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# Thermal Analysis in Switzerland

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**Abstract.** An overview about the state-of-the-art of the different techniques of thermal analysis is presented. Their advantages, some handicaps and their possibilities are given with some specific examples. A great number of the existing techniques are presently used in Switzerland, at universities, technical high schools, research institutes as well as in many different branches of industry. The applications are within all possible fields: research, development, in-process control and production. The Swiss Society for Thermal Analysis and Calorimetry (STK) has been founded in 1975 and activities were performed in several scientific areas during national and international venues. The STK is the vehicle for the exchange of scientific information, promotion and education in areas such as inorganic and organic chemistry, biochemistry and biophysics, polymers and material research. The methods of thermal analysis (TA) especially also with the to-day existing coupled instruments (TA-spectroscopy) are the basis for fundamental and applied investigations in the development of new chemical entities, new chemical and physical processes.

## What is Thermal Analysis?

Thermal analysis is a general term for all instrumental techniques in which a physical property of samples is measured as function of temperature or time. The number of techniques within thermal analysis is very large and the number of physical parameters which may be measured is even higher [1]. Several techniques which are used in Switzerland are described below.

When a material is heated, cooled or kept at a constant temperature over a certain period, a change in its structure or composition could occur. Physical or chemical transformations are often connected with a heat change. Differential scanning calorimetry (DSC) [2], which is an important thermal analysis technique, measures the difference between the heat flow into and out of the sample cell and the reference cell, in an atmosphere which may be controlled and in a temperature range from nearly zero up to 2500 K. Of course such a broad temperature range is only available using extrem different instruments. Modulated DSC allows the separation of overlapping reversible and irreversible events. This method is particularly valuable for the study of samples re-

vealing complex phenomena such as mixtures of amorphous and crystalline parts and also for the study of polymer blends. The first method developed by *Le Chatelier* in 1887 was the differential thermal analysis (DTA) where the temperature induced was measured in the sample and in the reference material directly. Another important method is the thermogravimetry (TG) which measures the loss of mass (or the increase) of a substance as a function of time or temperature between room temperature and +1000°. The two methods DTA and TG are also available as combined instruments.

Thermomechanical analysis (TMA) measures the expansion or contraction of substances between –170 and +1000°.

Dynamic mechanical analysis allows the measurement of thermomechanical properties applying selected mechanical frequencies to the sample. Dynamic dielectric instruments (DEA) are used for the measurement of the capacitive and conductive properties of materials in temperature intervals from –150 to 500° and in the frequency range from 10<sup>-5</sup> to 100 kHz. Another group of instruments are applied for the study of the rheological behaviour of materials and polymer solutions or as melts. All these methods are preferably used for the characterization of materials and polymers.

DSC and DTA instruments are also combined with microscopes (thermomicroscopy) which are mainly applied for the study of phase changes in solids and

emulsions. Water sorption and desorption isotherms can be measured with thermogravimetry. Today specific instruments, the so-called water sorption automaters, are commercially available for such applications.

The differentiation of DSC and DTA measuring principles is with modern instrumentation not very significant under normal applications, since due to calibration and instrument integrated data handling the instruments produce similar qualities of reported results. The sensitivity of a DSC or a DTA instrument is today with a sample mass of few milligrams in the order of 0.1 µW or in other words, 100 nW per mg, and 100 µW per g, respectively. Low energy transformations and highly diluted solutions of biochemical substances such as proteins were the starting point for the development of high sensitivity DSC instruments, normally constructed with cell volumes of ca. 1 ml [3]. These instruments widely used in the characterization of biological materials (cells, liposomes) and biochemical solutions are restricted to a narrow temperature range generally between –10 and +120°. The sensitivity is in the order of 100 nW per ml of solution which is up to three orders of magnitudes better than a normal DSC. Why should one work with very diluted solutions? There are several reasons such as high molecular weights of the biomolecules, low solubilities and last but not least, substances of which only extremely low sample masses exist, because of chemical or biotechnological processes involved or because of sophisticated extraction methods afforded. Solution calorimeters of the DSC type and isothermal calorimeters would be demanded for such applications with sensitivities of nW per ml what means about two orders of magnitudes better than the existing instruments. Reaching such high calorimetric sensitivities would bring the TA instrumentation in a competition with the currently used biochemical instruments and devices.

