Simultaneous DSC-synchronous XRD for understanding solid-state phase transformations

Professor Simon Gaisford

s.gaisford@ucl.ac.uk

Scope

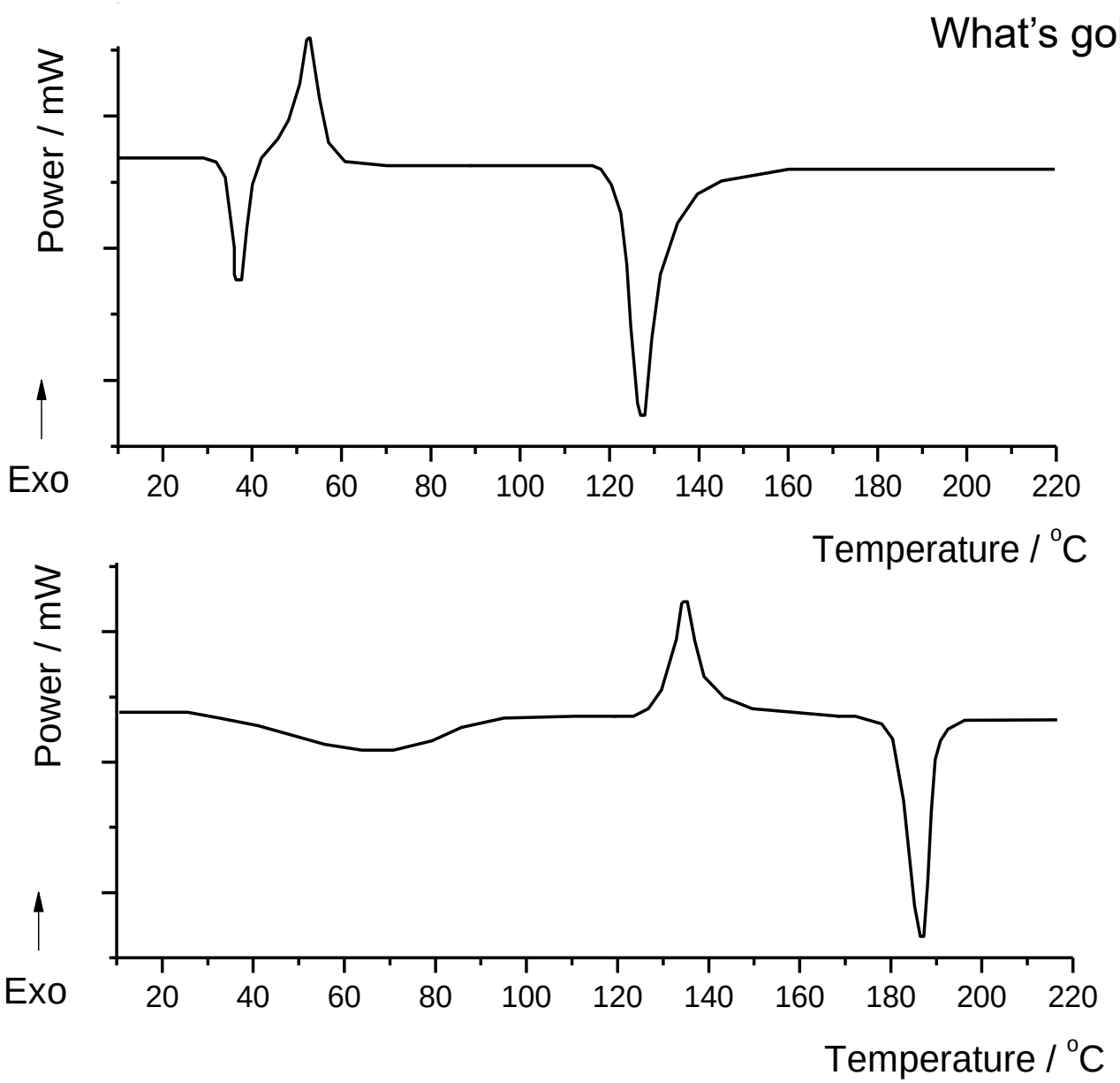
- Background to physical forms, especially in relation to pharmaceuticals
- Physical form identification by DSC
- Methods that might aid interpretation
- Hyphenated DSC techniques
- DSC-XRD
- Summary

DSC for physical form characterisation

- Methodology simple
- Put sample in a pan, heat it then look for peaks!
- Tricky part is interpretation of the data

- No molecular information and different processes can give similar peaks
- How to interpret?
  - LOOK at whether events are exo- or endothermic

What's going on here?

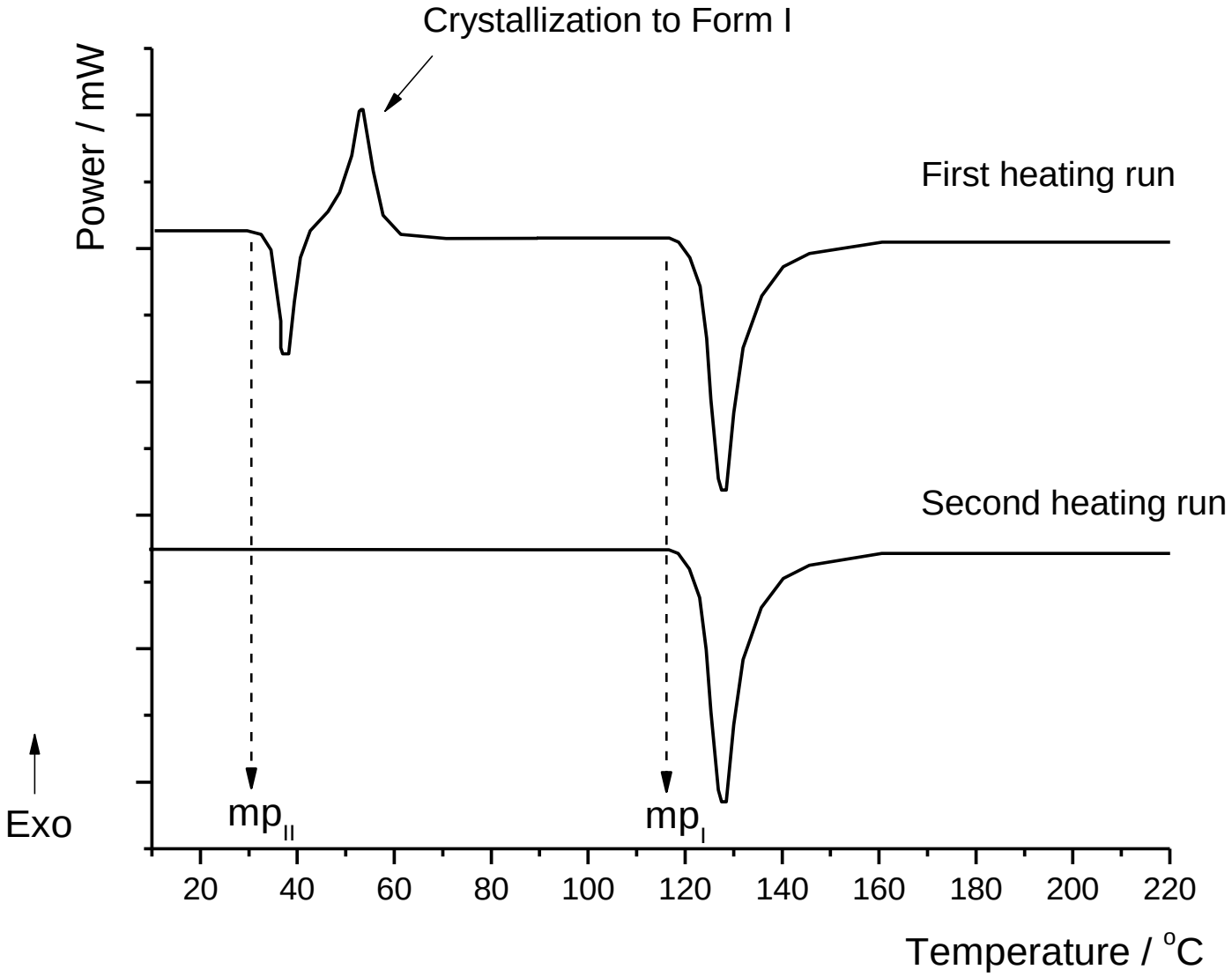


DSC for physical form characterisation

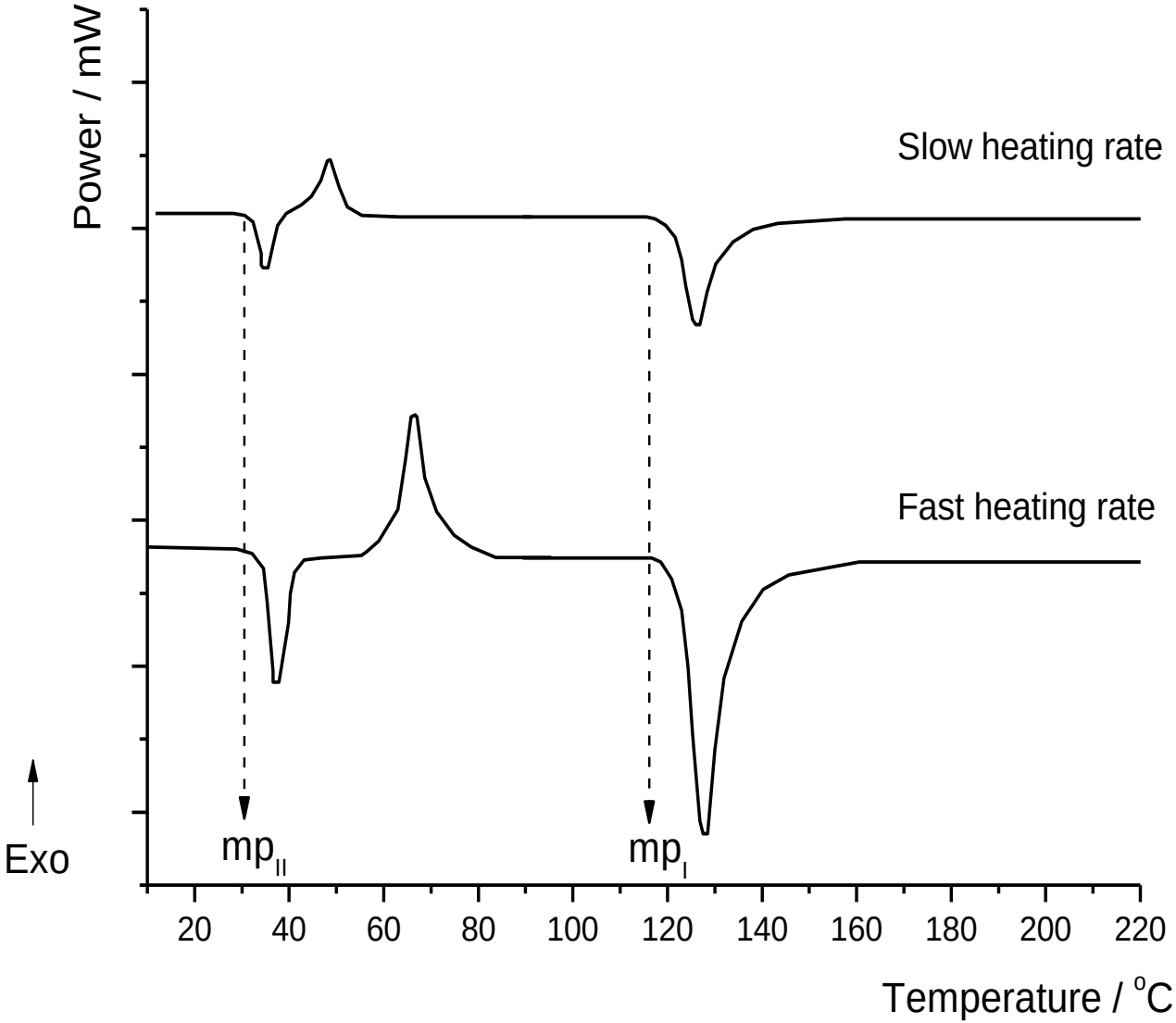
- Methodology simple
- Put sample in a pan, heat it then look for peaks!
- Tricky part is interpretation of the data

