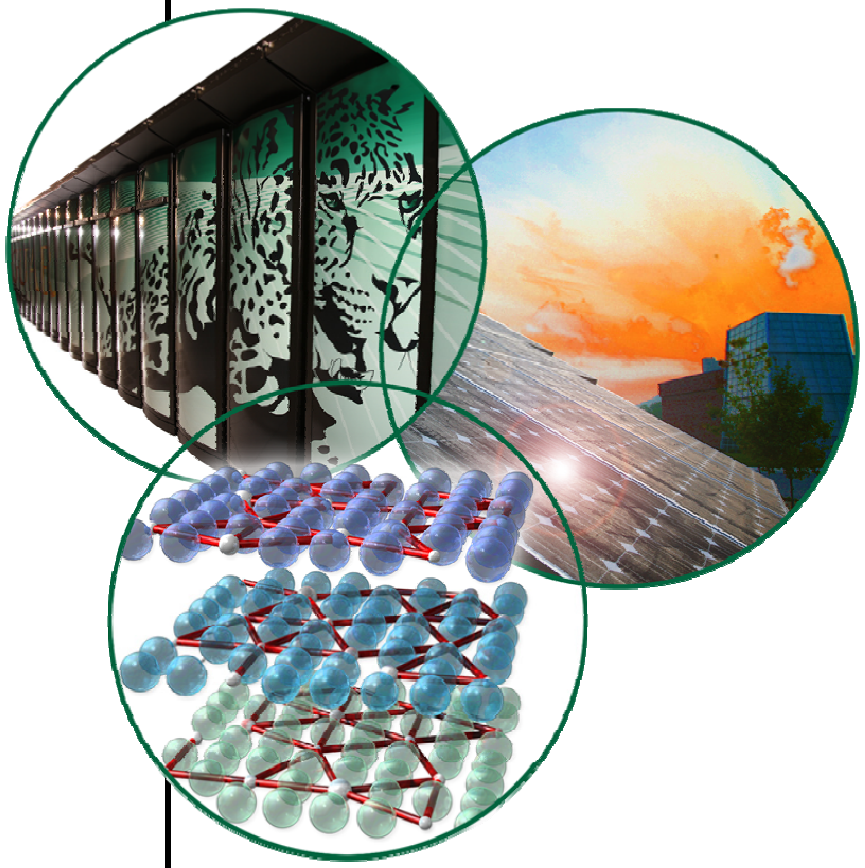
National School on Neutron and X-ray Scattering
June 24, 2010

Applications of

Small Molecule Crystallography

Xiaoping Wang
Neutron Scattering Science Division
Oak Ridge National Laboratory



U.S. DEPARTMENT OF ENERGY

OAK RIDGE NATIONAL LABORATORY
MANAGED BY UT-BATTELLE FOR THE DEPARTMENT OF ENERGY

Outline

- **Small Molecule Crystallography**
- **Accurate Molecular Structural Determination**
  - Impact on Science
- **Structure and Bonding**
  - Metal-Metal Multiple Bonds
  - From Small Molecule to Superamolecular Assembly
- **Case Studies**
  - Gas Adsorption Dynamic in a Meal-Organic Framework
  - Electronic Communications Between Dimetal Centers
  - Effects of Crystallization on Molecular Structure
  - Single Crystal to Single Crystal Chemical Reaction
- **Future Directions**
  - Single Crystal Crystallography in Higher Dimensions
  - Charge and Spin Density
  - Time Resolved Diffraction
  - Bridging the Gap in Small Molecule and Macromolecule Crystallography

Small Molecule Crystallography

- **Small molecule**

  A neutral or ionic compound of synthetic or biological origin but it is not a polymer, protein or nucleic acid:

  – Inorganic and Organic Compounds
  – Catalysts
  – Natural Products
  – Pharmaceuticals
  – Synthetic Chemicals

- **Small Molecule Crystallography**

  – Use single crystal X-ray/Neutron diffraction methods to determine the three dimensional structure of small molecules at atomic resolution.

  Chemical Crystallography

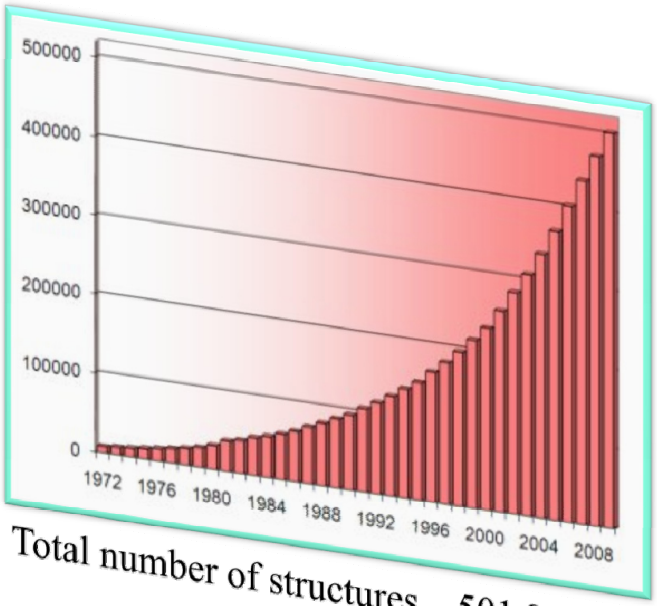
  – The relationship between molecular structure and chemical, biochemical or biological properties.

Cambridge Structural Database

Stores data for organic molecules & metal-organic compounds

http://www.ccdc.cam.ac.uk/

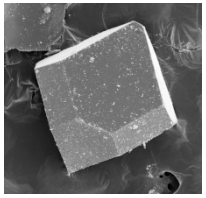
Basic Research at CCDC
Mean molecular dimensions
Studies of substituent effects
Statistical and numerical data analysis techniques
Structure correlation and reaction pathways
Conformational analysis
Hydrogen bond geometry and directionality
Weak hydrogen bonds
Nonbonded interactions not mediated by hydrogen
Crystal engineering
Crystallographic symmetry and molecular symmetry



Total number of structures 501 857

The CSD does not store:
Polypeptides and polysaccharides having more than 24 units.
Protein Data Bank http://www.rcsb.org/pdb/
Oligonucleotides. Nucleic Acids Data Bank http://ndbserver.rutgers.edu/
Inorganic structures
Inorganic Crystal Structure Database http://www.fiz-karlsruhe.de/icsd_content.html
Metals and Alloys CRYSTMET® http://www.tothcanada.com/

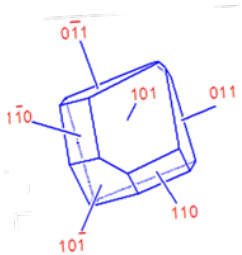
Single-Crystal Diffraction



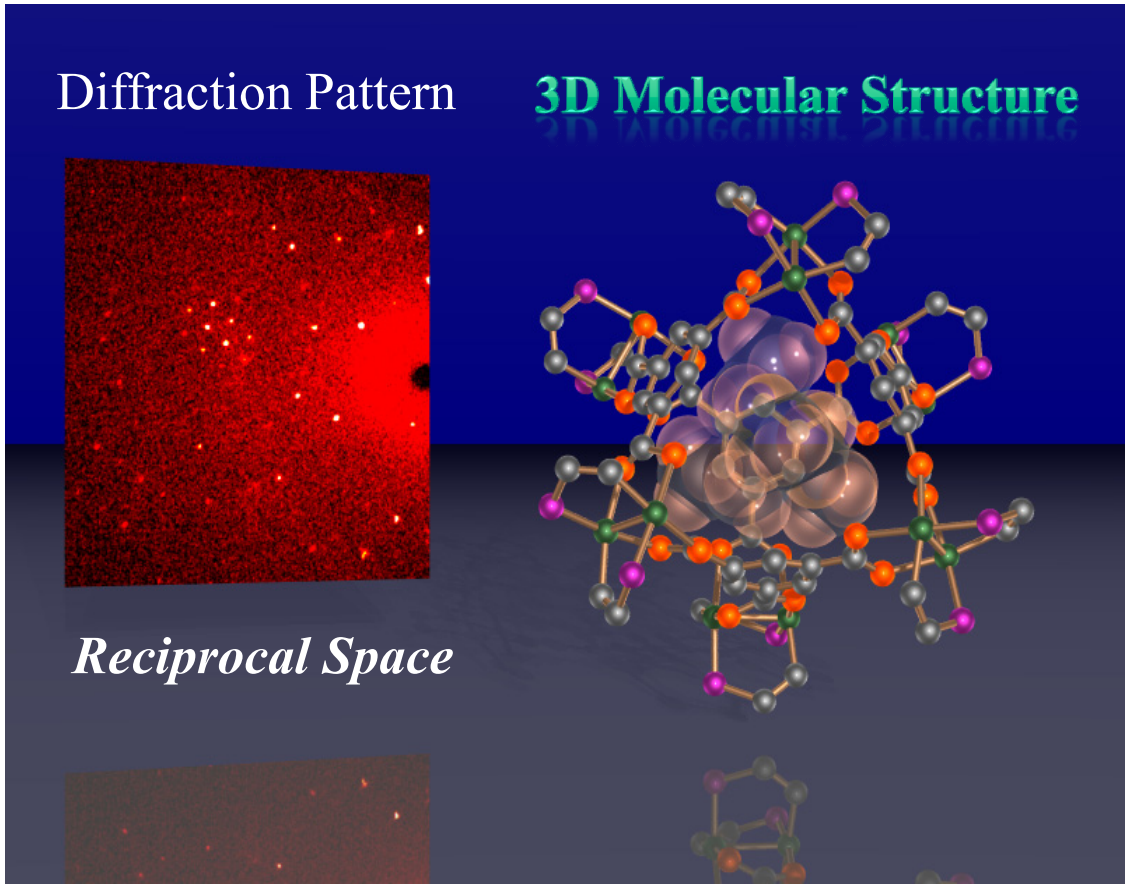
Single Crystal

Direct Space

Single Crystal Diffraction Experiment



Crystal Symmetry



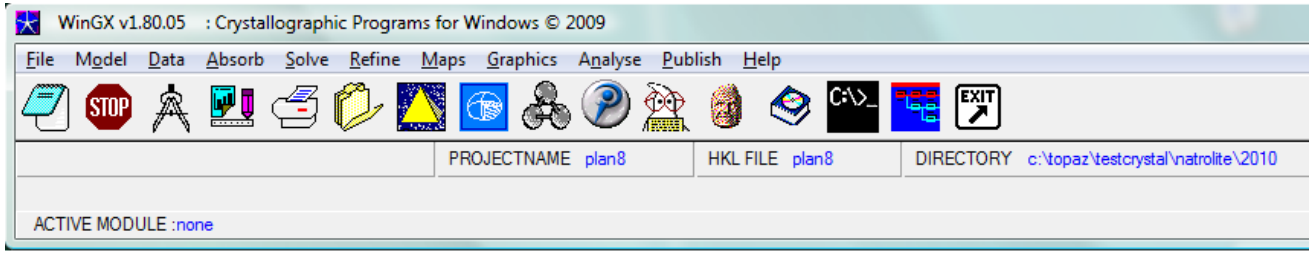
Programs for Single Crystal Structure Analysis

SHELX-97 Structure solution and refinement
http://shelx.uni-ac.gwdg.de/tutorial/english/index.html
http://www.chem.tamu.edu/xray/practicals/practical_shelx.pdf

JANA2006 Modulated structures
http://jana.fzu.cz/

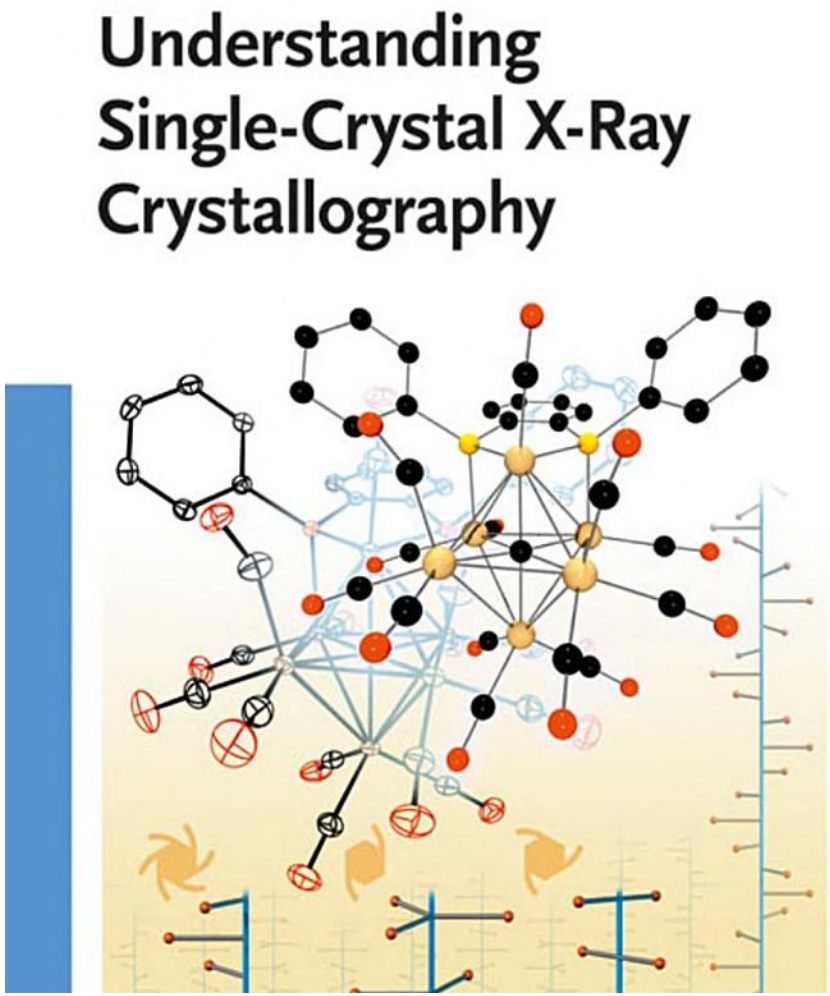
GSAS Single crystal and powder data
http://www.aps.anl.gov/Xray_Science_Division/Powder_Diffraction_Crystallography/GSASEXPGUI.html

WinGX Windows system of programs for solving, refining and analysing single crystal X-ray diffraction data for small molecules. http://www.chem.gla.ac.uk/~louis/software/wingx/



http://neutrons.ornl.gov/conf/NXS2008/Presentations/Xiaoping_Wang_SingleCrystal_Handout.pdf

Books in Single Crystallography



Dennis W. Bennett
ISBN: 978-3-527-32794-2
Paperback
831 pages
March 2010

http://www.wiley.com/WileyCDA/WileyTitle/productCd-3527327940.html

Accurate Molecular Structural Determination

- **Impact on Science**
  - 13 Nobel Prizes in chemistry and physiology or medicine awarded for work in the field of crystallography from 1956 to 2009.
  - Almost one in four chemistry prizes since 1956 have been for structure work.

M. Seringhaus and M. Gerstein, *Science,* **2007**,*315*, 412.

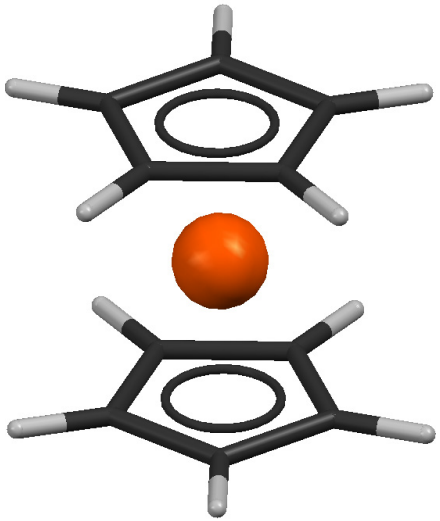
A critical stance is essential to science. Proving other people wrong is a favorite private and public satisfaction—there is nothing some scientists like better. But, excess zeal discounted, doubt serves as a powerful impulse to the advancement of knowledge. We document it here with the discovery of the structure of ferrocene,

P. Laszlo and **R. Hoffmann**, *Angew. Chem. Int. Ed*. **2000**, *39*, 123.

Molecular Structure of Ferrocence

$Fe(C_5H_5)_2$

T. J. Kealy, P. L. Pauson, *Nature* **1951**, *168*, 1039



G.Wilkinson, M. Rosenblum, M. C. Whiting, R. B.Woodward, *J. Am. Chem Soc*. **1952**, *74*, 2125.

Geoffrey Wilkinson

Ernst Otto Fischer

The Nobel Prize in Chemistry 1973

"for their pioneering work, performed independently, on the chemistry of the organometallic, so called sandwich compounds"

Bis-cyclopentadienyl Iron, a Molecular Sandwich
L. E. Orgel, J. D. Dunitz, *Nature* **1953**, *171*, 121.

Ferrocene: Ironclad History or Rashomon Tale?**

Pierre Laszlo and Roald Hoffmann*

P. Laszlo and R. Hoffmann, *Angew. Chem. Int. Ed.* **2000**, *39*, 123.

Peter Pauson, private communication, recalls that he had crystals of ferrocene in the fall of 1951. He was trying to decide whether to ask Jack Dunitz, or the senior organic crystallographer of the time, J. Monteath Robertson (real or adopted Scotsmen all). Pauson decided on Robertson. Who, according to Pauson, took the crystals to…Cornell, where he asked Lynn Hoard if someone could look at them. The crystals were assigned to a beginning graduate student, who failed to solve the structure.

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CHEMICAL & ENGINEERING NEWS

SCIENCE & TECHNOLOGY

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FIFTY YEARS OF FERROCENE CHEMISTRY

Journal celebrates the discovery of ferrocene and the birth of modern organometallic chemistry

RON DAGANI, C&EN WASHINGTON

On Dec. 15, 1951, two chemists at Duquesne University in Pittsburgh published a landmark paper reporting the synthesis of "a new type of organo-iron compound" they called dicyclopentadienyliron [*Nature*, **168,** 1039 (1951)].

F. Albert Cotton
(1930 – 2007)

What went on in Wilkinson's and Fischer's labs "was science at its best and most exciting," according to chemistry professor F. Albert Cotton of Texas A&M University. …

In his own recollections article in *JOMC*, Cotton characterizes Wilkinson and Fischer as two "young but mature chemists" who recognized the implications of a serendipitous discovery and pursued it with imagination and experimental skill.

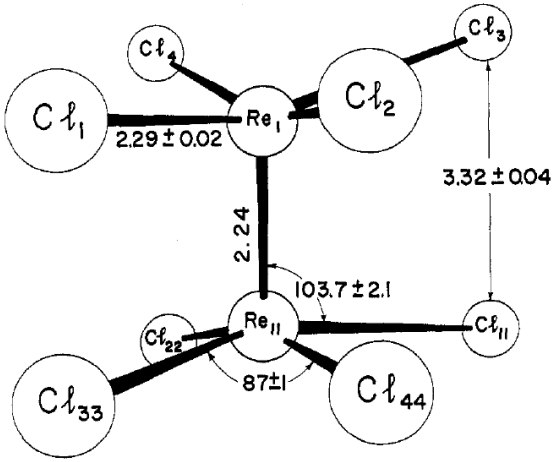
Structure and Bonding

The Crystal and Molecular Structure of Dipotassium Octachlorodirhenate(III) Dihydrate, $K_2[Re_2Cl_8] \cdot 2H_2O$[1]

By F. A. COTTON and C. B. HARRIS

Received September 22, 1964

Why not $K[ReCl_4] \cdot H_2O$?



Intensity data were collected by the equi-inclination Weissenberg method with Cu Kα radiation ...

Intensities were estimated visually using an intensity wedge prepared by timed exposures of one reflection from the same crystal.

