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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

## ARTICLE TYPE

## Drug solid solutions – a method for tuning phase transformations

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

This paper describes a methodology for the modification of phase transition temperatures using (+-)-methylmethcathinone solid solutions as an exemplar. This method serves to show that by varying the composition of the halide ion one can systematically alter the temperatures at which phase transitions can occur in order to evade the possibility of interconversion between polymorphs during processing or storage of materials.

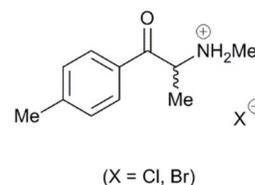
## Introduction

Crystal engineering has been at the forefront of structural science as a method by which one can alter the physical properties of a material by creating new solid-state forms.<sup>1-4</sup> The main experimental technique that is used is co-crystallisation whereby neutral molecules, that are solid under ambient conditions, crystallise together in stoichiometric quantities to form molecular complexes through the use of hydrogen bonding. Examples of the success of co-crystallisation as a methodology are increased resistance to hydration,<sup>5,6</sup> changing the luminescent properties<sup>7-9</sup> and even reducing the sensitivity of energetic materials.<sup>10</sup>

This area of research has been extended to investigate the use of ionic co-crystals (ICCs).<sup>11-13</sup> These are materials where one of the components is an ionic salt, e.g. calcium chloride, lithium benzoate, and can be created via similar synthetic pathways to co-crystals i.e. grinding, kneading with solvent and so on. One area related to this that does not seem to have been explored to a large extent is the area of solid solutions in the organic solid state where the anions or cations are exchanged to varying degrees.<sup>14</sup> Solid solutions using whole organic molecules have been lightly investigated as highlighted by Cherukuvada and Nangia in their review of eutectic systems.<sup>15</sup> Examples of molecular solid solutions include benzoic acid/4-fluorobenzoic acid,<sup>16</sup> oxandrogens,<sup>17</sup> Indoloacridines,<sup>18</sup> and Tritylnitrile/ tritylisonitrile<sup>19</sup> systems although very few have investigated the change in physical properties beyond a change in melting point. This technique is readily used in the inorganic solid state literature in order to alter the properties of materials such as superconductors.<sup>20,21</sup> We report the crystallisation of a series of solid solutions of (+-)-4'-methylmethcathinone (Scheme 1) not to try and improve its properties (as it is a 'legal high') but as an exemplar of how phase transitions may be altered by the use of solid solutions.

The crystal structure of (+-)-4'-methylmethcathinone hydrochloride (MeHCl) at room temperature was reported by Nycz et al. in 2011<sup>22</sup> but we have since discovered that it

undergoes a phase transition at low temperature (158 K). Herein we report the temperature induced phase transformation of the hydrochloride salt along with two novel forms of the hydrobromide salt. Furthermore we investigate the modification of the phase transformation temperature through the use of solid solutions.



Scheme 1: Basic structure of (±)-4'-methylmethcathinone

## Experimental

Synthesis and structural elucidation of compounds (**1a** and **1b**) can be found in the paper of Santali *et al*.<sup>23</sup>

## Single solvent screen

5 mg (0.02 mmol) of the required (±)-4'-methylmethcathinone salt was weighed accurately into 5 cm<sup>3</sup> vials before ~1 cm<sup>3</sup> of solvent was added (Table S1). The solutions were heated to 313 K and stirred until all the material was dissolved before cooling to room temperature. The vials were stored at room temperature and the solvent was allowed to evaporate to dryness. The colourless crystals were analysed using a range of techniques described below.

## Solid solution crystallisation

The solid solutions were crystallised via anti-solvent vapour diffusion using between 3-12 mg of (±)-4'-methylmethcathinone salts depending on their composition e.g. for the 70:30 Cl:Br solution 7.13 mg of hydrochloride was added together with 3.61 mg of hydrobromide. The solid was dissolved in a mixture of acetone and methanol (1:1, 4 ml) and placed inside a larger container containing hexane. The container was closed and the crystals appeared after two days.

