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;

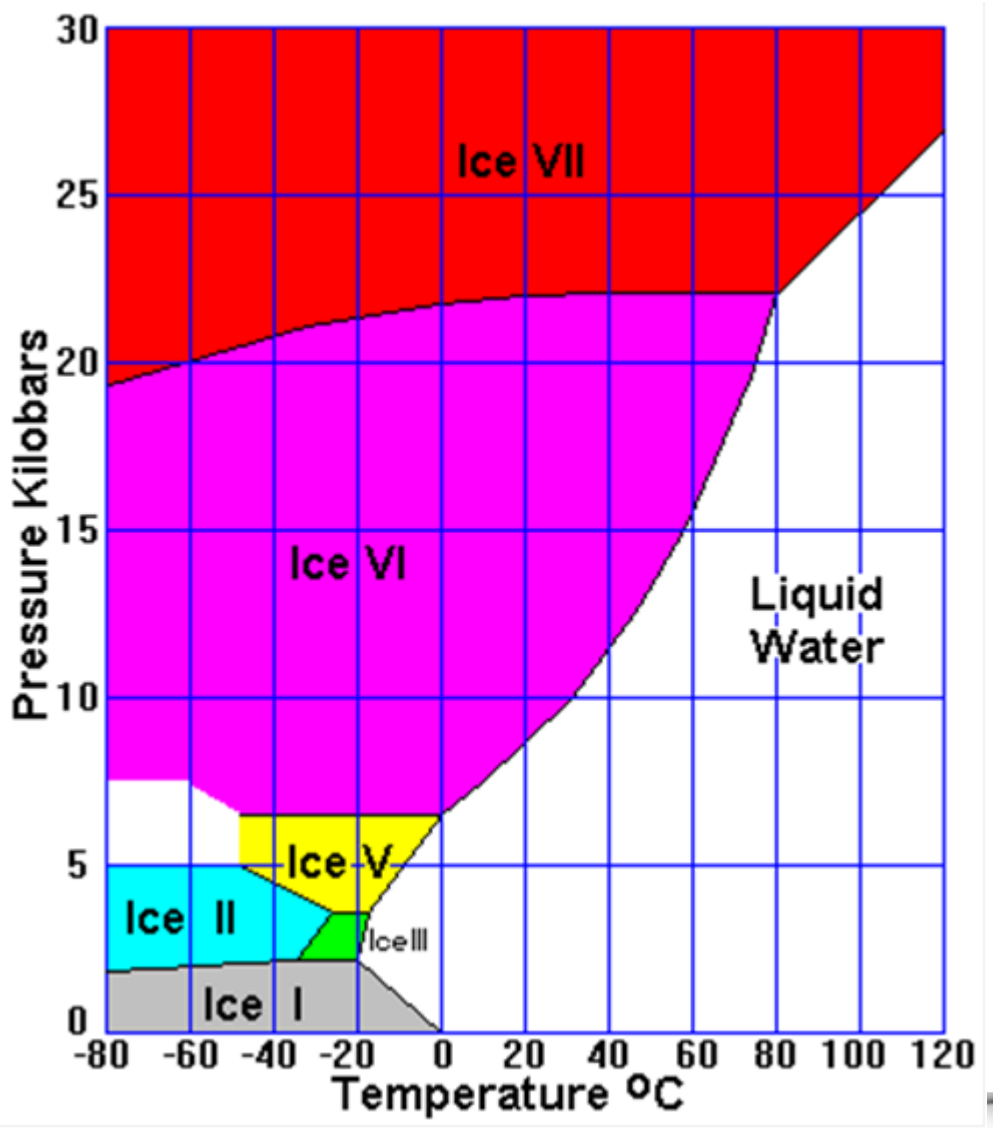
Pseudopolymorphs – the crystal lattice contains some amount of solvent (solvates, hydrates)

POLYMORPHISM

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

Crystal form	*Formation conditions*	*m. p. [°C]*
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

