Thermal Analysis

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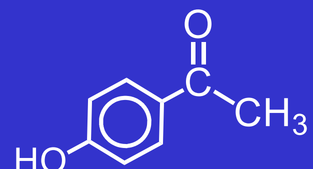
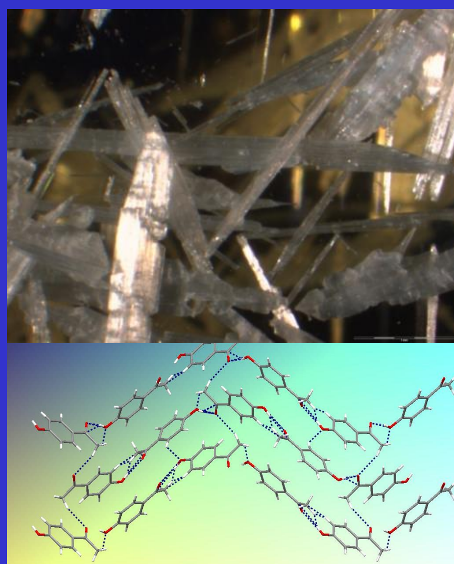
What is Thermal Analysis?

Physical and chemical transformations can often be induced in a sample by increasing or decreasing temperature

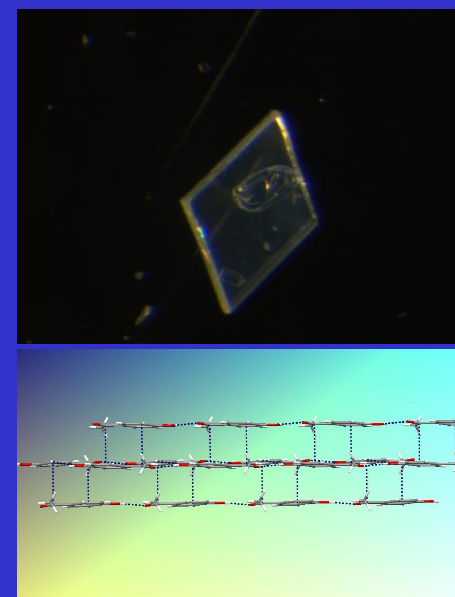
Representative Applications: Phase Transitions



Form II (Orthorhombic)



Form I (Monoclinic)



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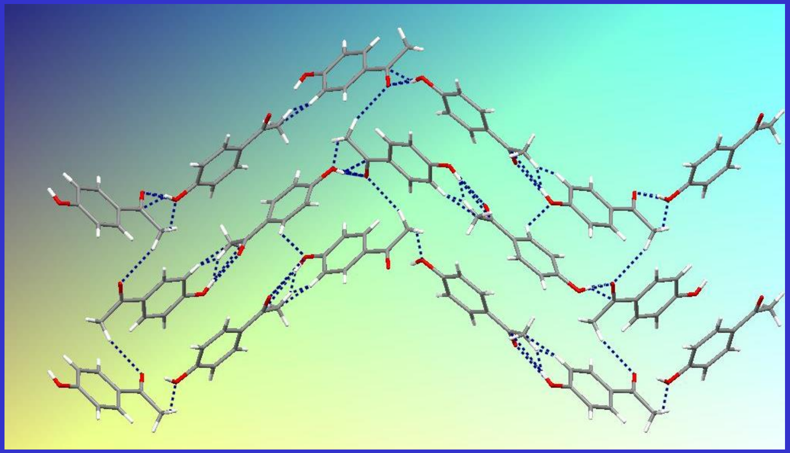
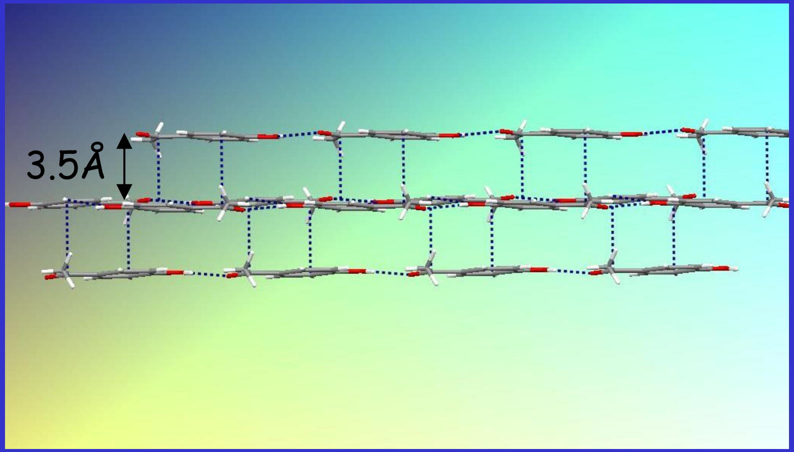
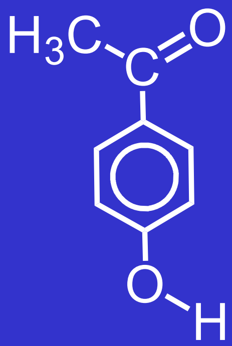
Crystal Growth & Design 2008, *8*, 2419-2430

Different Polymorphs Have Different Structures and Physical Properties



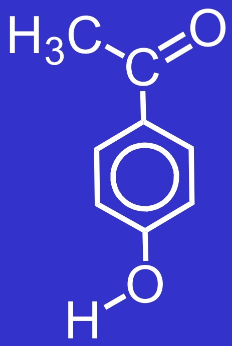




μ = 2.7 D

Form II

- Orthorhombic
- $P2_12_12_1$
- Z'=2
- $\rho_{150\ K}$ = 1.320 g.cm^{-3}
  $\rho_{298\ K}$ = 1.278 g.cm^{-3}



μ = 4.4 D

Form I

- Monoclinic
- $P2_{1/c}$
- Z' = 1
- $\rho_{150\ K}$ = 1.314 g.cm^{-3}
  $\rho_{298\ K}$ = 1.247 g.cm^{-3}

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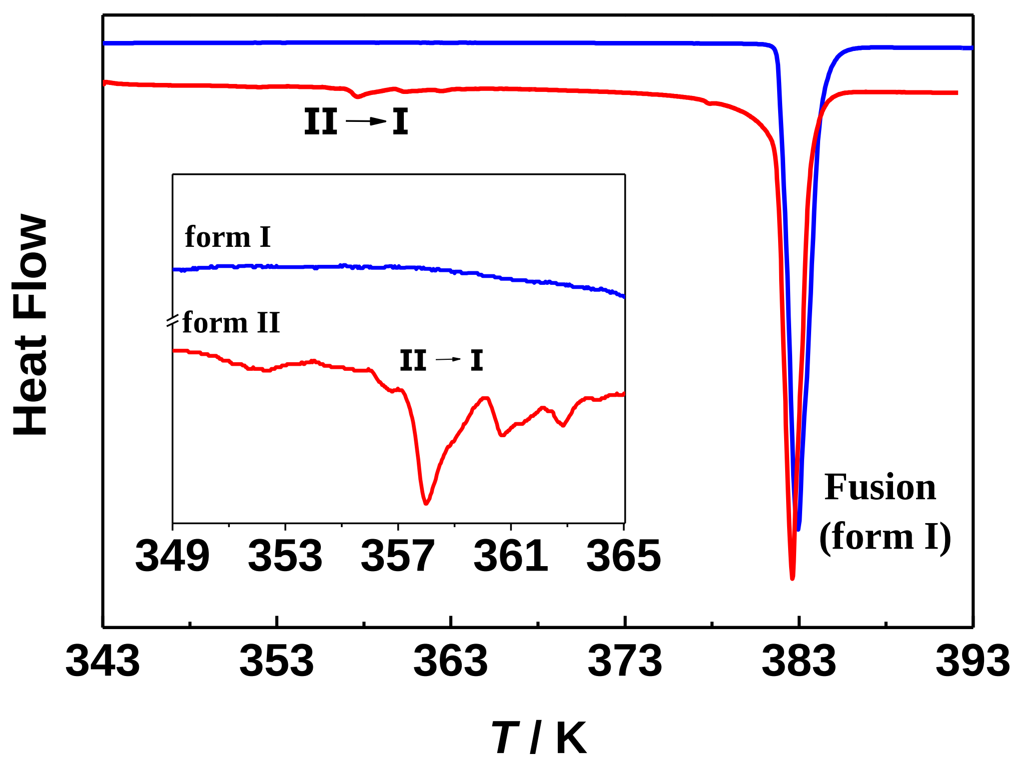
Differential Scanning Calorimetry (DSC)



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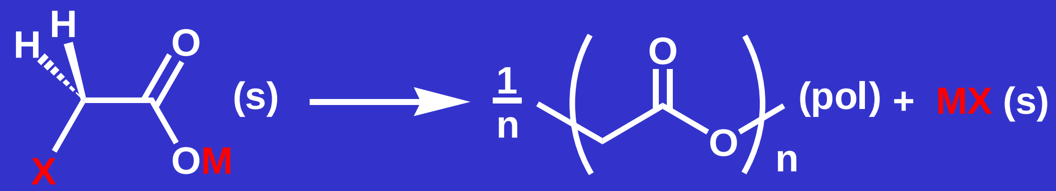
Representative Applications: Chemical Reactions



M = Li, Na
X = Cl, Br, I

Polyglycolide

471 K

$ClCH_2COONa$ (cr) → $NaCl$ (cr) + $-(CH_2COO)_n-$ (pol)

Sodium chloroacetate

Polyglycolide

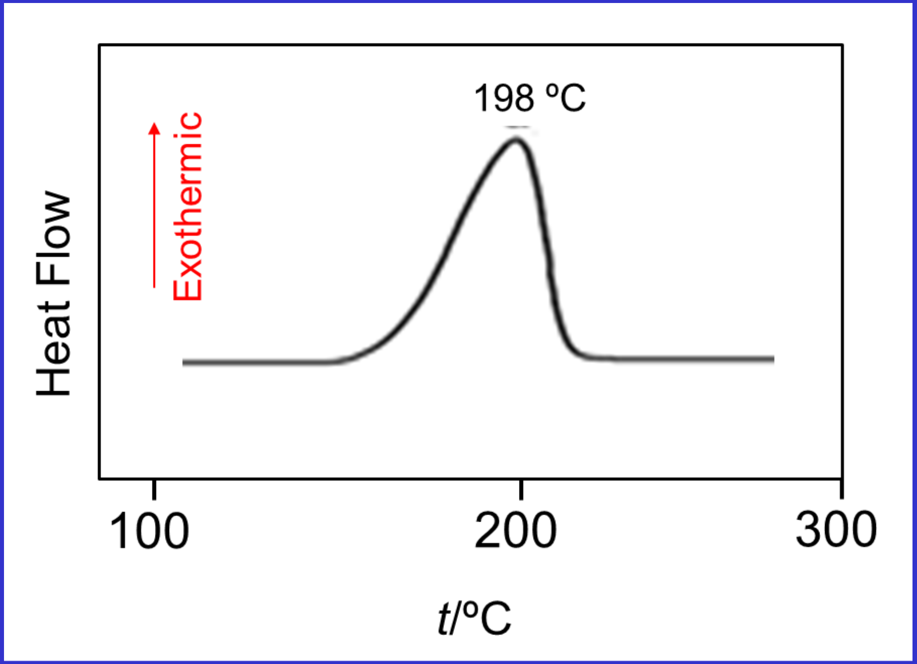
Detection of Chemical Reactions by DSC

198 ºC

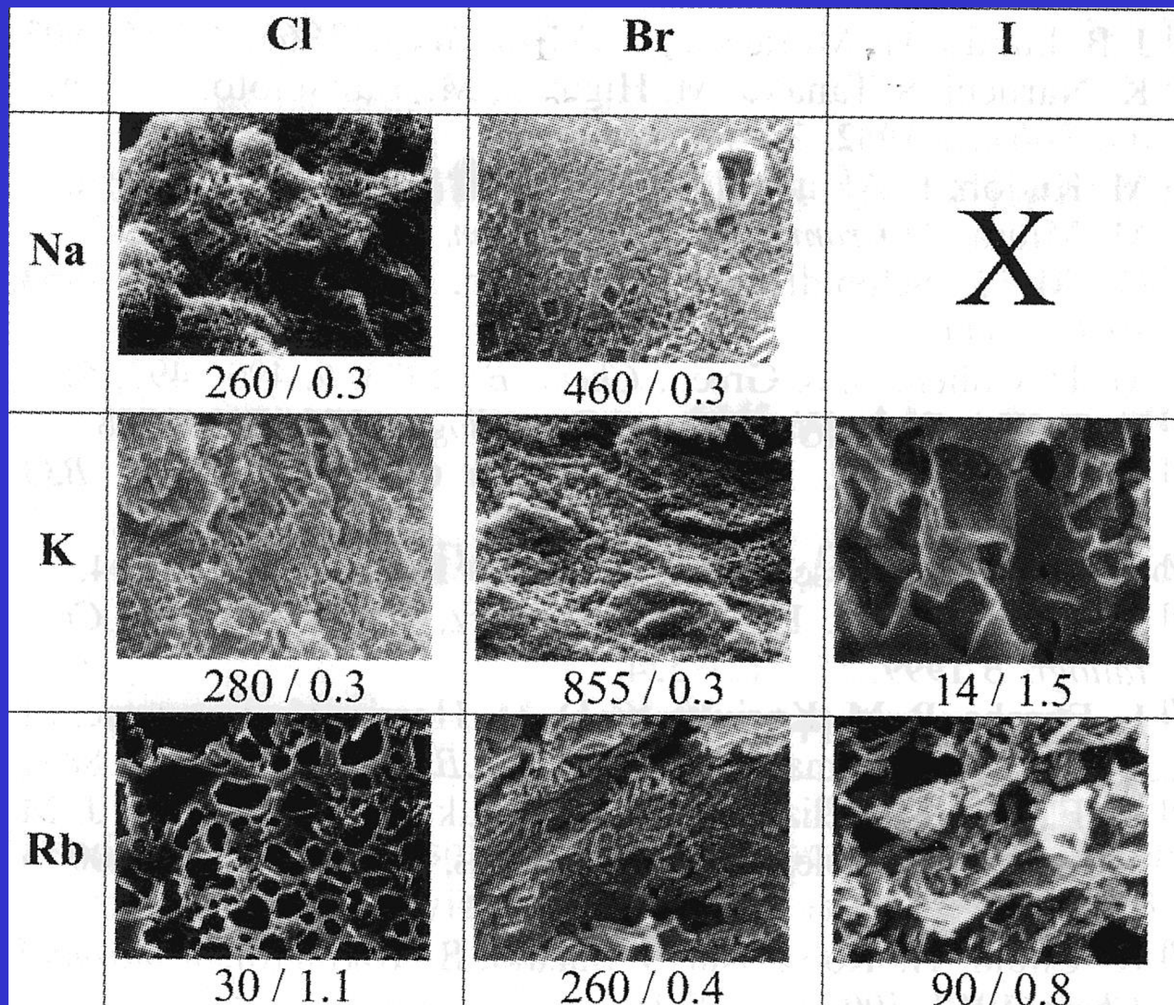
$ClCH_2COONa$ (cr) → $NaCl$ (cr) + $-(CH_2COO)_n-$ (pol)

Sodium chloroacetate

Polyglycolide

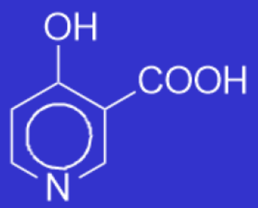


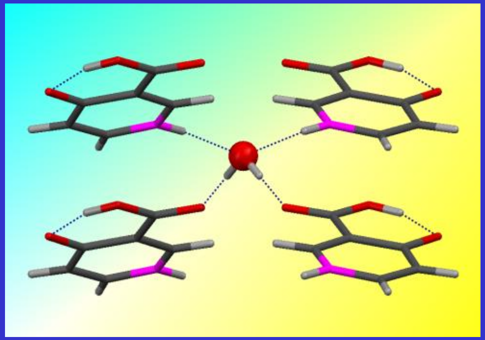
Scanning Electron Micrographs of Polyglycolide from Various Precursors

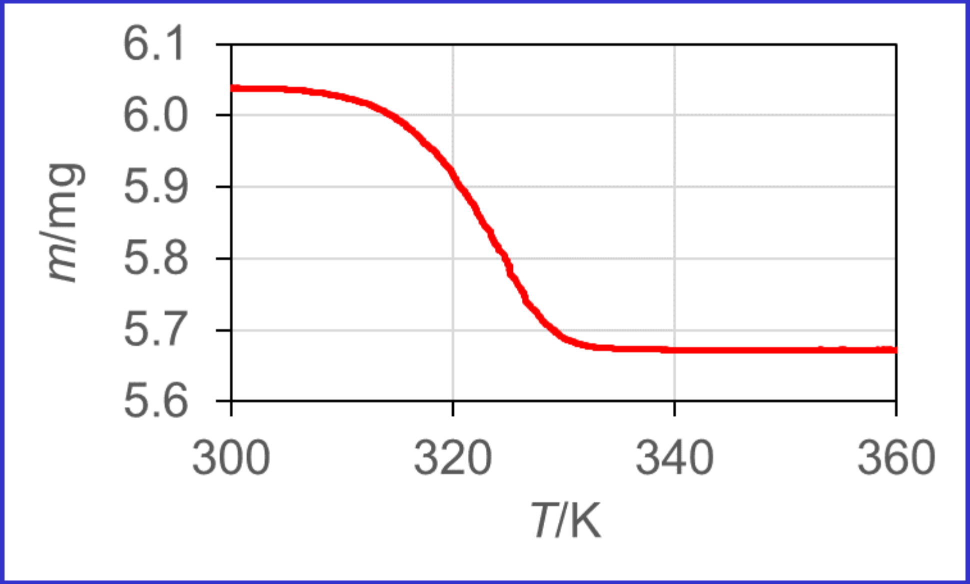


Dehydration: Detection by Mass Loss

$$4HNA \cdot 0.5H_2O(cr) \rightarrow 4HNA(cr) + 0.5H_2O(g)$$

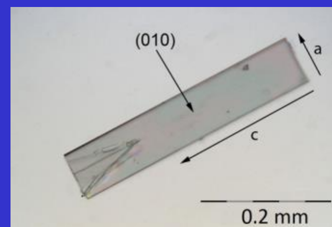




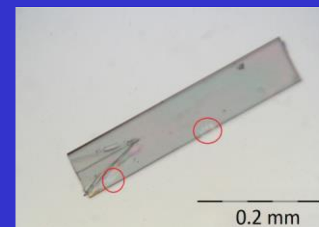


Dehydration: Detection by Microscopy

$$4HNA{\cdot}0.5H_2O(cr) \rightarrow 4HNA(cr) + 0.5H_2O(g)$$

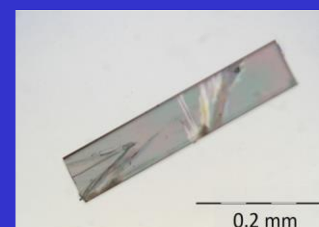


(a)

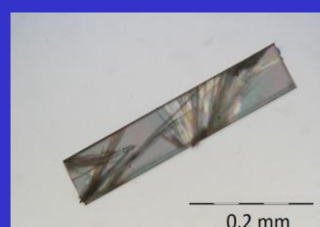


(b)

(c)



(d)



(e)

(f)

(g)

(h)

What is Thermal Analysis?

A group of techniques based on the observation of the transformations that substances undergo when subjected to programmed temperature changes

Very important for the characterization of solid materials!

Main Types of Thermal Analysis

Calorimetric Analysis:

- Termodynamic data: T_{fus}, $\Delta_{fus}H$, T_g, C_p
- Kinetic data: k, E_a for phase transitions and solid state reactions
- Purity

Thermogravimetry:

Mass change as a function of temperature

- Thermal decompositions in different atmospheres
- Vapor pressures

Main Types of Thermal Analysis

Thermomechanical analysis:

Study of mechanical properties of materials as a function of temperature

- e.g.: Compressibility and elasticity

Thermomicroscopy:

Variations of optical properties of substances as a function of temperature

- Morphological and structural variations

Thermal Analysis and Safety

Accident risk identification and analysis:

Since 2001, all Portuguese operators are required to submit a Safety Report on the handling and storage of hazardous substances to the Instituto do Ambiente. The report must contain information about:

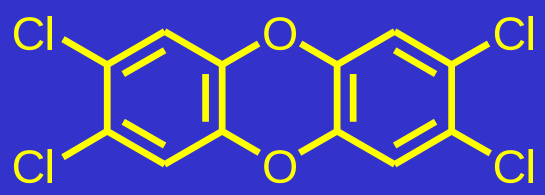
- Thermal stability
- Reactions and their kinetics (e.g. thermal decompositions)

Thermal Analysis and Safety

Identification of acident causes

Sveso Accident (Italy) **July 10, 1976**

- ICMESA herbicide producer
- Burst of a safety valve in a reactor
- 3000 kg of chemical products spread in the atmosphere
- 30 kg of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin)

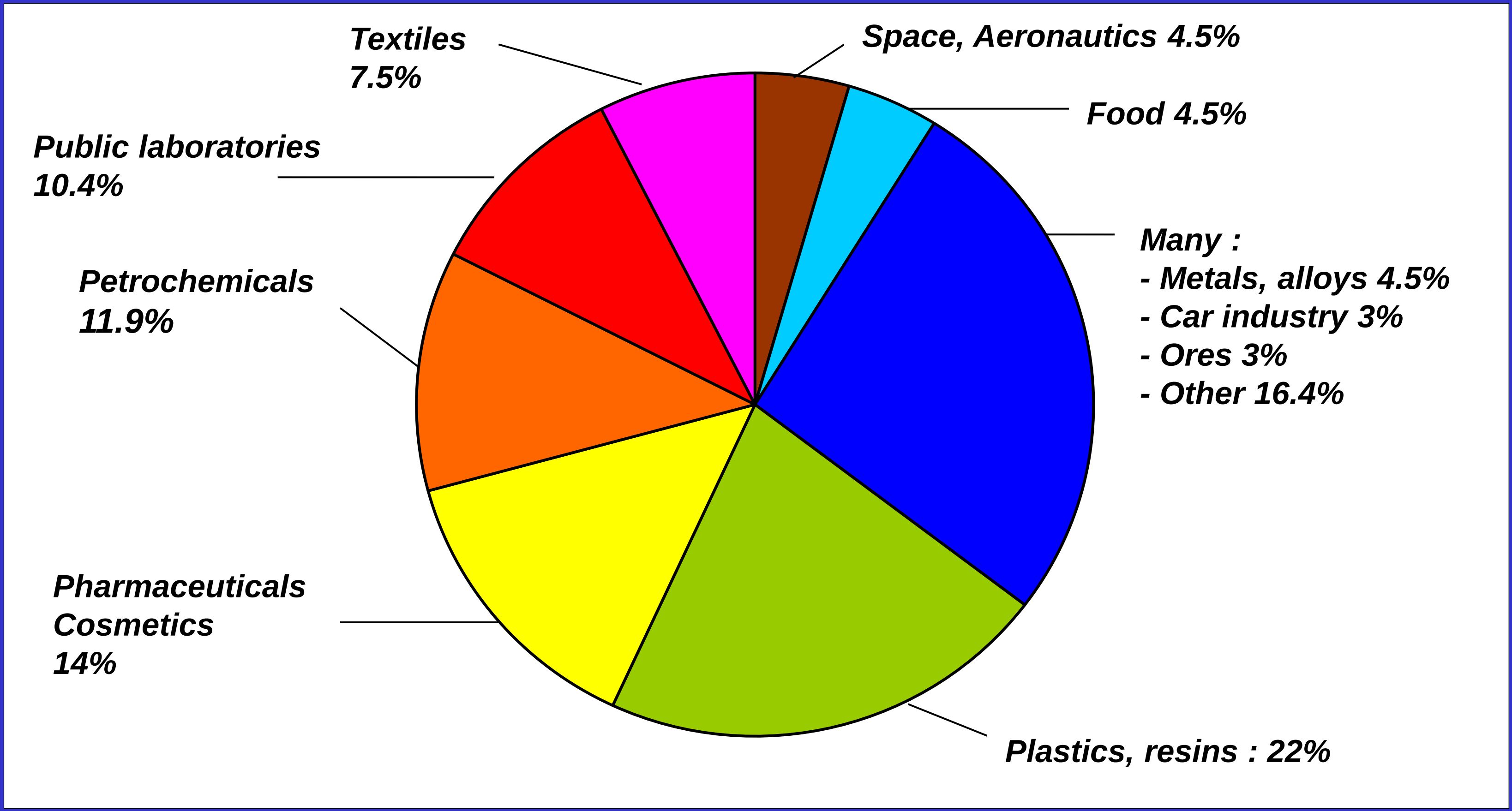


Highly toxic carcinogenic agent

Source:

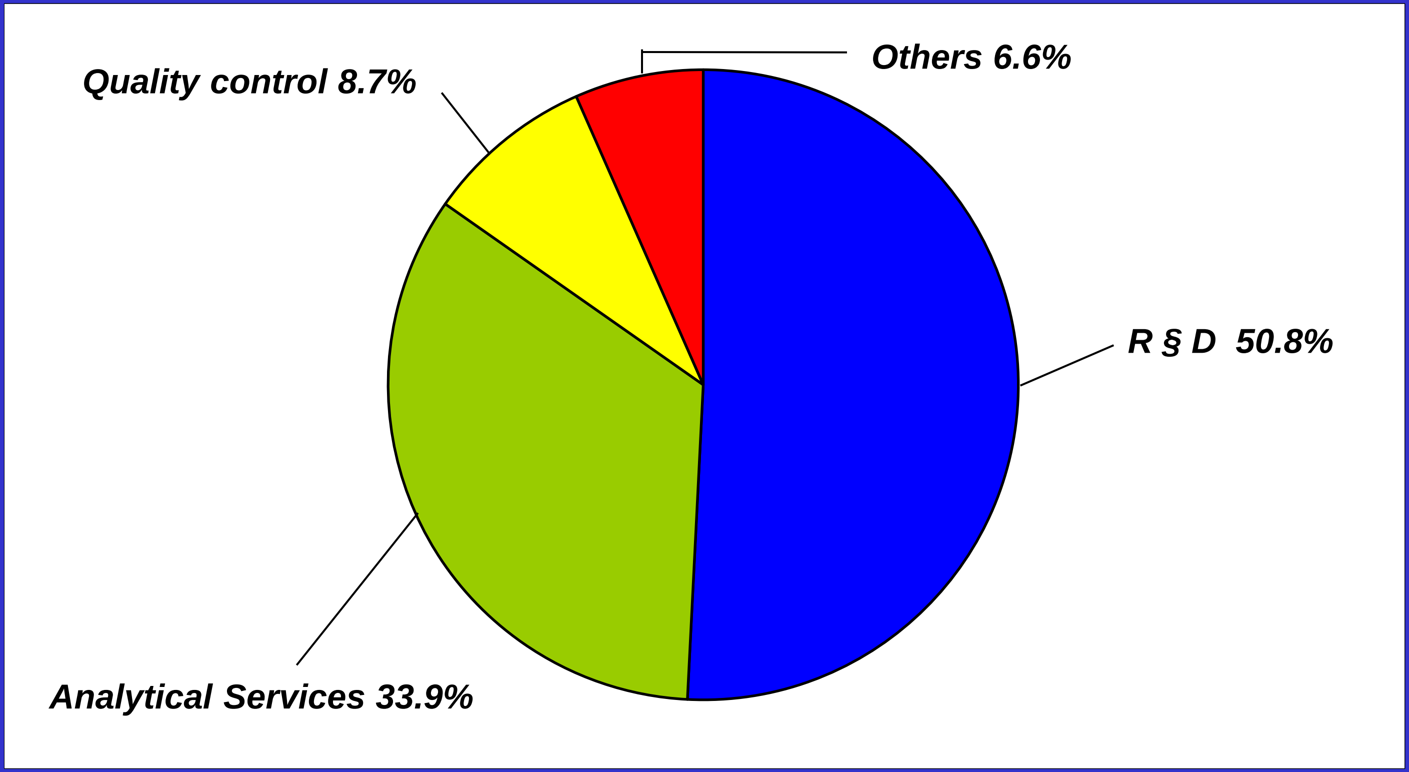
- Thermal decomposition of the reaction mixture at 200-220°C
- Conclusion obtained by differential scanning calorimetry (DSC) studies

Partiton by Industry



Pierre le Parlouër, Therm@l Consulting,
http://www.evitherm.org/presentations/wp7_presentation.ppt

Partiton by Laboratories



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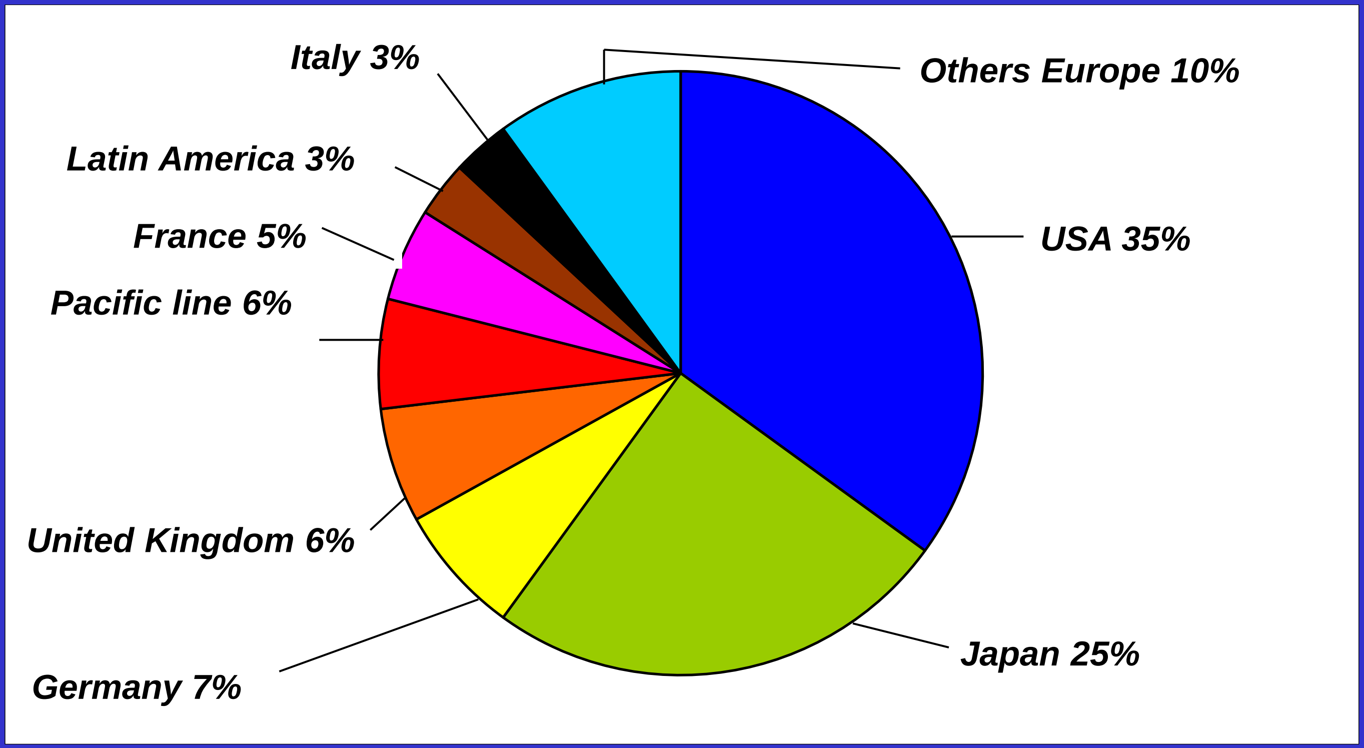
http://www.evitherm.org/presentations/wp7_presentation.ppt

Partiton by Country



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Main Types of Thermal Analysis

Thermomicroscopy

Variations of optical properties of substances as a function of temperature

- Morphological and structural changes

Calorimetric Analysis:

Differential Scanning Calorimetry

- Thermodinamic data: T_{fus}, $\Delta_{fus}H$, T_g C_p
- Kinetic data: k, E_a for phase transitions and solid state reactions
- Purity analysis

Thermogravimetry

Mass changes as a function of temperature

- Thermal decompositions in different atmospheres
- vapor pressures

Thermomechanical analysis :

Study of mechanical properties of materials as a function of temperature (e.g.: compressibility and elasticity)

Differential Scanning Calorimetry (DSC)

Essence of DSC

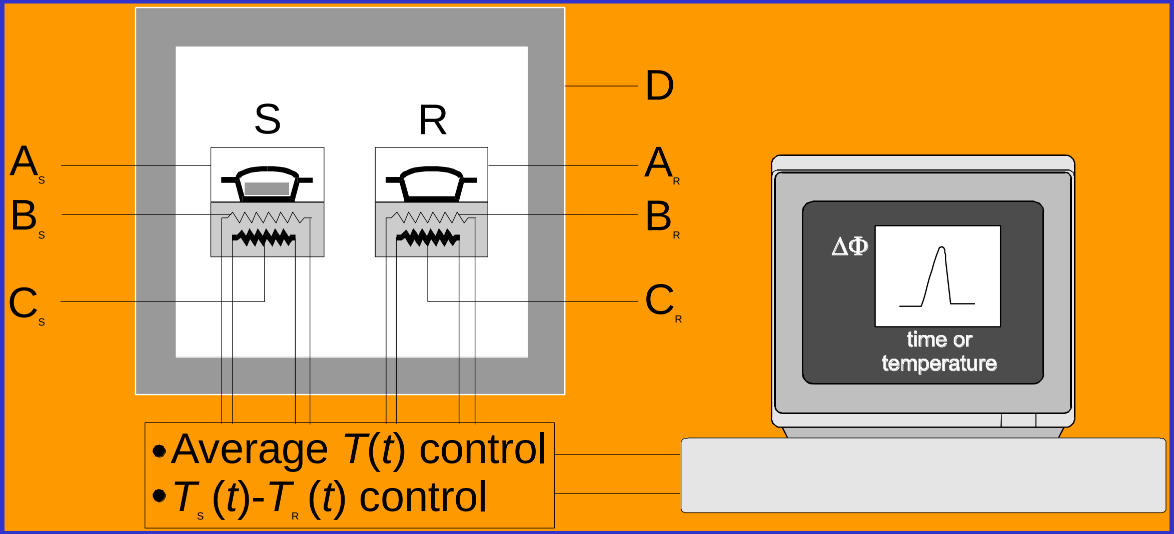
The physical and chemical transformations that accompany the heating or cooling of a substance are detected and characterized by monitoring the variation in the difference between the heat fluxes transmitted to a sample (S) and a reference material (R), as a function of temperature or of time, while S and R are subject to a programmed temperature variation

$$\Delta\Phi = \Phi_{\mathrm{S}} - \Phi_{\mathrm{R}} = (dQ/dt)_{\mathrm{S}} - (dQ/dt)_{\mathrm{R}}$$

Generally, the increase or decrease in temperature is linear. But the instruments can also be used in isothermal mode

Working Principle
(power compensation)

$$\Delta\Phi = \Phi_S - \Phi_R = (dQ/dt)_S - (dQ/dt)_R$$



Origins of DSC

Martine, 1739

Comparison of heating rates of equal volumes of mercury and water. First illustration of the possibility of applying thermal analysis to compare heat capacities of substances

Le Chatelier, 1887

The physical or chemical phenomena that occur when a material is heated or cooled can be identified measuring the variation of sample temperature as a function of time

Kurnakov, early 20th century

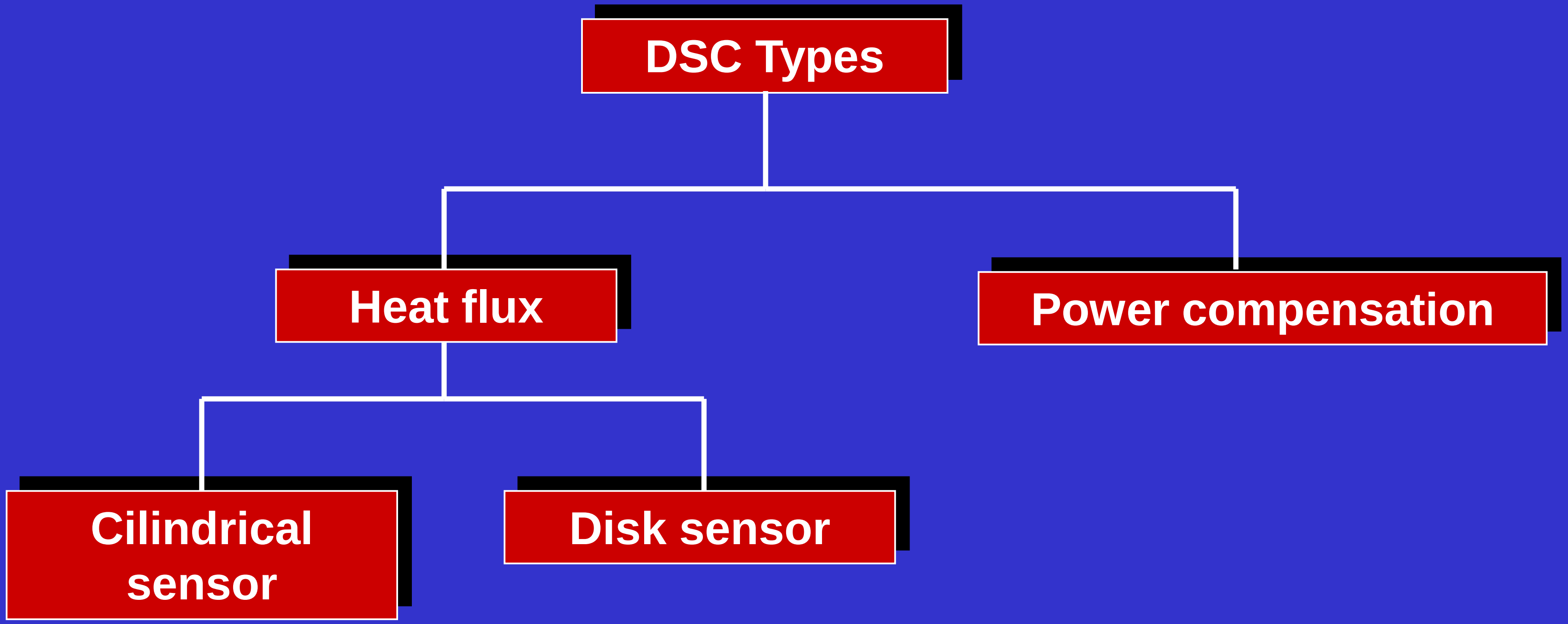
First Differential Thermal Analysis (DTA) Instruments

Watson, O'Neal, Justin & Brenner, 1964

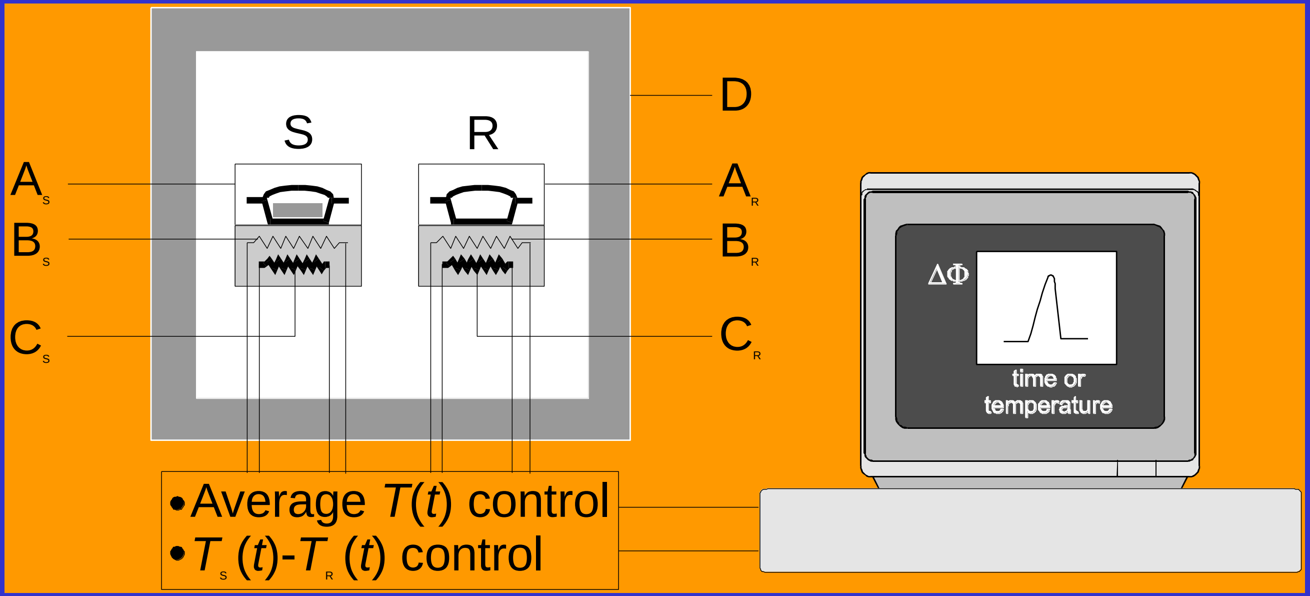
The first Differential Scanning Calorimeter
(it was of power compensation type)

(*Anal. Chem.* 1964, *36*, 1233-1238)

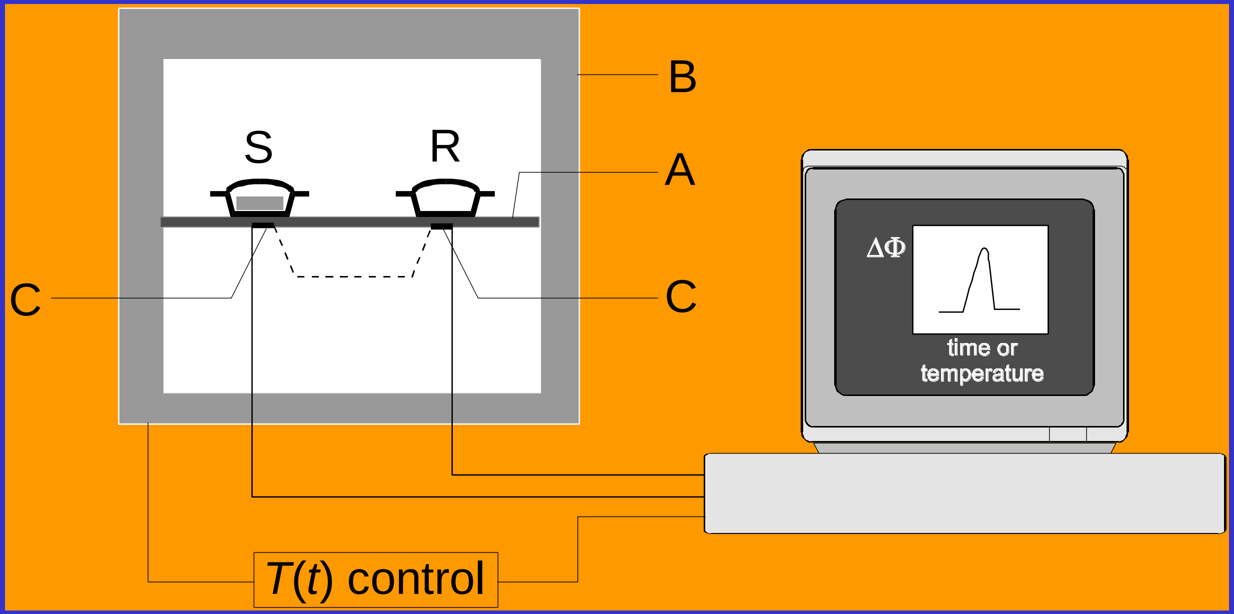
Main DSC Types



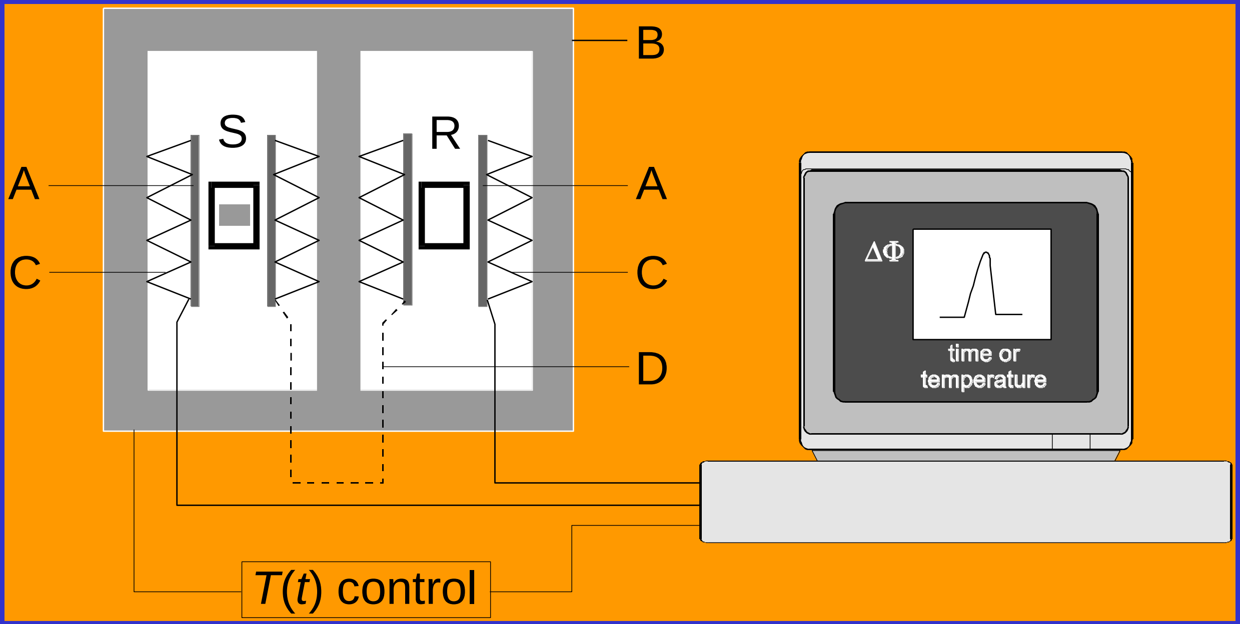
Power compensation DSC



Heat-flux DSC
(Disk type sensor)

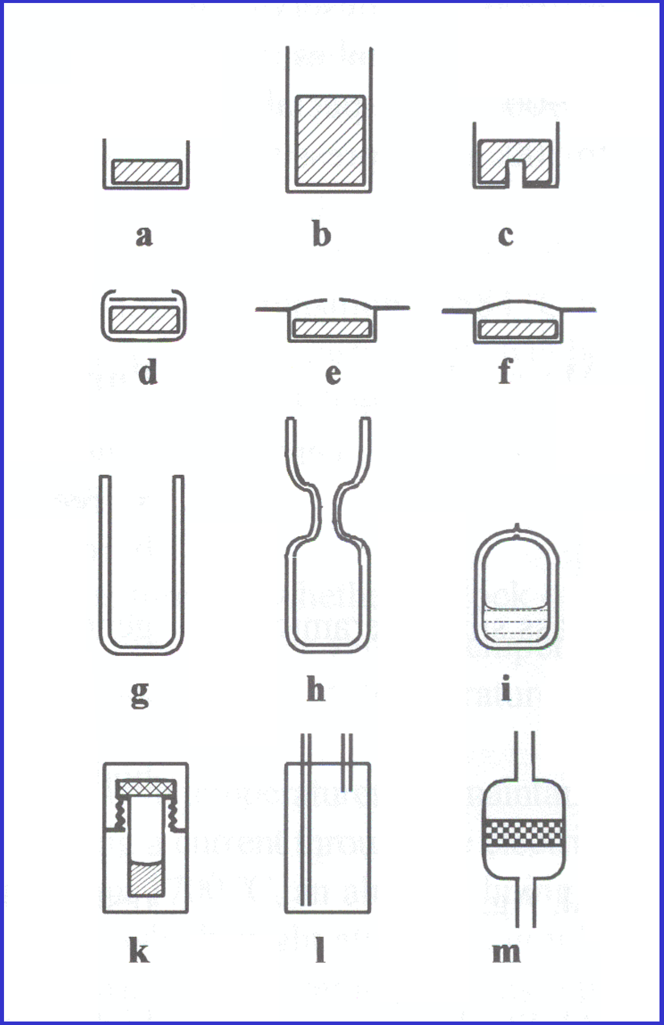


Heat-flux DSC
(Cylindrical type sensor)