### Single crystal X-ray diffraction

The X-ray intensities of the ( $\pm$ )-4'-methylmethcathinone salts and salt solutions were measured on a Bruker-Nonius APEX II diffractometer using Incoatec microsource (Mo-K $\alpha$  radiation) and an Oxford Cryosystems low temperature device operating at 123 K as standard.<sup>24</sup> Absorption corrections were carried out using the multiscan procedure *SADABS*. The structures observed at 293 K and 150 K were solved by direct methods (SIR-92)<sup>25</sup> and refined by full-matrix least-squares against  $F^2$  using all data (CRYSTALS).<sup>26</sup> H atoms were located in difference maps and initially refined with soft restraints on the bond lengths and angles to regularise their geometry (C-H in the range 0.93–0.98, N-H in the range 0.86–0.89 Å) and  $U_{\text{iso}}$  (H) (in the range 1.2–1.5 times  $U_{\text{eq}}$  of the parent atom), after which the positions were refined with riding constraints. All non-H atoms were modelled with anisotropic displacement parameters

### HCl VT study

For the HCl salt, the refined models at 293 K and 150 K served as the starting model for the refinements of Phase I and II, respectively, and followed the process as detailed above. The full crystallographic details of the variable temperature study are outlined in Table S2.

### Solid solutions

The structures of the solid solutions were refined as above but with a few alterations. The crystal structure of pure HCl was used as a starting model for the refinement of the solid solutions. The thermal parameters in this initial model indicated that the atom assigned to the electron density was incorrect. The anion was split into two sites and modified to be both Cl<sup>-</sup> and Br<sup>-</sup> with the occupancies set to 50 % and their fractional coordinates set to be equal. These occupancies were competitively refined.

Compound **1c\_6040** was refined as above however the data were weak and not as good as the other solutions. The crystal was the best crystal observed in the batch and so is presented. The only difference in the refinement of the structure was that vibrational and thermal similarity restraints were applied to the anions. Without these restraints the R-factor was 12.57 % and the thermal parameters were poor but once these restraints were applied the thermal parameters were a little better and the R-factor reduced to 11.9 %.

All crystal structures were visualised using the programs Materials Mercury.<sup>27</sup> Other structural analyses were carried out using PLATON.<sup>28</sup> Scheme 1 was created using Chemdraw 12.0.

### Solid solutions – Phase transition temperature analysis

The powder patterns for the low temperature and high temperature forms are very close even using Cu radiation (radiation of our powder X-ray diffractometers). It was felt that single crystal X-ray diffraction, whilst a little cumbersome for identifying phase transitions, would ultimately be the best method in the absence of Differential Scanning Calorimetry (see below). Fresh crystals of each salt solution (**1c\_7030**, **1c\_6040** & **1c\_3070**) were mounted on the diffractometer at 123 K and analysed using small matrix collections typically scanning 20° in omega at a step size of 0.5°. This was repeated at ~10 K intervals. Each dataset was analysed and indexed in order to identify when the phase transition had occurred. Selected unit cell parameters for each solution at various temperatures are given in Table ES5.

### Differential Scanning Calorimetry (DSC)

#### Low temperature (LT) DSC

The phase changes in ( $\pm$ )-4'-methylmethcathinone hydrochloride (**1a**) were measured using a nitrogen flushed Mettler Toledo DSC 30 differential scanning calorimeter. The scan rate of 2 K min<sup>-1</sup> and 10 K min<sup>-1</sup> for cooling and heating respectively during three cool-heat cycles for temperatures range of 298 to 133 K. The temperature and heat flow of the DSC instrument was calibrated with indium and zinc. The results were analysed using Mettler STARe software. Unfortunately, the low temperature DSC failed between the measurement of **1a** and the rest of the samples and so the phase transition was monitored via single crystal X-ray diffraction instead (see above).

#### High temperature (HT) DSC

The HT DSC plots were obtained using two pieces of equipment, the first being a DSC 822e, Mettler Toledo, UK and the second being a Netzsch STA 449 C.

Samples were prepared by carefully weighing between 1.51 and 3.33 mg of each sample into a 40  $\mu$ l aluminium pan, which was then hermetically sealed with a pinhole in the lid. An empty pin-holed 40  $\mu$ l aluminium pan was used as a reference in the Mettler Toledo DSC. Both pans were subjected to a nitrogen atmosphere. The pans were then heated at a rate of 10 K/min from 298 K to 530 K. The temperature and heat flow of the DSC instrument was calibrated with indium and zinc. The results were analysed using Mettler STAR software.

