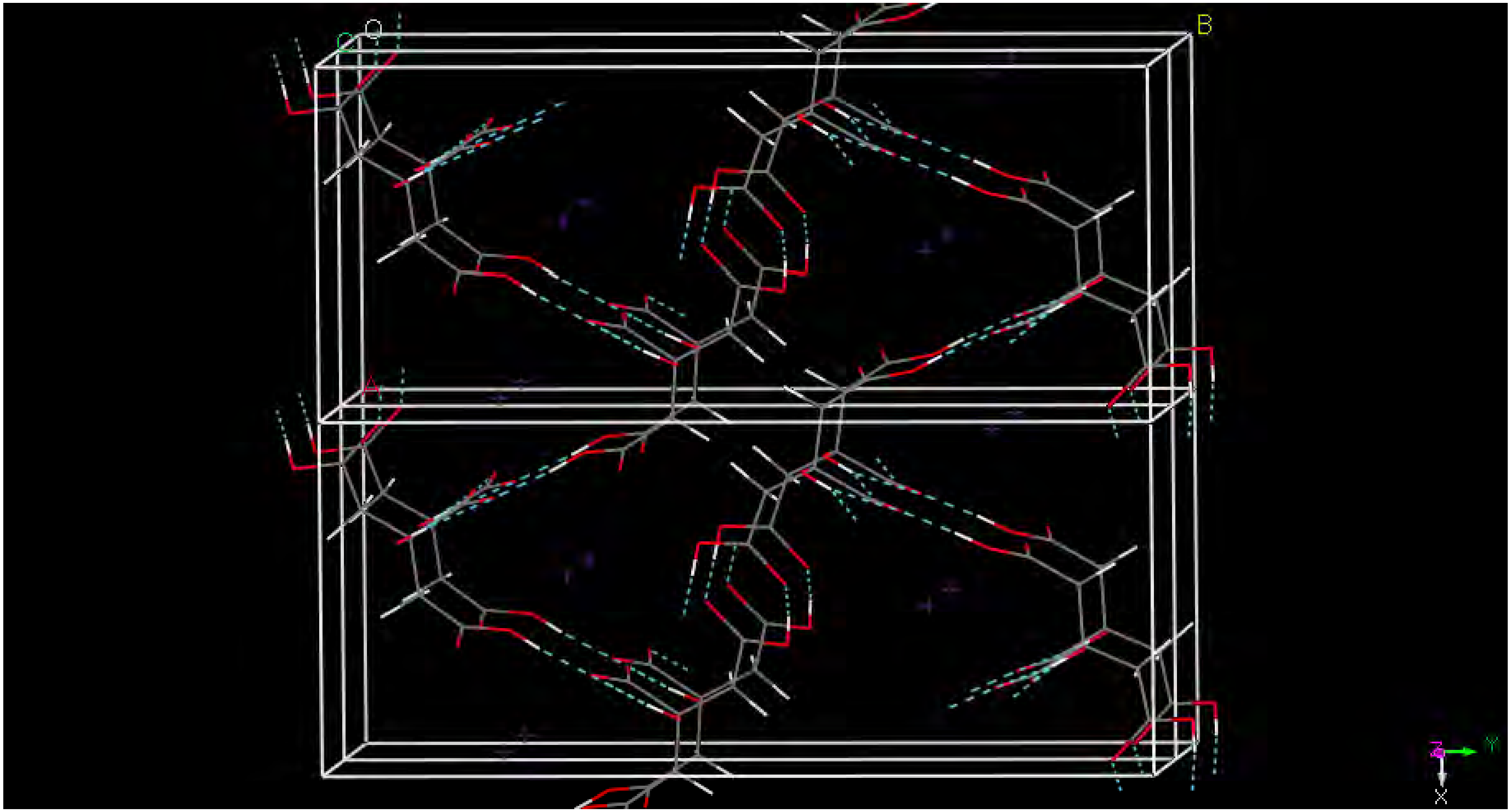
- $Pna2_1$, $Z = 4$
- $a = 8.7362(2)$
- $b = 20.5351(2)$
- $c = 5.1682(5)$
- $V = 927.17(9)$ (16.6 Å^3/non-H)


20307-5-3 Cs H2 citrate (RAMM013)
Hist 1
Lambda 1.5406 A, L-S cycle 475
Obsd. and Diff. Wt. Prf.
1.0
0.5
0.0
-0.5
-1.0
Wt. counts
10.0
20.0
30.0
40.0
50.0
60.0
70.0
2-Theta, deg

