Is There a Simple Relationship Between Different Phases, Phase Transitions and Stability of Drugs?

Milan D. Antonijevic

School of Science, University of Greenwich at Medway

Introduction

Research Interests

Examples of a solid state characterisation using conventional thermo-analytical instrumentation

Thermally Stimulated Current Spectroscopy (TSC) as a new mean of characterising materials

Conclusions

Educational Background

BSc Chemistry – 1997, University of Belgrade

Over 4 years – QA/QC, Pharmaceutical Industry, Serbia

PhD in Pharmaceutical Materials Science – 2005, Queens University Belfast

Academia (Lecturer in Pharmaceutical Analysis)

University of East Anglia (2004-2006)

University of Greenwich (2006-present)

Research Interests

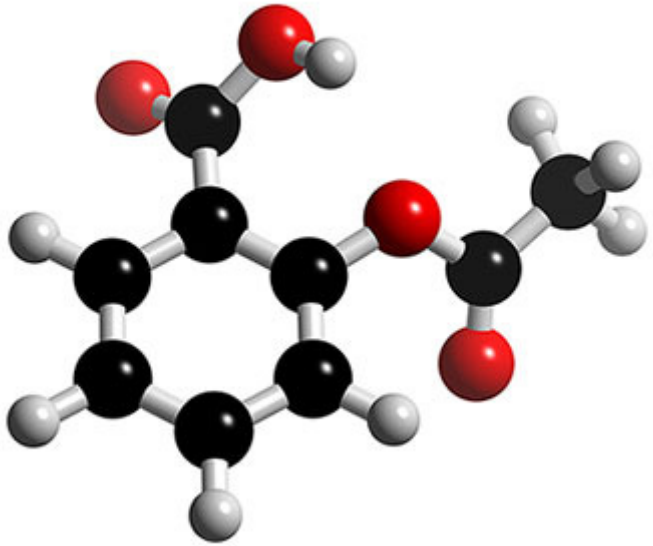
Solid-State characterisation

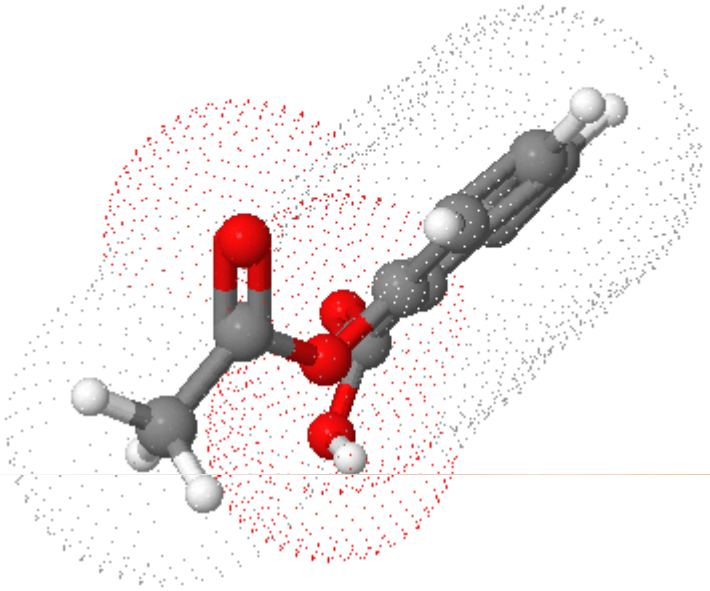
Understanding relationship between phase transitions and stability of different forms

Photo and thermal stability

Development of TSC as a new tool for characterisation of small (pharmaceutically important) molecules

Aspirin





Nice model drug

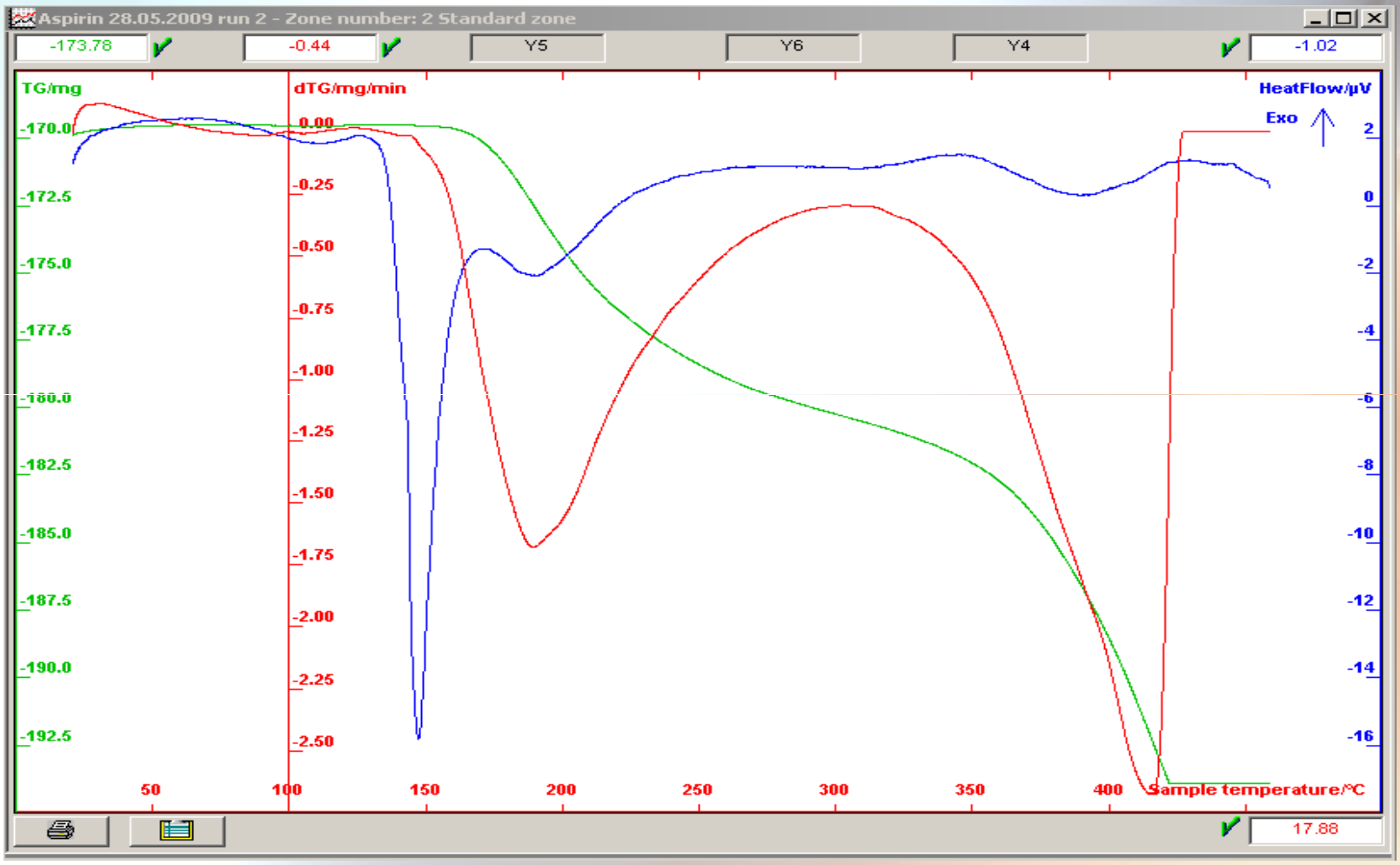
Cheap, non hazardous

Significant information available

Gaps in knowledge

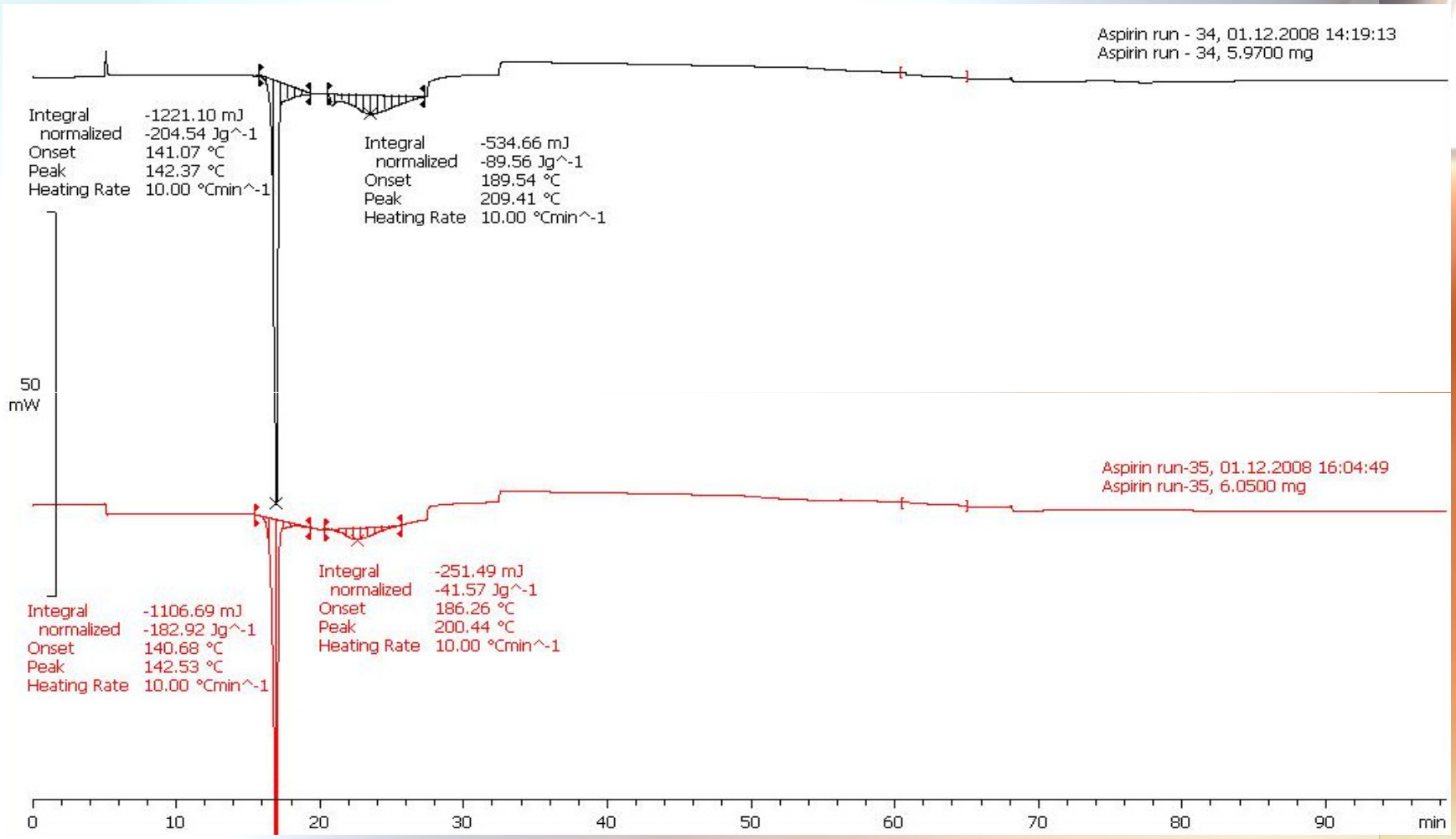
TGA Results

Stability in solid-state



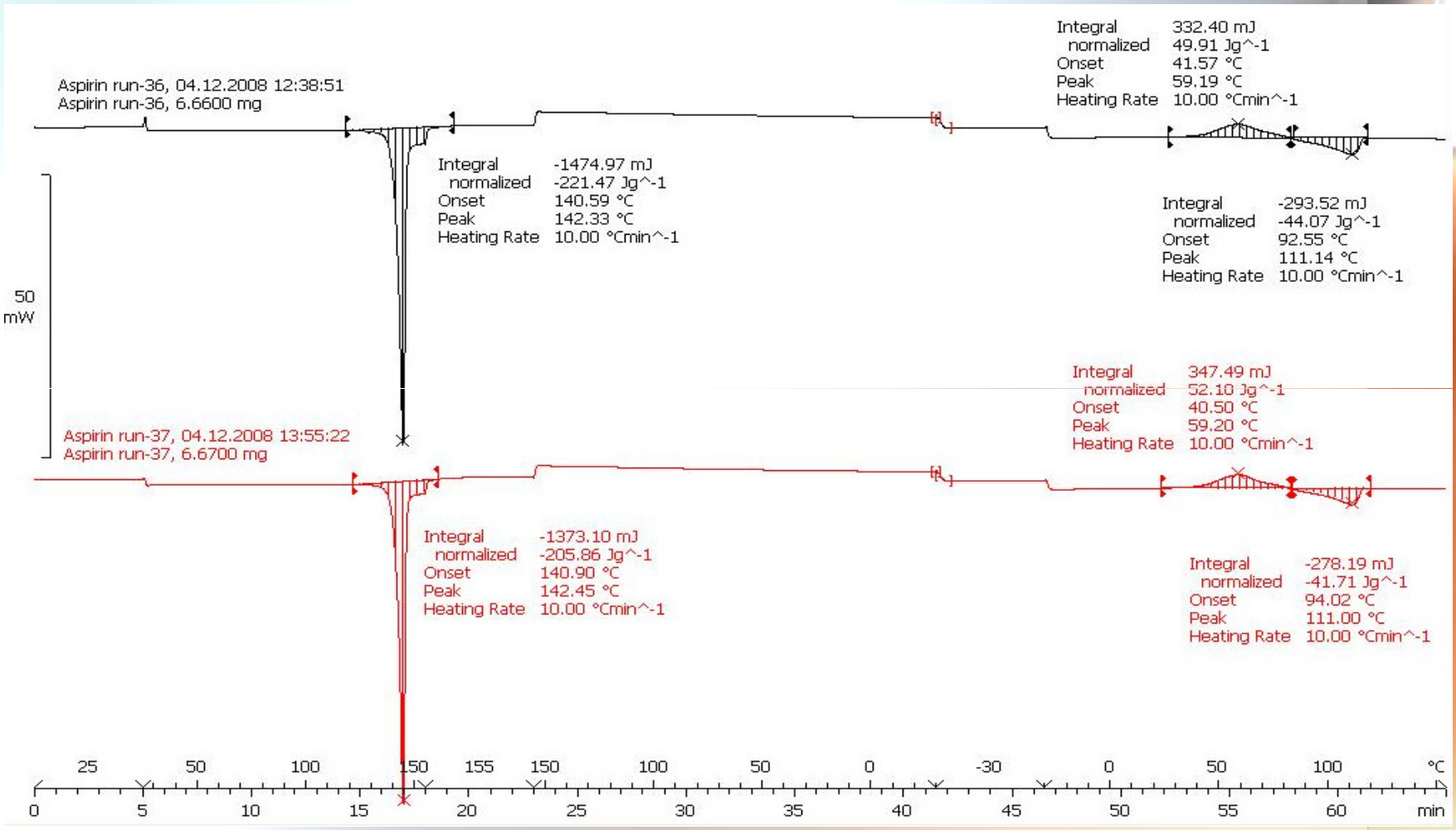
DSC Results

Aspirin (25to210°C/210to-30°C/-30to210°C@10)



