Small Molecule Crystallization

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Overview

Ø Basic Crystal Science
Ø Crystallization Process
Ø Our Research Projects
Ø Lab Tour
What is a Crystal?

New York

Crystal

London

Amorphous
Definition of Crystal

Ø Solid with short and long range order with atoms or molecules in a fixed lattice arrangement

Ø The distinction between a crystal and an amorphous solid is that between order and disorder over large distances

Ø Internal structure of crystals accessible by x-ray diffraction analysis
Crystal Structure

Unit cell parameters: $a$, $b$, $c$, $\alpha$, $\beta$, $\gamma$. 

lattice point

unit cell
# Seven Crystal Systems

<table>
<thead>
<tr>
<th>Crystal system</th>
<th>Unit cell dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubic</td>
<td>( \angle = 90^\circ; a = b = c )</td>
</tr>
<tr>
<td>Tetragonal</td>
<td>( \angle = 90^\circ; a = b \neq c )</td>
</tr>
<tr>
<td>Orthorhombic</td>
<td>( \angle = 90^\circ; a \neq b \neq c )</td>
</tr>
<tr>
<td>Monoclinic</td>
<td>( \angle \neq 90^\circ; a \neq b \neq c )</td>
</tr>
<tr>
<td>Triclinic</td>
<td>( \neq \angle \neq 90^\circ; a \neq b \neq c )</td>
</tr>
<tr>
<td>Trigonal</td>
<td>( \angle = 90^\circ; a = b = c )</td>
</tr>
<tr>
<td>Hexagonal</td>
<td>( \angle = 90^\circ; \angle = 120^\circ; a = b = d \neq c )</td>
</tr>
</tbody>
</table>
Space Groups

Ø 230 space groups
Ø For organic molecules, statistics shows that 95% of all compounds crystallize out in these 16 space groups

• P21/c monoclinic
• P21 monoclinic
• P21/m monoclinic
• P2/c monoclinic
• C2/c monoclinic
• C2/m monoclinic
• Cc monoclinic
• C2 monoclinic
• P-1 triclinic
• P1 triclinic
• P212121 orthorhombic
• Pbca orthorhombic
• Pnma orthorhombic
• Pna21 orthorhombic
• Pbcn orthorhombic
• Pca21 orthorhombic
• P21212 orthorhombic
X-Ray Diffraction

Structure Determination
Ø Need good quality single crystal

Send to Crystallographer.
Ø They determine lattice type, parameters i.e. a, b, c, α, β, γ atom positions and space group
Ø Space groups relate crystal symmetry on an atomic scale to possible arrangement of atom which possess that symmetry.
Ø Given systems and space group you can calculate all possible arrangement of atoms which meet this
Types of Crystals

Ø Ionic – Charged ions held in place on lattice by electrostatic forces (NaCl)
Ø Covalent – Atoms connected by framework of covalent bonds (Diamond)
Ø Molecular Crystals – Usually organic, composed of discrete molecules held together by weak attractive forces (Urea)
Ø Metallic Crystals – Ordered arrays of identical cations (Copper)
Morphology and Habit

Ø Crystal morphology is defined as the general appearance of crystals described by the Miller indices of the faces that show and give the crystals their characteristic shape.

Ø Crystal habit means the general shape of a crystal as given by the relative length of the various major axes.

Ø Both morphology and habit depend on growth conditions and can vary under different process conditions.
Morphology and Habit

Same morphological form but different habit

Different morphological form but same habit
Crystal Size Distribution

Ø CSD: the most widely applied quality test of a crystalline product
Ø Many industrial processes demand a narrow range of particle size as this results in good filtering, drying and free-flow ability
## Sizing Method

