Polymorphism

Polymorphism

It is the phenomenon in which the same chemical substance exhibits different internal crystal packing arrangements.

Polymorphism is an exclusively solid state phenomenon.

Polymorphs have distinct :

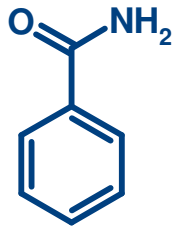
(i)Crystal structures (mutual arrangements of molecules, atoms or ions).

(ii)Physical and chemical properties.

Polymorphs can often have: different morphologies, solubility, colour, melting or sublimation temperatures, densities, thermal or electrical conductivities and other physical properties.

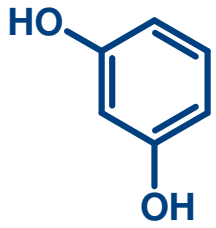
Early developments

Eilhardt Mitscherlich, in 1820, was the first to recognize polymorphism when he identified different crystal structures for **sodium arsenate phosphate**.

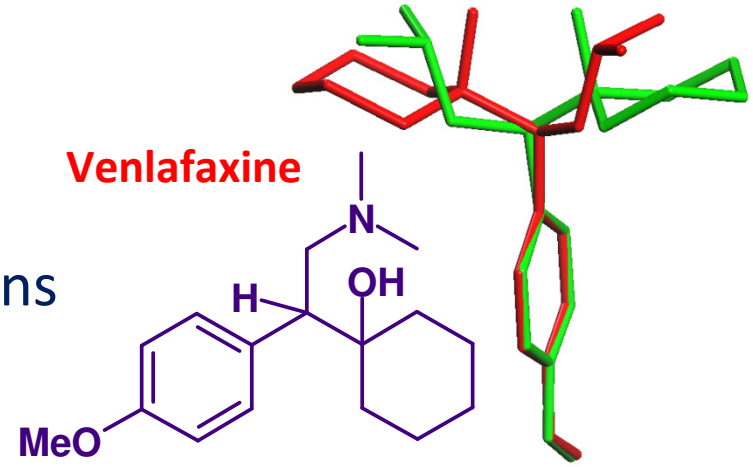


In 1832, **Friedrich Wöhler** and **Justus Liebig** discovered the first example of polymorphism in an organic solid, **benzamide**.

In 1938, **J. M. Robertson** and **Alfred Ubbelohde** used X-ray crystallography and determined the crystal structure of the dimorphs of **resorcinol (1,3-dihydroxybenzene)**.



Some types of polymorphism

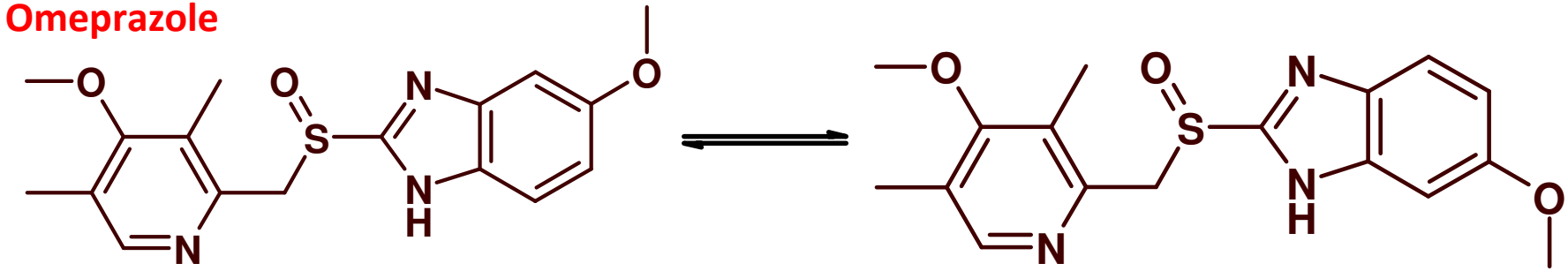


Conformational polymorphism

Each of the isolated crystal forms contains a different conformation of the same molecule

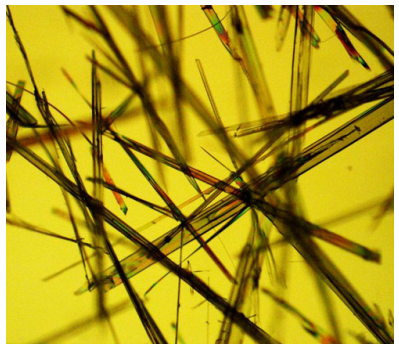
Tautomeric polymorphism

Crystal forms of tautomers are often considered to be polymorphs, because the tautomers generally equilibrate in solution at the temperature at which the solid forms are isolated.