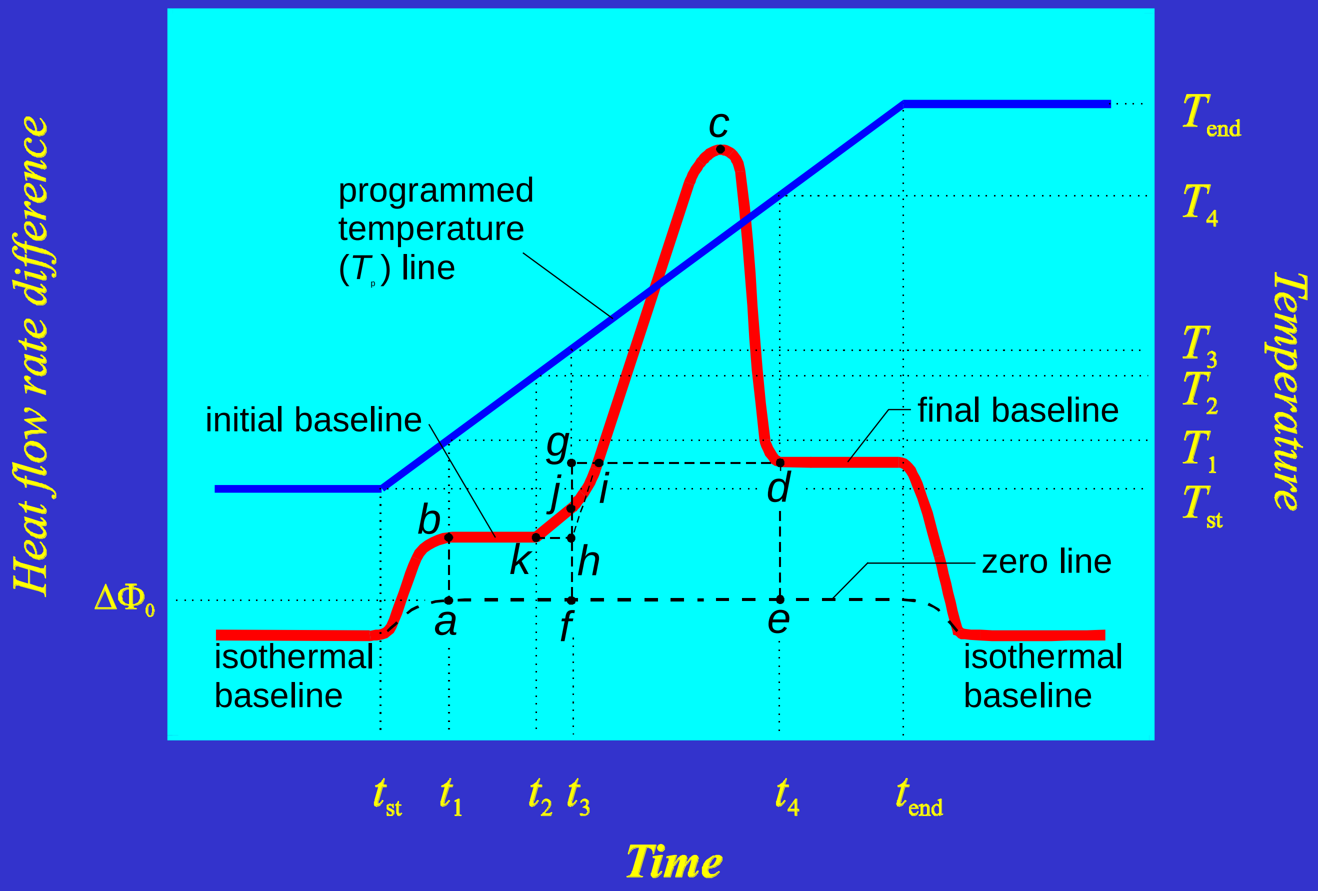
Some Typical Experimental Conditions

- Typical temperature range: 100 - 1000 K
- Heating rate: 0.1 K min^{-1} - 10000 K min^{-1}; (Most widely used: 5 K min^{-1} and 10 K min^{-1})
- Sample mass: 1 - 100 mg
- Sample inside a crucible (generally, aluminum)
- Purge gas (He, Ar, N_2)



Various crucible types and shapes

DSC Curve Characteristics



Quantitative Analysis of a DSC Curve
(Example: Melting curve)

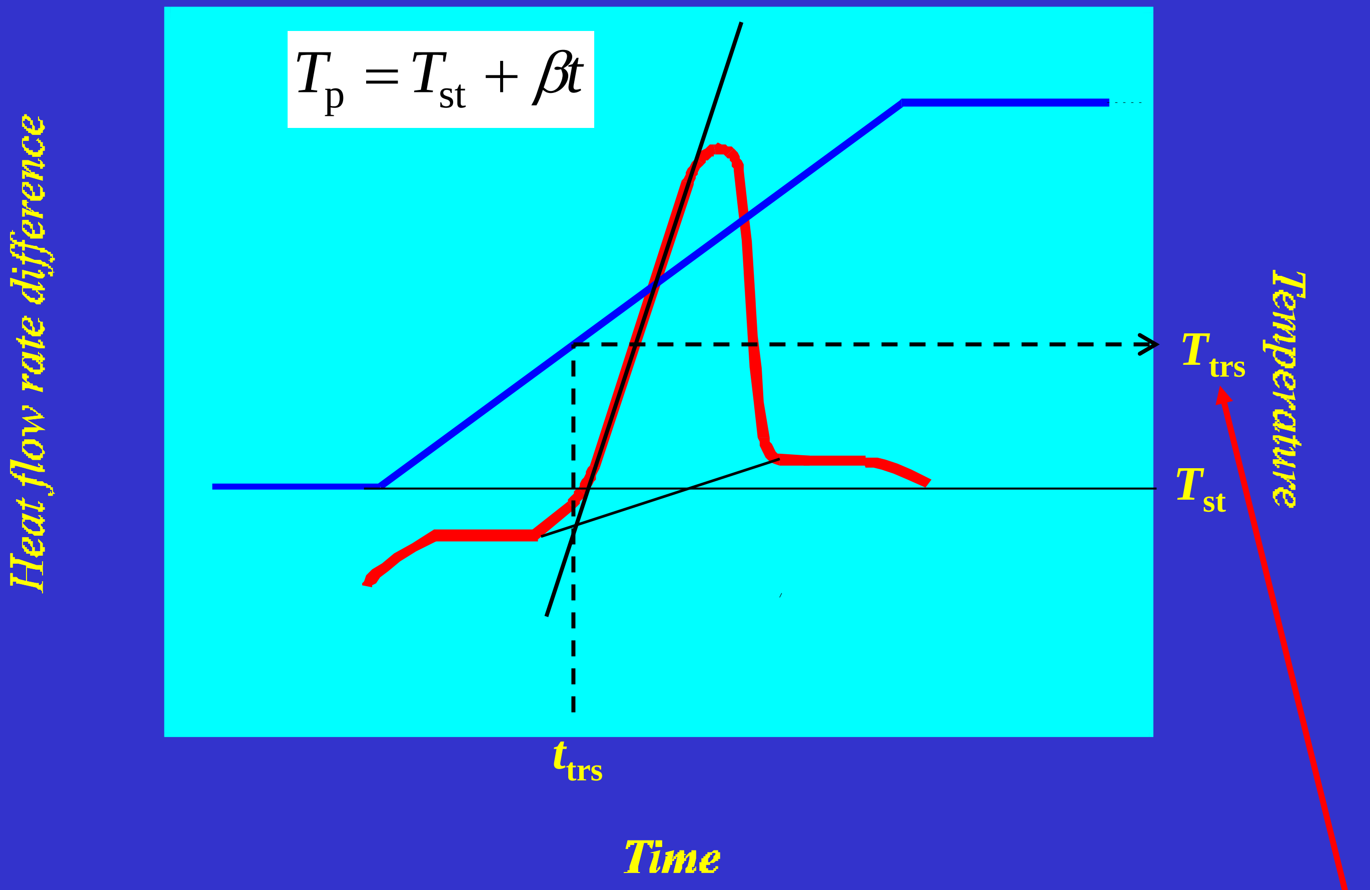
The analysis of a DSC melting curve can provide:

- Fusion temperature
- Enthalpy of fusion
- Purity

The determination requires:

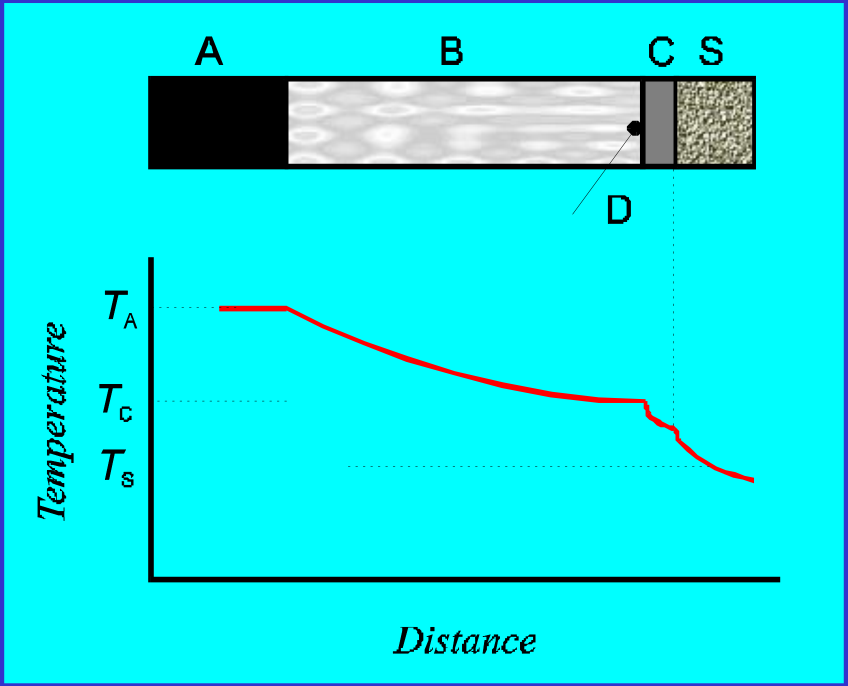
- Baseline definition
- Calibration of temperature scale
- Calibration of area in terms of enthalpy

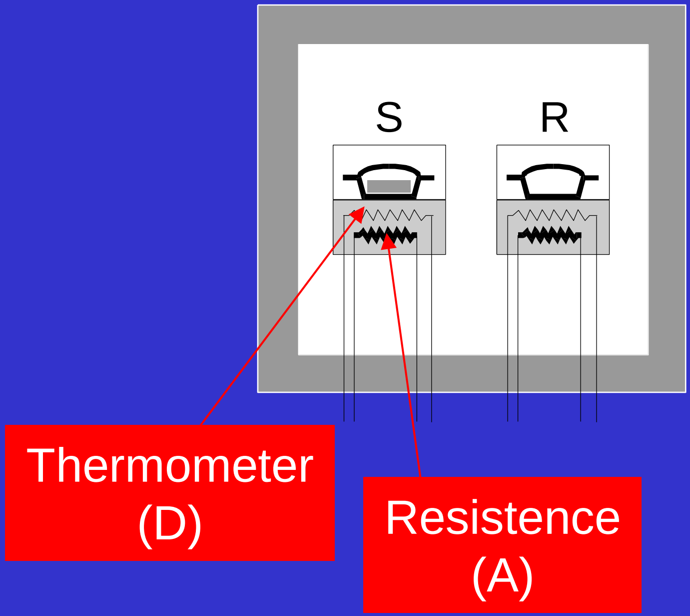
Determination of the Temperature of Fusion, T_{fus}



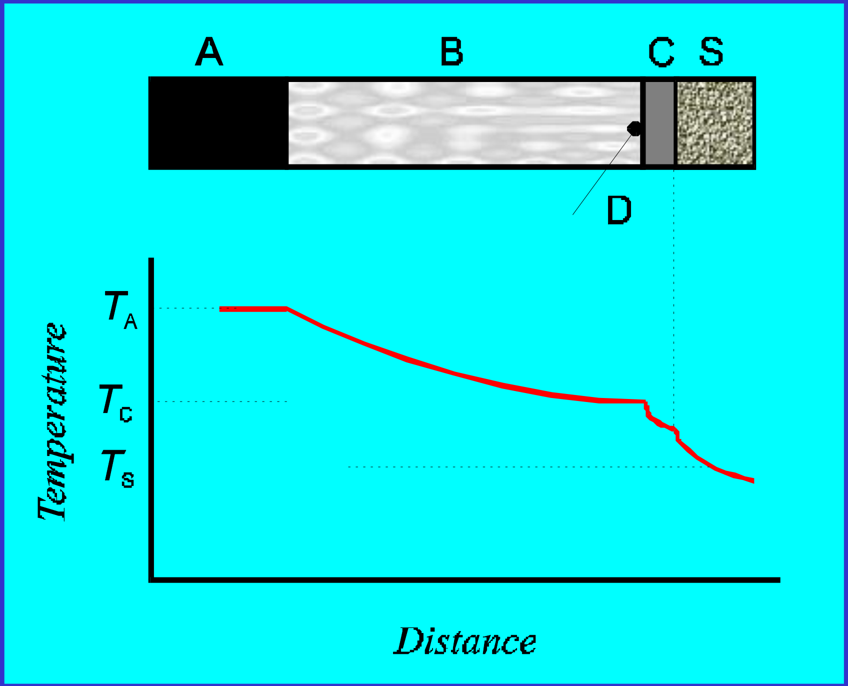
Represents the temperature of the sample surface in contact with the crucible at the start of the transformation

Calibration of the Temperature Scale (the problem of thermal lag)





Calibration of the Temperature Scale
(the problem of thermal lag)



Problem:

$$T_p = T_{st} + \beta t$$

T_p = programmed temperature
T_{st} = initial temperature
β = heating rate

$$T_p \neq T_s$$

T_s = sample temperature

- $T_p - T_s > 0$ heating
- $T_p - T_s < 0$ cooling
- Temperature gradient inside the sample

Determination of T_{fus}

1. Calibration of the temperature scale

a) Determine T_{fus} for different calibrants (e.g. In, Zn, Pb) and scan rates (β)

b) For each calibrant, determine $T_{fus}(\beta = 0)$ from plots of $T_{fus}(\text{exp})$ as a function of β

$$T_{fus}(\text{exp}) = T_{fus}(\beta = 0) + b\,\beta \qquad (1)$$

c) For each calibrant, determine the difference, δT, between the recommended temperature of fusion, $T_{fus}(\text{eq})$, and $T_{fus}(\beta = 0)$

$$\delta T = T_{fus}(\text{eq}) - T_{fus}(\beta = 0) \qquad (2)$$

d) Use a polynomial fit to find the relationship between δT and the experimental temperature, T, given by the instrument.

$$\delta T = a + bT + cT^2 + \ldots \qquad (3)$$

2. Determination of T_{fus} of a sample

e) Equation (3) can then be used to obtain $T_{fus}(\text{eq})$ of a sample from the experimentally determined $T_{fus}(\beta = 0)$ of that sample

$$T_{fus}(\text{eq}) = T_{fus}(\beta = 0) - \delta T \qquad (4)$$

Common Practice...

1. Calibration of the temperature scale of the apparatus for a specific scan rate, β, using a set of standards.

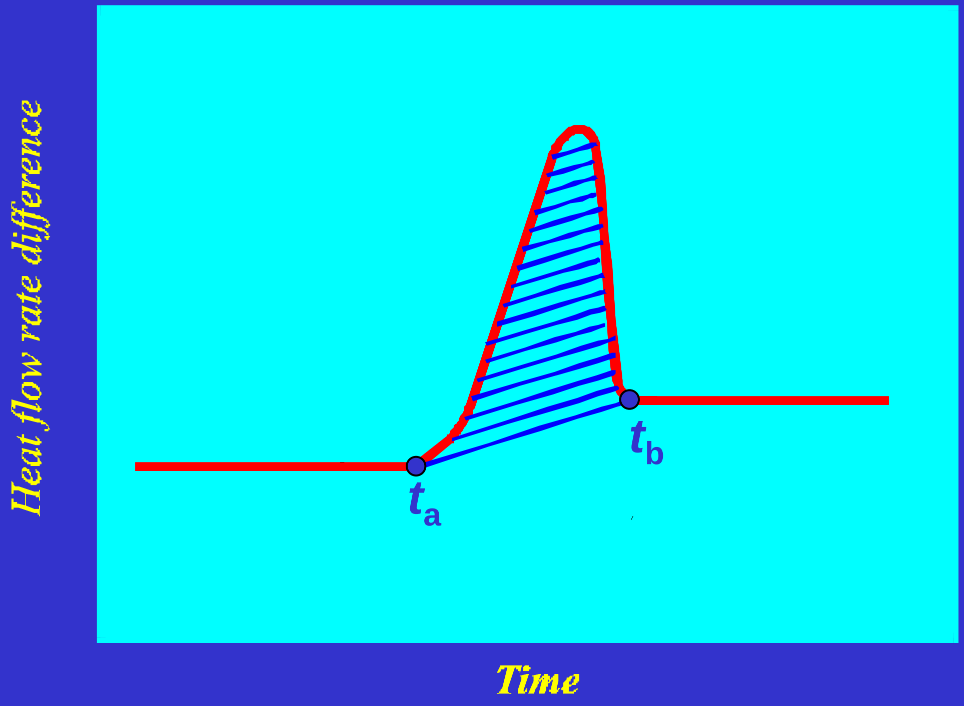
$$\delta T(\beta) = T_{fus}(eq) - T_{fus}(\beta) \qquad (5)$$

2. Determination of T_{fus} of a sample

Use equation (5) to obtain T_{fus}(eq) of the sample from the value of T_{fus} observed for the sample at the same heating rate.

$$T_{fus}(eq) = T_{fus}(\beta) - \delta T(\beta) \qquad (6)$$

Determination of the Enthalpy of Fusion, $\Delta_{fus}H$

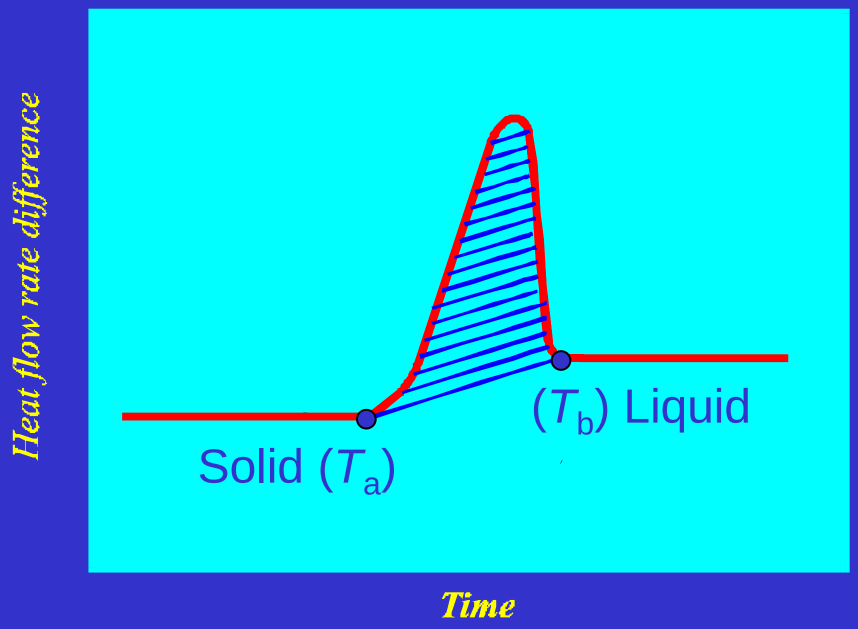


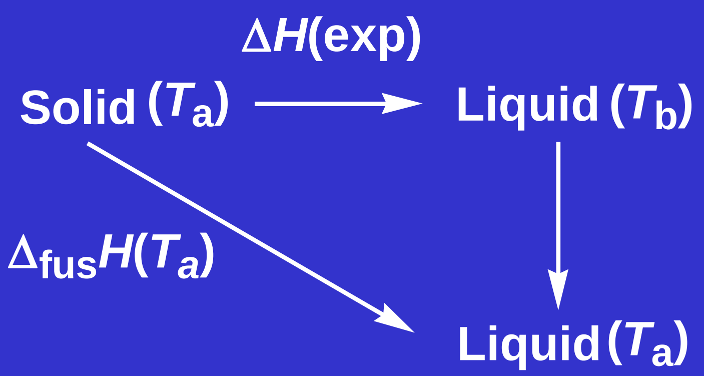
$$Q = \int_{t_a}^{t_b} \left[\left(\frac{dQ}{dt} \right)_S - \left(\frac{dQ}{dt} \right)_R \right] dt = k_Q A$$

Calibration

$$\Delta H(\exp)/\mathrm{J \cdot mol^{-1}} = \frac{M}{m} Q = \frac{M}{m} k_Q A$$

Determination of the Enthalpy of Fusion, $\Delta_{\text{fus}}H$, at a Specific Temperature





$$\Delta_{\text{fus}}H(T_{\text{a}}) = \Delta H(\text{exp}) + \int_{T_{\text{b}}}^{T_{\text{a}}} C_p(\text{l})\,dT$$

Determination of Purity by DSC

For details about this topic see paper available for download at Fénix

The determination of the purity of a given compound **A** by DSC is based on the cryoscopic depression phenomenon, also known as freezing point depression. This corresponds to the decrease of the fusion or freezing point of a solvent caused by the addition of a solute (the impurity), here denoted by **B**.

The difference, ΔT, between the temperatures of fusion of the pure (T*) and impure (T) compound is related to the overall impurity content x_B :

$$x_B = \frac{\Delta_{fus}H_m}{RT^{*2}}\Delta T \qquad \textbf{(1)}$$

$$\Delta T = T^* - T$$

where $\Delta_{fus}H_m$ is the molar enthalpy of fusion of the pure sample A. It should be noted that

- Equation (1) is based on the ideal solution model. Thus, it is only valid when $x_B \rightarrow 0$, i.e. for very pure compounds (typically for a molar percentage > 97%).
- x_B represents the overall impurity content, meaning that it may correspond to more than one type of impurity
- As such, purity is obtained without need to kown the nature of the impurities

Determination of Purity by DSC

A fusion endotherm for a pure compound is illustrated in Figure 1. Here T^* is the freezing point of the compound. The area ABC is proportional to the corresponding enthalpy of fusion, $\Delta_{fus}H_m$.

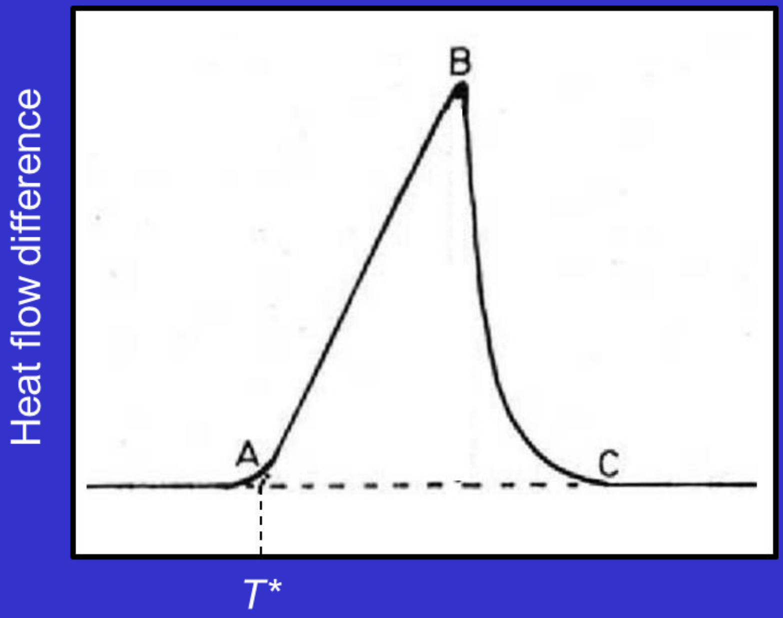


Figure 1. Idealized DSC curve for a pure sample The slope of AB is used to correct for thermal lag. T^* is the fusion temperature. Area ABC is proportional to the enthalpy of melting , $\Delta_{fus}H_m$.

Determination of Purity by DSC

The presence of an impurity B lowers the freezing point of the sample A (the solvent) and also increases the fusion range, giving a broader DSC endotherm as illustrated in the inset in Figure 2.