Another group of instruments with many applications in research and development are the isothermal high sensitivity calorimeters, available with sample volumes of 1–25 ml and operating between –50 to 150°. The variety of cells existing enable measurements of interactions between solid, liquid and/or gaseous phases, resulting in the determination of heats of dissolution, of mixing, of adsorption. Additionally, chemical and physical processes of extremely low energies can be observed for solid or liquid samples. Very precise determinations of crystallinity of an organic or inorganic substance can be

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achieved, not easily reached by any other method, as application of the measurement of the enthalpy of dissolution or of the measurement of the enthalpy of transformation. Processes of chemical reactions or physical transformations having a typical enthalpy change are directly measurable after an initial equilibrium time in real time for conversion rates of down to a few percent per year. Slow release processes for pharmaceutical and agrochemical substances as well as shelf life estimations of formulations and even safety problems are important fields of application in development and in the quality control using isothermal calorimetry.

The titration microcalorimetry is a research technique which enables to study binding processes, especially applied to

biochemical substances and biopolymers (e.g., DNA, enzymes) under isothermal conditions [4]. The cell volume is normally *ca.* 1 ml and in applying 10–50 injections of 5–25  $\mu$ l the biopolymer may react with the ligand molecules. The obtained titration curve is evaluated with a three parameter fit under certain assumptions. The values for the binding constant, the enthalpy and the entropy of binding and the number of binding sites are obtained in only one experiment.

A variety of different types of instruments are existing which combine a heated or even cooled sample cell, mainly with a controlled linear temperature program, with methods such as UV and visible spectroscopy. With these instruments, often no enthalpy change can be measured as

a function of temperature and time, however, with thermodynamic evaluation of the data, one can get under certain conditions results which may be compared with DSC results.

Also similar arrangements are commercially available such as X-ray diffraction (temperature resolved X-ray diffraction) or FT-IR or FT-IR microscopy, or even with *Raman* spectroscopy. Coupled instruments are commercially available or are existing in self-built versions in a combination of thermogravimetry or DSC directly coupled or over a chromatograph (GC, LC) with mass spectrometers or IR instruments (TG-MS, TG-IR or TG-FTIR, DSC(DTA)-MS, DSC-GC-MS...) [5]. These 'hyphenated' techniques combine the advantages of the unspecific but very sensitive thermal analysis with molecular specific data [6].

### What are the Advantages of Using Thermal Analysis?

The major advantages of these techniques are their sensitivities and versatilities, the speed of analysis, the automation and the huge range of applications. Thermal analysis can reveal results for substances of low purity and mixtures for which many of the other existing methods have rather great difficulties. Due to the different information delivered, thermal analysis methods are concurrent or complementary to other analytical methods such as the different spectroscopic methods or chromatography. Thermal analysis methods deliver unique information about heats of transformation for polymorphs. These techniques are used for material characterization, quality control and kinetic analysis in research and in industry for inorganic and organic substances, pharmaceutical and biological material as well as for food, cosmetics and polymers. These techniques find applications in the development of manufacturing processes: monitoring of crystallization, freeze-drying, purification of enantiomers as well as in the development of formulations: solid dispersions, liposomes, microcapsules, microemulsions, gels, creams or for stability studies. All methods of thermal analysis are also widely used in safety studies.

The examples given in Figs. 1–6 illustrate some typical applications of thermal analysis techniques. As demonstrated in Fig. 1 the purities of two samples manufactured by two processes can be compared by using only *ca.* 1 mg of sample within 1 h. The two presented melting curves are evaluated with a linearization

