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

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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

Physical forms in pharmaceuticals

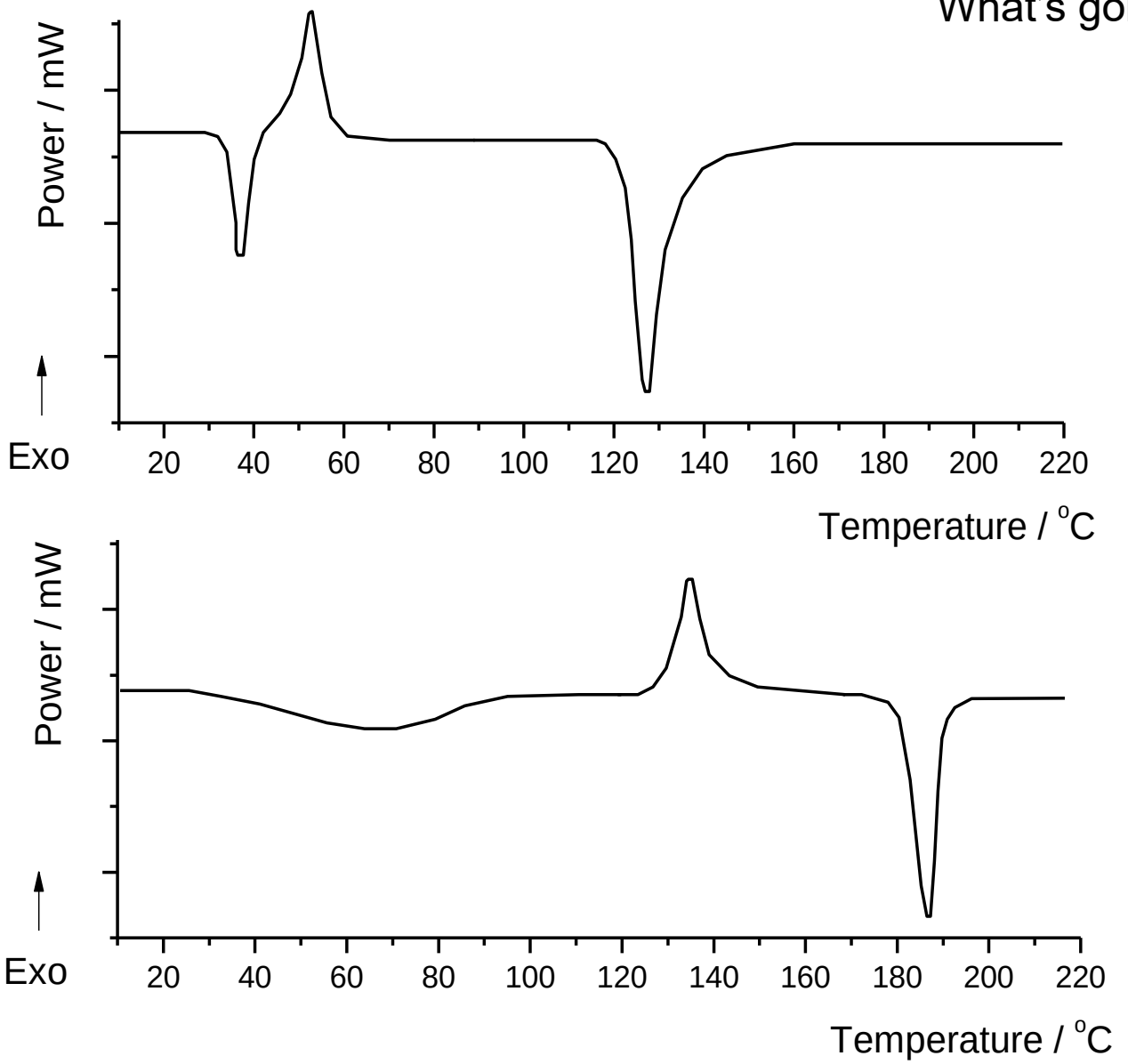
- Probably the biggest decision after selection of the drug molecule itself
- Why?
- Affects everything from solubility to dissolution, bioavailability, stability and manufacturing

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

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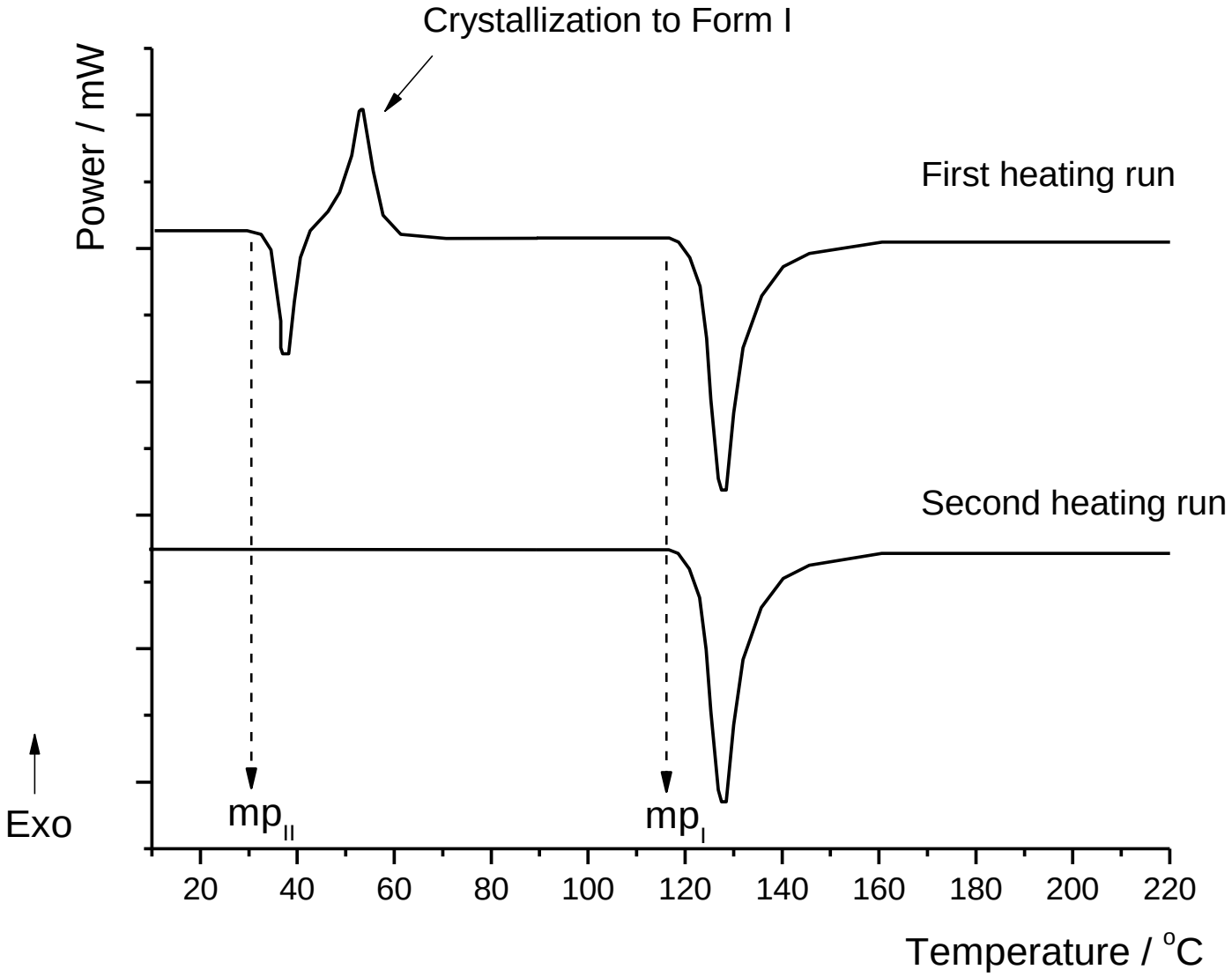
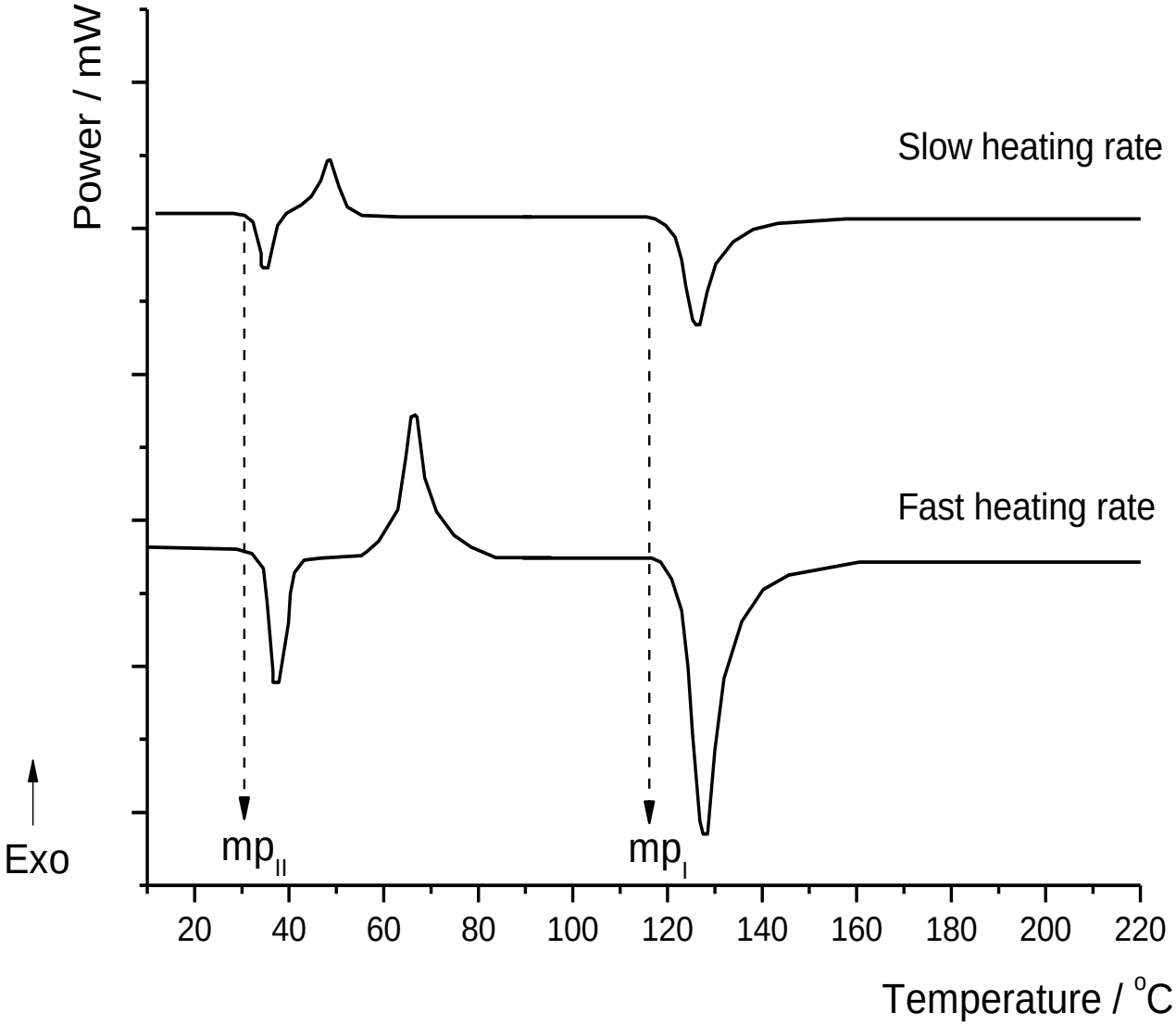
- No molecular information and different processes can give similar peaks
- How to interpret?
  - LOOK at whether events are exo- or endothermic
  - Much can be gained from altering DSC method, *especially* by reheating sample and by changing heating rate

