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# Polymorphism by differential scanning calorimetry [1]

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**Abstract**

After a basic introduction to polymorphism the most useful methods of detection of polymorphism are cited. A selection of typical DSC curves illustrates monotropic and enantiotropic solid–solid transition, allotropy, metastable–stable transition through the liquid state, pseudopolymorphic transition and mesophase transition. In addition, the calculation of an experimental free energy–temperature diagram is explained.

## INTRODUCTION

A substance is polymorphic if it can exist in different structural modifications, i.e. if the same chemical composition occurs in various modifications with different physical properties. The importance of polymorphism lies in the fact that physical properties (melting point, color, solubility, refractive index, hardness, conductivity, etc.) of a given compound vary between the polymorphic forms. The crystalline modifications melt into the same liquid phase.

Polymorphism (also called allotropy in the case of elements) is manifested by, for example, sulfur, carbon (graphite, diamond), phosphorus and numerous minerals and organic substances. Plastics can also be polymorphic, e.g. isotactic polypropylene.

Of great significance as far as the application is concerned are the polymorphic forms of pharmaceutically active substances [1, 2]. Since the solubility and dissolution rates are different the bioavailability is affected [2]. Their therapeutic efficiency depends strongly on the polymorph in question: the metastable form can be twice as active as the stable form.

The individual structural modifications are stable over particular temperature ranges and they are symbolized by greek letters or roman numerals. In addition, metastable states can also exist (symbolized for example by $\beta'$) whose slow transformation into stable forms can take hours or even years. In accordance with Ostwald's rule, melts of polymorphic

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[1] Dedicated to Hans Georg Wiedemann.

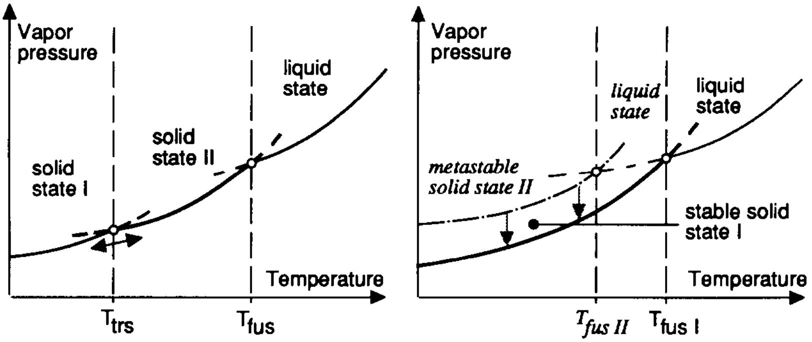

Fig. 1. Schematic representation of enantiotropic (left) and monotropic (right) phase diagram.

substances on cooling often first form the least stable modification and this then rearranges into the stable modification in stages. Quench cooling a melt often leads to the amorphous product which on heating undergoes glass transition followed by crystallization [3].

There are two types of polymorphism, enantiotropic and monotropic. The exothermal solid–solid transition of metastable into the stable form is called monotropic polymorphism (Fig. 1) and can occur only in the direction

$$\beta' \rightarrow \beta$$

and not in the reverse. The heat of fusion of the earlier melting $\beta'$ is smaller than that of $\beta$. (This rule only holds for melting point differences below approx. 20°C. With higher differences the $c_p$–temperature functions can interfere.) The difference is the heat of solid–solid transition. Metastable modifications can crystallize from the melt by rapid cooling or from saturated solutions in certain solvents.

Reversible solid–solid transitions are called enantiotropic polymorphism (Fig. 1). The transition $\alpha \rightleftharpoons \beta$ from the low temperature $\alpha$ into the high temperature $\beta$ form is endothermic. Therefore the heat of fusion of the earlier melting $\alpha$ is greater than that of $\beta$.

Phase diagrams describe the relation between the state of aggregation and the thermodynamic state properties temperature, pressure and concentration. The phase diagrams show the range of stability of the phases and the phase transitions, the latter are the regions in the diagram where two or more phases can coexist in equilibrium.