F. A. Cotton, C. B. Harris, *Inorg. Chem.* **1965**, *4*, 330.

Metal-Metal Multiple Bonds

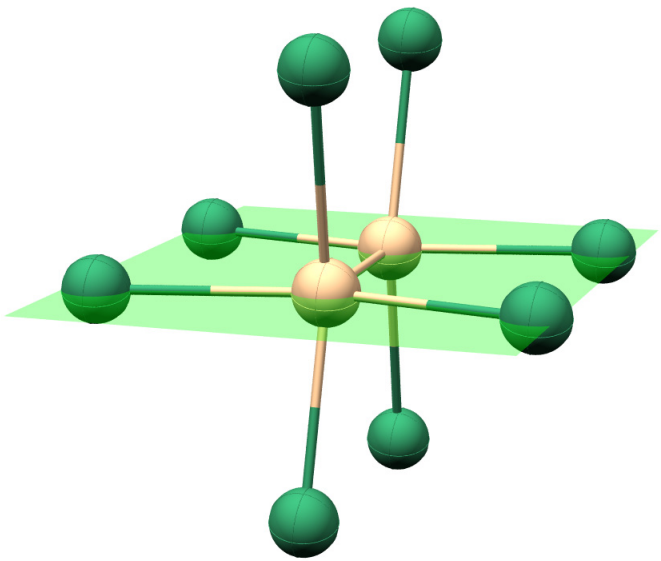
Metal–Metal Bonding in $[Re_2X_8]^{2-}$ Ions and Other Metal Atom Clusters[1]

By F. A. COTTON

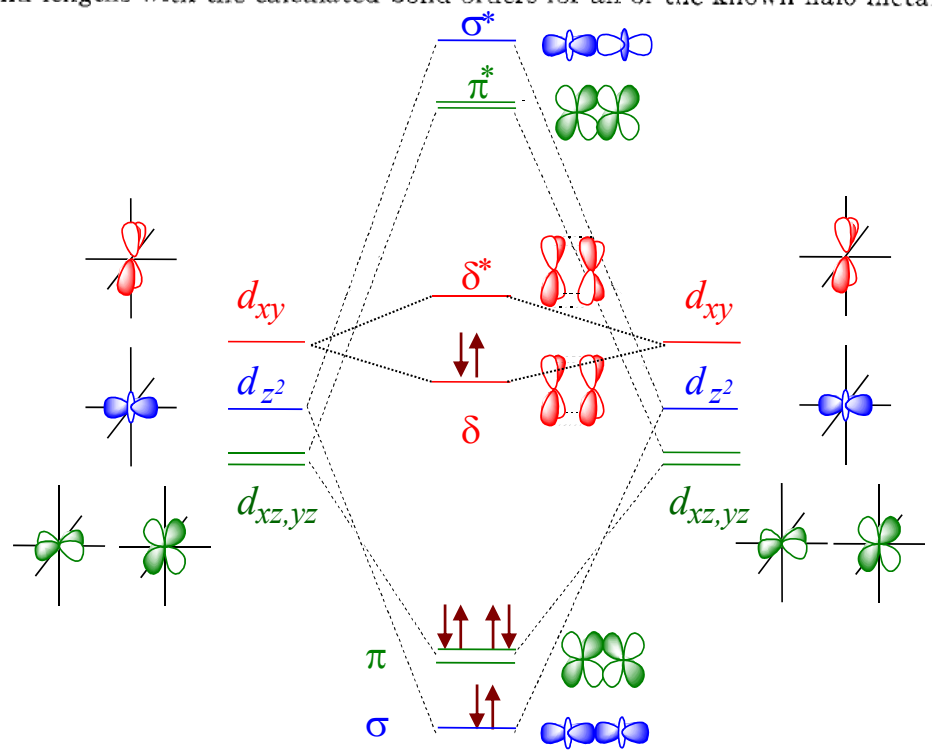
Received September 22, 1964

F. A. Cotton *et al.*, *Science*, **1964**, *145*, 1305.

The metal–metal bonding in the $[Re_2X_8]^{2-}$ ions is treated by a simple MO method similar to that previously used for other metal atom cluster compounds. A quadruple bond between the rhenium atoms is proposed and it is shown that this accounts for the eclipsed rotomeric configuration. The assignment of the absorption spectrum of $[Re_2Cl_8]^{2-}$ species is discussed. Finally, the consistency of observed bond lengths with the calculated bond orders for all of the known halo metal atom cluster compounds is demonstrated.



$[Re_2Cl_8]^{2-}$



Inorg. Chem. **1965**, *4*, 334.

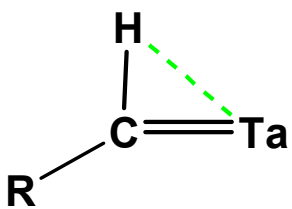
d^4 $\sigma^2\pi^4\delta^2$ d^4

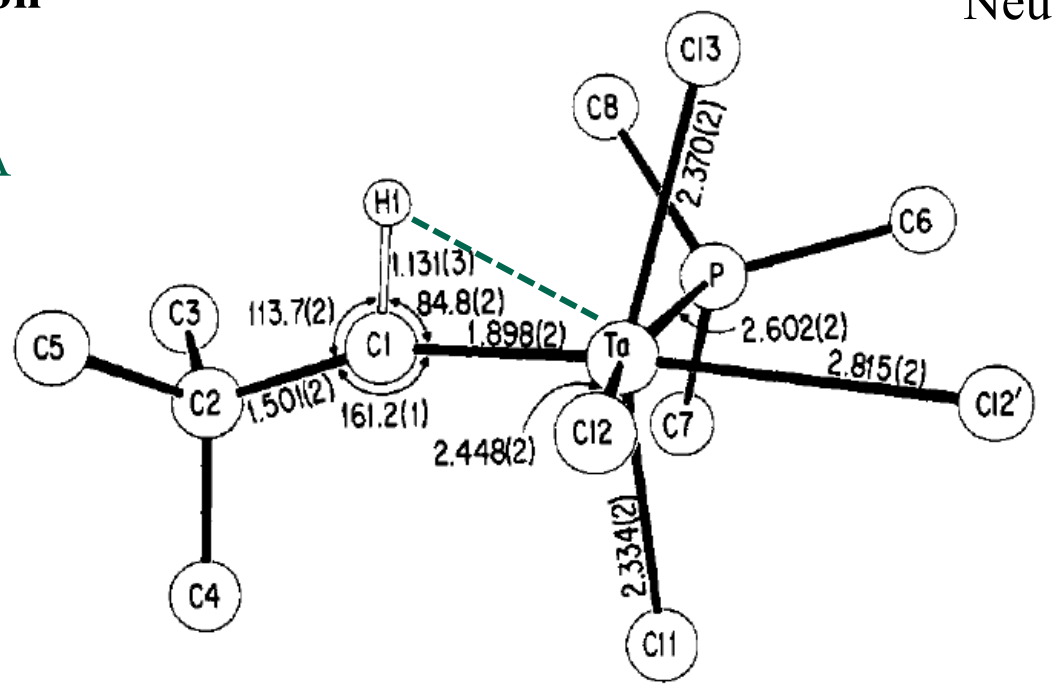
C−H−Metal Interactions in a Tantalum-Neopentylidene Complex

Agostic Interaction

Neutron

H1−Ta 2.119(4) Å





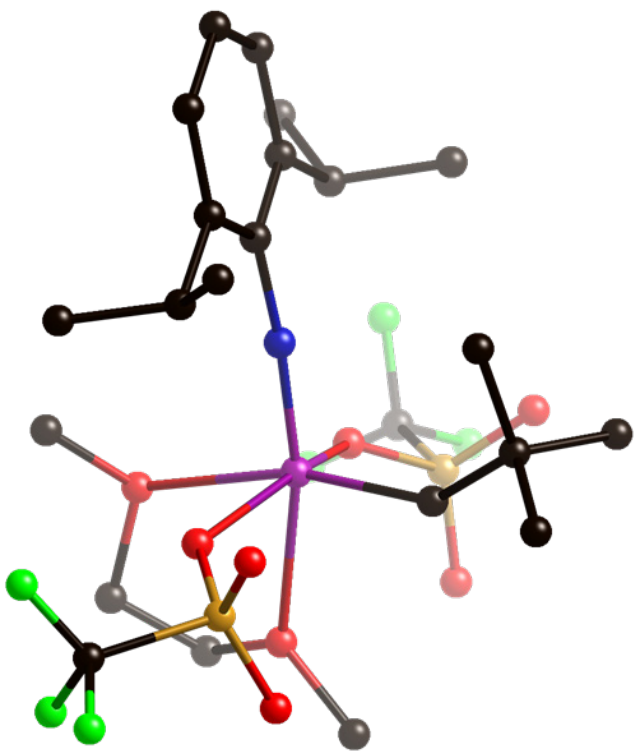
$[Ta(CHCMe_3)(PMe_3)Cl_3]_2$

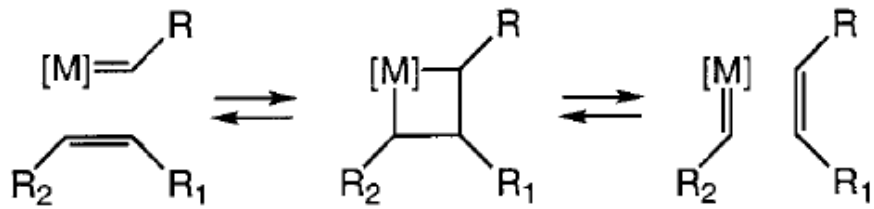
Activation of C-H bond is critical to olefin metathesis.

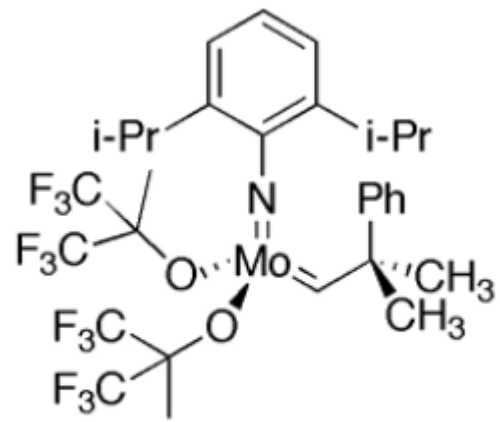
A. J. Schultz *et al, J. Am. Chem. Soc.* **1981**, *103*, 169.

Molybdenum-alkylidene Complexes

Development of the metathesis method in organic synthesis



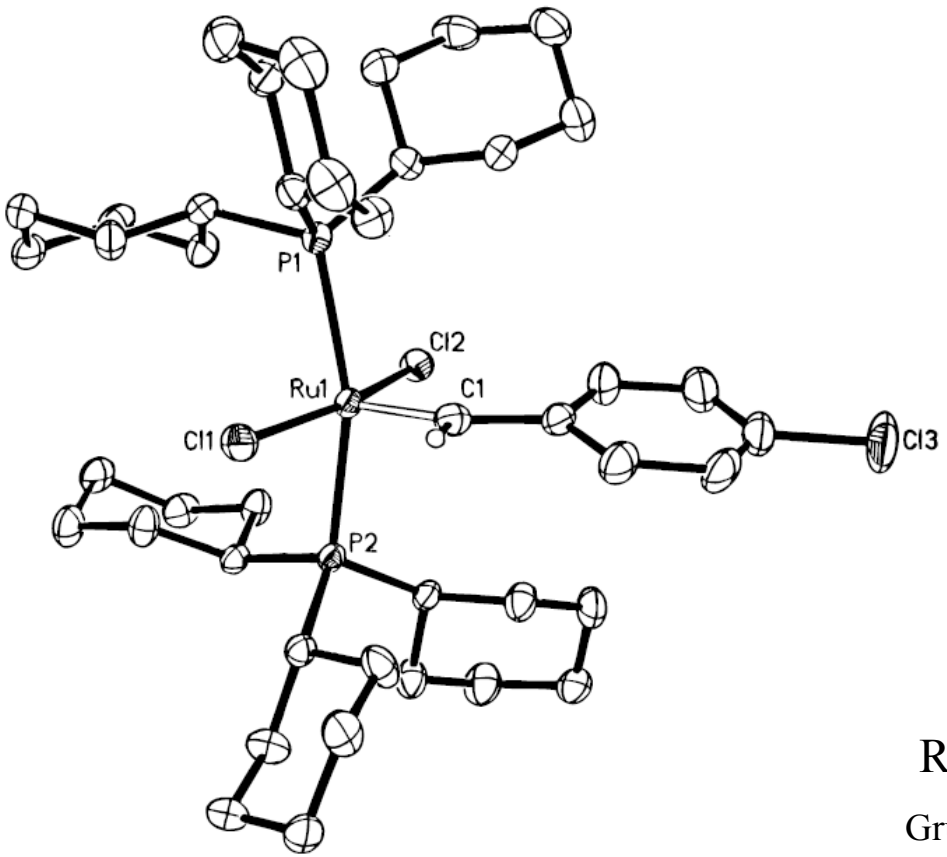


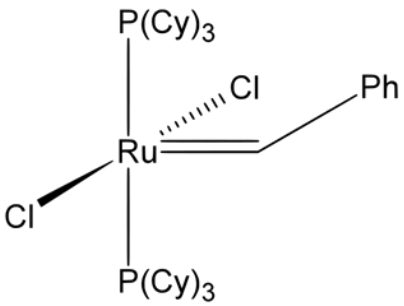


Schrock catalyst commercially available

R. R. Schrock, *et al J. Am. Chem. Soc.*, **1990**, *112* (10), 3875.

Grubbs Catalyst for Olefin Metathesis





1st generation Grubbs
Commercially available

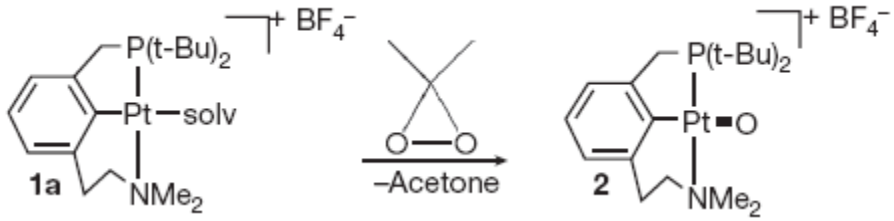
$RuCl_2(=CH\text{-}p\text{-}C_6H_4Cl)(PCy_3)_2$

Grubbs *et al. J. Am. Chem. Soc.*, **1996**, *118*, 100.

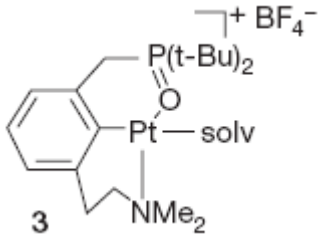
Robert H. Grubbs, Richard R. Schrock and Yves Chauvin
Nobel Prize in Chemistry 2005

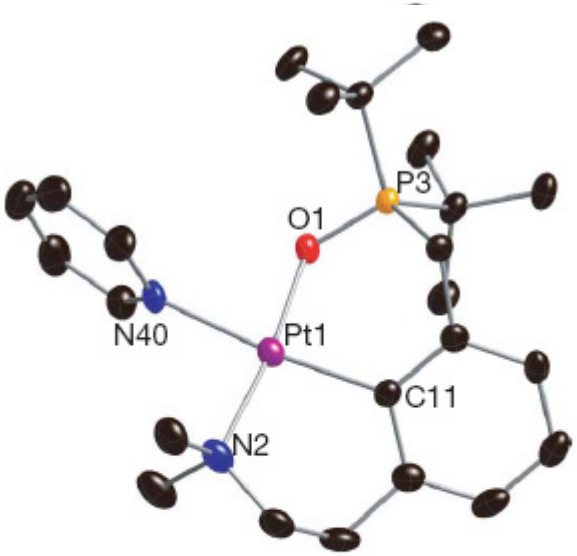
Structure of a Terminal Pt(IV)-Oxo Complex

Key intermediates in the photocatalytic oxidation of water to produce molecular oxygen.



Preparation and DFT structure of complex **2**.





Room temperature Intramolecular *oxo* transfer product.

E. Poverenov et al, *Nature*, **2008**, *455*, 1093.

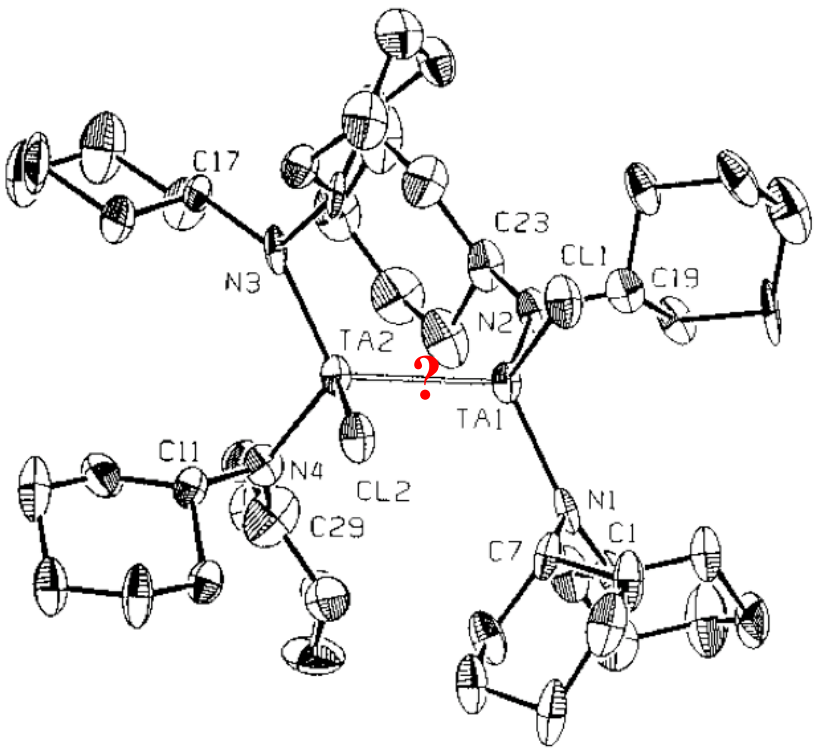
A Ta-Ta Bond without Bridging Ligands ?