- No molecular information and different processes can give similar peaks
- How to interpret?
  - LOOK at whether events are exo- or endothermic
  - Much can be gained from altering DSC method, *especially* by reheating sample and by changing heating rate

Reheating sample



A metastable polymorph at two heating rates



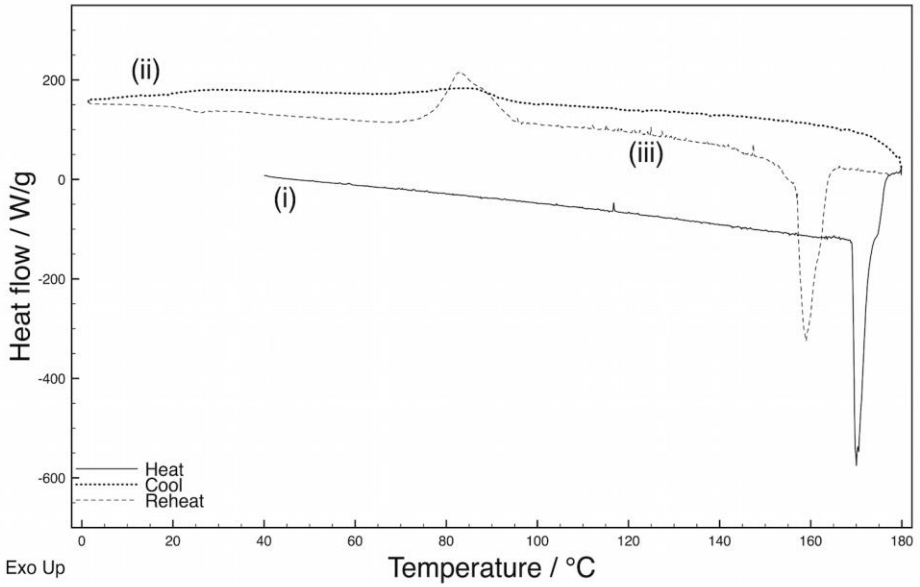
Additional analyses

- Can help interpretation with additional analyses
  - TGA
  - Hot-stage microscopy
  - Evolved gas analysis
  - Raman

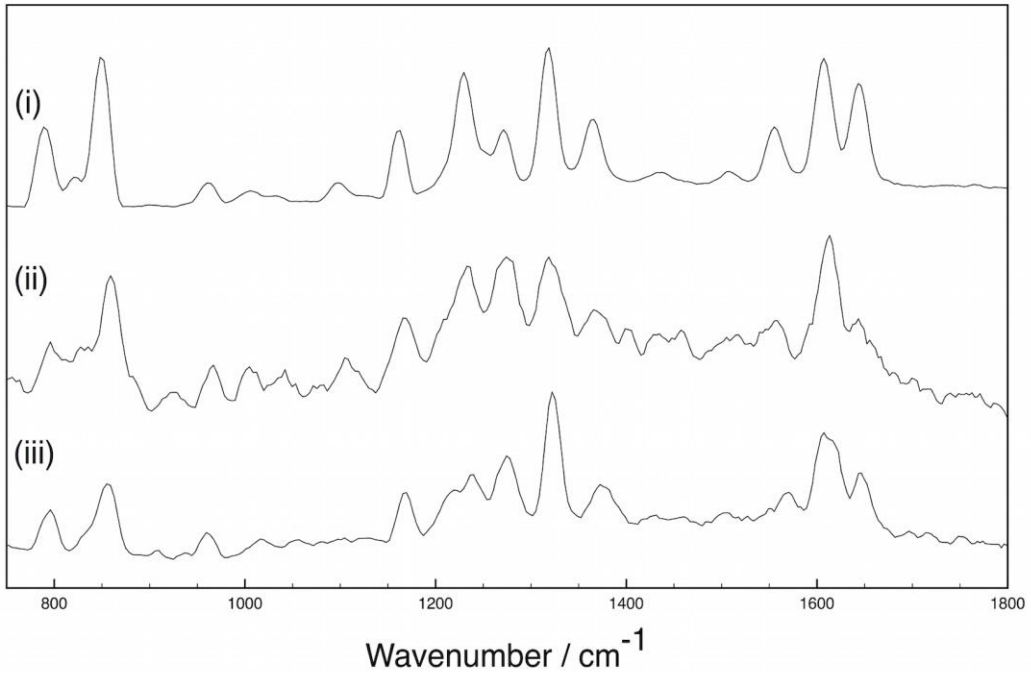
Telford et al (2016)
10.1039/c6cc05006a

Paracetamol

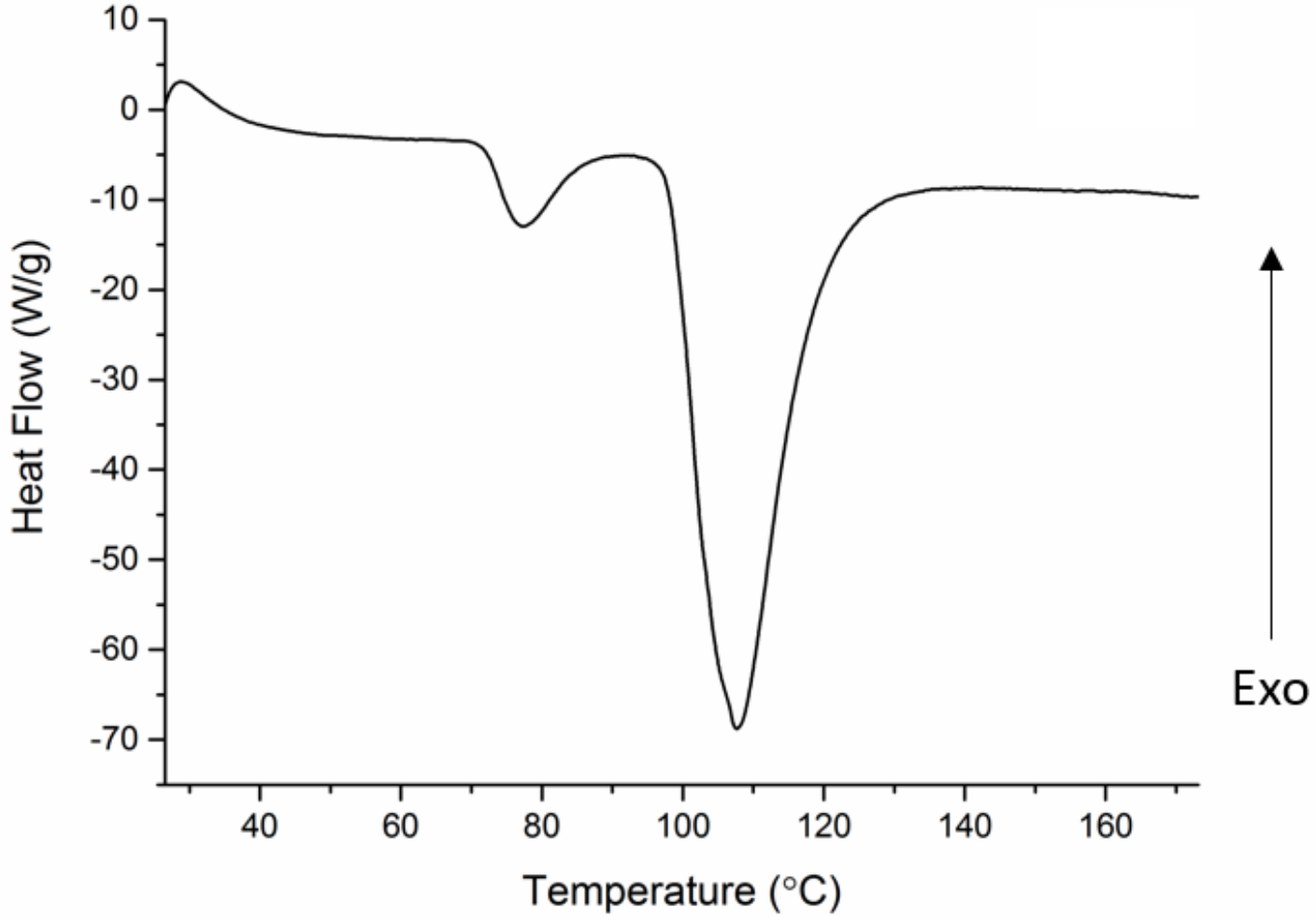
(a)



(b)

