



# POLYMORPHISM

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# POLYMORPHISM

The ability of a solid material to exist in multiple forms or crystal structures known as polymorphs;  
Polymorphs have different energy of their crystal lattices, and consequently different melting points, solubilities etc.

Do not mix up polymorphism with **crystal morphology** – a compound under different conditions crystallizes in different shapes – **habits**, but a polymorph is still the same;


**Pseudopolymorphs** – the crystal lattice contains some amount of solvent (solvates, hydrates)





# POLYMORPHISM

**Polymorphs** are crystalline materials that have the **same chemical composition**, but **different molecular packing**





## POLYMORPHISM VS. ALLOTROPY

**ALLOTROPY** – the existence of two or more different physical forms of a chemical element;

Example – graphite, diamond, fullerene

DOES IT MATTER?

When Napoleon invaded Russia, the soldiers' tin buttons disintegrated in the cold. They had to survive the Russian winter with open jackets!! (**tin pest**)

Some say it is only a legend

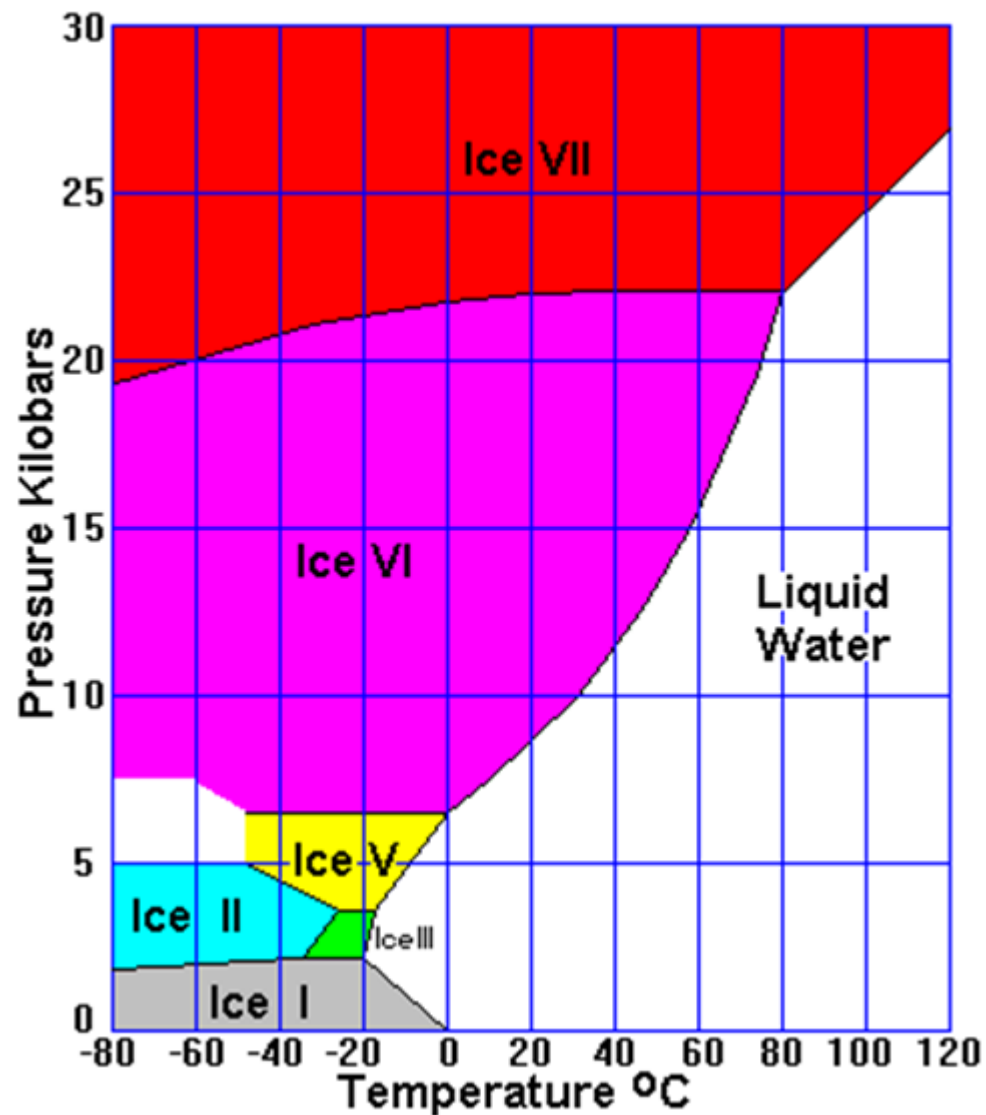


# POLYMORPHISM

Some polymorphs of ice

Kurt Vonnegut – Cat's Cradle -  
New water modification - **Ice Nine**  
– supposedly inspired by Irving  