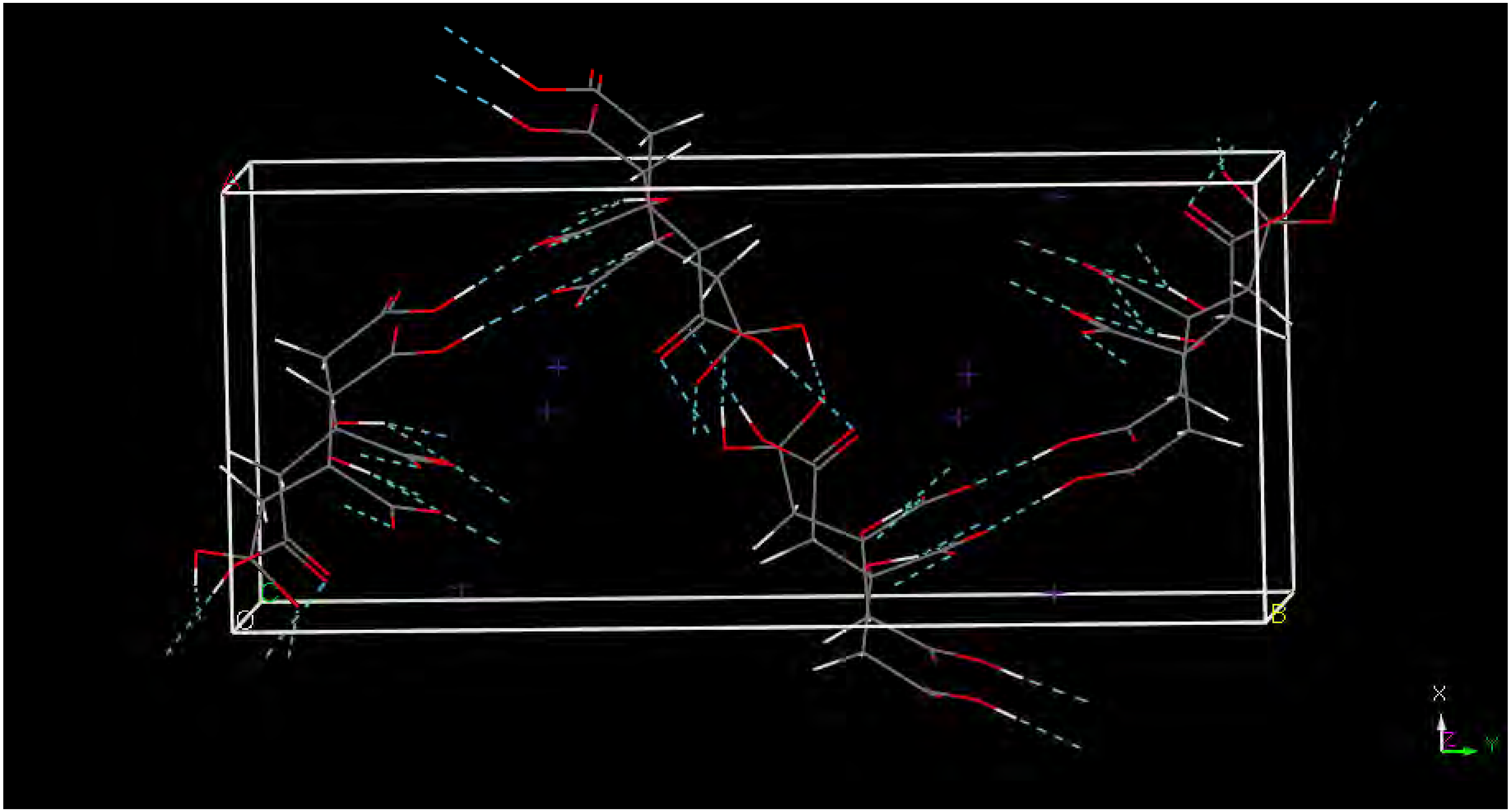
$Cs_1H_2C_6H_5O_7$ Citrate Anion



$Cs_1H_2C_6H_5O_7$ Crystal Structure



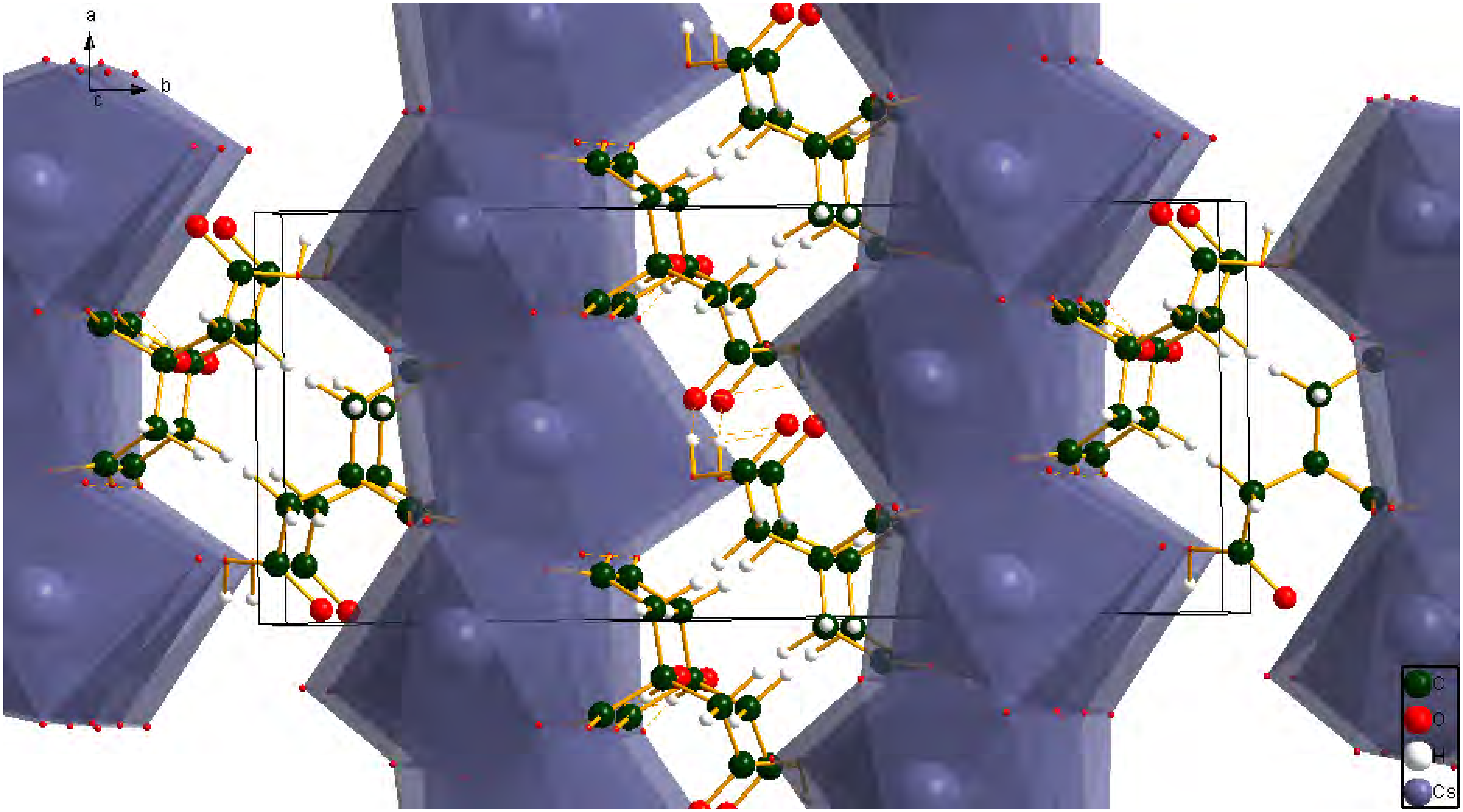
$Cs_1H_2C_6H_5O_7$ Rietveld and DFT



$Cs_1H_2C_6H_5O_7$ Hydrogen Bonds

	D-H, Å	**H···A, Å**	**D···A, Å**	**D-H···A, °**	**Overlap, *e***
O13-H16···O9	0.979	1.985	2.865	148.4	0.042
O13-H16···O10	0.979	2.149	2.691	113.3	0.028
O7-H20···O8	0.996	1.674	2.637	161.7	0.064
O11-H21···O10	1.028	1.575	2.600	174.4	0.095

$Cs_1H_2C_6H_5O_7$ Cs Coordination

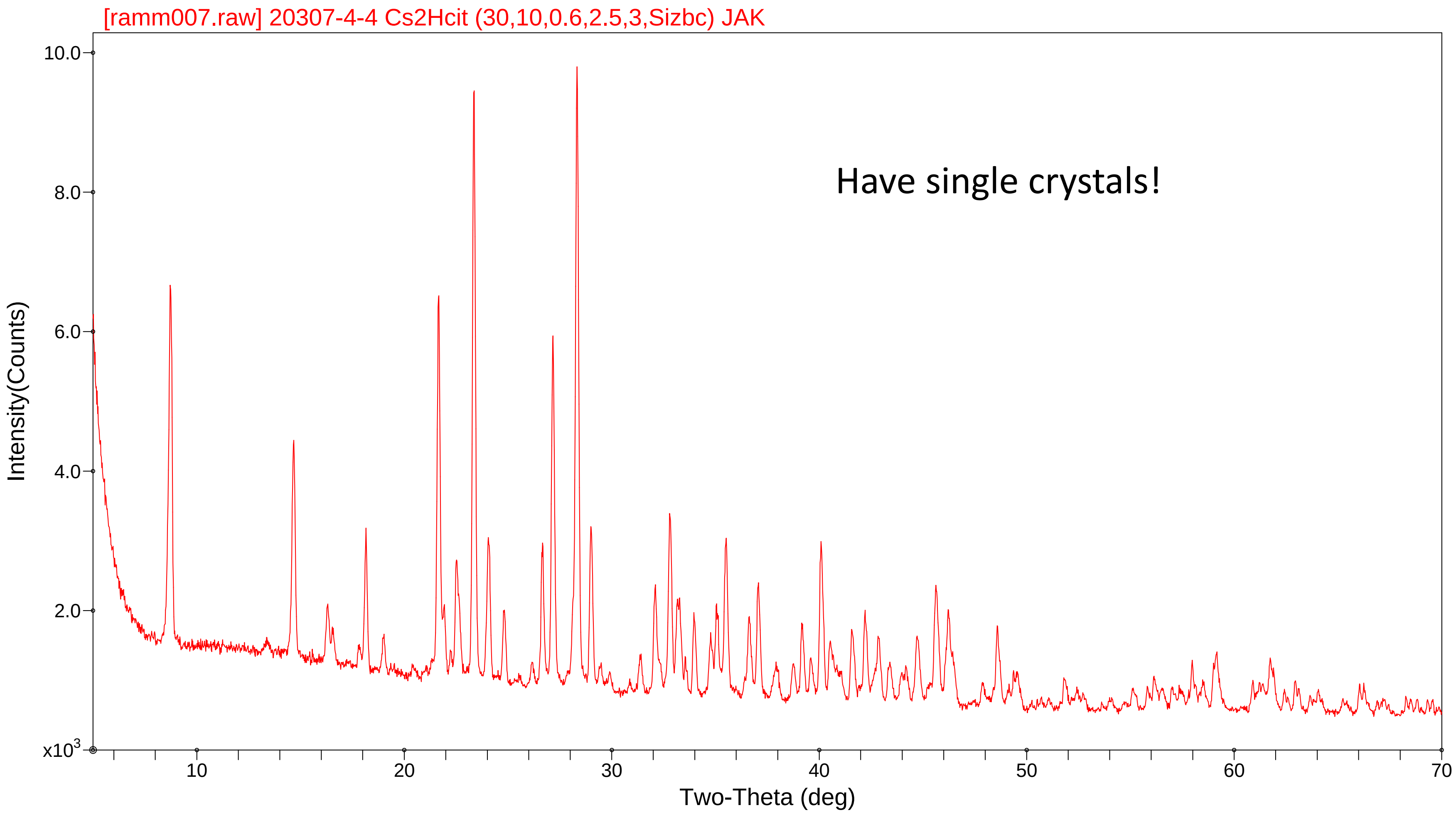


Cs19(9) BVS = 0.96

$Cs_2H_1C_6H_5O_7$

Amy Sarjeant

Northwestern



Have single crystals!