Reheating sample



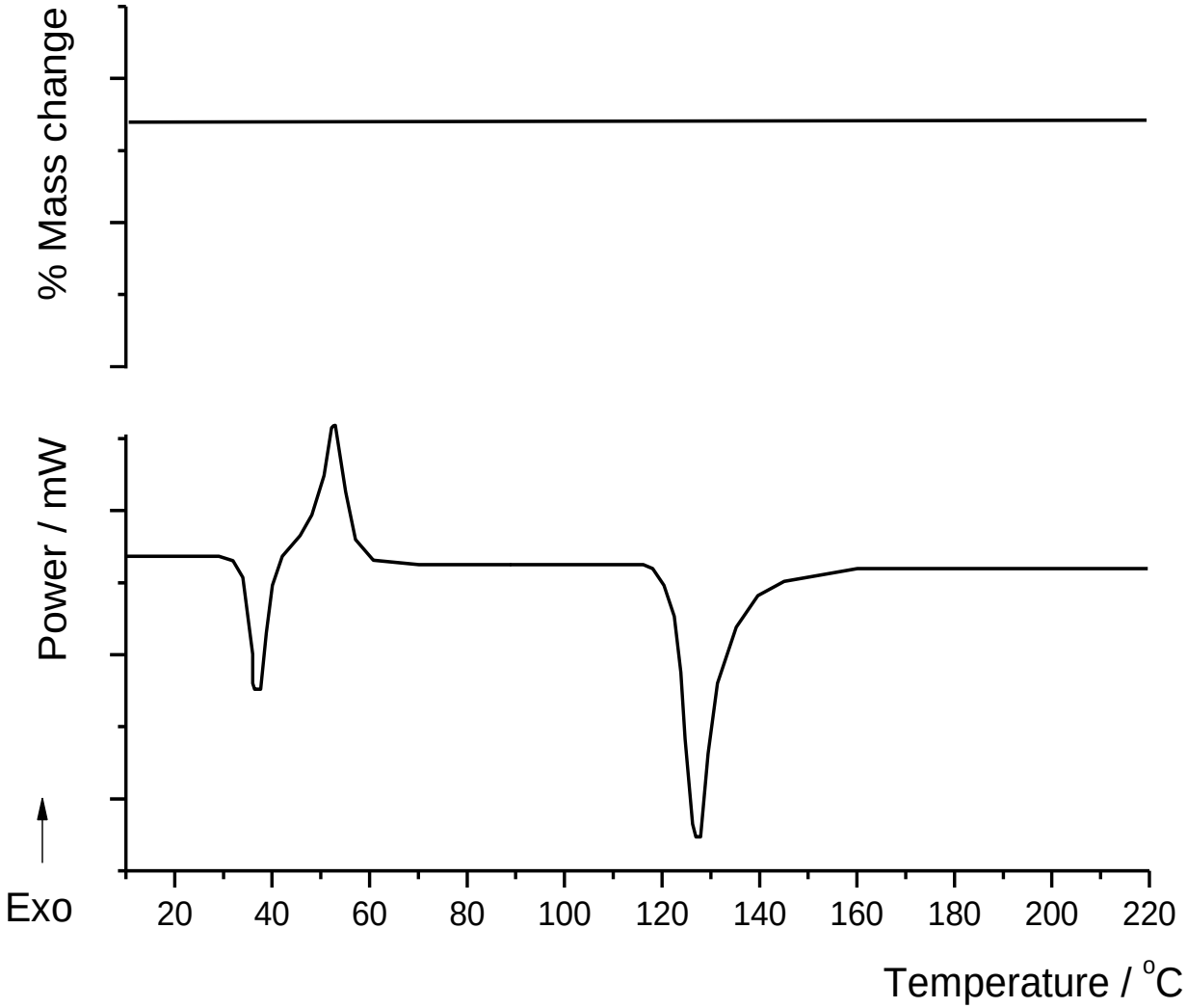
A metastable polymorph at two heating rates



