

Drug solid solutions – a method for tuning phase transformations

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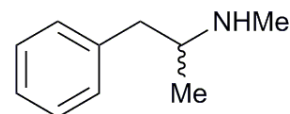
University of Strathclyde

11th March 2014

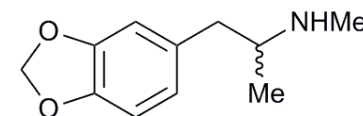
Mephedrone



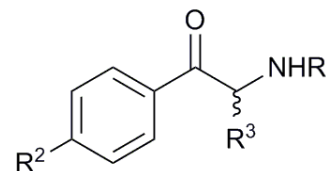
- Khat is a flowering plant native to the Horn of Africa
- Cathinones are psychoactives derived from Khat
- 'Legal highs' are materials that are structurally related to illicit materials
- Different enough to avoid legislative restrictions.
- 'Meow Meow' ((±)-4'-methylmethcathinone) reached prominence a few years ago due to deaths on clubbing scene
- Made illegal in 2010.



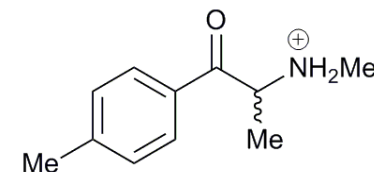
Methamphetamine



'Ecstasy'



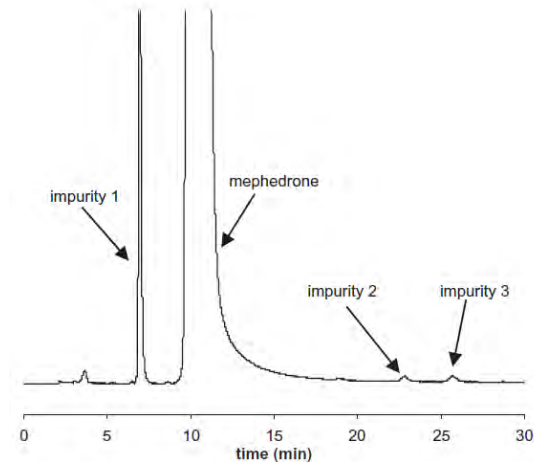
General cathinone backbone



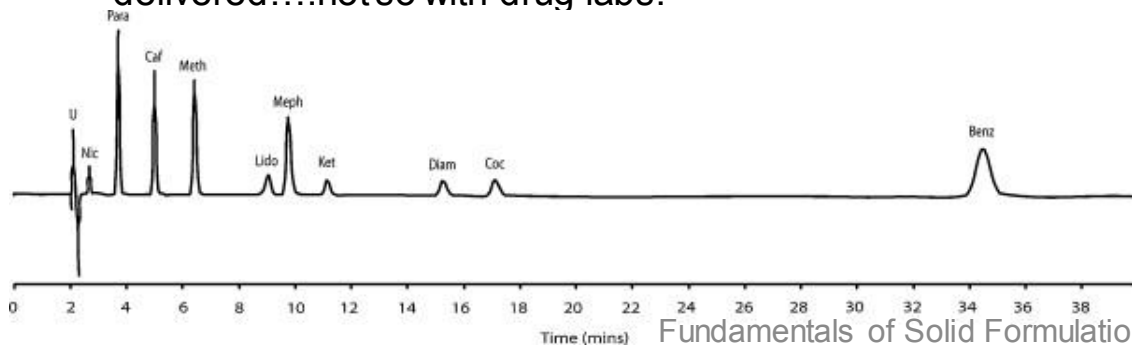
Methylmethcathinone

Mephedrone

- Street samples are rarely pure
- Many additives such as caffeine, paracetamol and benzocaine.
- Analytical protocols to identify constituents and even identifying specific labs
- But what about polymorphism?
- Polymorphs can affect solubility, bioavailability
- Regulated companies require extensive knowledge of compound so that a constant dose can be delivered....not so with drug labs.



N. Singh, P. Day, V.R. Katta, G.P. Mohammed, W.J. Lough *Journal of Pharmacy and Pharmacology*. 2010, (62)10, 1209 - 1210.



Santali, Cadogan, Daeid, Savage, Sutcliffe. *Journal of Pharmaceutical and Biomedical Analysis*. 2011, (56)2, 246–255.

Mephedrone hydrochloride



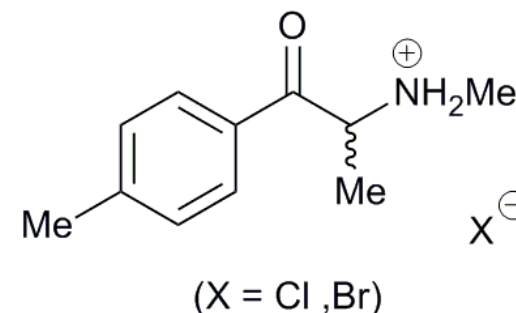
- Nycz *et al.* analysed mephedrone hydrochloride (rac) as part of a series of cathinone derivatives.
- Observed that it crystallised in monoclinic $P2_1/n$

$$a = 7.1349(7), b = 23.031(4), c = 7.4265(9) \text{ \AA}, \\ \beta = 90.477(11)^\circ, V = 1220.3(3) \text{ \AA}^3$$