For a great number of substances, crystallization from a solution in certain solvents gives solvates which on drying may give the anhydrous form with different properties, especially solubility or hygroscopicity. The solvent is often entrapped in crystals and escapes only during melting. When heated in a sealed container solvates normally melt at temperatures far lower than the anhydrous product. Hydrates and solvates can show similar behavior to polymorphs. This phenomenon is called pseudo-polymorphism [4].

Some organic compounds with long, linear and relatively rigid molecules do not go to the liquid state through one transition. Above the melting point an intermediate liquid phase called the mesophase appears, which represents the liquid crystalline state. This expression characterizes an isotropic liquid state. However some substances with globular molecules show a plastic crystalline state [5].

## DETECTION OF POLYMORPHISM

The different physical properties of polymorphs of the same substance allow them to be distinguished. The most useful methods with which to study polymorphism are as follows [6]: (i) DSC; (ii) thermo-optical analysis (TOA) [6] and polarization thermal microscopy; (iii) solubility; (iv) X-ray powder diffraction; (v) infrared spectroscopy.

## THE FREE ENERGY–TEMPERATURE DIAGRAM

The free energy–temperature diagrams ($G$–$T$) are the thermodynamic representation of phase diagrams, since the phase having the lowest free energy at a given temperature is always the stable phase at that temperature. With the specific heat ($c_p$) temperature function obtained by DSC, it is possible to calculate such a diagram.

$$\Delta G = \Delta H - T\Delta S$$

with $\Delta H$ being defined as

$$\Delta H = \int c_p \, \mathrm{d}T$$

$\Delta S$ can be measured as

$$\Delta S = \int (c_p/T) \, \mathrm{d}T$$

An example of such a diagram based on the specific heat determination of potassium perchlorate is shown in Fig. 2. Calculation of $\Delta G$, $\Delta S$ and $\Delta H$ has been done by means of the spreadsheet program Excel by Microsoft.

Schematic $G$–$T$ diagrams can be drawn based on the order of stability of the modifications, e.g. at room temperature, the order of the melting points and the respective heats of transition [7].

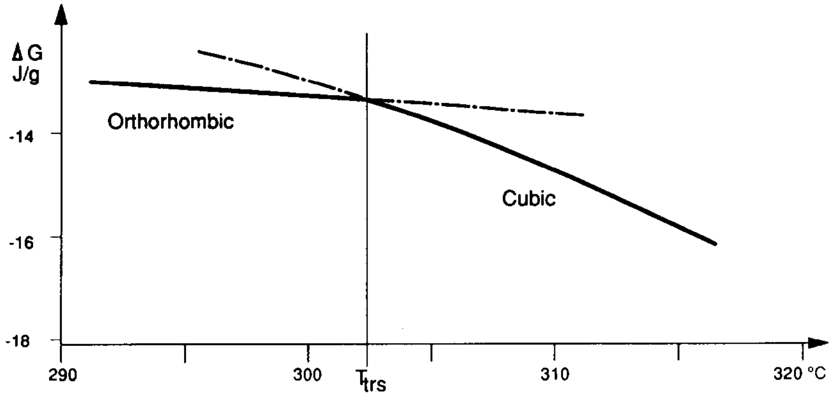

Fig. 2. Free energy diagram of potassium perchlorate showing the transition from orthorhombic to cubic form. The high transition temperature ($T_{trs}$) is due to a high heating rate during $c_p$ measurement (10°C $\mathrm{min}^{-1}$). The broken lines are extrapolated.

## DSC CURVES OF TYPICAL TRANSITIONS

This section illustrates the behavior of typical sample substances investigated by DSC. The respective original curves have been measured with various Mettler DSC modules.

### *Monotropic solid–solid transitions*

After premelting, for example, sulfapyridine (Fig. 3, top curve), it is quench cooled (hot crucible placed on a cold metal plate) to obtain the amorphous phase. On heating, a glass transition occurs, followed by cold crystallization (above $T_g$ the amorphous phase shows a tendency to crystallize (devitrify) of a metastable phase. This metastable phase transforms through an exothermal monotropic solid–solid transition into a more stable phase which finally melts.