Langmuir (General Electric Co.)

**Ice IX** really exists, it is stable at T  
below 140 K and pressure  
between 200 – 400 MPa;  
**Ice IX** fortunately does not have  
properties described in the novel!



# POLYMORPHISM

**McCrone criterion** – Polymorphs differ in crystalline structure, but molecules are identical in liquid and gaseous states;

**McCrone's statement** – every compound has different polymorphs, 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.

Polymorphs of cocoa butter

<i>Crystal form</i>	<i>Formation conditions</i>	<i>m. p. [°C]</i>
I	rapid cooling of the melt	17.3
II	rapid cooling of the melt at 2 °C/min	23.3
III	crystallization of the melt at 5–10 °C, converts into II at 5–10 °C	25.5
IV	crystallization at 16–21 °C	27.3
V	slow crystallization of the melt	33.8
VI	from form V after several months at RT	36.3

# POLYMORPHISM

## THE SIX POLYMORPHS OF CHOCOLATE



The molecules in cocoa butter can be stacked together in different ways - these are known as 'polymorphs'. Tempering chocolate is required to obtain only form V, the most desirable. This is achieved by allowing the chocolate to cool at room temperature, which leads to some of all the polymorphs except VI forming, then heating gently to just below the melting point of form V, so it is the major form remaining.

