Enabling cocrystallization of challenging systems: passing through a stable cocrystal solvate as a pathway to strenuous cocrystal forms

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Enabling cocrystallization of challenging systems: passing through a stable cocrystal solvate as a pathway to strenuous cocrystal forms

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ABSTRACT: Caffeine and maleic acid can form various cocrystal forms, which is a potential route to avoiding hydration issues of caffeine. This particular system was intensively studied as it not only shows co-crystal polymorphism, but also stoichiometrically diverse cocrystals with a 1:1 maleic acid: caffeine (MC) and a 1:2

maleic acid:caffeine (MC_2) form already identified. A cocrystallization process for MC was already developed. However, a process leading to pure MC_2 remained a challenge, as the stability zone of the MC_2 suspension is very narrow in most solvents. In this paper, we propose an alternative crystallization pathway towards this crystal form, passing through a stable solvate. Indeed, we identified a novel cocrystal solvate of MC_2 (MC_2.MeCN) in acetonitrile at 9°C. This cocrystal solvate is characterized by a large stability zone in the ternary phase diagram, and consequently, a crystallization process leading to this form can easily be devised. Upon filtration, and exposure to ambient atmosphere, MC_2.MeCN is quickly de-solvated leading to the pure MC_2 cocrystal phase. In this contribution, we therefore show that cocrystal phases, which are seemingly strenuous to crystallize from solution, can be accessed by thinking out-of-the-box and using the properties of unexpected alternative phases.

Keywords: caffeine:maleic acid cocrystals – ternary phase diagram – crystal engineering

1. Introduction

Many active pharmaceutical ingredients (API) exhibit unwanted physico-chemical properties, such as poor aqueous solubility, thermal degradation or polymorphic transition [1–3]. A well-established tool to deal with such issues is to change the crystalline phase of the compound, either by salt or cocrystal formation [4–6]. Salts are formed through acid-base reactions and hence require an acid or basic group, implying that such technique cannot extend to all API's. On the other hand, cocrystal formation, the formation of a crystalline single phase material composed of two or more different molecular and/or ionic compounds in a stoichiometric ratio, involves any kind of molecular interaction (hydrogen bonding, π- π interactions, Van der Waals,…). Its application spectrum is therefor much wider [6]. Besides, its effectiveness to address undesired solid state-related properties of materials has already been well demonstrated. Cocrystallization has already been successfully used to enhance solubility and bioavailability of pharmaceutical compounds, or to avoid phase transformation phenomena, such as polymorphic transformation, crystal hydration or deliquescence [5–9].

Different techniques are available on a laboratory scale to access cocrystals. (i) Cocrystallization from the melt consists in heating a physical mixture of the two coformers to form a liquid phase and cooling it down until recrystallization of the cocrystal phase occurs [10]. (ii) Solid-state grinding of the two coformers is a very efficient method in which the two solid powders of coformers are mixed and ground at high frequency. A drawback of these two methods is the difficulty to isolate selectively the cocrystal phase from the other solid phases or impurities [11,12]. (iii) Solution based cocrystallization regroups all the different methods that involve the use of a solvent, namely ripening (or solvent mediated transformation), evaporation and cooling crystallization [13–16]. Evaporative cocrystallization is performed by diluting both coformers in a volatile solvent and leaving the solution to evaporate. As the solvent evaporates, the concentration of both coformers increases until solubility of the cocrystal is reached and a solid cocrystal phase grows. Cooling crystallization consists in the formation of a solution of the two coformers, reaching supersaturation by cooling. In solvent mediated transformations, the coformers are left in suspension in conditions under which the cocrystal phase is the most stable phase. Cocrystallization occurs, in parallel to dissolution of both coformers [17].

Caffeine (Figure 1) is a pharmaceutical compound known to act as a central nervous system stimulant and smooth muscle relaxant. It is used as a formulation additive to boost the effect of analgesic remedies [21]. Two polymorphs, α and β, have been identified for caffeine: the α-form is most commonly encountered and the β-form only exists at higher temperature. The two polymorphs are enantiotropically related with a phase transition occurring at 145°C[22]. α-caffeine in itself is not ideal for pharmaceutical formulation[23] as the channel-like structure of this crystal form traps water molecules. The α-form is thus better described as a non-stoichiometric hydrate, containing between 0.8 and 1 equivalent of water depending on ambient atmosphere humidity and temperature. In 2005, Trask *et al.*, proposed to avoid water contamination of caffeine taking a cocrystallization approach, successfully identifying five different coformers cocrystallizing with caffeine [21]. Among these, maleic acid (Figure 1) showed the particularity of forming two stoichiometrically diverse cocrystals.

Figure 1. Detailed structure of caffeine (left) and maleic acid (right)

Due to this ability to form two stoichiometrically diverse cocrystals, the maleic acid:caffeine system was intensively studied. A pure 1:1 maleic acid:caffeine cocrystal (MC) phase could easily be obtained and single crystals isolated through solvent evaporation using dichloromethane as a solvent [21]. Interestingly, during the development of a crystallization process for the MC form, a metastable polymorph of this latter was encountered [24]. However, efforts in developing a crystallization process leading to the pure 1:2 cocrystal material remained challenging. Attempts to obtain the 1:2 cocrystal form by solution crystallization often resulted in the formation of a mixture of two crystal forms, either the 1:2 co-crystal and caffeine or a mixture of both the 1:2 (MC_2) and the 1:1 (MC) cocrystal phases [25–27]. Leyssens et al., were able to obtain the pure MC_2 form from solution using far out-of-equilibrium conditions [24]. Other successful attempts were mentioned using ultrasound-assisted solution cocrystallization (USCC) [28], solvent free continuous crystallization (SFCC)[29], or electro-spray deposition (ESD) [30]. Still, all these methods present critical drawback as they are either difficult to upscale (ESD and USCC) or do not allow purification of the product (SFCC). Furthermore, all are kinetically based, with no approach available to access thermodynamically the 1:2

phase in a robust manner. This is easily understood considering the extremely narrow stability zone of the 1:2 phase in most solvents.

In this paper, we present an out-of-the-box approach to access this phase in a robust manner. In our attempts to identify an alternative solvent allowing for a larger stability zone of the 1:2 cocrystal, we stumbled upon a thermodynamically stable cocrystal solvate working in acetonitrile. This form could easily be crystallized, and a very large stability zone for this solvate was found. Furthermore, upon filtration, the solvate could easily be de-solvated to yield the pure 1:2 cocrystal phase. We are here the first to present a thermodynamic crystallization approach towards the 1:2 phase, passing through a stable solvate phase. This is an original approach and shows that one can use the diversity in the solid state to find thermodynamically robust processes, even for those solid forms that are seemingly strenuous to crystallize.

2. Materials and methods

Materials. Caffeine (99% purity, CAS: 58-08-2), maleic acid (99% purity, CAS: 110-16-7), acetonitrile (99% purity, CAS: 75-05-8) and ethyl acetate (99% purity, CAS: 141-78-6) were purchased from Sigma-Aldrich and used without any further purification. 1:1 pure cocrystal phase was obtained by adding 390 mg of caffeine and 710 mg of

maleic acid (3 equivalents) to 10mL of ethyl acetate. The suspension was heated until complete dissolution, subsequently cooled down to 9°C and left over-night. The suspension was then filtered and washed with ethyl acetate. Pure 1:2 cocrystal phase was obtained mixing 290 mg of caffeine and 180mg of maleic acid (1 equivalent) in 10mL acetonitrile. The suspension was heated up until complete dissolution and stored at 9°C for two days. After two days, crystals appeared and the suspension was filtered and washed. The powder was left to dry under ambient conditions, leading to the 1:2 phase.