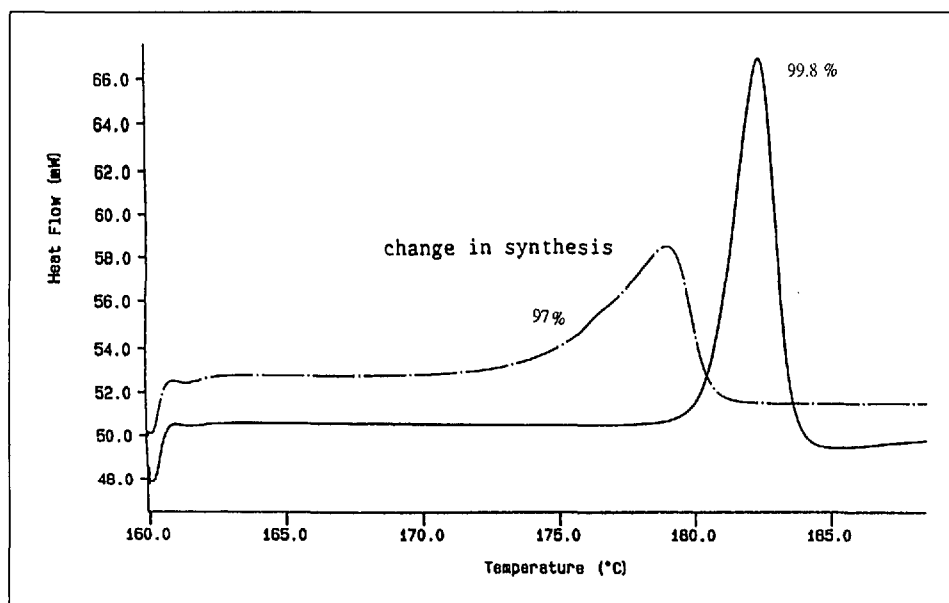


Fig. 1. DSC Purity analysis of two samples manufactured by different synthesis. Given are the purity values in respect of eutectic impurities.

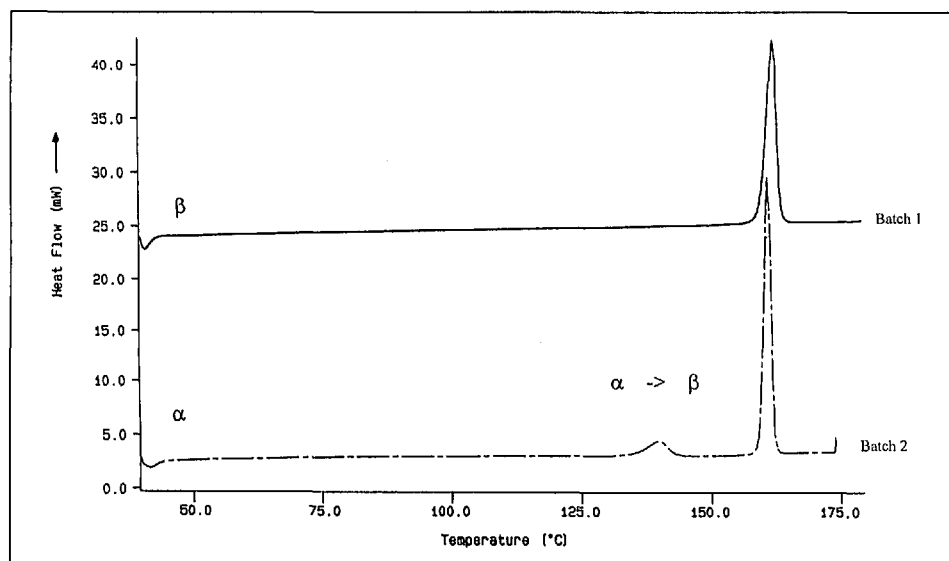


Fig. 2. DSC Scans of two polymorphs of a drug. Batch 1: metastable form at room temperature. Batch 2: stable form at room temperature.

procedure, yielding the determination of absolute eutectic purity without knowledge of the specific impurities.

The next example demonstrates the powerful application of DSC for the understanding of polymorphism of organic substances. Fig. 2 shows the scans of two batches of a drug which differ in their polymorphic forms. Batch 1 is the form  $\beta$  and batch 2 is the form  $\alpha$ . The small endotherm prior the melting point in batch 2 is an enantiotropic solid-solid transformation  $\alpha$  into  $\beta$ . The form  $\alpha$  is thermodynamically stable from room temperature until the transformation temperature. At higher temperatures, the form  $\beta$  is thermodynamically stable. Batch 1 has been obtained in the metastable state at room temperature for kinetic reasons.

The study of polymorphism and pseudo-polymorphism (hydrates, solvates) and salts is a pre-requisite for a proper knowledge of the solid state. The classical X-ray methods and temperature resolved X-ray diffraction, also IR and Raman methods for solid substances and thermogravimetry are the best techniques combined with DSC for a proper understanding of the polymorphic behavior of substances. A summary of such a study for tetracaine hydrochloride is given in Fig. 3 which demonstrates the complexity of the solid state of organic substances.