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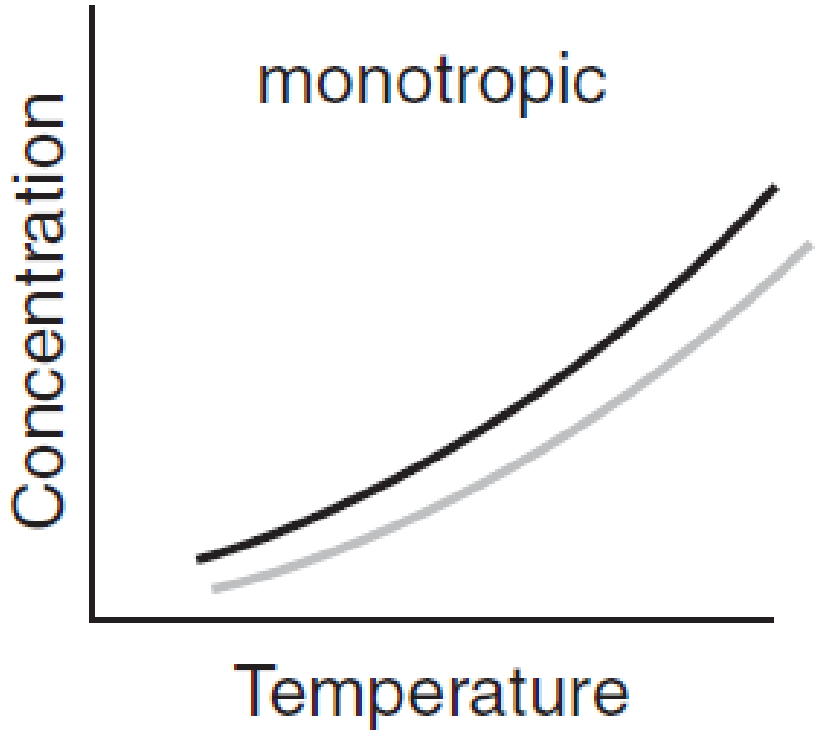
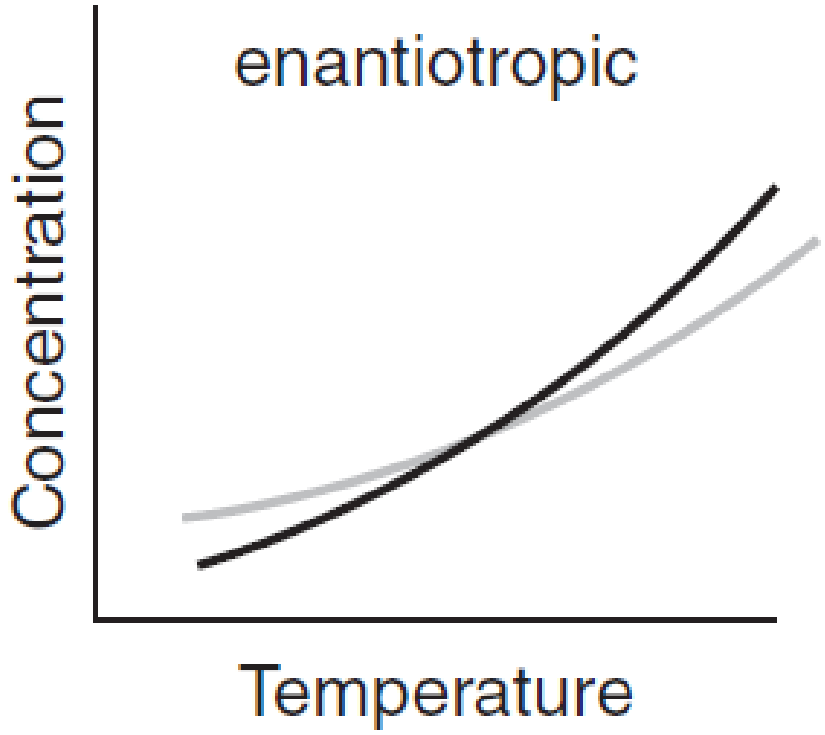
Monotropic polymorphs