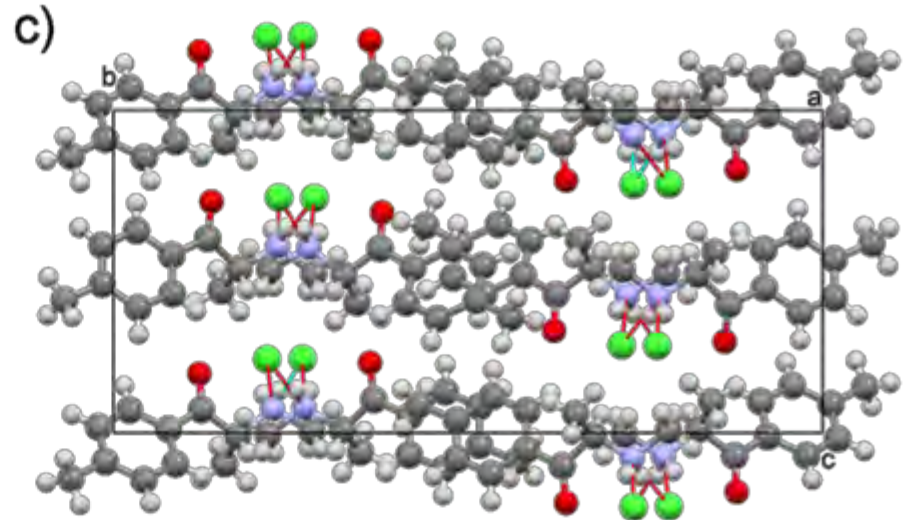
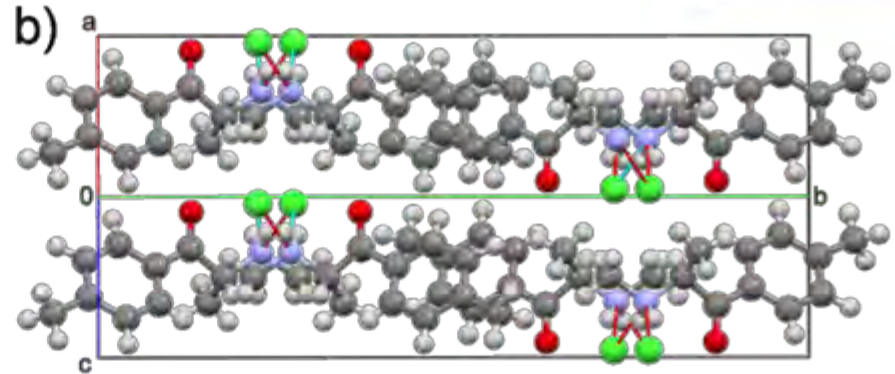
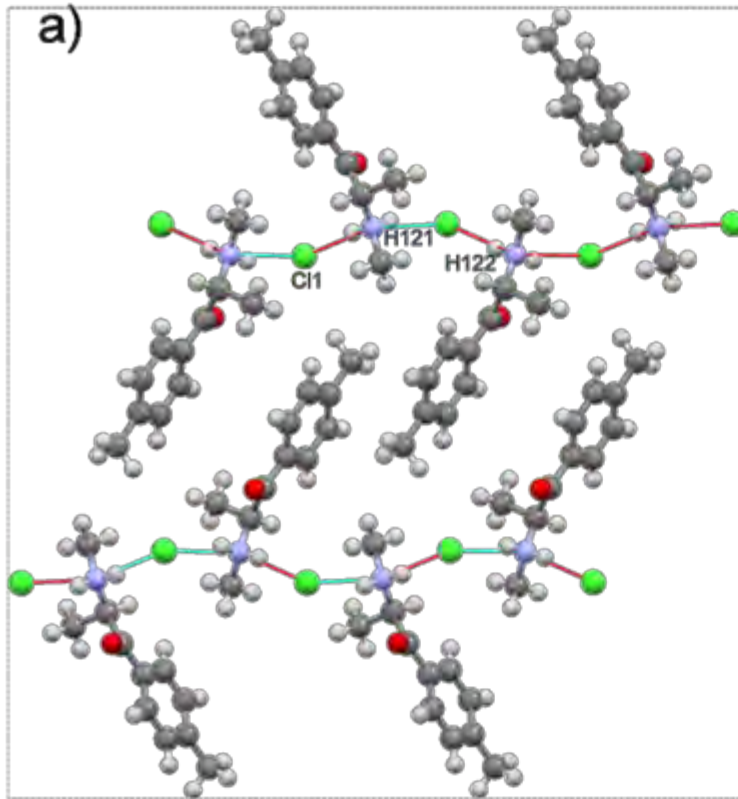
- Our own studies at 123 K showed a transition to a new phase had occurred ($P2_1/c$).

$$a = 10.0093 (3), b = 22.8207 (8), c = 10.4016 (4) \text{ \AA}, \\ \beta = 91.416 (2)^\circ, V = 2375.20 (14) \text{ \AA}^3$$

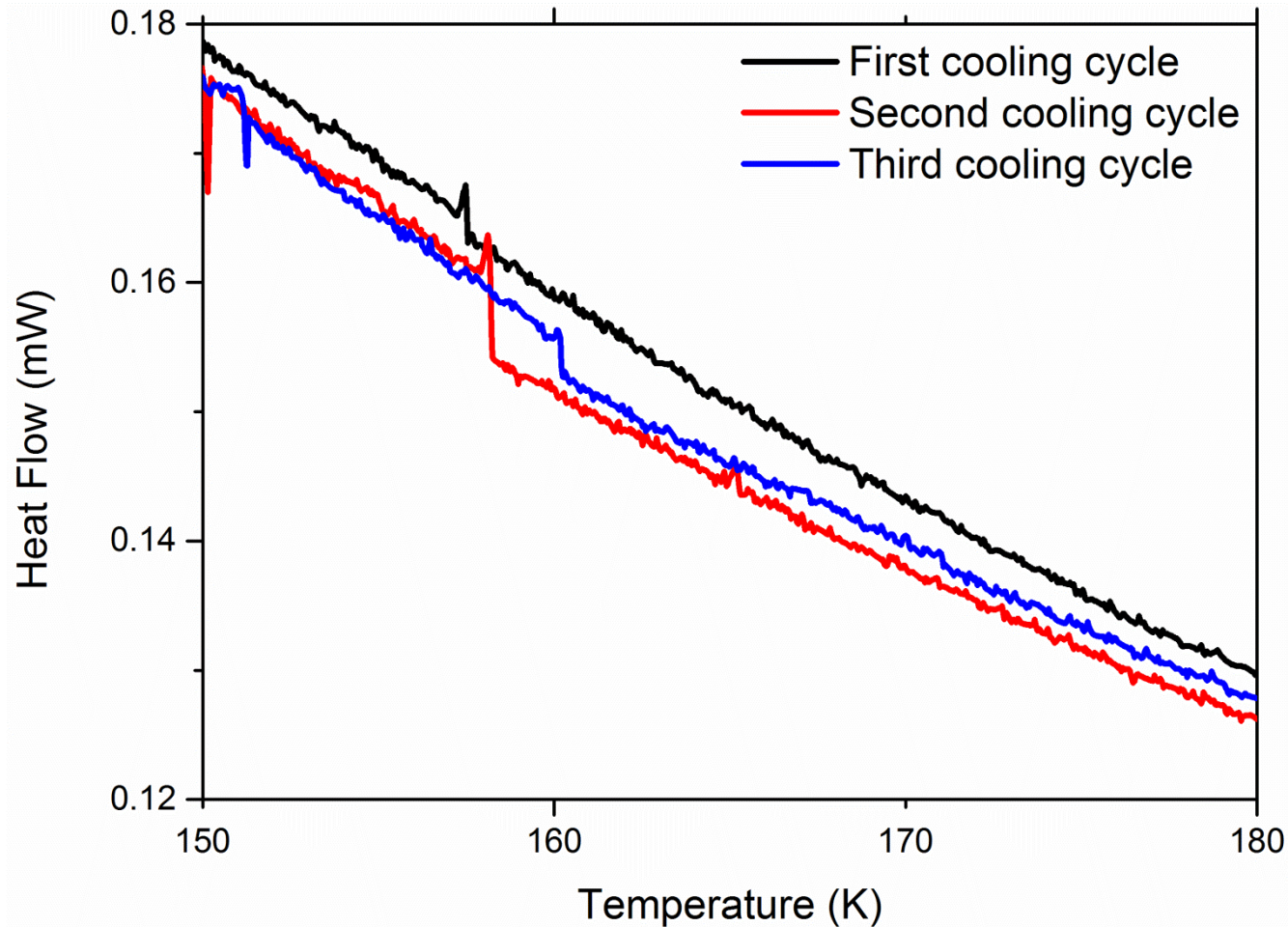
J. E. Nycz, G. Malecki, M. Zawiazalec and T. Pazdziorek,
Journal of Molecular Structure, 2011, 1002, 10-18.