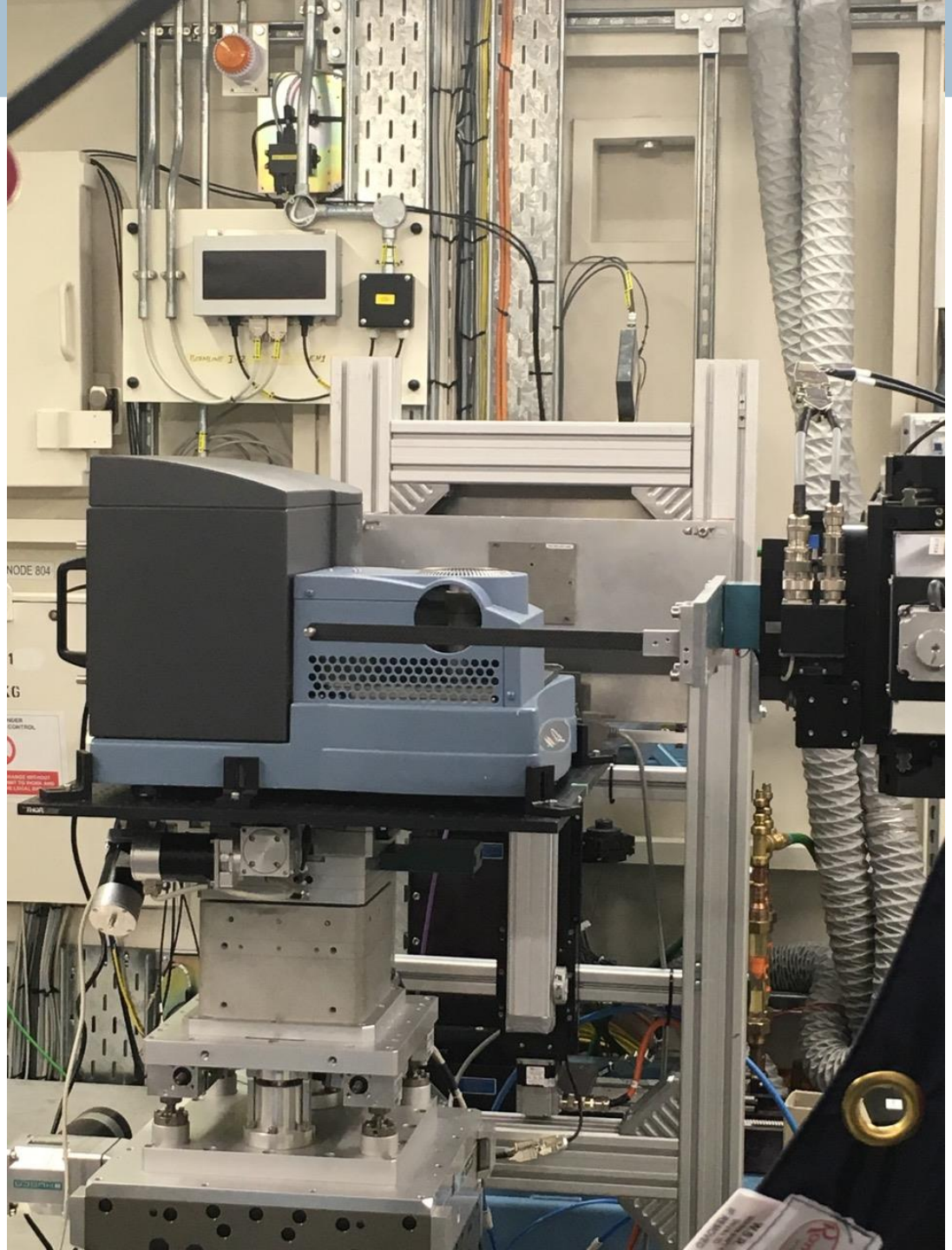


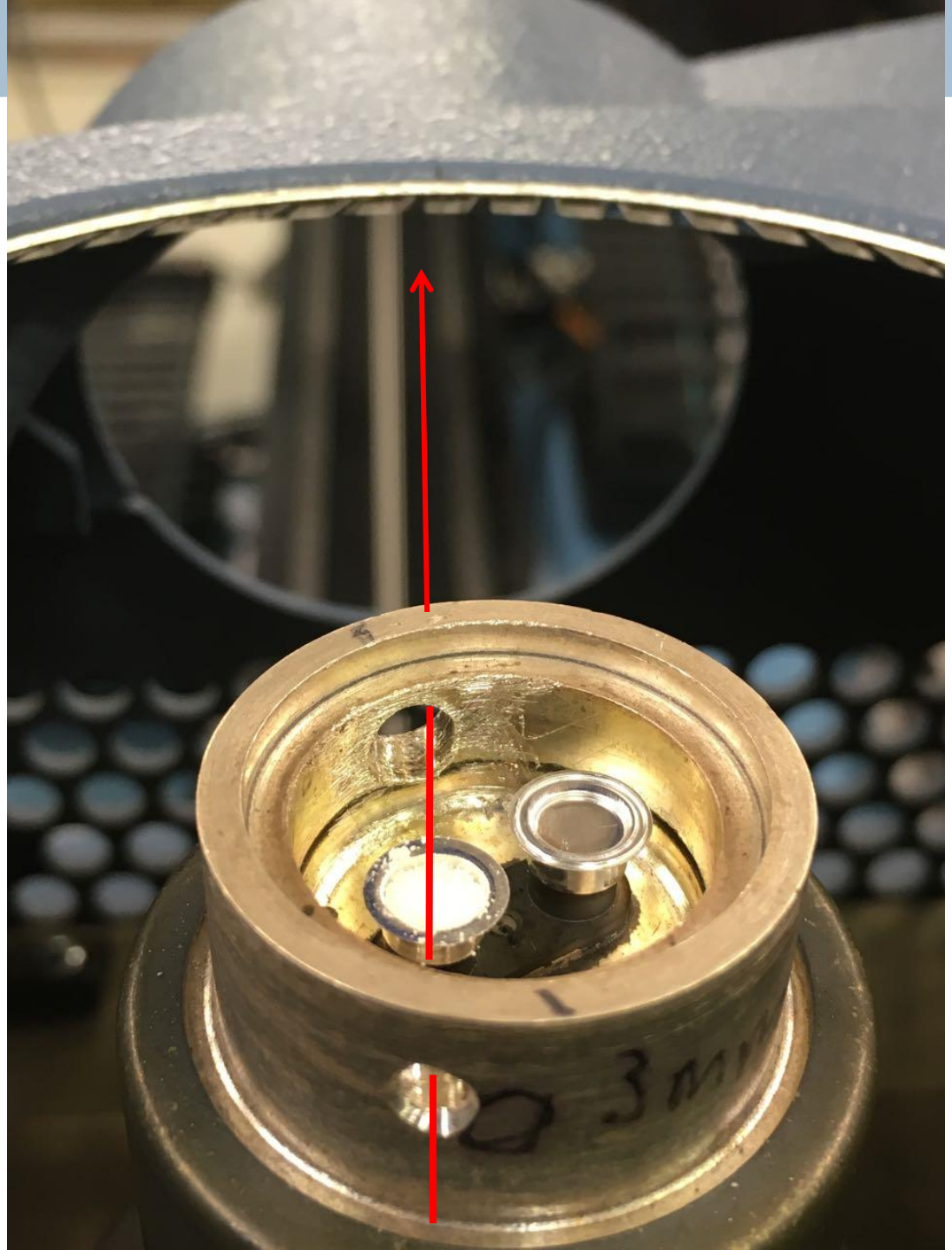
- Data for glutaric acid
- The question is, to what events should the peaks be assigned?



DSC for physical form characterisation

- ‘Gold standard’ analysis is single-crystal or powder XRD
- Takes a long time to record diffraction pattern
- We wanted to confirm physical form with PXRD in real-time, in the DSC pan
- Best done with a synchronous X-ray source