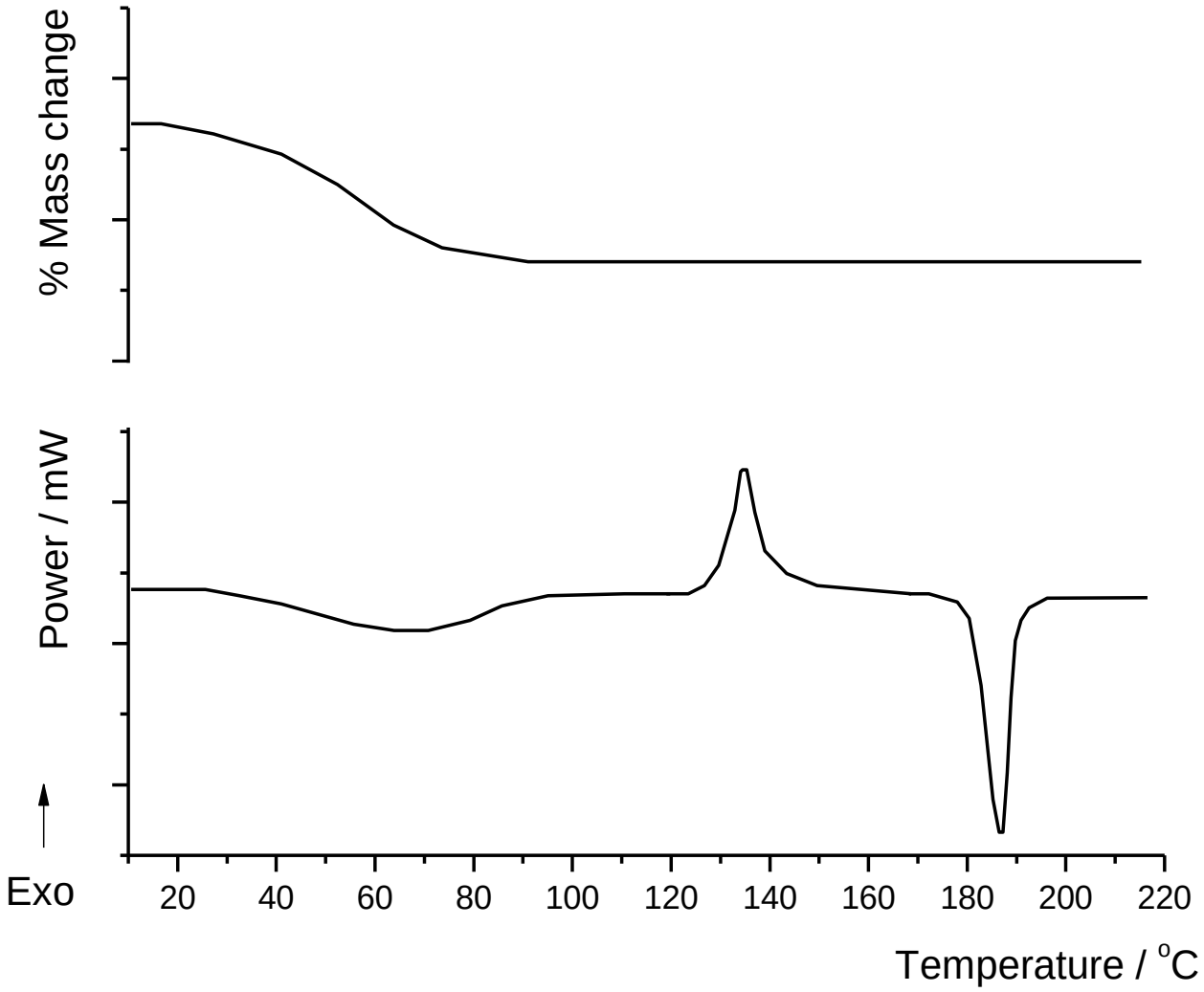
Additional analyses

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

TGA in event of polymorph conversion



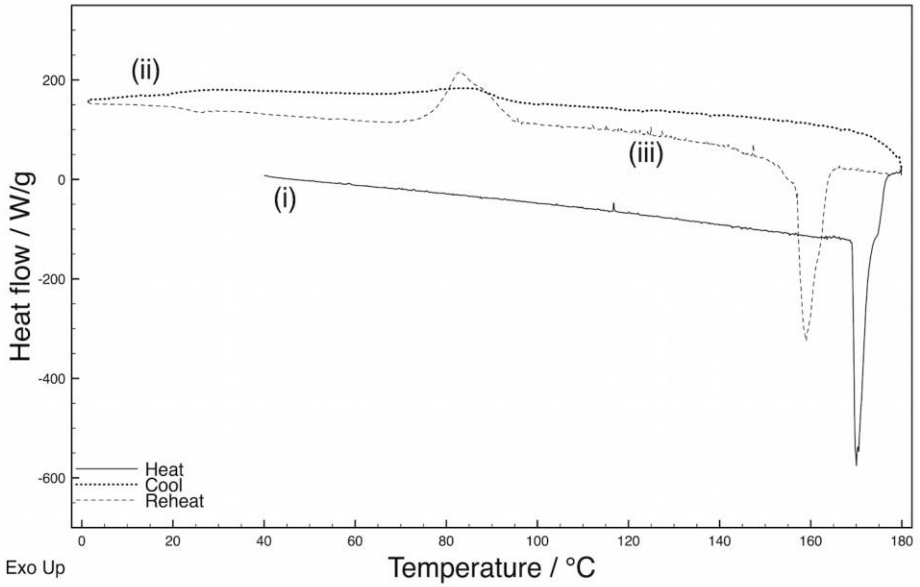
TGA in event of hydrate/solvate



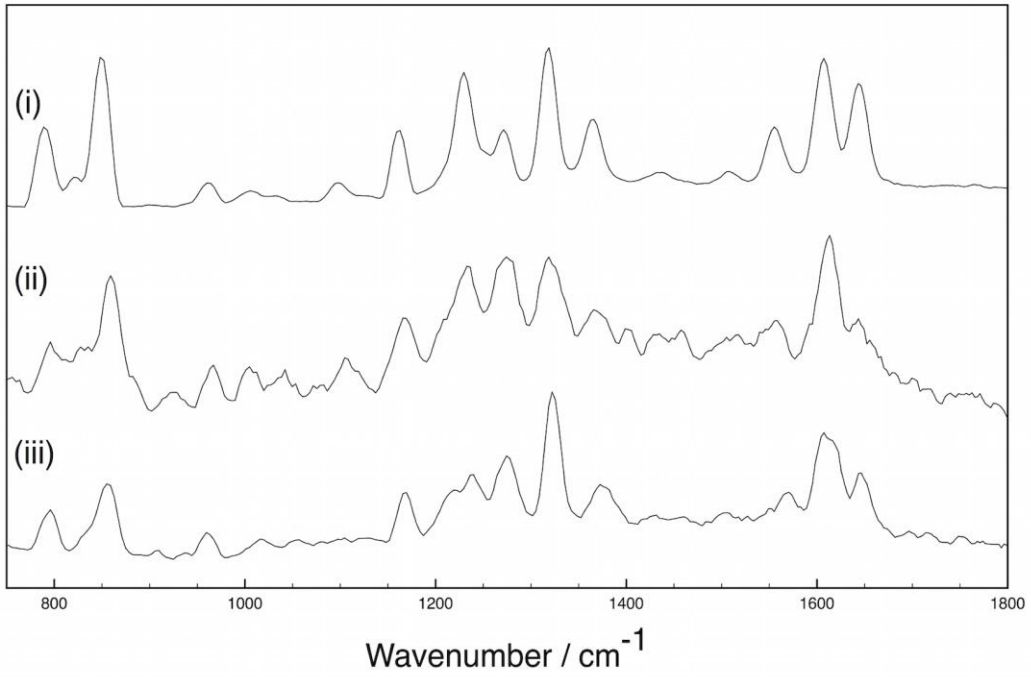
Telford et al (2016)
10.1039/c6cc05006a

Paracetamol

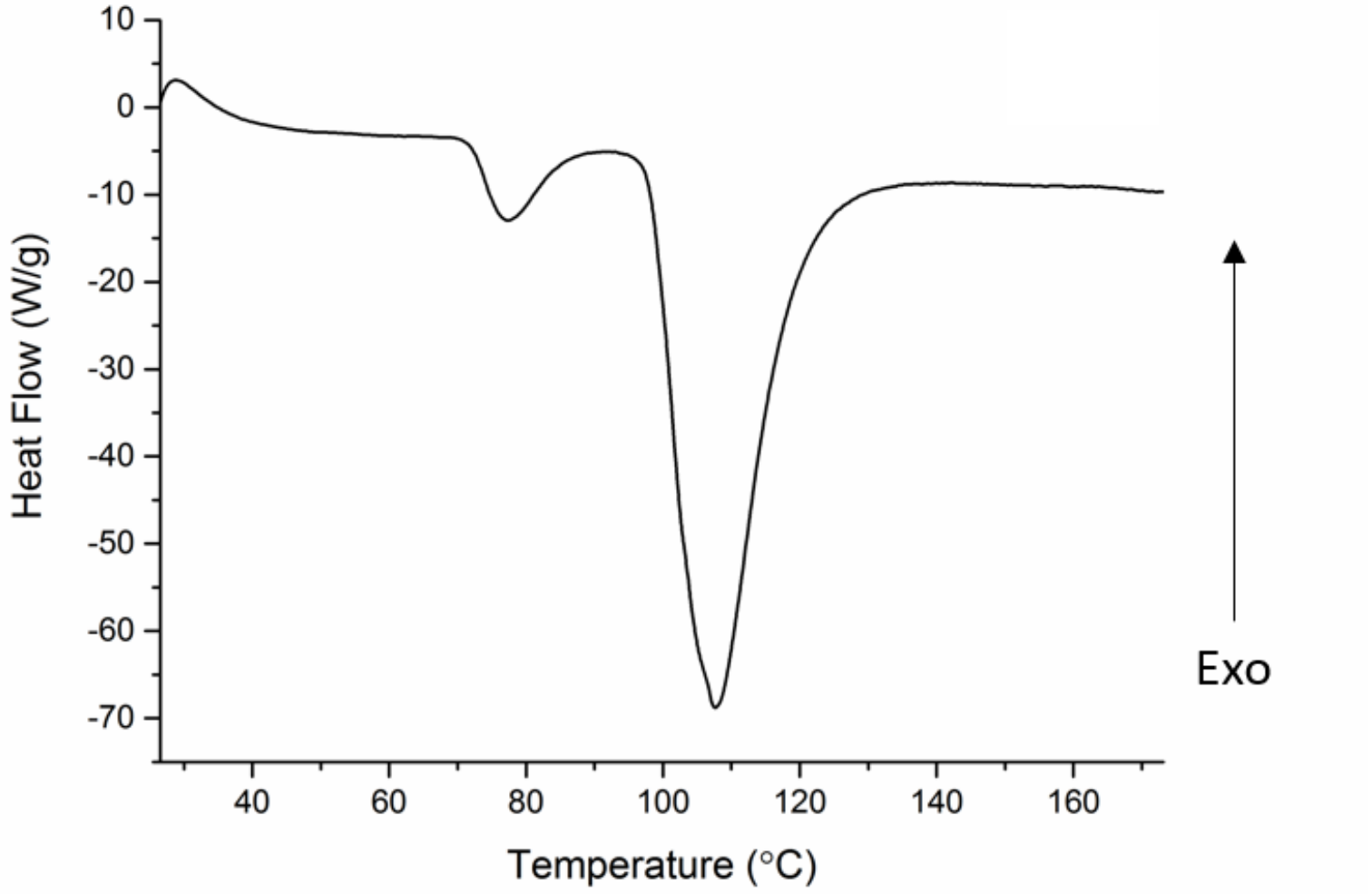
(a)



(b)