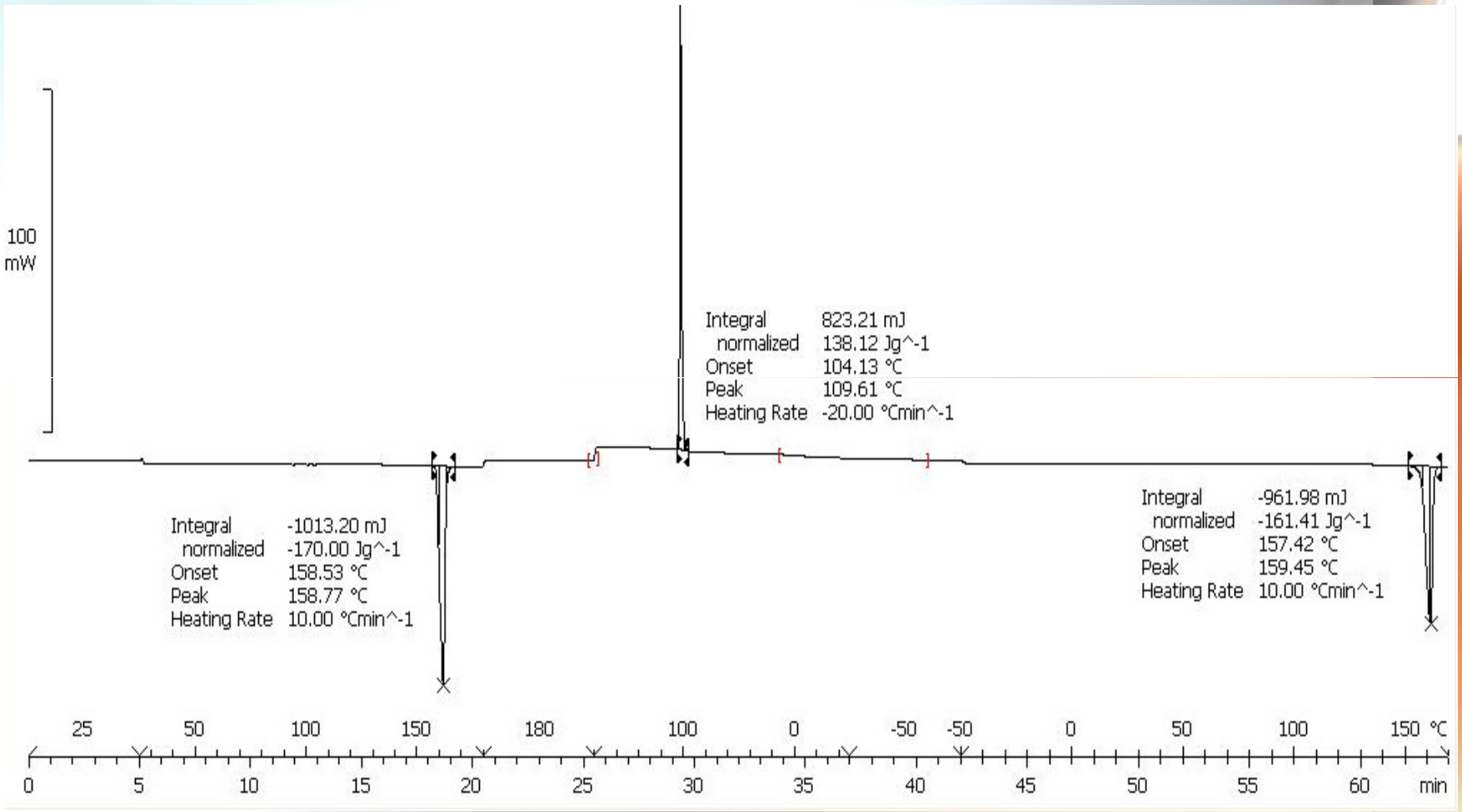
DSC Results

Aspirin



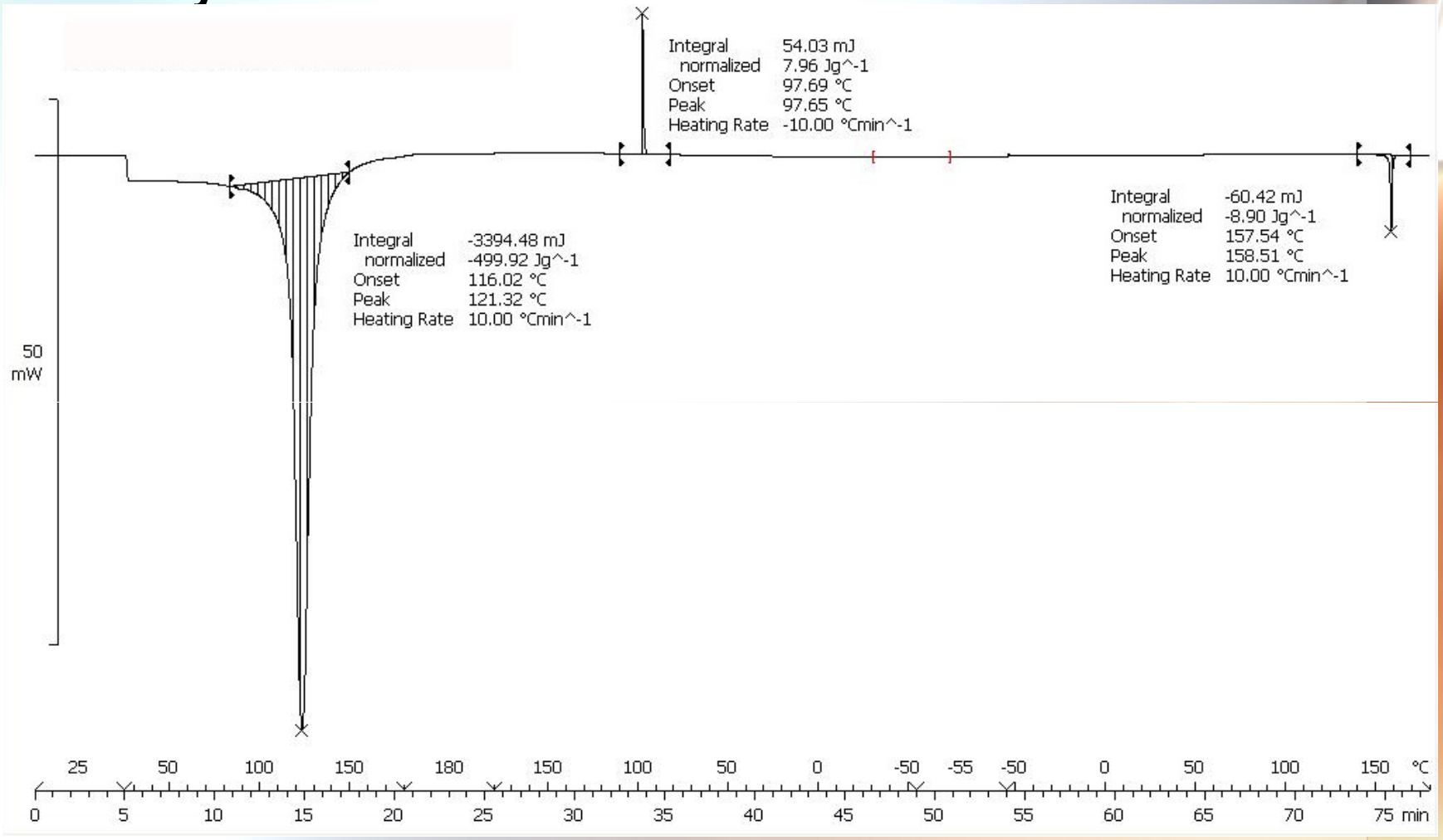
DSC Results

Salicylic Acid



DSC Results

Salicylic Acid + Acetic Acid



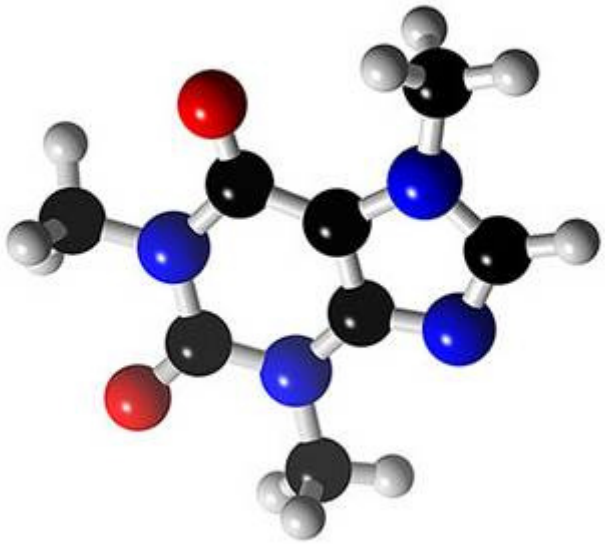
DSC Results

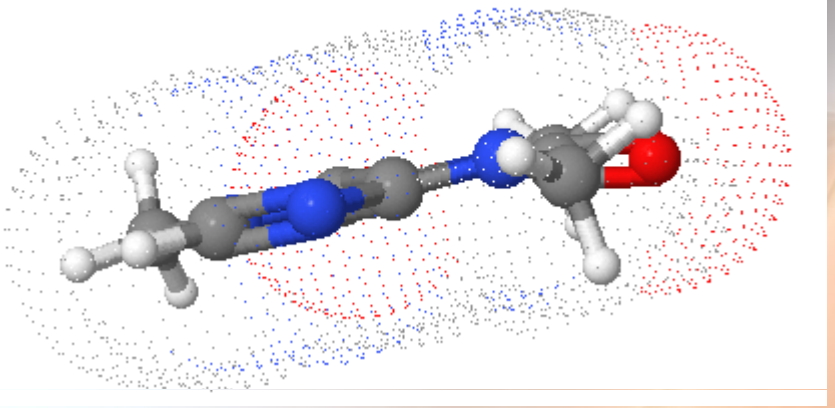
Correlation between presence of Acetic Acid and temperature of a phase transitions

	1st heating	2nd heating		
25-155/-55/155	Melting Point (°C)	Tg (°C)	Exo (°C)	Endo (°C)
Crimped pans				
cooling@5	141.2±0.6	-38.2±0.6	58.4±0.2	94.8±1.3
cooling@10	141.2±0.7	-38.2±0.6	58.5±0.4	94.4±1.2
cooling@20	140.6±0.5	-38.9±0.3	42.5±1.2	92.7±0.5
Pinhole pans				
cooling@5	141.0±0.4	-20.4±0.4	69.3±0.5	109.7±0.4
cooling@10	140.9±0.3	-24.5±0.8	61.2±1.3	102.8±0.6
cooling@20	140.6±0.4	-25.7±0.3	58.2±1.2	100.8±0.5

TA Instruments, London 2009

Caffeine





Polymorphic transition

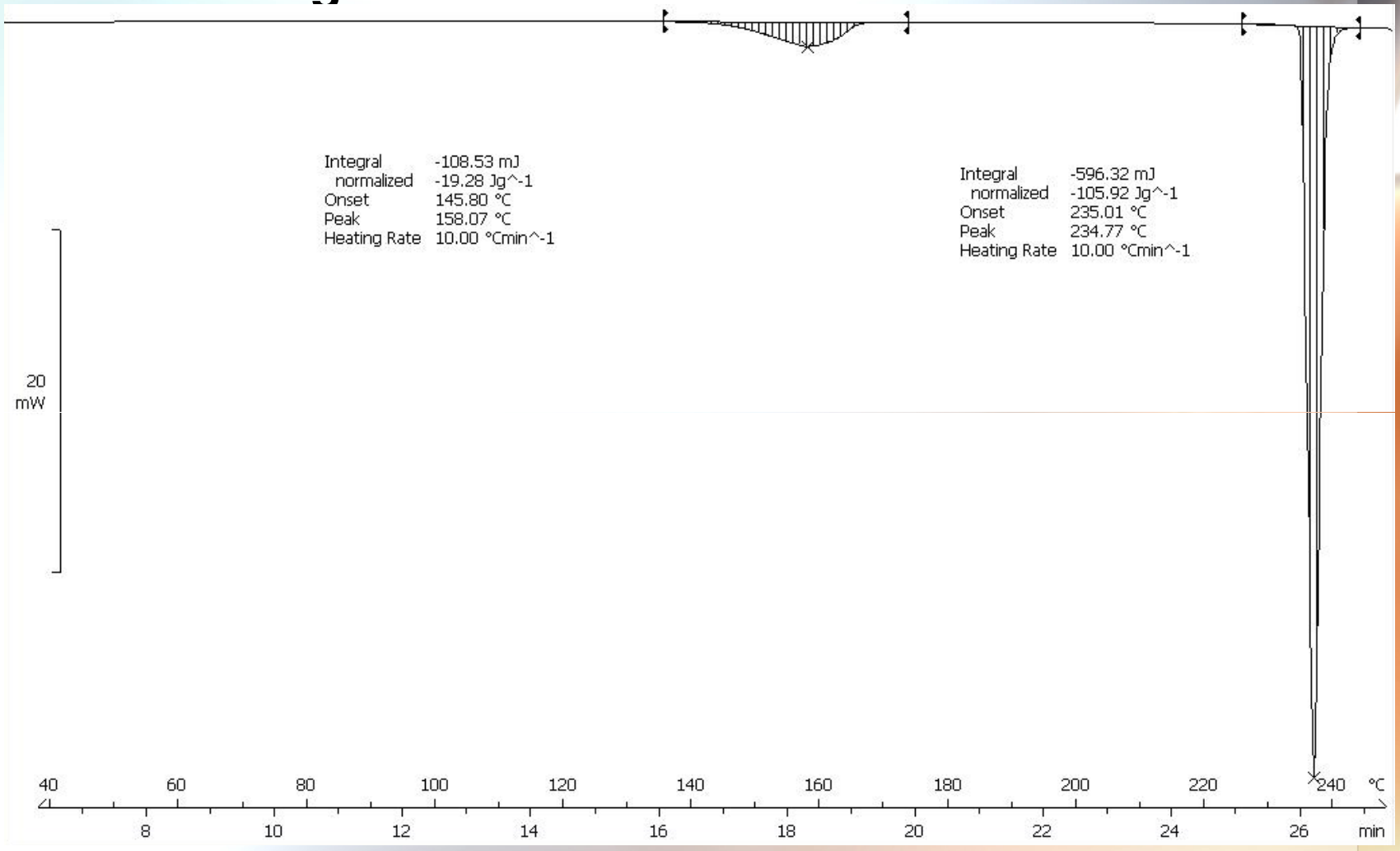
Form II is stable at room temperature

Form I is stable above 150°C

Xanthine alkaloid (theophylline, theobromine)

