UNIVERSITY OF LEEDS

This is a repository copy of *Mechanistic Understanding of Competitive Destabilization of Carbamazepine Cocrystals under Solvent Free Conditions*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/167284/

Version: Accepted Version

Article:

Alsirawan, MHDB, Lai, X, Prohens, R et al. (5 more authors) (2020) Mechanistic Understanding of Competitive Destabilization of Carbamazepine Cocrystals under Solvent Free Conditions. Crystal Growth & Design, 20 (9). pp. 6024-6029. ISSN 1528-7483

https://doi.org/10.1021/acs.cgd.0c00735

© 2020 American Chemical Society. This is an author-accepted version of an article published in Crystal Growth & Design. Uploaded in accordance with the publisher's self-archiving policy.

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose
university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

Supporting Information

Mechanistic Understanding of Competitive Destabilization of Carbamazepine Cocrystals under Solvent Free Conditions

MHD Bashir Alsirawan,[a] Xiaojun Lai,[b] Rafel Prohens,[c] Venu R. Vangala,[a] Petroc Shelley,[d] Thomas J. Bannan,[e] David O. Topping,[d,e] and Anant Paradkar*[a]

a. Centre for Pharmaceutical Engineering Science, University of Bradford, Bradford, D7 1DP, United Kingdom.

b. School of Chemical and Process Engineering, University of Leeds, Leeds, LS2 9JT, United Kingdom.

c. Polymorphism and Calorimetry Unit, University of Barcelona, Lluis Solé i Sabarís, 08028 Barcelona, Spain.

d. School of Earth and Environmental Sciences, University of Manchester, Manchester, M13 9PL, United Kingdom.

e. National Centre for Atmospheric Science, University of Manchester, Manchester, M13 9PL, United Kingdom.

Table of Contents

1. Experimental Section....3
    1.1. Cocrystal Preparation: 3
    1.2. Competitive destabilization experiments:....4
    1.3. Powder X-Ray Diffraction (PXRD) Analysis....4
    1.4. Differential Scanning Calorimetry (DSC): 4
    1.5. Thermogravimetric Analysis (TGA): 4
    1.6. Sublimation experiments:....5
    1.7. Raman Spectroscopy: 5
    1.9. Vapour pressure measurements using Knudsen Effusion Mass Spectrometry (KEMS):....5
    1.10. Hot Stage Polarized-Light Microscopy: 6
2. Supplementary Results: 7
    2.1. TGA and DSC results:....7
    2.2. Sublimation results: 11
    2.3. Hot Stage Polarized-Light Microscopy: 12
References: 15

1. Experimental Section

All materials and organic solvents were purchased from Sigma-Aldrich Company (UK), Ltd and were used as received.

1.1. Cocrystal Preparation:

CZ:SA cocrystals were prepared by dissolving CZ stable Form III (5.0 g; 21.16 mmol) and SA (2.58 g; 21.16 mmol) in 7:2 (v/v) chloroform/methanol (90 mL). In case of CZ:NT, CZ Form III (5.0 g; 21.16 mmol) and NT (3.88 g; 21.16 mmol) were dissolved in 8/2 (v/v) chloroform/methanol (60 mL) 40 C°. This was followed by solvent evaporation using Rota vapour apparatus at 20 rpm, 65 C°, and 400 mbar. The produced powder left under vacuum to remove all the solvent. Finally, the powder was gently passed through 500 μm sieve to break present lumps.

Table S1. Prepared cocrystals, polymorphs, and their CCDC reference codes:

Cocrystal	Polymorph	CCDC code
CZ:SA 1:1	Form I: Triclinic, $P\bar{1}$.	EXUQUJ
CZ:NT 1:1	Form I: Monoclinic, $P2_1/c$.	EXUQUJ01

CZ:SA triclinic Form I is formed by carbamazepine carboxamide homodimer with saccharin molecule via SA N-H…O CZ, and SA S=O…H CZ hydrogen bonding. While, CZ:NT involves the formation of carboxamide homosynthon linked to nicotinamide by multiple point amide-amide or NT N-H…O CZ and NT C=O…H CZ hydrogen bonding (Figure 1).