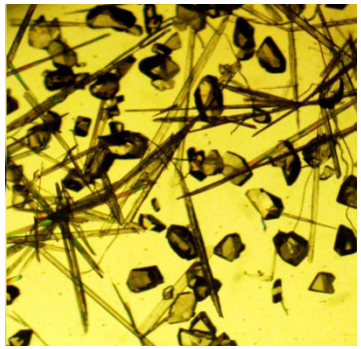


Some interesting phenomena

Concomitant polymorphs



(Form A)
1:1 $CHCl_3$:n-hexane
at 296K



Concomitant mixture of Forms A and B
1:1 $CHCl_3$:n-hexane
at 278 K

3-acetylcoumarin

Form B
glacial acetic acid
at 296K

Disappearing polymorphs

Crystal forms that fail to reappear after their initial isolation.

Pseudopolymorphs

Crystal forms in which an organic molecule is associated with differing amounts of solvent, say water

$M.H_2O$ $M.(H_2O)_{0.5}$ $M.(H_2O)_{1.5}$ $M.(H_2O)_2$

Occurrence of Polymorphism

Compounds that yield polymorphs readily.

Naphthazarin, pyrazine-2-carboxamide, thiourea and 2-thiobarbituric acid.

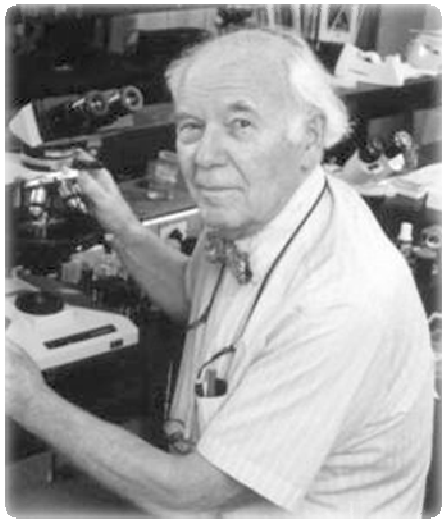
Compounds for which a second crystal form is not known

Benzoic acid, D-glucose, urea and naphthalene

Compounds that will yield new crystal forms provided a lot of experimentation is carried out.

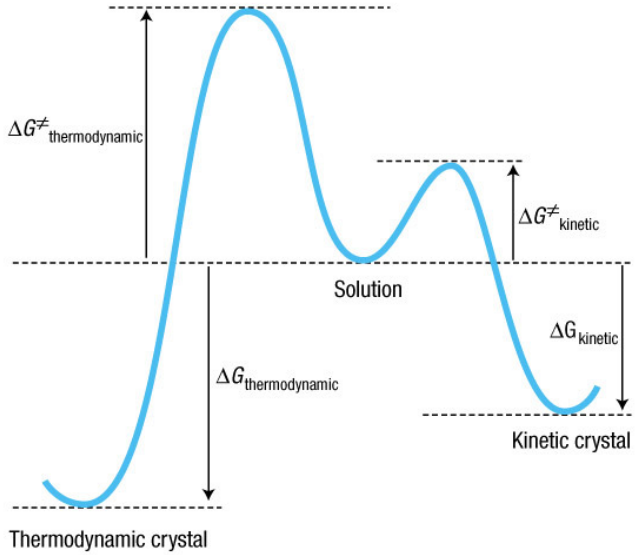
"every compound has different polymorphic forms and the number of forms known for a given compound is proportional to the time and energy spent in research on that compound."

Walter McCrone , in the 1970s



Thermodynamic and Kinetic factors

In a defined set of temperature and pressure conditions,
The most stable polymorph is called the **thermodynamic form** (**global energy minimum**)



The other polymorph or polymorphs are termed **kinetic or metastable forms** (**local minima**).

A metastable polymorph is thermodynamically unstable but it has a finite existence whose duration depends on its rate of transformation to more stable forms.