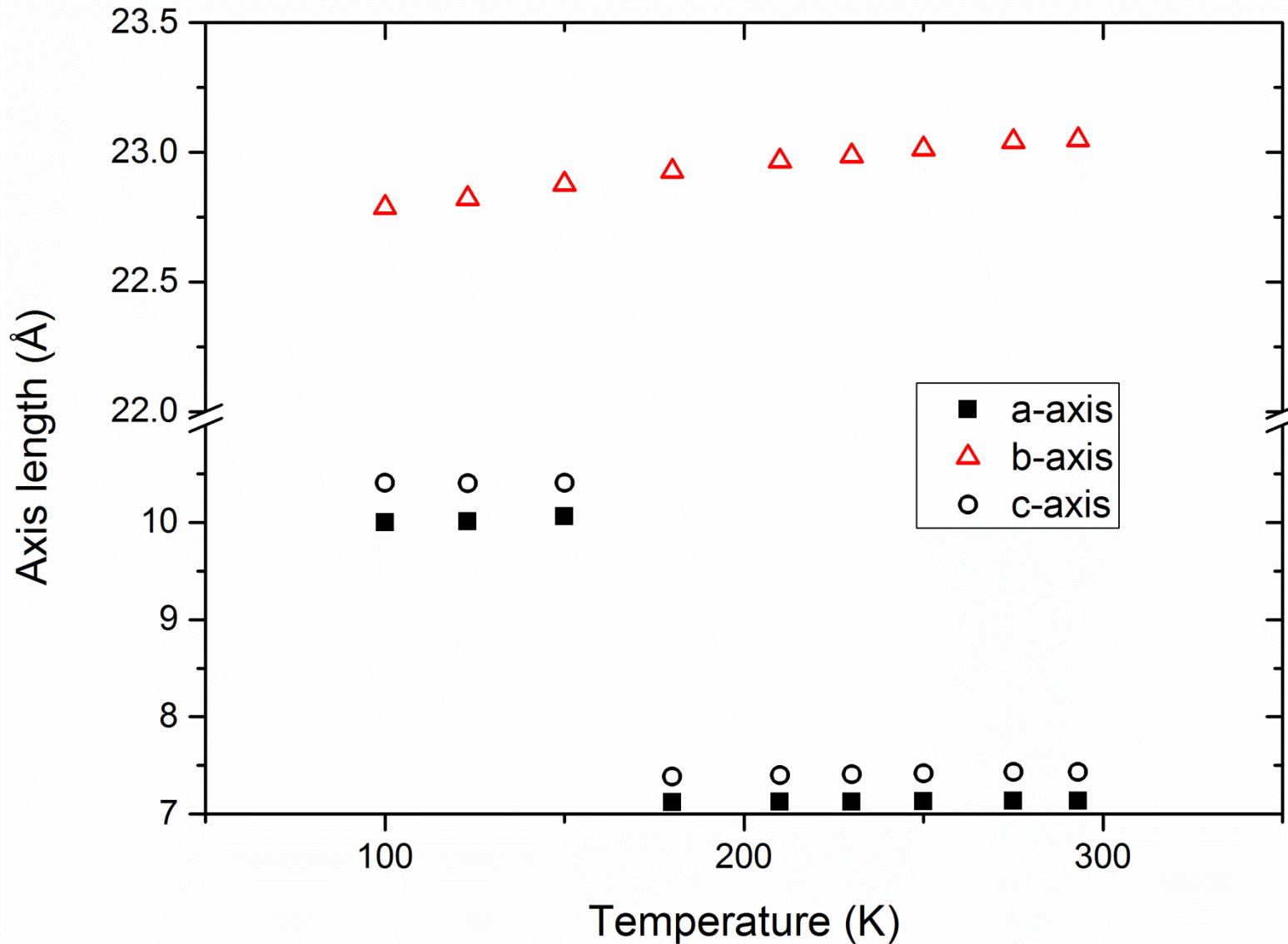
Mephedrone hydrochloride



Where does the phase transition occur?