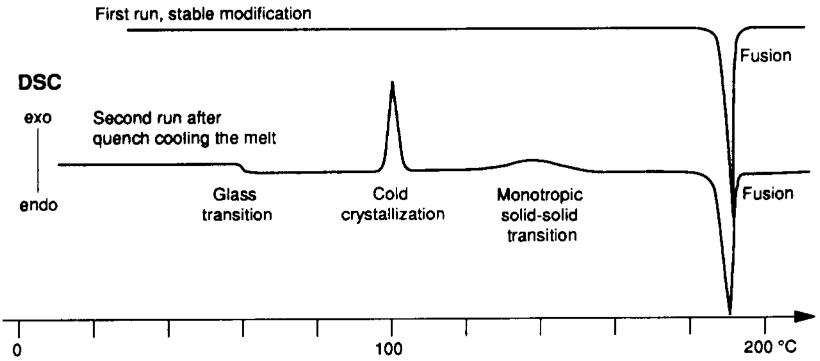

Fig. 3. DSC curve of 15 mg sulfapyridine heated at a rate of 5°C $\mathrm{min}^{-1}$. The melting point of the stable modification is 191°C (first run). Second run: here the monotropic solid–solid transition is observed.

## *Enantiotropic solid-solid transition*

Potassium perchlorate (Fig. 4) shows an enantiotropic solid-solid transition at 300°C corresponding to the phase transition from orthorhombic to cubic. During cooling, due to the time necessary for nucleation, the transition begins far below the equilibrium temperature.

Building up the new lattice requires the formation of nuclei. In small single crystals the probability of lattice defects leading to nuclei differs from individual crystal to crystal. This is demonstrated using a few grains: each grain shows an individual solid-solid transition (Fig. 5).

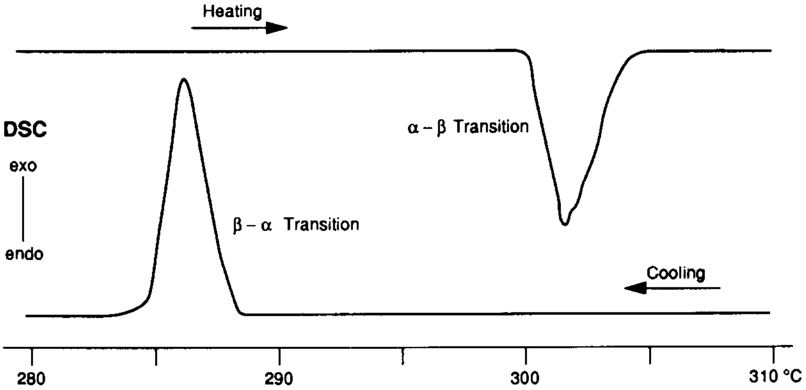

Fig. 4. DSC curve of a fine powder of $KClO_4$ showing the reversibility of the enantiotropic solid-solid transition. 15 mg of $KClO_4$ were placed in a pierced aluminum pan; heating and cooling rates were 2°C $min^{-1}$.