### FORM & MELTING POINT

### DESCRIPTION & PROPERTIES

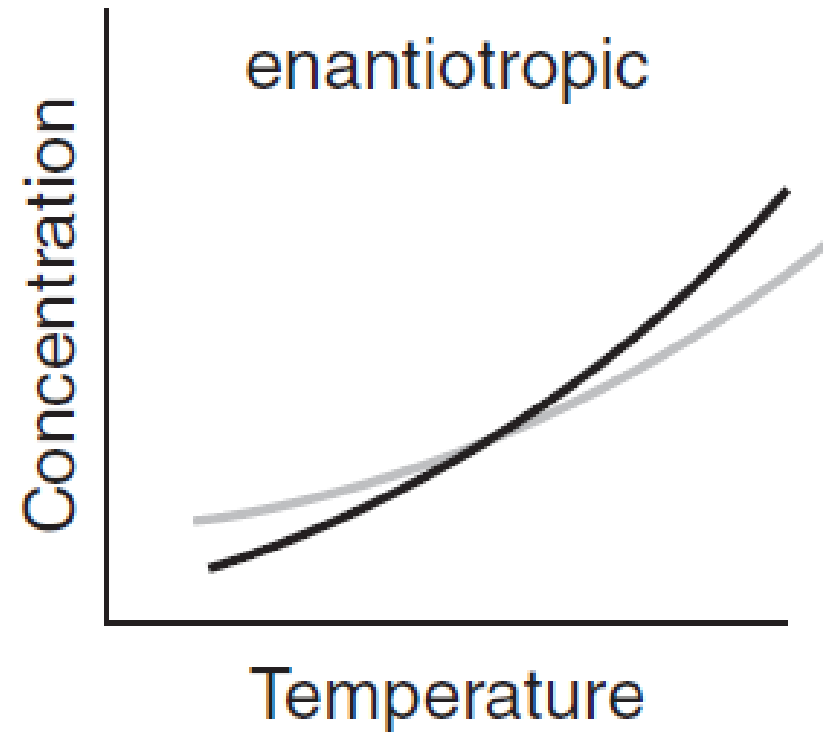
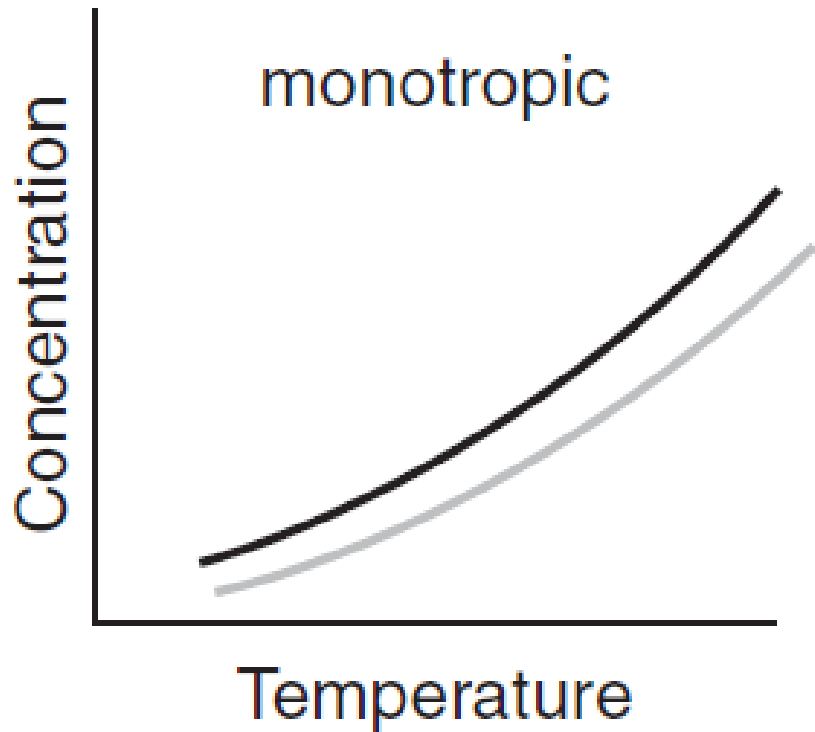
I	17.3 °C	<b>BOTH SOFT AND CRUMBLY WITH NOTICEABLE BLOOMING</b> Form I is produced by cooling melted chocolate rapidly (e.g. by putting it in the freezer).
II	23.3 °C	Form II is produced by cooling melted chocolate at 2°C per minute. Form I crystals also gradually become Form II after a short time of freezing temperature storage.
III	25.5 °C	<b>BOTH FIRM, BUT DON'T GIVE A GOOD 'SNAP', AND SHOW SOME BLOOMING</b> Form III is produced by cooling at 5-10°C. Form II becomes Form III after storage at low temperatures above freezing.
IV	27.3 °C	Form IV is produced by allowing melted chocolate to cool at room temperature; Form III also becomes Form IV after storage at room temperature for some time.
V	33.8 °C	<b>SHINY, SMOOTH TEXTURE, GOOD 'SNAP', AND MELTS IN THE MOUTH</b> Formed by tempering chocolate slowly at room temperature. Most desirable!
VI	36.3 °C	<b>HARD AND MELTS SLOWLY IN THE MOUTH, SHOWS SOME BLOOMING</b> Can't be formed from melted chocolate - can only be formed after solid, tempered chocolate has rested for at least 4 months.