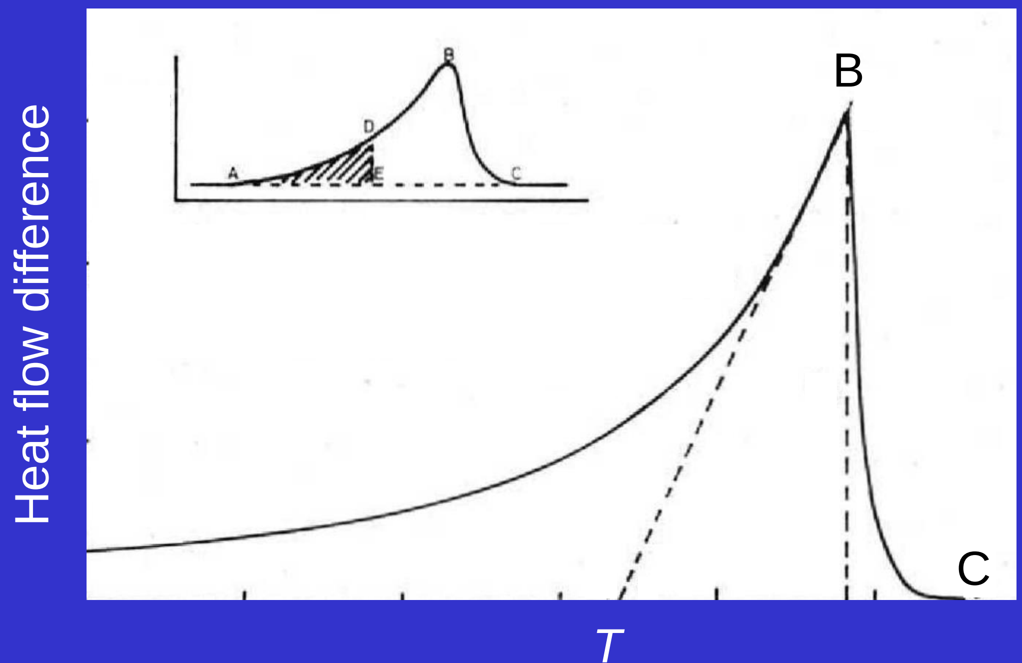


Figure 2. Idealized DSC curve for a an impure pure sample. *T* is the fusion temperature. Area ABC is proportional to the enthalpy of melting , $\Delta_{fus}H_m$.

At the unique temperature *T* (the freezing point of the impure sample) the mole fraction, x_B, is given by:

$$x_B = \frac{\Delta_{fus}H_m}{RT^{*2}}\left(T^* - T\right)$$

Relatioship Between Crysoscopic Depression and an Eutetic Phase Diagram

The origin of the broadening of the DSC endotherm can be understood with the help of the eutectic phase diagram and temperature time curve in Figure 3.

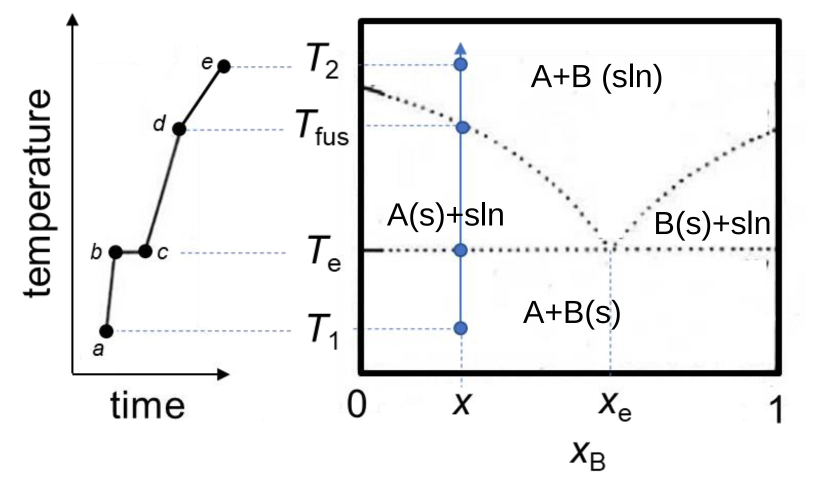


Figure 3. Heating curve of an impure solid (left) and its relationship with the corresponding eutectic diagram

If a sample A containing an impurity B with molar fraction *x* is heated from T_1 to T_2 the following observations can be made:

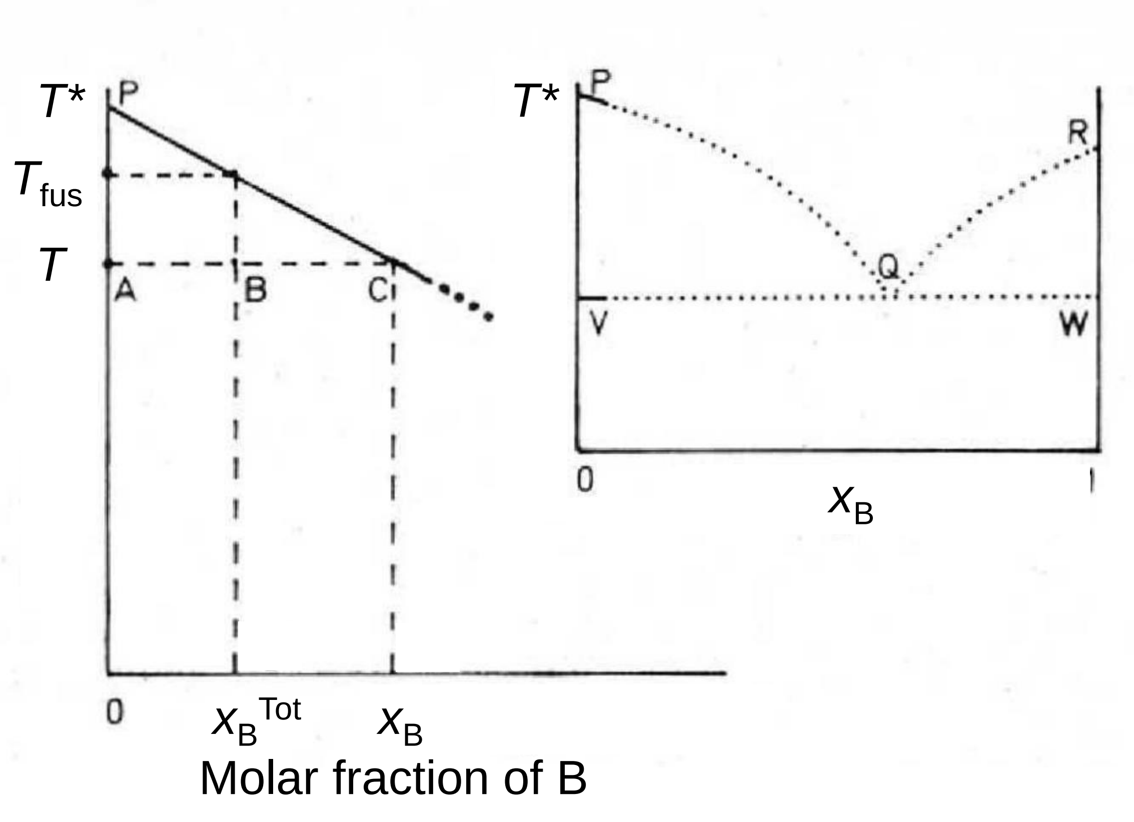
- Between points *a* and *b* in the temperature time curve, the sample is being heated fromT_1 and T_e (the eutectic point) and will remain solid.
- When the eutectic temperature, T_e, is reached at point b the first liquid will be formed. It consists ofa A+B mixture with a fixed composition (the eutectic composition) corresponding to a molar fraction x_e of impurity B. The temperature will remain constant until all eutectic solid has melted which occurs between points *b* and *c*. Because $x_e > x$ the liquid is richer in B than the initial sample.
- At point *c* all eutectic mixture has melted, and all B has been transferred into solution (only A remains in the solid state). The highest concentration of impurity in the liquid therefore corresponds to point *c*. Between points *c* and *d* the system is composed by solid A (only solid A) in equilibrium with the solution. As the temperature increases between points *c* and *d* from T_e to T_{fus}, solid A progressively melts and joins the solution. Thus, B is progressively diluted with A along the *c* to *d* pathway. At *d* a change in slope of the temperature-time curve is observed indicating that all A has gone into solution. This corresponds to the fusion temperature of the mixture, T_{fus} indicated by *T* in the DSC curve of Figure 2. From then on only the solution persists with a mole fraction of impurity *x* equal to that initially present in the solid state.

Determination of Purity by DSC

Low concentration region (x_B<0.05) of a simple eutectic phase diagram (inset). By the lever rule at point B, n_{solid}/n_{liquid} = BC/AB. C is the composition of the liquid in equilibrium with pure solid at T. Here $x_B > x_B^{tot}$.

The fraction of sample melted is:

$$F = n_l/(n_s + n_l) = AB/(AB+BC) = AB/AC = x_B^{tot} / x_B$$

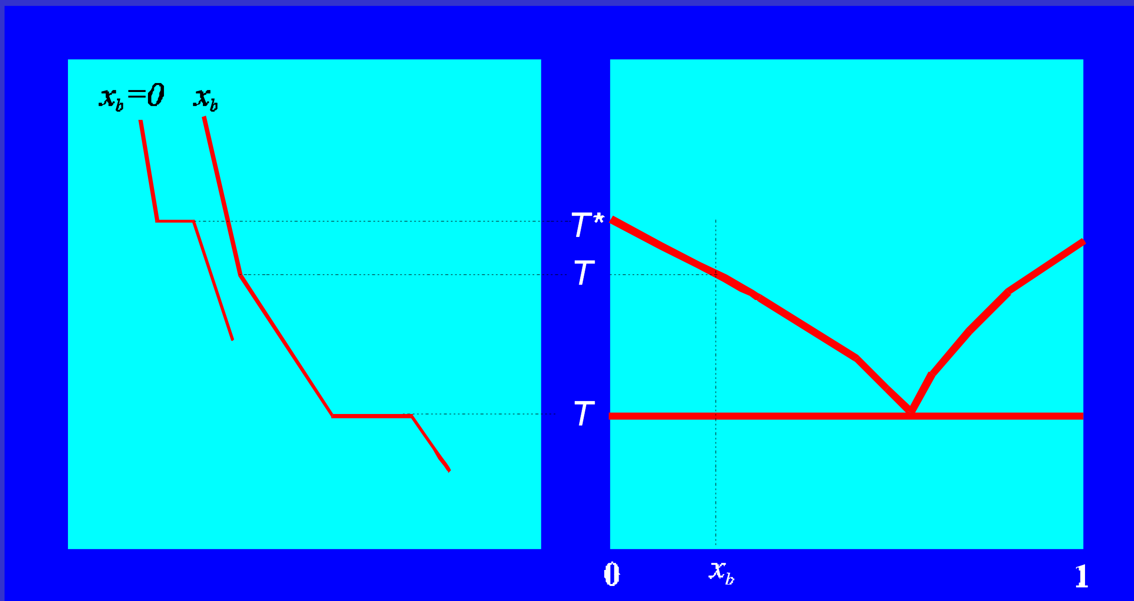


$$x_B^{tot} = \frac{\Delta_{fus}H_m}{RT^{*2}}\left(T^* - T_{fus}\right)$$

$$x_B = \frac{\Delta_{fus}H_m}{RT^{*2}}\left(T^* - T\right)$$

$$F = \frac{x_B^{tot}}{x_B} = \frac{T^* - T_{fus}}{T^* - T}$$

Determination of Purity by DSC



$$x_B = \frac{\Delta_{fus} H_m}{R T^{*2}} \left(T^* - T \right)$$

$$T = T^* - \frac{R T^{*2}}{\Delta_{fus} H_m} x_B$$

$$x_B = \frac{1}{F} x_B^{Tot}$$

F **= Fraction of sample melted**

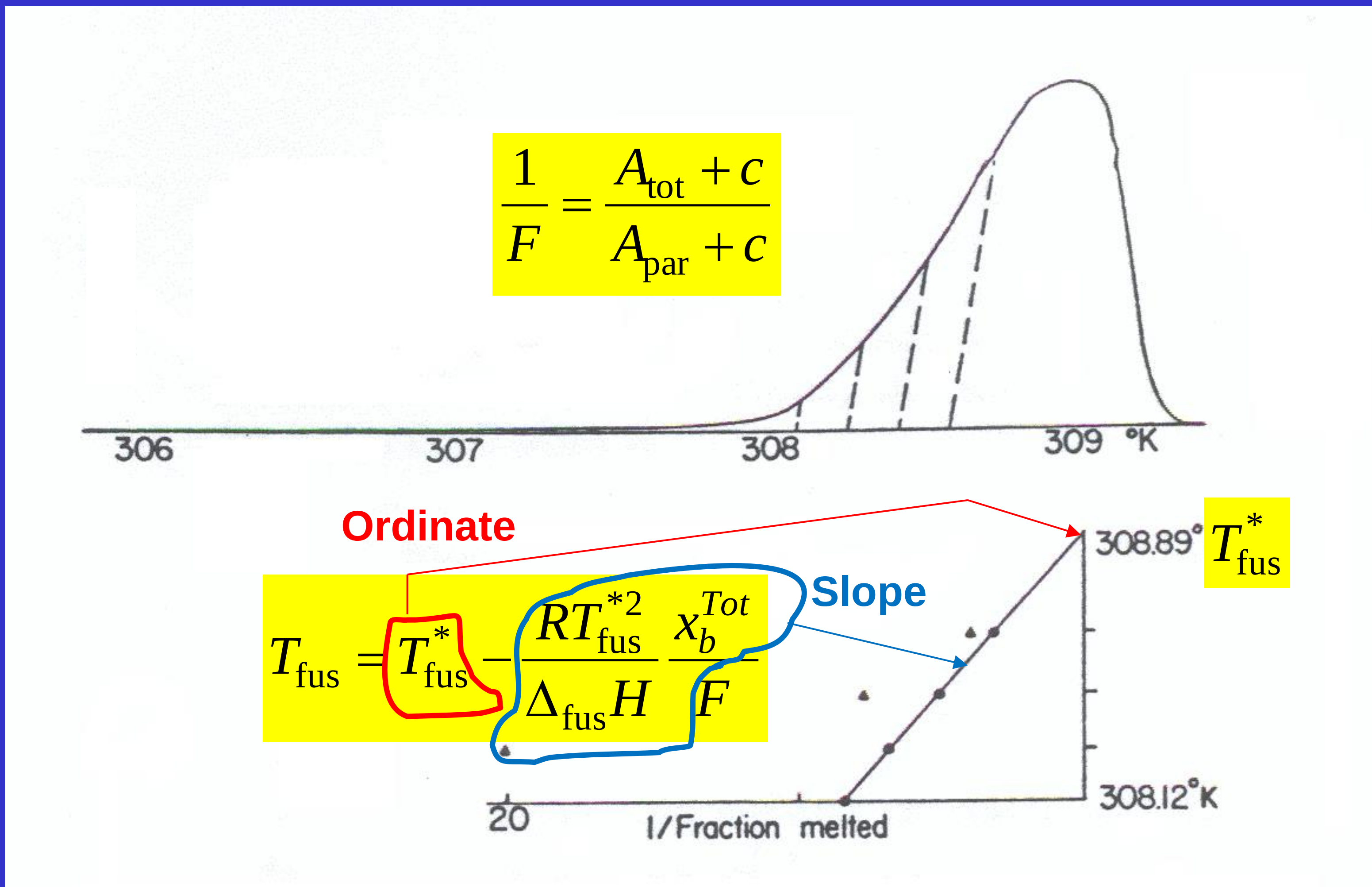
F **= 1 ⇒ All sample has melted**

F **= 0.01 (i.e. 1/*F* = 100) ⇒ 1% of sample has melted**

$$T = T^* - \frac{R T^{*2}}{\Delta_{fus} H_m} \frac{x_B^{Tot}}{F}$$

$$\frac{1}{F} = \frac{A_{tot} + c}{A_{par} + c}$$

Determination of Purity by DSC



$$\frac{1}{F} = \frac{A_{\mathrm{tot}} + c}{A_{\mathrm{par}} + c}$$

$$T_{\mathrm{fus}} = T_{\mathrm{fus}}^{*} - \frac{RT_{\mathrm{fus}}^{*2}}{\Delta_{\mathrm{fus}}H}\frac{x_b^{Tot}}{F}$$

T_{fus}^{*}

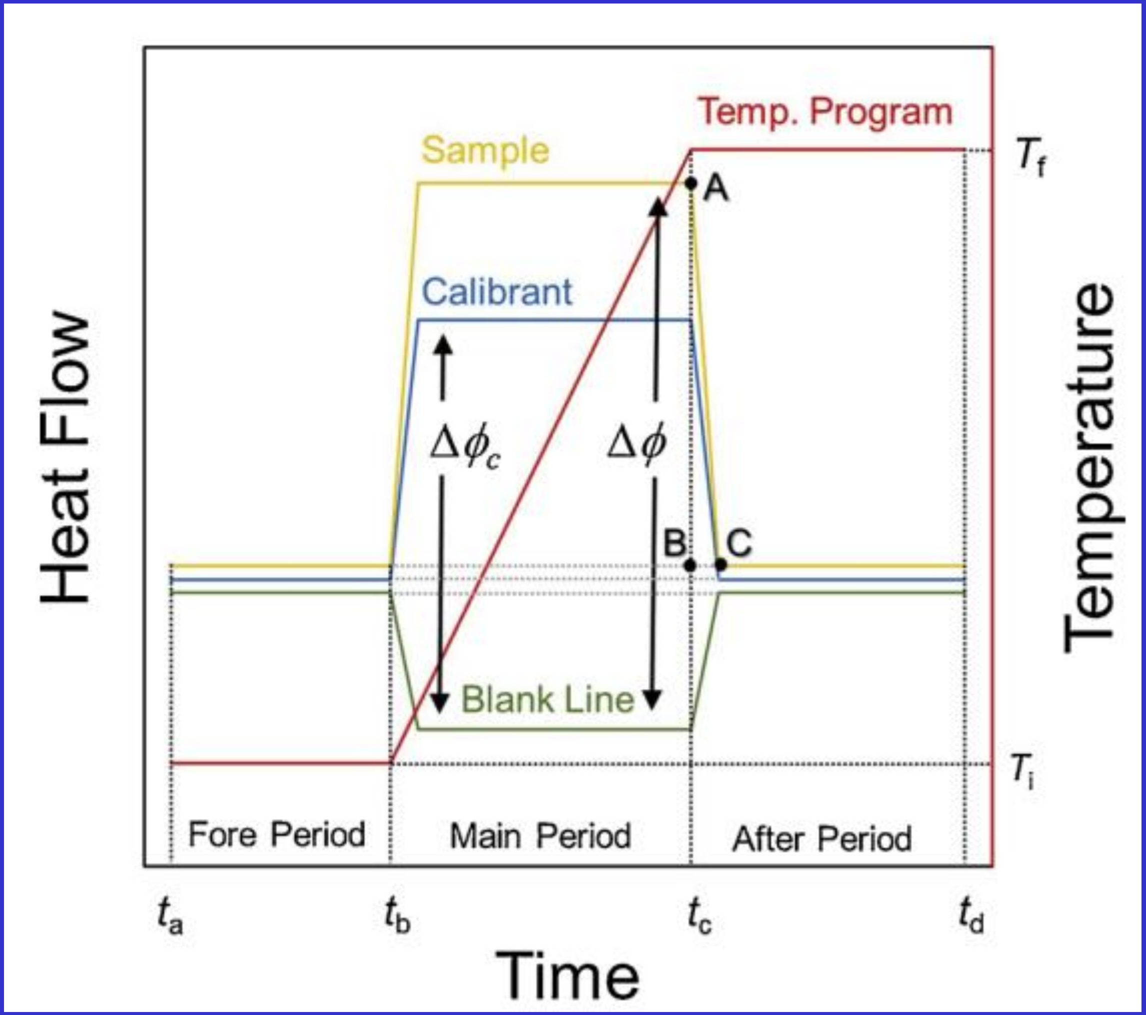
Determination of Purity by DSC

Some Typical Problems

- Solid solutions
- Volatile impurities
- Decomposition concomitant with fusion
- Polymorfism

Determination of Heat Capacity by DSC

For details about this topic see the two papers available for download at Fénix



$$C_{p,\mathrm{m}}(T) = k(T)\cdot\frac{M}{m\cdot\beta}\cdot\Delta\phi(T)$$

$$k(T) = \frac{C_{p,\mathrm{m}}(\alpha\text{-}Al_2O_3,T)_{\mathrm{Ref}}}{C_{p,\mathrm{m}}(\alpha\text{-}Al_2O_3,T)_{\mathrm{Obs}}}$$

Thermomicroscopy

Main Types of Thermal Analysis

Thermomicroscopy

Variations of optical properties of substances as a function of temperature

- Morphological and structural changes

Calorimetric Analysis: **Differential Scanning Calorimetry**

- Thermodinamic data: T_{fus}, $\Delta_{fus}H$, T_g C_p
- Kinetic data: k, E_a for phase transitions and solid state reactions
- Purity analysis

Thermogravimetry

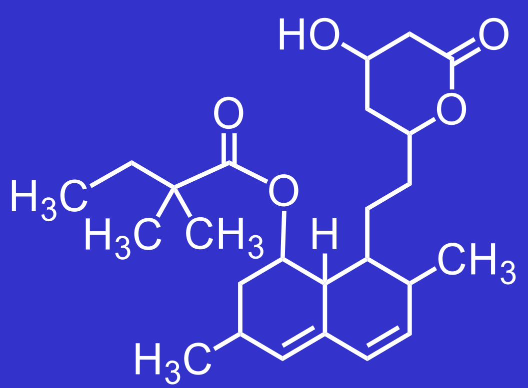
Mass changes as a function of temperature

- Thermal decompositions in different atmospheres
- vapor pressures

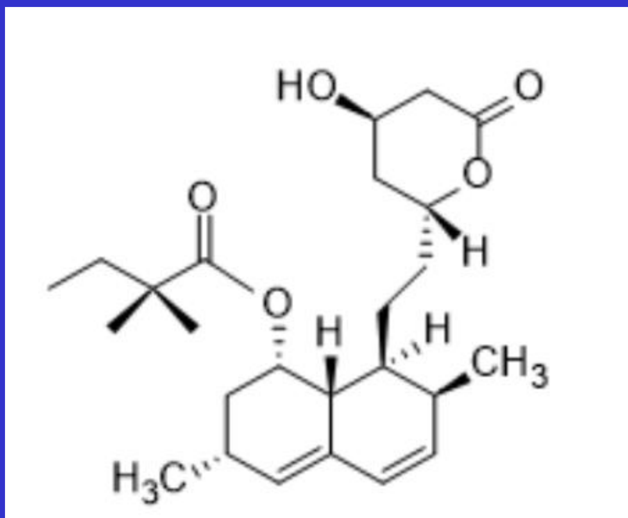
Thermomechanical analysis :

Study of mechanical properties of materials as a function of temperature (e.g.: compressibility and elasticity)

Phase Transitions: Is Polymorphism a Problem? (Simvastatin)

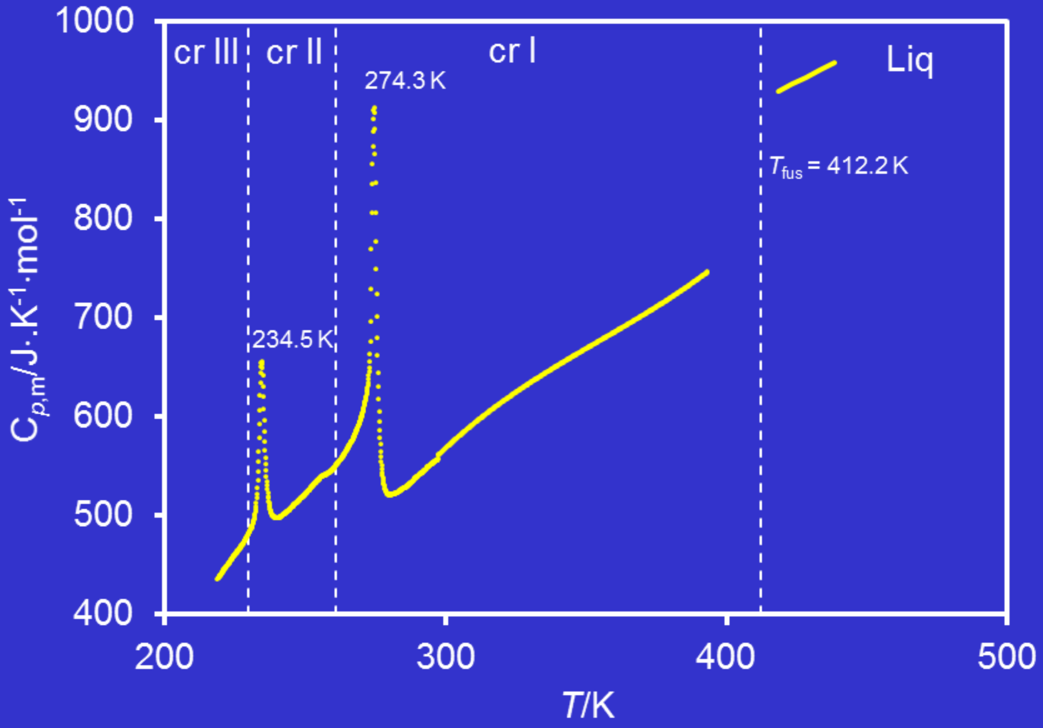


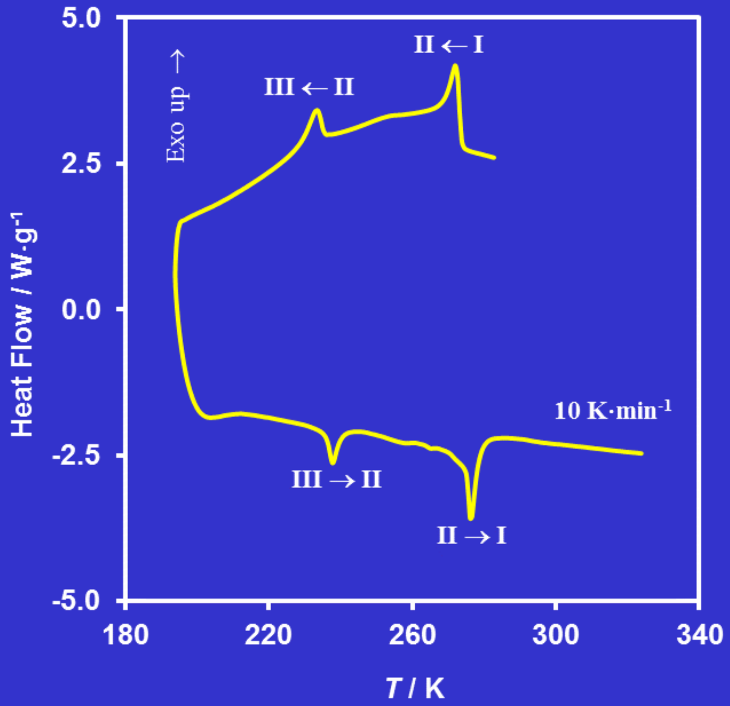
Phase Transition
(Simvastatin)



Temperature Domains of Polymorphs?