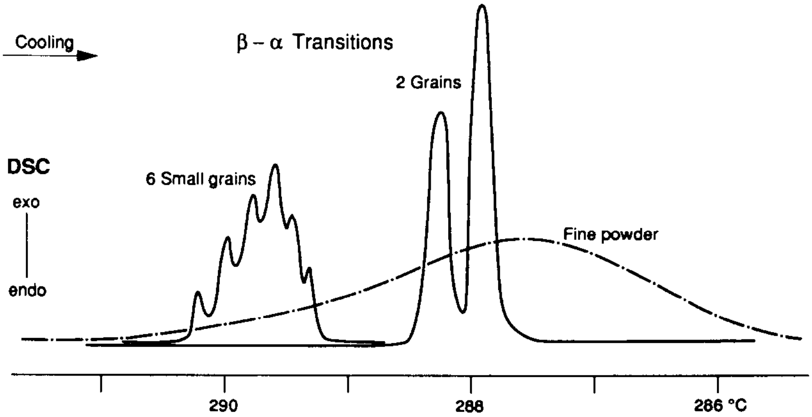

Fig. 5. DSC curves of potassium perchlorate during cooling at 1°C $min^{-1}$. The solid-solid transition of a powder with its large number of individual particles leads to Gaussian shape. The curves with 2 and 6 crystals illustrate the variations in individual transition temperatures.

### *Allotropy*

Sulfur provides a well known but quite complex example of allotropy. The stable form of sulfur at room temperature is the rhombic $\alpha$-sulfur consisting of $S_8$ molecules. At 95.6°C this transforms into monoclinic $\beta$-sulfur, which melts at 119°C. The resulting bright yellow liquid, $\gamma$-sulfur, readily polymerizes to form $\mu$-sulfur, which is reddish and highly viscous (Fig. 6, first run). On cooling at 1°C $\mathrm{min}^{-1}$ depolymerization takes place at around 160°C leading to a mixture of $S_4$ and $S_6$. This crystallizes at 50°C (Fig. 6). When heating the mixture of $S_4$–$S_6$ it melts at the "natural melting point".

If the sample is quench cooled (Fig. 7), for instance in liquid nitrogen,

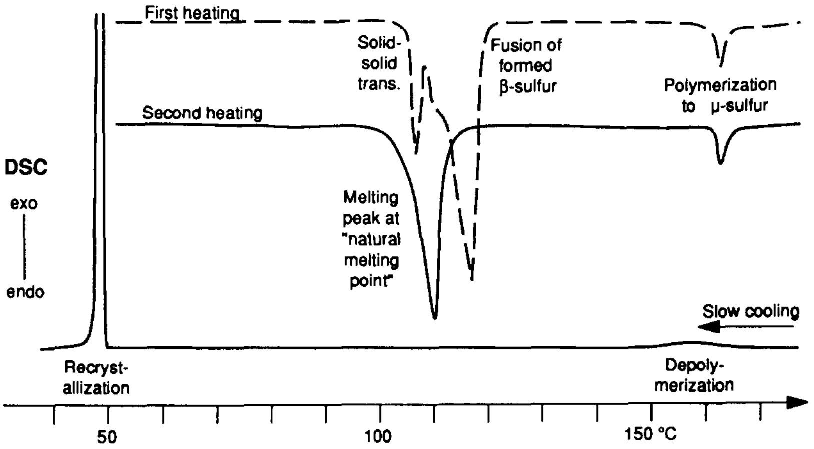

Fig. 6. DSC curves of 12 mg sulfur in a pierced aluminum pan. First heating at a rate of 5°C $\mathrm{min}^{-1}$, cooling to 30°C at 1°C $\mathrm{min}^{-1}$, and second heating at 5°C $\mathrm{min}^{-1}$.

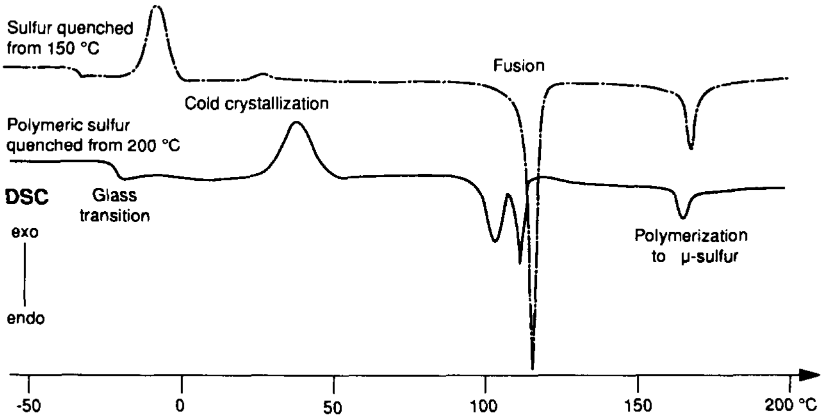

Fig. 7. DSC curves of sulfur quench cooled from 200°C (polymeric) and 150°C (non-polymeric); heating rate 5°C $\mathrm{min}^{-1}$.

