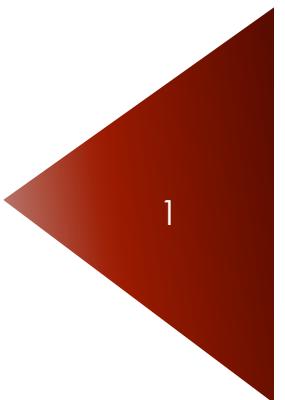


# **Applications of small molecule crystallography**

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Department of Chemistry and Biochemistry and Center for Nanoscience  
University of Missouri – St. Louis

**National School on Neutron and X-ray Scattering**  
Oak Ridge National Lab  
June 16, 2011



# **Small Molecule Applications**

**Academic Research**

**Governmental concerns (energy, weapons, explosives)**

**Pharmaceutical Industry (drug function, patents)**

**Chemical industry (synthesis, catalysts)**

**Agrochemical Industry (pesticides, herbicides)**

# What are small molecules?

## **Small molecules include:**

- › Organic and Inorganic synthetic materials
- › Drug molecules and ionic compounds
- › Natural products
- › Pesticides, herbicides, other agro-chemicals

## **Not included:**

- › Polymers
- › Proteins
- › Inorganic solids such as NaCl, other salts, metal oxides, etc.

Investigating macromolecular solids involves techniques that are different from small molecule systems.

# Where can you find small molecule data?

- **Cambridge structural database (CSD)**

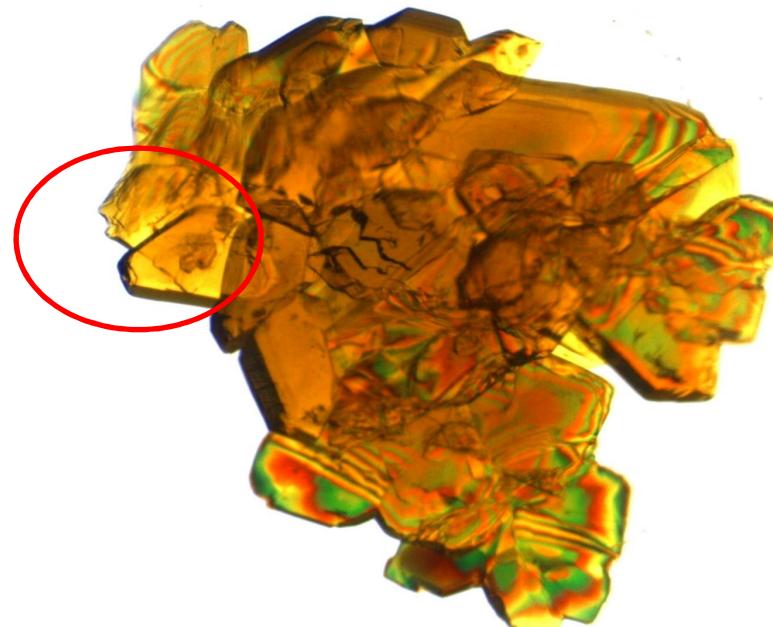
- › Contains most crystal structures containing organic groups (including organometallic and coordination compounds).
- › Most universities have a license to the database
- › The CCDC will also provide requested structures for free (you must know the deposition number(s) and the literature reference):  
<http://www.ccdc.cam.ac.uk/products/csd/request/>

- **Inorganic Crystal Structure Database (ICSD)**

- › Crystal structures of the elements and other inorganic molecules, ions, and solids only.
- › <http://www.fiz-karlsruhe.de/icsd.html>

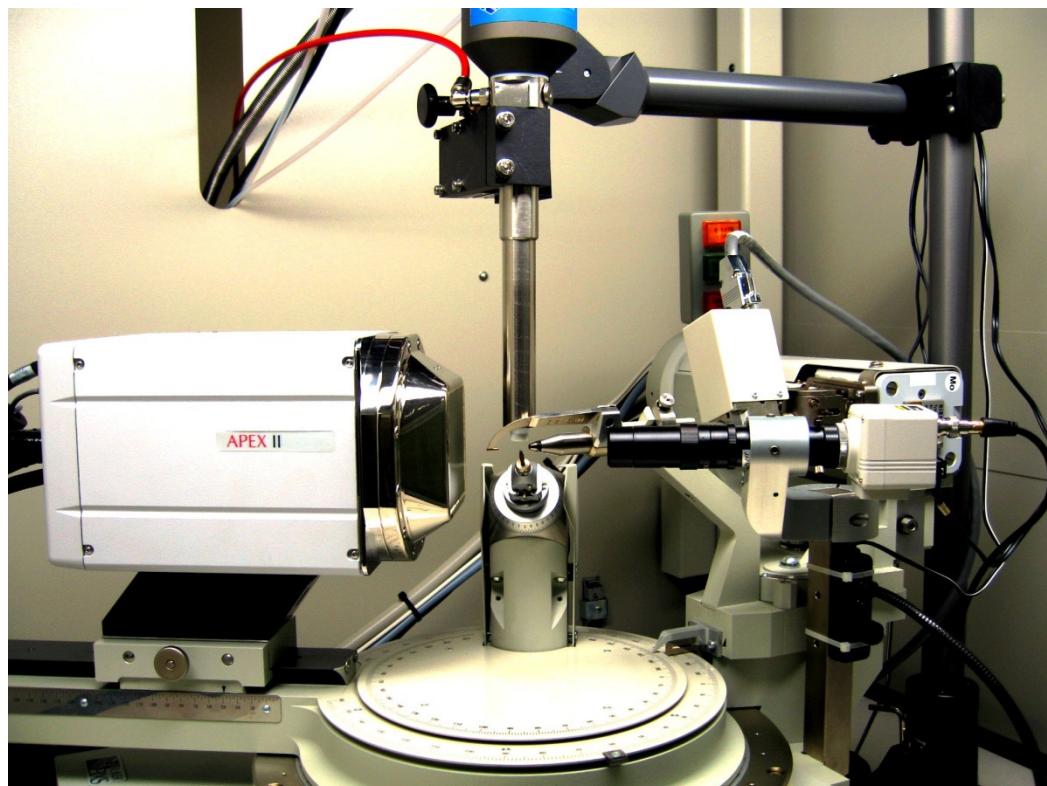
# What do you need to perform the experiment?