$Cs_2H_1C_6H_5O_7$ Crystal Data

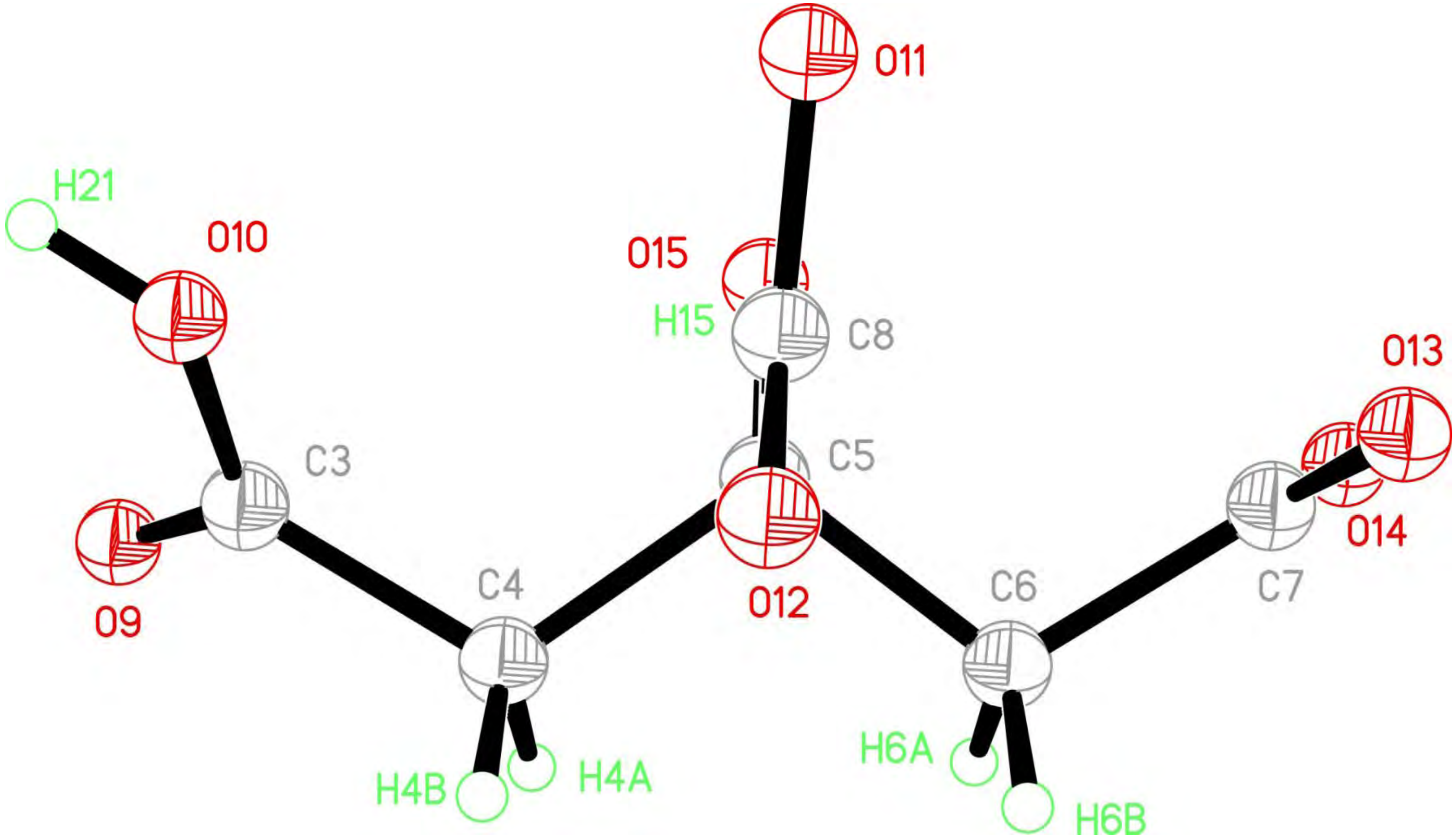
100K (single crystal)

- $P2_12_12_1$, $Z = 4$
- $a = 6.5435(2)$
- $b = 9.7653(3)$
- $c = 15.8501(4)$
- $V = 1012.81$

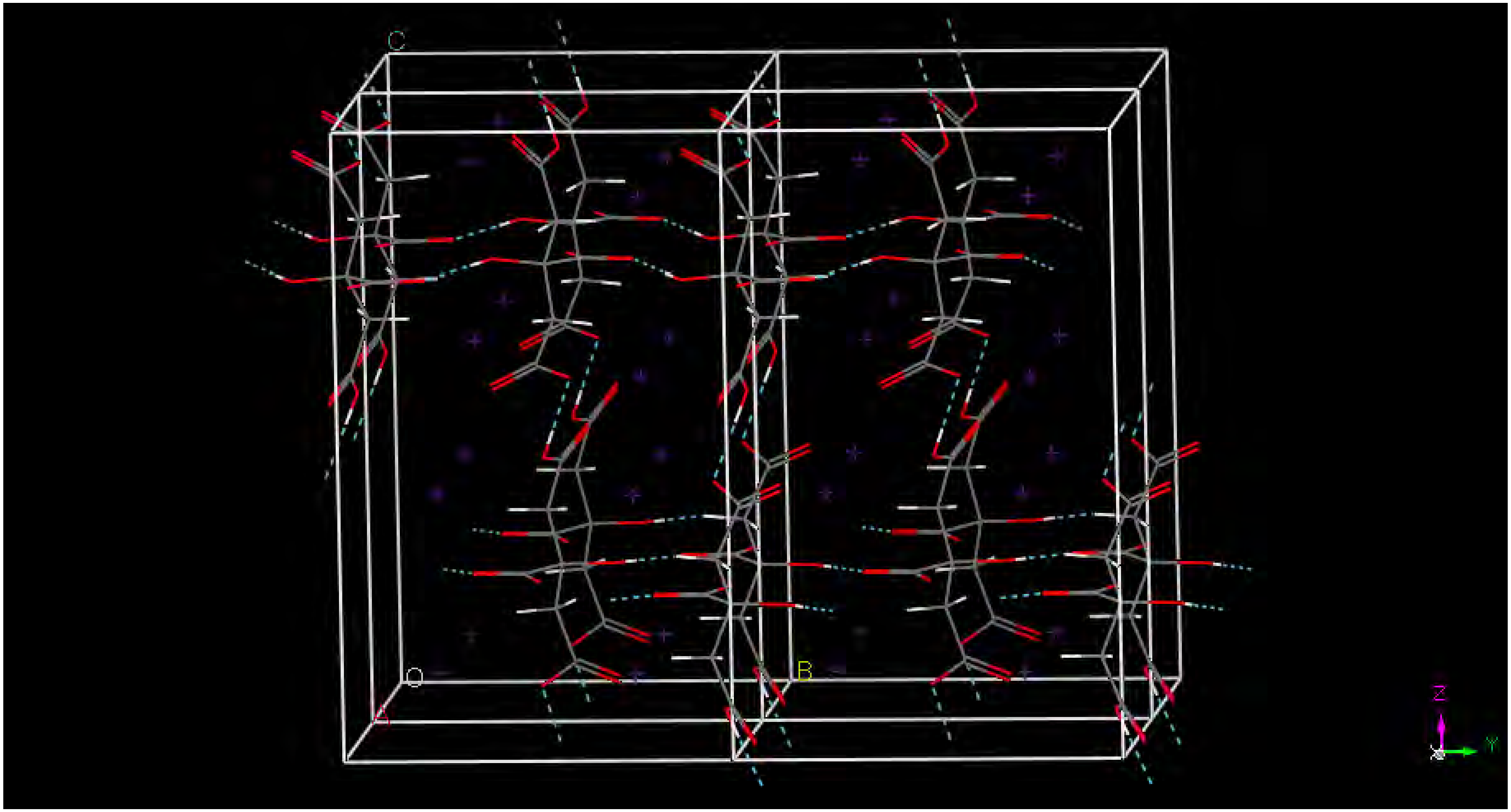
Ambient (powder)

- $P2_12_12_1$, $Z = 4$
- $a = 6.5967(3)$
- $b = 9.8460(5)$
- $c = 15.8864(7)$
- $V = 1031.84(8)$ (101.87%)
- (17.2 $Å^3$/non-H)