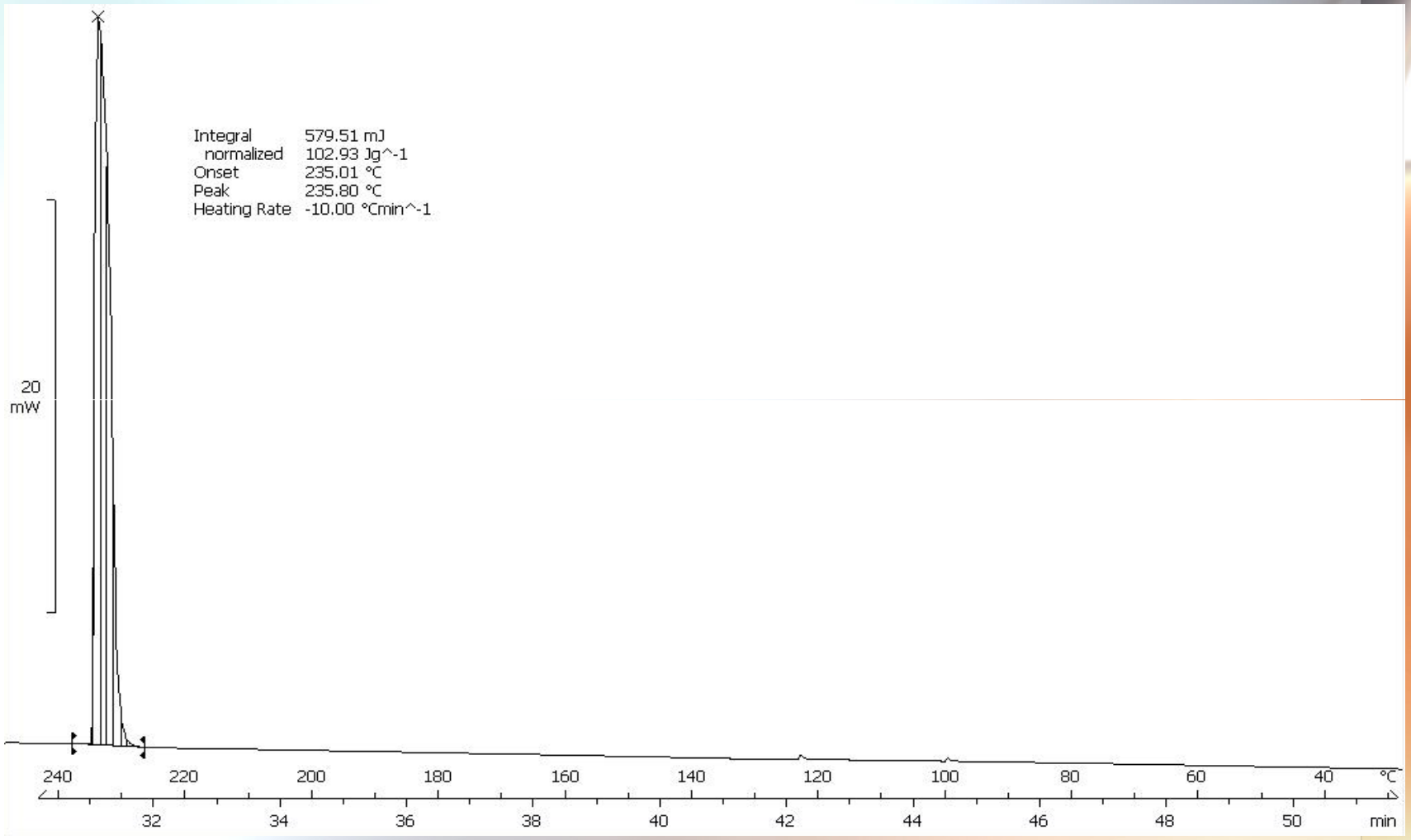
Caffeine Form II – DSC Results

1st heating



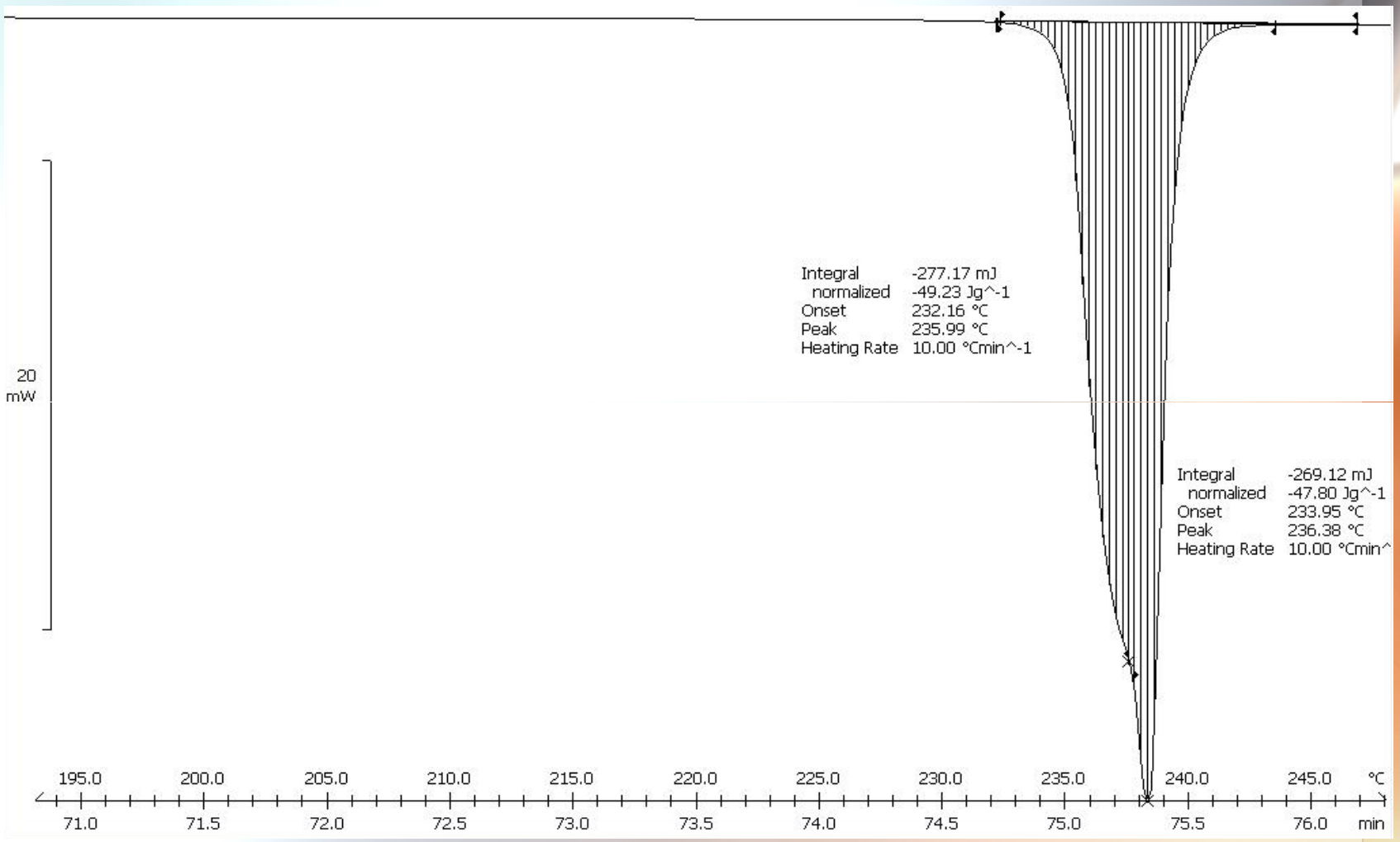
Caffeine Form II – DSC Results

cooling



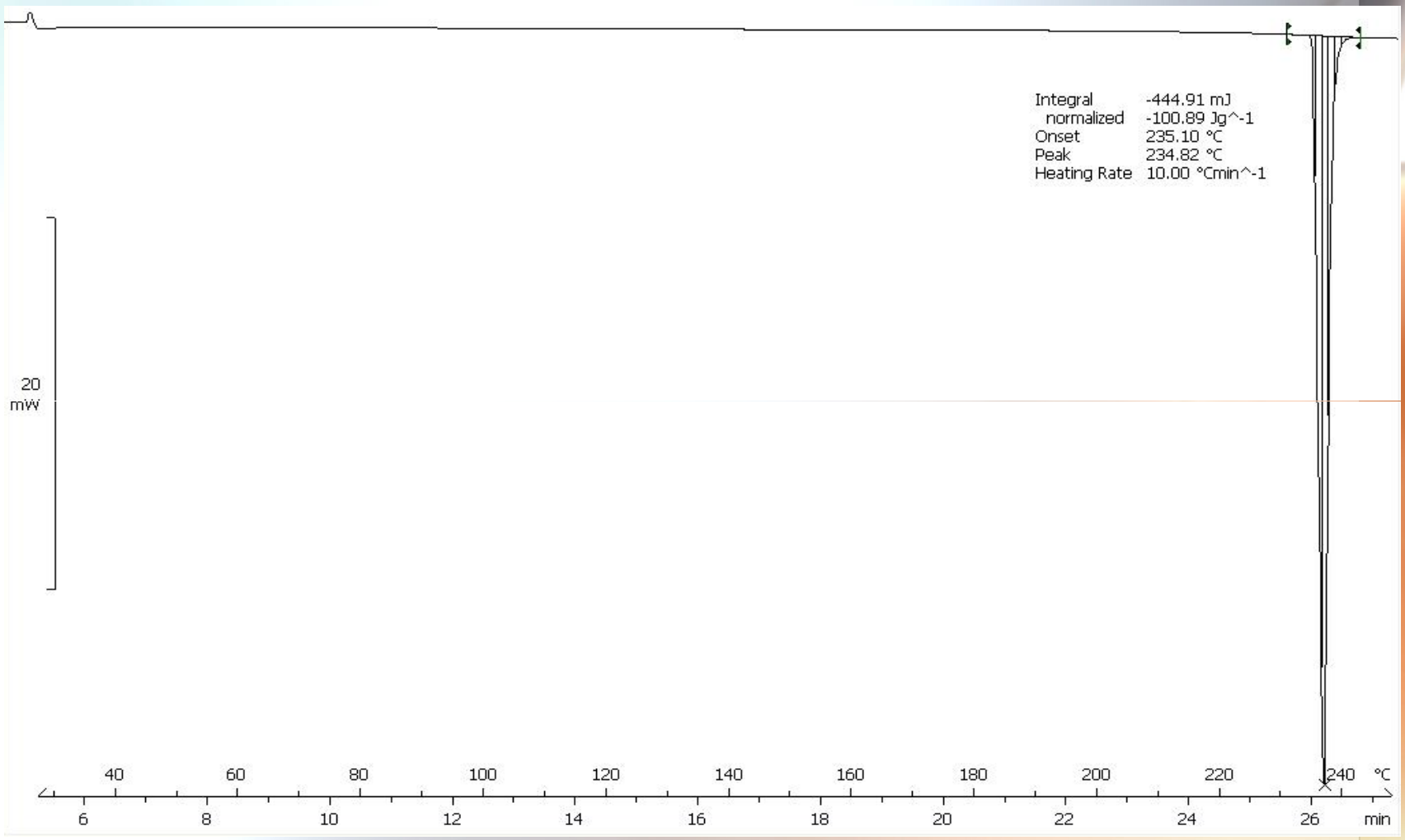
Caffeine Form II – DSC Results

2nd heating



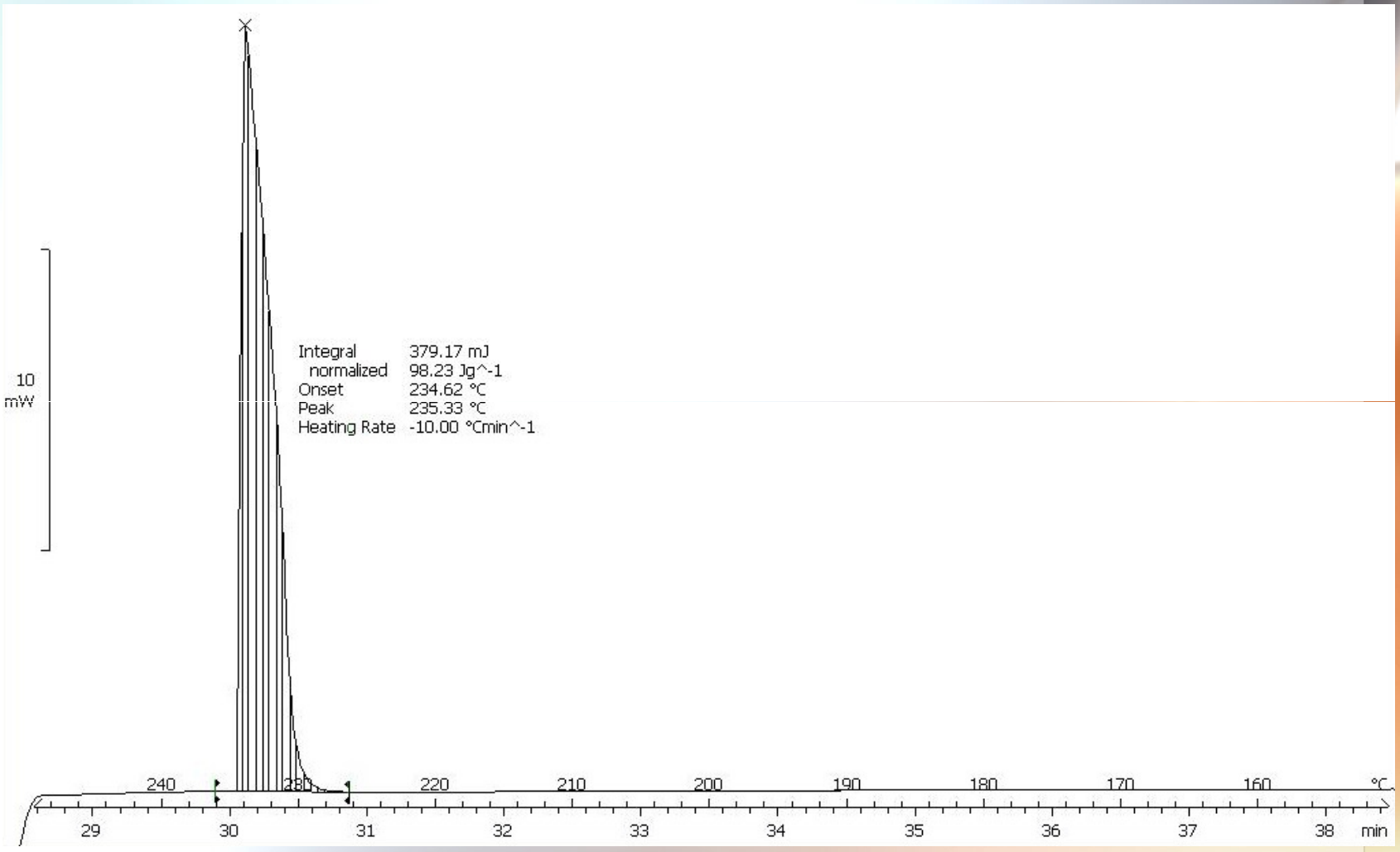
Caffeine Form I – DSC Results

1st heating



Caffeine Form I – DSC Results

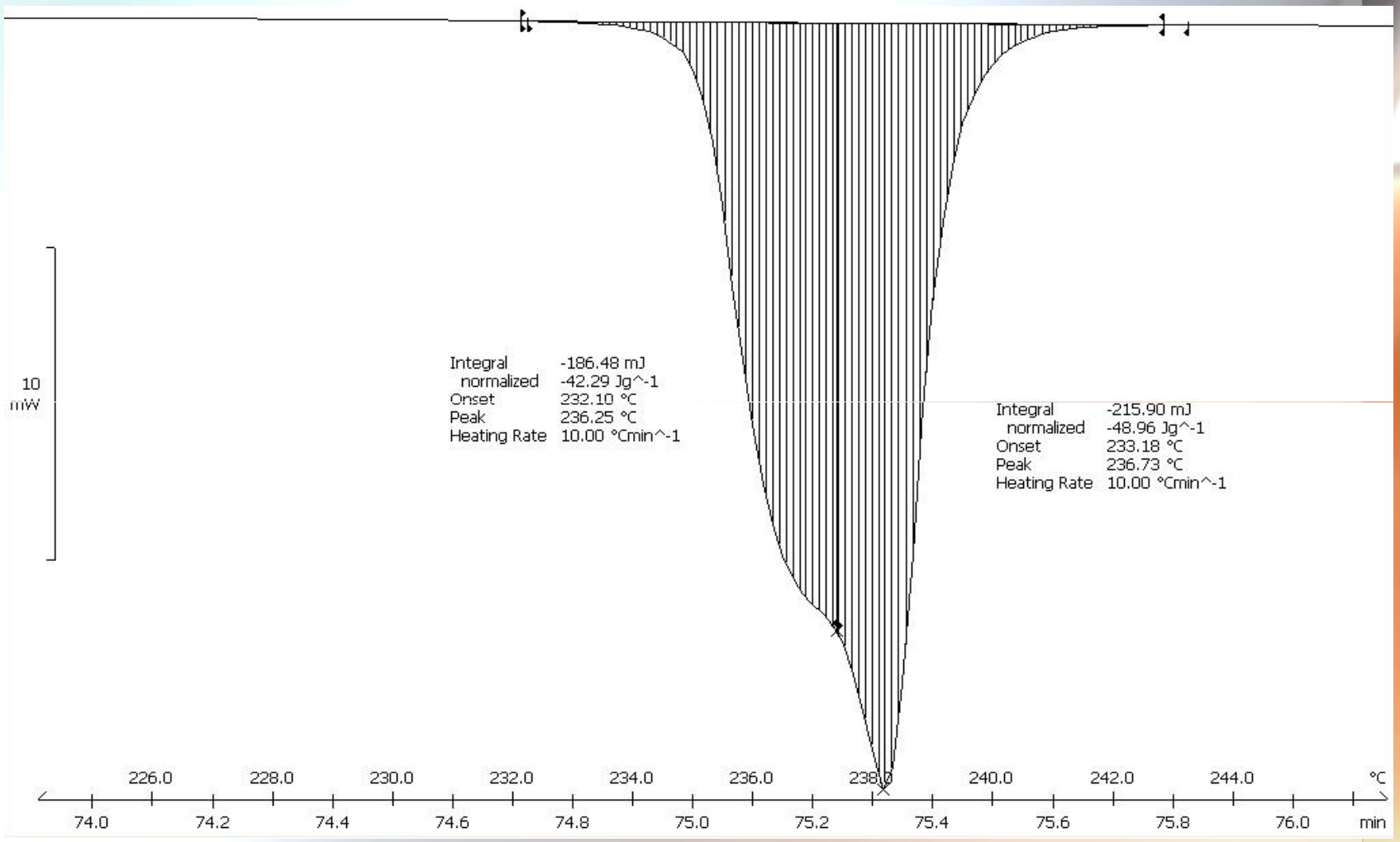
cooling



TA Instruments, London 2009

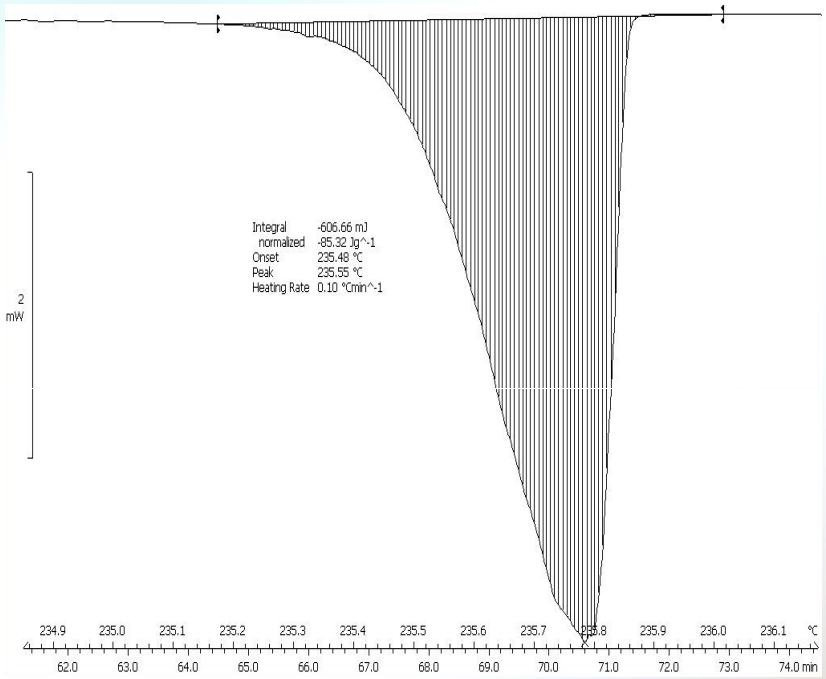
Caffeine Form I – DSC Results

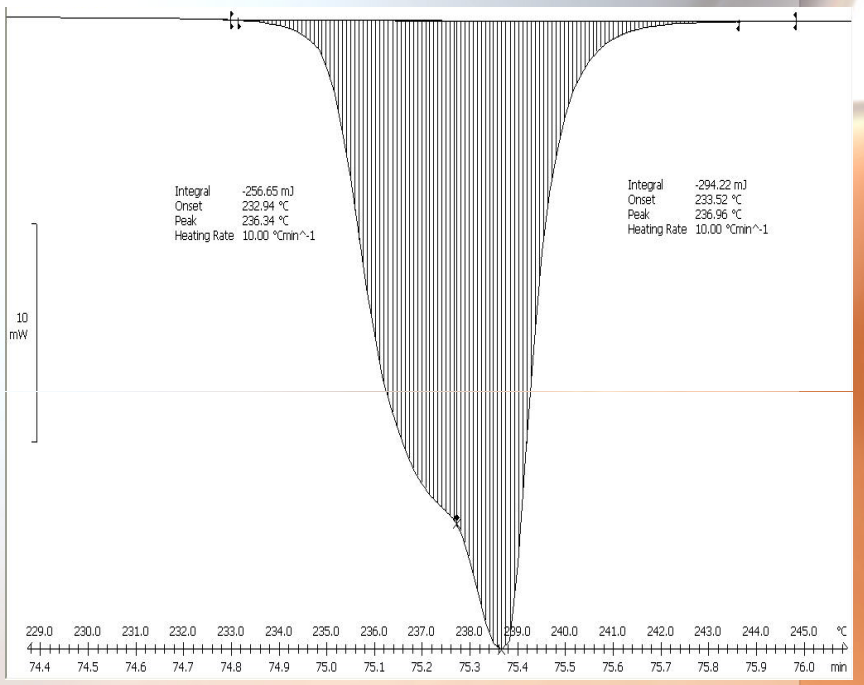
2nd heating



Caffeine Form I – DSC Results

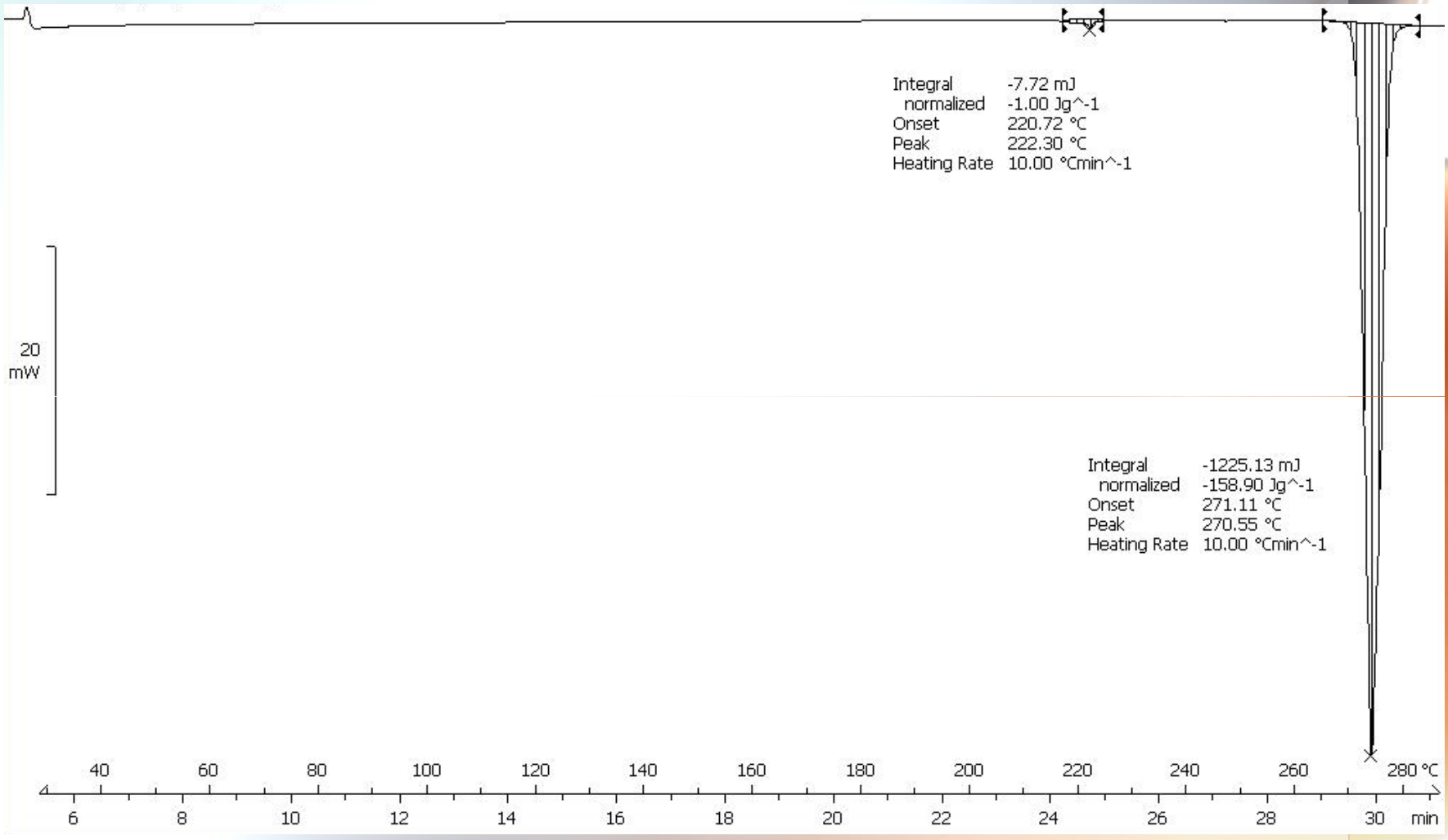
Melting of caffeine in1st and 2nd heating