1. A single crystal of appropriate dimension  
(depends on the instrument you're using)

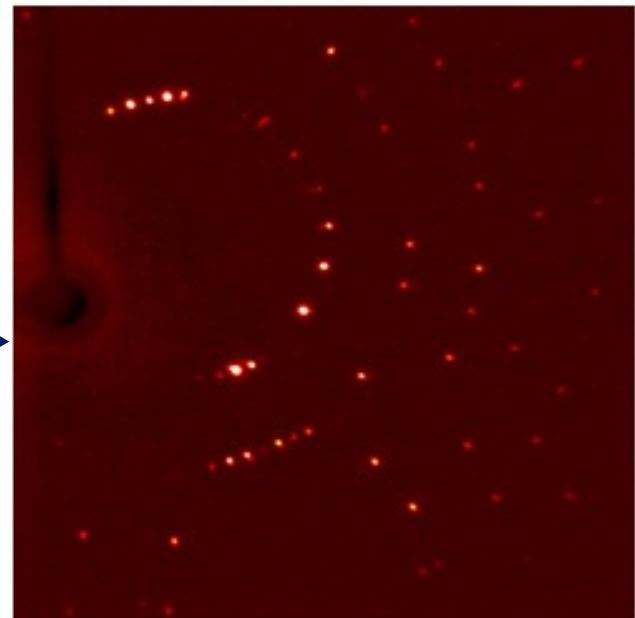


2. A diffractometer
3. A source of X-rays or Neutrons for diffraction

# Single Crystal Xray Diffractometer



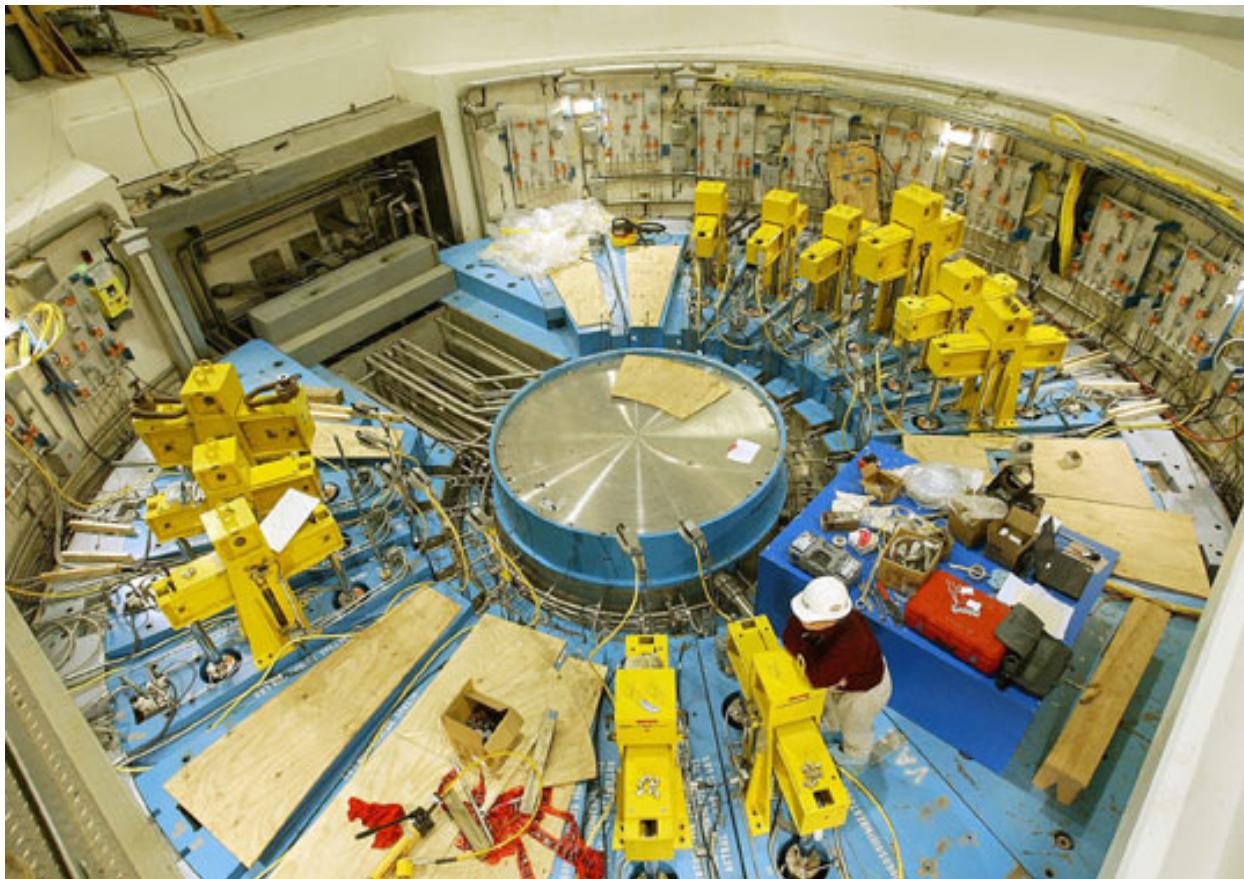
CCD detector, goniometer, X-ray source



Frames of data

**Crystal Structure**

# Neutron source here at ORNL



[http://dsc.discovery.com/news/2007/08/31/neutron\\_tec.html?category=technology&guid=20070831093000](http://dsc.discovery.com/news/2007/08/31/neutron_tec.html?category=technology&guid=20070831093000)

# What do we know from small molecule data?

## **Information from X-ray experiment:**

- › Position of atoms (except H)
- › Molecular shape
- › Molecular conformation
- › Bond lengths and angles
- › Absolute configuration
- › Intermolecular relationships (packing)
- › Location of electron density

**Neutron information:** all the above (except e-density) plus location of hydrogen atoms.

# Applications

## Crystal Structures

- Molecular Structure
  - Absolute configuration
  - Bonding (organic and inorganic)
- Supramolecular Structure
  - polymorphism, pharmaceutical, agrichemical
- Structure-Function relationships

## Locating e- and H

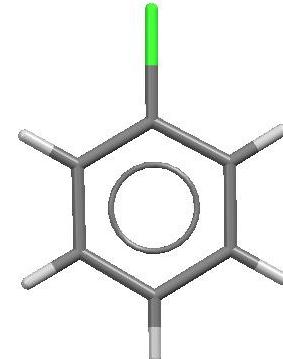
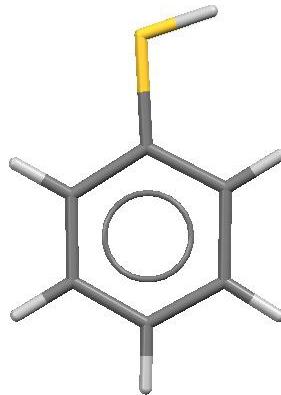
- Electron Density (X-ray)
- Hydrogen atoms (Neutron)

## Phase Transitions

- Low Temperature
- High Pressure

# Why is molecular structure important?

- ◉ **Molecule identification** (did I make what I said I made?)



Data will allow you to distinguish these by **electron density**, **scattering factors**, and/or **bond lengths and angles**. While S and Cl have nearly the same number of e-, you should be able to observe the H attached to S.

# Structural information is sometimes only available from single crystal structures

Lipscomb's 1976 nobel prize in chemistry was for work on boranes.

In his Nobel lecture he acknowledged the importance of X-ray diffraction to his work.

How would this work have been accomplished without “pictures” of the 3-D structures?

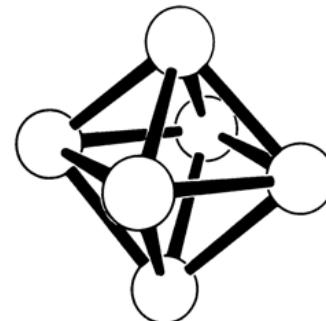
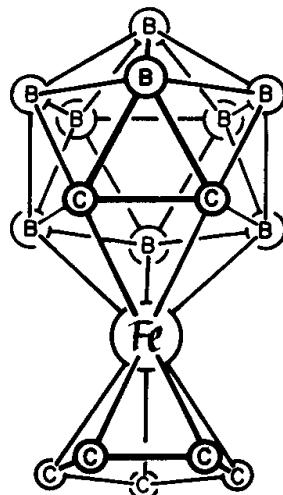


Fig. 1. The  $B_6$  octahedron, which occurs in certain metal borides, in which each boron atom is bonded externally to a boron atom of another octahedron. In  $B_6H_6^{-2}$  or  $C_2B_4H_6$ , a terminal hydrogen atom is bonded externally to each B or C atom.

Fig. 2. The  $B_{12}$  icosahedron, which occurs in boron carbide  $B_{12}C_3$ , in elementary boron, and in  $B_{12}H_{12}^{-2}$ . The three isomers of  $C_2B_{10}H_{12}$  also have this icosahedral arrangement in which there is one externally bonded hydrogen on each B or C atom.

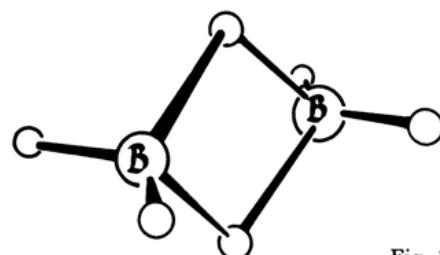
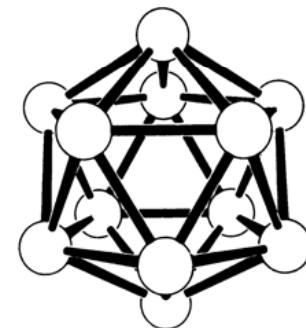
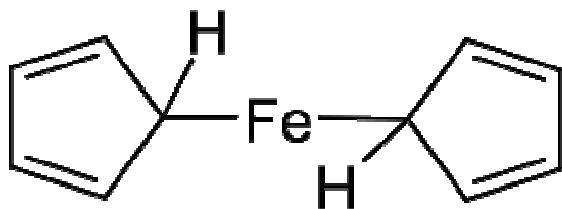


Fig. 3. The geometrical structure of  $B_2H_6$ .

# Structural information is sometimes only available from single crystal structures

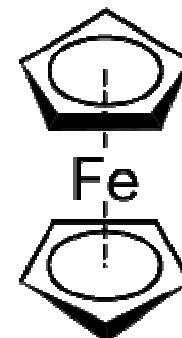
The structure of Ferrocene was at first thought to be:



T. J. Kealy, P. L. Pauson (1951). "A New Type of Organo-Iron Compound". *Nature* **168** (4285): 1039.

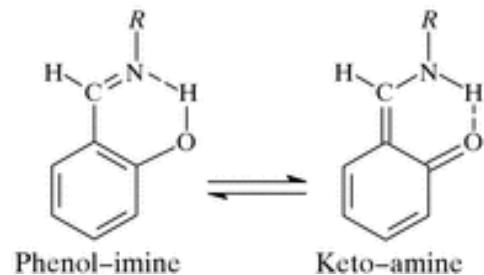
This was proven incorrect by Dunitz' structure, determined from X-ray diffraction data:

J. Dunitz, L. Orgel, A. Rich (1956). "The crystal structure of ferrocene". *Acta Crystallographica* **9** (4): 373–375



# Why is molecular structure important?

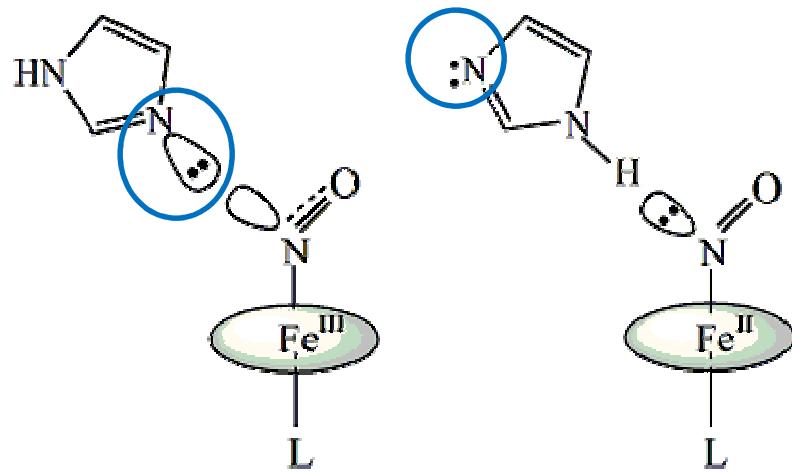
## ● Bond lengths and angles



Acta Cryst (2003). C**59**, o234-o236

Which tautomer/ form exists in the solid state?

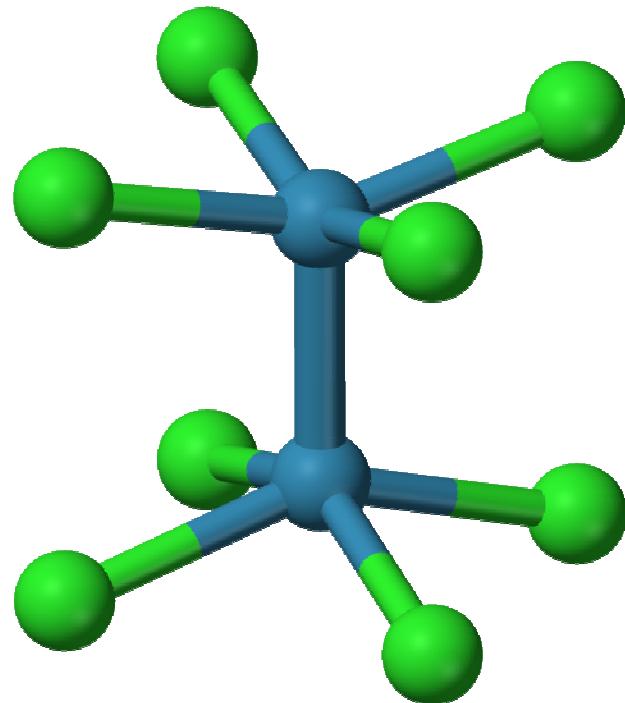
This affects reactivity!



