Ah! Crystallography!
Importance of Crystallography in Modern Science

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Crystallography deals with crystals

A crystal is a solid with an orderly, repeating arrangement of atoms
Crystals are everywhere!

Crystals are everywhere!

Transparent

Opaque

Translucent
Crystals are everywhere!

**Crystal Shape**
- General Shapes
  - prismatic
- Special named shapes
  - cube
  - dodecahedron
  - octahedron
  - Pyrite
  - Garnet
  - Magnetite
fibrous

Prismatic

Needles

Tabular
Crystals found in everyday life

Salt

Sugar

Diagram showing the structure of salt and sugar crystals.
Crystals found in everyday life

Diamond

Graphite

Fullerene
What is crystal?

- Historic definition before the advent of crystallography
  - A solid with well-defined faces

- Crystallographic definition
  - A material with a regularly repeating structural motif

- The strict definition
  - Any material that gives diffraction pattern with sharp 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*
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.
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.

Empty space is not allowed
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
Crystal faces: crystal usually bounded by a number of flat surfaces (faces).

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

\[4 + 4 + 4 = 12 \text{ edge}\]
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 located 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 are divided into 7 main groups.

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 with Pyritohedron Striations
- Cube
- Garnet
- Garnet - Dodecahedron
- Grossularite, Dodecahedra
- Spinel
- Fluorite
- Pyrite
- Trapezohedron
Three horizontal axes meeting at angles of 120° 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.
Rhombohedral Crystals

\[ \alpha = \beta = \gamma \neq 90^\circ \]
TETRAGONAL CRYSTALS

WULFENITE

APOPHYLLITE
  on Stilbite
ORTHORHOMBIC CRYSTALS
ORTHORHOMBIC CRYSTALS

STAUROLITE

Pinacoid View

Prism View
TRICLINIC CRYSTALS

Microcline, variety Amazonite
Abbé René Just Haüy (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 - \( \alpha \), \( \beta \), \( \gamma \)

- 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 \( 8 \times \frac{1}{8} = 1 \) lattice point.
Building a crystal
Translationally periodic arrangement of **points** in space

**Lattice**

- the underlying periodicity of the crystal
- atom or group of atoms associated with each lattice point

**Basis or Motif**

- how to repeat
- what to repeat

**Crystal**

Translationally periodic arrangement of **motifs**

**Crystal = Lattice + Motif**
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.
Elemental solids (Argon): Basis = single atom.

Polyatomic Elements: Basis = two or four atoms.

Complex organic compounds: Basis = thousands of atoms.
Seven unit cell shapes

- **Triclinic**
  \[ a \neq b \neq c \quad \alpha \neq \beta \neq \gamma \neq 90^\circ \]

- **Monoclinic**
  \[ a \neq b \neq c \quad \alpha = \gamma = 90^\circ, \beta \neq 90^\circ \]

- **Orthorhombic**
  \[ a \neq b \neq c \quad \alpha = \beta = \gamma = 90^\circ \]

- **Tetragonal**
  \[ a = b \neq c \quad \alpha = \beta = \gamma = 90^\circ \]

- **Rhombohedral**
  \[ a = b = c \quad \alpha = \beta = \gamma \neq 90^\circ \]

- **Hexagonal**
  \[ a = b \neq c \quad \alpha = \beta = 90^\circ, \gamma = 120^\circ \]

- **Cubic**
  \[ a = b = c \quad \alpha = \beta = \gamma = 90^\circ \]
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)**

\[ a \neq b \neq c, \, \alpha = \gamma = 90^\circ, \beta \neq 90^\circ \]
The 14 Bravais lattices

Orthorhombic (P)
\[ a \neq b \neq c, \alpha = \beta = \gamma = 90^\circ \]

Orthorhombic (C)
\[ a \neq b \neq c, \alpha = \beta = \gamma = 90^\circ \]

Orthorhombic (I)
\[ a \neq b \neq c, \alpha = \beta = \gamma = 90^\circ \]

Orthorhombic (F)
\[ a \neq b \neq c, \alpha = \beta = \gamma = 90^\circ \]
The 14 Bravais lattices