Preparation of the First Ditantalum(III) Complex Containing a Ta−Ta Bond without Bridging Ligands

Ludmila Scoles, Kamalesh B. P. Ruppa, and Sandro Gambarotta*

J. Am. Chem. Soc. ***1996,*** 118, 2529.

Crystal data.
monoclinic *C2/c,*
a = 48.833(1) Å
b =10.960(1) Å
c = 22.317(1) Å
α = 95.99(1)º



Ta−N	2.05(1) to 2.28(1) Å
C−C	0.86 to 1.70 Å

$[(Cy_2N)_2ClTa]_2$

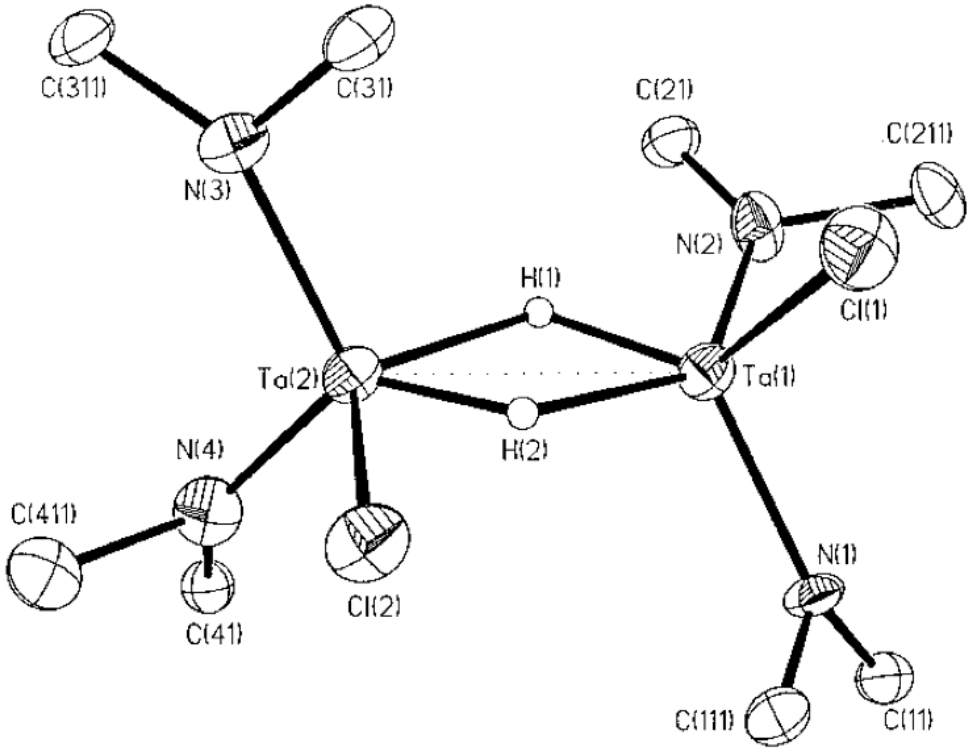
A Wonderful Bond that Wasn't There

A Wonderful Bond That Wasn't There: Reformulation of a Compound "Containing a Ta−Ta Bond without Bridging Ligands" as $[(Cy_2N)_2ClTa(\mu\text{-}H)]_2$

F. Albert Cotton,*,† Lee M. Daniels,†
Carlos A. Murillo,*,†,‡ and Xiaoping Wang†

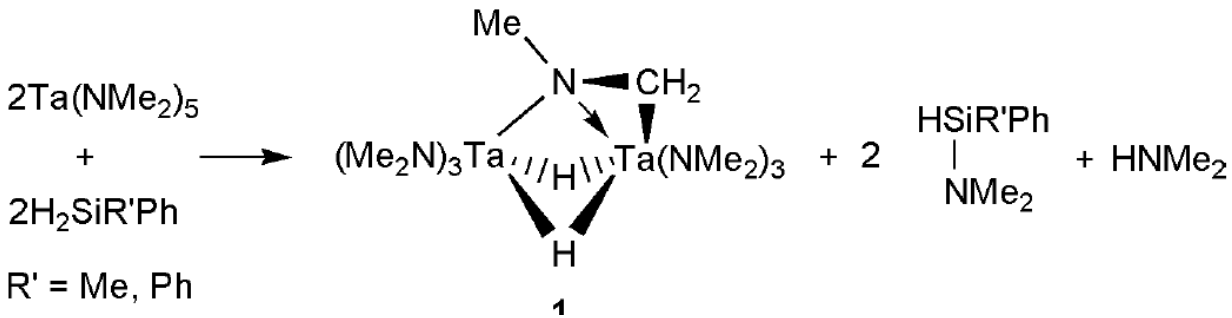
J. Am. Chem. Soc. ***1996,*** 118, 12449

Crystal data.
monoclinic *C2/c,*
a = 42.234(5) Å
b =10.804(1) Å
c = 22.765(2) Å
α = 94.702(8)º

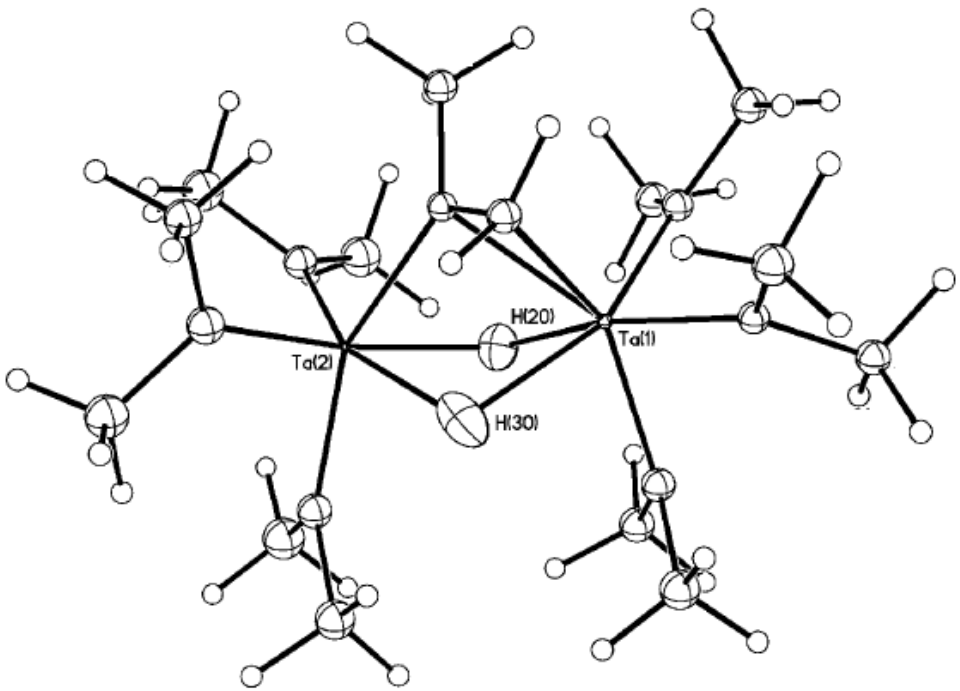


$[(Cy_2N)_2ClTa\text{-}(\mu\text{-}H)]_2$

β-H Abstraction Between Amide Ligands



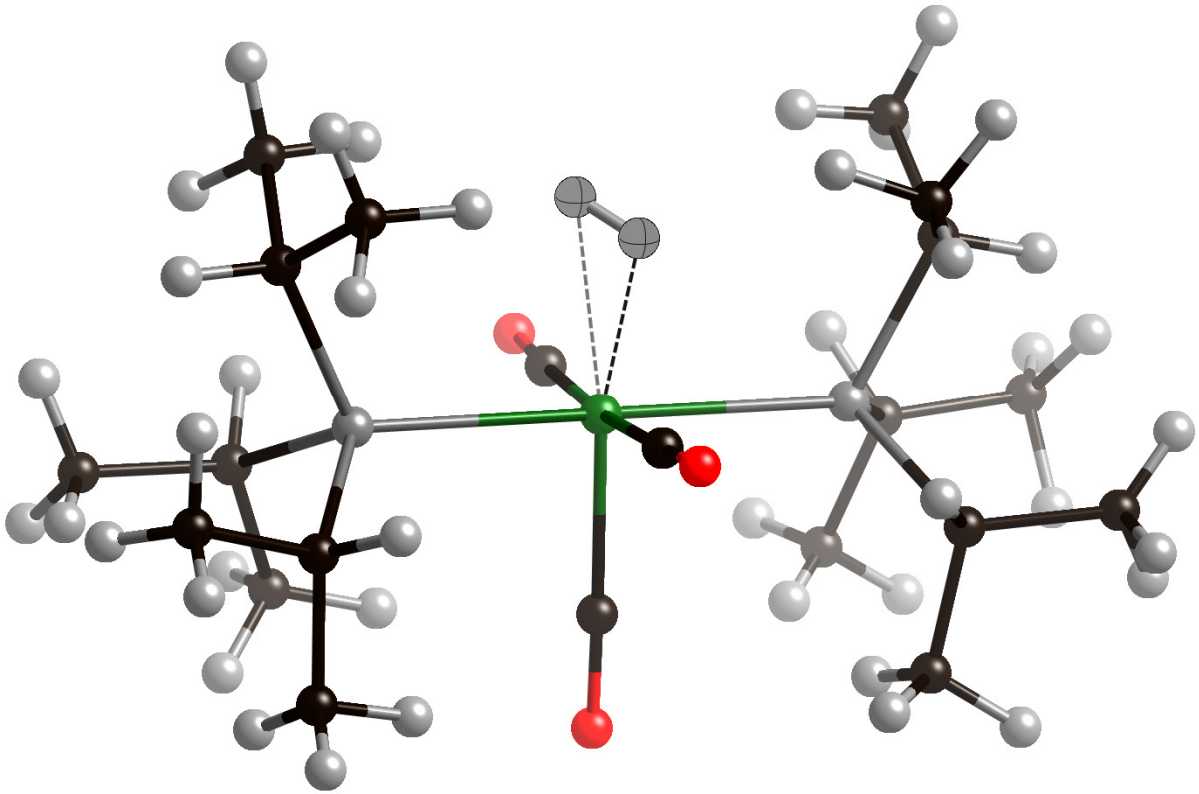
1



Neutron Structure
IPNS SCD
Now at LANSCE

Z. Xue et al, Chem. Commun., **2002**, 230

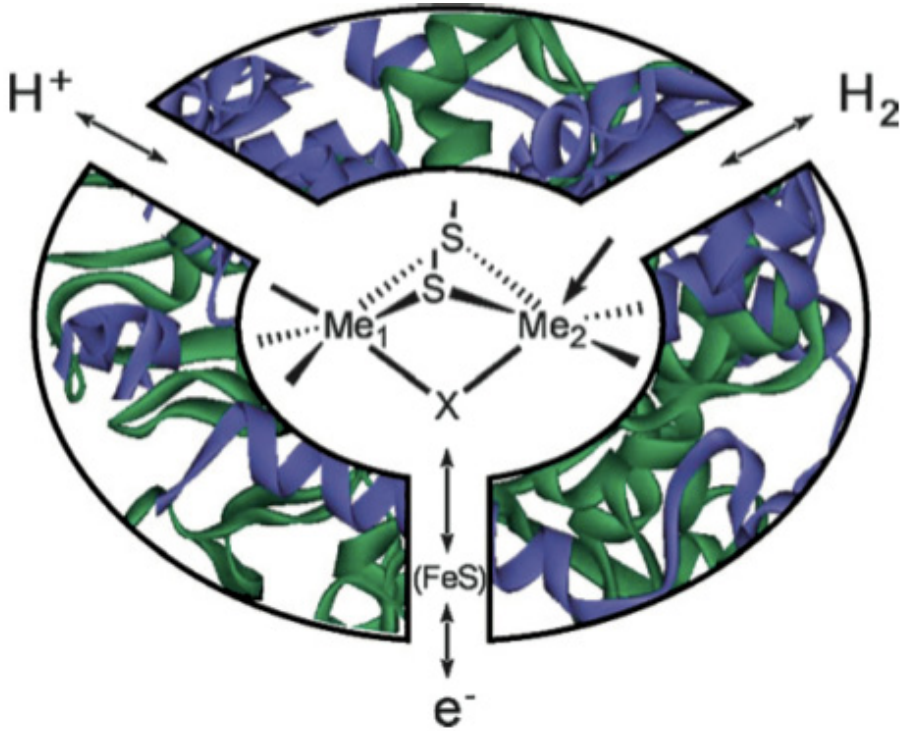
A Side-on Bonded H_2 Ligand - Cubas H_2 Bond



Structure of the first molecular hydrogen complex, $W(CO)_3(P\text{-}i\text{-}Pr_3)_2(\eta^2\text{-}H_2)$. Combined refinement of neutron and X-ray data.

G. J. Kubas et al, *J. Am. Chem. Soc.* **106**, *451-452* (1984)

Active Site in [NiFe]Hydrogenase Enzymes



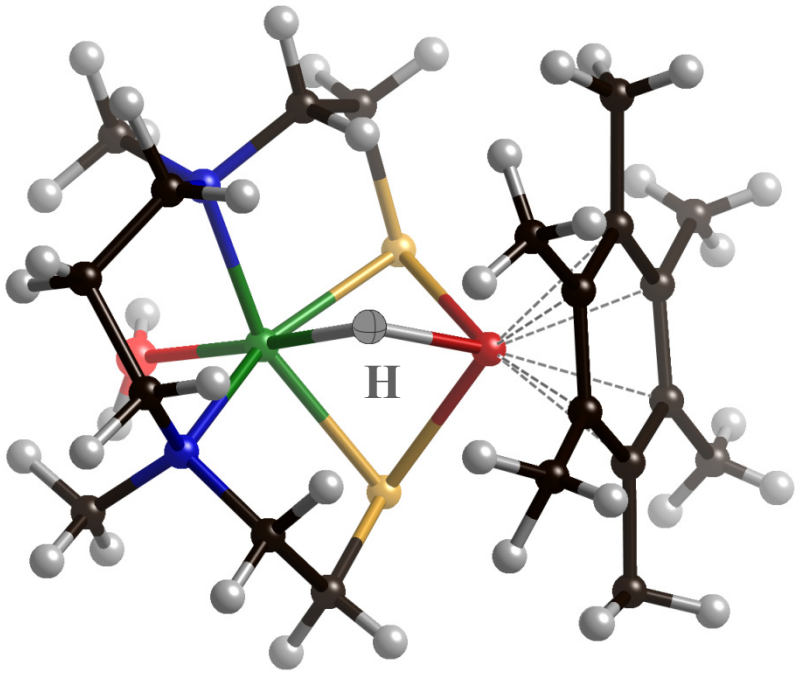
X = ?

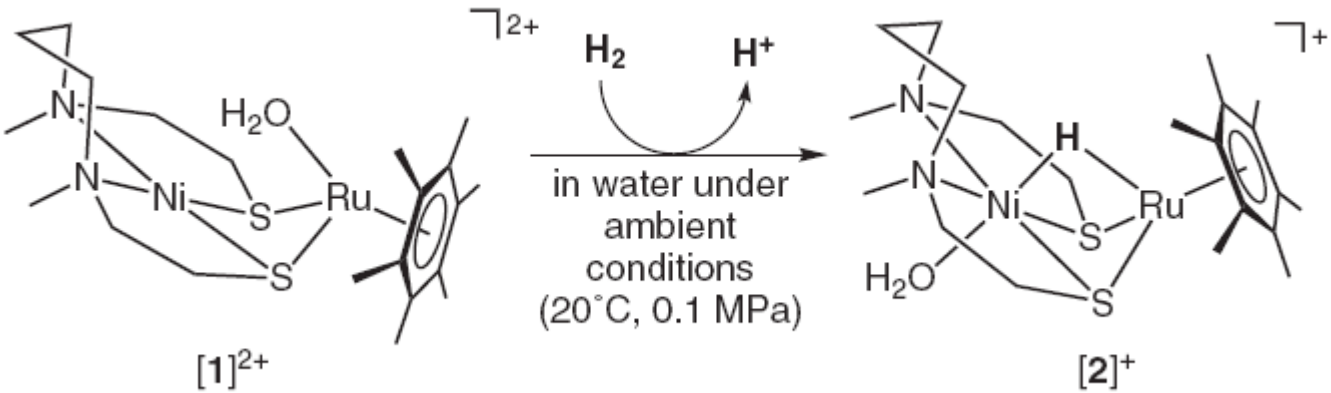
H_2O
OH^-
O_2^-

Coordination sphere of the
S-bridged bimetallic catalytic center.

Volbeda et al., *J. Am. Chem. Soc*. **1996**, *118*, 12989.
Lubitz et al, *Energy Environ. Sci*., **2008**, *1*, 15.

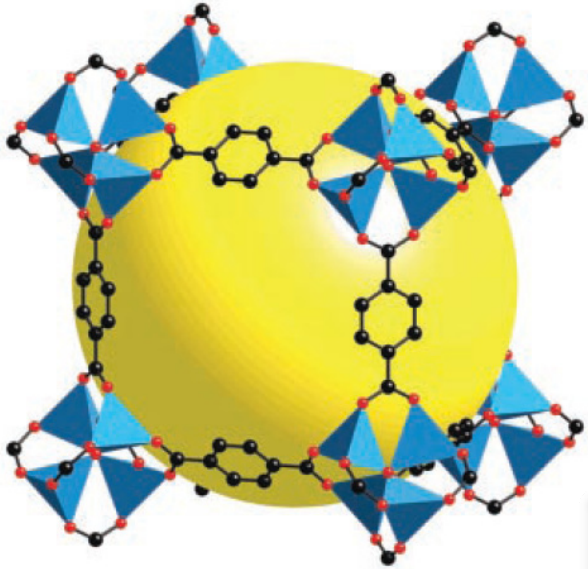
Model of the Active Site in Hydrogenase - Dinuclear Ni(μ-H)Ru Complex