# Metal-metal multiple bonds

- Synthesized in 1844, didn't confirm the quadruple bonding until Cotton published the crystal structure in 1965.

M-M multiple bonds: Knowledge about bond lengths allows us to understand and predict chemical bonding (which orbitals/molecular orbitals) are involved?

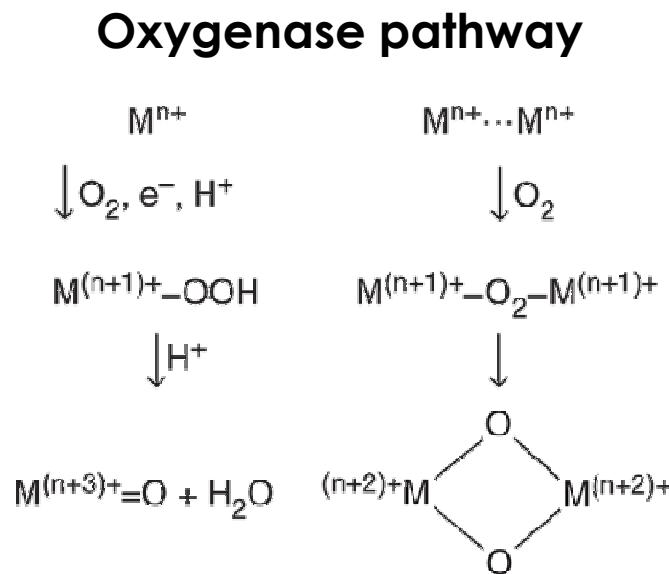


The octachlorodirhenate(III) anion,  $[\text{Re}_2\text{Cl}_8]^{2-}$ .

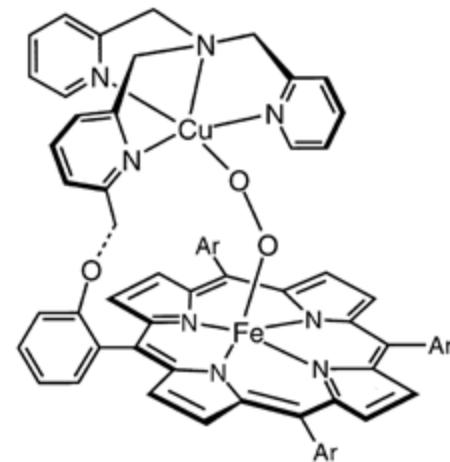
# Metal-ligand multiple bonds

Metal-Ligand multiple bonds, such as carbenes (Metal-carbon bonds) are important for prediction of synthetic pathways.

There are also biological applications for the binding of oxygen ligands:



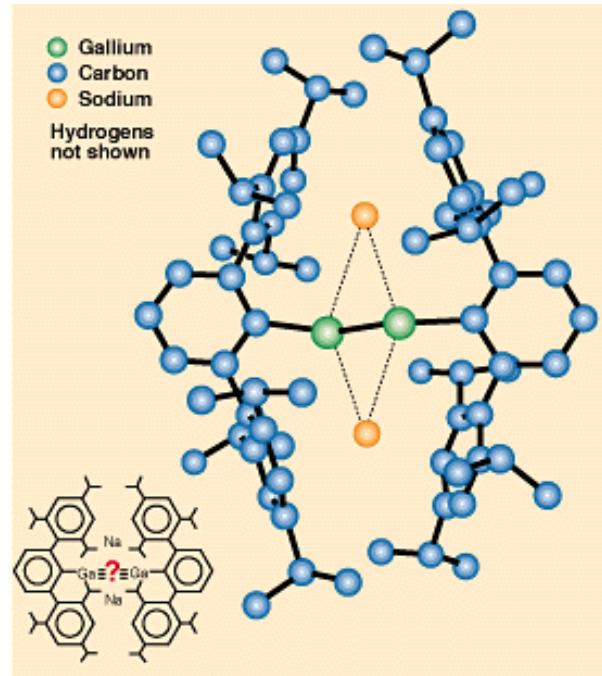
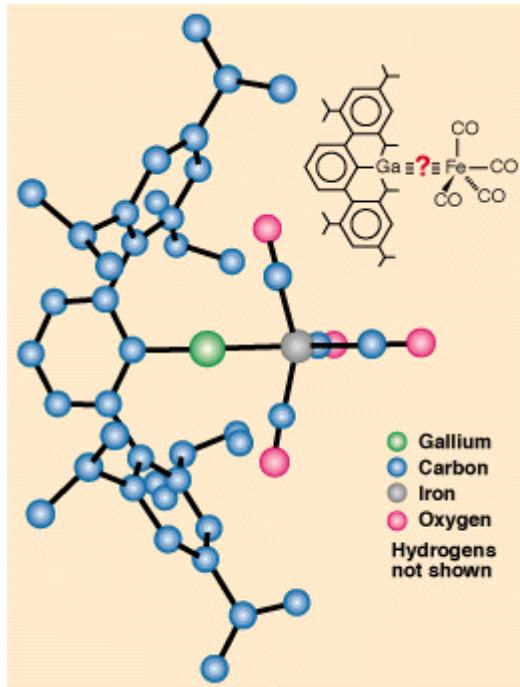
**Proposed structure for Cu-O-O-Fe intermediates for cytochrome oxidase.**



**ID structure, then match spectroscopy with that of the oxidase.**

# Multiple bond controversy

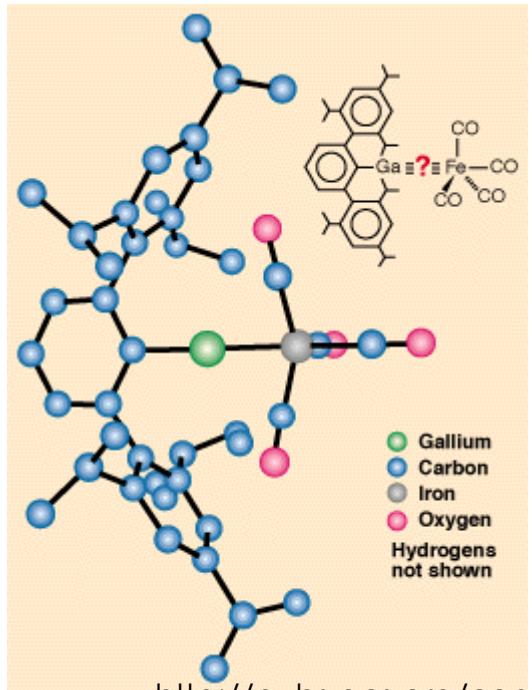
- Triple bond or just forced into close proximity?



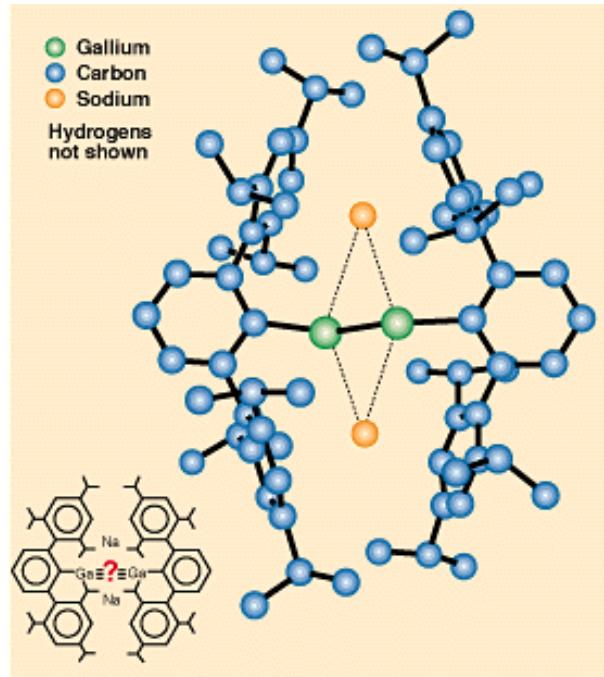
- Extremely short **Ga-Fe** and **Ga-Ga** bonds, respectively. (No-one is questioning the **validity** of the data).
- Problem: **bonding theory** didn't make sense. (What orbitals could combine to make a triple bond? None!)

# Multiple bond controversy

- Triple bond or just forced into close proximity?



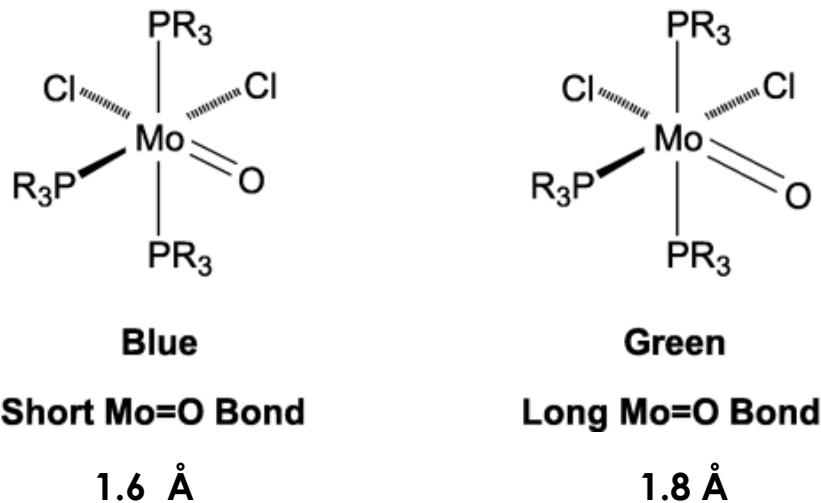
<http://pubs.acs.org/cen/hotarticles/cenear/980316/gal.html>



- Popular conclusion: The **sterics** of the ligand force the atoms close together, but still is only a double bond.
- Moral of the story: **interpretation** of the results is not always obvious! Close contacts aren't always attractive interactions, other things in the structure can force atoms together.