NODE 804



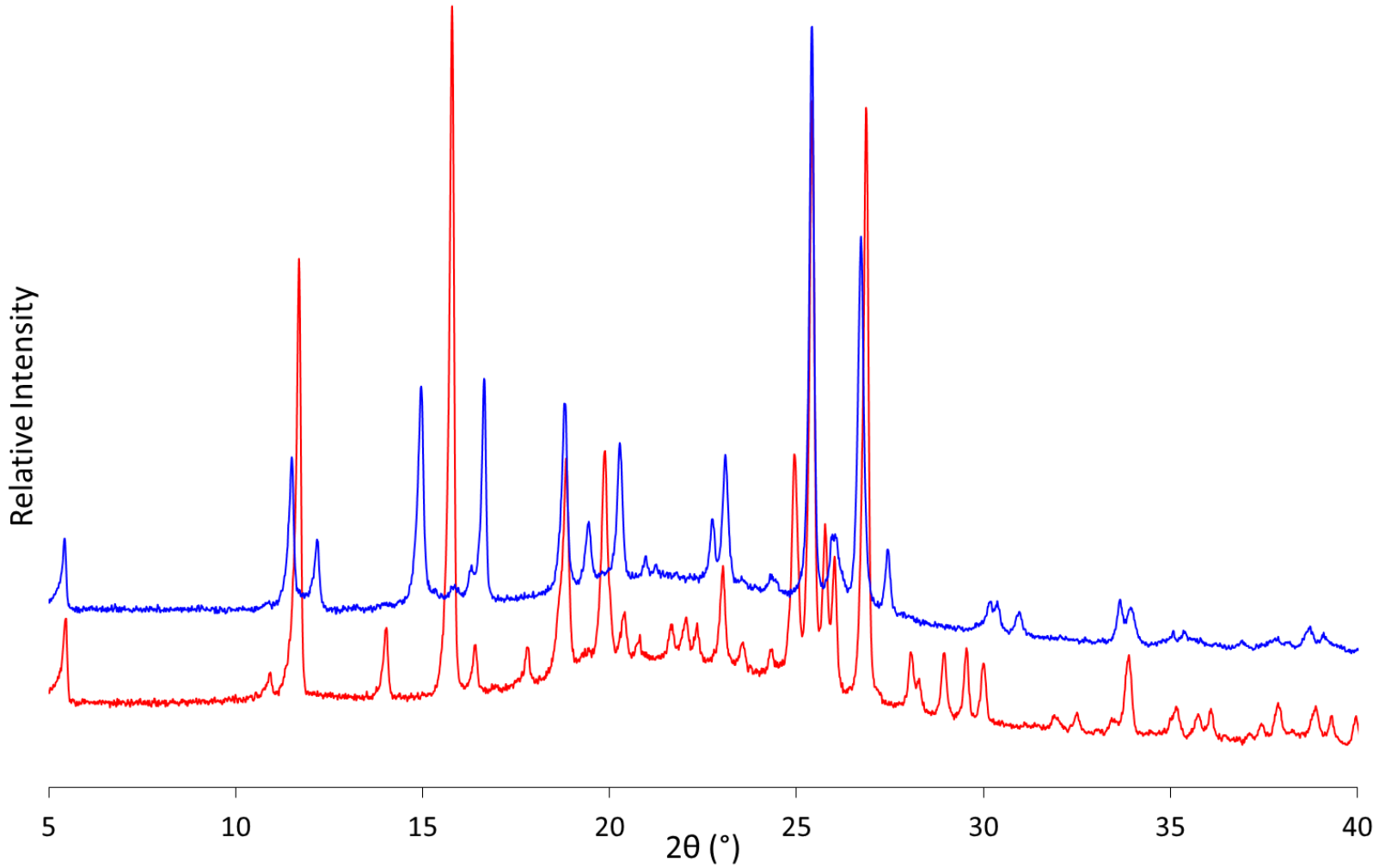
DSC
Q20

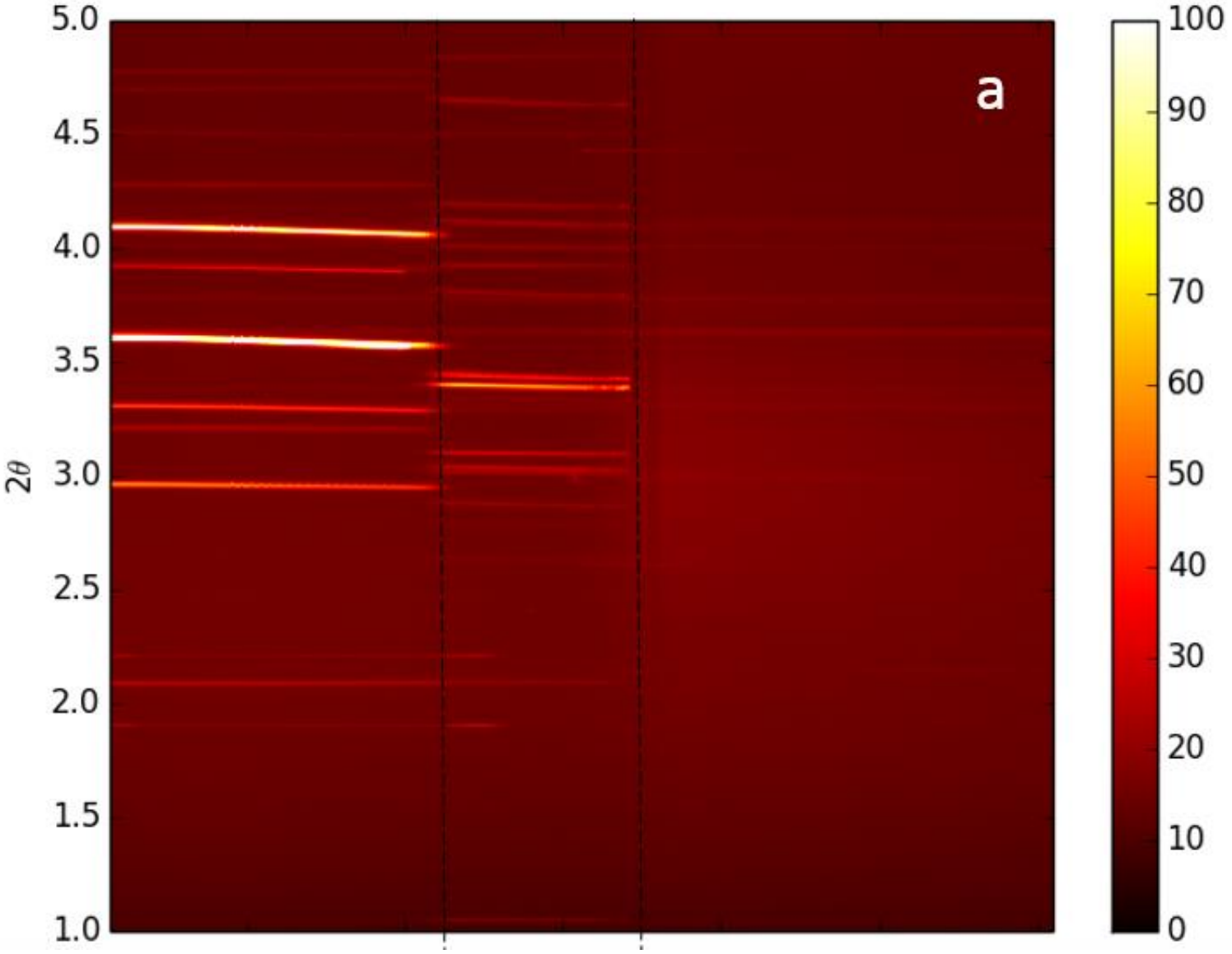
DSC for physical form characterisation

- Problem comes in *absolute* confirmation of form
- Can use *in-situ* Raman or NIR, but usually single-crystal or powder XRD is required
- Takes a long time to record diffraction pattern
- We wanted to confirm physical form with PXRD in real-time, in the DSC pan
- Best done with a synchronous X-ray source

- We were able to record a powder pattern in 4s, with a 2s pause, so 1 pattern every 1 ^{o}C

How to interpret XRD data?

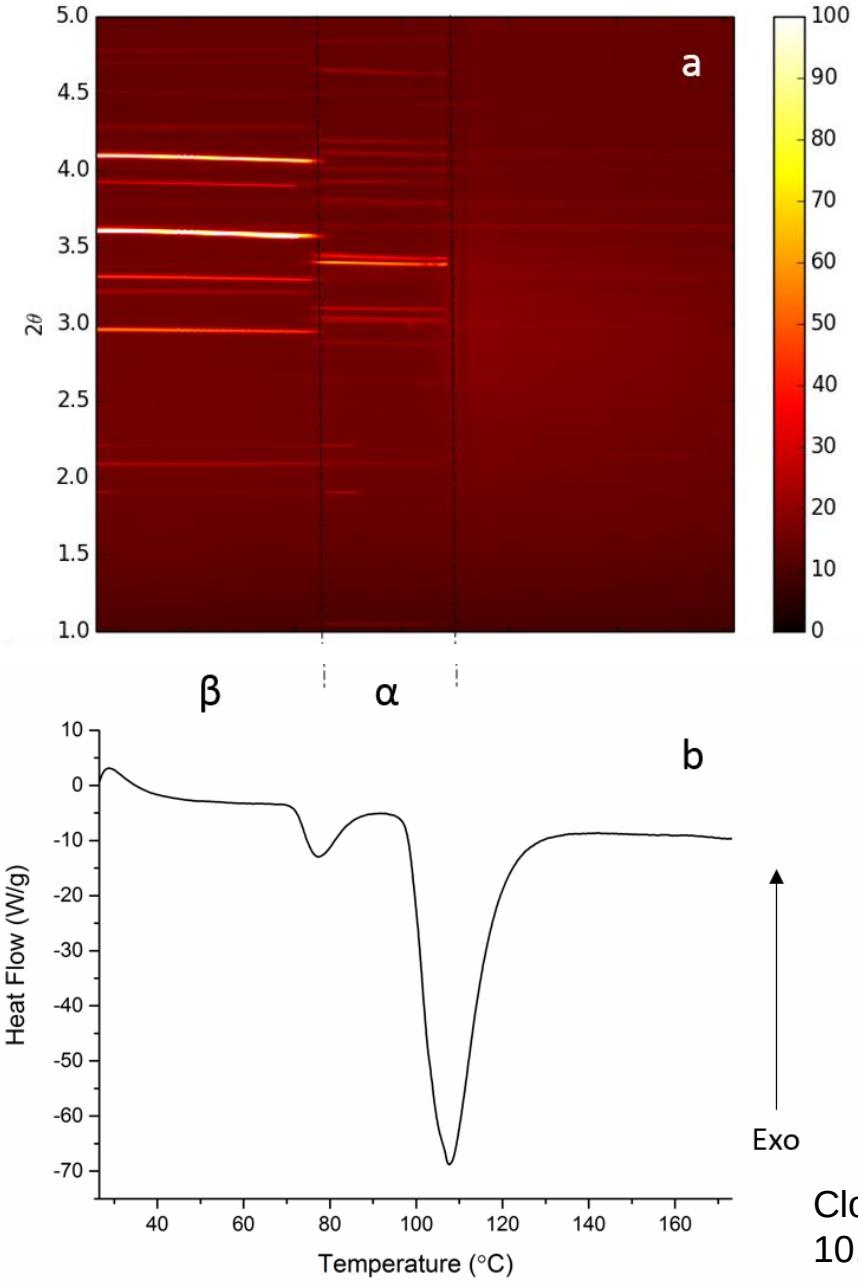



a
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
2θ
100
90
80
70
60
50
40
30
20
10
0

Glutaric acid:

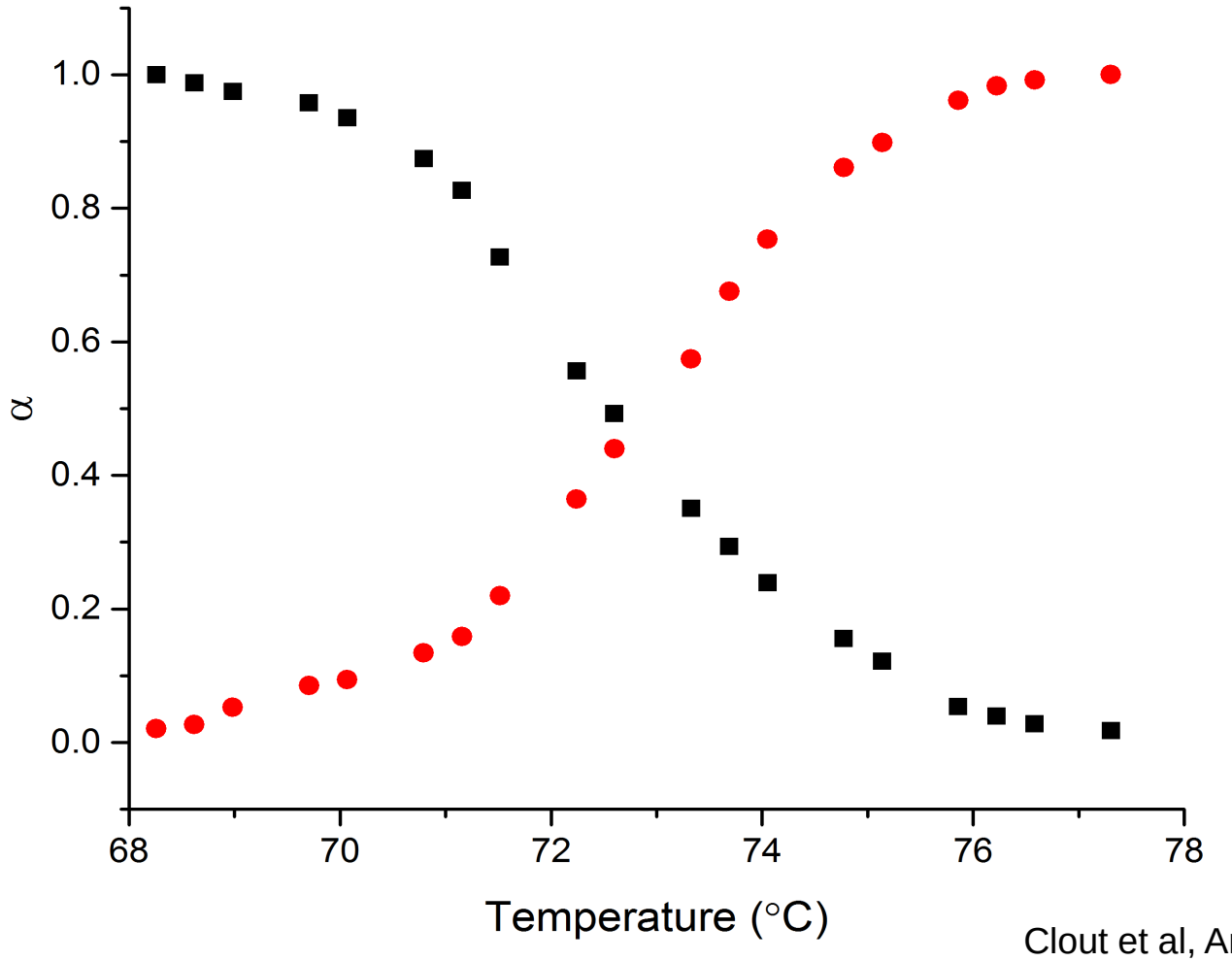
Two enantiotropic polymorphs

Solid-solid conversion
From β to α



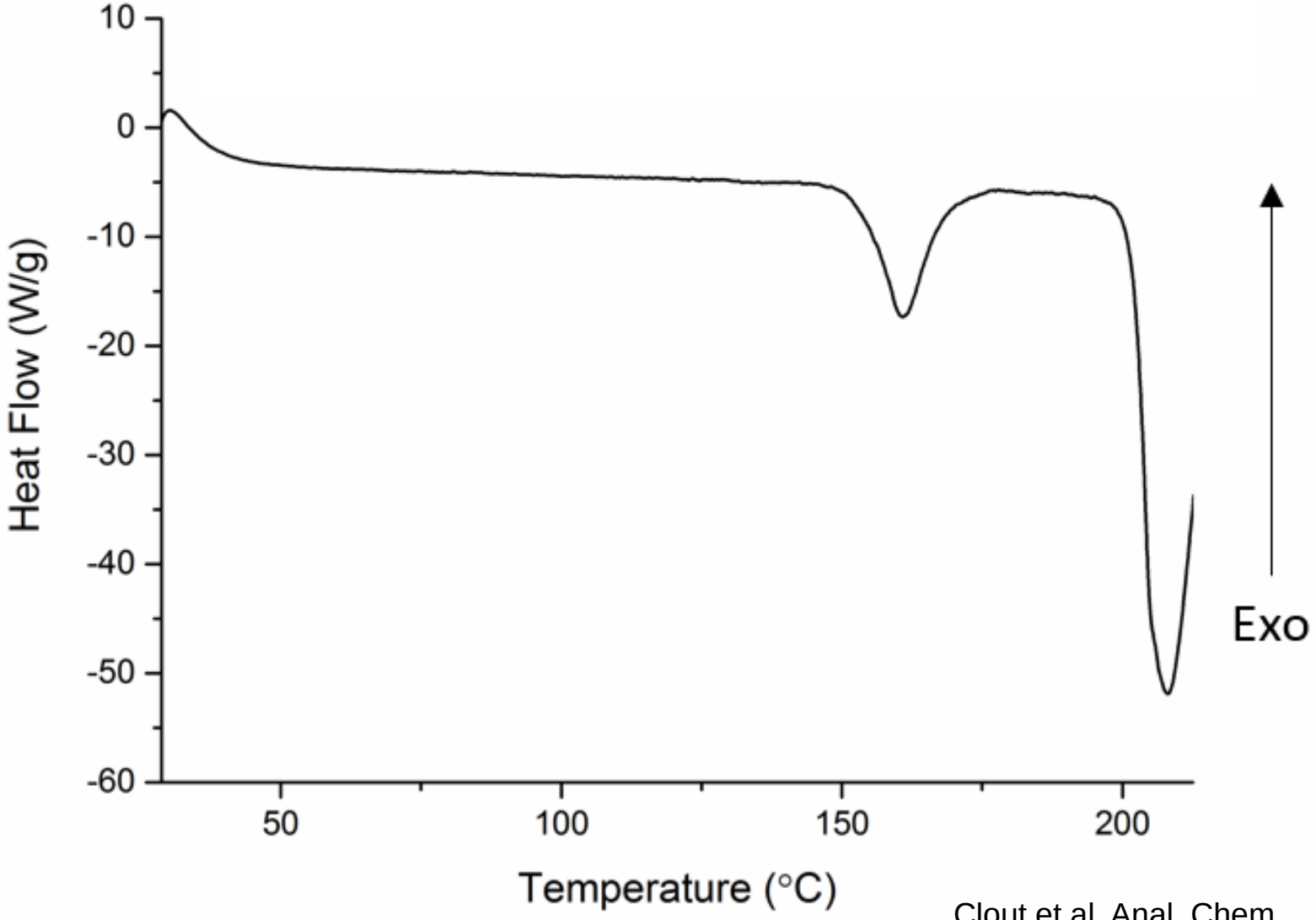
Clout et al, Anal. Chem.
10.1021/acs.analchem.6b02549

