HR-XRPD and Polymorph Stability

HR-XRPD, A CRUCIAL FACTOR IN THE DETERMINATION OF THE STABILITY HIERARCHY OF POLYMORPHS BY TOPOLOGICAL AND EXPERIMENTAL PRESSURE-TEMPERATURE DIAGRAMS

Ivo B. Rietveld, M. Barrio, J.-Ll. Tamarit, R. Céolin

Paracetamol

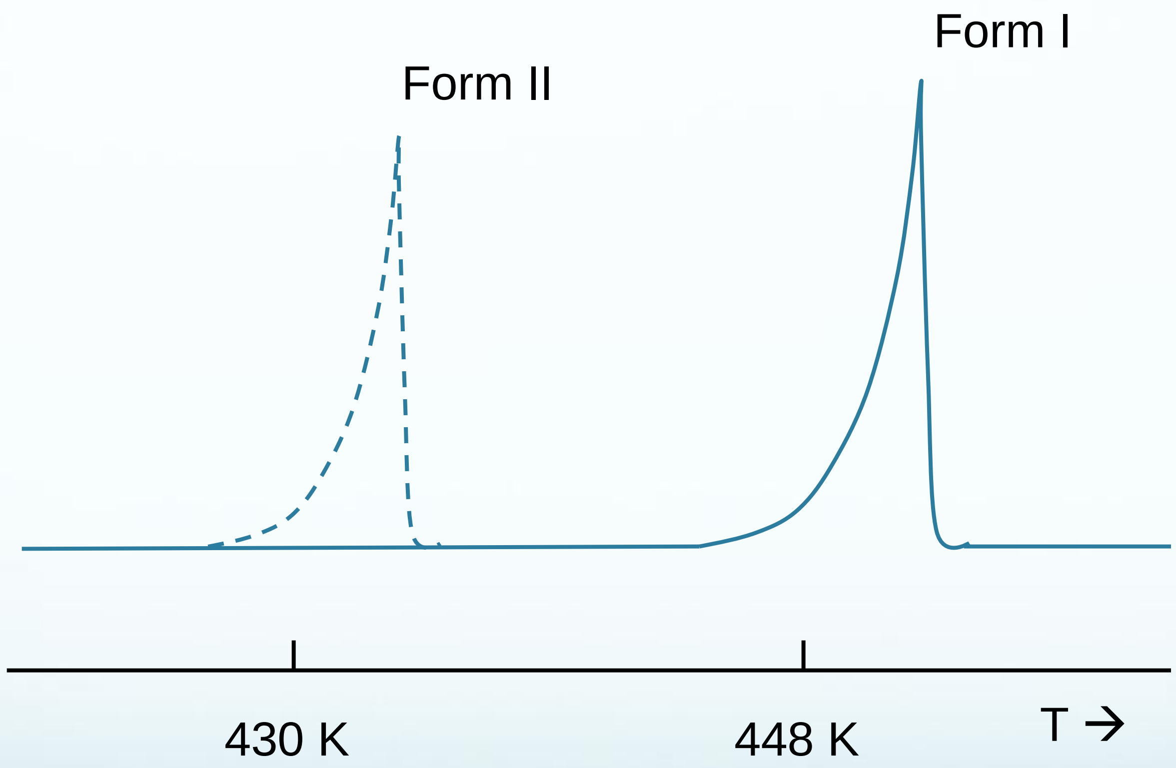
Two known polymorphs:

Form I: Monoclinic $P2_1/a$ fusion: 442.8 K, 191.4 J g^{-1}

Form II: Orthorhombic Pbca fusion: 430.2 K, 181.7 J g^{-1}

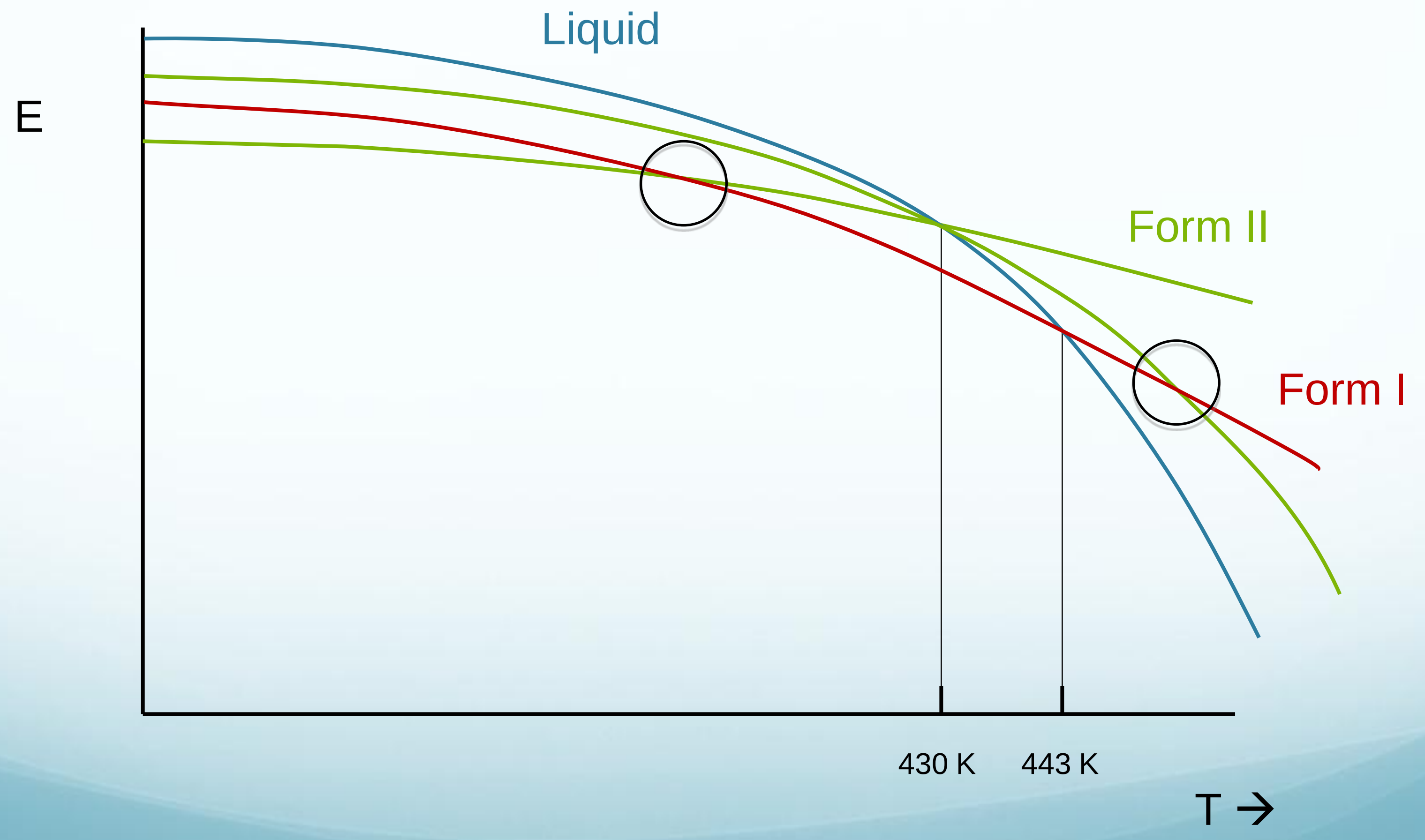
Which is the most stable?

Paracetamol



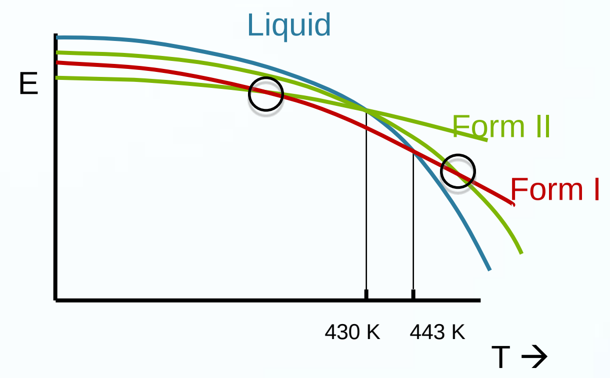
Paracetamol

Where is the equilibrium between form I and form II?



Gibbs Energy

$$G = H - TS$$

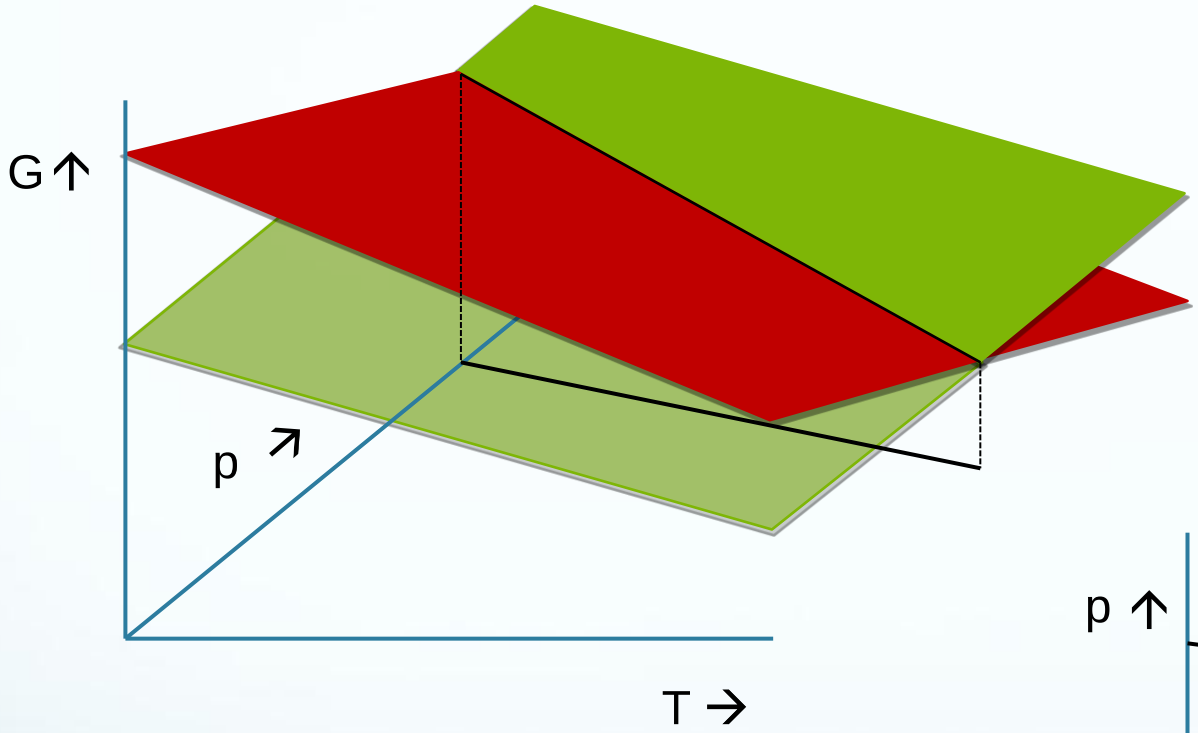


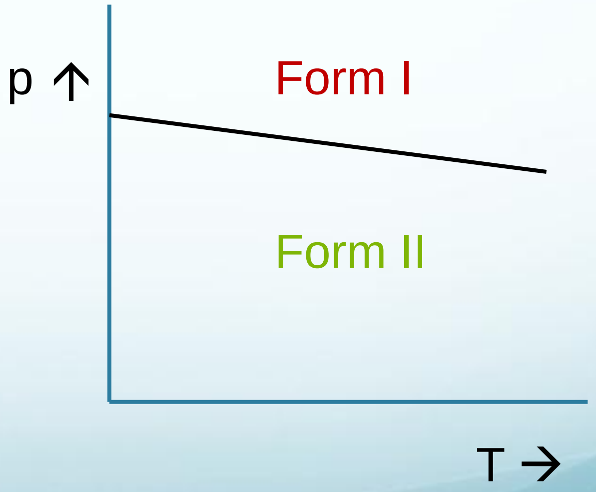
$$dG = -SdT + Vdp$$

G is *characteristic* for the variables:

Temperature and **Pressure**

Gibbs Energy





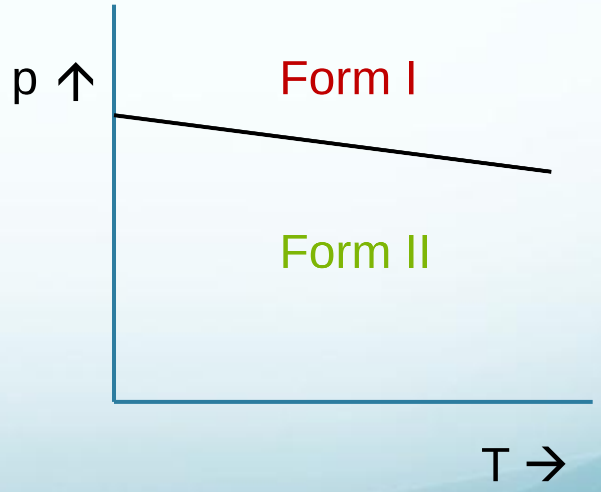
Clapeyron Equation

The slope of a two-phase equilibrium:

Calorimetry

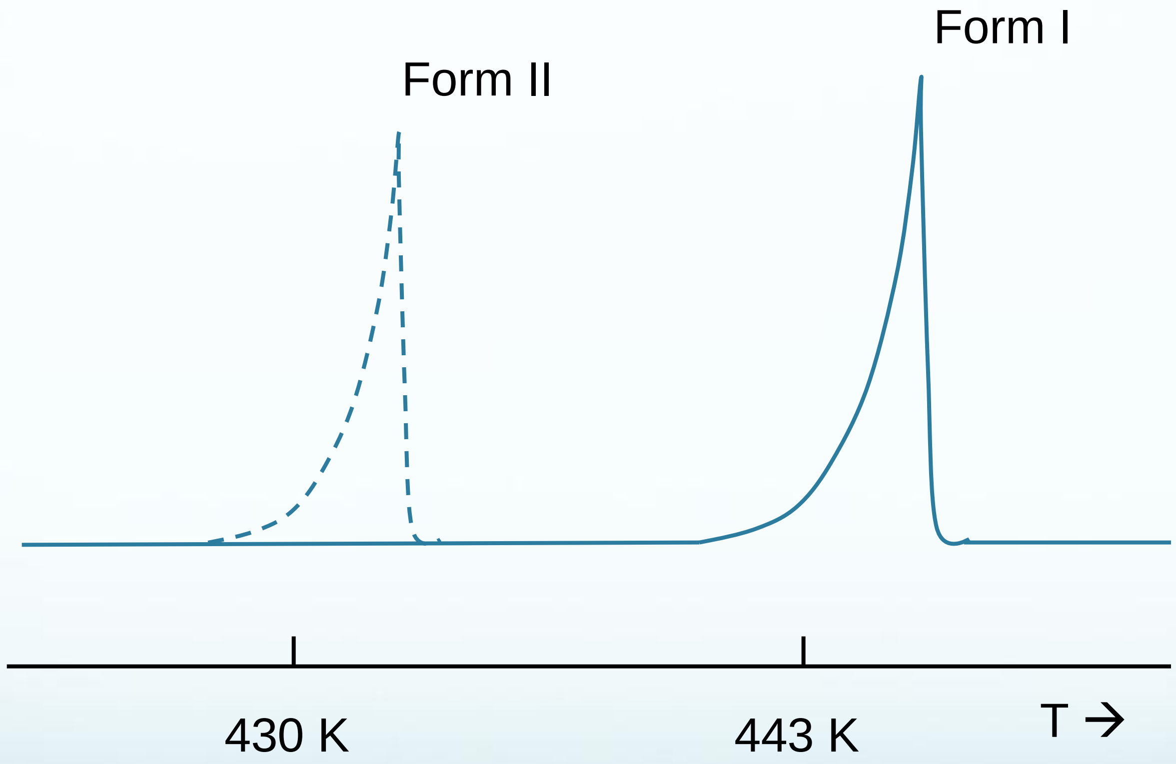
$$\frac{dp}{dT} = \frac{\Delta S}{\Delta v} = \frac{\Delta H}{T \Delta v}$$

X-ray diffraction

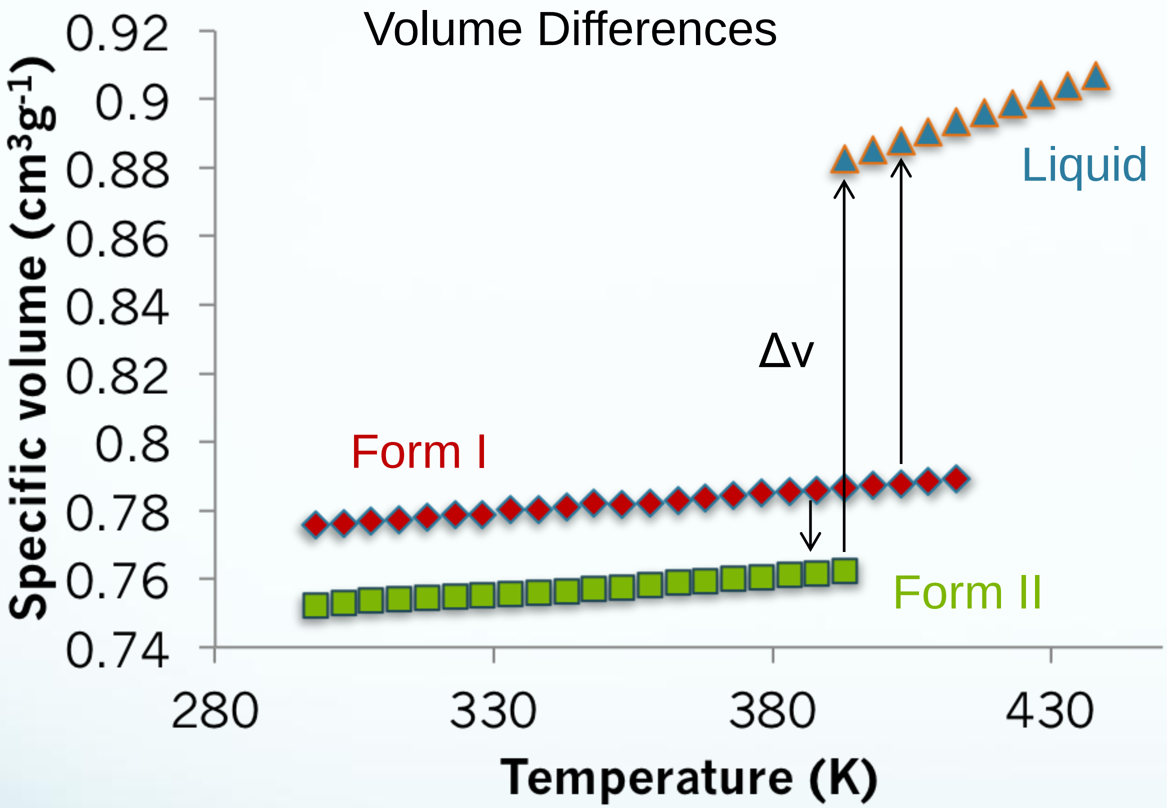


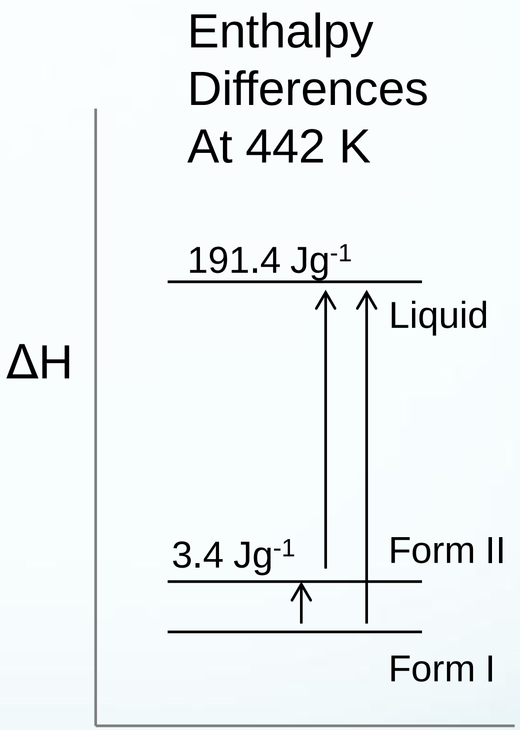
Pressure can be incorporated by X-ray diffraction without even measuring it!