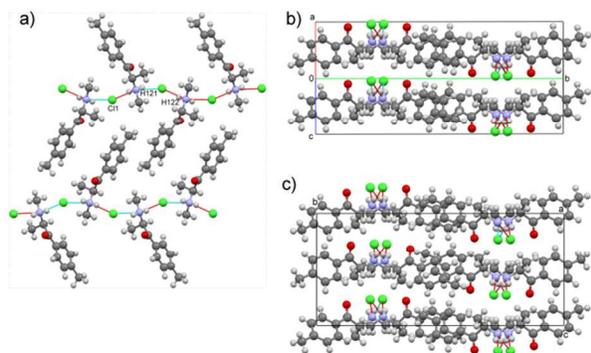
For the Netzsch system, samples were placed in 10  $\mu$ l aluminum pans, and a heating ramp was set in the range of 273–483 K at a rate of 10 K min<sup>-1</sup>. All analysis was performed using the Netzsch Proteus data analysis package. For all DSC traces see Supplementary Information (Figure S1 & 2).

## Results and Discussion

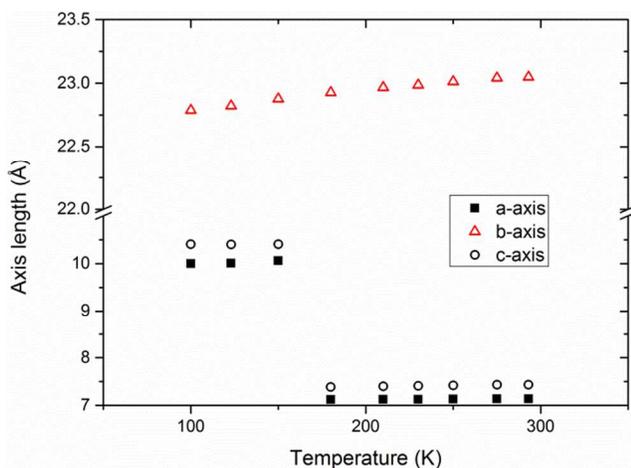
### Crystal structures of ( $\pm$ )-4'-methylmethcathinone hydrochloride and hydrobromide

The crystal structure of form I of ( $\pm$ )-4'-methylmethcathinone hydrochloride (**1a\_I**) was reported by Nycz *et al.*, in 2011.<sup>22</sup> The molecules crystallise with one formula unit in the asymmetric unit with the cation and anion interacting through NH...Cl<sup>-</sup> and N<sup>+</sup>H...Cl<sup>-</sup> hydrogen bonded chains along the [1 0 1] direction (N12...Cl11 3.063(2) & 3.104(2) Å). The orientation of the molecules alternate along the chain to allow interaction between the phenyl groups of the methylmethcathionate cation in neighbouring chains, related by an inversion centre (Figure 1).

On cooling, **1a\_I** undergoes a phase transformation to a new low temperature phase (**1a\_II**) at ~160 K via a single crystal to single crystal transition (Figure 2). Over the transition there is a doubling of the unit cell due to the molecules becoming crystallographically inequivalent. There are four independent hydrogen bonds in the structure as opposed to two in the LT phase (3.059(2) - 3.107(2) Å)(Table ES4). The structural changes that occur are very subtle (Figure 1b and c) with a slight change in position of the chains with respect to one another. Figure 1b and c are views along the chains and show the shift in the position of the chloride ions with respect to the chain above and below.

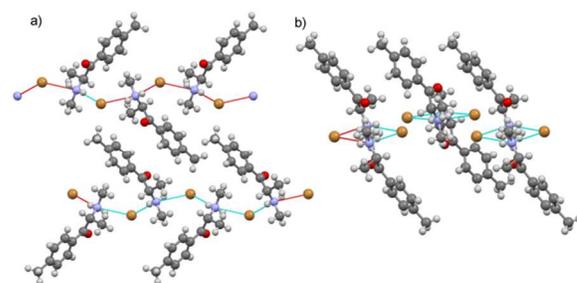


**Figure 1.** a) The basic chain structure of the hydrochloride salt. b) a view along the hydrogen bonded chains in b) **1a\_I** and c) **1b\_II**. Note the vertical alignment of the chloride ions in **1a\_I** but the slightly staggering of the ions in **1b\_II**.



**Figure 2.** A plot of the unit cell parameters for **1a** with varying temperature clearly indicating the phase transition.

Form I of ( $\pm$ )-4'-methylmethcathinone hydrobromide (**1b\_I**) crystallises in a similar hydrogen bonding motif to **1a\_I** where chains of cations and anions are formed along the [0 0 1] direction (N12...Br1 3.257(2) & 3.302(2) Å). **1b** exhibits polymorphism under ambient conditions and Form II (**1b\_II**) exhibits a hydrogen-bonded dimer motif ( $R_4^2(8)$ , (N12...Br1 3.243(1) Å; N12...Br1\* 3.324(1) Å) (Figure 3). **1b\_I** is the most predominant phase found under ambient conditions however **1b\_II** can be formed via crystallisation from methanolic and ethanolic solutions (Table S1). Relative stability studies were made by placing crystals of both phases, **1b\_I** and **1b\_II**, into a vial together with a saturated solution of **1b** in ethanol. Over a period of two weeks only the crystals of **1b\_I** remained showing that it is the more stable phase with the slow conversion of **1b\_II** to **1b\_I** in solution over time.