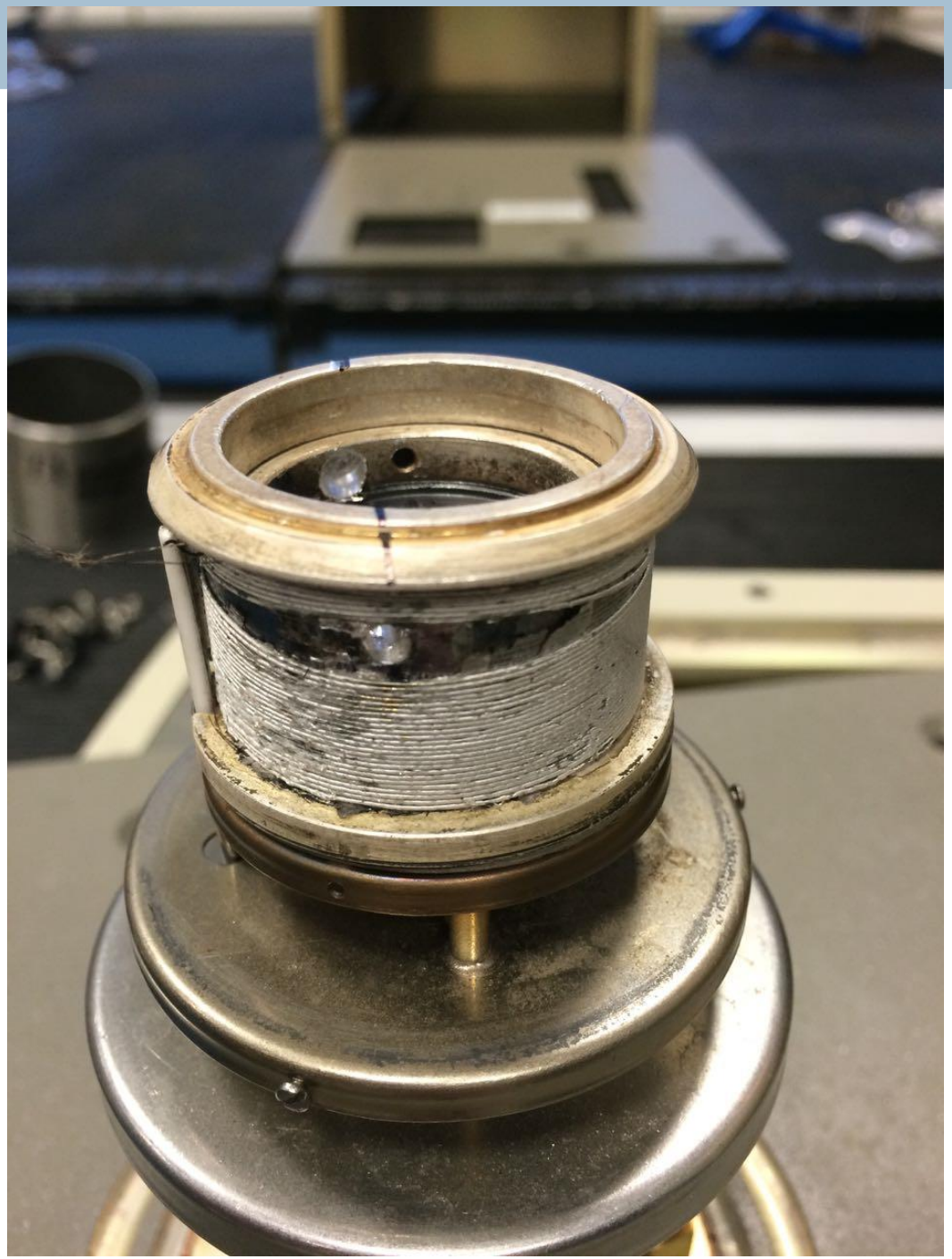


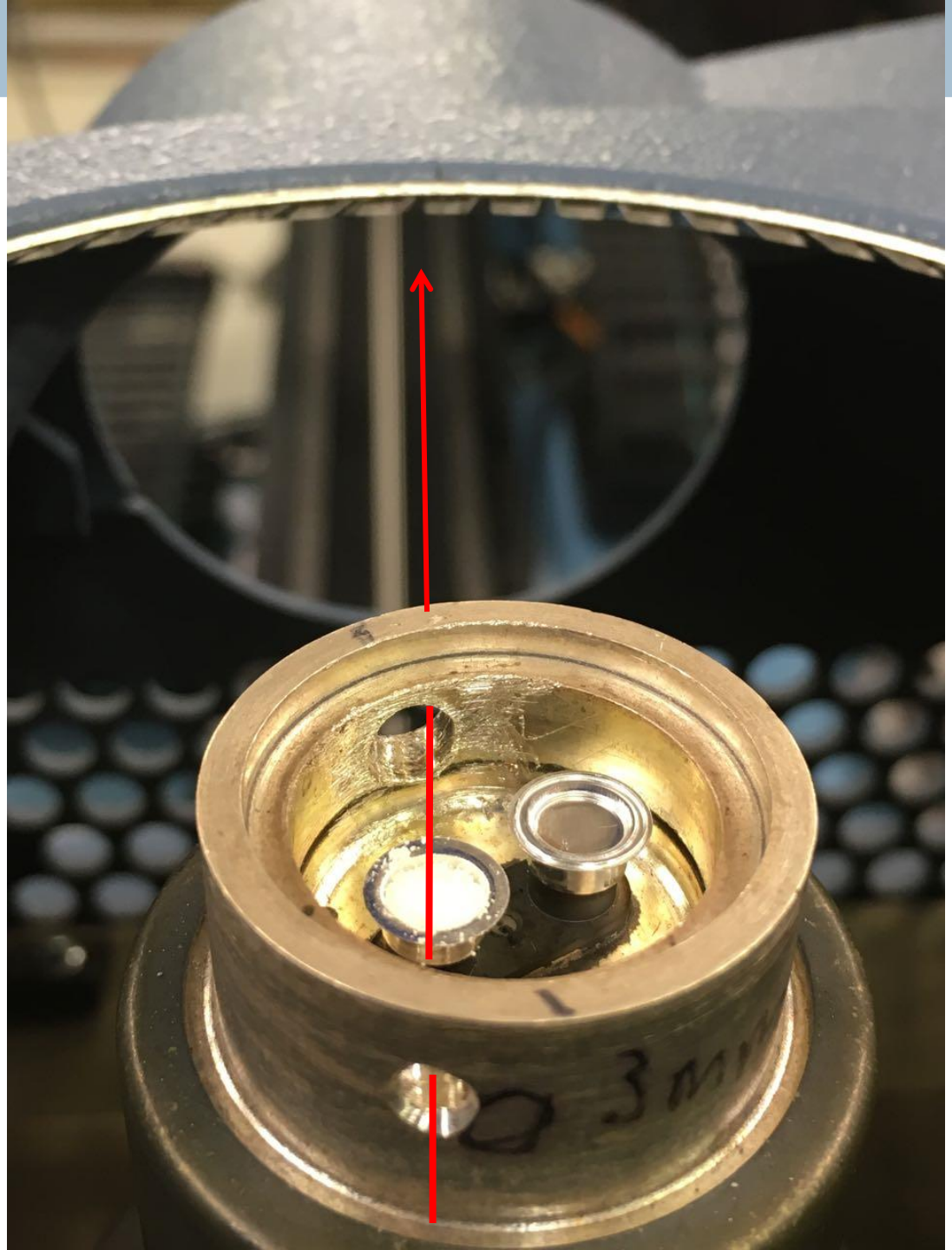
- Data for glutaric acid
- The question is, to what events should the peaks be assigned?

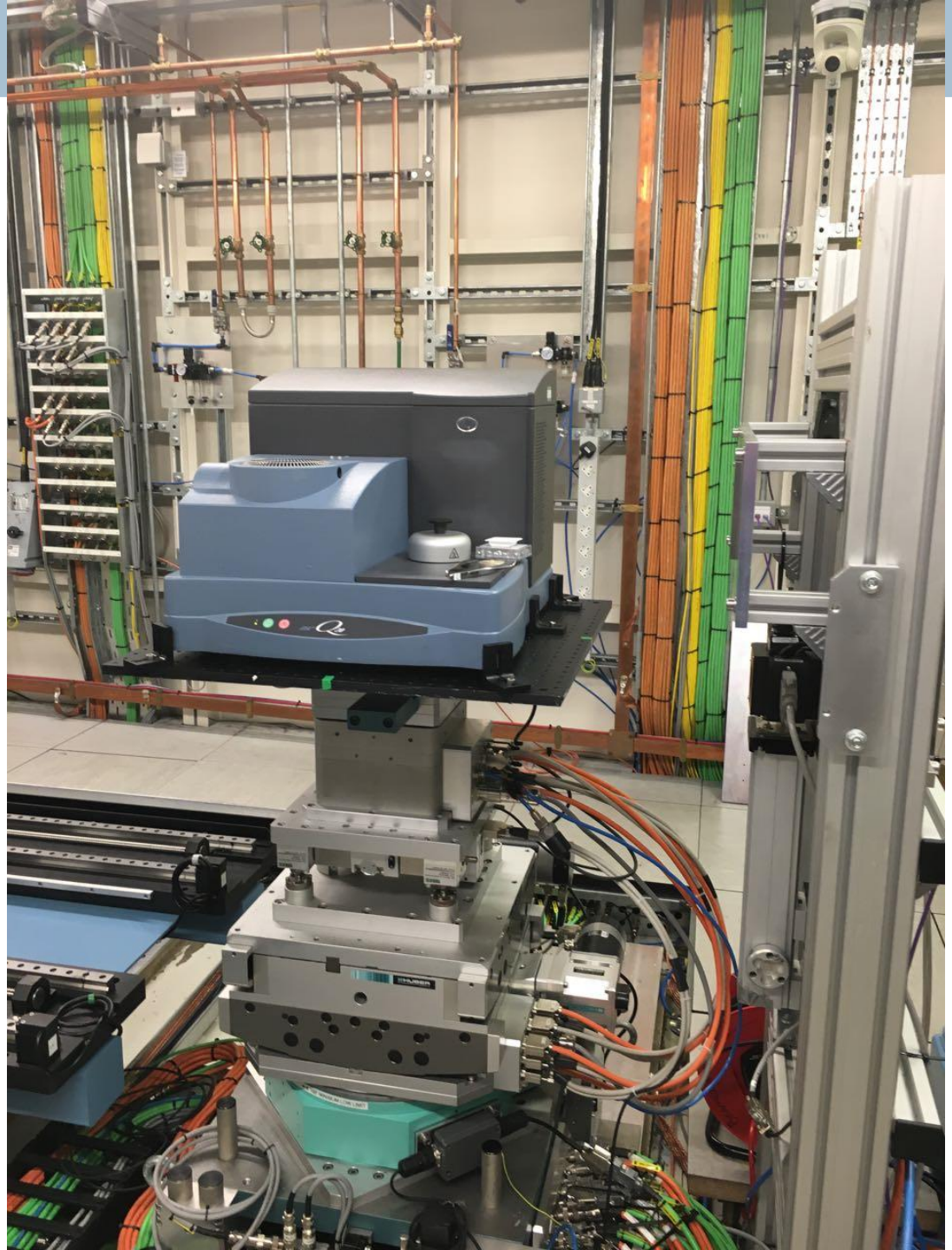


DSC for physical form characterisation

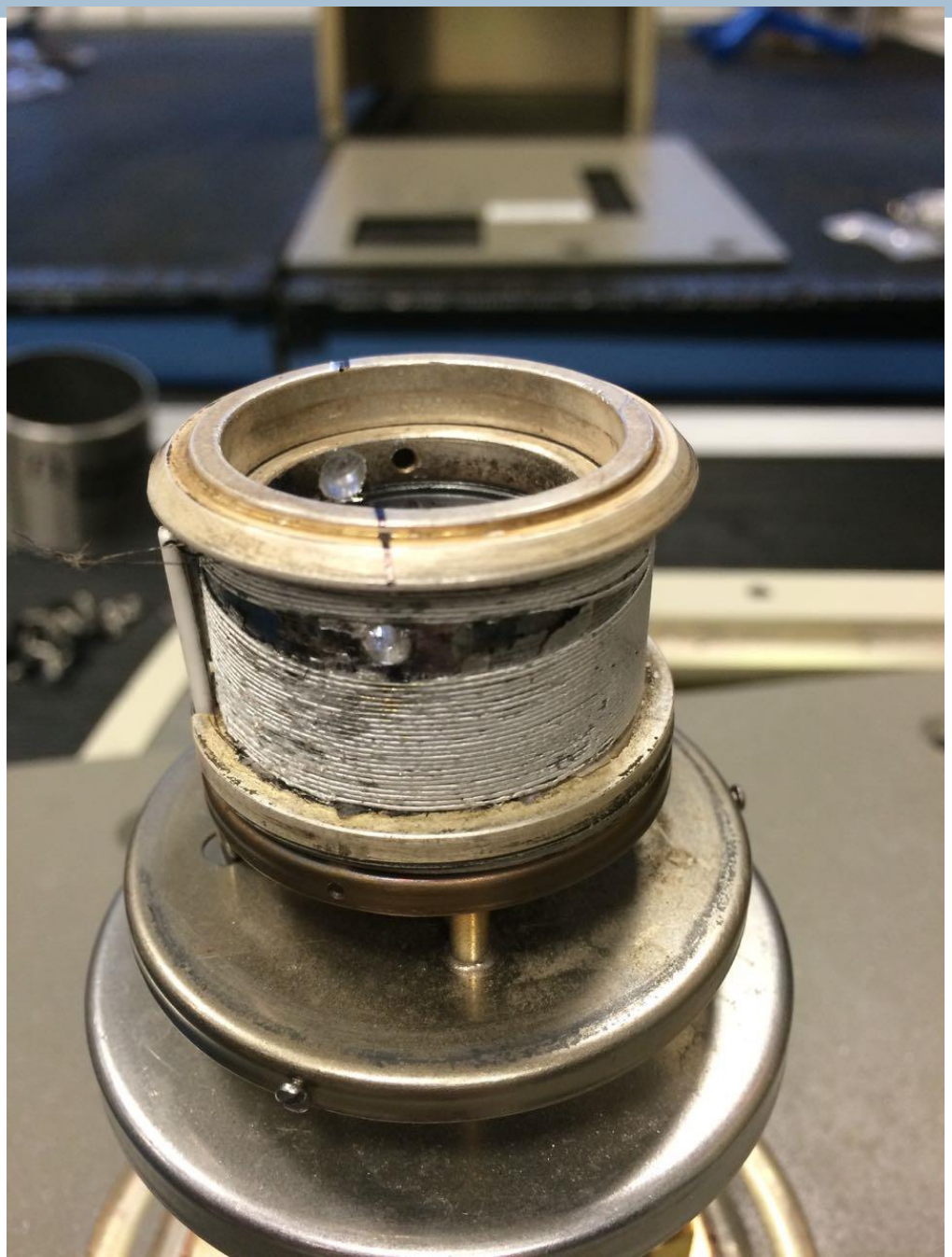
- ‘Gold standard’ analysis is single-crystal or powder XRD
- Takes a long time to record diffraction pattern
- We wanted to confirm physical form with PXRD in real-time, in the DSC pan
- Best done with a synchronous X-ray source