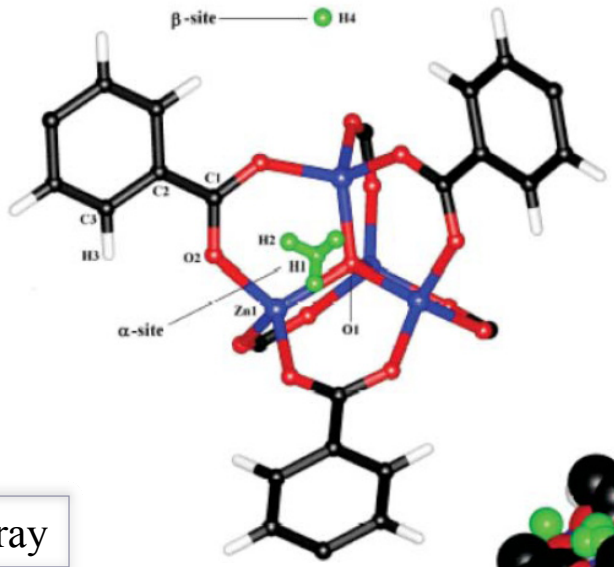


S. Ogo et al., *Science*, **2007**, *316*, 585.

Hydrogen Absorption Sites in MOF-5



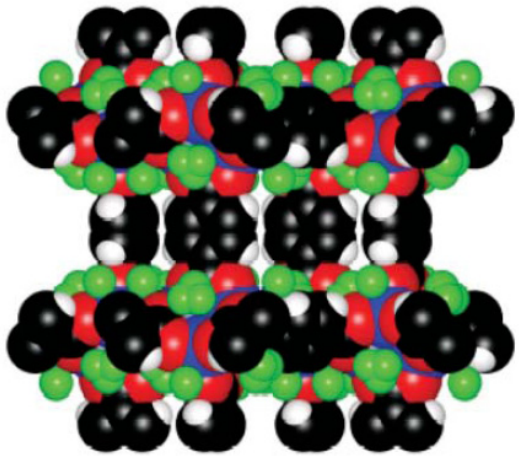
MOF-5



X-ray

Neutron

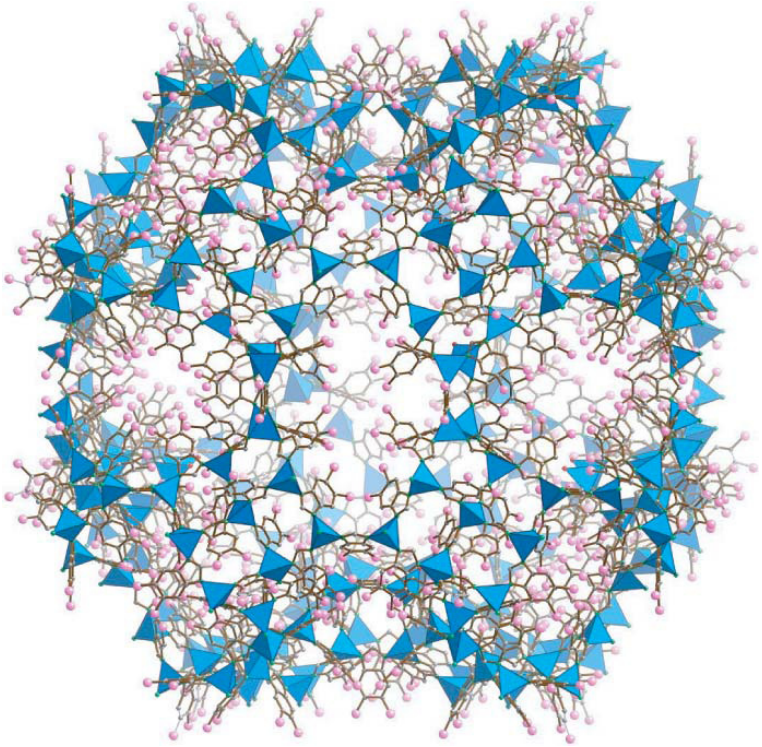
VIVALDI
ILL, France

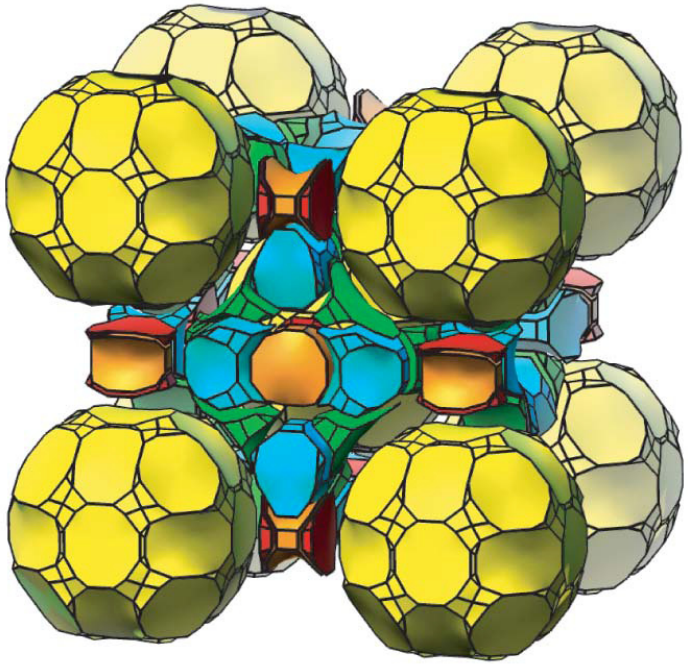


O. M. Yaghi et al, *Science*, **2003**, *300*, 1127

G. J. McIntyre et al, *Chem. Commun.*, **2006**, 278.

Zeolitic Imidazolate Framework, ZIF



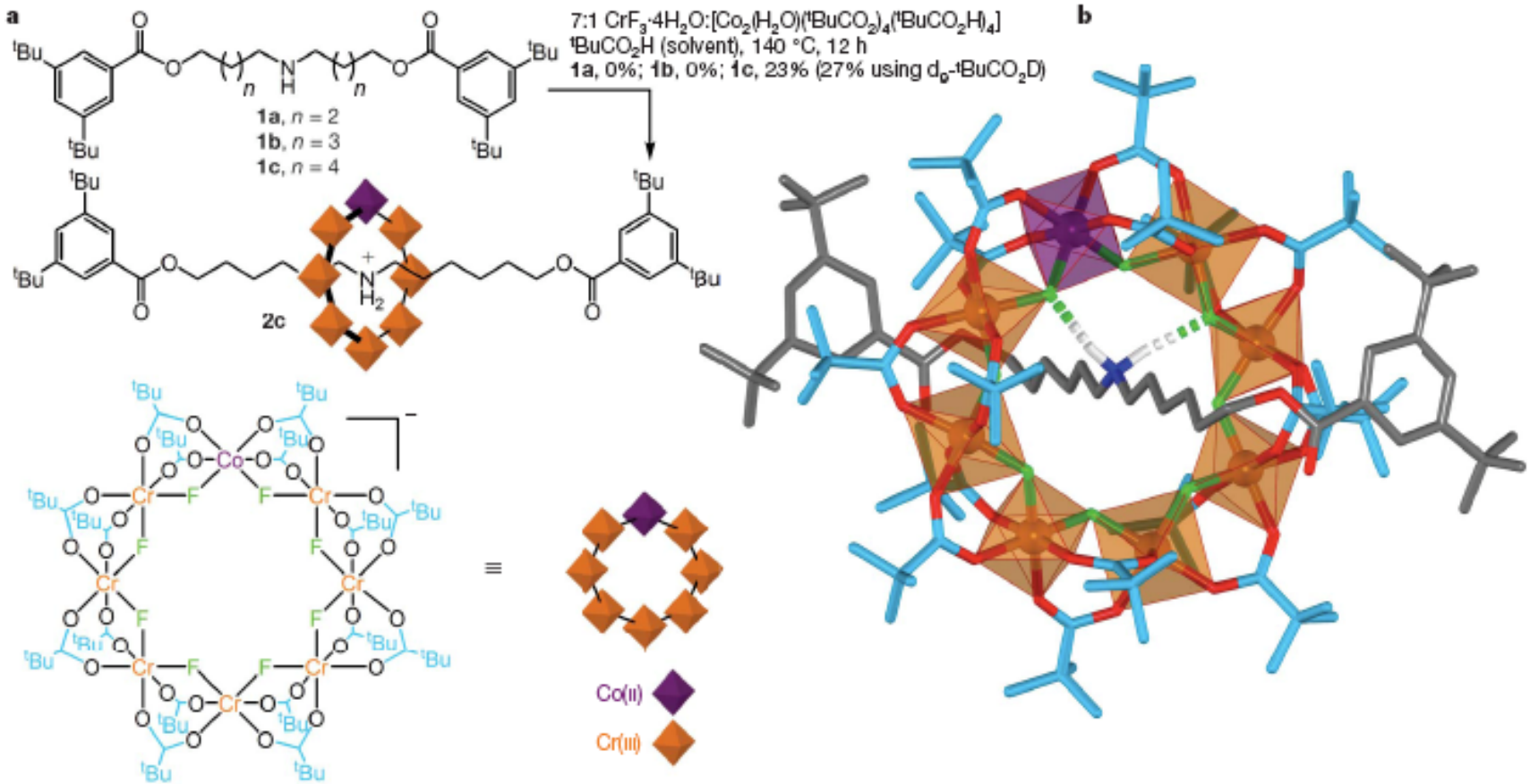


ZIF-100

Cubic
a =71.9797(4) Å
V =372,932(4)Å^3

O. M. Yaghi *et al Natural*, **2008**, *453*, 207

Hybrid Organic-Inorganic Molecular Shuttle



C. F. Lee et al, *Nature*, **2009**, *458*(19) 314.

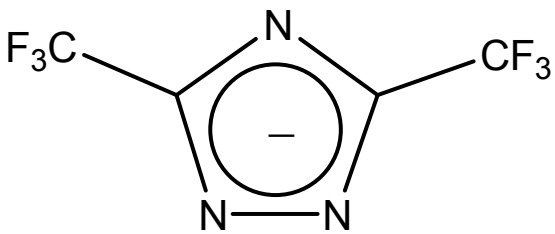
Functionalized Fluorous MOF

Higher Binding Energy

- H-bonding between H_2 and F atoms

Control at Molecular Level

-Gate function



organic

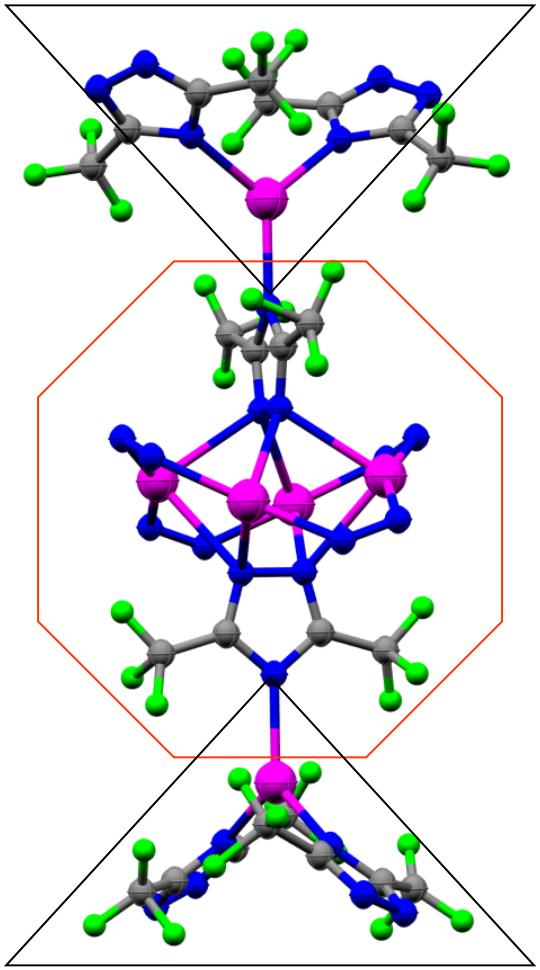
3,5-bis(trifluoromethyl)-1,2,4-triazolate, Tz

$\downarrow$ Ag^+

metal

$\{Ag_2[Ag_4Tz_6]\}_n$

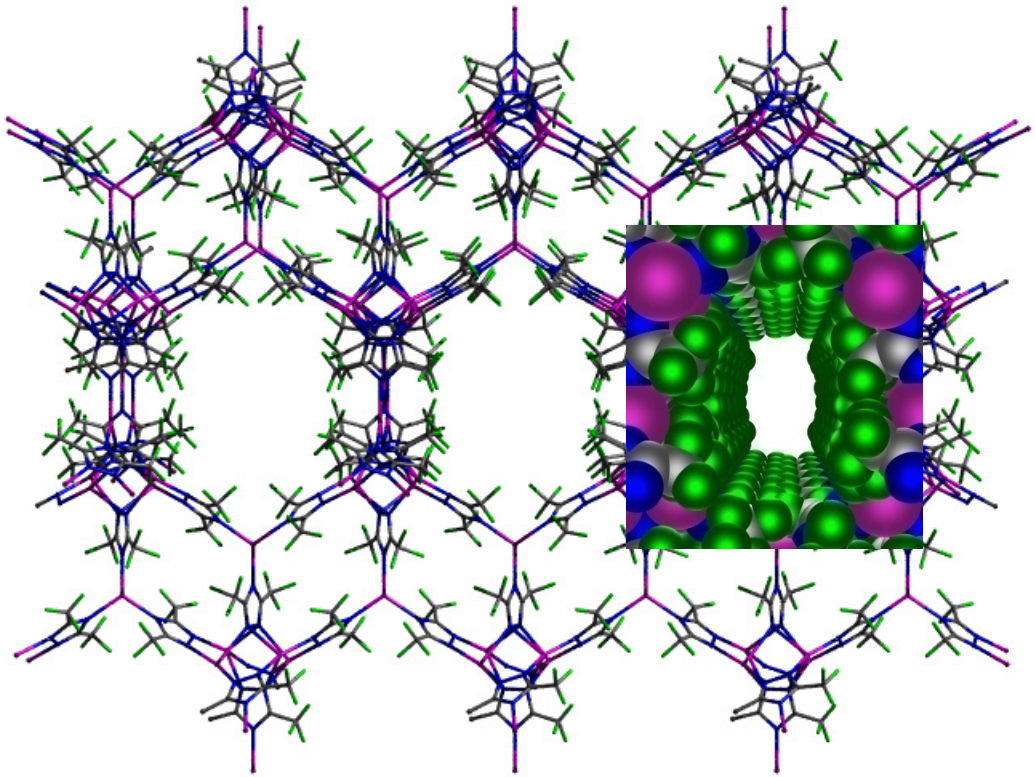
Synthesis

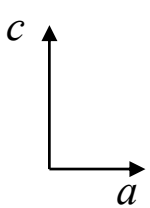


FMOF-1

C. Yang, X. P. Wang, M. A. Omary, *J. Am. Chem. Soc.* **2007**, 129, 15454.

Perfluorinated Channels in FMOF-1



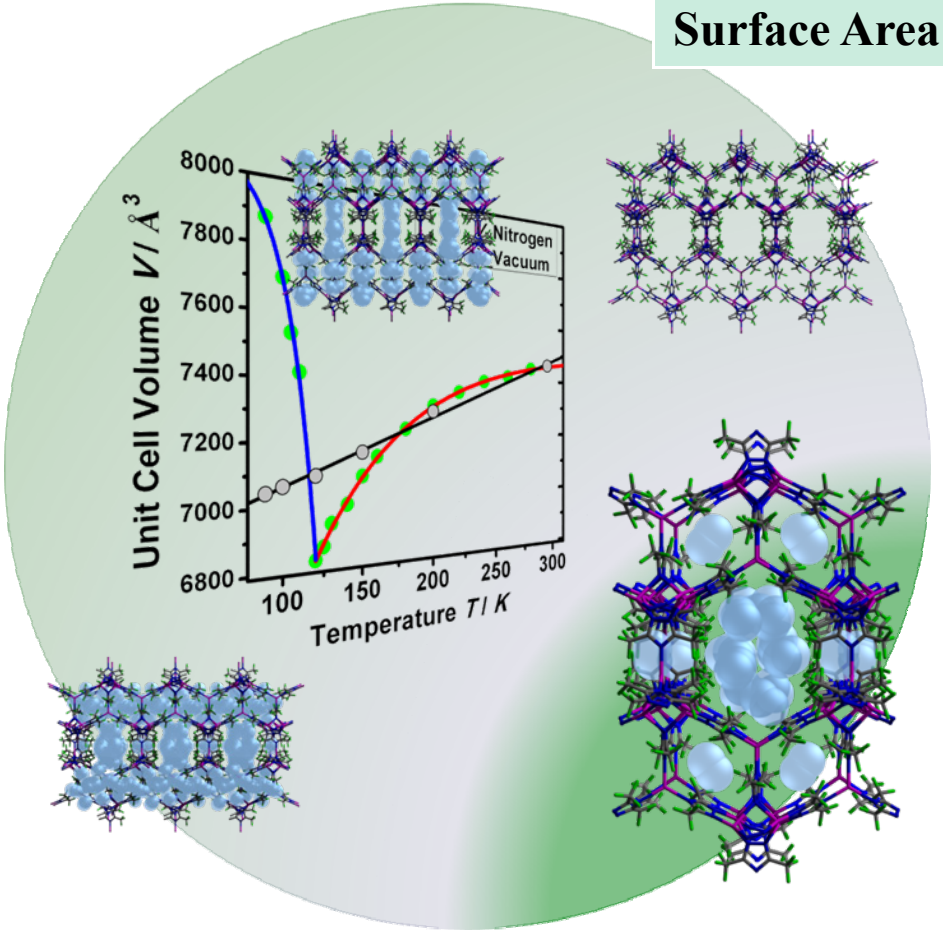


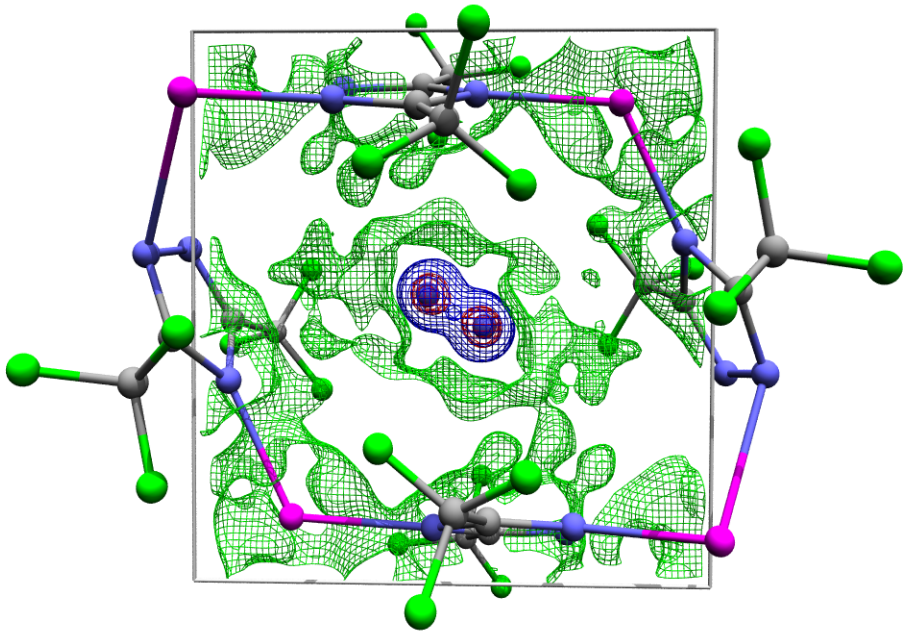
[*Evacuated Structure*]

***a* /Å**	14.0733(5)
***c* / Å**	37.675(3)

Gas Adsorption Dynamic Processes in FMOF-1

Temperature	295 K	119 K	90 K
V_{void}/V_{cell}	43.6%	37.8%	47.3%
$V_{void(small\ cage)}/V_{cell}$	1.1%	0%	4.1%
Surface Area m^2/cm^3	901.1	838.3	1005.0

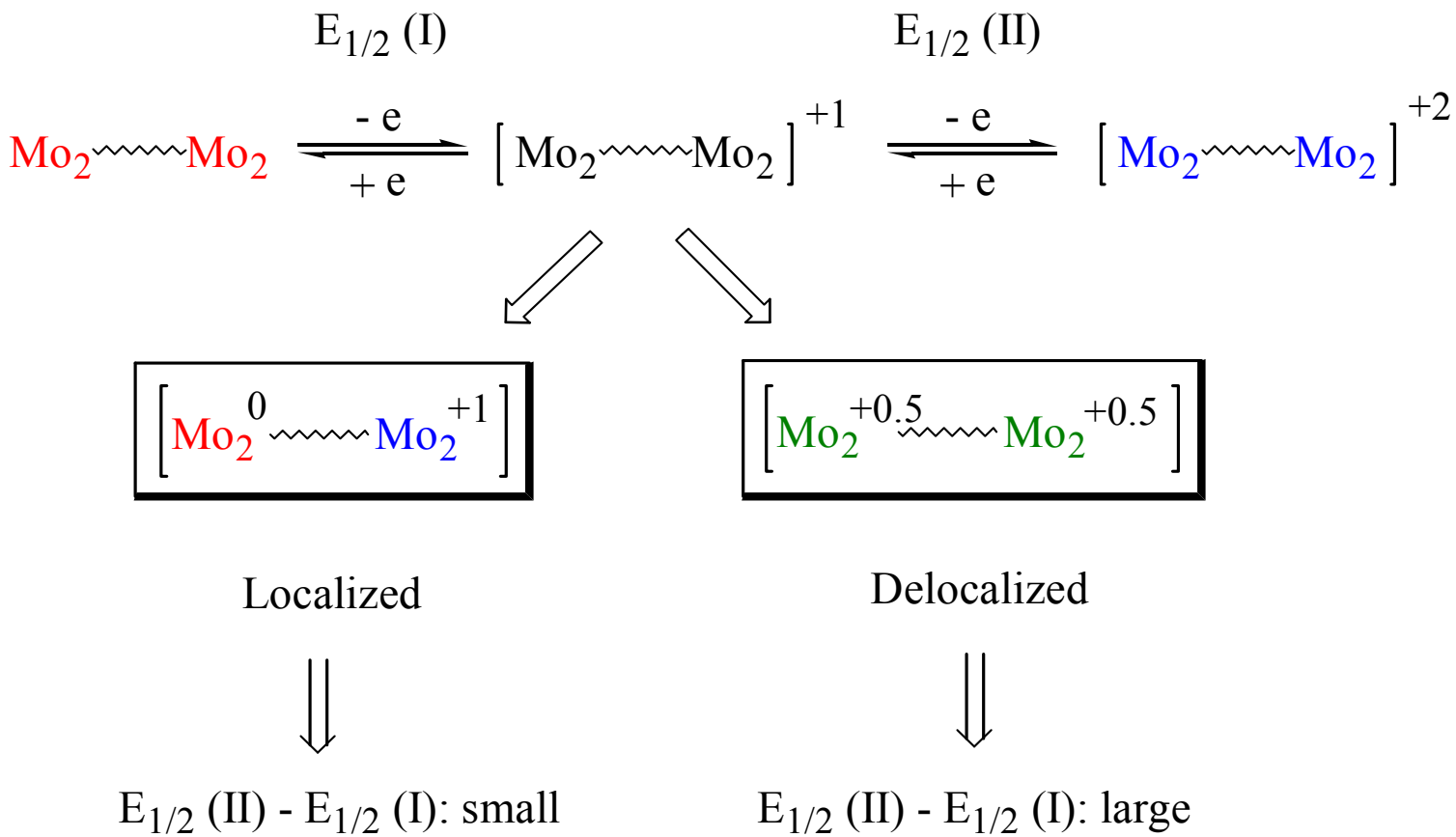




Filling of the small cavities with N_2 initiates the *Negative Thermal Expansion processes*.