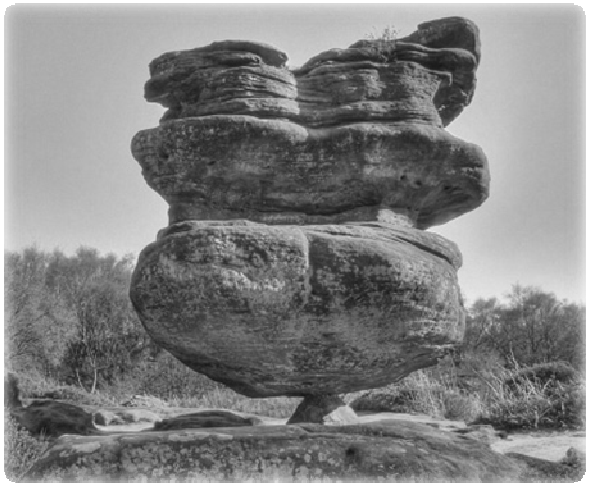
Thermodynamic versus Kinetic factors

When a compound exists in various solid state forms or polymorphs, two major issues need to be addressed:
(i) The relative stabilities and the transformations that can occur between the forms.
(ii) The time needed for the transformations to reach equilibrium.

Thermodynamics provides information about the first aspect (how far) and kinetics about the second (how fast).

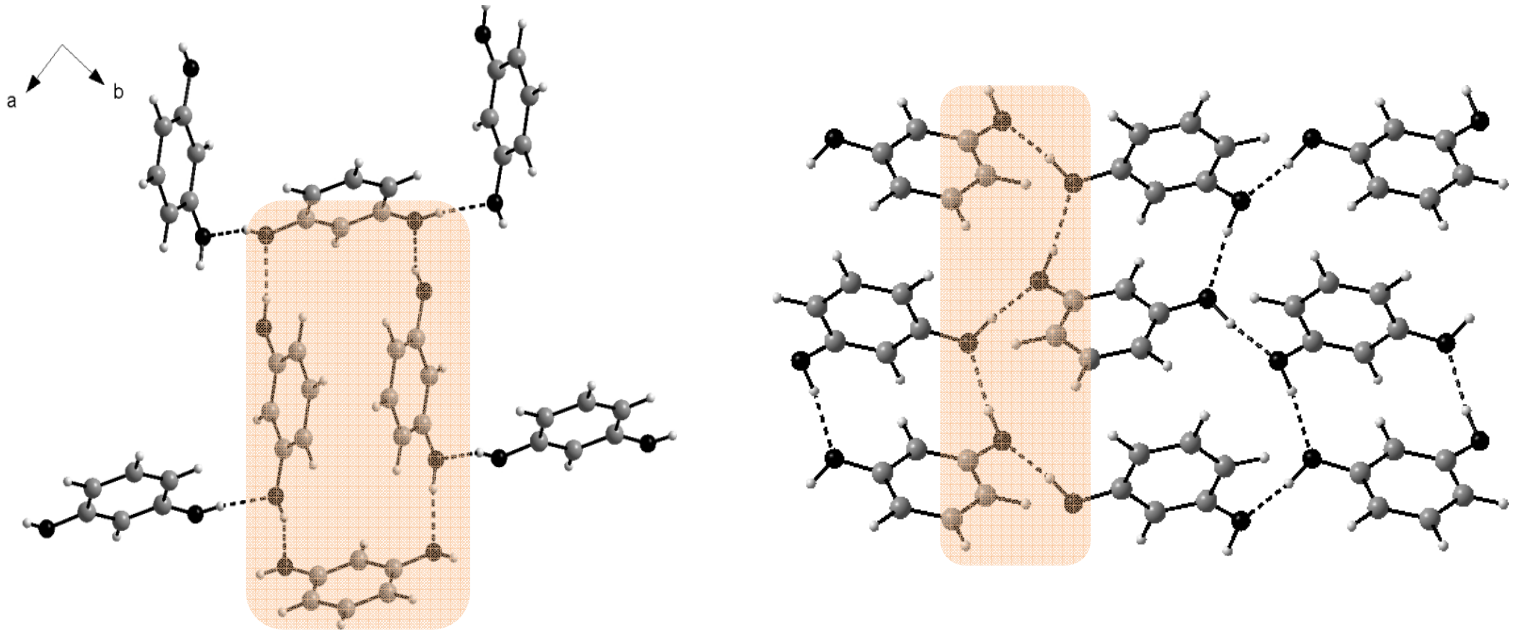
Ostwald's rule of stages

"when leaving an unstable state, a system does not seek out the most stable state, but rather the nearest metastable state which can be reached with least loss of free energy".



Polymorphism and Intermolecular Interactions

The same functional group and the same synthons
but differences in the overall packing.