PXRD. X-ray diffraction measurements were performed on a Siemens D5000 diffractometer equipped with a Cu X-ray source operating at 40 kV and 40 mA and a secondary monochromator allowing to select the $K\alpha_1$ radiation of Cu (λ = 1.5418 Å). A scanning range of 2θ values was applied from 2° to 50° at a scan rate of 0.6 min−1 and a step of 0.02°. Simulated patterns of the known starting compounds were calculated from their single crystal structures with Mercury 3.10 (version: August 2016).

Single crystal XRD. Single crystal X-ray diffraction was performed on a MAR345 image plate detector using Mo Kα radiation (0.71073Å) generated by a Rigaku UltraX 18S rotating anode (Xenocs Fox3D mirrors). Prior to measurement the crystal was

flash cooled at 150 K in a N_2 flow. Data integration and reduction were performed by CrysAlis^{PRO} (v1.171.35.19) and the implemented absorption correction was applied. Structures were solved by direct method using the SHELXS-97 program and refined by full-matrix least-squares on $|F|^2$ using SHELXL-2014 [31,32]. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed on calculated positions in riding mode with temperature factors fixed at 1.2 times U_{eq} of the parent atoms and 1.5 times U_{eq} for methyl groups.

Determination of TPD in acetonitrile and ethyl acetate. Ternary phase diagrams of caffeine and maleic acid in different solvents were determined as follows: mixtures of various composition in caffeine and maleic acid were prepared in 3 ml of either MeCN or AcOEt. Samples were stored at a controlled temperature of 20°C or 9°C in a Polar Bear Plus (Cambridge Reactor Design). Once the wanted temperature reached, vials were seeded with ~3mg of 1:1 and 1:2 cocrystals. After five days, the solid phase was filtered and its nature determined by PXRD, while a fraction of the supernatant was sampled and analyzed by HPLC to determine caffeine and maleic acid concentration. Even though the HPLC data allowed drawing the overall aspect of the TPD, for an

exact determination of eutectic points a more precise quantitative NMR (qNMR) based approach was used.

HPLC. 150µL of supernatant was sampled, weighed and diluted 15 times in a 3:7 MeCN:H_2O solvent. Caffeine and maleic acid concentrations were dosed using the following HPLC method: Device, Waters Alliance 2695. Column, Waters Sunfire C18 (4.6 × 100 mm, 3.5 µm). Detector, PDA 2998 (extraction at λ = 210 nm). T° = 40°C. Injection volume: 5 µL; Flow: 1.23 mL/min; Mobile phase A: H_2O + 0.1% H_3PO_4; Mobile Phase B: CH_3CN + 0.1% H_3PO_4; Gradient: 0 min → 10% B and 10%C; 1 min → 10% B and 10%C; 4.5 min → 90% B and 10%C; 7 min → 90% B and 10%C; Stop time: 7.5 min. A calibration curve was determined prior to analyzing, using concentrations ranging from 5 to 250 ppm (w/v) of either caffeine or maleic acid.

qNMR. 600µL of supernatant was sampled, weighed and left to evaporate in an NMR tube. The solid residue was dissolved in 0.8mL of deuterated acetonitrile and quantified by NMR. qNMR measurements were performed on a 300 MHz Bruker Avance, using 1,3,5-Trimethoxybenzene as an internal standard together with the compounds of interest, dissolved in deuterated acetonitrile. The relaxation time d1 was set to 20 s to ensure full relaxation of all protons, and 16 scans were performed for each sample.

DSC. DSC measurements were performed on a DSC 821 from Mettler Toledo. Samples were ground manually in a mortar and 7mg placed in a perforated 40µL aluminum crucible. The temperature was increased from 25°C to 180°C at a 10°C.min^{-1} rate.

Solubility curve determination. Solubility curves of caffeine and maleic acid in MeCN were determined using a Crystal 16 from Technobis. 1 mL solutions of various concentration in caffeine or maleic acid were prepared and heated from -5 to 40°C at a 0.02°C/min heating rate and stirred at 800rpm. Transmittance was recorded using a laser beam to record the clear point of each vial.

Upscaling the crystallization process for 1:2 maleic acid:caffeine cocrystal. Crystallizations were performed using an EasyMax 102 from Mettler Toledo in a 100 mL vessel. The stirring rate was set to 125 rpm and a temperature probe was put in direct contact with the solution. A suspension of 1.83 mol/L of caffeine and 2.19 mol/L of maleic acid in MeCN was first heated to 50°C and held for 1 hour to ensure complete dissolution of the material. The solution was then cooled down to 9°C at a 0.3 K/min rate. The suspension was left to equilibrate for 6 hours during which spontaneous crystallization occurred, and filtration was subsequently performed on a sieve under

vacuum and products were characterized by PXRD. To determine the robustness of the process, crystallization experiments were performed and seeded with different crystal forms. Solid material was always extracted and subsequently analyzed by PXRD.

3. Results and discussions

3.1. Solvent selection

Designing a robust cocrystallization process at scale is a challenge that requires an accurate knowledge of the thermodynamics of the system under consideration [17,33]. As three different components are involved in cocrystal formation, the solvent and the two coformers, isothermal ternary phase diagrams (TPDs) are frequently used. These thermodynamic diagrams state the nature of the solid and liquid phases depending on the overall composition of the system at a given temperature [34–36]. In the current case, obtaining pure MC or MC_2 co-crystal phase as the only stable phase in suspension is rather difficult due to the large solubility difference encountered between maleic acid and caffeine in most solvents. This often leads to a skewed TPD with narrow stability zones for the cocrystal phases [16]. By adjusting the relative solubility of both coformers, a more symmetrical diagram can be expected (Figure 2). In the case studied here, we

hoped to identify a solvent that shows accessibility zones for the 1:1 and in particular for the 1:2 cocrystal phase. Caffeine has a limited solubility in most solvents and identifying a solvent showing comparable solubility towards caffeine and maleic acid is not a straightforward task.

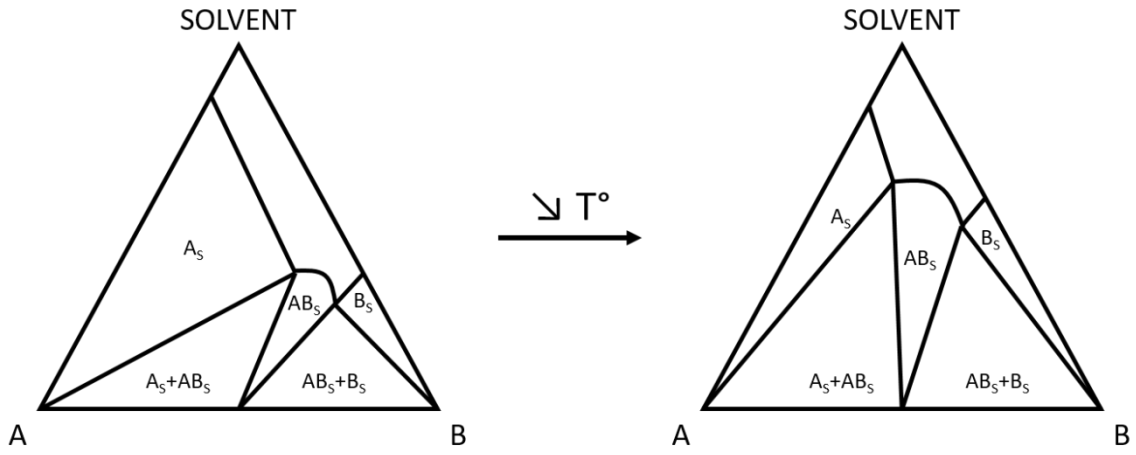

Figure 2. Theoretical TPD at a given temperature for a system of two coformers A and B, with strong solubility differences between both coformers. By adjusting the solubilities of both co-formers (e.g. by adjusting the temperature), a more symmetrical phase diagram can be obtained.