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Size Range [μm]</th>
<th>Size Parameter</th>
<th>Solid Content Range [Vol %]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sieving</td>
<td>5 - 125000</td>
<td>Sieve aperture diameter $d_{sa}$ of a sphere that would just pass through the aperture</td>
<td>-</td>
</tr>
<tr>
<td>Microscopy</td>
<td>0.5 - 150</td>
<td>Projected area diameter $d_{pa}$ of a circle that has the same area as the projected image</td>
<td>-</td>
</tr>
<tr>
<td>Laser Diffraction</td>
<td>0.1 – 1000</td>
<td>Number/ volume size distribution</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Focus Beam Reflectance</td>
<td>1 - 1000</td>
<td>Chord Length distribution</td>
<td>-</td>
</tr>
<tr>
<td>Measurement (LASENTEC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasonic spectroscopy</td>
<td>0.01 - 1000</td>
<td>Number/ volume size distribution</td>
<td>&lt; 50</td>
</tr>
</tbody>
</table>

**On-lined sizing**
Polymorphism

Ø The phenomenon of a chemical species having more than one possible crystal form e.g. Carbon (graphite: top and pencil and diamond: bottom) whilst remaining chemically identical

Ø Different forms maybe significantly different in terms of both their structures and physical & chemical properties
5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile

“ROY”

6 Polymorph Forms

McCrone’s Law

‘Every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound.’

Types of Polymorphism

Packing Polymorphism
Ø Packing and bonding arrangement of the structure in its different forms are significantly different

Conformational Polymorphism
Ø The existence of different conformers of the same molecule in different polymorphic modifications
Ø Low energy difference between various conformations

Pseudopolymorphism
Ø A new structure of a compound that is hydrated or solvated
Packing Polymorphism

Glycine (C\textsubscript{2}H\textsubscript{5}NO\textsubscript{2})

Conformational Polymorphism

Spiperone
($C_{23}H_{26}FN_3O_2$)

Form I

Form II

Polymorphic Properties

Packing Properties
Ø Molar volume, density, refractive index, conductivity, hygroscopicity

Thermodynamic Properties
Ø Melting and sublimation temperature, structural energy, Enthalpy, Heat capacity, Entropy, Free energy and chemical potential, Thermodynamic activity, Vapor pressure, Solubility

Kinetic Properties
Ø Dissolution rates, rates of solid state reactions, stability

Spectroscopic Properties

Surface Properties
Ø Surface free energy, interfacial tension, morphology

Mechanical Properties
Ø Hardness, tensile strength, compactability, handling, flow

Bioavailability
Characterization Methods

Crystallography: X-Ray Diffraction
Ø Single Crystal X-Ray Diffraction
Ø X-Ray Powder Diffraction

Morphology: Microscopy
Ø Polarizing Optical Microscopy
Ø Thermal Microscopy

Phase Transitions: Thermal Methods of Analysis
Ø Thermogravimetry
Ø Differential Thermal Analysis
Ø Differential Scanning Calorimetry

Molecular Motion: Vibrational Spectroscopy
Ø Infrared Absorption Spectroscopy
Ø Raman Spectroscopy

Chemical Environment: Nuclear Magnetic Resonance Spectrometry
Monotropic System

Ø One form is metastable relative to the other at all temperatures below the melting point
Ø Polymorphs are not interconvertible
Ø Solubility of the stable form is always lower than the metastable form
Monotropic System

L-glutamic acid $\text{C}_5\text{H}_9\text{NO}_4$
Enantiotropic System

- Polymorphic form dependent upon the temperature and pressure of the system
- Reversible transition point where relative thermodynamic stabilities change
- Transition point below melting point for any of the solid phase
L-Phenylalanine

Metastable form may exist for a long time;
Presence of the stable form results in solvent mediated phase transformation
Crystallization

Ø Formation of a crystalline phase from a parent phase, e.g. solution
Ø One of the oldest and most important unit operations, e.g. extracting salt crystals from sea water
Ø Over 90% of all pharmaceutical products contain drug substances
Crystallization Process

- Liquid Mixture
- Generation of Supersaturation: Driving force
  - Nucleation: Birth of Solid Phase
    - Ratio of Rate of Nucleation to Growth Controls Final Product
      - Crystal Habit, Crystal Purity
      - Size Distribution
  - Crystal Growth
    - Final Product
Definition of Supersaturation

\[ \Delta c = c - c^* \]

\[ S = \frac{c}{c^*} \]

\[ \sigma = \frac{\Delta c}{c^*} = S - 1 \]

\[ \Delta T = T^* - T_{cry} \]