Mephedrone hydrochloride



Mephedrone hydrobromide



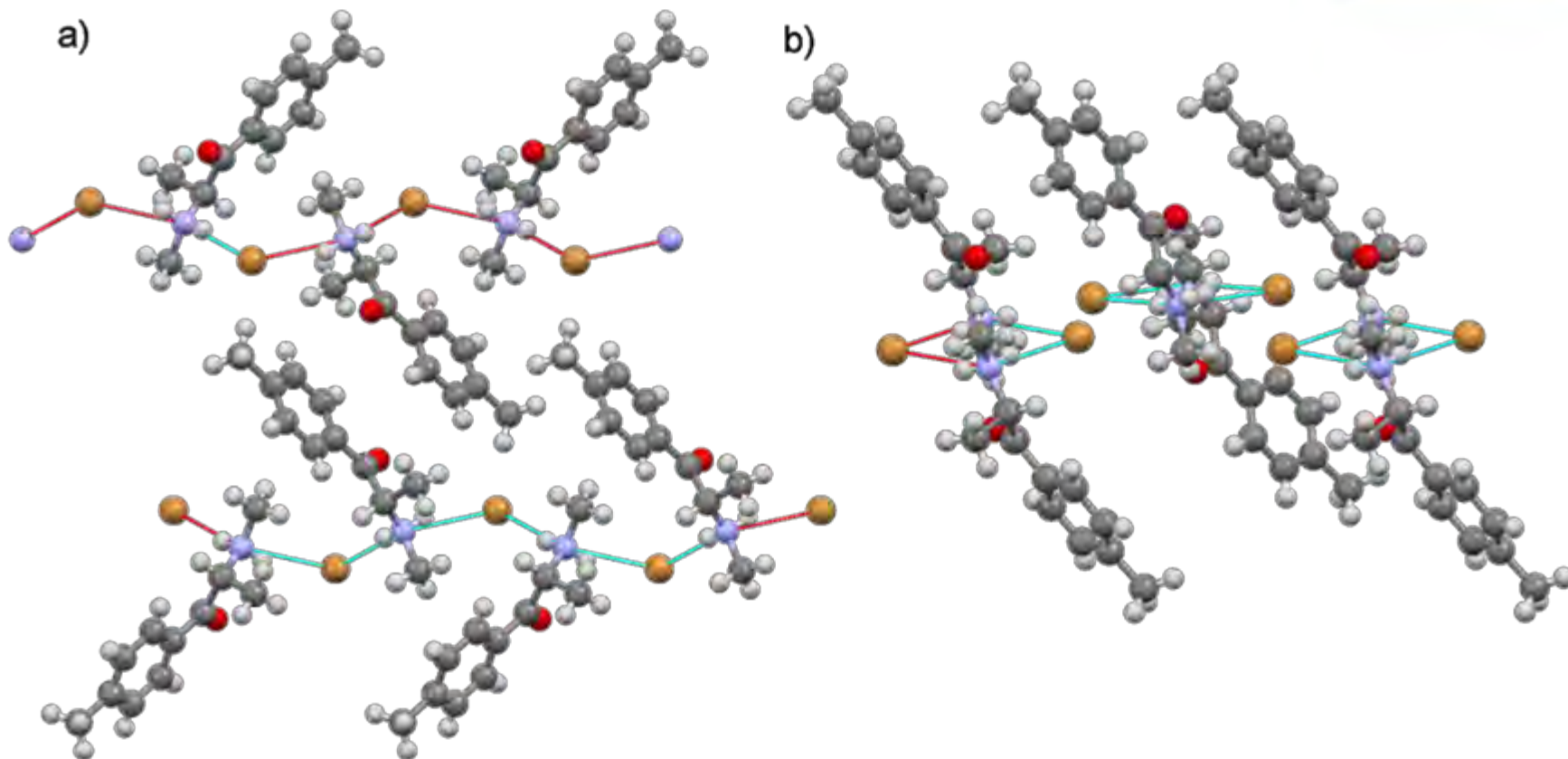
- Mephedrone hydrobromide (rac) crystallises in two polymorphs.
- Recrystallisation from most solvents gives Form I occurs monoclinic $P2_1/c$

$$a = 5.7804 (4), b = 19.7971 (14), c = 10.5967 (6) \text{ \AA}, \\ \beta = 100.841 (3)^\circ, V = 1190.99 (14) \text{ \AA}^3$$

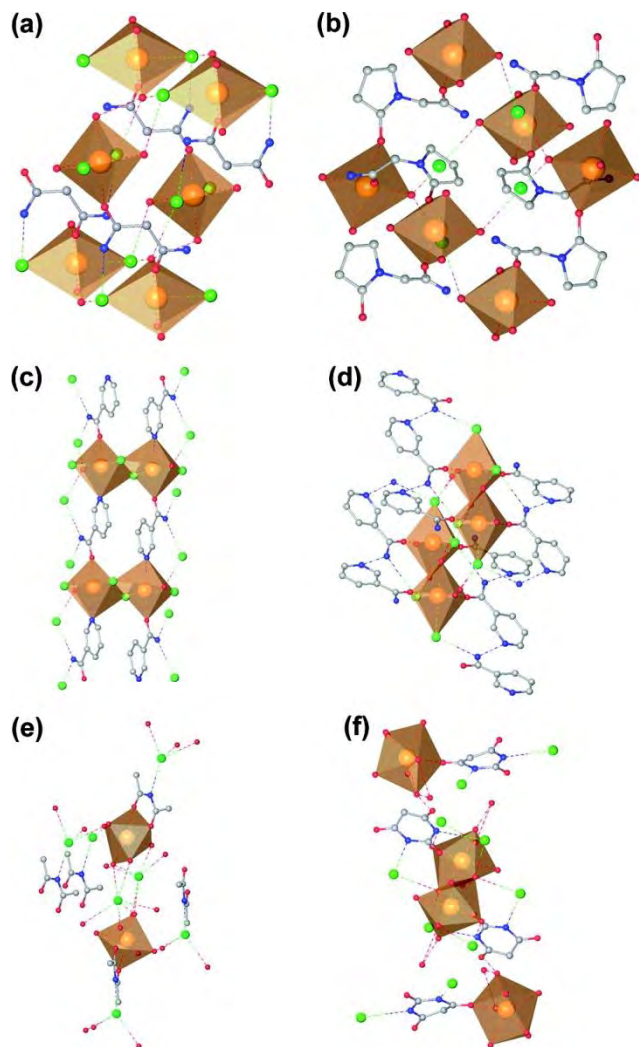
- Recrystallisation from methanol/ethanol gives Form II ($P2_1/c$).

$$a = 10.8355 (19), 10.2030 (17), 11.5425 (19) \text{ \AA} \\ \beta = 111.839 (8)^\circ, V = 1184.5 (4) \text{ \AA}^3$$

Mephedrone hydrobromide



Ionic co-crystals



- Braga and co-workers have investigated ionic co-crystals
- Reacted ionic salts e.g. CaCl_2 with organic materials to create novel entities
- “The possibility of increasing the thermal stability of an organic molecule or that of changing the dissolution and solubility properties by ionic co-crystallization may have important implications in all areas”

D. Braga, F. Grepioni, G. I. Lampronti, L. Maini and A. Turrina, *Crystal Growth & Design*, 2011, **11**, 5621-5627

Hypothesis



Can the temperature of the phase transition be altered via doping with bromide?