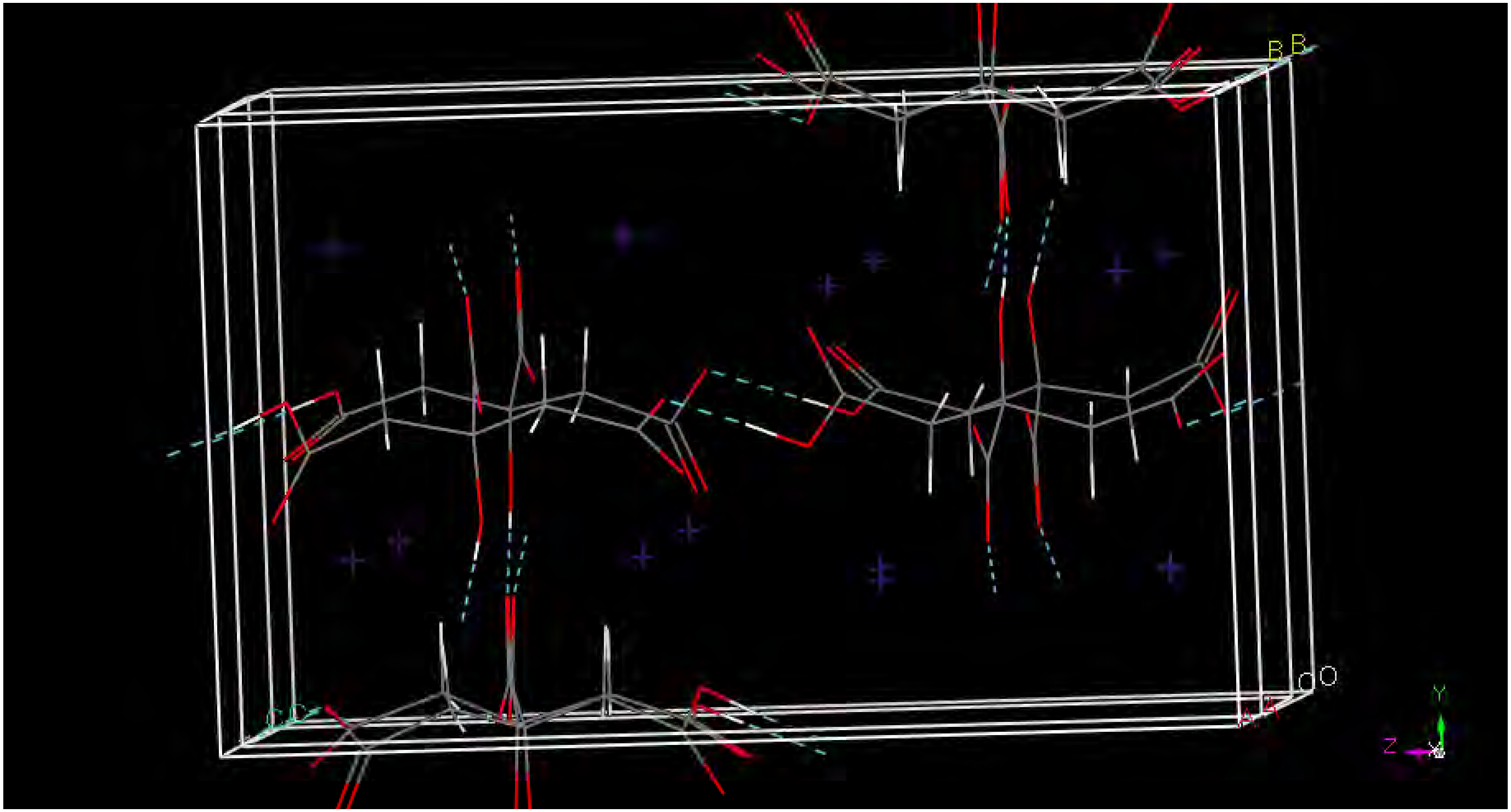
$Cs_2H_1C_6H_5O_7$ Citrate Anion



$Cs_2H_1C_6H_5O_7$ Crystal Structure



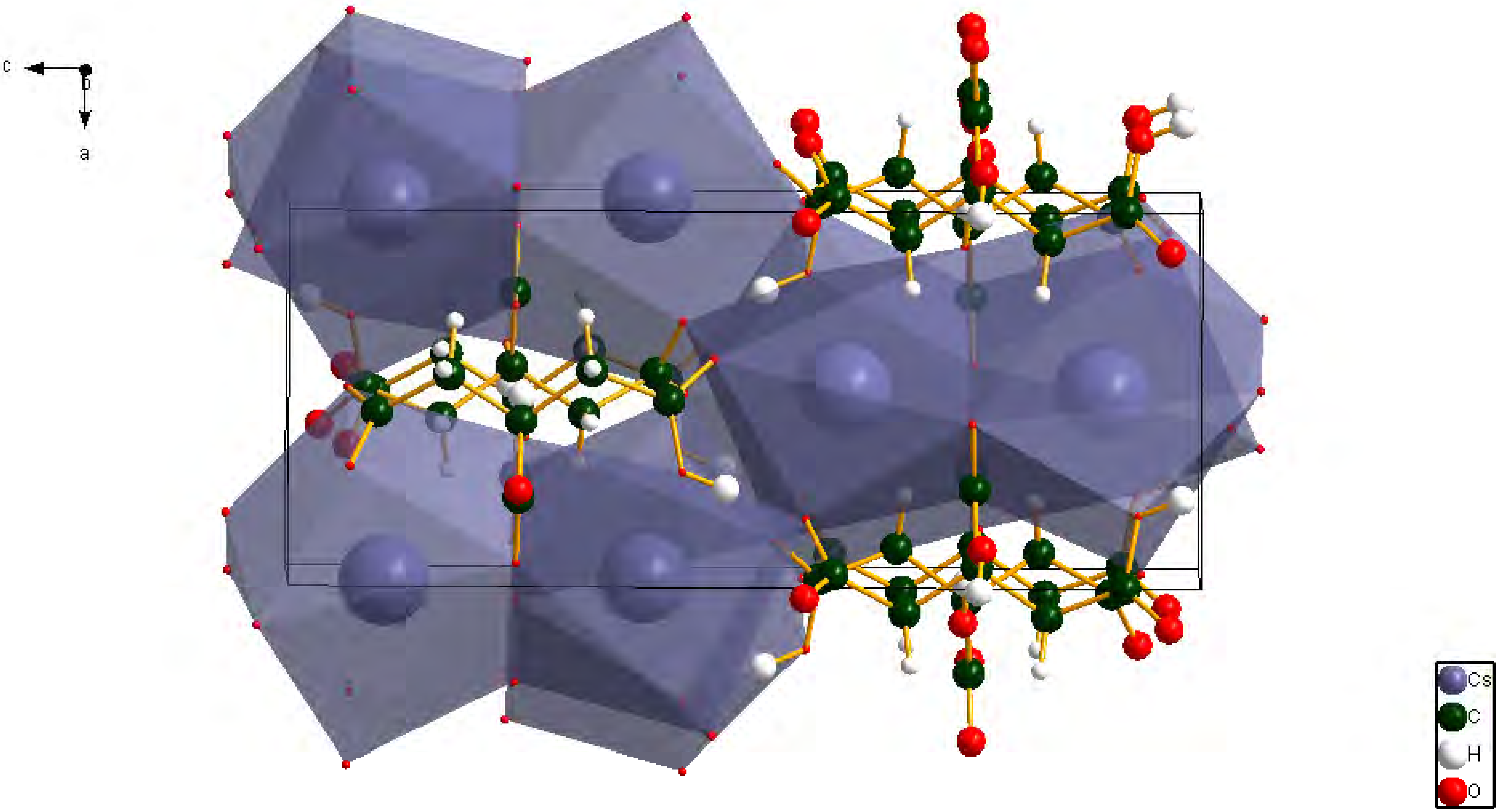
$Cs_2H_1C_6H_5O_7$ SC and DFT



$Cs_2H_1C_6H_5O_7$ Hydrogen Bonds

Cs2h1_0m	**D-H, Å**	**H···A, Å**	**D··A, Å**	**D-H··A, °**	**Overlap, *e***
O13-H21···O10	1.080	1.376	2.455	176.2	0.113
O15-H15···O12	1.003	1.601	2.603	175.9	0.081

$Cs_2H_1C_6H_5O_7$ Cs Coordination



Cs1(9) BVS = 1.02, Cs2(11) BVS = 1.01

$Cs_3C_6H_5O_7(H_2O)$

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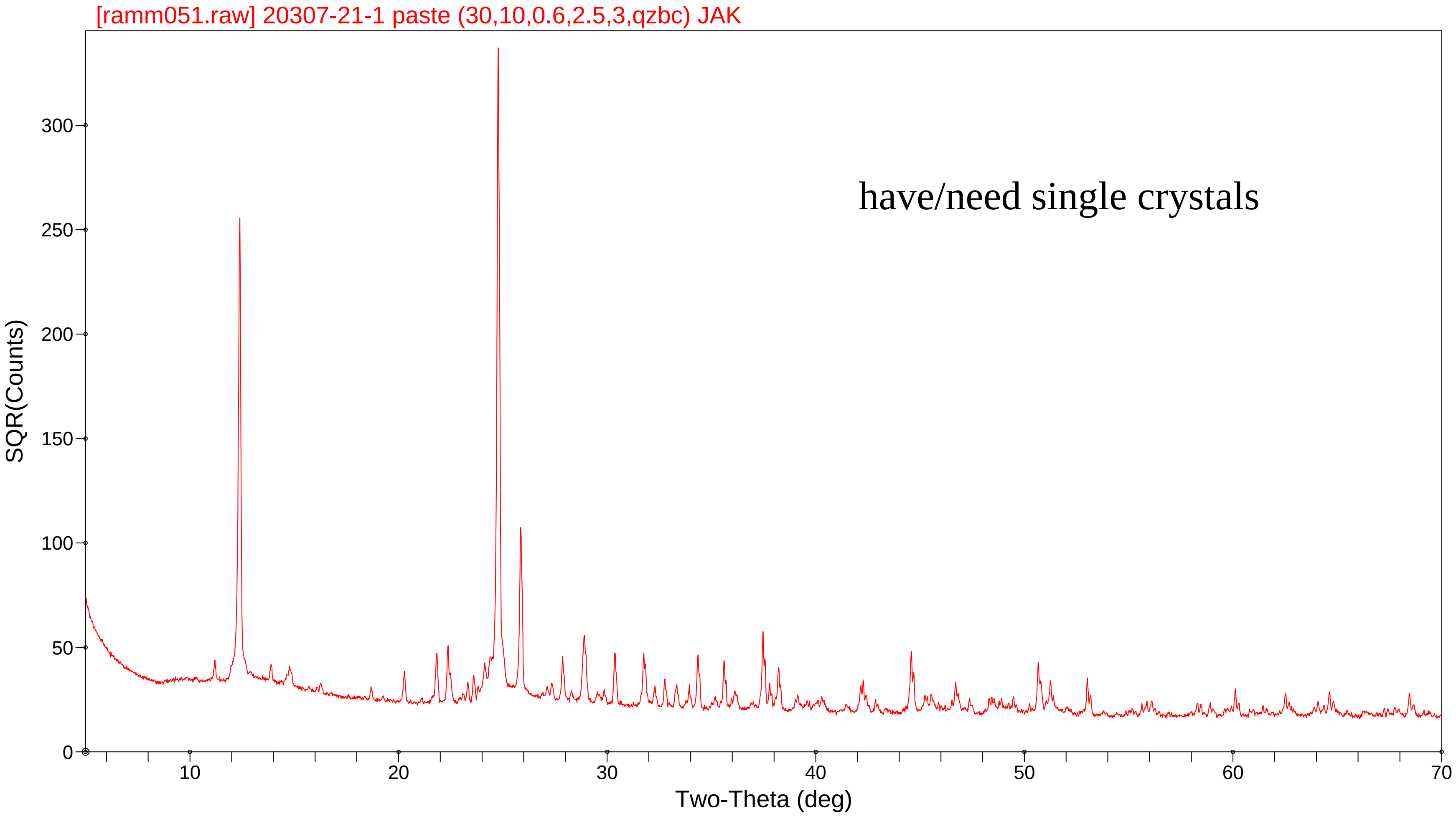