INCREASED STABILITY & DENSITY

# POLYMORPHISM

**Monotropic** polymorphs

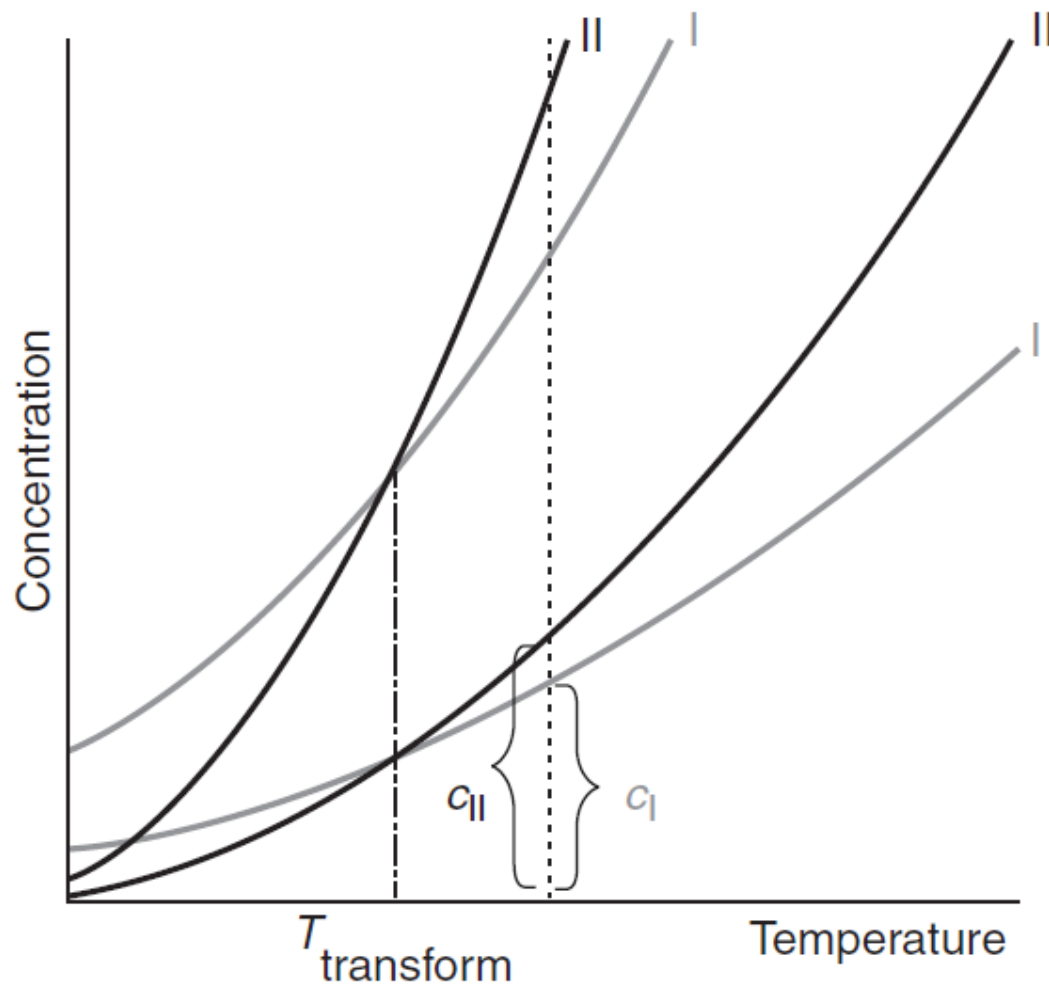
**Enantiotropic** polymorphs – more stable form depends on temperature





# POLYMORPHISM

Transition temperature for enantiotropic polymorphs is **independent** on a solvent;