Enantiotropic polymorphs – more stable form depends on temperature





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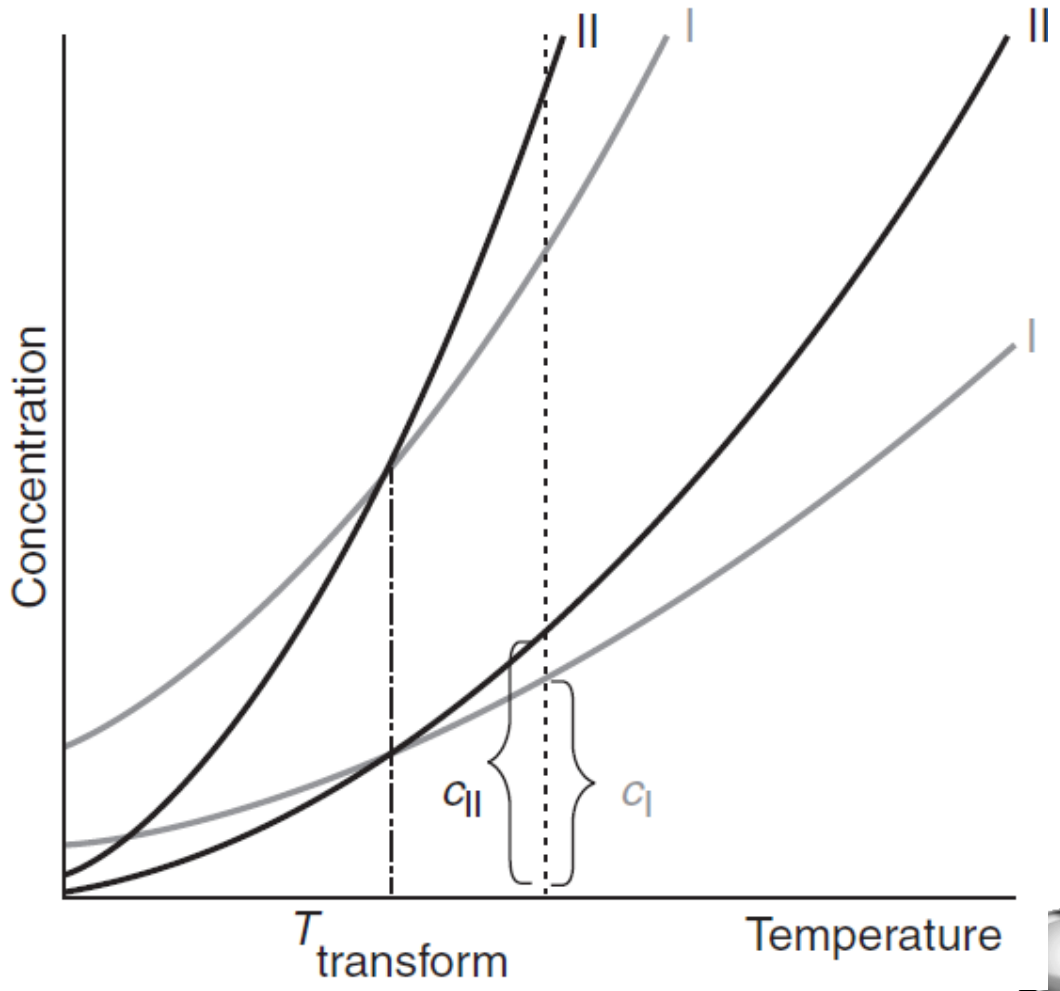
Transition temperature for enantiotropic polymorphs is **independent** on a solvent;



