Crystal Engineering of Materials: Aspects of Design, Synthesis and Applications

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Techniques most commonly used for solid-state characterization

**Diffraction methods:**
- X-ray single crystal X-ray diffraction
- X-ray powder X-ray diffraction (PXRD)

**Spectroscopic methods:**
- FT IR, Raman spectroscopy, Terahertz spectroscopy
- NMR spectroscopy

**Thermal methods:**
- Thermogravimetric analysis (TGA)
- Differential scanning calorimetry (DSC)
- Differential thermal analysis (DTA)

Typically, diffraction and spectroscopic methods are non-destructive, whereas thermal analysis often leads to the decomposition of the sample.

Solid-state analysis techniques

**Diffraction methods:**
- X-ray single crystal X-ray diffraction
- X-ray powder X-ray diffraction (PXRD)

What can diffraction methods teach us about the structure of organic materials?

**Type of solid material:**
- Single component or multi-component (solvate, salt, cocrystal)

**Solid-state structure:**
- Molecular structure
- Molecular arrangement

**Molecular recognition**

**Reaction mechanisms**

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The first step in understanding solids is in elucidating their organization:

- **Amorphous**: "Random" arrangement
- **Crystalline**: 3-dimensional periodicity

The solid state is "DYNAMIC" in that interconversion is possible between structures.

**Level 1: Is there order within the crystal?**

<table>
<thead>
<tr>
<th>molecule</th>
<th>low order</th>
<th>high order</th>
</tr>
</thead>
<tbody>
<tr>
<td>amorphous</td>
<td>&quot;random&quot; arrangement</td>
<td>crystalline</td>
</tr>
</tbody>
</table>

**Level 2: Variations of the order**

For a particular building block (molecule) there are many potential ways of solid-state ordering (polymorphs):

- **Crystalline form**
  - polymorph 1
  - polymorph 2
  - polymorph 3

Polytypes: a herringbone structure

Typically, only one polymorph is stable. The rest are metastable and may convert to the stable one.

**Level 3: More than one type of species in the crystal**

Solids can also be multicomponent systems: salts, cocrystals, hydrates, solvates, solid solutions, mixed crystals.

- Salt
- Cocystal
- Multicomponent crystals

- building block molecule
- salt former molecule
- cocrystal former molecule
- building block analogue
X-ray diffraction on a single crystal

The scattering of X-rays on a crystal can be mathematically described as the reflection of X-ray off different crystallographic planes.

The diffracted beams must be in constructive interference, hence "X-ray reflections" are observed only for some values of θ:

\[ 2d \sin \theta = n \lambda \] (Bragg's law)

- \( d \) = spacing between a set of crystallographic planes
- \( \theta \) = diffraction angle
- \( \lambda \) = X-ray wavelength
- \( n \) = integer

Intensity of diffracted radiation

Since there are many planes intersecting the unit cell, X-ray diffraction produces numerous reflections that are distributed in space around the crystal. Each reflection is defined by a characteristic set of Miller indices \((hkl)\) of the reflecting plane.

Measuring the positions of reflections allows determining the symmetry and shape of the unit cell.

The information on the molecules within the unit cell is obtained by measuring the intensities of X-ray reflections. The diffraction of X-rays is achieved on the electrons of each atom – there is a relationship between the electron density at a particular site in the unit cell \( \rho(x,y,z) \) and diffraction intensities \( I(hkl) \).

\[ F(hkl) \] is the Structure Factor, the amplitude of a diffracted beam: it is also the connection between X-ray intensity and electron density.

\[ F(hkl) = \sum f_j \rho \left( h\lambda + ky + kz \right) \]

\( f_j \) is the atomic scattering factor of the \( j \)th atom.
The intensity of diffracted radiation:

\[ F(hkl) = \sum_j f_j e^{2\pi i (hx_j + ky_j + lz_j)} \]

Heavier atoms contain more diffracting electrons and contribute more to the diffracted intensity: hydrogen is the poorest.

