Ah! Crystallography!
Importance of Crystallography in Modern Science

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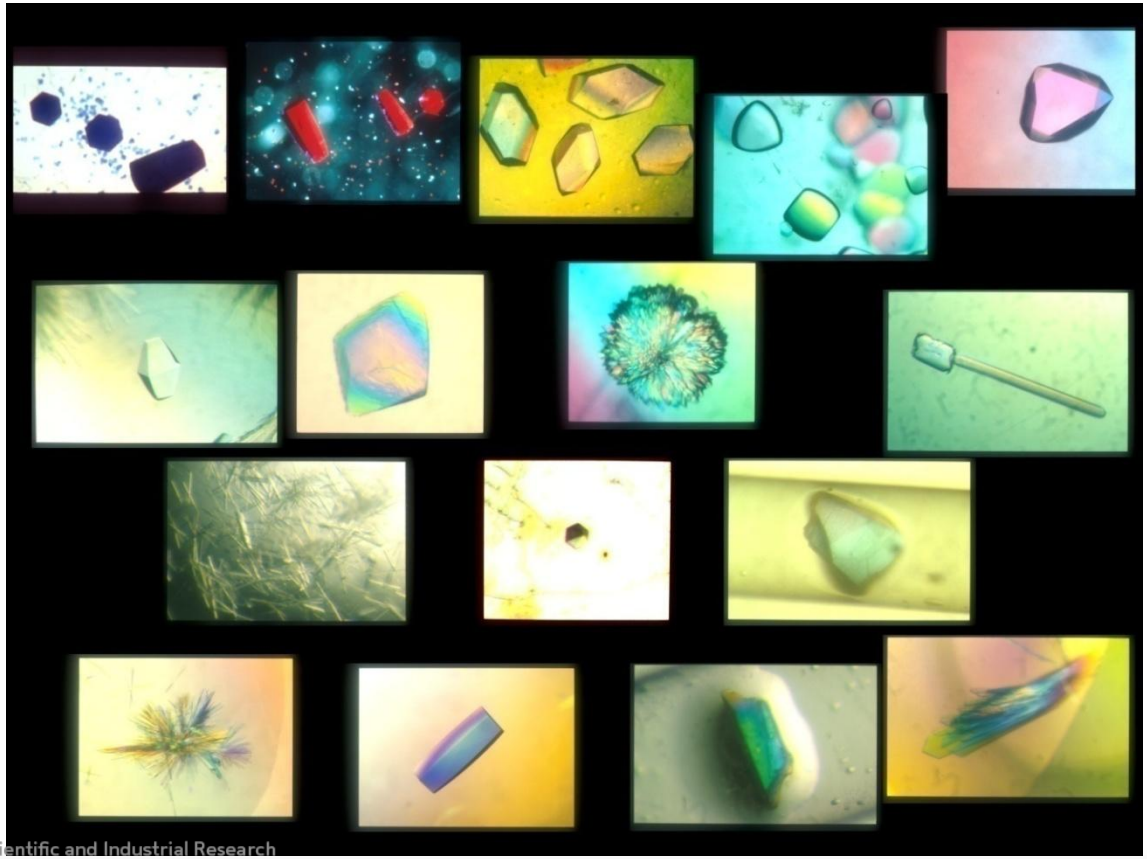
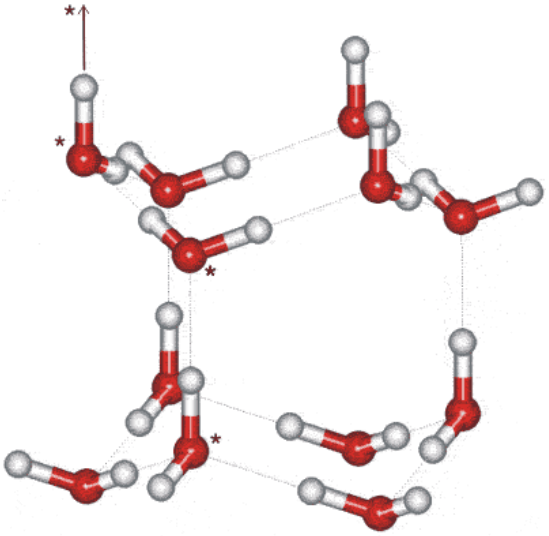
National Chemical Laboratory

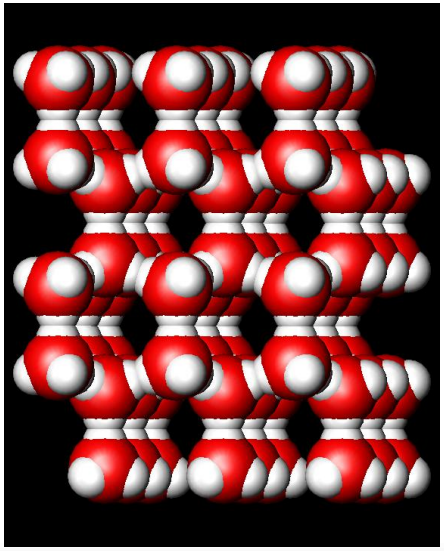
Crystallography deals with crystals

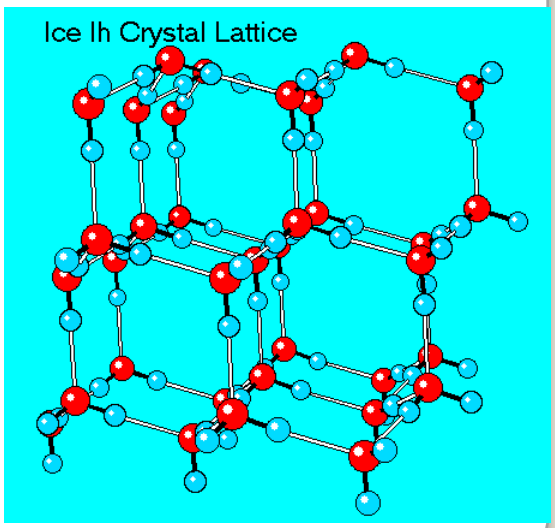
A crystal is a solid with an orderly, repeating arrangement of atoms



Crystals are everywhere!







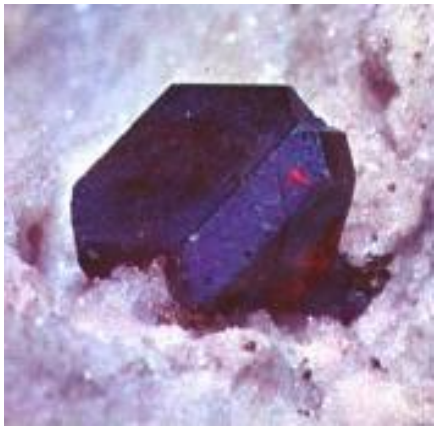
Hexagonal System, Sp. Gp. $P6_3/mmc$

Crystals are everywhere!

Transparent

Opaque

Translucent



Crystals are everywhere!

Crystal Shape

- General Shapes
  - prismatic

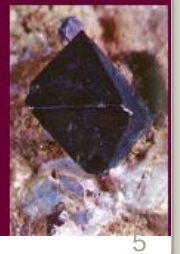
  - platy
  - blocky
  - tabular
  - bladed

Crystal Shape

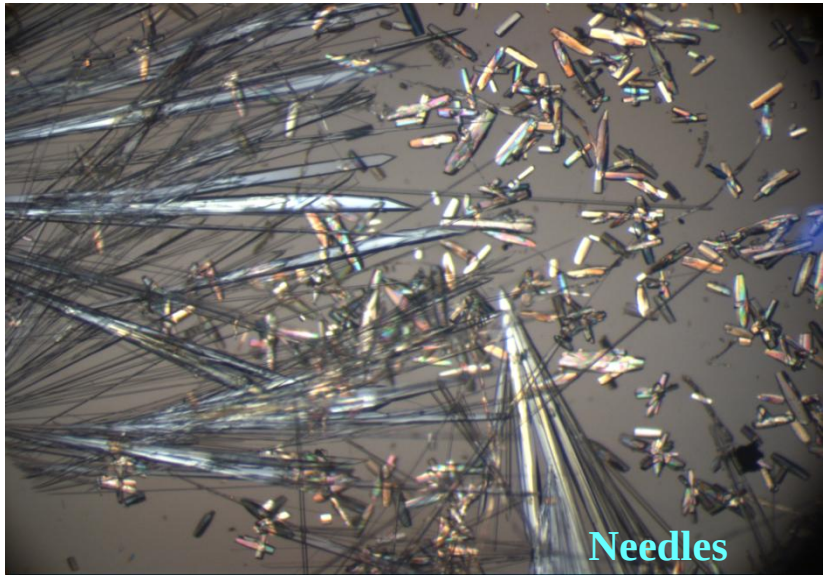
- Special named shapes
  - cube — Pyrite

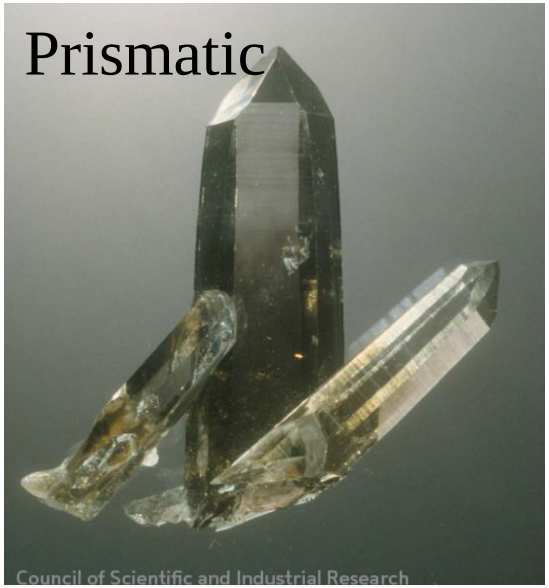
  - dodecahedron — Garnet

  - octahedron — Magnetite



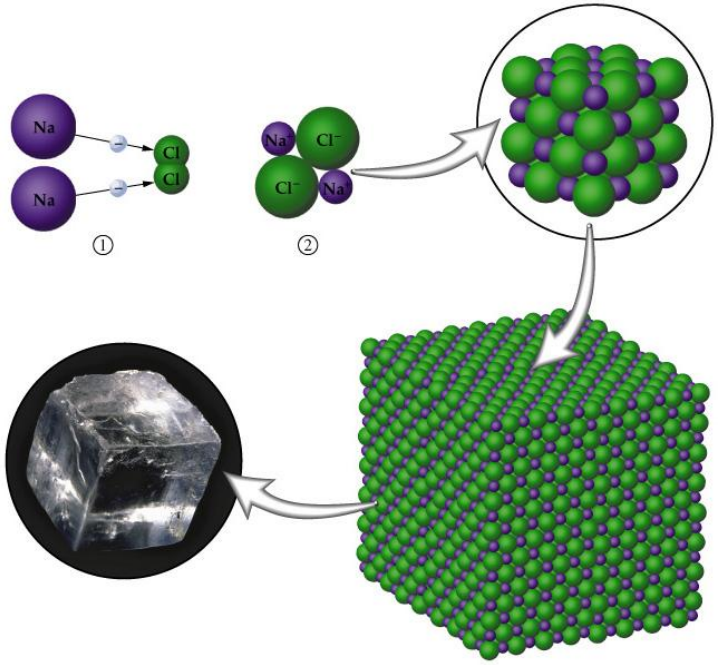

fibrous

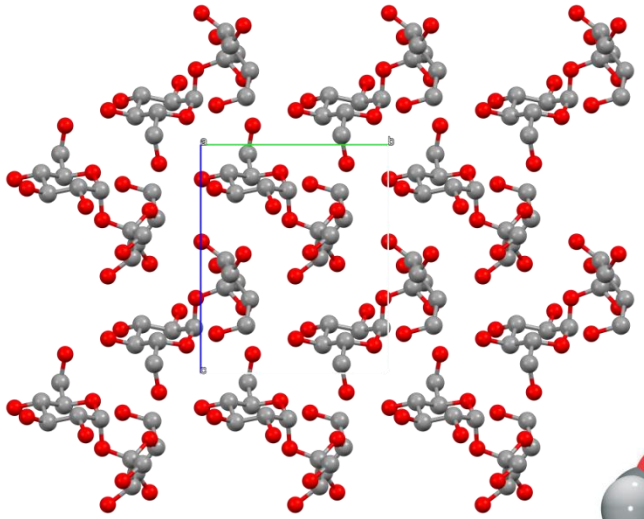

Needles

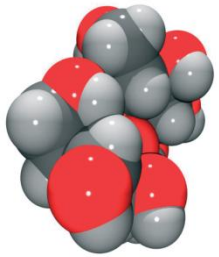

Prismatic
Council of Scientific and Industrial Research


Tabular

Crystals found in everyday life



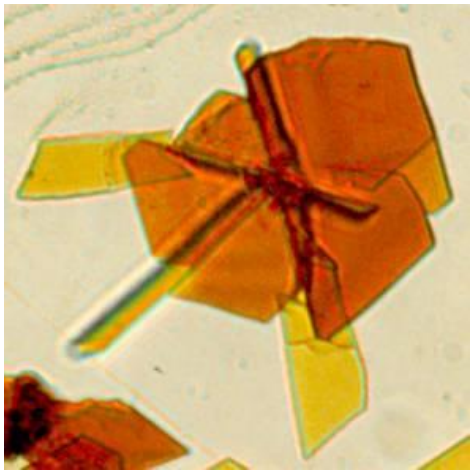




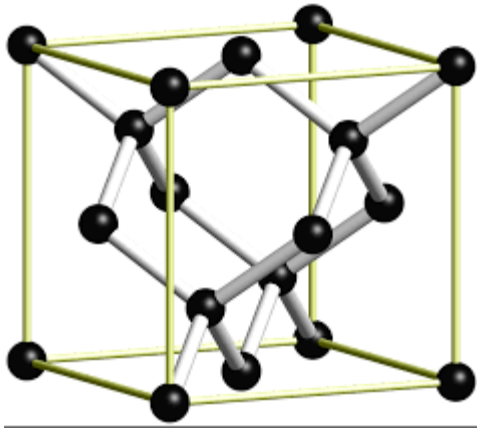
Crystals found in everyday life

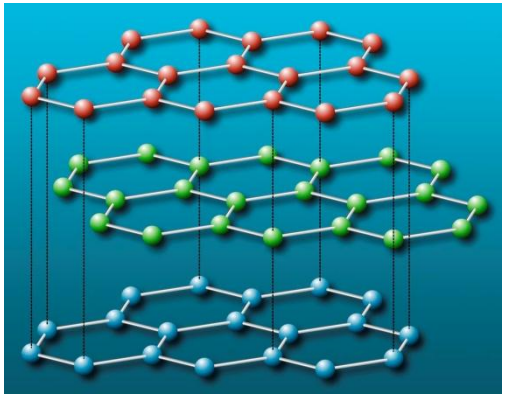
Diamond

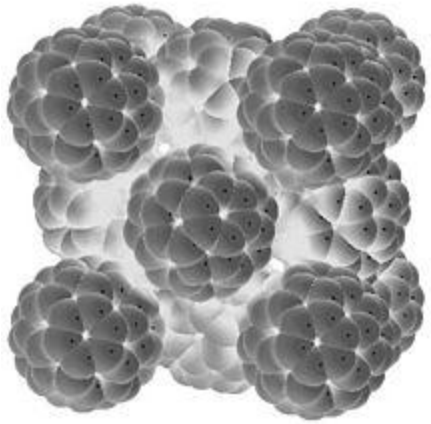
Graphite



Fullerene







What is crystal?

- **Historic definition before the advent of crystallography**

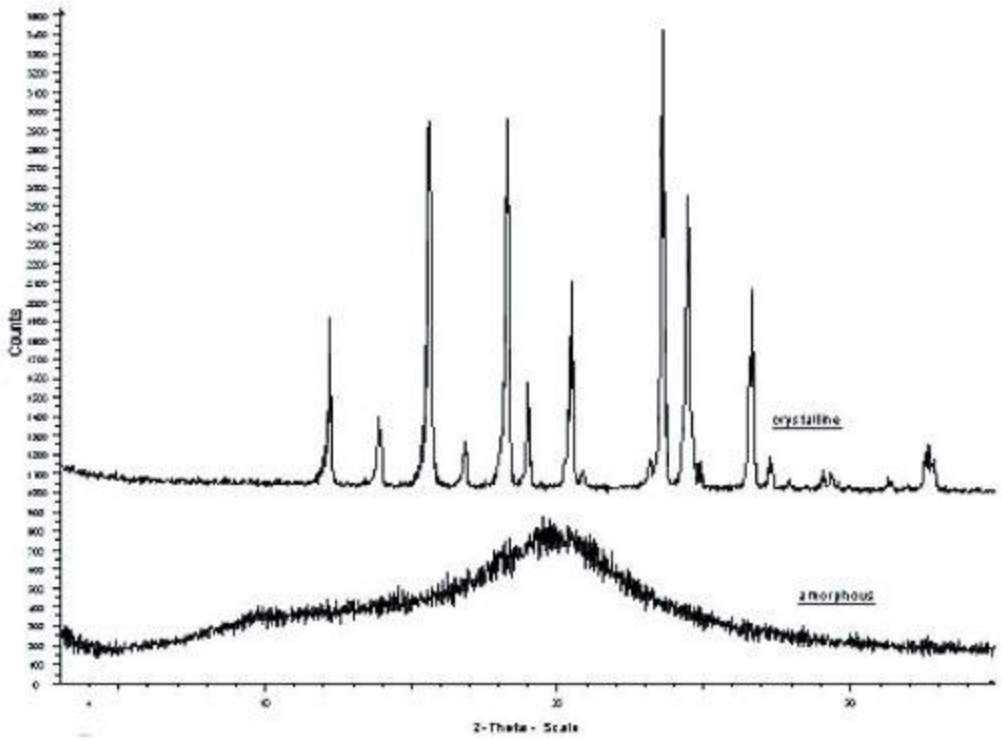
  -A solid with well-defined faces

- **Crystallogra**

  - A ma **f**

- **The strict d**

  - Any **p peaks**

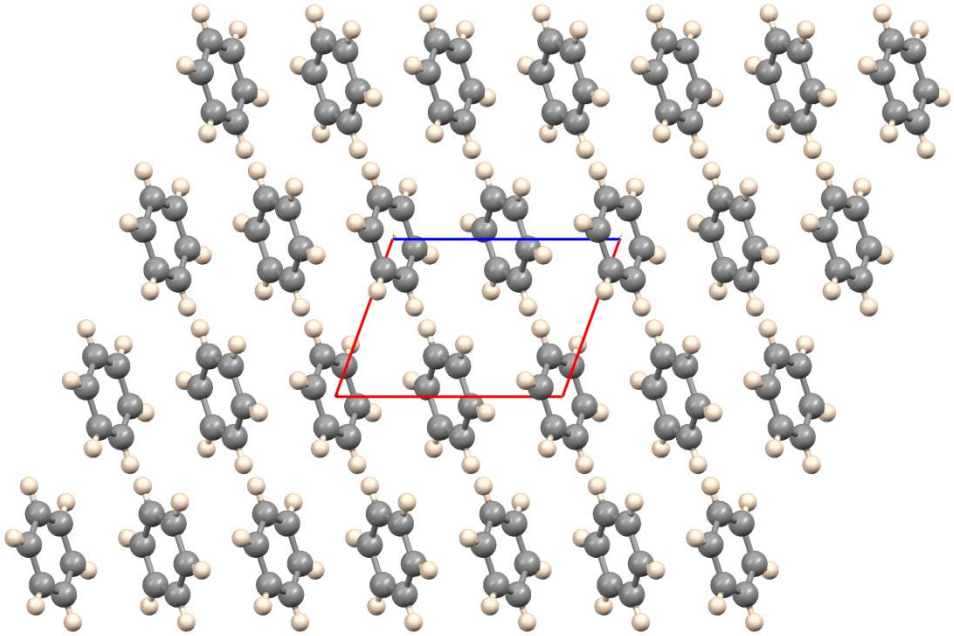


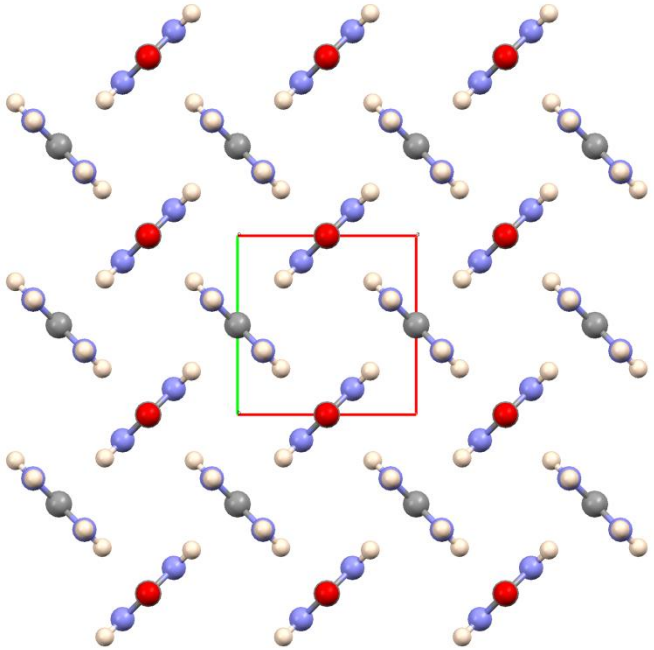
What is a Crystal?

What is not a Crystal?

What is a Crystal?

A Regular Arrangements of Atoms, Ions or Molecules

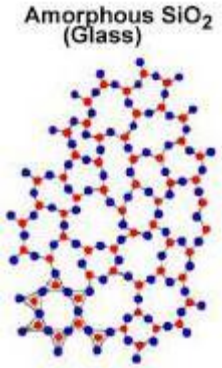


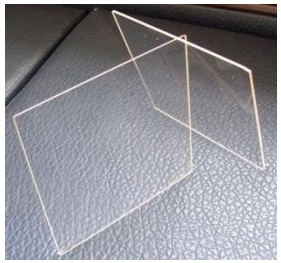


CLASSIFICATION OF SOLIDS BASED ON ATOMIC ARRANGEMENT

AMORPHOUS

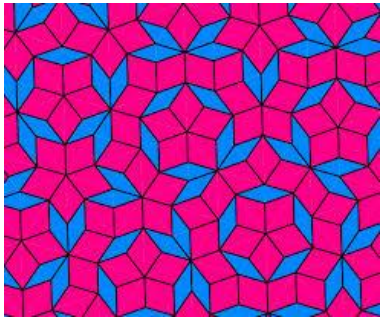
Short range order
+
No periodicity

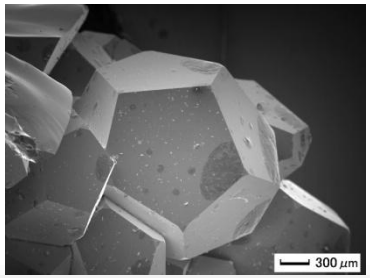




QUASICRYSTALS

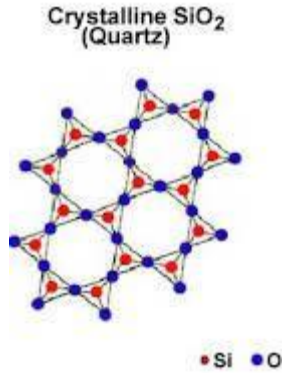
order
+
No periodicity





CRYSTALS

long range order
+
periodicity



Crystallography – what & why?

What?

- Science of the arrangement of atoms in molecules
- Science of the arrangement of molecules with respect to each other
- Implications for these arrangements for a myriad of areas of science from bioscience to nanotechnology
- *Not the science of crystals*

Crystallography – what & why?

Why?

- **Materials' properties are intimately related to their structures**

  Understanding certain properties requires knowledge of atomic arrangement, e.g. piezoelectric, polarization, optical activity, hardness, compressibility, solubility, colour , density etc.

- **This technique is essential for chemist's today for knowledge of accurate molecular structure, which is an essential for structure based functional studies to aid in the development of effective materials.**

Crystallography Developments: A Brief History

Geometrical Crystallography-

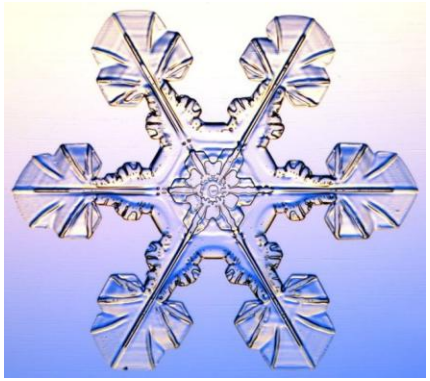
Study of external shape of crystal

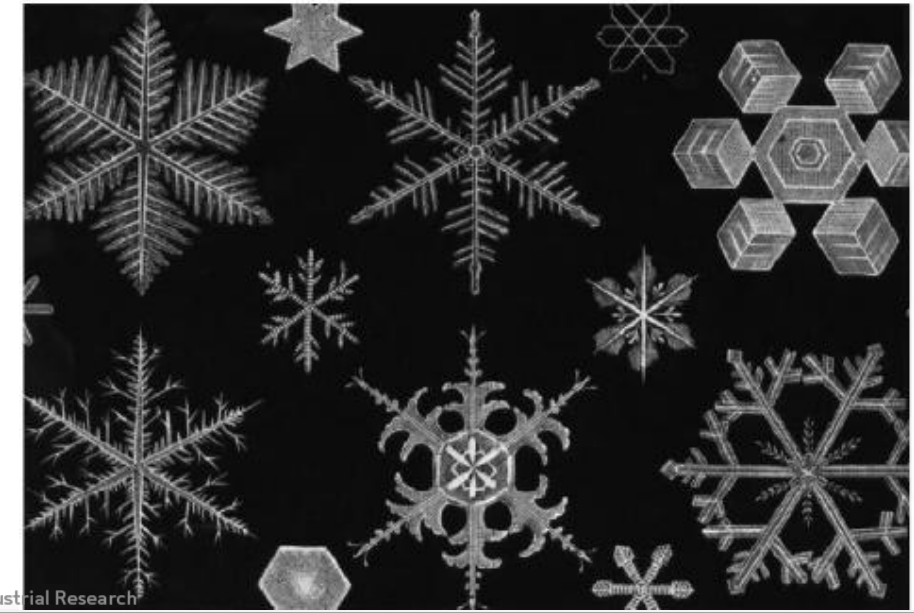
Early thoughts about crystals

Symmetry

- Crystals are solid - but solids are not necessarily crystalline
- Crystals have symmetry (Kepler,1611) and *long range order*

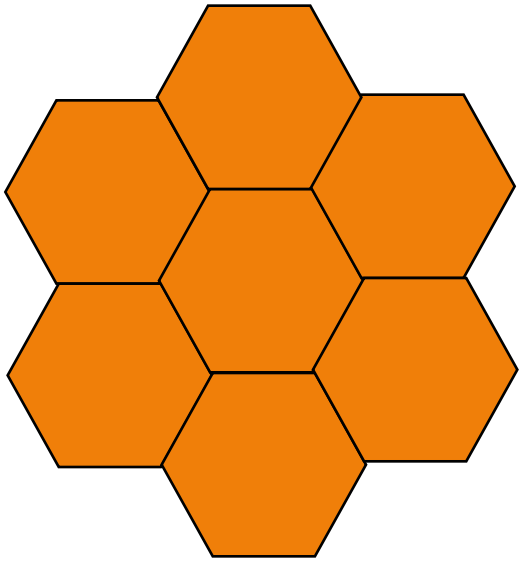
  - First speculation on the nature of six-fold symmetry of snowflakes based on the observation that small ice spheres can produce a regular polygon

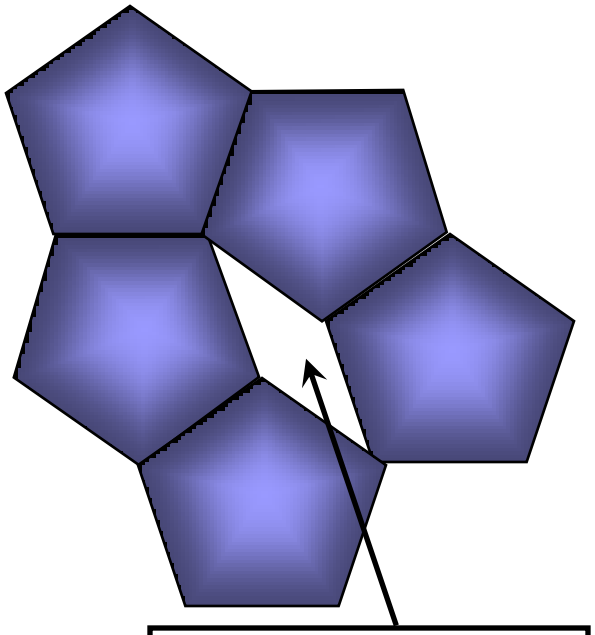


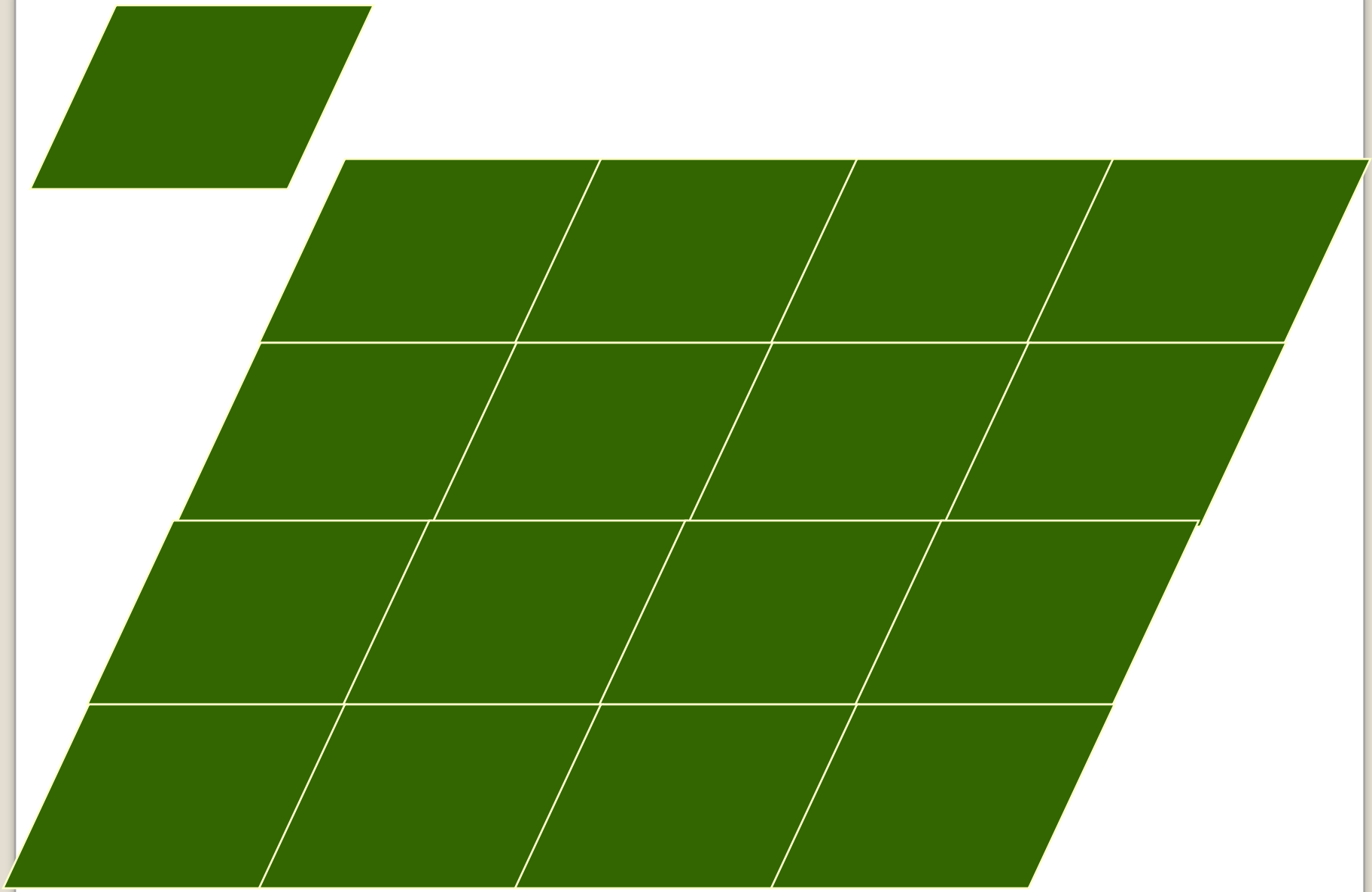


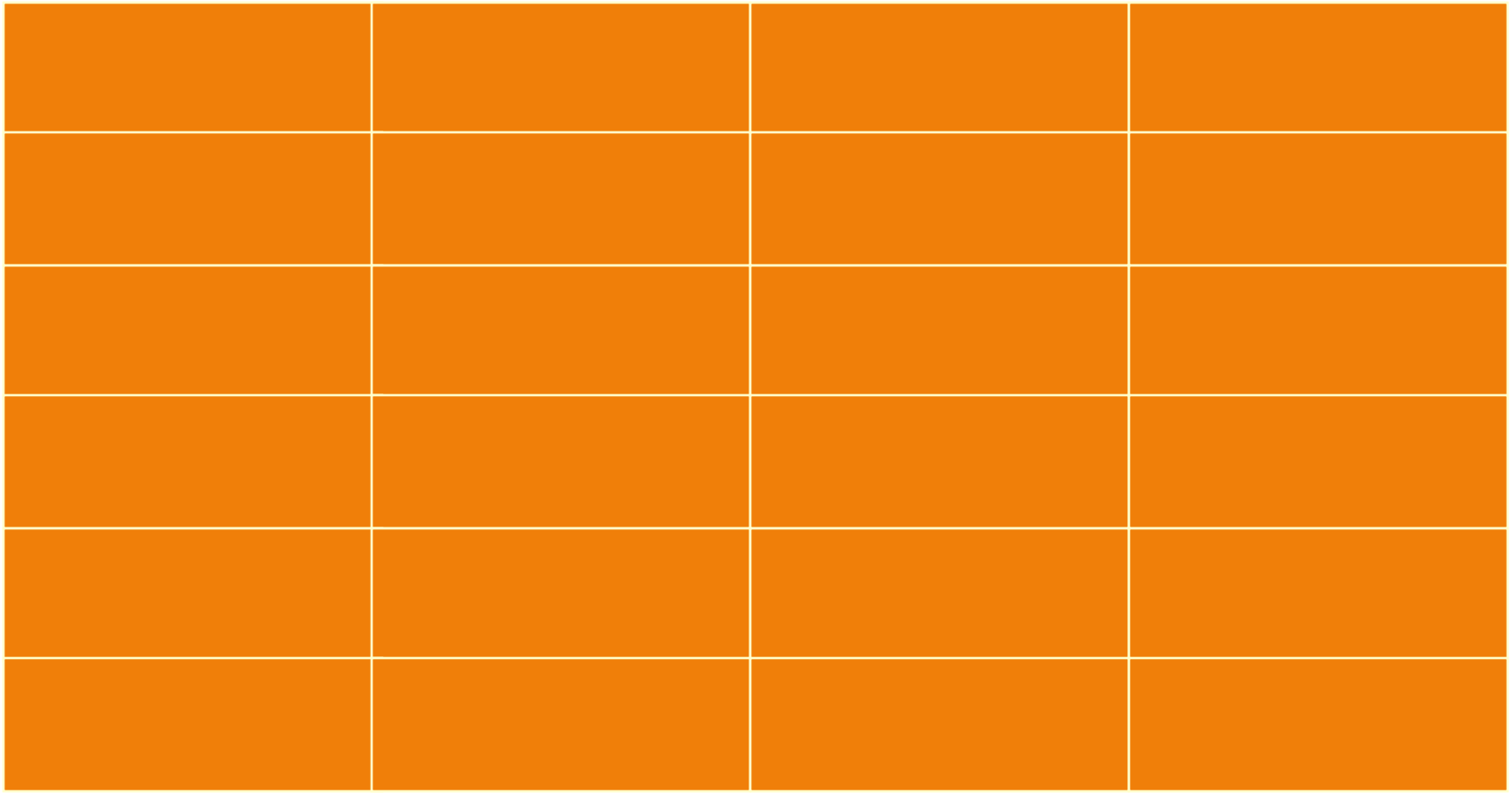
Group discussion

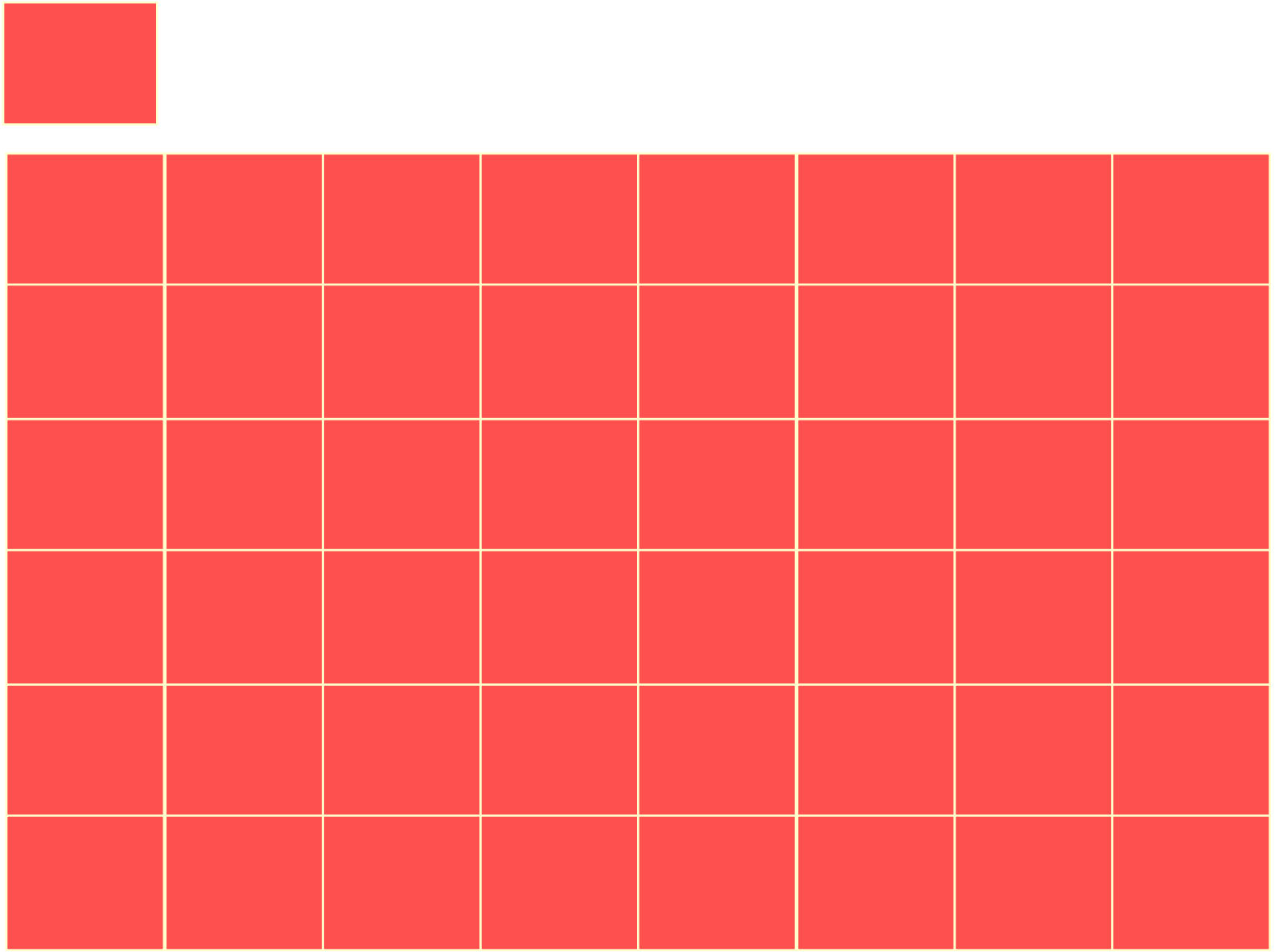
Kepler wondered why snowflakes have 6 corners, never 5 or 7. By considering the packing of polygons in 2 dimensions, demonstrate why pentagons and heptagons shouldn't occur.

