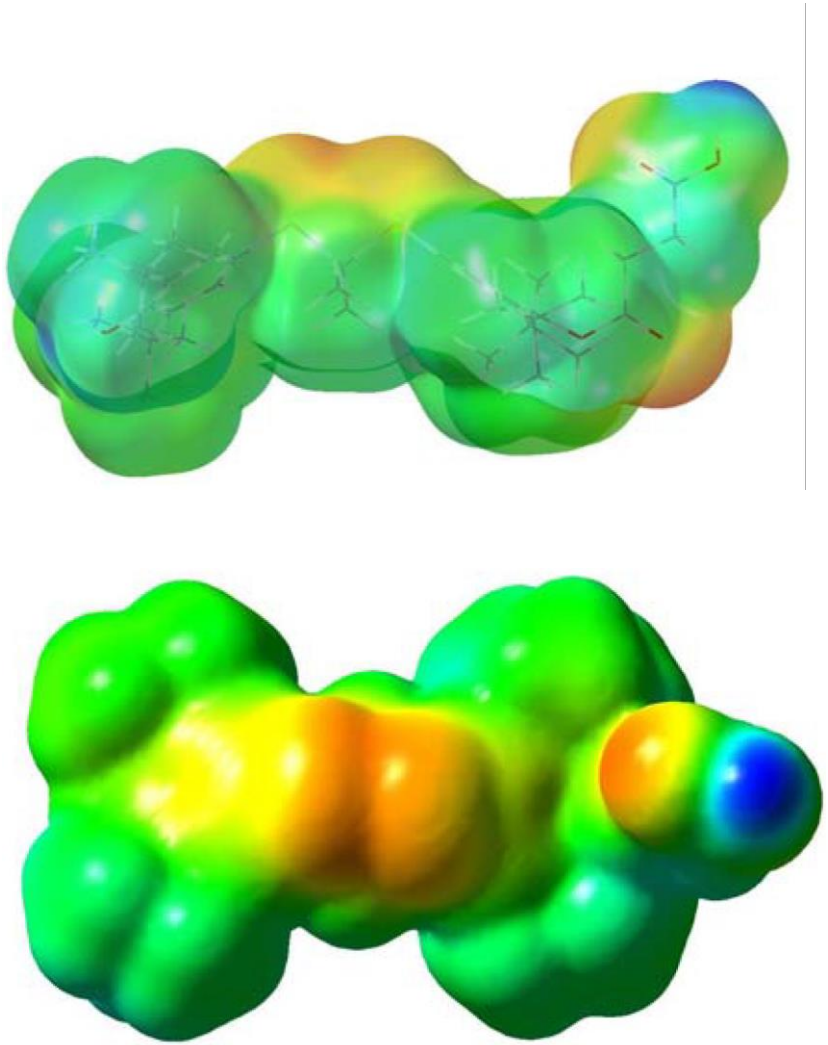
MUNI PHARM

Department of Natural Drugs

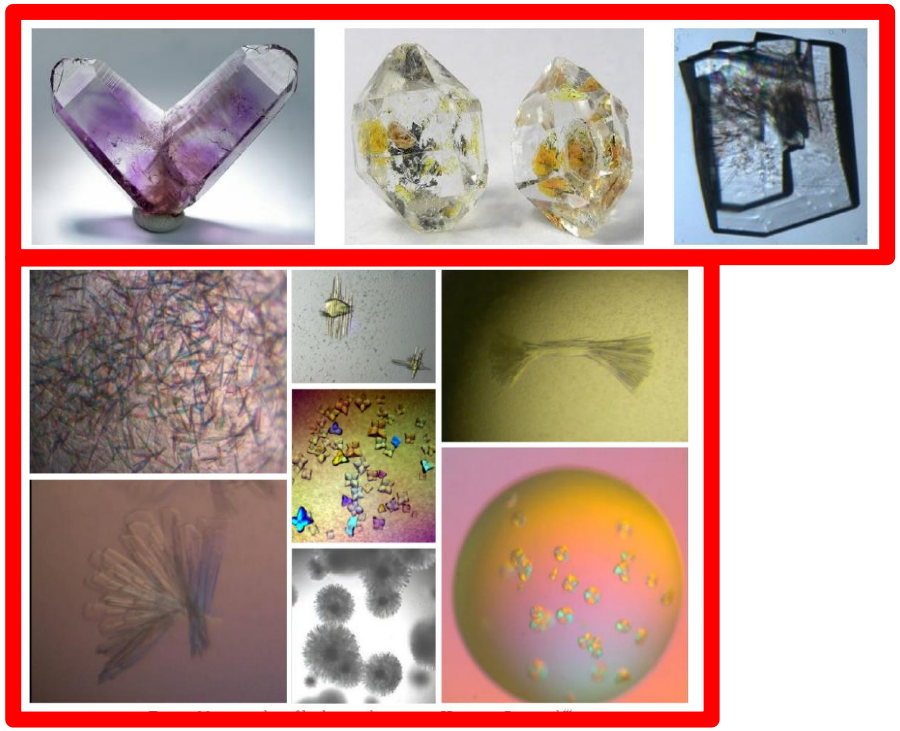
Supramolecular Pharmacy

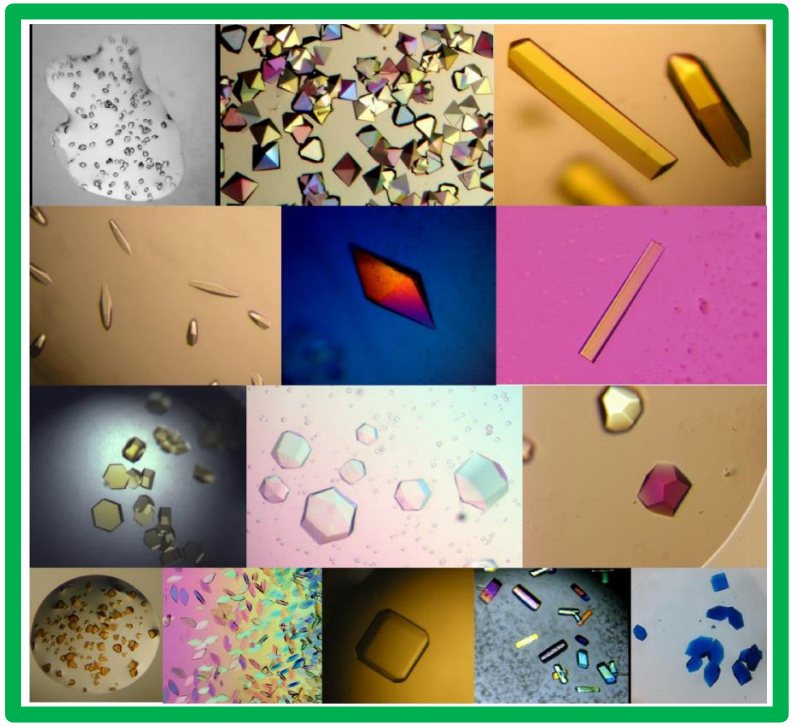
8. Polymorphism

Ondřej Jurček



Crystallization techniques and quality crystals

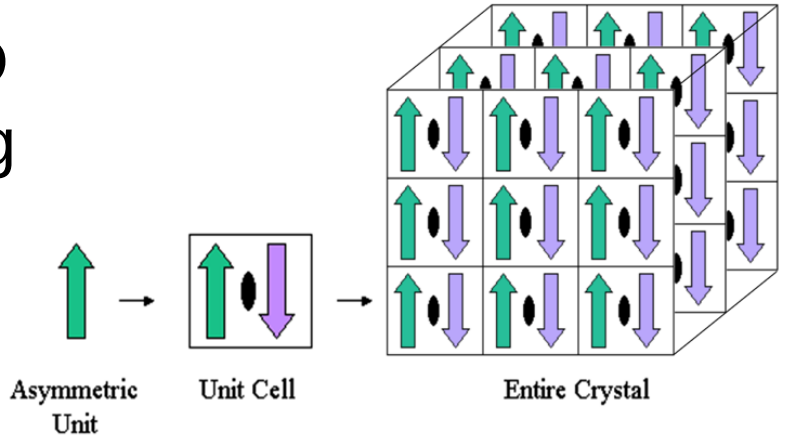


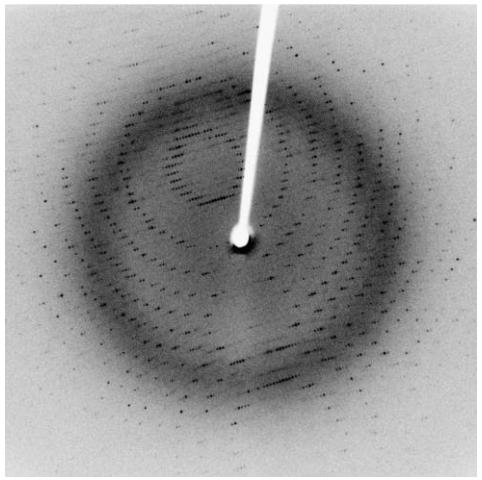


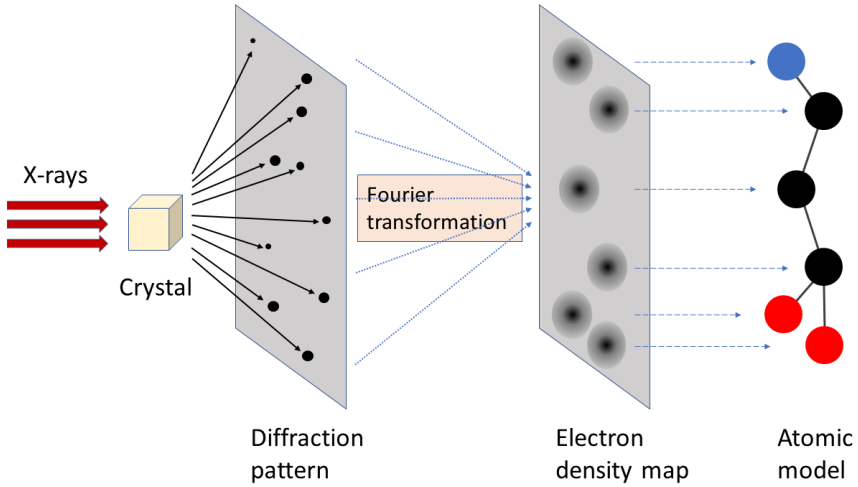
https://www.unifr.ch/chem/de/assets/public/PDFWordDocuments/Guide%20for%20crystallization.pdf

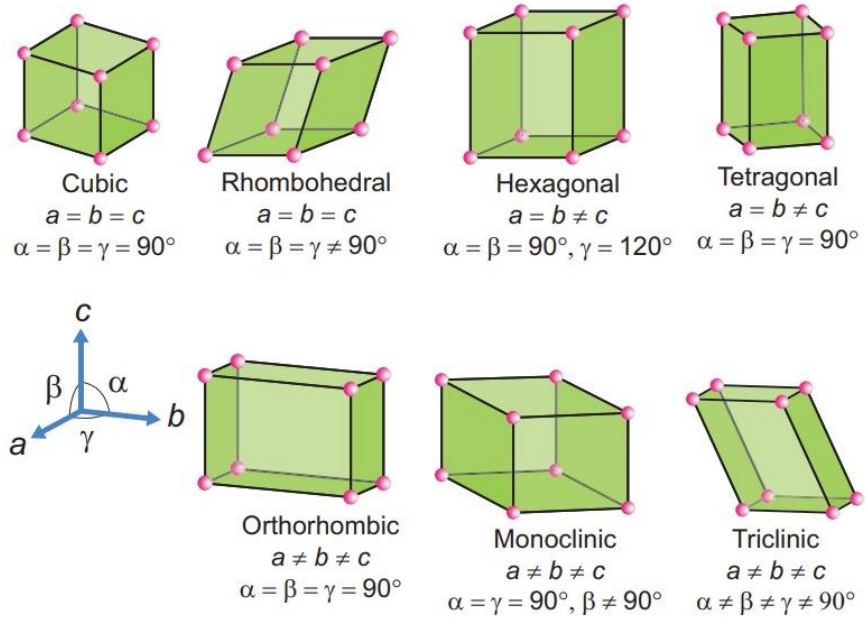
Crystal Structure Determination

- Unit cell determination, the smallest imaginary 3D unit in which the atoms are placed and multiplying this unit will build the whole macroscopic crystal
- Unit cell is defined by axes a, b, c, and angles α, β, γ – volume of unit cell
- Due to crystal symmetry seven types of primitive unit cells can exist