Connection between intensity and electron density:

In terms of electron density, the structure factor of any \( hkl \) reflection is obtained by integrating all the electron density throughout the entire unit cell:

\[ F(hkl) = \int F(x,y,z) e^{2\pi i (hx + ky + lz)} \, dV \]

The reverse – extracting electron density information from diffracted data is achieved through a Fourier transform:

\[ \rho(x,y,z) = \frac{1}{V} \sum_{h} \sum_{k} F(hkl) \cos 2\pi \left( hx + ky + lz \right) \]

Peaks of electron density obtained in this way correspond to atom positions.

The problem of locating hydrogen atoms:

The positions of hydrogen atoms cannot be readily deduced, as the number of electrons is small and the scattering power is small.

Sometimes it is possible to recognise electron peaks in the final difference electron density map:

after all heavy atoms have been accounted for, remaining peaks correspond to hydrogens and electron-rich regions of π-systems.
**Structural characterization of "difficult" molecules**

That the intensity of radiation scattered (diffracted) from a crystal is largely determined by the contribution of strongly scattering multi-electron atoms led to the "heavy atom" method for determination of complex molecular structures.

A large number of early structural characterizations have been enabled by bromine- or iodine-derivatization.


**Heavy atom method in protein crystallography**

The "heavy atom" approach is still very important in determining the crystal structures of proteins.

Derivatization is usually performed by "soaking" the crystals in solutions of platinum, palladium, gold or mercury compounds.

**Heavy atom method in non-covalent derivatization**

The synthesis of a brominated derivative is not a very efficient route to confirm the stereochemistry of a substrate!

An alternative is to form a complex between the actual substrate and a small molecule bearing a heavy atom.

Such a complex is called a cocrystal and is usually obtained following designs involving strong intermolecular (non-covalent) interactions.

Particularly important in that respect are hydrogen bonding and halogen bonding.
**“Intermolecular bonds”**

Typical strength $\approx 10^{-15}$ kcal mol$^{-1}$. A certain degree of directionality is required.

**Hydrogen bonds (H-bonds)**

$\text{A} - H - H - \text{B}$

- electron-rich atom or group
- high electronegativity (A) atom or group

**Halogen bonds (X-bonds)**

$\text{X} - \text{A}$

- electron-rich atom or group
- large, polarizable atom

**Determining the crystal structures of steroids**

Cocrystallization with brominated or iodinated phenols is a classical method to enable structural characterization of steroids.

The most important piece of information gained is the configuration of chiral centers.


**Cocrystallization in modern characterization**

Today, cocrystallization is used for cases when structural characterization is not possible because:

1) The substrate does not readily form crystals
2) The substrate is too unstable in its pure solid form
Resolving problems of structural characterization

The co-crystallization of a ladderane containing four chiral centers is an example of the case 1.

The use of halogen bonding interactions

Case 2 (cocrystallization to isolate otherwise unstable molecules) is illustrated by the recent cocrystallization of a halogenated cumulene:

Characterization of single-component solids

The occurrence of different crystal structures for the same chemical (and molecular) composition is known as polymorphism.

Polymorph characterization is traditionally out of the scope of organic synthesis – "all chemistry ends with crystallization"

However, further applications and processing require the full understanding not only of molecular structure, but also of crystal structure!

Frequently we cannot get single crystals (e.g. if we have a product from grinding experiments or just a compound that will not give good crystals)
Characterization of polymorphic purity of a solid sample (composition in terms of polymorphs) is easily achieved through X-ray diffraction on a powder.

Powder X-ray diffraction (PXRD) relies on the same principle as single crystal diffraction, but the sample is a collection of randomly oriented crystallites. X-ray diffraction results in rings of diffraction around the sample. The X-ray detector moves through each ring, providing a diffractogram.