Paracetamol



Paracetamol



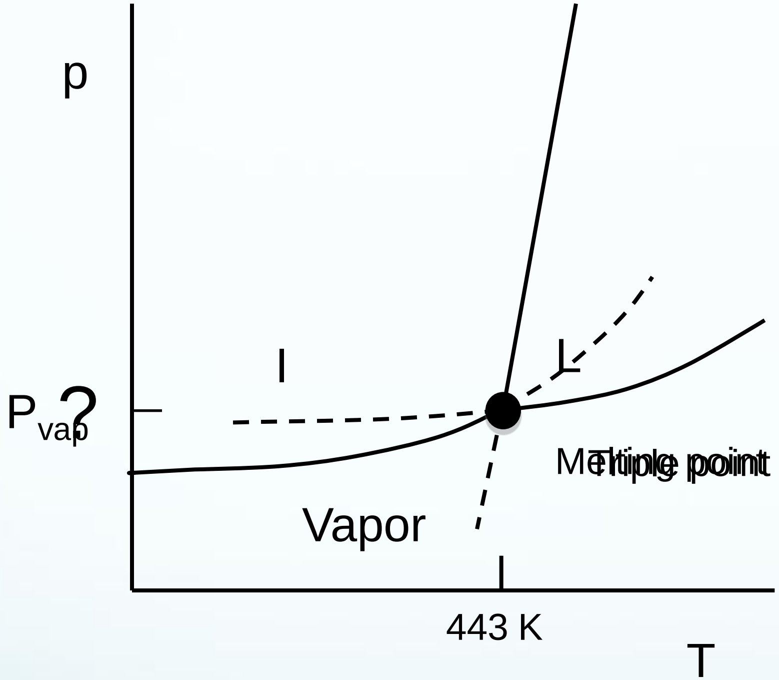


dp/dT (I→L) =3.7 MPa K^{-1}

dp/dT (II→L) = 3.1 MPa K^{-1}

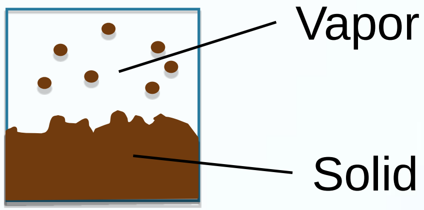
dp/dT (I→II) = -0.3 MPa K^{-1}

Pressure, Triple Points, and Alternation Rule



dp/dT (I→L) =3.7 MPa K^{-1}

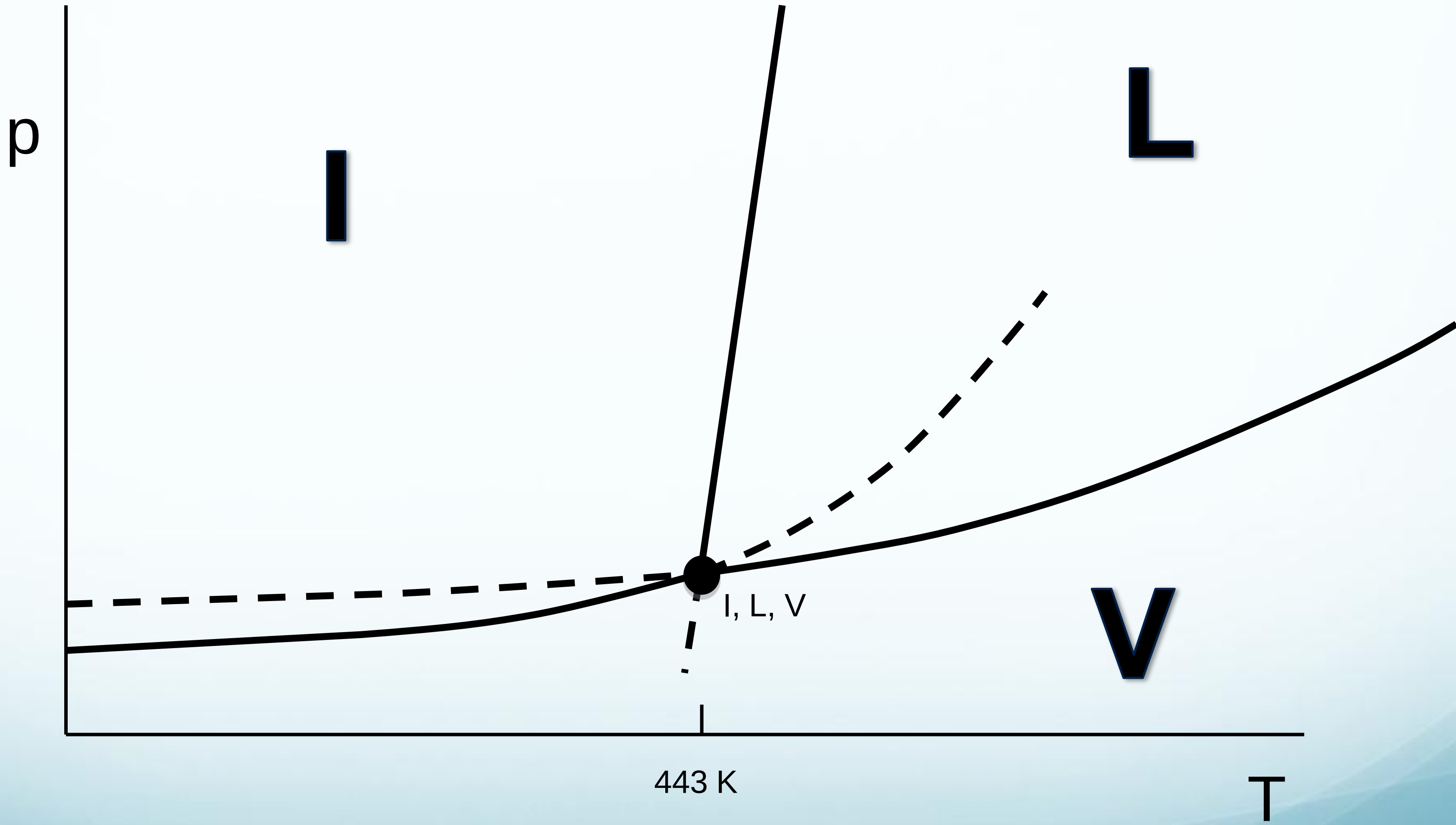
Rigid DSC capsule



The pressure of the system is its **vapor pressure**

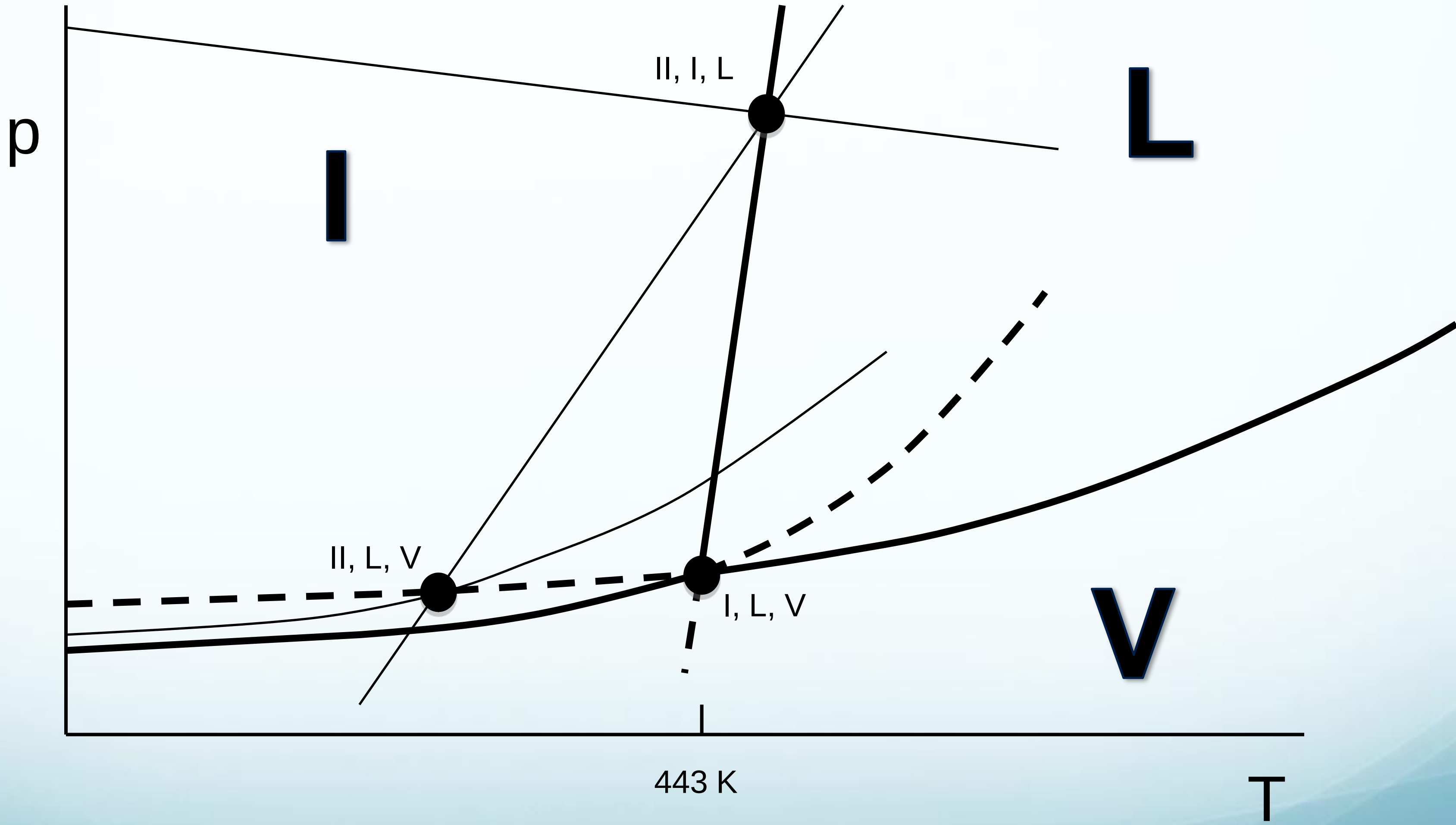
At Fusion: Three Phases
→ Triple point

Paracetamol



dp/dT (I→L) =3.7 MPa K^{-1}

Paracetamol

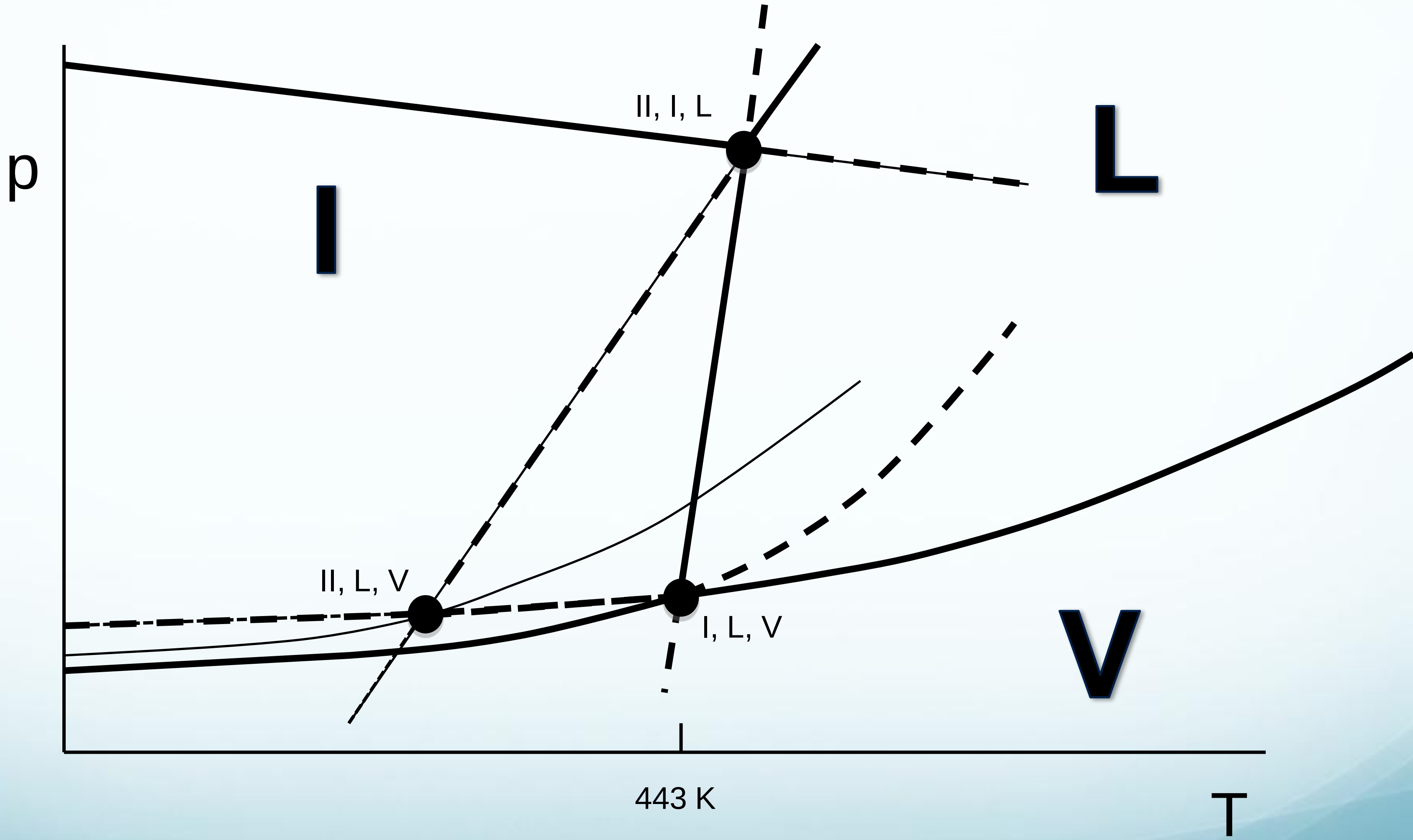


dp/dT (I→L) =3.7 MPa K^{-1}

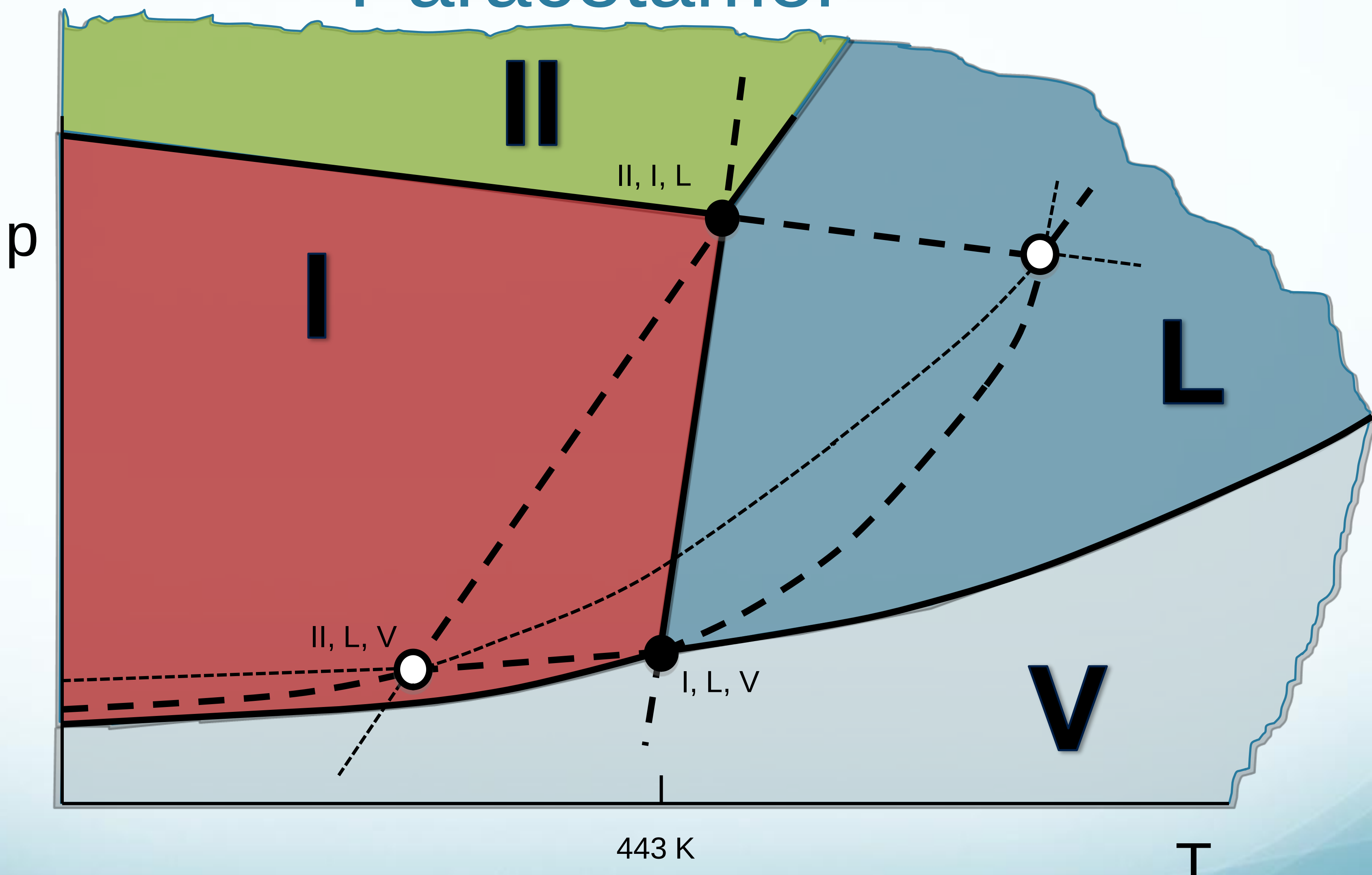
dp/dT (II→L) = 3.1 MPa K^{-1}

dp/dT (I→II) = -0.3 MPa K^{-1}

Paracetamol



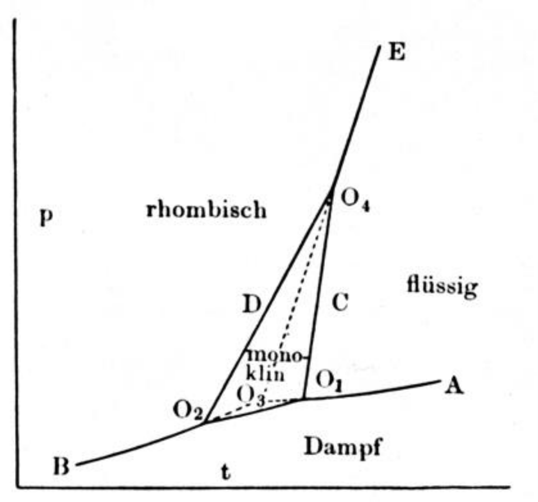
Paracetamol