Caffeine nevertheless shows moderate solubility in MeCN and AcOEt. For this reason, we started by establishing solubility curves of both coformers in these solvents (Figure 3). Caffeine and maleic acid show a similar evolution of their solubility with respect to temperature in AcOEt [24]. This is not the case in MeCN, where maleic acid

solubility increases more rapidly with temperature. This is likely due to the higher mobilization of polar interactions at higher temperature. Indeed, between 9°C and 20°C, caffeine and maleic acid solubility are increased by 34% and 31% respectively in AcOEt, while the same temperature change in MeCN increases the solubility by 42% for caffeine and 63% for maleic acid. Based on these results, one could expect that the ternary phase diagram would exhibit a wider zone for the 1:2 cocrystal crystallization at lower temperatures when working in MeCN. No significant differences are expected when working at different temperatures with AcOEt.

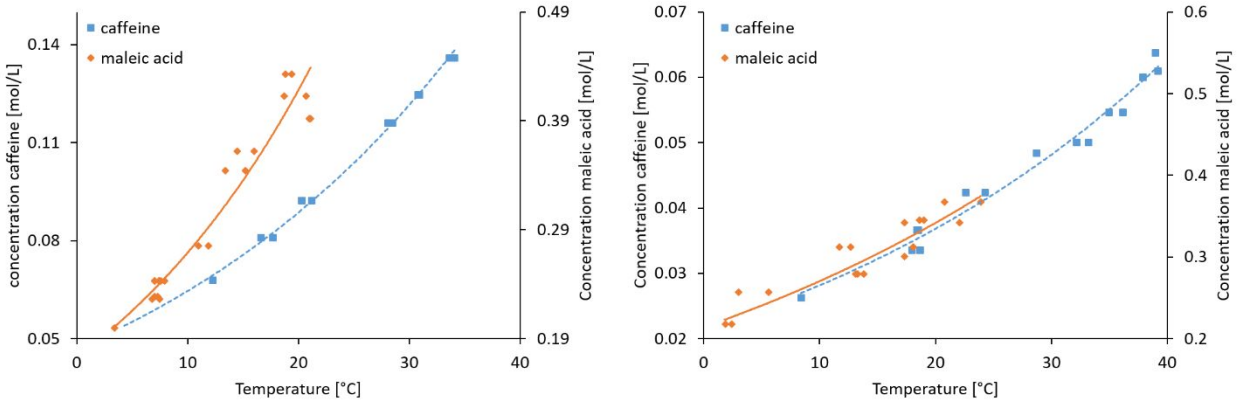

Figure 3. Solubility curves of caffeine and maleic acid in MeCN (left) and AcOEt (right)

3.2. Towards MC_2 cocrystallization

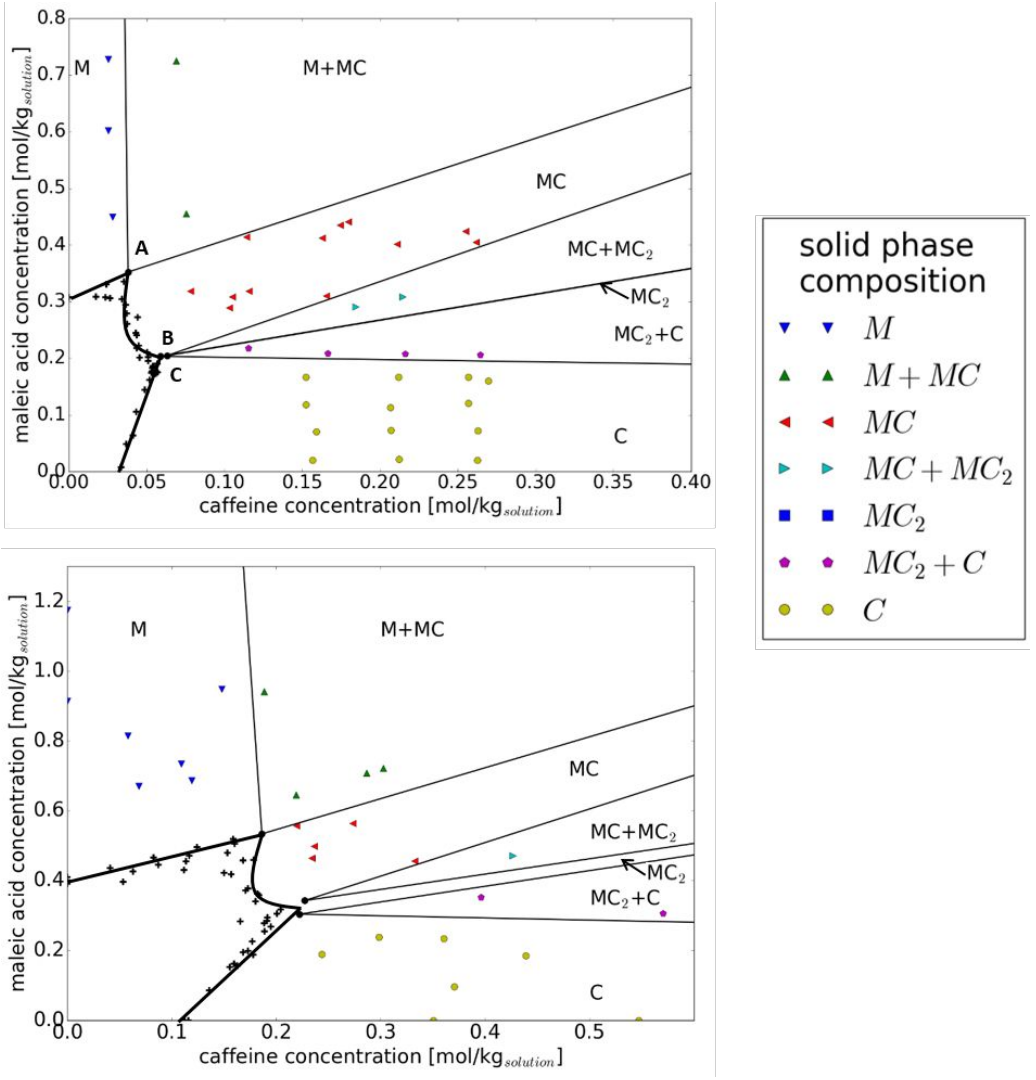

Figure 4. TPD of caffeine and maleic acid in AcOEt (up) and MeCN (down) at 20°C

The TPD in both solvents at 20°C show zones that allow the development of a robust cocrystallization process for caffeine, maleic acid as well as the 1:1 MC cocrystal form (Figure 4). Large stability zones containing two solid forms in suspension (M+MC; MC+MC_2; MC_2+C) can also clearly be observed. However, the zone where the 2:1 phase is the only stable phase in suspension is too narrow to be observed with the

precision at hand, confirming the difficulty to obtain this pure form by solvent crystallization. In addition, the determination of the different eutectic points by qNMR analysis shows that eutectics corresponding to mixtures of MC/MC_2 and MC_2/C are too close to be distinguished (Table 1). Indeed, MC/MC_2 and MC_2/C eutectic point coordinates are respectively [0.059 $mol_{caf}.L^{-1}$;0.191 $mol_{mal}.L^{-1}$] and [0.055 $mol_{caf}.L^{-1}$;0.190 $mol_{mal}.L^{-1}$] in AcOEt, and [0.20 $mol_{caf}.L^{-1}$;0.29 $mol_{mal}.L^{-1}$] and [0.19 $mol_{caf}.L^{-1}$;0.259 $mol_{mal}.L^{-1}$] in MeCN.