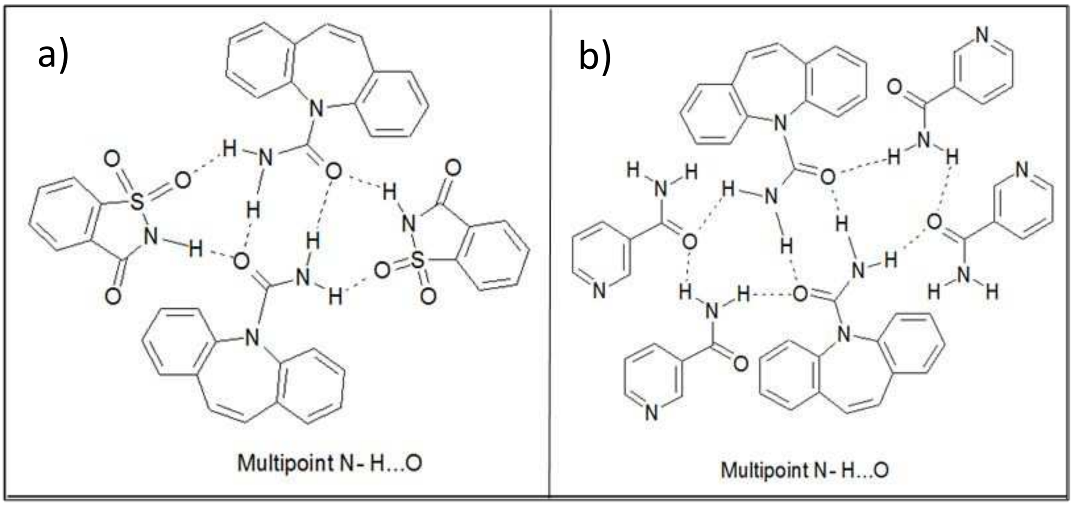

Figure S1: Molecular structure of a) CZ:SA, and b) CZ:NT.

1.2. Competitive destabilization experiments:

Following to cocrystals preparation, stoichiometric mixtures of CZ:NT + SA were subjected to different processing conditions. The selected conditions were, neat grinding using ball mill and heating (H) using variable temperature PXRD (VT-PXRD).

a. **Neat Grinding:**
   Neat grinding was conducted using Retsch MM200 ball mill, equipped with stainless steel 10-mL grinding jars and two 7-mm stainless steel grinding balls per jar. The grinding was performed at a rate of 25 Hz for a period of 90, and 120 minutes.

b. **Heating using VT_PXRD:**
   VT-PXRD analysis was performed using a Phillips PANalytical XPert-PRO diffractometer with a Cu-Kα radiation source tube and 1.54 Å X-ray wavelength. Emission filament voltage and amperage were 40 kV and 40 mA respectively. Selected scanning range was 5 to 30° 2θ with step size of 0.0334° was used. Heating was performed using HTK 1200N Capillary Extension chamber (Anton Paar) with RhPt thermocouple, and furnace heating range of 25 °C to 1200 °C, and 2 Theta range 1.5 to 88 °2θ. Two types of experiments were performed, polythermal ramping from 25 °C to 160 °C, at heating rate of 2 °C/min, and isothermal method which heats the sample to predetermined temperature and hold it for certain time. Data was handled using HighScore plus with ICDD database.

1.3. Powder X-Ray Diffraction (PXRD) Analysis

PXRD analysis was done using a Bruker D8 diffractometer with a Cu Kα radiation source tube and 1.54 Å X-ray wavelength. Emission filament voltage and amperage were 40 kV and 40 mA respectively. The scanning range of 5 to 30° 2θ with step size of 0.01 ° was used. Results were compared to the simulated patterns generated from the reported single crystal X-ray diffraction files from CCDC.

1.4. Differential Scanning Calorimetry (DSC):

The DSC was performed using DSC Q2000 from TA instruments. Approximately 2 to 4 mg of the sample was heated in the sealed standard aluminium pan from 25°C to 250°C at heating rate of 10 °C/min under nitrogen atmosphere. DSC data was analyzed using the TA Universal analysis software version 4.5A.

1.5. Thermogravimetric Analysis (TGA):

TGA was performed using TGA Q500 from TA instruments. Approximately 2 to 4 mg of the sample was heated from 30 to 700 °C with heat rate of 2 °C/min in open standard titanium pan under nitrogen atmosphere. TGA data was analysed using the TA Universal analysis software version 4.5A.