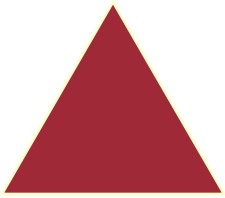


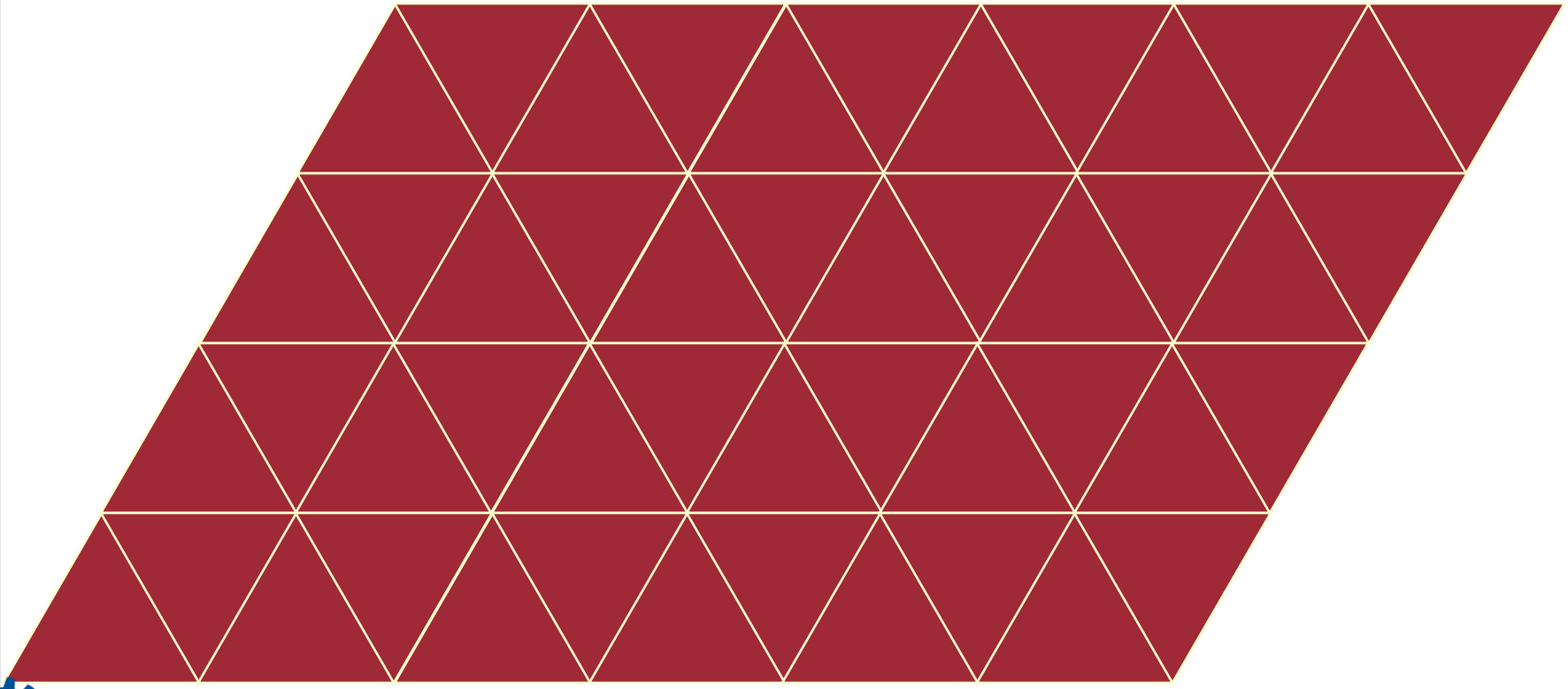


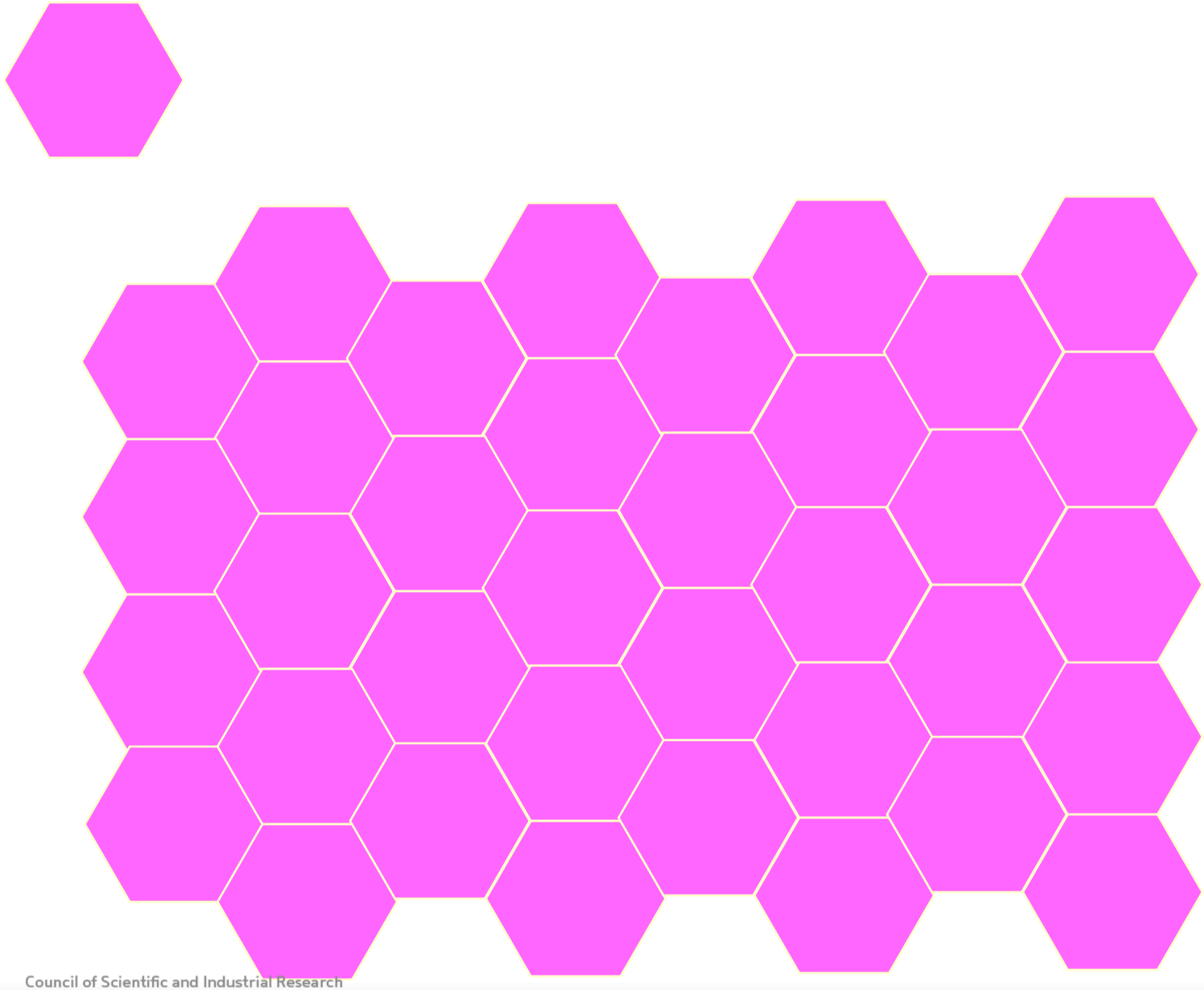


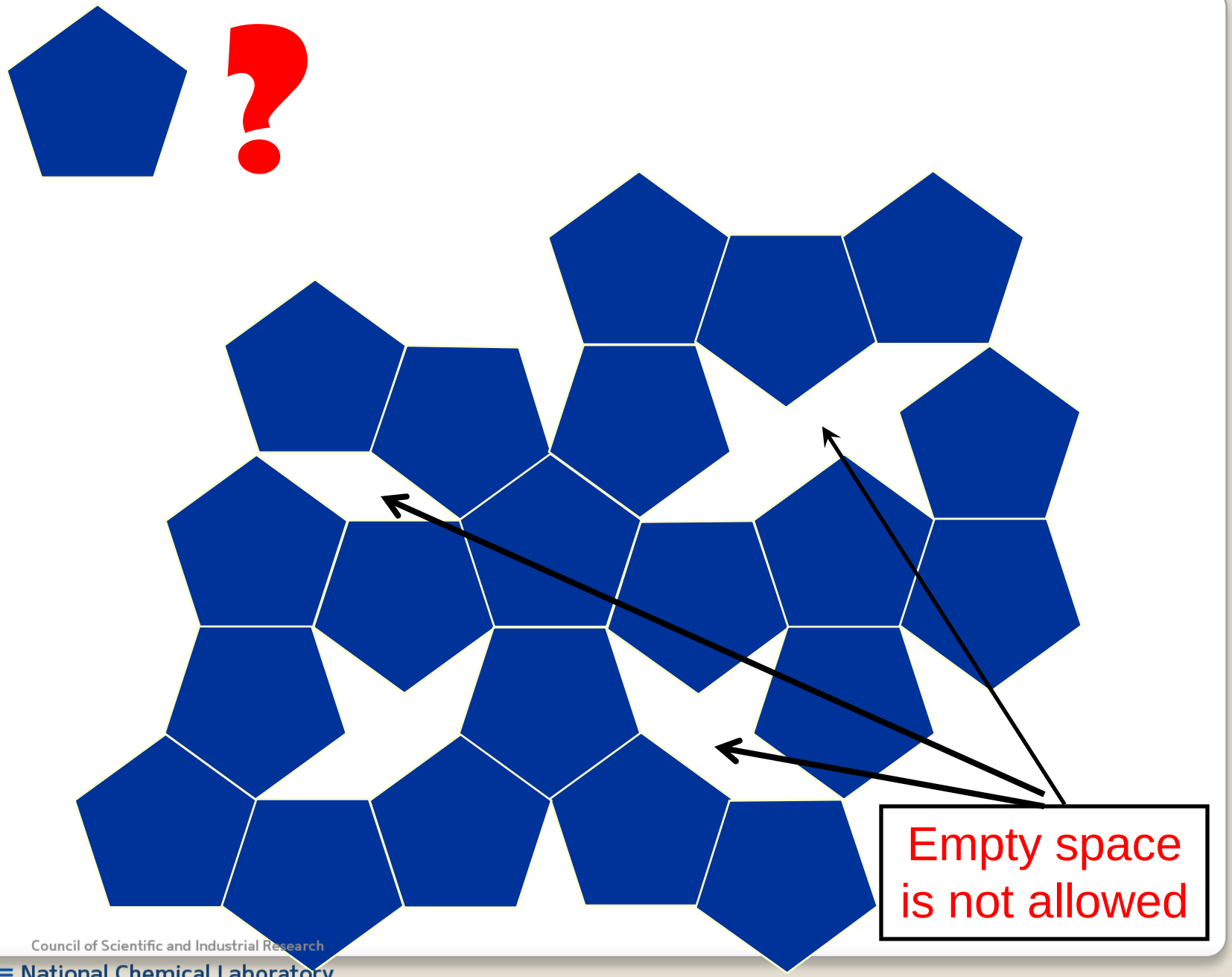








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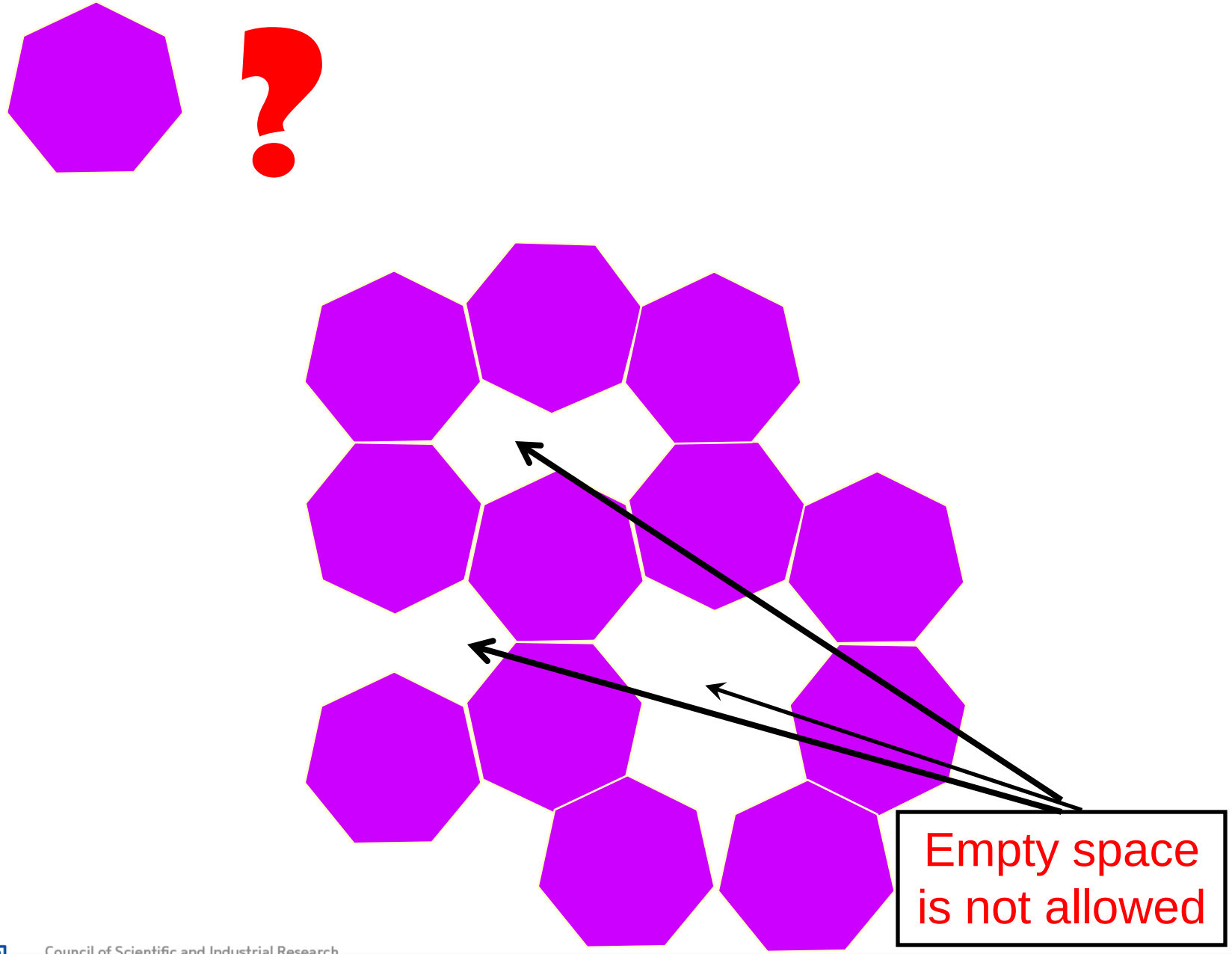
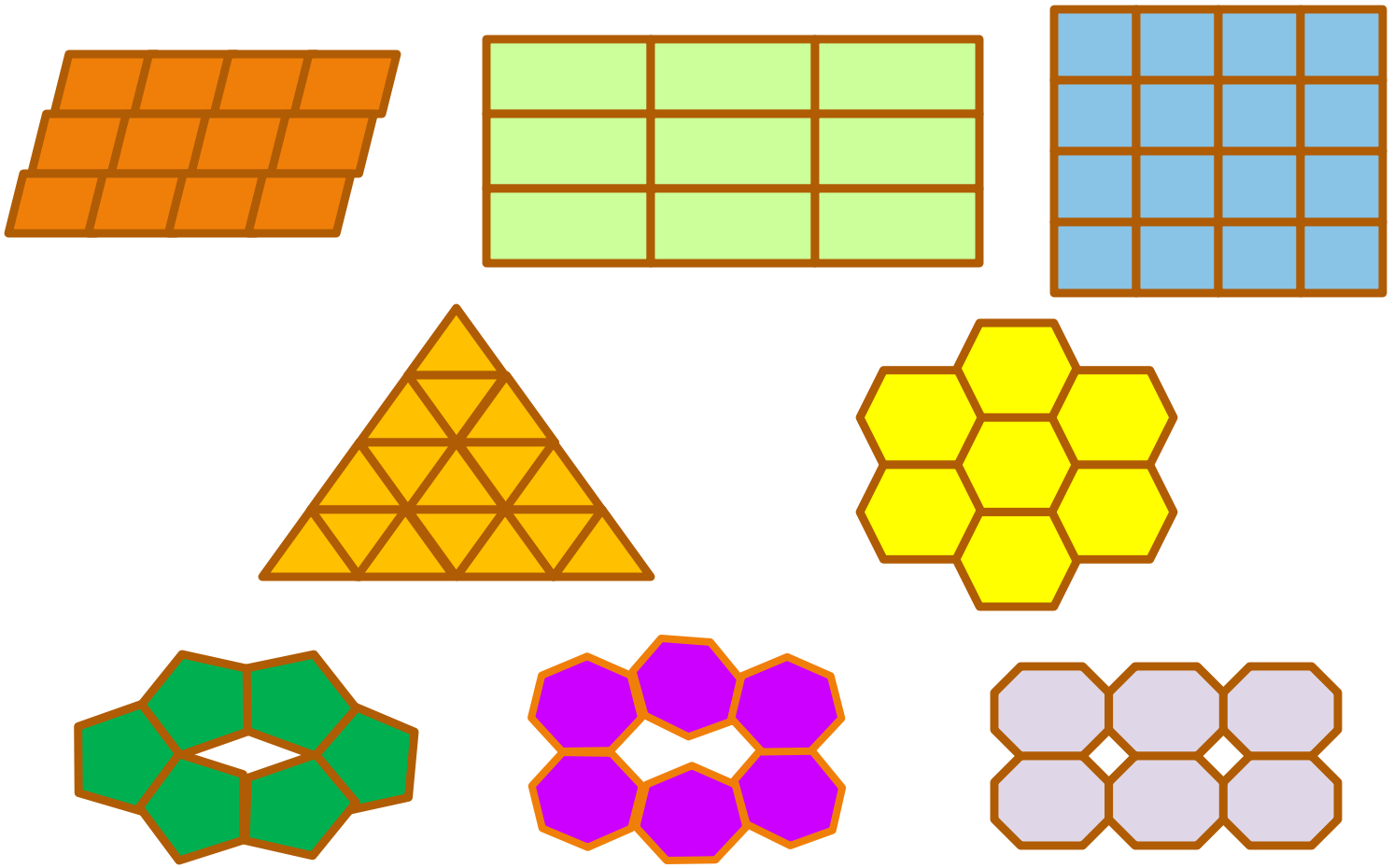
Empty space
is not allowed


Empty space
is not allowed

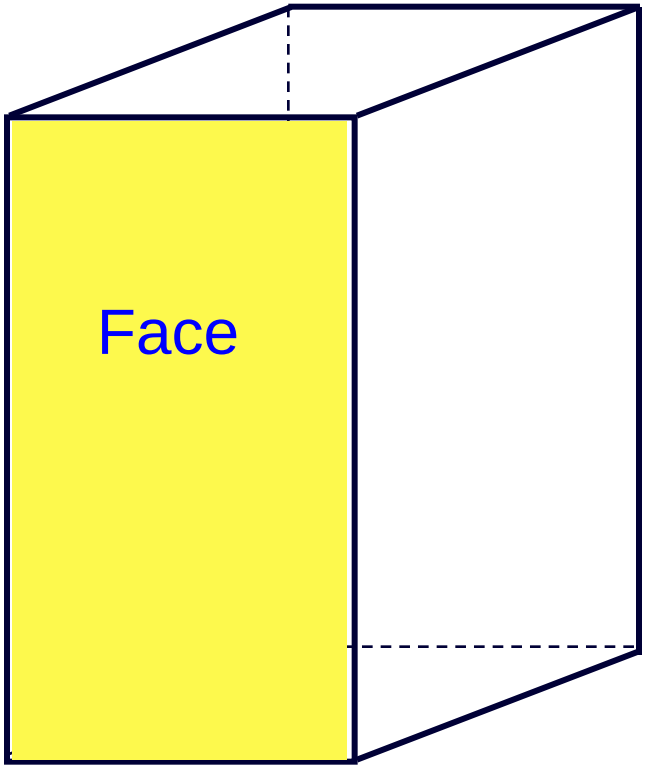
Space filling repeat patterns



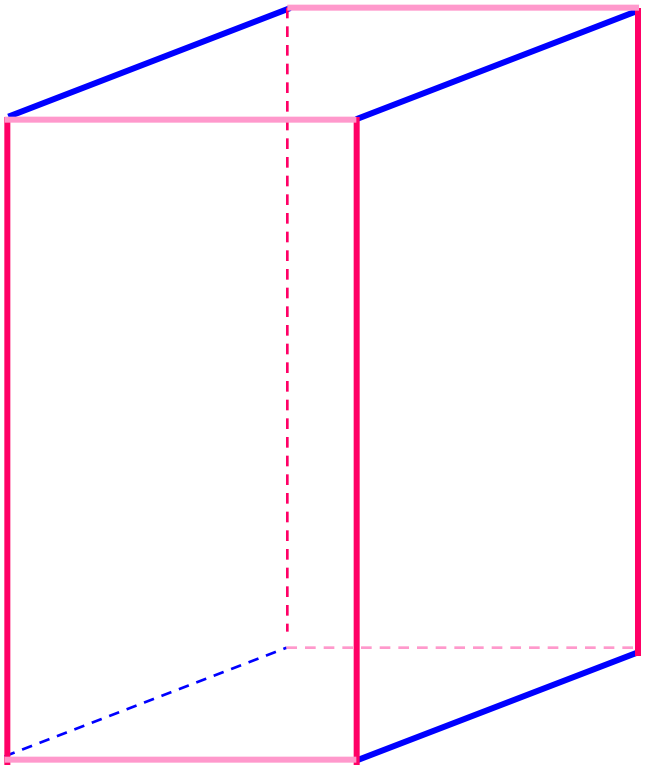
Only 2, 3, 4 and 6-fold rotations can produce space filling patterns

External Appearance of Crystals

Crystal faces: crystal usually bounded by a number of flat surfaces (faces).



Crystal edge: It is formed by intersection of two adjacent faces

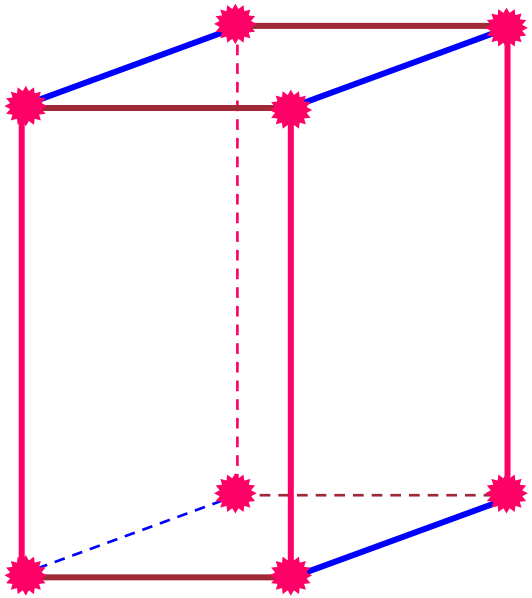


4 + 4 + 4 = 12 edge

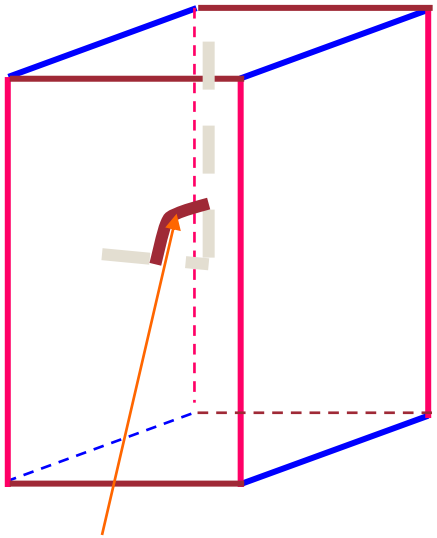
External parts of crystal

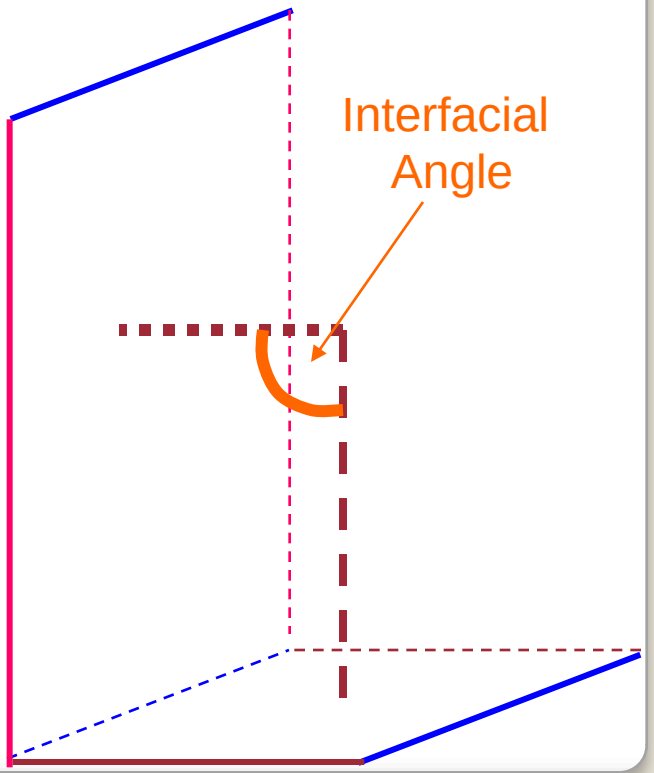
Solid angle: It is formed by intersection of more than two adjacent faces

Interfacial Angle: It is angle between two adjacent faces.
More accurately it is angle locates between two verticals drawn to any two adjacent faces.



4 + 4 = 8 Solid angle



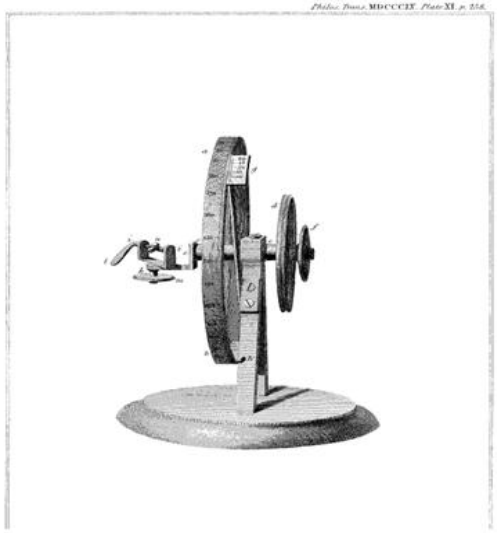


Law of constant interfacial angles

Angles between the crystal faces of a given species are constant

- ***Contact*** (A. Carangeot,1783): To determine the angle between two surfaces, one has to hold the crystal edge at the scissor opening between the limbs of the goniometer. The angle being measured is read from the scale.

- ***Reflecting*** (W.H. Wollaston, 1809): Instead of measuring the angle formed by the meeting of two faces of a crystal directly, it measured the angle formed by the meeting of rays of light reflected from them.



Classification of Crystals Based on their Shapes

Seven (7) Crystal Systems

1. Cubic	$a = b = c$;	$\alpha = \beta = \gamma = 90^\circ$
2. Hexagonal	$a = b \neq c$;	$\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$
3. Rhombohedral	$a = b = c$;	$\alpha = \beta = \gamma \neq 90^\circ$
4. Tetragonal	$a = b \neq c$;	$\alpha = \beta = \gamma = 90^\circ$
5. Orthorhombic	$a \neq b \neq c$;	$\alpha = \beta = \gamma = 90^\circ$
6. Monoclinic	$a \neq b \neq c$;	$\alpha = \gamma = 90^\circ$, $\beta = \neq 90^\circ$
7. Triclinic	$a \neq b \neq c$;	$\alpha \neq \beta \neq \gamma \neq 90^\circ$

CRYSTAL SYSTEMS

CRYSTAL SYSTEMS are divided into 7 main groups.

Fluorite Crystals

Pyrite Crystals

The first group is the ISOMETRIC (Cubic). This literally means "equal measure" and refers to the equal size of the crystal axes.

ISOMETRIC BASIC CRYSTAL SHAPES

Octahedron

Cube

Cube with Pyritohedron Striations

Trapezohedron

Grossularite, Dodecahedra

HEXAGONAL CRYSTALS

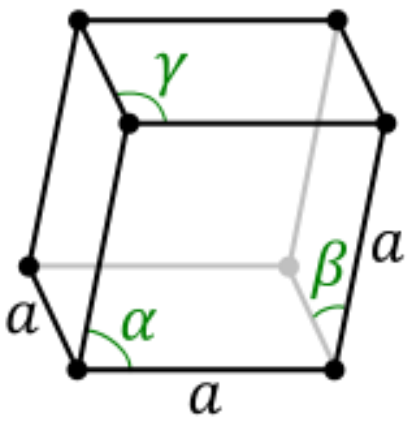
Three horizontal axes meeting at angles of 120^{o} and one perpendicular axis.

This model represents a hexagonal **PRISM** (the outside hexagon - six sided shape). The top and bottom faces are called **PINACOIDS** and are perpendicular to the vertical “c” axis.

BERYL

Rhombohedral Crystals

$\alpha=\beta=\gamma \neq 90°$



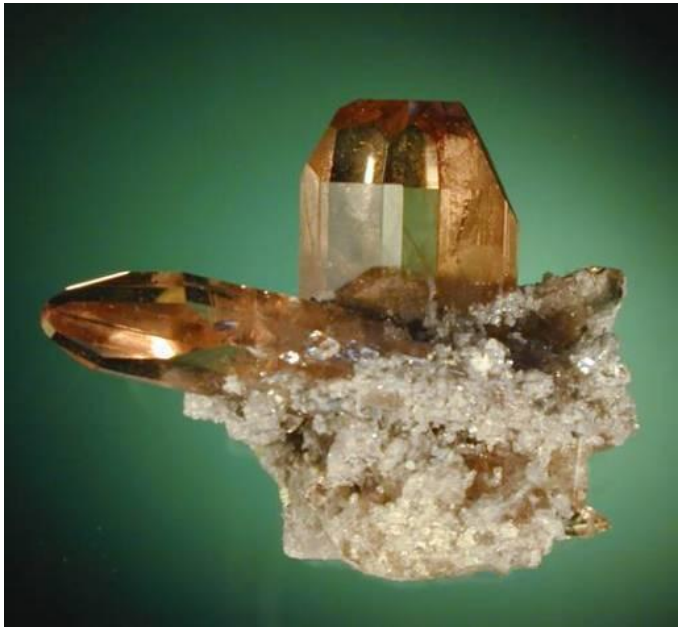
TETRAGONAL CRYSTALS

WULFENITE

APOPHYLLITE

on Stilbite

ORTHORHOMBIC CRYSTALS

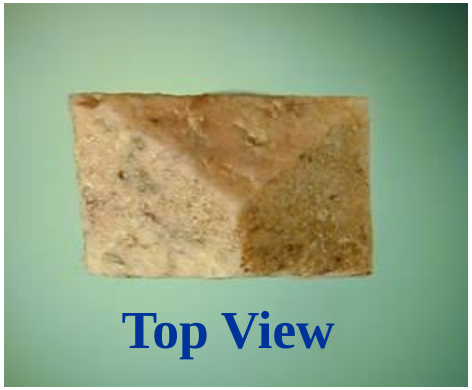


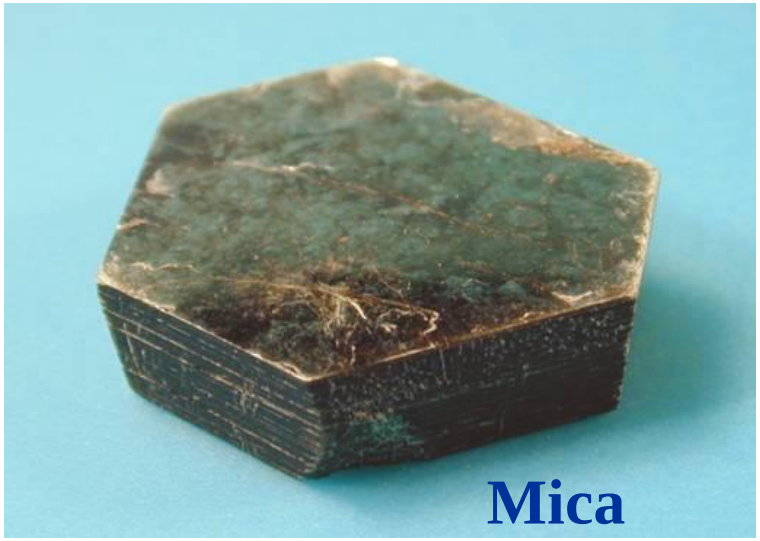
ORTHORHOMBIC CRYSTALS

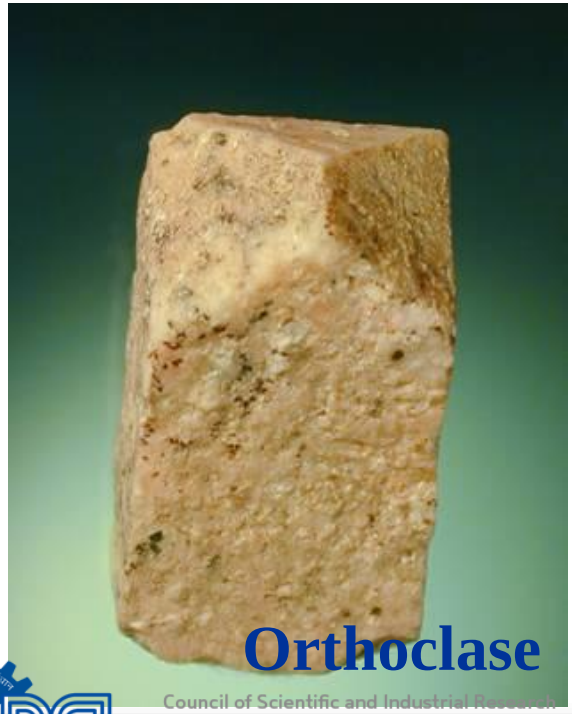
Pinacoid View

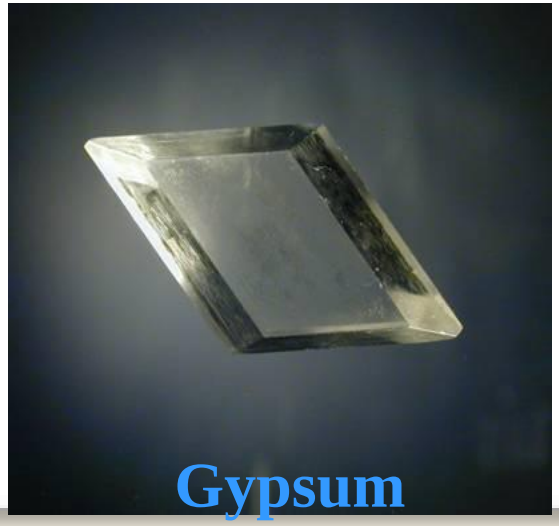
Prism View

MONOCLINIC CRYSTALS









TRICLINIC CRYSTALS

Microcline, variety
Amazonite

Geometrical Crystallography

- **Abbé René Just Haűy** (1743 – 1822): Father of Crystallography

Gabriel Delafosse

Auguste Laurent

Christian Samuel Weiss

Crystal Structure Model

Symmetry in Crystal

Auguste Bravais (1811 -1863)

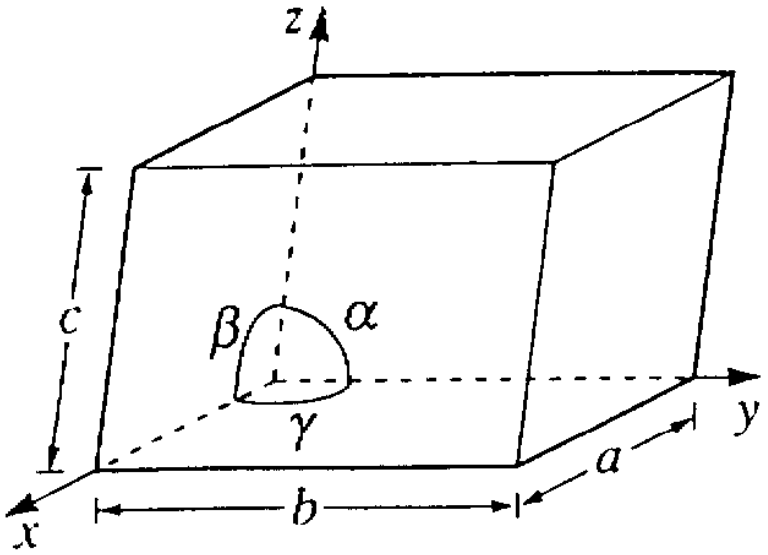
Bravais, a graduate of the **École Polytechnique** and a professor of physics, worked out a ***mathematical theory of crystal symmetry*** based on the concept of the **crystal lattice, of which there were 14**.

The Unit Cell

"The smallest repeat unit of a crystal structure, in 3D, which shows the full symmetry of the structure"

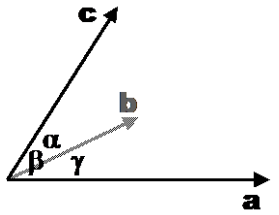
The unit cell is a box with:

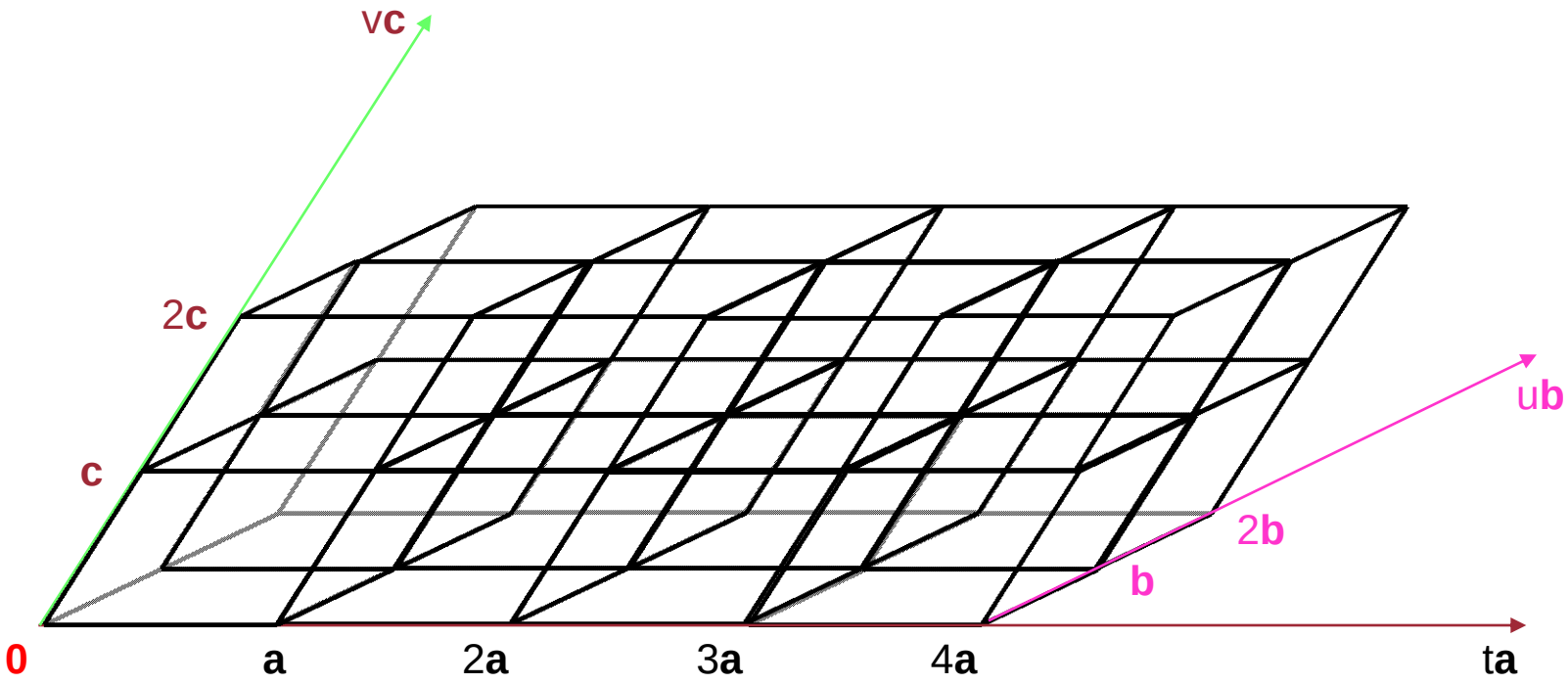
- 3 sides - a, b, c
- 3 angles - α, β, γ



- **Only 1/8 of each lattice point in a unit cell can actually be assigned to that cell.**
- **Each unit cell in the figure can be associated with 8 x 1/8 = 1 lattice point.**

Building a crystal





Lattice

Translationally periodic arrangement of **points** in space

Crystal

Translationally periodic arrangement of **motifs**

Crystal = Lattice + Motif

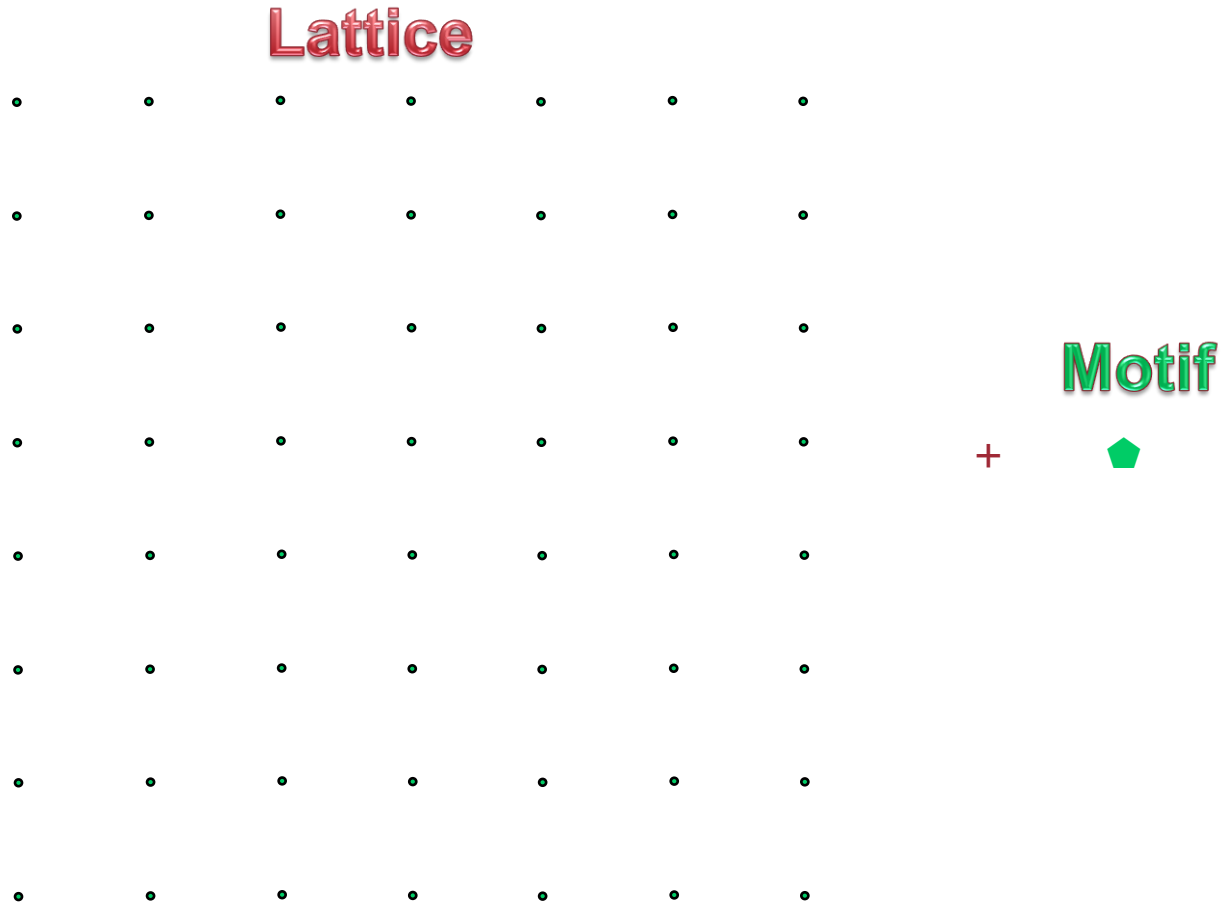
Lattice ➢ the underlying periodicity of the crystal

Basis or Motif ➢ atom or group of atoms associated with each lattice points

Lattice ➢ how to repeat

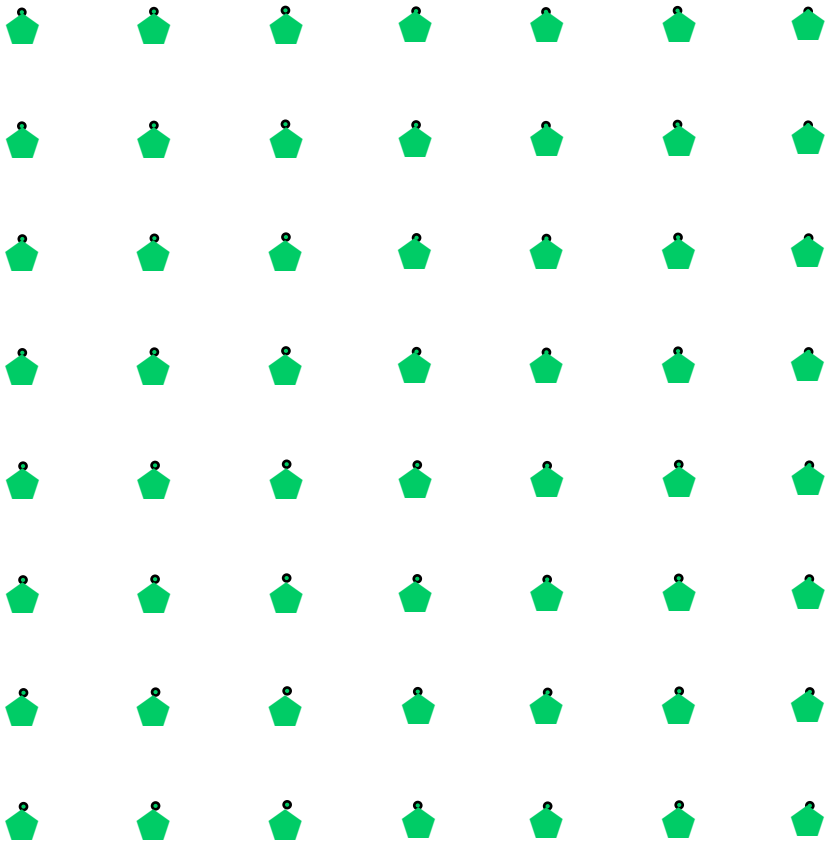
Motif ➢ what to repeat

- Crystal structure can be obtained by attaching atoms, groups of atoms or molecules which are called basis (motif) to the lattice sides of the lattice point.