The two-dimensional information obtainable using single crystal X-ray diffraction is condensed into one dimension using PXRD. Significant overlap of peaks makes it difficult to extract structural information – there are two approaches:

1) Extracting individual intensities, followed by structure solution and refinement
2) Building a model structure and fitting the experimental and calculated diffraction patterns.

Structures of many simple molecules are not known: 

Identification of polymorphs and amorphous phases using PXRD

The lack of order in an amorphous phase makes it "invisible" to PXRD.

Note the use of the simulated i.e. expected PXRD pattern.

Identification of polymorphs by diffraction "fingerprinting"

"ROY"

three possible degrees of rotational freedom.

Why is polymorphism important?

Polymorphism = the observation of different crystal structures (forms) for the same molecule i.e. different three-dimensional arrangements in the crystal.

We can compare diamond and graphite – both pure carbon but different crystal structures and properties (allotropes).
**Patenting – not the molecule but the crystal!**

Drugs of this type are typically used to treat both duodenal and gastric ulcers. At one time Zantac was earning $2 billion per annum.

**GSK (UK) vs. Novopharm (Canada)**

Major legal dispute over patents: not because of pharmacological reasons or the identity of the molecule — but because of the structure of the crystals formed — **polymorphic form!**

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**Conformational polymorphism**

The two forms of Ranitidine HCl are **conformational polymorphs**

![Form 1](image1)  ![Form 2](image2)

Polymorphism is **helped** by the flexibility of the molecule - an illustration of the problem that affects most modern high molecular weight drugs!

Balance between intra and intermolecular forces.
A more “household” example

Example of paracetamol: 4-(acetylamino)phenol
Two established polymorphs: 1 and 2
Hydrogen-bonding patterns are very similar in both

Compaction and making tablets

Form 1 contains corrugated layers, that are not easily compressed as flat layers of form 2.

Molecular assembly via intermolecular bonds

Molecules within the crystal join through these non-covalent interactions to form molecular assemblies: supermolecules
Lehn: “Supermolecules are to molecules and the intermolecular bond as molecules are to atoms and the covalent bond.”
Considering a crystal as a product of supramolecular synthesis

During crystallisation of an organic solid, patterns of intermolecular interactions are established, representing "an extension of synthesis". Indeed we will use the term "synthons". Analysis of crystal structures reveals that some patterns are frequently encountered:

These robust patterns of interactions are "supramolecular synthons". So we can say: supramolecular synthesis through (co)crystallisation.

Supramolecular synthons can be utilised to design a supramolecular synthesis, like traditional synthons of organic chemistry.

So we can say: supramolecular synthesis through (co)crystallisation.

The product of such a supramolecular synthesis is a two- (or more) component crystal: a cocrystal.

Explaining reactivity through solid-state analysis

Crystal structure determination is an excellent means to explain reactions that happen in solids. Classical example is [2+2] photodimerization of C=C double bonds in olefins (alkenes): the first study was performed on cinnamic acid.

Topochemical postulates: 
1) Olefin groups must be parallel 
2) d \leq 4.2 \text{ Å}
Stereochemistry of the cinnamic acid dimer is controlled by the arrangement of molecules in the reacting crystal:

- α-cinnamic acid
- β-cinnamic acid
- γ-cinnamic acid

Explaining reactivity

The topochemical postulates learned from studies of solid-state [2+2] photodimerizations have been put to use in the syntheses of cyclophanes and ladderanes:

Expected products are unusual strained molecules composed of fused cyclobutane rings: ladderanes.
Explaining reactivity

Both strained frameworks are obtained in a 100% yield!