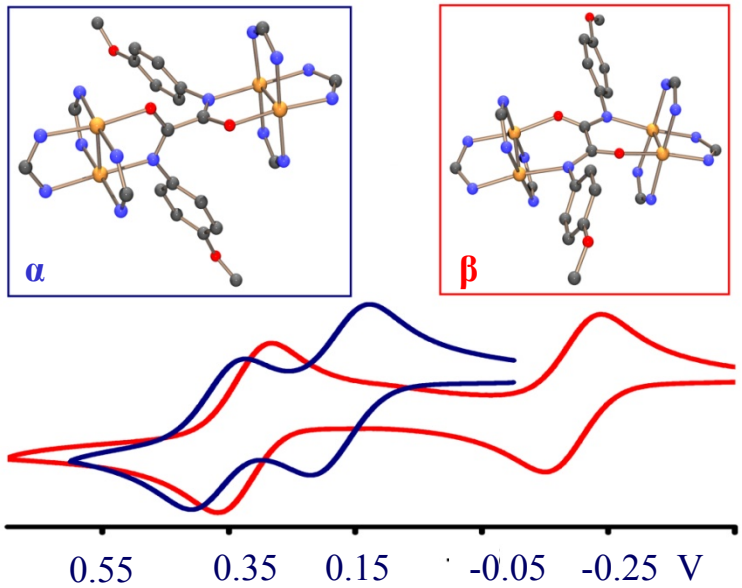
C. Yang, X. P. Wang, M.A. Omary, *Angew. Chem. Int. Ed.* **2009**, *48*, 2500.

Electronic Communication Between Dimetal Units



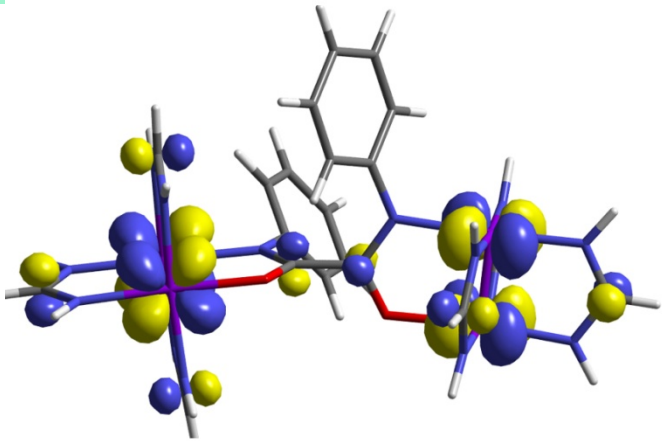
F. A. Cotton *et al*, *J. Am. Chem. Soc*. **2004**, *126*, 14822.

Conformational Effects of Oxamidate Linkers

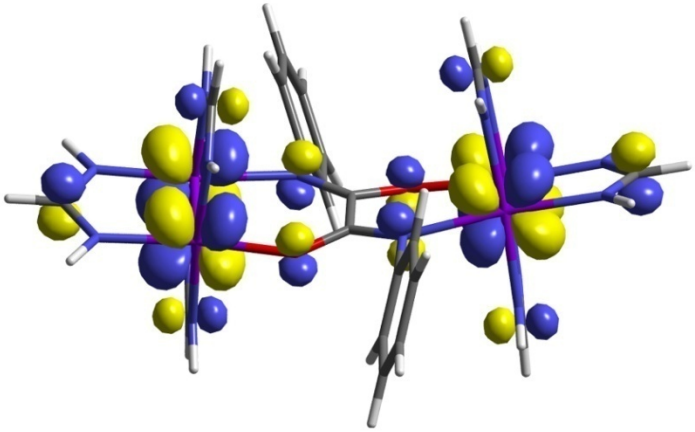


	α	β
$\Delta E_{1/2}$	191 mV	540 mV
K_C	1.7×10^3	1.3×10^9

$[Mo_2(DAniF)_3]_2(AniNC(O)C(O)NAni)$



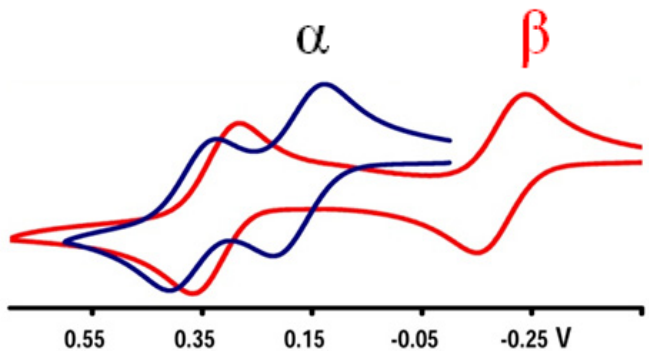
α-*gauche*-HOMO (-3.71 eV)



β- HOMO (-3.29 eV)

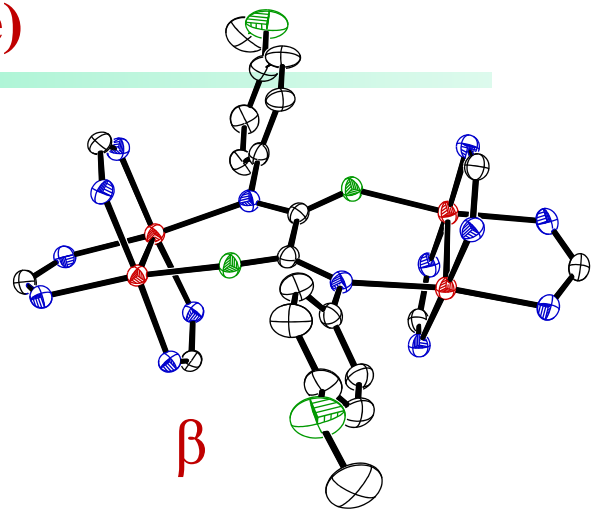
Chemical Oxidation of

β-$[Mo_2(DAniF)_3]_2$(*N*,*N'*-di-*p*-anisyloxamidate)

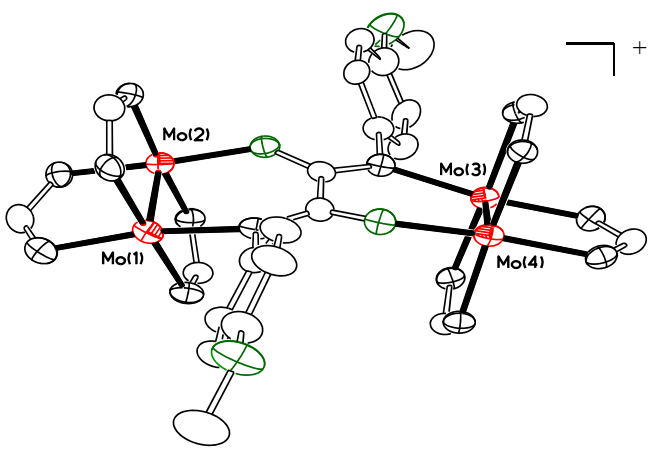


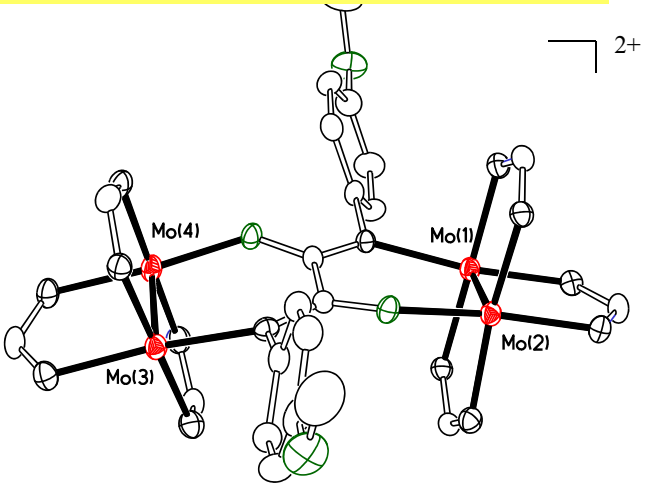
$\Delta E_{1/2}$ = 523 mV

$K_C = 6.9 \times 10^8$



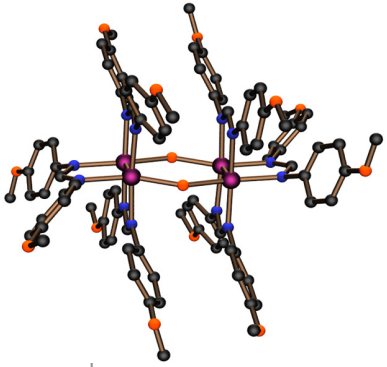
	Neutral	Singly oxidized	Doubly oxidized
Mo—Mo bonds	2.0944(4) Å	2.111(1), 2.114(1) Å	2.1446(8), 2.1418(8) Å



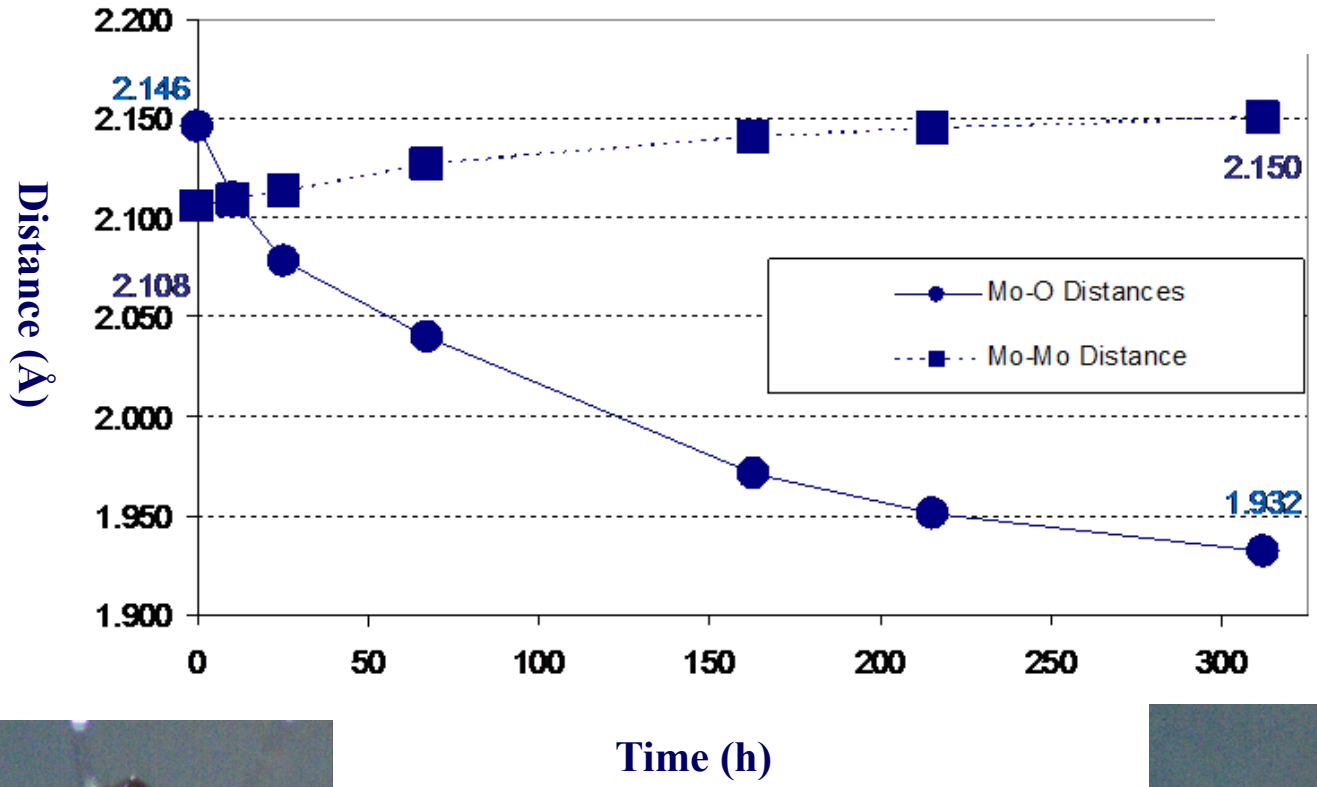


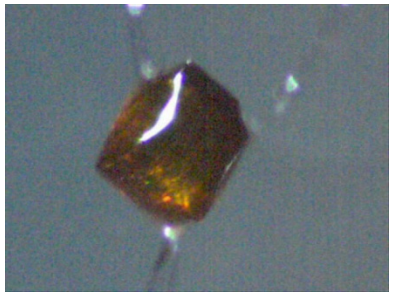
F. A. Cotton *et al*, *J. Am. Chem. Soc*. **2004**, *126*, 14822.

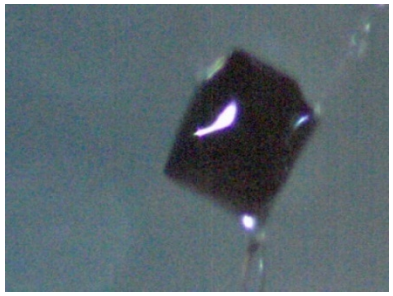
Oxidation Reaction in a Single Crystal



Time Dependence of Mo–Mo and Mo–O Distances







F. A. Cotton et al, *Inorg. Chem*. **2007**, *46*, 3245

Unit Cell Transformation

$P\bar{1}$, Z=2
a = 14.8324(18) Å
b = 17.394(2) Å
c = 17.804(2) Å
α = 87.946(2)°
β = 88.125(2)°
γ = 86.966(2)°
V = 4582(1) Å^3

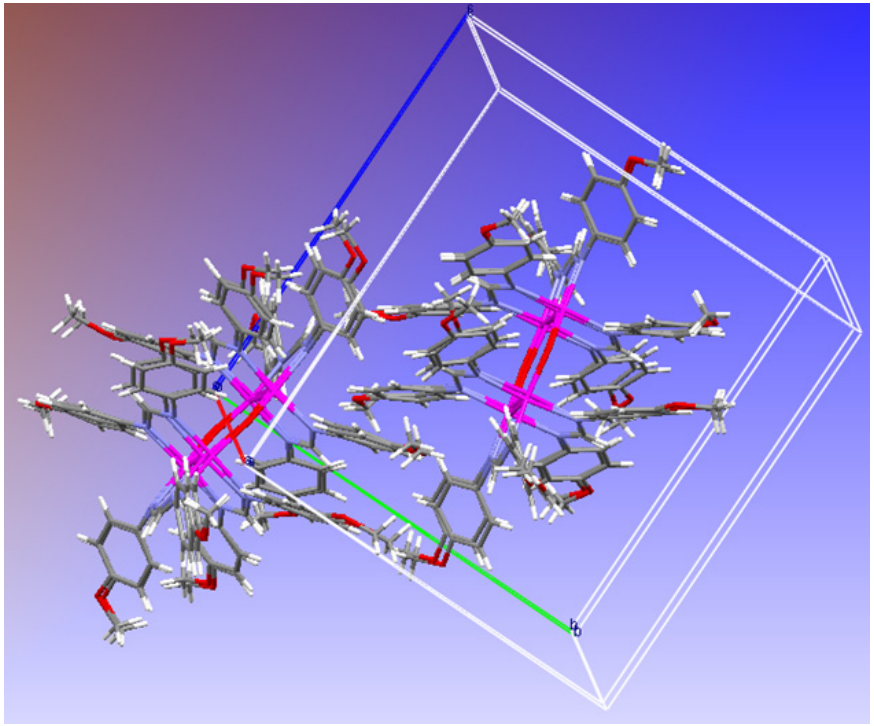
t=00 h

$P\bar{1}$, Z=2
a = 14.661(3) Å
b = 17.247(3) Å
c = 17.539(3) Å
α = 91.456(3)°
β = 91.093(3)°
γ = 95.927(3)°
V = 4408(2) Å^3

t=312 h

(-1 0 0, 0 1 0, 0 0 -1)

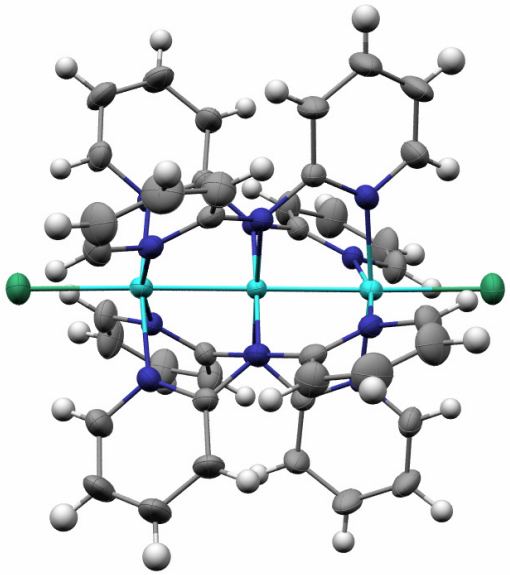
$P\bar{1}$, Z=2
a = 14.8324(18) Å
b = 17.394(2) Å
c = 17.804(2) Å
α = 92.054(2)°
β = 88.125(2)°
γ = 93.034(2)°
V = 4582(1) Å^3

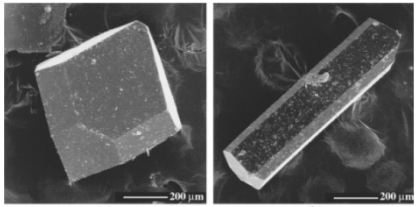


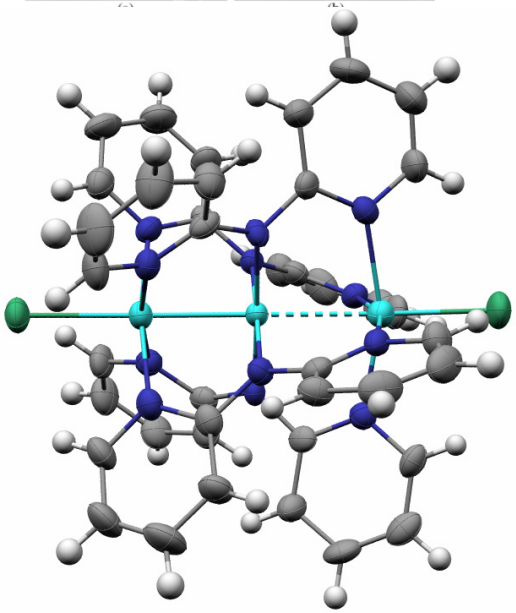
Effects of Crystallization on Molecular Structure

Can crystal structure determine molecular structure?
For $Co_3(dpa)_4Cl_2$, yes

F. Albert Cotton,*[a] Carlos A. Murillo*[a,b] and Xiaoping Wang[a]







(s-$Co_3(dpa)_4Cl_2 \cdot CH_2Cl_2$)

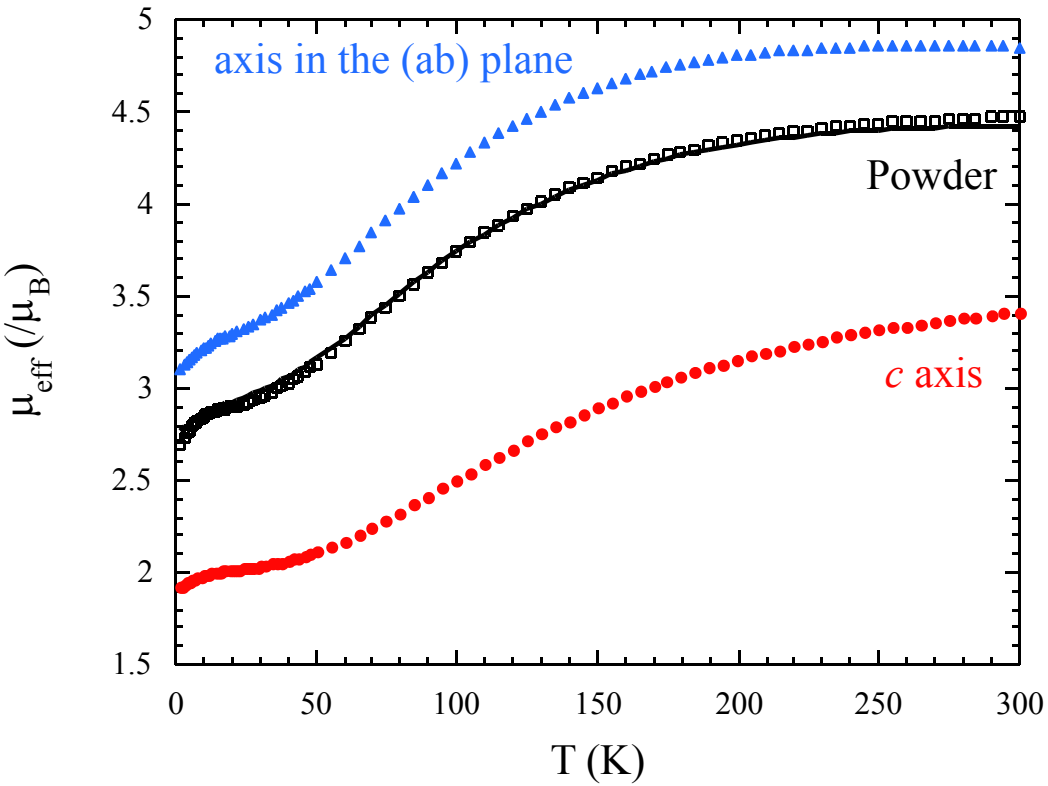
Cl(1) — Co(1) — Co(2) — Co(1A) — Cl(1A)
2.4881(8) **2.3369(4)** **2.3369(4)** 2.4881(8) Å

(u-$Co_3(dpa)_4Cl_2 \cdot 2CH_2Cl_2$)

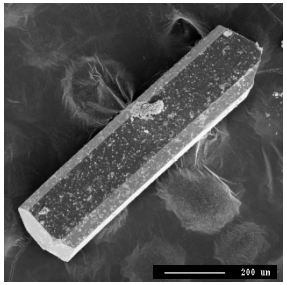
Cl(1) — Co(1) — Co(2) ···· Co(3) — Cl(2)
2.434(2) **2.299(1)** **2.471(1)** 2.363(2) Å

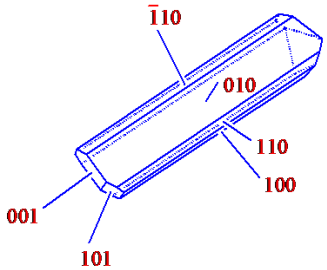
J. Chem. Soc., Dalton Trans., **1999**, 3327.