Co-crystallisation



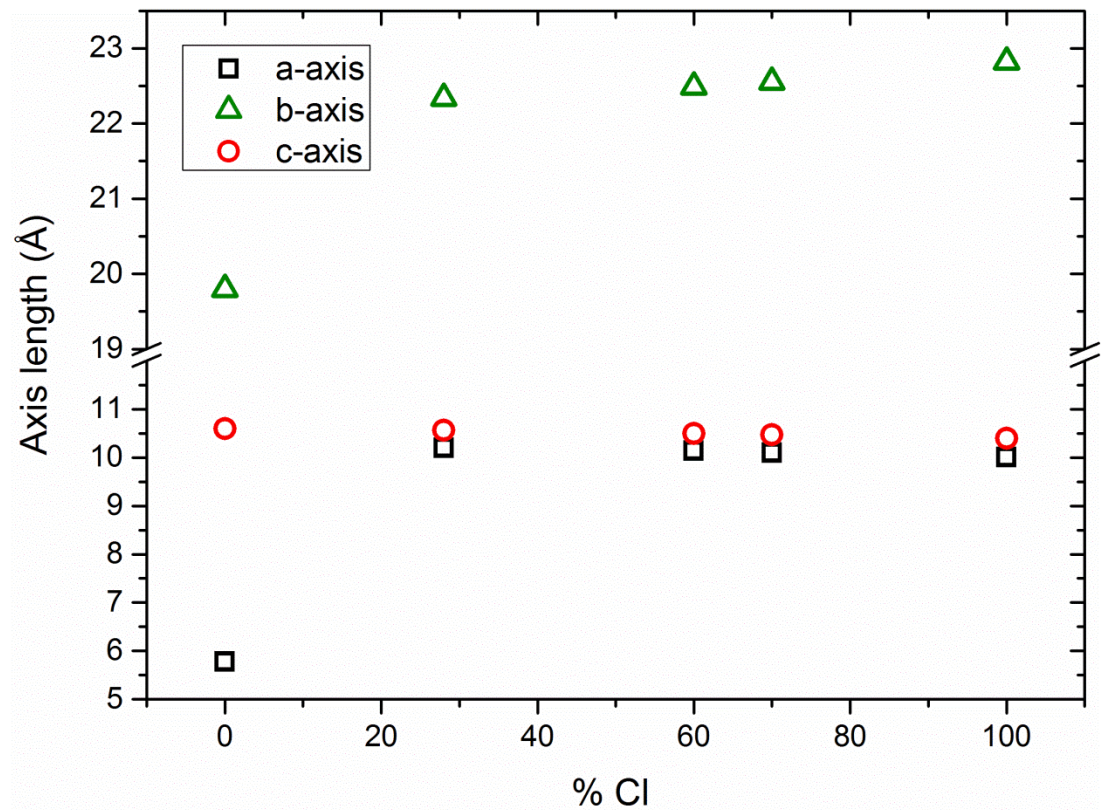
- Molar ratios of 70:30, 50:50 and 30:70 HCl:HBr were weighed out and recrystallised from an acetone:methanol mixture.
- Only powder produced – vapour diffusion used to form single crystals