Single-crystal-to-single-crystal transformations

A single-crystal-to-single-crystal (SCSC) is a homogeneous topotactic reaction:

i) The lattice of a solid product shows one or a small number of crystallographically equivalent, definite orientations relative to the lattice of the parent crystal

ii) The reaction proceeds throughout the bulk of the reactant

Technological applications

(holographic memories; crystalline polymers)

In situ study of chemical reactions

(X-ray single crystal diffraction)

SCSC photodimerization

Benzylbenzylidenecyclopentanone (BBCP)

Note similarity to cinnamic acid
Monitoring reaction course

large structural changes - the crystal eventually cracks

[2+2] photodimerization of cinnamic acid: normally not SCSC!

\[ \text{α-Cinnamic acid} \rightarrow \text{Truxinic acid} \]

Crystal decomposition is a result of rapid product buildup near the surface of the crystal because of strong and non-uniform absorption.

Mismatch between product and reactant size and shape leads to the "precipitation" of product crystallites: polycrystalline or amorphous material results.

SCSC reactivity obtained by using radiation with weaker absorption: "tail-end irradiation method"

Tail-end absorption wavelengths penetrate uniformly in the crystal, enabling a homogeneous reaction.

Thus, [2+2] photodimerisation of α-cinnamic acid can be accomplished in SCSC manner.
Monitoring other reaction mechanisms

Slow diffusion of a small molecule into an open structure (porous) host containing a bulky (therefore locked in) complementary reactant is a technique that allows in situ monitoring of structural transformations of traditional organic synthesis.

The technique is being promoted as the use of "self-assembled molecular flasks"

Most important requirement: ensure the explored system remains a single crystal throughout

In situ observation of the transformation of an amine into an imine

Energy profile for the aldimine condensation

The reaction involves an elusive hemiaminal intermediate.

Direct observation of an unstable reaction intermediate by X-ray diffraction and structure determination.
Coordination polymers

A rapidly developing family of materials are based on combining inorganic and organic groups.

In general, the inorganic fragment provides structural directionality and physicochemical properties that are specific for metals: colour, magnetism, redox behaviour, luminescence (especially with rare earth - lanthanide - metals).

The organic fragment is a linker and can also provide loci for numerous chemical and/or physical functionalities (hydrogen bonding, reactive sites, colour, luminescence, photovoltaic behaviour and many more).

Obviously this area requires good understanding of both organic and inorganic (coordination) chemistry! http://www.youtube.com/watch?v=iyooGndaXvY

Coordination polymers

This type of materials can be considered half-way between purely organic (molecular) and inorganic (e.g. oxides, zeolites) materials.

Therefore, coordination polymers are also known as hybrid inorganic-organic materials.

Constituents are held together through metal-ligand coordination bonds, with typical strength of \(150-200\) kJ mol\(^{-1}\).

This is stronger than most intermolecular hydrogen bonds (\(50-100\) kJ mol\(^{-1}\)), with two important consequences:

1) The formation of coordination polymers is reversible under mild synthetic conditions, giving rise to well-organized crystalline materials.

Coordination polymers

2) The resulting nets (frameworks) can persist even after minor "events".

Typical events include:
1) loss of included guest (solvent or a gas)
2) chemical reactions within or on the framework.

The bond strengths in hybrid materials are below those observed in similar inorganic materials, e.g. Si-O bonds in zeolites (ca \(400-450\) kJ mol\(^{-1}\)).

Hybrid materials tend to be less thermally stable and high-temperature applications are difficult to support.
Coordination polymers = porous frameworks (sometimes)

The ability to form open crystalline frameworks has led to the term **porous metal-organic frameworks (MOFs)**

What are the benefits?

Imagine a porous structure to which you could impart any particular architecture and any desired property.

For example, the guest and the framework could interact through weak forces (e.g., hydrogen bonding). This would lead to selectivity in inclusion of guests.

Types of hybrid inorganic-organic materials

The simplest - and also most blurred - division is into:

- coordination polymers
- metal-organic frameworks

This course is organized around this division.

Simple coordination polymers are non-porous at nanometer scale.

Metal-organic frameworks (MOFs) are open structures which may exhibit permanent porosity at the nanometer scale.