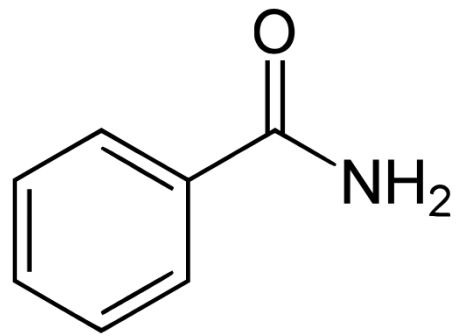




Book: Analytical methods in supramolecular chemistry, 2nd edition, Wiley, Kari Rissanen – chapter Crystallography and crystal engineering, book edited by C. Schalley

Polymorphism

- Polymorphism is the ability of a chemical compound to exist in more than one crystal packing arrangement in the solid state and hence exhibit different packing of the molecules and generally different crystal unit cell dimensions
- Formation of polymorphism can be influenced by solvent, temperature, humidity and the presence of seeds or additives, or crystallization method
- Solid crystals can also change form, sometime irreversibly, as a function of temperature, pressure, humidity changes or just time
- The first description of polymorphism was made in 1832 by Friedrich Wöhler (the father of organic synthesis) and Justus von Liebig when they examined crystallization of benzamide - it initially forms silky needle-shaped crystals on cooling an aqueous solution but over time these turn into rhombic crystals (there are three polymorphs in the end as found later)



Polymorph properties

- Different polymorphs exhibit different physical properties such as electrical or thermal conductivity, filtering, drying, flow, tableting, dissolution and processing characteristics and hence can have different bioavailability
- Ostwald's step rule conceived by Wilhelm Ostwald states that it is the least stable polymorph that crystallizes first with increasingly more stable forms crystallizing out in next steps

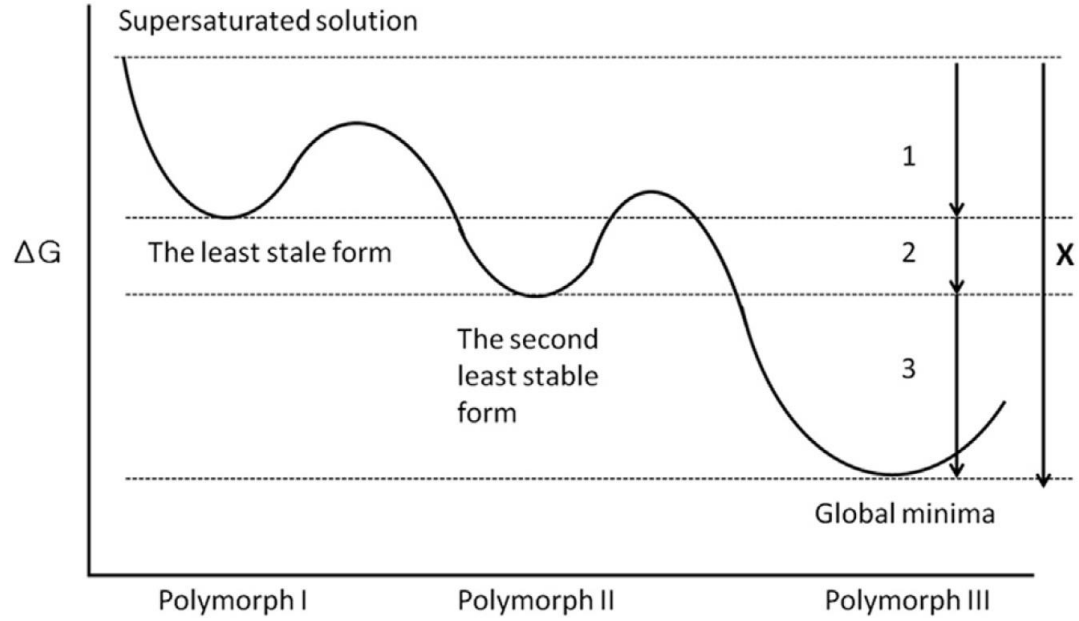
Thermodynamic properties
- Melting and sublimation temperatures, and vapor pressure
- Enthalpy, entropy, and heat capacity
- Free energy, chemical potential, and solubility

Packing properties
- Molar volume and density
- Conductivity, electrical and thermal
- Refractive index
- Particle morphology
- Hygroscopicity
- Color

Kinetic properties
- Dissolution rate
- Rates of solid state reaction
- Physical/chemical Stability
- Rate of nucleation/crystal growth

Surface properties
- Surface free energy
- Interfacial tensions
- Habit

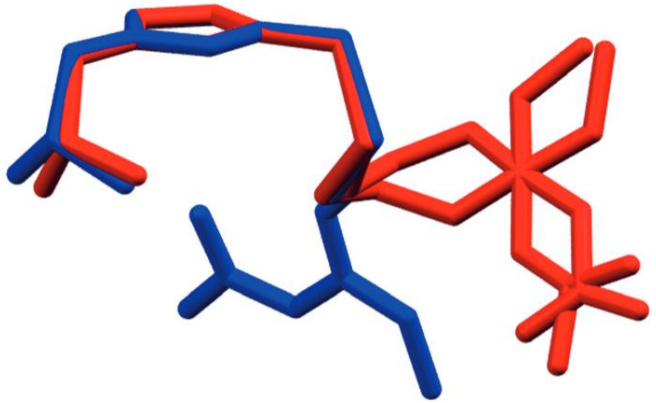
Mechanical properties
- Hardness
- Tensile strength
- Compactibility and tableting
- Handling, filtration, flow and blending
- Cleavage



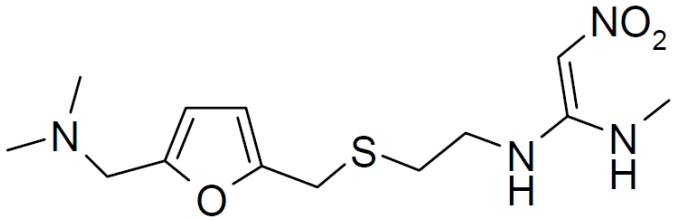
E. H. Lee *Asian J. Pharm. Sci.* 2014, 9, 163-175.

Polymorphism – Legal Issues

- Great impact in pharmacy - particular crystal form of API (polymorph) can be separately patented as distinct inventions next to patent of API development
- If particular polymorphs are patented after the original API patent then upon the expiry of the API patent, rival generic drug companies are prevented from marketing their own versions of the drug
- Conversely, if a rival discovers a new solid form of an API they can separately patent this new polymorph and secure exclusive rights over other companies when the API patent expires



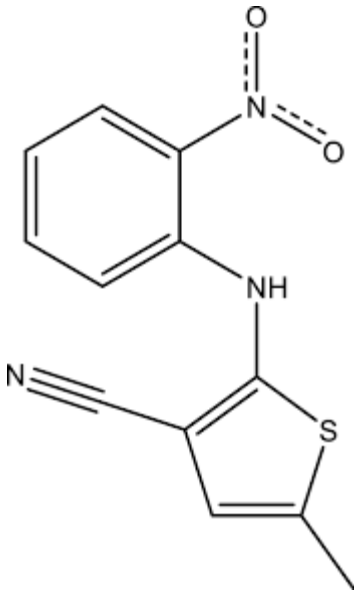
- Ranitidine hydrochloride (Zantac) a stomach acid production inhibitor was discovered 1976, came to market 1981
- GlaxoSmithKline defended its patent for the polymorph type II of ranitidine hydrochloride against competitors when the patent on polymorph type I had expired
- 2019-2020 – *N*-nitrosodimethylamine (NDMA) found as impurity, cancerogenic compound, withdrawal from market

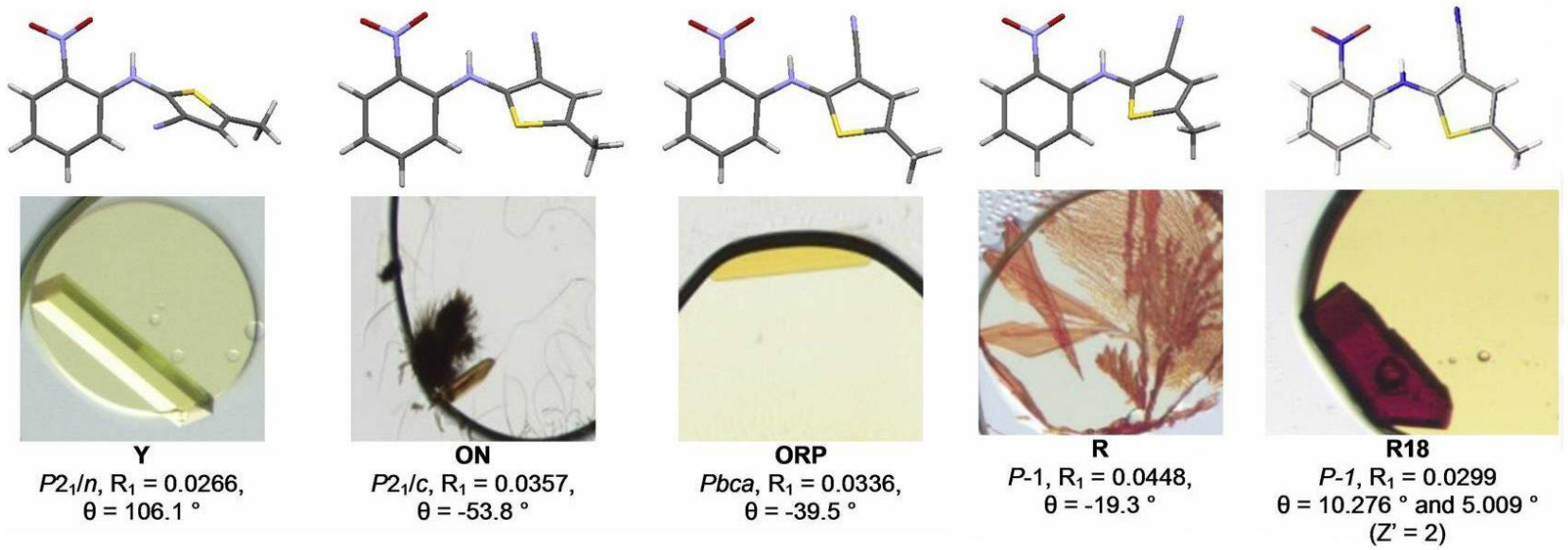


Polymorphism

- Walter McCrone once famously said ‘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’

- ROY (5-methyl-2-[(nitrophenyl)amino]-3-thiophenecarbonitrile) = 10 polymorphs Red-Orange-Yellow