Co-crystallisation

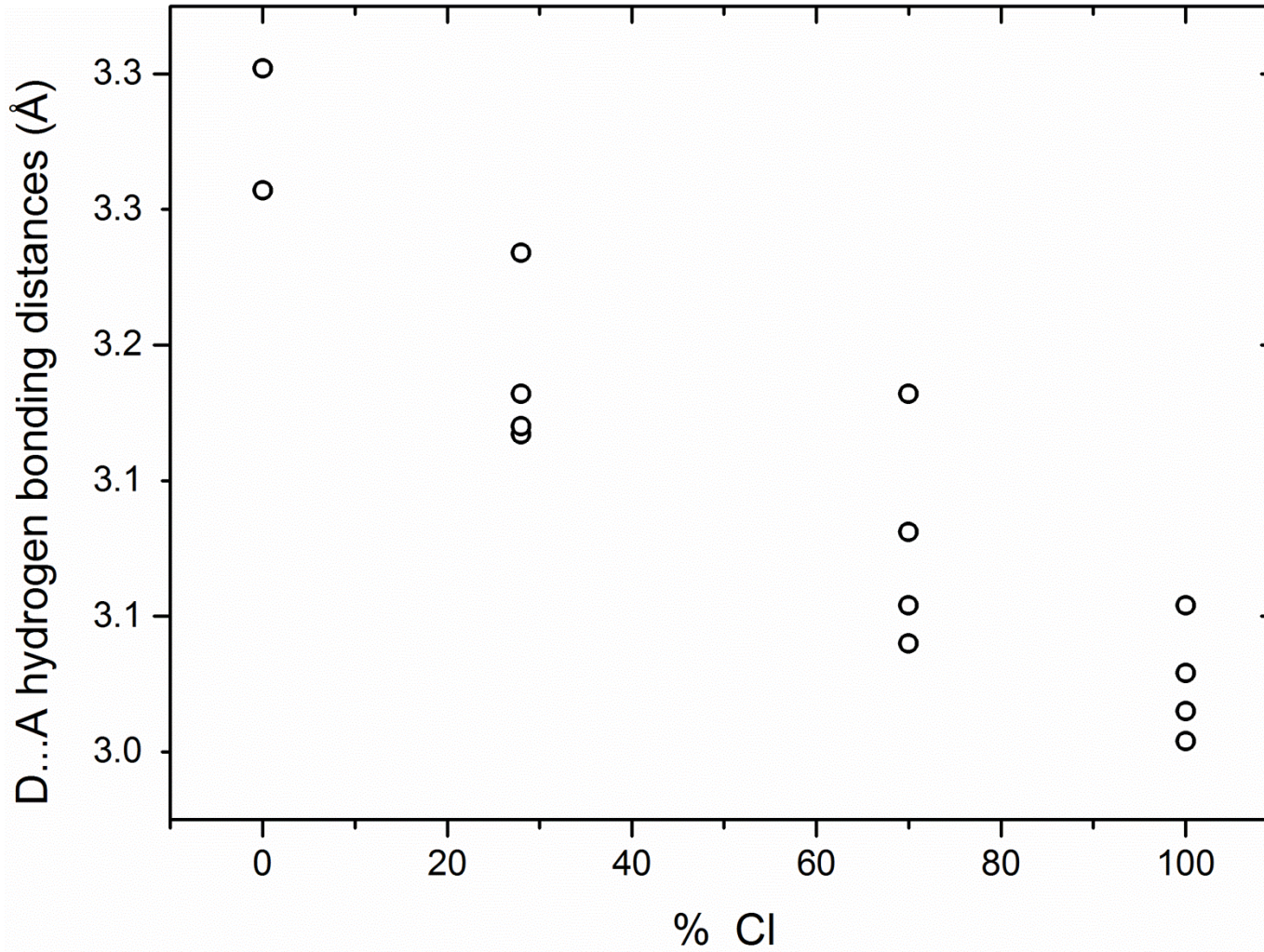


- SXD studies showed that from these crystallisations we isolated a 70:30, 60:40 & 28:72 solid solutions

- All the solid solutions exhibited low and high temperature forms
- Unit cell parameters similar to HCl salt



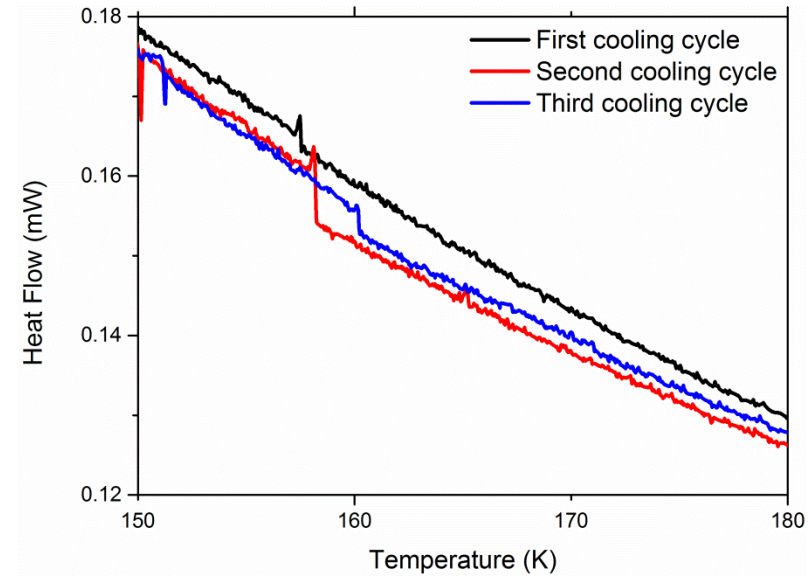
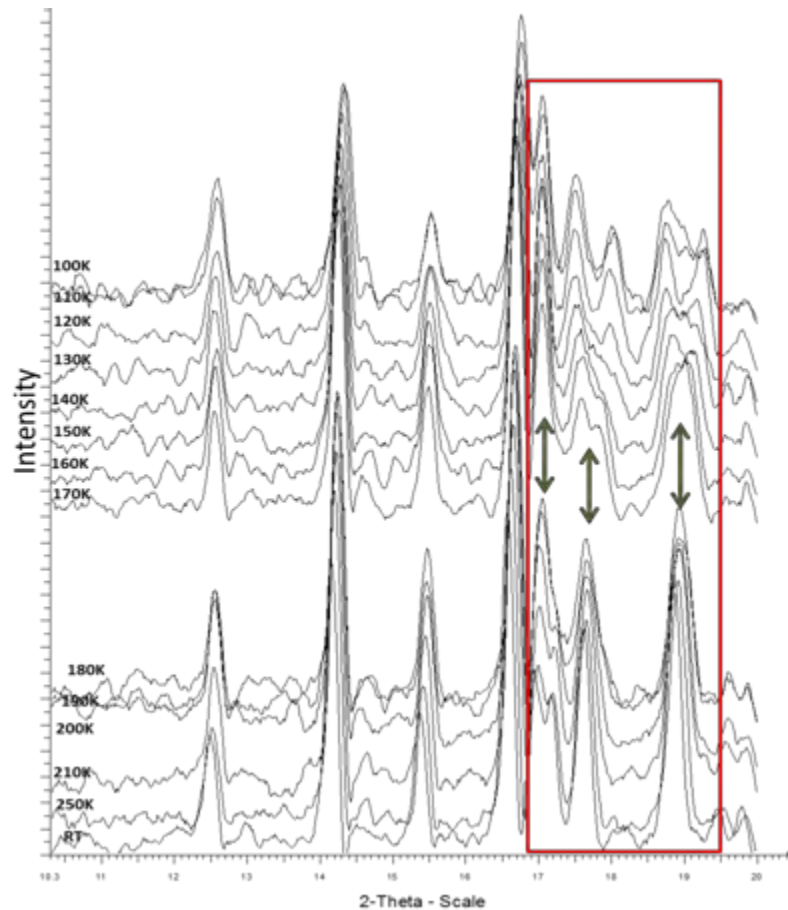
Hydrogen bonding



Phase transition temperature



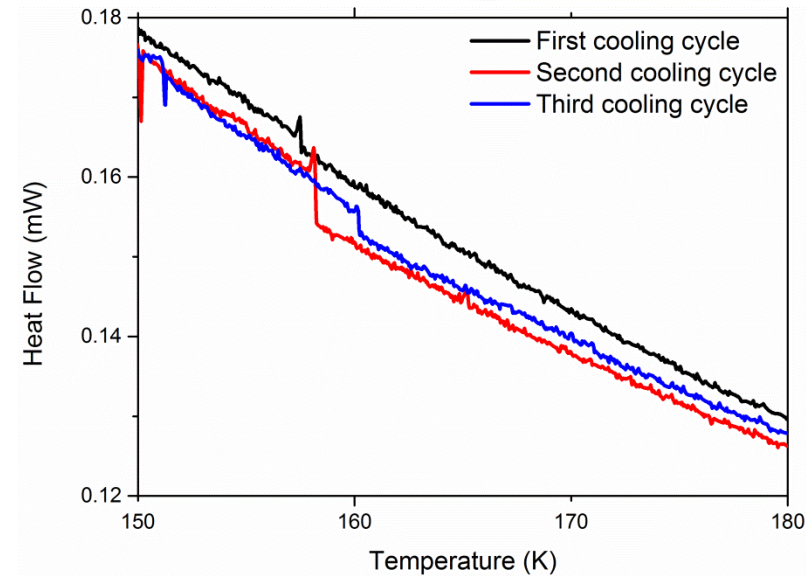
- Mephredone.HCl showed a transition between 158-160 K.