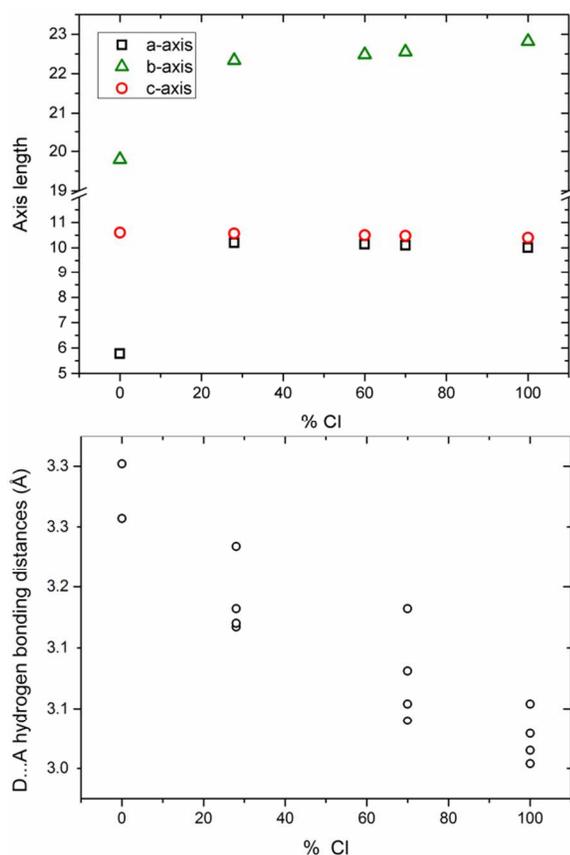


**Figure 3.** a) The hydrogen bonded chains in **1b\_I** and b) the dimer motifs present in **1b\_II**.

Due to the similarities in the hydrogen bonding motifs of **1a\_I** and **1b\_I** we investigated the possibility of substituting bromide ions into the crystal structure to observe whether co-crystals or solid solutions could be observed and if so which three-dimensional arrangement would be preferred.

#### Solid solutions of MeHCl & MeHBr

Various molar ratios (70:30, 50:50, 30:70) of **1a** and **1b** were added to a (1:1) solution of acetone and methanol and subjected to anti-solvent vapour diffusion methods using hexane as an anti-solvent. Via this route we were able to obtain crystals of sufficient quality for single crystal X-ray diffraction. At 123 K the unit cell parameters for all these crystals largely matched those of **1a\_I** but with slight differences in axes lengths (Table S2). It was only during refinement that we were able to identify that the substitution had taken place due to unusual anisotropic temperature factors and a stubbornly high R-factor. By altering the model to include the substitution of Cl<sup>-</sup> with Br<sup>-</sup> ions we were able to refine the structures to a satisfactory R-factor thereby indicating the successful synthesis of a solid solution. Starting with initial compositions of 70:30, 50:50 and 30:70 we have been able to create solid solutions with compositions 70:30, 60:40, and 28:72 HCl:HBr. Figure 4a and Table S2 show the unit cell parameters of the different compositions of crystal which change smoothly from 100 % hydrochloride to 100 % hydrobromide. As one would expect with the change in size of the counterion the hydrogen bonding parameters in these forms changes linearly with the percentage composition (Figure 4b). Further analysis of these solid solutions was made via differential scanning calorimetry (DSC). Figure S2 shows the DSC traces for the pure compounds as well as for the solid solutions. DSC measurements of **1a\_I**, **1b\_I** and **1b\_II** show that they melt at 524 K, 486 K and 476 K, respectively. The melting points of the different solutions (Figures S2c, d and e) show an increase from the melting point of the hydrobromide (Figure S2a and b) to the the melting point of the hydrochloride (Figure S2f). In general the melting events for the solid solutions show a broader transition than the pure phases, an observation that has been made of solid solutions.<sup>15</sup>



**Figure 4.** a) The unit cell parameters as a function of %Cl composition. b) The hydrogen bonding lengths for the solutions (Å).