Differential Scanning Calorimetry





$\Delta_{trs}H_m$(III→II) = 0.36±0.01 kJ·mol^{-1}

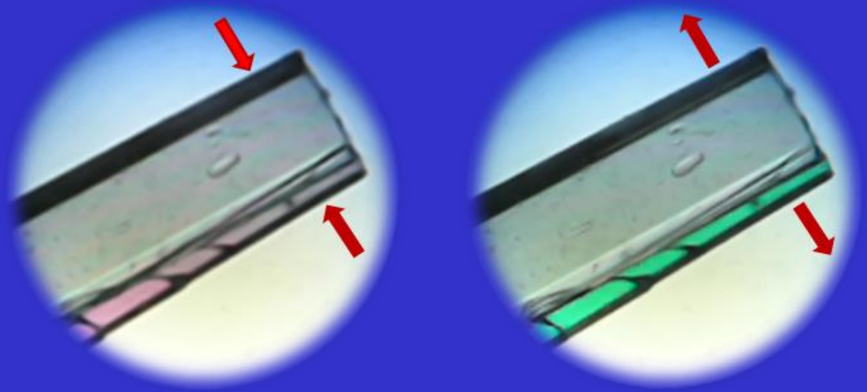
$\Delta_{trs}H_m$(II→I) = 0.55±0.02 kJ·mol^{-1}

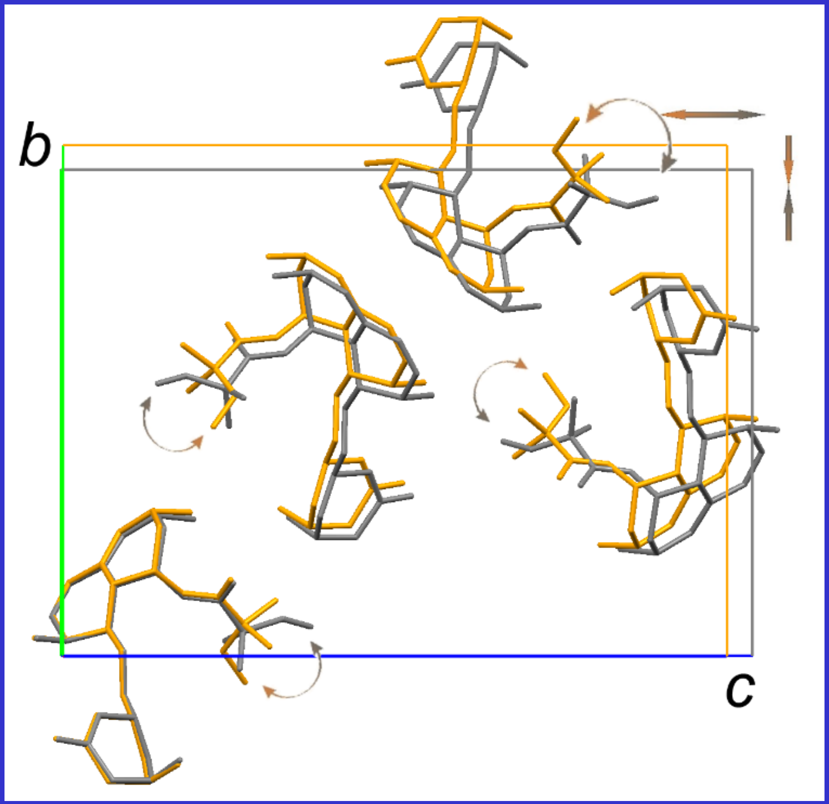
$\Delta_{fus}H_m$ = 30.4±0.2 kJ·mol^{-1}

<300 K Netzsch 204 F1 Phoenix
>300 K Perkin-Elmer DSC 7

Phase Transition: A Molecular View (Simvastatin)

Form II → Form I
271 K





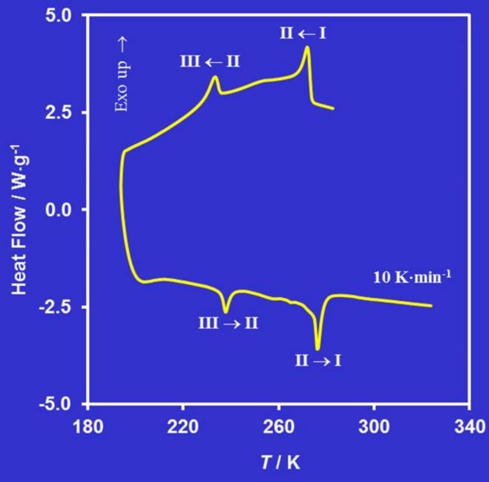
Form II (grey) → Form I (yellow)

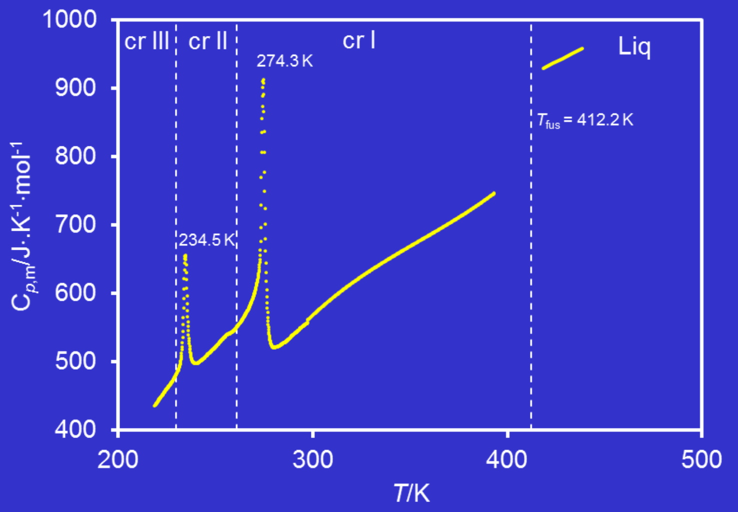
Message to Take Home

It is probably not a serious issue for pharmaceutical formulations because:

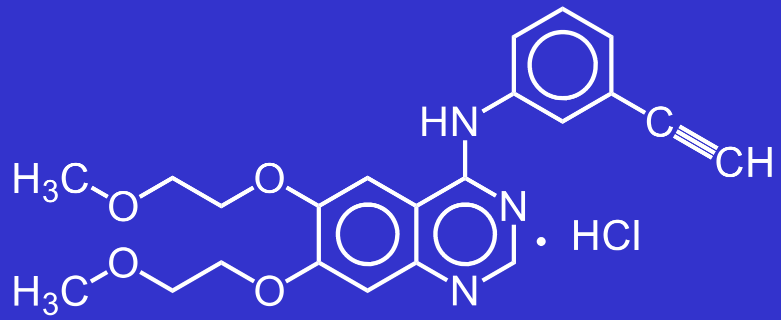
(i) The III and II polymorphs readily convert to form I at ambient temperature.

(ii) Only form I is present between ambient temperature and the fusion temperature.



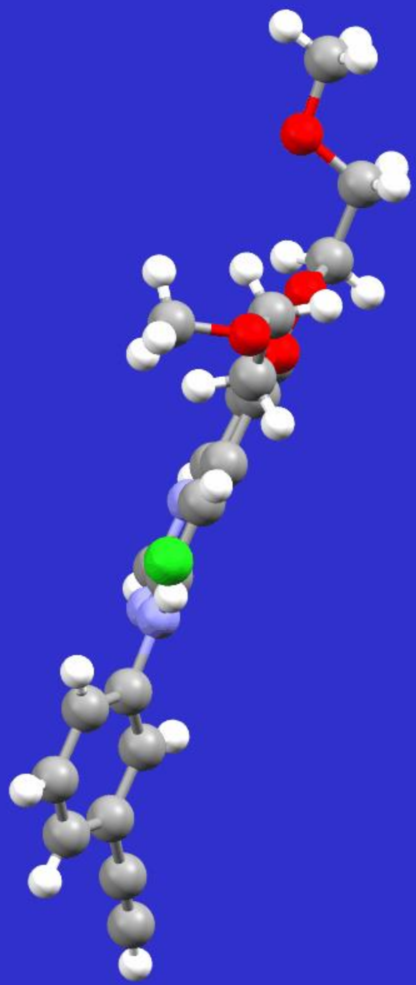


Erlotinib hydrochloride (EtbHCl): Two polymorphs A & B



<u>Applications</u>

- Lung cancer
- Pancreatic cancer

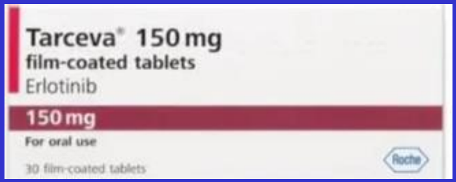


Polymorphism as an opportunity

A textbook example of the importance of crystal polymorphism for drug development and patent litigation

9 years of patent litigation

- 2004 Marketed by Roche under tradename Tarceva



- 2006 Introduced in India

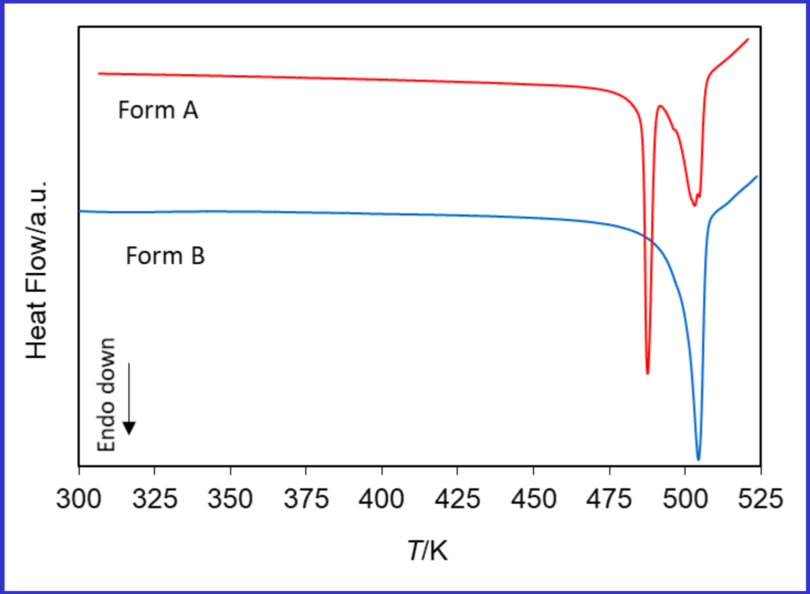
  Cipla started selling EtbHCl (polymorph B) under tradename Erlocip at 1/3 of Roche's price

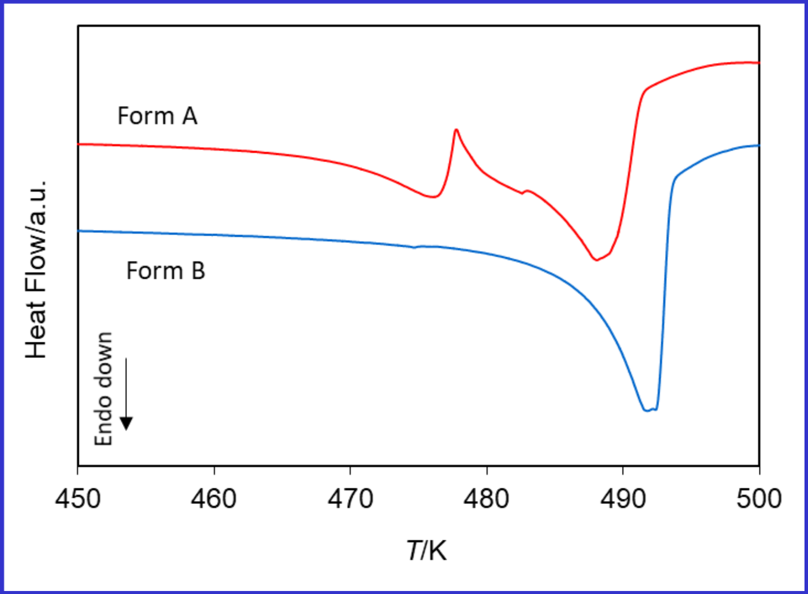
- 2008 Roche vs. Cipla litigation started in India

  Cipla claimed that Roche patent did not specifically cover polymorph B

- 2017 (May) The two companies reached a settlement

Phase Transition (DSC Results) (Erlotinib·HCl)

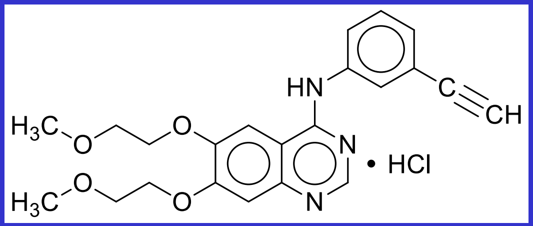


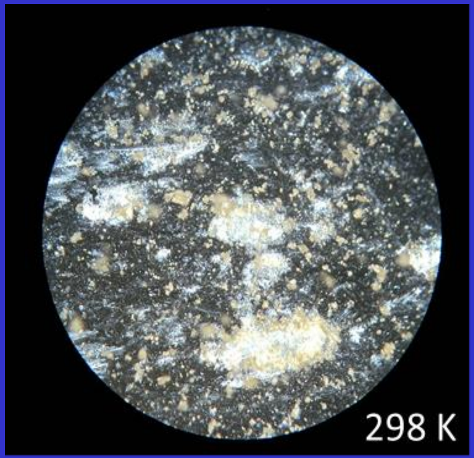


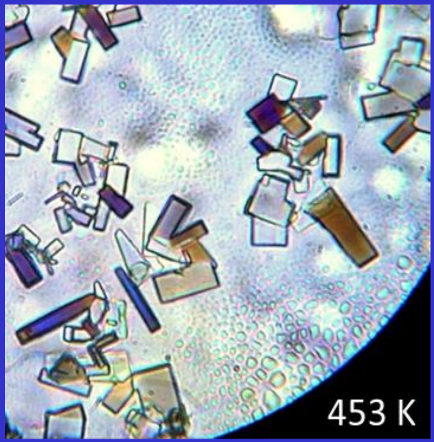
10 K·min^{-1}

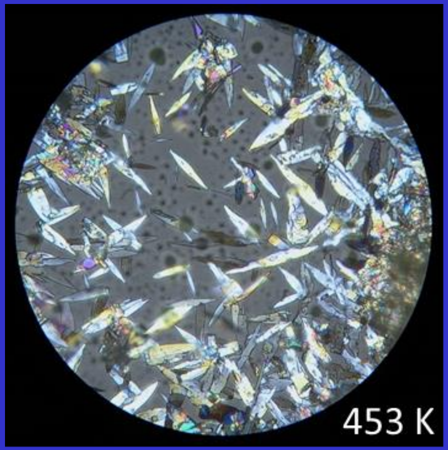
1 K·min^{-1}

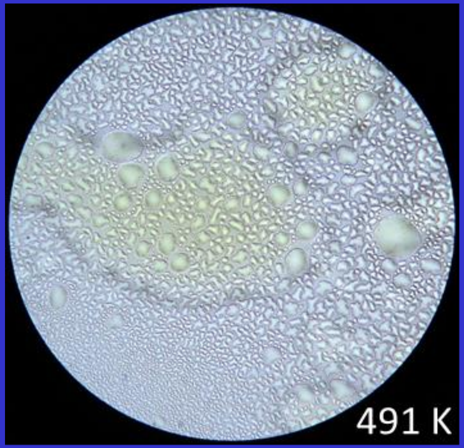
Phase Transition (Erlotinib·HCl)







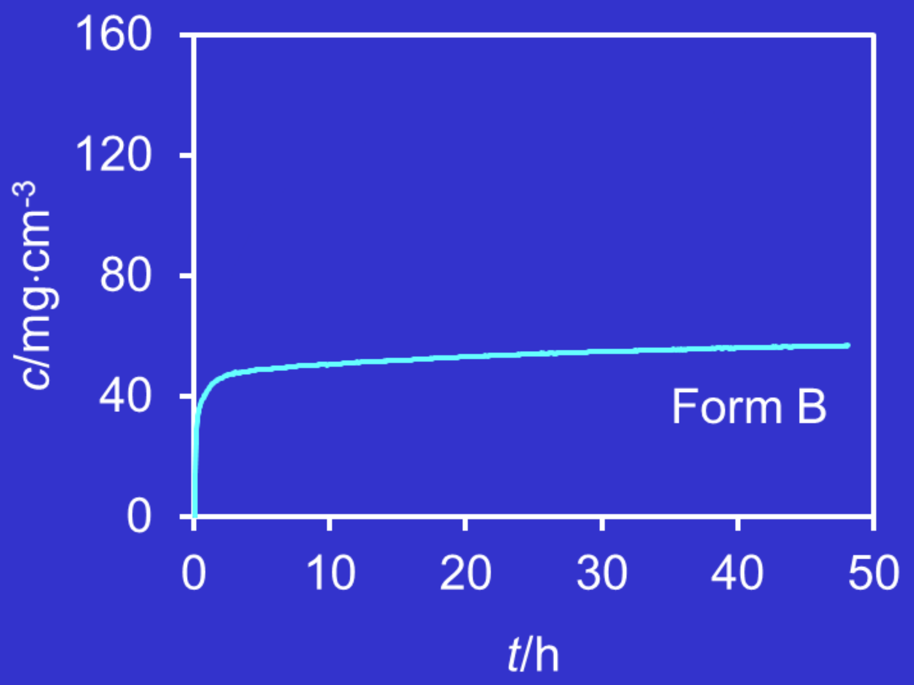




Polymorphism as an Opportunity
Erlotinib·HCl Solubility

Solvent: Simulated gastric fluid without enzymes

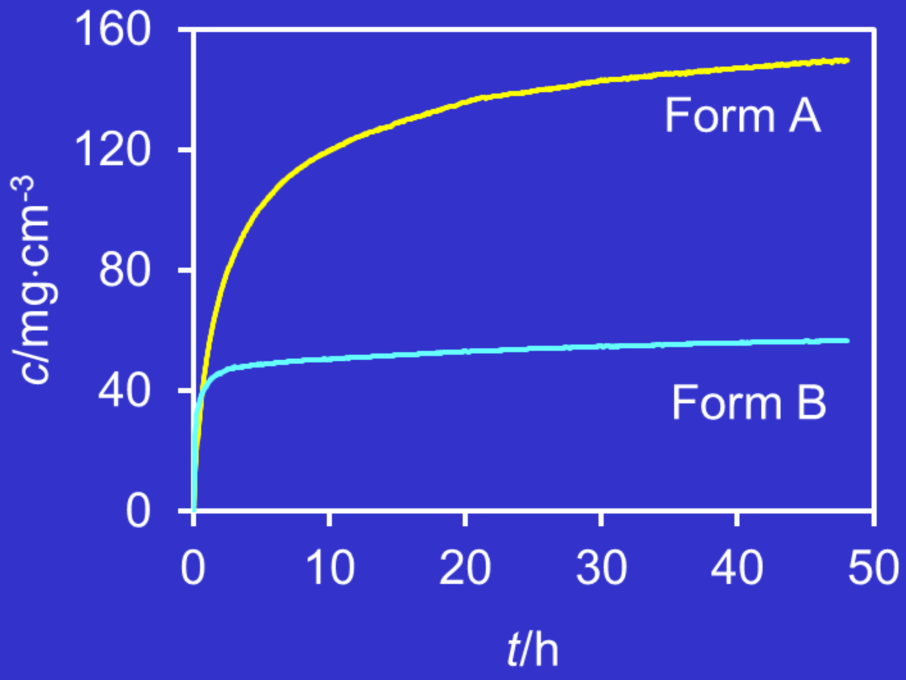
T = 298 K

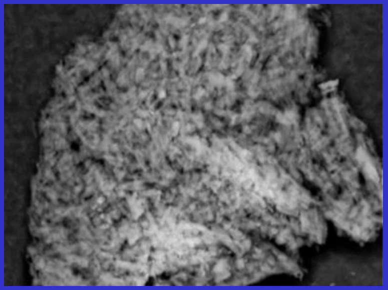


Form B
(marketed)

