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

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Paracetamol

Two known polymorphs:

**Form I:** Monoclinic P2₁/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

Form II

Form I

430 K

448 K

T →
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

Form I

Form II
Clapeyron Equation

The slope of a two-phase equilibrium:

\[
\frac{dp}{dT} = \frac{S}{v} = \frac{H}{T v}
\]

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

Form II

Form I

430 K

443 K

T →
Paracetamol

Volume Differences

Enthalpy Differences At 442 K

\[ \Delta v \]

\[ \Delta H_{\text{Liquid}} \]

Form I

Form II

Specific volume (cm$^3$g$^{-1}$)

Temperature (K)

280

330

380

430

0.74

0.76

0.78

0.80

0.82

0.84

0.86

0.88

0.90

0.92

\[ dp/dT \ (I \rightarrow L) = 3.7 \text{ MPa K}^{-1} \]

\[ dp/dT \ (II \rightarrow L) = 3.1 \text{ MPa K}^{-1} \]

\[ dp/dT \ (I \rightarrow II) = -0.3 \text{ MPa K}^{-1} \]

191.4 Jg$^{-1}$

3.4 Jg$^{-1}$
Pressure, Triple Points, and Alternation Rule

The pressure of the system is its vapor pressure.

The pressure of the system is its vapor pressure.

At Fusion: Three Phases → Triple point

\[ dp/dT \ (I \rightarrow L) = 3.7 \, \text{MPa K}^{-1} \]

Rigid DSC capsule

Vapor

Solid

443 K

Vapor

Triple point

Melting point 443 K

\[ p \]

\[ P_{\text{vap}} \]
Paracetamol

\[
dp/dT (I \rightarrow L) = 3.7 \text{ MPa K}^{-1}
\]
Paracetamol

\[ dp/dT (I \rightarrow L) = 3.7 \text{ MPa K}^{-1} \]
\[ dp/dT (II \rightarrow L) = 3.1 \text{ MPa K}^{-1} \]
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Paracetamol

Bakhuis-Roozeboom
4 Phases $\rightarrow$ 4 Phase Diagrams - 1901
Paracetamol
Experimental Verification

Experimental Triple Point
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
P2_{1}/c

T_{fus}: 400 K
ΔH_{fus}: 36.6 kJ mol^{-1}

Form II

374 K
28.8 kJ mol^{-1}
Biclotymol

Volume of form I and liquid

Melting peaks versus pressure
High Pressure DTA

E = Sample (échantillon)
T = Reference (témoin)

Supply of pressure transmission liquid

Heater block

Thermocouples

Manometer

Piston

\[ \Delta T \]
Biclotymol

Form II - L

Form I - L

Pressure (MPa)

Temperature (K)

-150
-100
-50
0
50
100

320
350
380
410
440
Biclotymol

Le Chatelier

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

T $\rightarrow$

Observation
Form II into Form I
transition exothermic

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

I $\rightarrow$ II

T $\rightarrow$

![Graph showing the transition of Form II to Form I with temperature and pressure axes]
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\textsubscript{1}2\textsubscript{1}2\textsubscript{1}
P-T, Necessary Data

DSC: temperature and enthalpy

X-ray: Volume difference
P-T, Necessary Data

DSC: temperature and enthalpy

DSC: T II $\rightarrow$ I and heating rate
Clapeyron Equation:
\[
\frac{dp}{dT} = \frac{H}{T} \frac{1}{v}
\]

The slope of a phase equilibrium

By DSC, high pressure DTA and X-ray:
- Transition temperature
- Enthalpy of transition
- Volume change at transition

Topological Pressure – Temperature Diagram
Construction of P-T Diagram

Pressure (MPa) vs. Temperature (K)

Melting point solid II 
\( P, T, \Delta H \)

Boiling point 
\( T = 590 \text{ K} \)
\( \Delta H = 65 \text{ kJ/mol} \)
\( P = 1 \text{ bar} \)

\[ \ln P = \frac{H}{RT} + B \]
Dimorphism stability regions (P, T)
Specific volume of liquid

without measurement

\[
\frac{dp}{dT} = \frac{H}{T \cdot v}
\]

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?


Form I  
Monoclinic  
P2₁/n, Z = 4

Form II  
Orthorhombic  
Pbca, Z = 8
Benfluorex
High Pressure Data

Lines parallel…
- Measured
- Calculated
No $v_{\text{spec}}$ of liquid

No triple point!?
From melting enthalpies:
\[ H_{II} < H_I \]

From X-ray measurements
\[ v_{II} < v_I \]

Le Chatelier:
- \( P \rightarrow \) decreases
- \( V \rightarrow \) decreases
- \( T \rightarrow \) increases
- \( H \rightarrow \) increases

Triple point down
Inconsistent

Triple point up
Consistent
Benfluorex

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

Temperature (°C)

Area = 521.388 mJ
Delta H = 104.2775 J/g
Onset = 160.98 °C
Peak = 162.50 °C

Heat from 100.00°C to 180.00°C at 1.00°C/min

Black: 0.05 K/min
Red: 0.1 K/min

Sample Weight: 5.000 mg

Comment:
benfluorex lotto 0640718 n°9 pesato il 9-07-10 5 mg misurato con testa a -30°C dai 100°C
Solid-solid transition heating rate dependent and disappearing in II melt
Benfluorex II is stable at room temperature (RT).
Pressure – Temperature - Composition

D-Camphor

DL-Camphor
Experimental P-T data

Solid-solid equilibria!

Vapor pressure $\approx 0.05$ MPa
P-T-x Phase Diagram of the camphor melting transition
Pressure is the pressure of the system, not 1 atm!

Always check heating rate dependence of solid-solid transitions!
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

\[ H_{II} \rightleftharpoons H_{I} \]
\[ T \rightarrow \]
\[ p \uparrow \]
\[ v_{II} \]
\[ v_{I} \]

Clapeyron

\[ \frac{dp}{dT} = \frac{S}{v} = \frac{H}{T} v \]

Vapor pressure

\[ \ln P = \frac{H}{RT} + B \]

Alternation Rule

Triple points

Each case is a different puzzle!
4 phases (solid 1, solid 2, liquid, vapor): 4 phase diagram options
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