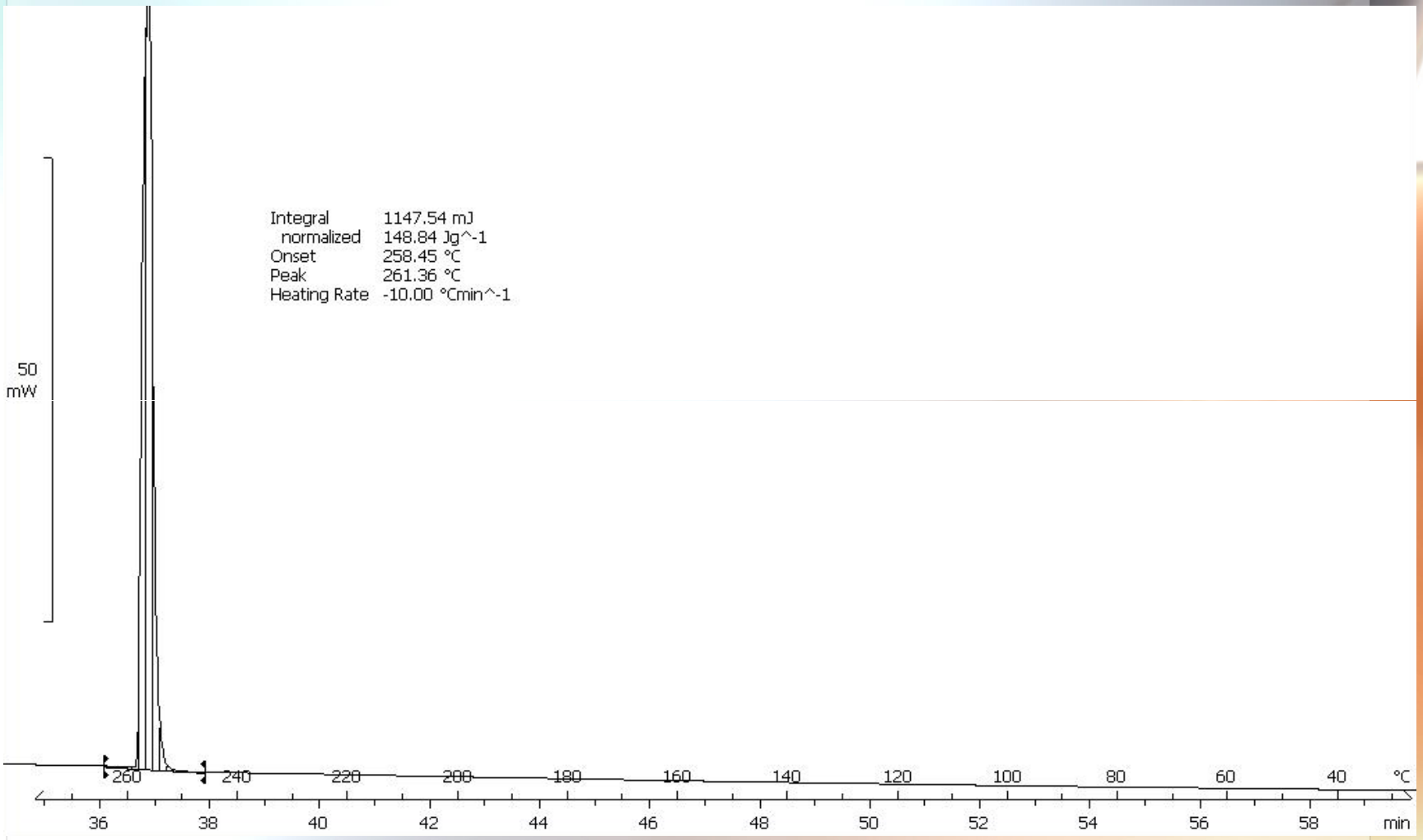
Theophylline - DSC

1st heating



Theophylline

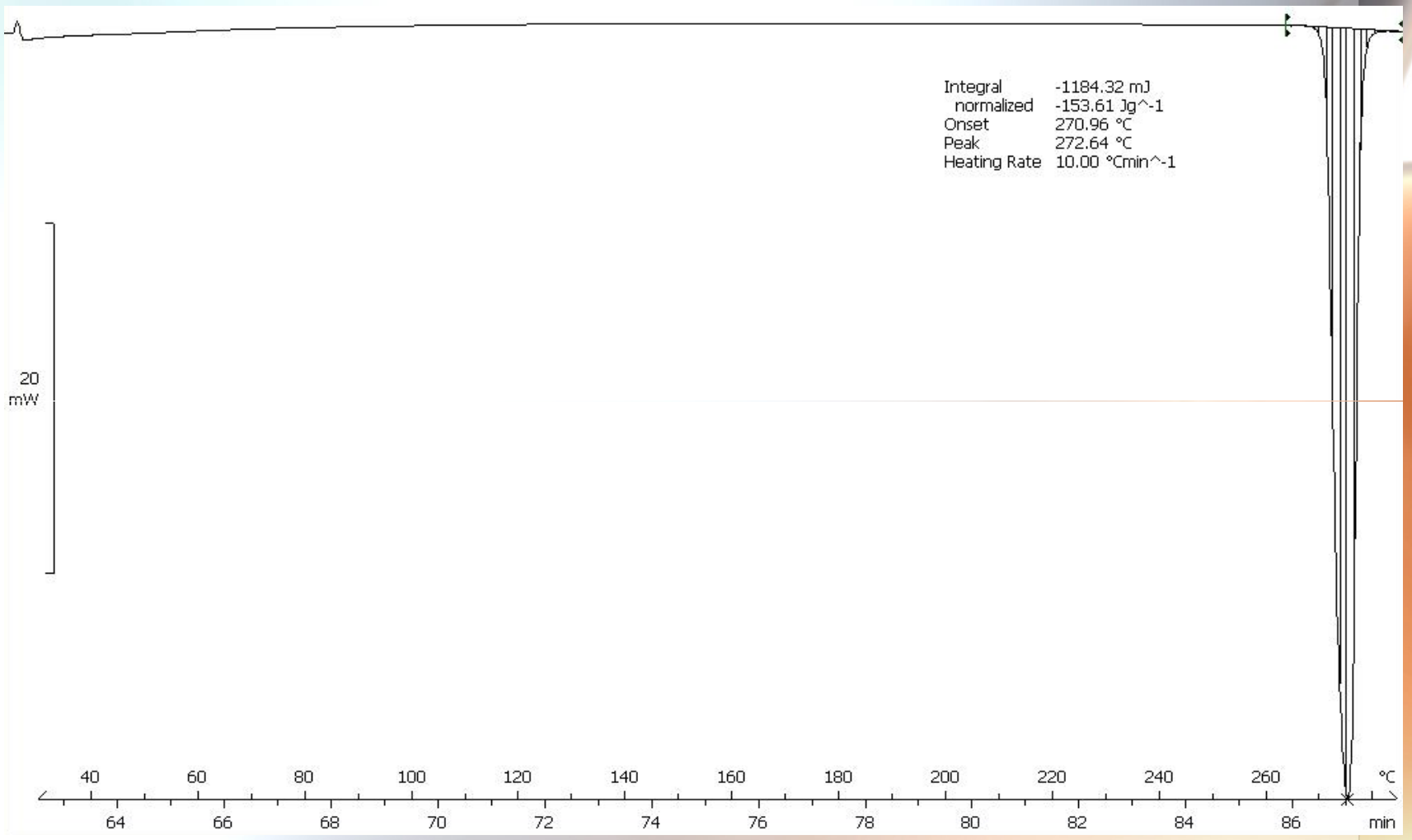
cooling



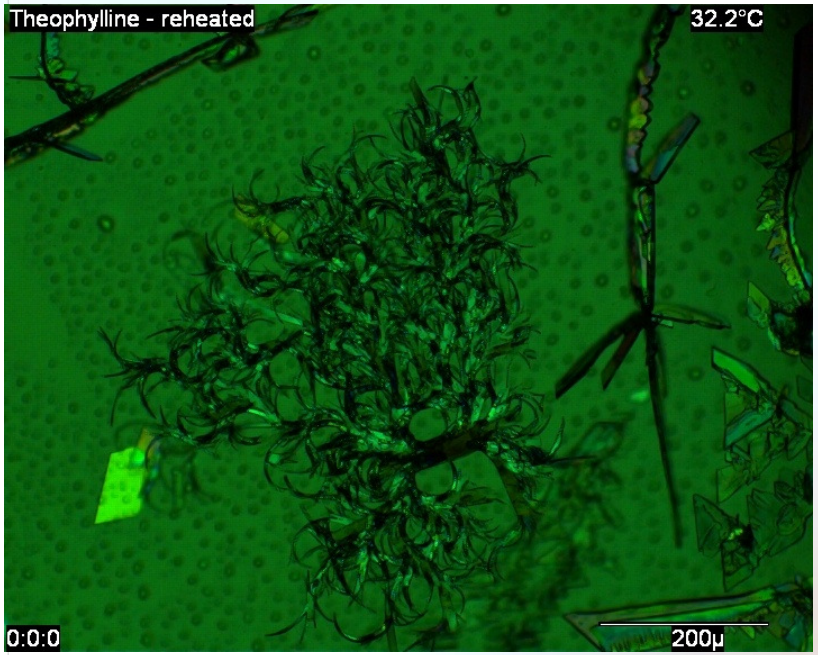
TA Instruments, London 2009

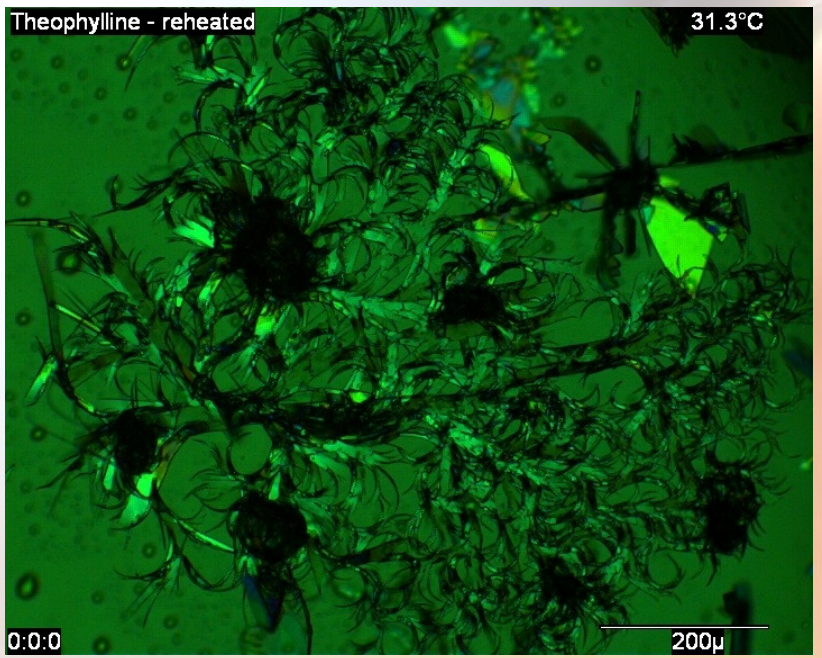
Theophylline

2nd heating



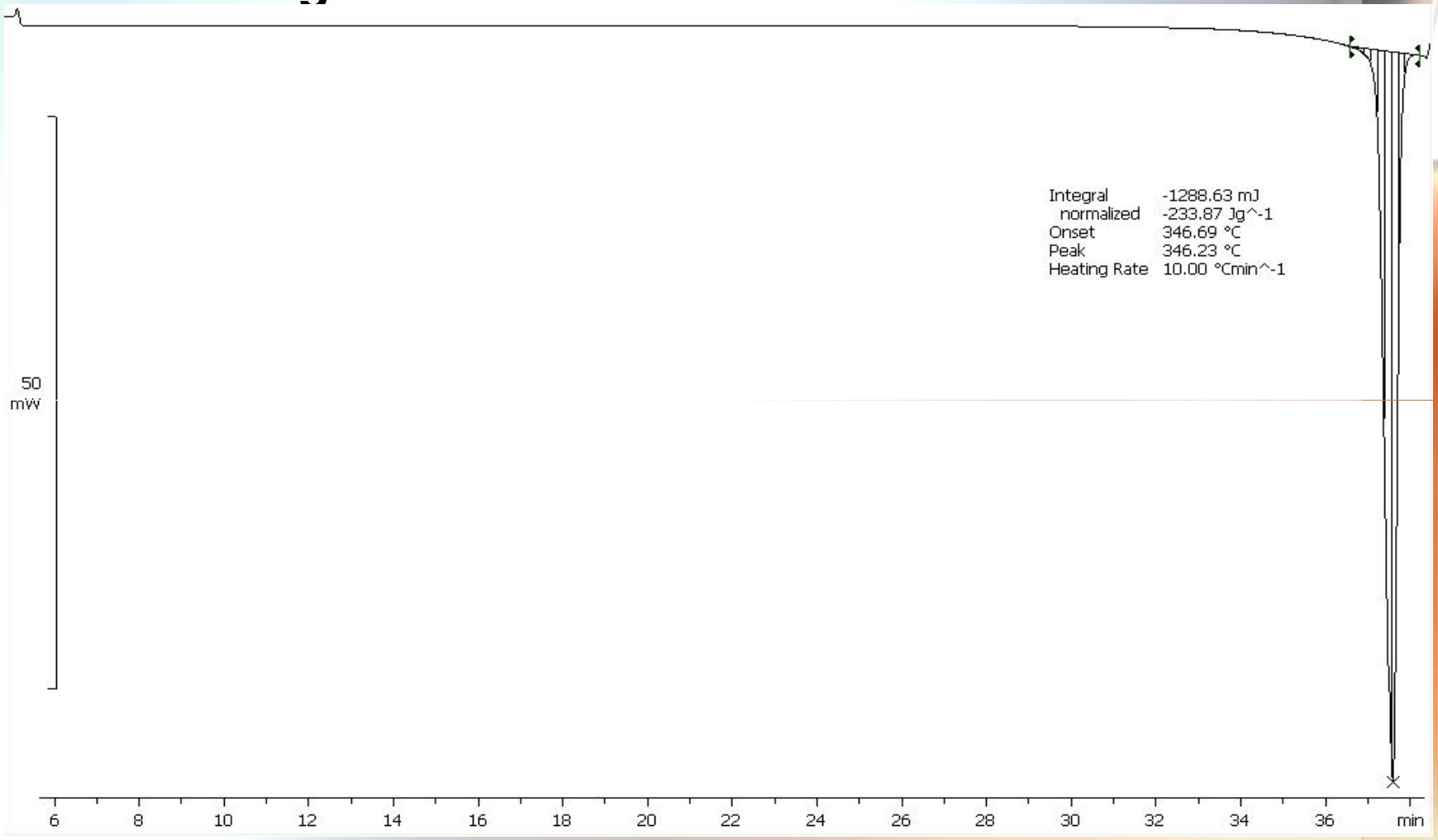
Theophylline





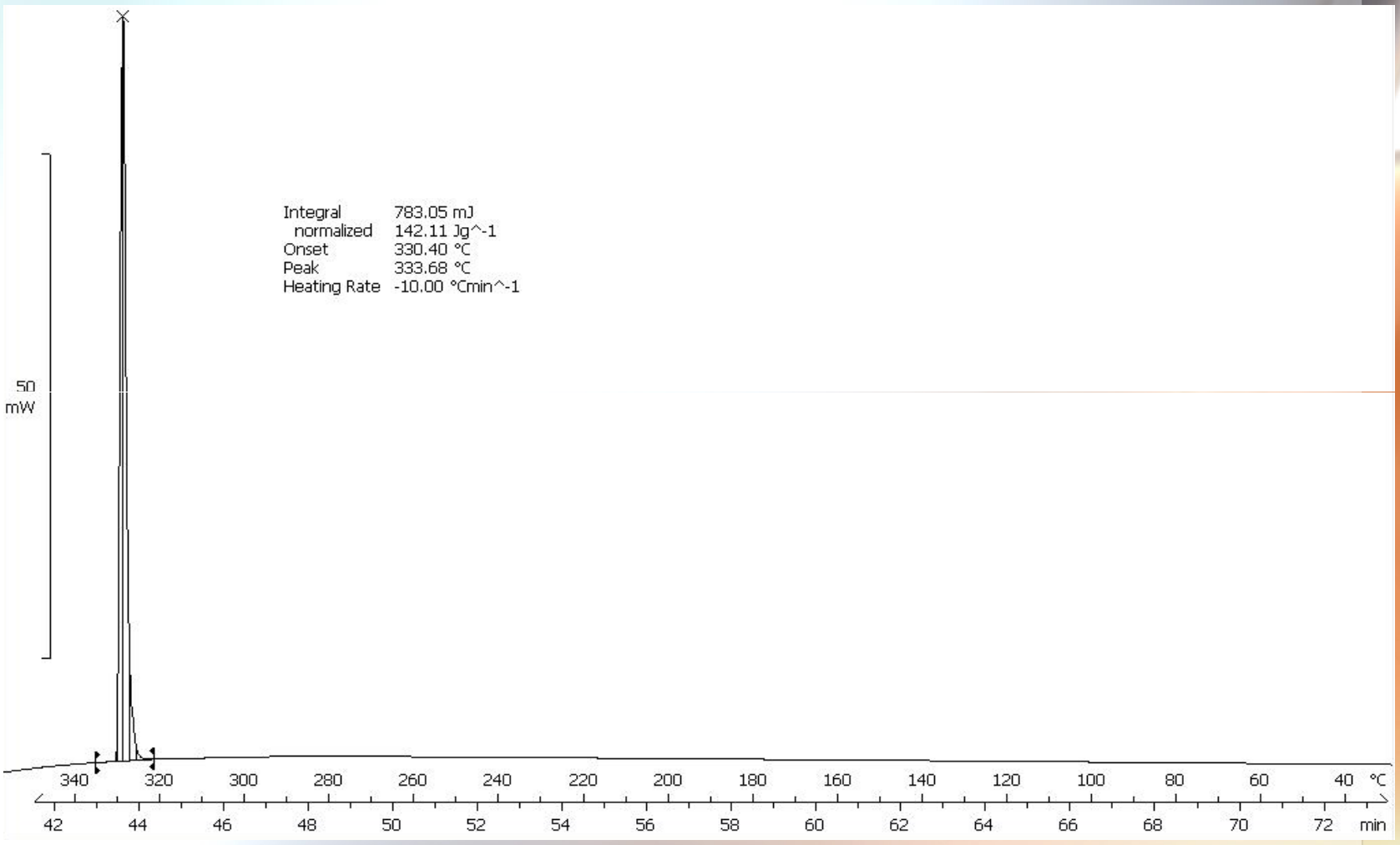
Theobromine

1st heating



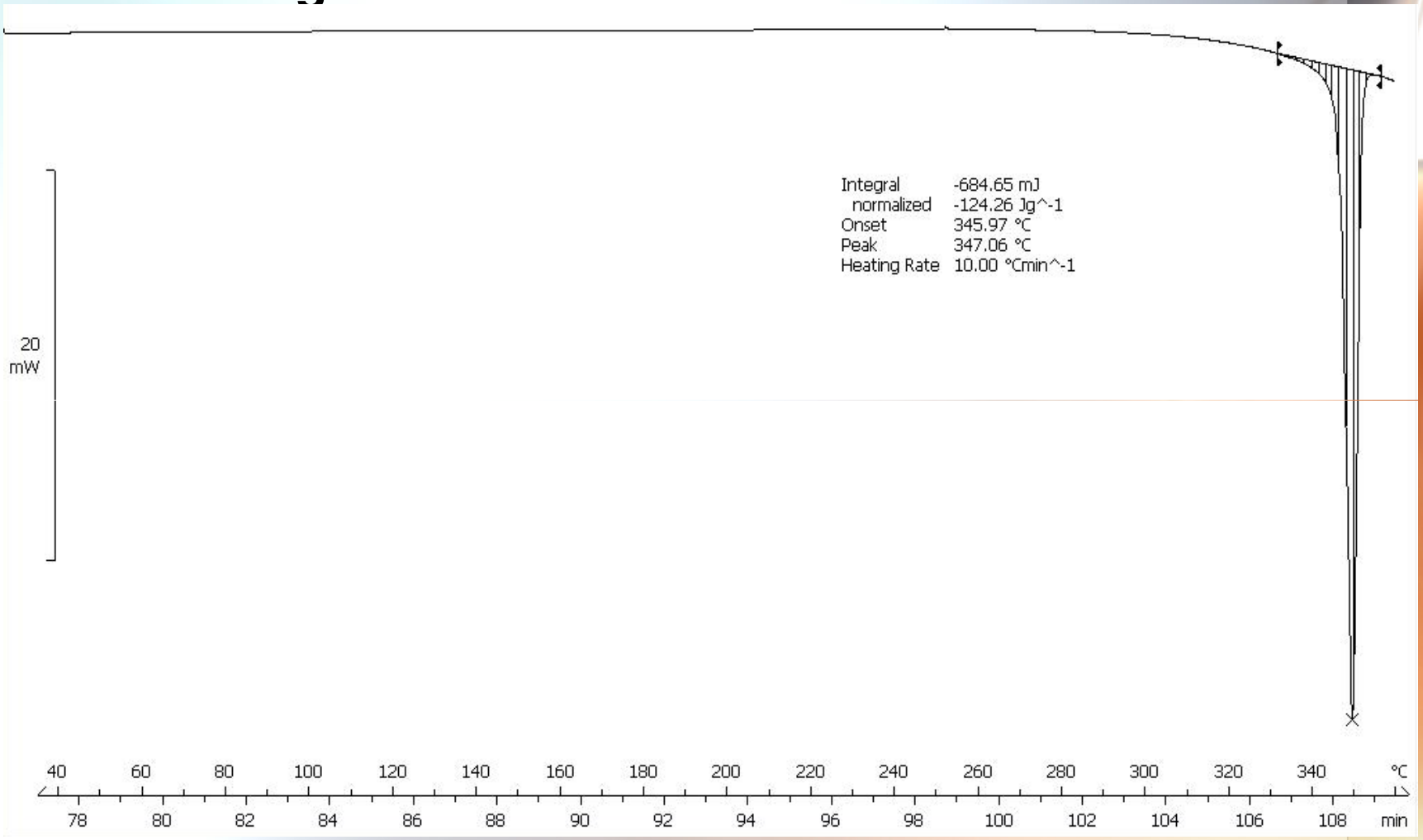
Theobromine

cooling



Theobromine

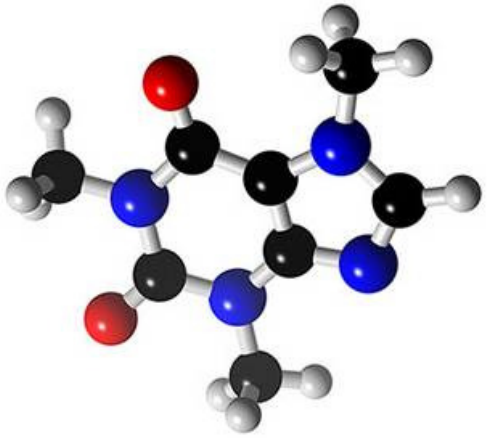
2nd heating

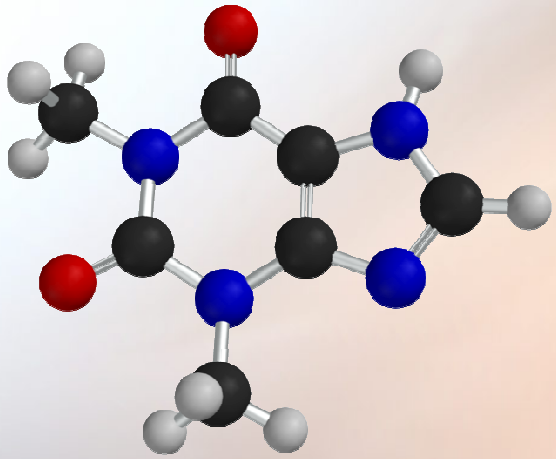


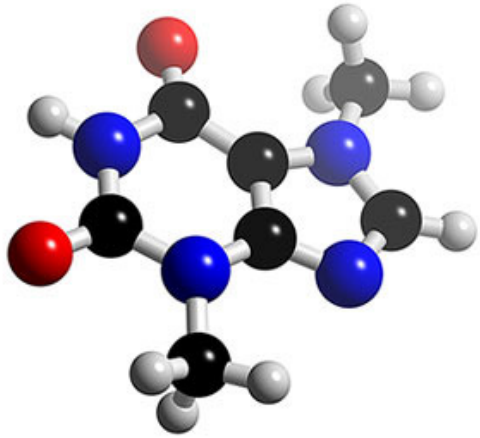
Caffeine, Theophylline, Theobromine

Caffeine and Theobromine – sublime rapidly

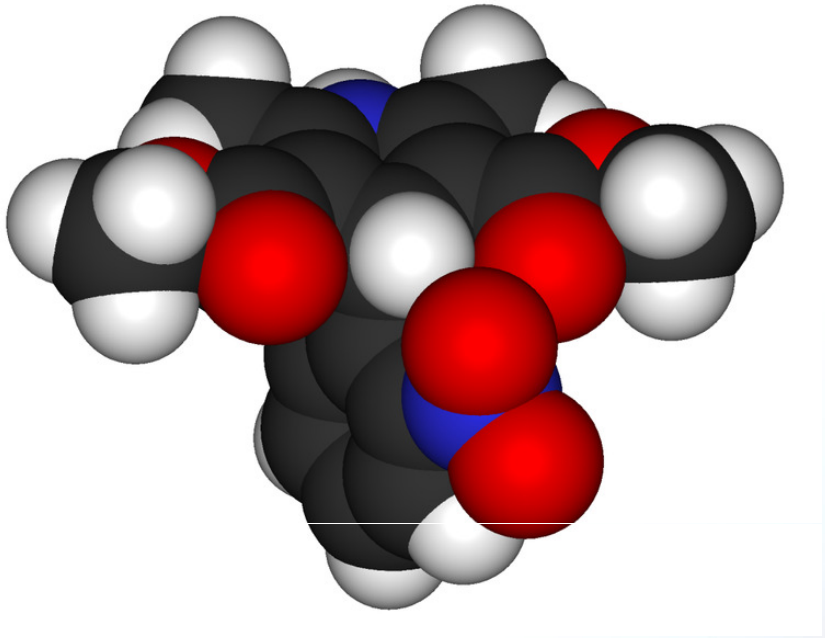
	Melting point (°C)	Phase Transition (°C)	Recystallisation (°C)
Caffeine	~ 235	~ 145	~ 235
Theophylline	~ 271	~ 220	~ 260
Theobromine	~ 346	-	~ 333