By selecting specific XRD reflections, can look at loss of β and creation of α



Clout et al, Anal. Chem.
10.1021/acs.analchem.6b02549

Sulphathiazole

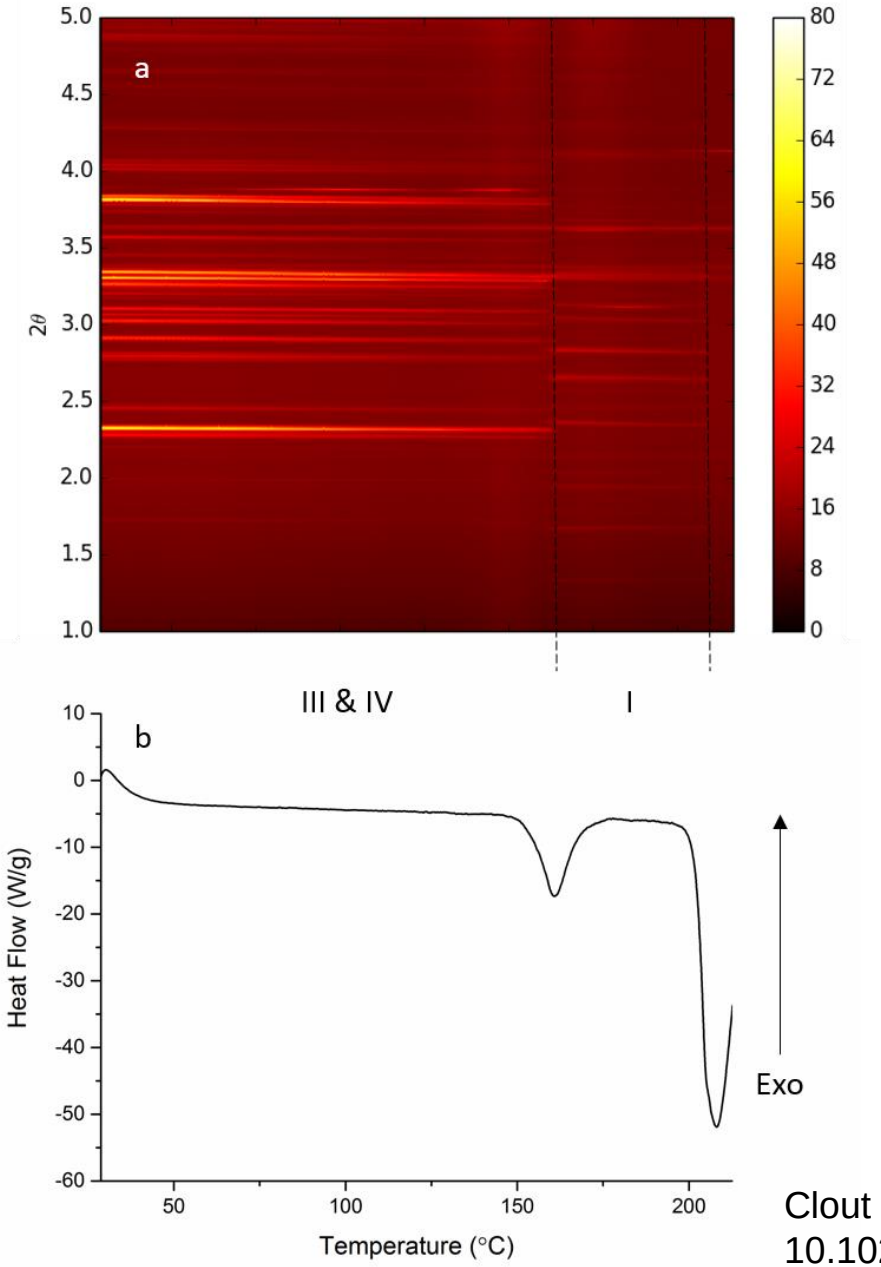


Clout et al, Anal. Chem.
10.1021/acs.analchem.6b02549

Sulphathiazole:

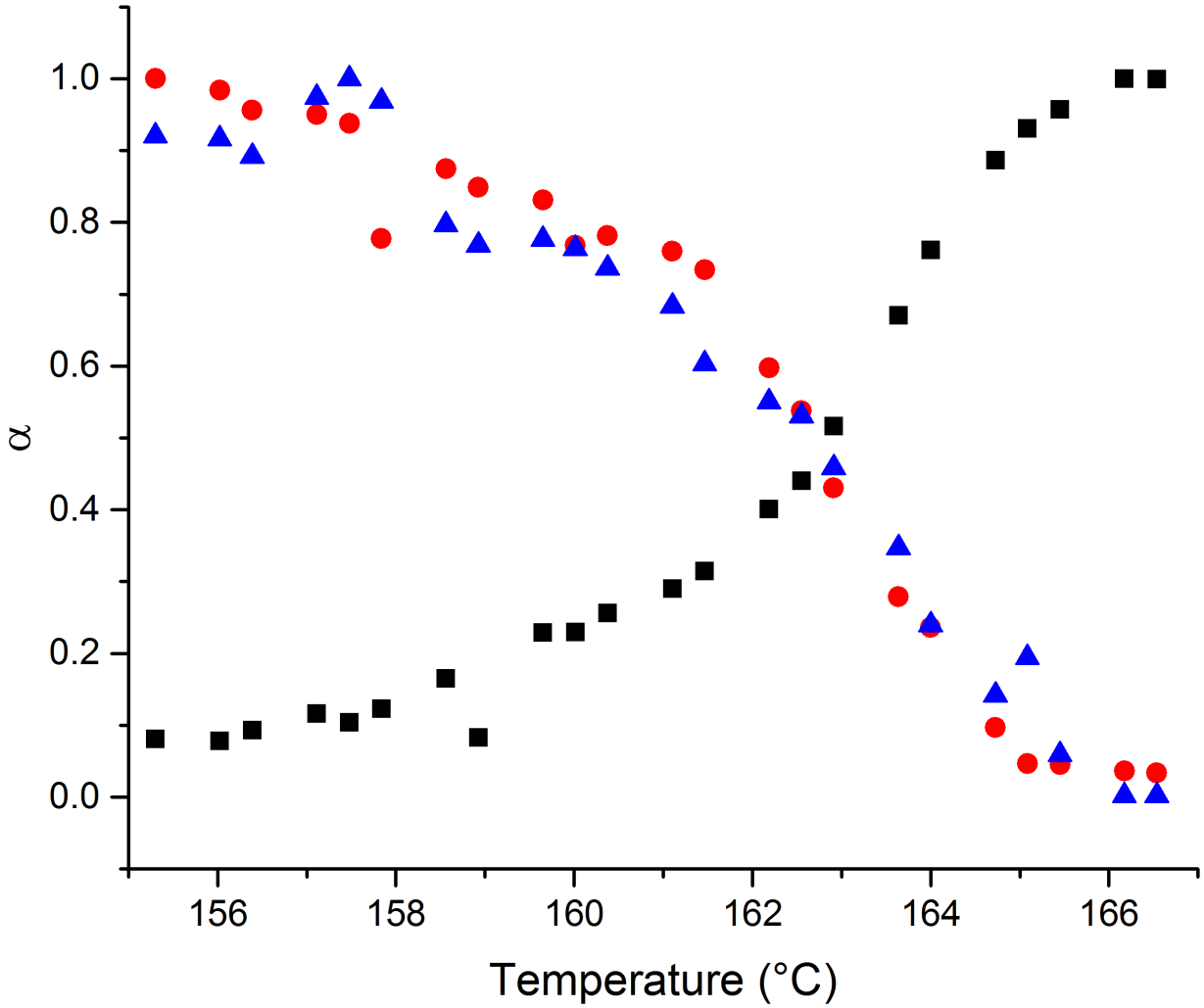
Three enantiotropic polymorphs

Solid-solid conversion from a mixture of forms III and IV to form I



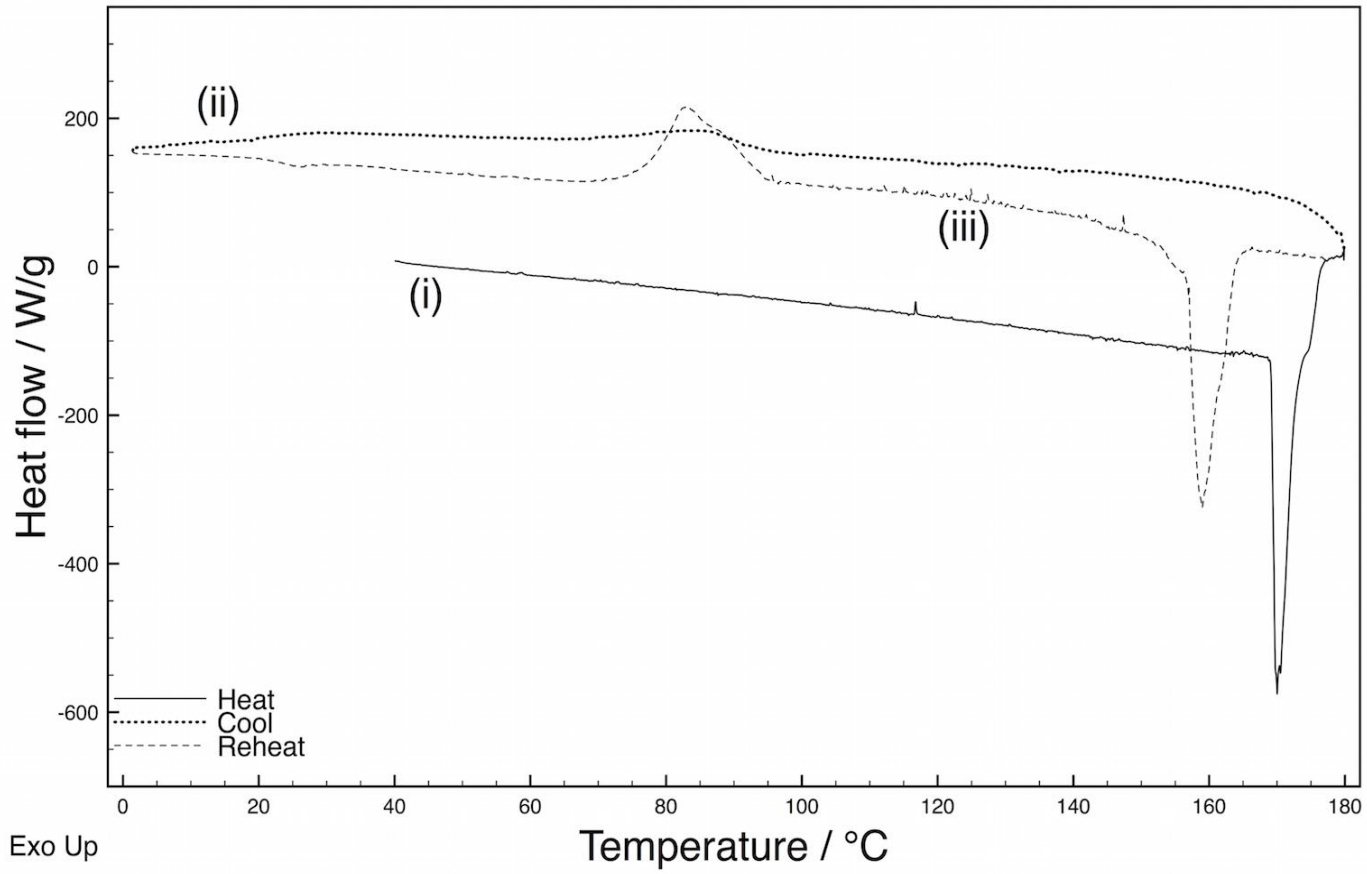
Clout et al, Anal. Chem. 10.1021/acs.analchem.6b02549

Again, can see loss of Forms III and IV and creation of Form I



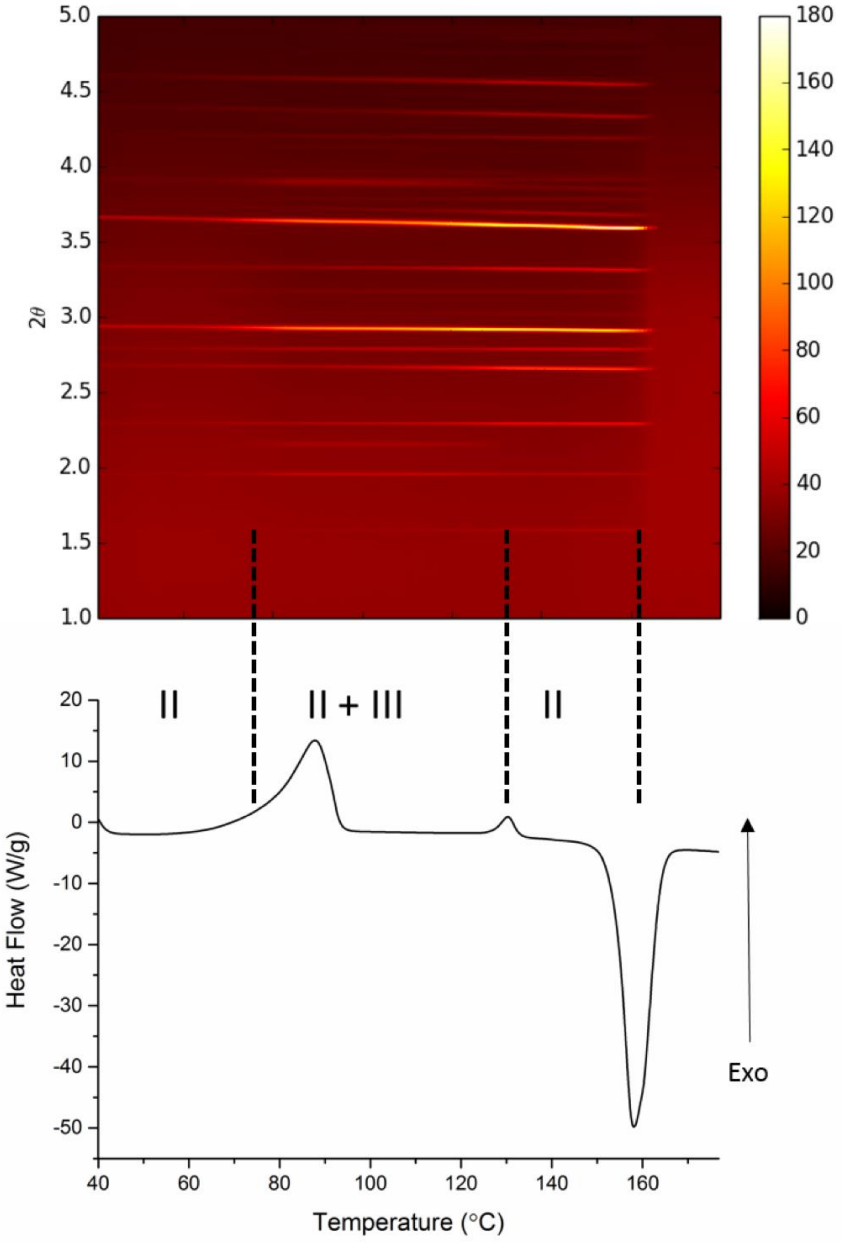
Clout et al, Anal. Chem.
10.1021/acs.analchem.6b02549

(a)


(ii)
(iii)
(i)
200
0
-200
-400
-600
Heat flow / W/g
Heat
Cool
Reheat
0
20
40
60
80
100
120
140
160
180
Exo Up
Temperature / °C