have/need single crystals

$Cs_3(C_6H_5O_7)(H_2O)$ Crystal Data

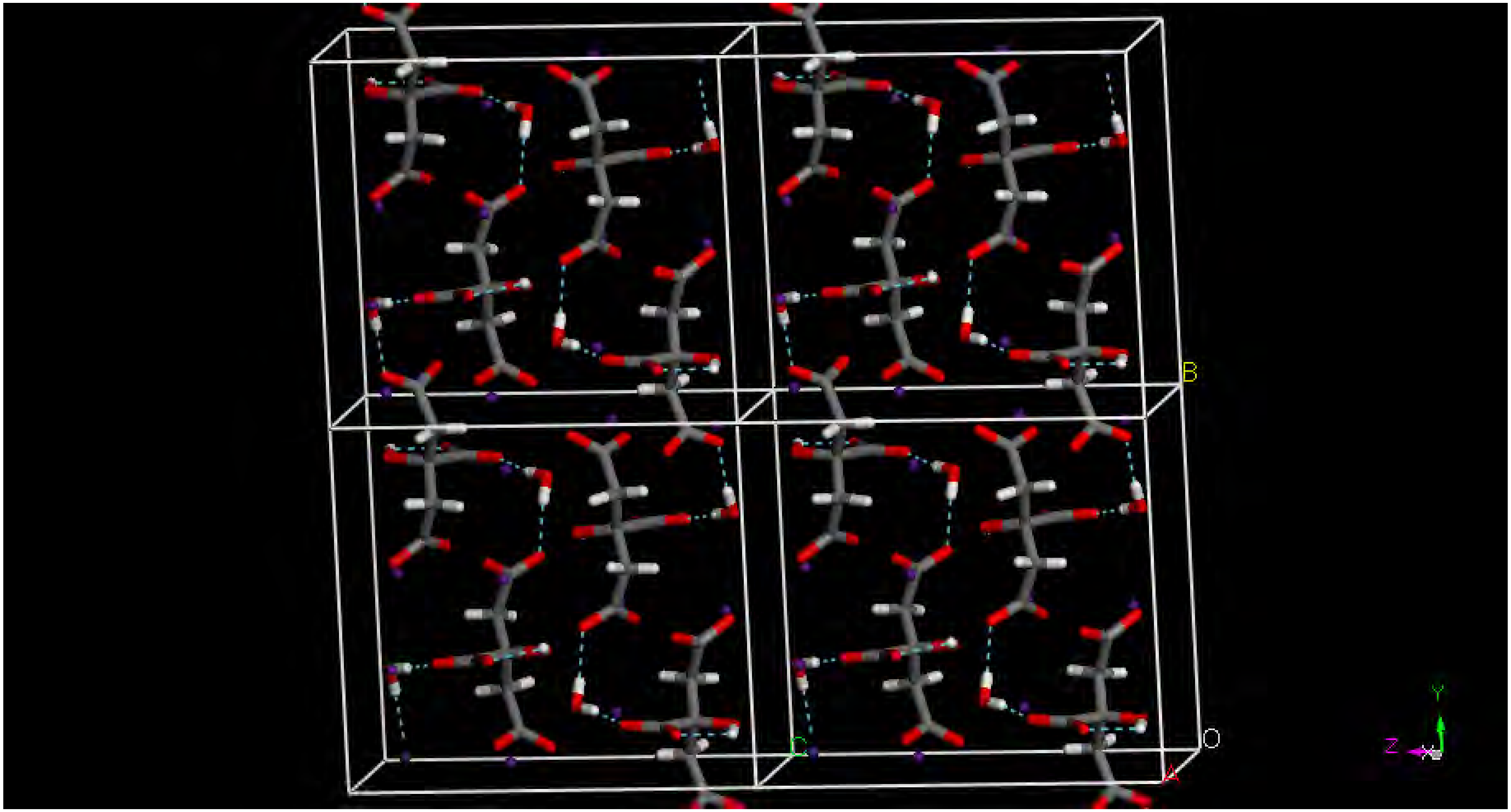
100K (single crystal)

- $P2_1/n$, $Z = 4$
- $a = 7.7529(3)$
- $b = 12.0281(4)$
- $c = 13.8043(5)$
- $\beta = 97.000(2)$
- $V = 1277.69(8)$

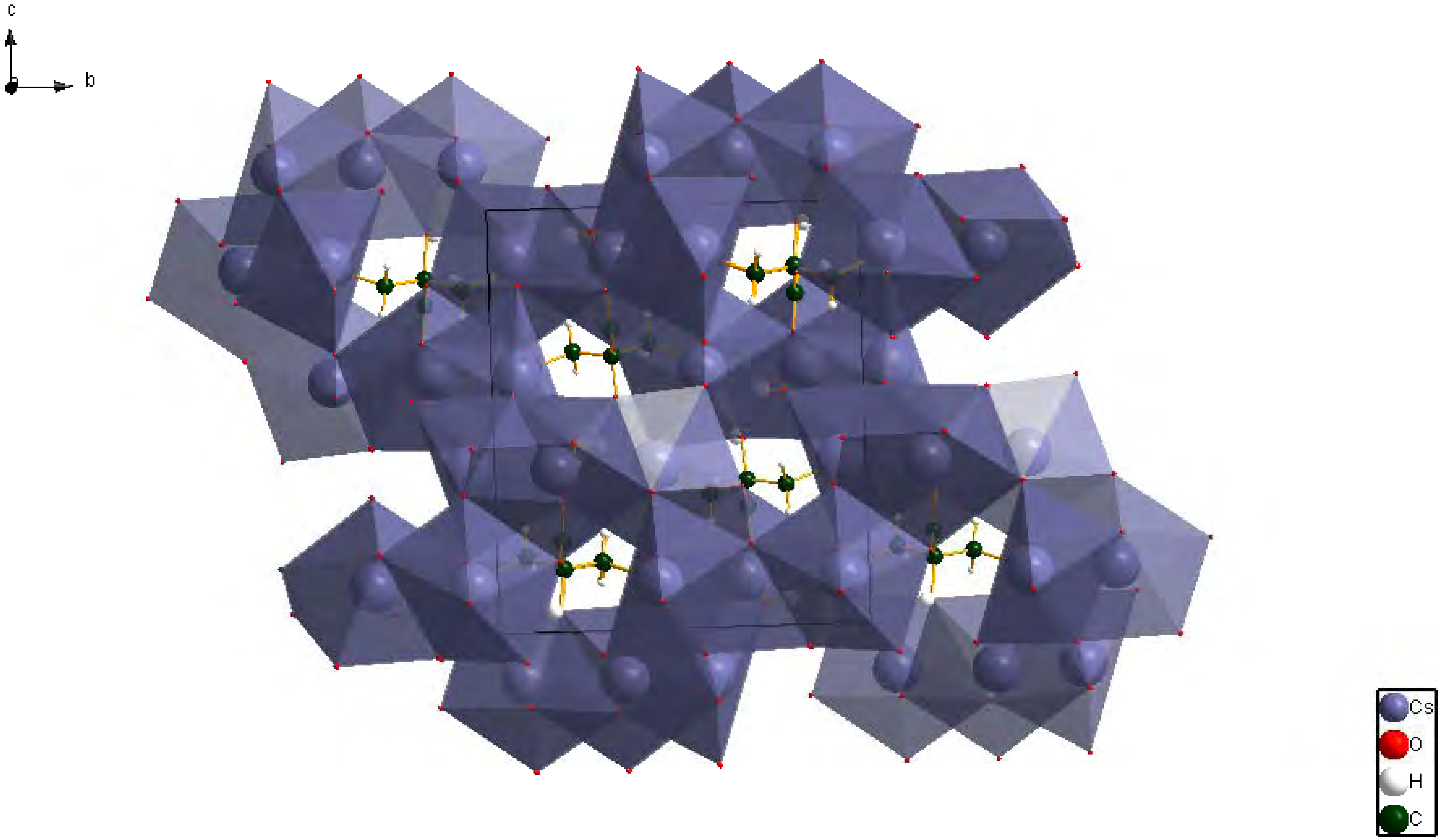
Ambient (powder)

- $P2_1/n$, $Z = 4$
- $a = 7.8851(4)$
- $b = 12.2109(8)$
- $c = 14.0367(8)$
- $\beta = 97.280(4)$
- $V = 1340.63(14)$ (104.9%) (19.7 Å^3/non-H)

