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 $P2_1/a$  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

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**
The slope of a two-phase equilibrium:

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

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

Volume Differences

Form I

Form II

Δv

Liquid

Enthalpy Differences At 442 K

191.4 J g⁻¹

Form II

3.4 J g⁻¹

Form I

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

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

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

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

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Paracetamol

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Paracetamol
Bakhuis-Roozeboom
4 Phases → 4 Phase Diagrams - 1901
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

<table>
<thead>
<tr>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2₁/c</td>
<td></td>
</tr>
<tr>
<td>(T_{\text{fus}}):</td>
<td>(T_{\text{fus}}):</td>
</tr>
<tr>
<td>400 K</td>
<td>374 K</td>
</tr>
<tr>
<td>(\Delta H_{\text{fus}}):</td>
<td>(\Delta H_{\text{fus}}):</td>
</tr>
<tr>
<td>36.6 kJ mol(^{-1})</td>
<td>28.8 kJ mol(^{-1})</td>
</tr>
</tbody>
</table>
Biclotymol

Volume of form I and liquid

Melting peaks versus pressure
High Pressure DTA

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

**Diagram:***
- Thermocouples
- Manometer
- Piston
- Supply of pressure transmission liquid
- Heater block

**Equipment:**
- High Pressure DTA apparatus with various components and labeled parts.
Biclotymol

Le Chatelier

\[ H_{\text{phase A}} < H_{\text{phase B}} \]

\[ T \rightarrow \]

Observation
Form II into Form I
transition exothermic

\[ H_{\text{form I}} < H_{\text{form II}} \]

\[ \text{I} \leftrightarrow \text{II} \]

\[ T \rightarrow \]

![Graph showing the phase transition of Biclotymol](attachment:image.png)

- Form II - L
- Form I - L
- Form I 
- Form II
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 $Pbca$
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
Topological Pressure – Temperature Diagram

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

DSC: T, D\text{H} ; X-ray + V_{\text{liq}}: \Delta v
Construction of P-T Diagram

Boiling point
T = 590 K
ΔH = 65 kJ/mol
P = 1 bar

\[ \ln P = \frac{H}{RT} + B \]
Dimorphism stability regions (P, T)
Specific volume of liquid without measurement

\[ \Delta V(\text{I-L}) \rightarrow V_{\text{liquid}} \]

\[ \frac{dp}{dT} = \frac{H}{T \nu} \]

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!?
Benfluorex

From melting enthalpies:
\( H_{\text{II}} < H_{\text{I}} \)

From X-ray measurements
\( v_{\text{II}} < v_{\text{I}} \)

Le Chatelier:

\[ P \uparrow \quad V \downarrow \quad T \rightarrow \quad H \uparrow \]

Triple point down

Inconsistent

Consistent

Triple point up
Benfluorex

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

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

Onset = 160.98 °C
Peak = 162.50 °C

Area = 521.388 mJ
Delta H = 104.2775 J/g
Benfluorex

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

II stable at RT
Pressure – Temperature - Composition

D-Camphor

DL-Camphor
Experimental P-T data

Solid-solid equilibria!

Vapor pressure ≈ 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

Temperature (K)

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

280 330 380 430

T$_g$

10%
Toolbox
Conclusions 3/4

Le Chatelier

\[ H_{\text{II}} < H_{\text{I}} \]

\[ \text{p} \uparrow \]

\[ \text{v}_{\text{II}} \]

\[ \text{v}_{\text{I}} \]

\[ T \rightarrow \]

Clapeyron

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

Vapor pressure

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

Alternation Rule

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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