Thermogravimetry allows also a complete composition analysis as demonstrated in Fig. 4 for calcium oxalate monohydrate. Processes, which are of higher complexity in the products generated, afford for a molecular elucidation the coupled methods or also an off-line investigation applying additionally spectroscopic methods.

Figs. 5 and 6 demonstrate the study of the thermal denaturation of the growth factor TGF- $\beta$ 3 at pH 2.5. In Fig. 5 the denaturation is observed by UV at 278 nm with a sample which is heated with a linear heating rate. The derivative of the UV-absorption curve is calculated and is compared to the calorimetric curve directly measured in a micro-DSC showing an interesting comparison of the results of linear heated UV spectroscopy with the findings of a calorimetric method (see Fig. 6).

### STK (Schweizerische Gesellschaft für Thermoanalytik und Kalorimetrie) and Its Activities

The Swiss Society of Thermal Analysis and Calorimetry was founded in 1975. The foundation members elected Prof. H.R.

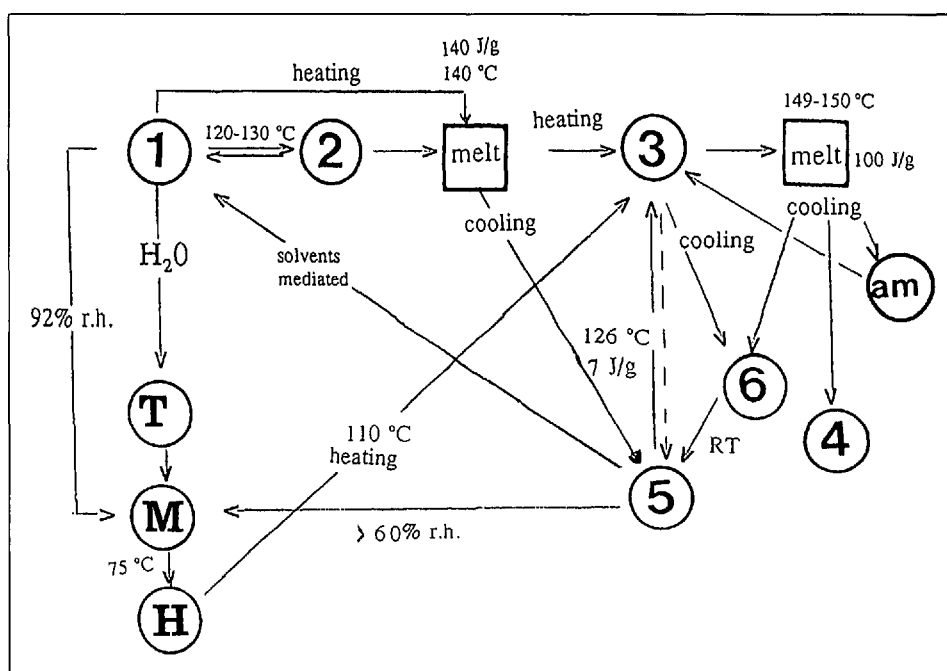


Fig. 3. Study of polymorphic behavior of tetracaine hydrochloride. 1-6: crystalline polymorphs, am: amorphous form, T: tetrahydrate, M: monohydrate, H: hemi-hydrate.