Table 1. Concentrations in caffeine and maleic acid determined by qNMR and nature of the solid phase in equilibrium at the eutectic points in AcOEt and MeCN at 20°C

Point	Solid phase composition	AcOEt – 20°C		MeCN – 20°C	
		x_{caf} [mol.L^{-1}]	X_{mal} [mol.L^{-1}]	x_{caf} [mol.L^{-1}]	X_{mal} [mol.L^{-1}]
A	M-MC	0.036±0.001	0.334±0.002	0.16±0.04	0.47±0.01
B	MC-MC_2	0.059±0.001	0.191±0.001	0.20±0.01	0.29±0.01
C	MC_2-C	0.055±0.001	0.190±0.002	0.19±0.01	0.259±0.002

As for caffeine and maleic acid, MC solubility is higher in MeCN than in AcOEt. Indeed, the MC solubility product (K_{sp}) is estimated as 0.075 $mol^2.L^{-2}$ in MeCN and

0.012 $mol^2.L^{-2}$ in AcOEt.[a] Similarly, K_{sp} for MC_2 is estimated as 0.0116 $mol^3.L^{-3}$ in MeCN and $6.65*10^{-4}$ $mol^3.L^{-3}$. In both cases, the system is incongruent with respect to the crystallization of the 1:1 phase, as one could expect looking at the solubility ratio of caffeine to maleic acid (0.107 in AcOEt and 0.212 in MeCN). Nevertheless, the TPD shows a strong increase in solubility for both caffeine and maleic acid upon addition of the other component.

Ideally, we wanted to render these diagrams even more symmetrical, hoping to increase the stability zone of the 2:1 phase. Based on the solubility curves, lowering the temperature seemingly has a more important impact in MeCN with the solubility ratio increasing from 0.212 to 0.243 going from 20°C to 9°C, whereas almost no impact on the ratio (0.107 at 20°C and 0.104 at 9°C) is observed in AcOEt. Indeed, in the TPD diagram in AcOEt at 9°C (Figure 5), the two eutectics delimiting the zone for pure MC_2 cocrystallization are once more close to each other (Table 2). In addition, the caffeine to maleic acid concentration ratio of the different eutectics are similar at 20°C and 9°C,

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[a] K_{sp} values have been estimated using eutectic point A for MC and eutectic point B for MC_2

as was the case for the coformers' solubility ratio (point A: 0.11 at 20°C and 0.10 at 9°C – point B/C: 0.31/0.29 at 20°C and 0.25/0.31 at 9°C). This confirms that a decrease in temperature shifts the solubility lines in the TPD in a similar manner for all solid forms in AcOEt.

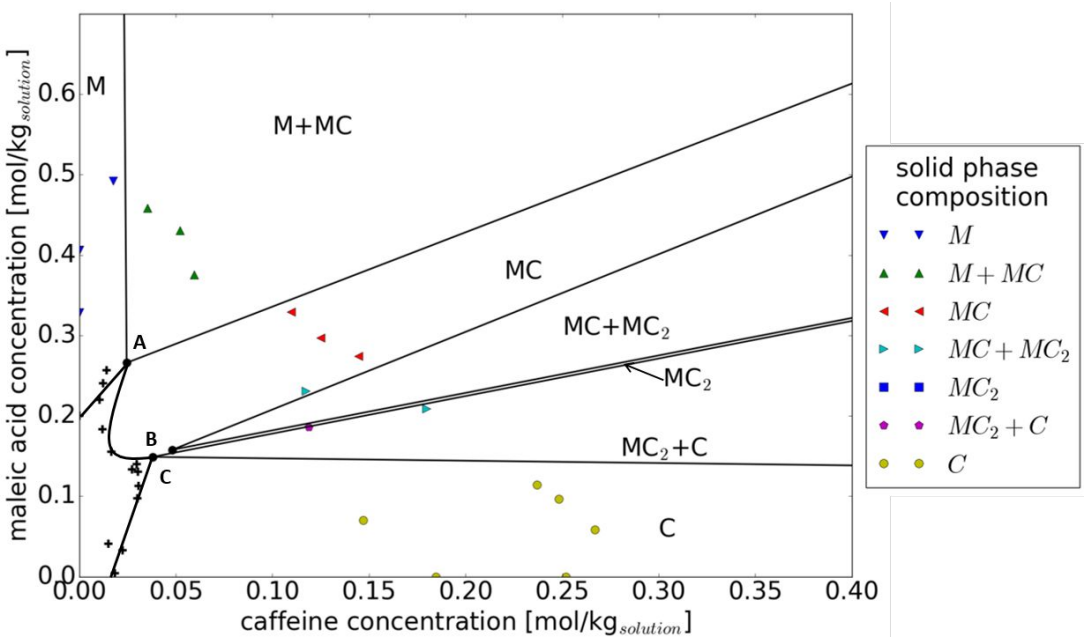


Figure 5. TPD of caffeine and maleic acid in AcOEt at 9°C

Table 2. Concentrations in caffeine and maleic acid determined by qNMR and nature of the solid phase in equilibrium at the eutectic points in AcOEt at 9°C

Point	Solid phase composition	AcOEt – 9°C	
		x_{caf} [mol.L^{-1}]	X_{mal} [mol.L^{-1}]
A	M-MC	0.0229±0.0003	0.249±0.001

B	MC-MC_2	0.0351±0.0004	0.138±0.001
C	MC_2-C	0.0448±0.0007	0.146±0.001

Based on the data above, we had more hope of strongly affecting the TPD by a temperature decrease using MeCN. To our surprise, constructing this diagram at 9°C led to the discovery of an unexpected new crystal form. Visually, the typical needle-shaped crystals one would expect for any of the known forms did not appear [24]. Instead, translucent plate-like crystals came out of solution (Figure 6). These were analyzed by single crystal XRD and identified as a maleic acid:caffeine:acetonitrile (1:2:1) cocrystal solvate (MC_2.MeCN). The crystal structure was determined by single crystal XRD under a flow of liquid nitrogen at 150K to prevent desolvation. MC_2 and MC_2.MeCN do not show clear filiations in terms of crystal structure, however as they share a similar space group, it is possible that a topotactict desolvation process occurs. The study of the desolvation process has, however, not been studied in detail. In a similar mindset, co-crystal solvates have already been shown to be intermediates to produce specific polymorphs.[18–20]

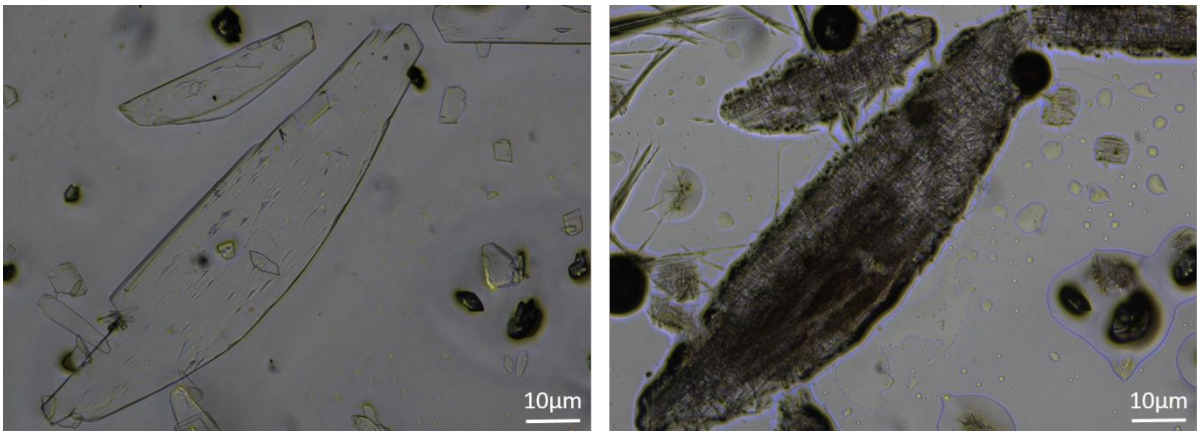


Figure 6. MC_2.MeCN cocrystal in MeCN at 9°C (left) and after 40 minutes in ambient atmosphere at 15°C (right) under microscope

The crystal structure obtained by single crystal XRD reveals the formation of a 1:2 maleic acid: caffeine solvated cocrystal. The cocrystal crystallizes in a monoclinic space group *Pc* (see Supporting Information 1). In the asymmetric unit, the two molecules of caffeine are linked to maleic acid through hydrogen bonds between the nitrogen with sp^2 hybridization of caffeine and the carboxylic function of maleic acid. An internal hydrogen bond between the two carboxylic groups of maleic acid contributes to stabilize the conformation of maleic acid. Two hydrogen bonds, designated as D according to Etter's notation [37], form non-cyclic U-shaped trimers involving two caffeine and one maleic acid molecules (Figure 7a). The different U-shaped trimers are head-to-toe oriented, forming sequential alignment of caffeine

molecules and maleic acid molecules. Solvent molecules are located in the space left between the different trimers, stabilized by Van der Waals interactions (Figure 7b).