1.6. Sublimation experiments:

These experiments were conducted using sublimation apparatus, (Sigma Aldrich, Germany) (Figure S2). Sublimation experiments were carried out by placing around 1 g of sample either as pure material or a mixture in sublimation reservoir. Then, the reservoir was attached to the top side of the apparatus and all were placed in a controlled temperature paraffin oil bath. Tape water was passed through the top side to precipitate any produced sublimate.

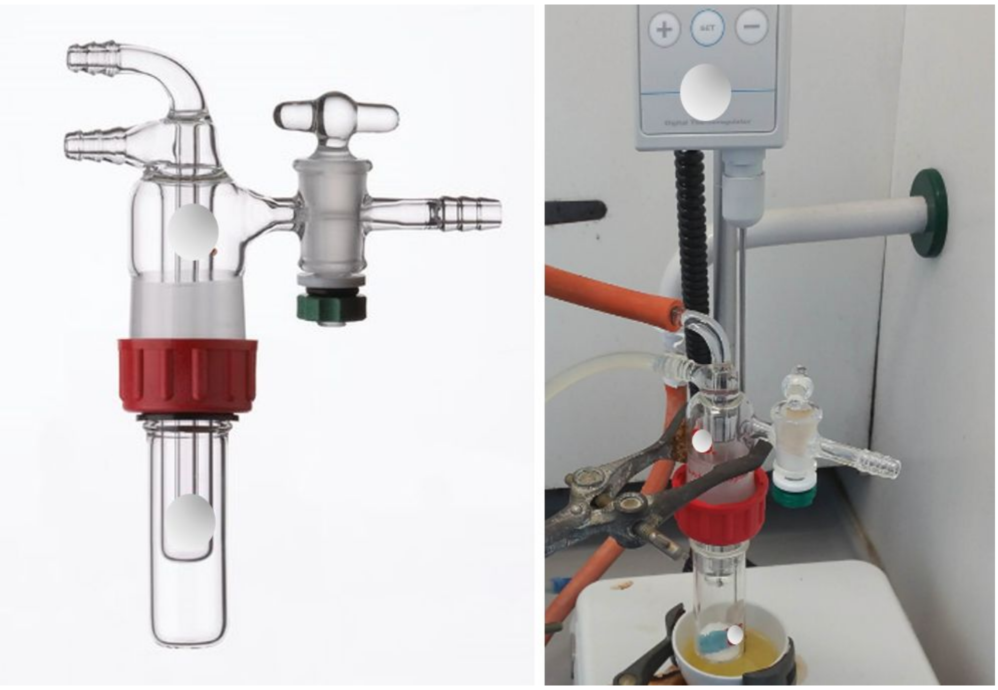

Figure S2: Sublimation apparatus.

1.7. Raman Spectroscopy:

Raman spectra of samples were obtained using a Renishaw *InVia* Reflex dispersive Raman microscope equipped with a 785 nm near-infrared diode laser (Renishaw, Wotton-under-Edfe, UK) and 5x objective lens generating a 5 μm diameter laser spot. Scans were performed at 2 cm^{-1} resolution and 10 second exposure time with extended scanning mode from 200-1800 cm^{-1}. Data were obtained using WIRE 3.4 software backage.

1.9. Vapour pressure measurements using Knudsen Effusion Mass Spectrometry (KEMS):

Knudsen Effusion Mass Spectrometry (KEMS) system has been used [1,2,3] to determine vapour pressures. For a more detailed overview see Booth et al.[2]

KEMS system was calibrated using a reference compound of known vapour pressure is used. In this study tetraethylene glycol (PEG-4) (P298 = 1.69 x 10^{-2} Pa),[4] was used as the reference compound. The homologous polyethylene glycol (PEG) series covers a range of 1 x 10^{-2} to 1 x 10^{-7} Pa and has been validated using multiple different experimental techniques, including the KEMS, in the work by Krieger et al.[4] The reference compound is placed in a temperature-controlled Knudsen cell. The cell has a chamfered orifice through which the sample effuses creating a molecular beam. The size of the orifice is <1/10 the mean free path of the gas molecules in the cell. This ensures that the particles effusing through the orifice don't disturb the thermodynamic equilibrium of the cell. The molecular beam is then ionised via electron impact at 70 eV and sampled using a quadrupole mass spectrometer. After correcting for the ionisation cross section, the signal generated is proportional to the vapour pressure.