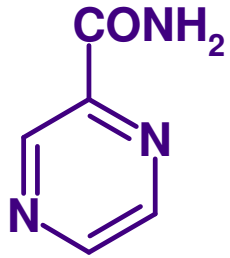


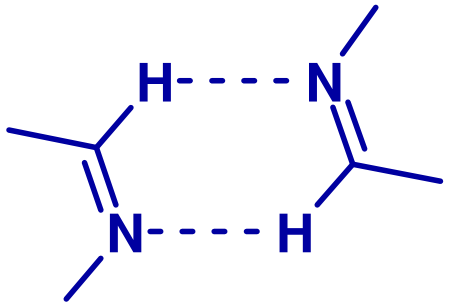
Resorcinol

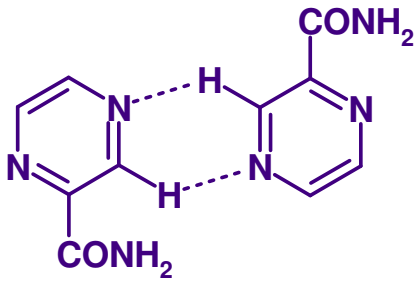
Polymorphism and Intermolecular Interactions

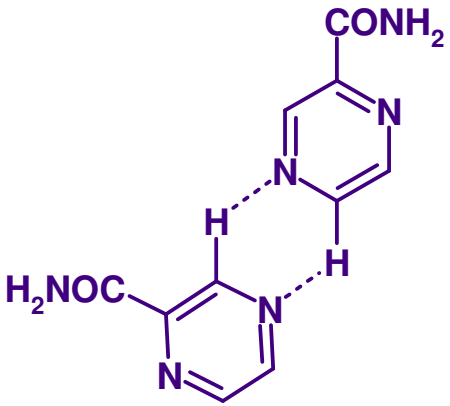
The same functional group and the same synthons but the multiple occurrences of these groups in different and distinctive molecular locations