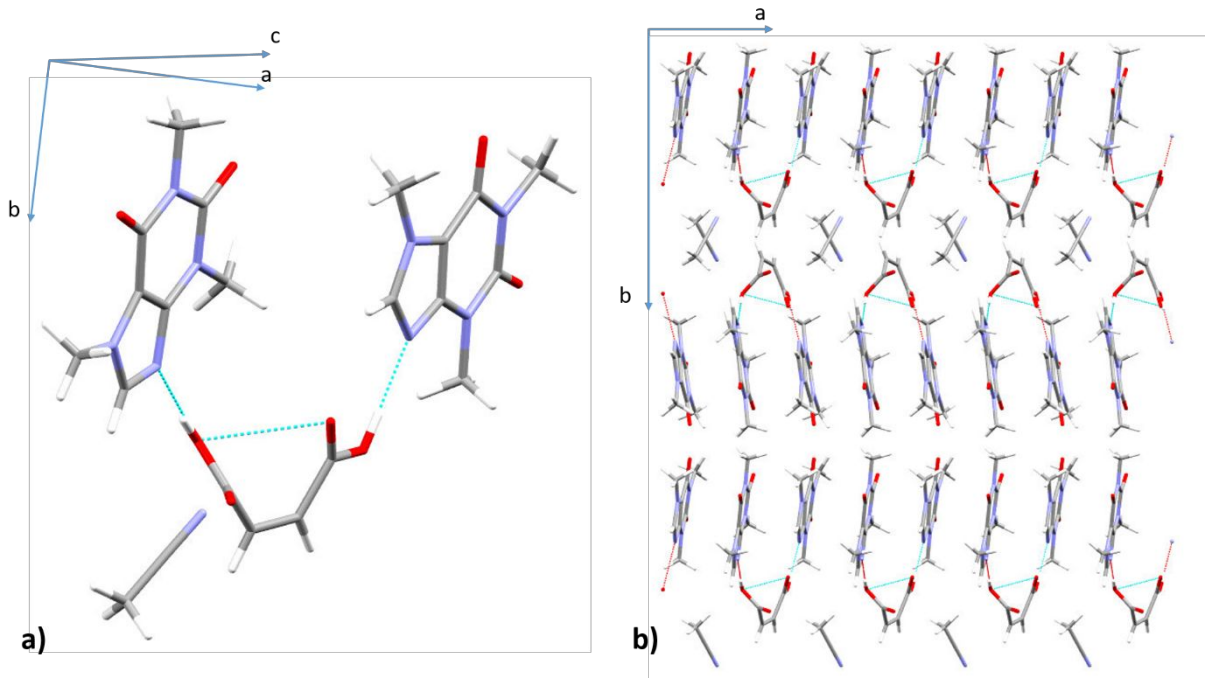


Figure 7. Trimer constituting the MC_2.ACN cocrystal (left) and view of the packing along the c-axis (right)

As was expected from the solubility study, the TPD in MeCN at 9°C is more symmetrical than the one at 20°C due to the similar solubility of the coformers. In addition to the effect of temperature, the apparition of a solvated form changes the equilibria between the different solid forms. Indeed, the MC_2 crystal form is no longer thermodynamically stable at that temperature as the MC_2.MeCN is. Consequently, the different eutectic points can clearly be distinguished (Table 3) and the different zones

for pure cocrystal formation, either MC or MC_2.MeCN, are well defined and accessible experimentally (Figure 8).

Table 3. Concentrations in caffeine and maleic acid determined by qNMR and nature of the solid phase in equilibrium at the eutectic points in MeCN at 9°C

Point	Solid phase composition	MeCN – 9°C	
		x_{caf} [mol.L^{-1}]	X_{mal} [mol.L^{-1}]
A	M-MC	0.08±0.01	0.3193±0.0004
B	MC-MC_2	0.10±0.01	0.24±0.02
C	MC_2-C	0.11±0.01	0.136±0.003

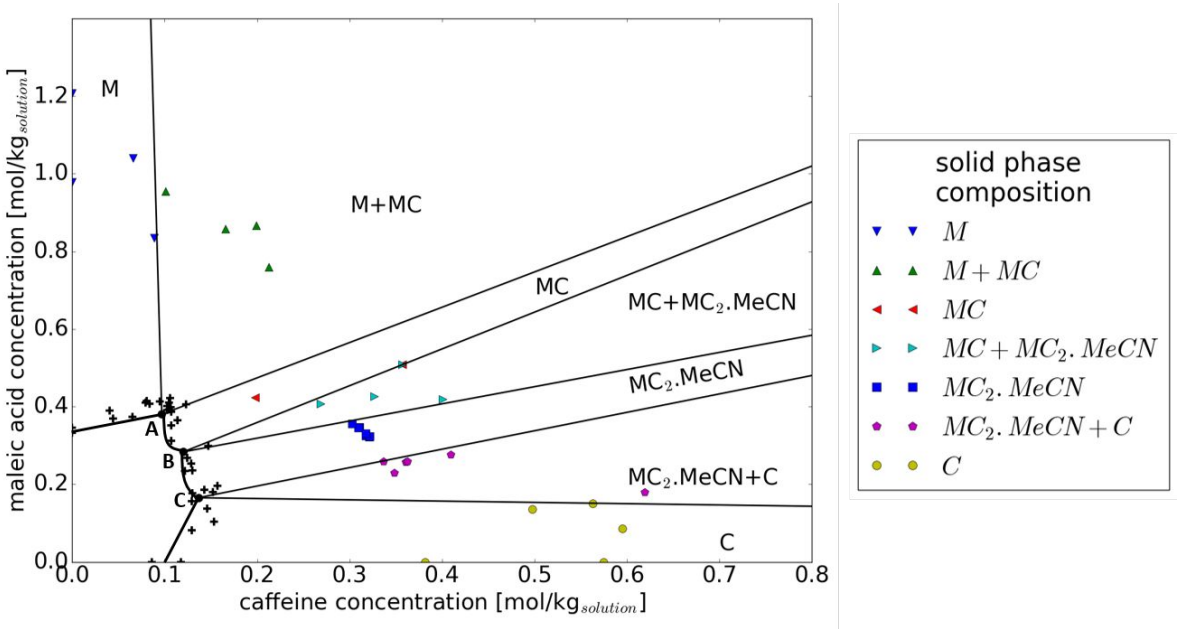


Figure 8. TPD of caffeine and maleic acid in MeCN at 9°C

TPD determination at 9°C and 20°C also allowed determining the heat of dissolution (ΔH_d) of the MC crystal form in AcOEt and MeCN. Indeed, based on solubility data obtained experimentally, we were able to calculate the K_{sp} of MC at 20°C and 9°C in both solvents. Finally, we were able to determine ΔH_d using Van't Hoff equation that indicated the dissolution of MC is less endothermic in MeCN than in AcOEt (Table 4).