Telford et al (2016)
10.1039/c6cc05006a

Paracetamol



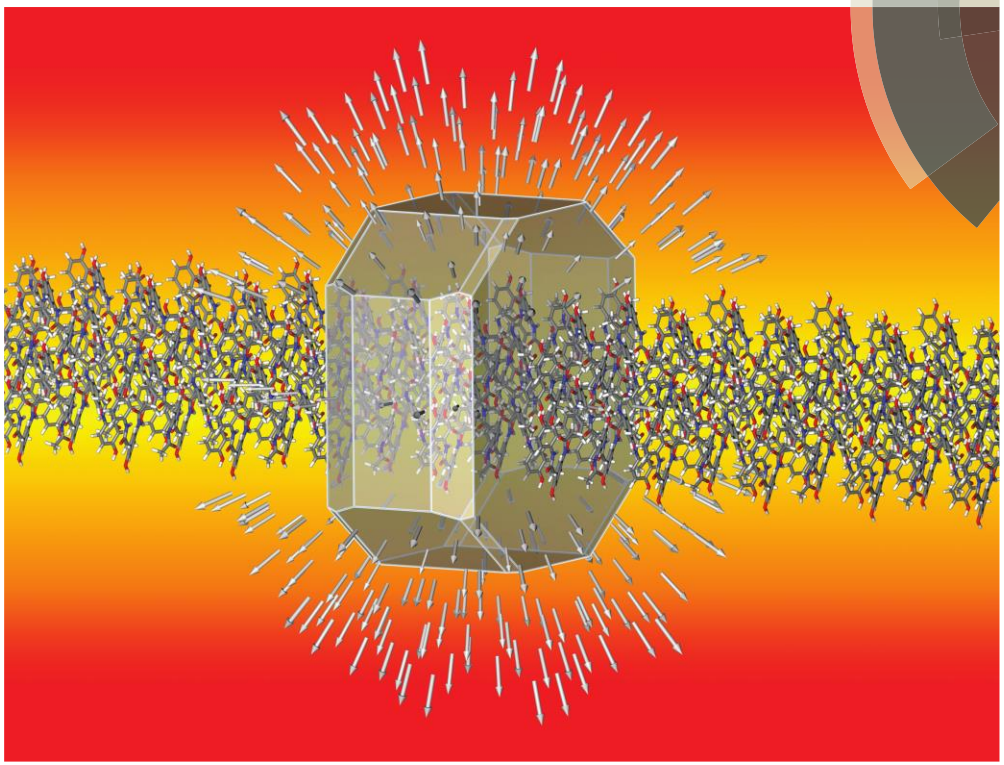
UCL

Volume 52 | Number 81 | 18 October 2016 | Pages 12001–12118

ChemComm

Chemical Communications

www.rsc.org/chemcomm



ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

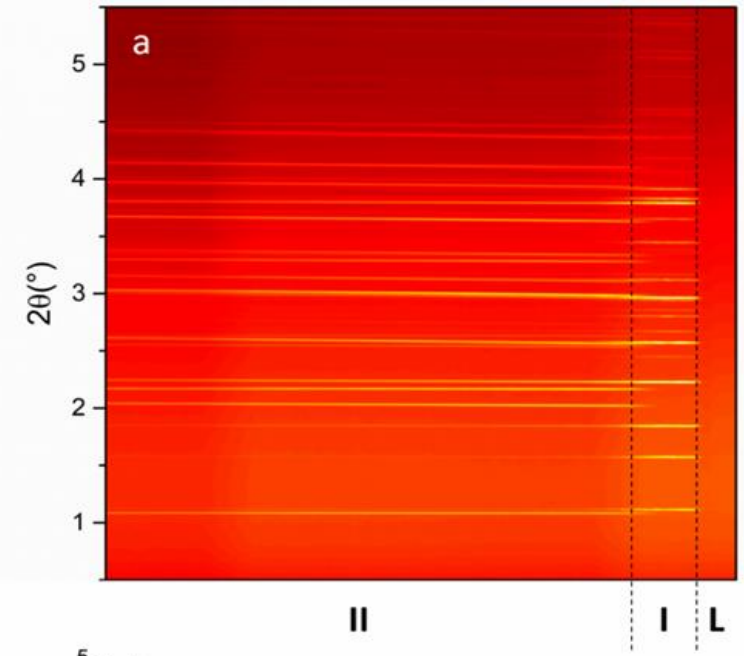
COMMUNICATION

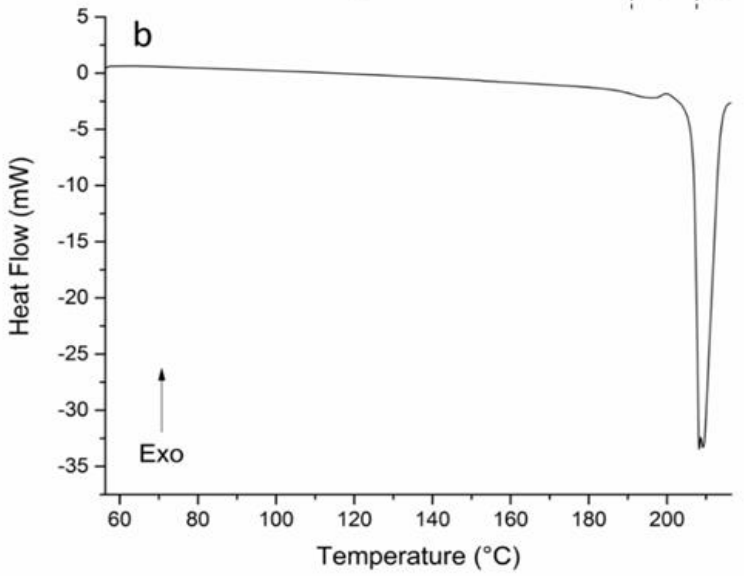
Ian J. Scowen *et al.*

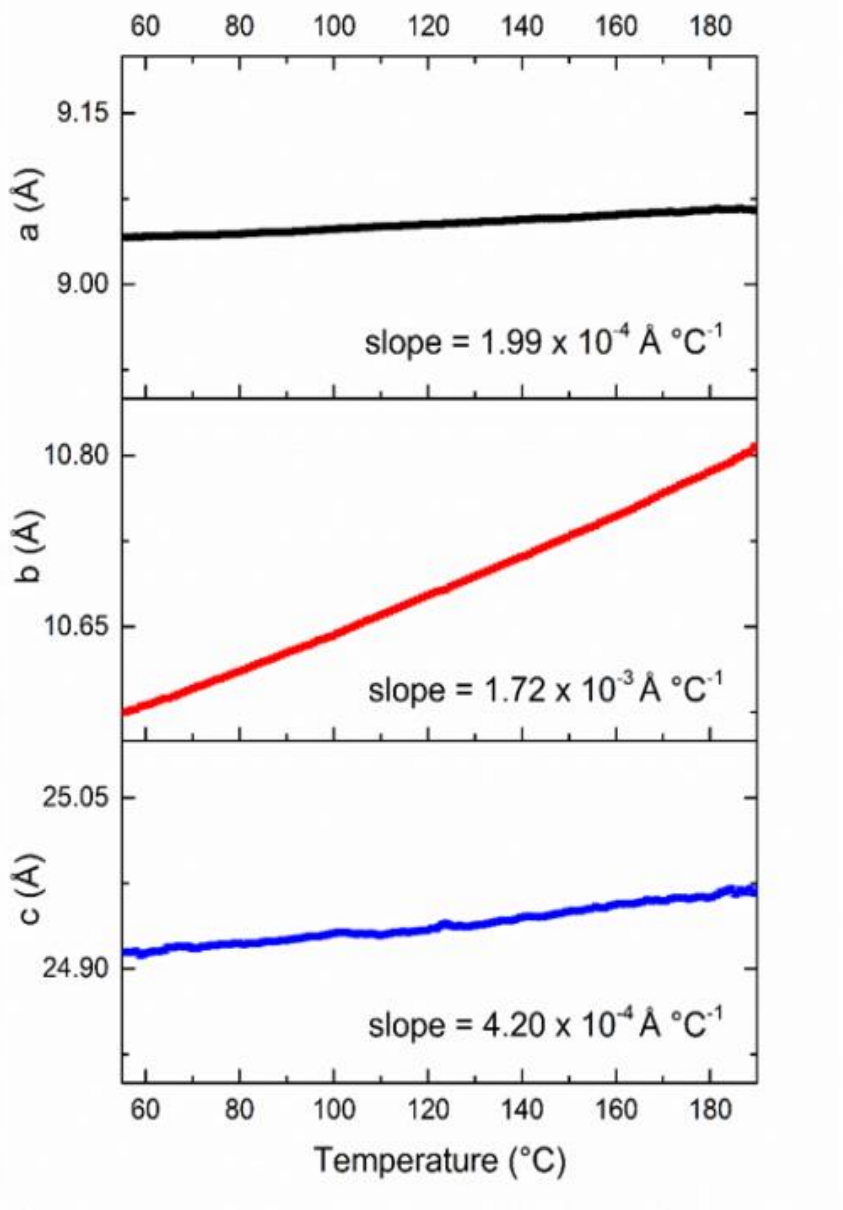
Stabilisation of metastable polymorphs: the case of paracetamol form III