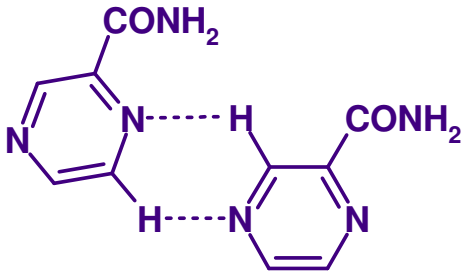
Pyrazinamide





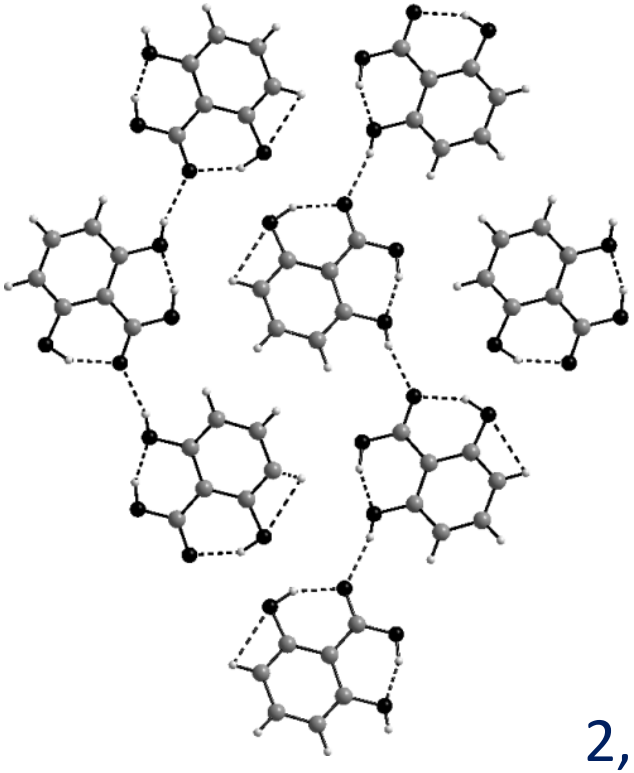


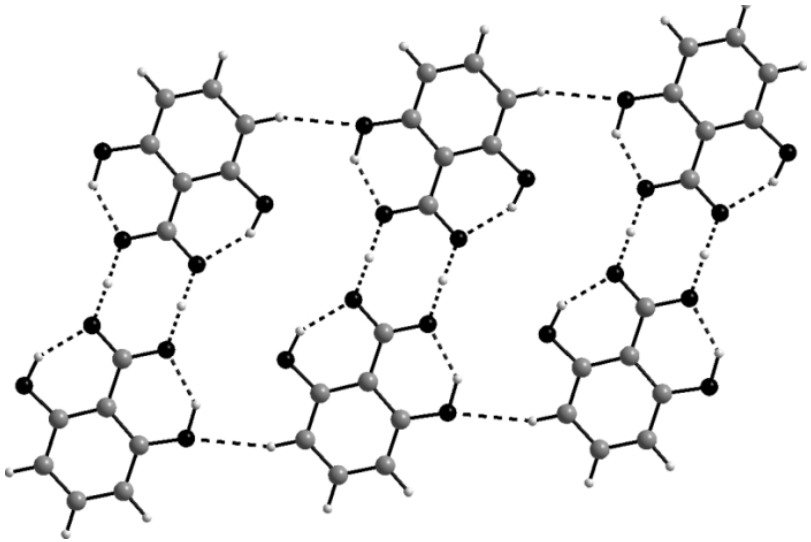




Polymorphism and Intermolecular Interactions

Different synthons and different packing arrangements.



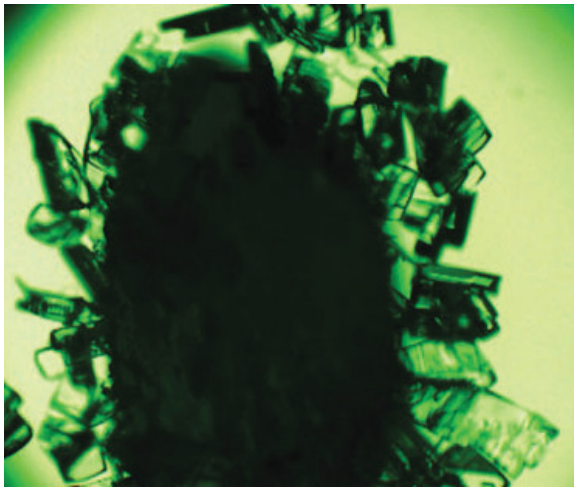


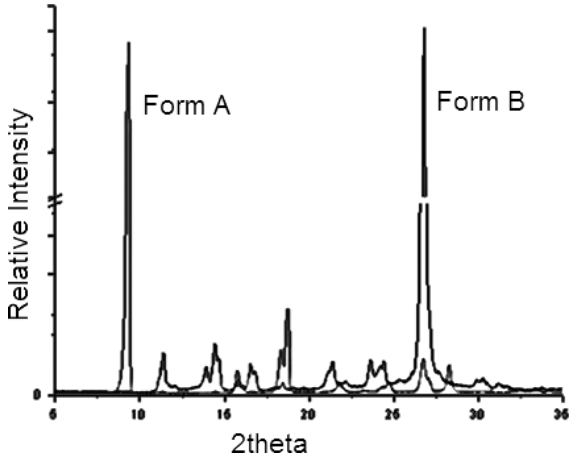
2,6-Dihydroxybenzoic acid

Methods of Polymorph Characterization

Hot Stage Microscopy

Sample is viewed using some form of optical microscopy while a hot stage is employed to control the temperature of the sample.





Powder X-ray Diffraction

Information obtained about:

- Phases present (peak positions)
- Phase concentration (peak areas) and
- Amorphous content (background hump)

Thermal Analysis

Differential Scanning Calorimetry, DSC

- Phase transition
- Glass transition
- Melting
- Crystallization
- Decomposition

The thermal events result in altering the total heat capacity of the system and this is observed as a peak

Thermogravimetry, TGA

Monitors weight change as a function of temperature

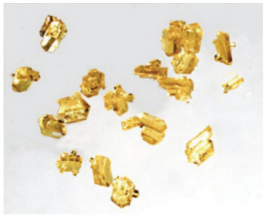
- Useful to characterize solvates, hydrates and host-guest compounds
- Quantifying stoichiometry
- Assessing stability

Properties of Polymorphs

Colour

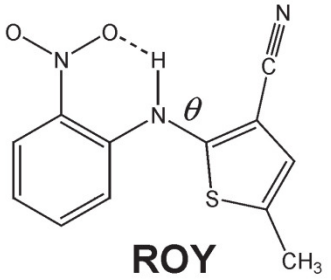
Polymorphs of ROY

(1) **R** P-1
mp 106.2 °C
θ = 21.7°

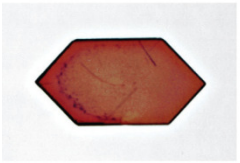


(2) **Y** $P2_1/c$
mp 109.8 °C
θ = 104.7°

(3) **ON** $P2_1/c$
mp 114.8 °C
θ = 52.6°

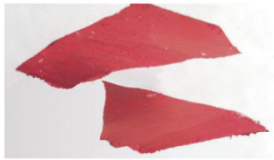


ROY



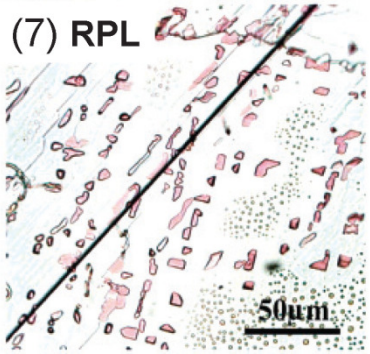
(4) **OP** $P2_1/c$
mp 112.7 °C
θ = 46.1°