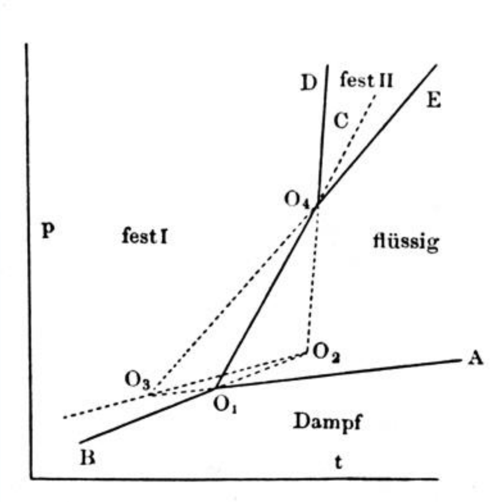


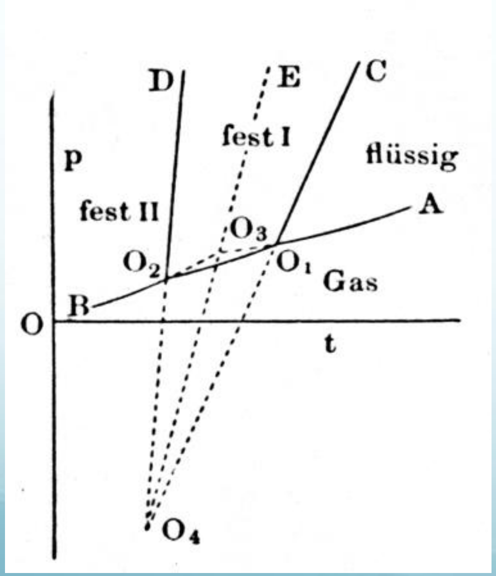
Espeau et al, J. Pharm Sci 94 (3), **2005**, 524-539

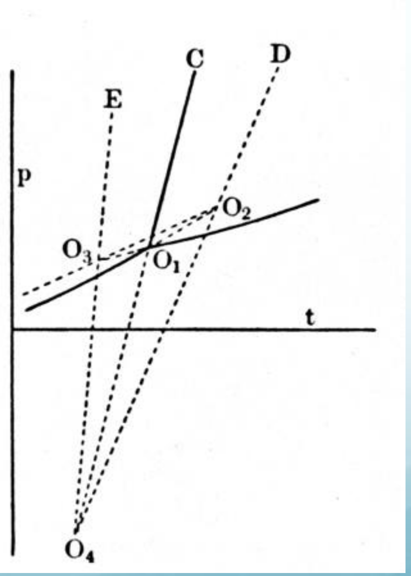
Bakhuis-Roozeboom

4 Phases → 4 Phase Diagrams - 1901



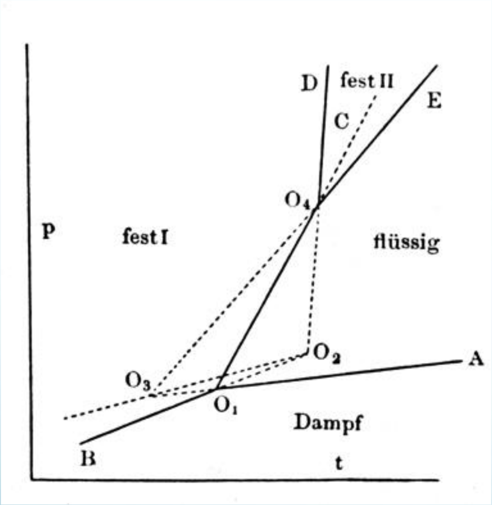


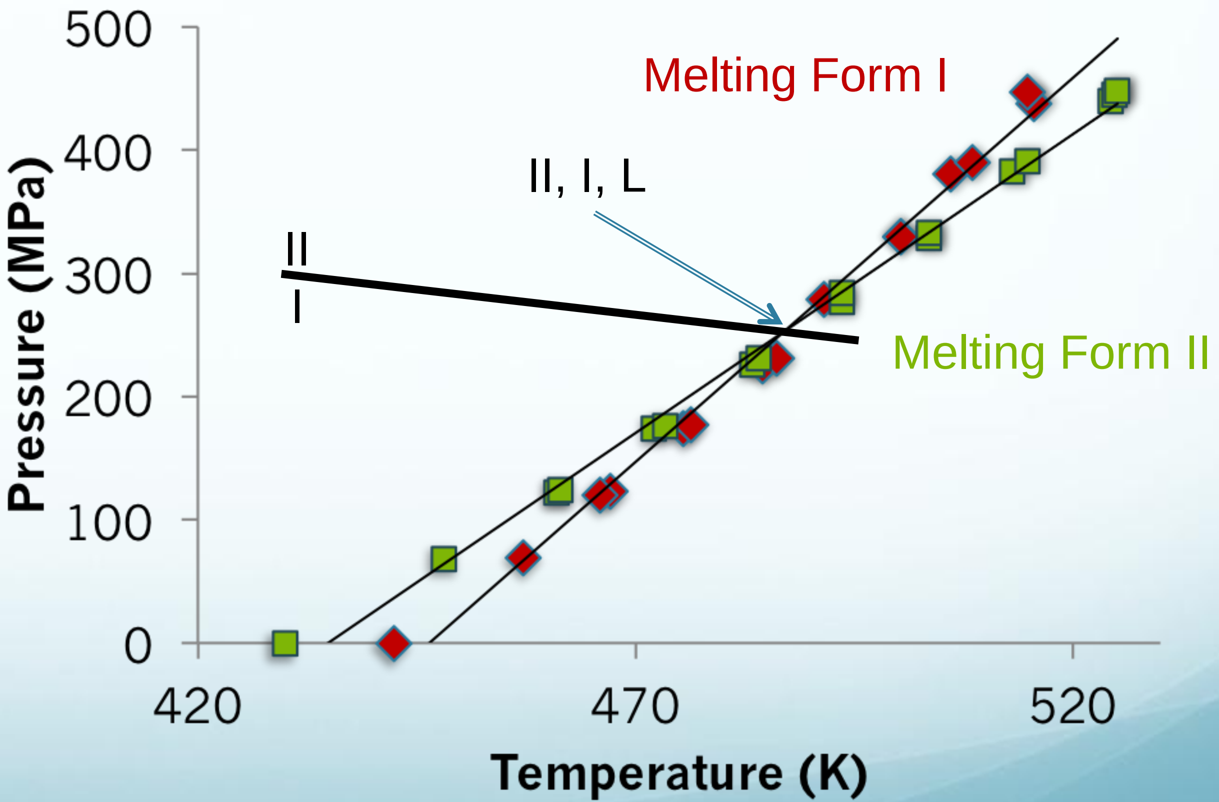




Paracetamol
Experimental Verification

<u>Experimental Triple Point</u>
T = 489.6 K
p = 258.7 MPa

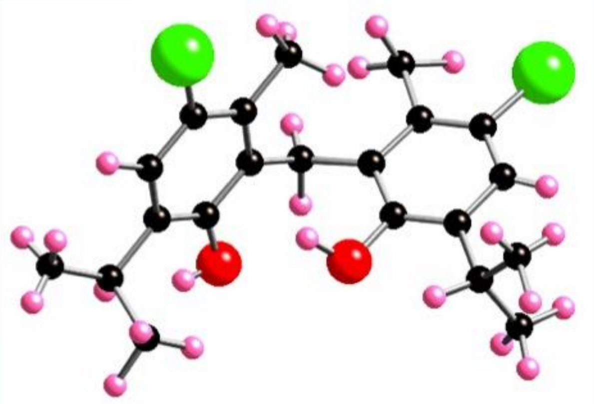


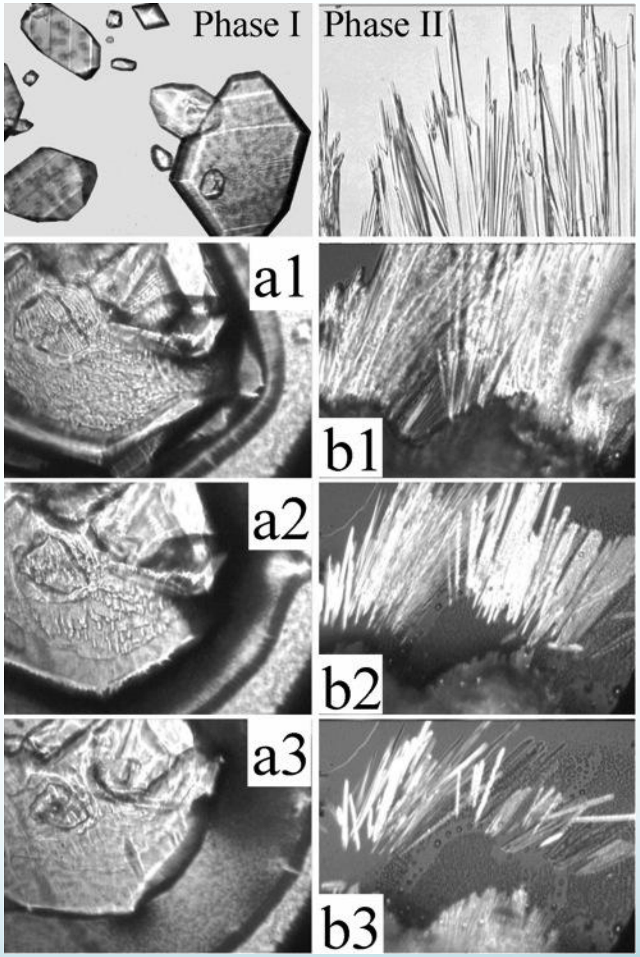


J. Ledru et al., J Pharm Sci 96 (10), **2007**, 2784-2794

Biclotymol

Pulmonary antiseptic

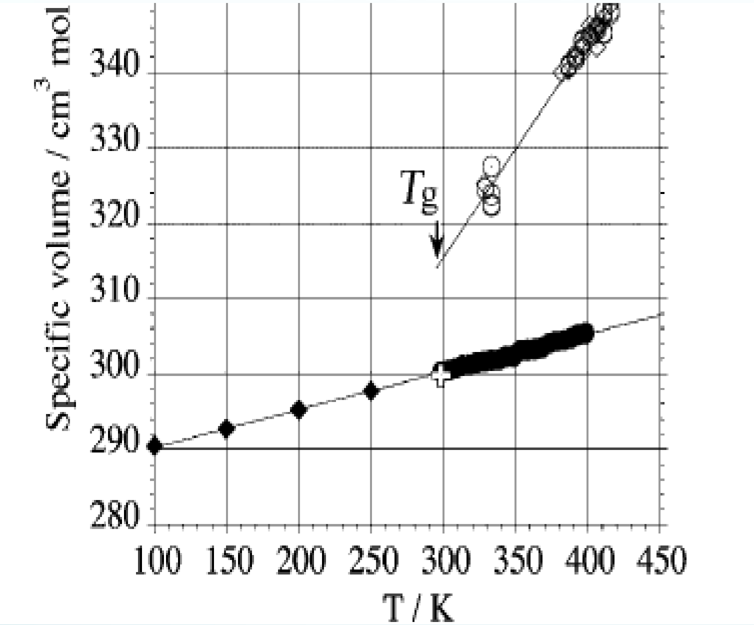




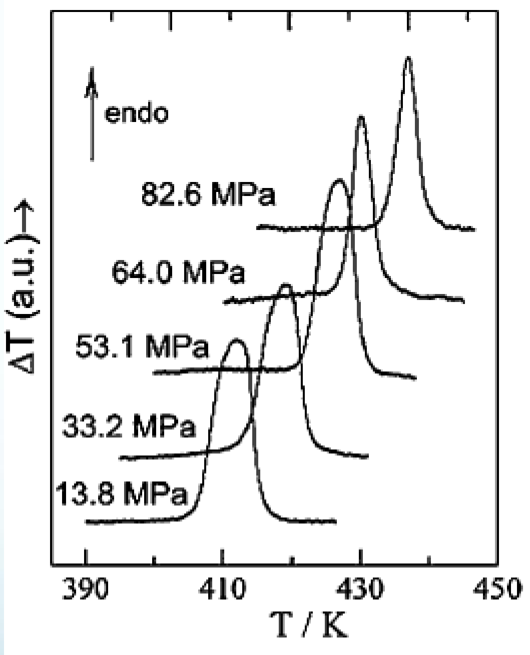
	Form I	Form II
	$P2_1/c$	
T_{fus}:	400 K	374 K
ΔH_{fus}:	36.6 kJ mol^{-1}	28.8 kJ mol^{-1}