Polymorphism as an Opportunity
Erlotinib·HCl Solubility

Solvent: Simulated gastric fluid without enzymes
T = 298 K

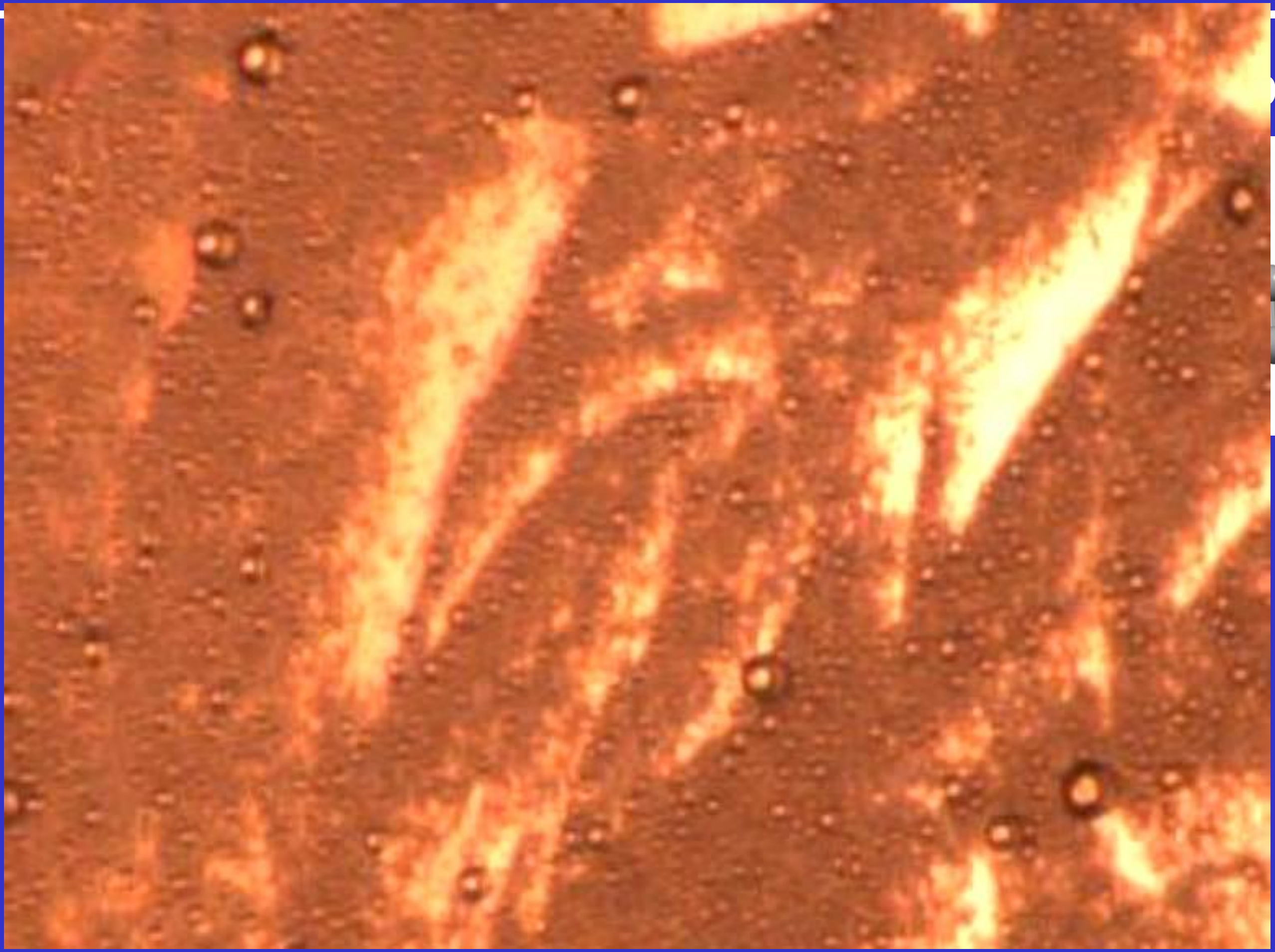




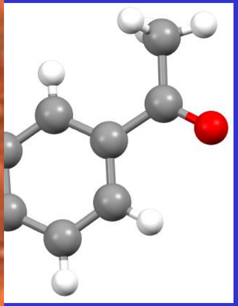
Form A

Form B
(marketed)

Crystal Growth from Melt and Polymorphism

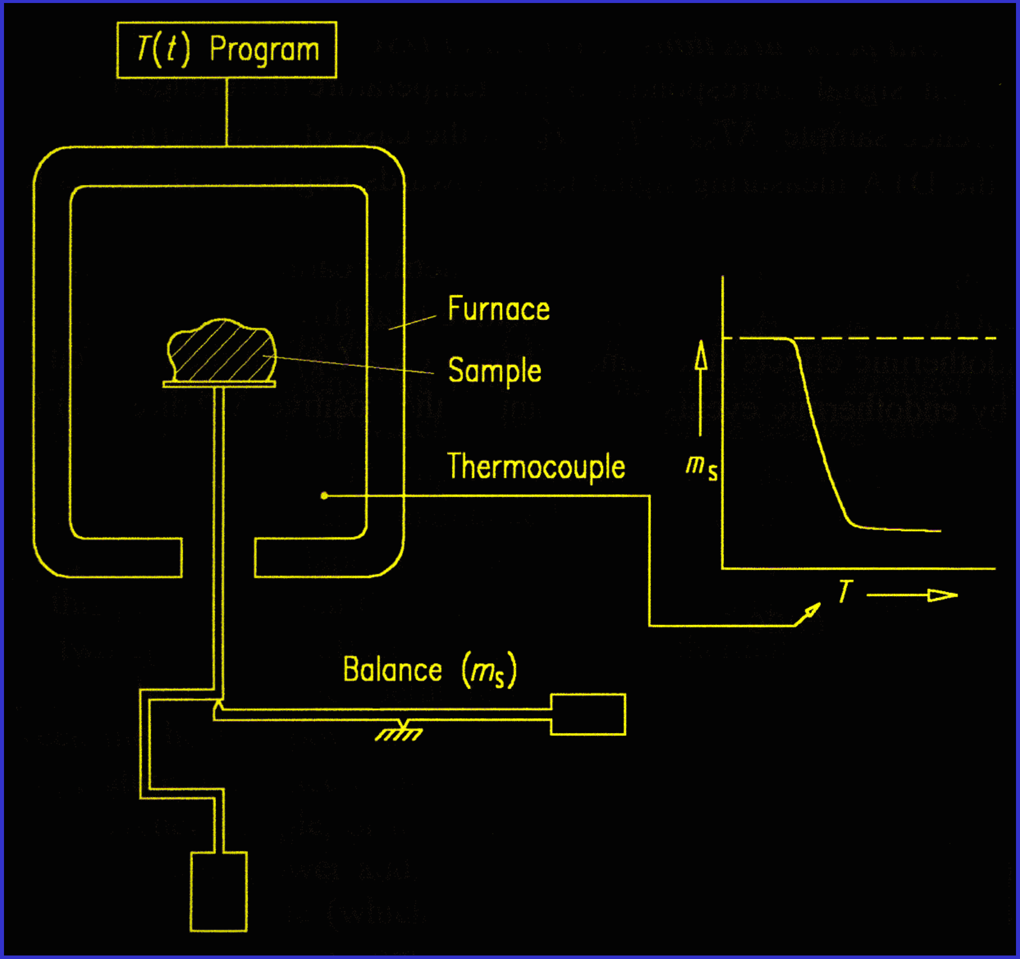


henone

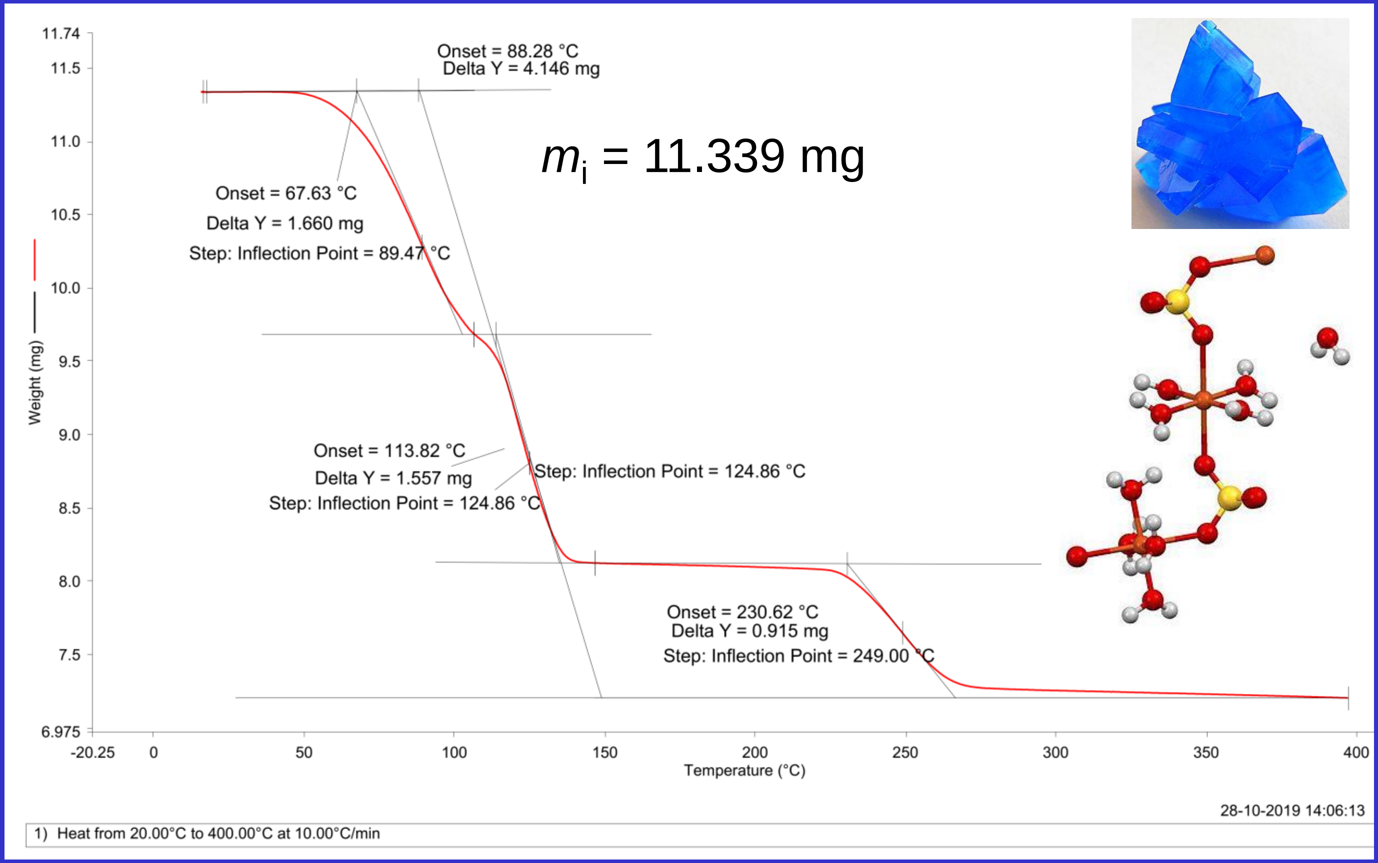


Thermogravimetry

Thermogravimetric Analysis (TGA)



TG Analysis of $CuSO_4{\cdot}5H_2O(cr)$ Dehydration



Step 1 $CuSO_4{\cdot}5H_2O(cr) \rightarrow CuSO_4{\cdot}3H_2O(cr) + 2H_2O(g)$

Step 2 $CuSO_4{\cdot}3H_2O(cr) \rightarrow CuSO_4{\cdot}H_2O(cr) + 2H_2O(g)$

Step 3 $CuSO_4{\cdot}H_2O(cr) \rightarrow CuSO_4\,(cr) + H_2O(g)$

Sources of Errors in TGA

Typical sources of error in TGA are:

1. Buoyance effect. If an empty crucible is heated there is usually an apparent weight change as temperature increases. This is due to the change in buoyancy of the gas in the sample environment with the temperature, the increase convection and possible effect of heat from the furnace in the balance itself. In most modern thermobalances, this effect is negligible. However, if necessary, a blank run with empty crucible can be performed over the appropriate temperature range. The resultant record can be used as a correction curve for subsequent experiment performed in the same condition.

2. Condensation on balance suspension. Condensation of the sample on the balance suspension will also affect the observed mass loss and consequently the shape of the TG curve .This can be avoided by maintaining a dynamic atmosphere around the sample in the furnace so that all the condensable product may be driven by the flowing gases.

Sources of Error in TGA

3. Random fluctuation of balance mechanism.

4. Reaction between sample and container.

5. Convection effect from furnace

6. Turbulence effect from gas flow

7. Induction effect from furnace

Errors of type 3 can be avoided by proper placing of balance in the laboratory. Error 5 can be minimized by an appropriate choice of sample container. Errors 5-7 have to be considered in the design of the furnace, the balance and its suspension system. By avoiding excessive heating rate and proper gas flow rate some of the above mentioned errors may be reduced.

Calibration of TG Systems

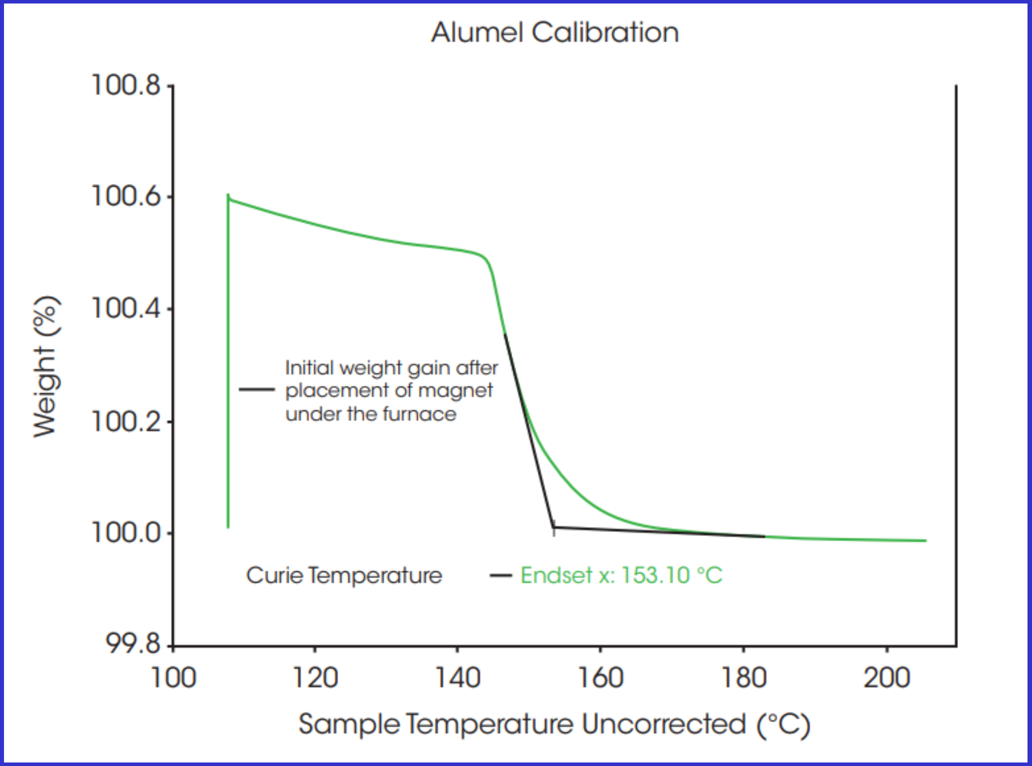
Because of the errors mentioned it is necessary to calibrate thermobalance before use.
Calibration of the mass scale can be done by placing a standard mass in the sample container.
Calibration of the temperature scale can be performed using ferromagnetic standards. In a magnetic field these substances shown detectable mass changes associated with phase transitions that occur at well known temperatures.

In this technique, a Curie standard material is placed in an empty, tared TGA pan located near a strong magnet. The material is then heated. At the Curie temperature, the magnetic properties disappear and the reduced attraction for the magnet results in a sharp apparent weight loss or gain (depending on the TGA furnace design). This point (temperature) is sharp and reversible, and hence ideal for calibration.

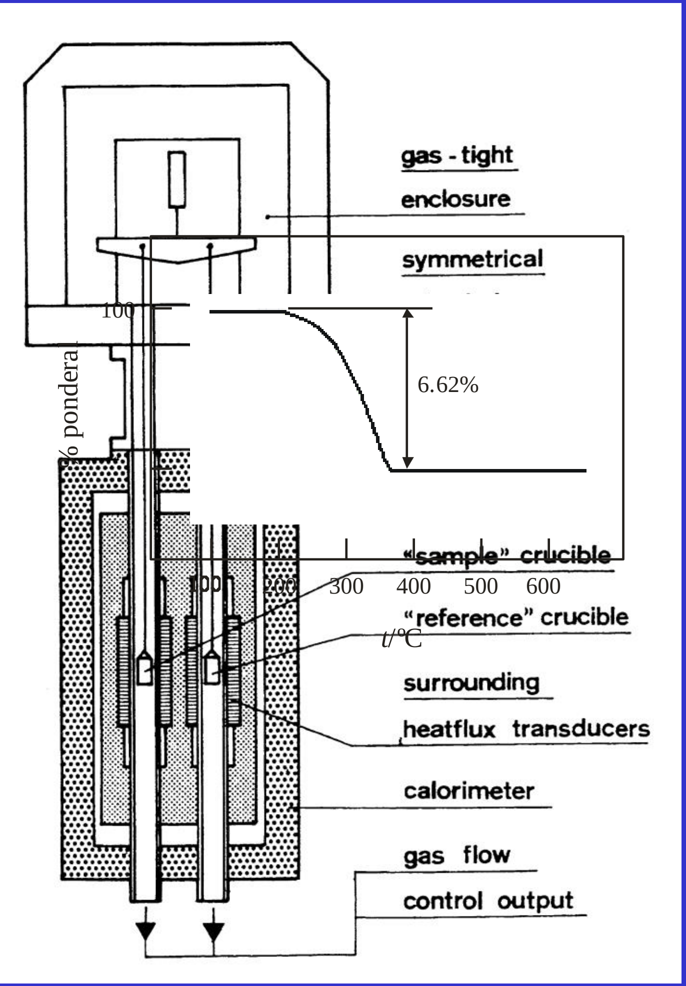
Calibration of TG Systems

Alumel: alloy consisting of approximately 95% nickel, 2% aluminium, 2% manganese, and 1% silicon

Curie temperature (T_C), or **Curie point:** temperature above which certain materials lose their permanent magnetic properties

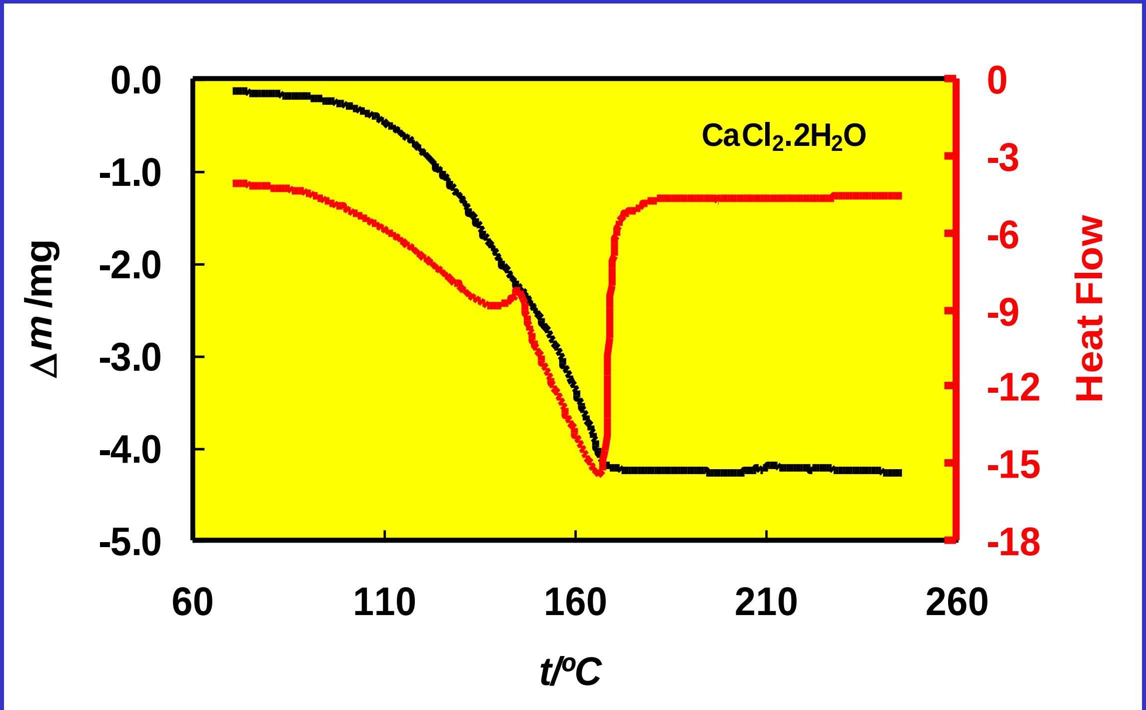


Hyphenated Methods
(TG – DSC)



TG-DSC Analysis of $CaCl_2{\cdot}2H_2O$

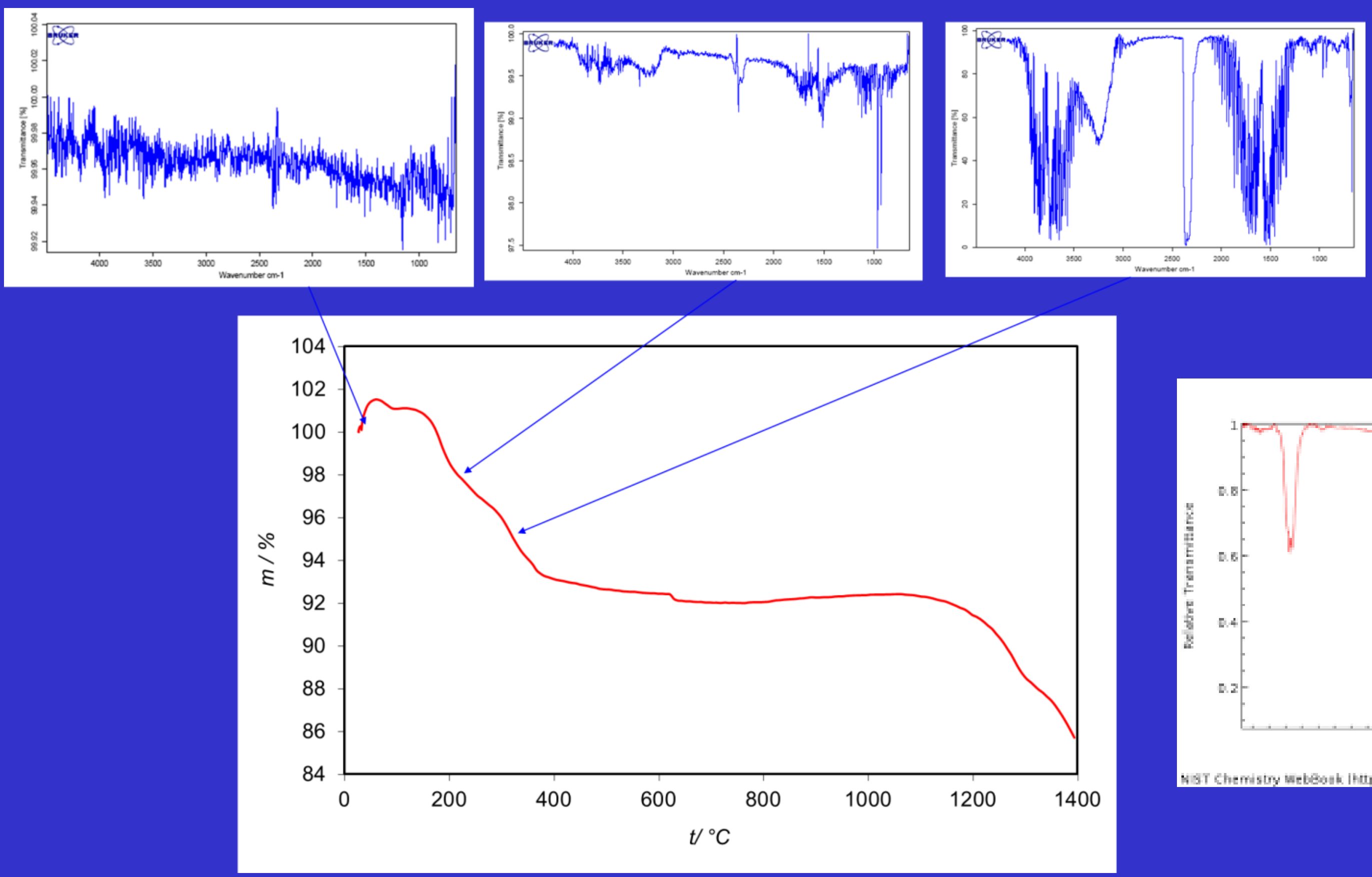
$$CaCl_2{\cdot}2H_2O(cr) \rightarrow CaCl_2(cr) + 2H_2O(g)$$

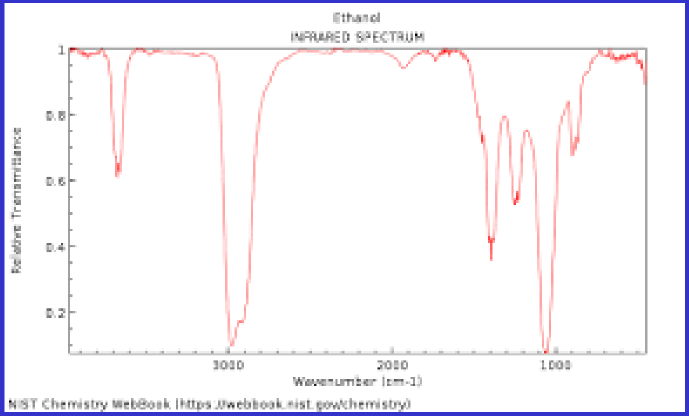


- $m_{initial}(CaCl_2{\cdot}2H_2O)$ = 16.1 mg
- $n_{initial}(CaCl_2{\cdot}2H_2O) = 1.095\times10^{-4}$ mol
- $M(CaCl_2.2H_2O)$ = 147.0146 g mol^{-1}
- $M(H_2O)$ = 18.0153 g mol^{-1}
- $m(H_2O$, predicted) = 3.9 mg
- $m(H_2O$, observed) = 4.0 mg