DSC
Q20

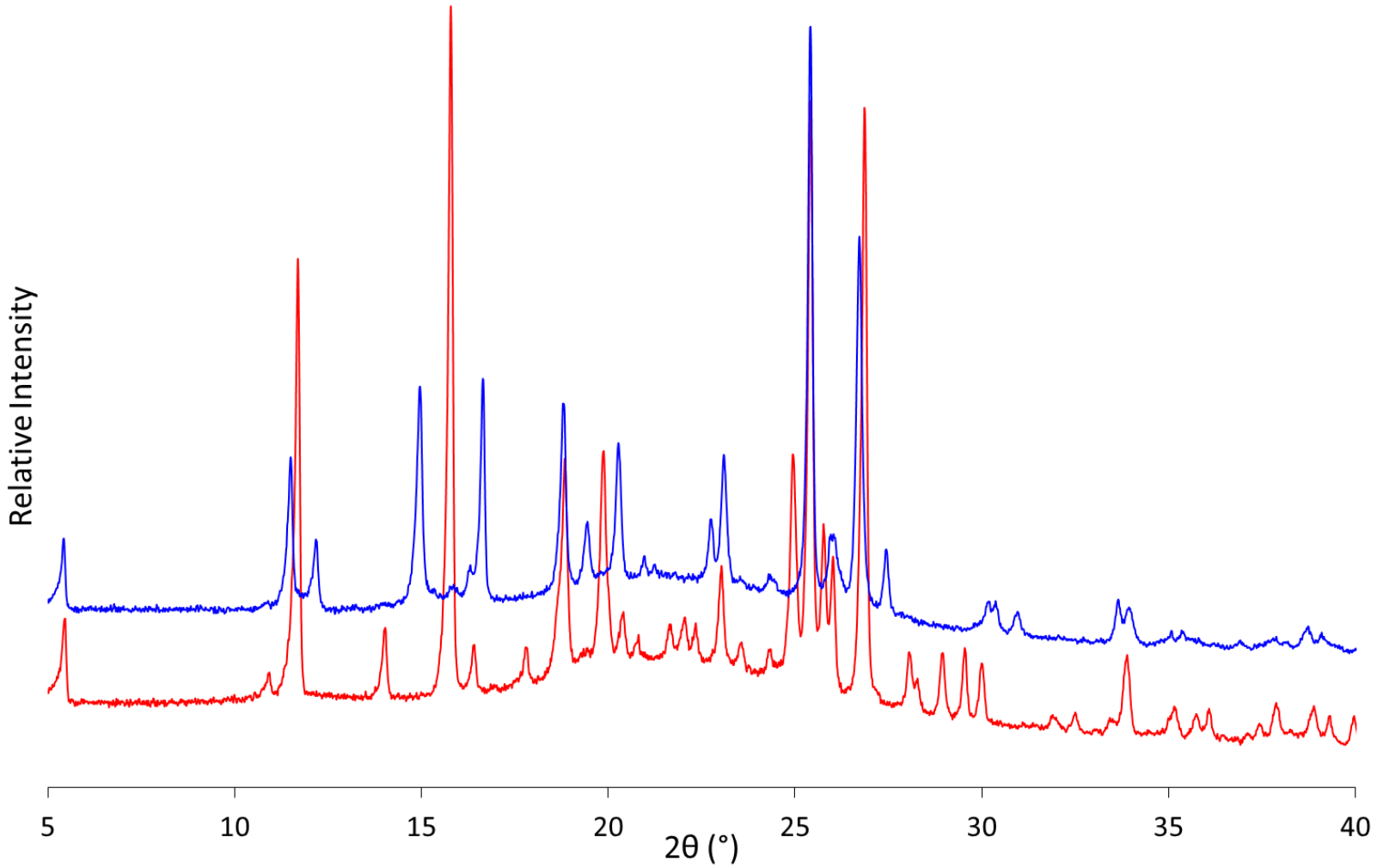


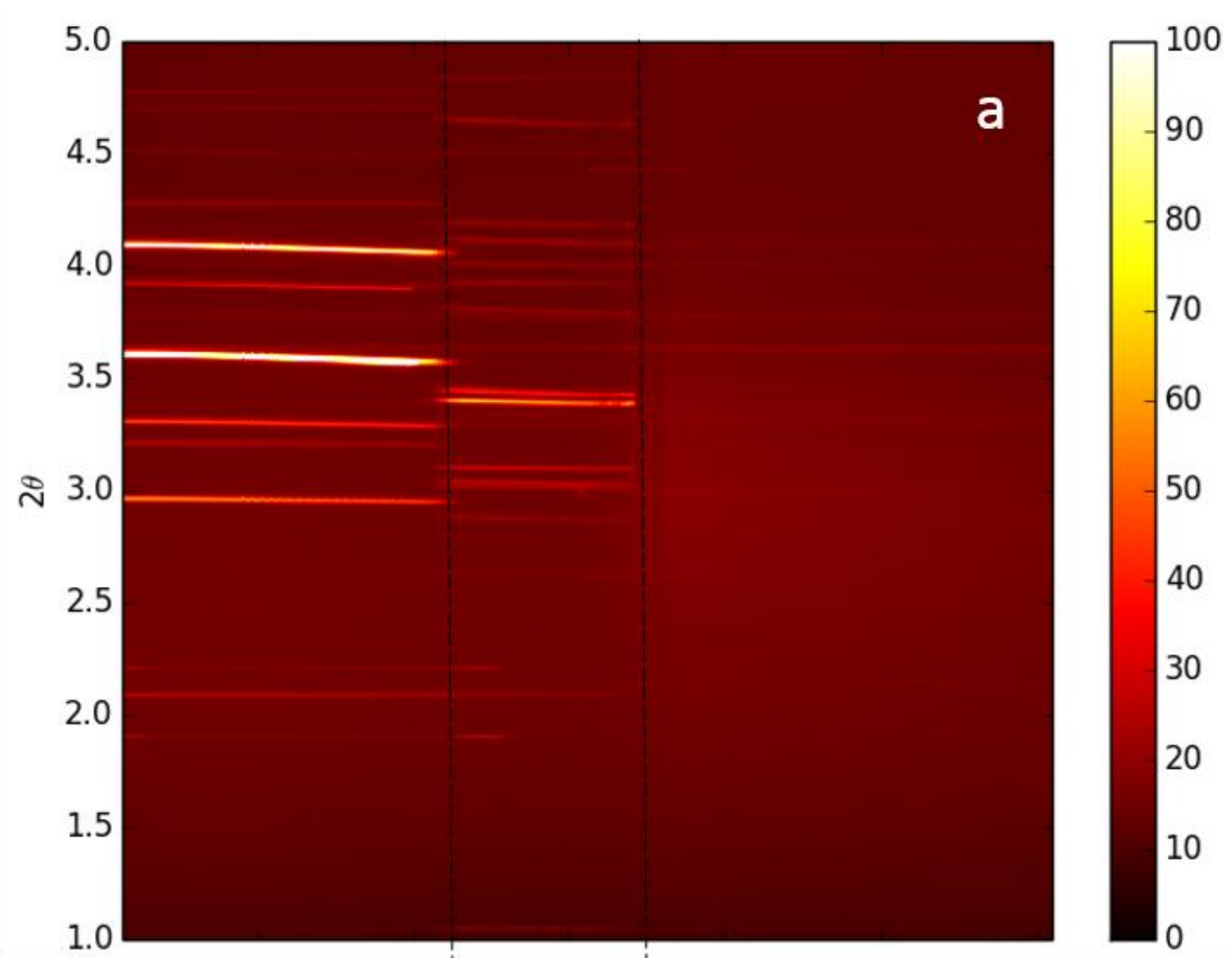
DSC for physical form characterisation

- 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?

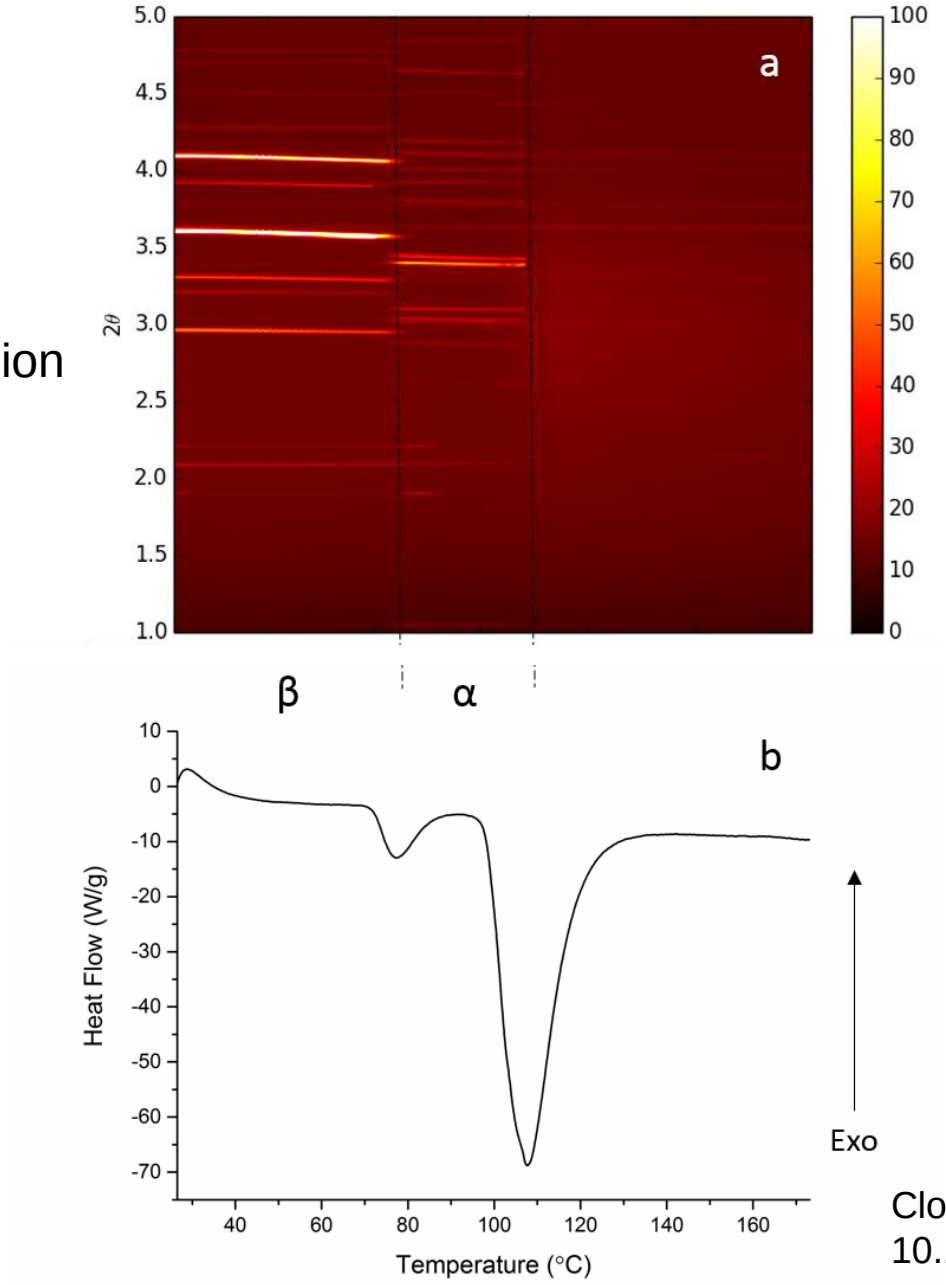



a
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
2θ
100
90
80
70
60
50
40
30
20
10
0