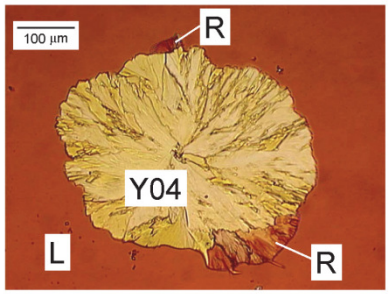
(5) **YN** P-1, mp 99 °C
θ = 104.1°



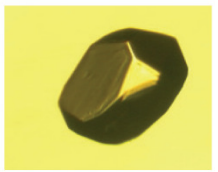
(6) **ORP** Pbca
mp 97 °C, θ = 39.4°

(7) **RPL**

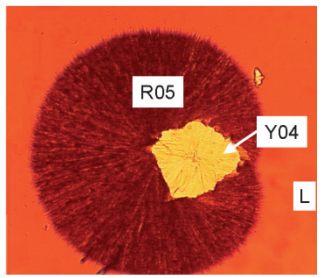




(8) **Y04**



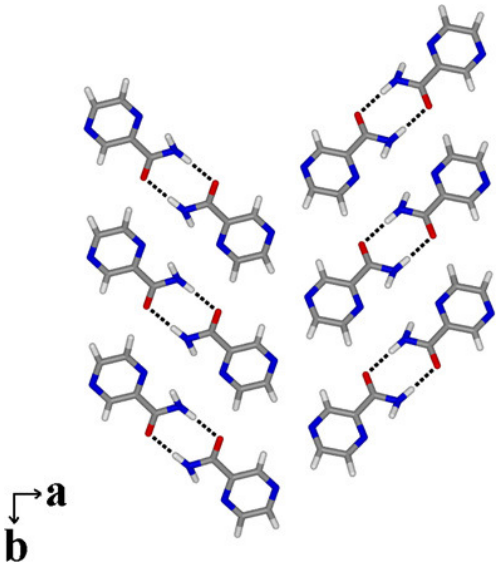
(9) **YT04** $P2_1/c$
mp 106.9 °C
θ = 112.8°

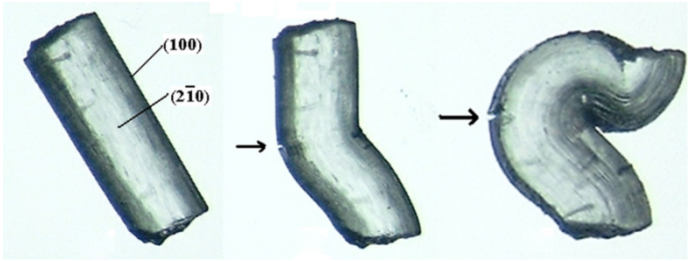


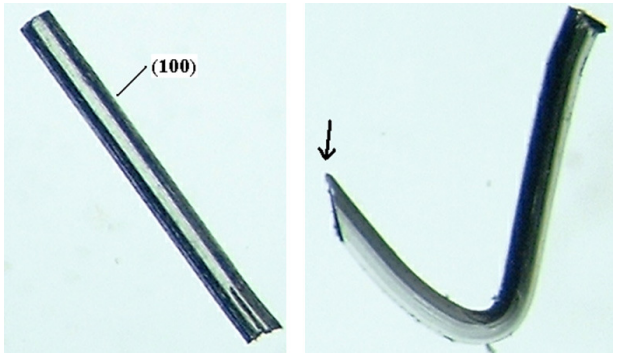
(10) **R05**

Properties of Polymorphs

Mechanical Properties

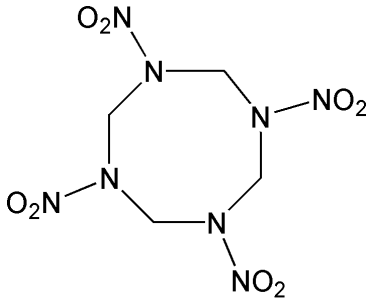


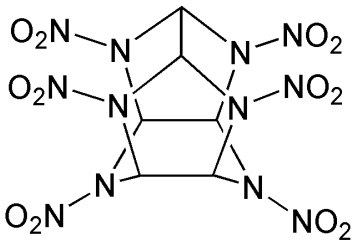




Chemical Reactivity

Polymorphism in Energetic Materials





Polymorphism and the Pharmaceutical Industry

Formulation and Activity: Differences in crystal morphology can affect processing properties like filtering, drying, flow, tableting, rate of dissolution, shelf life and bioavailability.