C* : equilibrium concentration for a given temperature

C : solution concentration; T*: saturated temperature;

Tcry: Crystallization temperature
# Generation of Supersaturation

<table>
<thead>
<tr>
<th>Mode</th>
<th>Supersaturation generation method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling</td>
<td>Reduction in temperature</td>
</tr>
<tr>
<td>Evaporation</td>
<td>Lost of solvent</td>
</tr>
<tr>
<td>Dilution</td>
<td>Adding anti-solvent</td>
</tr>
<tr>
<td>Reaction</td>
<td>Generation of solute</td>
</tr>
<tr>
<td>Vacuum</td>
<td>Cooling, flashing evaporation</td>
</tr>
</tbody>
</table>
Ø Supersaturated zone:
Spontaneous nucleation is expected

Ø Metastable zone:
Spontaneous nucleation is impossible

Ø Stable zone:
Nucleation is impossible
Metastable Zone Width

Ø Metastable zone width (MSZW) is a critical parameter in the crystallisation process as it reveals the nucleation behaviour of the system.

Ø MSZW is a nucleation kinetic-limited parameter that is highly dependent on process conditions.

Ø Many factors may influence the value of MSZW, e.g. rate of cooling, agitation, the presence of foreign particles and impurities.
Effects of Cooling Rate & Agitation

- Ø MSZW decreases as stirrer speed increases.
- Ø MSZW widens at N>400rpm.
- Ø MSZW widens as cooling rate rises.

Cooling crystallization of aqueous L-glutamic acid solutions.
Nucleation

Primary Nucleation:
- Nucleation in crystal free system

Homogeneous:
- Spontaneous

Secondary Nucleation:
- Induced by the presence of crystals

Heterogeneous:
- Induced by the presence of foreign particles
Homogenous Nucleation

Gibbs Free Energy Change

\[ \Delta G = \Delta G_s + \Delta G_v \]

\[ \Delta G_s = 4\pi r^2 \gamma \]
\[ \Delta G_v = -\left(\frac{4\pi r^3}{3v_m}\right)RT \ln(1 + S_B) \]

- \( r \): radius of cluster
- \( v_m \): specific volume of solute molecules
- \( S_B \): supersaturation of the solution
- \( \gamma \): solid-liquid interfacial tension
Free Energy Diagram

\[ \Delta G_s \]

Free energy, \( \Delta G \)

\[ \Delta G_v \]

Size of nucleus, \( r \)

\[ \Delta G \]

Potential E

Metastable

Unstable

Stable

Displacement

Nucleus

Embryos

Growing crystals

Critical nucleus

Work of nuclei formation

Particle size

Work of bringing the body to the unstable state

\[ \Delta G_{\text{crit}} = \frac{4}{3} \pi \sigma r_c^2 \]
Heterogeneous Nucleation

Ø Heterogeneous nucleation: caused by dust, dirt, rough spots on walls, etc
Ø In industrial processes, homogeneous nucleation is rare
Ø Nucleation is usually heterogeneous and/or secondary
Heterogeneous Nucleation

Ø Lower energy barrier

\[ \Delta G_{het} = \phi \Delta G_{hom} \]

\[ \phi = \frac{(2 + \cos\theta)(1 - \cos\theta)^2}{4} \]

\[ 0 < \phi < 1 \]
Empirical Nucleation Model

\[ J = k_n \Delta c_{\text{max}}^m \]

\[ \Delta c_{\text{max}} = c - c^* \]

- \( J \): Nucleation rate
- \( k_n \): Nucleation rate constant
- \( m \): Nucleation order
- \( C^* \): Equilibrium concentration at nucleation temperature
- \( C \): Solution concentration
Secondary Nucleation