# POLYMORPHISM

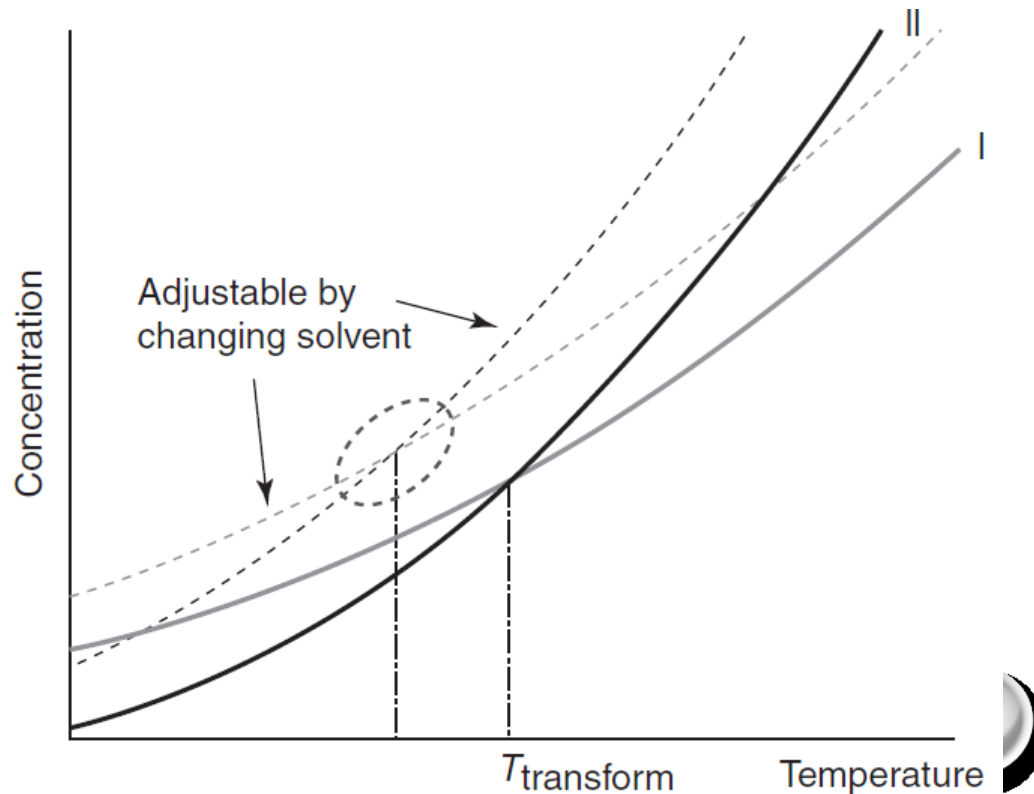
At the transition point of a dimorphic enantiotropic system both polymorphs have the same thermodynamic potential and **the same solubility**;

The transition temperature is only related to the solid lattice structures and therefore independent of the solvent from which the polymorphs are crystallized.