TG – FTIR Analysis of Ethanol Removal from Fluorapatite

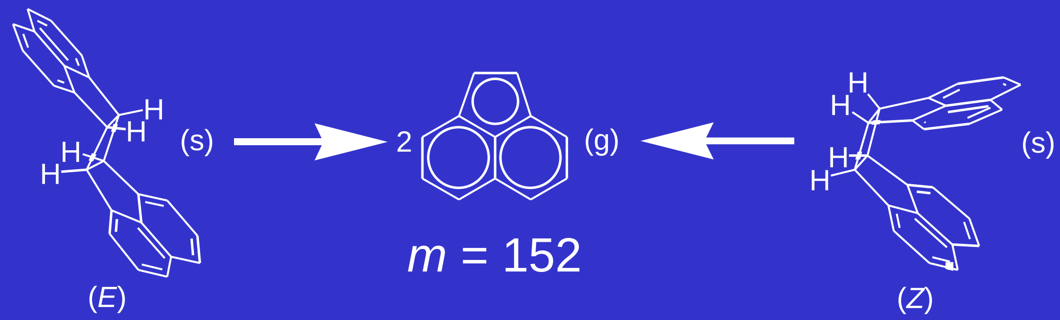
$Ca_{10}(PO_4)_6F_2 \cdot C_2H_5OH$

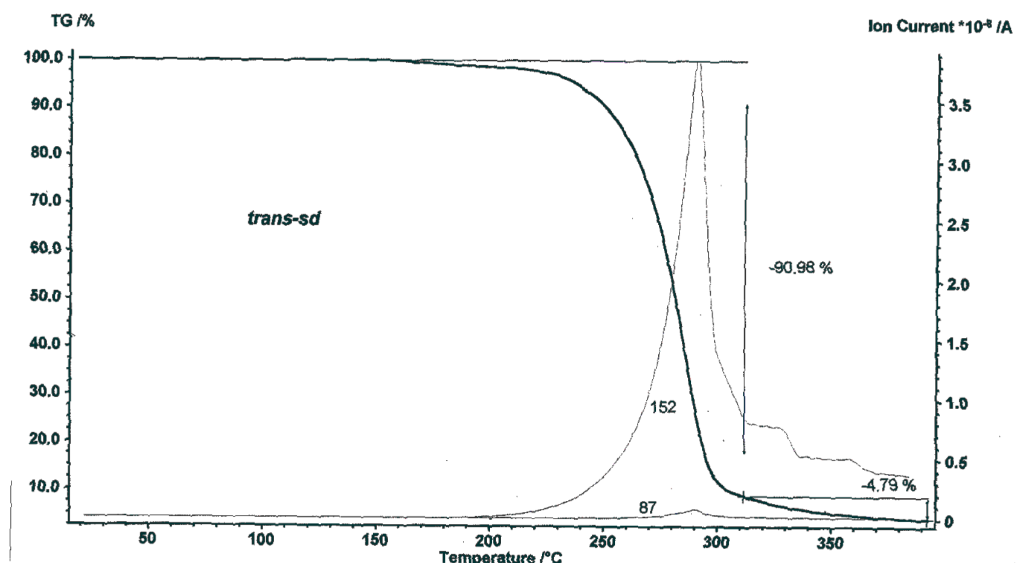




Ethanol FT-IR spectrum

TG – MS Analysis of the reaction trans-Heptacyclene → 2 Acenaphtylene





[#] Instrument	File	Identity	Sample	Date	Mass	Segment	Range	Atmosphere	Correction
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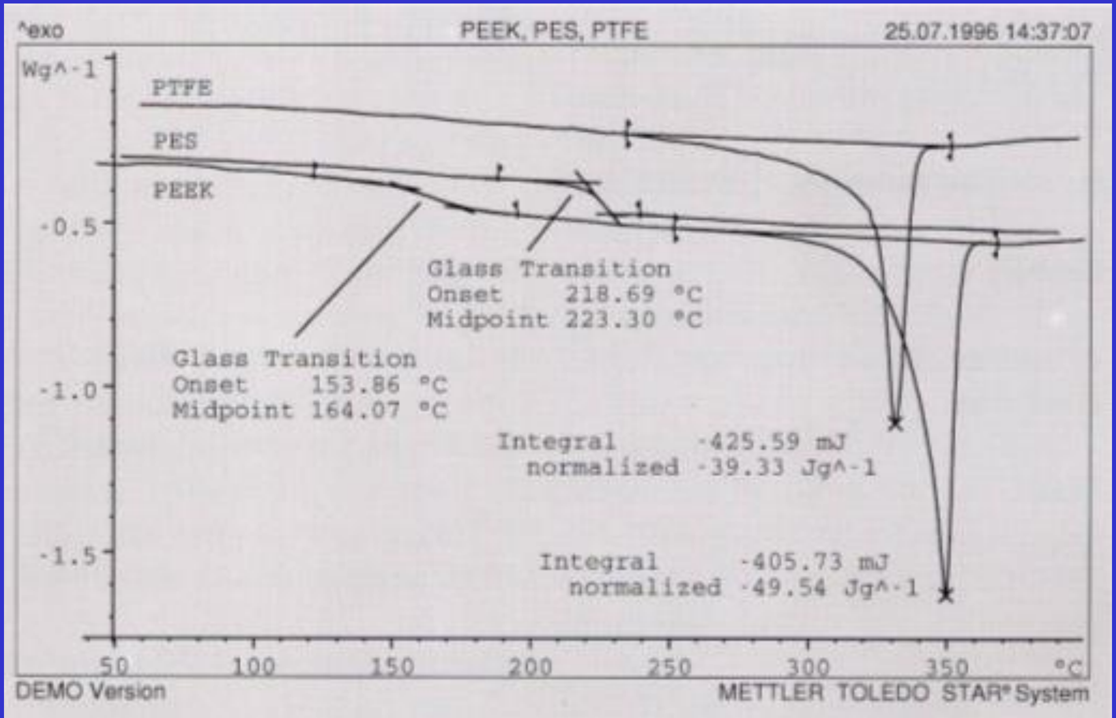
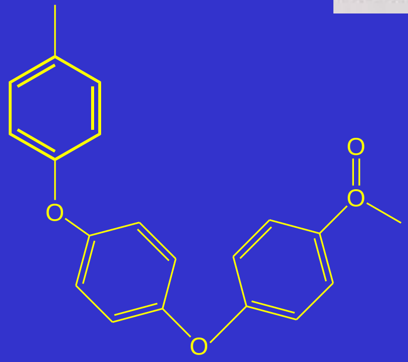
[2] Balzers MID	132008_m152_t4.30.AS...	132008	152 59.73 [%]	11.09.00 11:03:56		1/1	23 °C/5.1(K/min)/387 °C		0
[3] Balzers MID	132008_m87_t4.30.ASC	132008	87 41.15 [%]	11.09.00 11:03:56		1/1	23 °C/5.1(K/min)/387 °C		0

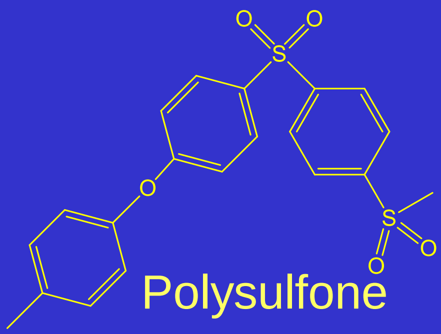
Case Studies

Applications: Identification of Polymers

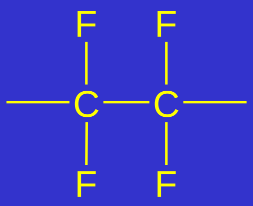




Polyether ether ketone (PEEK)

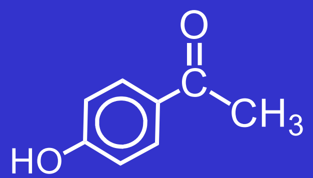


Polysulfone (PES)



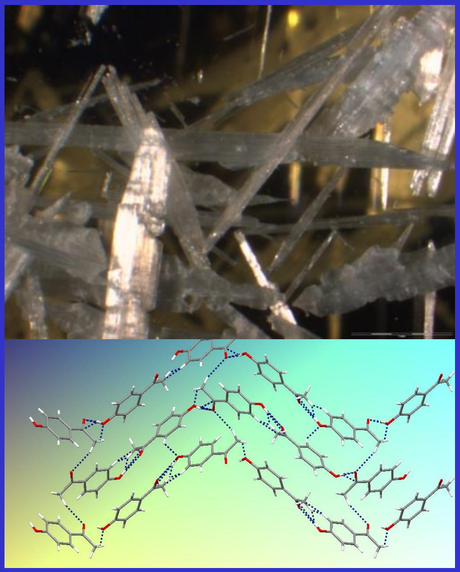
Polytetrafluoroethylene (PTFE)

Applications: Detection of Polymorphism

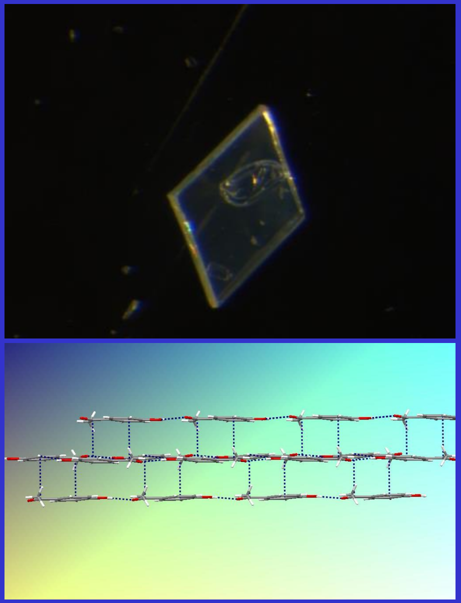


4’-Hydroxyacetophenone

Form II (Orthorhombic)

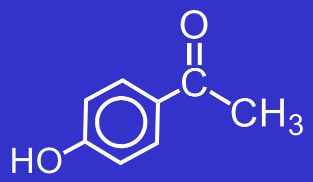


Form I (Monoclinic)

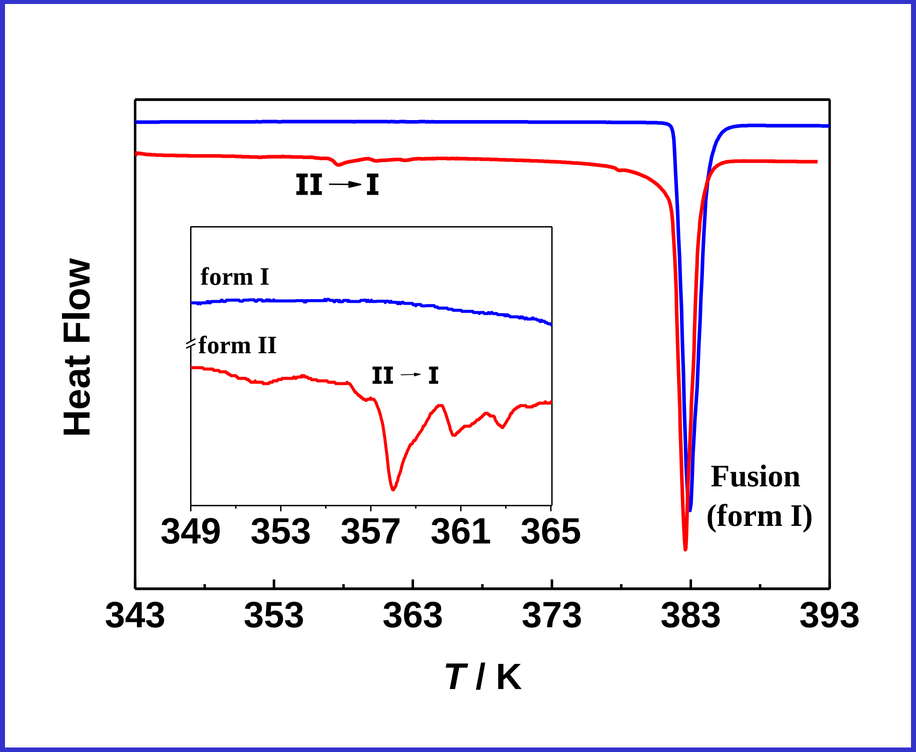


C. E. S. Bernardes, M. F. M. Piedade, M. E. Minas da Piedade
Crystal Growth & Design 2008, *8*, 2419-2430

Applications: Detection of Polymorphism

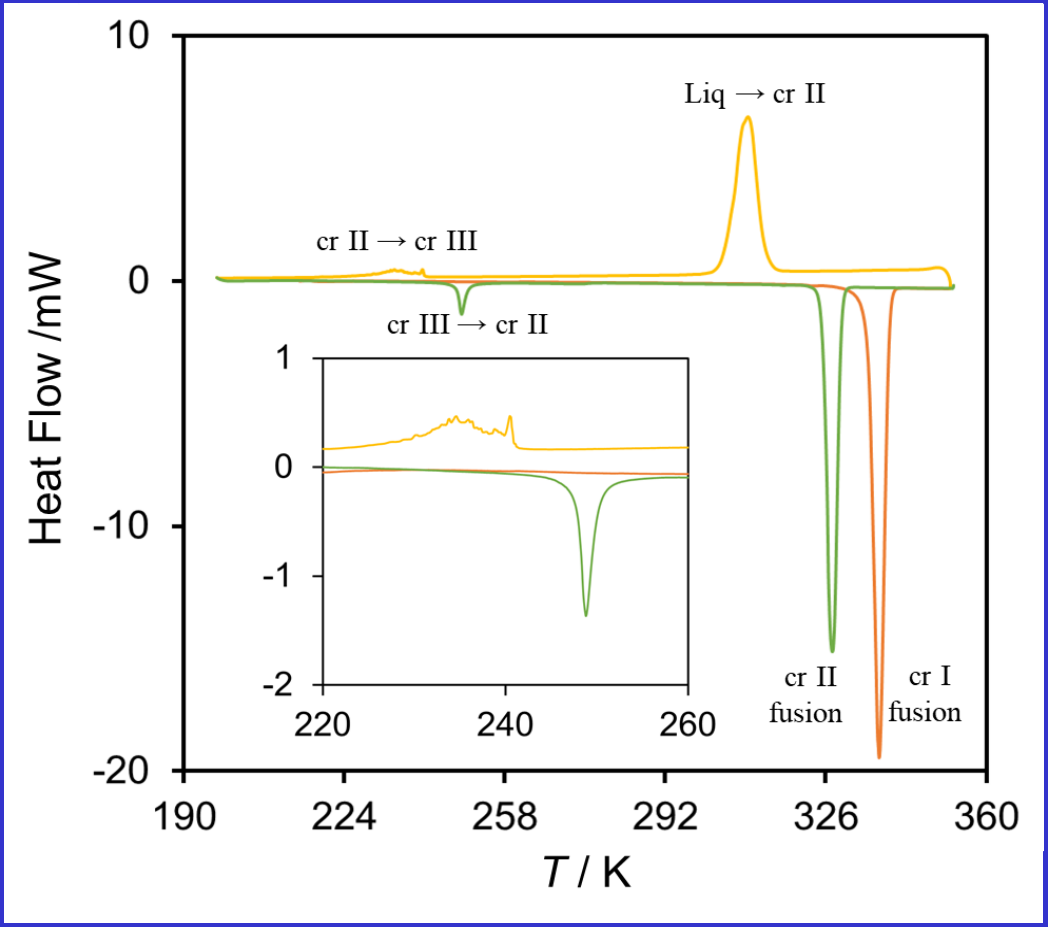


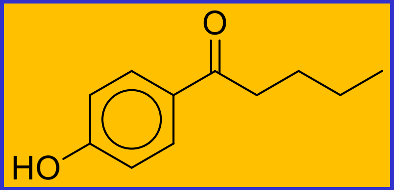
4'-Hydroxyacetophenone



C. E. S. Bernardes, M. F. M. Piedade, M. E. Minas da Piedade
Crystal Growth & Design 2008, *8*, 2419-2430

Applications: Detection of Polymorphism





4´-Hidroxyvalerophenone

R. G. Simões, C. S. D. Lopes, M. F. M. Piedade, C. E. S. Bernardes, H. P. Diogo, M. E. Minas da Piedade
Crystal Growth & Design 2008, *8*, 2419-2430

Applications: Stability of Explosives

Center for Fire & Explosives, Forensic Investigations, Training & Research (CENFEX)

Proficiency Testing for the Thermal Sensitivity of Pentaerythritol Tetranitrate (PETN) and Cyclotrimethylenetrinitramine (RDX) utilizing Differential Scanning Calorimetry (DSC)

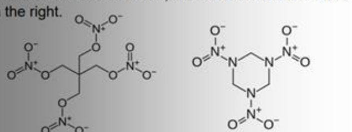
Matthew K. Green, Ph.D. – School of Forensic Sciences, CENFEX Fire and Explosives Laboratory

Julianne Green – School of Forensic Sciences, Undergraduate Laboratory Intern

INTRODUCTION

DSC, or Differential Scanning Calorimetry, can be used as a method of testing the thermal sensitivity of energetic materials. DSC is the most commonly used thermal analysis technique due to its ease of operation and rapid analysis. Furthermore, this instrumentation provides precise, reproducible heat flow measurements.[1] Thermal sensitivity testing determines the potential hazards of energetic materials when exposed to increasing levels of heat. Heat capacity measurements are particularly relevant when mixing, drying, transferring, and/or storing energetic materials.[1]

Two commonly used explosives are PETN and RDX. PETN, or pentaerythritol tetranitrate, is a high explosive that is used in military detonating cord and blasting caps.[2] RDX, or cyclotrimethylenetrinitramine, is used extensively in military munitions.[3] The chemical structures are shown below, PETN on the left and RDX on the right.



As a means to increase the validity of thermal sensitivity testing, proficiency tests can be performed to improve protocols and standardization. The Explosives Testing Users Group (ETUG), organized by Safety Management Services, Inc., developed a "Round Robin" testing project, and selected thermal analysis of PETN and RDX. For this research, a TA Instruments, Inc. SDT 650 was used to test the thermal sensitivity of the explosive standards. This research demonstrates the DSC proficiency testing performed at the CENFEX Fire and Explosives Research Laboratory. Results from the laboratory were compared to federal, national, and international laboratories participating in the Round Robin testing project. Statistical analyses demonstrated similarities among participating laboratories and identified potential protocol and standardization

MATERIALS

Instrument:
- SDT 650 – TA Instruments, Inc.

Supplies:
- Tzero pans and lids – TA Instruments, Inc.
- Tin metal calibrant – TA Instruments, Inc.
- RDX – Omni Distribution, Inc.
- PETN – Omni Distribution, Inc.

PROFICIENCY TESTING

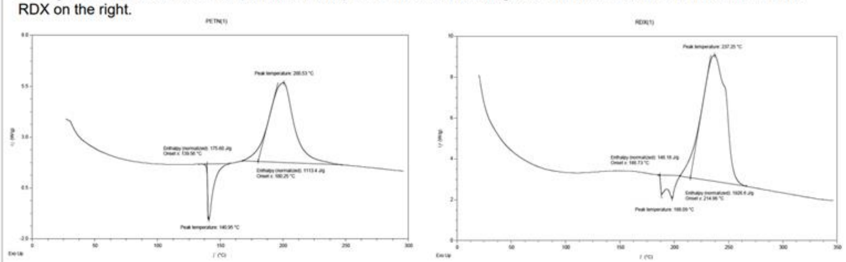
Procedure:

1. DSC Calibration Verification
2. PETN and RDX Analyses
3. Result Comparison and Statistical Analysis

Step 1:
- Three separate tin calibrant samples were analyzed using the SDT 650 DSC/TGA Instrument from TA Instruments, Inc.
- The melting point of tin was determined for each calibrant sample, and the average was calculated to be 232.14°C
- The acceptable range listed in the ETUG DSC Round Robin Procedure[4] is 230.9°C to 232.9°C
- Observed results demonstrated successful DSC calibration

Step 2:

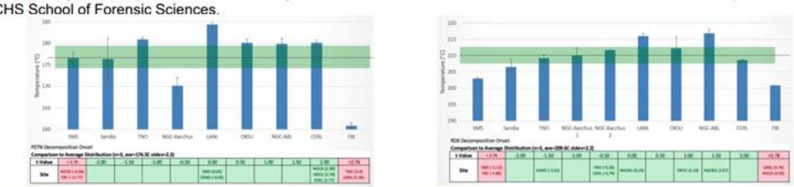
For PETN and RDX, three proficiency tests were completed to determine both the average melting temperature and average decomposition onset temperature. Examples of observed thermograms are shown below, PETN on the left and RDX on the right.



Results: Average melting and decomposition temperatures for PETN – 139.59°C and 180.35°C
Average melting and decomposition temperatures for RDX – 186.74°C and 212.00°C

Step 3:

At the Explosives Testing Users Group 2018 Meeting in Park City, Utah, results from each participating laboratory were presented and discussed. Reported values were compared via statistical analysis. Result comparison graphs[5] for decomposition onset temperatures are listed below, PETN on the left and RDX on the right. Each bar represents a participating laboratory, with "OKSU" showing results from the CENFEX Fire and Explosives Research Laboratory at OSU-CHS School of Forensic Sciences.



RESULTS SUMMARY

- Thermal analysis is a crucial component of characterizing explosive materials
- Differential Scanning Calorimetry (DSC) analysis is the most common and understood method of thermal characterization
- Explosives Testing Users Group (ETUG) Round Robin completed to improve standardization within the field of energetics characterization
- Results obtained at the CENFEX Fire and Explosive Research Laboratory reflect consistency, for tin metal and both selected energetic materials, PETN and RDX
- 9 national and international laboratories participated in the proficiency testing exercise
- CENFEX Fire and Explosives Research Laboratory results matched with the group average temperatures for:
  - Tin melting onset
  - PETN melting onset
  - PETN decomposition
  - RDX decomposition
- Substantial deviation from the group mean was observed for RDX melting onset
- Following procedural adjustments, average values for PETN and RDX temperatures can potentially be established for certification by the Explosives Testing Users Group

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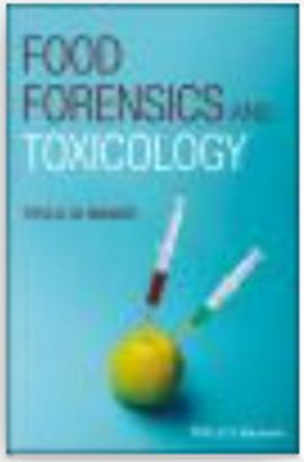
1. Conkling and Mocella, Chemistry of Pyrotechnics: Basic Principles and Theory, 2nd Edition, 2011.
2. Beveridge, Forensic Investigation of Explosions, 2nd Edition, 2012
3. United States Environmental Protection Agency,
4. Explosive Testing User's Group Round Robing Testing Procedure, Safety Management Services, 2018.
5. Guymon and Snow, ETUG DSC Summary of Results, 10th Annual Explosives Testing Users Group Meeting, 2018

ACKNOWLEDGEMENTS

John Frucci III, Ed.D. – CENFEX Executive Director
Robert Allen, Ph.D. – School of Forensic Sciences Chair



BOOK CHAPTER

Application of Thermal Methods in Food Forensics

Msagati, Titus A. M

Food Forensics and Toxicology, 2017, p.361-377

Thermal methods of analysis are highly useful in food forensic analyses, because most foods are susceptible to variations in their physical parameters that eventually alter the chemistry of food constituents that are associated with the quality of foods, including texture, taste, aroma, stability, and taste. The analyst must be conversant with the principles involved in these methods so as to correctly choose the appropriate method of analysis for a particular sample. Different food types can be characterized by using thermal methods of analysis. The thermal methods include thermalgravimetric analysis (TGA), differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermomechanical analysis (TMA). TGA has been widely used in the characterization of moisture content, as well as water of crystallization of foods. In food forensics, DSC has proved to be very useful in the determination the stability and energy changes in samples that are subjected to thermal treatment.