# Another Controversy

- “Bond-stretch isomers”: two isomers of a complex differing only in one bond length.



- Why only one Mo=O stretch in IR?
- After 15 years, the truth: contaminated with MoCl<sub>3</sub>PR<sub>3</sub>
- Moral of the story: crystal structures identify an average of what is in the structure, not individual molecules.

See: G. Parkin Chem. Rev. **93** (1993), p. 887

# What do we know from small molecule data?

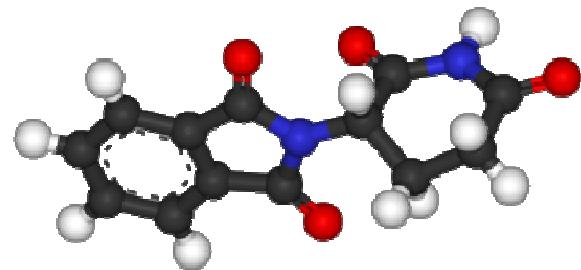
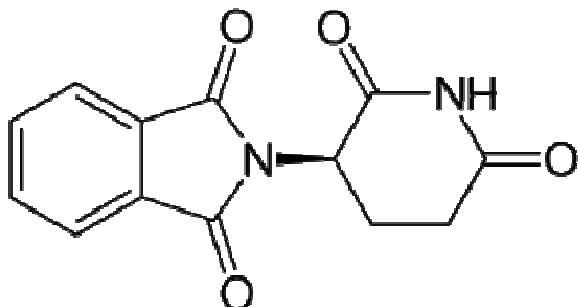
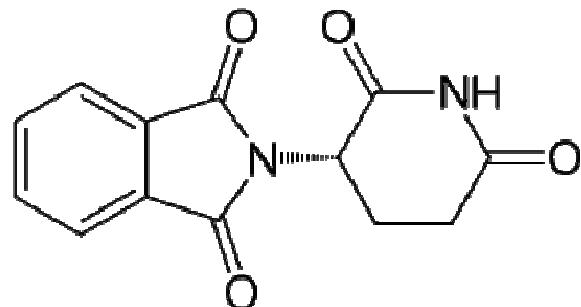
## Information from X-ray experiment:

- ✓ Position of atoms (except H)
- ✓ Molecular shape
- ✓ Molecular conformation
- ✓ Bond lengths and angles
  - > **Absolute configuration**
  - > **Intermolecular relationships (packing)**
  - > **Location of electron density**

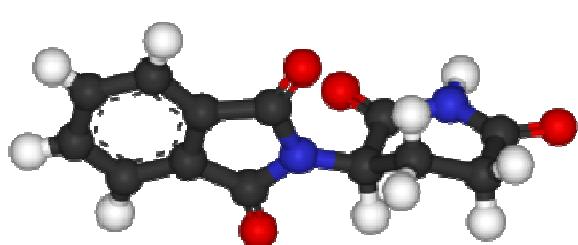
**Neutron information:** all the above (except e-density) plus location of hydrogen atoms.

# Absolute Configuration

Usually determined using Cu K $\alpha$  radiation:



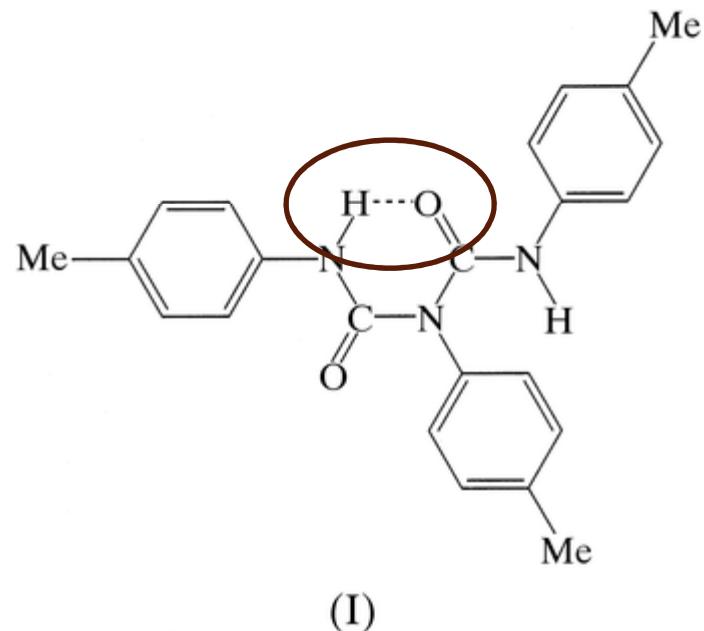
**(S)-thalidomide**  
Combats morning sickness



**(R)-thalidomide**  
Causes birth defects (teratogen)

# Intramolecular interactions

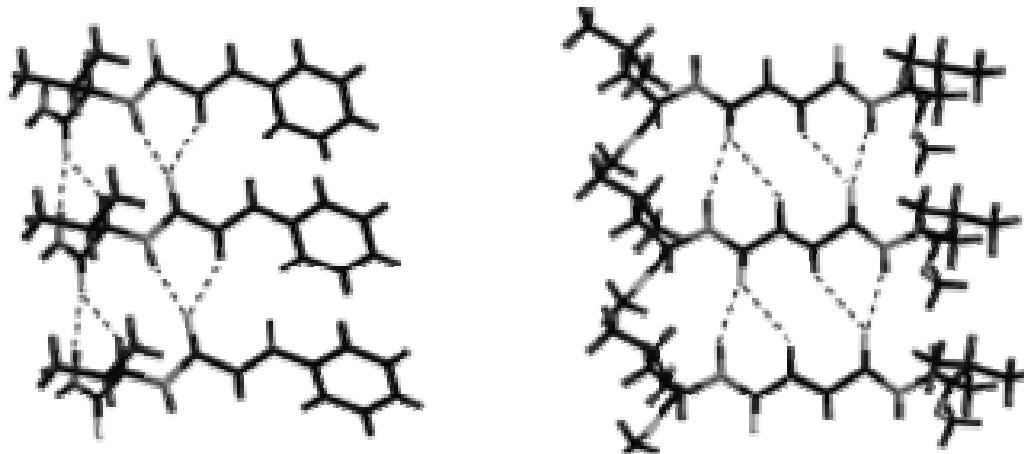
Intramolecular hydrogen bond forces the molecule to be flat:



*Acta Cryst* (2000). C**56**, e529-e530

# Intermolecular interactions

Not just regular hydrogen bonds:

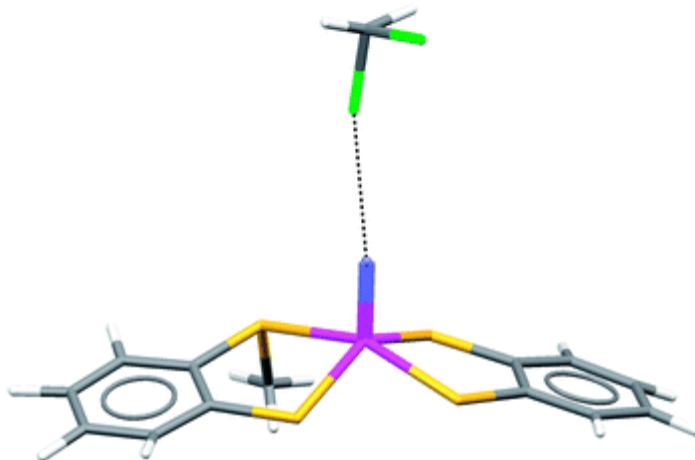
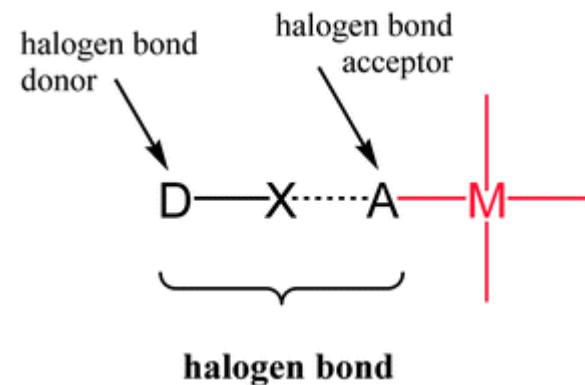