### Phase transition temperature

One of the main reasons for investigating this system was the fact that the crystal undergoes a phase transition to a new phase on cooling. Our hypothesis at the outset of this investigation was that the addition of a secondary counterion to the crystalline form would alter the temperature at which the phase transition takes place. In order to investigate this we used variable temperature single crystal diffraction in order to observe the transition to the high temperature phase. Small datasets consisting of ~100-800 reflections were taken at 5-15 K intervals starting at the data collection temperature, 123 K. The first compound to undergo this investigation was **1c\_7030**. At 123 K it is present in the LT cell and it remains in this phase until ~165 K where there are indications that a phase transition is taking place. On warming the diffraction pattern begins cleanly with diffraction from a single crystal of the LT phase but deteriorates as it approaches 165 K. At this temperature a number of reflections were observed that could be indexed to the HT cell (208). At 170 K the transition is complete. Unit cell parameters from the exploration of the phase boundaries can be found in Table ES5 for each of the component mixtures. This is a modest rise from pure **1a** (158-160 K) but indicates that the other solid solutions may cause a more substantial change in temperature.

The crystal of **1c\_6040** was the poorest crystal of those investigated. Despite this we were able to track the change in the

unit cell parameters with temperature. At both 180 and 190 K the diffraction data could be indexed with both the LT and HT cells around 180-190 K indicating the phase transition was occurring at these temperatures. The number of reflections that could be indexed to the HT phase at 180 K was reduced compared with the 190 K data and signifies the HT phase is being phased out. This still indicates a 20-30 K rise in the transition temperature over **1a**.

The initial dataset of **1c\_3070** showed that at 123 K this compound was also present in the LT phase. On warming successive data collections showed the LT phase persisted to 235 K where the HT phase started to grow in as per the other solid solutions. At 250 K the pattern can be indexed purely as the HT phase. This phase transition temperature is approx. 80 K higher than pure **1a** and is the largest change in the series which would be consistent with the composition of the crystal. In all of these investigations time does not seem to be a factor, i.e. later frames still present reflections from both the LT and HT phase. A caveat to this statement is that the time for the data collection was approximately 45 minutes and so further residence at a specific temperature, i.e. a few hours, may allow the phase transition to occur.

There are few instances of this type of solid solution in the literature where the counterion has been substituted to affect a physicochemical change and very few in which the anion has been changed. The ferroelectric compound Rochelle salt (Potassium sodium tartrate tetrahydrate) has been studied to some extent with variation in composition with substitution of ammonium as the cation.<sup>29-33</sup> These studies have shown that the physical properties can be altered via this method but a systematic approach to the substitution was not investigated. The results from our experiments are a remarkable observation as we have shown that by varying the quantities of each counterion we can tune a phase transition temperature by up to 80 K whilst retaining the same three-dimensional packing arrangement. There is a clear potential in this method for the modification of the transition temperatures in other salt materials, including pharmaceuticals. This is particularly relevant if a phase transition of a material occurs close to a standard operating or processing temperature. By applying solid solution methodologies we can synthesise materials that have similar physical properties, such as solubility, but with a lower risk to interconversion on processing.

### Conclusions

We have been able to use the concept of solid solutions to alter the physicochemical properties of the compound including the phase transition temperatures and melting points. To the best of our knowledge this is the first instance by which a systematic substitution of halide ions has been used to alter the properties of a pharmaceutically relevant complex. We have shown that by adding increasing quantities of bromide ions to the hydrochloride salt we can alter the phase transition temperature by up to 80 K. The ability to tune these properties will undoubtedly have an impact on materials processing and storage where one will be able to alter the phase transition temperature of a material if it falls out with a particular operating temperature range.

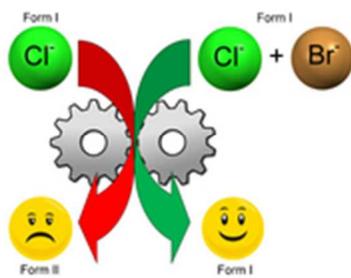
## Acknowledgements

The authors would like to thank The Leverhulme Trust for funding (AD) and the SIPBS for their contribution to the upgrade of the diffractometer to a microsource.

## Notes and references

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- † Electronic Supplementary Information (ESI) available: DSC traces for 1a at low temperature and high temperature. DSC traces for 1b and 1c\_7030, 1c\_6040, 1c\_3070 at high temperature. Full crystallographic and hydrogen bonding parameters for all structures. Unit cell parameters observed for the phase transformation. See DOI: 10.1039/b000000x/
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Tuning phase transformation temperatures through the use of solid solutions.



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