**Tetragonal (P)**
$a=b \neq c$, $\alpha=\beta=\gamma=90^\circ$

**Tetragonal (I)**
$a=b \neq c$, $\alpha=\beta=\gamma=90^\circ$

**Hexagonal (P)**
$a=b \neq c$, $\alpha=\beta=90^\circ$, $\gamma=120^\circ$

**Rhombohedral (R)**
Trigonal P
$a=b=c$, $\alpha=\beta=\gamma \neq 90^\circ$
The 14 Bravais lattices

Cubic (P)
\[a=b=c, \ \alpha=\beta=\gamma=90^\circ\]

Cubic (I)
\[a=b=c, \ \alpha=\beta=\gamma=90^\circ\]

Cubic (F)
\[a=b=c, \ \alpha=\beta=\gamma=90^\circ\]
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.”
Rotation, reflection and inversion operations generate a variety of unique arrangements of lattice points (i.e., a shape structure) in three dimensions.
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 $\sigma$ 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
The inversion, i

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

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.
**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’s Institute.
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.
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

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.
X-ray Crystallography – in a nutshell

**Bragg’s law**

**Reflections**

\[
\begin{array}{cccc}
 h & k & l & I \\
 0 & 0 & 2 & 3523.1 \\
 0 & 0 & 3 & -1.4 \\
 0 & 0 & 4 & 306.5 \\
 0 & 0 & 5 & -0.1 \\
 0 & 0 & 6 & 10378.4 \\
\end{array}
\]

\[
\frac{1}{\sigma(I)}
\]

**Electron density:**

\[
\rho(x, y, z) = \frac{1}{V} \sum \sum \sum |F(h, k, l)| \exp[-2\pi i (hx + hy + lz) + i\alpha(h, k, l)]
\]
Bragg's Law

\[ \frac{ACB}{2d \sin \theta} \]

For NaCl

\[ AB = 2.8 \times 10^{-8} \text{ cm} \]
W. H. & W. L. Bragg,
X-Rays and Crystal Structure (1915)

- Birth of "X-ray Crystallography"

Photos
Top: William Henry Bragg (1862 – 1942);
Bottom William Lawrence Bragg (1890-1971)
Swedish postage stamp with 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
The crystal is getting cooled to **120K** (-153 °C, -243 °F)
X-ray Diffractometer:
**Crystal Structures of Carbon Allotrope**

*W. L. Bragg (1890-1971)*


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

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

*Buckminster Fullerene, 1985, H. Kroto*
Inorganic Structures

Copper


CaF₂, (1914)

CaCO₃, (1914)

Pyrite, FeS₂, (1914)

Inorganic Structures

**Spinel, MgAl₂O₄**


**Rutile and Anatase forms of Titanium Dioxide, TiO₂**

**Sodium Nitrate, NaNO₃**

Inorganic Structures

Wurtzite (ZnS), 1920


Hexagonal Structure

Cubic Structure

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.
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.”
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.

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.
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.
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.
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
Structure solved in 1950
by John Kendrew

Hemoglobin
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 a pioneer in the field of DNA research.


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

Solving the Structure of DNA

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 of the DNA.
Contribution from INDIA

Triple Helix structure of collagen and Ramachandran plot

Prof. G. N. Ramachandran,
Ribosome Crystal Structure

The Nobel Prize in Chemistry 2009

“for studies of the structure and function of the ribosome”

Venkatraman Ramakrishnan
© 1/3 of the prize
United Kingdom

Thomas A. Steitz
© 1/3 of the prize
USA

Ada E. Yonath
© 1/3 of the prize
Israel

L7/L12
peptidyl transferase center

mRNA

decoding site

50S

30S
The Journey

Year 1913

Cl⁻  Na⁺

NaCl

Year 2009

70S ribosome

W. L. Bragg

Venkatraman Ramakrishnan

Council of Scientific and Industrial Research
National Chemical Laboratory
Applications

Drug Design

Structure of few anti-cancer drugs

1. Gefitinib (EGFR)
2. Erlotinib (EGFR)
3. Imatinib (BCR-ABL)
4. Nilotinib (BCR-ABL)
5. Bisindolylmaleimide (PRKCBII)
6. 17β-estradiol (ligand for estrogen receptor alpha)
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

Binding pocket of Sunitinib in the TRK KIT.