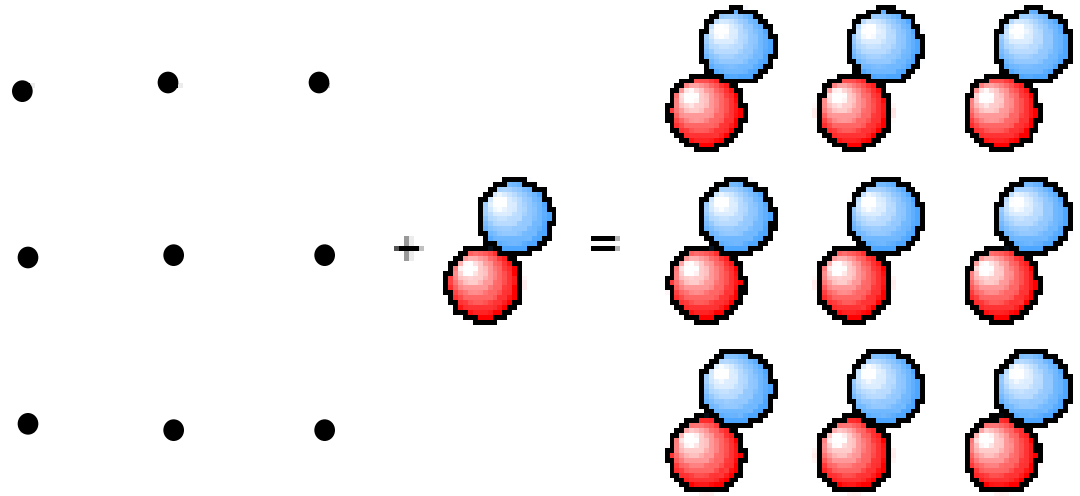


Crystal

=



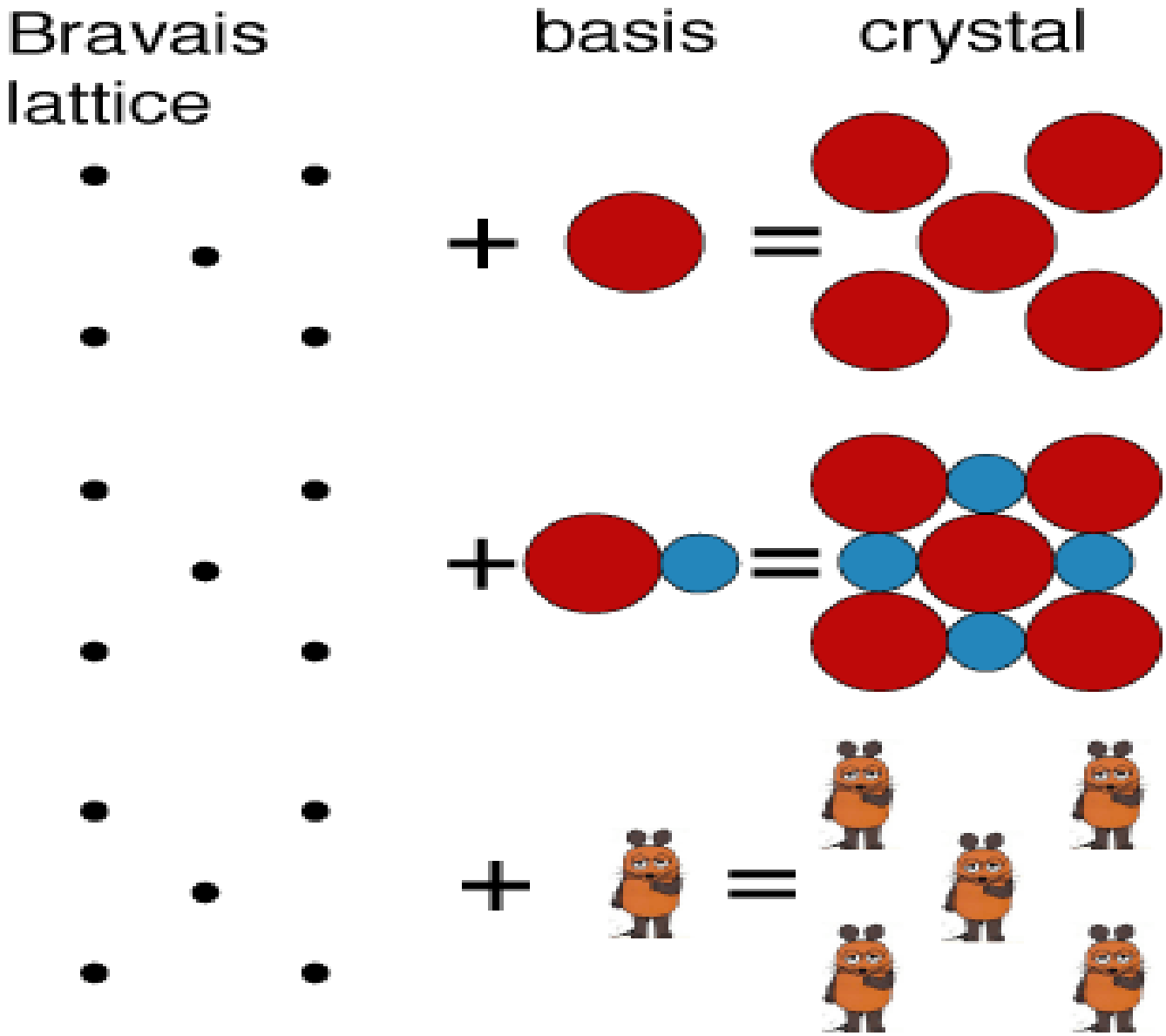
Crystal Structure = Crystal Lattice + Basis



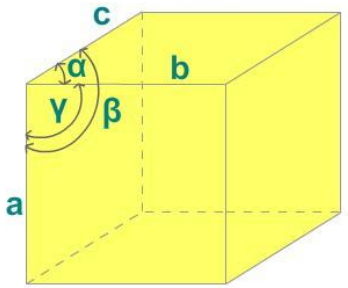
Elemental solids (Argon): **Basis = single atom.**

Polyatomic Elements: **Basis = two or four atoms.**

Complex organic compounds: **Basis = thousands of atoms.**


Bravais lattice
basis
crystal

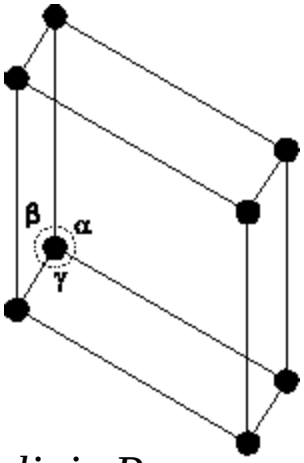
⇒ Seven unit cell shapes



(≠ should be read "not constrained to be.")

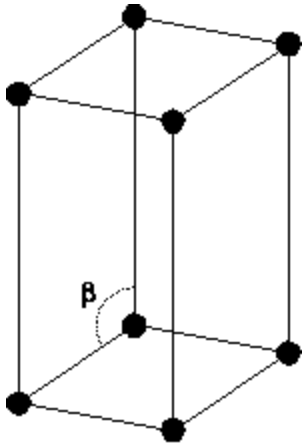
• Triclinic	$a \neq b \neq c$	$\alpha \neq \beta \neq \gamma \neq 90°$
• Monoclinic	$a \neq b \neq c$	$\alpha = \gamma = 90°, \beta \neq 90°$
• Orthorhombic	$a \neq b \neq c$	$\alpha = \beta = \gamma = 90°$
• Tetragonal	$a = b \neq c$	$\alpha = \beta = \gamma = 90°$
• Rhombohedral	$a = b = c$	$\alpha = \beta = \gamma \neq 90°$
• Hexagonal	$a = b \neq c$	$\alpha = \beta = 90°, \gamma = 120°$
• Cubic	$a = b = c$	$\alpha = \beta = \gamma = 90°$

The 14 Bravais lattices



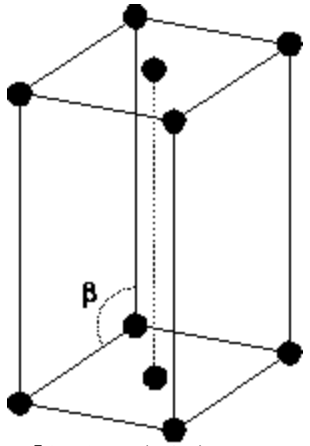
Triclinic P

$a \neq b \neq c,\ \alpha \neq \beta \neq \gamma$



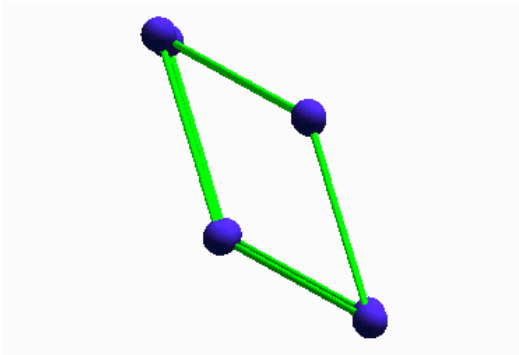
Monoclinic P

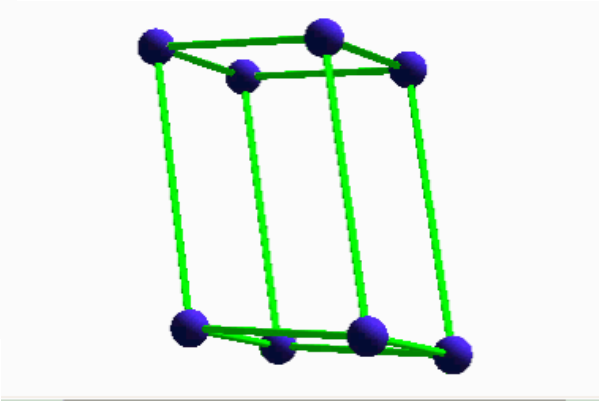
$a \neq b \neq c,\ \alpha = \gamma = 90^{\circ}\ \beta \neq 90^{\circ}$

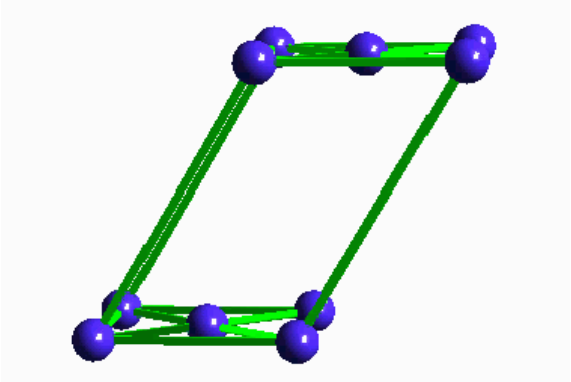


Monoclinic (C)

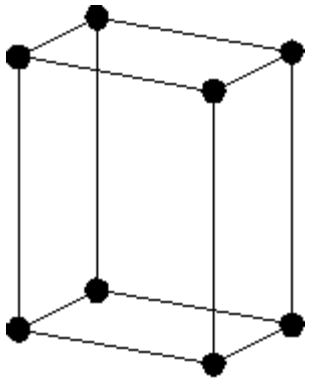
$a \neq b \neq c,\ \alpha = \gamma = 90^{o}\ ,\ ß \neq 90^{o}$





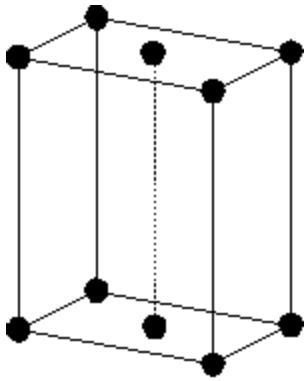


The 14 Bravais lattices



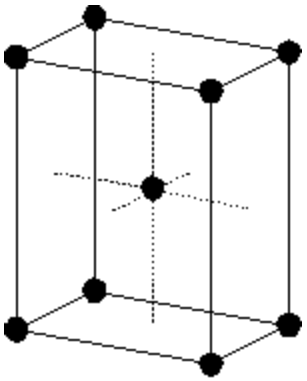
Orthorhombic (P)

$a \neq b \neq c$, $\alpha=ß=\gamma=90^o$



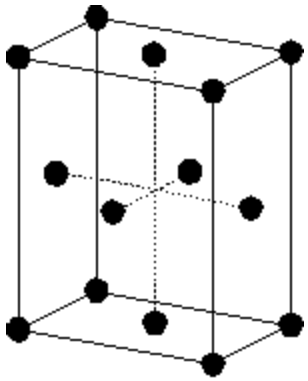
Orthorhombic (C)

$a \neq b \neq c$, $\alpha=ß=\gamma=90^o$



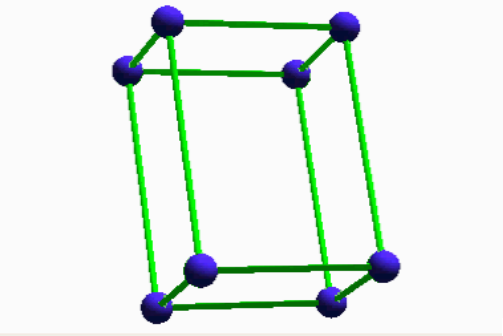
Orthorhombic (I)

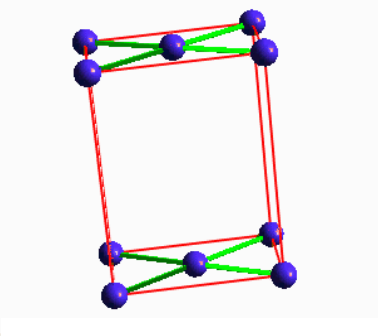
$a \neq b \neq c$, $\alpha=ß=\gamma=90^o$

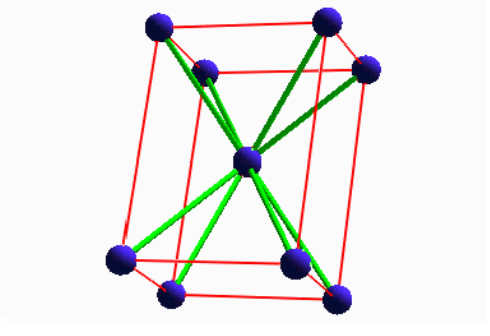


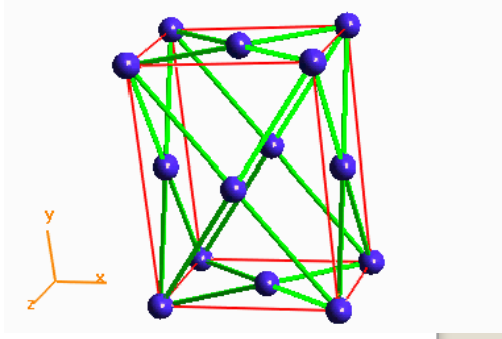
Orthorhombic (F)

$a \neq b \neq c$, $\alpha=ß=\gamma=90^o$

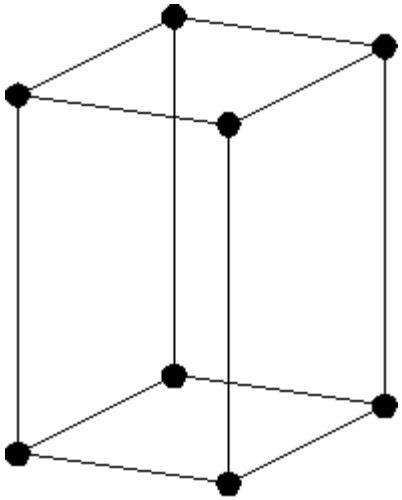






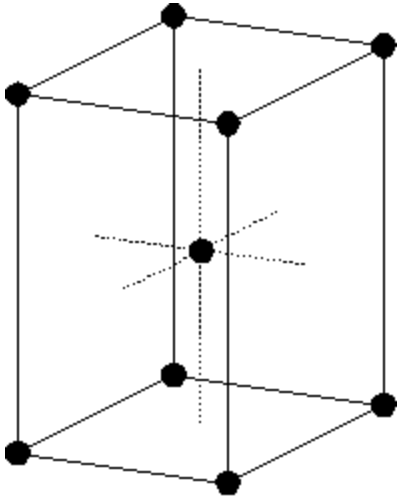


The 14 Bravais lattices



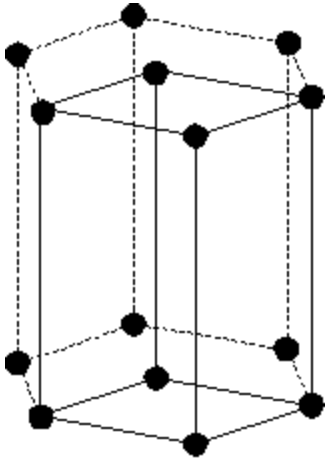
Tetragonal (P)

$a=b \neq c,\ \alpha=ß=\gamma=90^o$



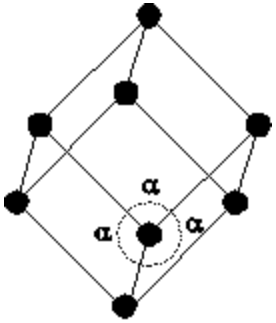
Tetragonal (I)

$a=b \neq c,\ \alpha=ß=\gamma=90^o$



Hexagonal (P)

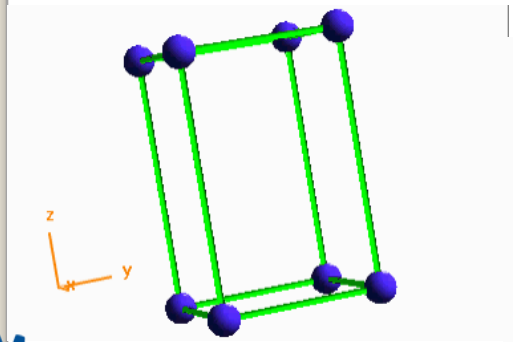
$a=b \neq c,\ \alpha=ß=90^o,\ \gamma=120^o$

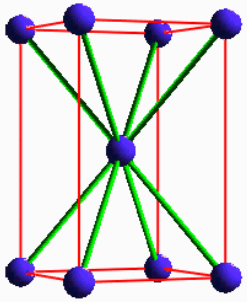


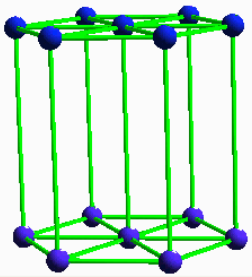
Rhombohedral (R)

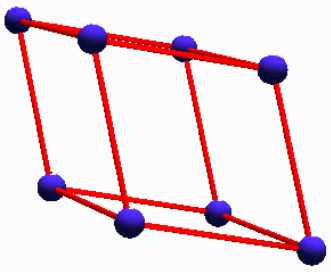
Trigonal P

$a=b=c,\ \alpha=ß=\gamma \neq 90^o$

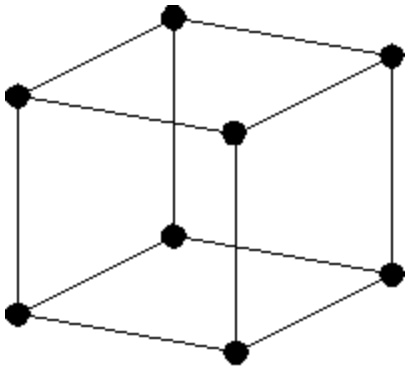






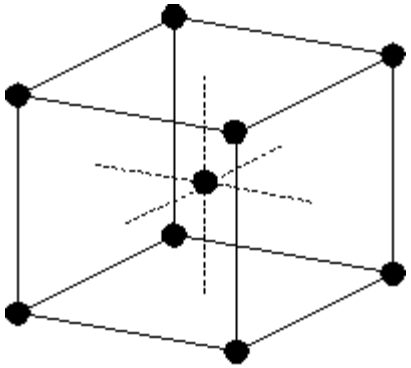


The 14 Bravais lattices



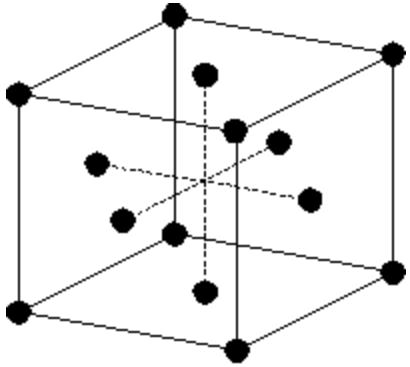
Cubic (P)

$a=b=c,\ \alpha=ß=\gamma=90^o$



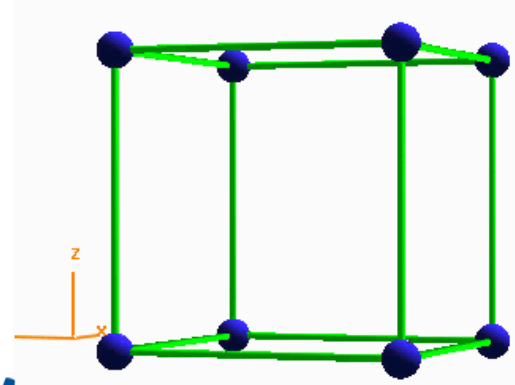
Cubic (I)

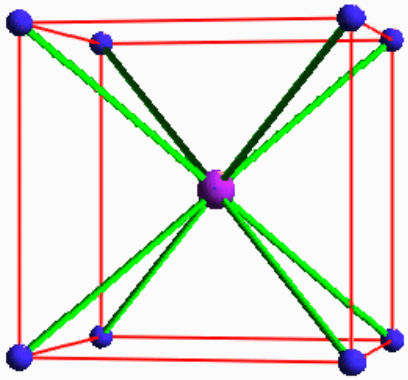
$a=b=c,\ \alpha=ß=\gamma=90^o$

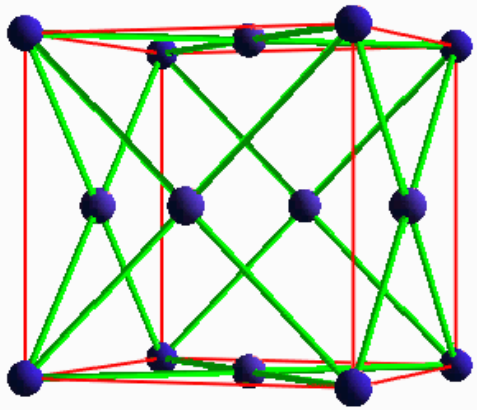


Cubic (F)

$a=b=c,\ \alpha=ß=\gamma=90^o$







Symmetry Elements and Operations

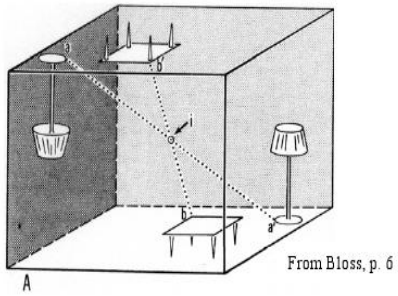
*"**Symmetry elements*** define the (conceptual) motion of an object in space,

the ***symmetry operation***, leads to an arrangement that is indistinguishable from the initial arrangement."

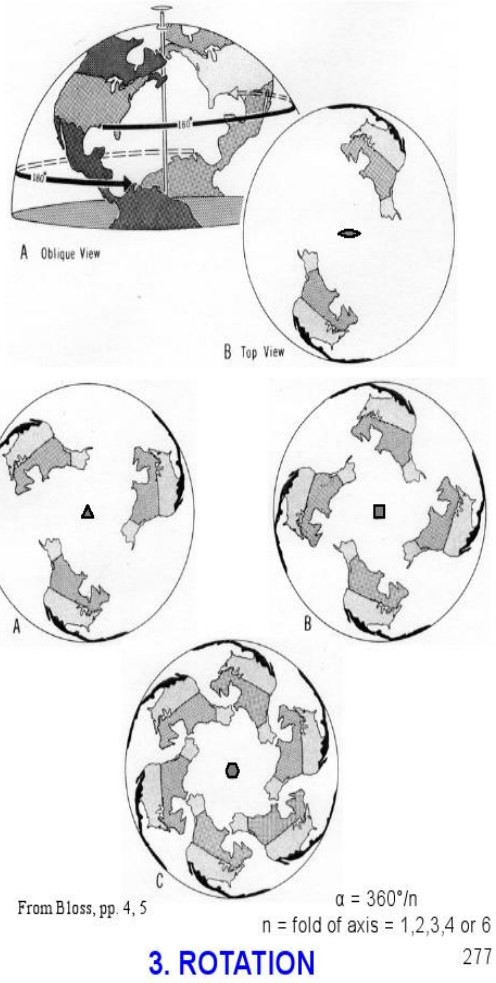
Symmetry Operations & 32 Point Groups

Rotation, reflection and inversion operations generate a variety of unique arrangements of lattice points (i.e., a shape structure) in three dimensions.

2. REFLECTION = *m*

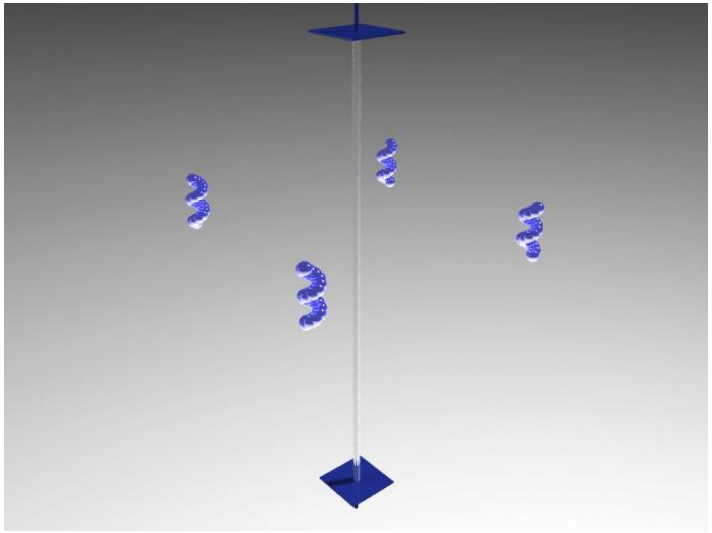


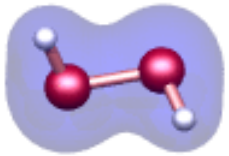
4. INVERSION = *i*



3. ROTATION

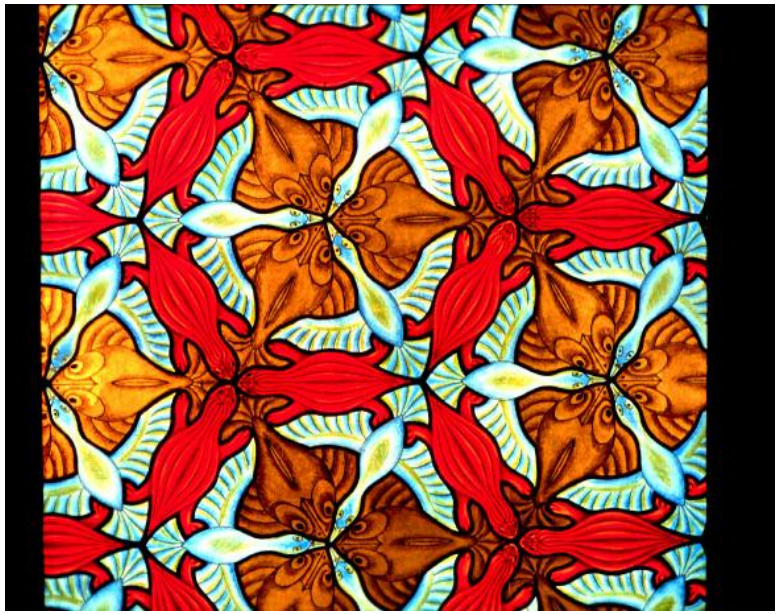
Rotational symmetry





Rotation about an axis:
1, 2, 3, 4 or 6

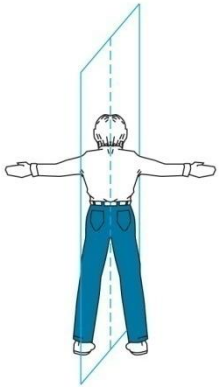
Rotational symmetry

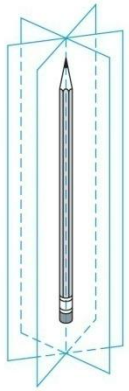


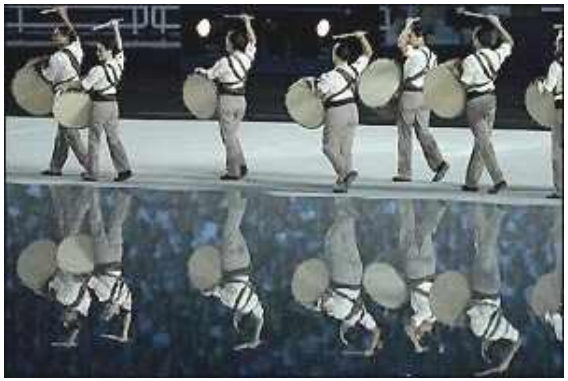
ESCHER'S DRAWING

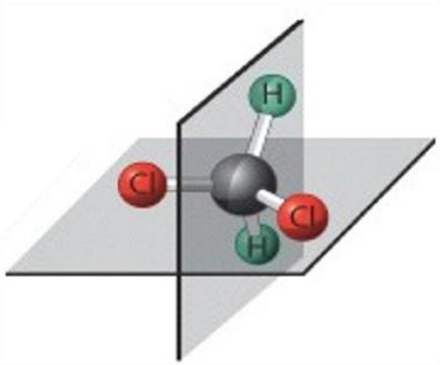
Mirror Plane Symmetry

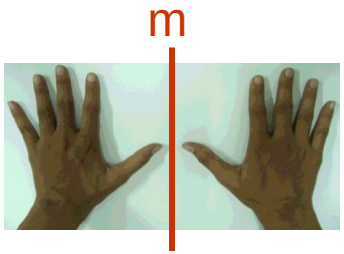
"Arises when one half of an object is the mirror image of the other half"

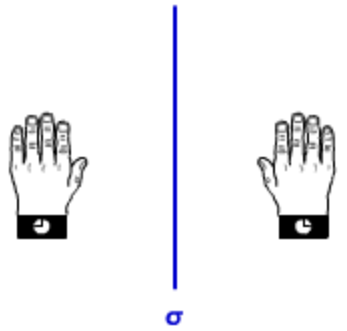




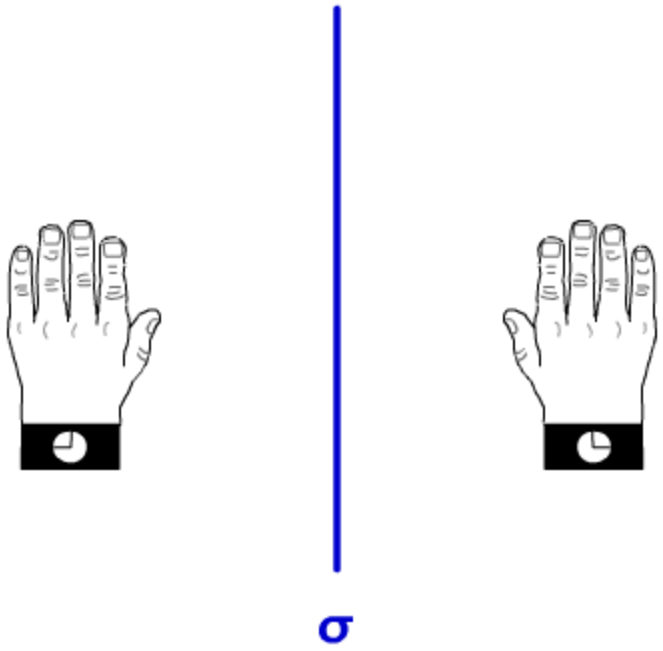








Mirror Symmetry



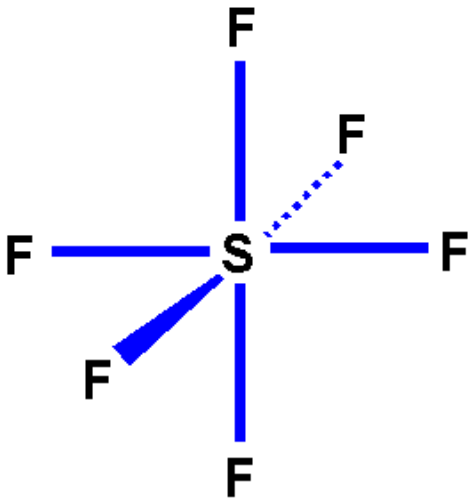
Right and left hands are identical by reflection through a mirror plane.

Imagine σ as a plane pointing into the page. This mirror plane is the symmetry element.

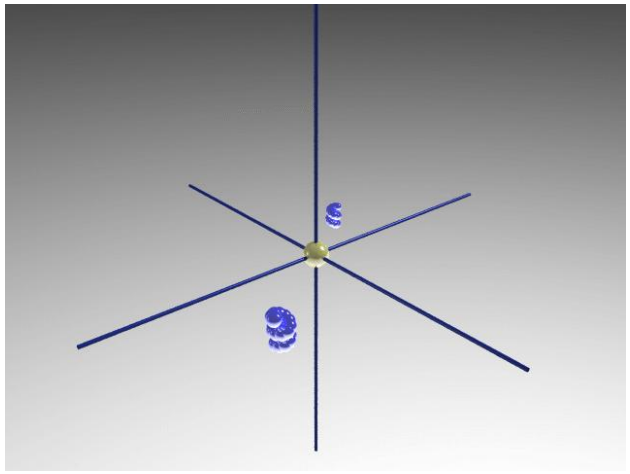
The motion of taking one hand through the plane to give its reflection is the symmetry operation.

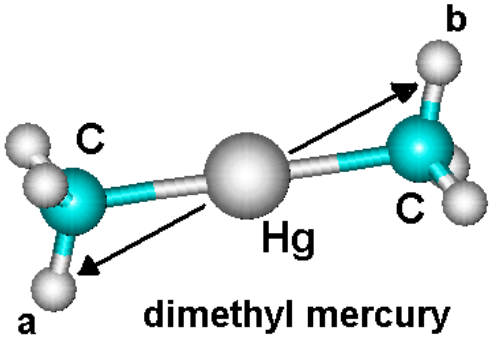
Centre of Symmetry (i)

"present if you can draw a straight line from any point, through the centre, to an equal distance the other side, and arrive at an identical point"

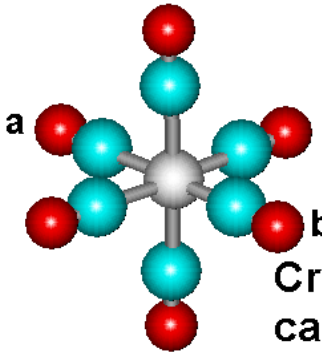


Centre of symmetry at **S**





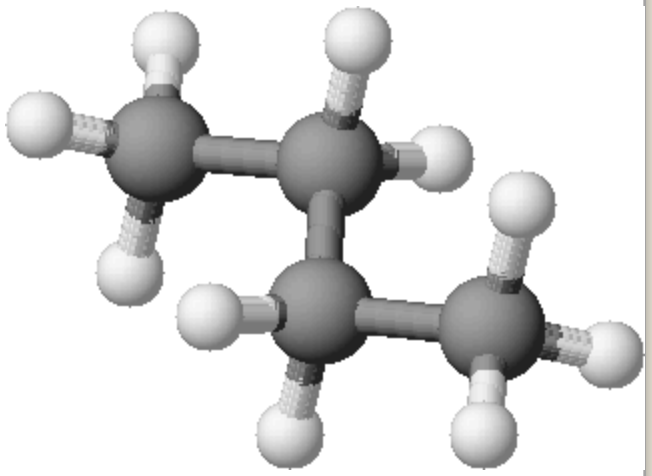
dimethyl mercury

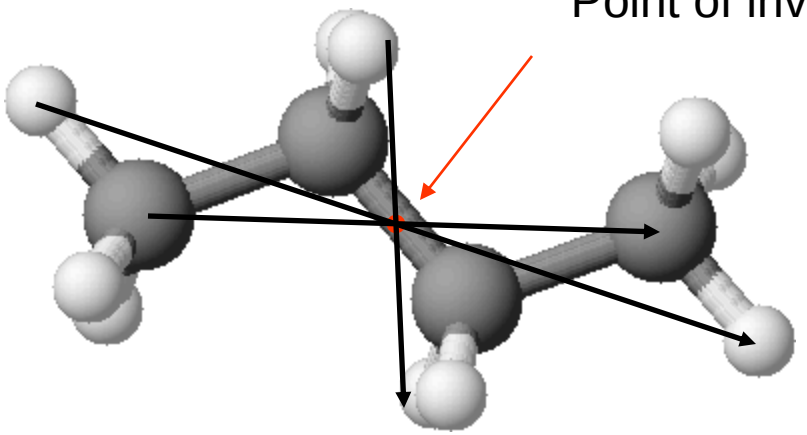


Cr(0) hexa-carbonyl

The inversion, i

- Centre of symmetry
  - reflection through the centre of the molecule to an equal distance on the opposite site.





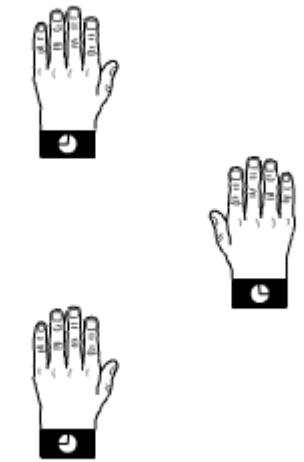
Space groups

The combination of all available symmetry operations (32 point groups), together with translation symmetry, within the all available lattices (14 Bravais lattices) lead to 230 Space Groups that describe the only ways in which identical objects can be arranged in an infinite lattice. The International Tables list those by symbol and number, together with symmetry operators, origins, reflection conditions, and space group projection diagrams.

Arthur Moritz Schönflies
(1853-1928)

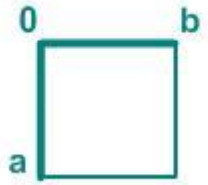
Yevgraf Stepanovich Federov
(1853-1919)

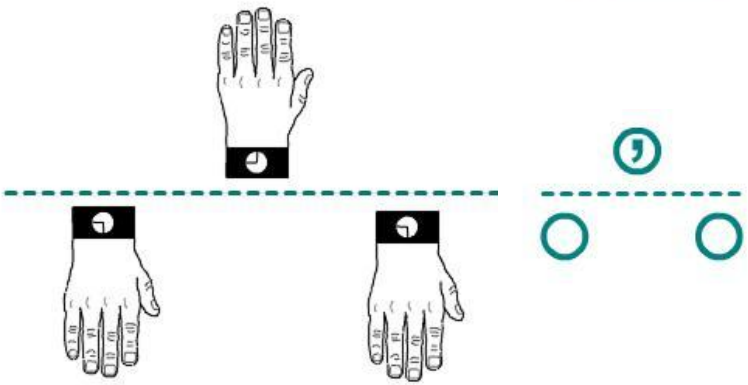
Reflection Plane: Glides



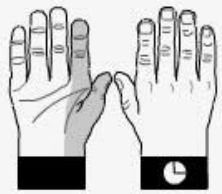
The glide plane is perpendicular to the page.

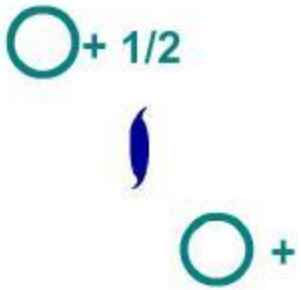
A glide consists of a reflection followed by a translation.