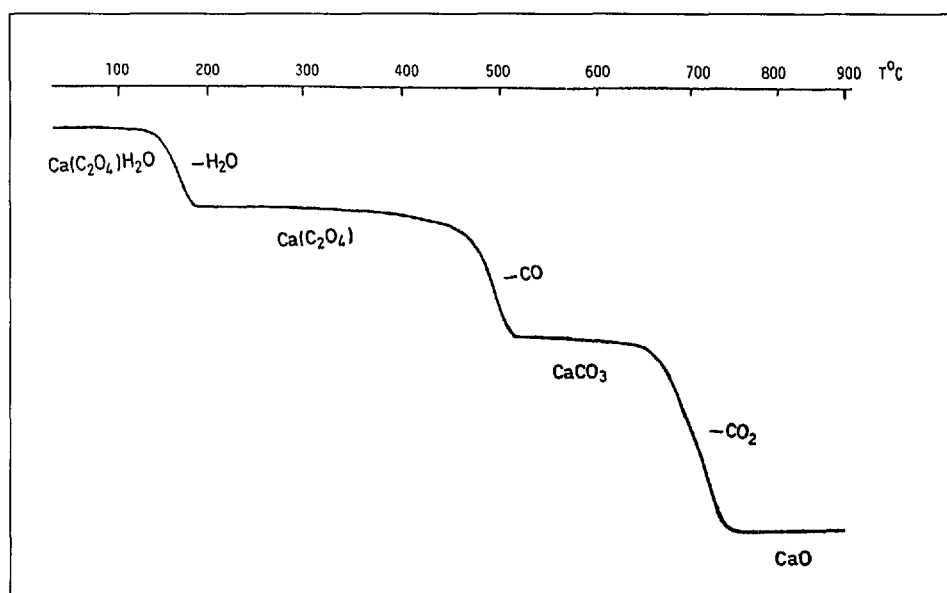


Fig. 4. Thermogravimetric curve of calcium oxalate monohydrate showing the distinct steps obtained by heating

Oswald as president for the period of 1975-1978. Since 1979, Dr. E. Marti is the president of STK. The society grew more than expected by its foundation members and has now ca. 130 members. Members are from all parts of Switzerland, from university, industry and manufacturers of instrumentation. The collaboration allows a high degree of exchange of scientific information. As an example, the knowledge of inorganic solid-state chemistry and solid-state characterization has been transferred with the STK as vehicle to the organic chemistry, not only within the scientific societies, but also as a global network to the chemical companies [7-9].

STK is member of the ESTAC (European Society for Thermal Analysis and Calorimetry) and of the international society ICTAC (International Confederation for Thermal Analysis and Calorimetry) which covers 46 countries with 550 members. ICTAC works in collaboration with IUPAC, establishes clear nomenclature and standardization and promotes conferences and education courses of thermal analysis. In 1992 a new European society namely eurostar was born with a nucleus of the scientific colleagues of the president of the STK. eurostar is organizing scientific conferences in Europe and the PhandTA3 (3rd Symposium/Workshops

on Pharmacy and Thermal Analysis) will be held in October 1997 at the Centro Stefano Franscini, Monte Verità, Ascona. The basic goal of the board members of eurostar is the organization of subject focussed conferences, similar to the Gordon Research Conferences following the ideas of Dr. P. Rhyner, the long-time president of the 'Schweizerischer Chemiker Verband'.

Every year national meetings of STK as well as from time to time joined meetings with the French, the Italian or the German partner society take place for *e.g.*, at Geneva, Freiburg, Basel. The symposium ESTAC 3 was organized by the board members of STK 1984 in Interlaken with more than 300 participants. This symposi-

um has been achieved because of the great number of publications and lectures of Swiss members in international journals and conferences in fields of pharmacy, food, biology, inorganics, process safety and even archeology. Several members of STK represent thermal analysis in national and international organizations for the promotion of these techniques. STK promotes research of high level and is presenting nearly every year an Award for 'Applied Chemical Thermodynamics'. In 1997, the Award is dedicated to Prof. J.W. Stucki, Pharmacological Institute of the University of Bern. The prize for 'Young Scientists' has been introduced five years ago because the scientific achievements for the normal award is practically impos-

sible to reach for a young scientist. The prize 'Young Scientists' is 1997 given to Prof. Annette Bauer-Brandl, University of Tromsø, Norway, for 'Pharmaceutical Technology'.

## Trends

The thermal analysis techniques are now applied practically in all fields of research and industry. Standard substances for the different measured parameters are available from national laboratories. Furthermore, the manufacturers offer automatic reliable instruments with high throughput which are qualified, making the technique also more appropriate for high-volume, routine quality control analyses.

The thermal analysis methods cover such a broad field of research, development and production including quality control, that it is difficult to keep such a fast growing diversity under a single organization. Therefore, the answer to this problem is to organize also symposia which are focussed on a single subject. The instrumentation has been strongly broadened since the foundation of the STK. Combined or coupled techniques (TG-MS, DSC-X-ray, DSC-IR, TG-FTIR) and the instruments applicable for isothermal and non-isothermal investigations of biochemical substances are the most attractive enlargements. The near future will bring new inventions in the direction of calorimeters based on micro-sensors with sensitivities in the range of picojoule. Research investigations have been formulating in this high sensitivity regions an ultimate goal, which will be revolutionary, namely the direct measurement of the heat of reaction for single molecules.