Biclotymol

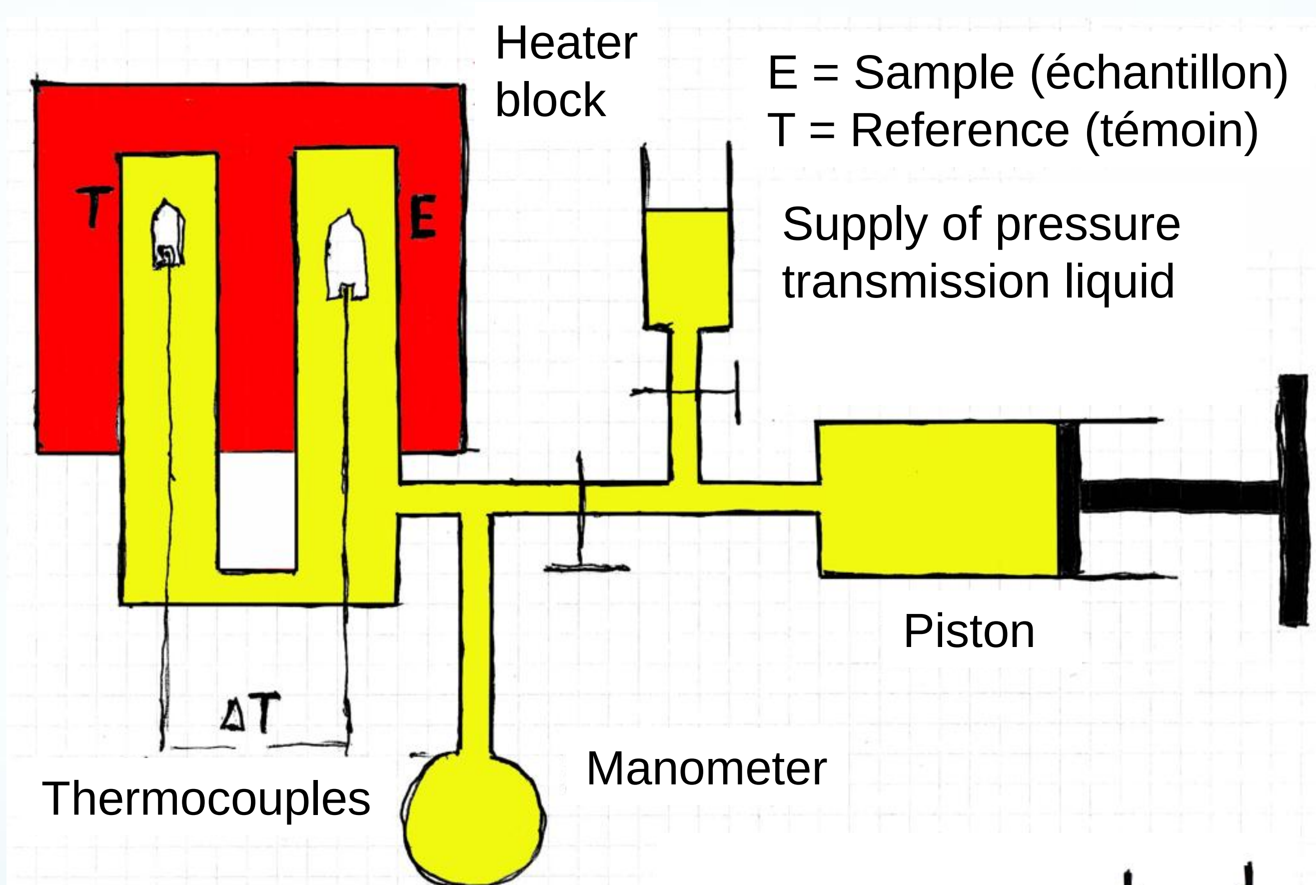
Volume of form I and liquid

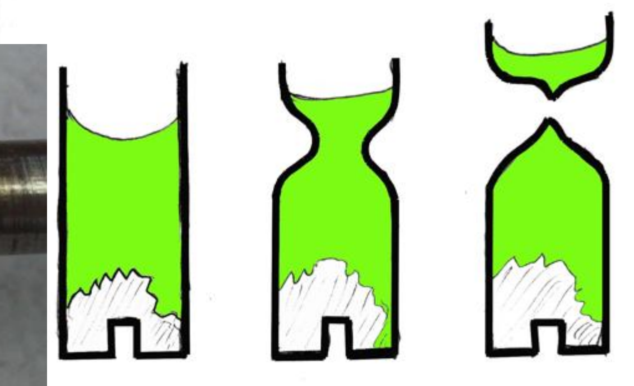


Melting peaks versus pressure

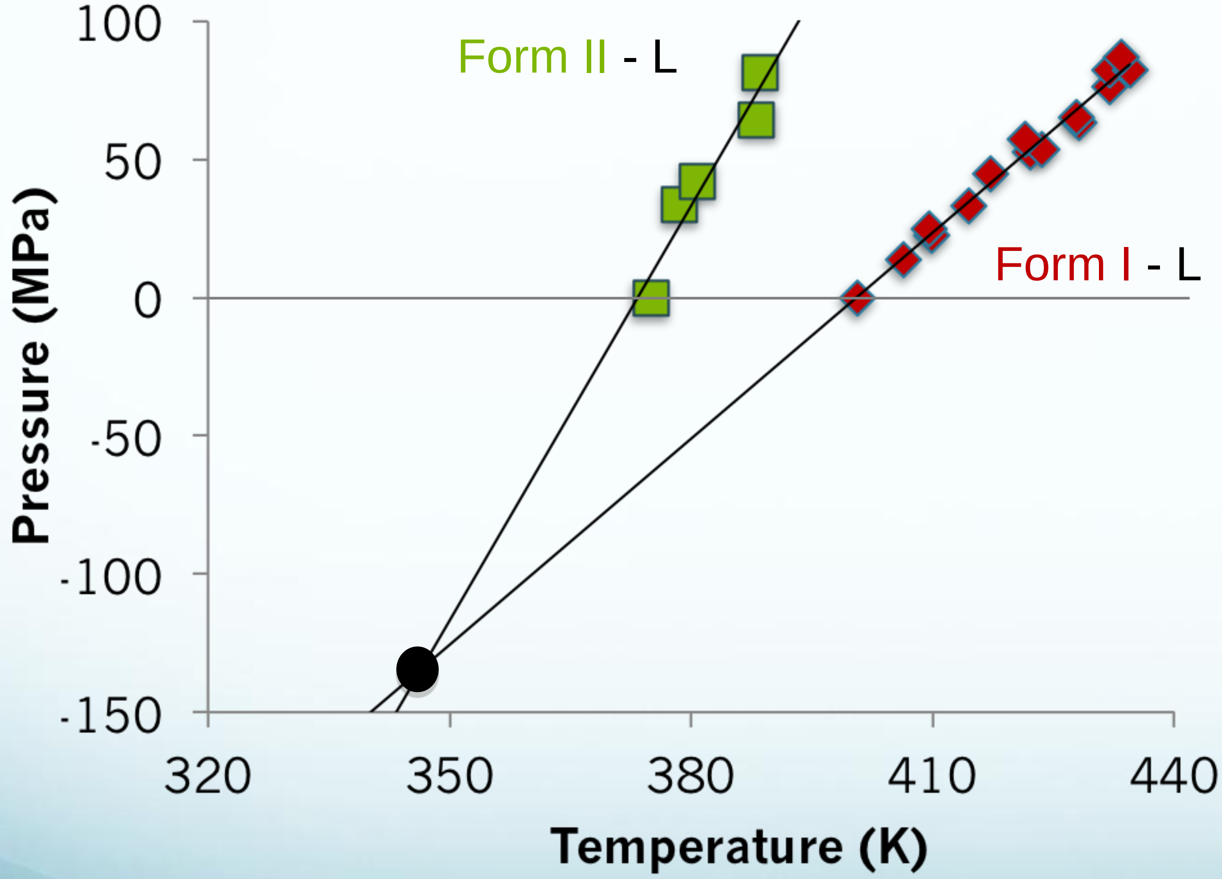


High Pressure DTA

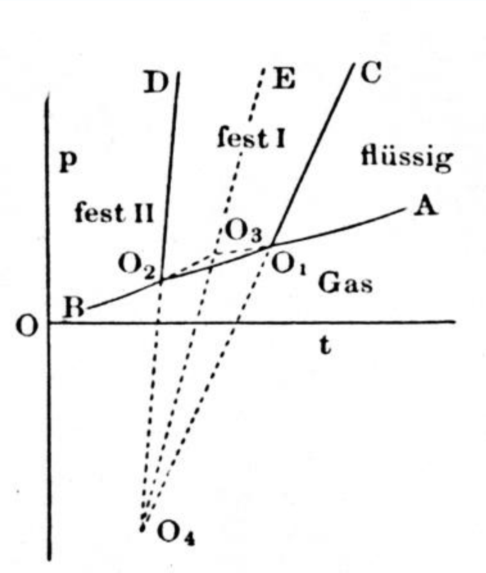




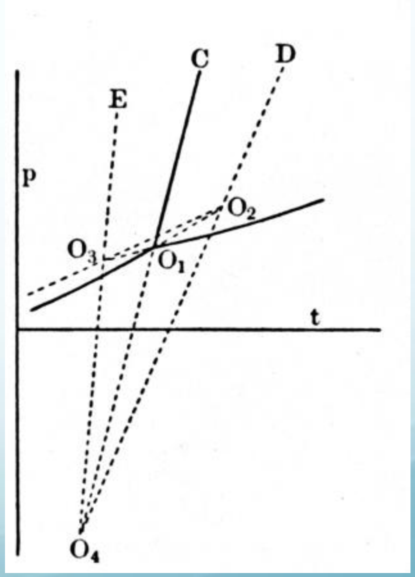
Biclotymol



Form II - L
Form I - L
Pressure (MPa)
100
50
0
-50
-100
-150
320
350
380
410
440
Temperature (K)