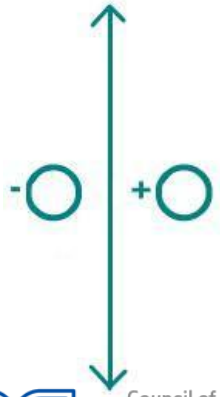


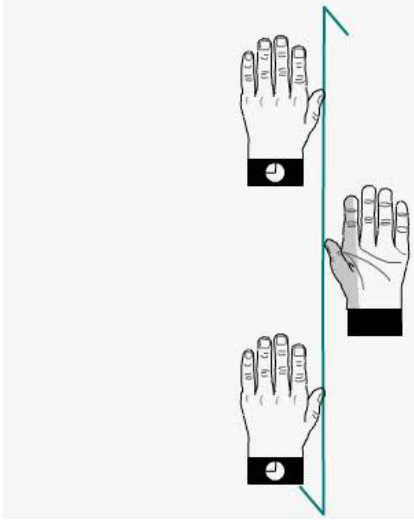


Rotation Axis: Screw



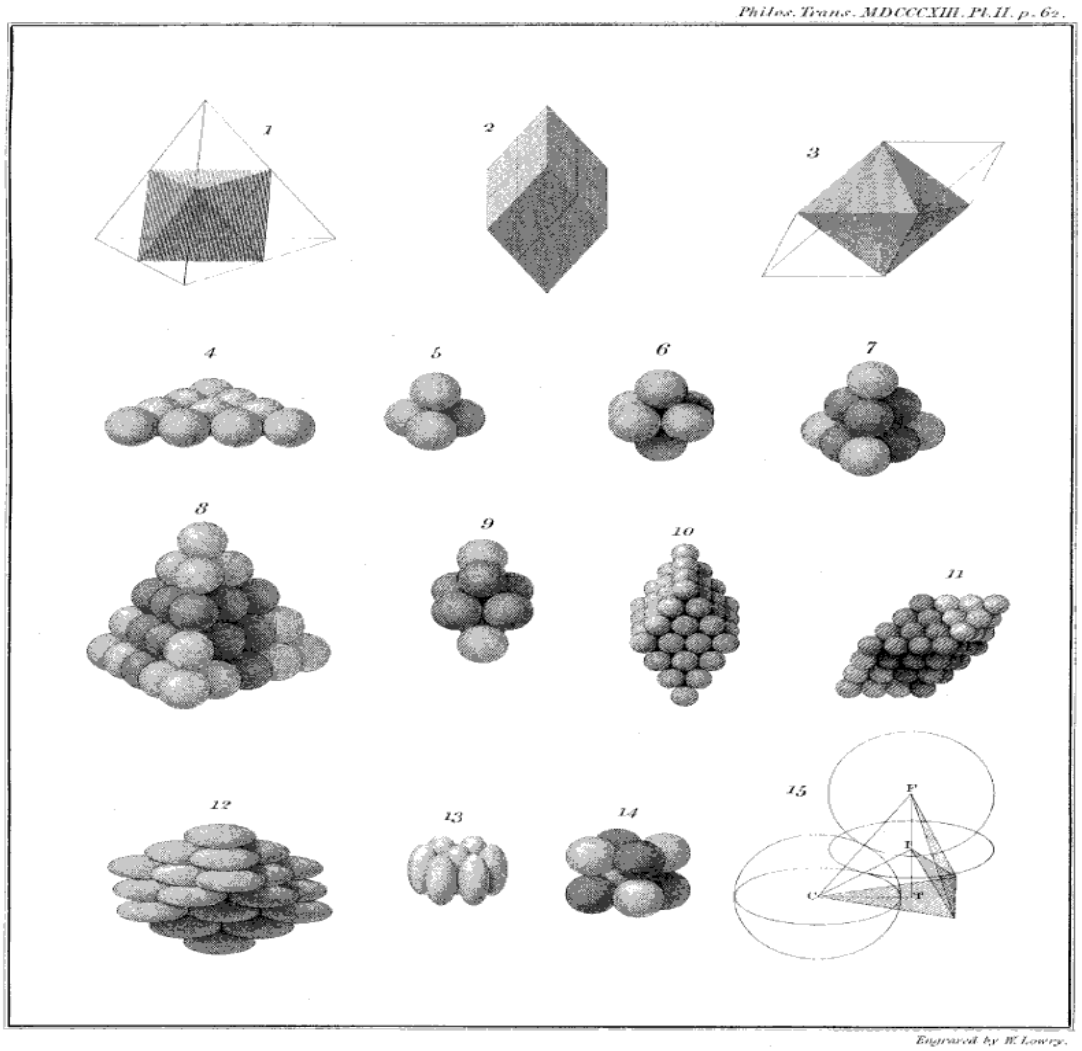




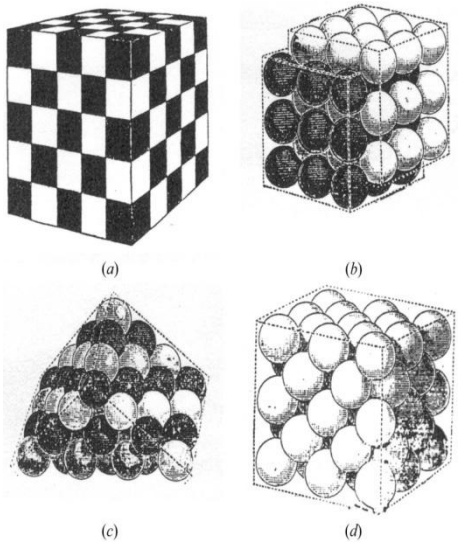


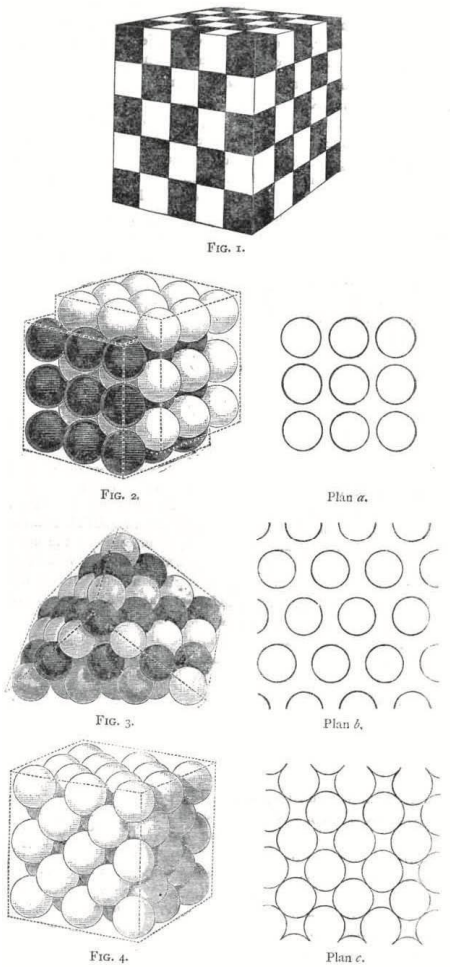
Theoretical Model of Crystal Structure

William Hyde Wollaston.



William Barlow (1845-1934)





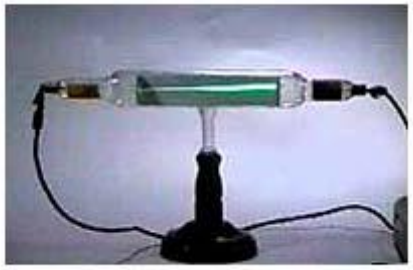
Barlow's theories of the properties of crystals were based on *the close packing of atoms*."

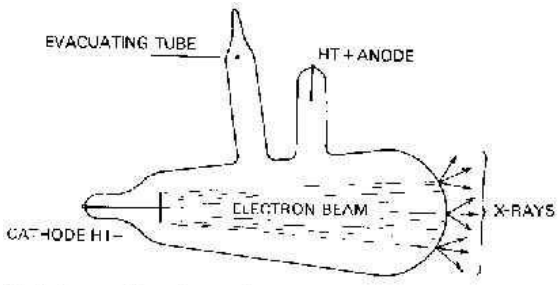
Independently of Schönflies and Federov , Barlow derived the 230 space groups.

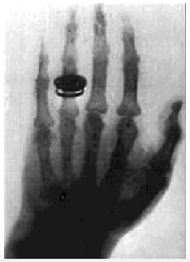
William T. Hosler, "Barlow, William," *Complete Dictionary of Scientific Biography*. 2008. Encyclopedia.com. 20 May, 2012. http://www.encyclopedia.com

X-Ray Diffraction: Discovery of X-Rays

- Nov., 1895: **W. Röntgen** discovered that **when certain substances are exposed to the beam of a cathode ray tube, a new kind of penetrating ray capable of fogging photographic plates even when shielded** was emitted –
- He called it "x-rays". These x-rays also ionized gases through which they passed.

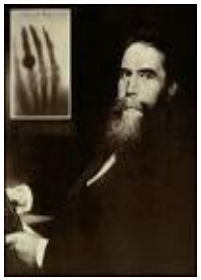






Bertha Röntgen's Hand 8 Nov, 1895

X-Ray Diffraction: Ludwig-Maximilians University of Munich Group in 1912



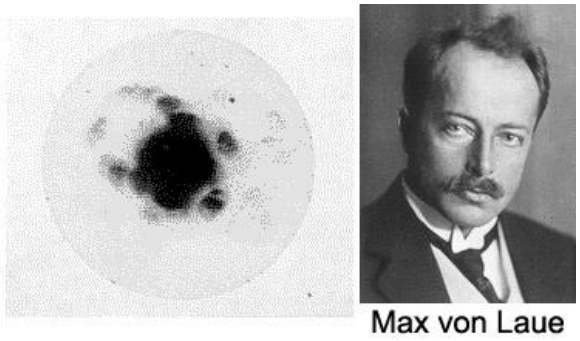
- **Röntgen**, director of the physics laboratory.
- **Arnold Sommerfeld**, Director of the Institute for Theoretical Physics. Experimental work on wave-nature (and wave length) of x-rays.

- **Paul von Groth**, professor of mineralogy, world renowned authority on crystallography and mineralogy. Interested in atomic/molecular meaning of crystal structure.

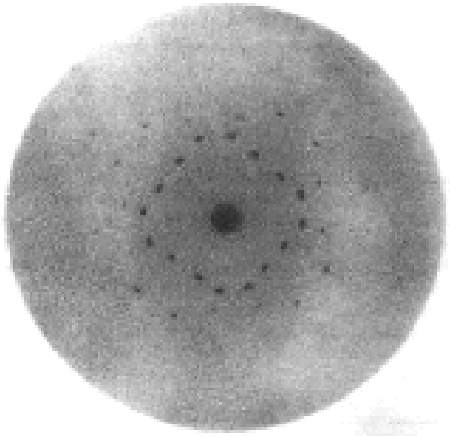
- **Paul Peter Ewald**, student of Sommerfeld, working on propagation of x-rays in single crystals.
- **Max von Laue**, *Provatdozent* in Sommerfeld' Institute.

X-Ray Diffraction: April, 1912

The first kind of scatter process to be recognised was discovered by Max von Laue who was awarded the Nobel prize for physics in 1914 *"for his discovery of the diffraction of X-rays by crystals".* His collaborators Walter Friedrich and Paul Knipping took the picture on the right in 1912. It shows how a beam of X-rays is scattered into a characteristic pattern by a crystal. In this case it is copper sulphate.

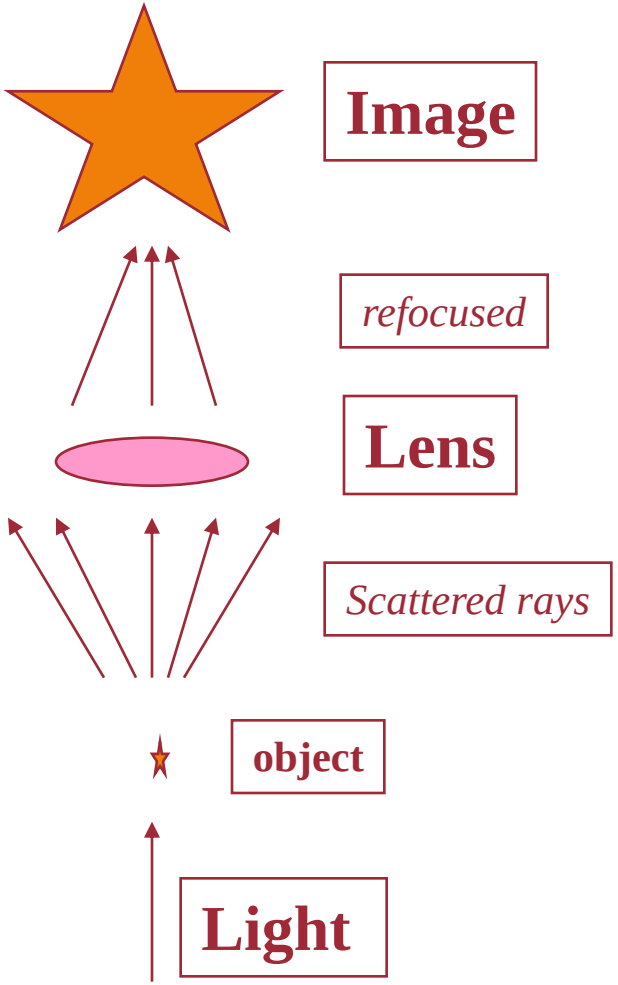


Max von Laue



X-ray diffraction pattern of copper sulphate

Optical microscope -
to view an enlarged image of an object (dimensions mm)

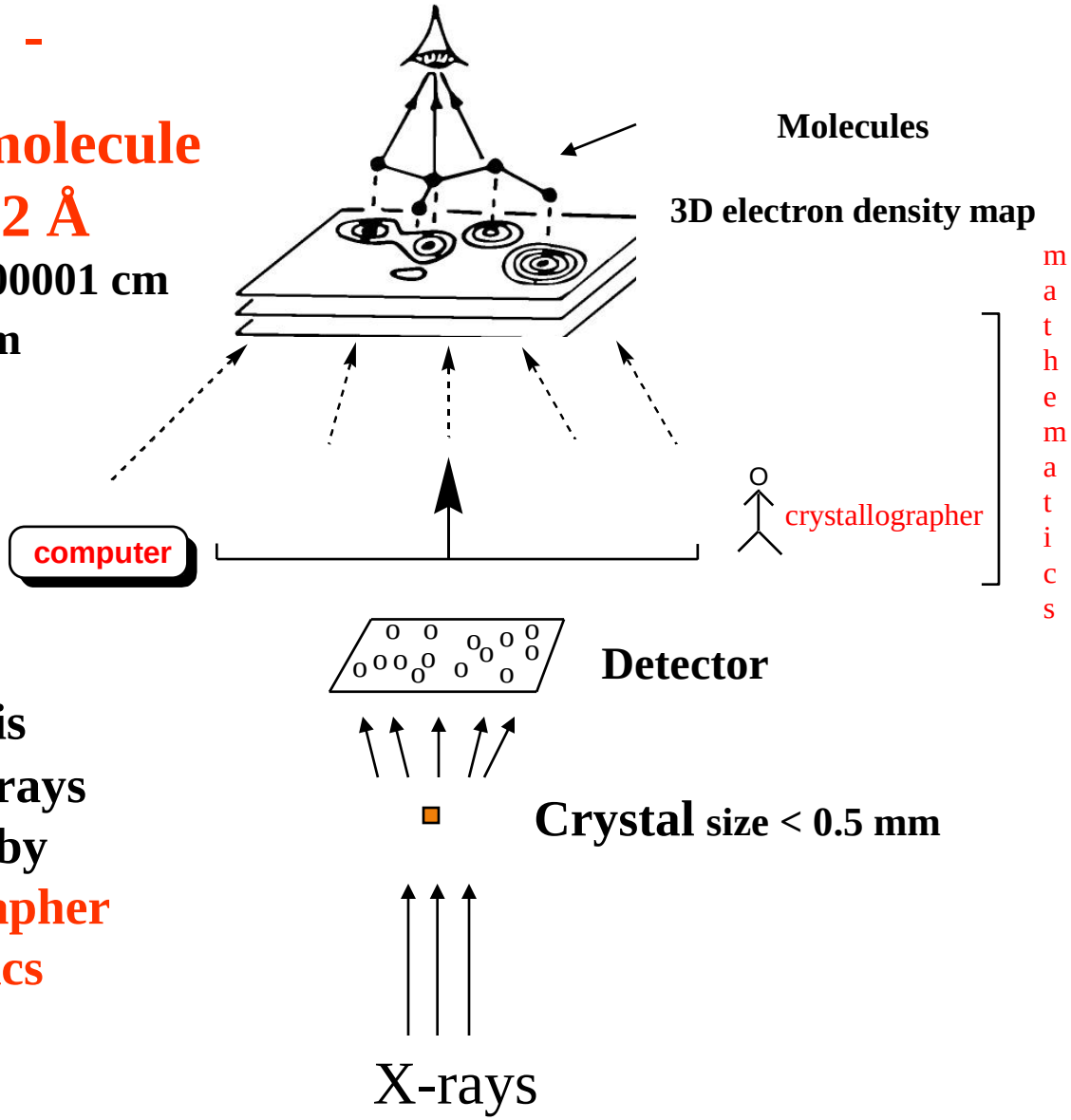


X-ray diffraction -

to view atoms in a molecule separated by 1-2 Å

1 Angstrom (Å) = 0.00000001 cm

$= 10^{-8}$cm = 10^{-10} m

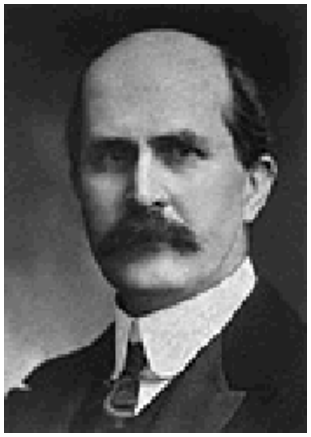


No lens exists which is capable of refocusing X-rays So the lens is replaced by a computer, a crystallographer and a lot of mathematics

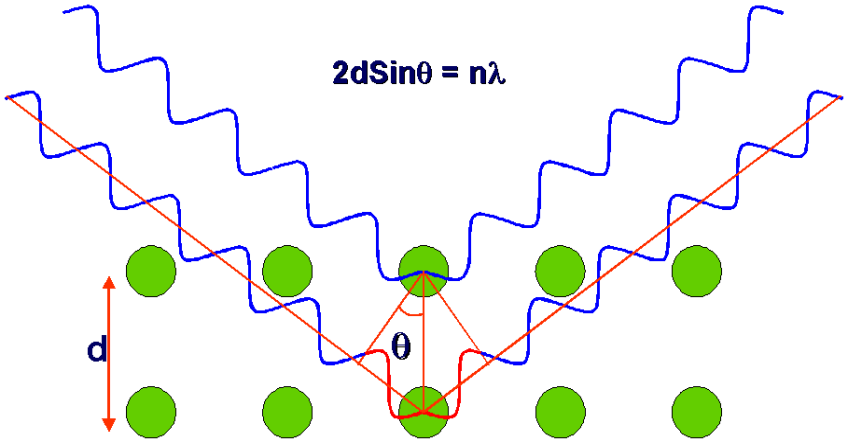
Ref: ***Crystal Structure Analysis: A Primer***. J. P. Glusker & K. N. Trueblood. Oxford University Press

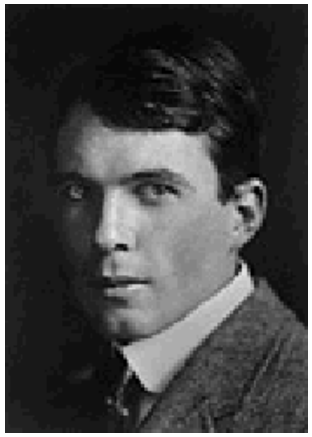
X-Ray Diffraction

- W. L. Bragg presented a simple explanation of the diffracted beams from a crystal.
- The Bragg derivation is simple but is convincing only since it reproduces the correct result.



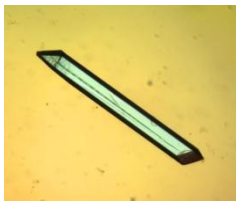
Sir W. H. Bragg (1862-1942)



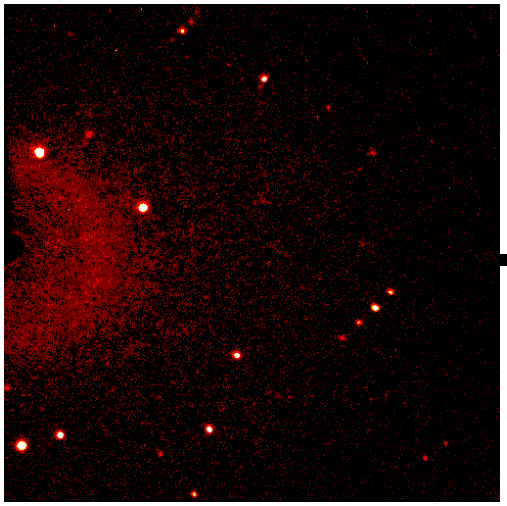


W. L. Bragg (1890-1971)

X-ray Crystallography – in a nutshell



Bragg's law



REFLECTIONS

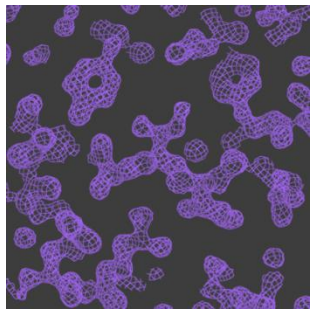
h	k	l	I	σ(I)
0	0	2	3523.1	91.3
0	0	3	-1.4	2.8
0	0	4	306.5	9.6
0	0	5	-0.1	4.7
0	0	6	10378.4	179.8

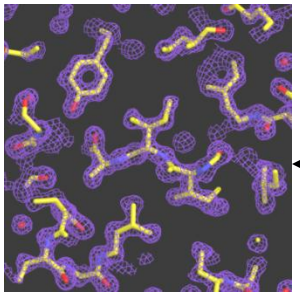
FT

REFLECTIONS

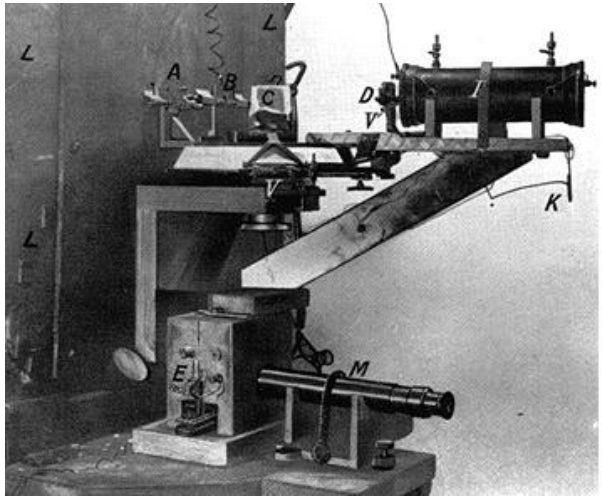
h	k	l	F	σ(F)
0	0	2	3523.1	91.3
0	0	3	-1.4	2.8
0	0	4	306.5	9.6
0	0	5	-0.1	4.7
0	0	6	10378.4	179.8

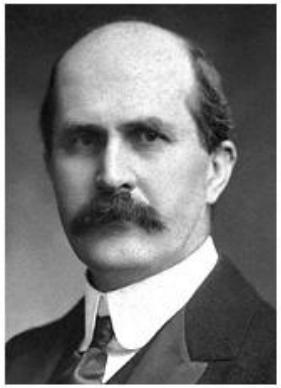
? Phase Problem ?
Direct Method
Heavy Atom Method



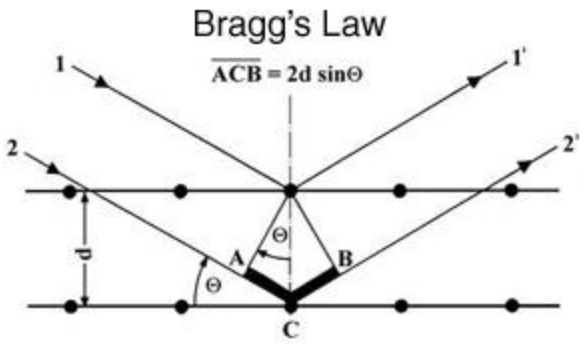


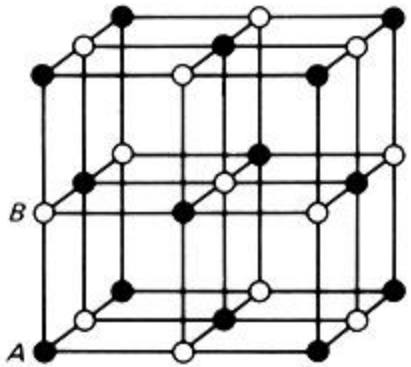
Electron density: $\rho(x\,y\,z) = 1/V \sum\sum\sum |\mathbf{F}(h\,k\,l)| \exp[-2\pi i\,(hx + hy + lz) + i\alpha(h\,k\,l)]$





William Henry Bragg



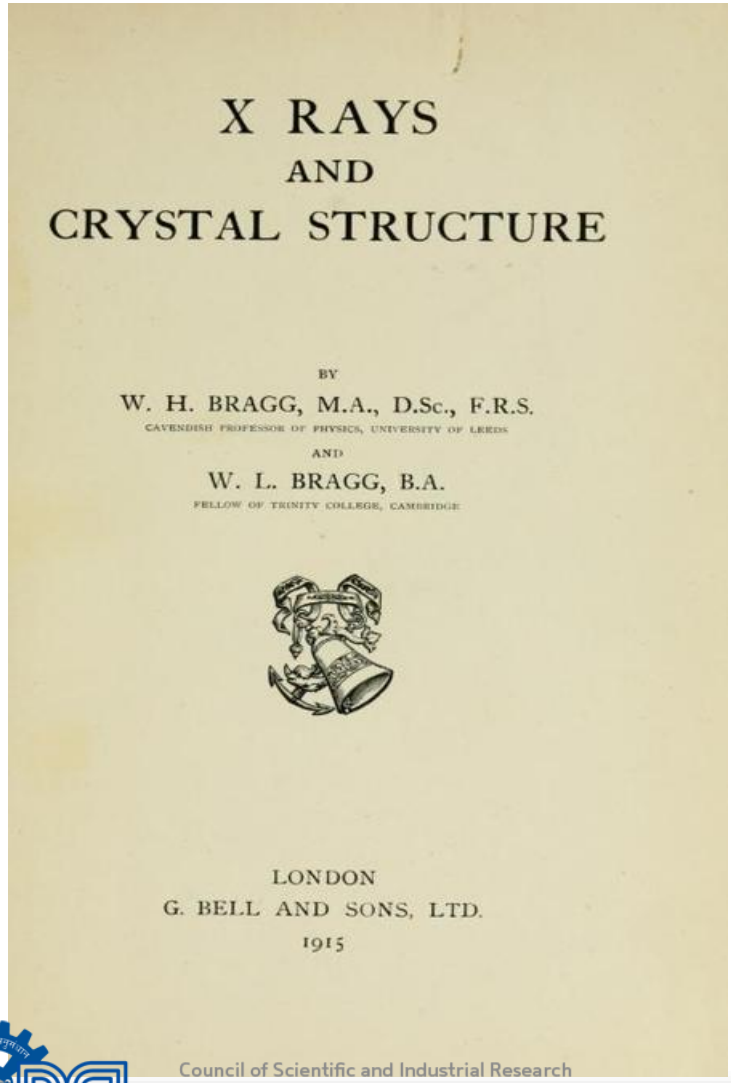


For NaCl

$AB = 2{\cdot}8 \times 10^{-8}$ cm

William Lawrence Bragg

W. H. & W. L. Bragg,
X-Rays and Crystal Structure (1915)

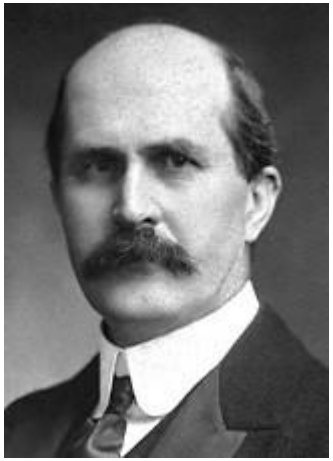


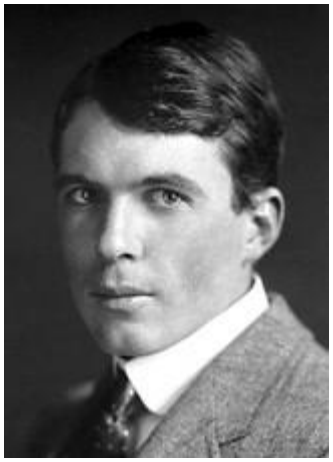
X RAYS
AND
CRYSTAL STRUCTURE

BY
W. H. BRAGG, M.A., D.Sc., F.R.S.
CAVENDISH PROFESSOR OF PHYSICS, UNIVERSITY OF LEEDS
AND
W. L. BRAGG, B.A.
FELLOW OF TRINITY COLLEGE, CAMBRIDGE

LONDON
G. BELL AND SONS, LTD.
1915

-Birth of "X-ray Crystallography"





Photos

Top: William Henry Bragg (1862 – 1942);

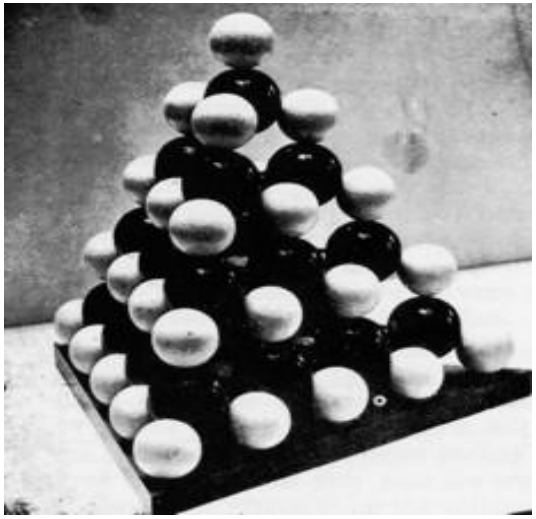
Bottom Wlliam Lawrence Bragg

(1890-1971)

Swedish postage stamp with Braggs

Zinc Blende: Von Laue & the Braggs

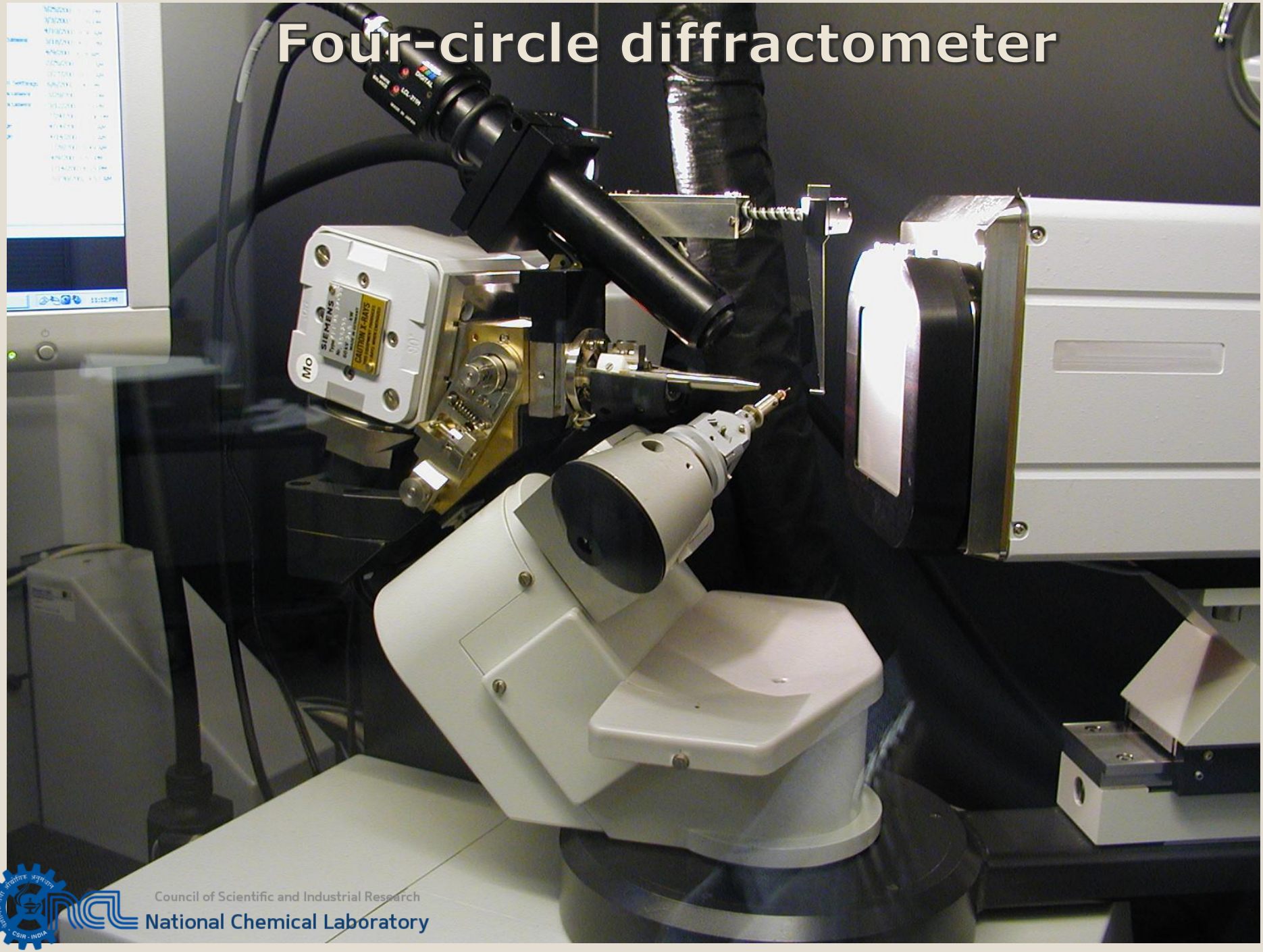
- "The most satisfying result was on von Laue's photograph of diffraction from zinc blende crystals.



- **Von Laue had assumed that atoms in zinc blende are arranged in a simple cubic lattice, but if this was true Bragg's law wouldn't explain the diffraction pattern.**

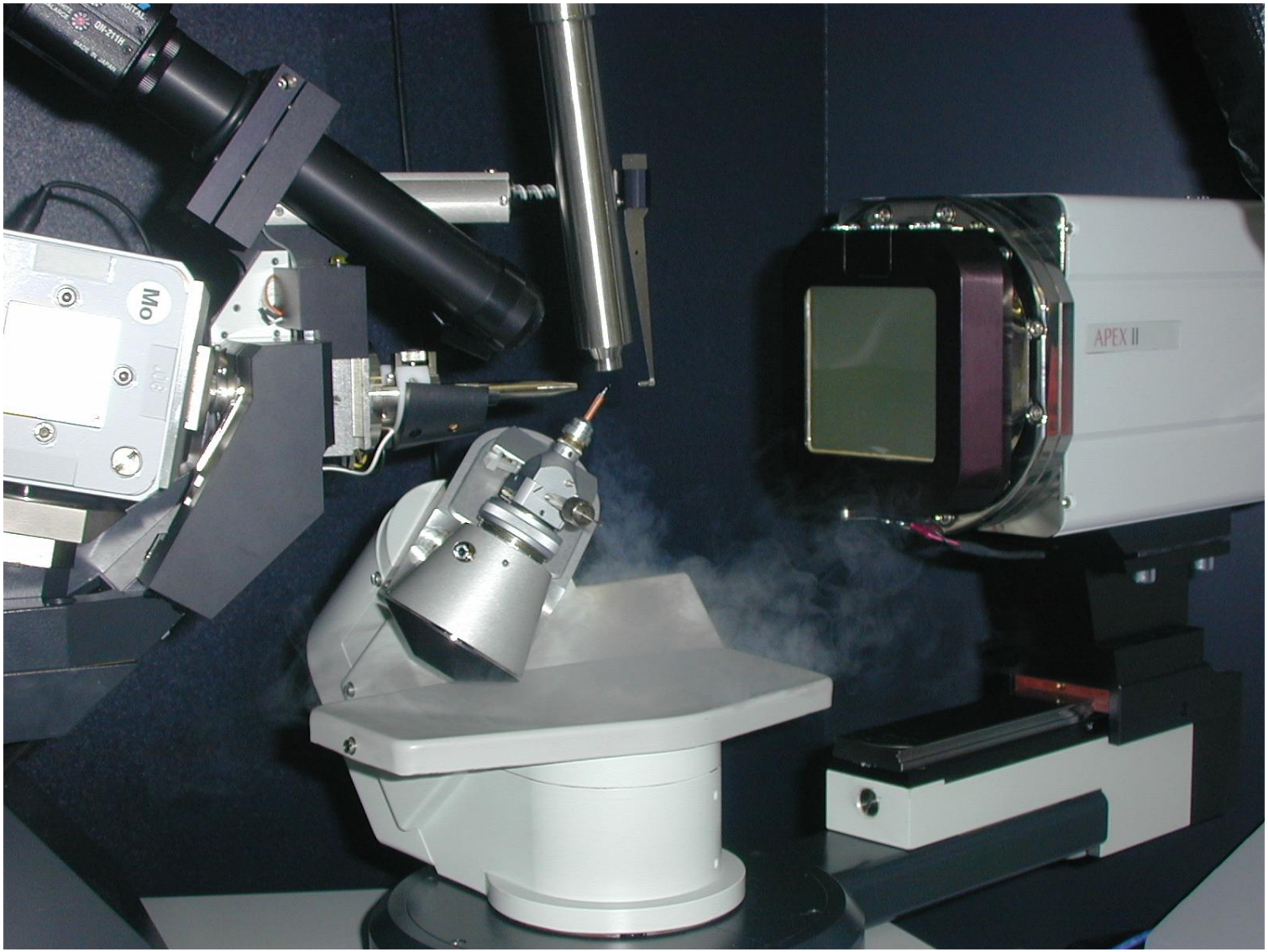
- But **if the arrangement of atoms was…arranged in a *face centred cubic lattice***, the diffraction pattern was explained perfectly."

Four-circle diffractometer

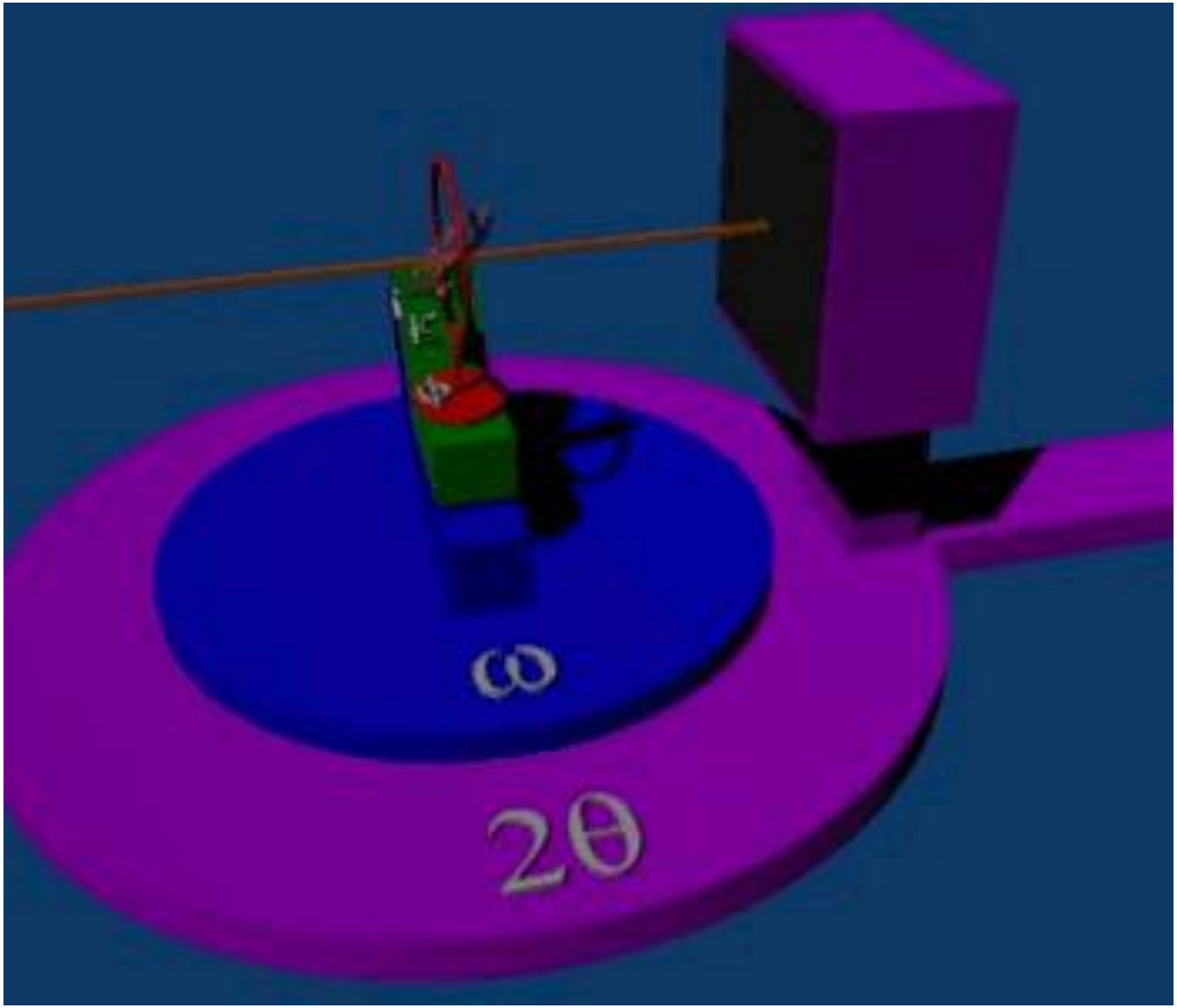


Council of Scientific and Industrial Research
National Chemical Laboratory

The crystal is getting cooled to 120K (-153 ºC, -243 ºF)

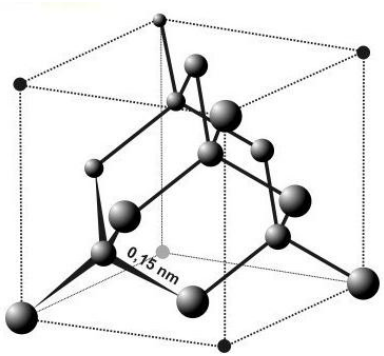


X-ray Diffractometer:

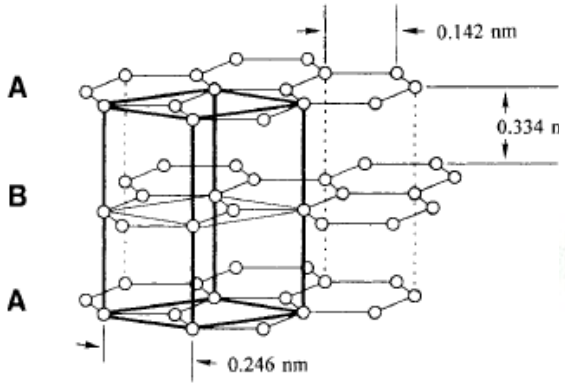


Crystal Structures of Carbon Allotrope

W. L. Bragg (1890-1971)



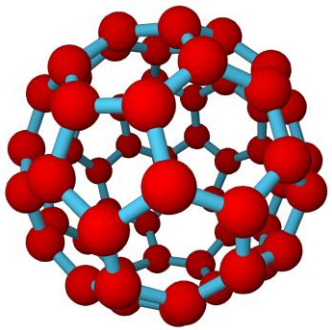
Bragg WH, Bragg WL (1913). "The structure of the diamond". *Nature* **91** (2283): 557

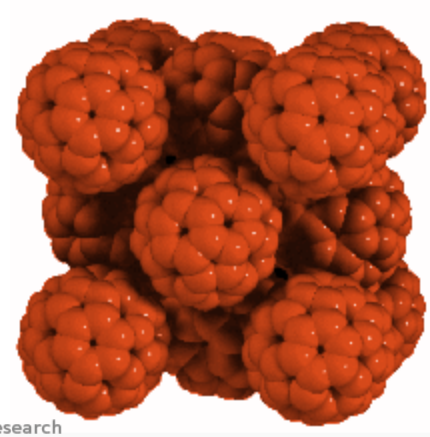


J. D. Bernal, **1924**

Graphite has a layered structure that consists of rings of six carbon atoms arranged in widely spaced horizontal sheets.