Magnetic Property of *u*-$Co_3(dpa)_4Cl_2 \cdot 2CH_2Cl_2$



$$\chi = \frac{1}{3}(2\chi_{\perp} + \chi_{\parallel})$$

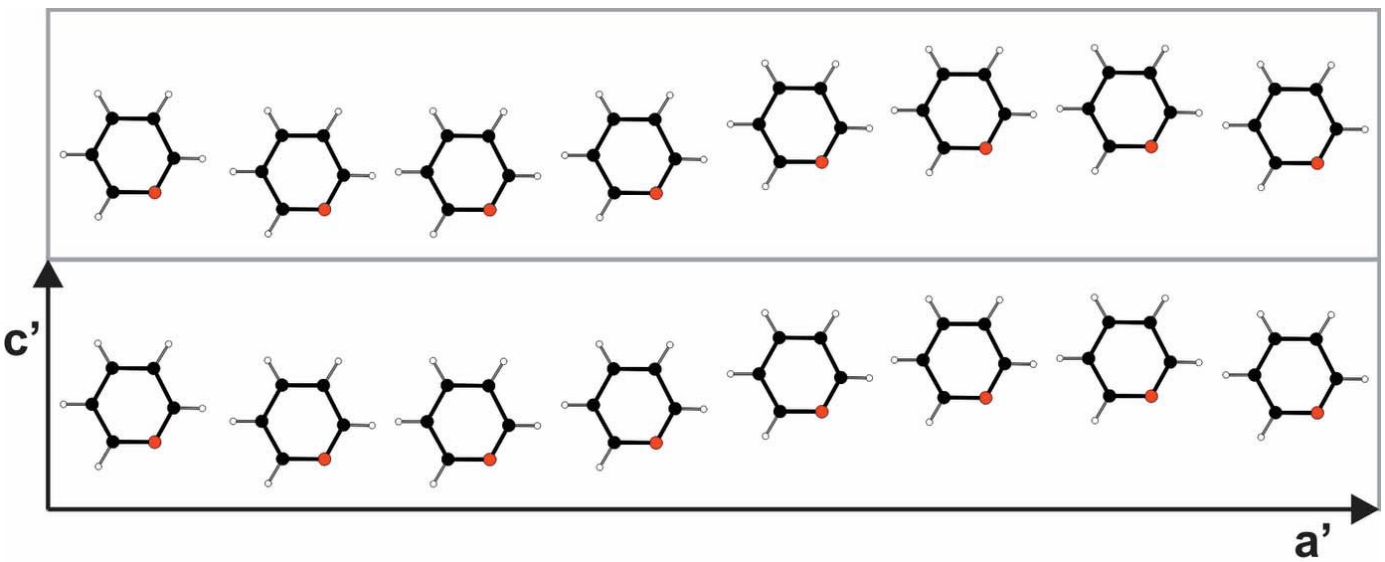


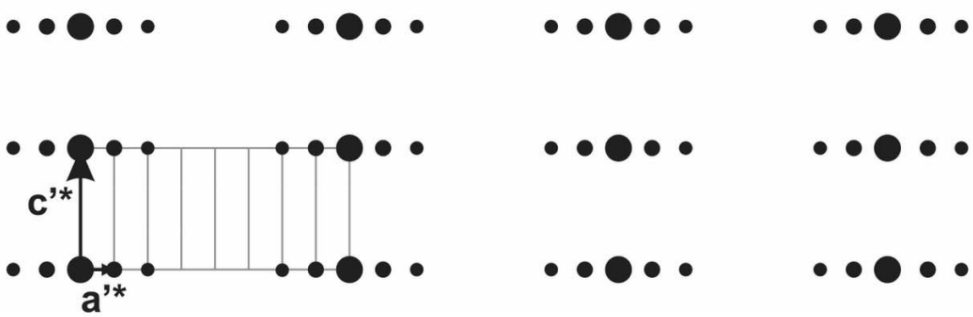


Spin Crossover S = 1/2 To S = 3/2

Clerac, R.; Cotton, F. A.; Daniels, L. M.; Dunbar, K. R.; Kirschbaum, K; Murillo, C. A.; Pinkerton, A. A; Schultz, A. J; Wang, X. P, *J. Am. Chem. Soc.* **2000**, *122*, 6226

Going Beyond Three Dimensional Space

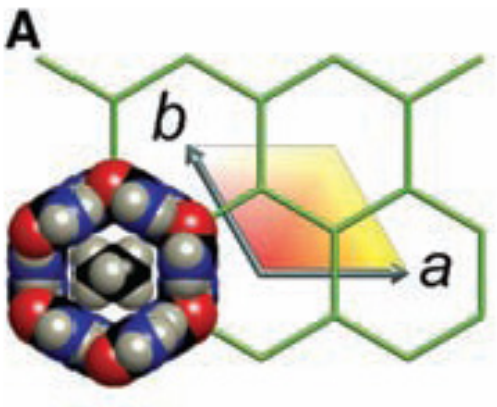


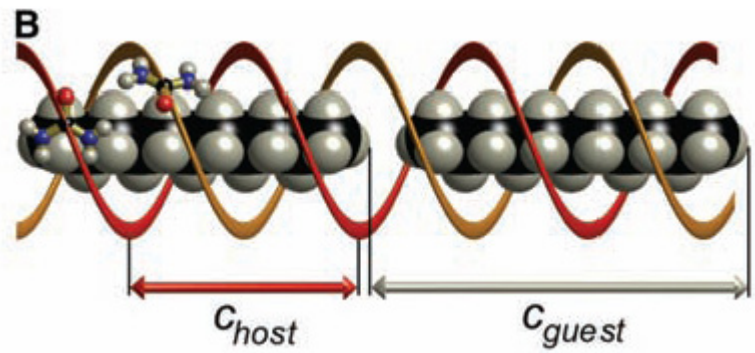


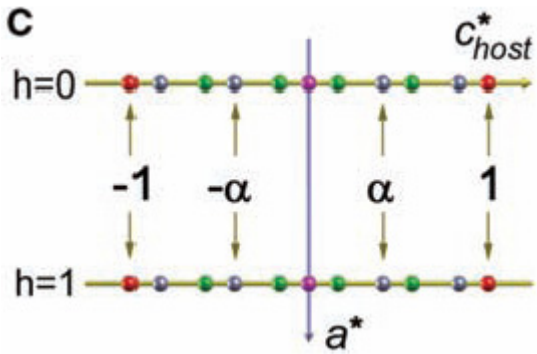
$$\mathbf{q} = 0.125\mathbf{a}^* + 0\mathbf{b}^* + 0\mathbf{c}^*$$

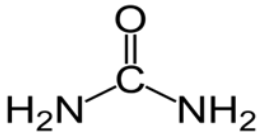
T. Wagner and A. Schönleber, *Acta Cryst*. **2009**, *B65*, 249.

Aperiodic Crystals









urea-d_4

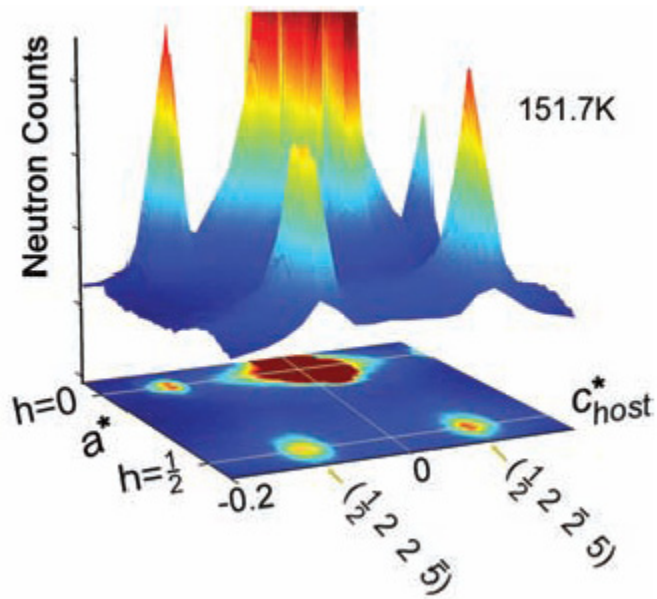
$C_{19}D_{40}$

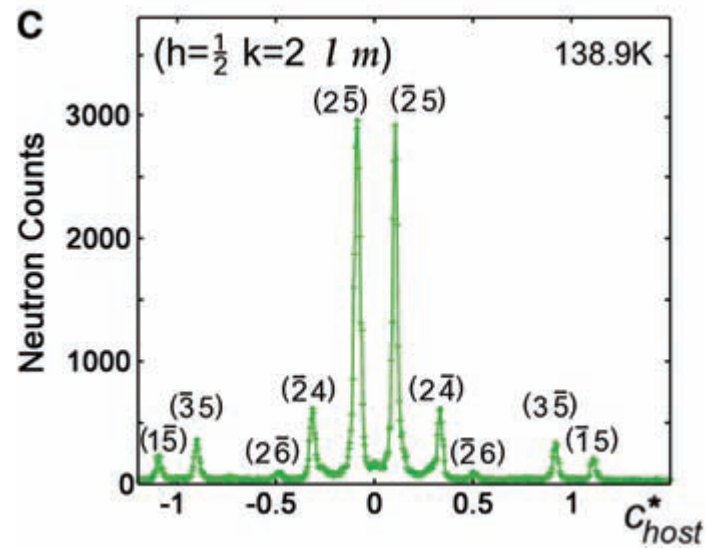
nonadecane-d_{40}

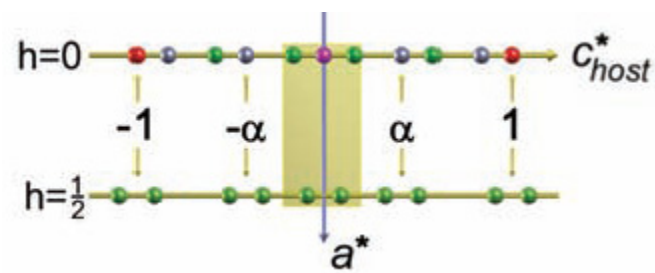
B. Toudic et al, *Science*, **2008**, *319*, 69.

Symmetry Breaking in Superspace

ISIS SXD







$$G_{hklm} = h\mathbf{a}^* + k\mathbf{b}^* + l\mathbf{c}^*_{host} + m\mathbf{c}^*_{guest}$$

A molecular solid can change from one structure to another in a way that can only be described properly using four-dimensional space.

B. Toudic *et al*, *Science*, **2008**, *319*, 69.

Charge Density Analysis

X-Ray Intensity

Theory

Geometry

Bonding?

Bonding

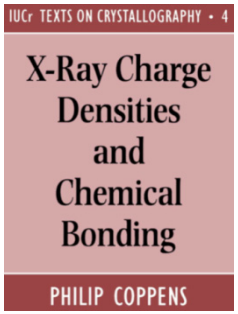
Geometry?

Electron Density

Deformation density
Topological analysis

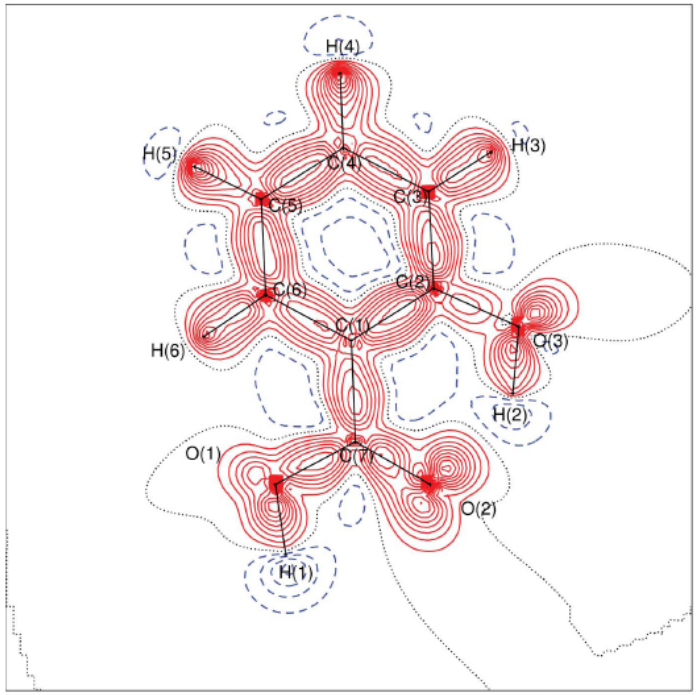
[Charge Density]

Chemical Bonding
Molecular Property
Intermolecular Interaction

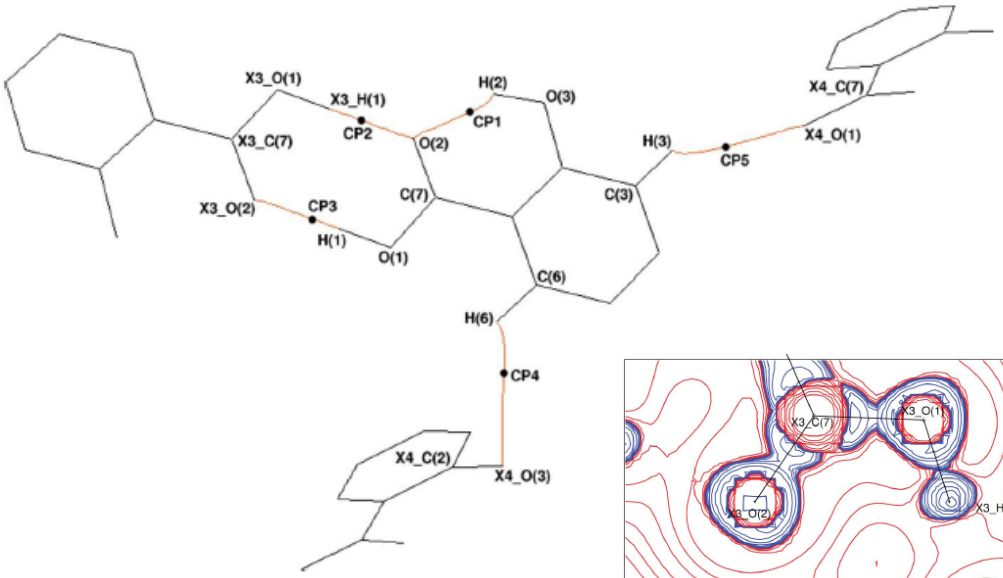


P. Coppens, *Angew. Chem. Int. Ed.* **2005**, *44*, 6810.

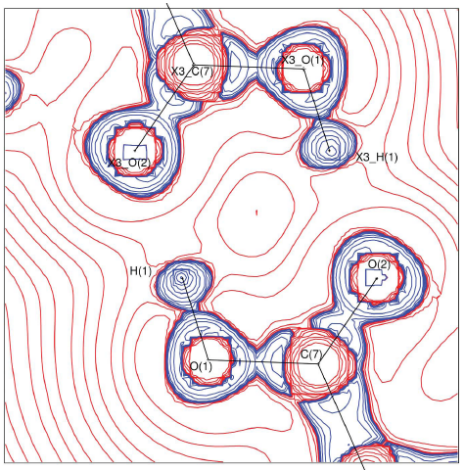
Cooperative Features in a Bioactive Molecule



Static deformation-density map for salicylic acid.



Bond-paths (BCP) along the hydrogen bonds

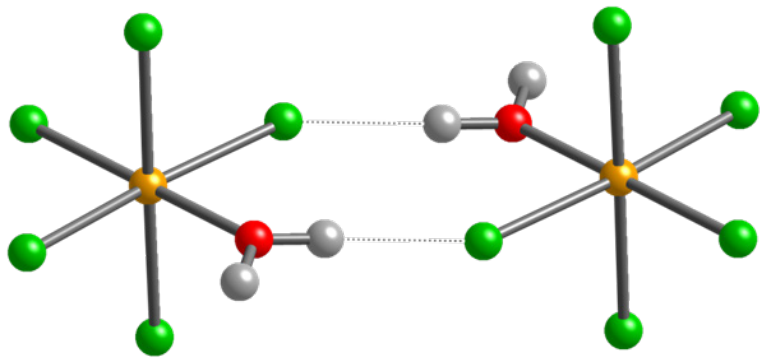


Laplacian distribution of the O—H···O hydrogen bonds.

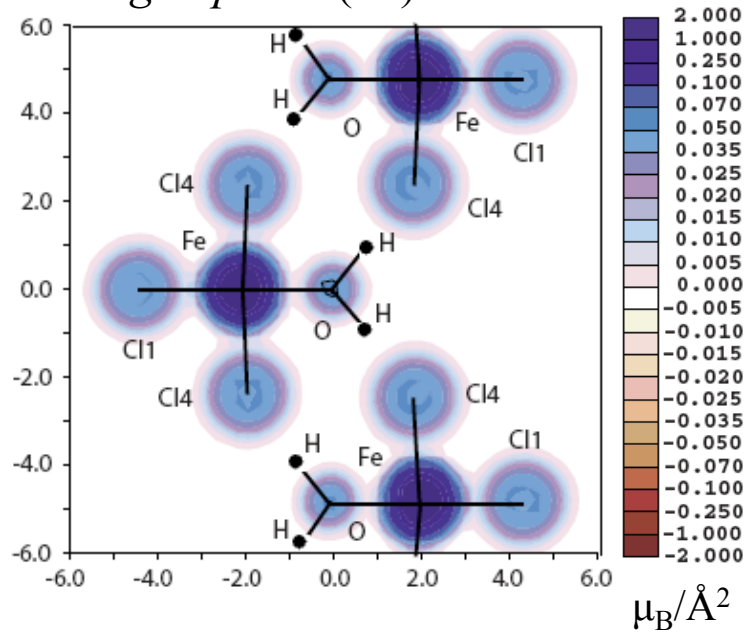
Munshi and Guru Row, *Acta Cryst*. **2006**, *B62*, 612.