D
E
C
fest I
flüssig
p
fest II
A
O3
O2
O1
Gas
B
O
t
O4



C
D
E
p
O2
O3
O1
t
O4

Biclotymol

Le Chatelier

$H_{phase\ A} < H_{phase\ B}$

T →

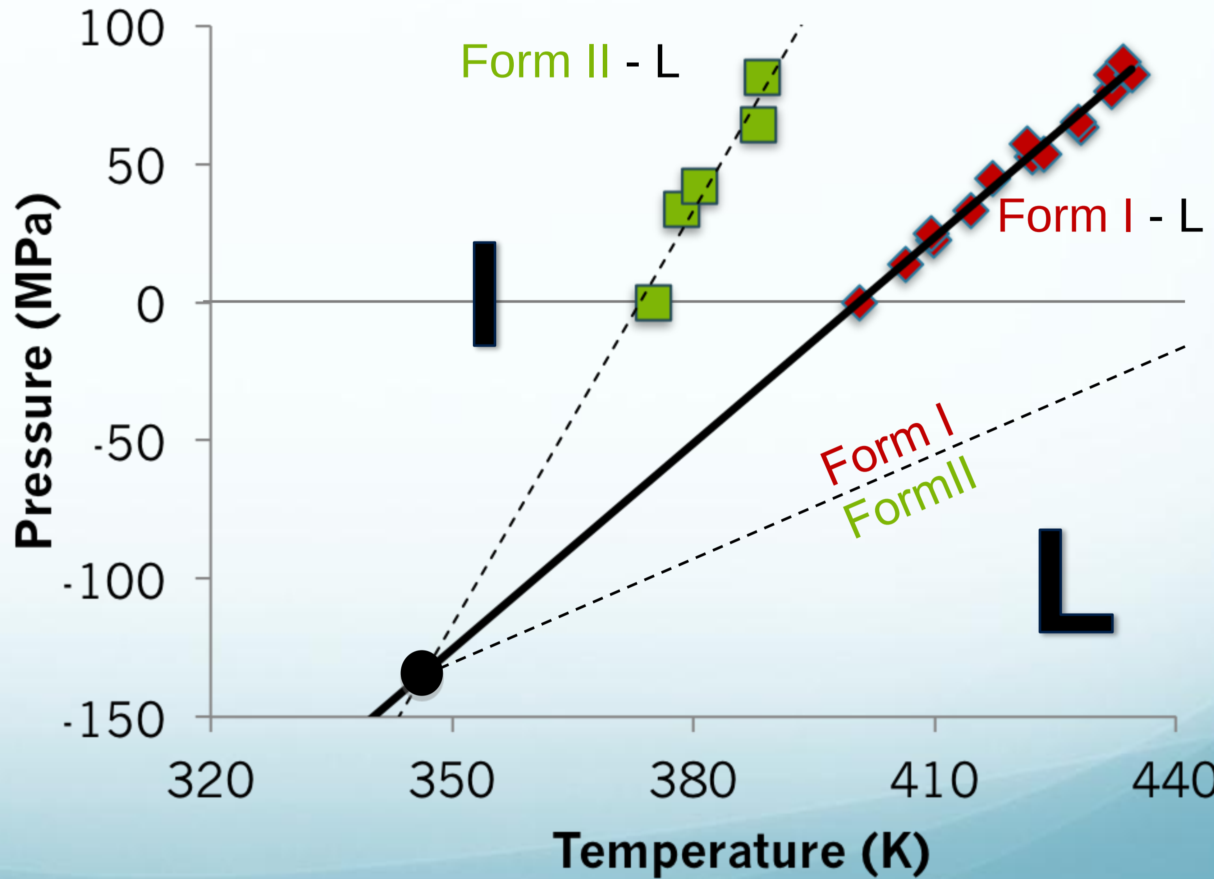
Observation

Form II into Form I transition exothermic

$H_{form\ I} < H_{form\ II}$

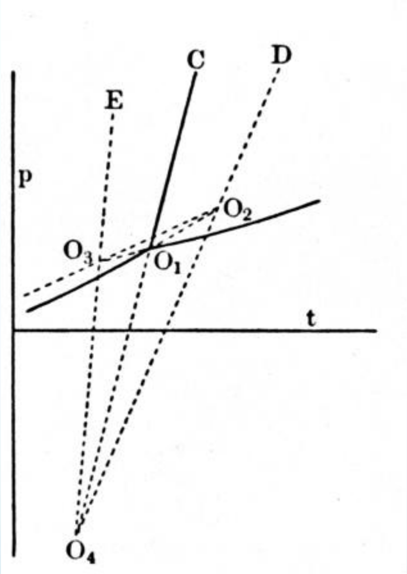
I II

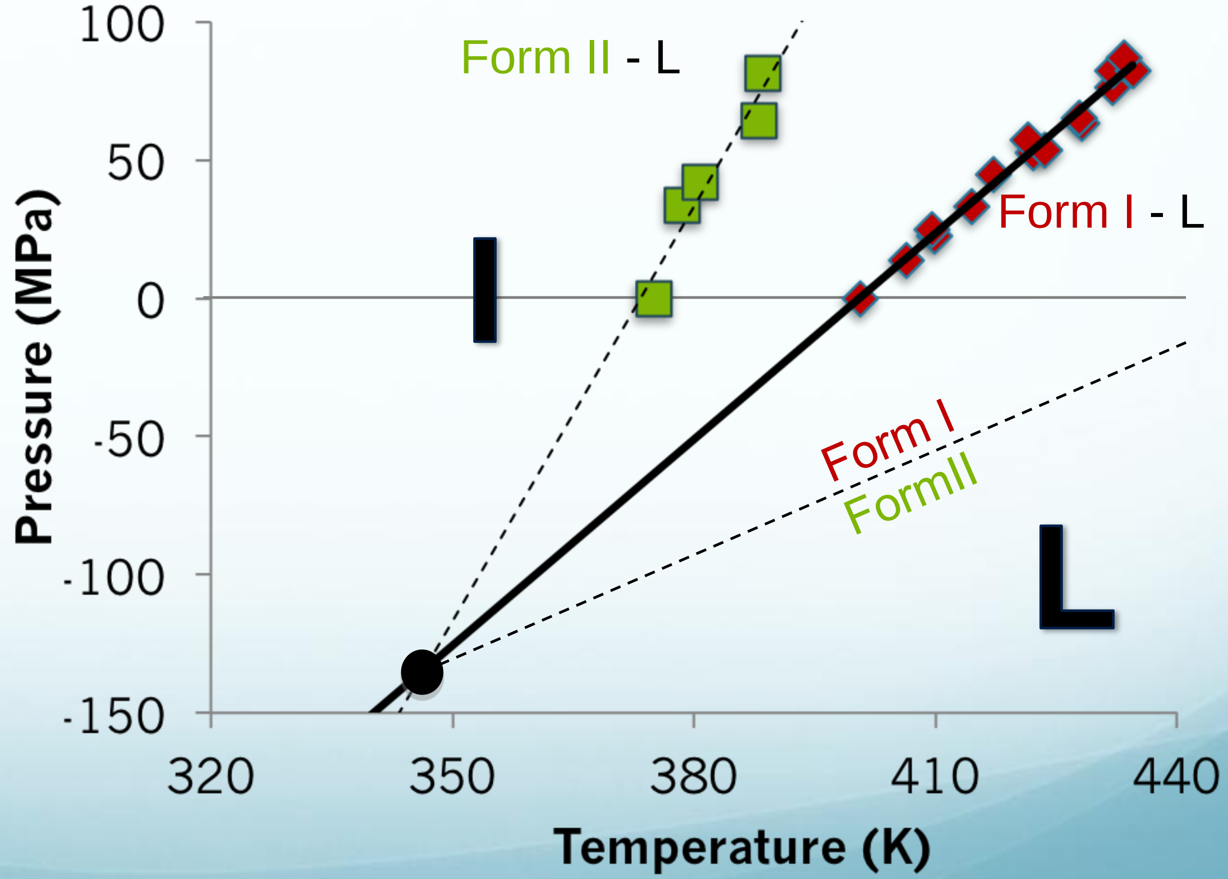
T →



Biclotymol

Overall monotropy

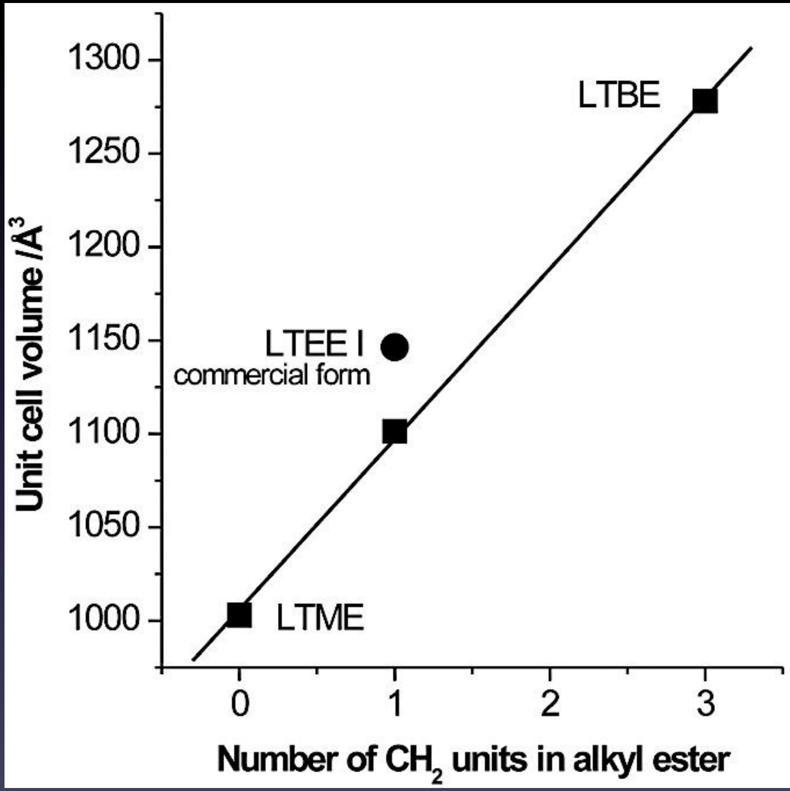


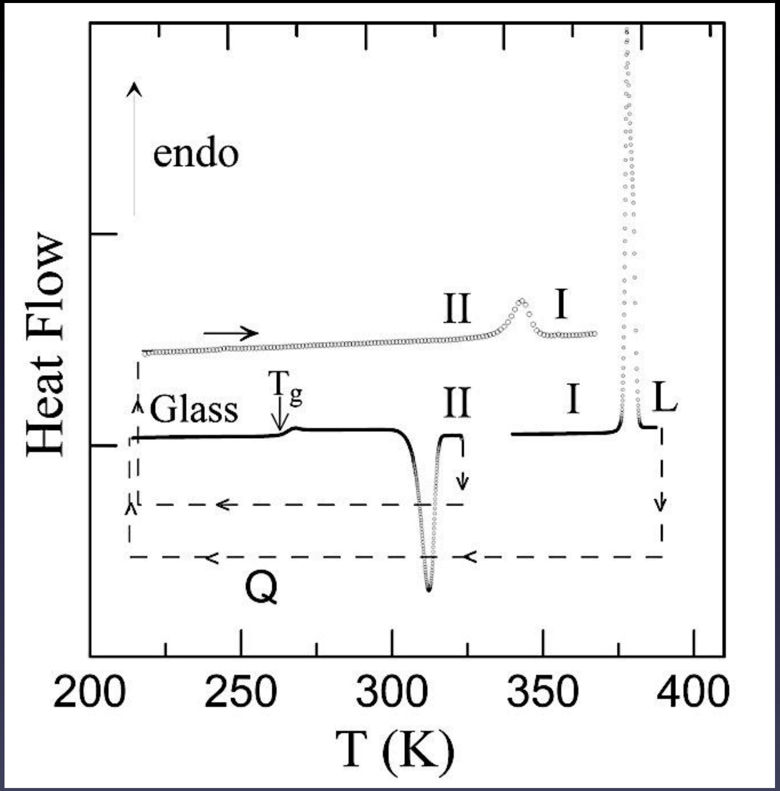


Céolin et al. J. Pharm Sci 97 (9), **2008**, 3927-3941

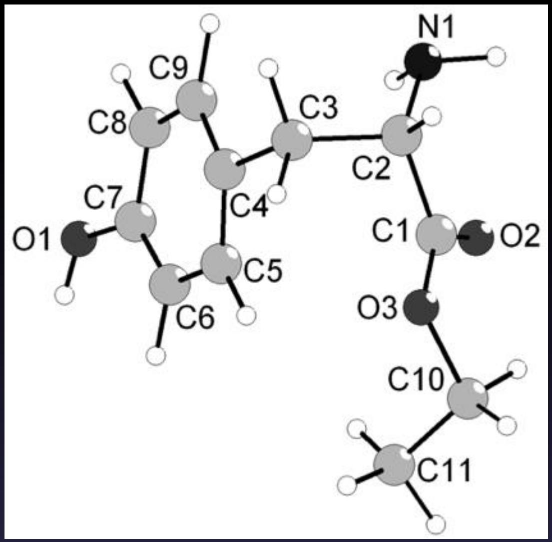
Dimorphic Tyrosine Ethyl Ester

Prodrug against tyrosine deficiency



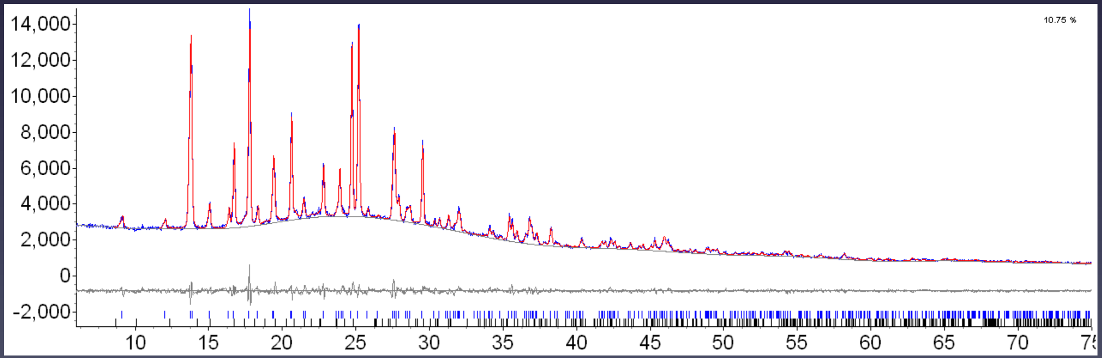


Crystal Structure

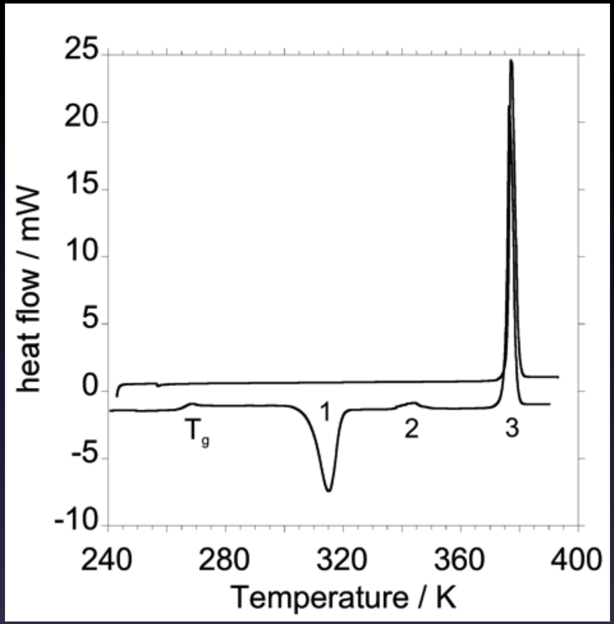


Ethyl ester, Phase II:

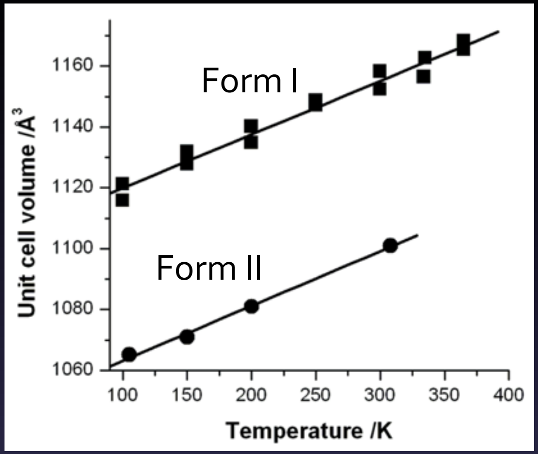
orthorhombic $P2_12_12_1$



P-T, Necessary Data

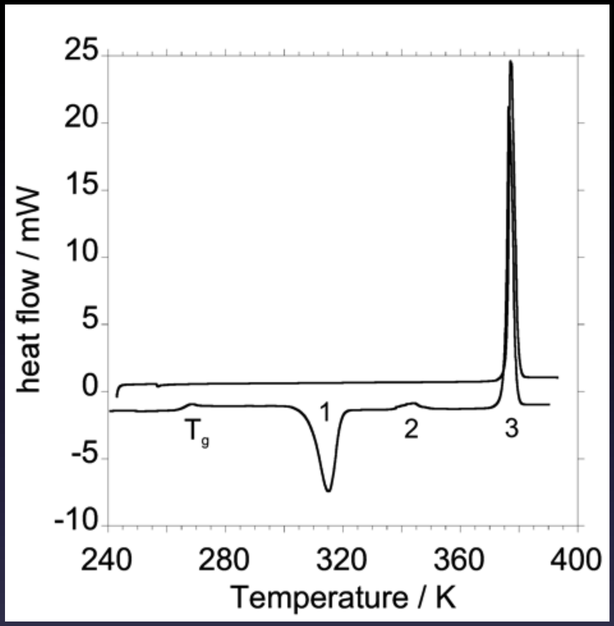


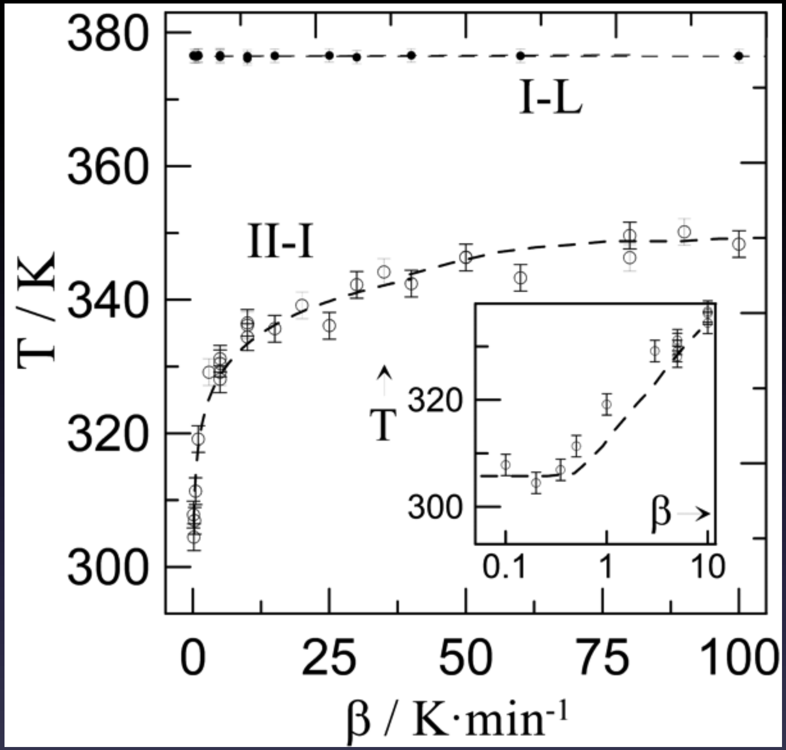
DSC: temperature and enthalpy



X-ray: Volume difference

P-T, Necessary Data





DSC: temperature and enthalpy

DSC: T II → I and heating rate

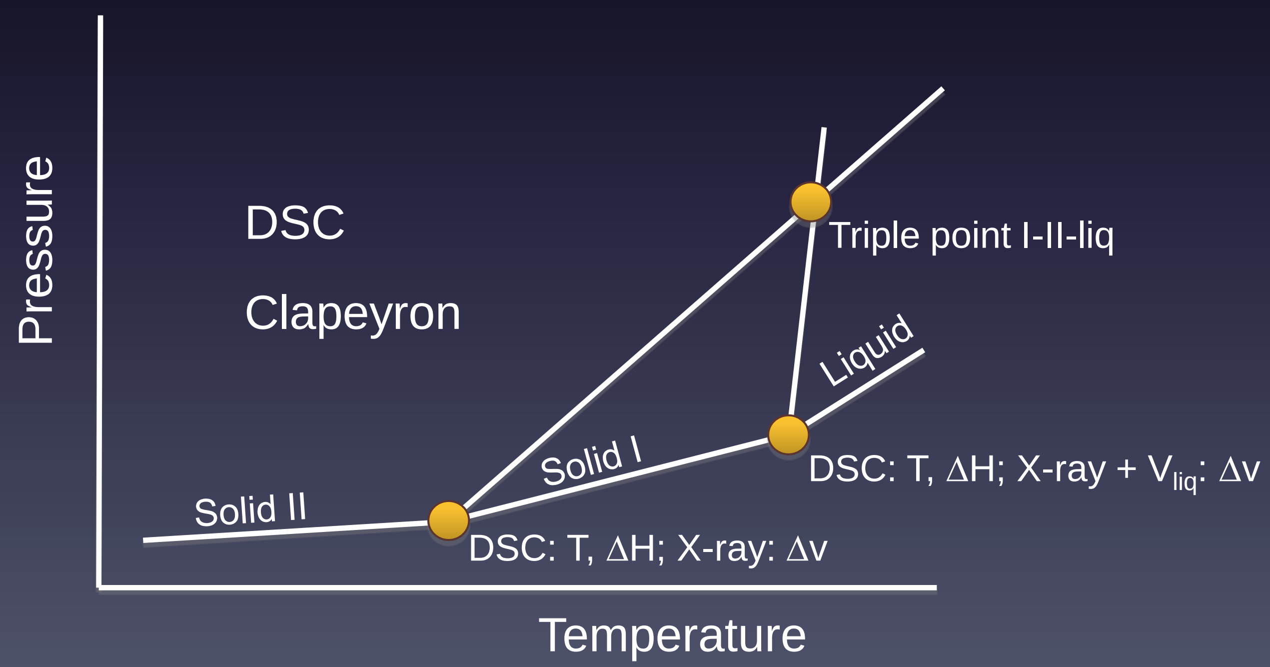
Topological Pressure – Temperature Diagram

Clapeyron Equation: $$\frac{dp}{dT} = \frac{\Delta H}{T\Delta v}$$

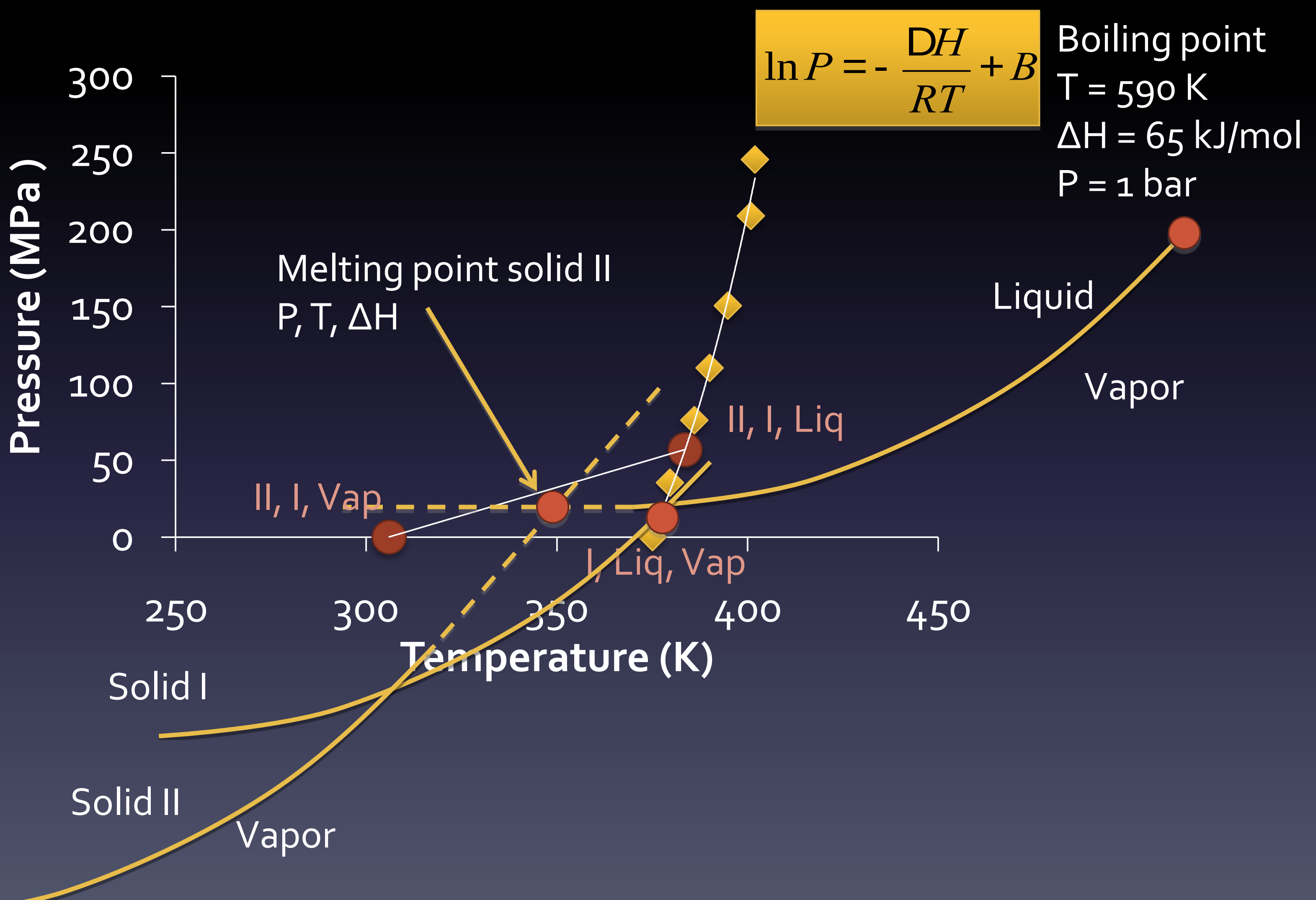
The slope of a phase equilibrium

By DSC, high pressure DTA and X-ray:

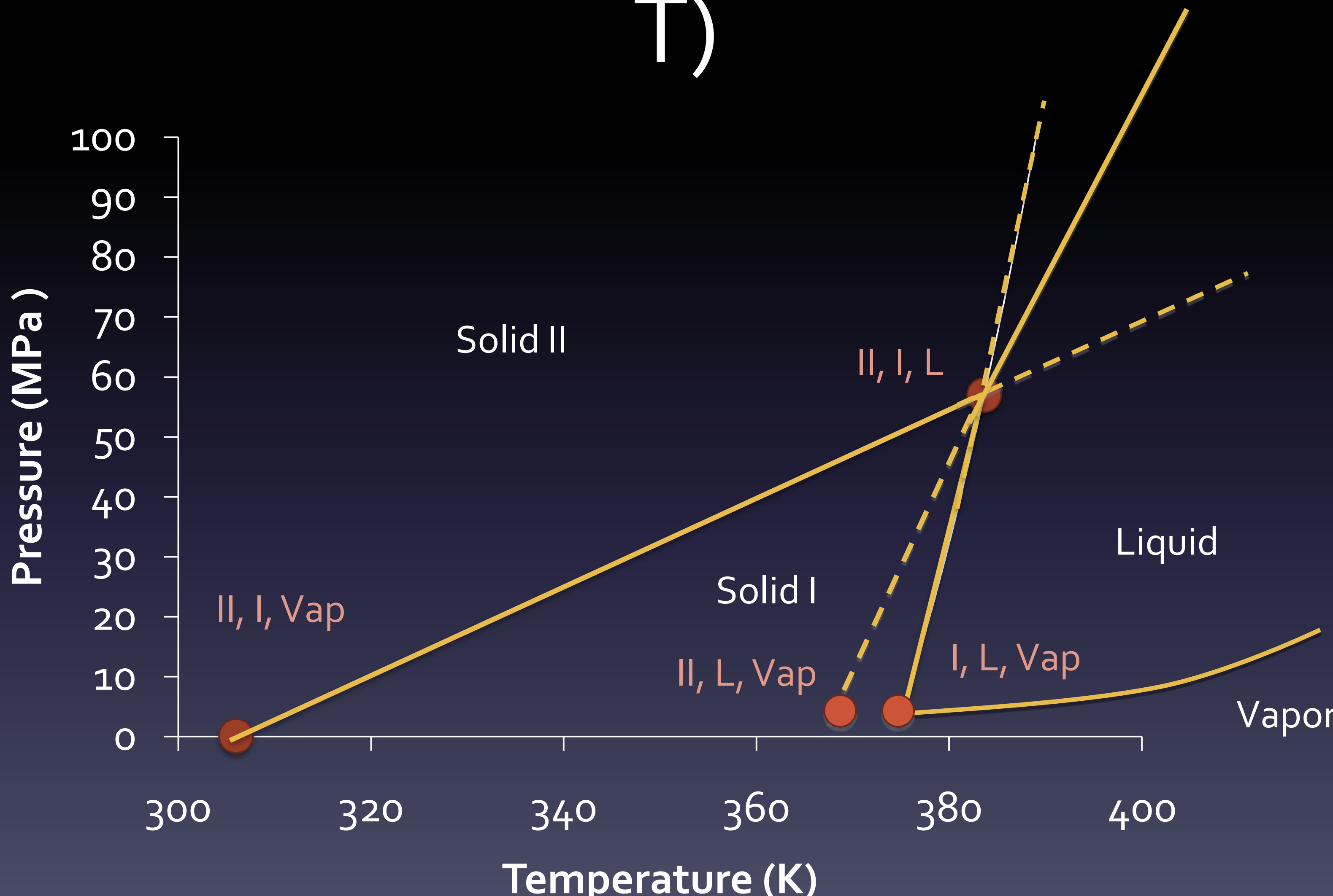
- Transition temperature
- Enthalpy of transition
- Volume change at transition