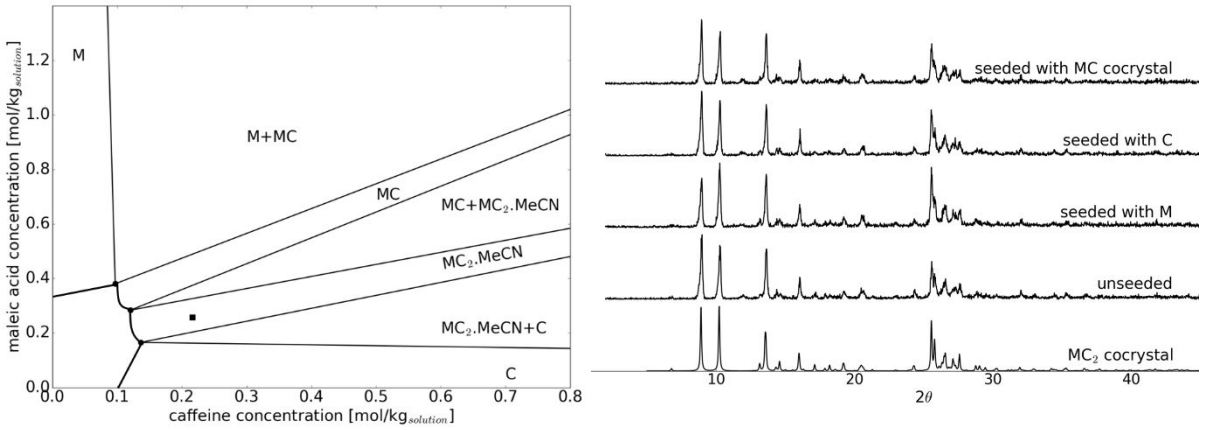
Table 4. Determination of MC heat of dissolution in AcOEt and MeCN

AcOEt		MeCN	
$K_{sp}^{20°C}$	1.20±0.02*10^{-2}	$K_{sp}^{20°C}$	8±2*10^{-2}
$K_{sp}^{9°C}$	5.7±0.1*10^{-3}	$K_{sp}^{9°C}$	2.6±0.2*10^{-2}
ΔH_d (kJ/mol)	47±2	ΔH_d(kJ/mol)	67±3

3.3. Crystallization process for MC_2 recovery

The findings above paved the way for the development of thermodynamically robust MC2 cocrystallization process, starting from a 75mL clear supersaturated solution in conditions for which MC2.MeCN is the thermodynamically stable form (Figure 9-left, black dot). Such a solution was prepared adding 2.67g of caffeine and 1.91g of maleic acid (1.2 equivalents) to 75mL of MeCN. The suspension was heated to 50°C and held for 1 hour to ensure complete dissolution of the material. The solution was then cooled down to 9°C at a 0.3 K/min rate. The suspension was left to equilibrate for 6 hours,

after which filtration was performed on a sieve under vacuum and products were characterized by PXRD. To determine the robustness of the process, crystallization experiments were performed and seeded with different crystal forms at the onset of the isothermal hold at 9°C. Solid material were always extracted and subsequently analyzed by PXRD. In principle, the thermodynamic outcome should be the 1:2 cocrystal solvate[b] as it is the only stable form in suspension under these conditions. Our results show that, no matter the type of seeding form used (M, C, MC, MC_2), this solvate is always obtained at the end of the process, even if one does not seed, implying this form is also the one that crystallizes out spontaneously (Figure 9-right).



[b] The MC_2 form was obtained as confirmed by PXRD analysis after filtration, as the MC_2.MeCN form desolvates spontaneously upon exposure to ambient atmosphere.

Figure 9. Conditions for the upscaling experiment (left) and PXRD analysis of the crystalline products (right)

A scale-up process was suggested for the MC_2 cocrystal form using these conditions. To prepare seed material, an initial 4g slurry of MC_2.MeCN crystals in suspension was left to equilibrate at 9°C for 2 days and used as a seeding material.[c]

Then 3.56 g of caffeine and 2.55 g of maleic acid were added to 100ml of MeCN. The solution was first heated up to 55°C to ensure complete dissolution of caffeine and maleic acid. It was then cooled down to 9°C at a 2 K/h rate. After 15 minutes at 9°C, the solution was seeded with the 4g seeding suspension and left to equilibrate for 6 hours. Upon filtration and drying, 2.01g of material (58% yield with respect to caffeine) was recovered and analyzed by PXRD and DSC (see supporting information). The quantity of material recovered accounts for 92% of the theoretical yield based on the TPD, with the 8% loss explained by filtration and residues remaining in the crystallization vessel.

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[c] The composition used is once more identical to the one represented by the black dot in Figure 9.

4. Conclusion

This study evidenced the importance of solvent and temperature in the development of a cocrystallization process. Under specific conditions, this can lead to crystallization of defined forms difficult to predict (solvate at lower temperature or cocrystals with 'original stoichiometry'). These forms can potentially give access to other forms phase transformations. In particular, we are the first to propose a robust way to obtain the 1:2 maleic acid:caffeine cocrystal. This latter form shows such a small stability zone in most solvents, that direct crystallization of this form is strenuous. Here we present an innovative pathway to this form, by co-crystallization of the 2:1 co-crystal solvate in MeCN. This solvate can easily be obtained by co-crystallization from solution, and desolvates to the 2:1 co-crystal form under ambient conditions, hereby offering a thermodynamic robust cocrystallization pathway to this form. This paper thus highlights the fact that one can use intermediate forms, to achieve seemingly difficult to get co-crystal forms.

5. Supporting information

- Crystal data and structure refinement for MC_2.MeCN

- DSC and PXRD characterization of process's product

This material is available free of charge via the Internet at http://pubs.acs.org.

6. Acknowledgements

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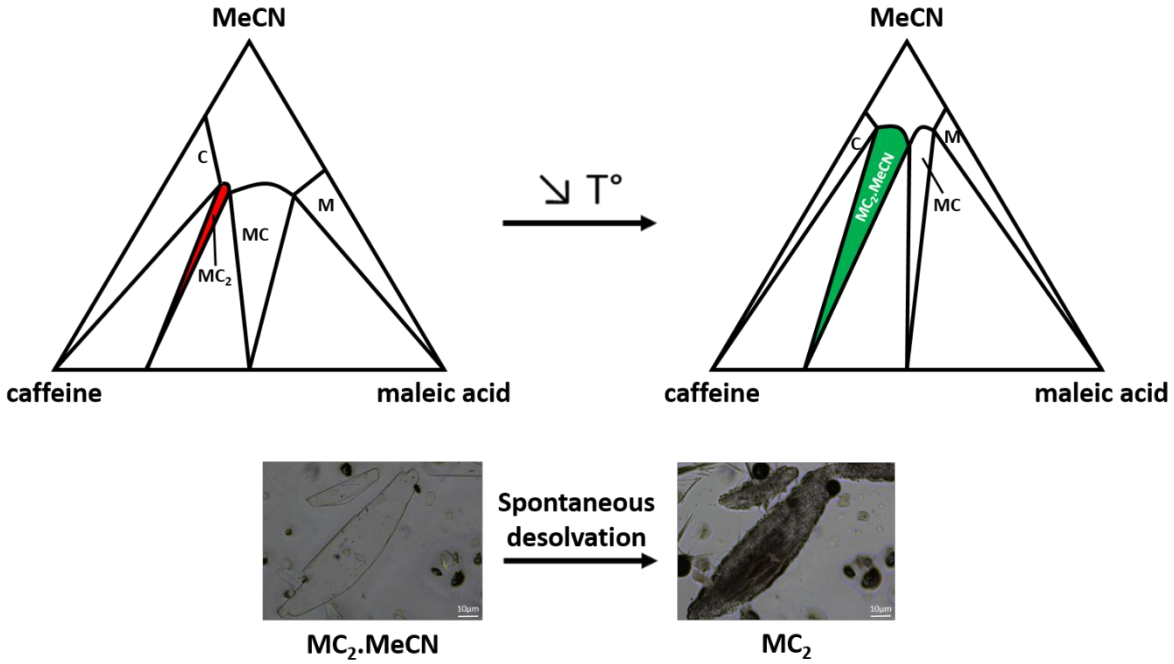
For Table of Contents Use Only

Enabling cocrystallization of challenging systems: passing through a stable cocrystal solvate as a pathway to strenuous cocrystal forms.