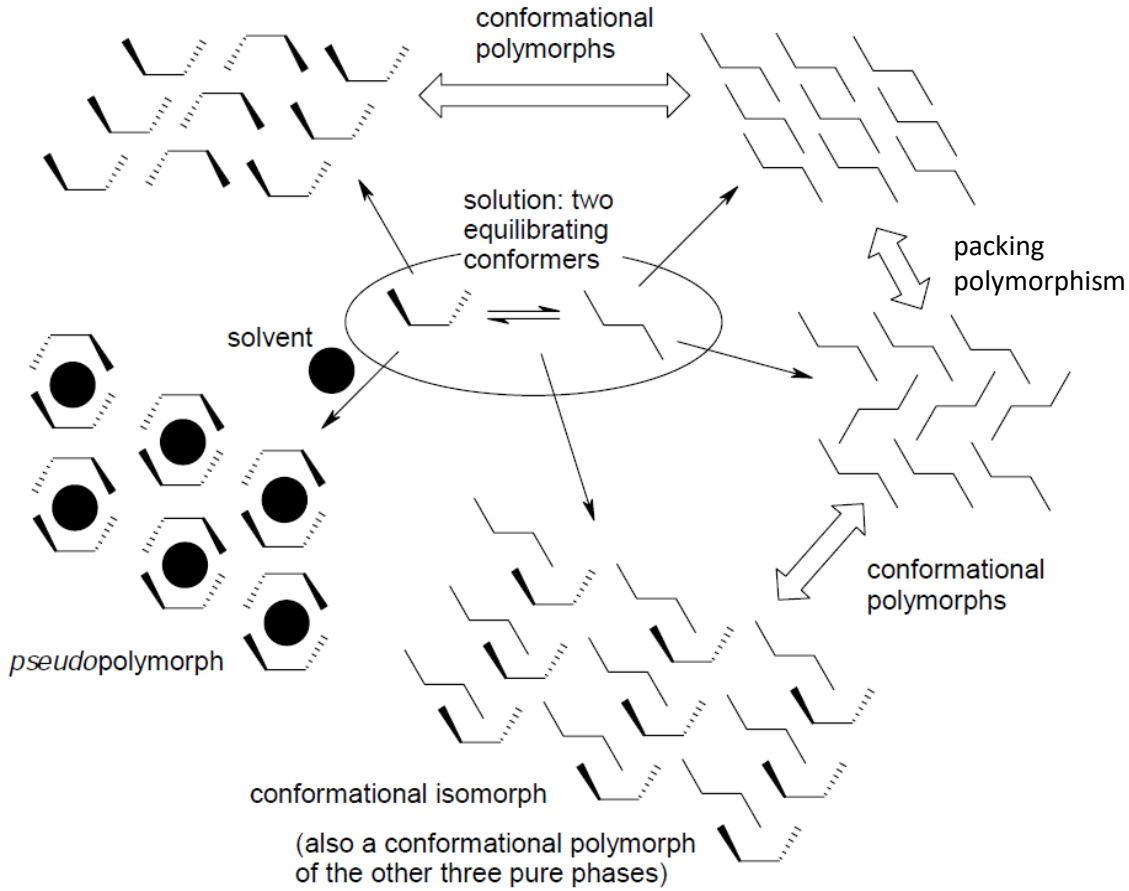




Rohani et al. *Curr. Med. Chem.* 2009, 16, 884-905 & Wikipedia.

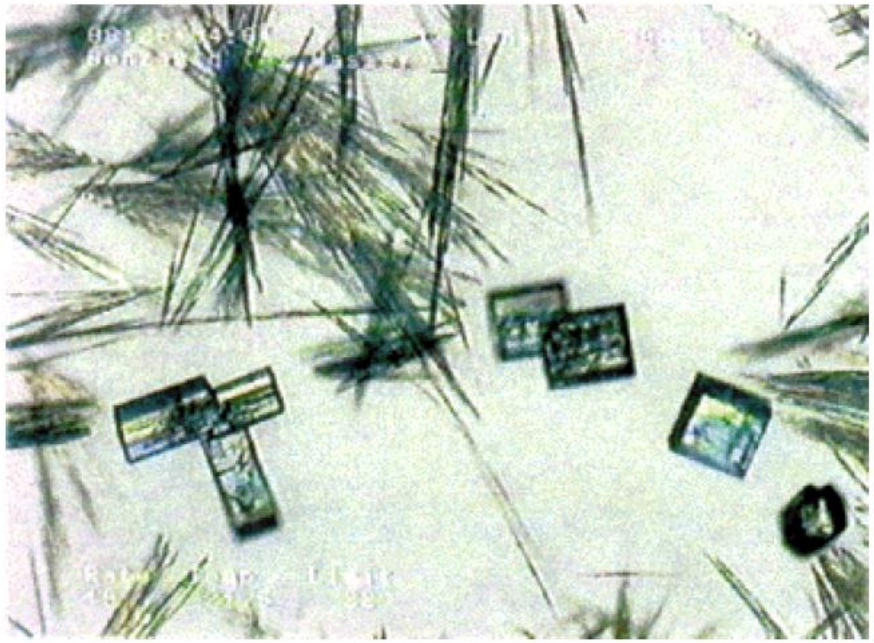
Polymorphism

- The term **pseudopolymorph** is a synonym for hydrate (when the co-crystallized guest is water) or solvate (when the guest is a solvent molecule other than water). Pseudopolymorphs are also sometimes referred to as solvatomorphs.
- **Packing polymorphism × conformational polymorphism**
- **Concomitant polymorphs** – a solid crystalline phase of a given compound resulting from at least two crystalline arrangements of the molecules of that compound in the solid state
- **Disappearing polymorphism**
- **Supramolecular polymorphism**



Concomitant polymorphs

- The first recognized example of a polymorphic organic substance was also an example with concomitant polymorphs (Wöhler+Liebig, 1832) – dimorphism of benzamide

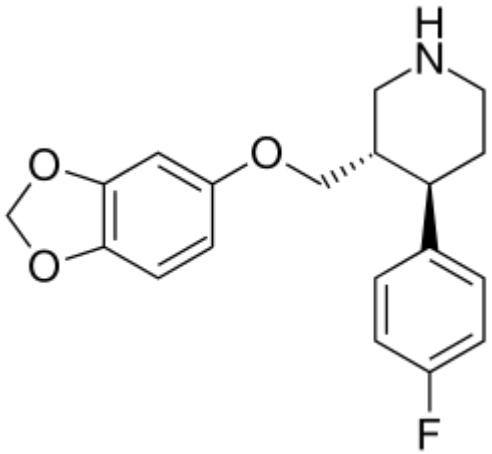


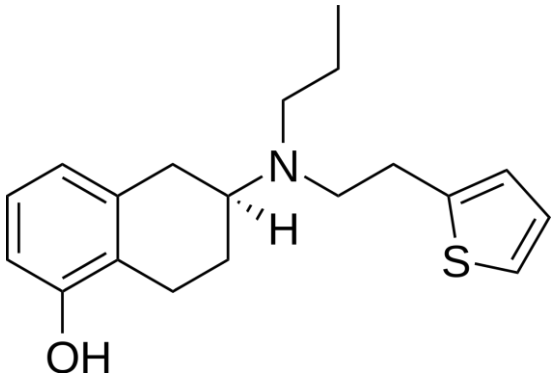
Bernstein et al. *Angew. Chem. Int. Ed.* 1999, *38*, 3440-3461.

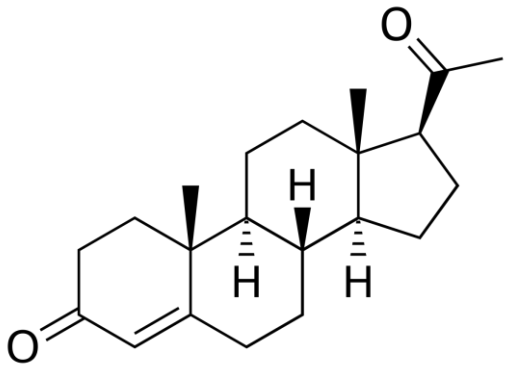
Disappearing polymorphism

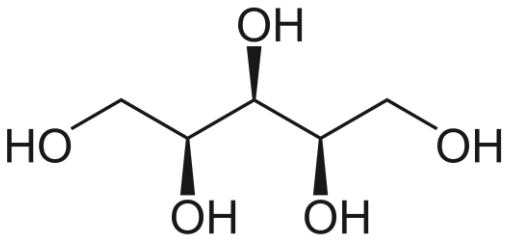
- Seemingly stable crystal structure is suddenly unable to be produced, instead transforming into a polymorph, or differing crystal structure with the same chemical composition, during nucleation

- Paroxetin, rotigotine, progesterone, beta-melibiose, xylitol, etc.





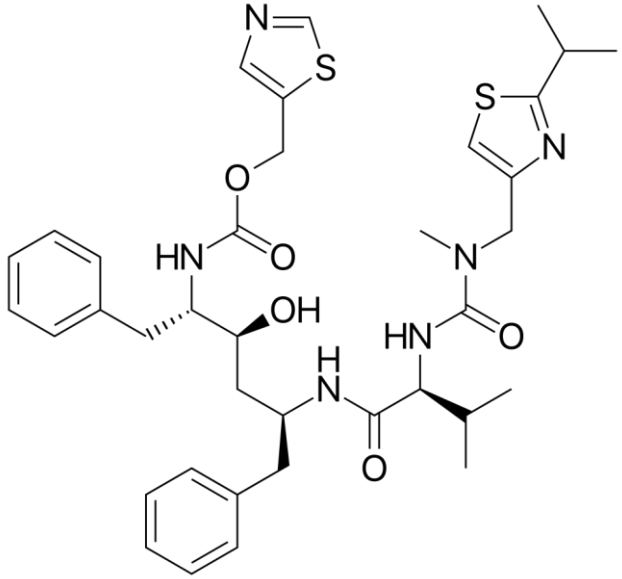




a) Dunitz et al. *Acc. Chem. Res.* 1995, 28, 193—200; b) Bučar et al. *Angew. Chem. Int. Ed.* 2015, 54, 6972 –6993.