Glutaric acid:

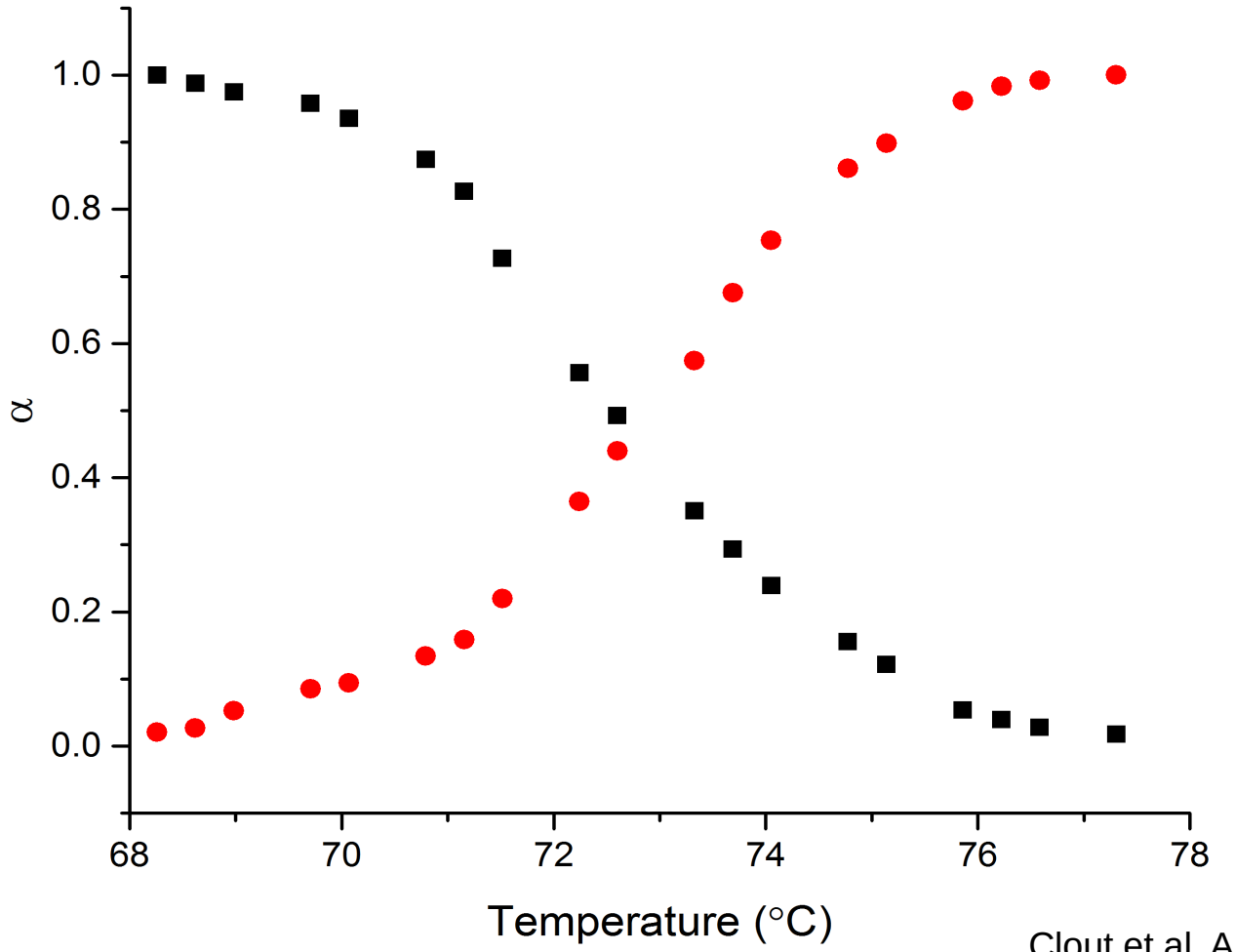
Two enantiotropic polymorphs

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



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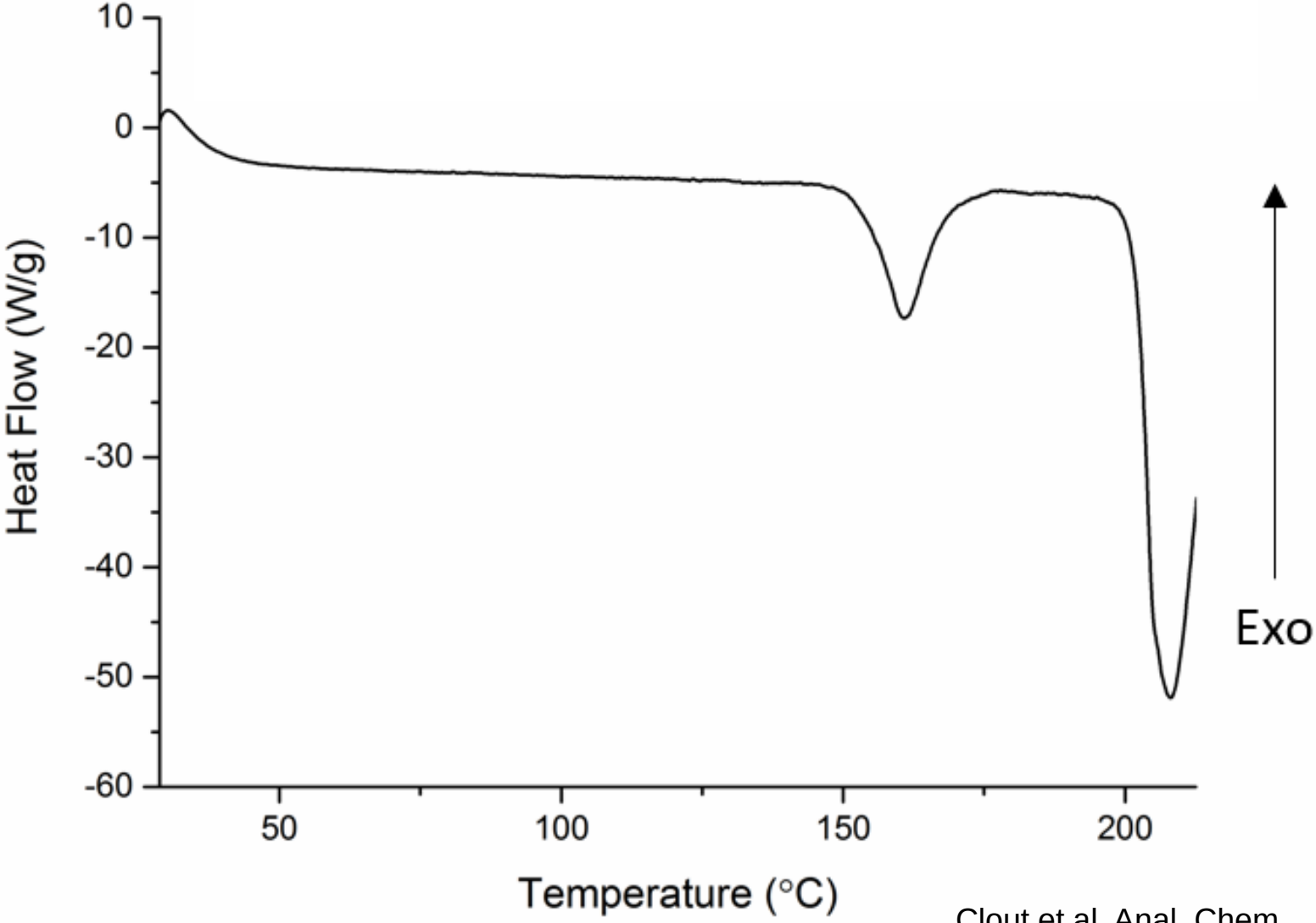
Sulphathiazole