Tetrahedral arrangement of C-atoms and length of C-C bond 1.52 Å

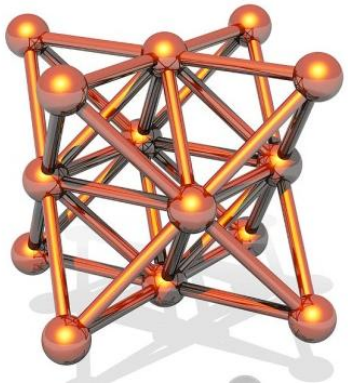




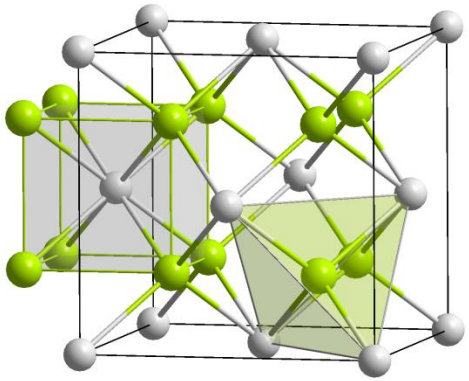
Buckminster Fullerene, 1985, H. Kroto

Inorganic Structures

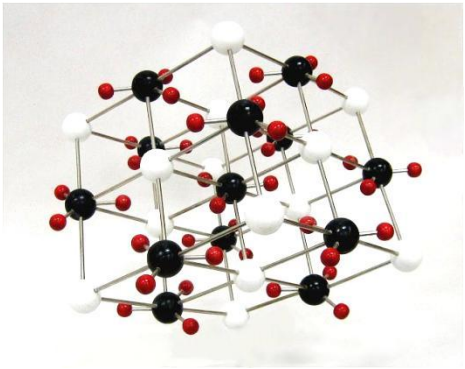
Copper



Bragg WL (1914). "The Crystalline Structure of Copper". *Phil. Mag.* **28** (165): 355

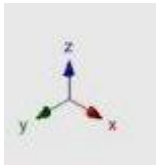


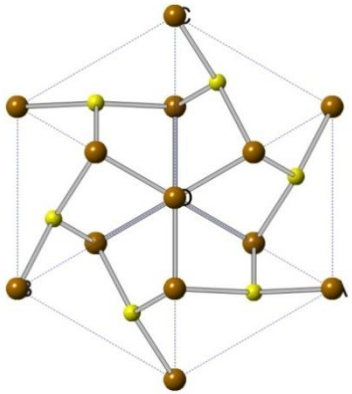
CaF_2, (1914)

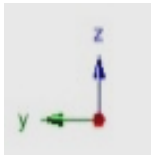


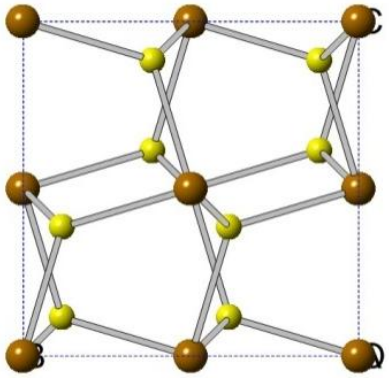
$CaCO_3$, (1914)

Pyrite, FeS_2, (1914)





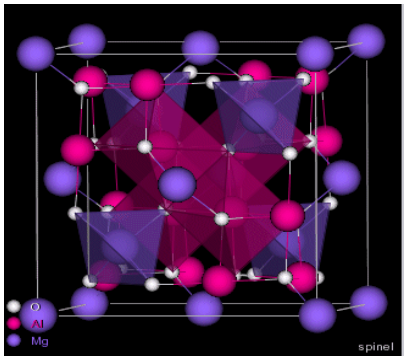




Bragg WL (1914). "The analysis of crystals by the X-ray spectrometer". *Proc. R. Soc. Lond.* **A89** (613): 468

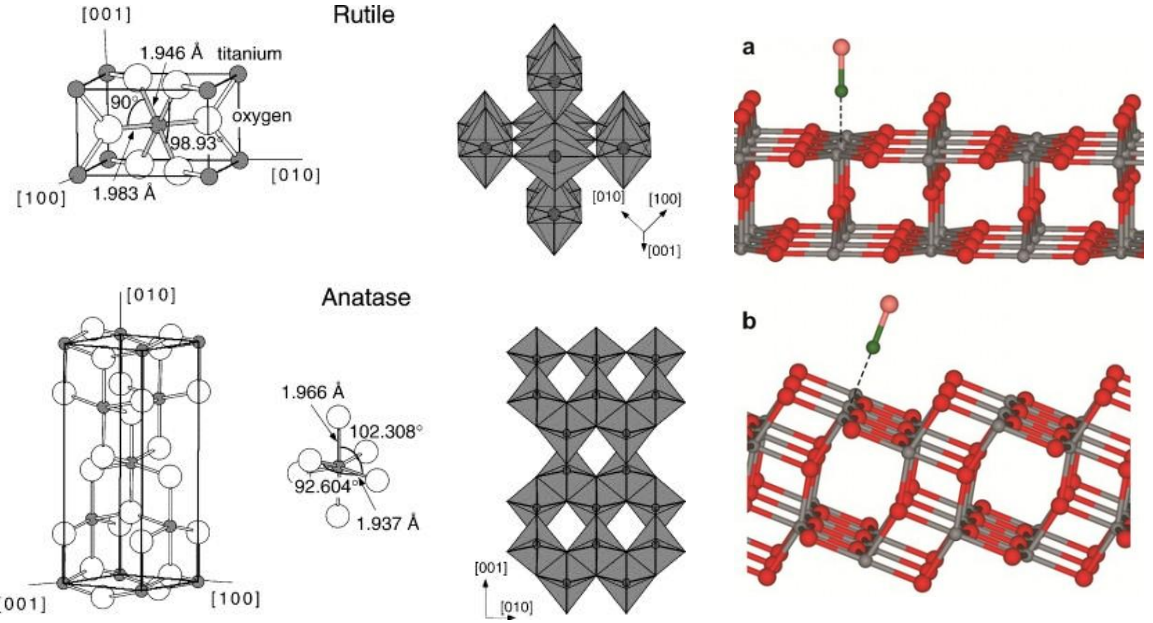
Inorganic Structures

Spinel, $MgAl_2O_4$



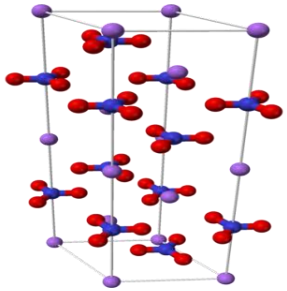
Bragg WH (1915). "The structure of the spinel group of crystals". *Phil. Mag.* **30** (176): 305.

Rutile and Anatase forms of Titanium Dioxide, TiO_2



Vegard L (1916). "Results of Crystal Analysis". *Phil. Mag.* **32** (187): 65.)

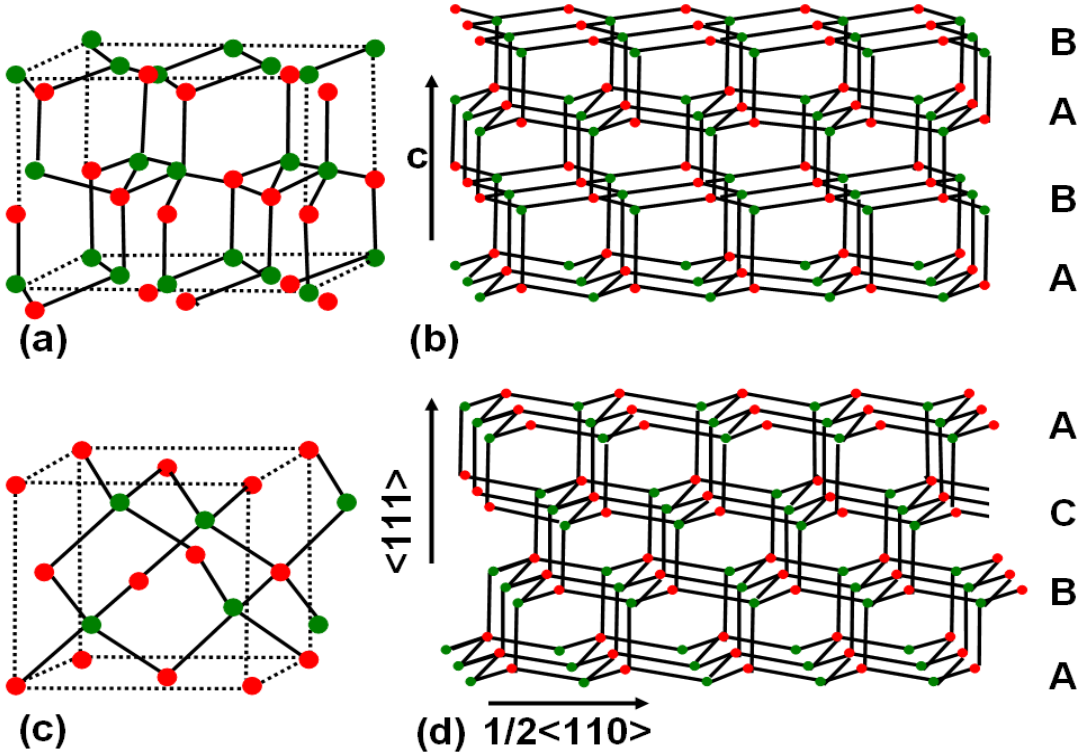
Sodium Nitrate, $NaNO_3$



1919

Inorganic Structures

Wurtzite (ZnS), 1920



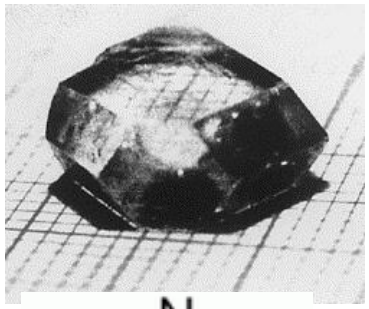
Hexagonal Structure

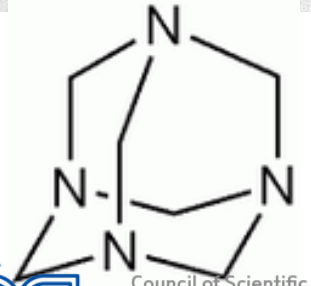
Cubic Structure

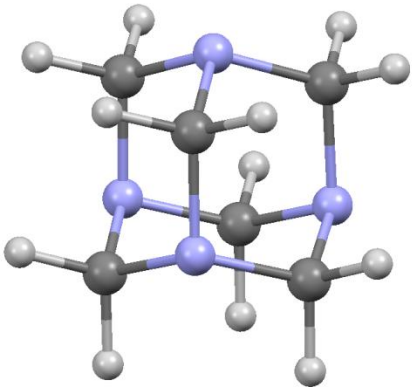
Bragg WL (1920). "The crystalline structure of zinc oxide". *Phil. Mag.* **39** (234): 647.)

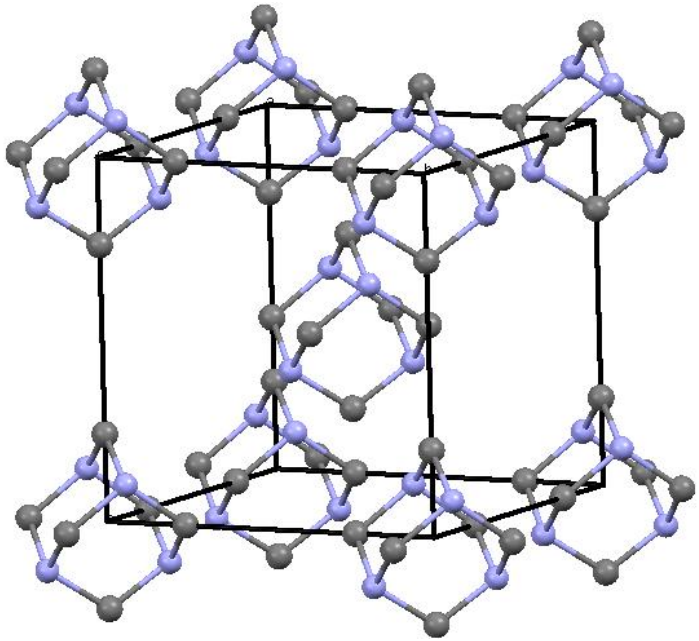
Application to Organic Compounds

In 1923: The first Structure of an Organic compound, **Hexamethylenetetramine**, was solved in 1923 by Dickinson and Raymond. This was followed by several studies of long-chain fatty acids, which are an important component of biological membranes.









K. Lonsdale and Benzene Structure: Structural Chemistry and X-Ray Diffraction

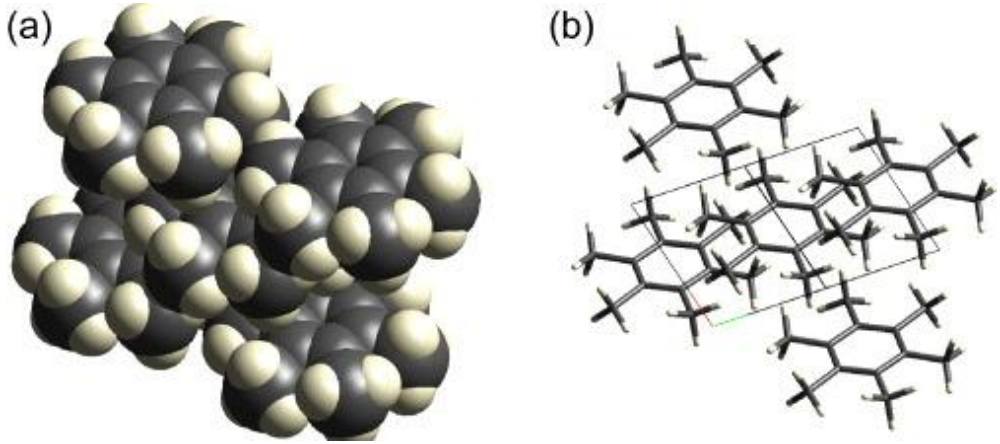
Earlier, Assumption about benzene structure

- The molecule exists in the crystal as a separate entity.
- The benzene carbon atoms are arranged in ring formation.
- The ring is hexagonal or pseudo-hexagonal in shape.

The above reasoning, in fact, supplies a definite proof, from an X-ray point of view, that the chemist's conception of the benzene ring is a true representation of the facts."

K. Lonsdale and Benzene Structure: Structural Chemistry and X-Ray Diffraction

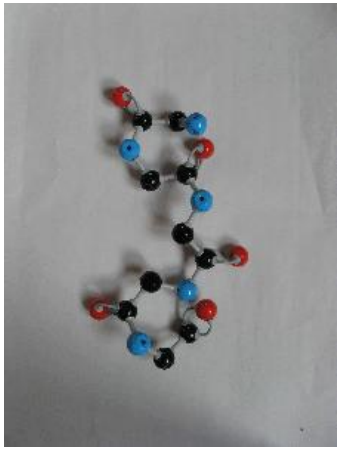
Hexamethylbenzene established the hexagonal symmetry of benzene and showed a clear difference in bond length between the aliphatic C–C bonds and aromatic C–C bonds; this finding led to the idea of resonance between chemical bonds, which had profound consequences for the development of chemistry.



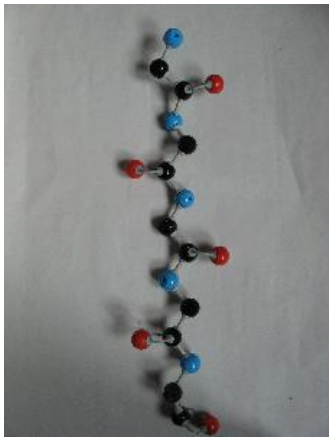
Lonsdale K (1928). "The structure of the benzene ring". *Nature* **122** (3082): 810.Bibcode:1928Natur.122

Understanding the molecular structure of wool - the changing shape of keratin

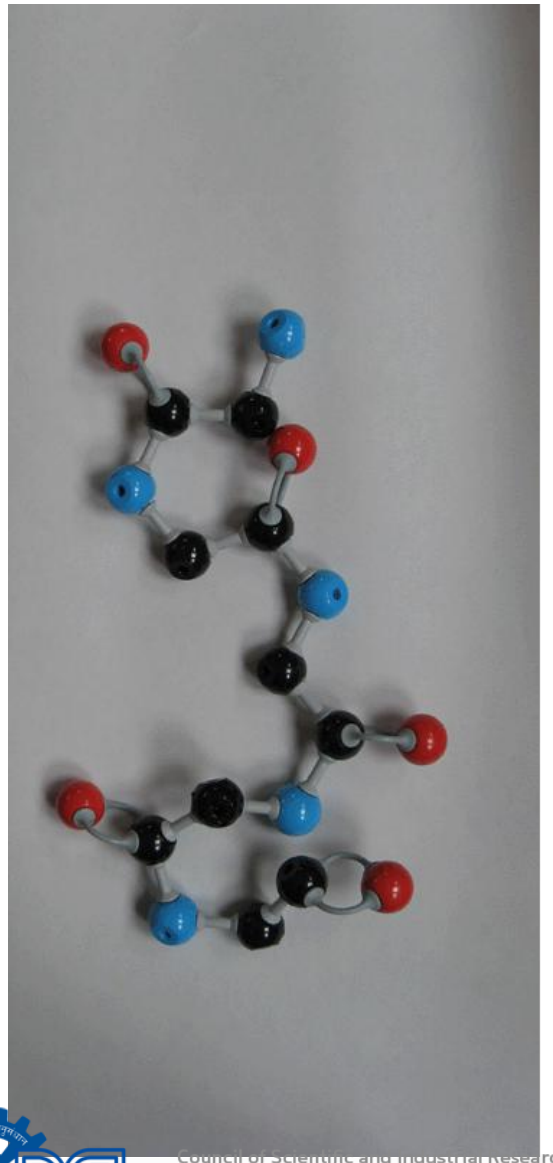
The principal component of hair is a protein molecule called keratin. All protein molecules consist of long chains of small molecular units, the amino acids, of which there are 20 different kinds. Each keratin molecule in hair consists of many hundreds of amino acid units, arranged in an irregular order, although not a random one by analogy, the letters in this sentence are in an irregular order, but the sentence has meaning. The order in keratin determines how the molecules fit together, giving the hair strength and flexibility.



The long chains of keratin could be compacted, called the alpha-form (shown left) or stretched out, called the beta-form (shown right). Using his X-ray analysis, Astbury showed that the elasticity or stretchiness of wool fibres was due to the compacted alpha-keratin protein fibres unfolding into the more extended beta-form.



Birth of Structural Molecular Biology



William **Thomas** Astbury 1898-1961

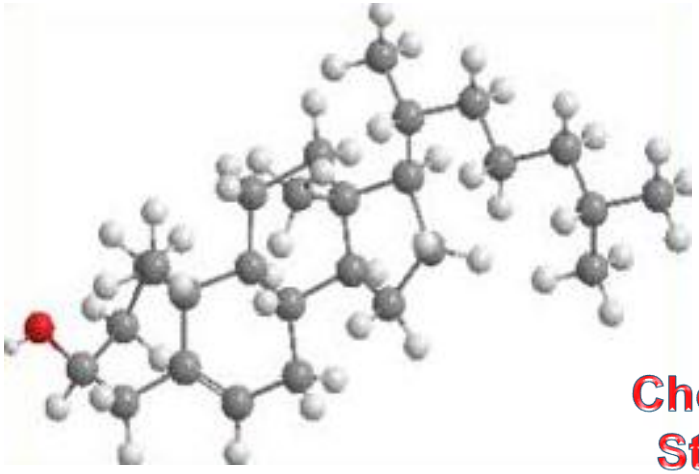
Whilst this discovery was of great interest to the textile industry, its real significance was *that it showed how the macroscopic properties of biological materials could be understood in terms of changes in the shape of their constituent protein molecules.*

This was to lead to a novel approach to understanding biological systems, that Astbury referred to as *molecular biology*.

Dorothy Hodgkin

First to determine the three-dimensional structure of a complex bio-organic molecule.

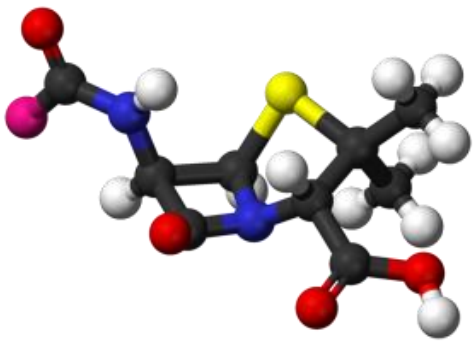
- She determined the structure of cholesteryl iodide by x-ray diffraction in 1941-42 (published in 1945) in complete three-dimensional detail, at a time when no one else was determining complex structures in three dimensions because of the formidable calculations involved.



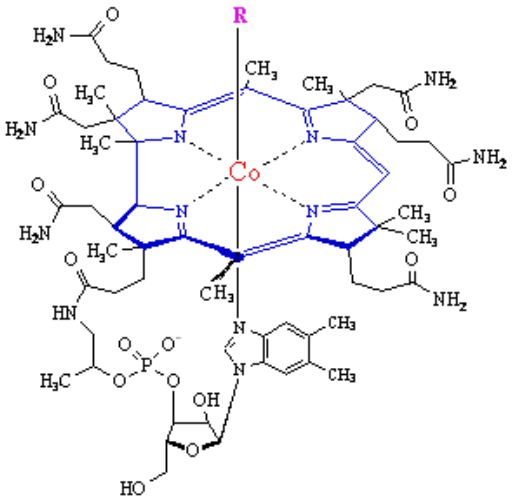
Cholesterol Structure

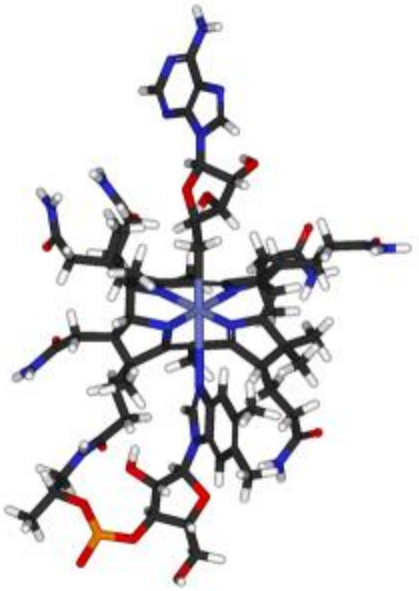
Dorothy Hodgkin

Determined the structure of penicillin in 1944 (published in 1949), again in three-dimensional detail. Before her work there was only fragmentary and conflicting evidence on the structure, from chemical analysis, of this rather unstable molecule, which was of immense importance as an antibiotic during and immediately after World War II.



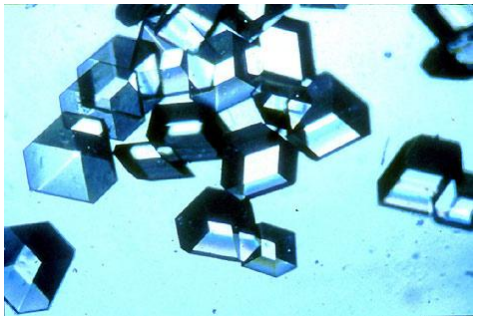
Determined the structure of vitamin B-12 in 1956, using one of the first high-speed digital computers. This was by far the most complex molecule whose three-dimensional architecture had been established, and some of its unusual structural features were quite unanticipated.

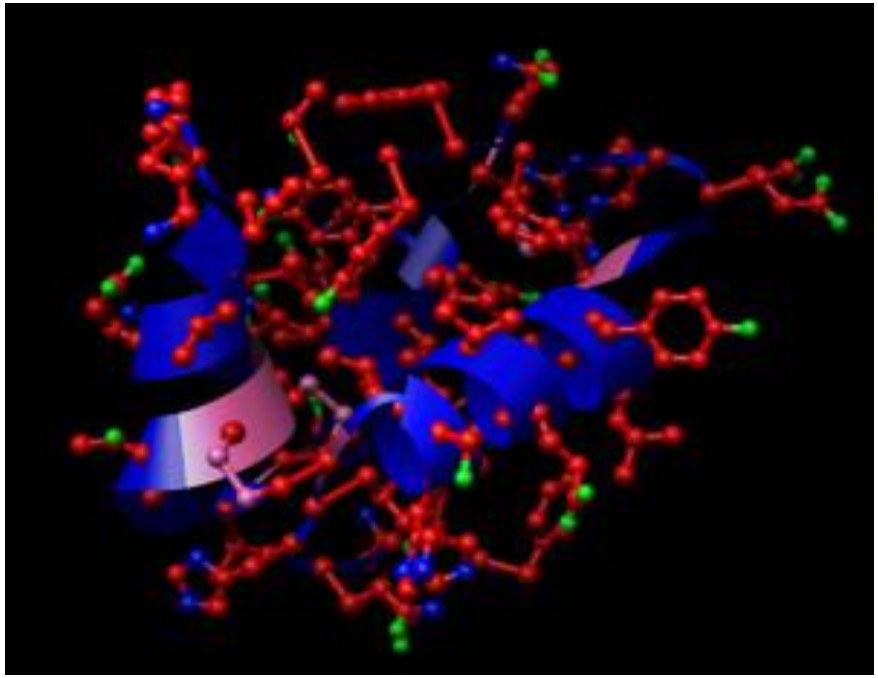




Dorothy Hodgkin

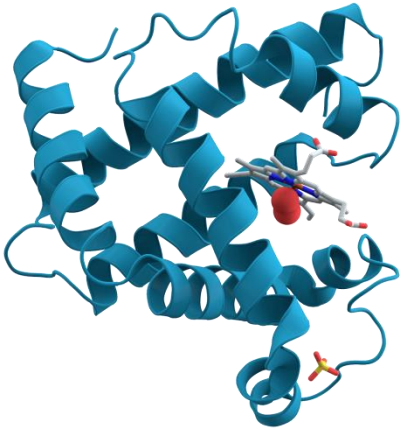
Determined the structure of insulin in 1969. This culminated a study pursued over three decades. The details of the structure provided insight into the function of this vital hormone.



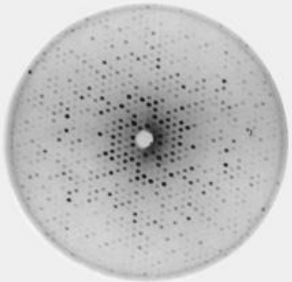


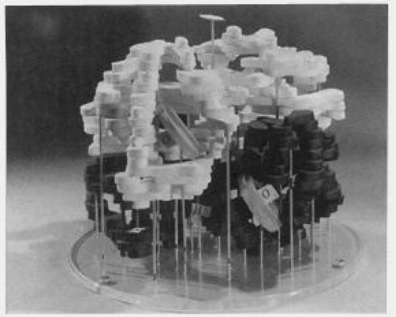
Crystal Structure of Myoglobin and Hemoglobin

Myoglobin



Hemoglobin





Structure solved in 1950
by John Kendrew

Structure solved in 1959
by Max Perutz

Both shared
1962 Nobel Prize
for Chemistry

Crystal Structure of DNA

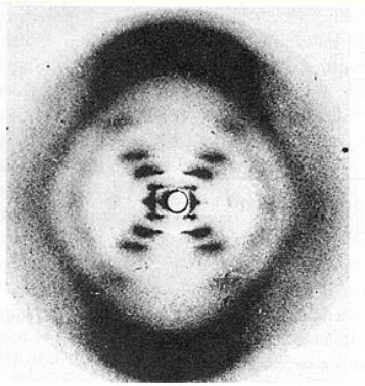
- **In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure**
- **He was pioneer in the field of DNA research**

Astbury W, (1947). "Nucleic acid". *Symp. SOC. Exp. Biol.* **1** (66).

Sir William Astbury

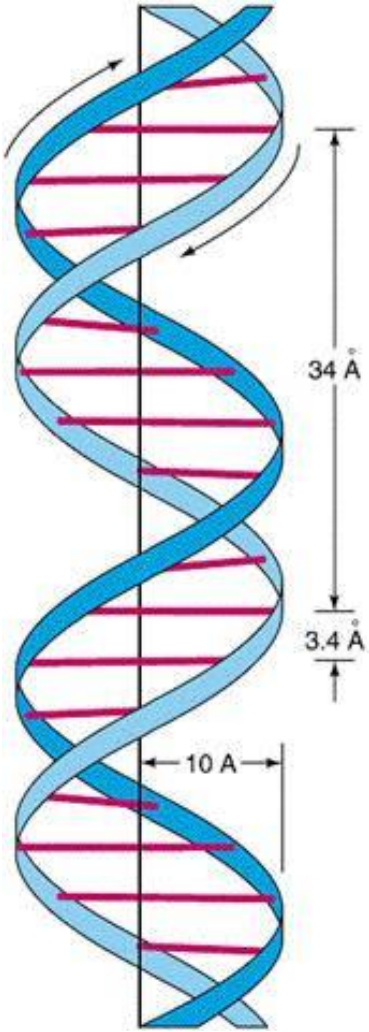
- **X-ray diffraction image of the double helix structure of the DNA molecule, taken 1952 by Raymond Gosling, commonly referred to as "Photo 51", during work by Rosalind Franklin on the structure of DNA**

X-Ray diffraction: Rosalind Franklin



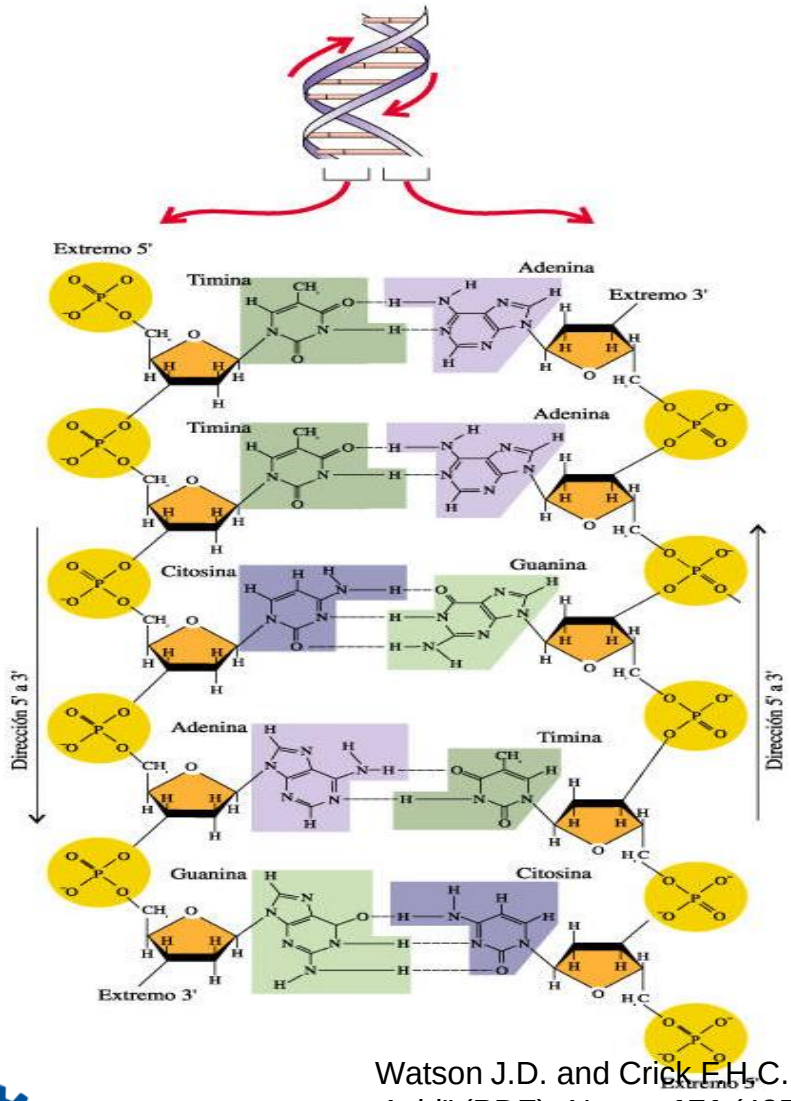
Crystal Structure of DNA

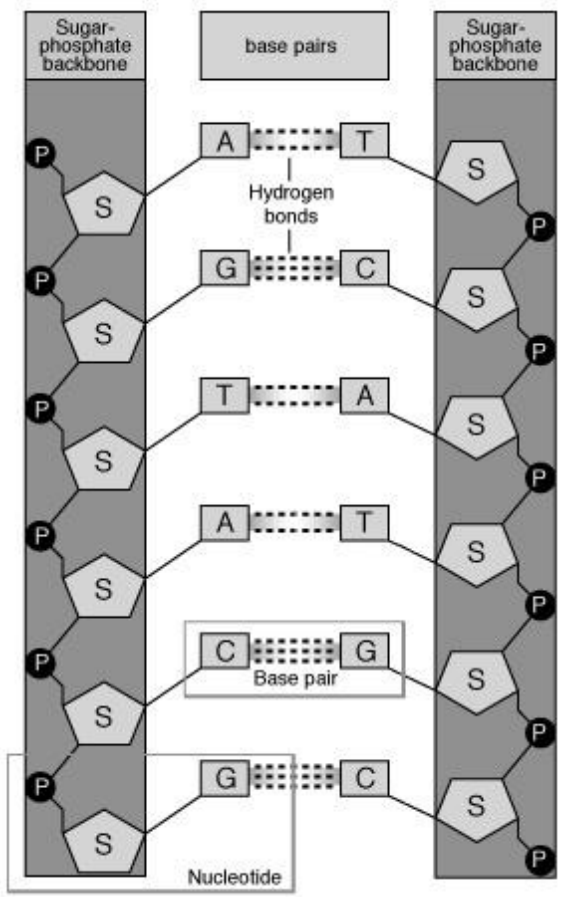
James Watson &
Francis Crick



In 1953, **James Watson** and **Francis Crick** suggested what is now accepted as the first correct double-helix model of DNA structure in the journal *Nature*. Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51") taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases are paired — also obtained through private communications from Erwin Chargaff in the previous years.

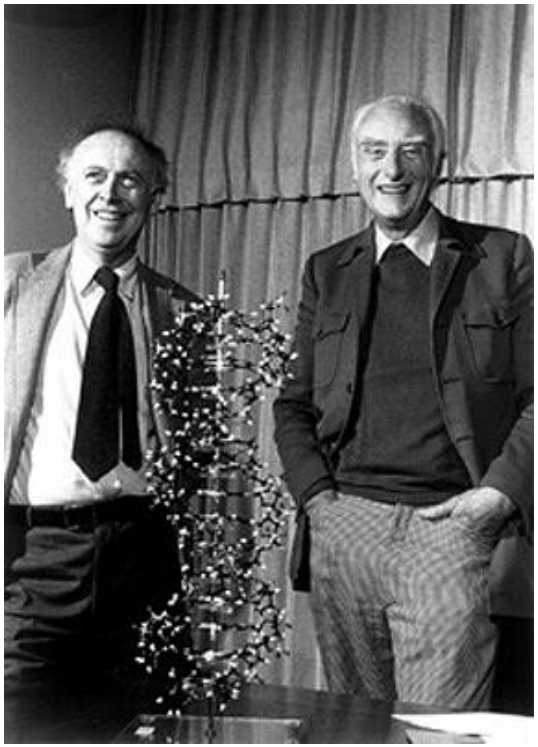
Solving the Structure of DNA

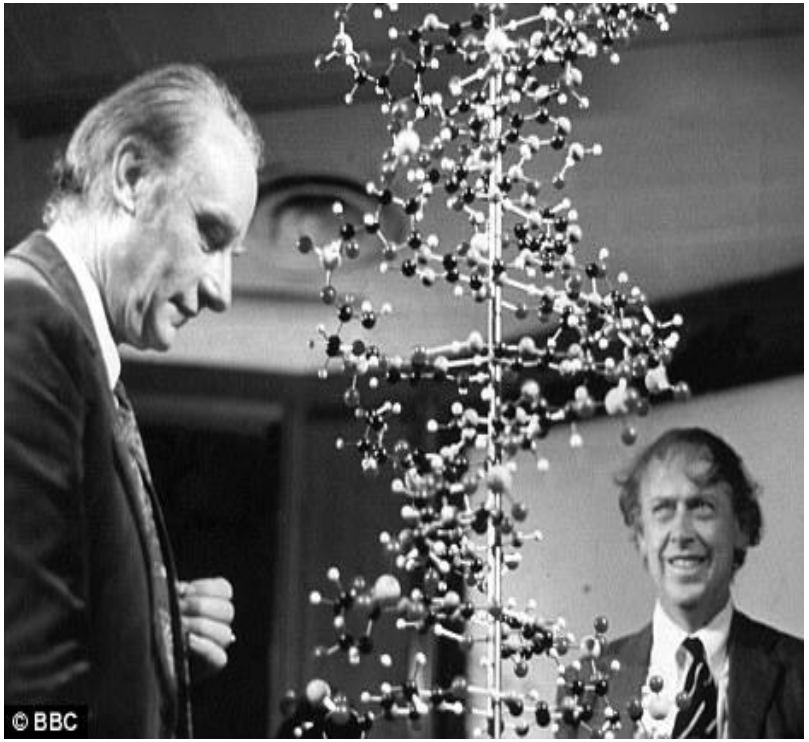




Watson J.D. and Crick F.H.C. (1953). "A Structure for Deoxyribose Nucleic Acid" (PDF). *Nature* **171** (4356): 737–738. Bibcode:1953Natur.171..737W

Solving the Structure of DNA



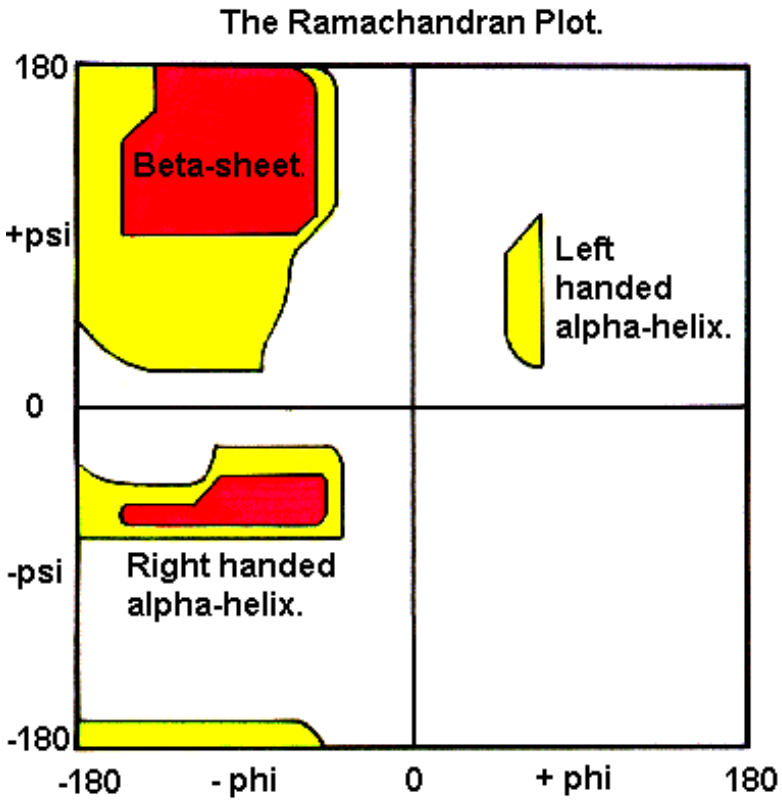


Watson and Crick's DNA model

In 1962 James *Watson*, Francis *Crick*, and Maurice Wilkins jointly received the Nobel Prize in physiology or medicine for their 1953 determination of the structure DNA.