Disappearing polymorphism - Case of Ritonavir

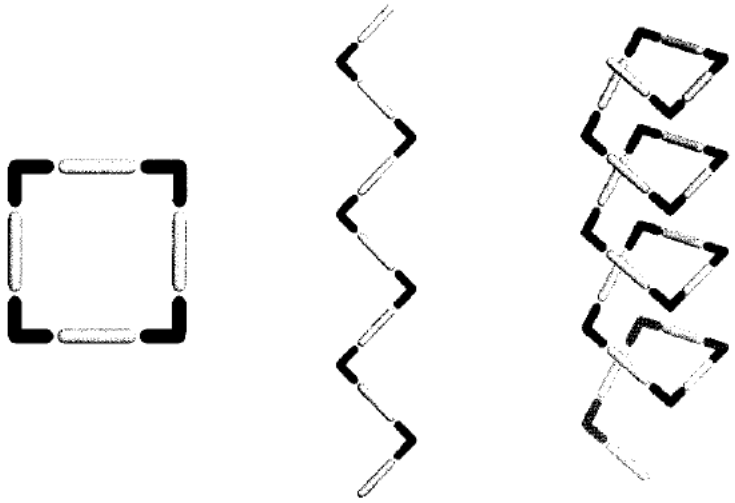
- Abbott Laboratories introduced the anti-AIDS (later anti-COVID-19) drug ritonavir in 1996
- 18 months on the market a previously unknown more stable polymorph II was suddenly detected during manufacture (reason unknown, subtle alteration in manufacturing conditions or even seeding by microscopic particles of the second polymorph) and it became major
- New form was only half as soluble as the first and so was also the bioavailability

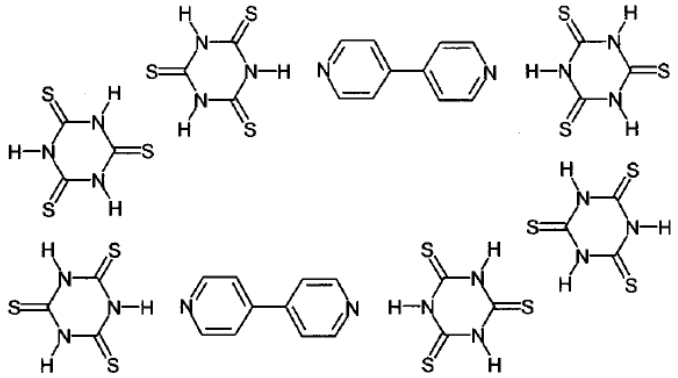


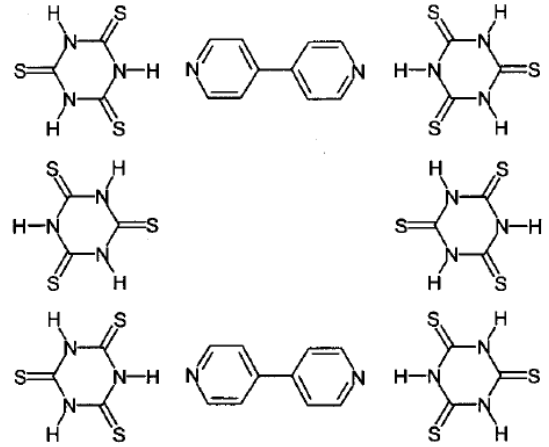
- Disappearing polymorph (loss of 250 mil. USD) → refrigerated gelcap with pre-dissolved mixture of both
- In 2000 - tablet formulation of lopinavir/ritonavir (Kaletra)
- In 2010 - tablets produced in a solid dispersion by melt-extrusion were found to remain in form I

Supramolecular isomerism (polymorphism)

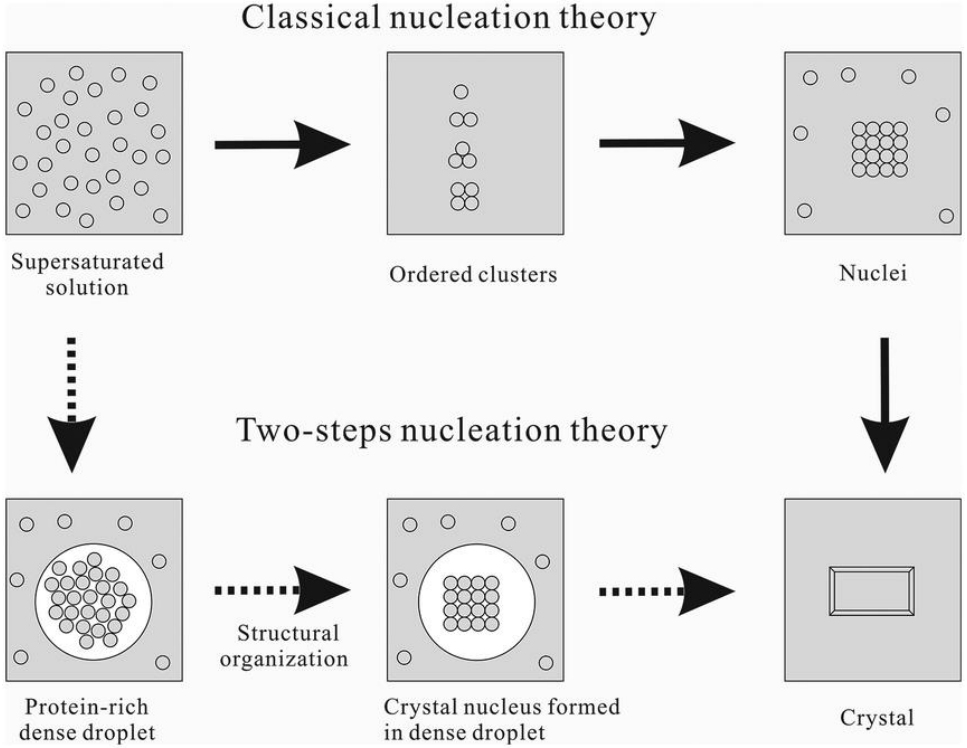
- Defined by Zaworotko: „existence of more than one type of network superstructure for the same molecular building blocks“
- Related to structural isomerism at the molecular level

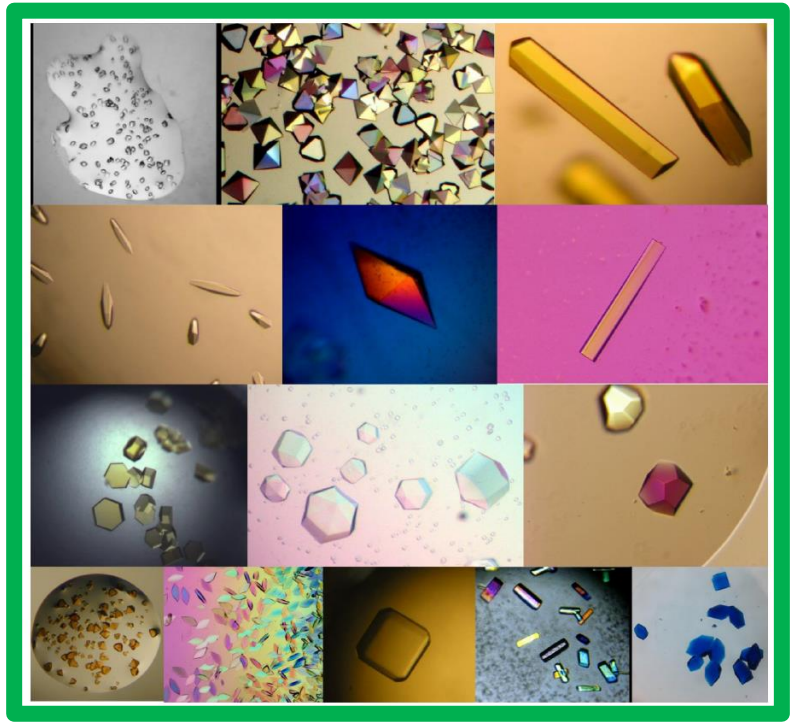






Crystallization





Zhou et al. *CrystEngComm* 2017, 19, 1143-1155.

Crystallization of polymorphs

- Polymorph screening is conducted by crystallizing substances from a single or mixed solvent via cooling crystallization, evaporation, or antisolvent crystallization using a set of 96 solvents
- 15 categories using cluster statistical analysis where solvent parameters such as hydrogen-bond acceptor/donor propensity, polarity/dipolarity, dipole moment, dielectric constant, etc. are variables
- Heating and cooling rates, crystallization temperature, evaporation rate, the degree of supersaturation, the rate of agitation, pH of the media can affect crystallization
- High throughput screening approach is adopted with multiple crystallization wells reflecting systematic variation of solvent, supersaturation etc. followed by rapid in situ technique such as Raman spectroscopy

Crystallization from a single or mixed solvents/HTS [62–66]
Thermal activation of the solid substrates [67]
Crystallization from the melt [73–75]
Desolvation/dehydration of solvates/hydrates by heat or by reslurry [85,91]
Crystallization in nano-confined structures [96,98,100]
Seeding/pseudoseeding [101,102]

Solution mediated polymorphic transformation/slurry conversion method [103–106]
Solid-state polymorphic transformation [85,107]
Mechanical activation of the solid substance [11,108],
Crystallization in a capillary tube [109,110]
Exposure to vapor at high or low humidity [111–113]
Exposure to organic vapor [90]

Directed crystallization on molecular substrates [37–42]
Crystallization in the presence of tailor-made additives [44–58]
Laser induced crystallization [114,115]
Crystallization from a supercritical fluid [116–118]
Structure prediction [119–123]

E. H. Lee *Asian J. Pharm. Sci.* 2014, 9, 163-175.

Polymorphism transitions

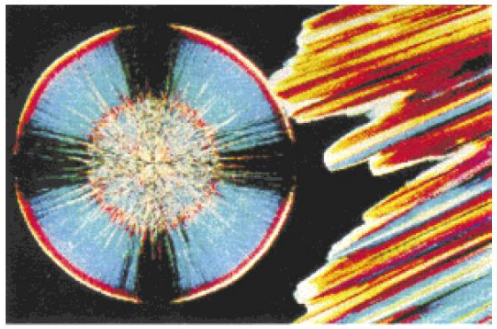
- Two types of polymorphous transition:
  i) enantiotropic – characterized by transformation temperature $T_{A \rightarrow B}$, it is often reversible and well-defined,
  ii) monotropic – has no $T_{A \rightarrow B}$, polymorph transition pass over liquid phase (crystallization from a different solvent)

  - Pharmaceutics are often undergoing monotropic transformation

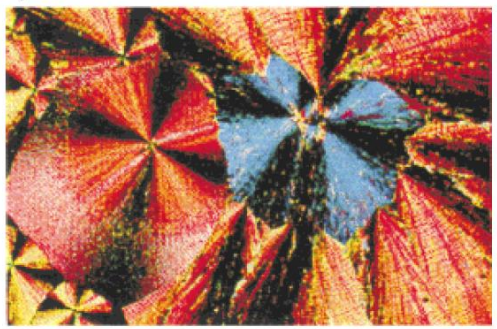
  - Uncontrolled transition might happen during final crystallization of API, long-lasting standing of the product in the parent solution, during drying, micronization, tablet pressing, during wet granulation, or even in the tablet during storing
  - Seeding can help in control of polymorphism

Analysis of Polymorphs

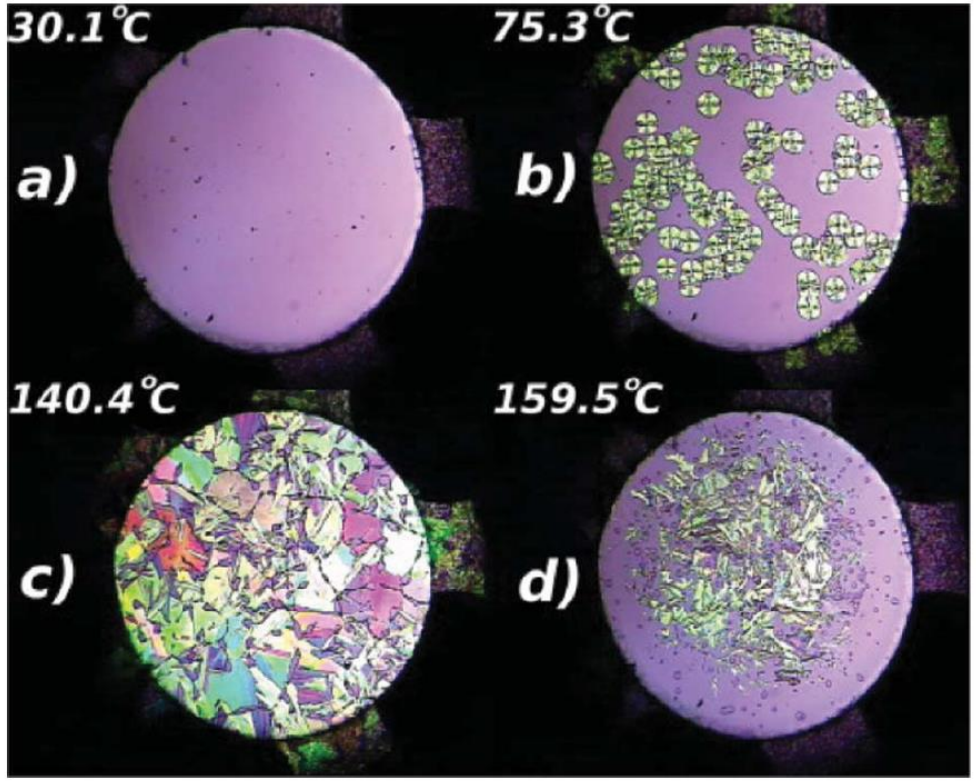
- Obvious change of properties of crystalline materials, *e.g.*, color, solubility, melting point, etc.
- Differential scanning calorimetry
- Thermogravimetry
- Vibrational spectroscopy (IR, Raman)
- Single crystal X-ray diffraction
- Powder X-ray diffraction
- Solid state magic angle spinning NMR
- Polarised optical hot-stage microscopy
- Neutron diffraction



Phenobarbital



Nicotinamide



Paracetamol

a) Brog et al. *RSC Adv.* 2013, 3, 16905; b) Bernstein et al. *Angew. Chem. Int. Ed.* 1999, 38, 3440-3461.