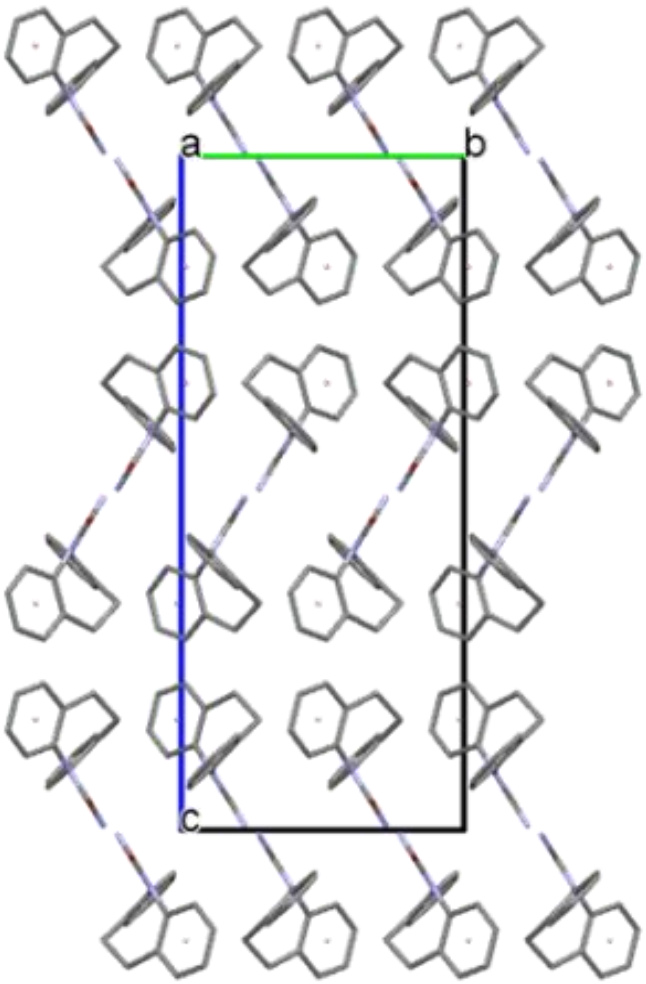
175 YEARS

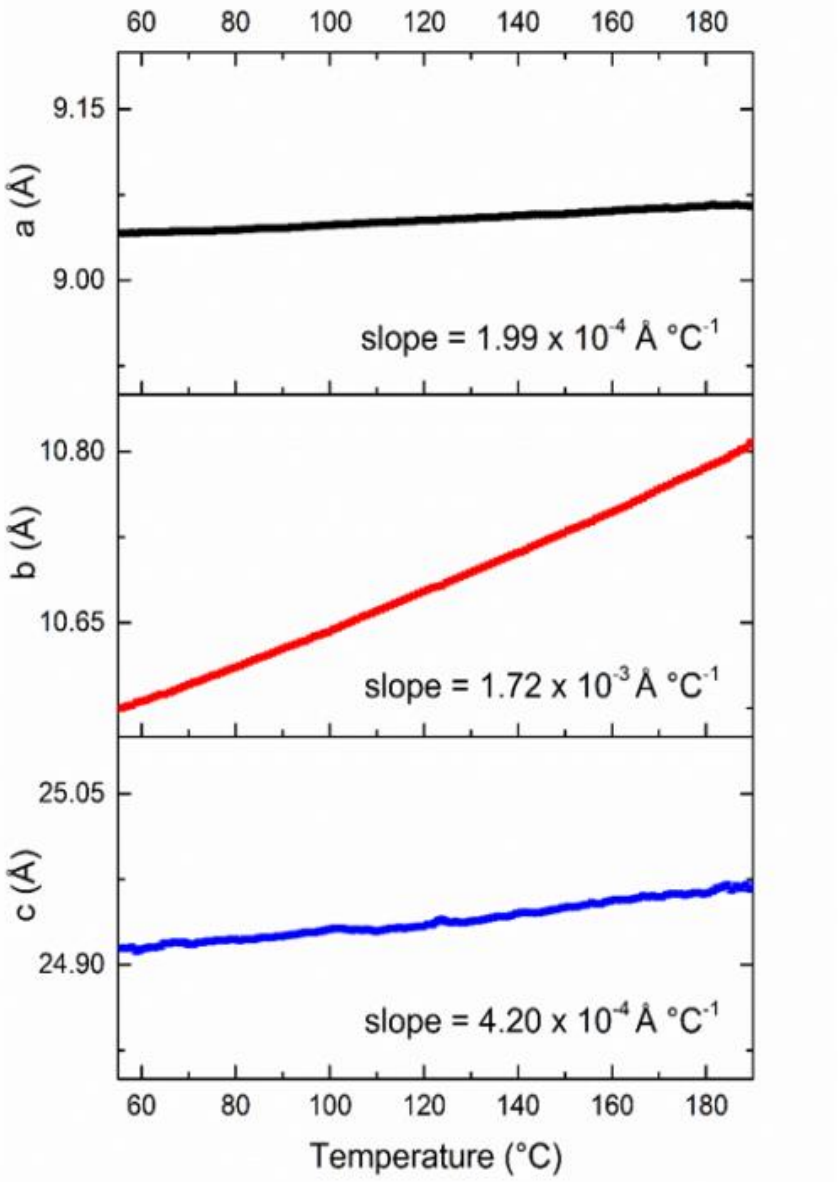
10,11-dihydrocarbamazepine

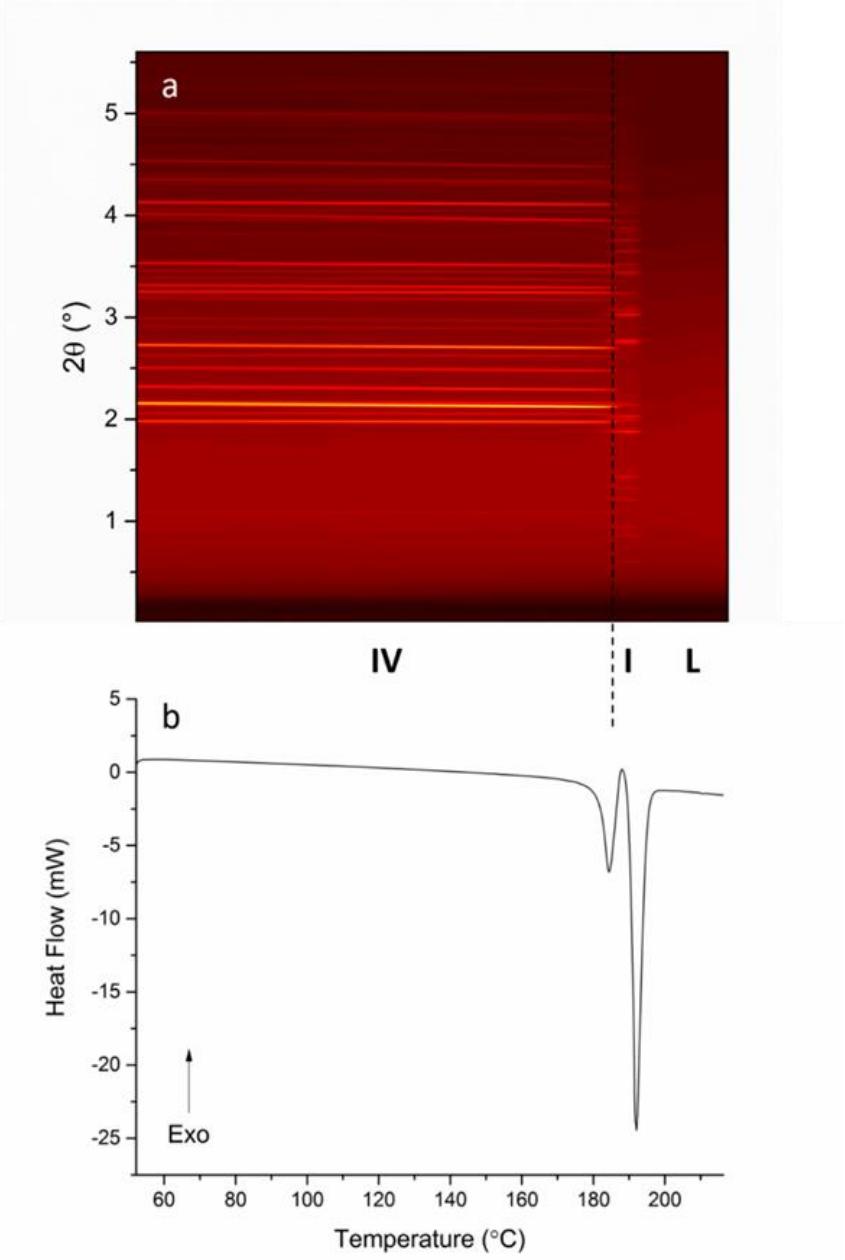


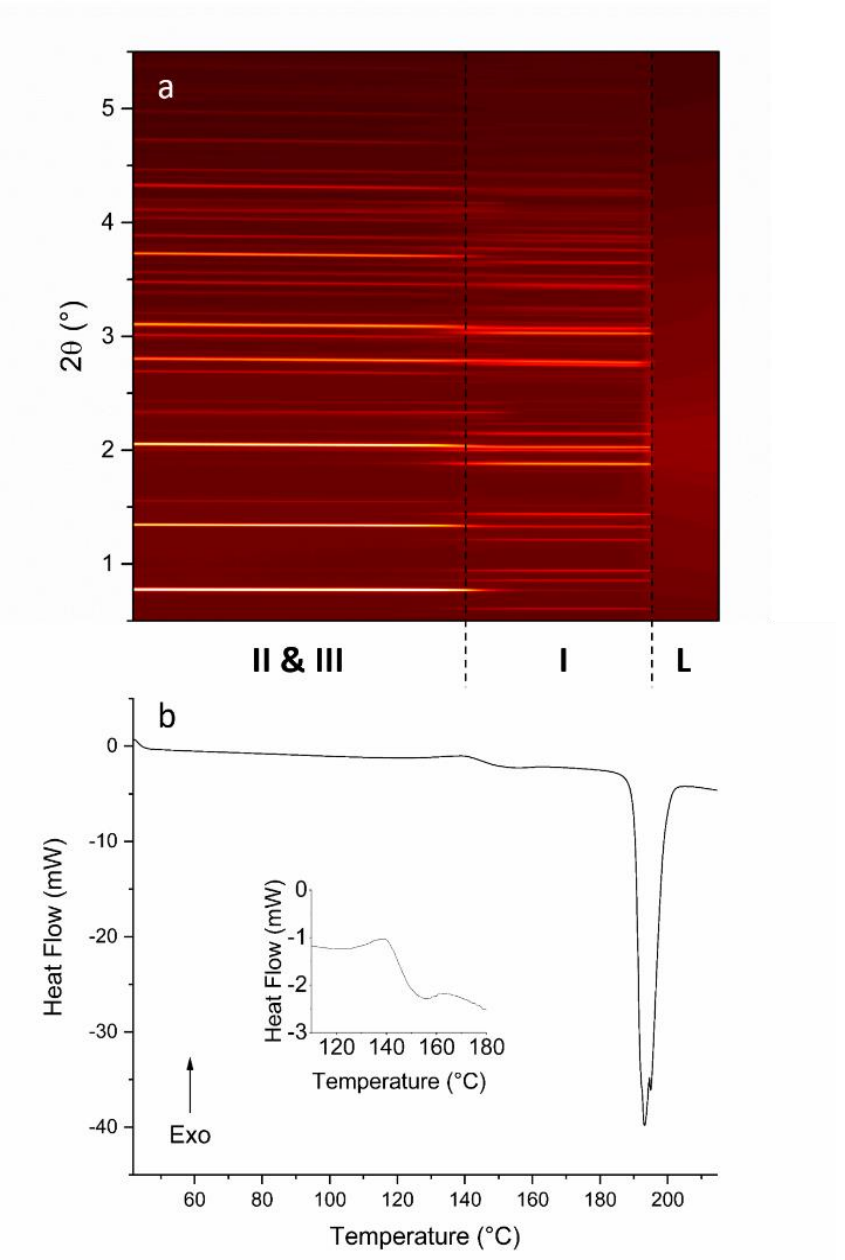


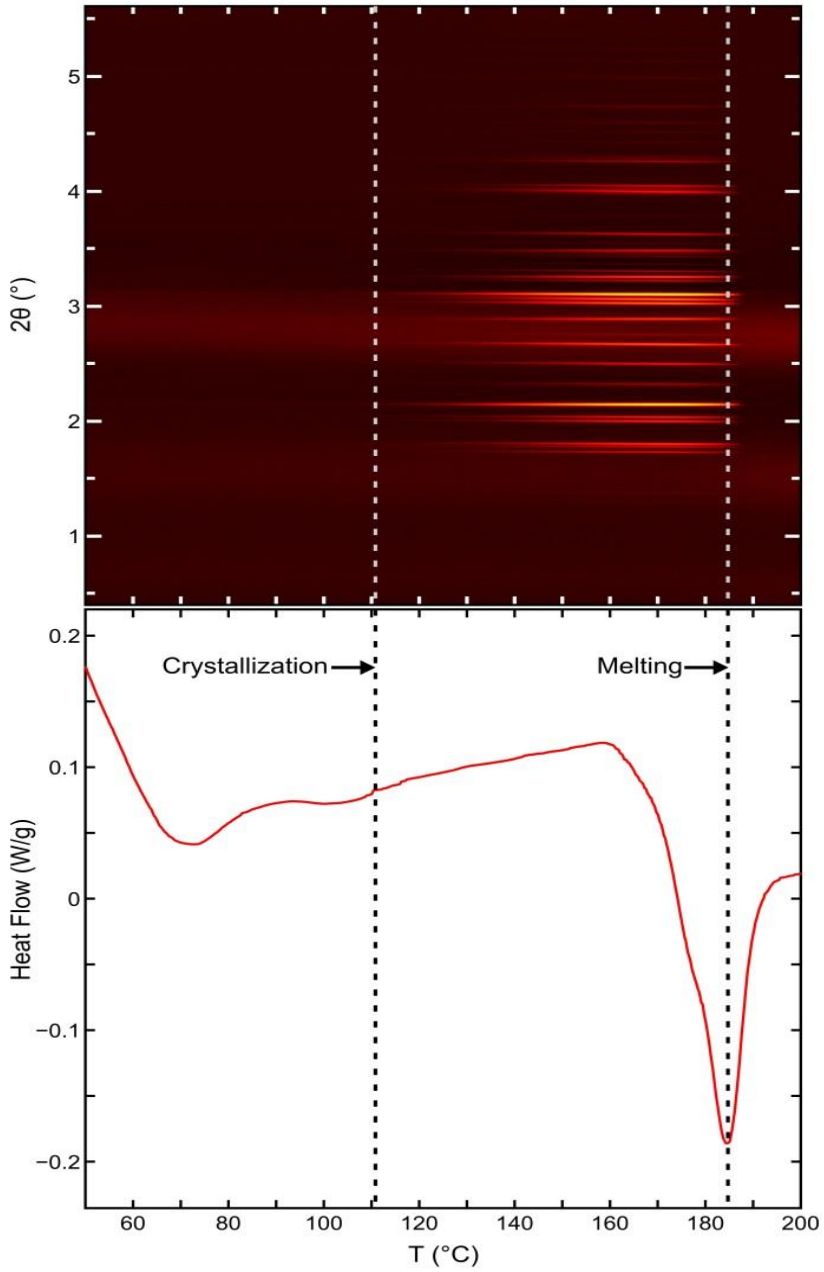



a
b
c

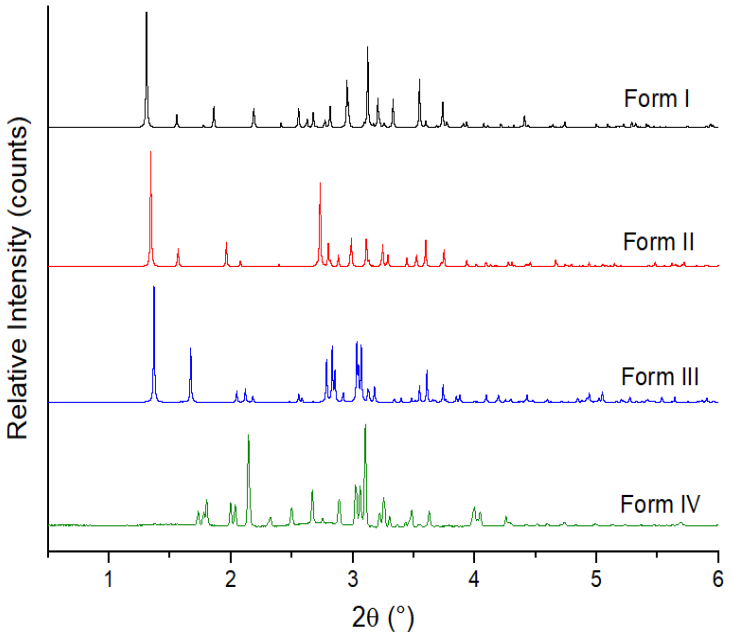

60
80
100
120
140
160
180
9.15
9.00
a (Å)
slope = 1.99 x 10-4 Å °C-1
10.80
10.65
b (Å)
slope = 1.72 x 10-3 Å °C-1
25.05
24.90
c (Å)
slope = 4.20 x 10-4 Å °C-1
Temperature (°C)

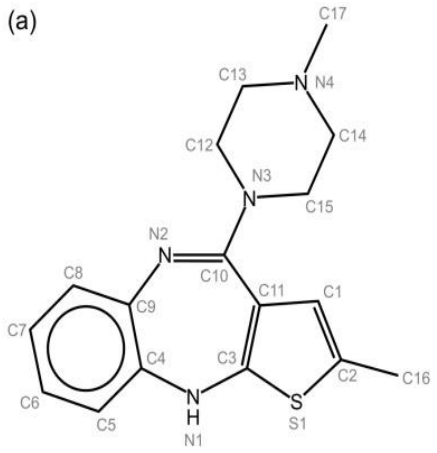

a
2θ (°)
IV
I
L
b
Heat Flow (mW)
Exo
Temperature (°C)


a
2θ (°)
II & III
I
L
b
Heat Flow (mW)
Exo
Temperature (°C)


2θ (°)
Crystallization
Melting
Heat Flow (W/g)
T (°C)

Olanzapine


Form I
Form II
Form III
Form IV
Relative Intensity (counts)
2θ (°)


(a)
(b)

Summary

- DSC excellent for seeing phase transitions, but absolute assignment to physical forms tricky
- Simultaneous XRD capable of following change in form in real-time
- TA DSC is very easy to modify for this use
- Initial experiments have shown that solid-solid transitions occur without an intermediate liquid phase
- If you have systems of interest, contact us and we will schedule them on the Diamond Beam

Thanks to…

- Gareth Williams
- Asma Buanz
- Alex Clout
- Sean Askin
- Richard Telford and Ian Scowen
- Sally Price, Derek Tocher and Jeremy Cockcroft
- Jas Mahey and TA Instruments

1949 version

2016 version

diamond is a DSC's best friend