Binding of sitagliptin within DPP-IV.
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 (P2₁/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

Table II. Single Crystal X-Ray Data

A: Comparison of Torsion Angles in Ritonavir Forms

<table>
<thead>
<tr>
<th>Torsion Angle</th>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (N-Methyl Urea)</td>
<td>−5 (cis)</td>
<td>−179 (trans)</td>
</tr>
<tr>
<td>B</td>
<td>72</td>
<td>−77</td>
</tr>
<tr>
<td>C (carbamate)</td>
<td>−178 (trans)</td>
<td>−8 (cis)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2₁ (#4)</td>
<td>P2₁P2₁P2₁ (#19)</td>
</tr>
<tr>
<td>Z value</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dcalc</td>
<td>1.28 g/cm³</td>
<td>1.25 g/cm³</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>a = 13.433 (1) Å</td>
<td>a = 10.0236 (3) Å</td>
</tr>
<tr>
<td></td>
<td>b = 5.293 (2) Å</td>
<td>b = 18.6744 (4) Å</td>
</tr>
<tr>
<td></td>
<td>c = 27.092 (4) Å</td>
<td>c = 20.4692 (7) Å</td>
</tr>
<tr>
<td></td>
<td>β = 103.102 (9) Å</td>
<td>V = 1876.0 (8) Å³</td>
</tr>
<tr>
<td></td>
<td>V = 3831.5 (2) Å³</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ethanol/Water</th>
<th>99/1</th>
<th>95/5</th>
<th>90/10</th>
<th>85/15</th>
<th>80/20</th>
<th>75/25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form I</td>
<td>90 mg/mL</td>
<td>188</td>
<td>234</td>
<td>294</td>
<td>236</td>
<td>170</td>
</tr>
<tr>
<td>Form II</td>
<td>19 mg/mL</td>
<td>41</td>
<td>60</td>
<td>61</td>
<td>45</td>
<td>30</td>
</tr>
</tbody>
</table>

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)

Four polymorphs known, $\alpha$, $\beta$, $\gamma$, $\delta$; $\delta$ form is least stable whereas $\beta$ form is most stable

$\alpha$-Form: Blue

$\beta$-Form: Red

$\gamma$-Form: Green

$\delta$-Form: Orange
Cyclo tetramethylene tetranitramine (HMX)
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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Image 1</th>
<th>Image 2</th>
<th>Properties</th>
</tr>
</thead>
</table>
| fluoxetine HCl            | ![Image](image1) | ![Image](image2) | • melts 158 °C  
• less soluble |
| succinic acid             | ![Image](image3) | ![Image](image4) | • melts 186 °C |
| 2:1 fluoxetine HCl : succinic acid cocrystal | ![Image](image5) | ![Image](image6) | • melts 134 °C  
• more soluble |

Source: E. Barash, SSCI, an Aptuit Company.
API: 2-[4-(4-chloro-2-fluorophenoxy)phenyl] pyrimidine-4-carboxamide

How high can dissolution rates be?

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

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

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>oxalic acid</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure" /></td>
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<td><img src="image16.png" alt="Structure" /></td>
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<td><img src="image18.png" alt="Structure" /></td>
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<tr>
<td><img src="image19.png" alt="Structure" /></td>
<td>4,4’-bipyridyl</td>
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<td><img src="image20.png" alt="Structure" /></td>
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Crystal Packing of Paracetamol-Oxalic Acid Cocrystal

pc:oxa (1:1) cocrystal
Crystal Packing of Paracetamol-Oxalic Acid Cocrystal

pc:oxa (1:1) cocrystal
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?

Caffeine

\[ C_8H_{10}N_4O_2 \]

MW=194.19  
pK_a=3.6

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

Caffeine hydrate  
(CAFINE from CSD)
Combine caffeine with each of the acids to form a series of new crystals and study hydration properties.