The difference is blurred and can be a source of confusion:

- porous MOFs have sometimes been addressed as porous coordination polymers (PCPs).
- porous MOFs can sometimes appear in non-porous interpenetrated forms - akin to different polymorphs.
Classification of hybrid inorganic-organic materials

The most general description of hybrid inorganic-organic structures is based on dimensionality of inorganic and metal-organic connectivity.

<table>
<thead>
<tr>
<th>Dimensionality of inorganic connectivity, ( n )</th>
<th>Dimensionality of metal-organic connectivity, ( n' )</th>
<th>Overall dimensionality, ( n + n' )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

These combined define the overall dimensionality of the structure.

Inorganic connectivity is defined by metal-metal or metal-oxygen-metal contacts.

Metal-organic connectivity is defined by metal-organic ligand-metal contacts.

An alternative classification

Another popular classification is based only on the term coordination polymers and deals with structural transformations and reversibility of guest loss.

This classification allows comparison with other materials:
- behaviour of most molecular (hydrogen-bonded) systems resembles 1st generation hosts
- behaviour of zeolites resembles 3rd generation ones.

Structural nomenclature of hybrid inorganic-organic materials 1

Example - a very simple coordination polymer (cationic):

Overall dimensionality - 1D
Inorganic dimensionality - 0 (no M-X-M fragments)
Metal-organic dimensionality - 1

Useful observation:
octahedrally coordinated ion + linear bridging ligand = infinite chains
Structural nomenclature of hybrid inorganic-organic materials

Overall dimensionality - 2D
Inorganic dimensionality - 1
(Co-Cl-Co chains fragments)
Metal-organic dimensionality - 1

Node and linker concept

We are mostly interested in structures in which inorganic dimensionality is 0.

The design of frameworks is easily understood using the concepts of "node" and "linker".

Nodes create multiple connecting sites and linkers are usually linear.

Design of three-dimensional coordination polymers

The design of three-dimensional structures is based on analyzing known nets - in a way similar to retrosynthetic analysis in organic chemistry.

For example, a diamondoid net is constructed by combining tetrahedral units.

A good tetrahedral ion is Cu⁺.

Combining Cu⁺ with a neutral organic ligand based on tetraphenylmethane gives a cationic diamond-like structure!
A simpler take on diamondoid structures is combining tetrahedral and linear elements! The metal takes on the role of a node, and the organic bit can be a simple linker.

It is tremendously important to use poorly-coordinating ligands: BF$_4^-$, PF$_6^-$ etc.

The node in a three-dimensional metal-organic structure (MOF) can also consist of more than one metal ion.

The most promising metal-organic framework materials are based on inorganic clusters - secondary building units.

Secondary building units (SBU) provide geometrical diversity and are larger than individual metal ions - this open up more room in the porous material.

Common types of SBUs used in MOF synthesis:
- Paddlewheel unit
- Carboxylate oligomers and polymers
- M$_4$O units
- IRMOFs (isoreticular MOFs)
- MILs (Materials Institute Lavoisier)
- a wide range of structures and SBUs
Possibilities in coordination polymer synthesis

A wide range of structures can be obtained by combining different rigid nodes and linkers.

Different topologies can arise from the same combinations of building blocks.

This argument can also be applied to zeolites:


Inverted metal-organic frameworks (IMOFs)

In this take on the design of open metal-organic structures, the node and the linker exchange places.

The node is now an organic molecule, and the linker is a metal-organic complex with (in the simplest cases) linear connectivity.

Coordination frameworks are isoreticular

The design of coordination polymers and metal-organic frameworks depends on the isoreticular nature of the structure: the ability to form an identical net (framework, lat. reticulum) regardless of the size or substitution pattern of our building blocks.

Design of open (and porous) frameworks from scratch is still not possible - discovery is very important.

Isoreticularity was first demonstrated in the IRMOF family.

Material also known as MOF-5.
Isoreticular nature of IRMOF materials

Modifications to the linker bring about unusual physical properties

Interpenetration of open frameworks (IRMOFs)

Two or more identical frameworks can become mechanically locked (or interwoven) - result can be a material that is based on an open framework but is not porous!