$Cs_3(C_6H_5O_7)(H_2O)$



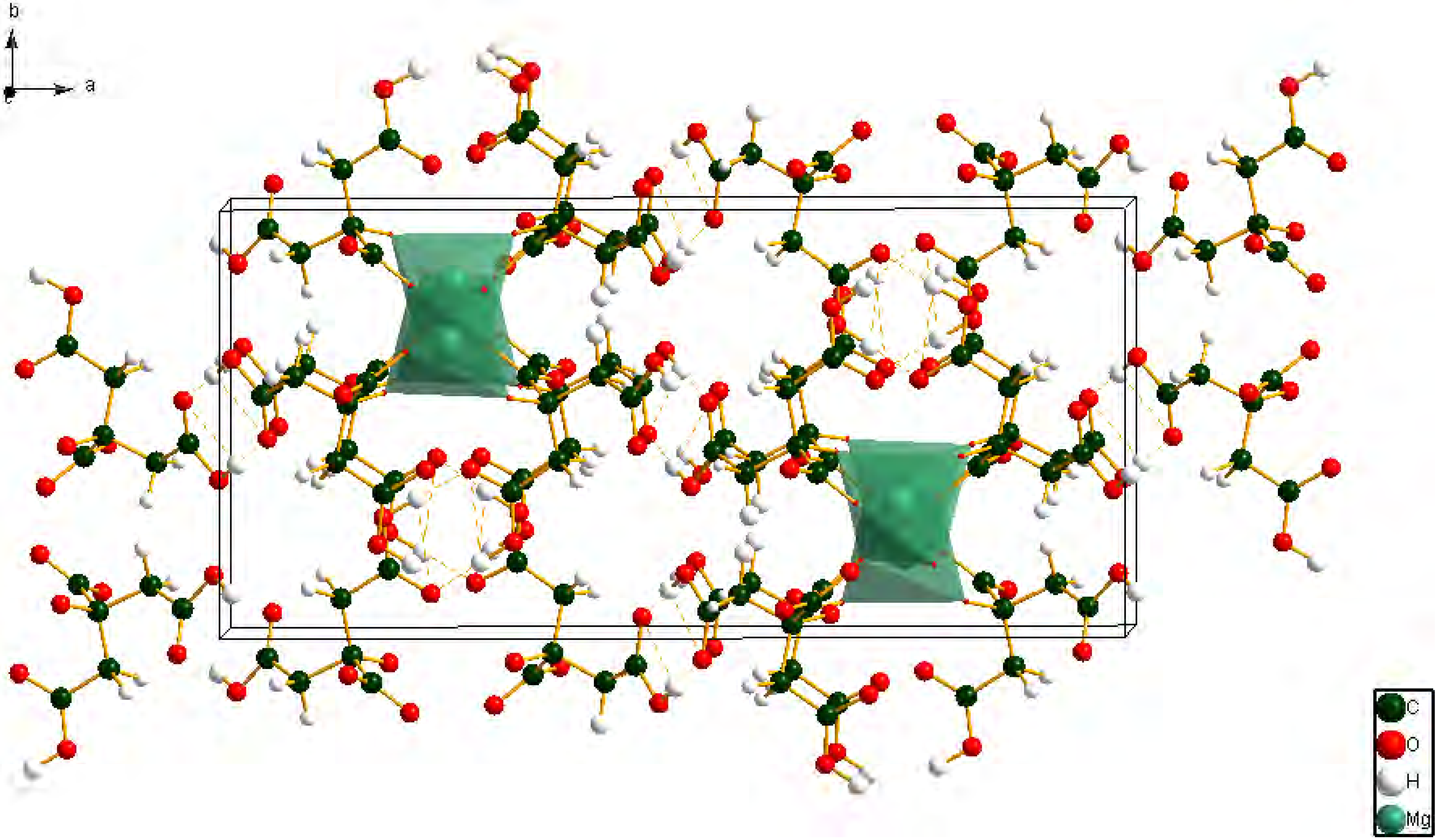
$Cs_3(C_6H_5O_7)(H_2O)$

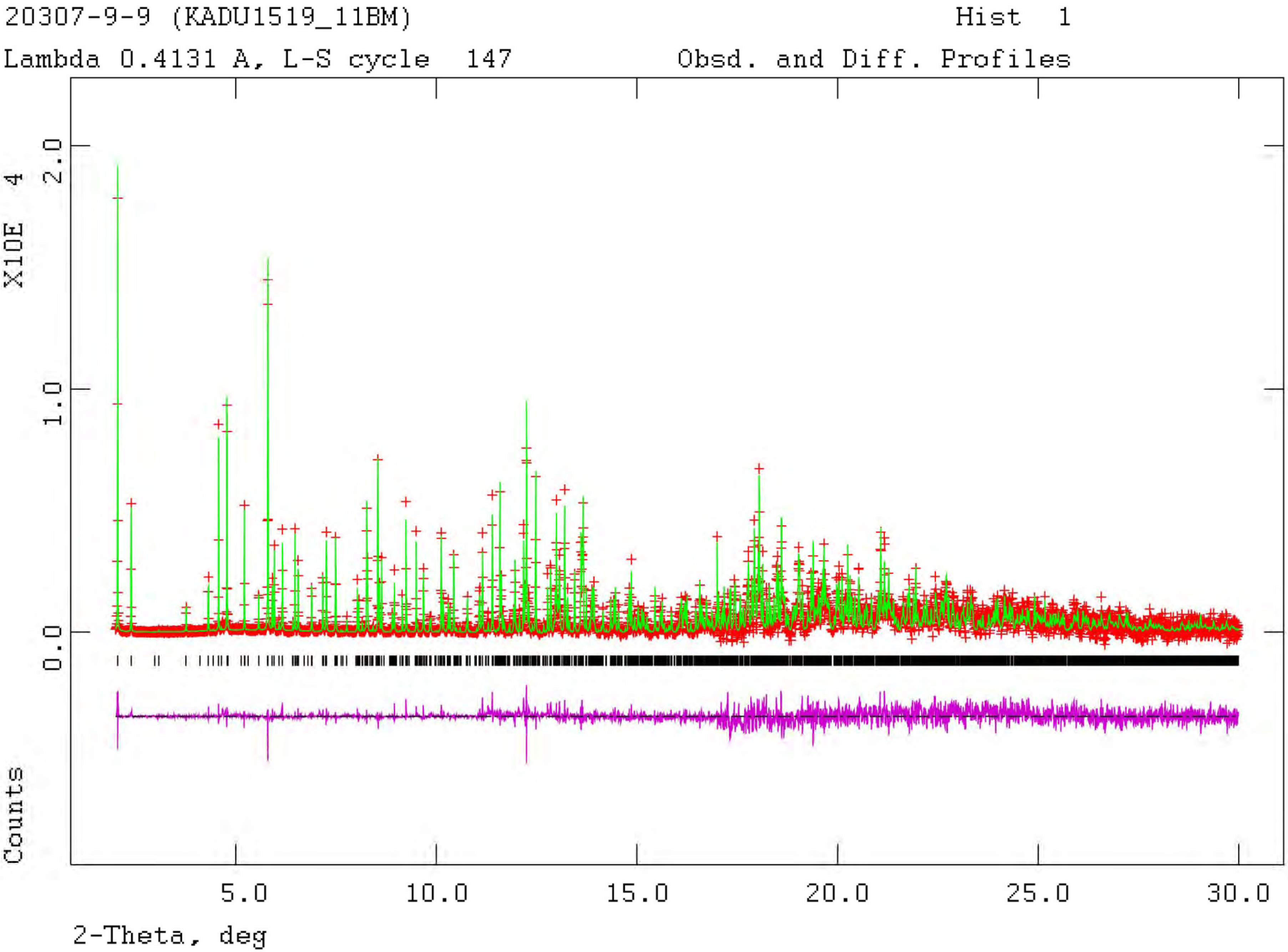


New Group 2 Citrates

11-BM mail-in