Spin-Density Distribution in $K_2FeCl_5 \cdot H_2O$

Polarized Neutron Diffraction D23 at ILL



High Spin Fe(III)



Color Projection of the spin-density fit in the plane containing the Fe–O–H⁻*Cl–Fe pathway* from the multipole expansion approach.

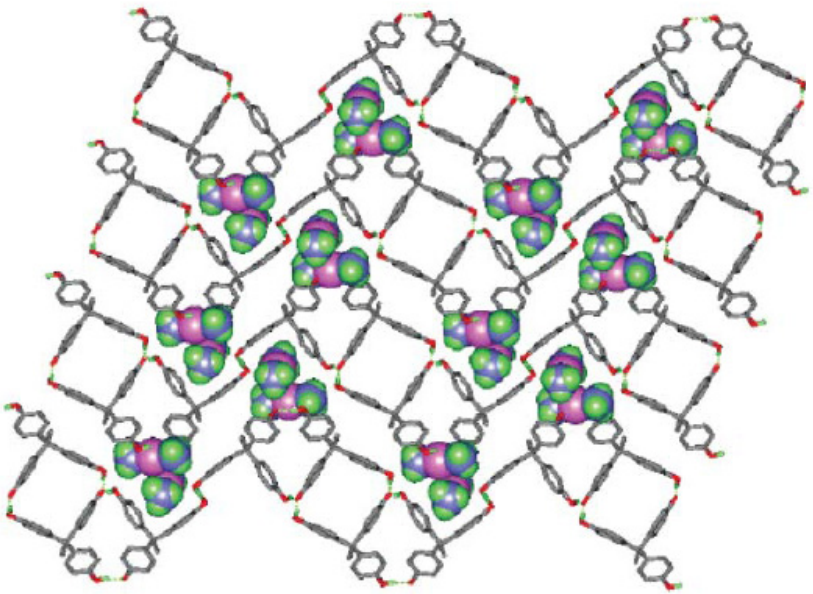
Luzón et al, *Physical Review B,* **2008**, *78*, 054414.

Time Resolved Diffraction

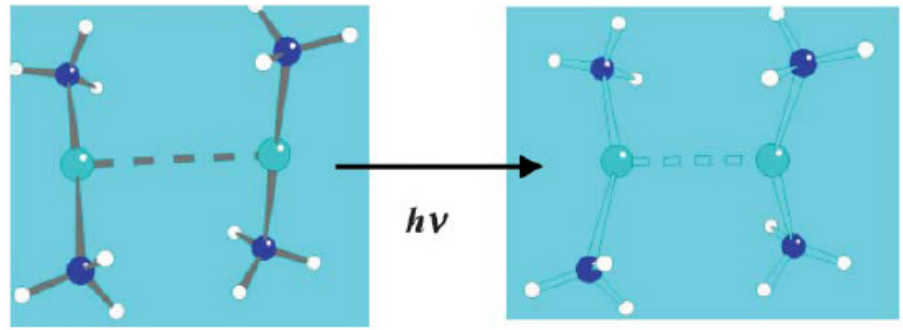
Reversible — Molecular excitation
Irreversible — (Photo)-initiated chemical reaction

15-ID at APS

Supramolecular
Time-resolved diffraction



$[Cu(NH_3)_2]_2[THPE]_2 \cdot 3.25H_2O$



Contraction of the Cu–Cu distance in the $[Cu(NH_3)_2]_2$ 2+ ion (from 3.02 to 2.72 Å)

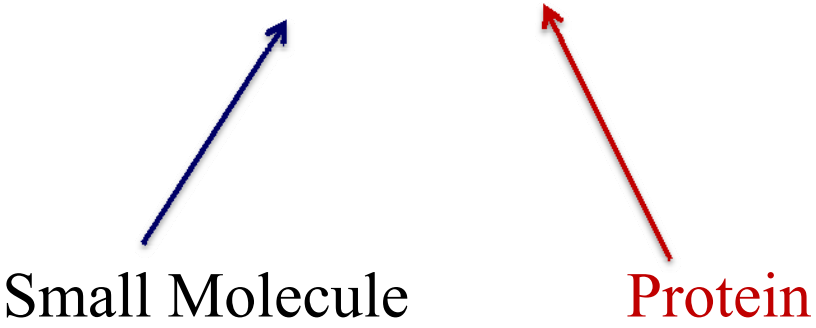
Pulsed laser-excitation (532 nm) at 17 K
A triplet excited state lifetime of 4.2 ms
Pause repeat frequency at12 kHz.

P. Coppens *et al*, *CrystEngComm*, **2006**, *8*, 735.

Perspectives in Neutron Crystallography

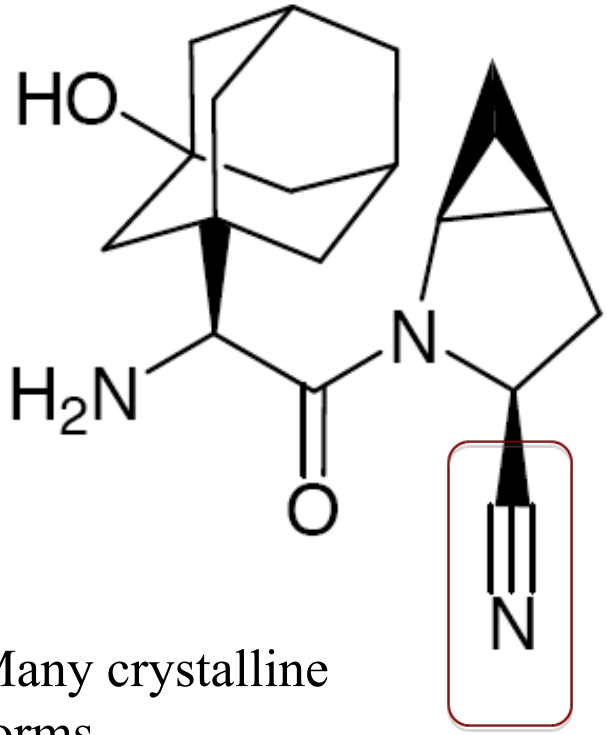
- **Bridging the Gap in Small Molecule and Macromolecule Crystallography**

  – Chemical Reaction between Ligand and Receptor



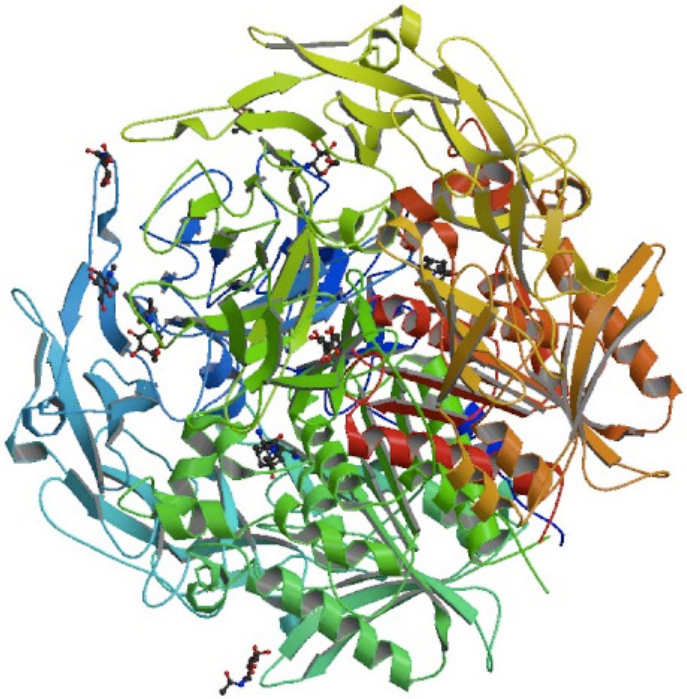
ONGLYZA (Saxagliptin)

Saxagliptin is a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes.



$\cdot H_2O$

Many crystalline forms



DPP-IV:Saxagliptin Cocrystal

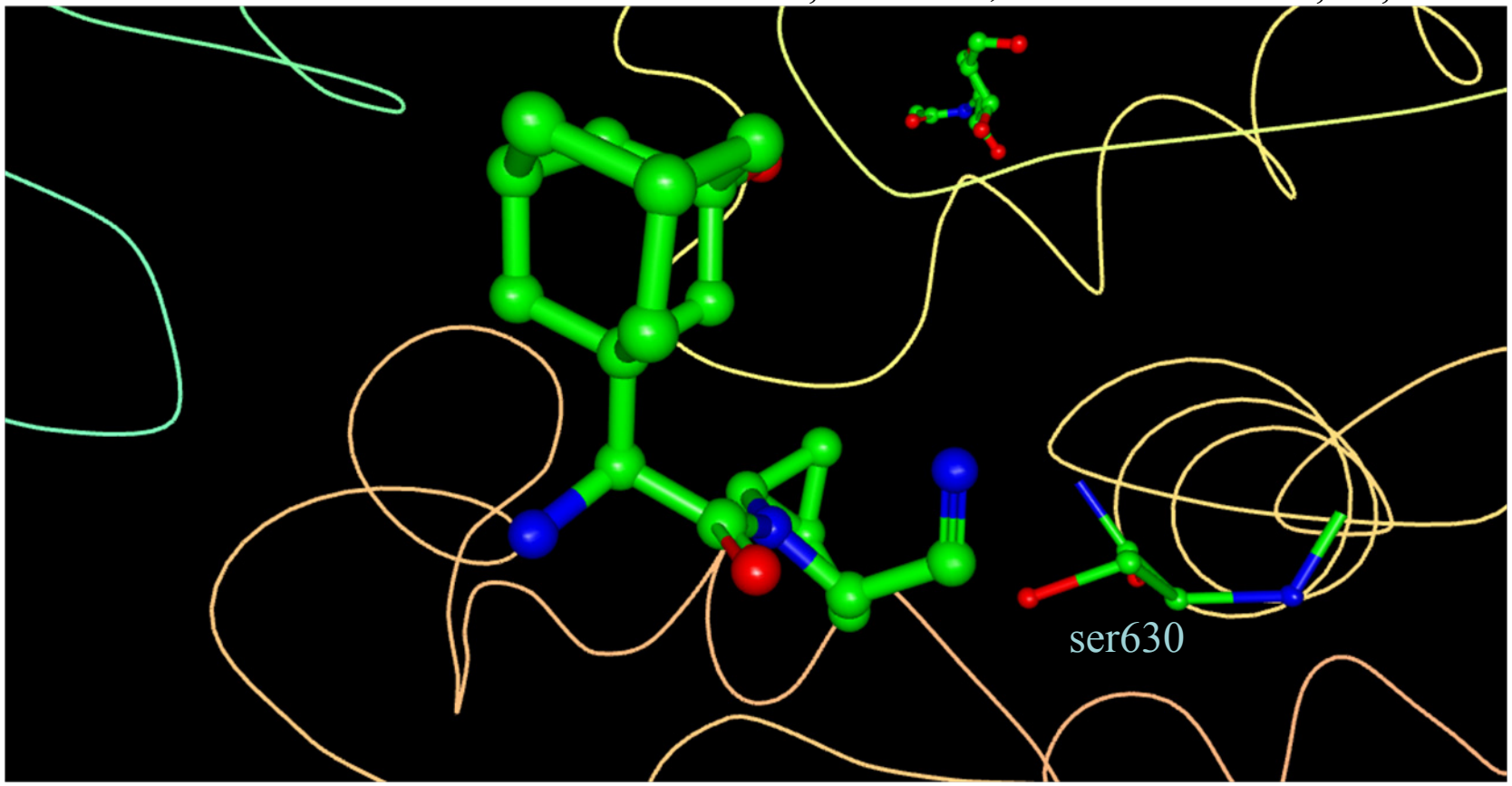
2.35 Å resolution

Metzler, W.J. *et al, Protein Sci*. **2008**, *17*, 240-50.

Crystal Structure of DPP-IV:Saxagliptin

Covalent bonding between S630 and the inhibitor nitrile carbon.

Metzler, W.J. *et al, Protein Sci*. **2008**, *17*, 240-50.

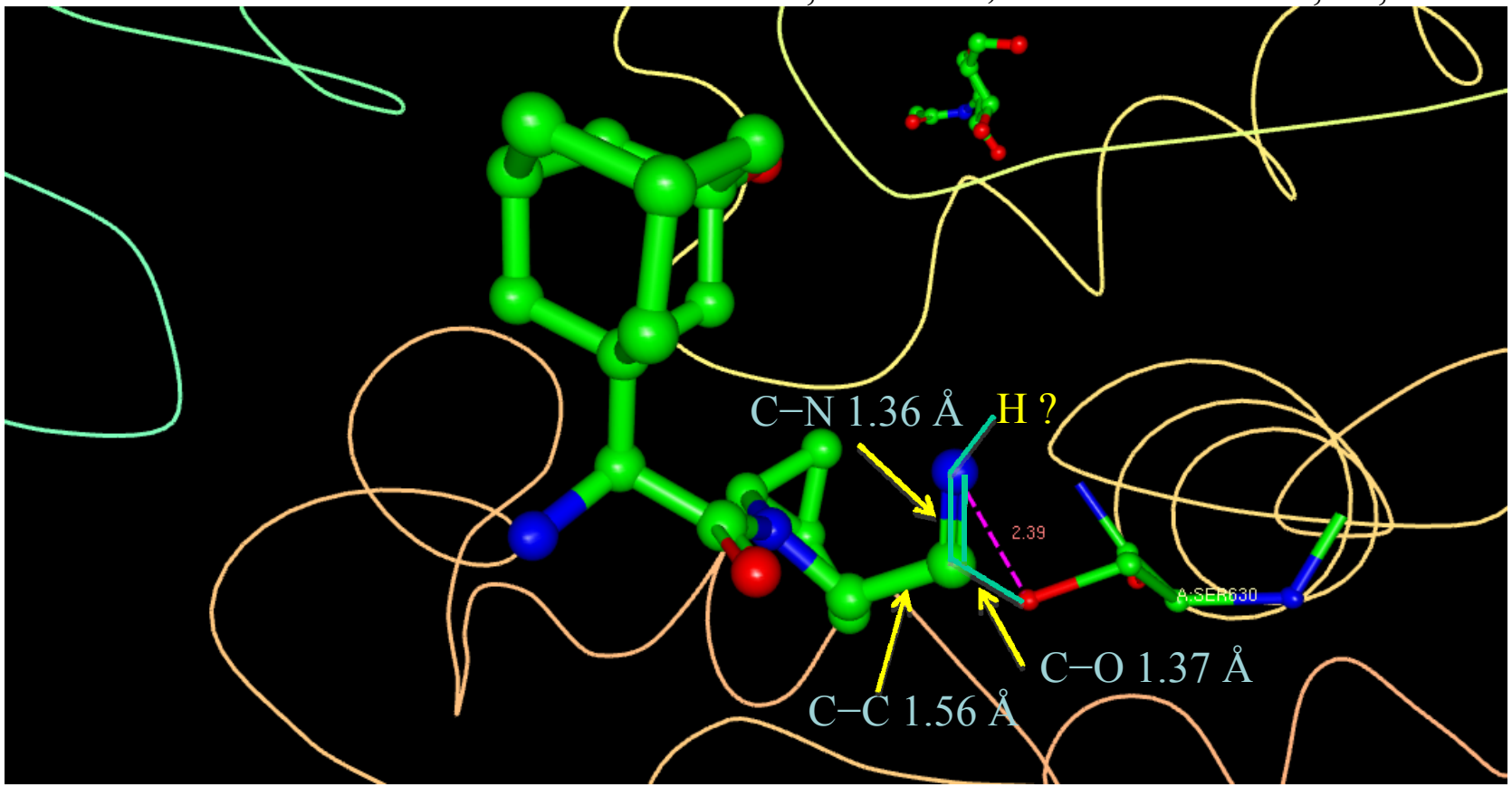


http://www.pdb.org/pdb/explore/explore.do?structureId=3BJM

Crystal Structure of DPP-IV:Saxagliptin

Covalent bonding between S630 and the inhibitor nitrile carbon.

Metzler, W.J. *et al, Protein Sci*. **2008**, *17*, 240-50.



http://www.pdb.org/pdb/explore/explore.do?structureId=3BJM

Reaction of Coordinated Acetonitrile

Pergamon

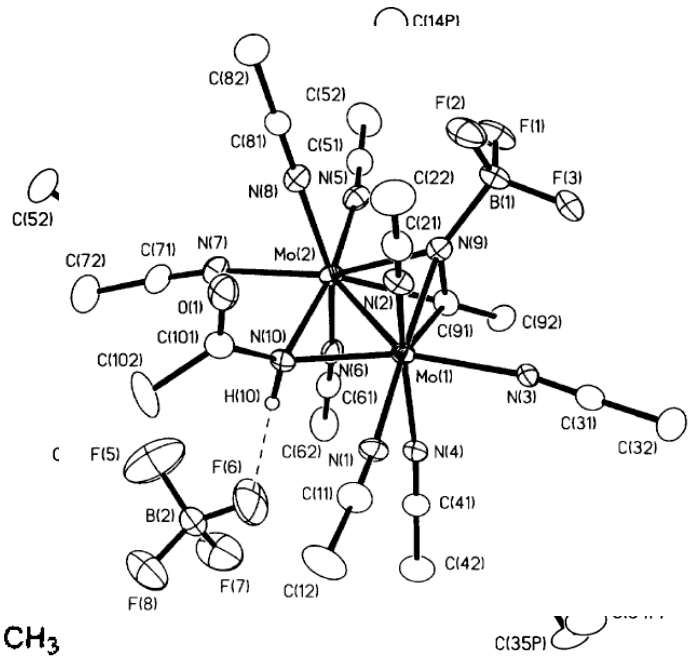
PII : S0277–5387(97)00470–1

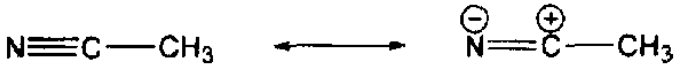
Polyhedron Vol. 17, No. 17, pp. 2781–2793, 1998

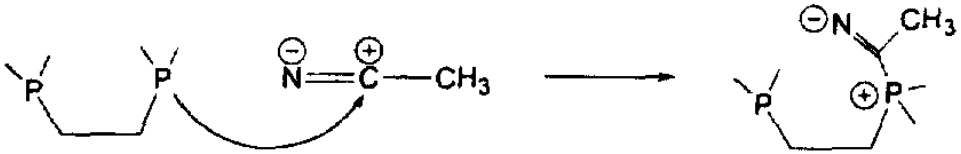
0277–5387/98 $19.00+0.00

From end-on coordination of acetonitrile molecules to crosswise bridging ; formation of iminophosphino and acetamidate ligands in a dimolybdenum complex by further reactions with nucleophiles†

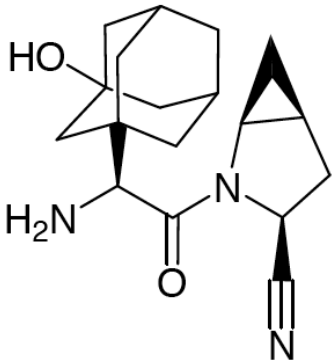
F. Albert Cotton,[a]* Lee M. Daniels,[a] Carlos A. Murillo[a,b]* and Xiaoping Wang[a]