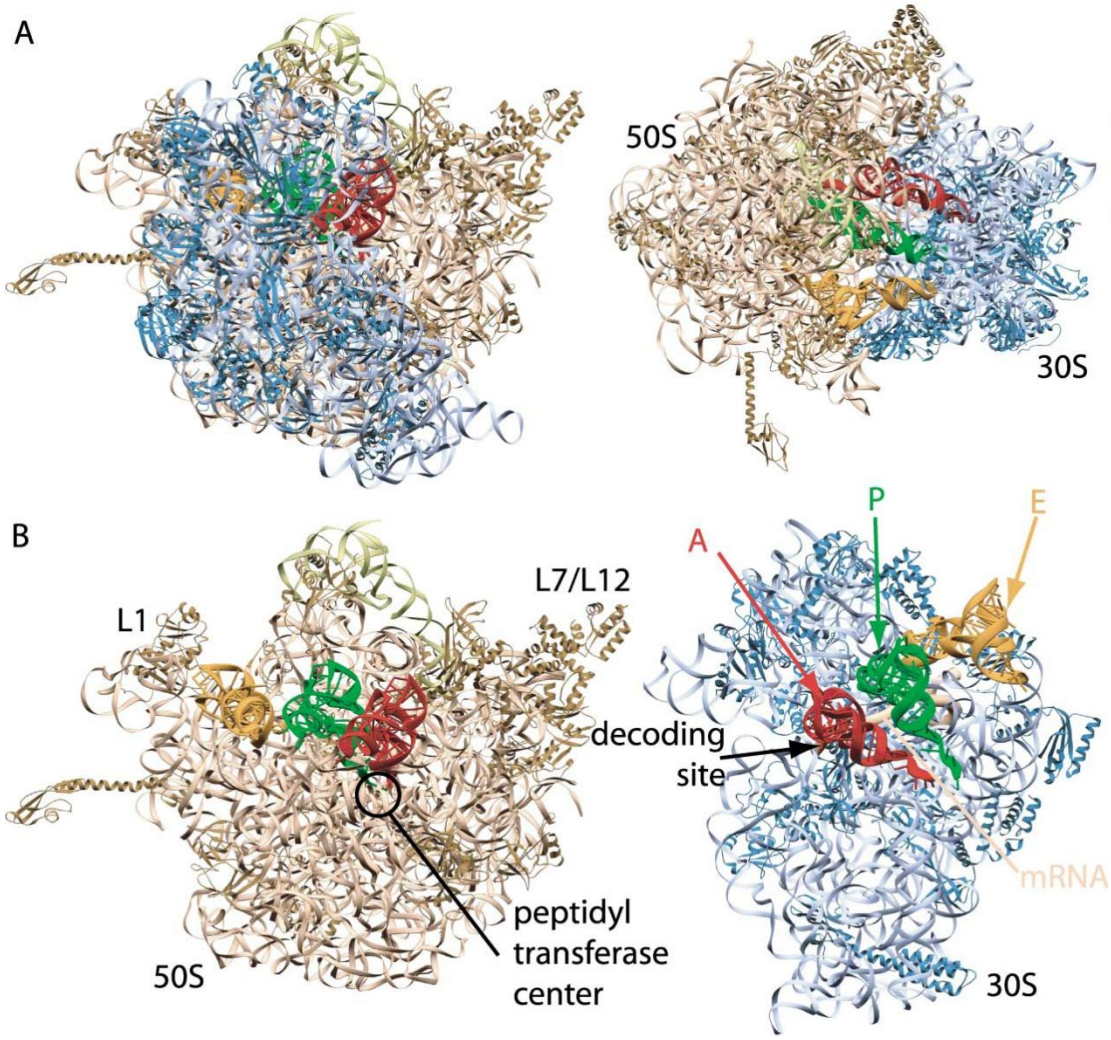
Contribution from INDIA

Triple Helix structure of collagen and Ramchandran plot



Prof. G. N. Ramchandran,

Ribosome Crystal Structure



Chemistry

The Nobel Prize in Chemistry 2009

"for studies of the structure and function of the ribosome"

Photo: MRC Laboratory of Molecular Biology

Venkatraman Ramakrishnan

1/3 of the prize

United Kingdom

MRC Laboratory of Molecular Biology
Cambridge, United Kingdom

Credits: Michael Marsland/Yale University

Thomas A. Steitz

1/3 of the prize

USA

Yale University
New Haven, CT, USA;
Howard Hughes Medical Institute

Credits: Micheline Pelletier/Corbis

Ada E. Yonath

1/3 of the prize

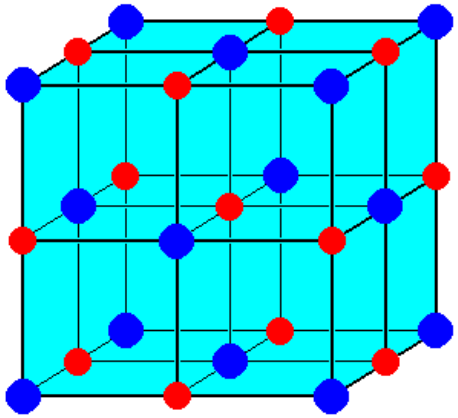
Israel

Weizmann Institute of Science
Rehovot, Israel

W. L. Bragg

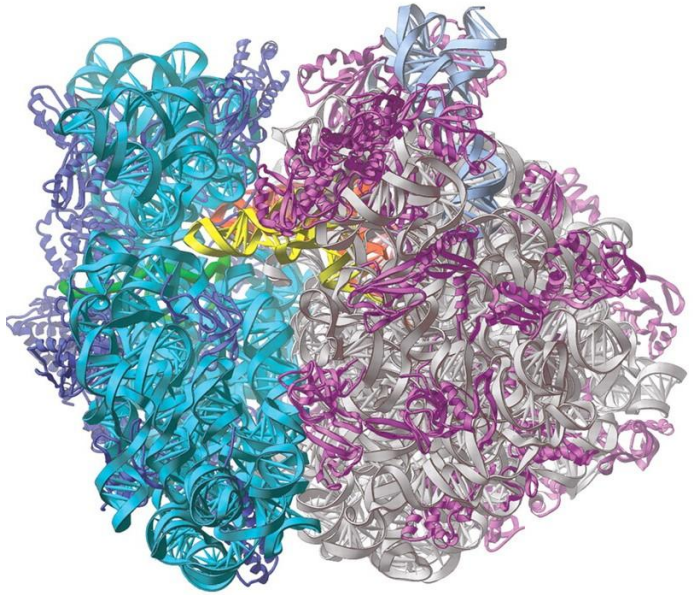
Venkatraman Ramakrishnan

The Journey



Year 1913

NaCl

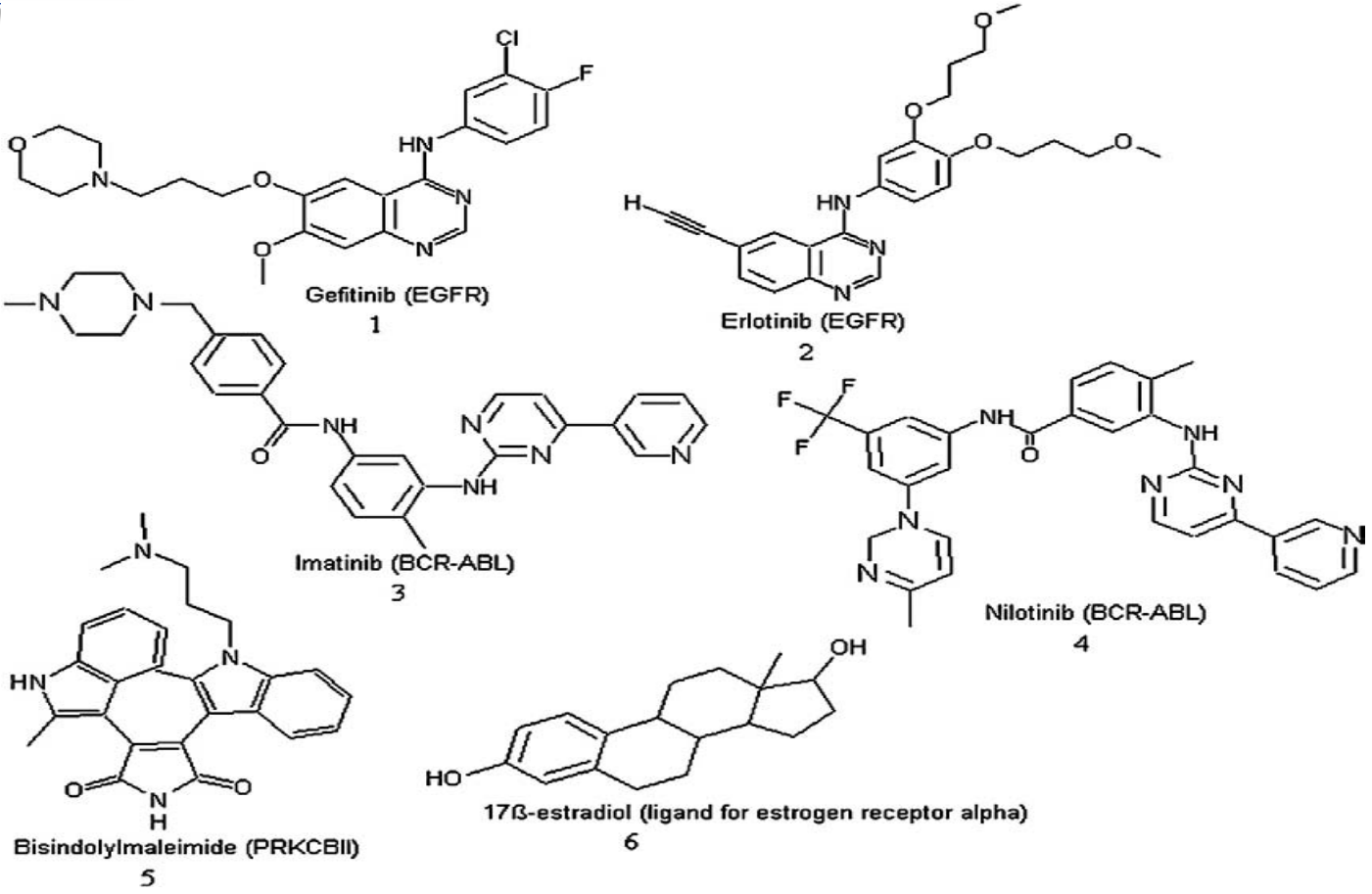


70S ribosome

Year 2009

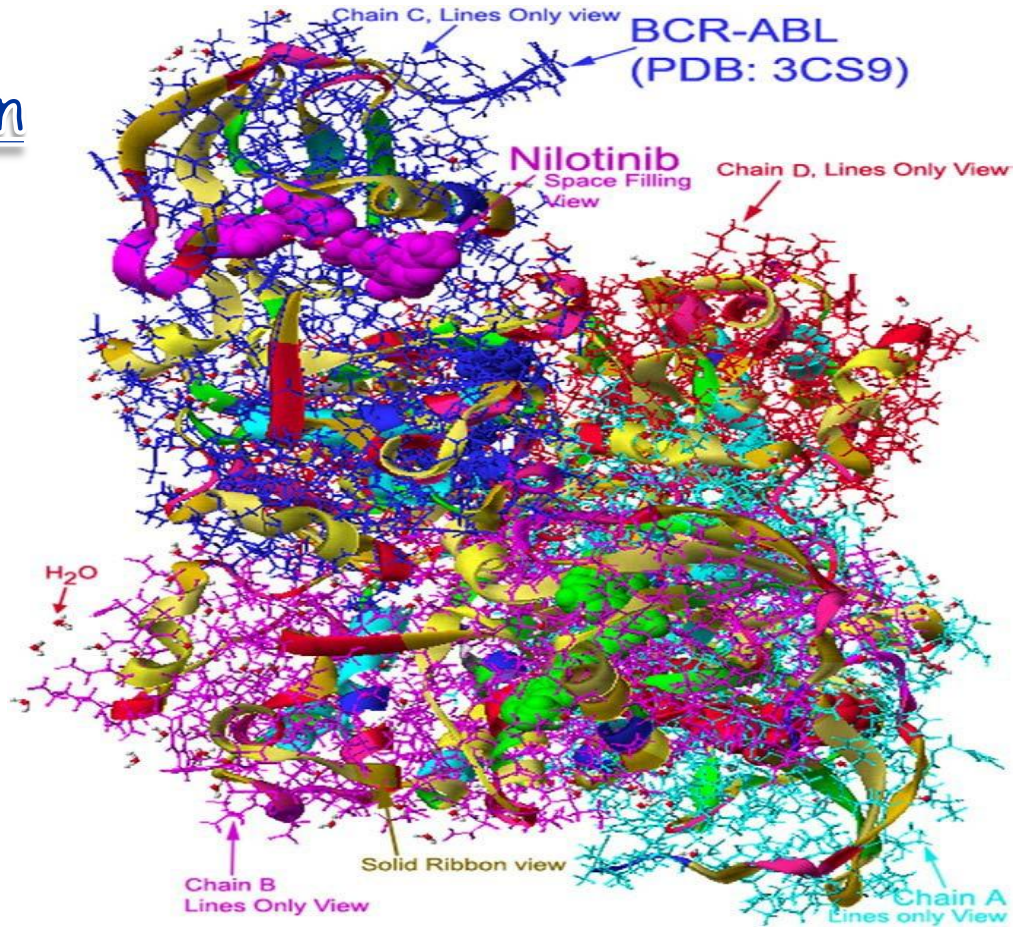
Applications

Drug Design



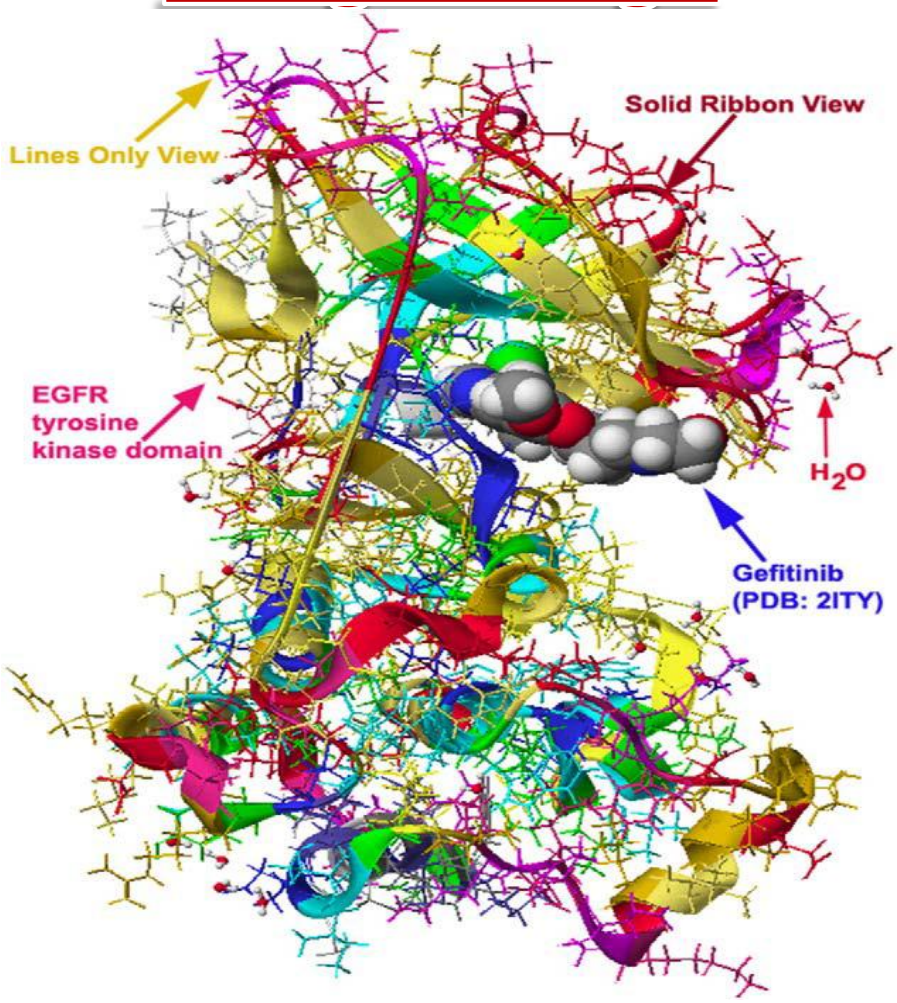
Structure of few anti-cancer drugs

Drug Design



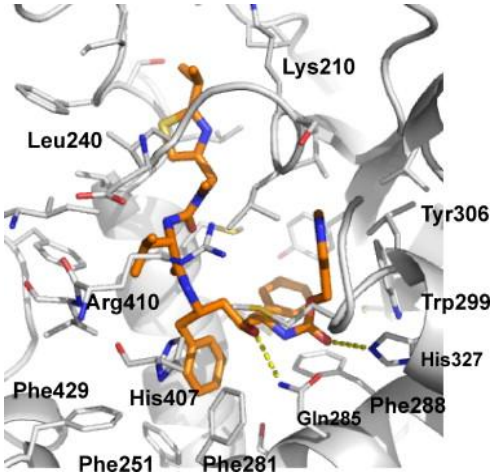
BCR-ABL kinase domain: showing the binding pocket of nilotinib (purple) bound to the active site of the target BCR-ABL in Chain C. In this figure, BCR-ABL is the cluster of four chains (chain A , chain B [purple], chain C [blue], and chain D [red]).

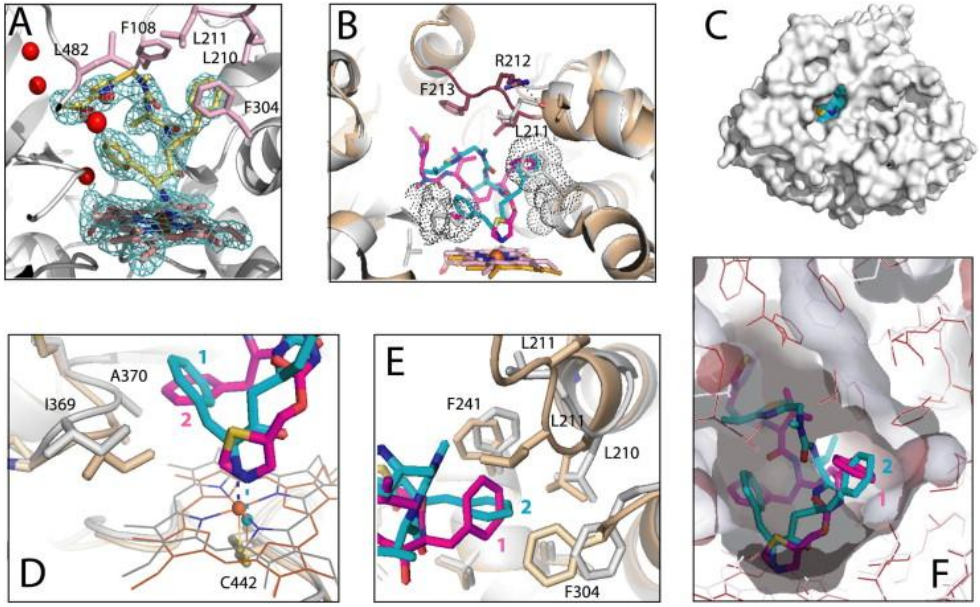
Drug Design



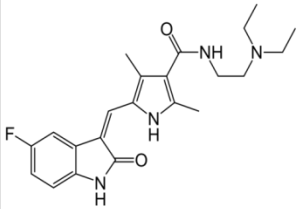
The tyrosine kinase domain of the EGF receptor: showing the binding of gefitinib.

Binding of Ritonavir with Protein

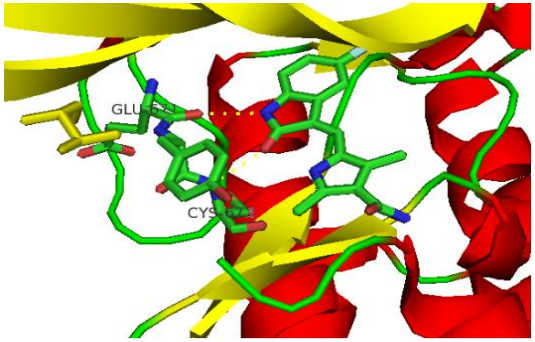




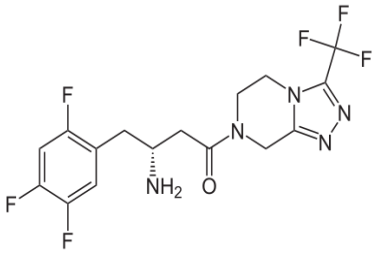
Interaction of Ritonavir with human Cytochrome



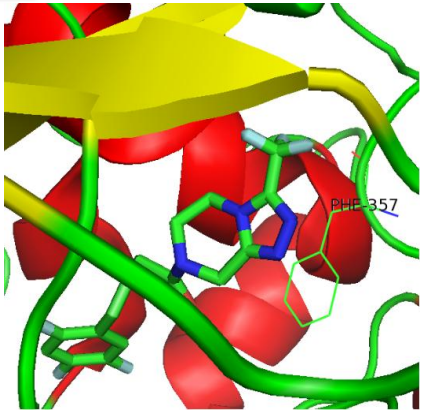
Sunitinib



Binding pocket of Sunitinib in the TRK KIT.



Sitagliptin



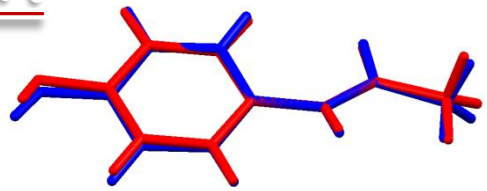
Binding of sitagliptin within DPP-IV.

Polymorphism

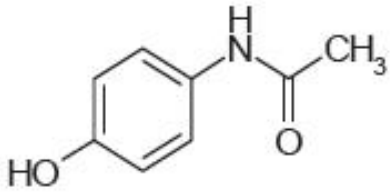
The ability of a compound to exist in more than one crystal form i.e. different molecular arrangements in the crystal lattice.

- **Packing Polymorph**
- **Conformational Polymorph**

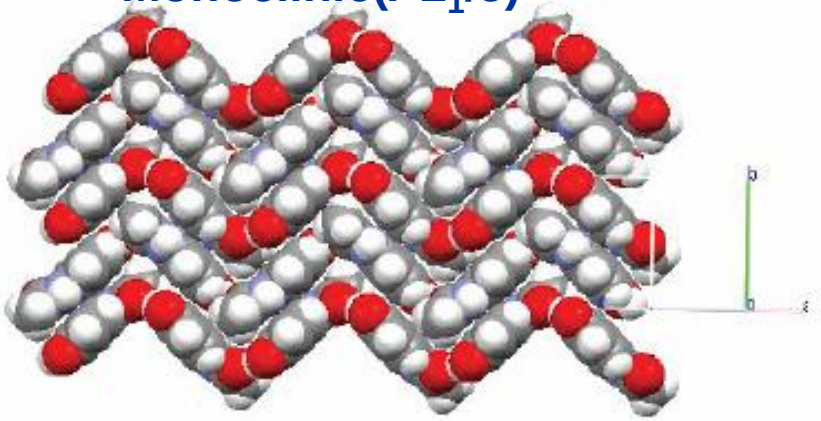
Packing Polymorph



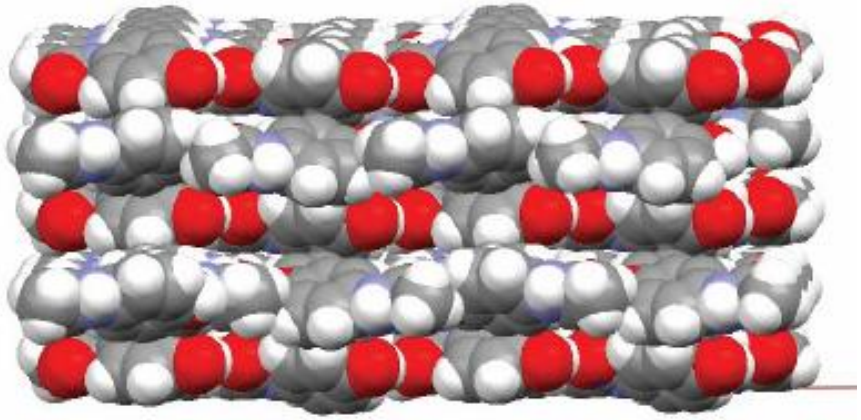
Paracetamol



Monoclinic($P2_1/c$)



Orthorhombic (*Pbca*)



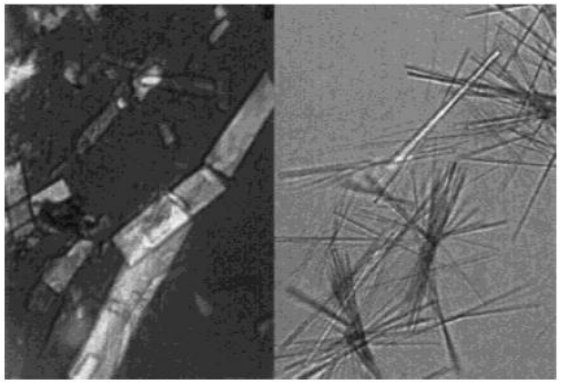
Form I, the stable polymorph, forms corrugated layers and is difficult to compress into tablets)

Form II is metastable and difficult to crystallise. It does, however, compress into tablets.

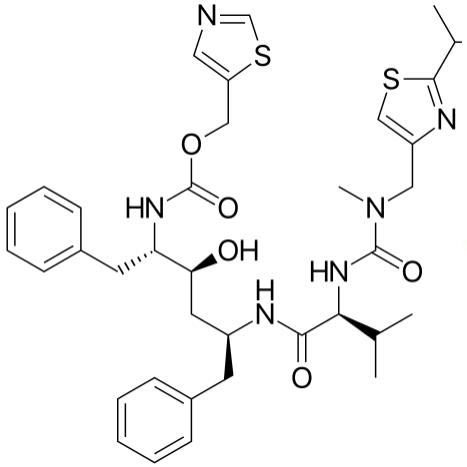
***J. Pharm. Sci*., 1983, 72, 232**

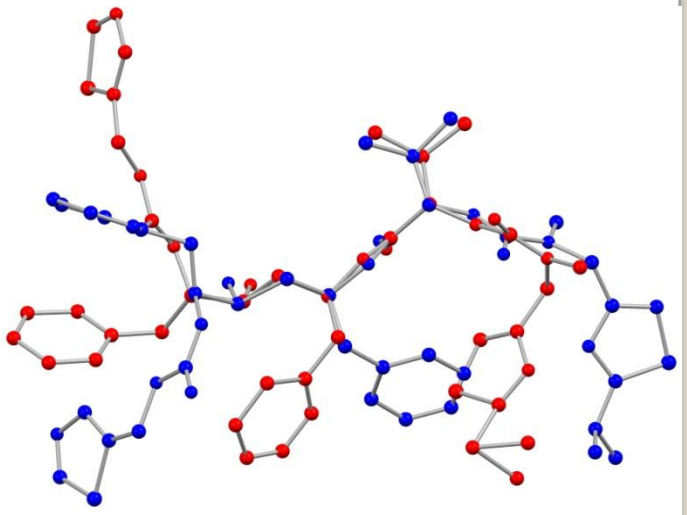
Conformational Polymorph

Ritonavir



Form I Form II





Form I – red, Form II - blue

Table II. Single Crystal X-Ray Data

A: Comparison of Torsion Angles in Ritonavir Forms

Torsion Angle	Form I	Form II
A (N-Methyl Urea)	–5 (cis)	–179 (trans)
B	72	–77
C (carbamate)	–178 (trans)	–8 (cis)

B: Single Crystal X-ray Data for Form I and Form II Ritonavir

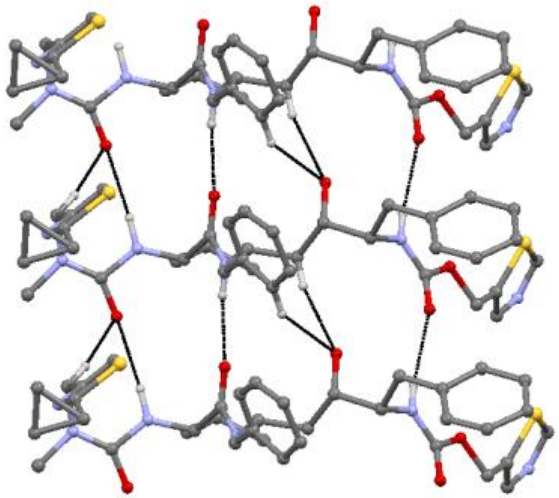
Parameter	Form I	Form II
Crystal system	monoclinic	orthorhombic
Space Group	$P2_1$ (#4)	$P2_1P2_1P2_1$ (#19)
Z value	2	4
Dcalc	1.28 g/cm^3	1.25 g/cm^3
Lattice Parameters	a = 13.433 (1) Å	a = 10.0236 (3) Å
	b = 5.293 (2) Å	b = 18.6744 (4) Å
	c = 27.092 (4) Å	c = 20.4692 (7) Å
	β = 103.102 (9) Å	
	V = 1876.0 (8) Å^3	V = 3831.5 (2) Å^3

Table I. Solubility Profile in Various Hydroalcoholic Solvent Systems at 5°C

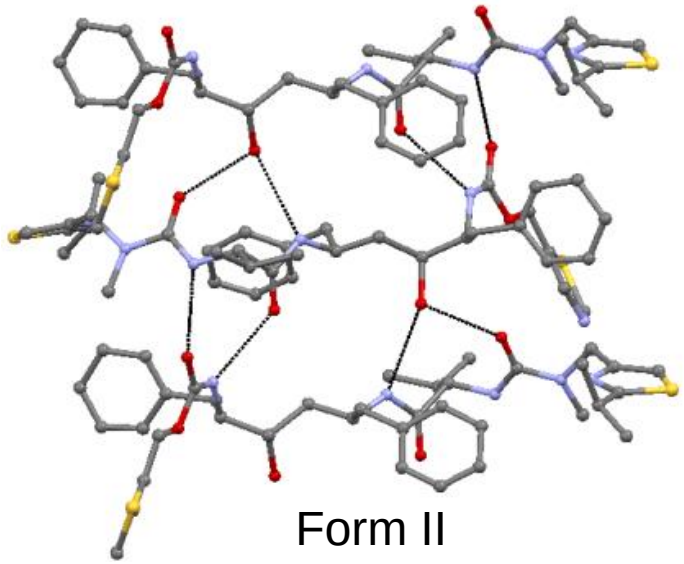
Ethanol/Water	99/1	95/5	90/10	85/15	80/20	75/25
Form I	90 mg/mL	188	234	294	236	170
Form II	19 mg/mL	41	60	61	45	30

Morris, J. et al. Pharmaceutical Research, Vol. 18, No. 6, 2001

Retonavir Polymorphs: Difference in Molecular Arrangements



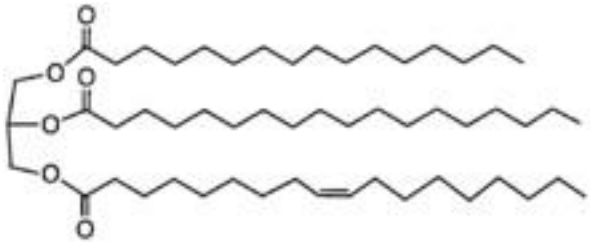
Form I



Form II

- **In Chocolates:**

Cocoa butter - The main ingredient of chocolate.

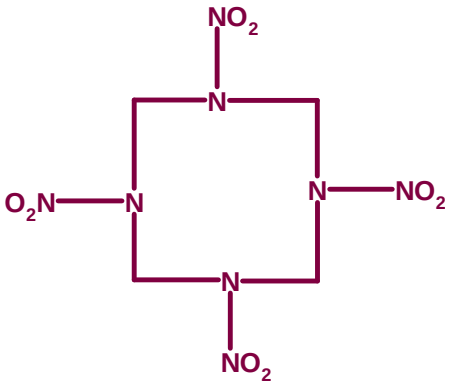


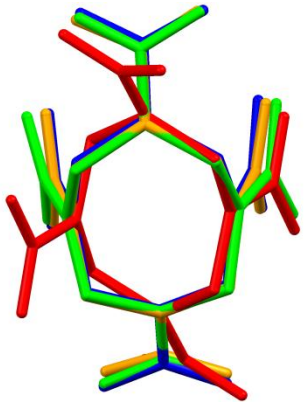
Six Polymorphs of Cocoa Butter

The fats in cocoa butter can crystallize in six different forms. The six different crystal forms have different properties.

Conformational Polymorphism

Cyclo tetramethylene tetranitramine (HMX)





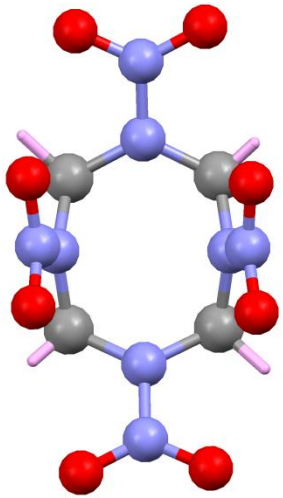
α-Form: Blue

β-Form: Red

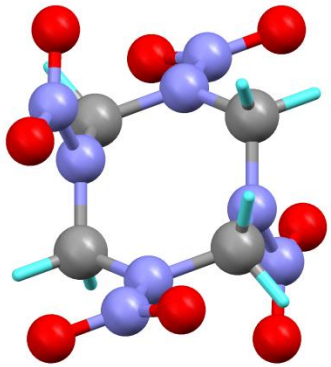
γ-Form: Green

δ-Form: Orange

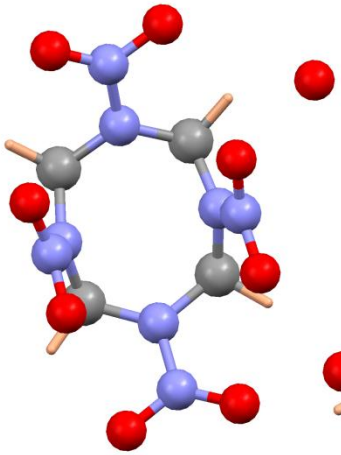
Four polymorphs known, α, β, γ, δ; δ form is least stable whereas β form is most stable

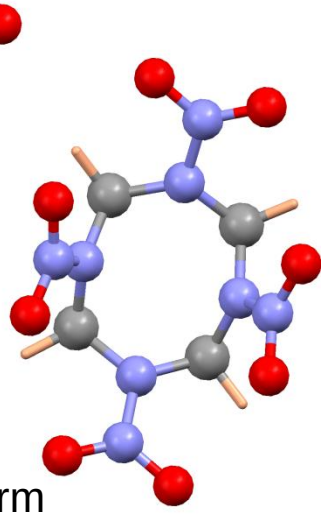


α Form

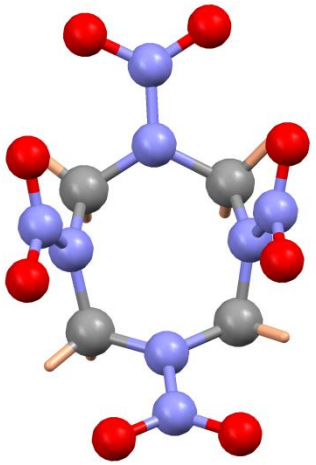


β Form





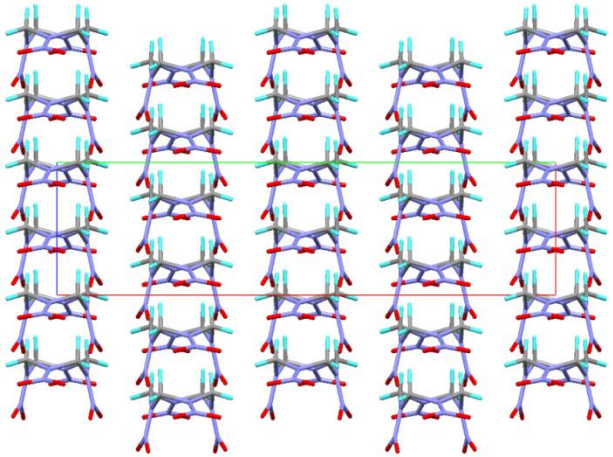
γ Form



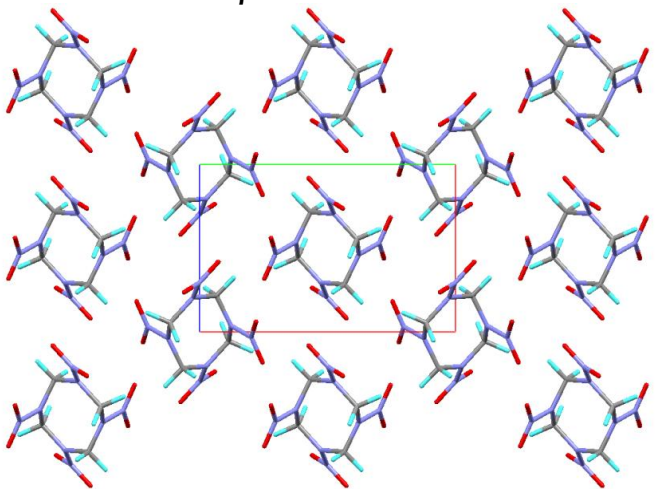
δ Form

Cyclo tetramethylene tetranitramine (HMX)

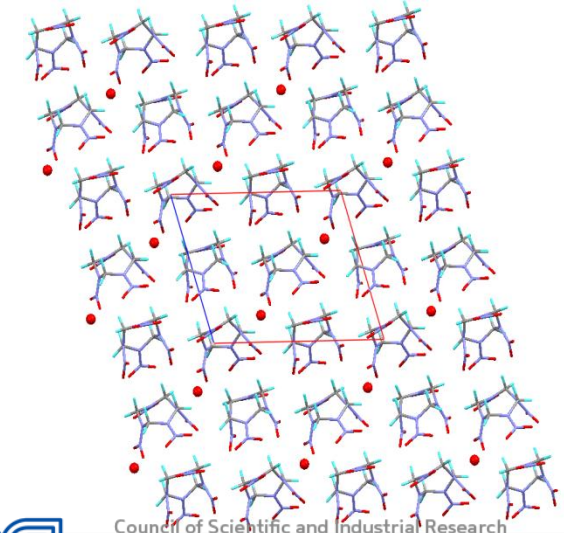
α Form



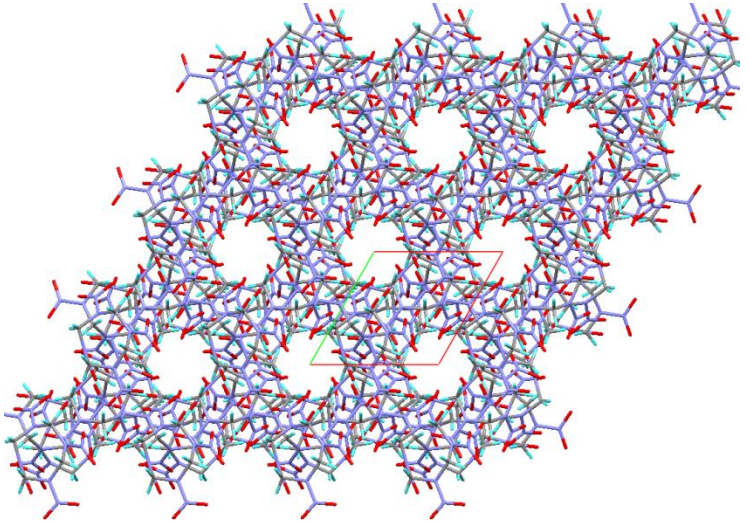
β Form



γ Form



δ Form

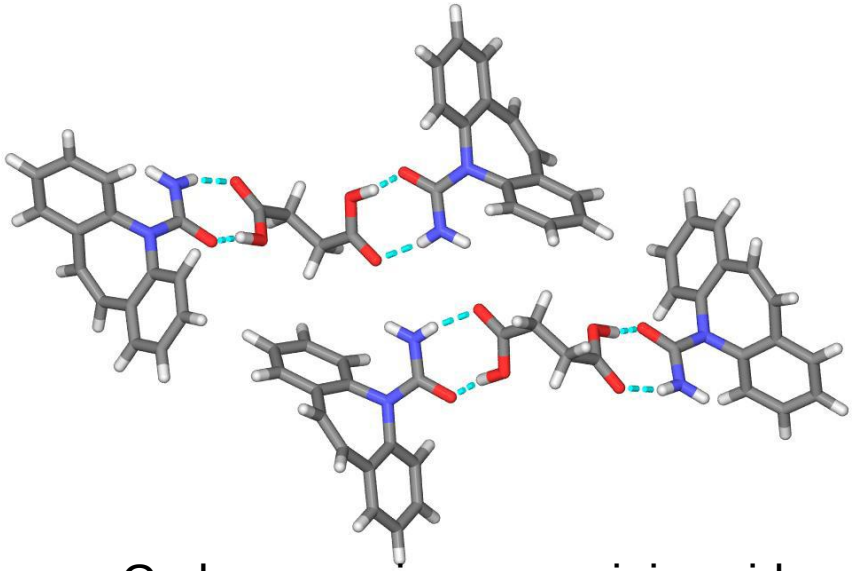


Cocrystal Design

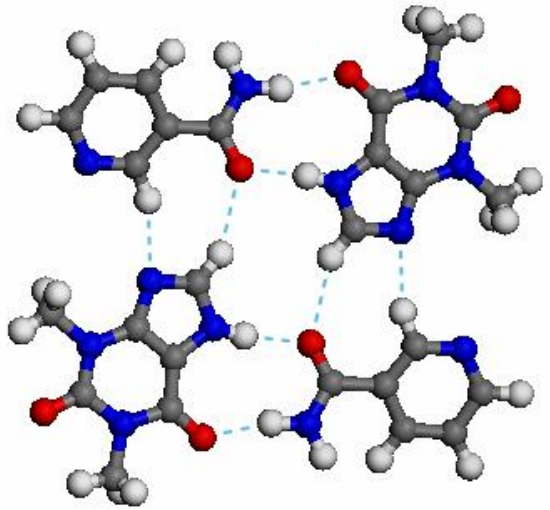
What is Cocrystal?