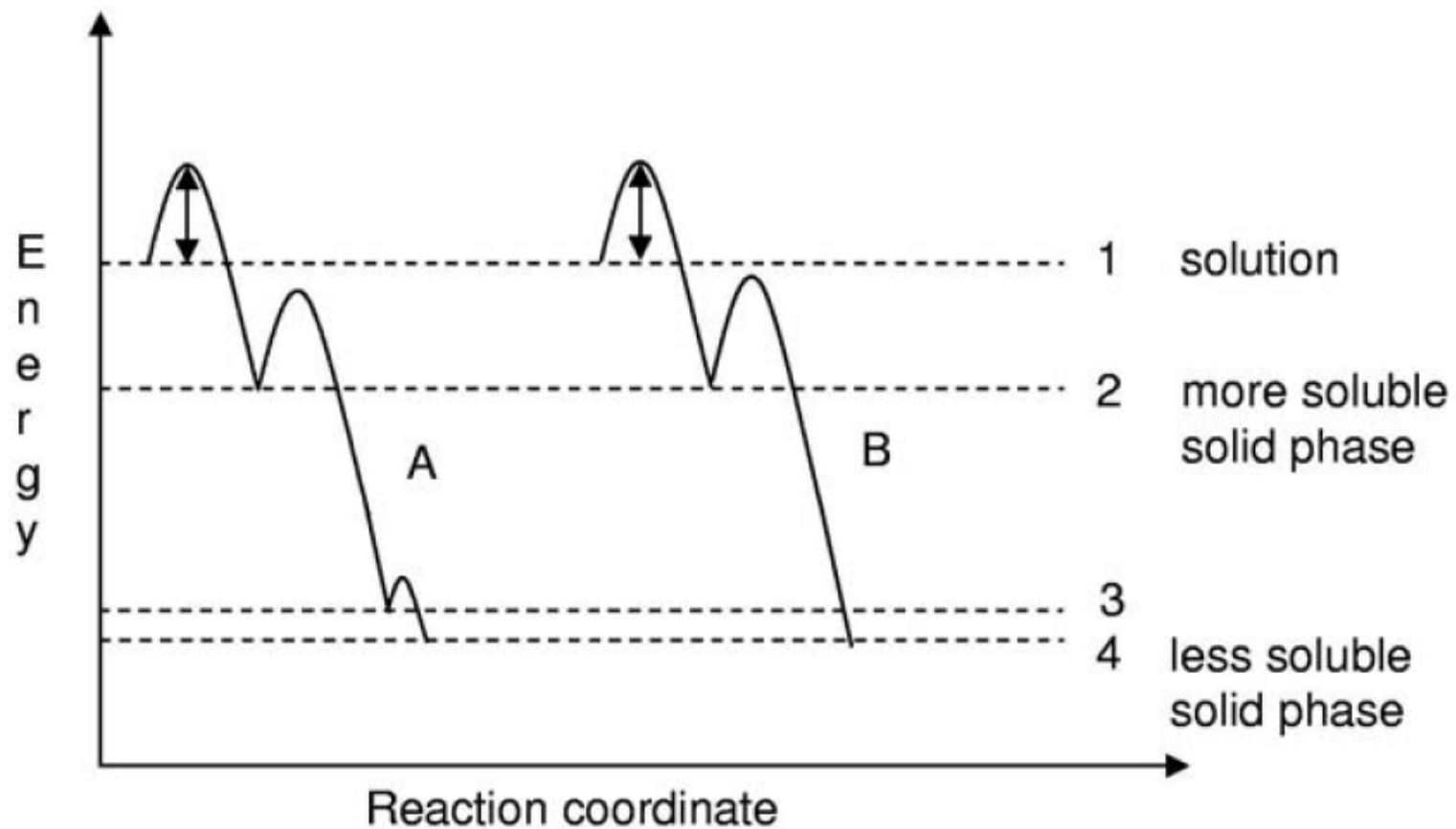
# POLYMORPHISM

- Metastable zone width is however strongly influenced by selected solvent;
- Ostwald's step rule – for several possible polymorphs (in metastable zone) less stable polymorph is formed preferentially;
- Possible formation of **different** polymorphs in **different** solvents;
- Concomitant polymorphism**



# POLYMORPHISM

## Ostwald's step rule – graphical description



# POLYMORPHISM

## • **Burger (Ramberg) rules**

### • Heat of Transition rule

- Polymorphs are enantiotropically related if endothermic heat of transition from a lower melting form to a higher melting form is observed;

### • Heat of Fusion rule

- Polymorphic pairs are enantiotropically related if the low melting form has the higher heat of fusion, otherwise they are monotropically related;