direct methods

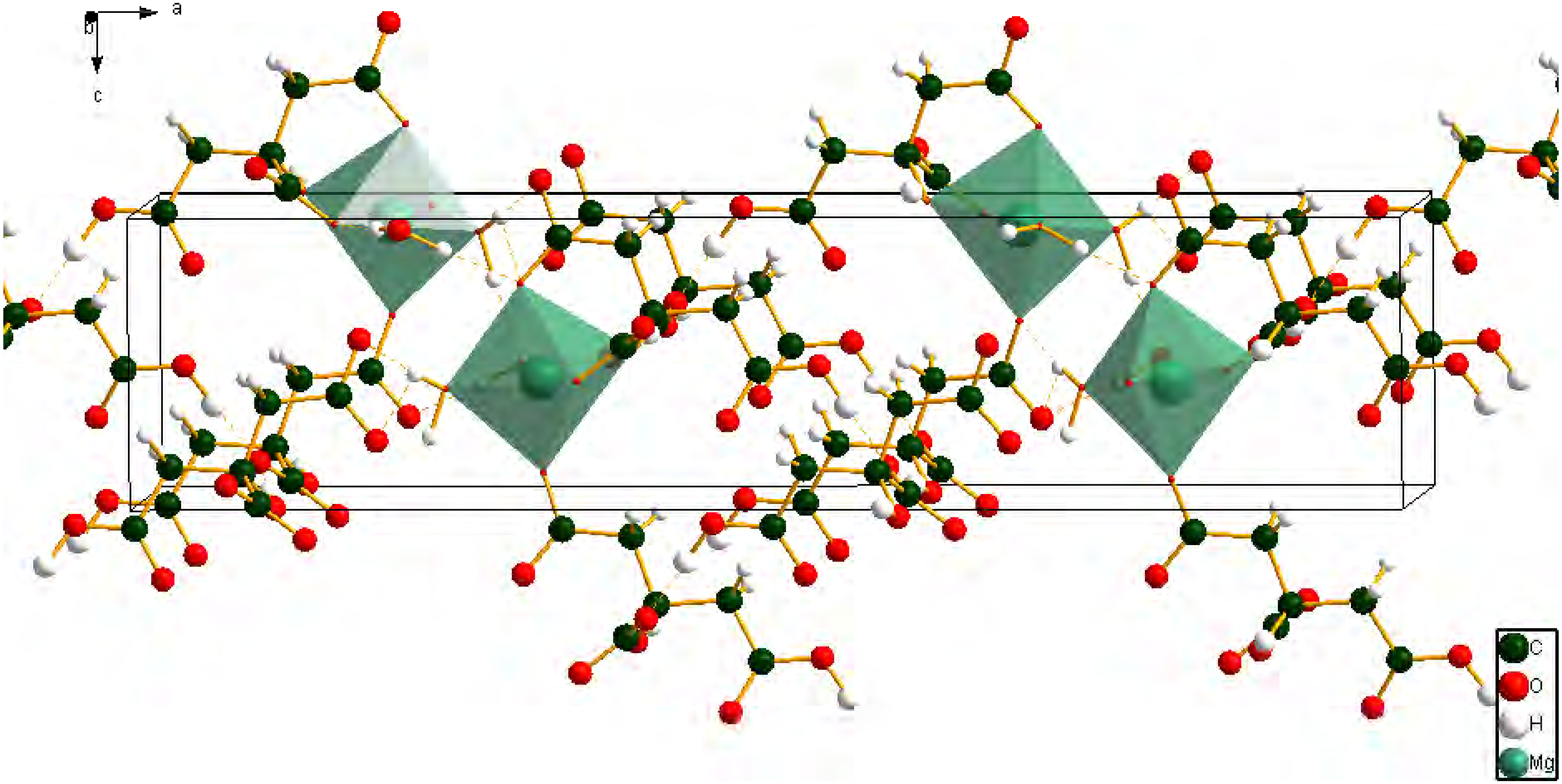
$Mg(H_2C_6H_5O_7)_2$

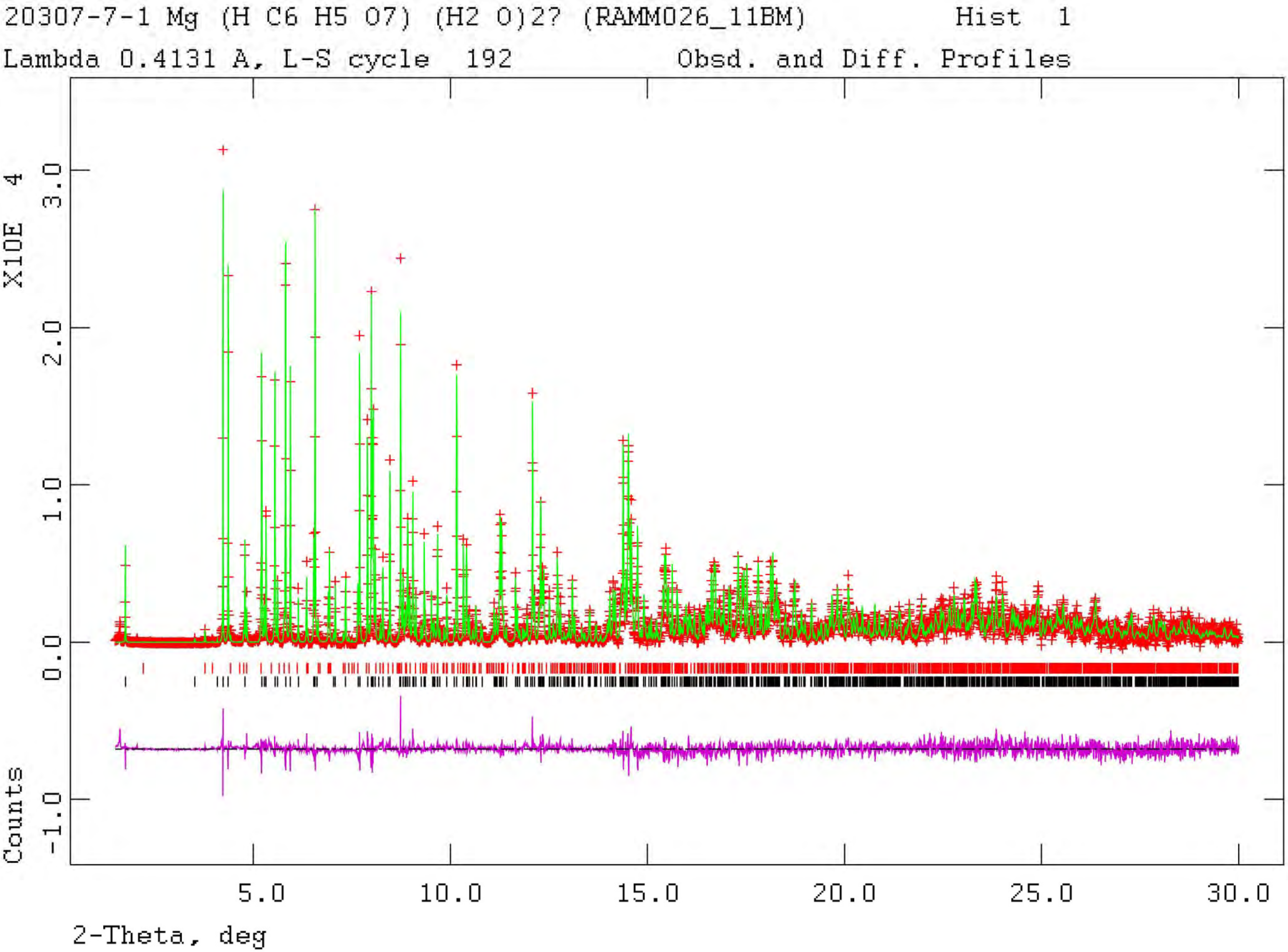




Scaling: 3.0(2.0X) 11.0(10.0X) 17.0(40.0X)