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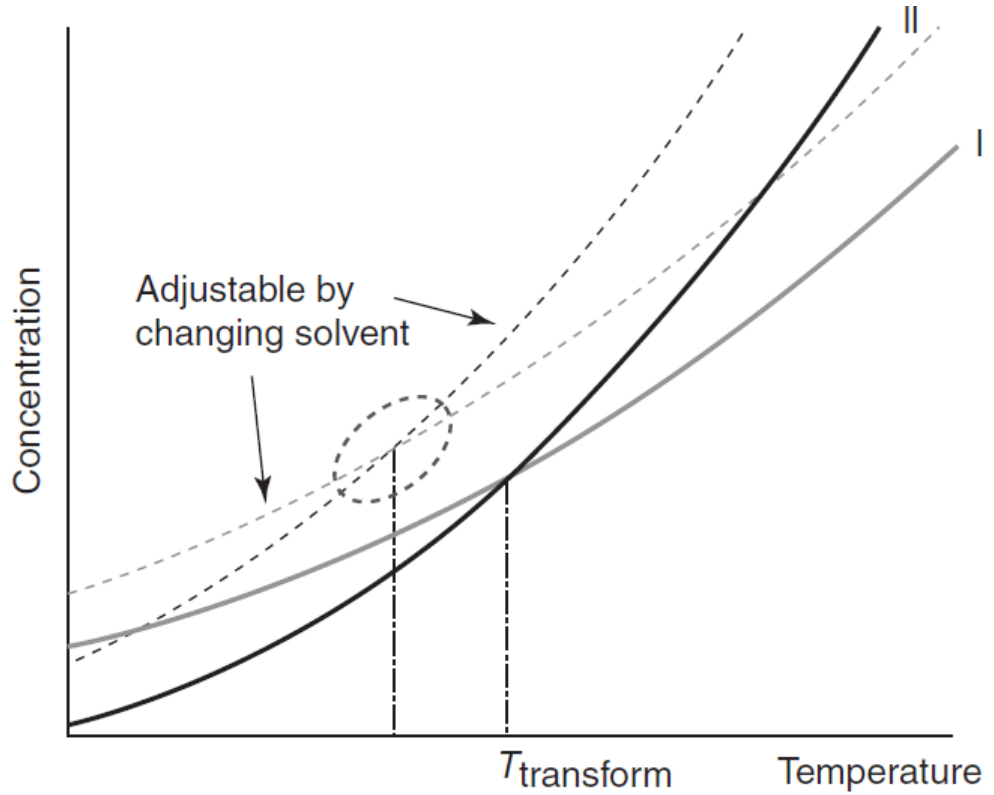
Metastable zone width is however strongly influenced by selected solvent;

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



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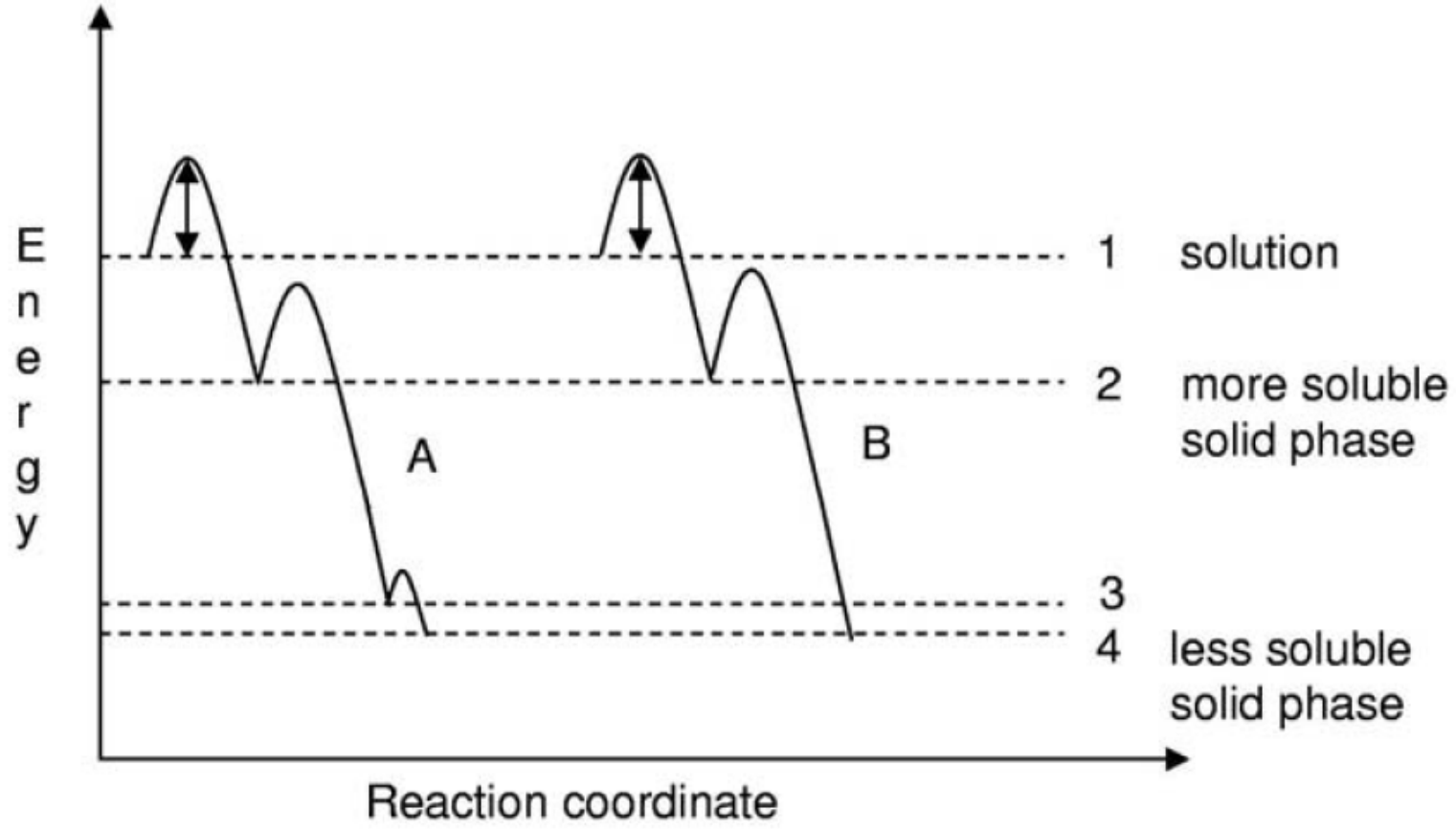
Ostwald's step rule – graphical description