Analysis of Polymorphs

Techniques	Analysis time	Sample (mg)	Destructiveness	Preparation	Quantitation	
PXRD [112,126,127]	3–8 min	10–30	X	Simple	O	Difficult to differentiate the mixtures, first-line to analyze polymorphs, HTS
DSC [128–130]	20–30 min	2–4	O	Simple	O	Easy to detect the mixtures Thermodynamic relationships
TGA	20–30 min	~10	O	Simple	X	Existence of solvates/hydrates Idea of how strong solvents interact with molecules
Single crystal X-ray	1–2 day	Single crystal	O	Difficult	X	Definitive tool
FTIR (Pellet)	10–20 min	3~ (pellet)	O	Difficult	O	Molecular interactions
FTIR (ATR)	10–20 min	10~	X	Simple	O	No sample preparation
FTIR (Probe)	3 s	10~	X	Simple	O	On-line monitoring
FT-Raman [131,132]	~20 min	10~	O	Simple	O	Molecular interactions, HTS
FT-Raman (Probe) [133]	3 s	3~	X	Simple	O	On-line monitoring
HSM [134]	20–30 min	2–3	X	Simple	X	Visual observation
ssNMR [135–137]	1 h	20–30	O	Difficult	O	Racemate, Chirality

DSC – differential scanning calorimetry; TGA – Thermogravimetry analysis; HSM – Hot-stage microscopy; HTS – High-throughput screening; O = Yes X = No.

E. H. Lee *Asian J. Pharm. Sci.* 2014, 9, 163-175.

Polymorphism in pharma companies

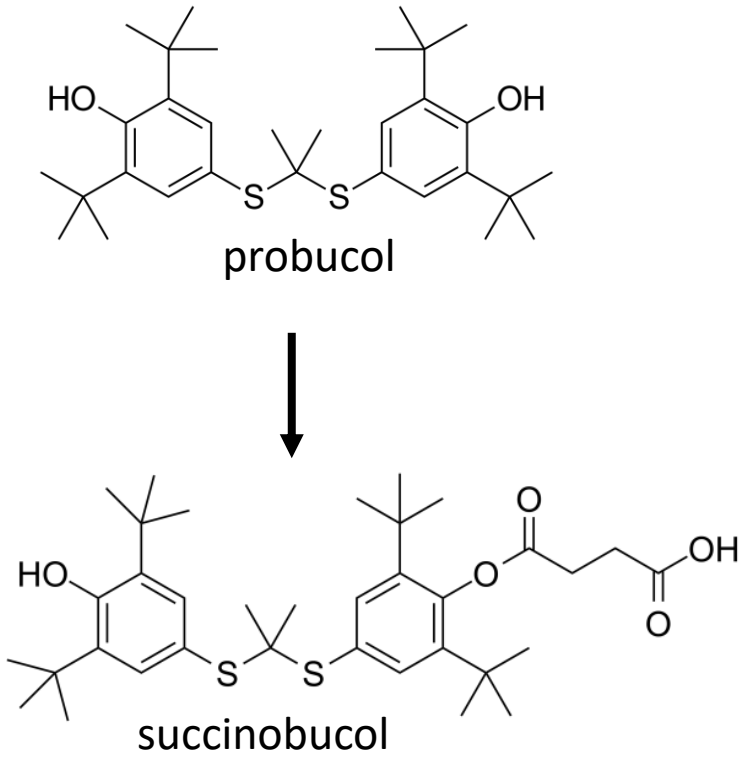
- Polymorph screening must undergo every new API

- For pharmaceutical companies, the problem of polymorphism is rather a blocking than a creative element. Sometimes the differences between two polymorphs are tiny and tiny are the differences in properties (*e.g.*, polymorphs of aspirin - acetylsalycilic acid).

- Polymorphism is closely watched by regulatory authorities and no pharmaceutical manufacturer can afford to ignore it.

Shtukenberg et al. *Cryst. Growth Des.* 2017, 17, 6, 3562–3566.

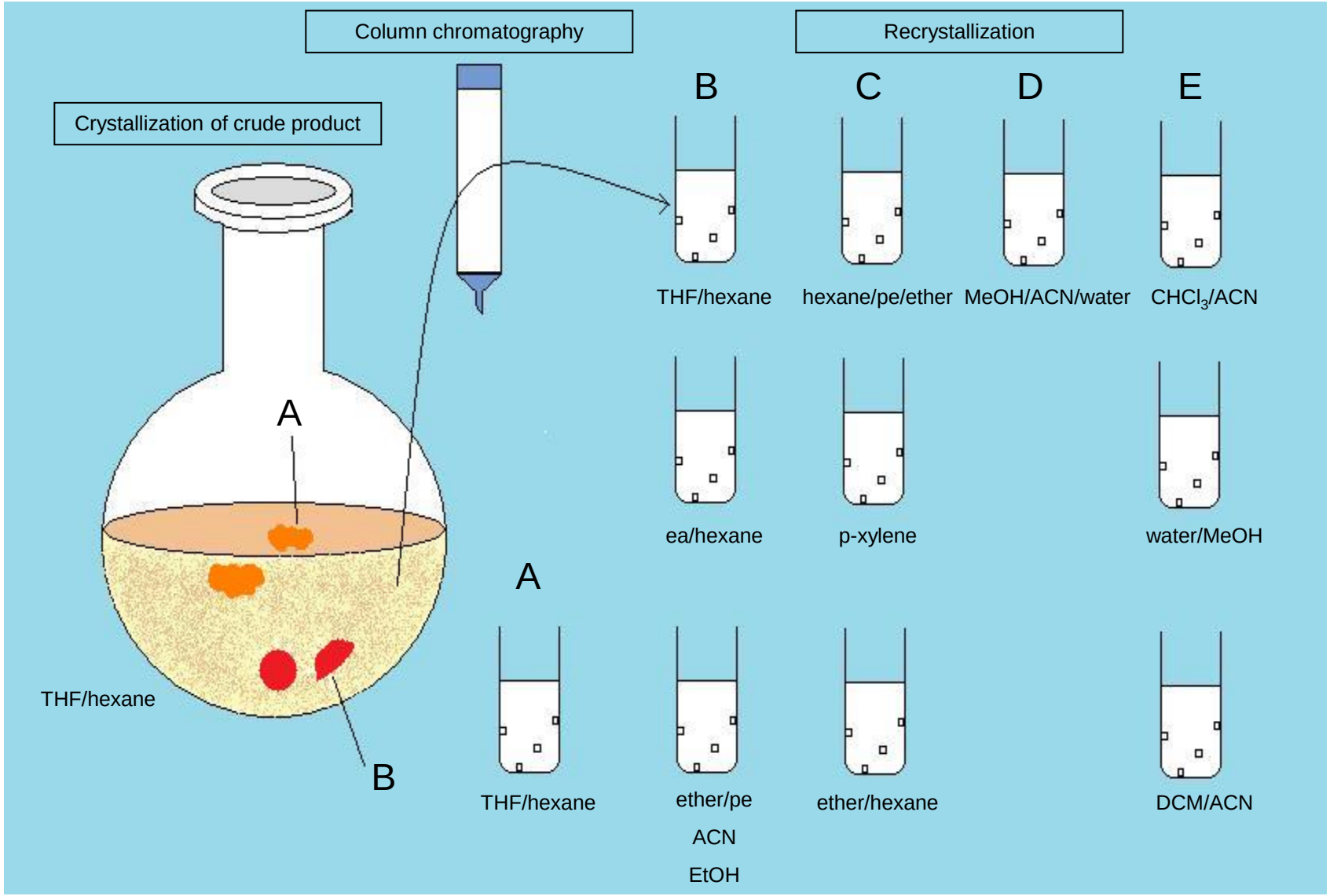
Probucol and Succinobucol: Example from our Lab

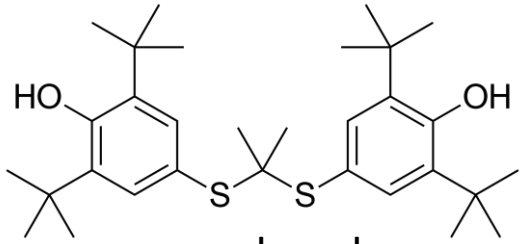


Succinobucol

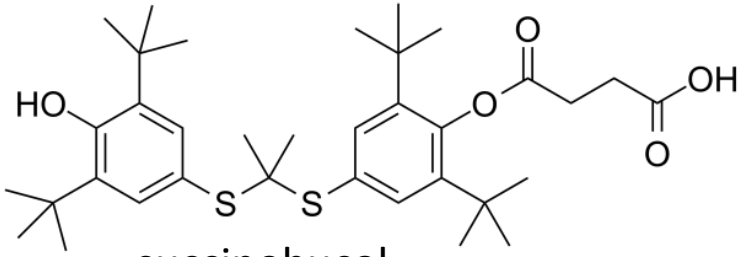
- LDL reduction effect
- anti-inflammatory
- antioxidant
- anti-restenotic
- antihyperglycemic effects