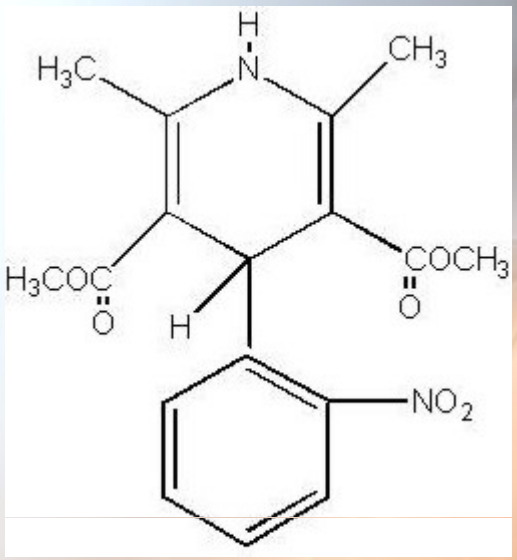






Nifedipine





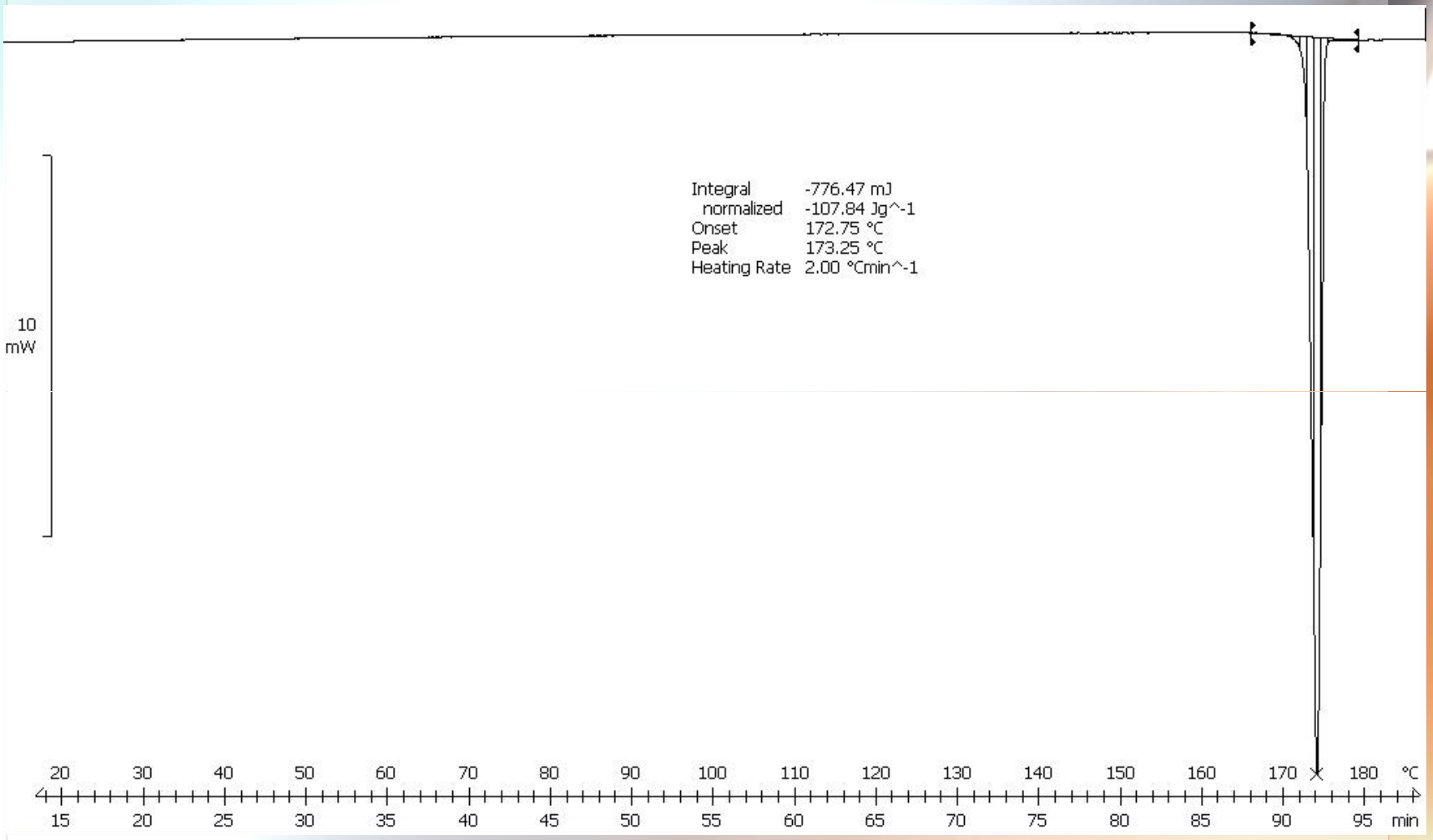
Exists in several polymorphic forms

May exist in amorphous form

Photo sensitive

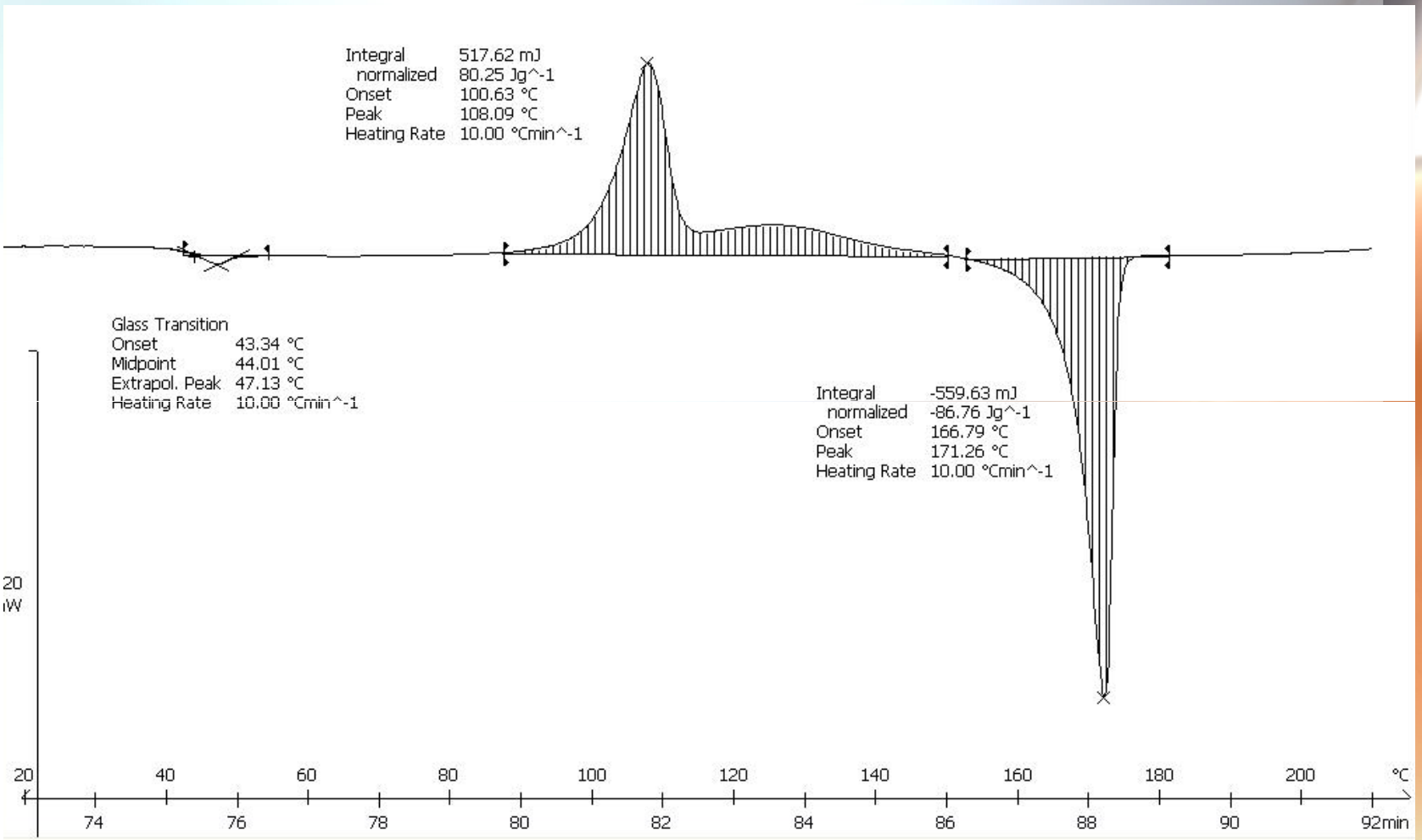
Nifedipine

As received – 1st heating



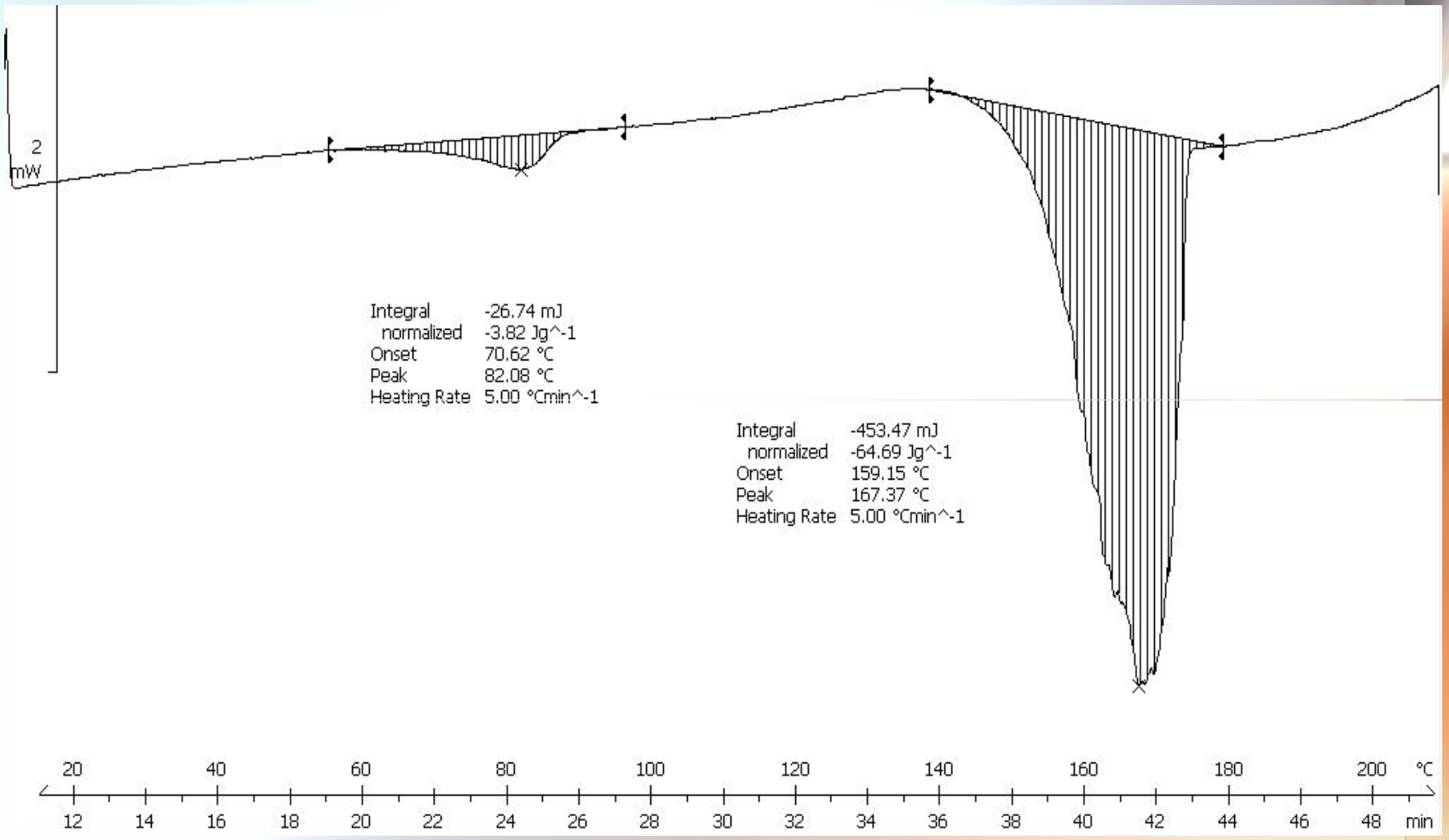
Nifedipine

As received – 2nd heating



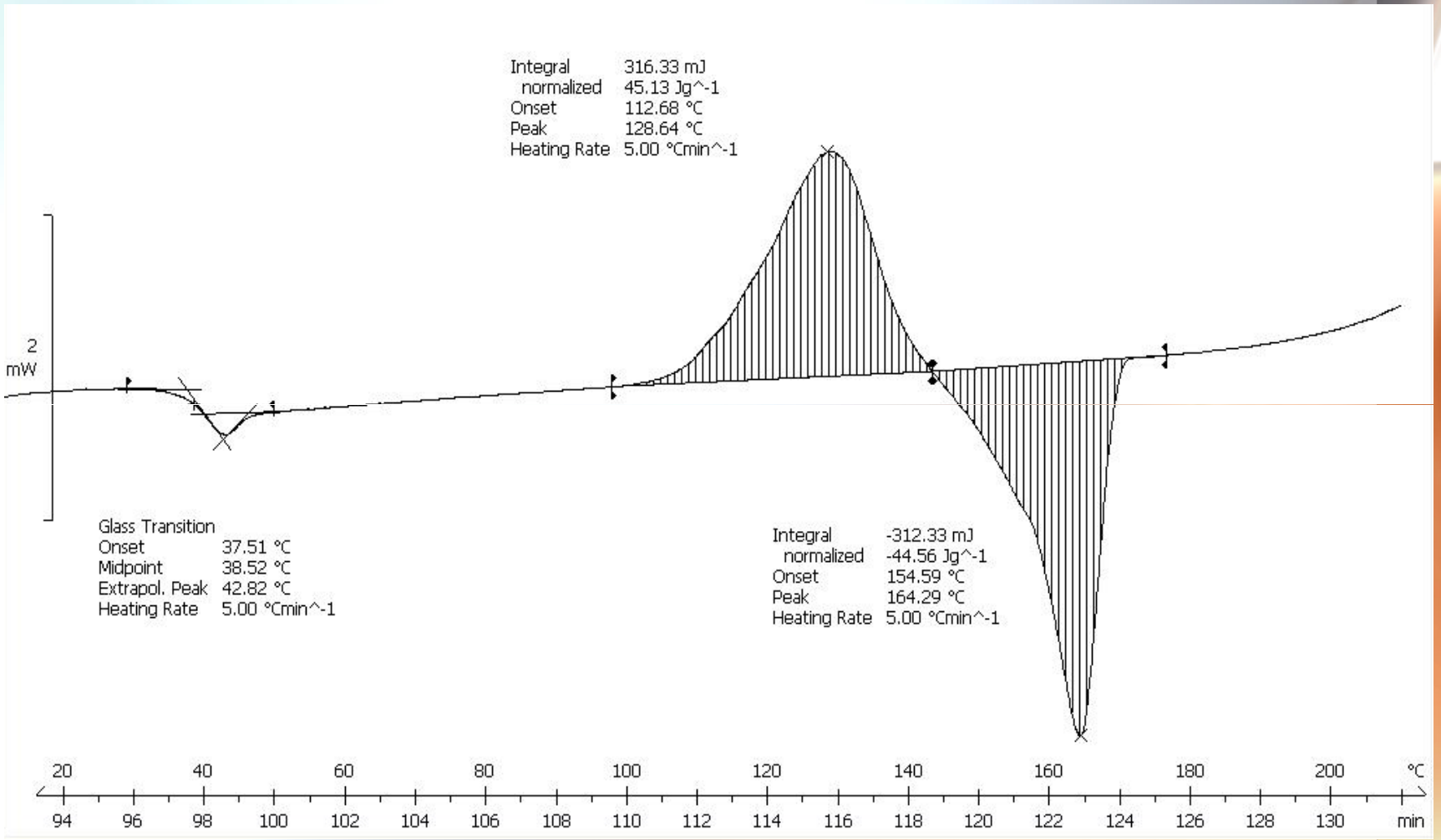
Nifedipine

UV irradiated – 1st heating



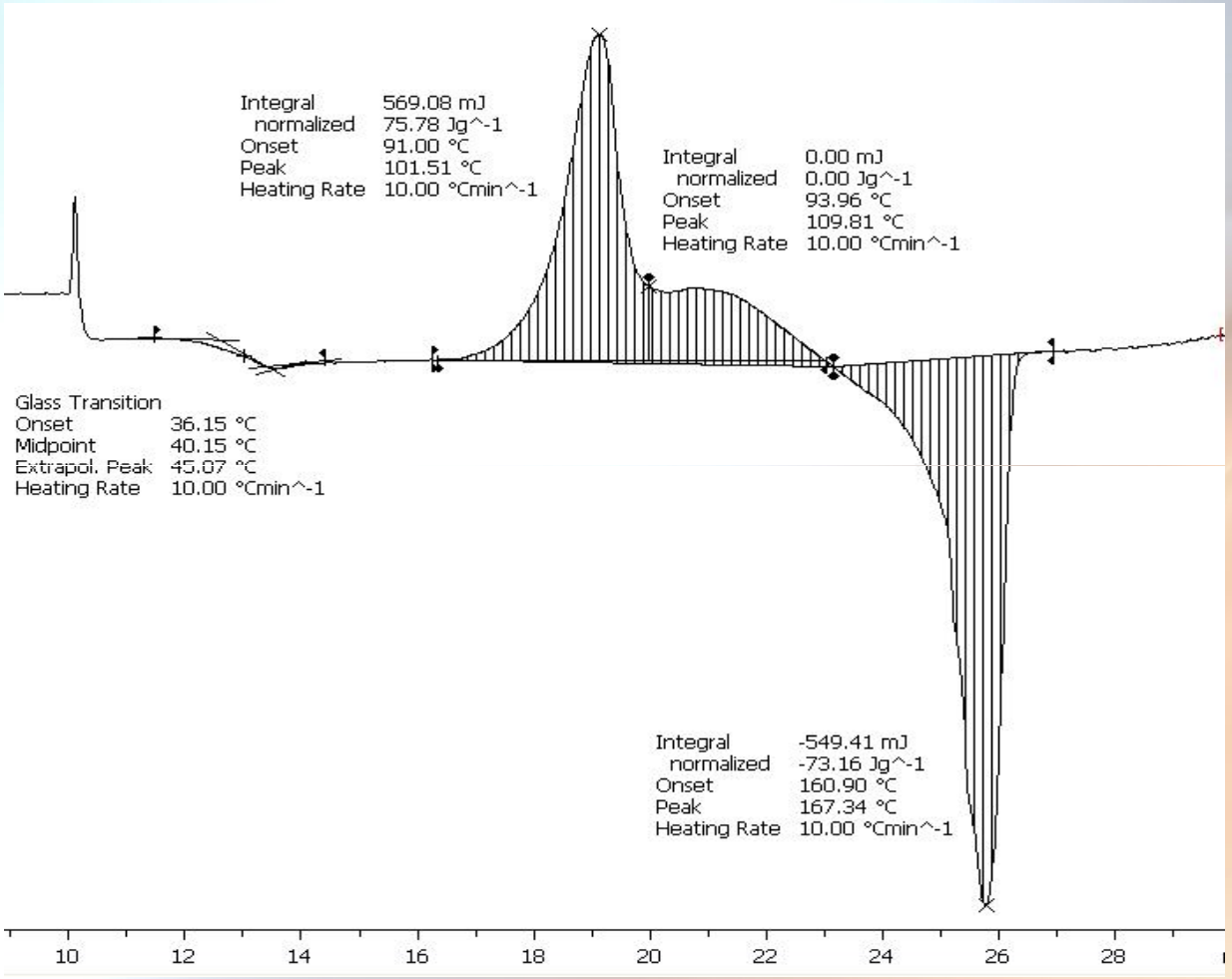
Nifedipine

UV irradiated – 2nd heating



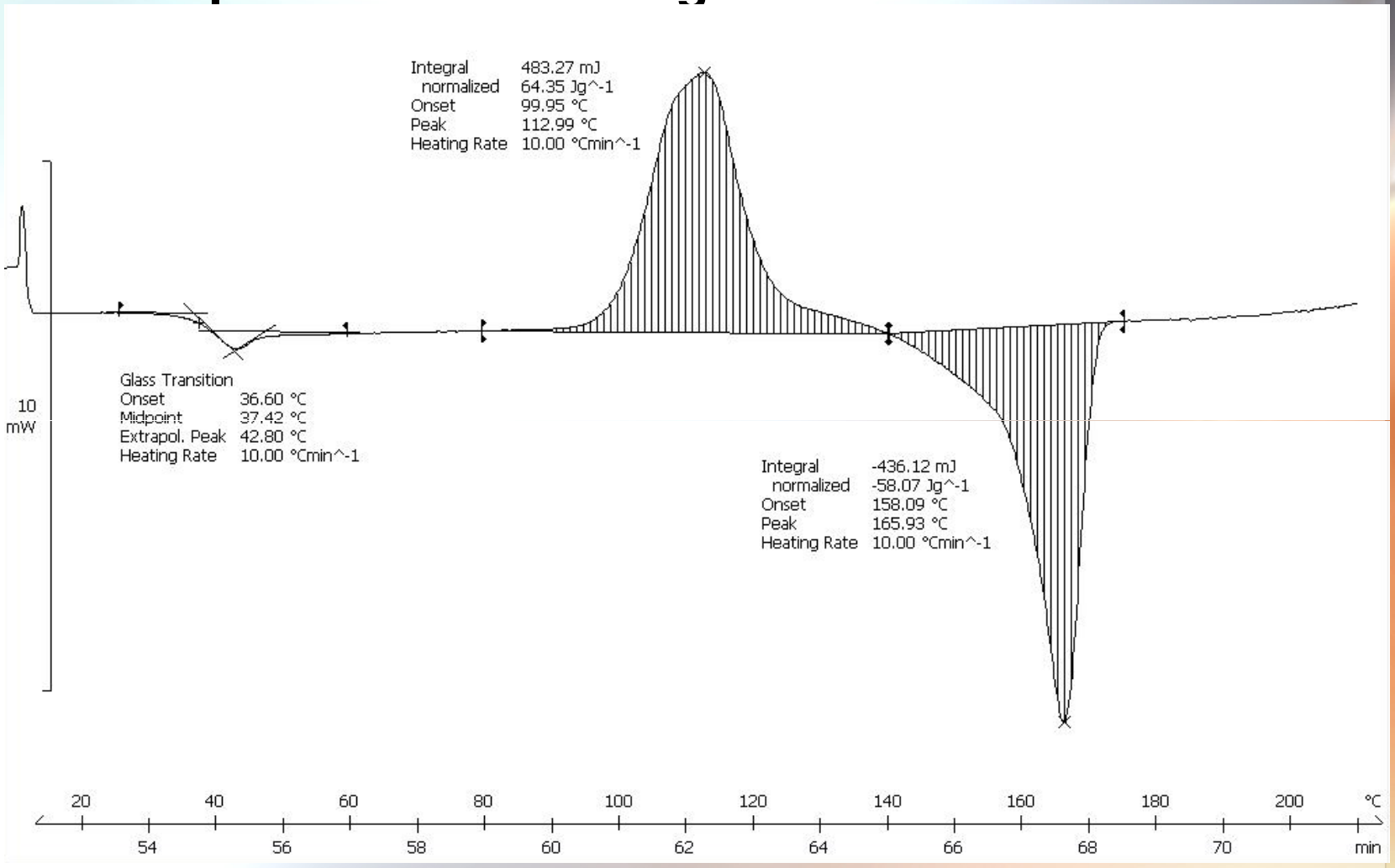
Nifedipine

Amorphous – 1st heating



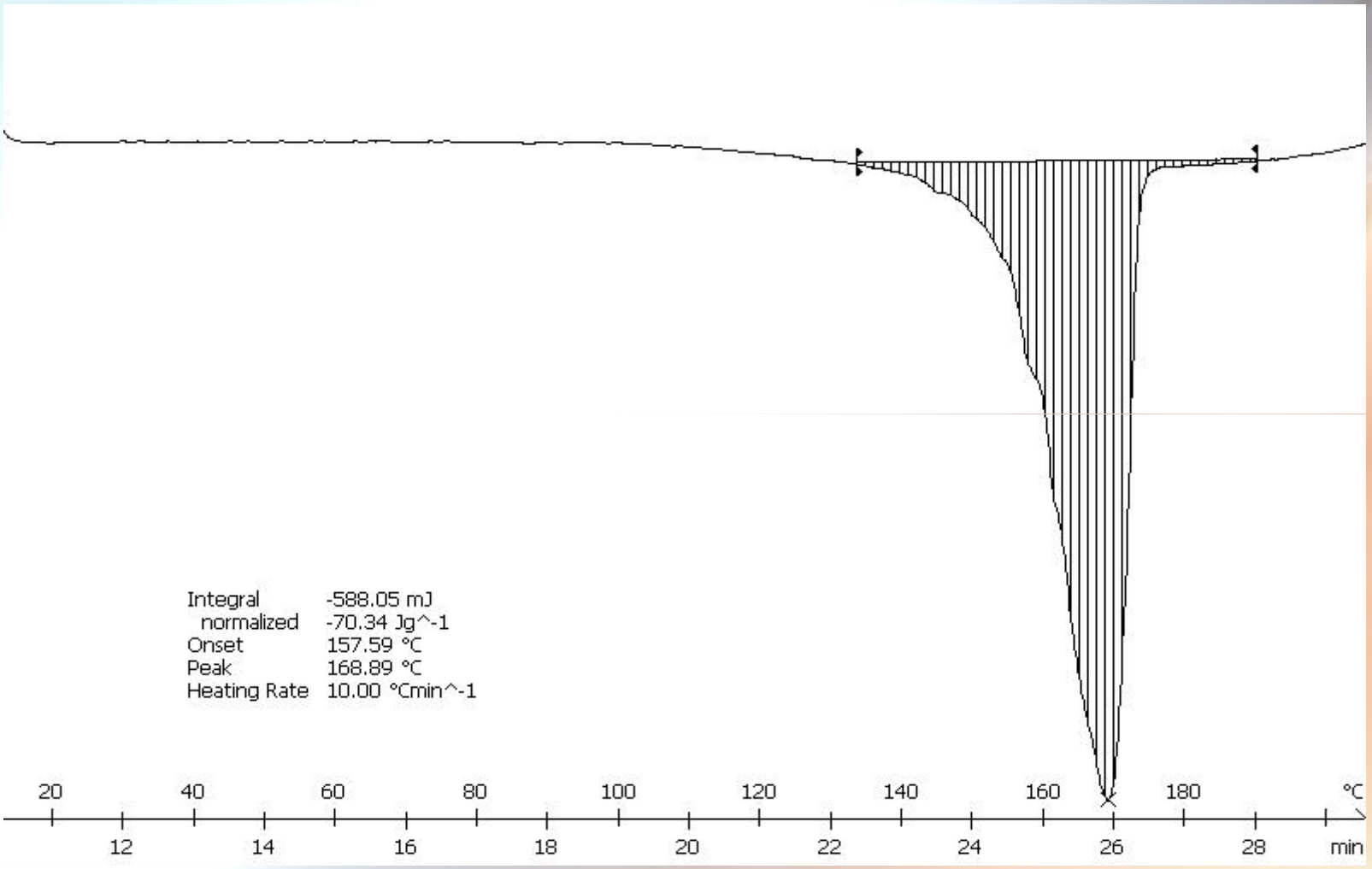
Nifedipine

Amorphous – 2nd heating



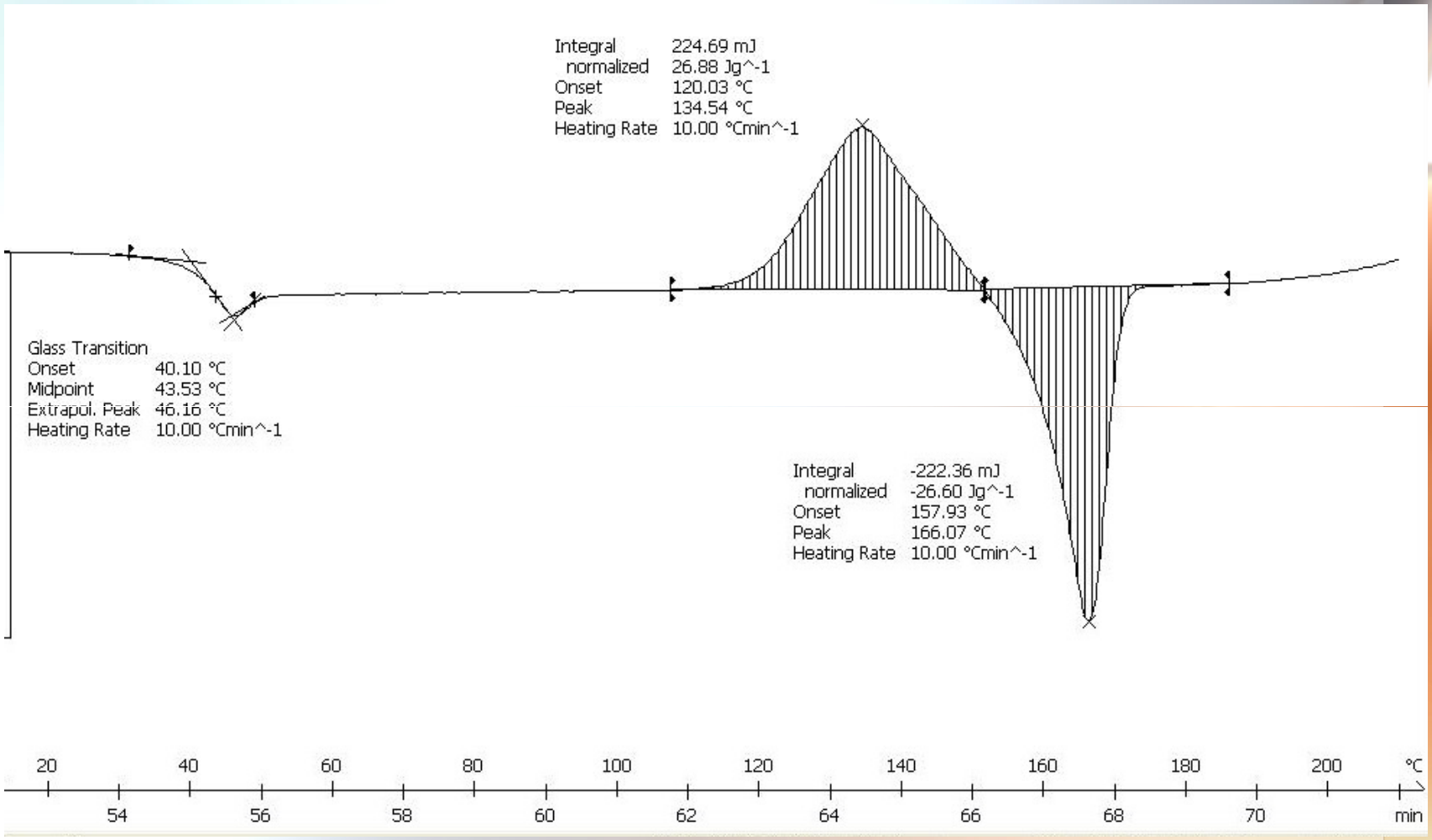
Nifedipine

Amorphous UV irradiated – 1st heating



Nifedipine

Amorphous UV irradiated – 2nd heating



TA Instruments, London 2009

Conclusion