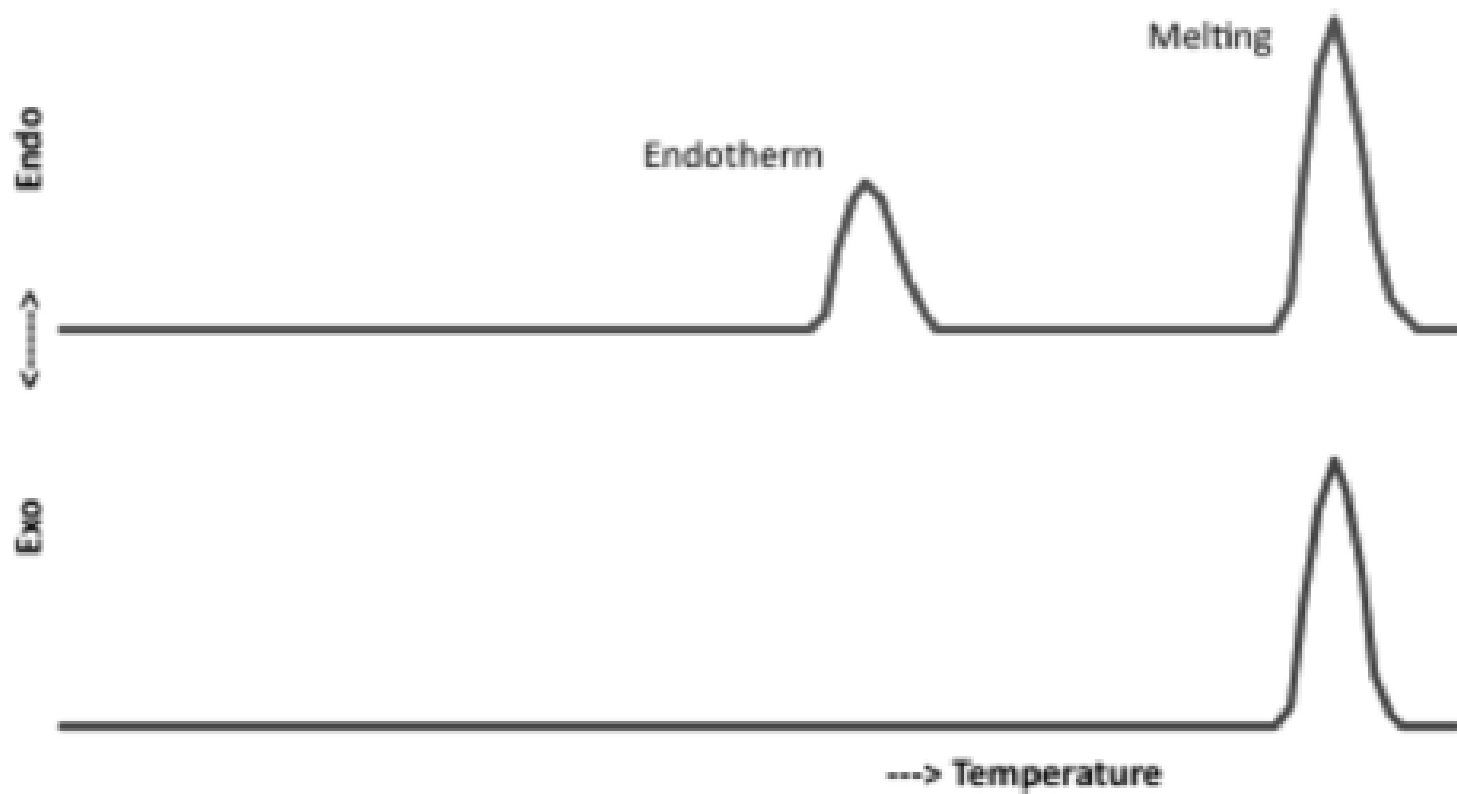
### • Entropy of Fusion rule

- Polymorphs are enantiotropically related if the high melting form has the lower entropy of fusion, otherwise they are monotropes;

It is recommended to confirm DSC results with experimental microscopic observations, solubility determination or slyrrying;