**CH---O hydrogen bonds** recurr in this system (IR shows increase in bond lengths)

**Application:** small molecule mimic of biological systems – binding in proteins.

# Halogen bonding

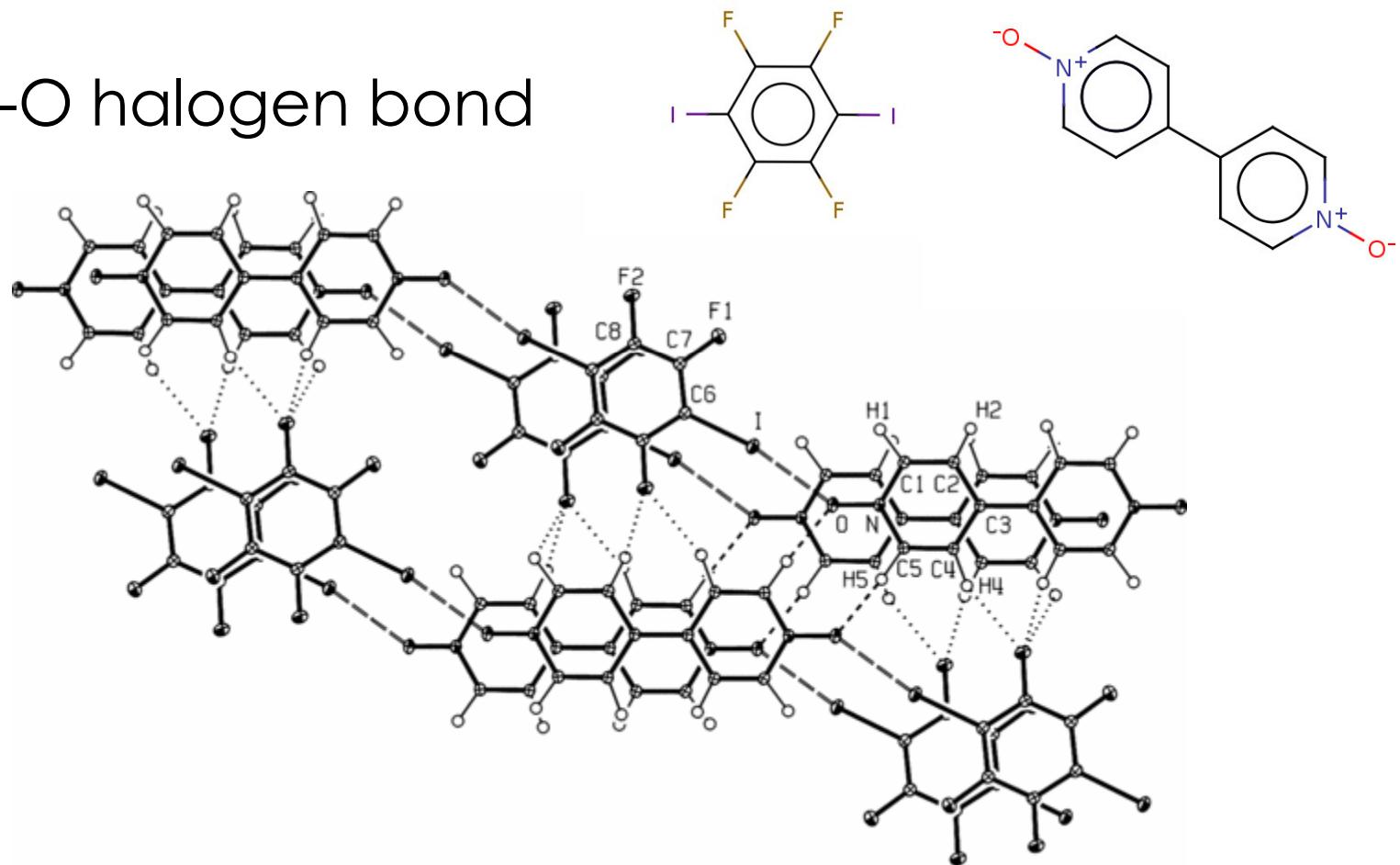
- Halogen – halogen
- Halogen – nitrogen



Brammer et. al *CrystEngComm*, 2008, **10**, 1712-1727

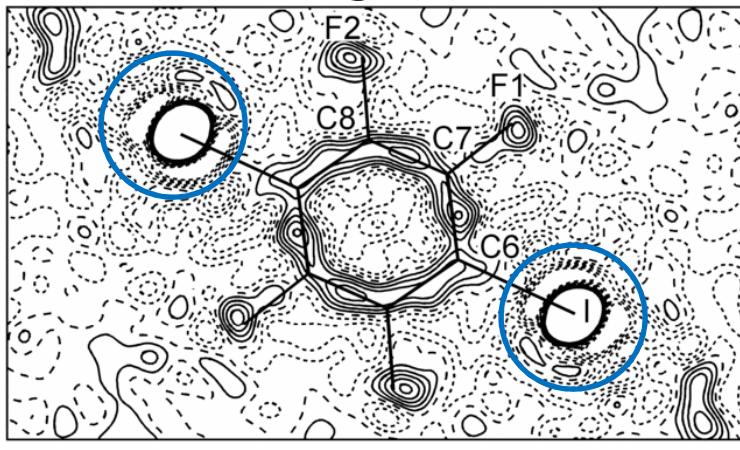
# Electron Density measurements (X-ray)

- I---O halogen bond

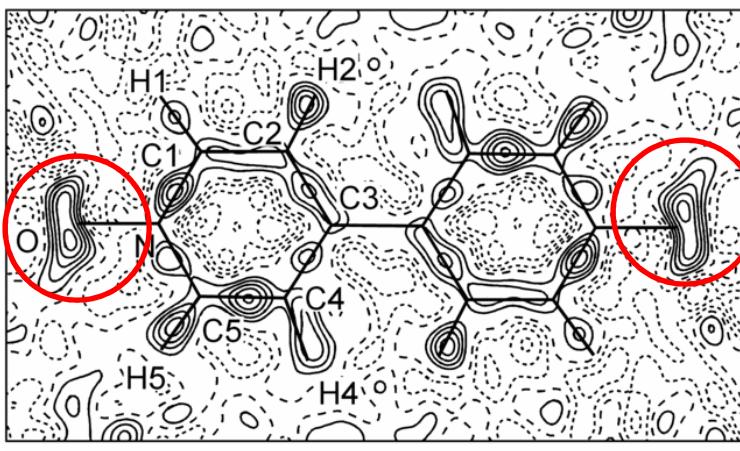


# Electron Density measurements

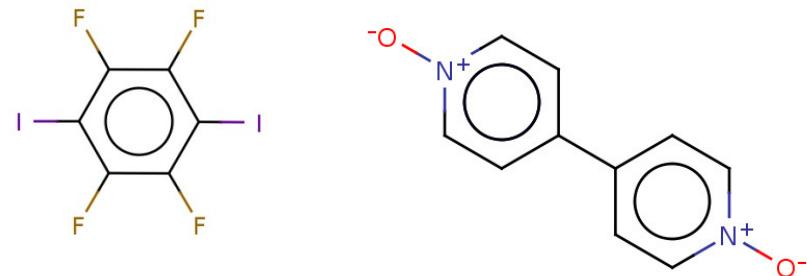
## ● I---O halogen bond



(a)



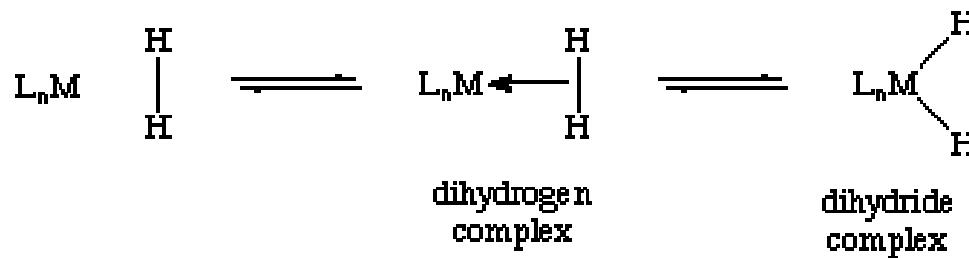
(b)



Electron density studies are conducted at low temperatures over long periods of time.

This residual electron density map shows electron density at Oxygen and positive charge at Iodine, indicating attractive electrostatic **I---O** interaction.

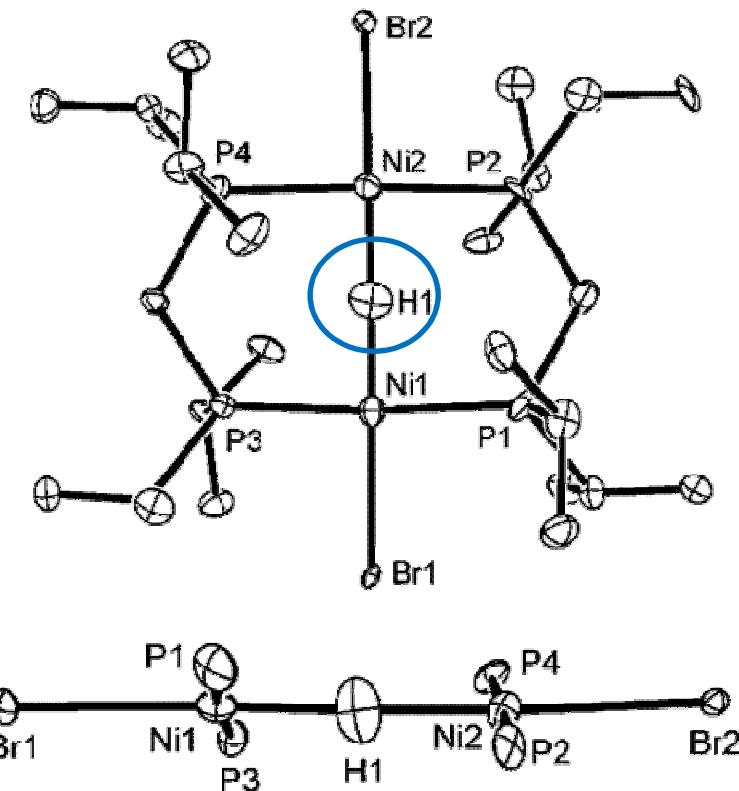
# Dihydrogen ligand (Neutron)



- Application: these are typically intermediates in **metal-catalyzed hydrogenation** reactions.
- Knowing structure allows chemists to identify reaction mechanisms (and therefore predict new reactions).
- Hydrogen atoms are not observable by X-ray diffraction.

# Hydrogen ligands (Neutron)

- Locating the exact position of this hydrogen atom would be absolutely impossible by X-ray diffraction.