before or after the polymerization, an amorphous solid is formed. Upon heating the amorphous polymeric sulfur exhibits a glass transition at −30°C followed by cold crystallization at 30°C. It melts after the $\alpha \rightarrow \beta$ transition. $\gamma$-Sulfur (quench cooled from 150°C) has a lower glass transition. After the cold crystallization of $\beta$-sulfur it melts and finally polymerizes again.

### *Metastable–stable transition through the liquid state*

The behavior of phenylbutazone illustrates a metastable–stable transition through a liquid state. When phenylbutazone (Fig. 8) is heated for the first time it melts at 105°C, the melting point of the stable modification. Often the melt formed does not crystallize upon rapid cooling, instead it forms a glass. During a second heating a metastable modification, with a lower melting point frequently crystallizes. During or after fusion the stable crystals can grow, provided there is nucleation of the stable form. Some direct monotropic solid–solid transition below the melting point of the metastable phase causes the small exotherm just before fusion. On further heating the stable form also melts.

Using the high heating rate of 25°C $\text{min}^{-1}$ the metastable form (conserved by cooling after cold crystallization) melts and the formation of the stable form is suppressed. Due to the high heating rate the peak appears broadened.

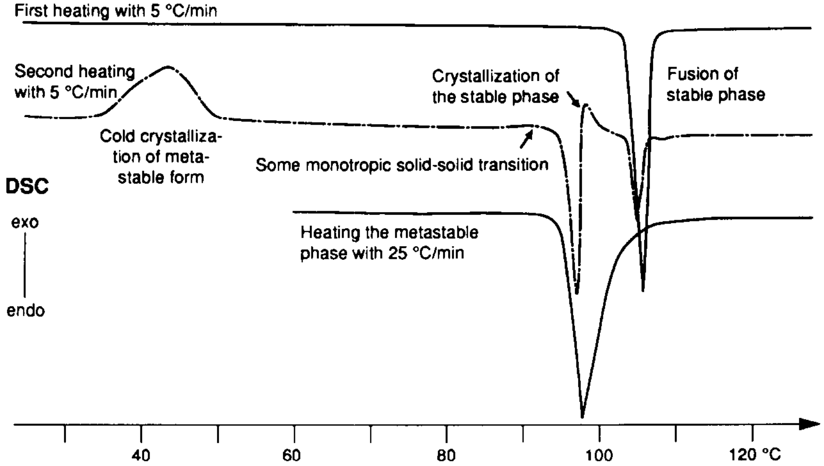

Fig. 8. DSC curves of 5.5 mg phenylbutazone. First run: $\alpha$ form melts at 105°C. Second run: at 40°C a metastable modification crystallizes from the amorphous form and melts at 92°C. During fusion the stable phase appears (indicated by the exothermal peak) which melts at 105°C.

## *Other types of transition*

### *Formation of the meatastable phase through the liquid state*

Cooling of a melt of 4-nitrotoluene (Fig. 9) often results in recrystallization of the stable form. Sometimes (in about 20% of cases) a modification with a lower melting point appears.