Once the calibration process is completed it is possible to measure a sample of unknown vapour pressure. When the sample is changed it is necessary to isolate the sample chamber from the measurement chamber using a gate valve so that the sample chamber can be vented, whilst the ioniser filament and the secondary electron multiplier (SEM) can remain on and allow for direct comparisons with the reference compound. The vapour pressure of the sample can be determined from the intensity of the mass spectrum, if the ionisation cross section at 70 eV, and the temperature at which the mass spectrum was taken are known. The samples of unknown vapour pressure are typically solid, so it is the solid-state vapour pressure that is determined.

After the solid state vapour pressure, P (P_a), has been determined for multiple temperatures, the Clausius-Clapeyron (Eq 1) can be used to determine the enthalpy and entropy of sublimation as shown in Booth et al.[2]

$$\ln P = \frac{-\Delta H_{sub}}{\mathrm{R}T} + \frac{\Delta S_{sub}}{R} \quad \text{(Eq 2)}$$

where T is the temperature (K), R is the ideal gas constant (J mol-1 K-1), ΔH_{sub} is the enthalpy of sublimation (J mol-1) and ΔS_{sub} is the entropy of sublimation (J mol-1 K-1). P was obtained over a range of 30 K in this work starting at 298 K. The reported solid-state vapour pressures are calculated from a linear fit of ln P vs $1/T$ using the Clausius-Clapeyron equation.

1.10. Hot Stage Polarized-Light Microscopy:

Zeiss Axioplan-2 microscope was used, and images were processed using Axiovision (4.5) software. Heating was performed using a Linkam hot stage (THMS600) with linksys 32 patch as controlling software. Most of thermal treatment steps used heating rate of 10 °C/min. Crystals identities were confirmed using Raman microscopy.