$Mg(HC_6H_5O_7)(H_2O)_2$



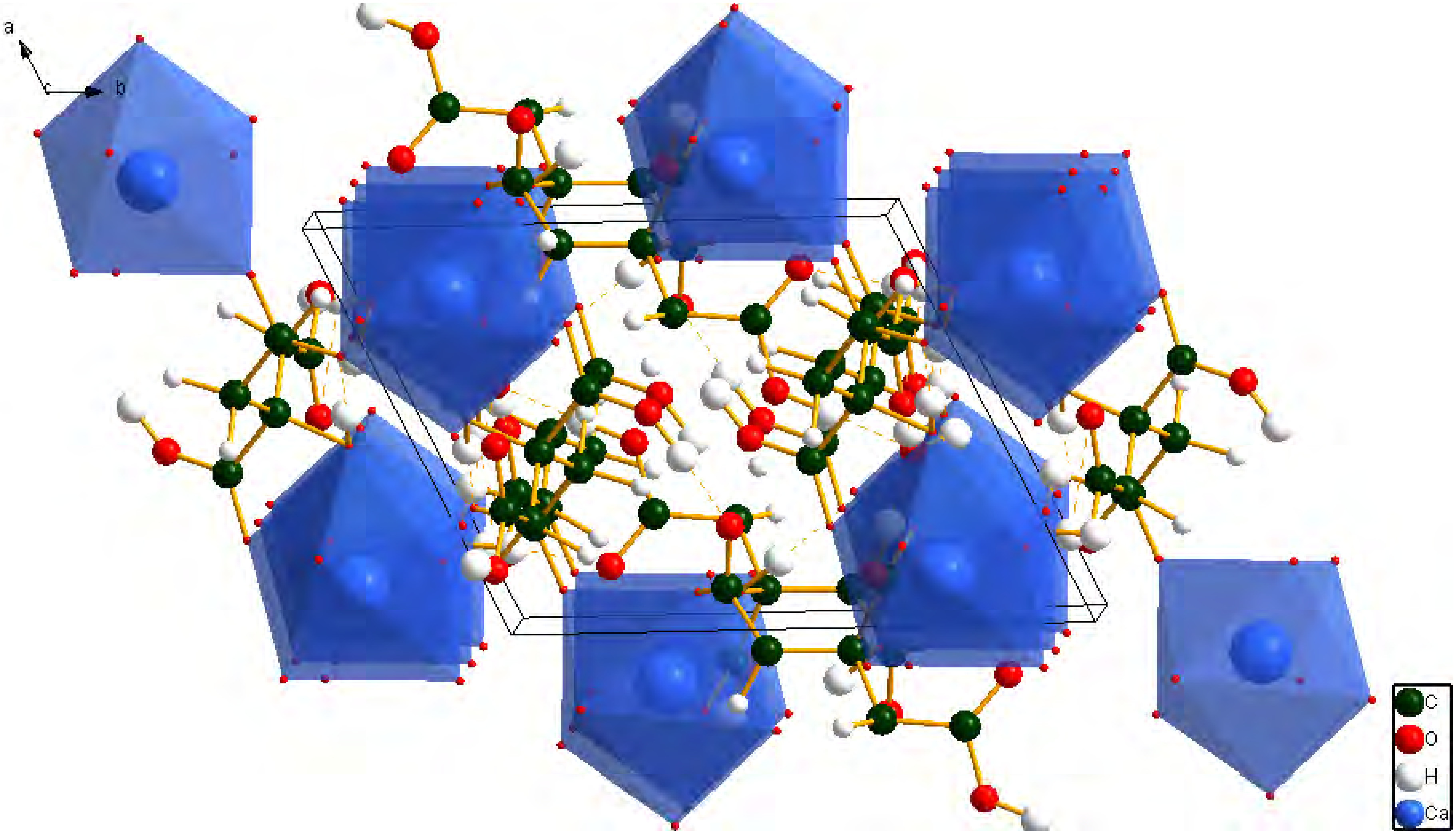


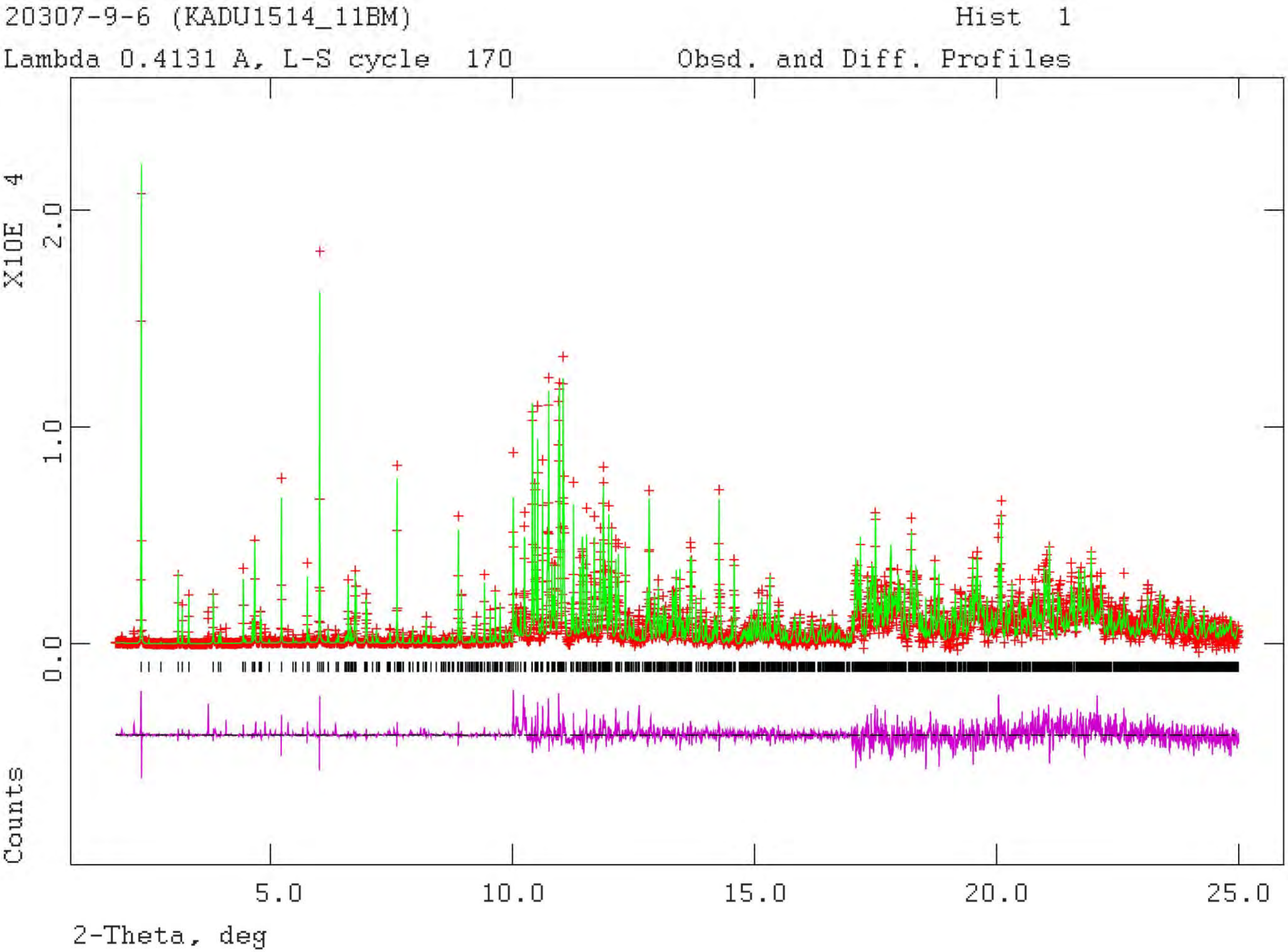
20307-7-1 Mg (H C6 H5 O7) (H2 O)2? (RAMM026_11BM) Hist 1

Lambda 0.4131 A, L-S cycle 192 Obsd. and Diff. Profiles

Scaling: 5.0(5.0X) 14.0(20.0X) 22.0(40.0X)

$[Ca(H_2C_6H_5O_7)_2(H_2O)](H_2O)$





Scaling: 10.0(10.0X) 17.0(40.0X)

Which CO_2H ionizes first?
pKa = 3.128, 4.761, 6.396

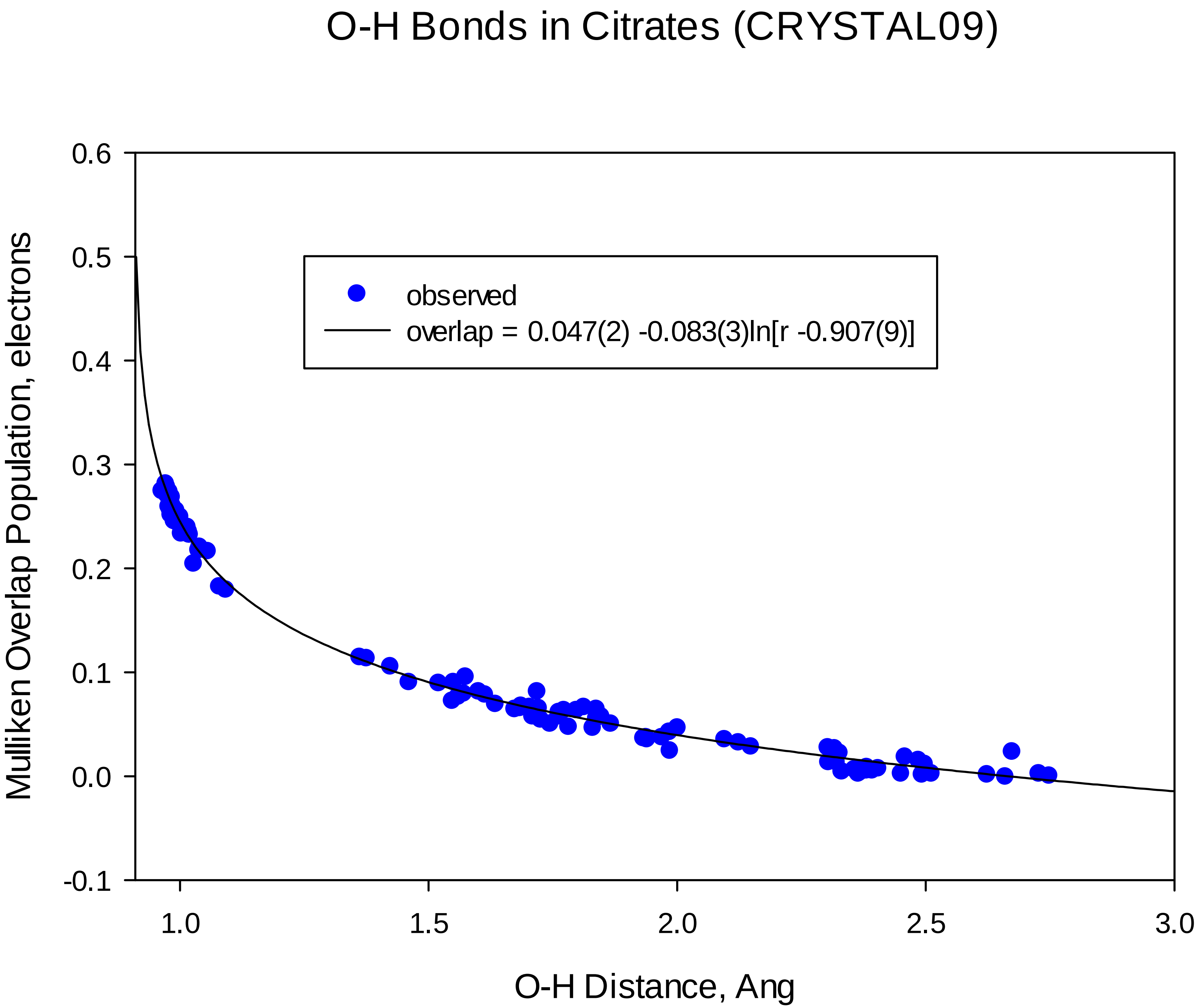
LiH_2	Central	$LiH_2(H_2O)$	Central
NaH_2	Central Terminal		
KH_2	Central	$KH_2(H_2O)_2$	Terminal
RbH_2	Central		
CsH_2	Central		
$Mg(H_2cit)_2$	Central		
		$Ca(H_2cit)_2(H_2O)_2$	Terminal

Which CO_2H ionizes last?

		$Na_2Hcit(H_2O)_{1.5}$	Terminal
K_2H	Terminal		
Rb_2H	Terminal		
Cs_2H	Terminal		
		$MgHcit(H_2O)_2$	Terminal
		$CaHcit(H_2O)_3$	Terminal

Order of Ionization: central, terminal, terminal

But hydration and packing
can affect order?


O-H Bonds in Citrates (CRYSTAL09)
Mulliken Overlap Population, electrons
O-H Distance, Ang
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
1.0
1.5
2.0
2.5
3.0
observed
overlap = 0.047(2) -0.083(3)ln[r -0.907(9)]

Volume/non-H in Group 1 and 2 Citrates