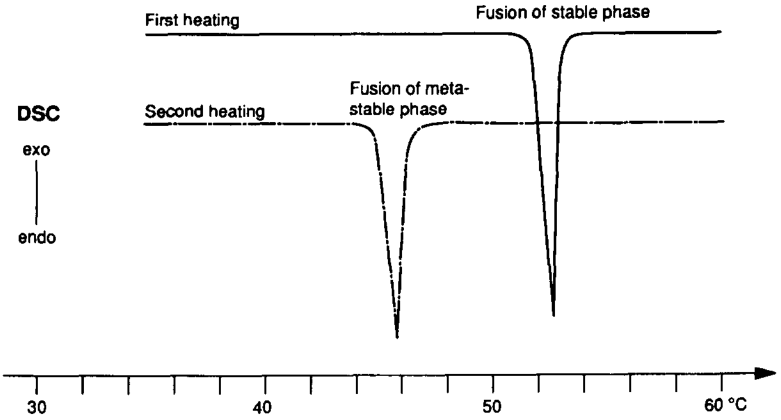

Fig. 9. DSC curves of 4-nitrotoluene: stable form with a melting point of 51.5°C. The metastable form obtained after cooling melts at 45°C.

### *Pseudopolymorphic transition*

The dehydration of calcium sulfate dihydrate (Fig. 10) occurs in two steps which more or less overalp depending on heating rate and sample preparation.

$CaSO_4 \cdot 2H_2O = CaSO_4 \cdot 0.5H_2O + 1.5H_2O$

$CaSO_4 \cdot 0.5H_2O = CaSO_4 + 0.5H_2O$

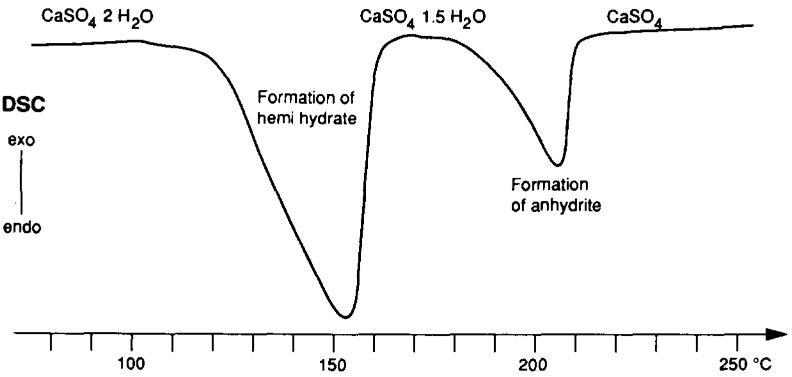

Fig. 10. DSC curve of gypsum ($CaSO_4 \cdot 2H_2O$) is an example of pseudo-polymorphism. In self-generated atmosphere using a heating rate of 5°C $min^{-1}$ the two dehydration peaks are well separated.

### *Mesophase transitions*

The DSC curve of, for example, cholesteryl myristate (Fig. 11) shows the temperature range of existence of the mesophases in a liquid crystal.

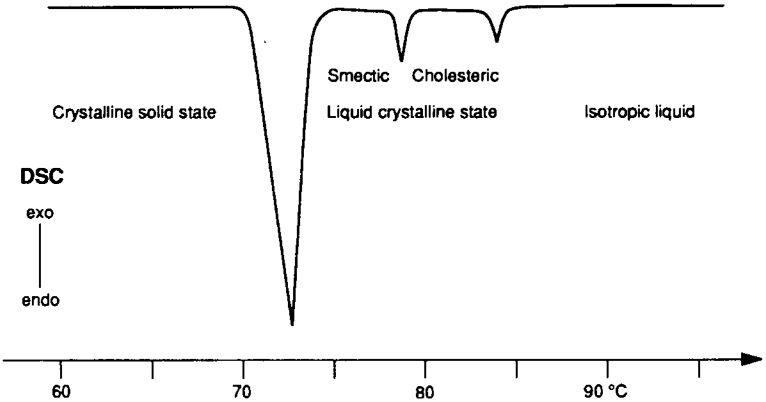

Fig. 11. The DSC curve of cholesteryl myristate. The melting peak is followed by the two transition peaks of the mesophases.

## CONCLUSION

All polymorphic transitions are related to a change in enthalpy. Therefore they can be investigated by DSC. For the interpretation of the DSC curves some knowledge of polymorphism is necessary. This paper, with a selection of typical curves, should serve to build up the basic knowledge.

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