# POLYMORPHISM

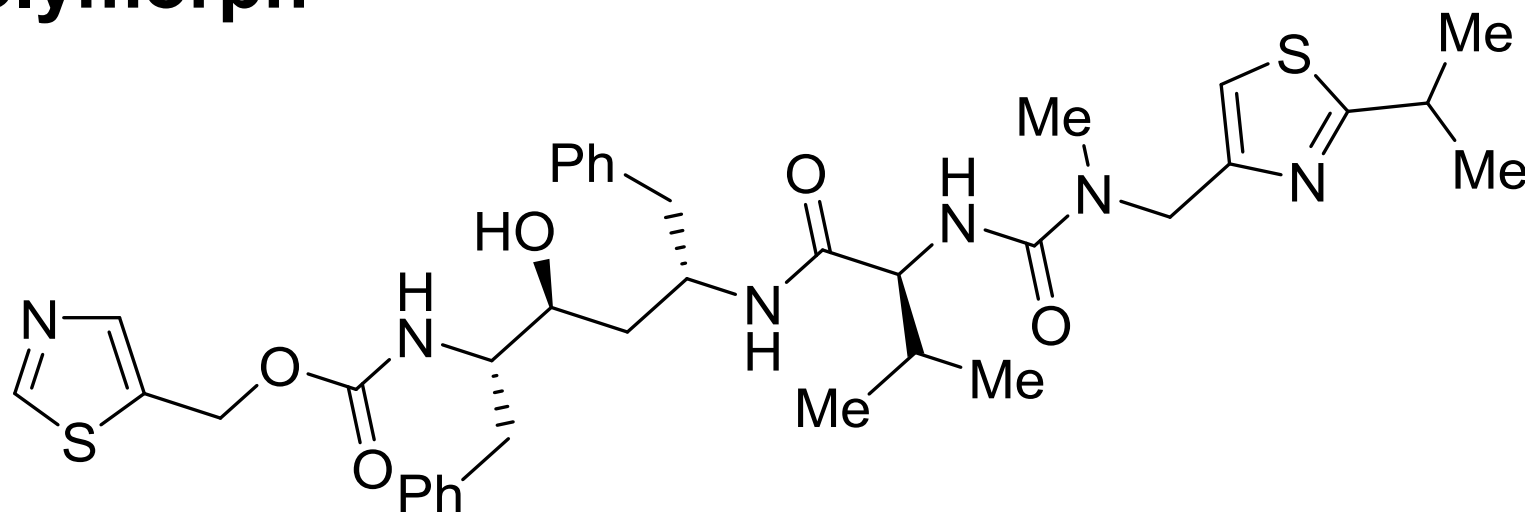
- Burger (Ramberg) rules
- Heat of Transition rule



# POLYMORPHISM

Disappearing polymorph

Ritonavir Case



Protease inhibitor for HIV (Abbott, Norvir™)

Chemburkar, S.R. *et al* *Org. Process Res. Dev.* 4, 413 (2000)

# POLYMORPHISM

## Disappearing polymorph

### Ritonavir Case

NDA (New Drug Application) filed in December 1995;  
Two years after some lots of the product (semisolid gel capsules with Form I) failed a dissolution specification;  
The new crystal form (Form II) was found;  
Form II is thermodynamically more stable than Form I  
Samples of Form II brought to a laboratory to study – within a few days **all** of the lots of ritonavir turned to Form II;  
Form I manufacturing failed from this point and “disappeared”





# POLYMORPHISM


## Disappearing polymorph

### Ritonavir Case

#### Causes:

- Small amounts of impurity
- Residual solvent

#### Solutions:

- Develop new manufacturing process for the preparation of Form I and also Form II;
  - Develop new formulations with either Form.
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# POLYMORPHISM

Disappearing polymorph

Ritonavir Case



Form I

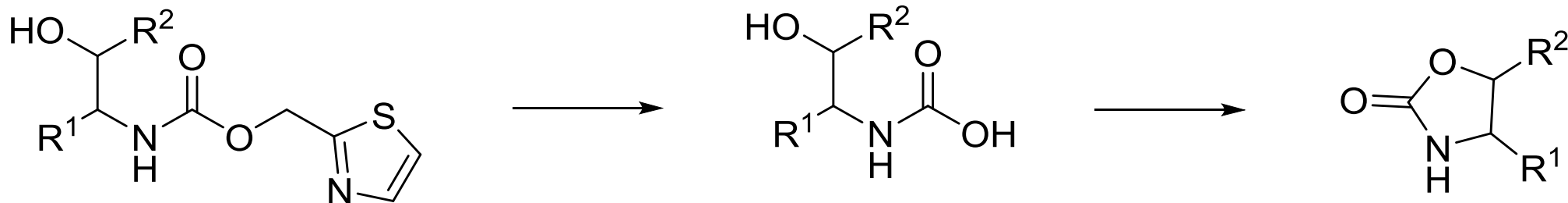


Form II

# POLYMORPHISM

Disappearing polymorph

Ritonavir Case





# POLYMORPHISM

## Disappearing polymorph

Dunitz, J.D. *et al Acc. Chem. Res.* 28, 193 (1995)

Bučar, D.-K. *et al Angew. Chem. Int. Ed. Engl.* 54, 6972 (2015)