Construction of P-T Diagram

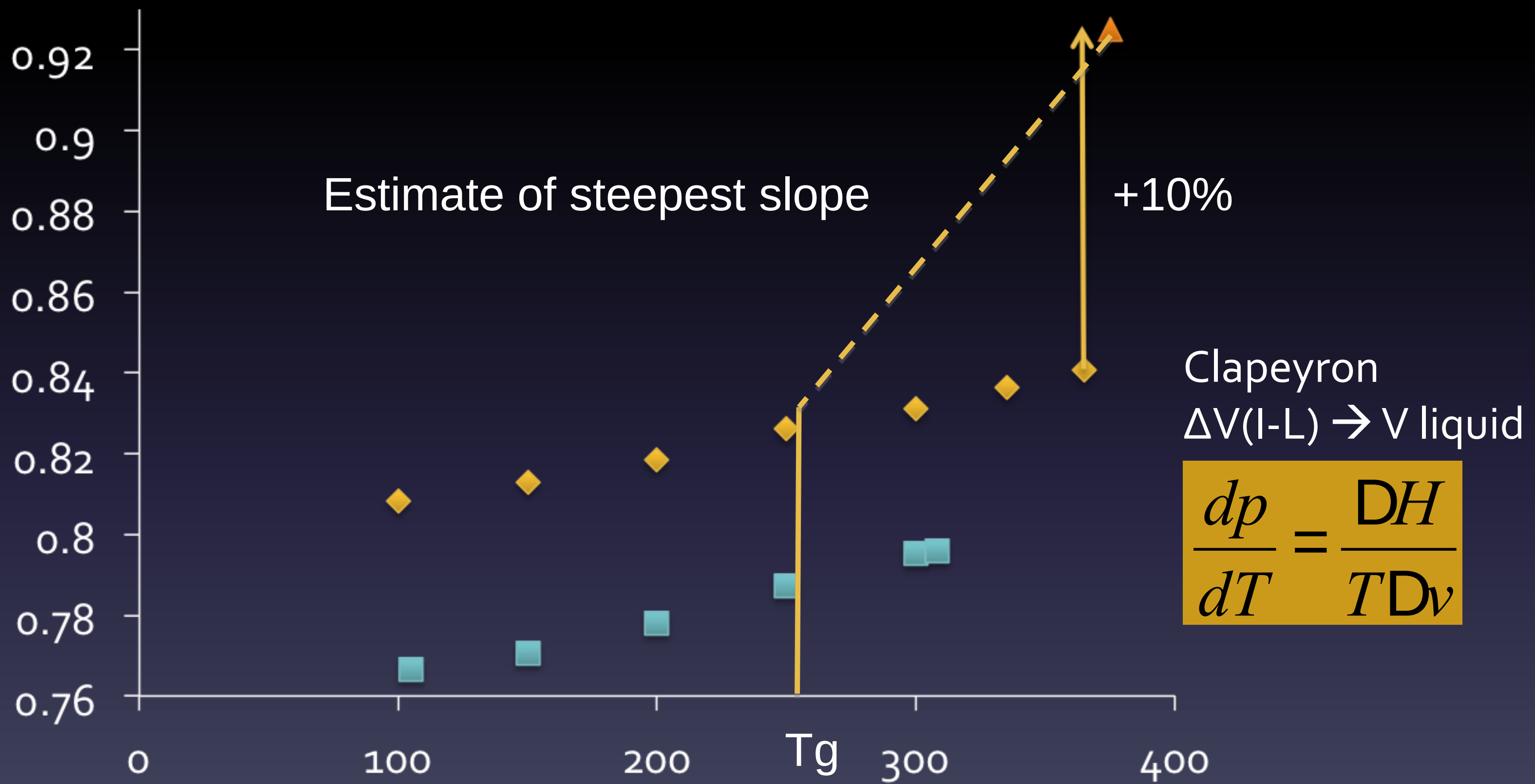


Dimorphism stability regions (P, T)



Specific volume of liquid

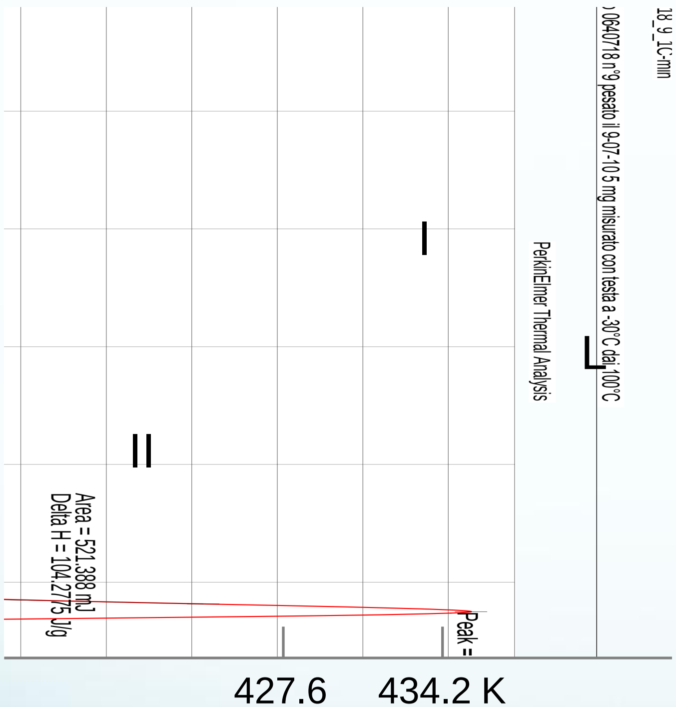
without measurement



Céolin, Rietveld, J Therm Anal Calorim 102, **2010**, 357-360
Rietveld et al. J Pharm Sci submitted (tyrosine ethyl ester, previous slides)

Benfluorex (Mediator)

anorectic and hypolipidemic agent



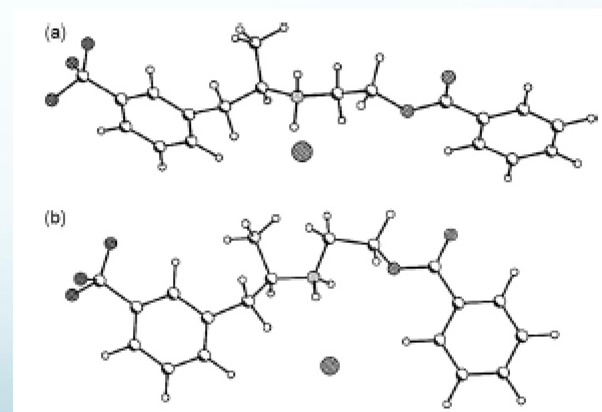
Form I highest melting point

Stable form?

Maccaroni et al. J. Pharm. Biomed. Analysis 53, **2010**, 1-6

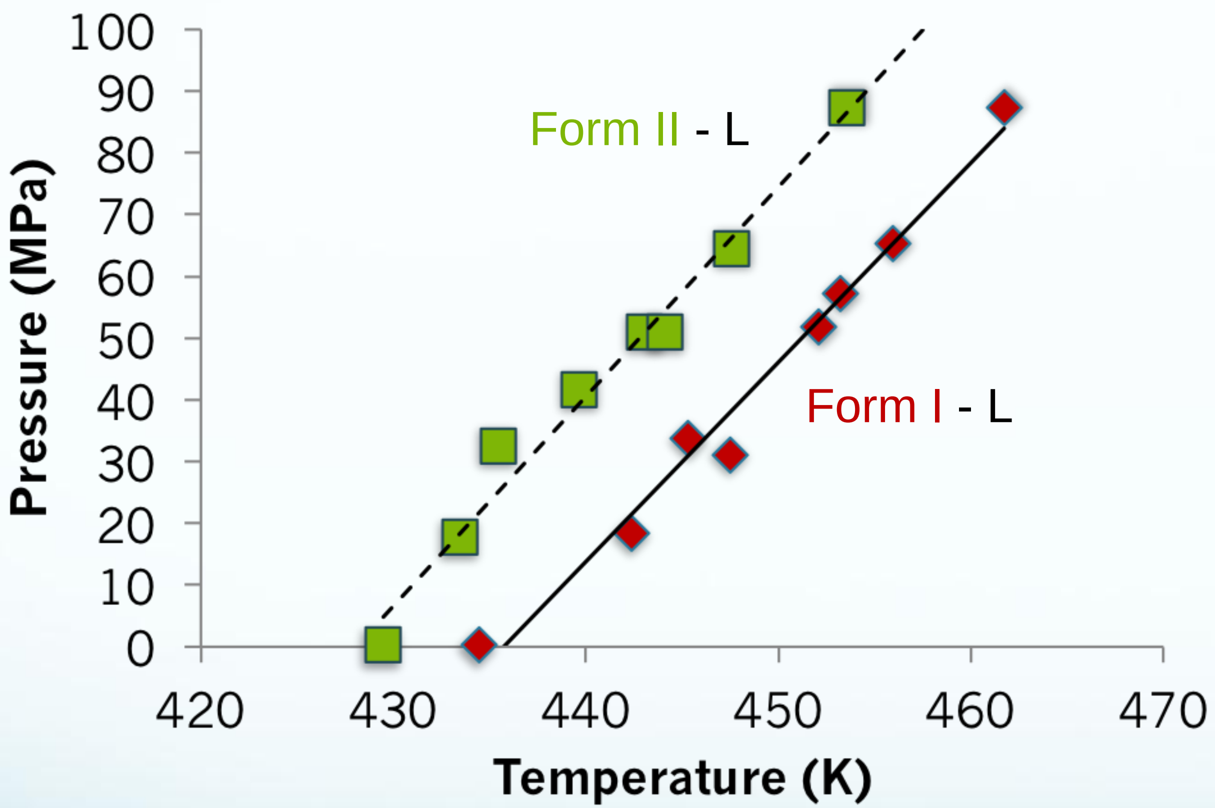
Form I
Monoclinic
$P2_1/n$, Z = 4

Form II
Orthorhombic
Pbca, Z = 8



Benfluorex

High Pressure Data



Lines parallel…

- Measured

- Calculated

No v_{spec} of liquid

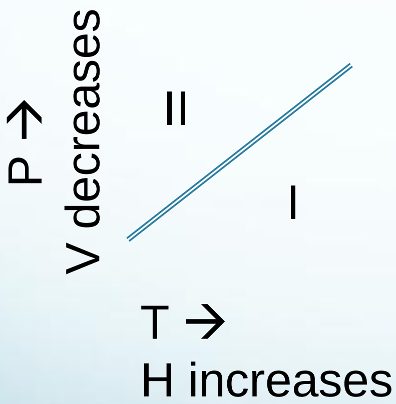
No triple point!?

Benfluorex

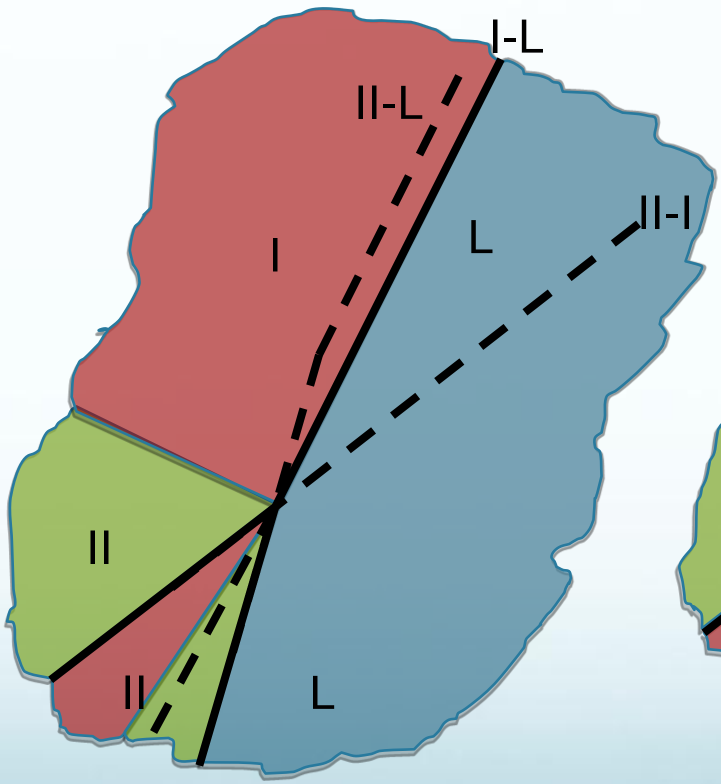
From melting enthalpies:
$H_{II} < H_{I}$

From X-ray measurements
$v_{II} < v_{I}$

Le Chatelier:

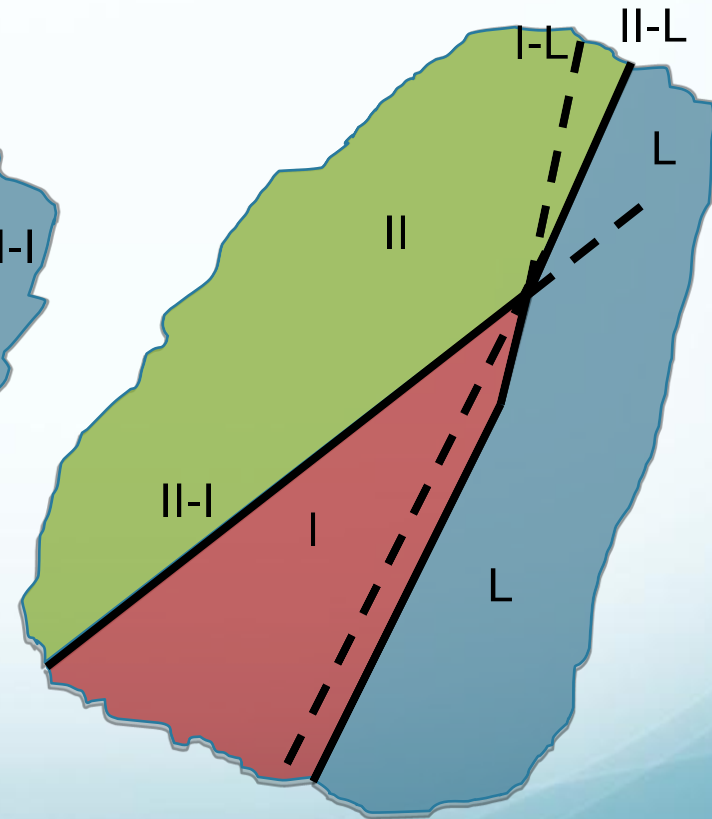


Triple point down



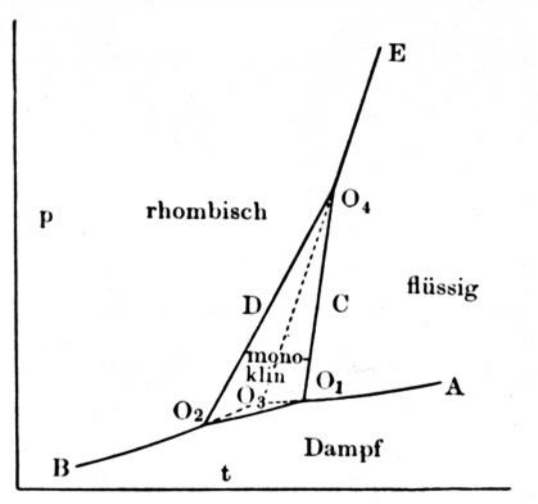
Inconsistent

Triple point up

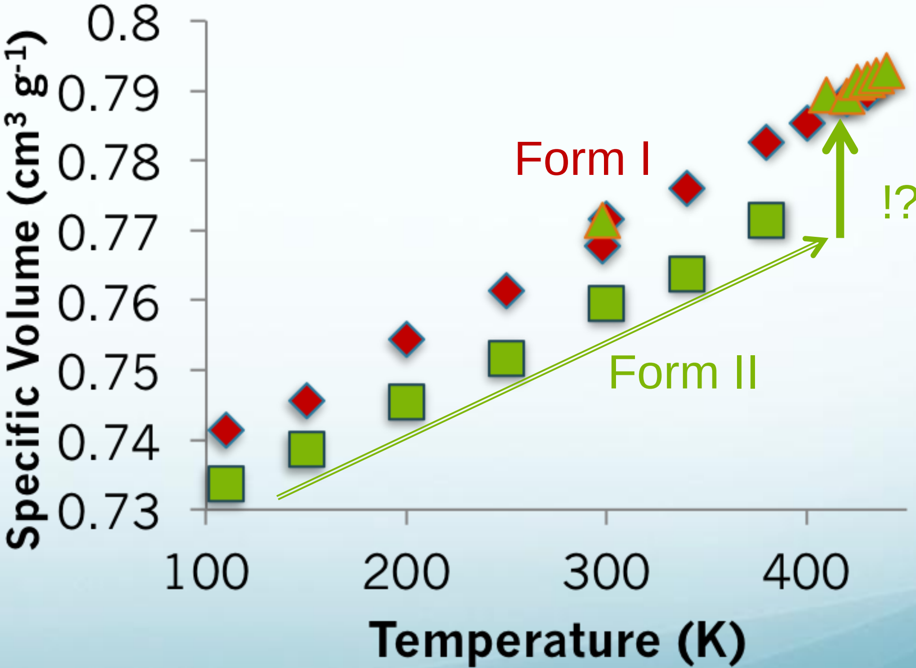


Consistent

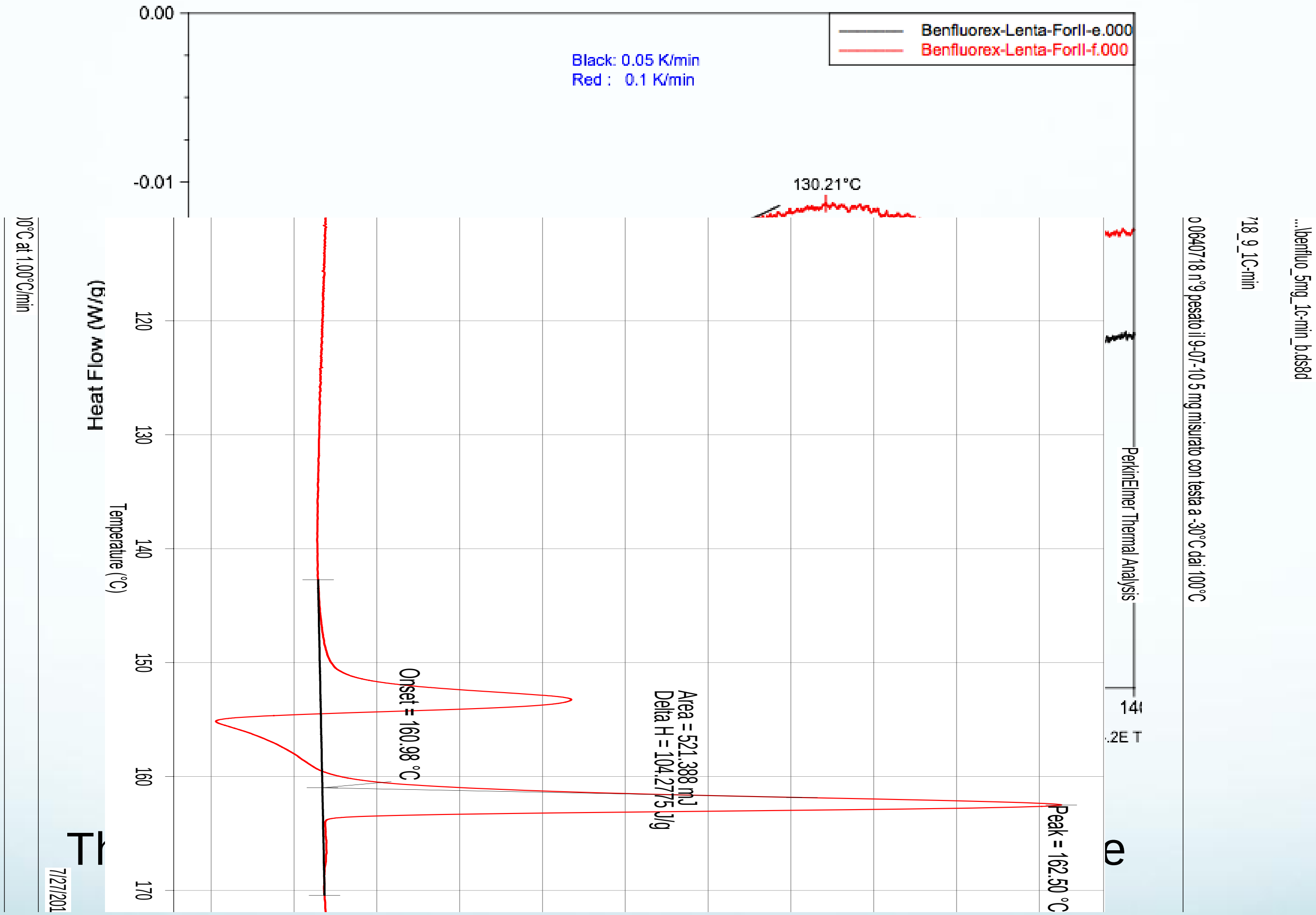
Benfluorex



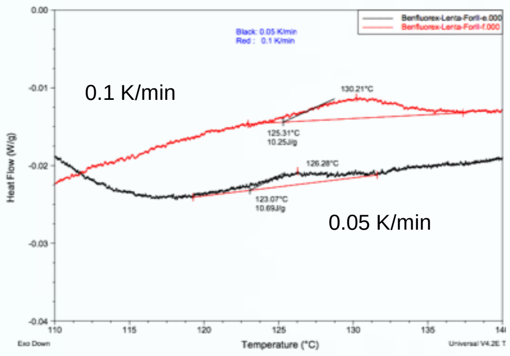
A transition at about 420 K!
Invisible in all DSC measurements

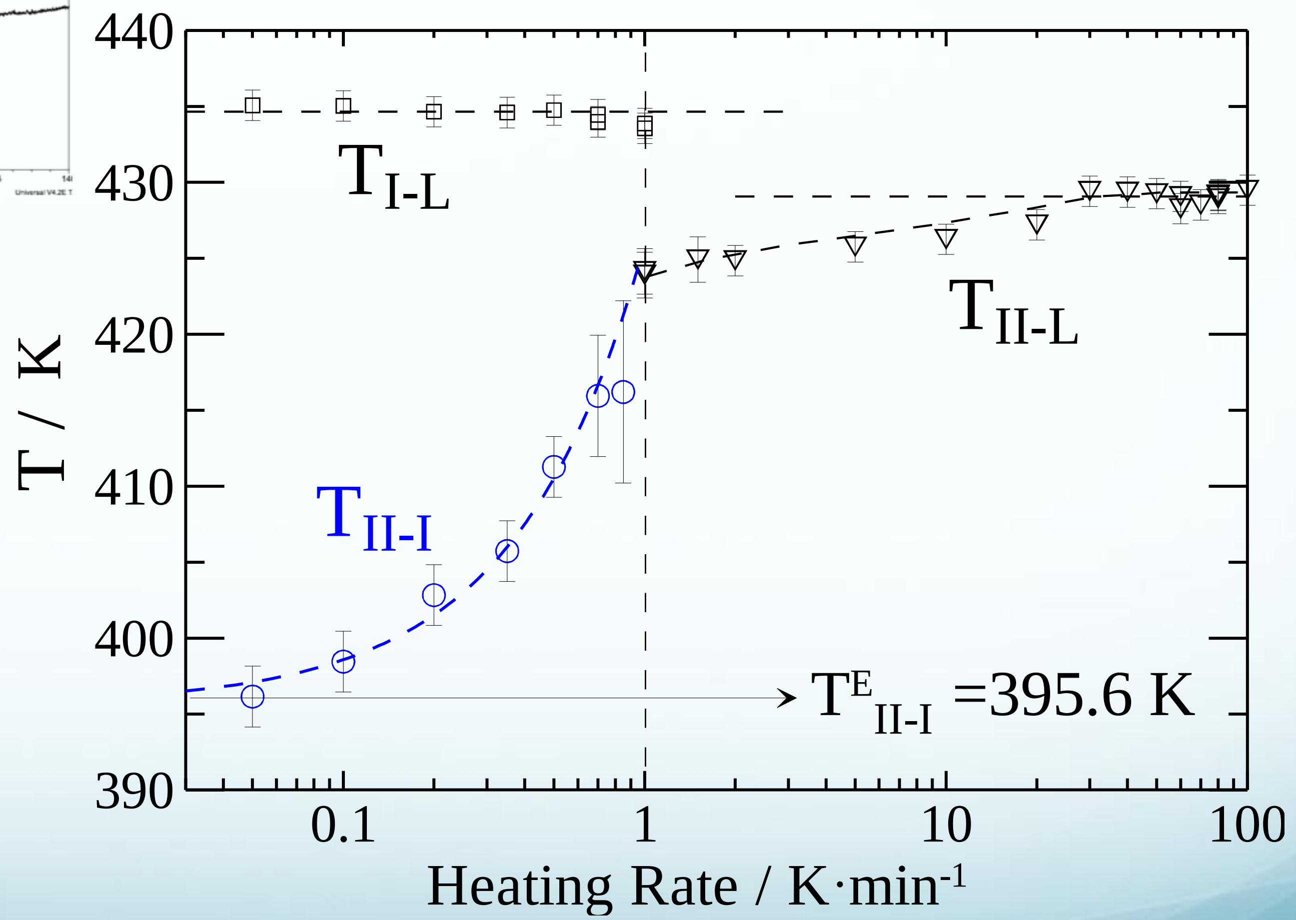


Benfluorex


0.00
-0.01
Black: 0.05 K/min
Red : 0.1 K/min
Benfluorex-Lenta-ForII-e.000
Benfluorex-Lenta-ForII-f.000
130.21°C
Heat Flow (W/g)
Temperature (°C)
Onset = 160.98 °C
Area = 521.388 mJ
Delta H = 104.2775 J/g
Peak = 162.50 °C
PerkinElmer Thermal Analysis

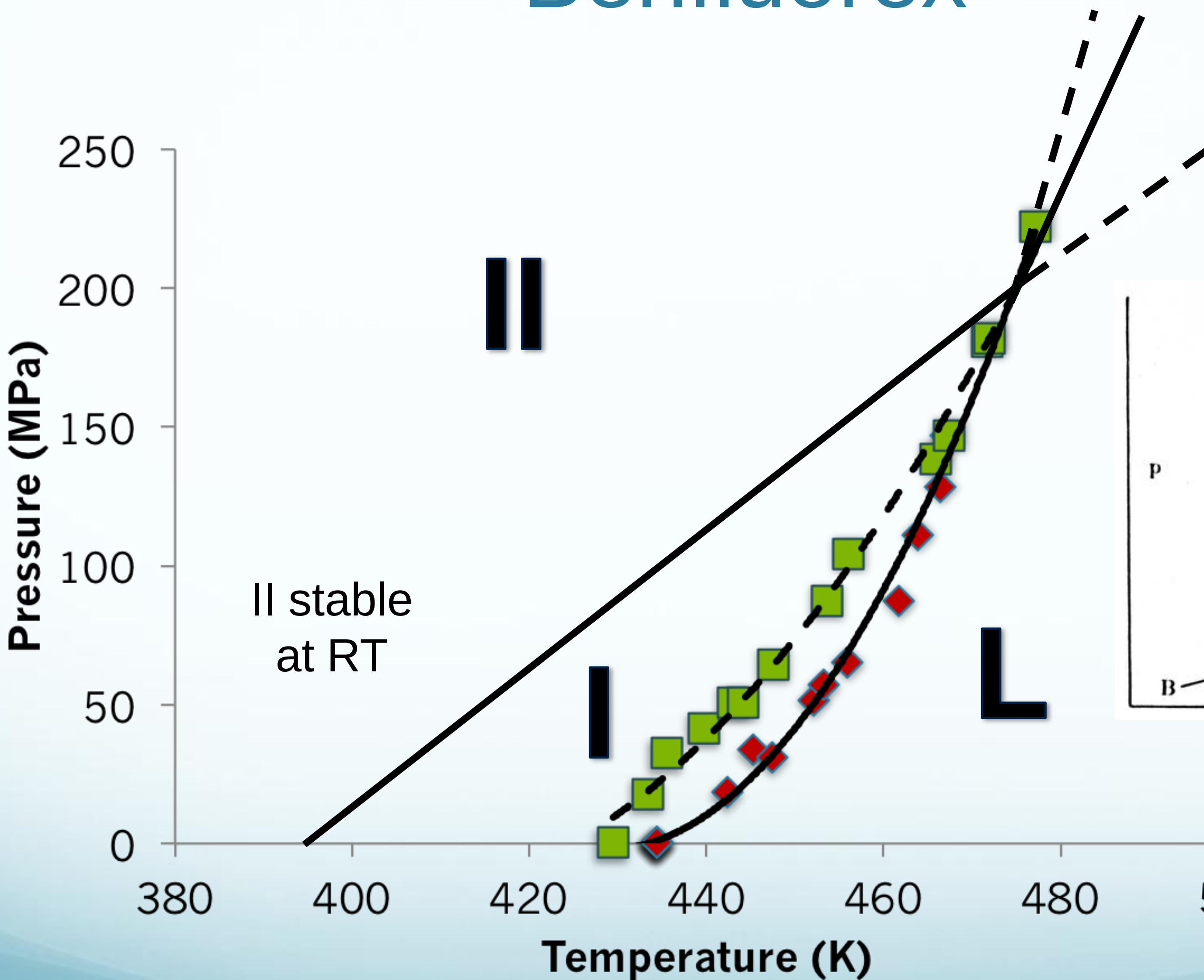
Benfluorex



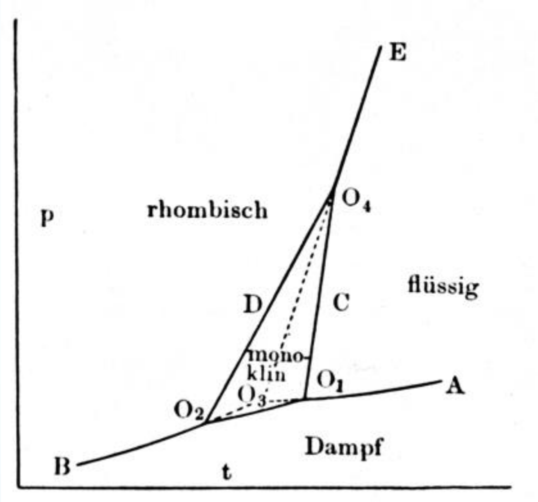


Solid-solid transition heating rate dependent and disappearing in II melt

Benfluorex

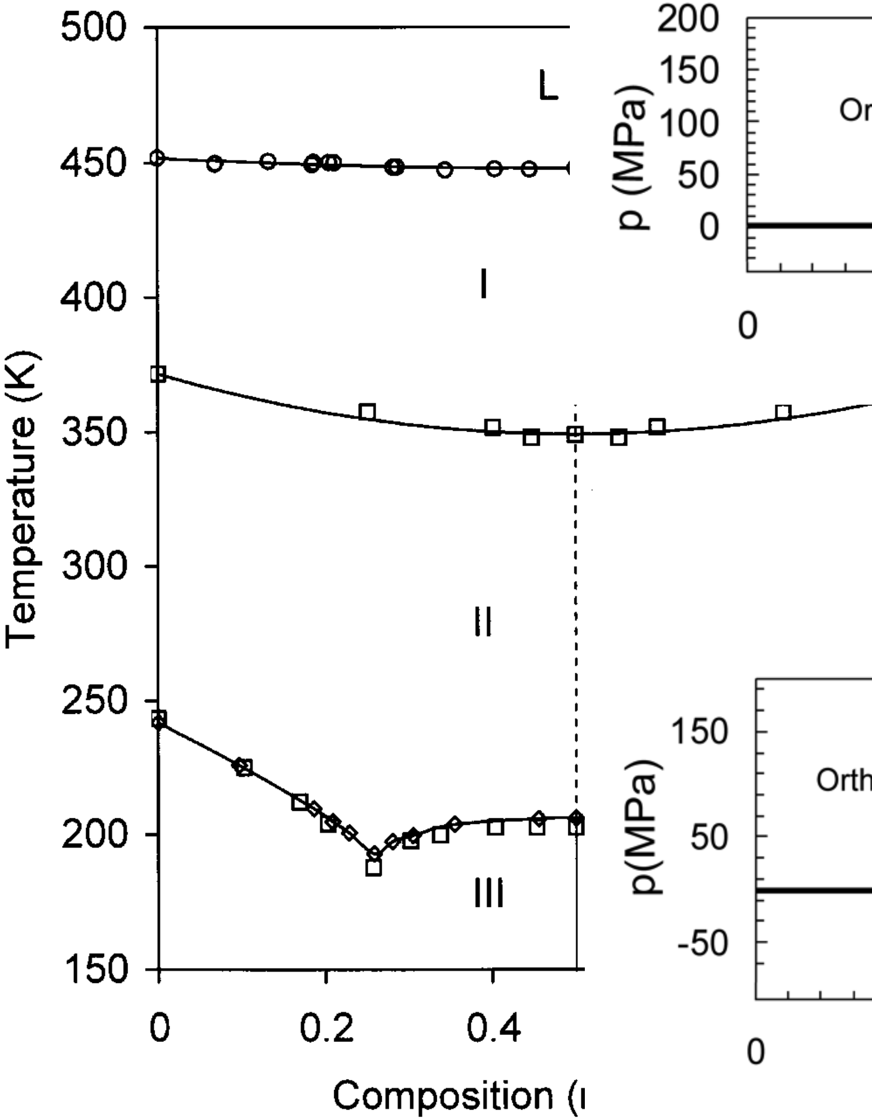


Pressure (MPa)
250
200
150
100
50
0
380
400
420
440
460
480
500
Temperature (K)
II
I
L
II stable
at RT

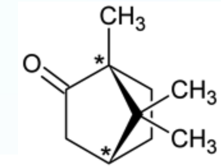


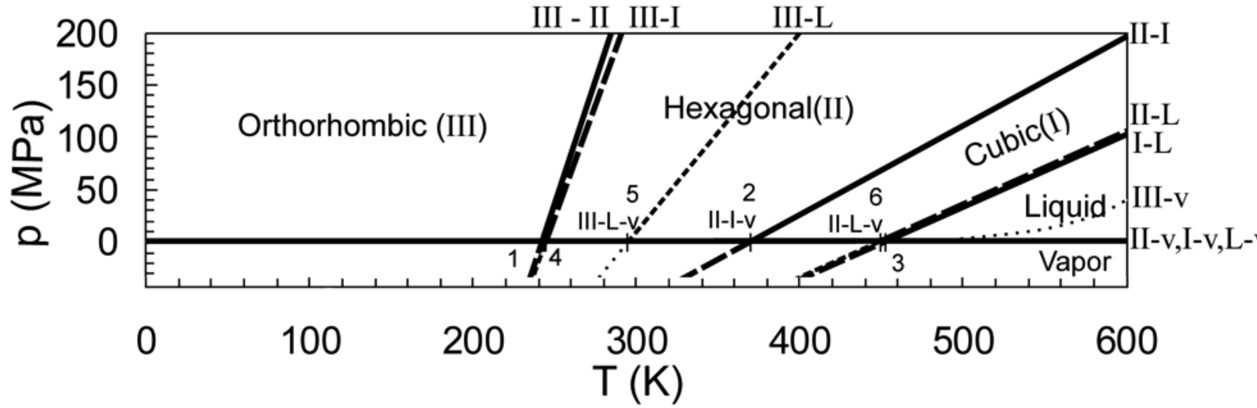
p
rhombisch
flüssig
E
O4
D
C
mono-
klin
O3
O1
A
O2
Dampf
B
t