Crystalline Nifedipine more prone to photo degradation compare to amorphous

Less stable crystalline form may be formed upon the exposure of crystalline Nifedipine to the UV light

	1st heating				2nd heating			
	Tg (°C)	Tc (°C)	PT (°C)	Tm (°C)	Tg (°C)	Tc (°C)	PT (°C)	Tm (°C)
Crystalline				~ 172	~ 45	~ 100	~ 135	~ 166
Crystalline-UV		Tm - 72		~ 159	~ 37		~ 135	~ 154
Amorphous	~ 36	~ 91	~ 102	~ 160	~ 37	~ 99		~ 158
Amorphous-UV				~157	~ 40	~ 120		~157

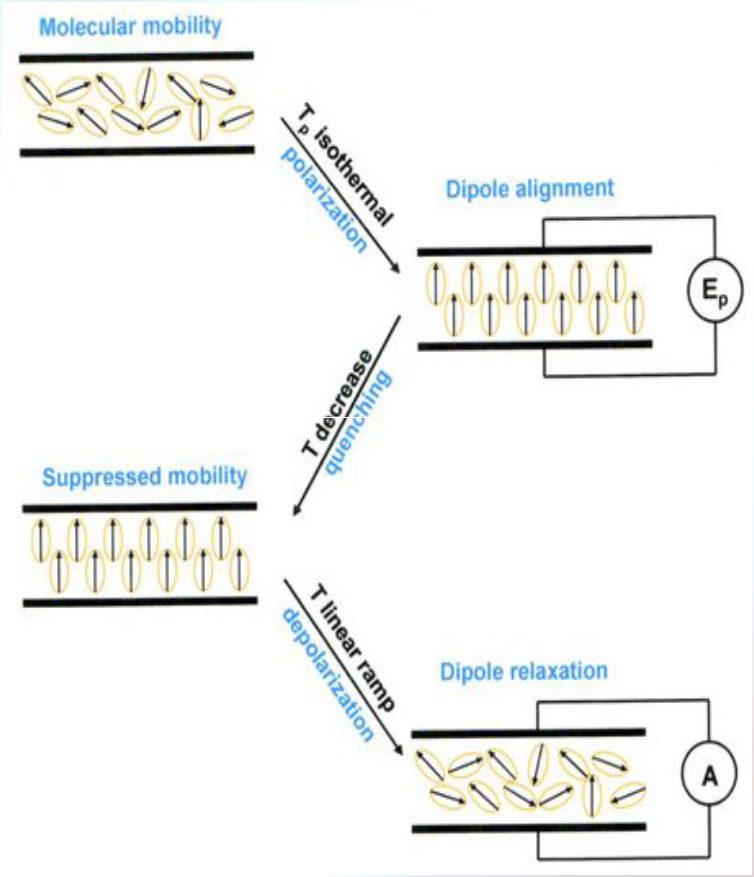
Thermally Stimulated Current Spectroscopy (TSC)

TSC is a general term applied to the measurement of current generated by temperature-activated relaxation of molecular dipoles in response to the application of a static electric field

- **1936, Frei and Grotzinger**

- **electrets, ionic crystals**
- **waxes, resins**
- **ceramics, plastic**

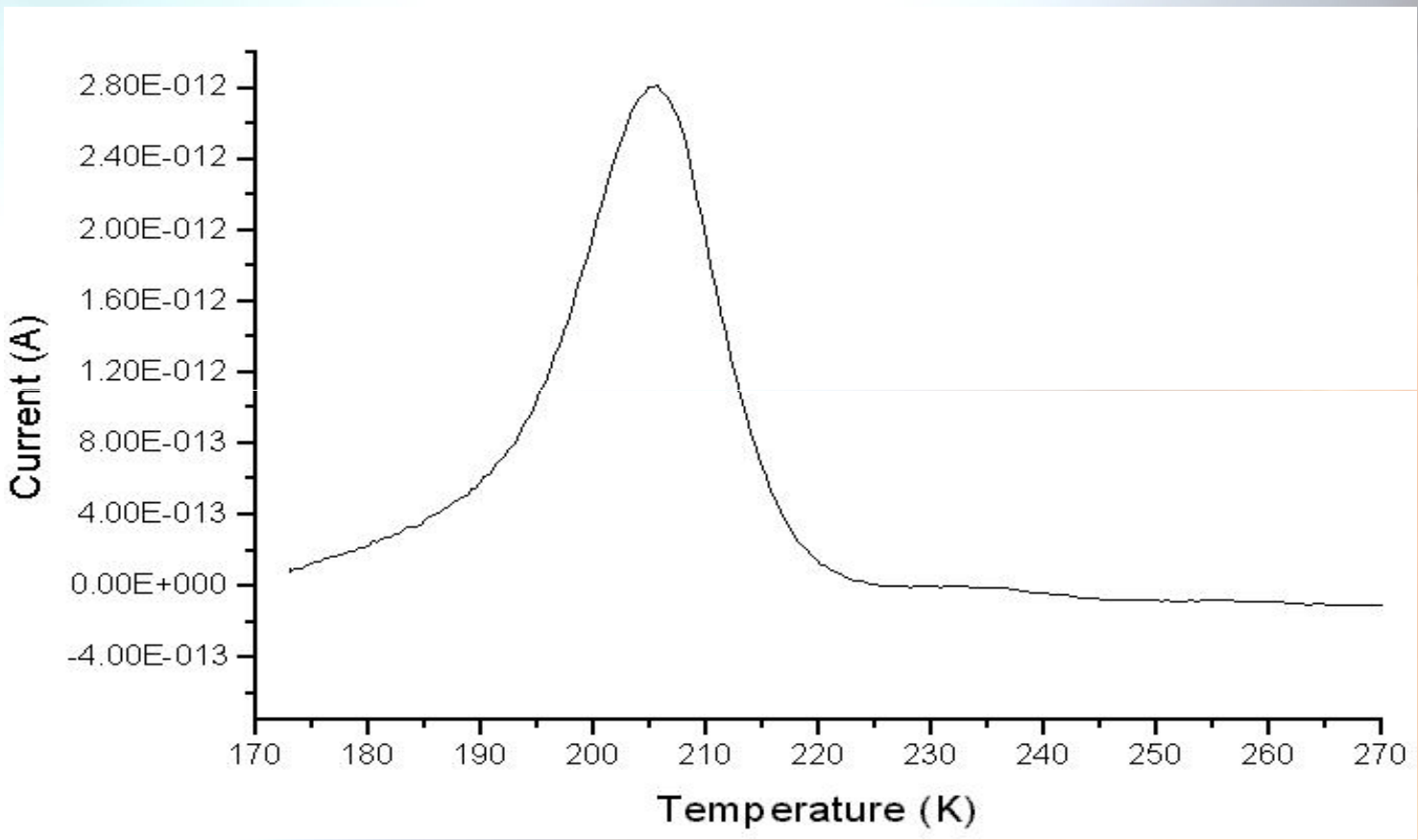
TSC origin



Experimental variables:

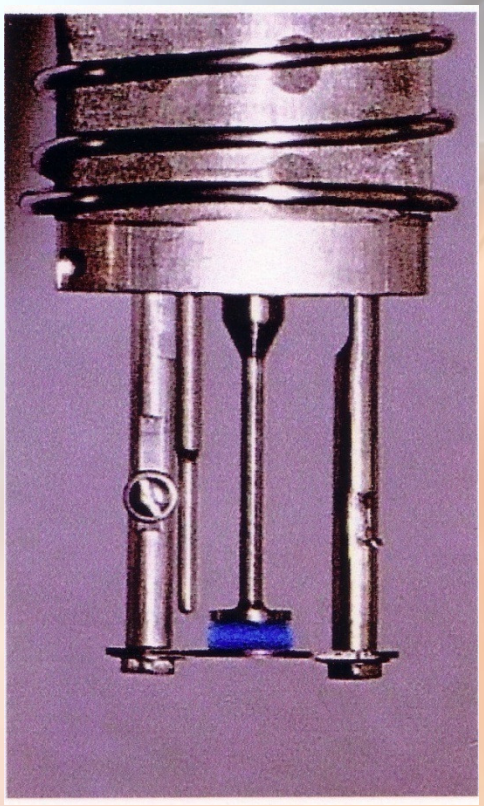
- Temperature of polarization
- Time of polarization
- Polarization field
- Cooling rate
- The lowest temperature
- Time at lowest temperature
- Heating rate
- Final temperature
- Temperature of stabilization

TSC spectrum



Main parts of the instrument

- Thermostated sample holder
- Vacuum system
- Heating and Cooling unit
- DC generator
- Current detector (10^{-4} to 10^{-16} A)
- Recording unit



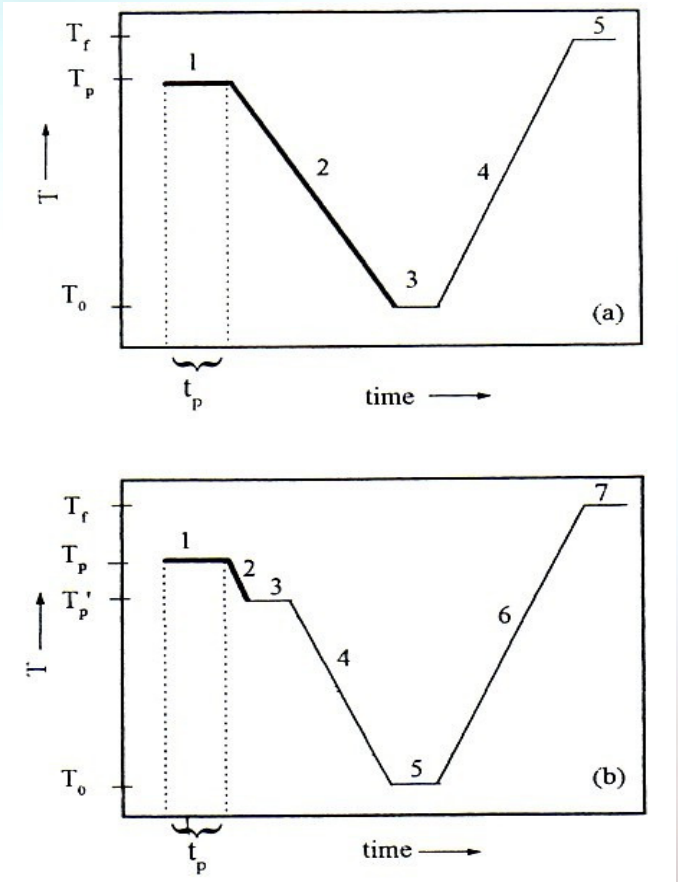
Amorphous Materials

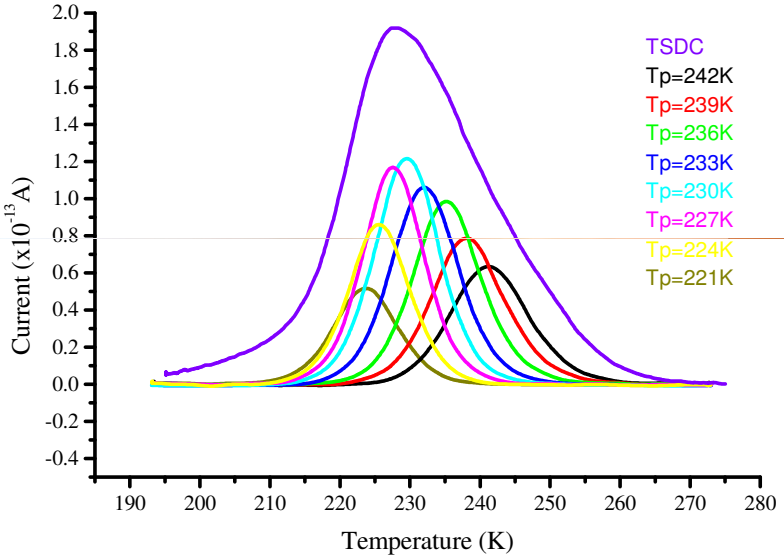
Glass transition is characterised by:

Heat capacity change (DSC)

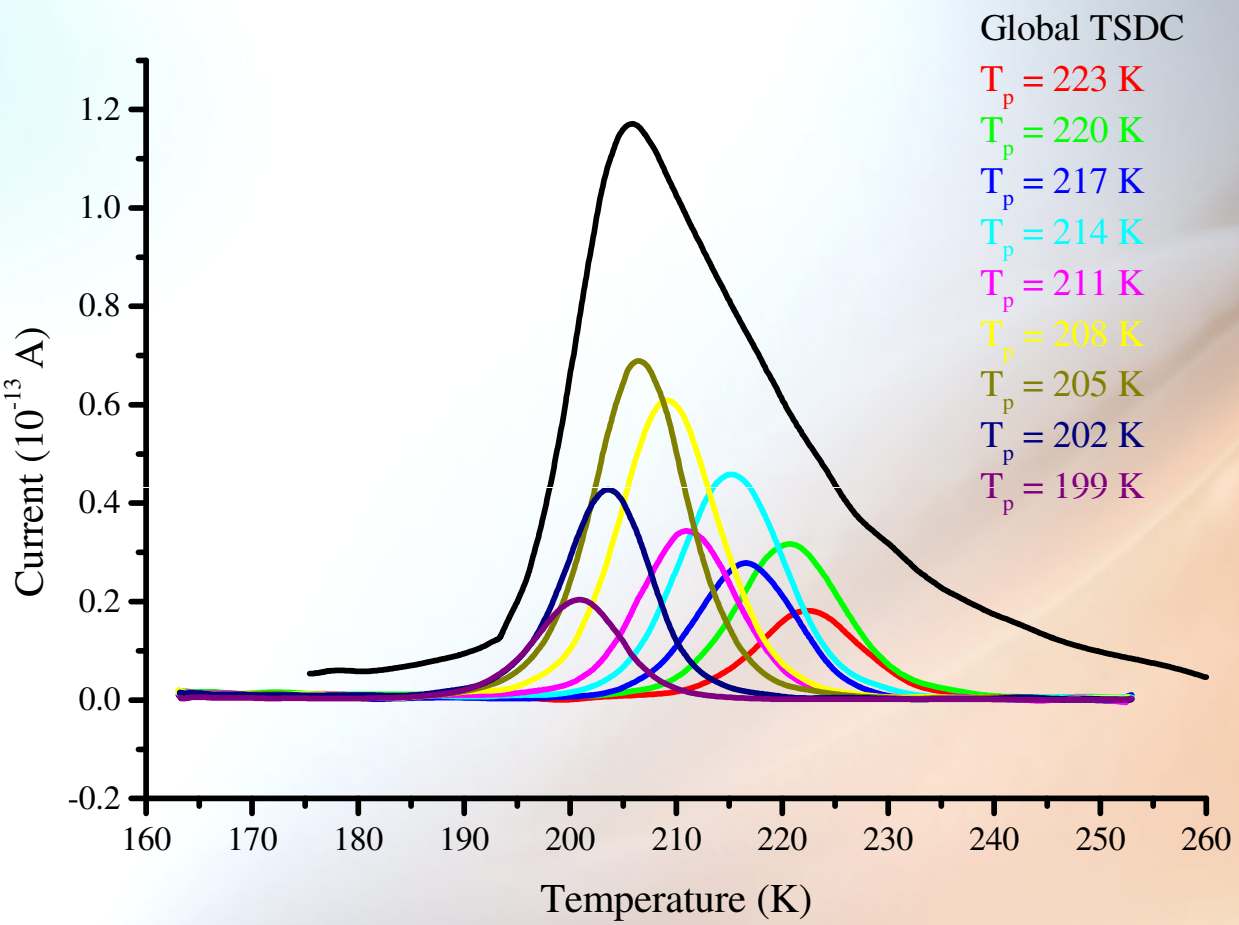
Visco-elastic changes (TSC)

TW-TSDC

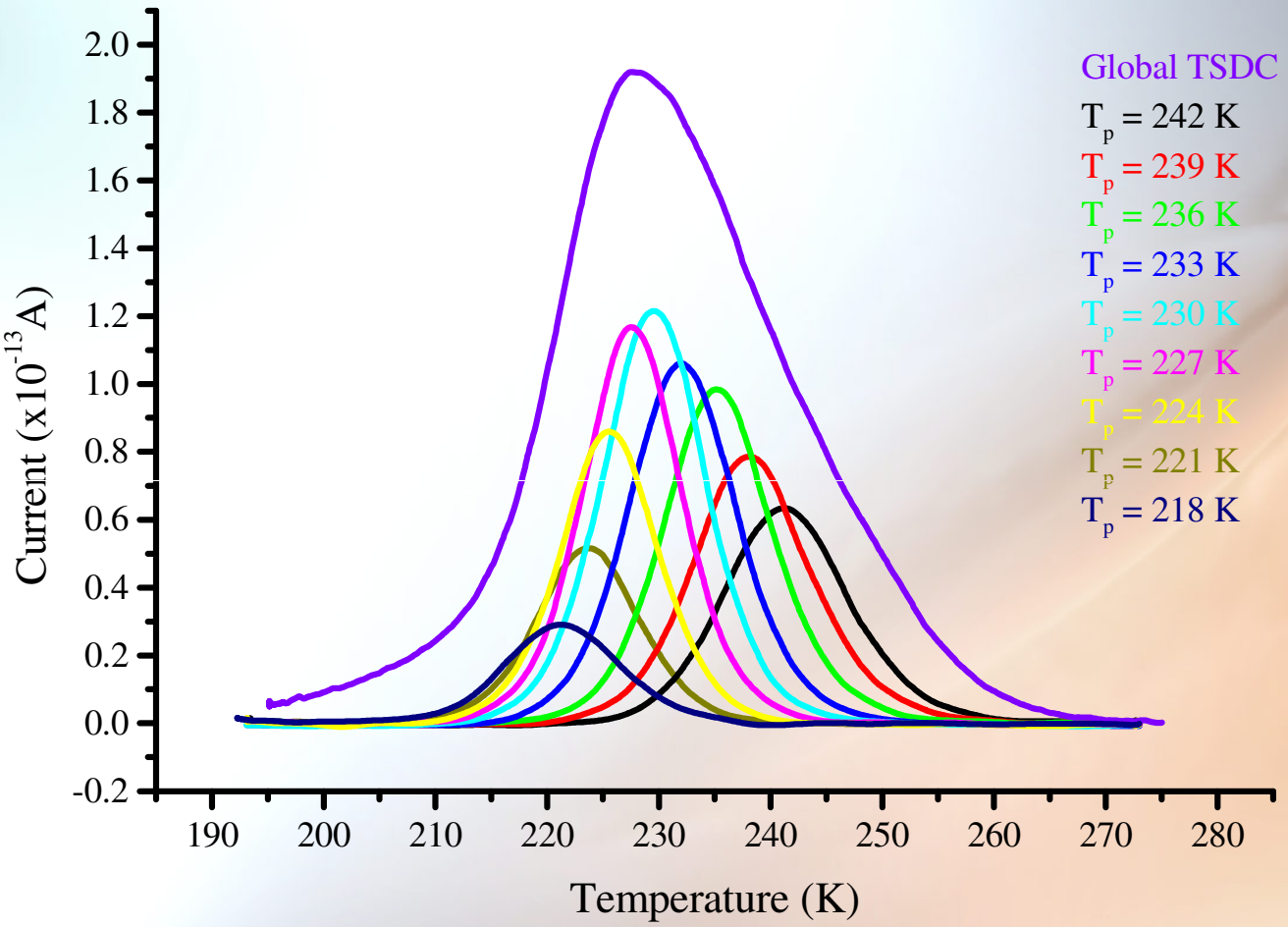

T_f
T_p
T_0
T
1
2
3
4
5
(a)
t_p
time
T_f
T_p
T_p'
T_0
T
1
2
3
4
5
6
7
(b)
t_p
time


Current (x10^{-13} A)
Temperature (K)
TSDC
Tp=242K
Tp=239K
Tp=236K
Tp=233K
Tp=230K
Tp=227K
Tp=224K
Tp=221K