Strong OH···N Hydrogen bond
Weaker CH···O Hydrogen bond
Caffeine Cocrystal

Caffeine: OA
2 : 1

Caffeine: MA
2 : 1

<table>
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<th>7 days</th>
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<td>✓</td>
</tr>
</tbody>
</table>
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
# Introduction to Advanced Porous Crystalline Materials

**Zeolites**

- **Discovery**: 1756
- **Pore size**: <1 nm
- **Surface area**: 904 m$^2$g$^{-1}$
- **Functionality**: No
- **Stability**: High
- **Applications**: Adsorption, catalysis, etc.

**Metal-organic framework (MOFs)**

- **Discovery**: 1995
- **Pore size**: 0.3 nm to 10 nm
- **Surface area**: 7000 m$^2$g$^{-1}$
- **Functionality**: Yes
- **Stability**: Low-Moderate
- **Applications**: Multifunctional materials

**Covalent-organic framework (COFs)**

- **Discovery**: 2005
- **Pore size**: 0.7 nm to 5 nm
- **Surface area**: 4650 m$^2$g$^{-1}$
- **Functionality**: Yes
- **Stability**: Moderate-High
- **Applications**: Multifunctional materials

---

Metal-organic frameworks (MOFs)
Example of Metal-organic frameworks (MOFs)

\[
\text{H}_2\text{BDC} + \text{Zn(NO}_3\text{)}_2\cdot4\text{H}_2\text{O} \rightarrow \text{Zn}_4\text{O(BDC)}_3\cdot(\text{DEF})_7
\]

Different doped MOF crystals

Applications of Metal-organic frameworks (MOFs)

- Gas storage
- Gas separation
- Chiral separation
- Non-linear optics
- Proton conduction
- Drug delivery
- Chemical sensing
- Magnetism
- 1D MOFs
- 2D MOFs
- 3D MOFs

- Photoluminescence
- Catalysis
- ORR Catalyst
- Charge carrier mobility

Council of Scientific and Industrial Research
National Chemical Laboratory
Covalent Organic Frameworks

1) Crystalline porous polymers

2) Composed of light-weight elements

3) Linked together by strong covalent bonds

4) High thermal stability

Cote et al. Science, 2005, 310, 1166-1170
Linkers used for Covalent Organic Frameworks

a) 1. Trimerization of boronic acids
   ![Chemical structure of COF-1](image1)
   ![Chemical structure of CTF-1](image2)

2. Trimerization nitride
   ![Chemical structure of COF-LZU1](image3)

3. Schiff base reaction
   ![Chemical structure of COF-LZU1](image4)
   ![Chemical structure of COF-5](image5)

4. Boronate ester
   ![Chemical structure of COF-LZU1](image6)
   ![Chemical structure of COF-5](image7)

b) Boronic acids
   ![Chemical structures of boronic acids](image8)

   Catechols and acetonides
   ![Chemical structures of catechols and acetonides](image9)

   Amines
   ![Chemical structures of amines](image10)

   Aldehydes
   ![Chemical structures of aldehydes](image11)
Synthesis and Applications of COFs

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


2) Photoconducting material


3) Heterogeneous catalysis


15 mol/kg, at 298 K, 1 bar
International Union of Crystallography

Laue centennial
A celebration of 100 years of X-ray diffraction

journals.iucr.org/a

International Year of Crystallography 2014
Prospectus
| **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 *(Chemistry)*     |
| 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 *(Chemistry)*           |
| Hauptmann & Karle               | 1985  | Development of direct methods for the determination of crystal structures *(Chemistry)*         |
| J. Deisenhofer, R. Huber, H. Michel | 1988 | Determination of the 3D structure of a photosynthetic reaction center *(Chemistry)*              |
| Pierre-Gilles de Gennes         | 1991  | Methods of discovering order in simple systems can be applied to polymers & LC *(Physics)*     |
| 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 *(Chemistry)* |
| R. MacKinnon                    | 2003  | Potassium Channels *(Chemistry)*                                                                |
| D. Kornberg                     | 2006  | Studies of the molecular basis of eukaryotic transcription *(Chemistry)*                        |
| 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)*                                                |
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.