Succinobucol re-crystallization





probucol



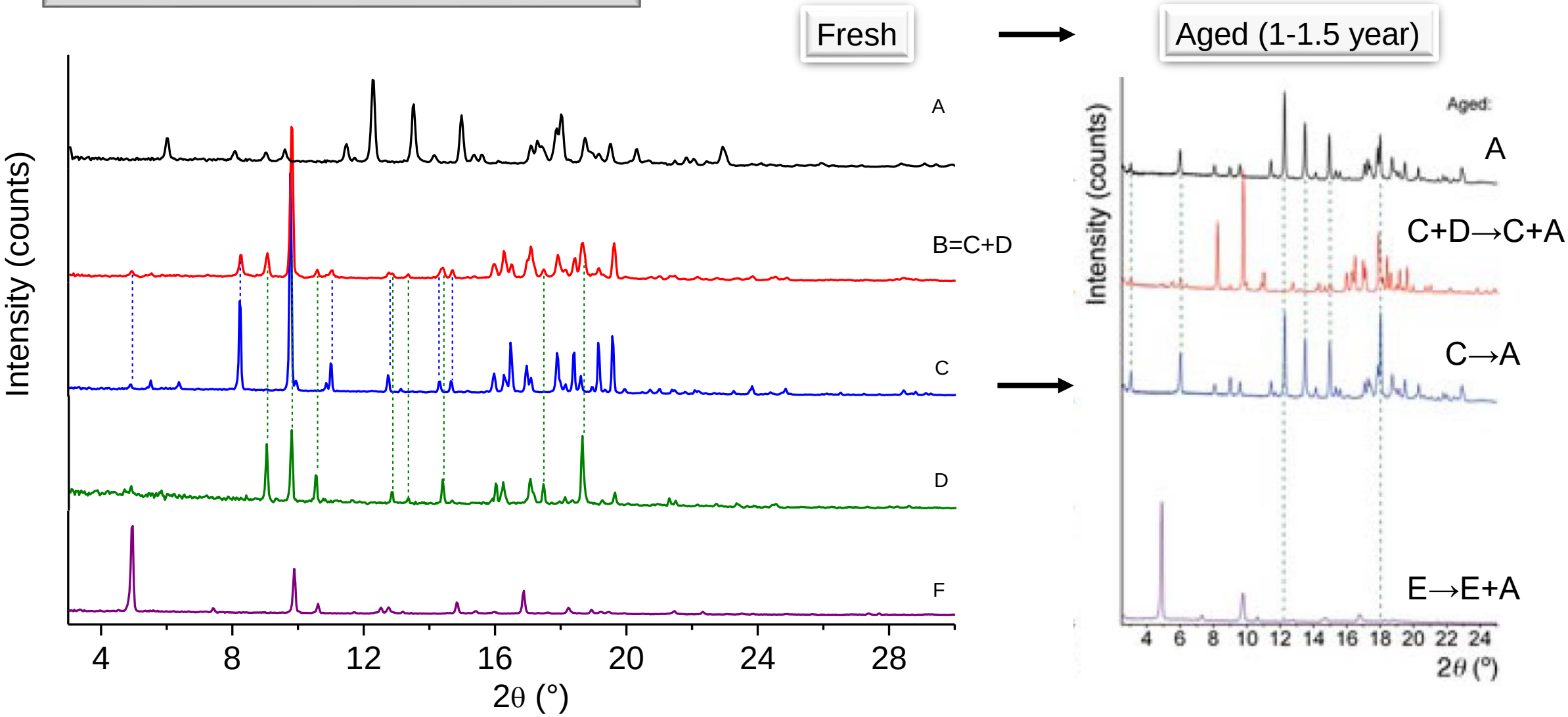
succinobucol

5 different crystalline solids were obtained where 4 different polymorphs of succinobucol were found

Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794.

Succinobucol polymorphism studies

Powder X-ray diffraction (PXRD)

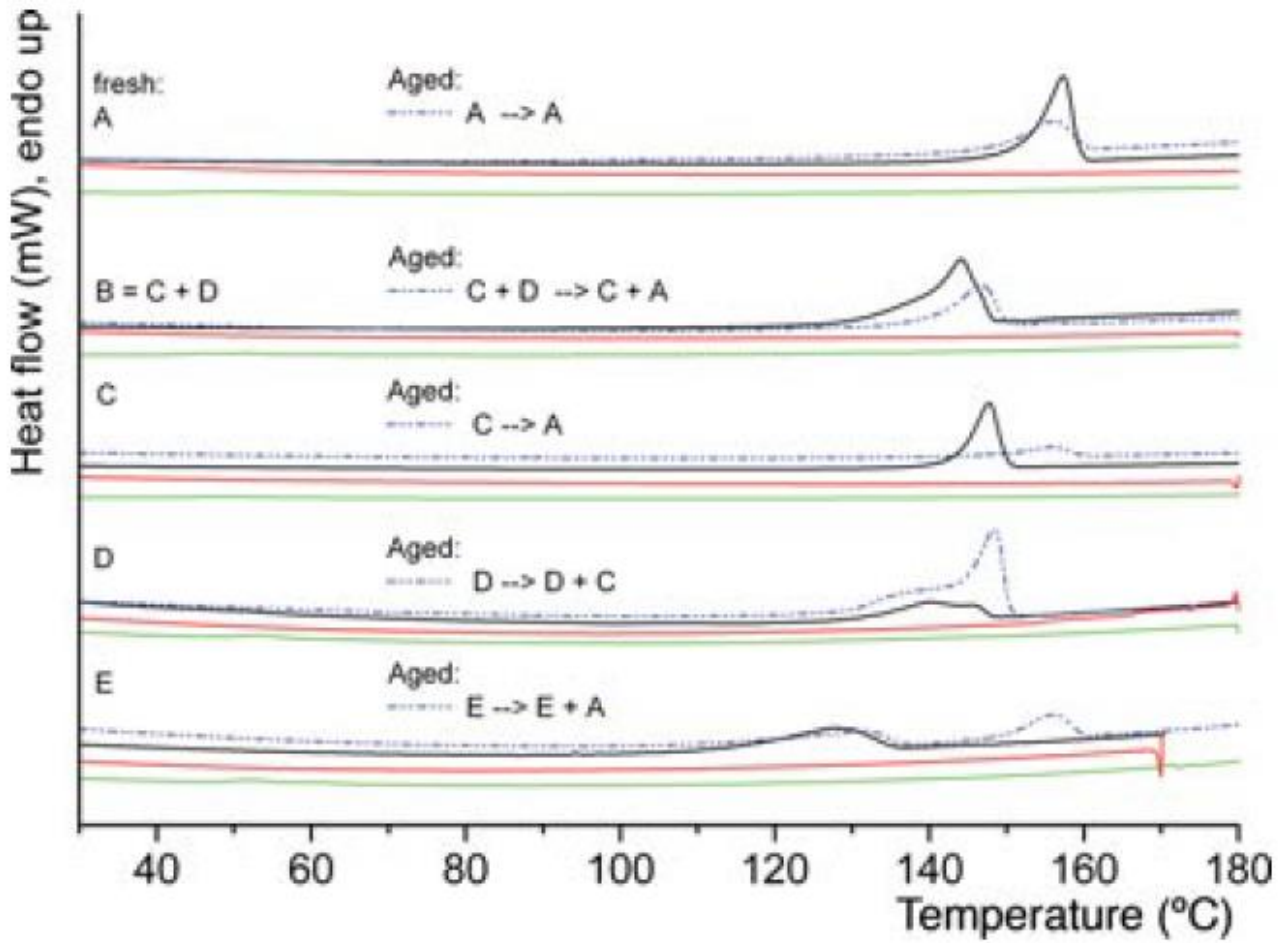


Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794.

Succinobucol polymorphism studies

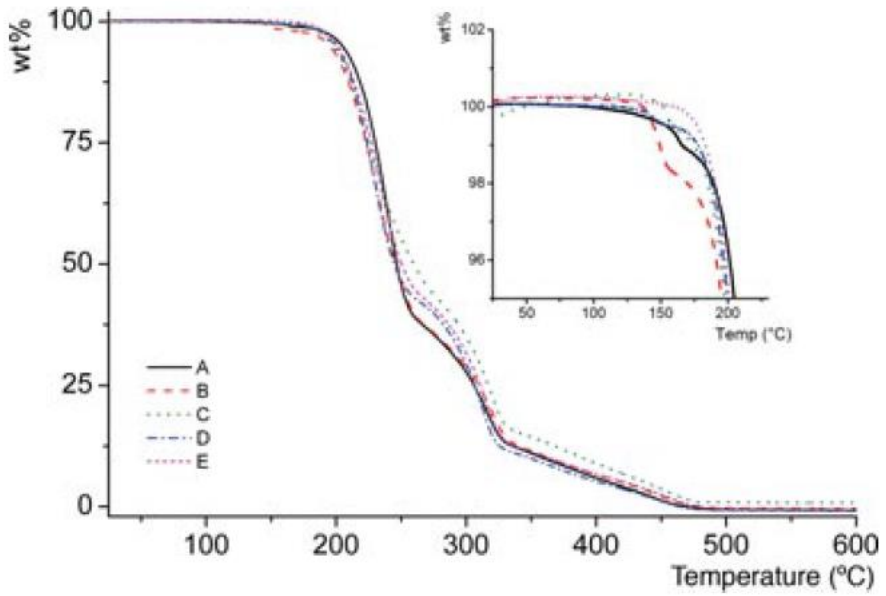
Differential scanning calorimetry (DSC)

Fresh → Aged (1-1.5 year)



Sample	1st heating T_m, ΔH °C, (kJ/mol)	2nd heating T_g, ΔC_p °C, [kJ/(mol/°C)]	Decomposition T_d (°C)
A	157.3 (42.01)	43.7 (0.165)	191
B	144.1 (42.12)	41.7 (0.114)	198
C	147.7 (45.51)	43.2 (0.201)	186
D	140.2 (20.47)	49.1 (0.226)	186
E	135.6 (36.56)	46.7 (0.237)	187

Thermogravimetry (TGA)

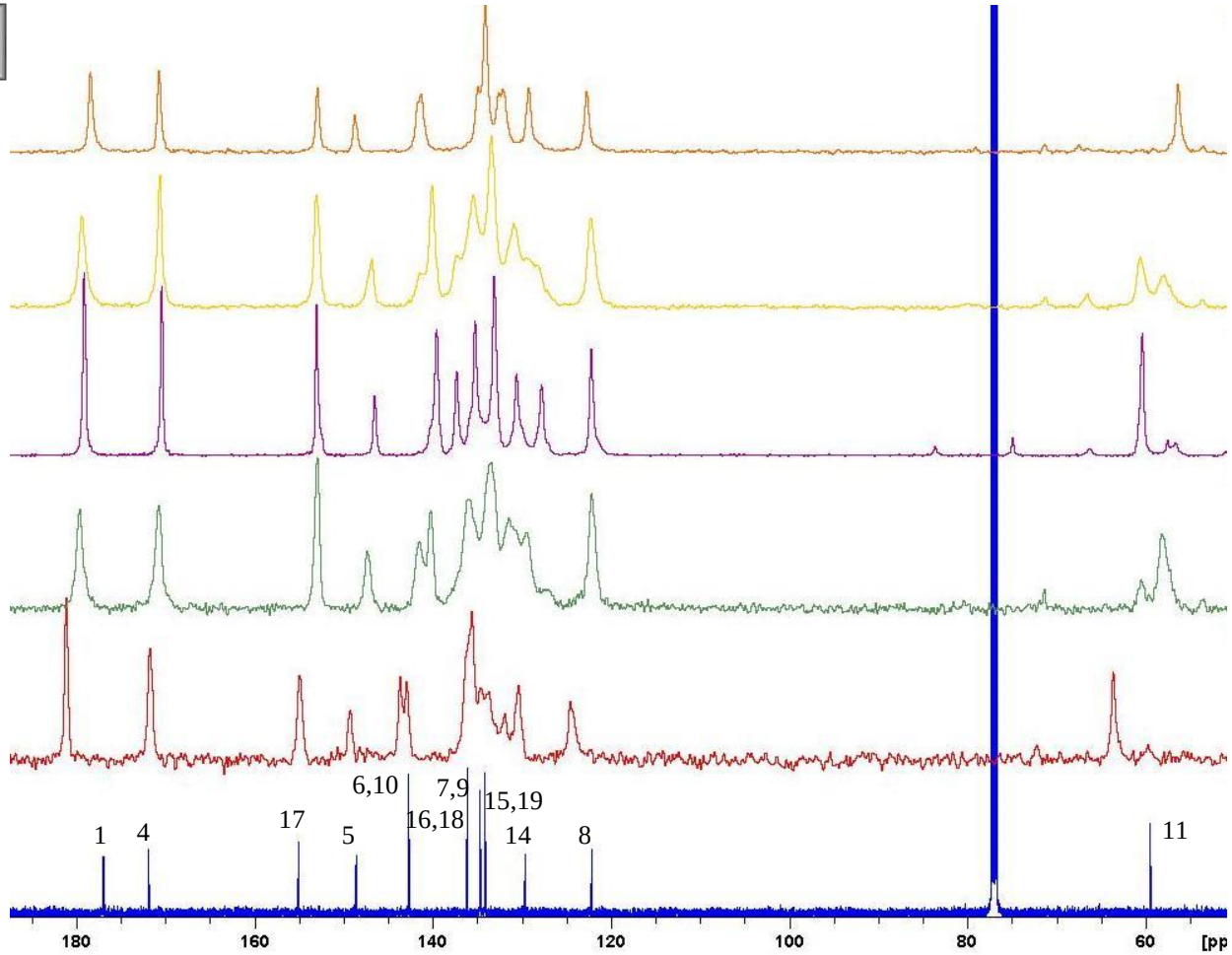


Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794.