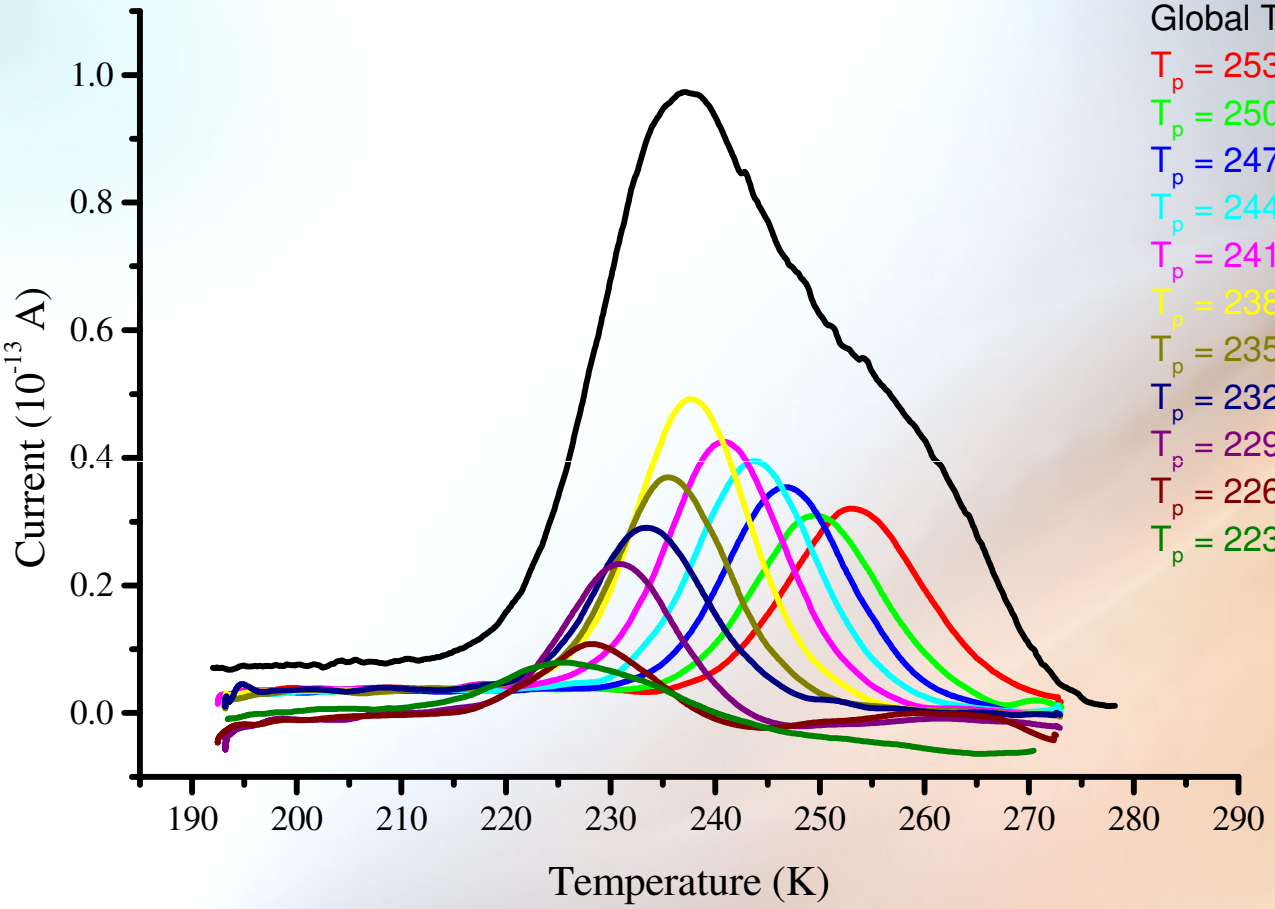
TSC PEG 4000 - Aldrich



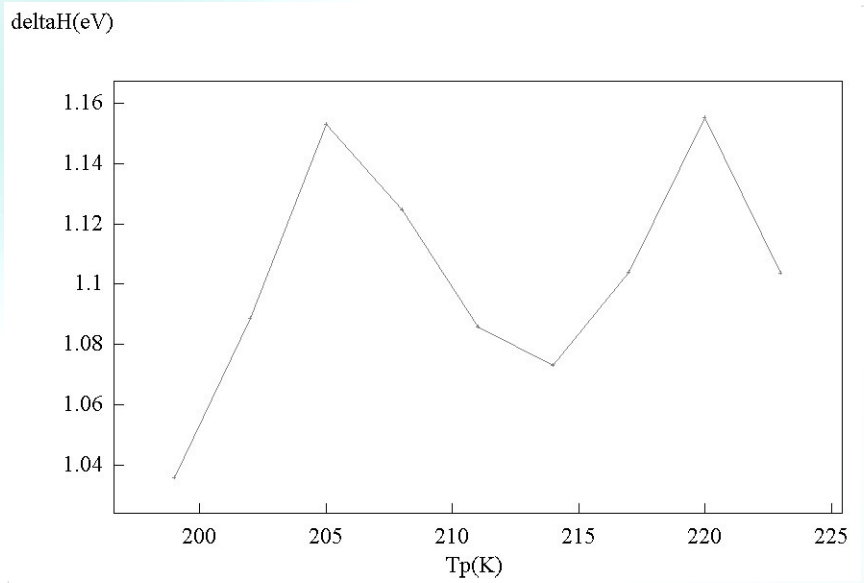
TSC PEG 6000 - BDH

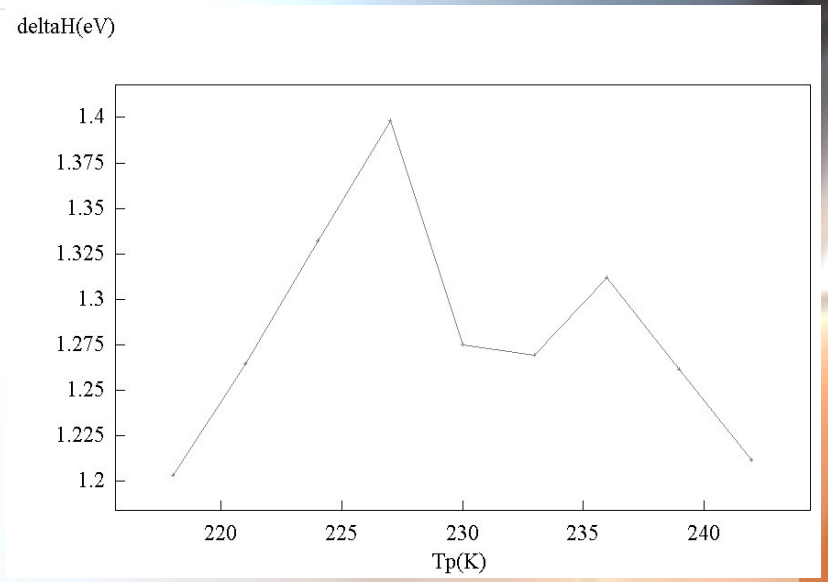


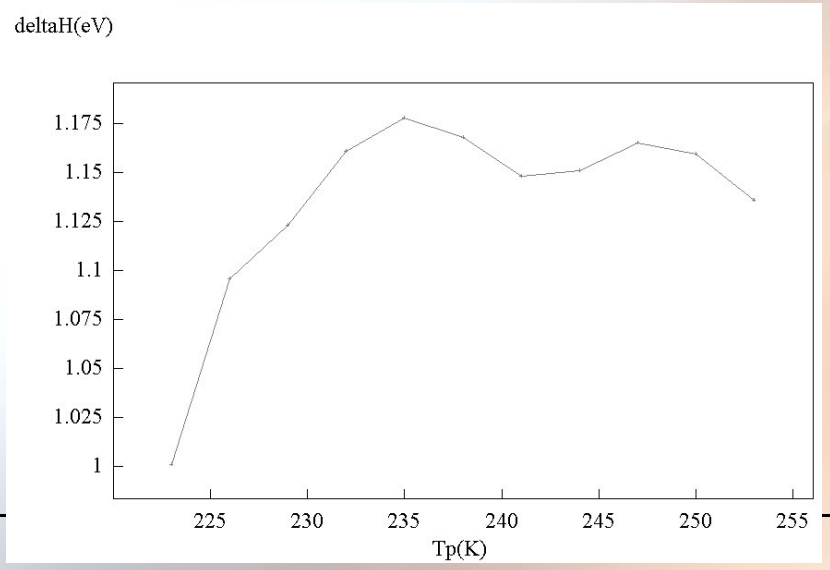
TSC PEG 20000 - Clariant



TSC PEG 4000/6000/20000



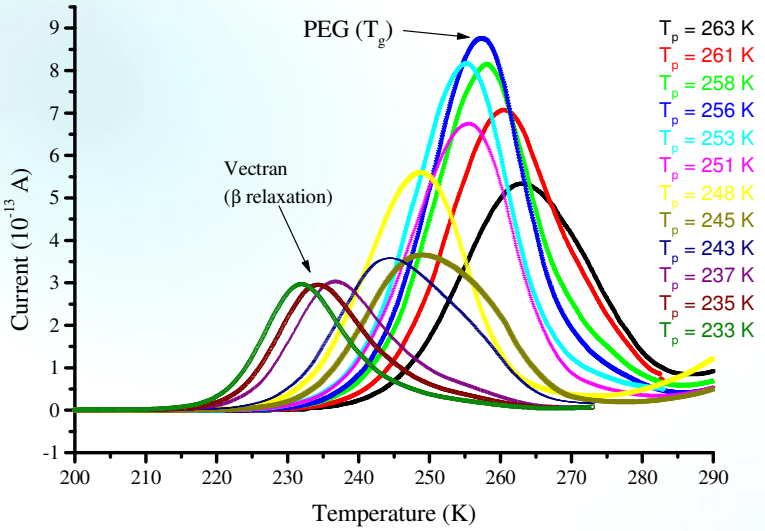


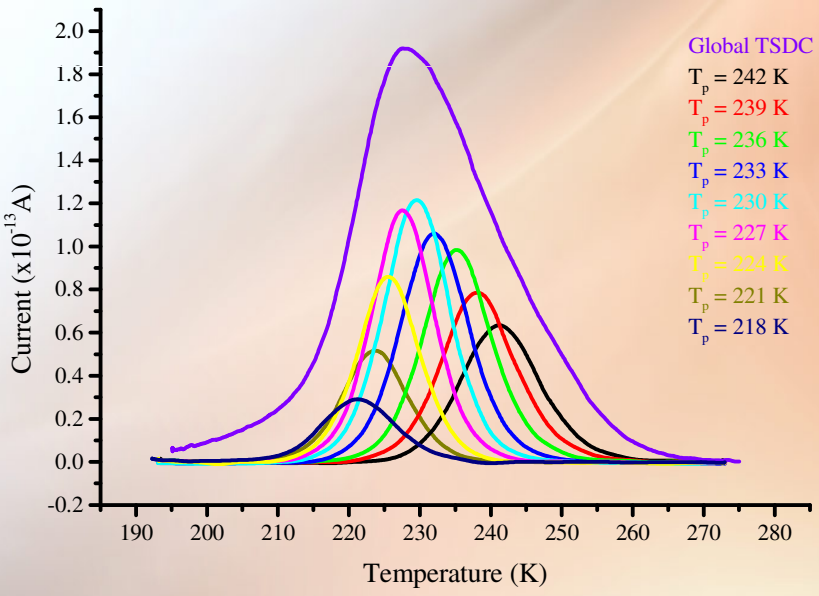


TSC PEG 4000/6000/20000

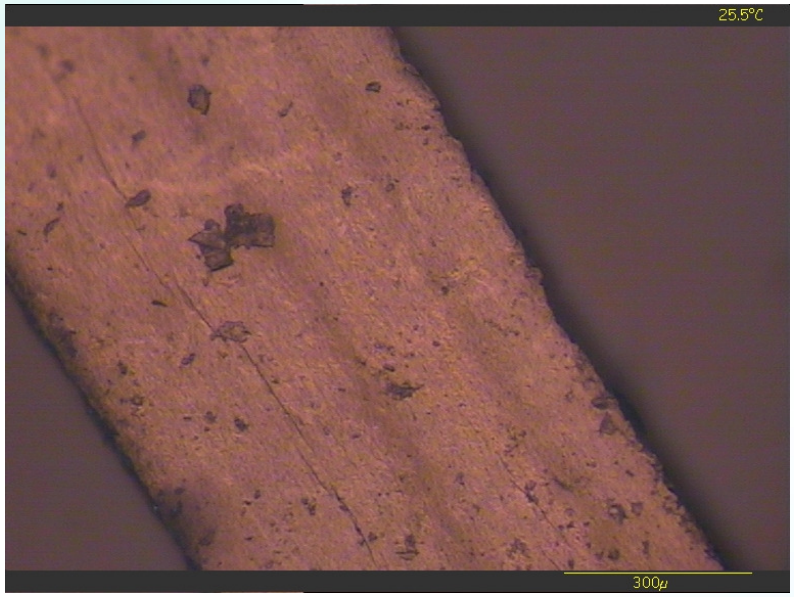
	PEG 4,000	PEG 6,000	PEG 20,000
Melting T (K)	326 - 331	328 - 333	333- 340
TW T_{g1} (K)	205	227	235
TW T_{g2} (K)	220	236	247
TSDC T_g (K)	205.8	223.2	237.1
ΔH TW T_{g1} ($kJmol^{-1}$)	111.25	134.91	112.43
ΔH TW T_{g2} ($kJmol^{-1}$)	111.46	116.96	113.64
Fragility index T_{g1}	28.3	31.0	25.0
Fragility index T_{g2}	26.5	25.9	24.0

TSC PEG 6000 – Lancaster/BDH



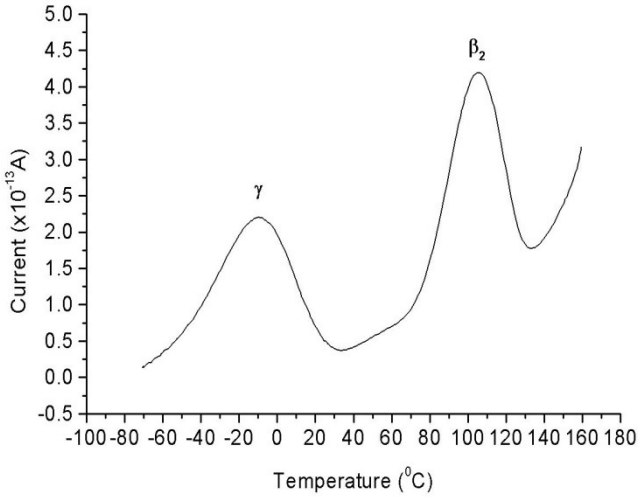


HS Microscopy PEG 6000 – Lancaster/BDH

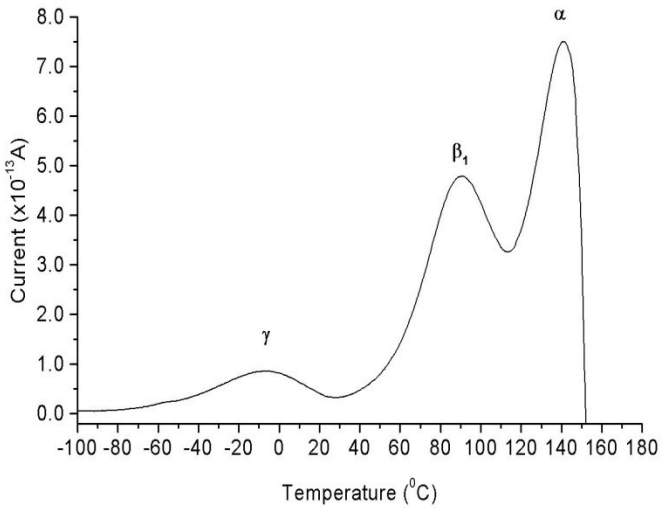


Caffeine - TSDC Results

Form I

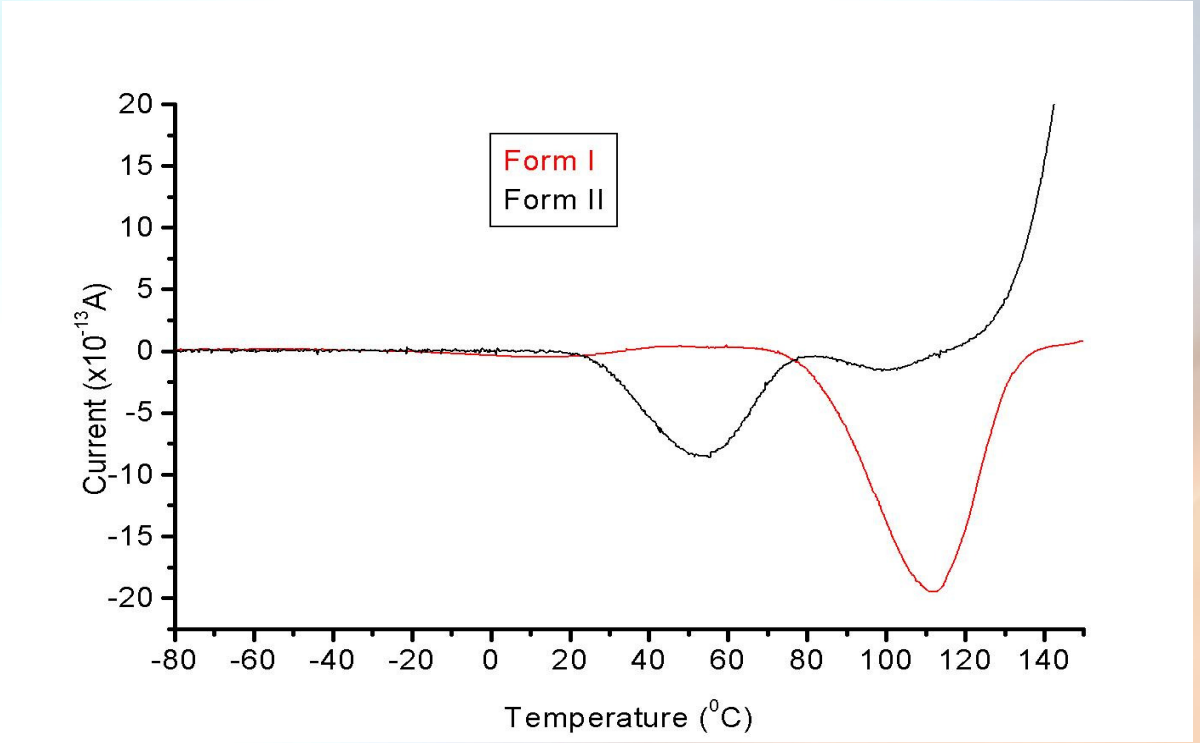


Form II



α-process	139ºC	Form II only - *polymorphic transition*
γ-process	-8ºC	Forms I and II - *orientation of side group*
β_1-process	91ºC	Form II
β_2-process	107ºC	Form I - *orientation/mobility of sub-unit*

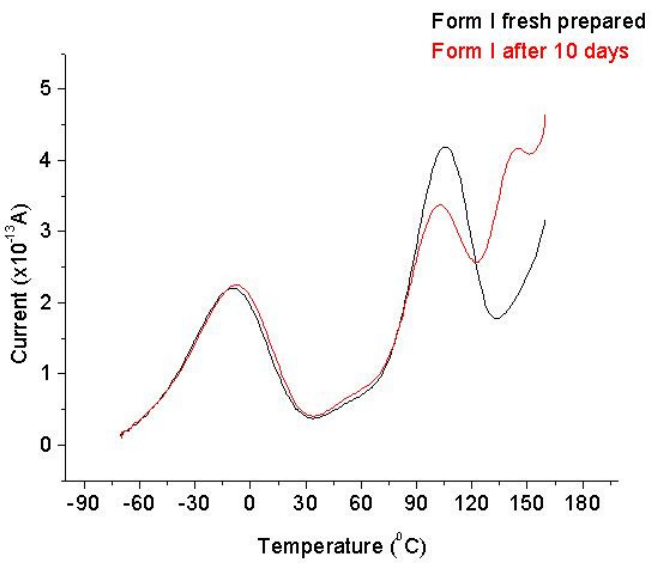
Caffeine - SDC Results



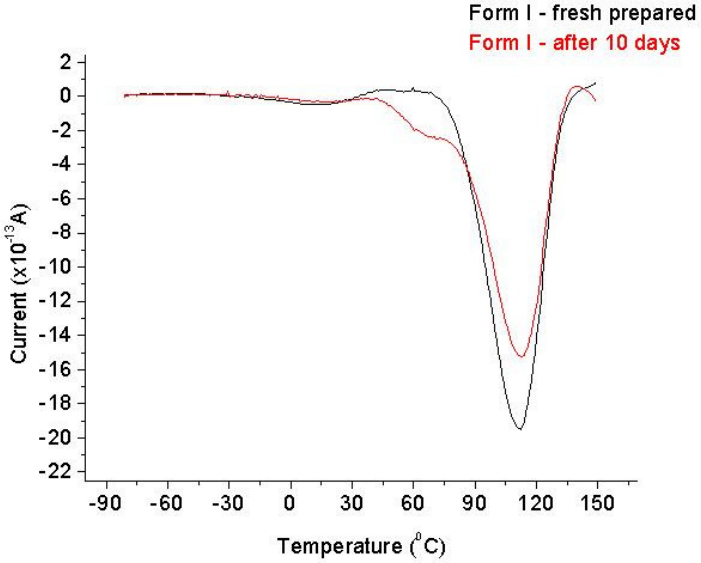
Form I - negative peak at -8°C and 112°C
Form II - negative peak at 52°C

Kinetic Parameters - TSC Method

TSDC

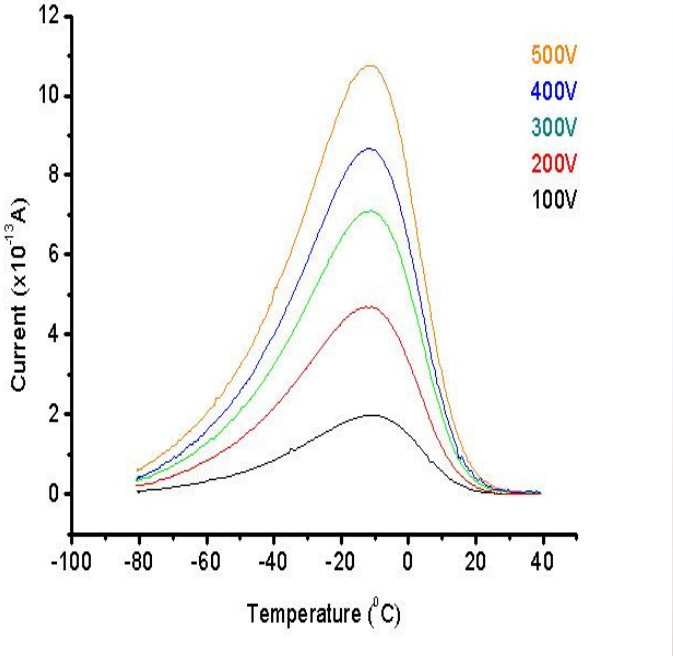


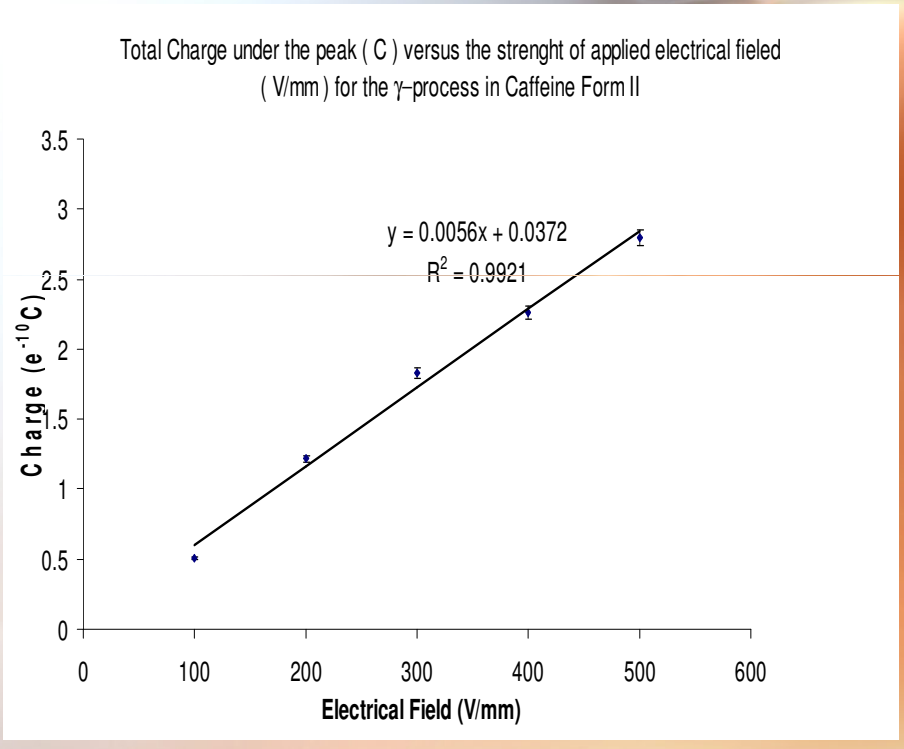
SDC



Validation Characteristics TSC Method

Signal-to-Noise





Conclusions

TSC technique:

- **Appears as a powerful technique for the detection of the polymorphs and polymorphic transitions, weak glass transitions and second order transitions in materials.**

- **Ability to detect movements of side groups makes this thermal technique potentially applicable in the field of structural analysis, and could even expand its thermodynamic use.**

Conclusions

There have been well established correlations between phases and phase transitions such as:

Stability of amorphous phase (Tg – 50°C)

Stability of pseudo-polymorphs (solvent-drug inter.)

Stability of polymorphs (difference in energy)

Poorly understood relationships:

Width of the phase transition process

Importance of second order transitions (β and γ)

Acknowledgments

MSc students

Rahul Patil

Amit Narayankar

Abdul Syed

IESTE student

Ivana Lazarevic

Erasmus student

Inmaculada Andres Tome