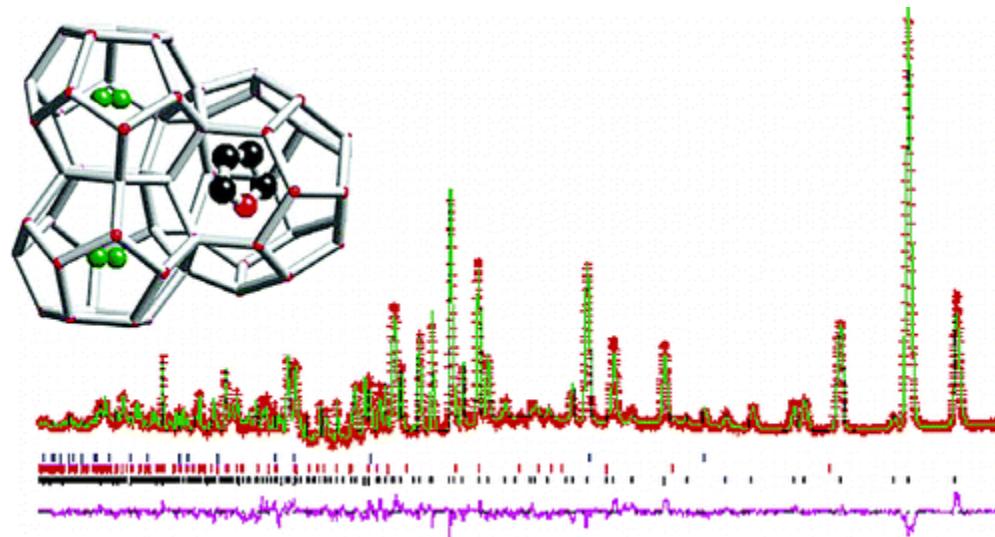


# High Pressure studies

- Clathration may occur only at high pressures:

**Molecular Hydrogen Occupancy in Binary THF-H<sub>2</sub> Clathrate Hydrates  
by High Resolution Neutron Diffraction**

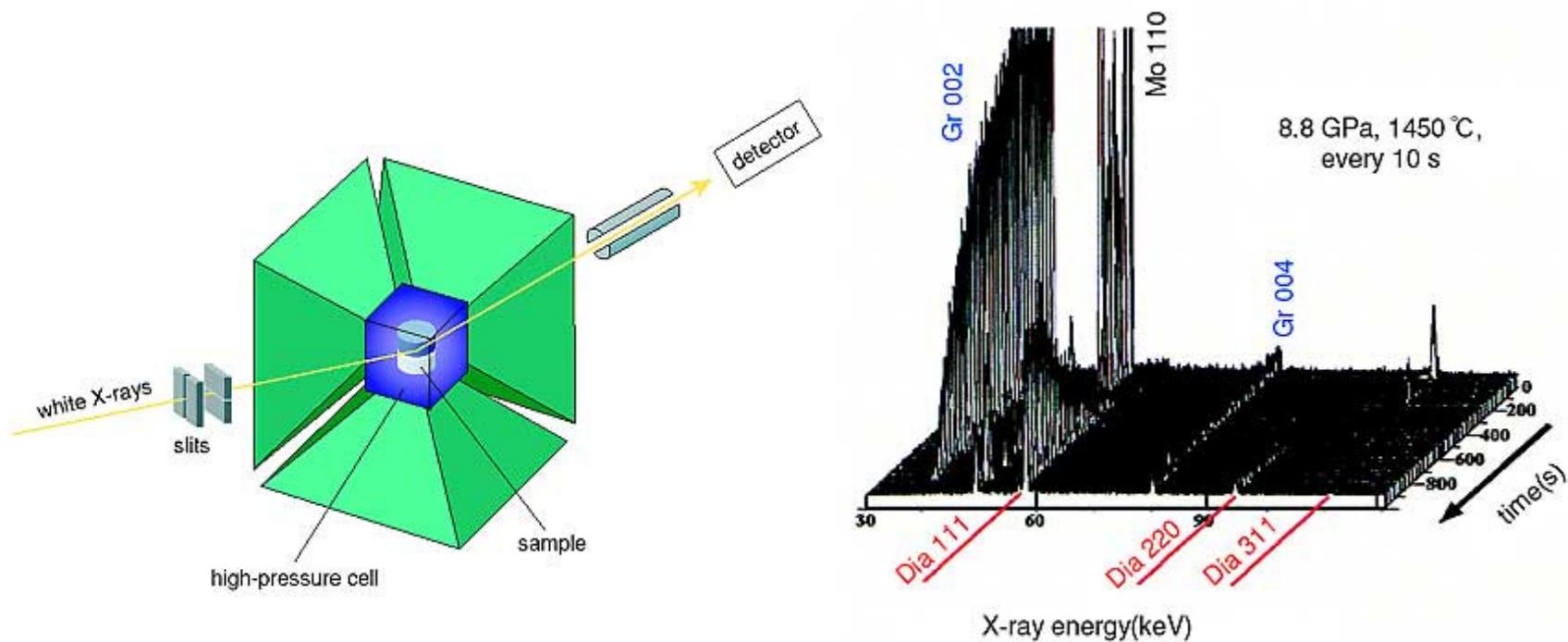
(experiments performed by lecturer Art Schultz)



- Application: Hydrogen storage/transportation

# In-situ reactions using high pressure cells

Observe diamond peak growing in over time under high pressure.



T. Okada et al., In Situ X-ray Observations of the Decomposition of Brucite and Graphite-Diamond Conversion in Aqueous Fluid at High Pressure and Temperature, Phys. Chem. Minerals., 29, 439 (2002).

# Materials with practical applications

- Crystal structure information provides structure.
- X-ray and Neutron diffraction can also be used to interrogate materials.

First – some materials and why we care...

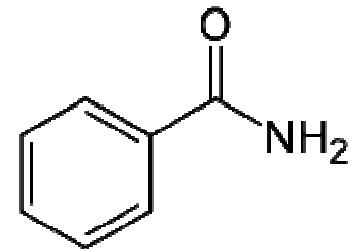
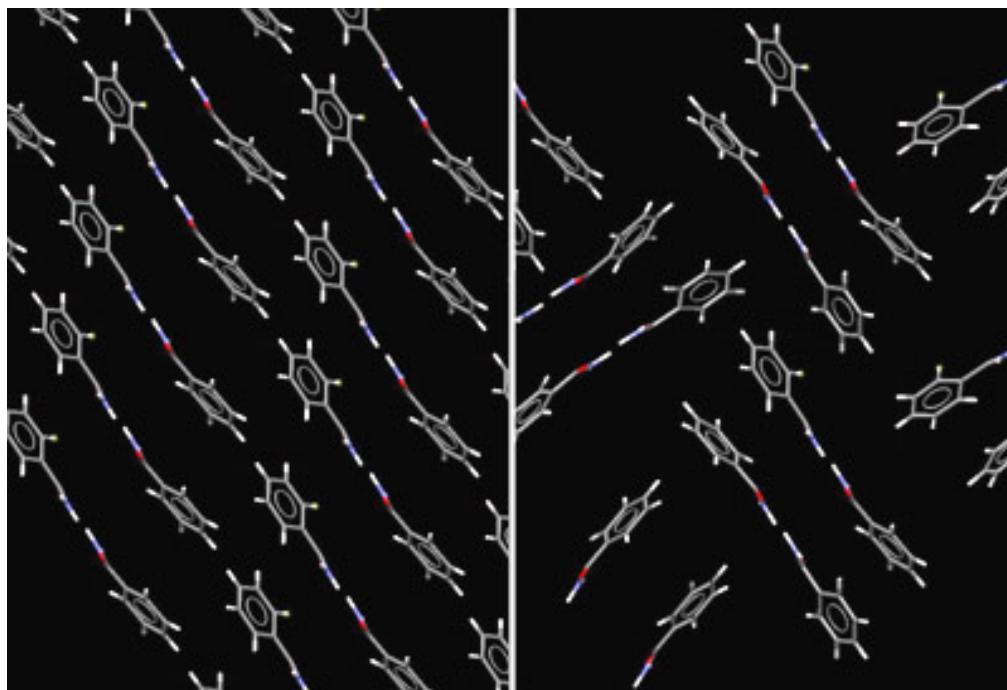
# Supramolecular structure and function

## Structure-Function relationships

- Polymorphism
- Pharmaceuticals
- Agrichemical
- Supramolecular materials:
  - > MOFs
  - > POMs
- Magnetic Materials

# Polymorphism

- The same molecule can have two different crystal packing arrangements. These are called polymorphs.
- Two forms of benzamide:



H-bonded dimers pack in two different ways.

# Polymorphism

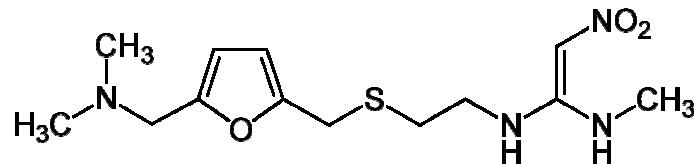
Properties of polymorphic crystals can be quite different:

- Melting point
- Rate of dissolution
- Stability
- Hardness

All of these properties are significant for drug formulations

# Zantac patent controversy

- Zantac: antacid
- Patents for Polymorph I was approved for GlaxoSmithKline. As its patent expired, they got a patent for Polymorph II.
- Other companies began making generic versions, and Glaxo sued.
- Result: Pharmaceutical companies try to get as many polymorphs as possible for their drug molecules! (Also solvates, co-crystals, etc...)