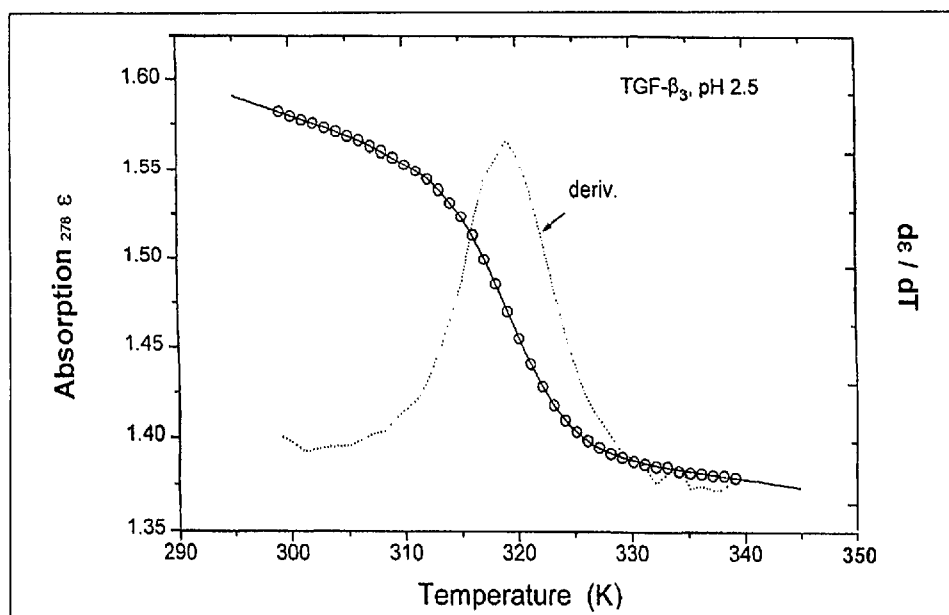


Fig. 5. Temperature dependence of the UV absorbance for TG- $\beta_3$  at pH 2.5 and the derivative of this curve at 278 nm

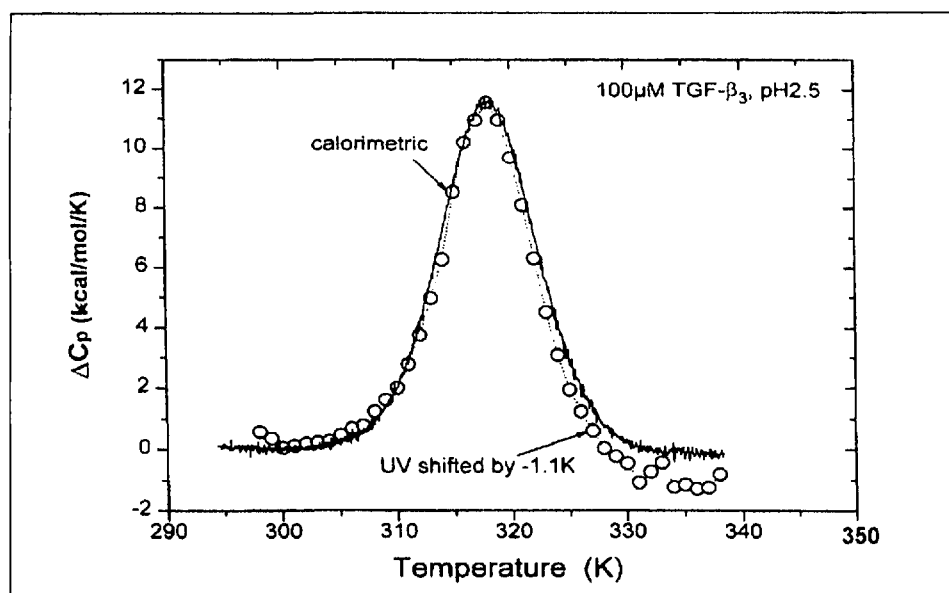


Fig. 6. Comparison of the calorimetric denaturation curve for TG- $\beta_3$  at pH 2.5 with the derivative curve obtained from the UV absorbance of the denaturation process according to Fig. 5

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