A + B ⟷ **A-B**

A crystal containing two or more neutral solid component together



Carbamazepine – succinic acid



theophylline – nicotinamide

Cocrystals

- are crystals that contain two or more different molecular components
- components are solids at room temperature
- often rely on hydrogen-bonded assemblies between neutral molecules of the active pharmaceutical ingredient (API) and other components
- are a homogenous (single) crystalline phase with well-defined stoichiometries AB, AB_2, etc

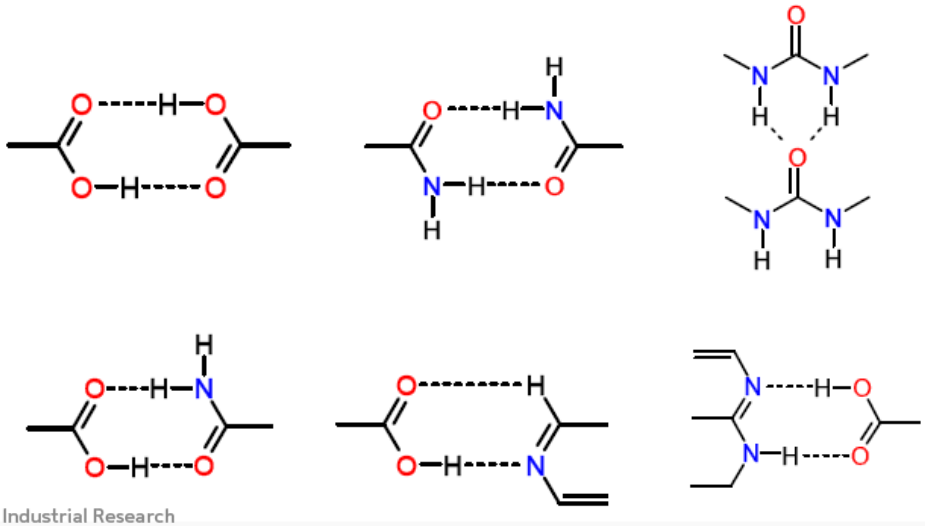
Why cocrystal?

- Cocrystal generates different crystalline form of a compound.
- Modify significant properties
  - ◇ Solubility
  - ◇ Dissolution rate
  - ◇ Bioavailability
  - ◇ Chemical stability
  - ◇ Moisture uptake
  - ◇ Mechanical behavior
- Intellectual property and patents

Cocrystals

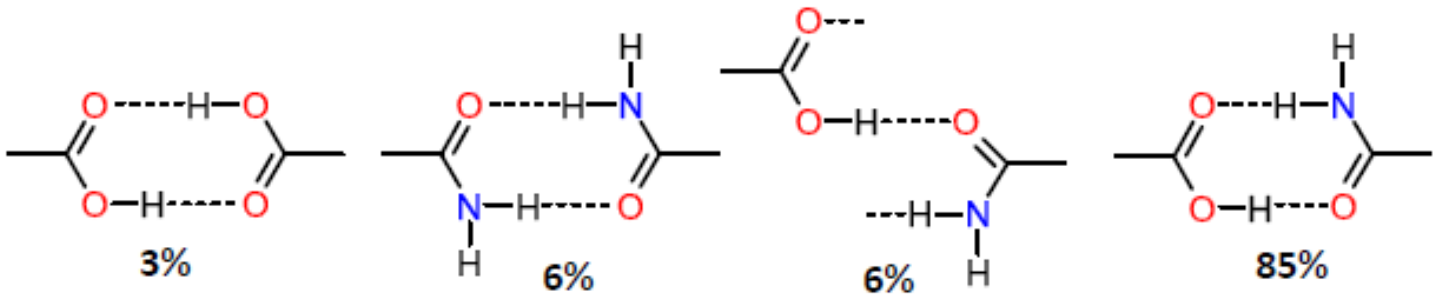
- One of the components of a cocrystal may serve as a co-crystal former.
- The components interact via non-covalent interactions such as hydrogen bonding, ionic interactions, van der Waals interactions and π-stacking interactions.

Common hydrogen bonded synthons used in crystal engineering



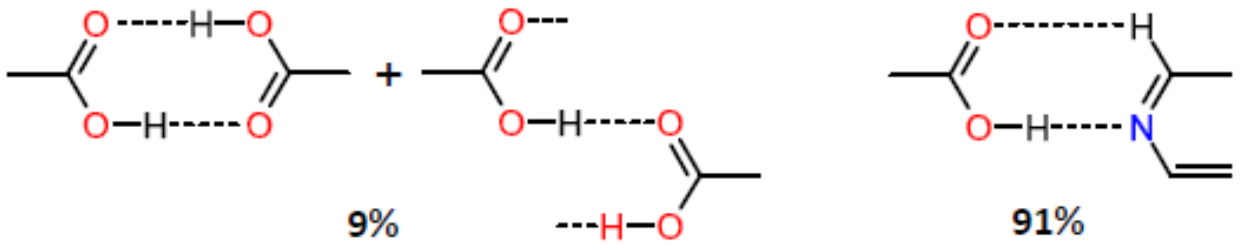
Hydrogen bond selectivity preferences

Carboxylic acid and primary amide



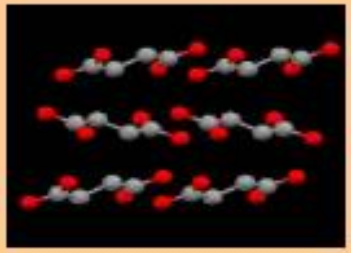
CSD Version 5.29, January 2008 update

Carboxylic acid and pyridine

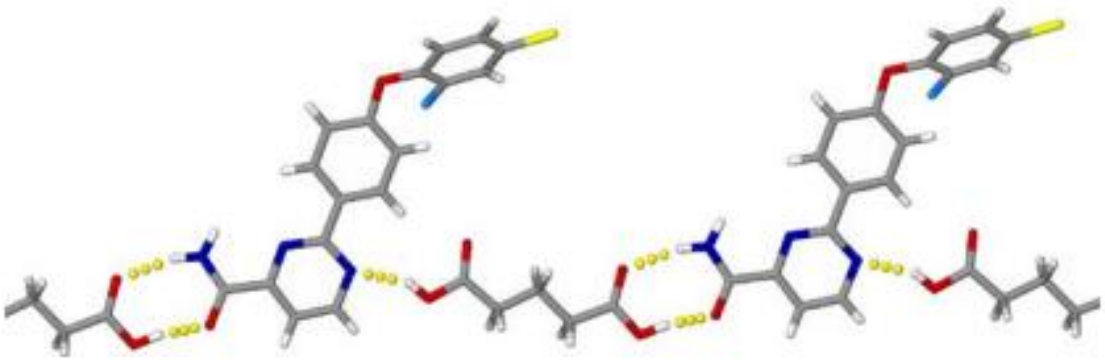


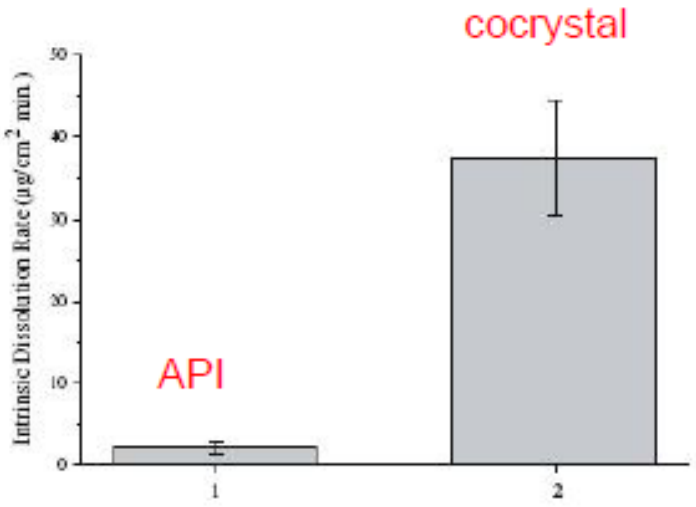
*T. Steiner, Acta Crystallogr., **2001**, B57, 103*

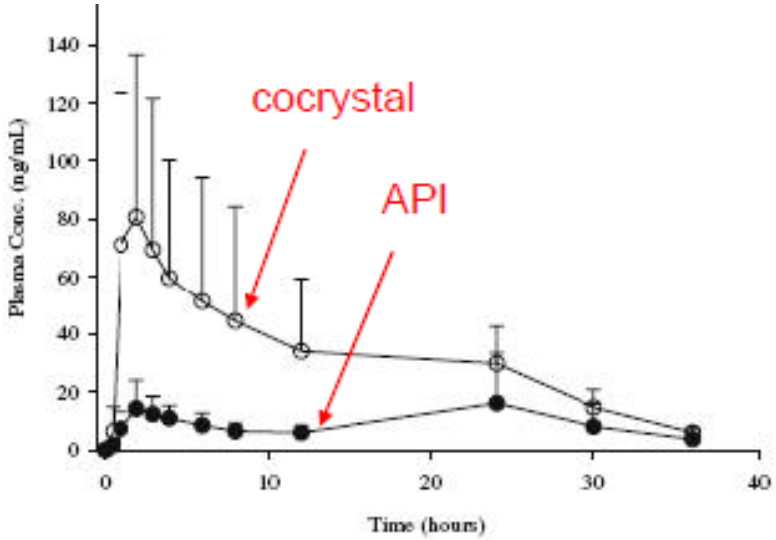
Realizing the Benefits

fluoxetine HCl			• melts 158 °C • less soluble
succinic acid			• melts 186 °C
2:1 fluoxetine HCl : succinic acid cocrystal			• melts 134 °C • more soluble

Source: E. Barash, SSCI, an Aptuit Company.



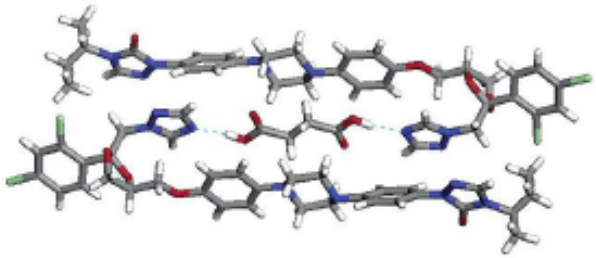




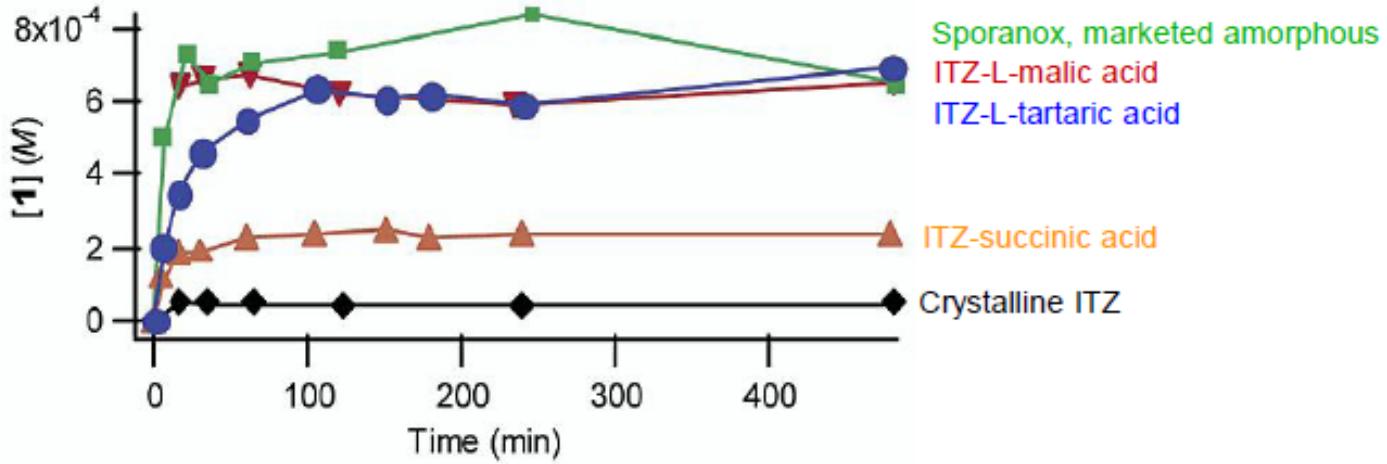
API: 2-[4-(4-chloro-2-fluorophenoxy)phenyl] pyrimidine-4-carboxamide

McNamara D,, Childs, S, et al., Pharm. Res., 2006

How high can dissolution rates be?



Itraconazole-succinic acid cocrystal



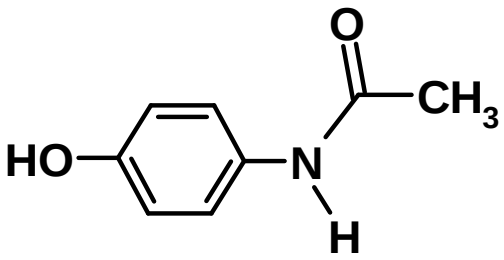
Cocrystal dissolution rates can be as high as for amorphous form of ITZ.

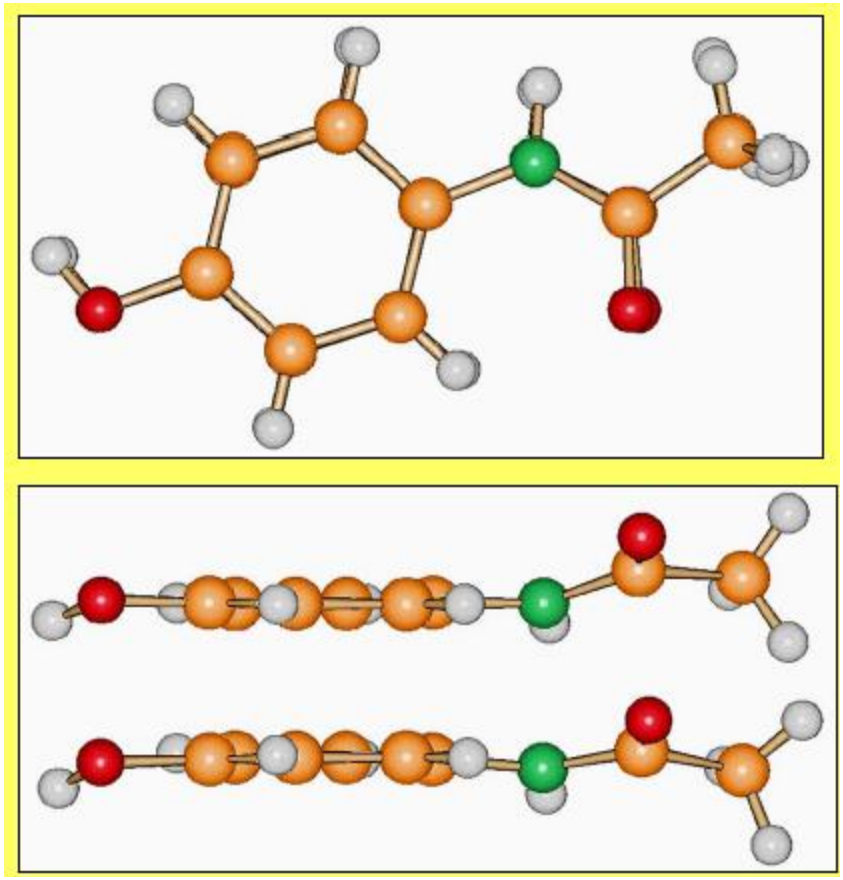
Remenar, Morissette, Peterson, Moulton, MacPhee, Guzman, and Almarsson. "Crystal engineering of novel cocrystals of a triazole drug with 1,4-dicarboxylic acids." *Journal of the American Chemical Society.* 125: 8345-8457 (2003).

Case Study 1

Cocrystals Screening Based on Paracetamol

Two Molecules Possess an almost identical conformation





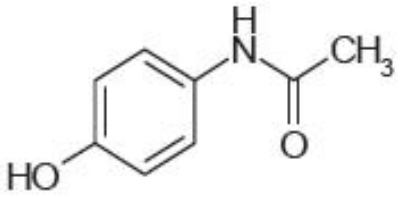
Form I
on top of
form II

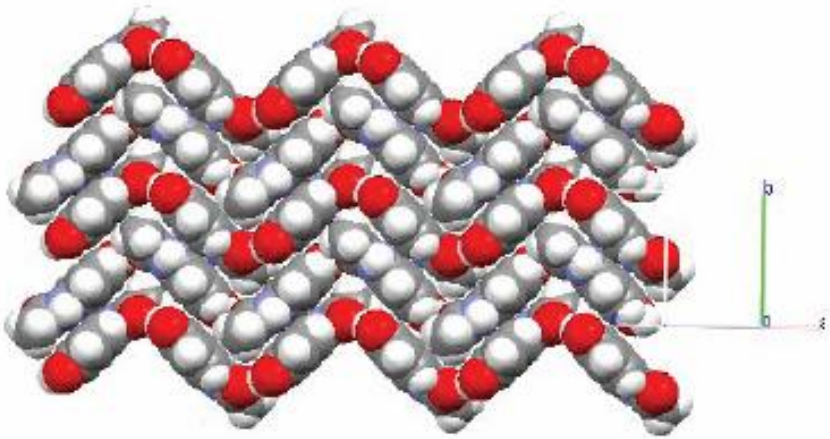
Form I

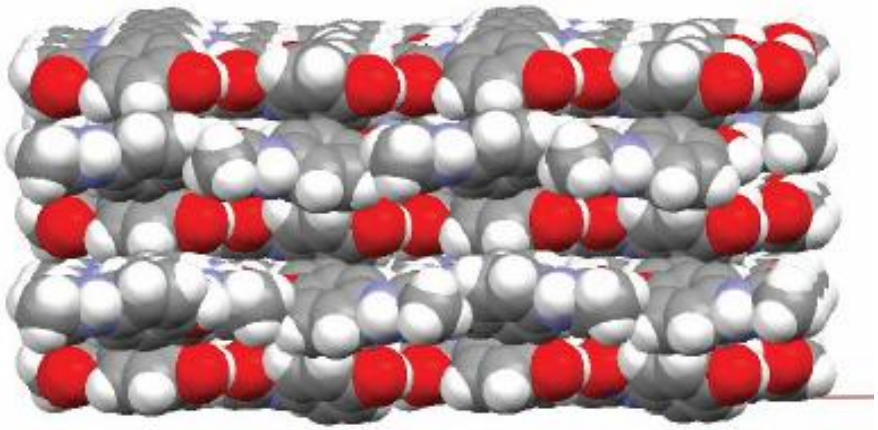
Side View

Form II

Compaction Property







Form I, the stable polymorph, forms corrugated layers and is difficult to compress into tablets)

Form II is metastable and difficult to crystallise. It does, however, compress into tablets.

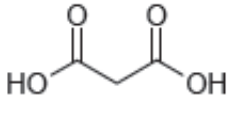
Screening for Compressible Cocrystals

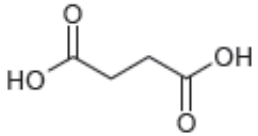
The aim therefore was to prepare various cocrystals of paracetamol and study mechanical properties with a view to being able to form tablets

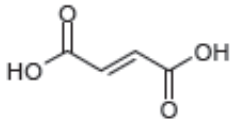
- How to select possible cocrystal formers? And how to screen?
  - They selected 20 selected possible cocrystal formers
  - Used the simple method of grinding and liquid assisted grinding to screen for cocrystallisation.

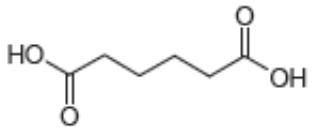
Range of cocrystal formers

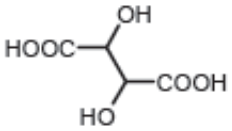

oxalic acid

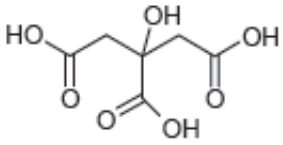

malonic acid

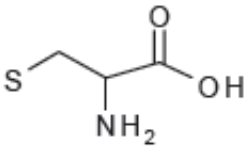

succinic acid

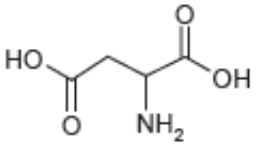

fumaric acid

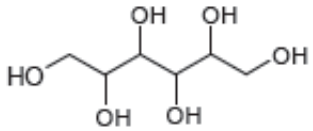

adipic acid

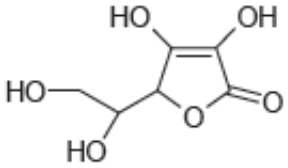

tartaric acid

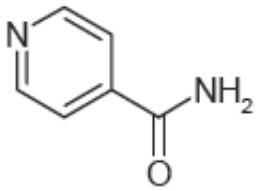

citric acid

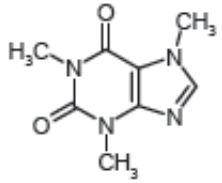

cysteine

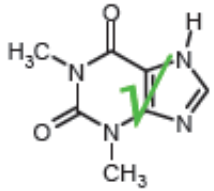

aspartic acid

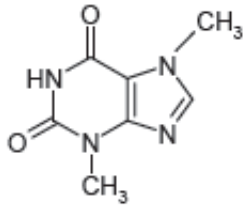

D-mannitol

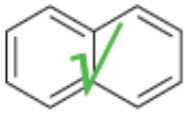

ascorbic acid

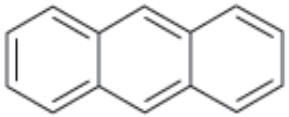

nicotinamide

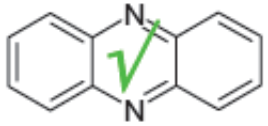

caffeine


theophylline

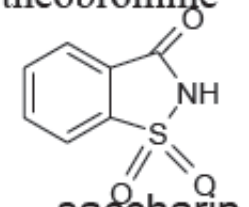

theobromine


naphthalene

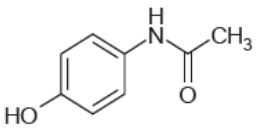

anthracene

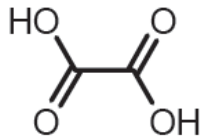

phenazine


4,4'-bipyridyl

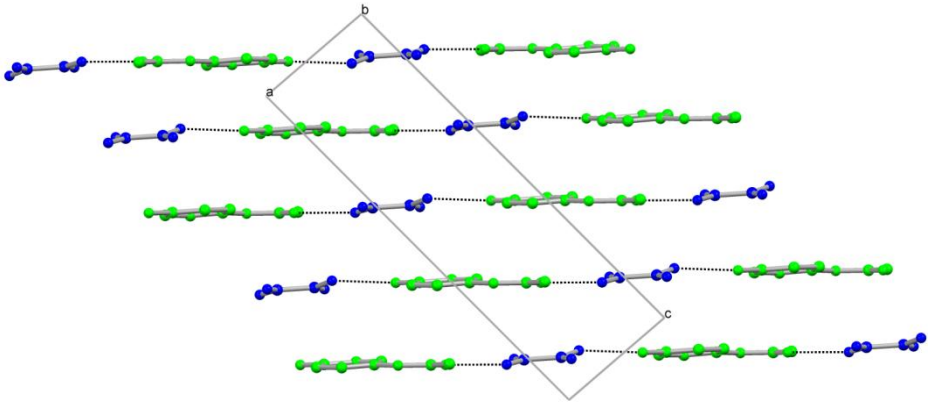

saccharin

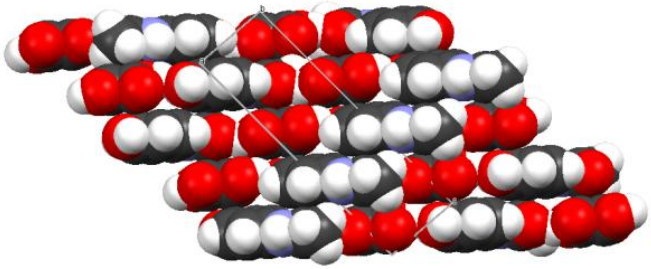
Crystal Packing of Paracetamol-Oxalic Acid Cocrystal



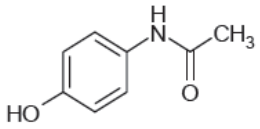


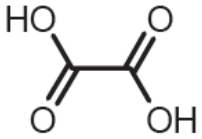
pc:oxa (1:1) cocrystal





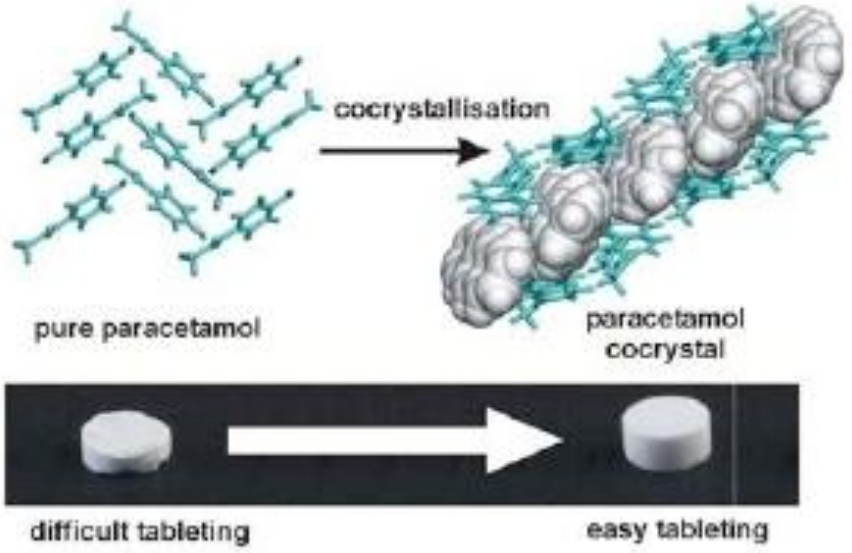
Crystal Packing of Paracetamol-Oxalic Acid Cocrystal





pc:oxa (1:1) cocrystal

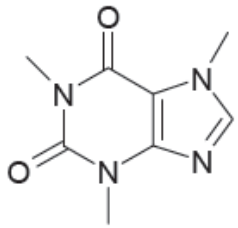
hydrogen and halogen bonds.



Case Study 2

Example of Caffeine Hydration

- Bulk stability in the context of hydrate formation.
- How to “stabilise” a molecule that otherwise crystallizes in an unstable/reactive form?



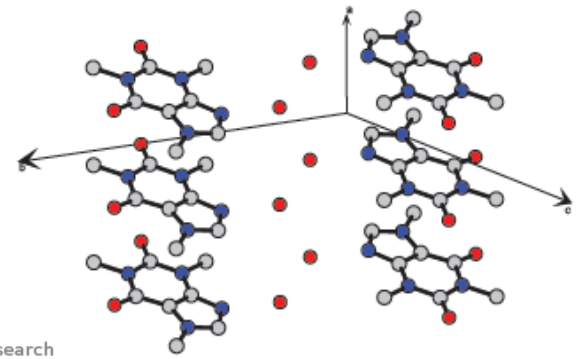
$C_8H_{10}N_4O_2$

Caffeine

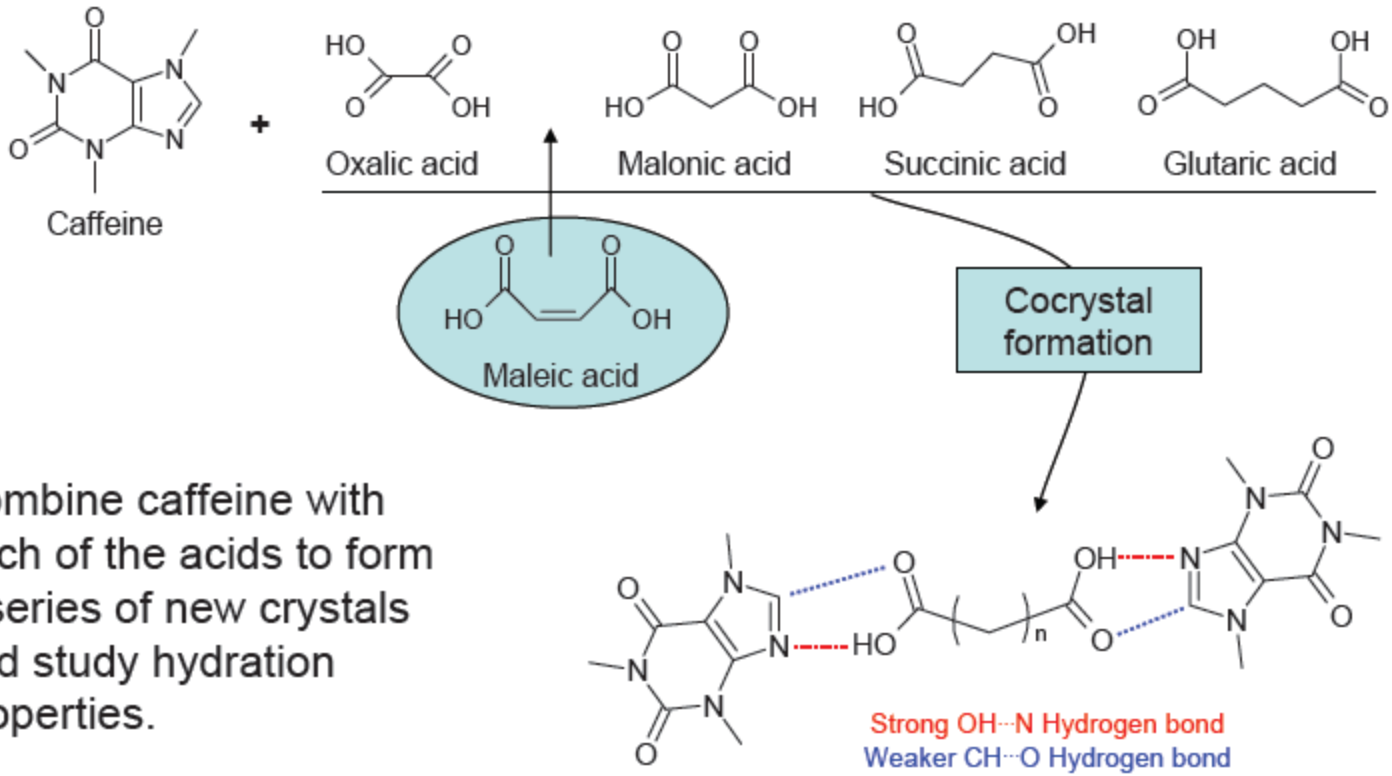
MW=194.19
pKa=3.6

Picks up water from the atmosphere to form the hydrate. Properties will therefore change.

Caffeine hydrate
(CAFINE from CSD)



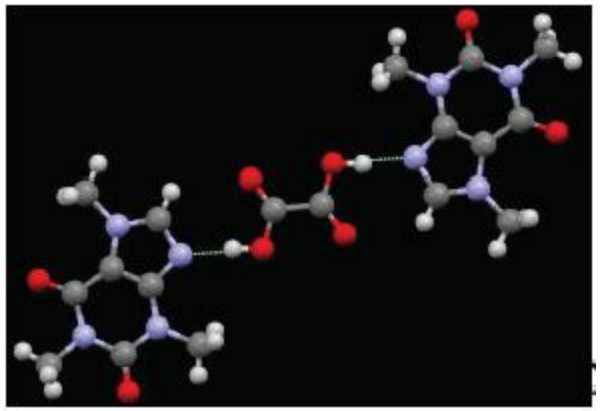
Cocrystal Designing



Combine caffeine with each of the acids to form a series of new crystals and study hydration properties.

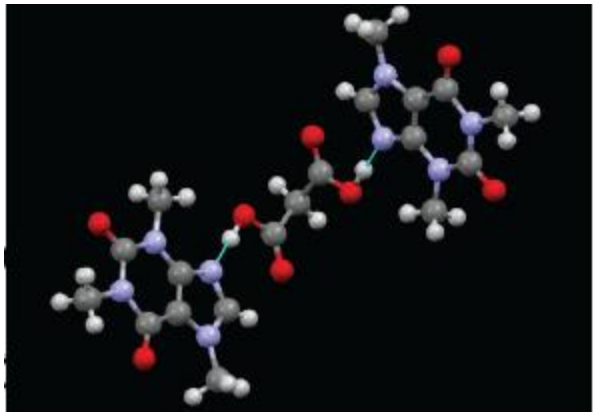
Caffeine Cocrystal

Caffeine: OA
2 : 1



RH	1 day	3 days	7 days	7 weeks
0%	✓	✓	✓	✓
43%	✓	✓	✓	✓
75%	✓	✓	✓	✓
98%	✓	✓	✓	✓

Caffeine: MA
2 : 1



RH	1 day	3 days	7 days	7 weeks
0%	✓	✓	✓	✓
43%	✓	✓	✓	✓
75%	✓	✓	✓	✓
98%	✓	✓	✓	✗

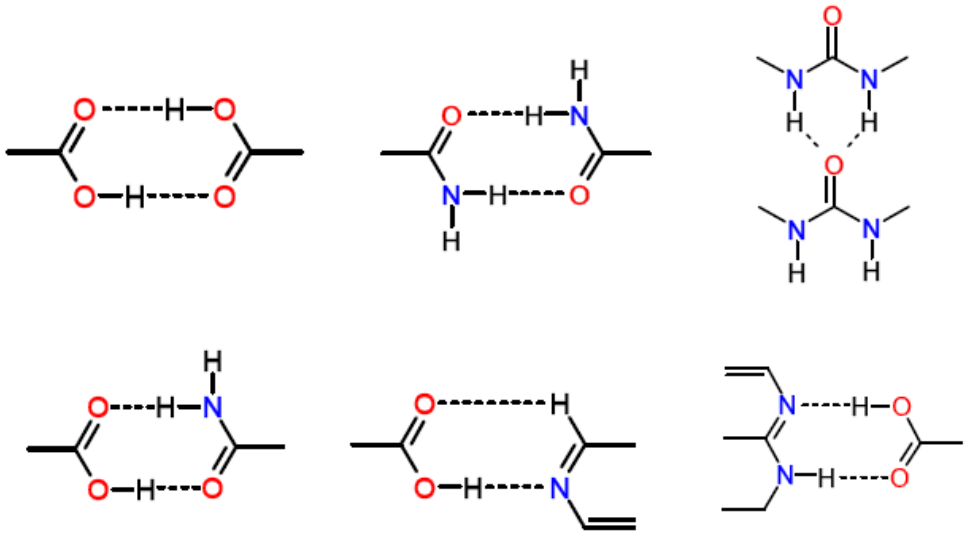
Crystal Engineering

Pioneer of Crystal Engineering

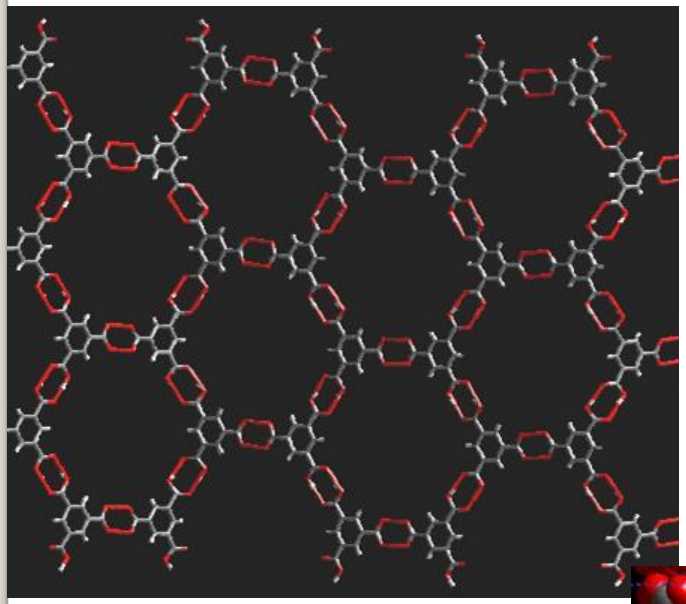
Prof. G. R. Desiraju

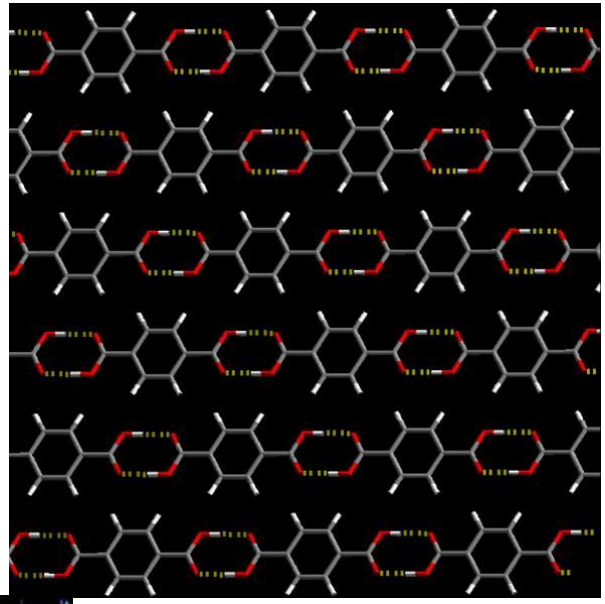
The understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties

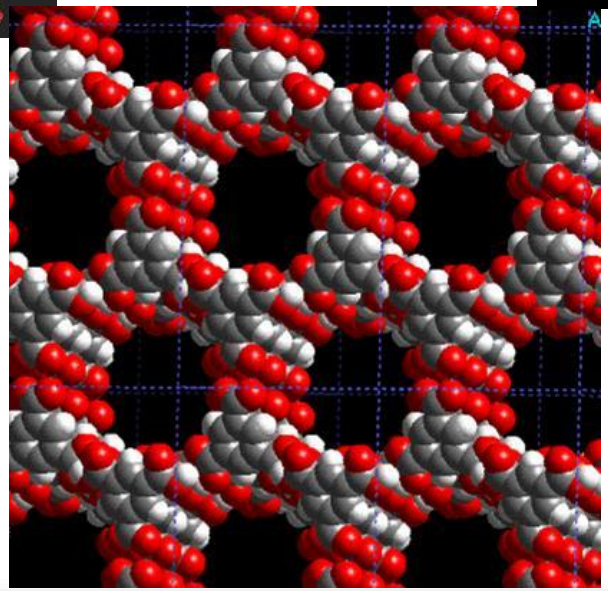
Common hydrogen bonded synthons used in crystal engineering



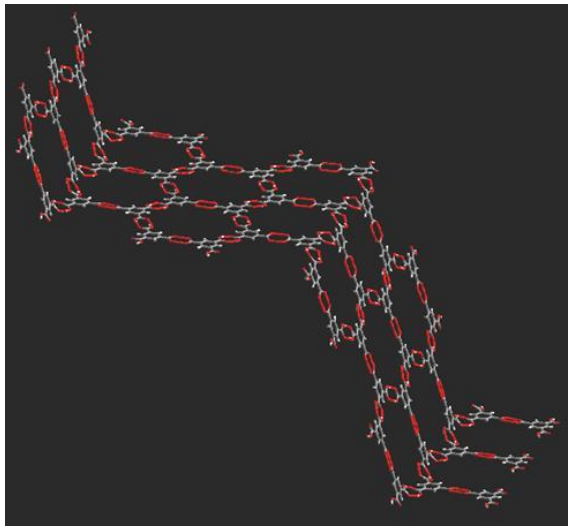
Crystal Engineering

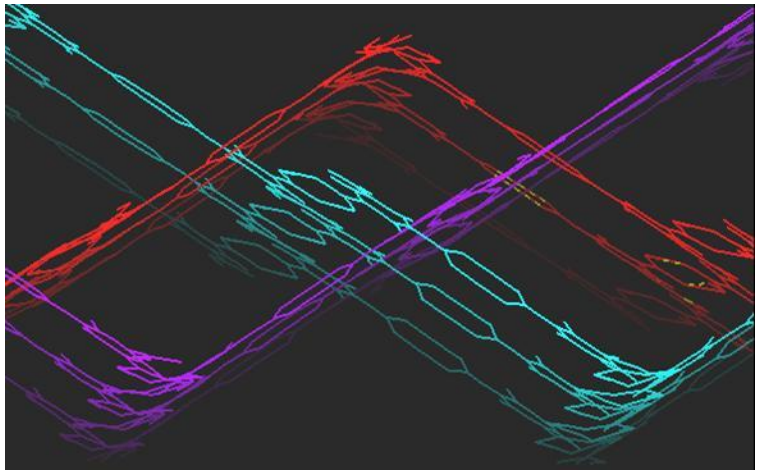


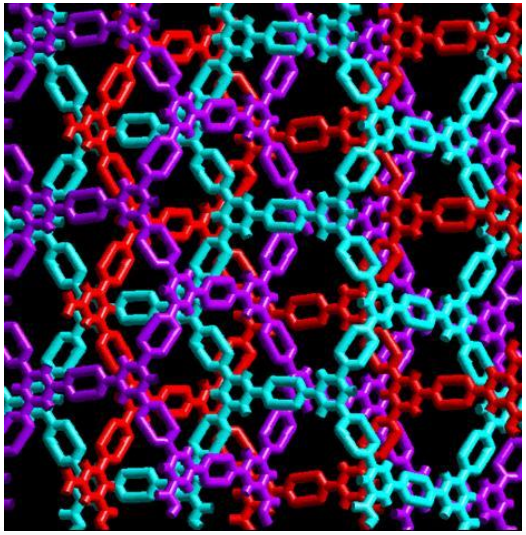




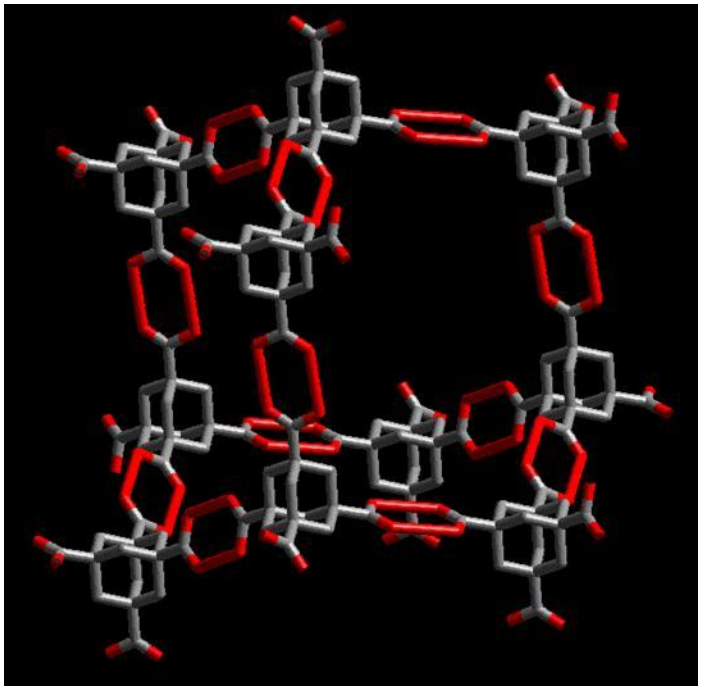
Crystal Engineering

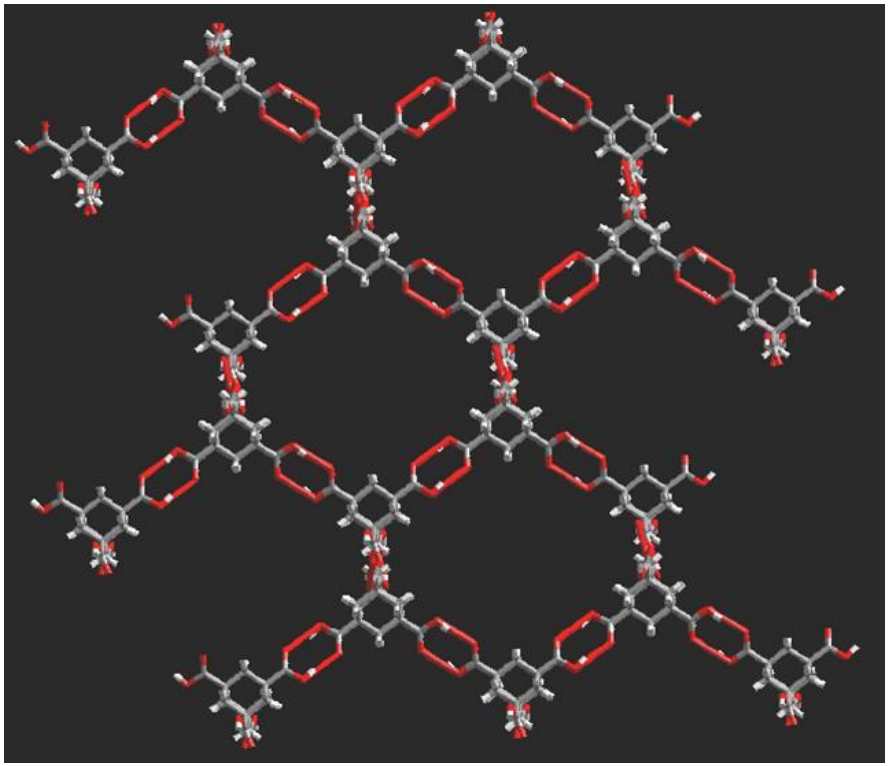




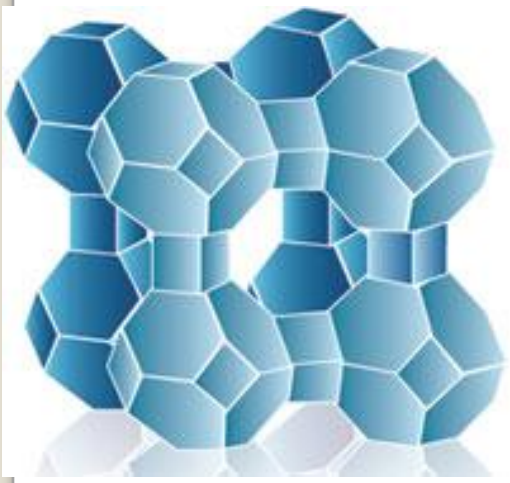


Crystal Engineering

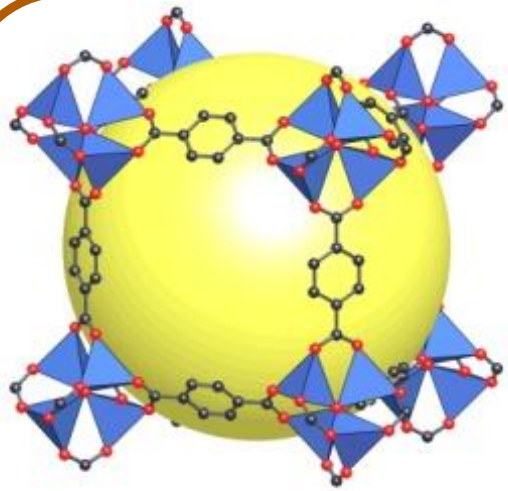




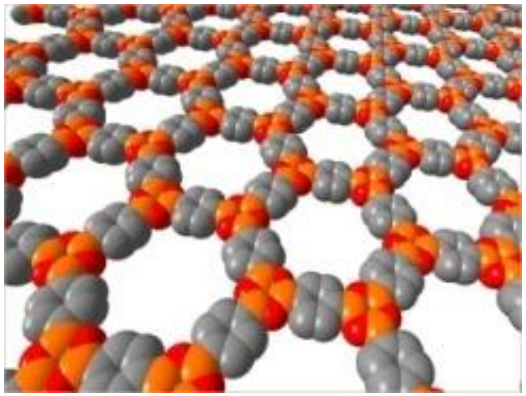
Introduction to Advanced Porous Crystalline Materials