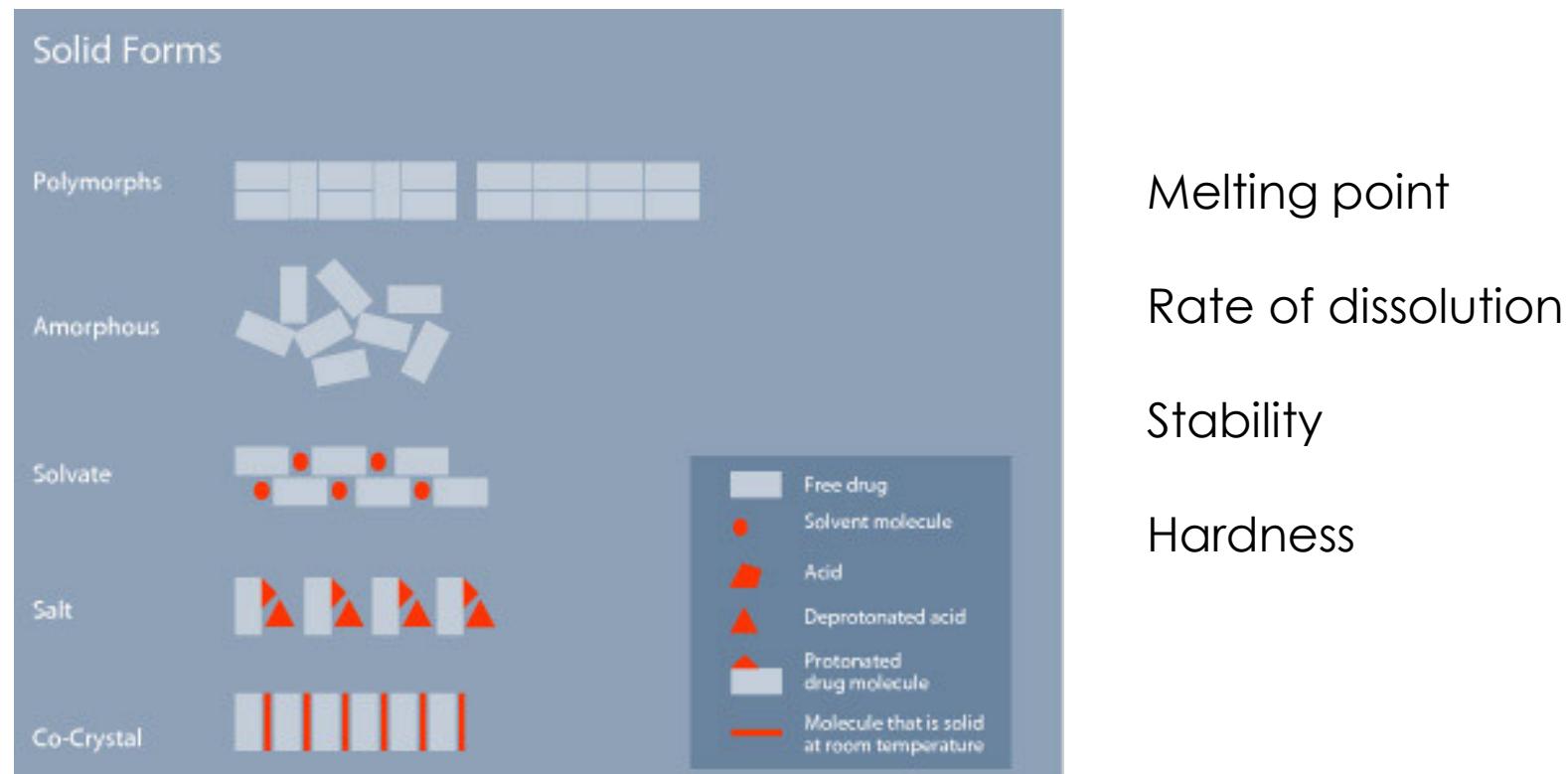


# Co-crystals, clathrates, solvates

- **Solvates** (and **hydrates**): solvent molecules crystallize in the lattice along with the solvent or ions.
- **Cocrystals**: two or more molecules that are solids at room temperature crystallize in the lattice.
- **Clathrates**: more old-school term for co-crystals and/or solvates

# Co-crystals, clathrates, solvates

The cocrystallizing agent can dramatically change the properties of the solid:



# Agrichemicals

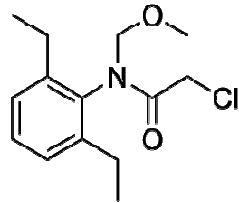
Similar to drug molecules, these tend to promote or inhibit plant growth and plant characteristics.

- These can be environmentally harmful...
- On the EPA website, the list of **just** organics includes 53 molecules.

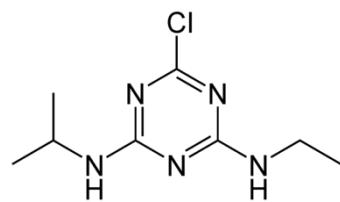
The maximum accepted level of 23 of these molecules is **zero** parts per million (ppm).

## Examples:

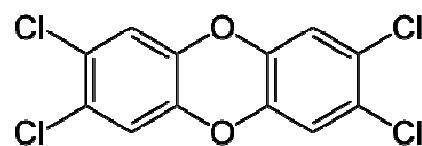
Alachlor (herbicide):



Atrazine (herbicide):



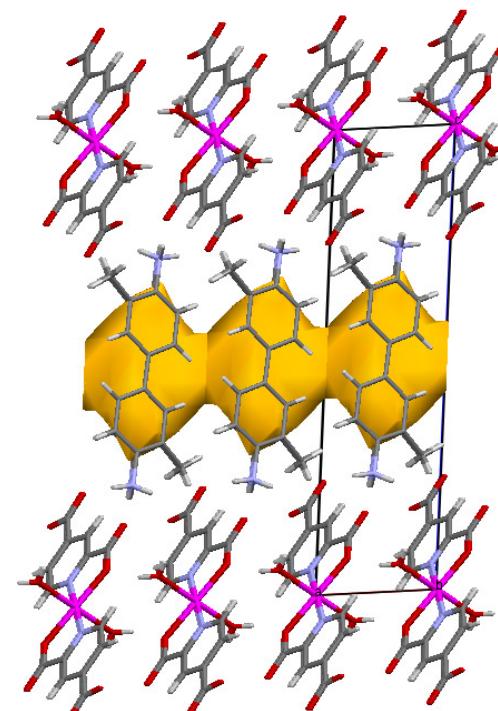
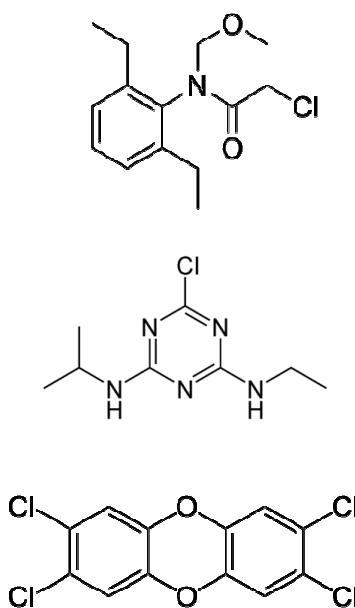
Dioxin (2,3,7,8-TCDD):



**Challenge for  
materials  
chemists:  
Build containers for  
these molecules.**

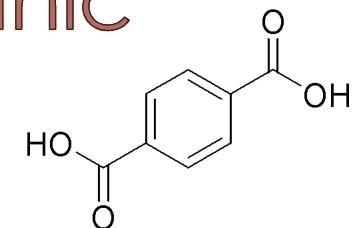
# Container systems: Synthesized from molecular building blocks

- ID structure using diffraction methods (how else can you?)
- Void space in yellow: will our pesticides fit?

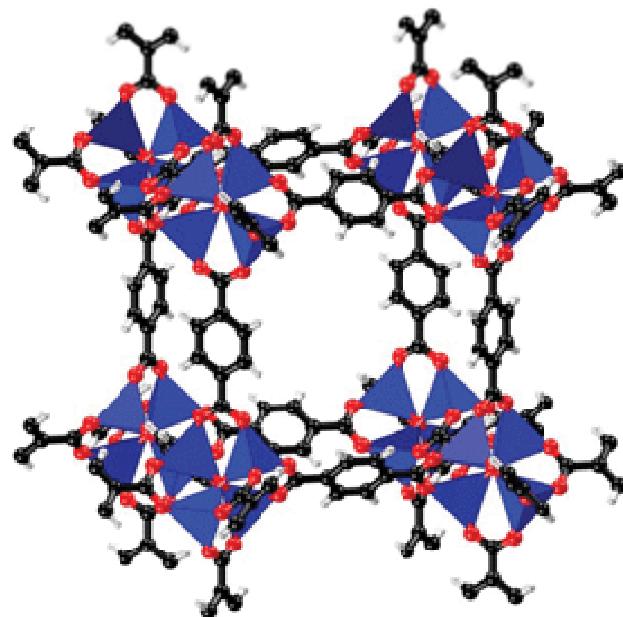


Beatty et al, unpublished results.