Ø Nucleation caused by interaction of existing crystals with vessel, impeller or by collisions
Ø The main source of nuclei in many industrial applications
Ø Empirical model: B secondary nucleation rate

\[ B = k_n N^i M_{T}^{j} \Delta C^{m} \]
Secondary Nucleation of Potassium Chloride
Secondary Nucleation

Ø Higher secondary nucleation rate using steel impeller

Ø Secondary nucleation rate increases as agitator speed rises
Crystal Growth

(1) Transport from bulk to boundary layer
(2) Diffusion to crystal surface
(3) Absorb onto surface and partial desolvation
(4) Diffusion to energetically favorable sites
(4*) Diffusion away
(5) Integration at a kink and total desolvation
Molecule Incorporation

Single molecule incorporation on flat areas of a crystal face is not energetically favorable.

Molecule is bonded both to a step face as well as to the surface.

Most energetically favorable: three sides of molecular cube are bonded (kink site).

Surface Structure of a Growing Crystal
Crystal Growth Theories

Mononuclear Model

Polynuclear Model

Birth and Spread Model
BCF (Burton Cabrera Frank) Theory

Ø Dislocations in the crystal are the source of new steps (dislocations are a certain type of irregularity in the structure of the crystal lattice)

Ø Screw dislocation provides a way for the steps to grow continuously.

Spiral Growth from a Screw Dislocation
Empirical Growth Model

Mass Deposition Rate

Overall Linear Growth Rate

\[ R_G = \frac{1}{A_T} \frac{dm}{dt} = k_G \Delta c^g \]

\[ G = \frac{dL}{dt} \quad R_G = 3^{\frac{\alpha}{\beta}} \rho G \]

\( g \): Growth order is generally between 0 and 2.5, most commonly equal to 1;

\( k_G \): Overall rate constant, depends on temperature, crystal size, hydrodynamics and presence of impurities;

\( A_T \): Total surface area of the crystals

\( m \): Mass of the crystals; \( L \): Mean crystal size;

\( \alpha, \beta \): Volume and area shape factors; \( \rho \): Crystal density
**Particle Engineering**

**Physicochemical**
- Chemical purity
- Crystal Habit
- Crystal Structure (Polymorphism/hydrate/imperfection)
- Thermodynamic properties

**Physicotechnical**
- Mechanical properties (compressibility)
- Packing & flowability

**Particulate Properties**
- Crystal size, shape & surface

“Designer” Particles

**Bioavailability (solubility)**
- Chemical and physical stability
Seeding Technology

Objectives:
Ø Design the crystallization process to achieve a certain final product size using seeds
Ø By seeding the preferable polymorph form, obtain desired crystal morphology and polymorph or pseudo-polymorph
**Approach**

- **MultiMax reactor system**
  - 4x50ml scale
  - Temperature
  - Stirring rate
  - Dosing rate

- **PXRD**
  - Polymorphic form

- **BET**
  - Particle surface area

- **Lasentec FBRM**
  - In-situ particle sizing
Model

\[ \frac{dn(L,t)}{dt} + G \frac{\partial n(L,t)}{\partial L} = B_{\text{nuc}} \delta (L_i - L_0) \]

\[ G(T) = k_g (T) \Delta c^g (T) = \frac{dL}{dt} \]

\[ B_{\text{nuc}} = k_N N^a M_{\text{tol}}^b \Delta c^c \]

\[ \frac{d\Delta c}{dt} = - \frac{dc^*}{dT} \cdot \frac{dT}{dt} - N_G - N_{\text{nuc}} \]

\[ c^* (T) = a_1 T^2 + a_2 T + a_3 \]
Seed properties: size, shape, mass, surface

Nucleation and crystal growth kinetic parameters

Measured final crystal size distribution

Population Balance Model

Simulated final crystal size distribution & yield

Optimization & design

Verification
What do we do?

Ø Crystallization process development and optimization
Ø Nonphotochemical laser-induced nucleation of small molecules and proteins
Ø Template-directed nucleation and growth of molecular crystals
Ø Electrodynamically levitating single solution droplet to study the activity of supersaturated small molecule and protein solutions
Questions?