Phase transition temperature

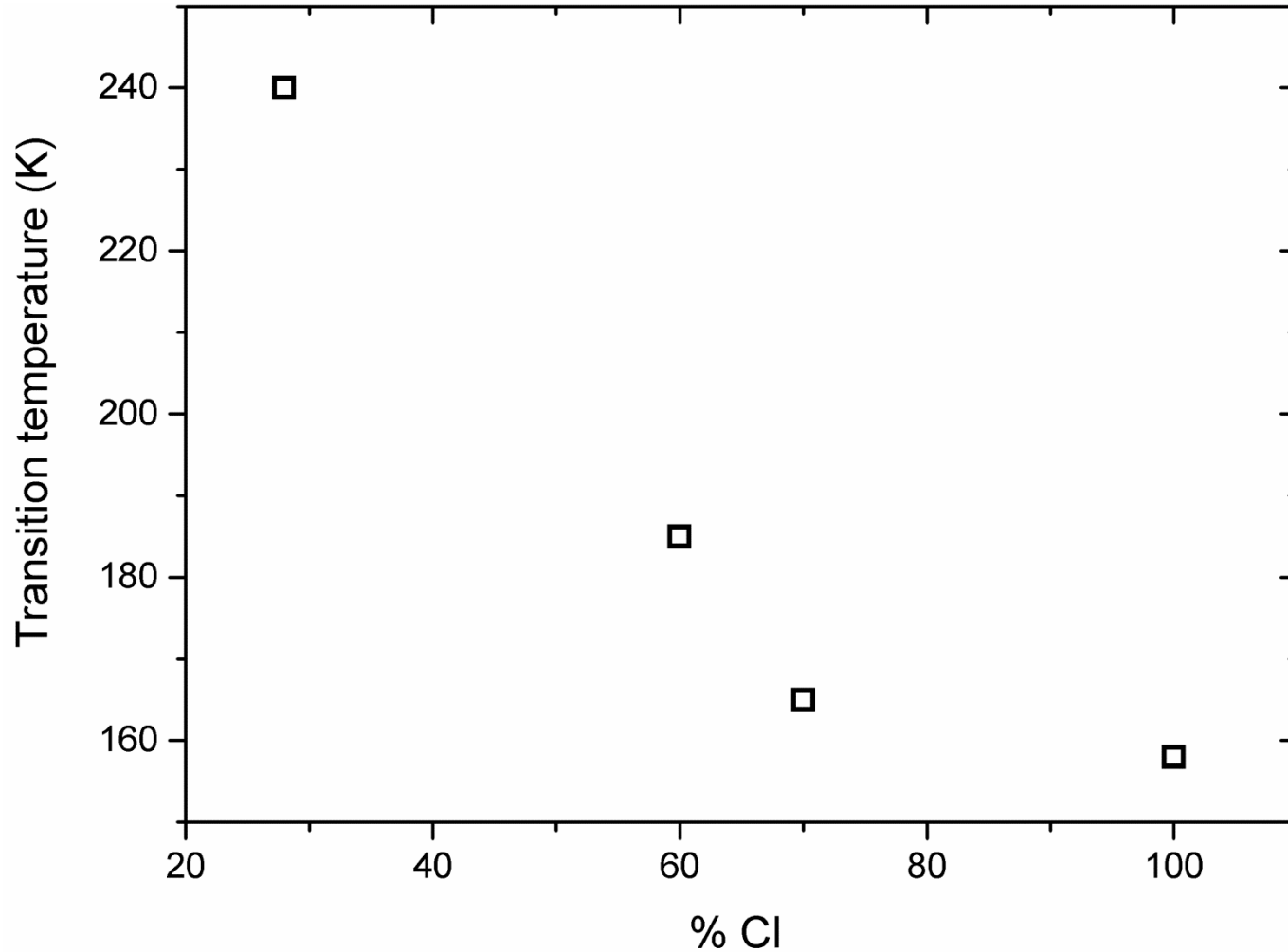


- Mephredone.HCl showed a transition between 158-160 K.
- Solid Solution transition temperatures via SXD.
- Monitored unit cell parameters as a function of temperature.
- All solid solutions could be indexed with both LT and HT unit cell parameters over the transition period.