Increasing the length of the linker opens up space and increases the chances of interpenetration!

Possible solutions:
1) make your linkers simultaneously thicker
2) conduct reactions in the presence of large guest molecules

Increasing the length of the linker opens up space and increases the chances of interpenetration!
The organic component allows introducing different modes of functional behaviour into metal-organic materials. μ-acetato bridges can be used to arrange metal ions at ca. 3.5 Å distances. An option already known to us is photoactivity: [2+2] photodimerisation leading to interesting new molecules. Bonding of potentially photoactive linkers to such nodes could lead to desired reactivity.

There are two types of acetate ligands in this system: bridging and terminal. The terminal groups are not very important for arranging the metal ions and could perhaps be exchanged to provide a wider range of materials.

Photoactive coordination polymers exhibiting SCSC reactivity

In a single-crystal-to-single-crystal (SCSC) reaction, the crystal of the reactant does not fall apart due to internal strains - it simply transforms into a crystal of the product. Replacing the terminal acetates with trifluoroacetates leads to a material with SCSC reactivity.

One answer is that the weak forces between molecules have changed, making the crystal more robust. This illustrates the modularity of coordination polymers - the ability to fine-tune individual components and change the physicochemical behaviour of the material.
Practical use of metal-organic frameworks (MOFs)

MOFs are generally expected to involve an open structure with permanent porosity.

**Primary function** is for molecular storage.

The most interesting task is hydrogen storage, this is a difficult task and further applications have now come to focus on acetylene/methane/fuel gas storage and storage of CO₂.

**Required loading limit:**
A functional storage device based on H₂ should contain at least 6.5% by weight of hydrogen. When the overall design of the device is taken into account, this should be at least around 8-9%.

**Three principal directions of research:**
1) Increase the capacity for hydrogen/other gases by making larger pores.
2) Increase capacity for hydrogen/other gases by enhancing gas-framework binding.
3) Make your MOF lighter!

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**MOF-5**

MOF-5 is the archetypal metal-organic framework material.

The first MOF that was industrially manufactured on kilogram scale.


MOF-5

Surface area: 2500-3000 m² g⁻¹
Hydrogen storage capacity: 4.5% by weight at 77 K, 1% by weight at R.T./20 bar
for comparison, active carbon is between 0.1-0.3%

Hydrogen absorption takes place largely on the surface of the organic ligand

Stability problems of MOF-5

Unfortunately, the material is highly sensitive to air moisture
In a model simulation, the water molecule readily displaces the acetate bridge, suggesting a potential mechanism of MOF sensitivity

At or near room temperature, even 1 mol% of water in the surrounding atmosphere damages the structure

Hydration stability of known MOF types
Zeolitic imidazolate frameworks (ZIFs)

The geometry of the imidazole-metal-imidazole fragment resembles the geometry of the O-Si-O fragment in SiO2 and zeolites.

Larger building blocks provide larger pore sizes.

Post-synthetic modification (PSM) of metal-organic frameworks

A very recent trend in MOF materials chemistry.

"Crystal as a molecule" concept.
PSM of frameworks based on Zn₄O units

PSM using long aliphatic chains can impart a hydrophobic (water-repelling) character to MOFs

Stabilising MOF-5 structures using PSM

The extent of (super)hydrophobic behaviour is controlled by the extent of the PSM reaction

Ultra light zeolitic imidazolate frameworks

Following a net-based strategy, tetrahedral Zn²⁺ nodes in ZIFs can be replaced by alternative terahedral species
A combination of Li⁺ and B³⁺ effectively replaces two Zn²⁺ in terms of shape and charge: a relative atomic weight of 18 (7+11) instead of 130 (2x65)

Leads to materials with densities under 1 g cm⁻³

Another way to increase the gravimetric density of hydrogen storage!