Legal issue: A mixture of polymorphs is chemically pure but it is not pure in a crystallographic sense because it consists of crystals with different crystal structures.

A drug has both chemical and crystallographic properties that may be independently entitled to patent protection.

Polymorphs and patents

US006894051B1

(12) **United States Patent**
Zimmermann et al.

(10) **Patent No.: US 6,894,051 B1**
(45) **Date of Patent: May 17, 2005**

(54) **CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIMIDINEAMINE DERIVATIVE, PROCESSES FOR ITS MANUFACTURE AND ITS USE**

(75) Inventors: **Jürg Zimmermann**, Basel (CH); **Bertrand Sutter**, Hésingue (FR); **Hans Michael Bürger**, Allschwil (CH)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 311 days.

(21) Appl. No.: **09/463,097**

(22) PCT Filed: **Jul. 16, 1998**

(86) PCT No.: **PCT/EP98/04427**

§ 371 (c)(1),
(2), (4) Date: **Jan. 18, 2000**

(87) PCT Pub. No.: **WO99/03854**

PCT Pub. Date: **Jan. 28, 1999**

(30) **Foreign Application Priority Data**

Jul. 18, 1997 (CH) 1764/97

(51) **Int. Cl.**[7] **A61K 31/506**; C07D 401/14
(52) **U.S. Cl.** **514/252.18**; 544/295
(58) **Field of Search** 544/295; 514/252.18

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Primary Examiner—Emily Bernhardt
(74) *Attorney, Agent, or Firm*—George R. Dohmann

(57) **ABSTRACT**

The invention relates to a new crystalline form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide of formula 1, which may be used for example for tumor therapy.