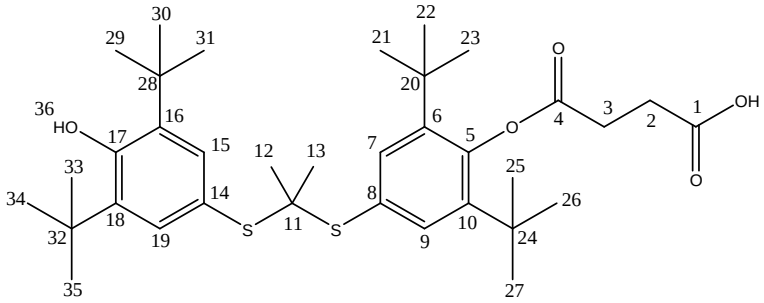
Succinobucol polymorphism studies

Solid state nuclear magnetic resonance (ssNMR)

^{13}C



A



B as a mixture of C and D

C

D

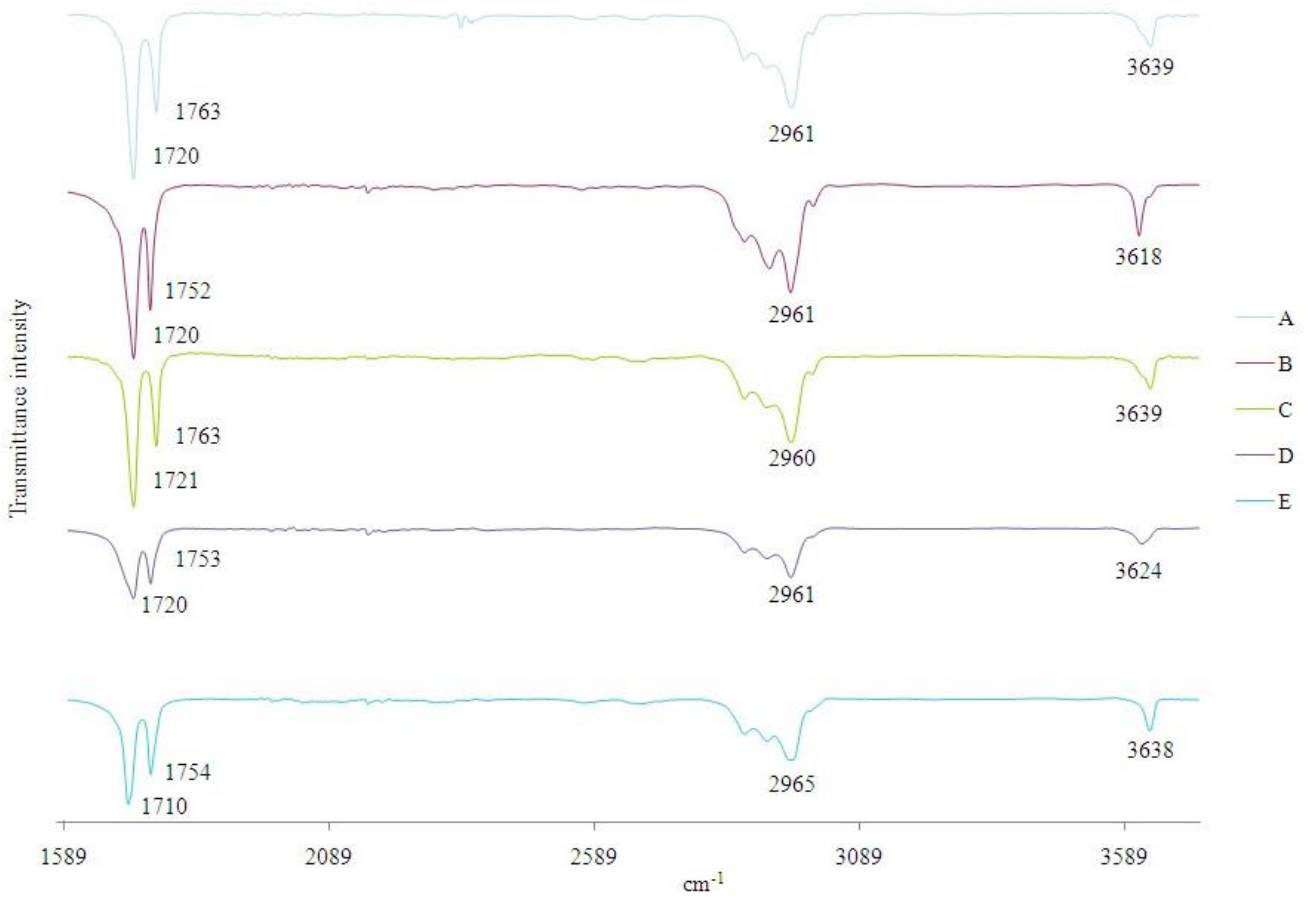
E

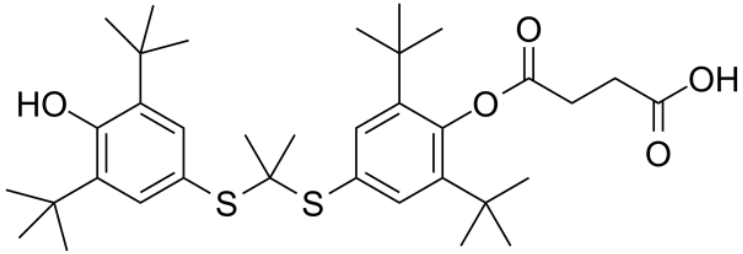
liquid ^{13}C NMR

Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794.

Succinobucol polymorphism studies

Infrared (IR) spectroscopy





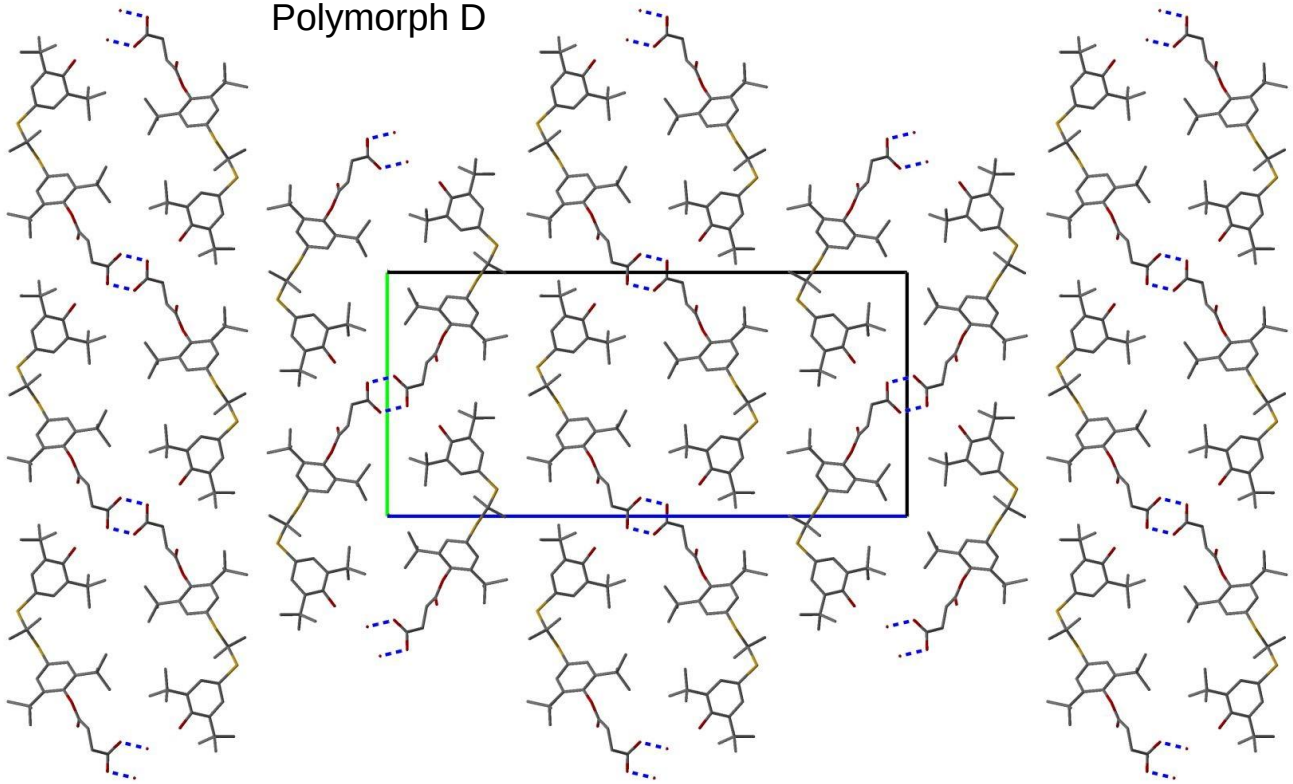
Group	A	B	C	D	E
-OH stretching	3639 m	3618 m	3639 m	3624 m	3638 m
t-butyl C-H stretching	2961 s	2961 s	2960 s	2961 s	2965 s
-C=O stretch in -COOH	1720 vs	1720 vs	1721 vs	1720 vs	1710 vs
-C=O stretch in -COOR	1763 s	1752 s	1763 s	1753 s	1754 s
bending in succinyl	1360 s	1365 s	1359 s	1364 s	1364 s

Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794.