Pressure – Temperature - Composition

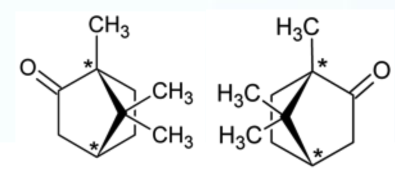


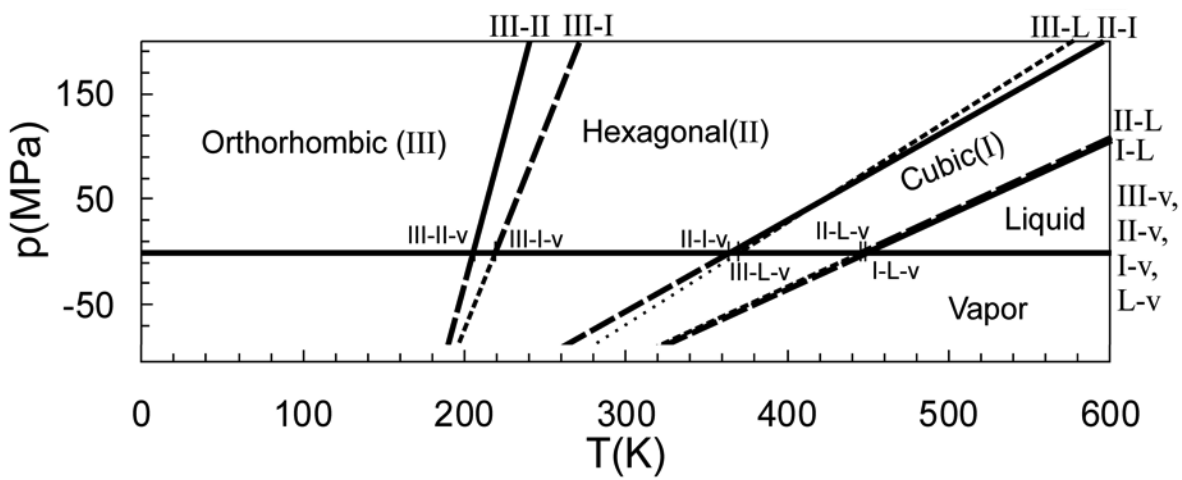
D-Camphor



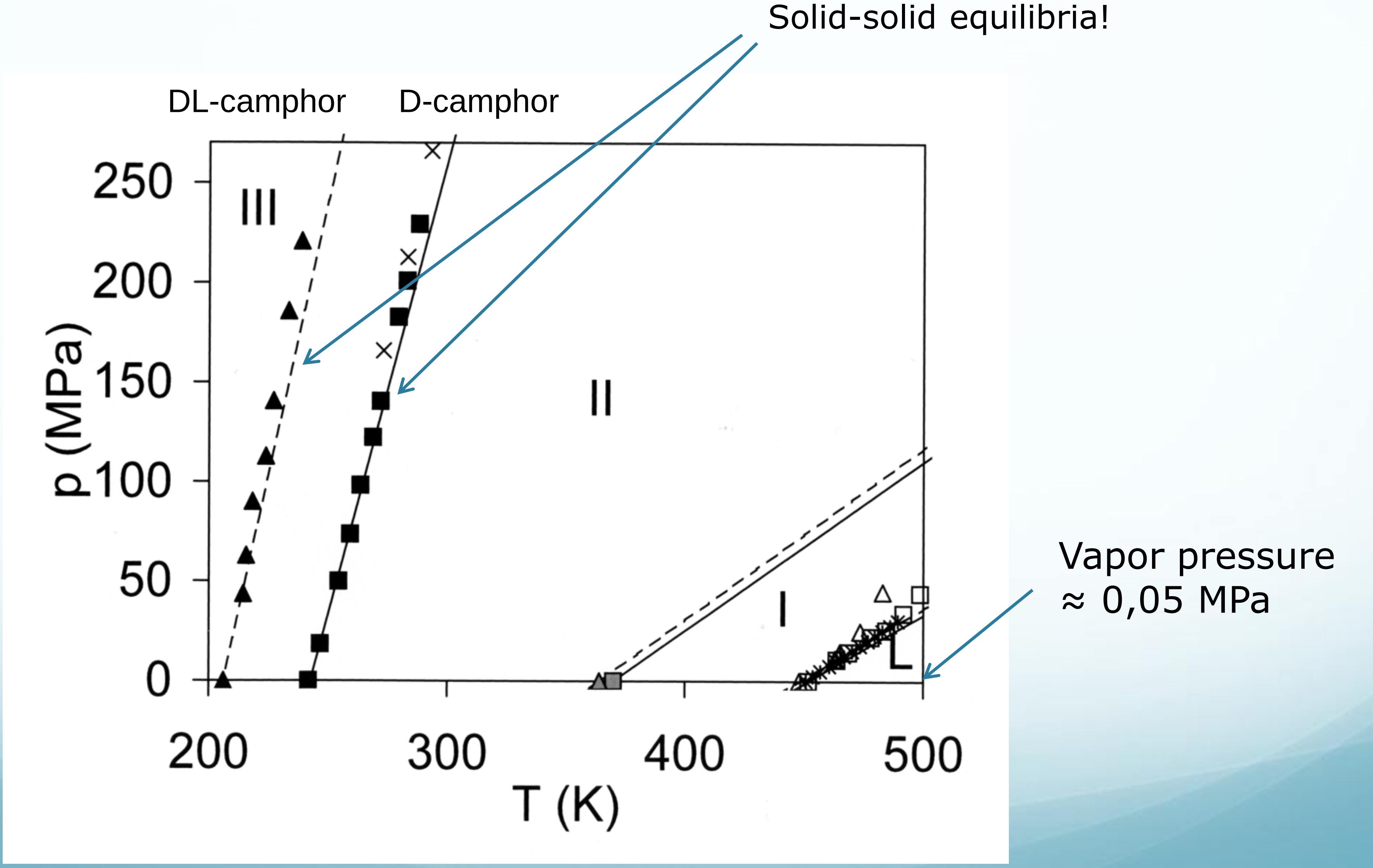


DL-Camphor

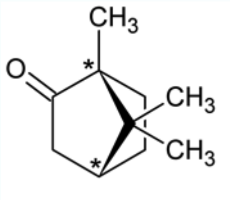


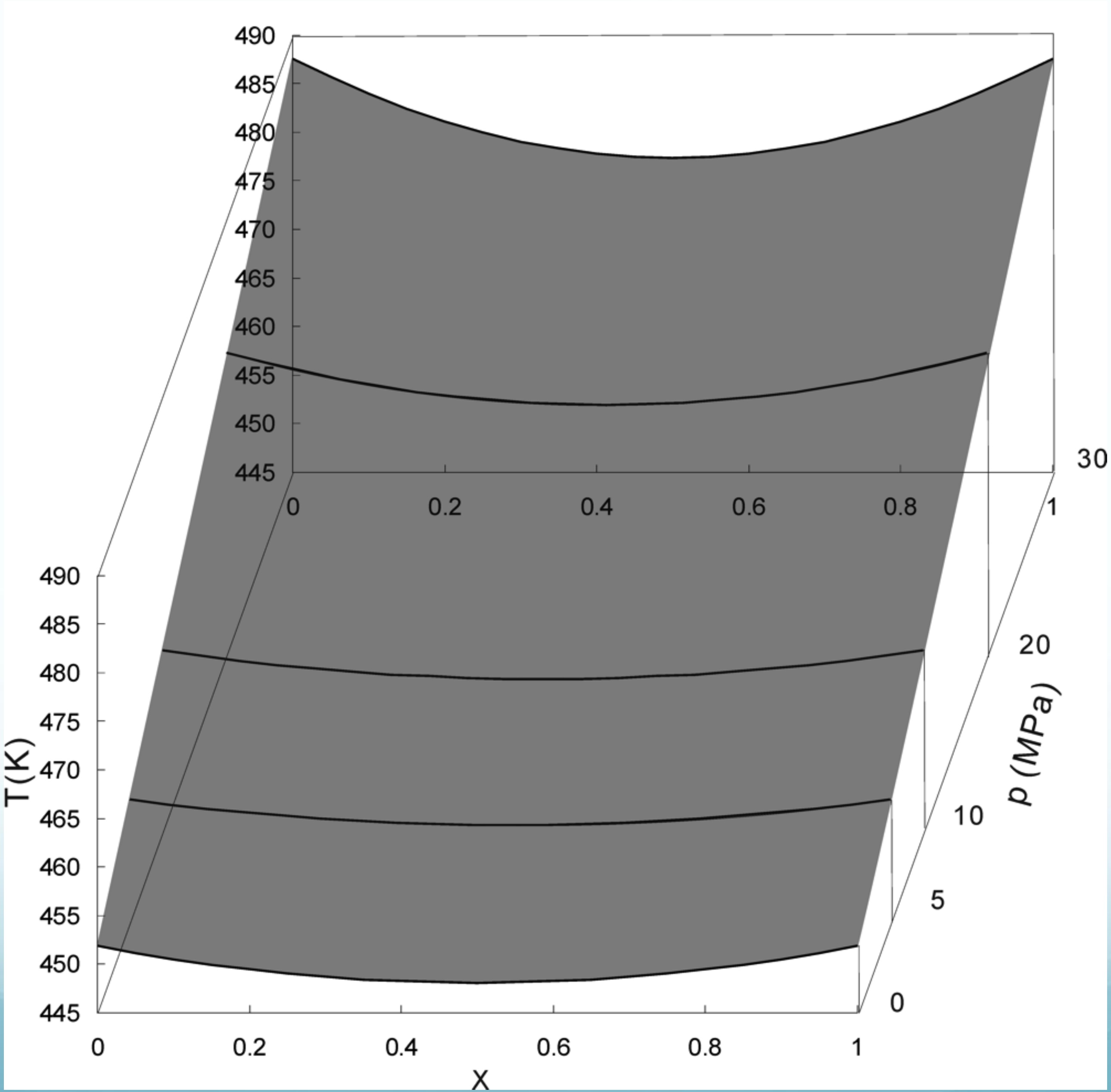


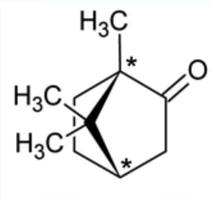
Experimental P-T data



P-T-x Phase Diagram of the camphor melting transition



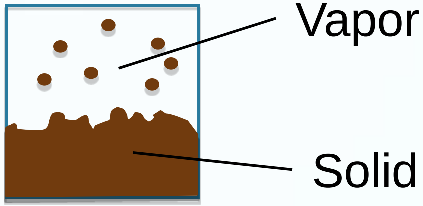




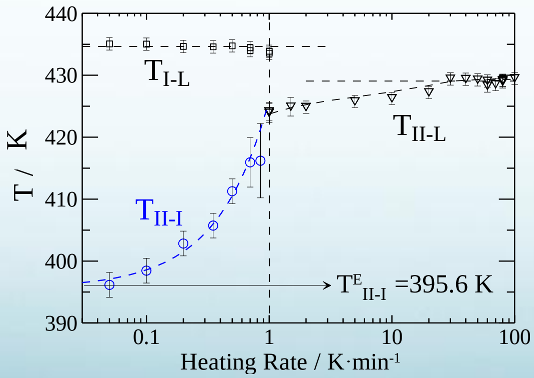
Toolbox

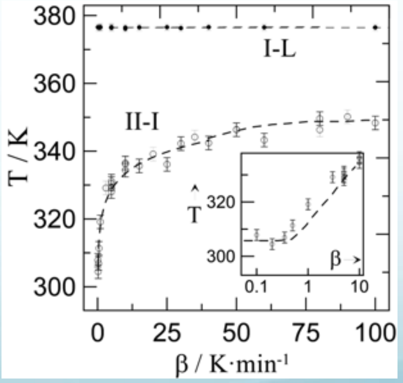
Conclusions 1/4

Pressure is the pressure of the system, not 1 atm!



Always check heating rate dependence of solid-solid transitions!



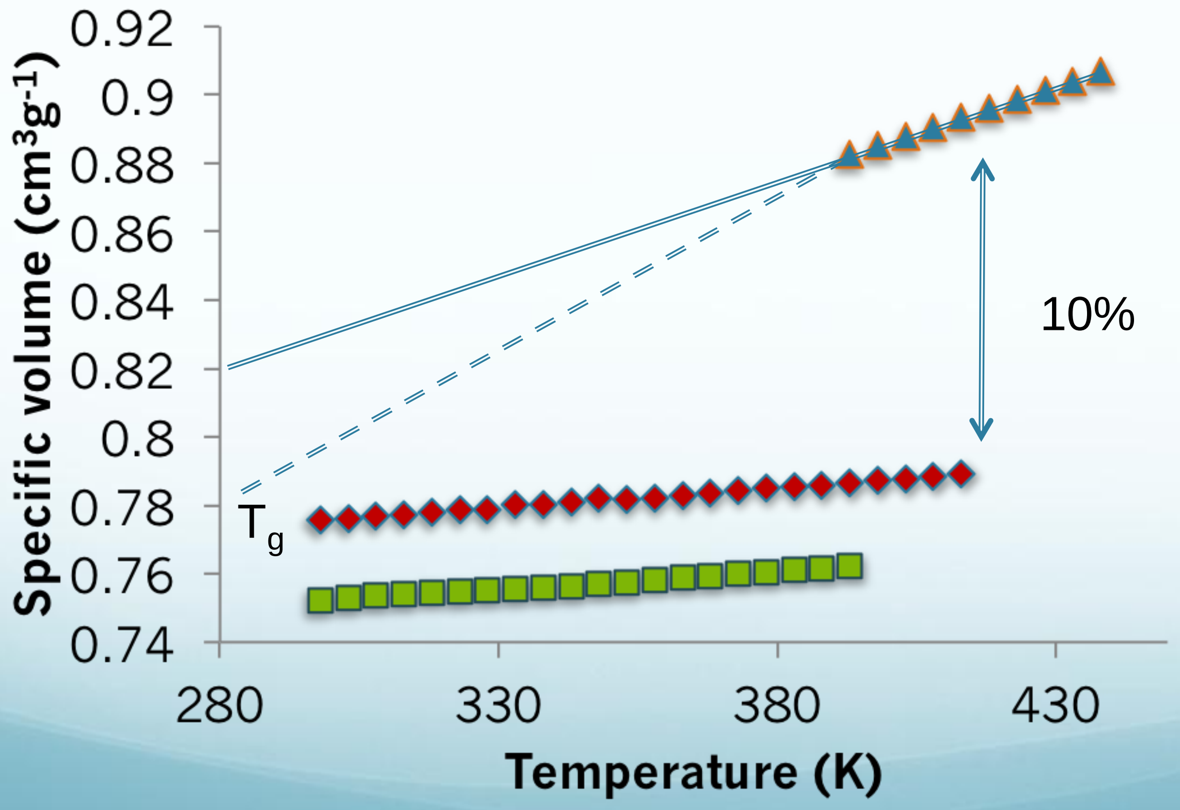


Toolbox

Conclusions 2/4

Required data:
DSC
X-ray
High Pressure – Differential Thermal Analysis

Glass transition
Liquid volume



Specific volume of liquid serves the topological approach

Toolbox

Conclusions 3/4

Le Chatelier

$H_{II} < H_{I}$

T →

p ↑

v_{II} < v_{I}

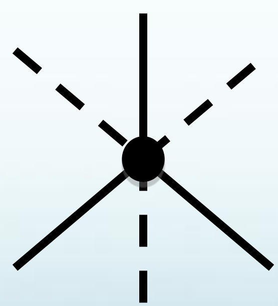
Vapor pressure

Clapeyron

$$\frac{dp}{dT} = \frac{\Delta S}{\Delta v} = \frac{\Delta H}{T \Delta v}$$

$$\ln P = -\frac{\Delta H}{RT} + B$$

Alternation Rule

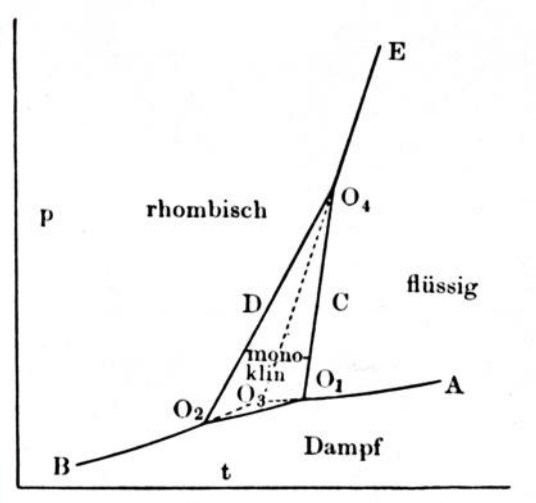


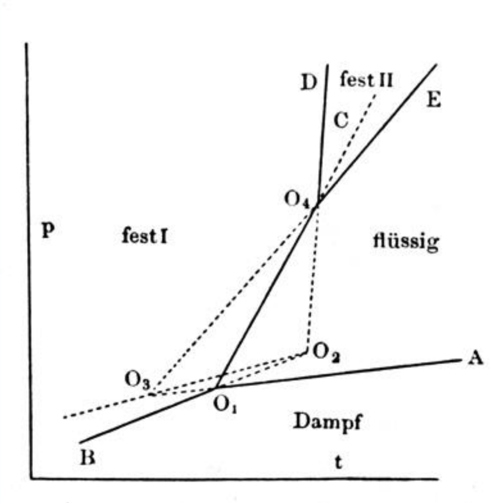
Triple points

Each case is a different puzzle!

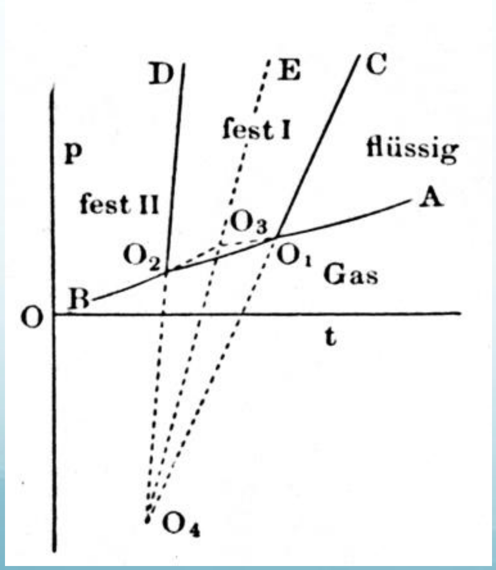
Toolbox

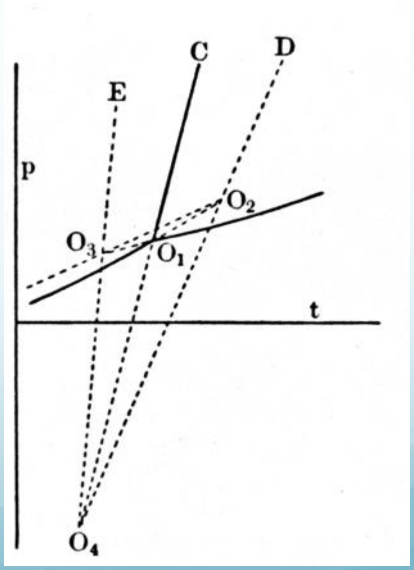
Conclusions 4/4





4 phases (solid 1, solid 2, liquid, vapor): 4 phase diagram options





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