Applications: Forensic Science

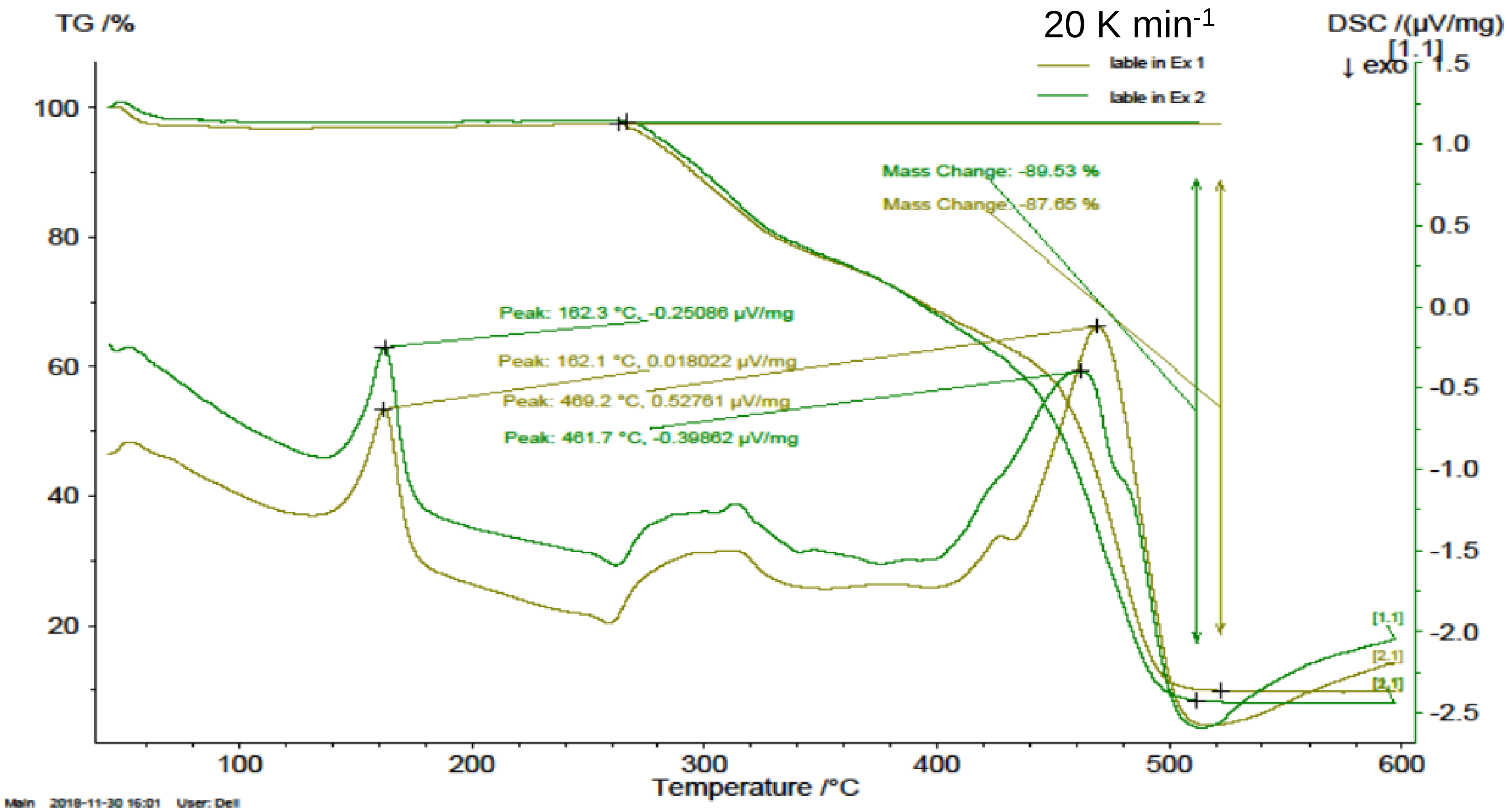
Comparison of Cardboard Pieces as Physical Evidence in Murder Case Using Simultaneous Thermal Analysis

K. S. Kapgate, R. V. Phadke, C. B. Ghoti, S. S. Apte, V. J. J. Thakre

Forensic. Res. Criminal Investig. **2020**, *1*, 25-31

In the present case **the accused used a cardboard box to dispose of a body** in a murder case. A cardboard piece along with label stick to it was seized from riverside. The cardboard box piece thrown in the river to dispose the body had a company label stick on it. The same label was observed on the cardboard boxes seized from the company office. Thermal properties of the cardboard box collected at the crime scene and from the company site were found to be different. The peak observed at about 357°C was of opposite nature. The origin of this difference was studied by DSC and TG using different conditions and different control samples. The results revealed that the differences were due to to their treatment in making originating from binder in cardboard making.and that the cardboard used to dispose the body was indeed obtained from the seized company.

The probable reason for the phenomenon was related moistened of the cardboard with water. In this case the glue or corrugated sheet get dissolved in water and only cellulose is left behind. The sample then shows an endothermic rather than an exothermic peak as observed for the same cellulose without glue. The phenomenon was again confirmed using cotton and filter paper as control sample.

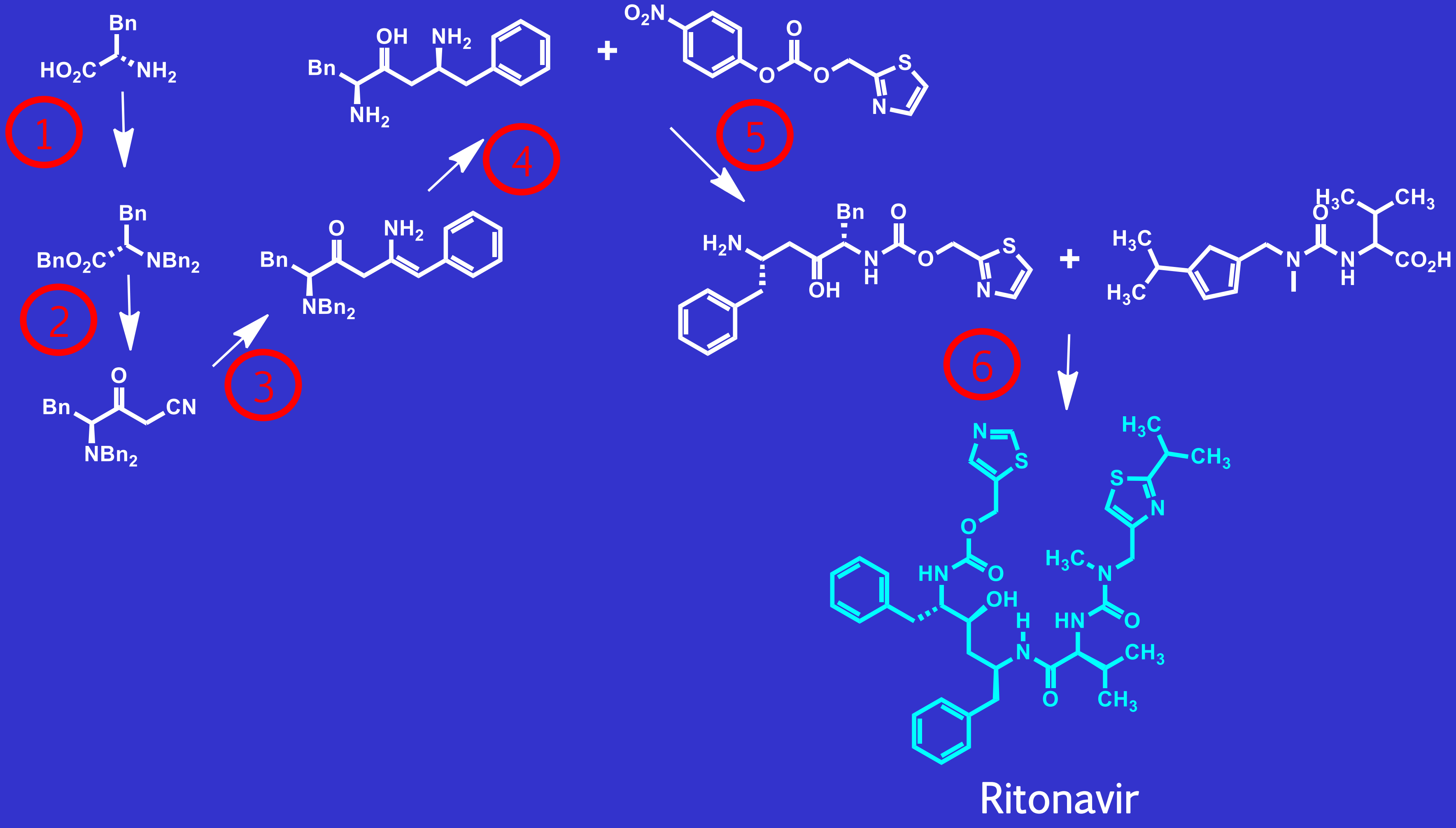


TG /%
20 K min-1
DSC /(μV/mg)
[1.1]
↓ exo
lable in Ex 1
lable in Ex 2
Mass Change: -89.53 %
Mass Change: -87.65 %
Peak: 162.3 °C, -0.25086 μV/mg
Peak: 162.1 °C, 0.018022 μV/mg
Peak: 469.2 °C, 0.52761 μV/mg
Peak: 461.7 °C, -0.39862 μV/mg
[1.1]
[2.1]
[1.1]
100
80
60
40
20
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
100
200
300
400
500
600
Temperature /°C
Main 2018-11-30 16:01 User: Dell

The Ritonavir Case

$C_{37}H_{48}N_6O_5S_2$

Synthesis



Bn
HO_2C
NH_2
1
Bn
BnO_2C
NBn_2
2
O
Bn
CN
NBn_2
3
O
NH_2
Bn
NBn_2
4
OH
NH_2
Bn
NH_2
+
O_2N
O
O
O
S
N
5
Bn
O
H_2N
N
H
O
S
N
OH
+
H_3C
CH_3
O
H_3C
N
N
H
CO_2H
H_3C
6
N
S
H_3C
CH_3
S
N
O
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N
OH
H
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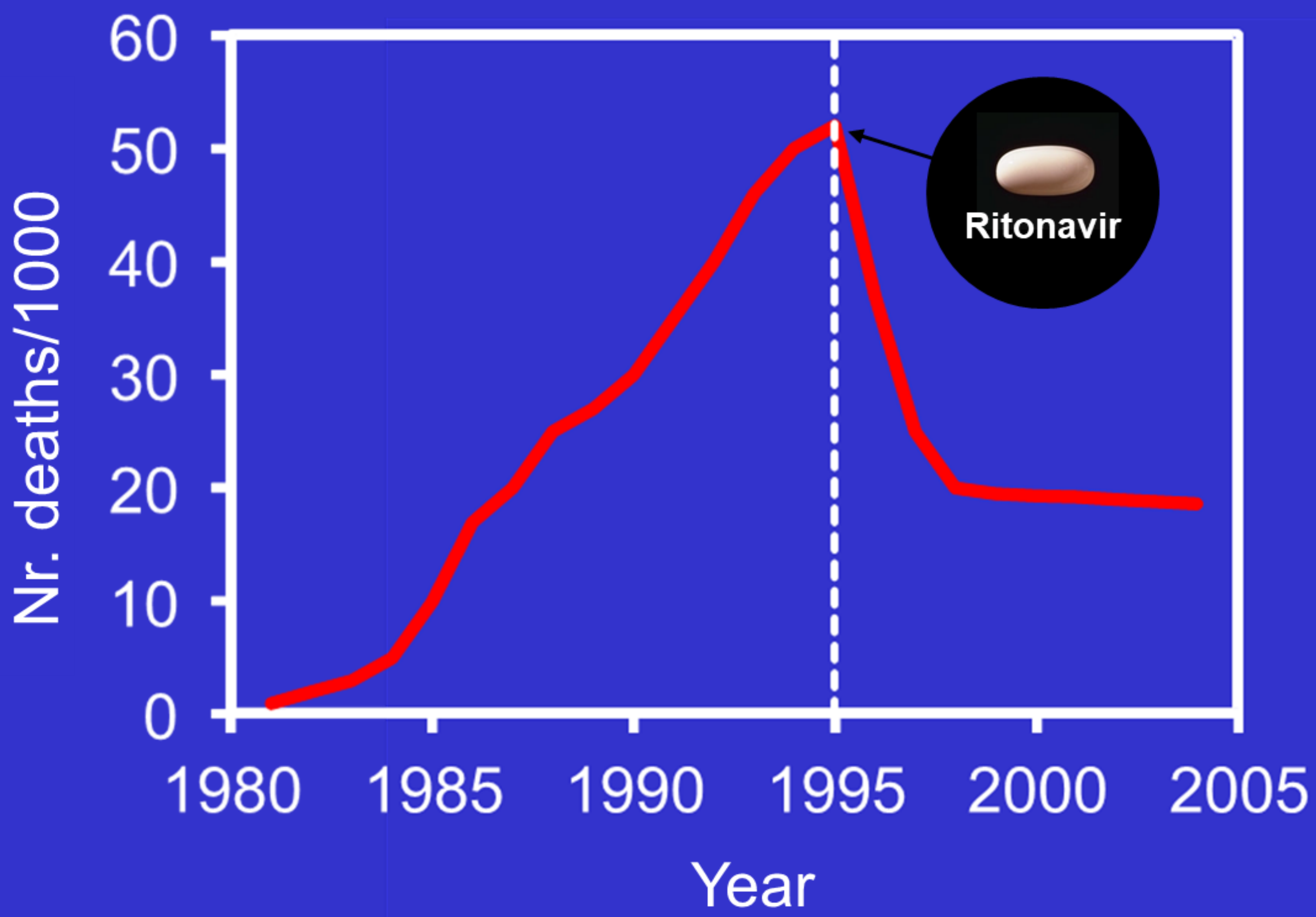
N
CH_3
O
CH_3
Ritonavir

Number of HIV Related Deaths



Chronology of the Ritonavir Case

Discovery by Abbott laboratories

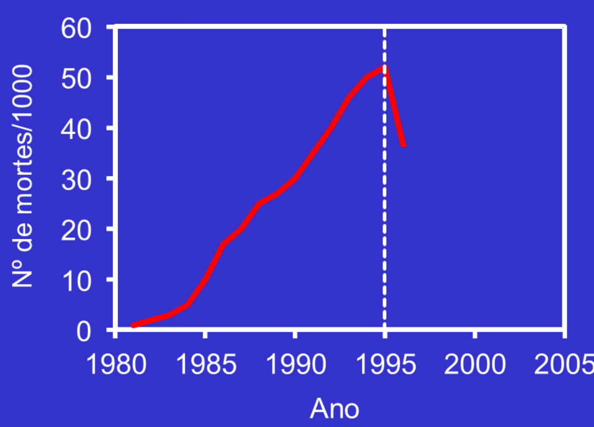
1992

Drug application to FDA (NDA) filed

1995

FDA approval. Commercialization started

1996



Several lots failled dissolution test

- Ritonavir production stopped
- Abbott into a market crisis: Ritonavir stock depleting very quickly
- Risk of patients without treatment

1998

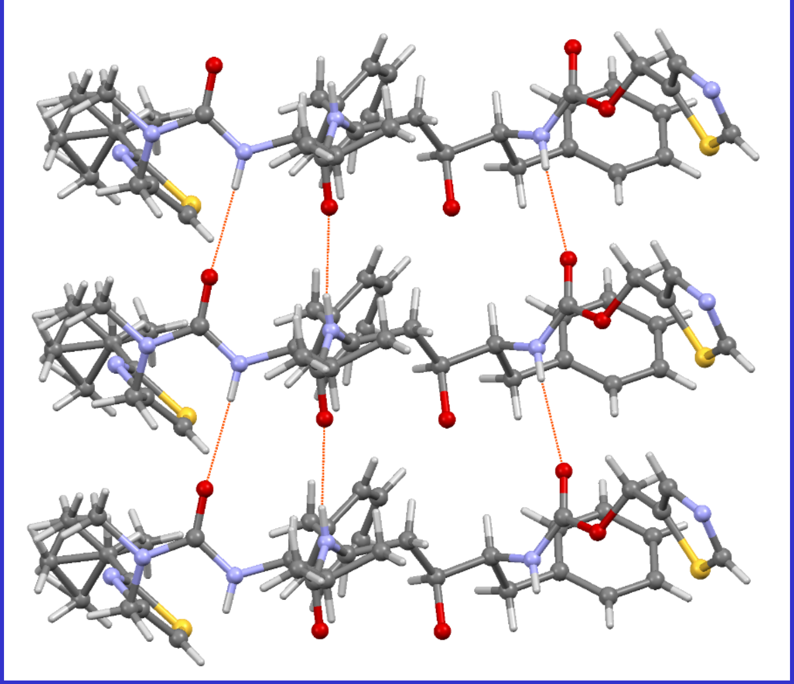
New formulation

- 600 scientists
- Loss > 250 M€

1999

Origin of the Problem: 2 Polymorphs

Form I (marketed)



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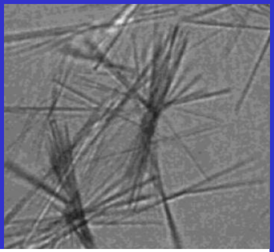
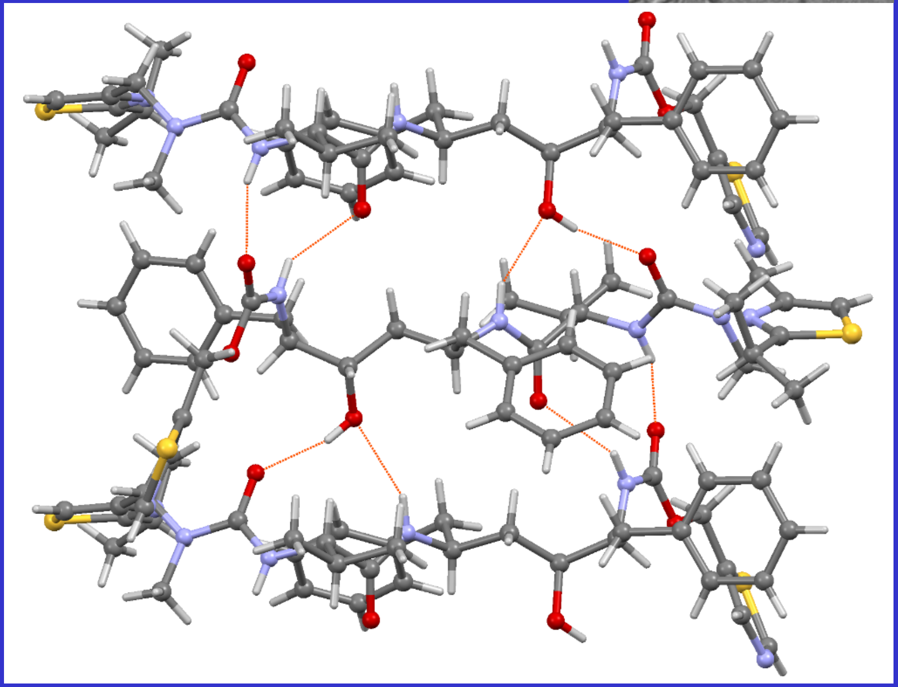
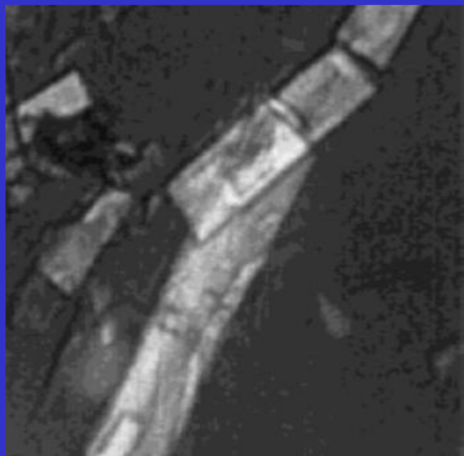
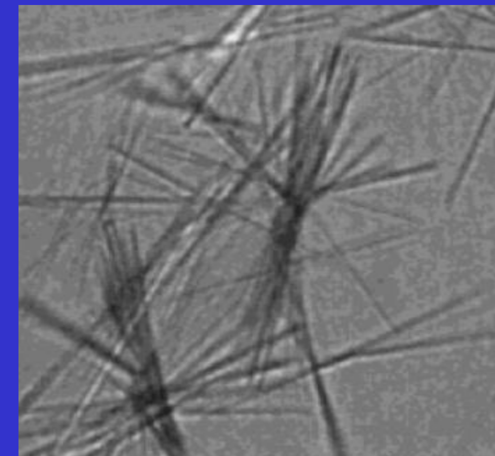




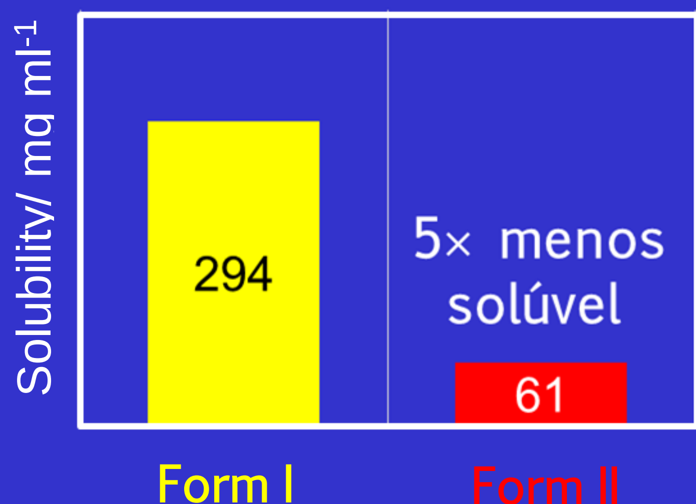
… with Very Different Solubilities



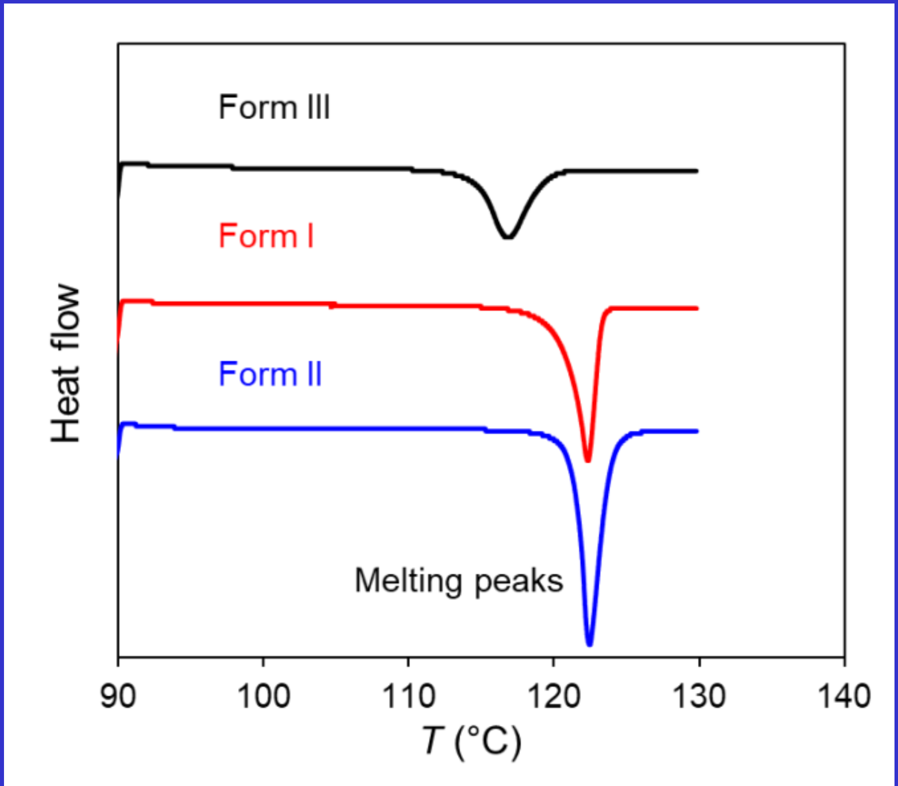
Form I



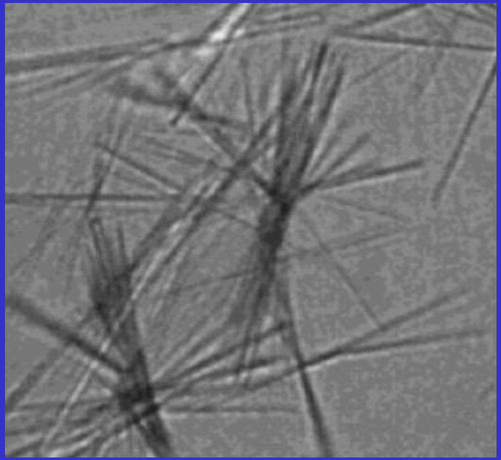
Form II



Distinguishing Ritonavir Polymorphs using DSC and Microscopy



Form I



Form II