Clout et al, Anal. Chem.
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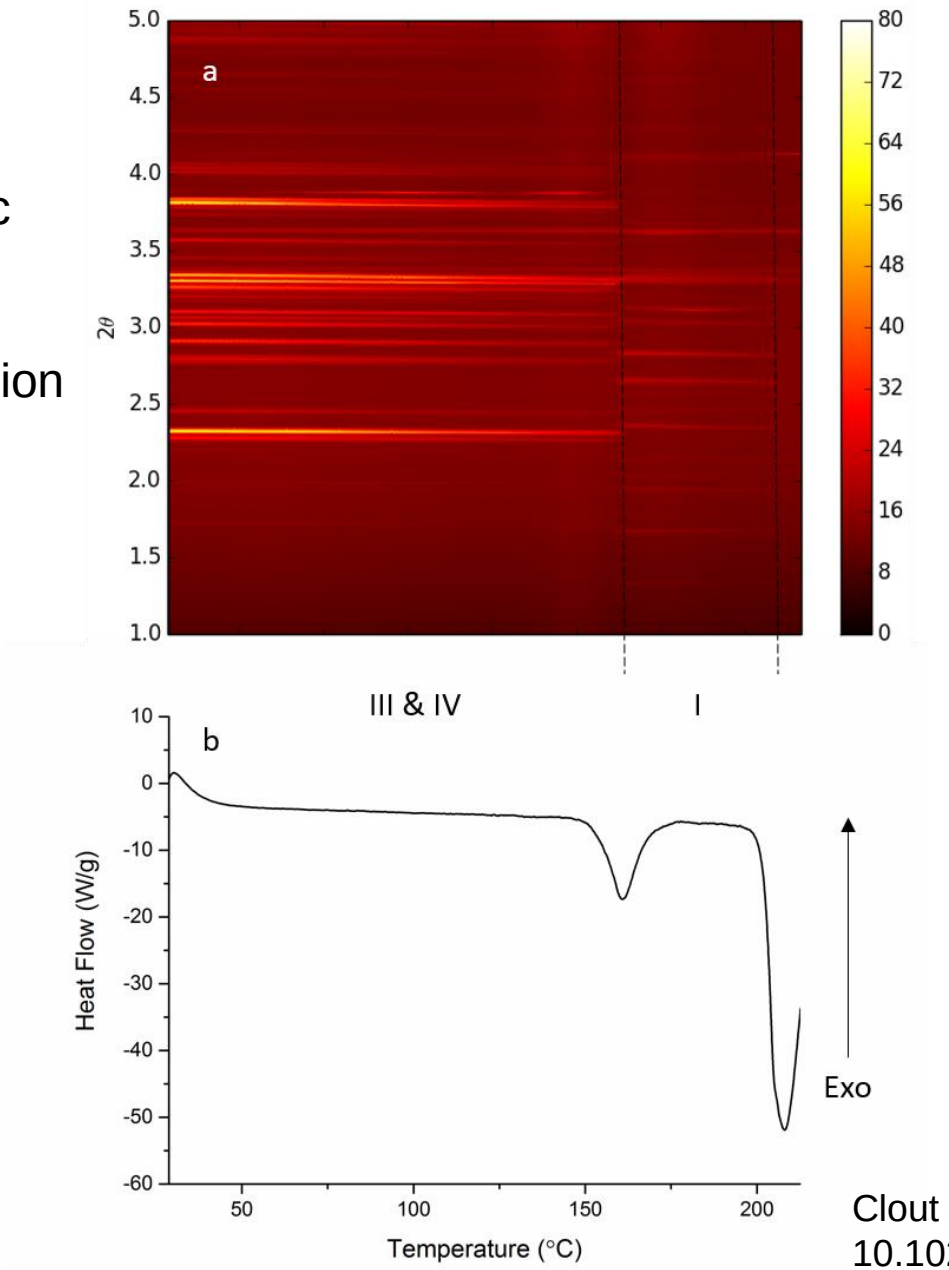
Sulphathiazole:

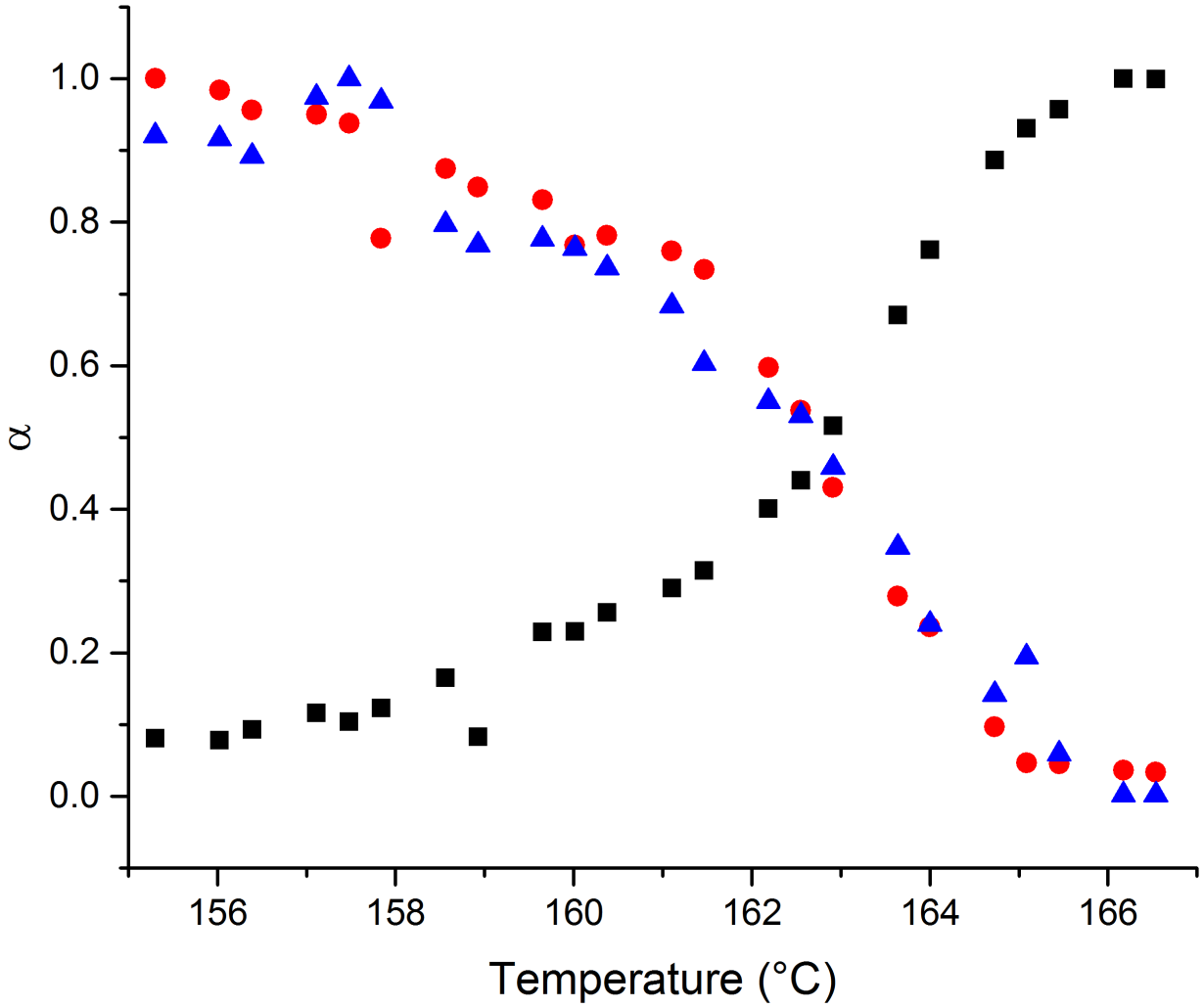
Three enantiotropic polymorphs

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.
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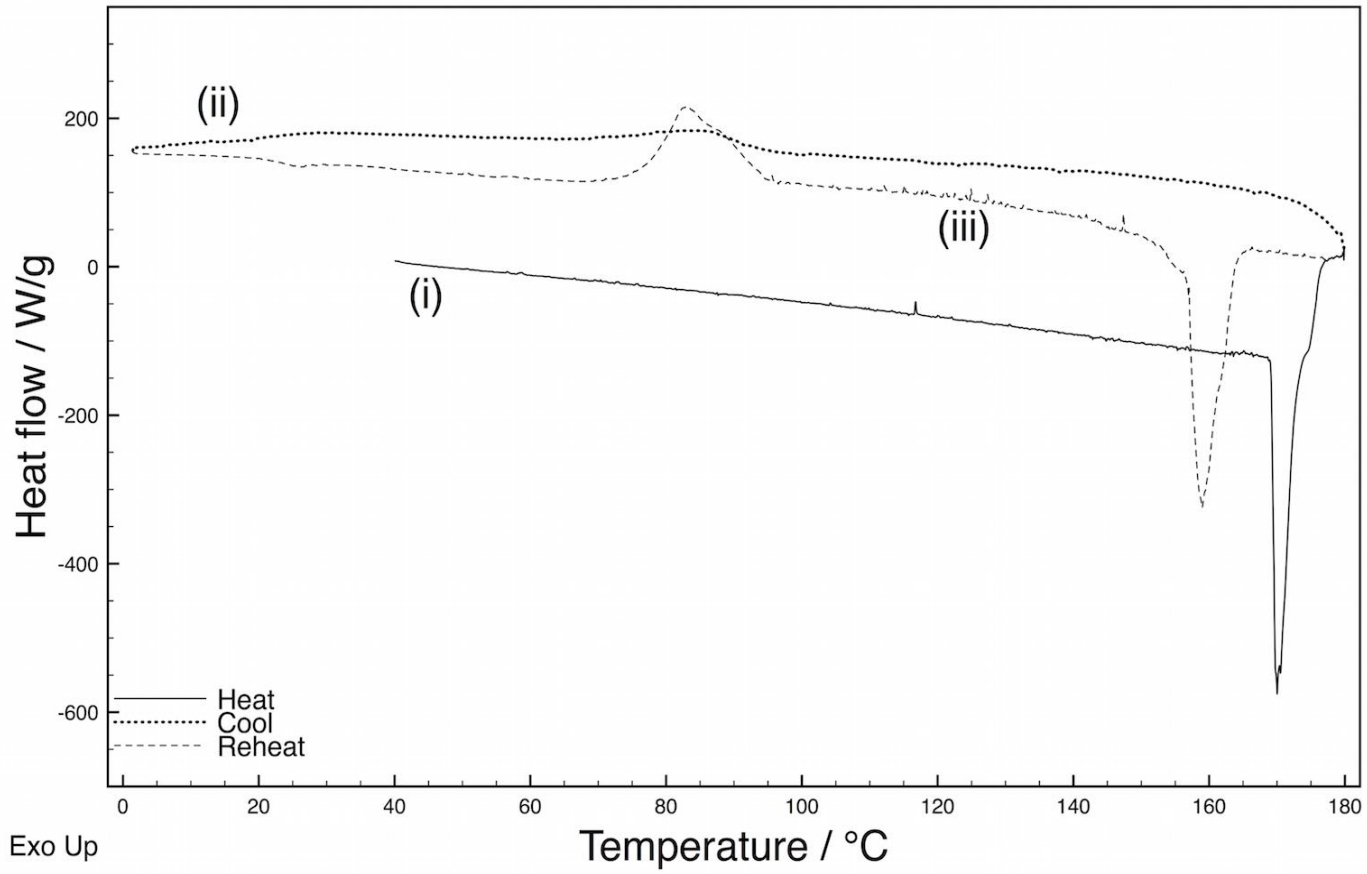
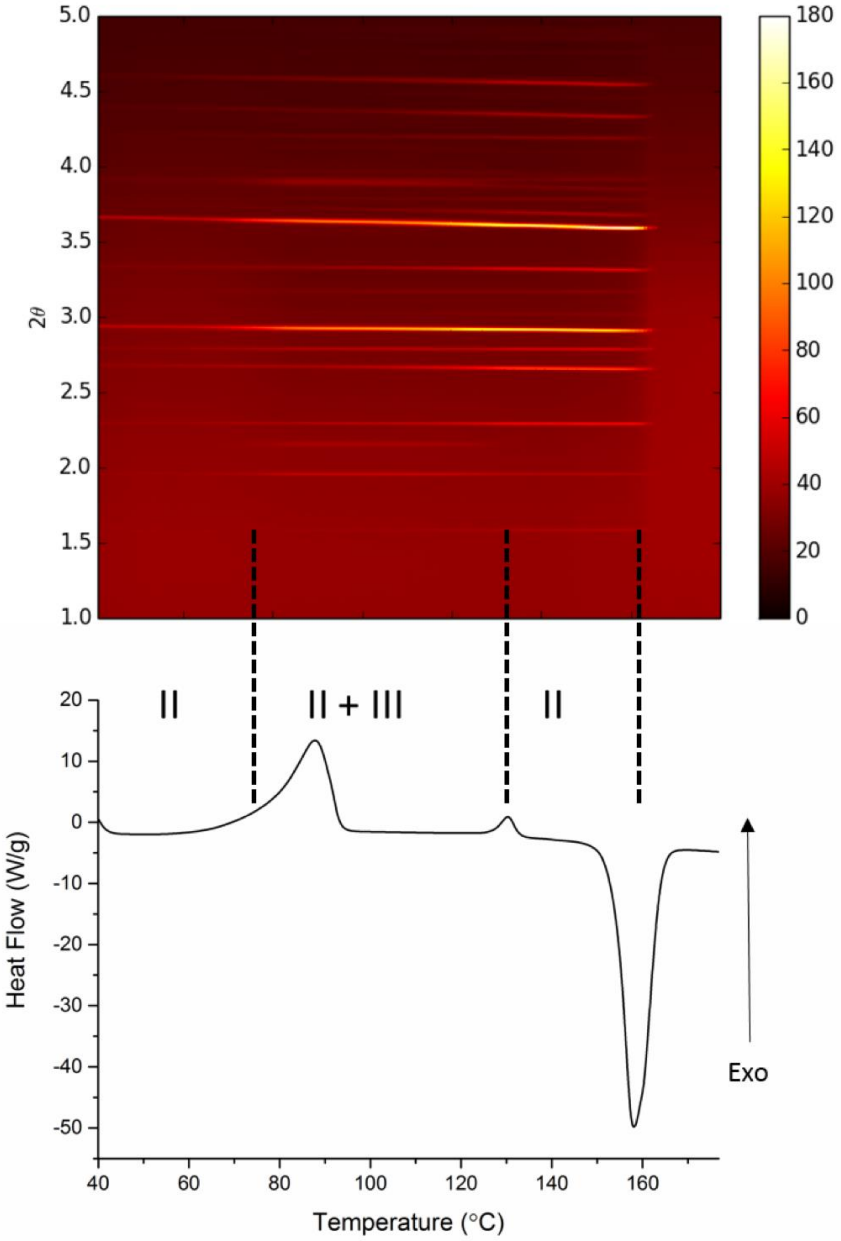
(a)