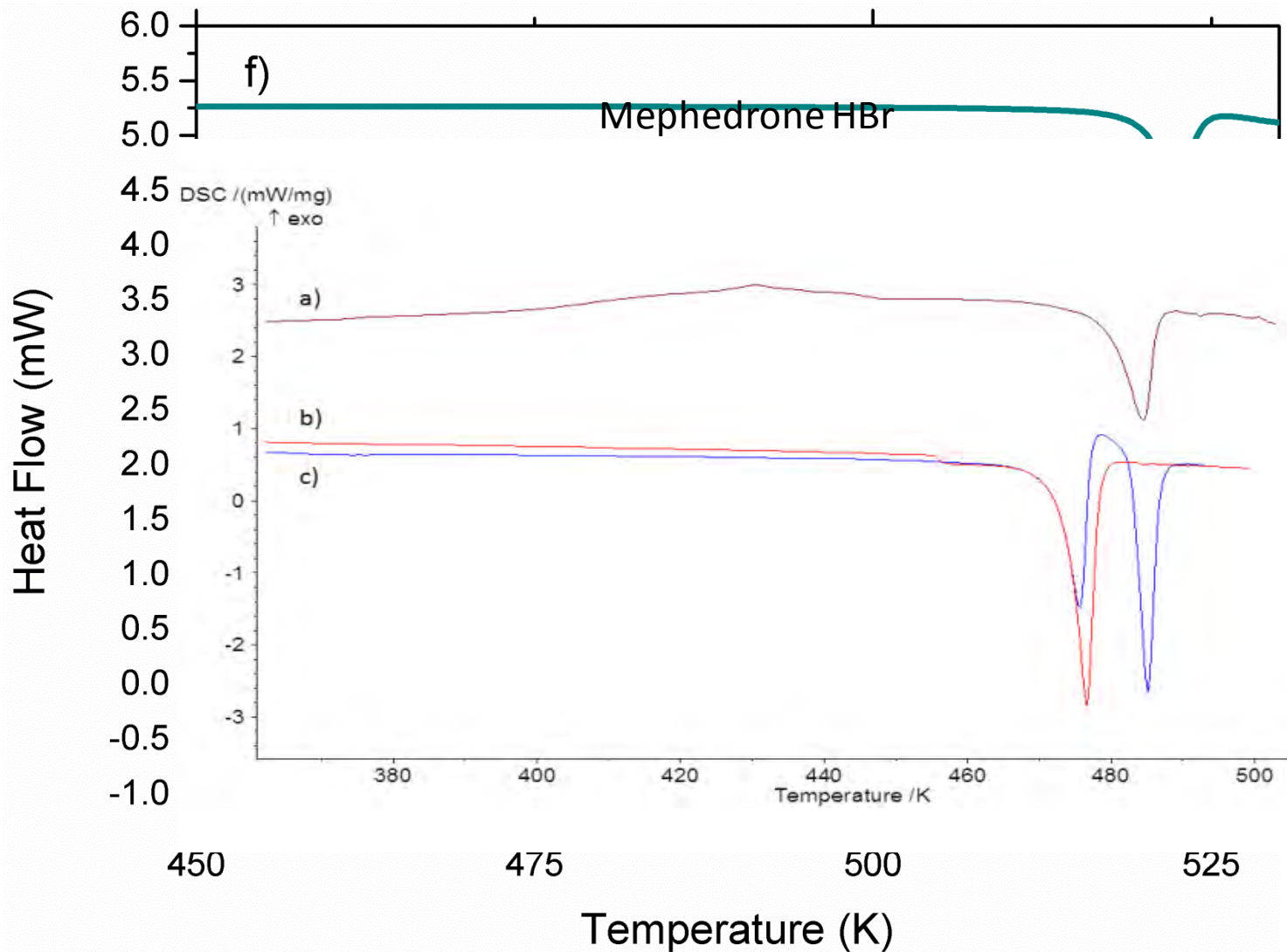


30% Cl						
Temp (K)	a (Å)	b (Å)	c (Å)	β (°)	Volume (Å ³)	No. reflections
250	7.332(7)	22.43(4)	7.615(11)	93.23(9)	1251(3)	184
240	7.36(2)	22.48(5)	7.676(19)	93.38(4)	1268(9)	156
240	10.42(2)	22.59(4)	10.61(2)	90.62(3)	2496(14)	384
235	7.310(2)	22.42(2)	7.632(5)	93.3(4)	1248.9(15)	165
235	10.299(8)	22.51(2)	10.567(6)	90.15(5)	2450(3)	581
220	10.286(3)	22.478(7)	10.5846(19)	90.369(17)	2447.1(12)	774

Phase transition temperature



Melting points of solid solutions



**Mephedrone.
HCl**

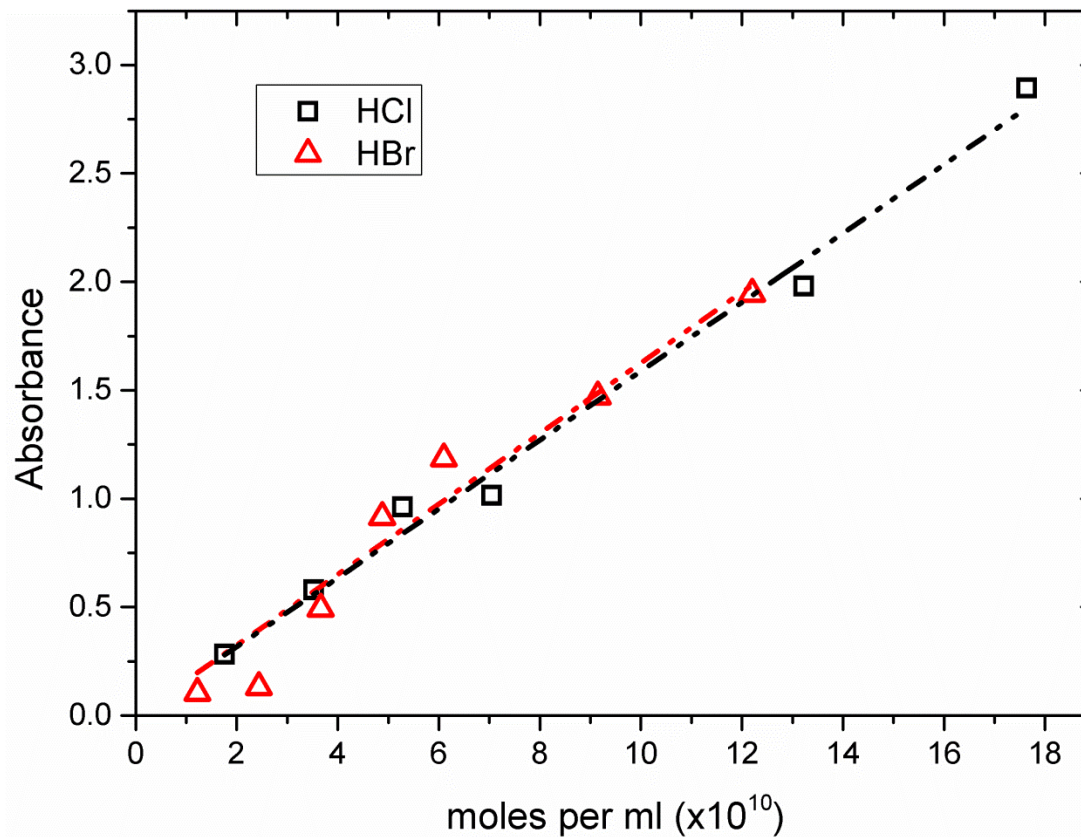
**SS-
70:30**

**SS-
60:40**

**SS-
28:72**

Solubility

- Solubility measured for both HCl and HBr salts via UV absorbance measurements
- Both materials showed similar solubilities.



Conclusions



- We have shown that the phase transition temperature of mephedrone. HCl can be altered via the use of solid solutions
- Potential in this method to be used where a transition temperature is close to any processing temperature.
- In this case, the solubility remained constant whilst other properties were changed.

Acknowledgements



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- Pauline Maclure



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