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

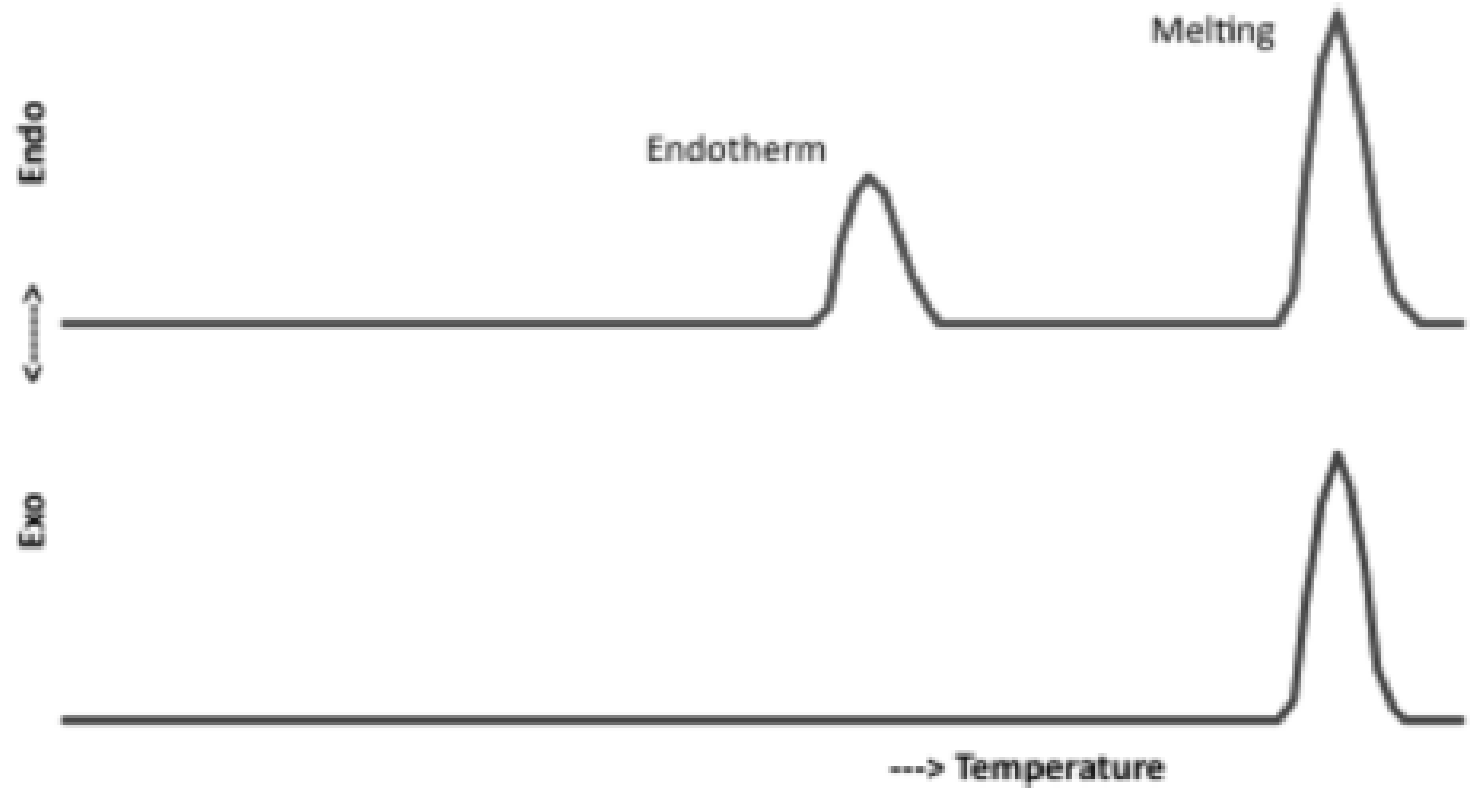
- Polymorphs are enantiotropically related if the high melting form has the lower entropy of fusion, otherwise they are monotropes;