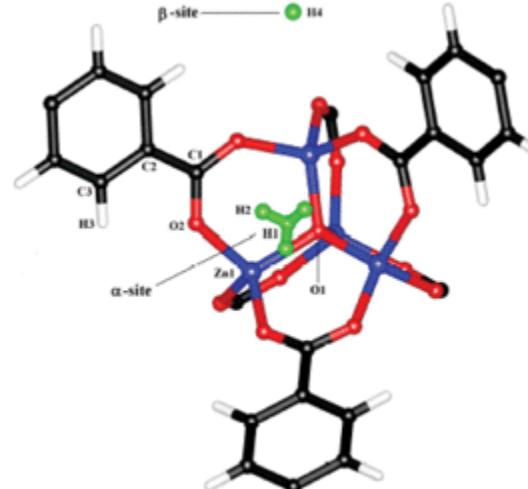
# Container systems: Metal-organic Frameworks (MOFs)



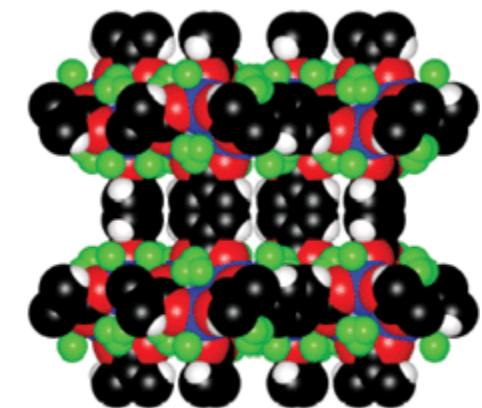
- Infinite cubic framework from  $Zn_4O$  node and BDC ligands.
- Observe  $H_2$  binding in porous materials using **Neutron Diffraction**:



Yaghi MOF



(a)

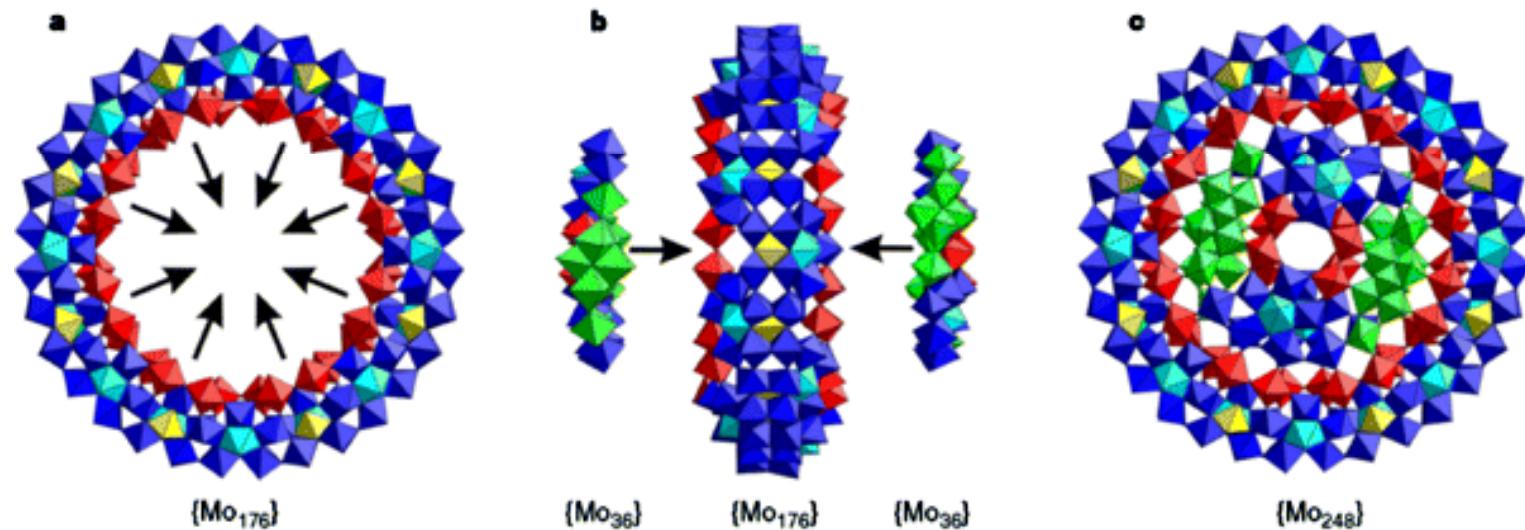


(b)

Formula at 5 K is  $Zn_4O(BDC)_3 \cdot 8H_2$

# Polyoxometallates

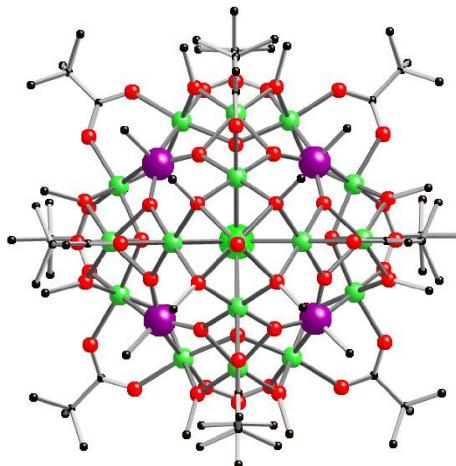
- 1D Structure (How else could you?)



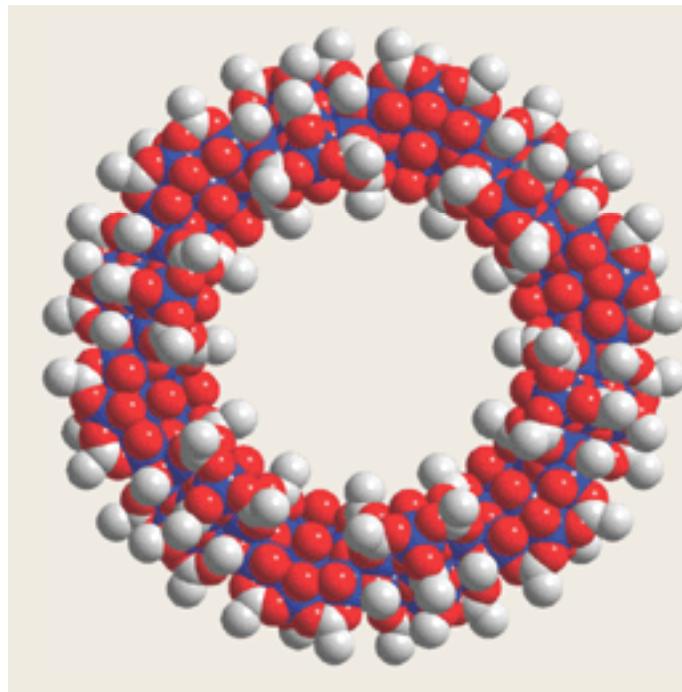
- Huge hollow metal oxides

# Other systems suitable for X-ray and Neutron investigation

- Superconductors
- Single Molecule Magnets (SMMs) based on  $Mn_xO_y$  cages.



<http://afm.ch.man.ac.uk/NewLigandCages.html>

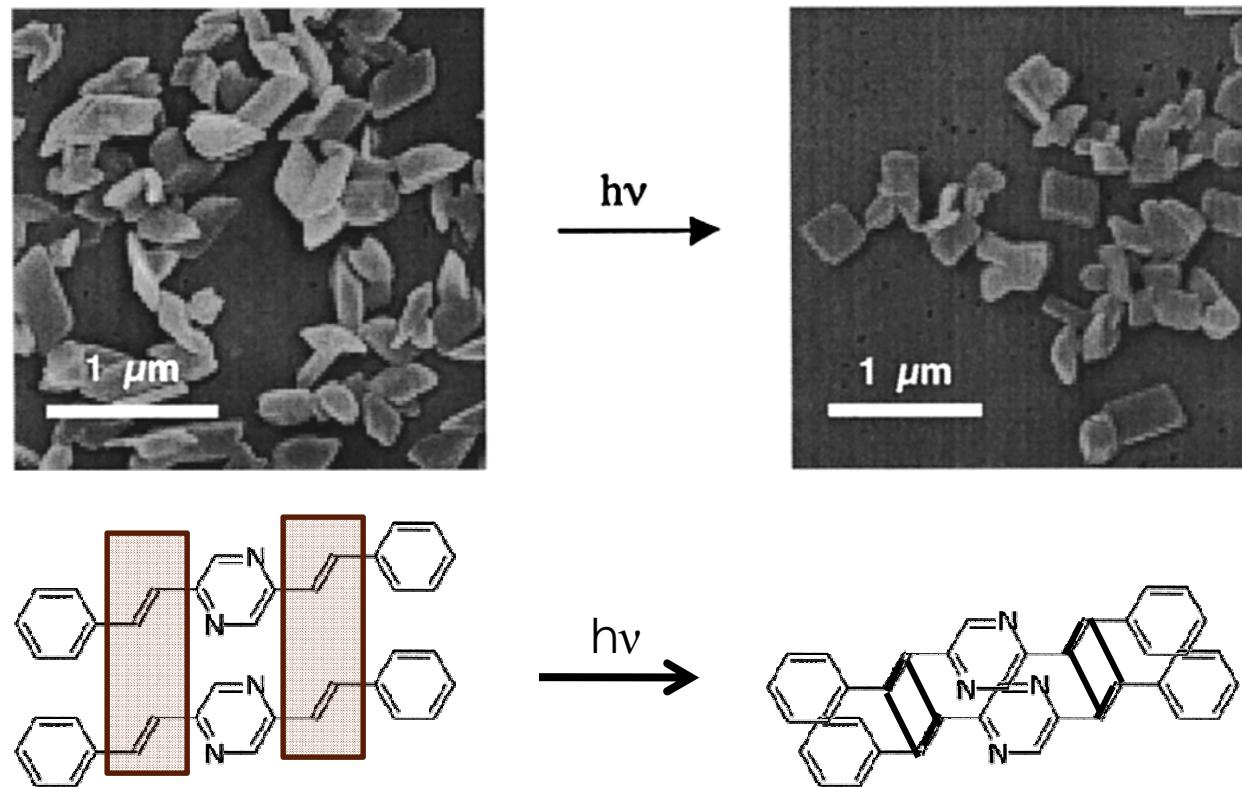


Giant  $Mn_{84}$  SMM

Christou et al, Angewandte Chemie Volume 116,  
Issue 16, pages 2169–2173, April 13, 2004

# Single-crystal to single-crystal transformations

- Molecule undergoes 2+2 cycloaddition upon irradiation with UV light:



# Complementary Methods

Remember, X-ray and Neutron diffraction methods are great, and usually give us a clear picture, but we use many complementary techniques to characterize and interrogate our solids:

- Solid State NMR (structure prediction)
- Theoretical methods (structure prediction)
- FT-IR (bond lengths vs IR stretch)
- Powder diffraction (structure solution)
- Protein crystallography (binding sites)

Thank you!