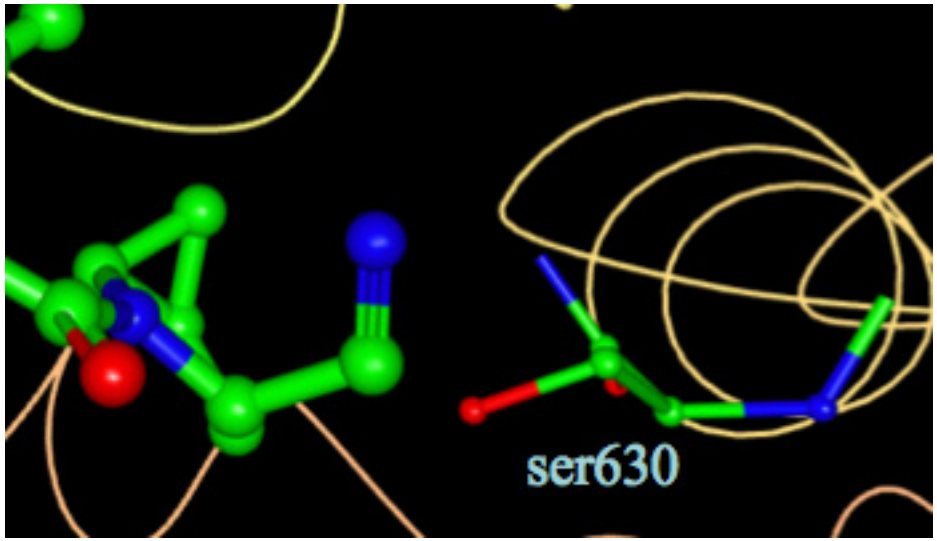


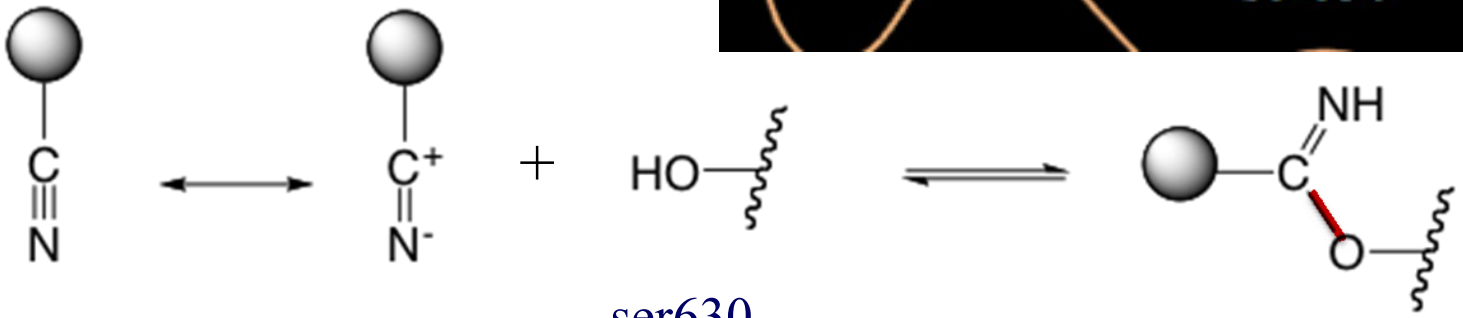


A Covalent Bond Formed in DPP-IV:Saxagliptin



Saxagliptin





ser630
DPP-IV

An imidate product

Need a neutron structure to understand inhibitor bonding

Research Facilities - Synchrotron Sources

ChemMatCARS (15-ID) at APS, Argonne National Laboratory

Very high-energy synchrotron radiation ~6 to 32 KeV

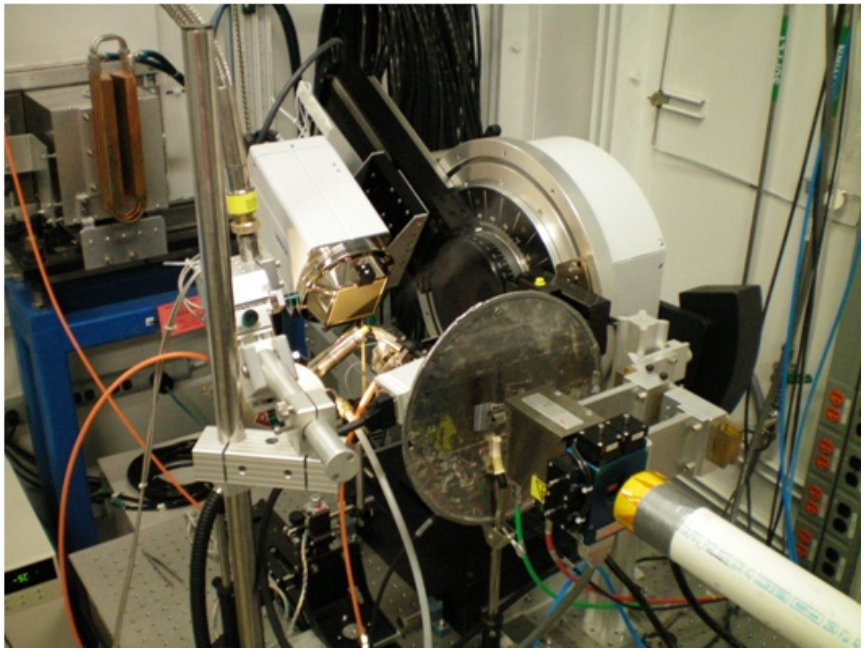
- Extinction-free diffraction

Use of much smaller crystals
Beam size 80 to 500 μm

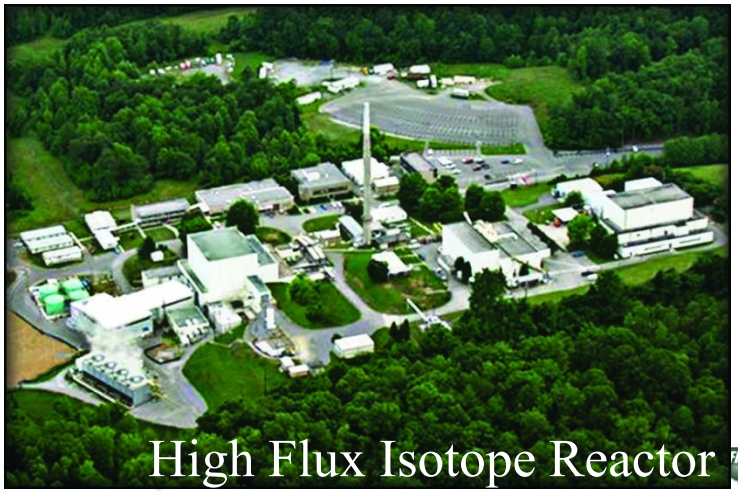
- Minimize extinction and absorption

Low temperatureLiquid Helium cryostat T = 15-70 K

- Reduced ADPs

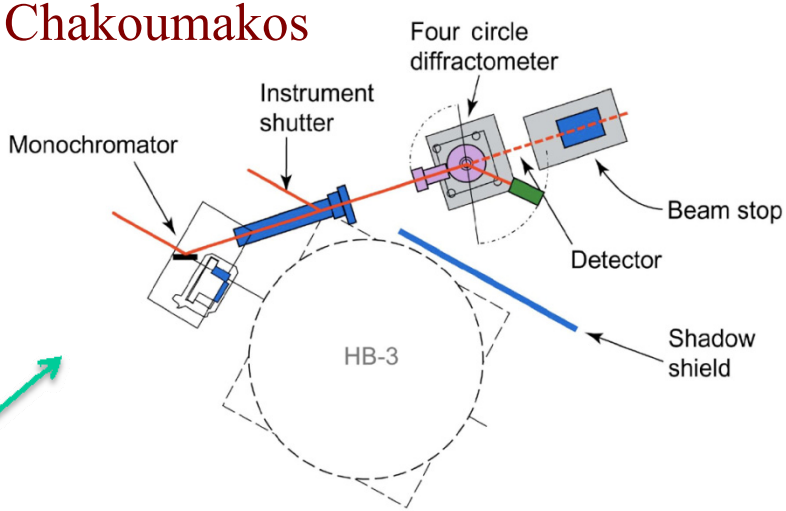


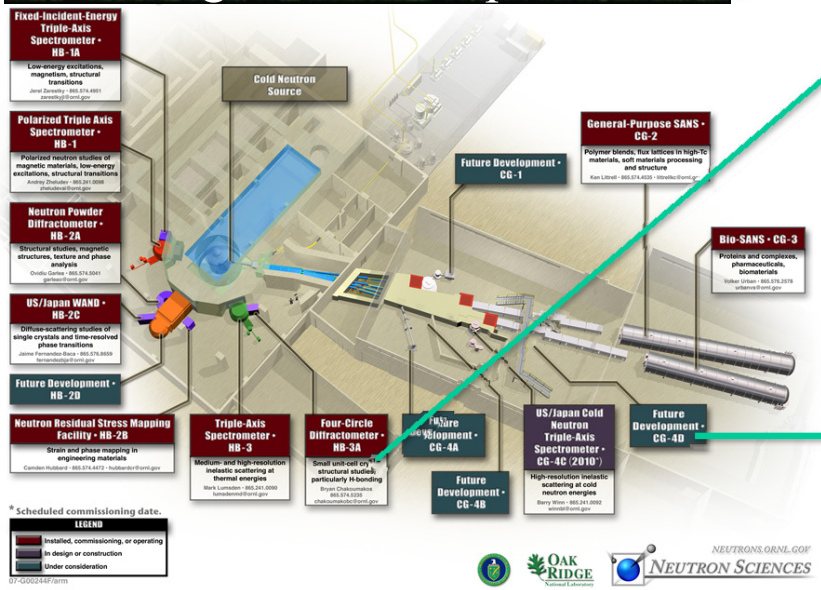
Neutron Source -HFIR Single Crystal Instruments

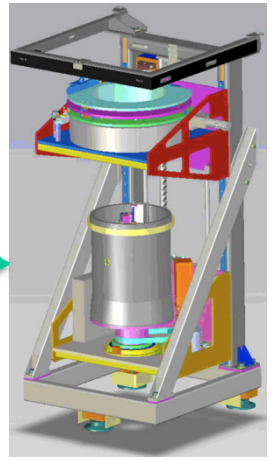


Four-Circle Diffractometer (HB-3A)

Bryan Chakoumakos







Laue Diffractometer (IMAGINE)

Funded by NSF

Tibor Koritsanszky

Flora Meilleur

SNS Single Crystal Instruments

SNAP (BL-3)

Atomic Structure

Extreme Conditions

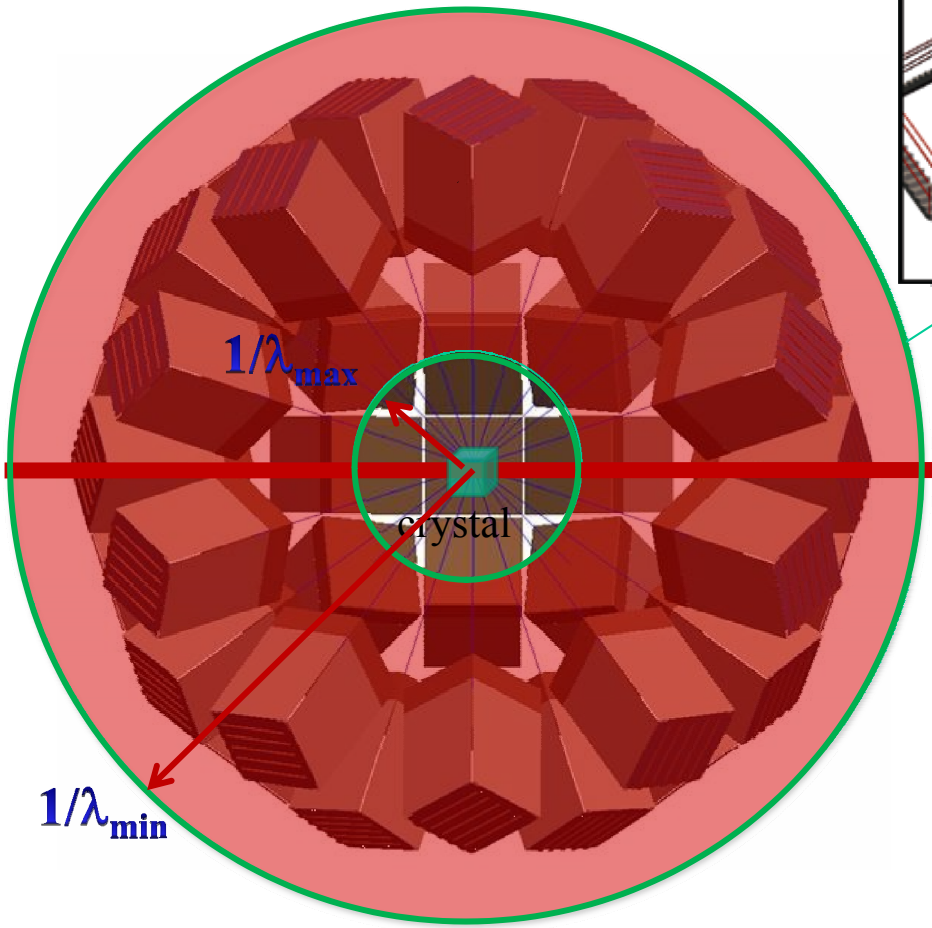
High Pressure

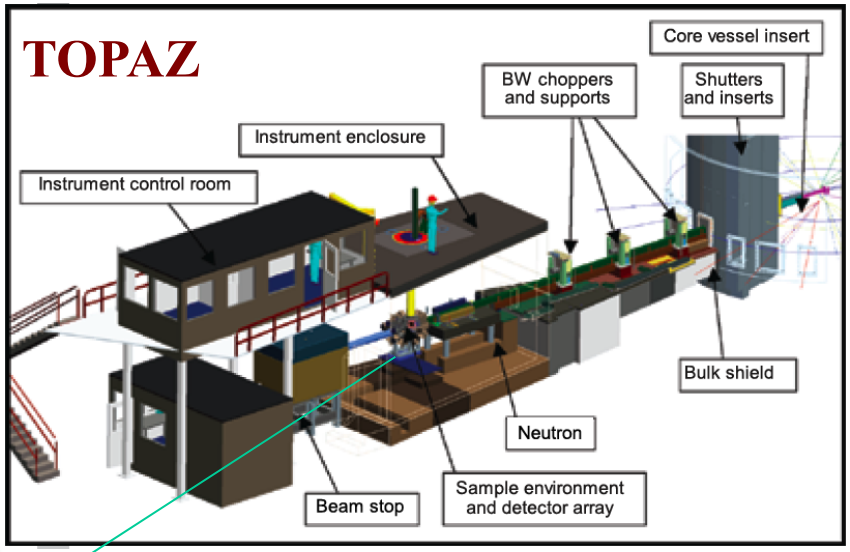
High Temperature

Time-resolved Laue Neutron Diffraction

Neutron time of flight

$$\lambda = 2d\sin\theta = \frac{h}{mv} = \frac{ht}{mL}$$



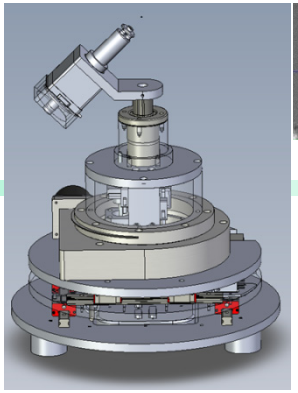


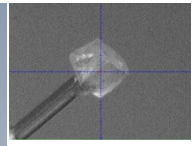
Time-resolve

3-*D* Reciproca

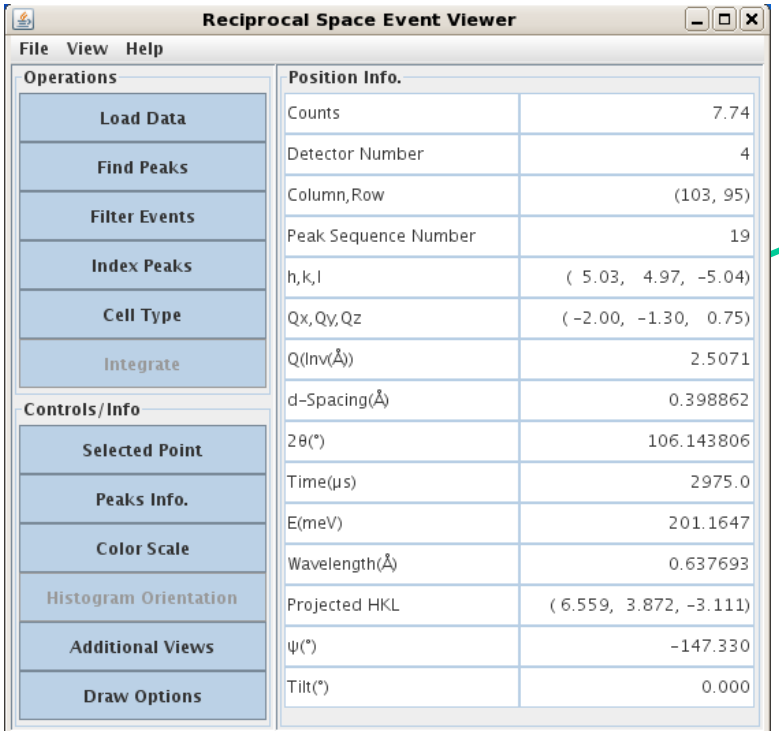
Detector pixel size	6.2 x 10^{-6} sr (1 mm)
Detector angles	0–180°
Wavelength bandwidth	3.35 Å
Frame 1	0.5–3.85 Å
Resolution	0.1%
Sample size	0.001 mm^3 < S < 1 mm^3

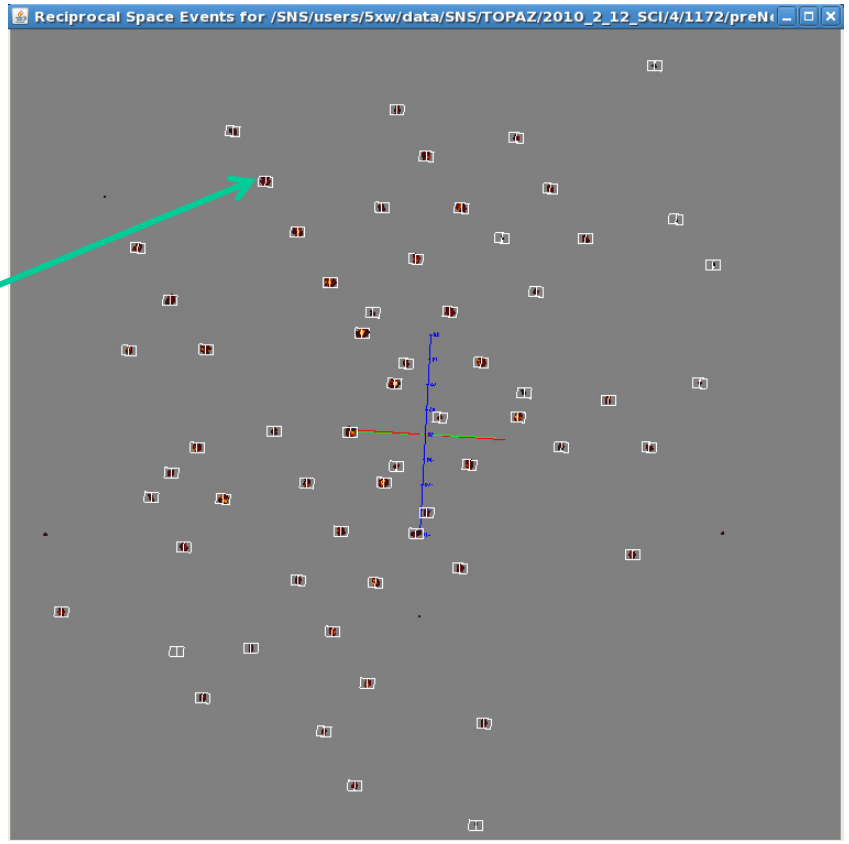
ISAW – Neutron Event Data Viewer





Live data stream is plotted into 3D ***Q***-space
Peaks are searched and indexed
Cell parameters and UB-matrix are refined





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