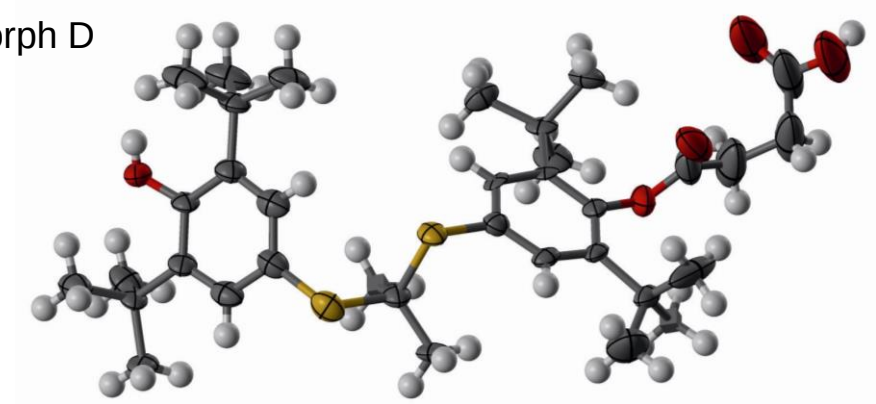
Succinobucol polymorphism studies

Single crystals X-ray diffraction (SCXRD)

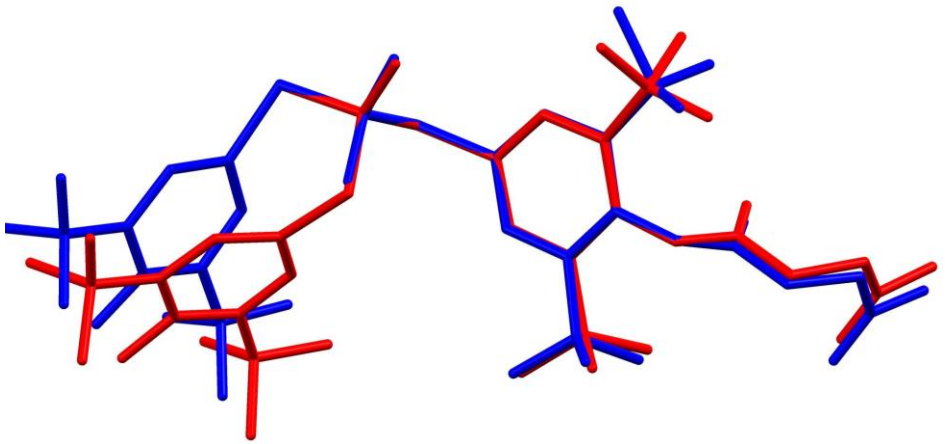
Polymorph D



Polymorph D



Overlap of polymorphs C and D



Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794.

Succinobucol conjugation with steroids

- **Probucol, succinobucol, and phytosterol derivatives**

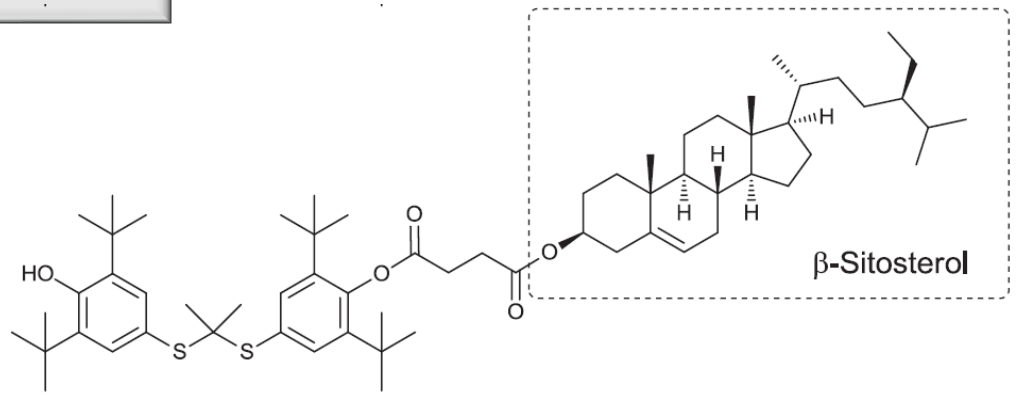
Succinobucol

- LDL reduction effect
- anti-inflammatory
- antioxidant
- antirestenotic
- antihyperglycemic effects

+

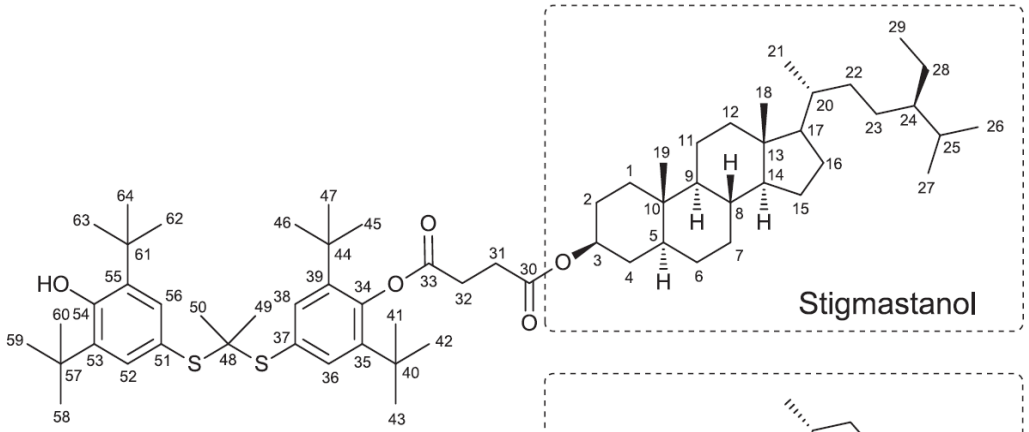
Phytosterols

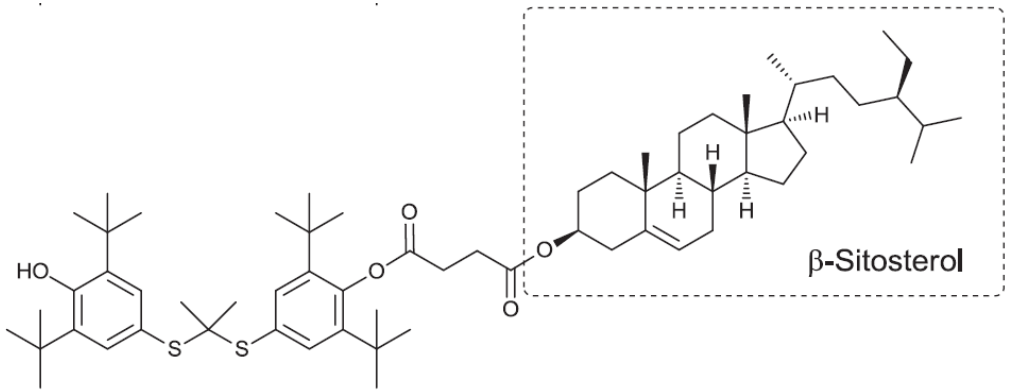
- lowering of cholesterol serum level (especially LDL), block cholesterol absorption
- aiming of the drug into hepatopancreatic system

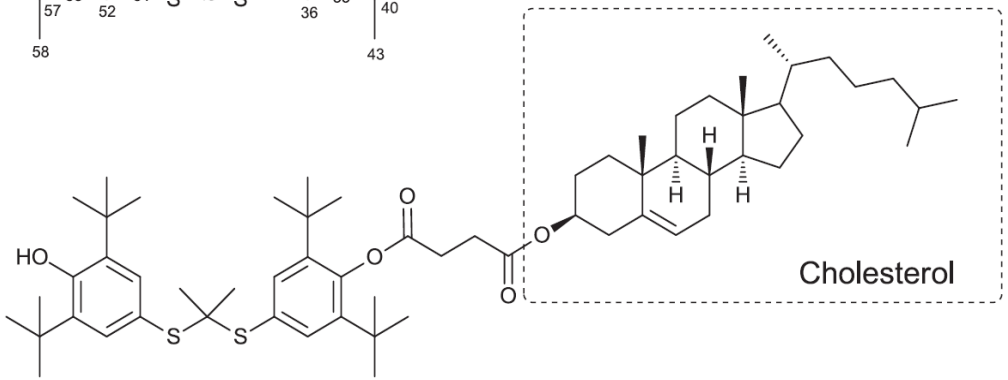


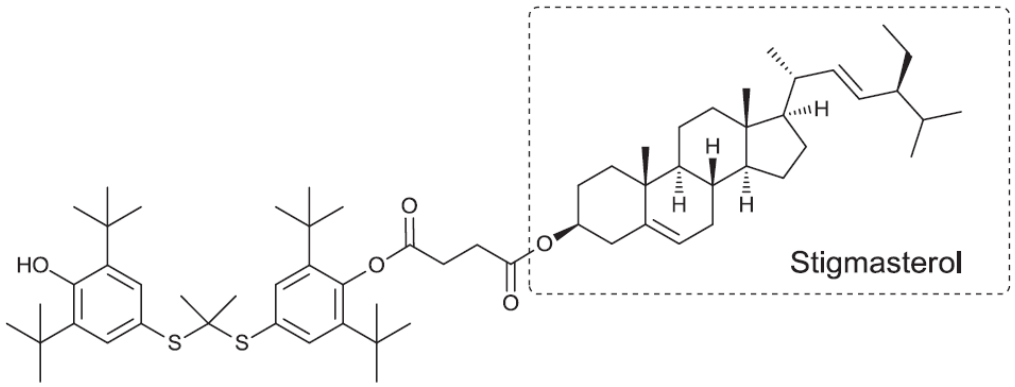
a) Jurček et al. *J. Pharm. Sci.* 2012, 101(5), 1794; b) Jurček et al. *Molecules* 2011, 16, 9404-9420; c) Ikonen et al. *J. Mol. Struct.* 2012, 1011, 25–33.

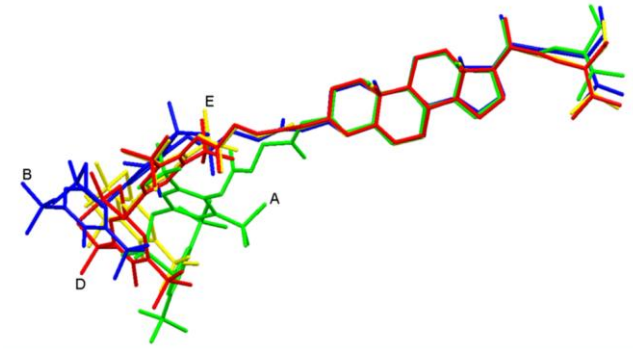
Succinobucol-sterol conjugates

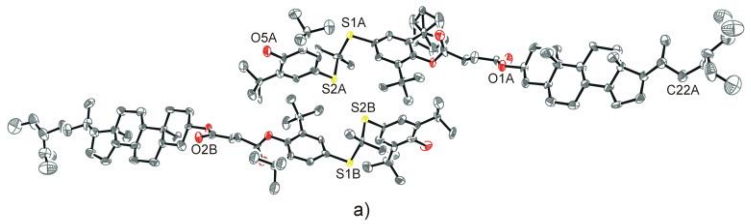


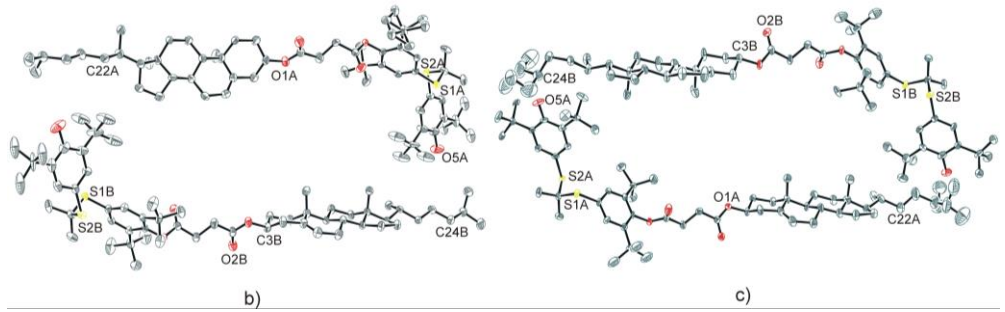












a) Jurček et al. *Molecules* 2011, 16, 9404-9420; b) Ikonen et al. *J. Mol. Struct.* 2012, 1011, 25–33.

In the next class…

Porous solid materials, Metal-Organic Frameworks (MOFs)

Thank you for your attention!