J.B. de Maere d'Aertrycke, R. Payen, L. Collard, K. Robeyns, D. Croker, T. Leyssens



Selecting the right solvent and temperature conditions allowed accessing a strenuous cocrystal form. Decreasing the temperature in acetonitrile, a new solvated cocrystal form is obtained. Upon exposure to ambient atmosphere, this form desolvates spontaneously and leads to the cocrystal form desired.

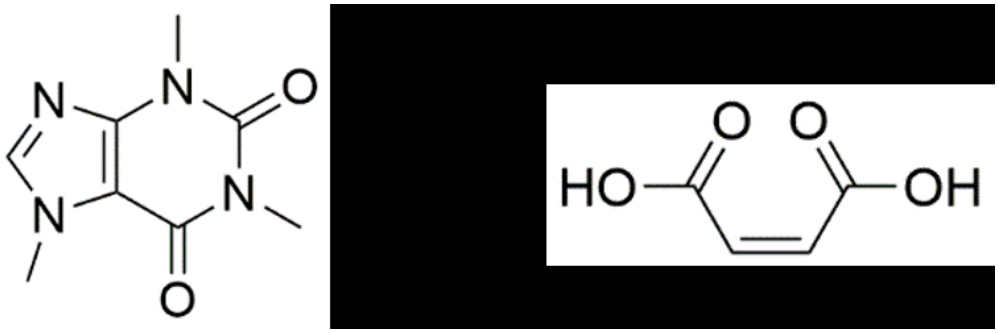


Figure 1. Detailed structure of caffeine (left) and maleic acid (right)

128x41mm (150 x 150 DPI)

Figure 2. Theoretical TPD at a given temperature for a system of two coformers A and B, with strong solubility differences between both coformers. By adjusting the solubilities of both co-formers (e.g. by adjusting the temperature), a more symmetrical phase diagram can be obtained.

244x96mm (150 x 150 DPI)

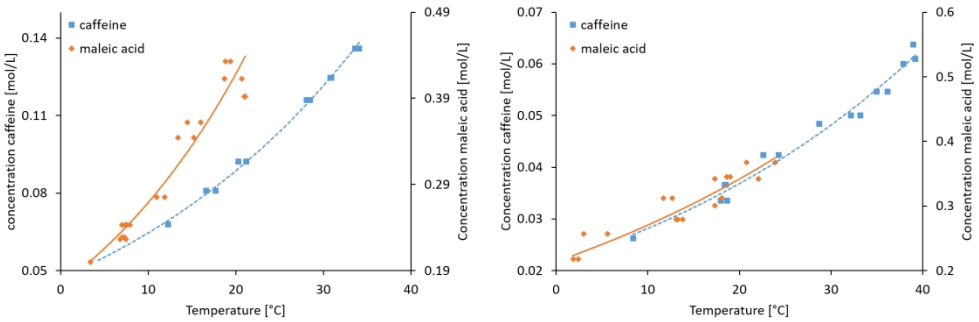


Figure 3. Solubility curves of caffeine and maleic acid in MeCN (left) and AcOEt (right)

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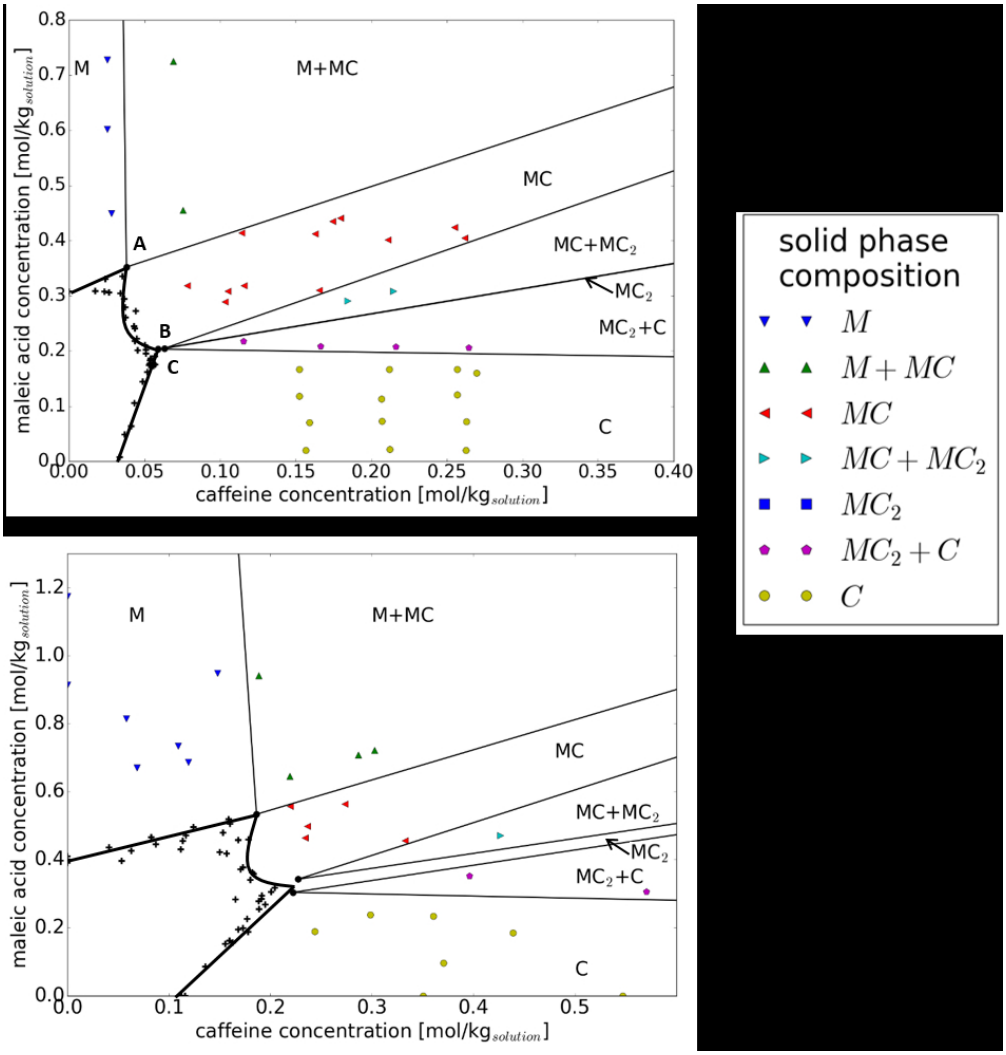