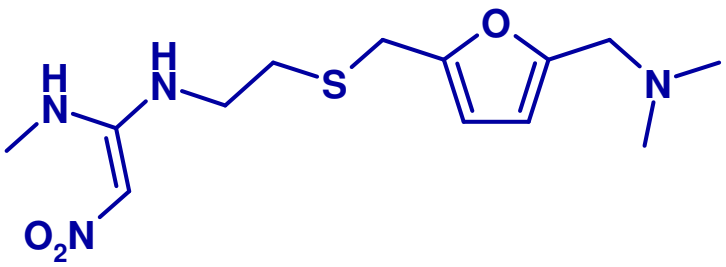
18 Claims, 2 Drawing Sheets

- Novelty
- Non-obviousness
- Utility

Case Studies from the Pharmaceutical Industry

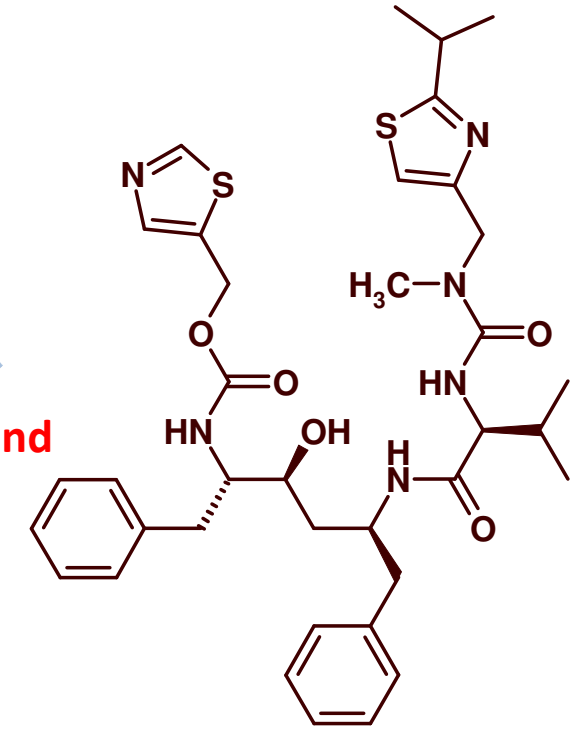
Ranitidine

Legal issue



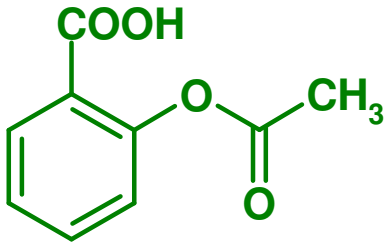
Ritonavir

Phase transformation and therapeutic issue



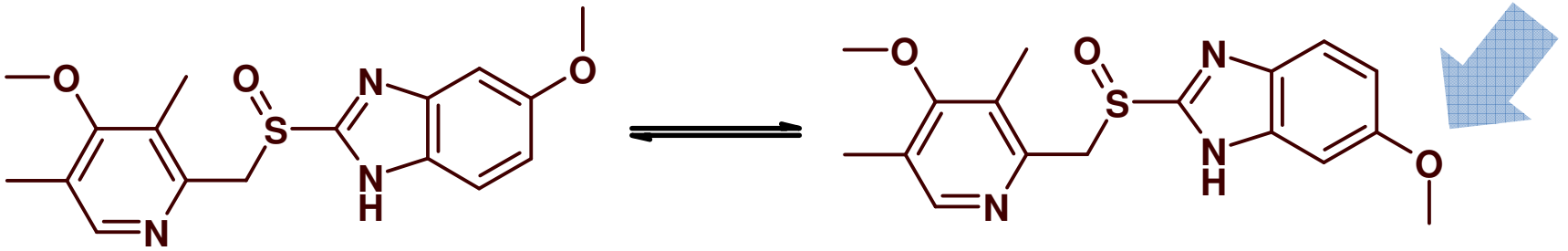
Aspirin

Intergrown crystal domains



Omeprazole

Tautomeric polymorphism



Points to be kept in mind:

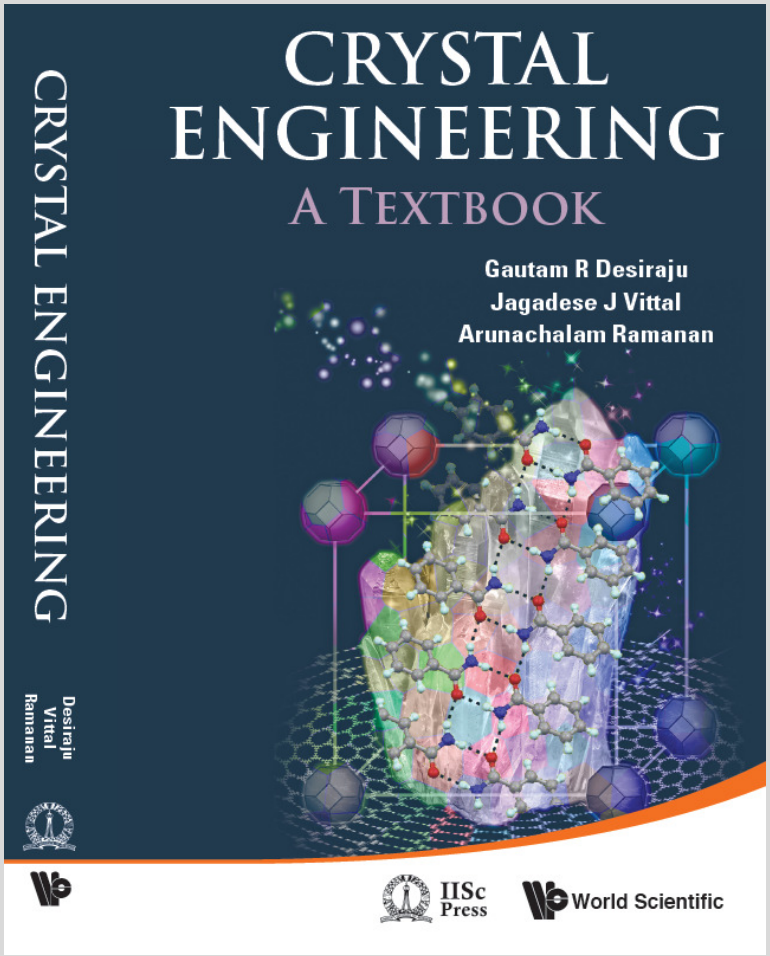
Polymorphs are different crystal forms of the same chemical compound. Polymorphism is a solid state phenomenon.

Polymorphs can exhibit different physical and chemical properties.

Competing intermolecular interactions result in dominance of kinetic factors during crystallization.

A trade-off between kinetics and thermodynamics can lead to polymorphism.

Polymorphism occurs frequently in organic solids and notably in drug molecules because they contain flexible functional groups capable of hydrogen bonding.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