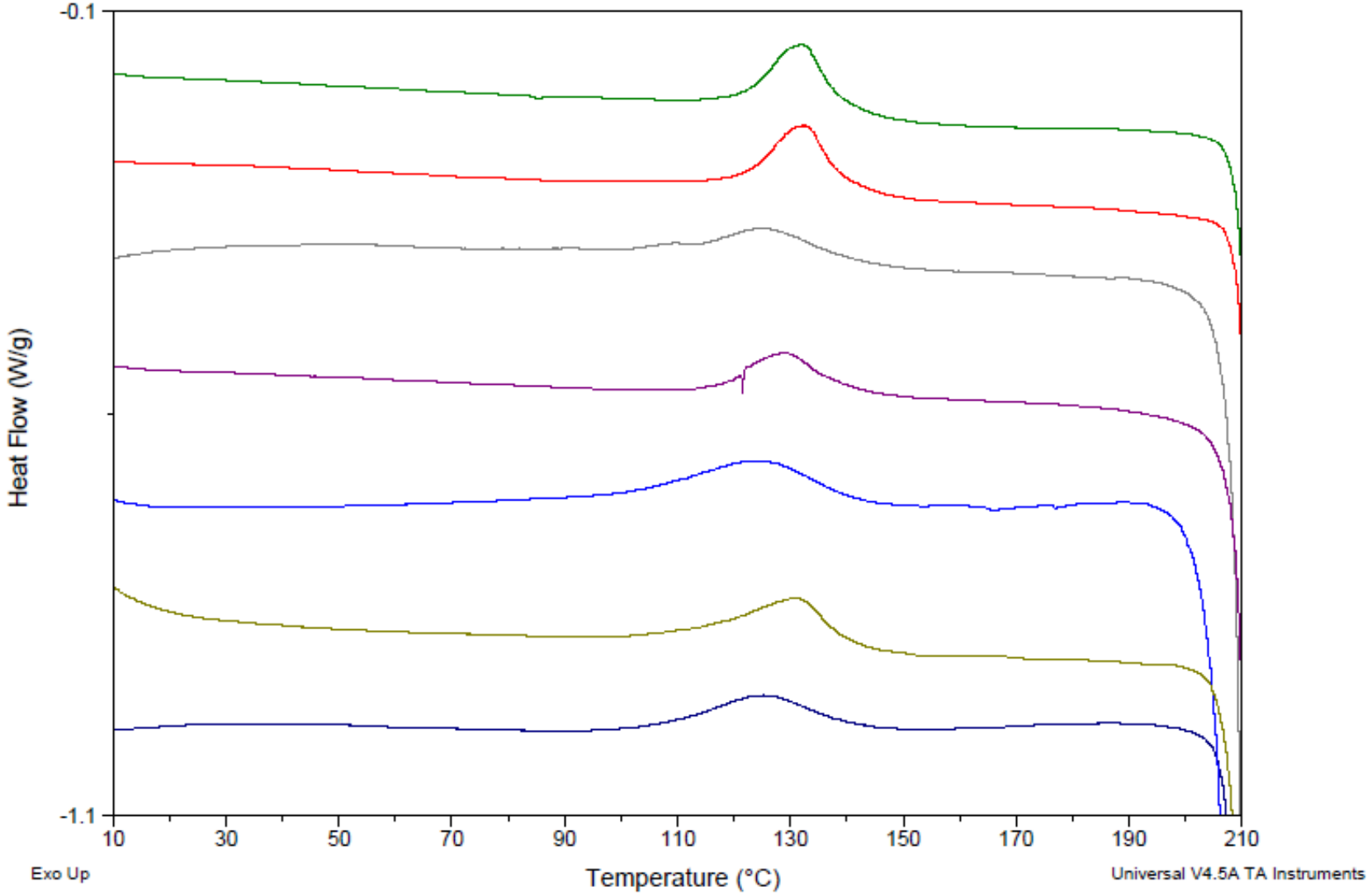

(ii)
(iii)
(i)
200
0
-200
-400
-600
Heat flow / W/g
Heat
Cool
Reheat
0
20
40
60
80
100
120
140
160
180
Exo Up
Temperature / °C

Telford et al (2016)
10.1039/c6cc05006a

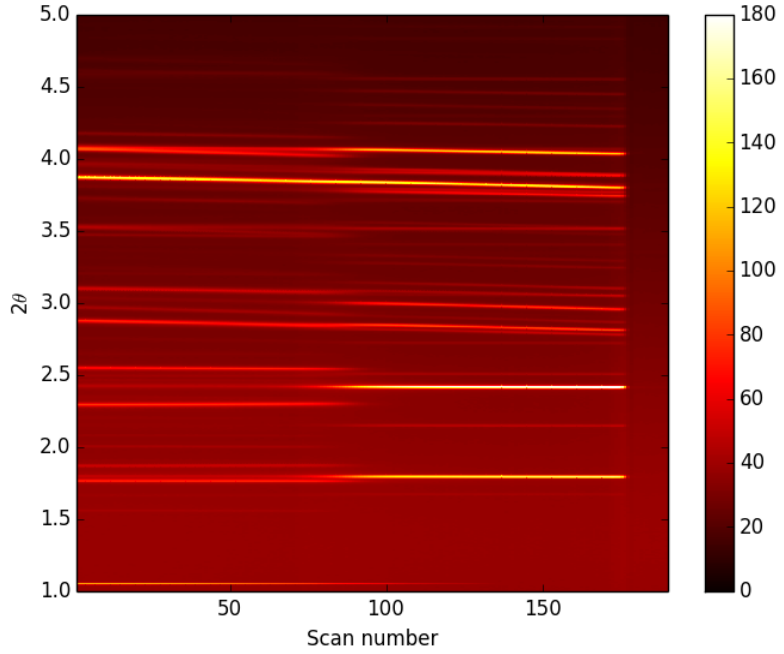
Paracetamol



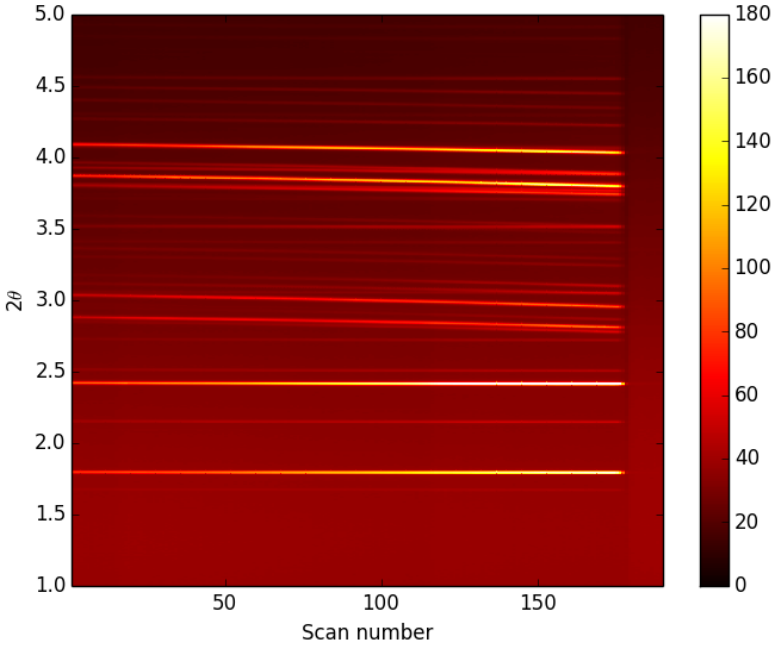
DSC of tolfenamic acid Form VII



TA VII



TA I



Heating 10 ^{o}C/min

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
- Richard Telford and Ian Scowen
- Sally Price, Derek Tocher and Rona Watson
- Jas Mahey and TA Instruments

1949 version

2016 version

diamond is a DSC's best friend