Figure 4. TPD of caffeine and maleic acid in AcOEt (up) and MeCN (down) at 20°C

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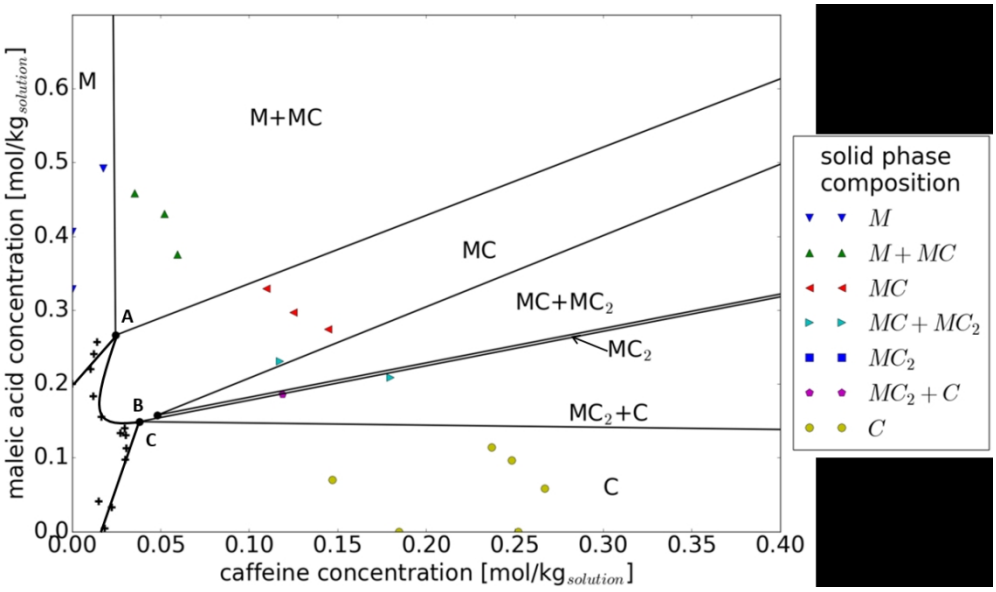

Figure 5. TPD of caffeine and maleic acid in AcOEt at 9°C

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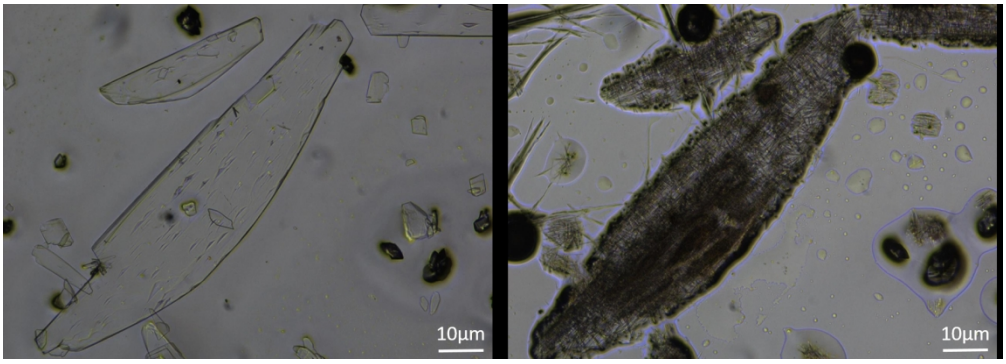

Figure 6. MC2.MeCN cocrystal in MeCN at 9°C (left) and after 40 minutes in ambient atmosphere at 15°C (right) under microscope

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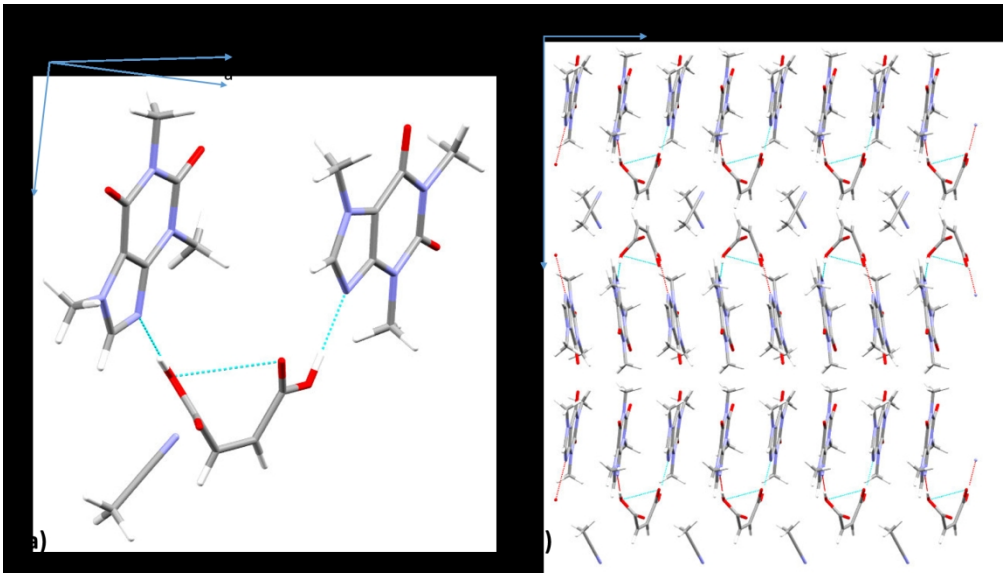

Figure 7. Trimer constituting the MC2.ACN cocrystal (left) and view of the packing along the c-axis (right)

321x182mm (150 x 150 DPI)

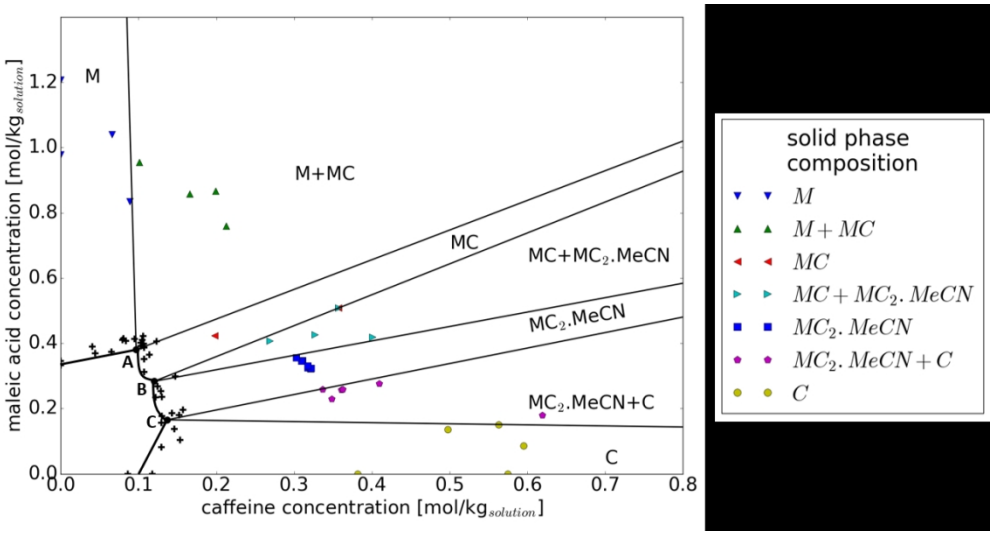

Figure 8. TPD of caffeine and maleic acid in MeCN at 9°C

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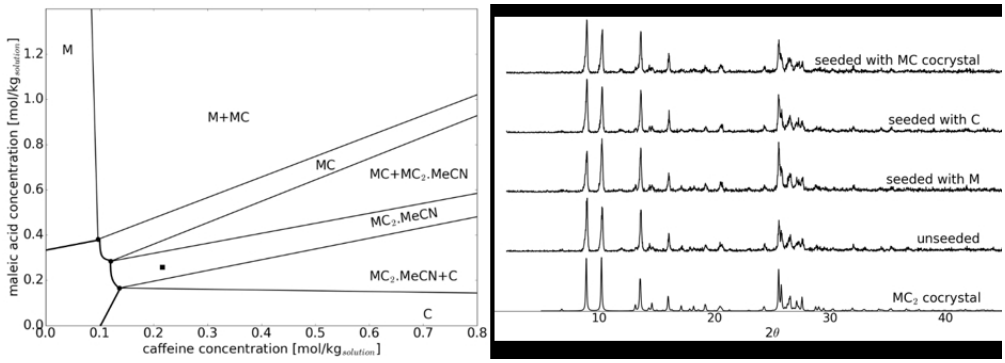

Figure 9. Conditions for the upscaling experiment (left) and PXRD analysis of the crystalline products (right)

158x56mm (150 x 150 DPI)