Zeolites



Metal-organic framework

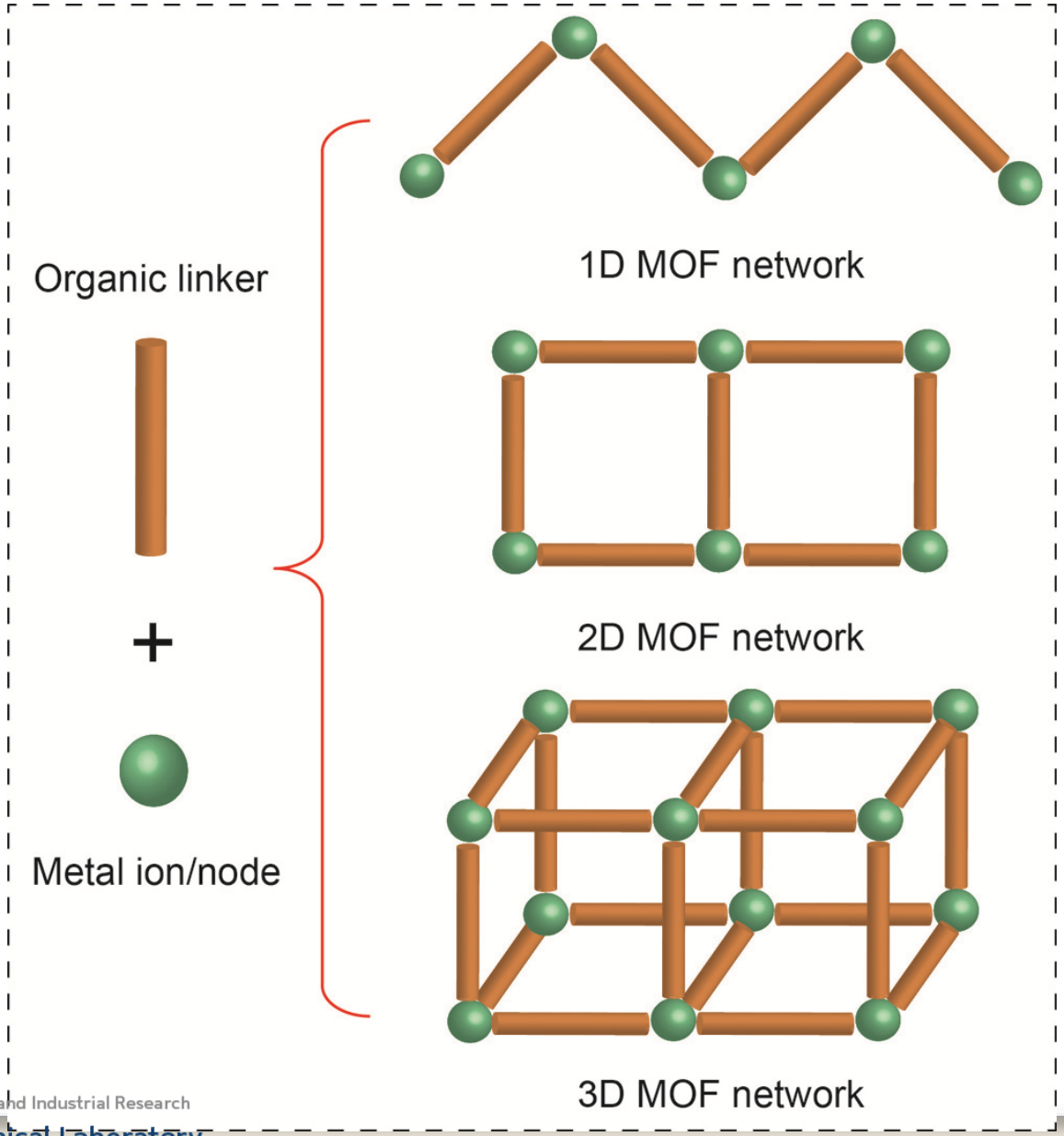


Covalent-organic framework

	Zeolites	MOFs	COFs
Discovery	1756	1995	2005
Pore size	<1 nm	0.3 nm to 10 nm	0.7 nm to 5 nm
Surface area	904 m^2g^{-1}	7000 m^2g^{-1}	4650 m^2g^{-1}
Functionality	No	Yes	Yes
Stability	High	Low-Moderate	Moderate-High
Applications	Adsorption, catalysis, etc.	Multifunctional materials	Multifunctional materials

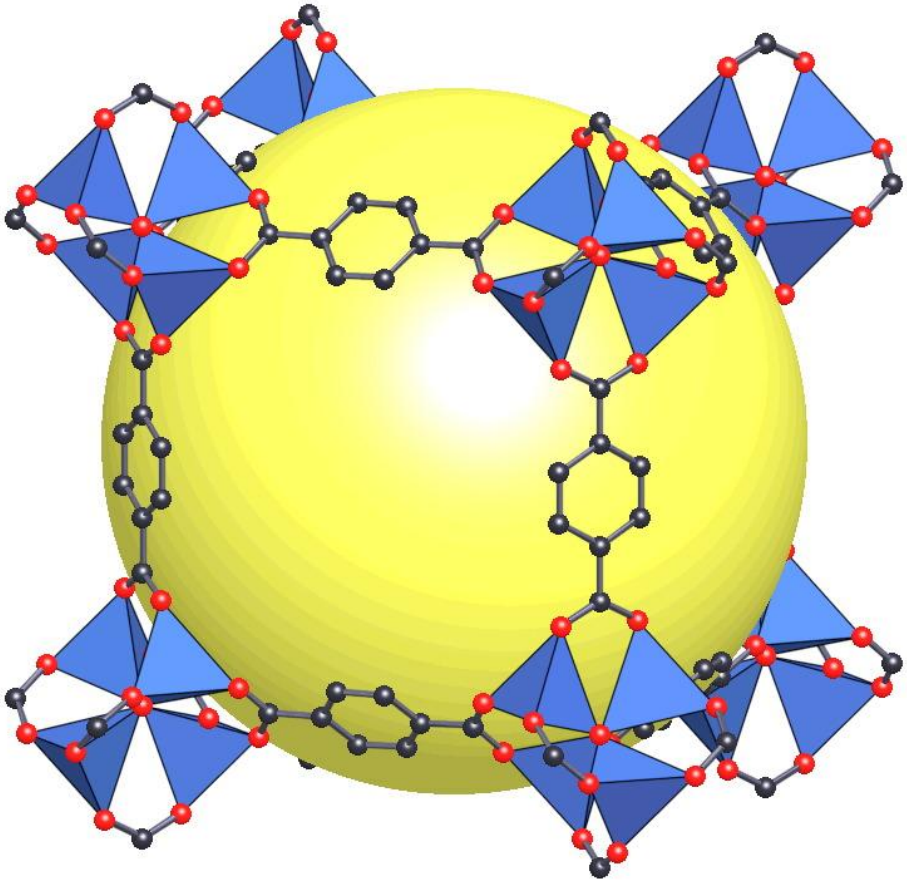
Yaghi et al., *J. Am. Chem. SOC.* ***1995****,117, 10401,* Cote *et al., Science,* **2005**, 310, 1166.

Metal-organic frameworks (MOFs)

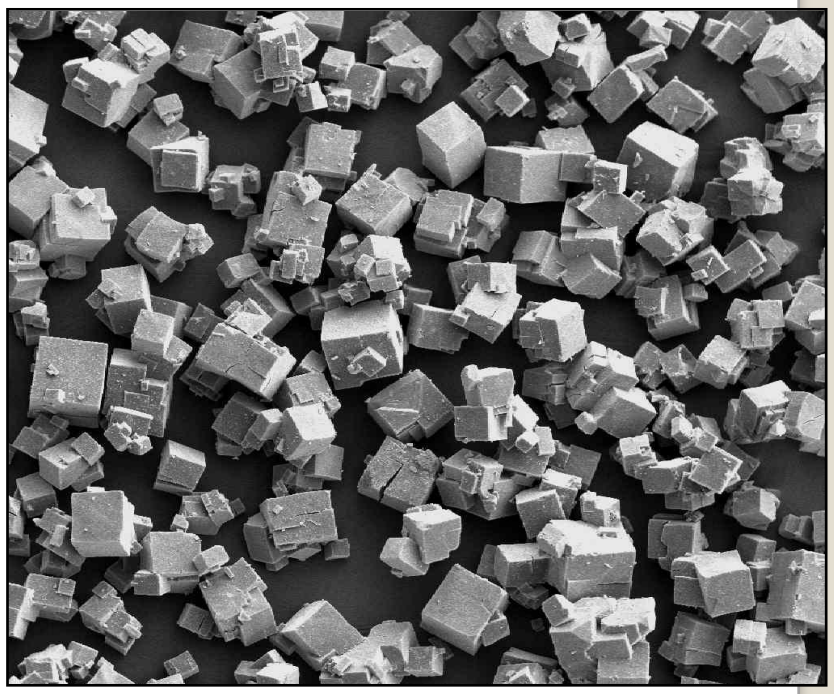


Example of Metal-organic frameworks (MOFs)

$$H_2BDC + Zn(NO_3)_2 \bullet 4H_2O \xrightarrow{DEF\ (12mL)} Zn_4O(BDC)_3 \bullet (DEF)_7$$



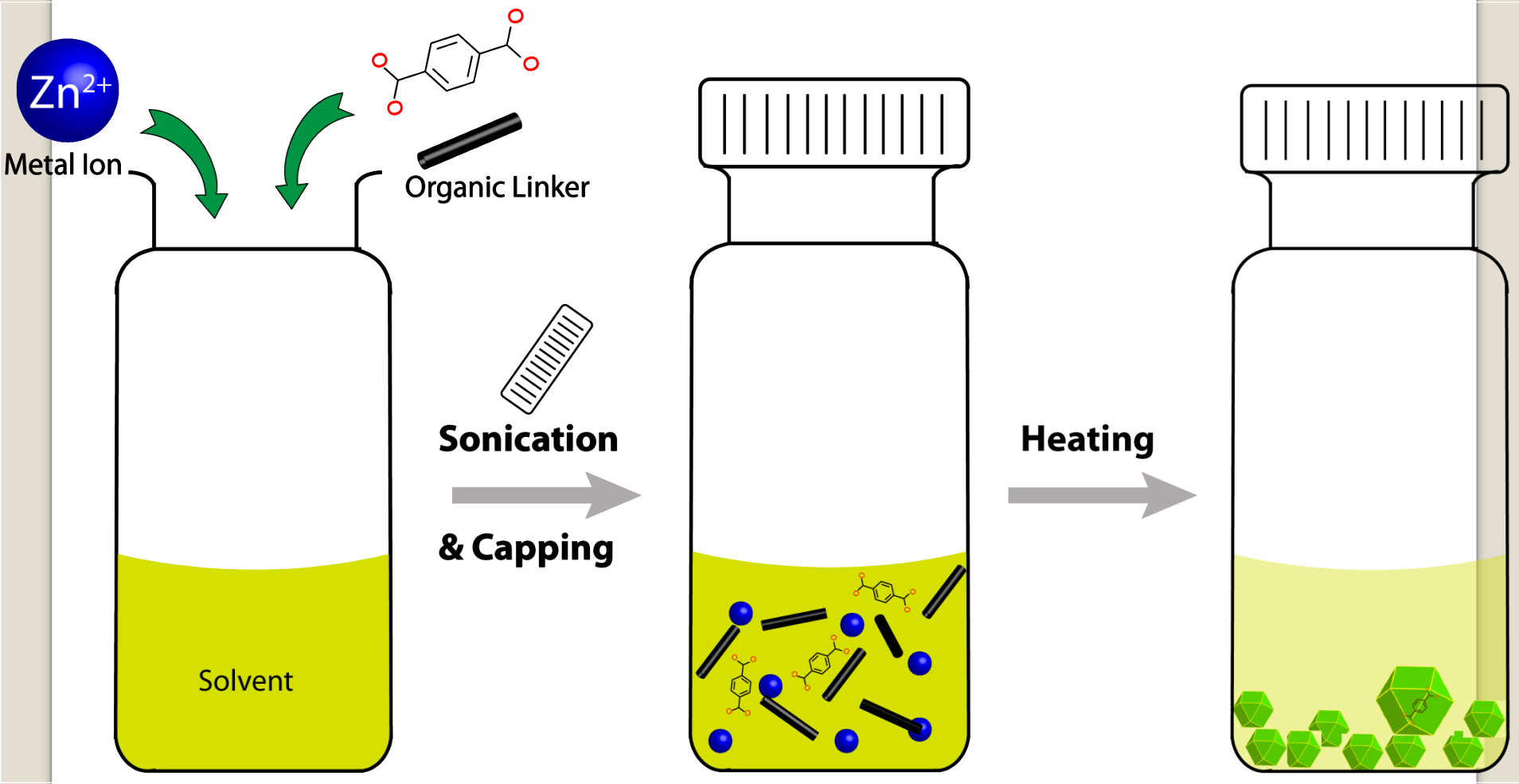
$Zn_4O(O_2C\text{-}C_6H_4\text{-}CO_2)_3$



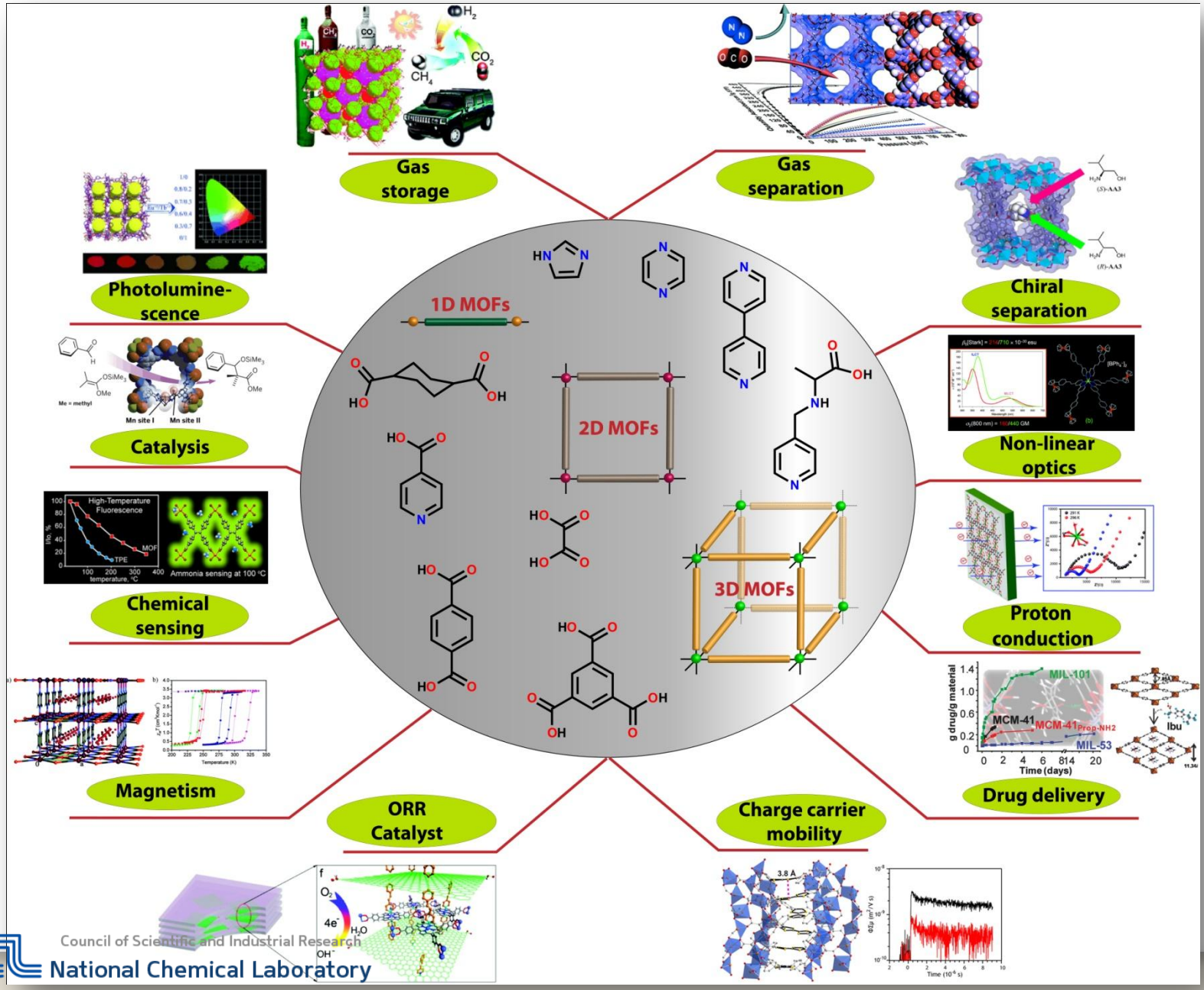
Different doped MOF crystals

H. Li, M. Eddaoudi, M. O'Keeffe, O. M. Yaghi. *Nature* (1999) *402*, 276-279

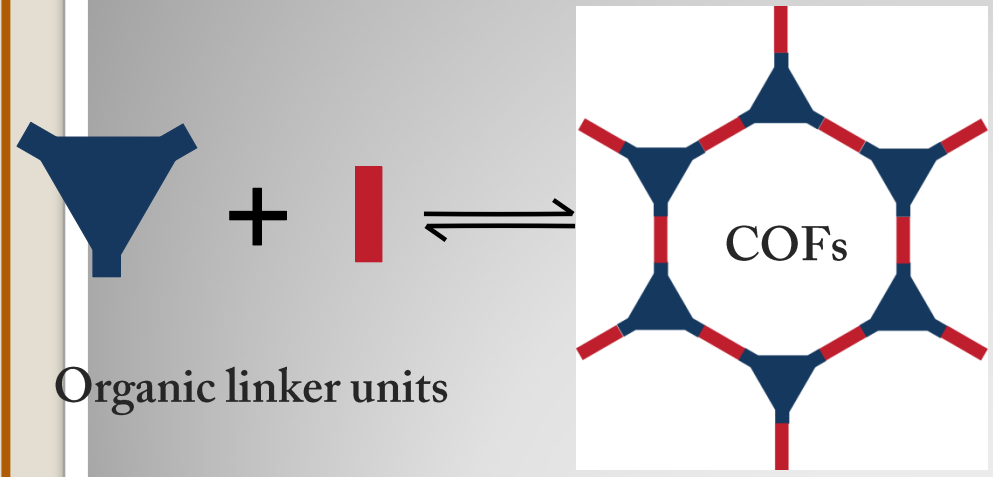
General Route for MOF Synthesis



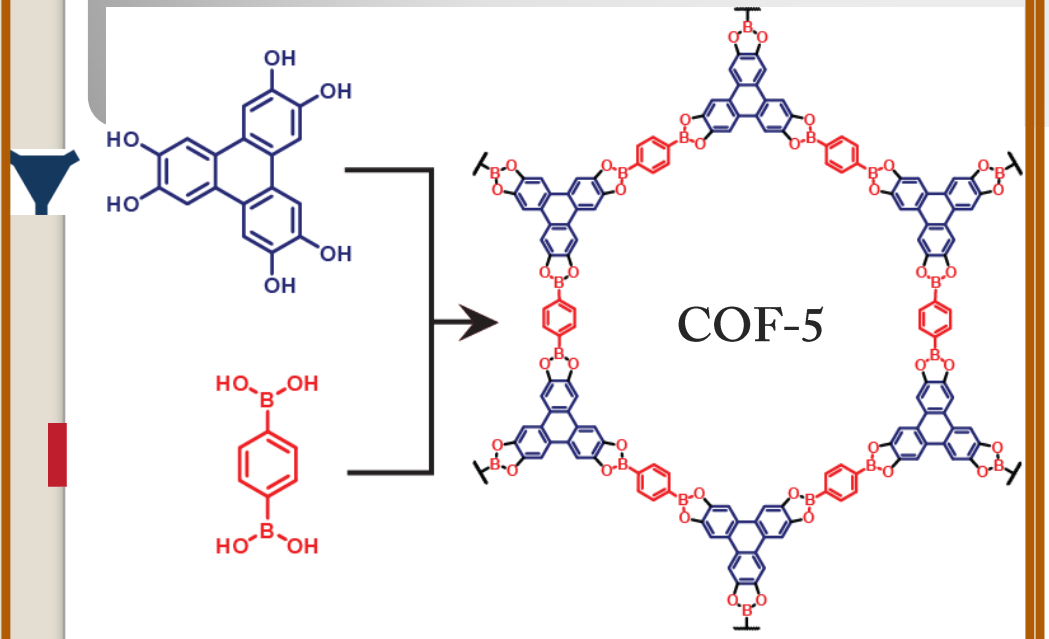
Applications of Metal-organic frameworks (MOFs)



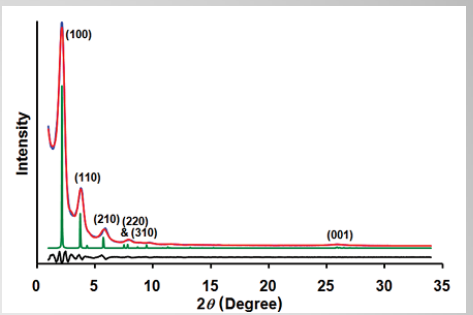
Covalent Organic Frameworks



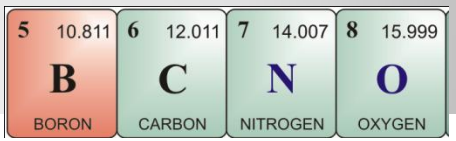
Organic linker units



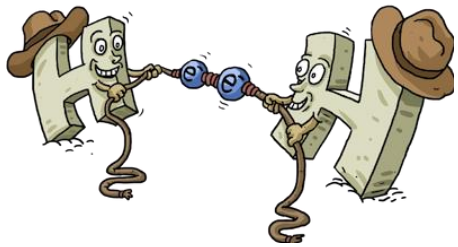
1) Crystalline porous polymers



2) Composed of light-weight elements



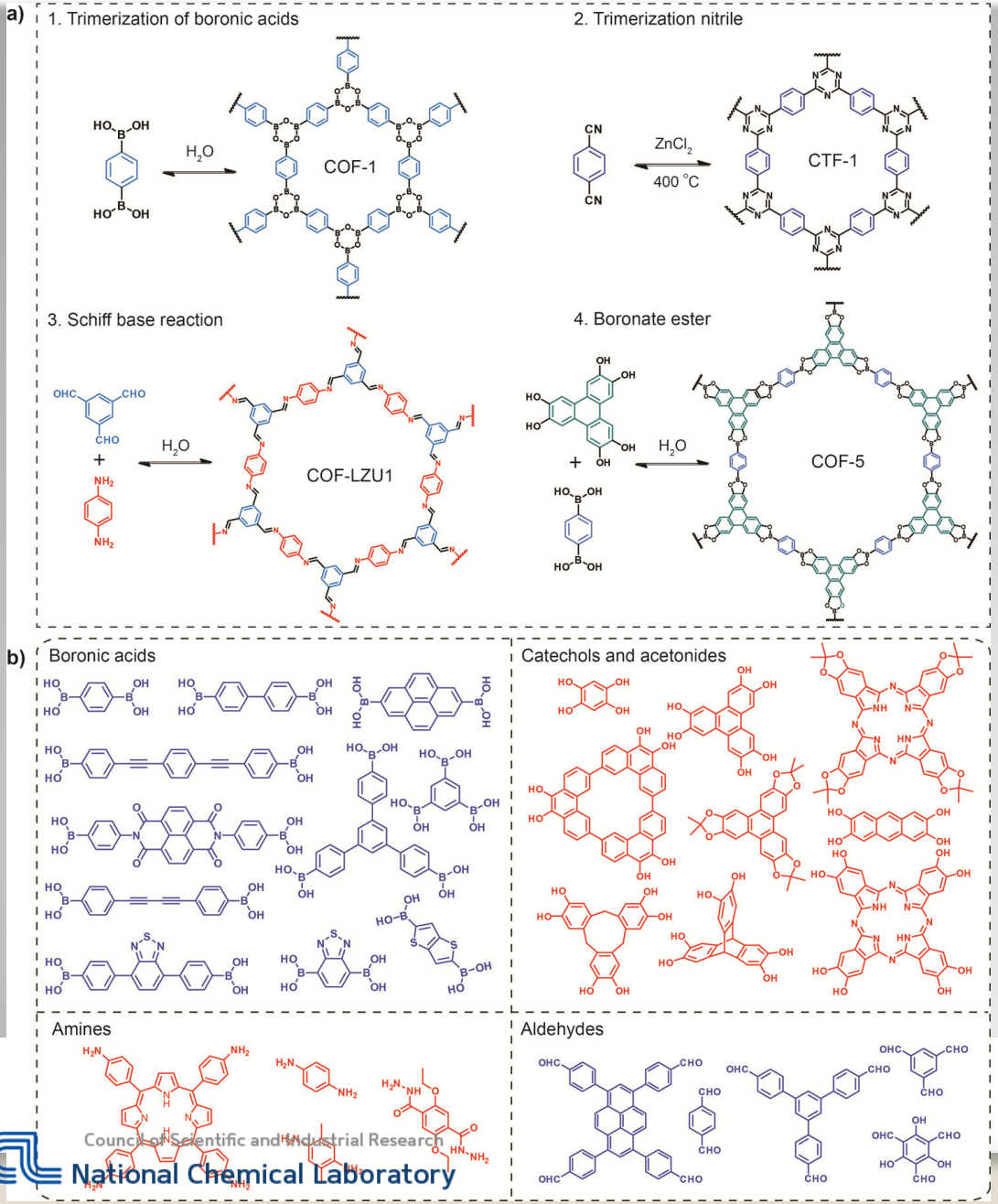
3) Linked together by strong covalent bonds

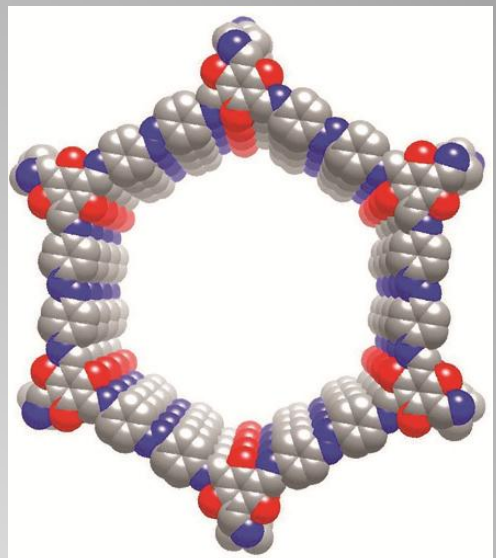


4) High thermal stability

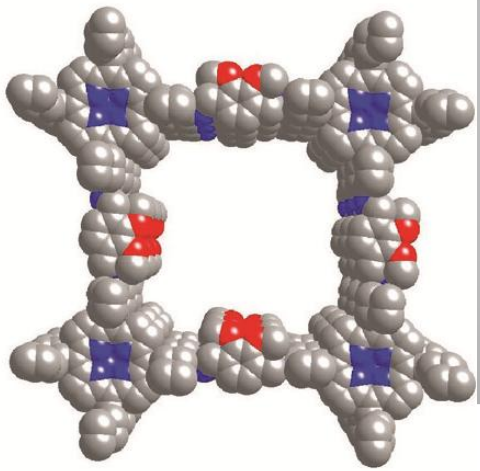
Côté et al. *Science*, **2005,** *310,* 1166-1170

Linkers used for Covalent Organic Frameworks





TpAzo



2,3-DmaTph

Synthesis and Applications of COFs

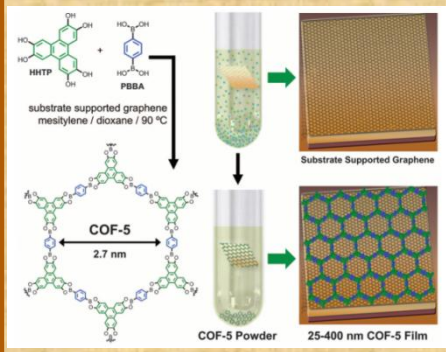
Solvothermal

Ionothermal

Mechanochemical

Microwave

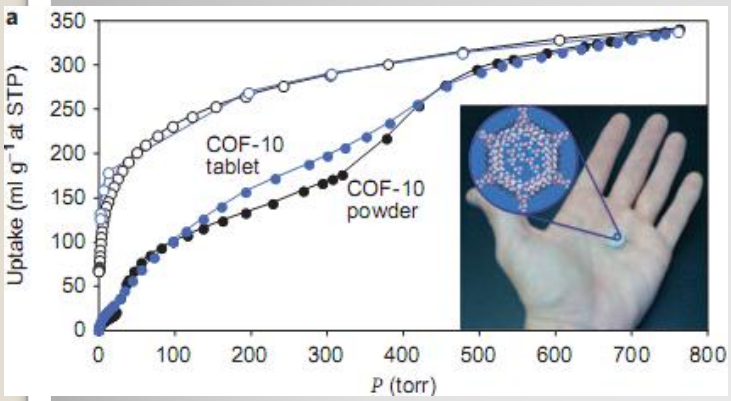
Growth on template



Biswal *et al.*, *J. Am. Chem. Soc.*, **2013**, *135*, 5328.

Dichtel *et al.*, *Science*, **2011**, *332*, 228.

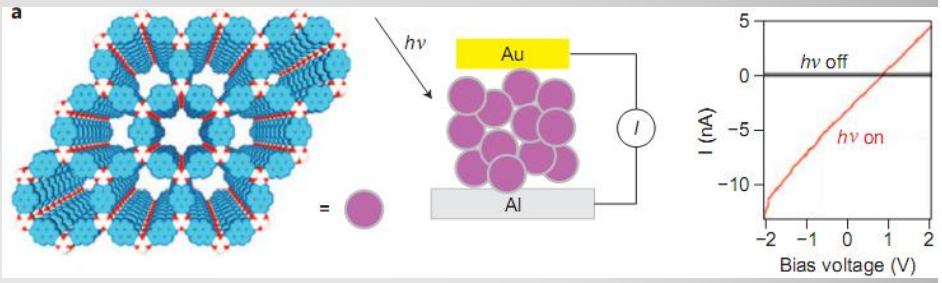
1) Gas storage (H_2, CO_2, CH_4, NH_3)



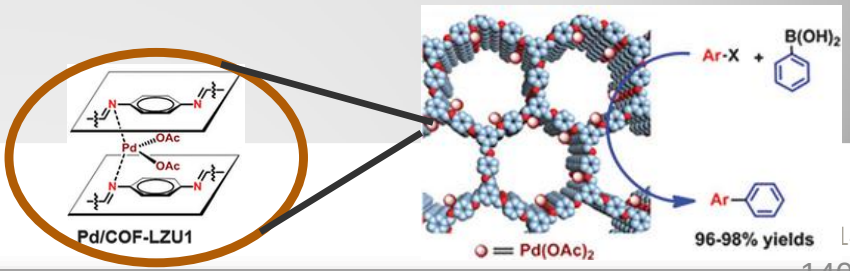
15 mol /kg,
at 298 K, 1 bar

Doonan *et al.*, *Nat. Chem.*, **2010**, *2*, 235.

2) Photoconducting material

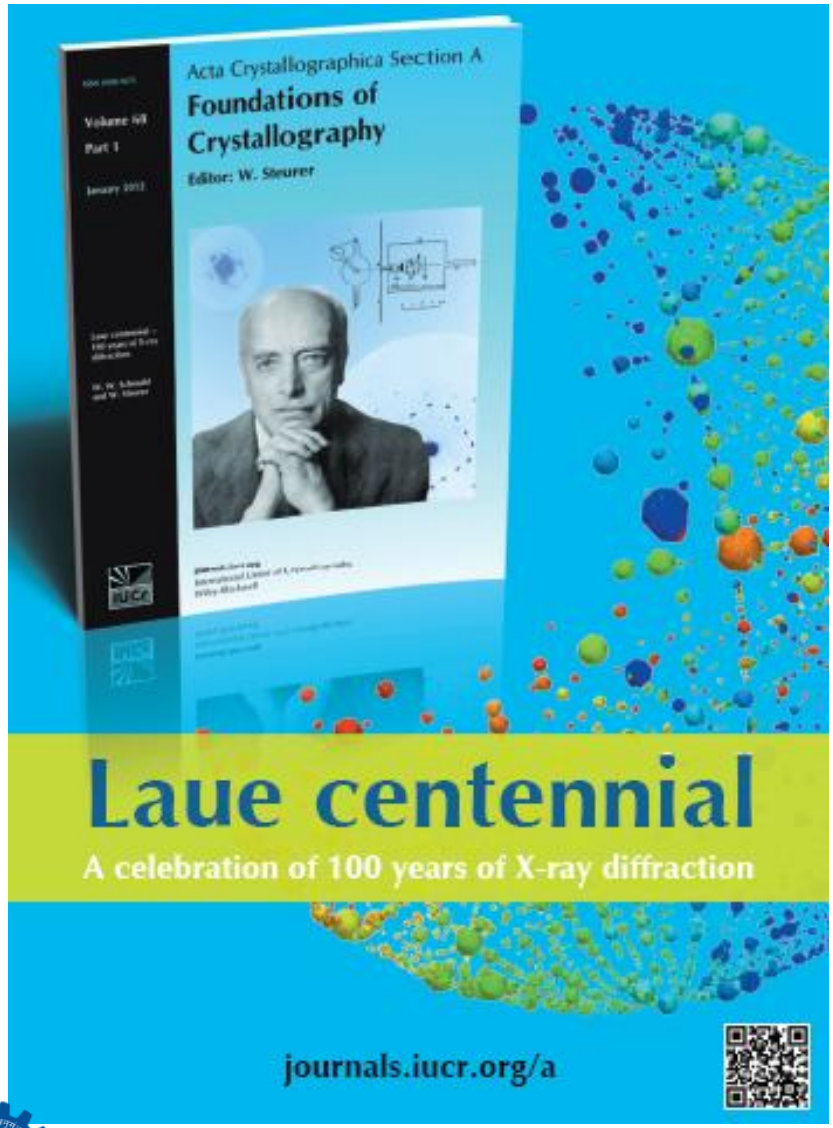


3) Heterogeneous catalysis



Wang *et al.*, *J. Am. Chem. Soc.*, **2011**, 133, 1981.

International Union of Crystallography

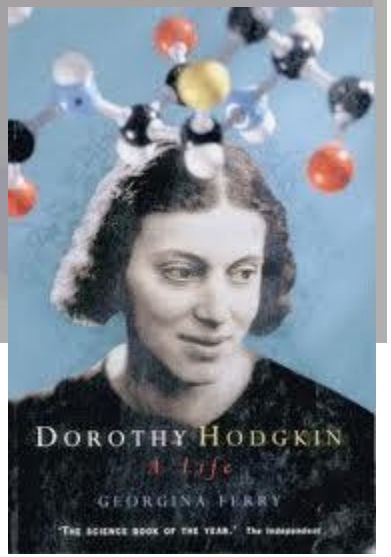


Nobel Prizes in Crystallography and Diffraction

• **W. C. Röntgen**	**1901**	*Discovery of X-rays (Physics)*
• **M. Von Laue**	**1914**	*Diffraction of X-rays by crystals (Physics)*
• **W.H. Bragg & W.L. Bragg**	**1915**	*Use of X-rays to determine crystal structure (Physics)*
• **Charles Glover Barkla**	**1917**	*Discovery of the characteristic Röntgen radiation of the elements (Physics)*
• **A. H. Compton**	**1927**	*Physics, Scattering of X-rays by electrons (Physics)*
• **Louis-Victor de Broglie**	**1929**	*Wave nature of the electron (Physics)*
• **C. J. Davisson, G. P. Thomson**	**1936**	*Diffraction of electrons by crystals (Physics)*
• **J.B. Sumner**	**1946**	*For his discovery that enzymes can be crystallized (Chemistry)*
• **L. C. Pauling**	**1954**	*Nature of chemical bond and its application in structure of complex substances (C)*
• **Perutz and Kendrew**	**1962**	*For determining the structure of globular proteins (Chemistry)*
• **Crick, Watson and Wilkens**	**1962**	*Medicine, Double Helix (Physiology or Medicine)*
• **D. Hodgkin**	**1964**	*Structure of vitamin B, Penicillin (Chemistry)*
• **Barton and Hassel**	**1969**	*Concept of conformation (Chemistry)*
• **C.B. Anfinsen**	**1972**	*Folding of protein chains (Chemistry)*
• **Lipscomb**	**1976**	*Structure of boranes (Chemistry)*
• **A. Klug**	**1982**	*Crystallographic electron microscopy and nuclei acid-protein complexes (C)*
• **Hauptmann & Karle**	**1985**	*Development of direct methods for the determination of crystal structures (C)*
• **J. Deisenhofer, R. Huber, H. Michel**	**1988**	*Determination of the 3D structure of a photosynthetic reaction center (C)*
• **Pierre-Gilles de Gennes**	**1991**	*Methods of discovering order in simple systems can be applied to polymers & LC (P)*
• **Georges Charpak**	**1992**	*Discovery of the multi wire proportional chamber (Physics)*
• **C. G. Shull, B. N. Brockhouse**	**1994**	*For their pioneering research in neutron scattering (Physics)*
• **R. F. Curl, H. W. Kroto, R. E. Smalley**	**1996**	*For their discovery of the fullerene form of carbon (Chemistry)*
• **P.D. Boyer, J.E. Walker, J.C. Skou**	**1997**	*Elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP) and discovery of an ion-transporting enzyme (C)*
• **R. MacKinnon**	**2003**	*Potassium Channels (Chemistry)*
• **D. Kornberg**	**2006**	*Studies of the molecular basis of eukaryotic transcription (Chemistry)*
• **V. Ramakrishnan, T.A. Steitz, A.E. Yonath**	**2009**	*Studies of the structure and function of the ribosome (Chemistry)*
• **D. Shechtman**	**2011**	*For the discovery of quasicrystals (Chemistry)*

Dorothy Hodgkin – (1910-1994)

A great advantage of x-ray structure analysis as a method of chemical structure analysis is its power to show totally unexpected and surprising structure with, at the same time, complete certainty.




Thank You!