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

POLYMORPHISM

- **Burger (Ramberg) rules**

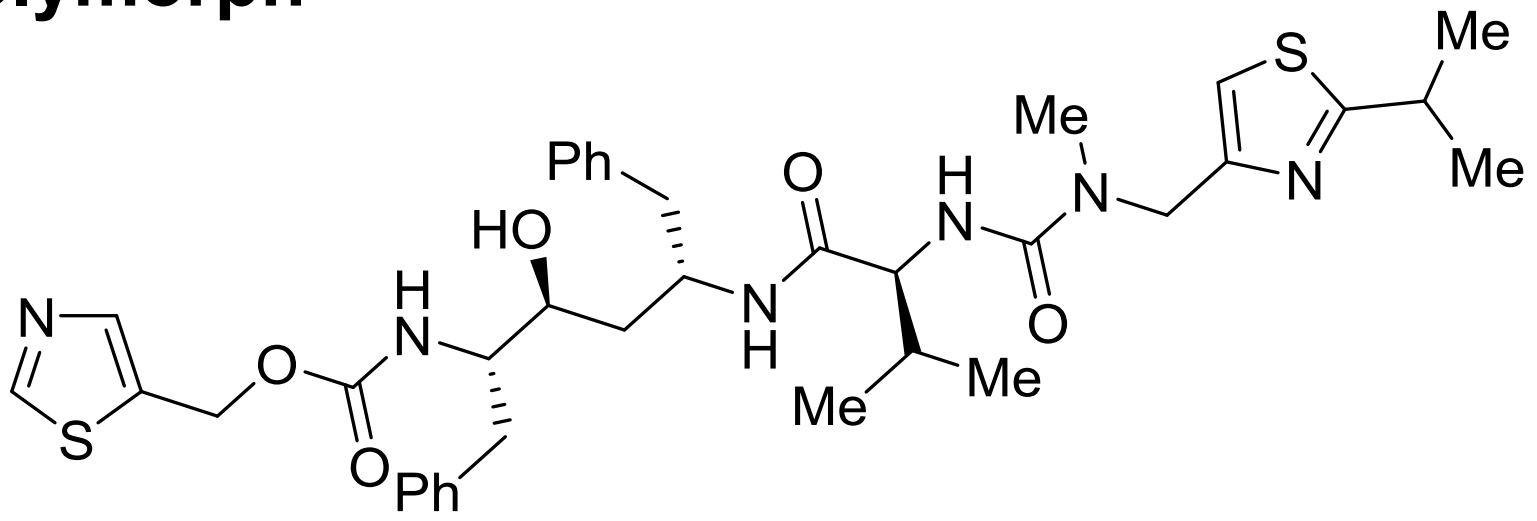
Heat of Transition rule



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 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.

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**)