2. Supplementary Results:

2.1. TGA and DSC results:

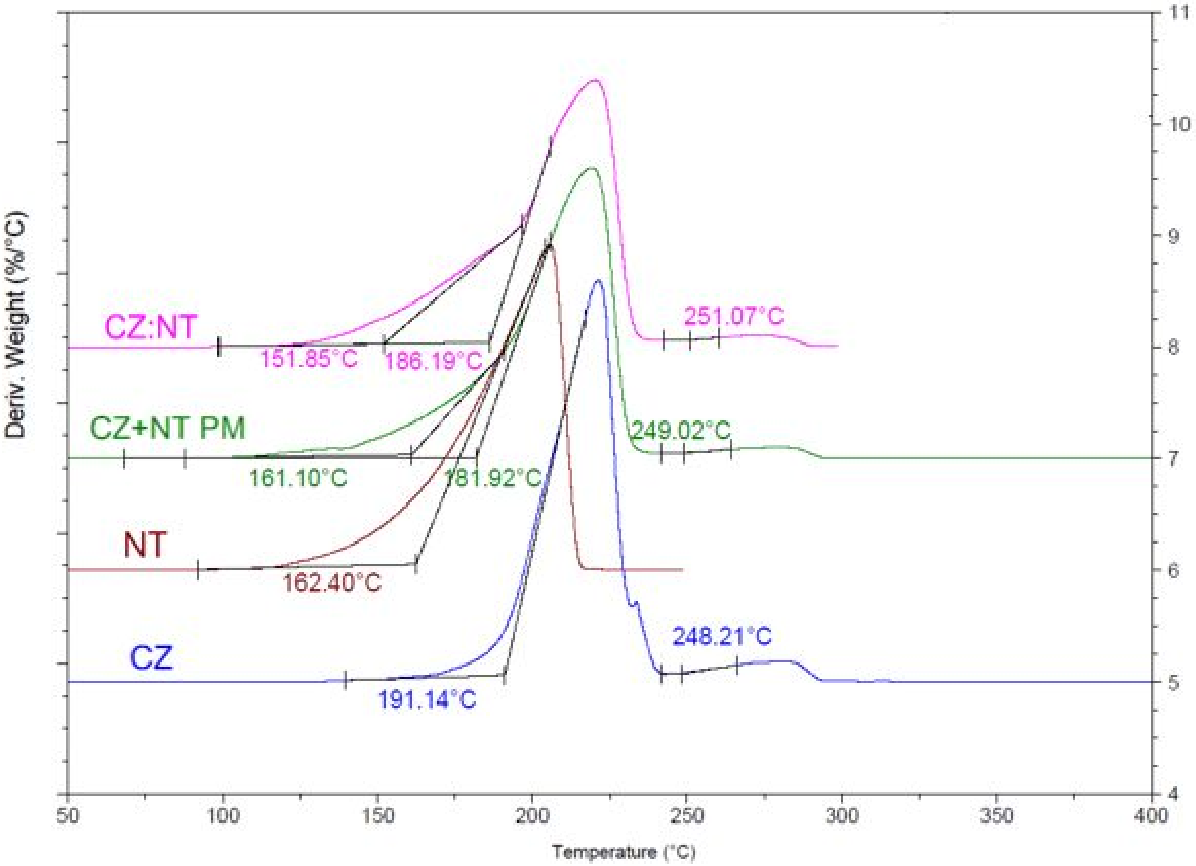

Figure S3: DTA thermograms of CZ:NT cocrystal, related pure compounds and 1:1 physical mixture (PM).

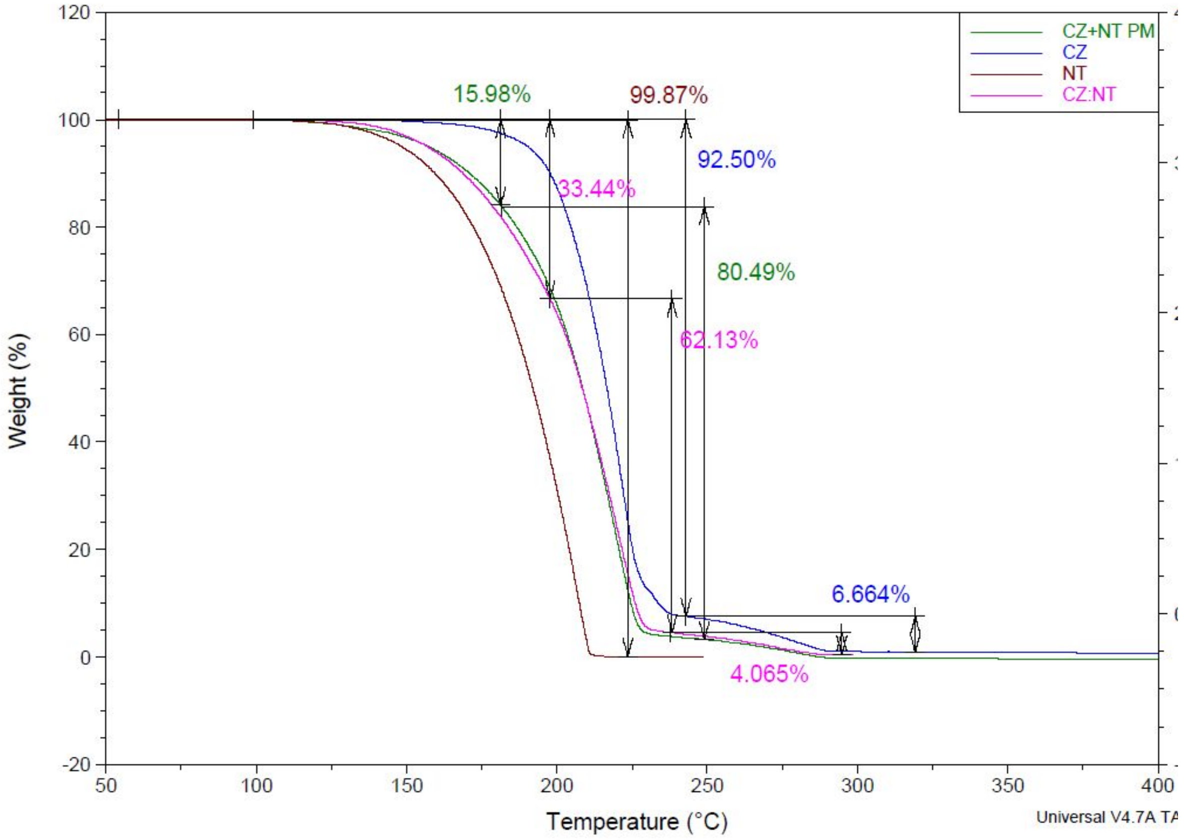

Figure S4: TGA thermograms of CZ:NT cocrystal, related pure compounds and 1:1 physical mixture (PM).

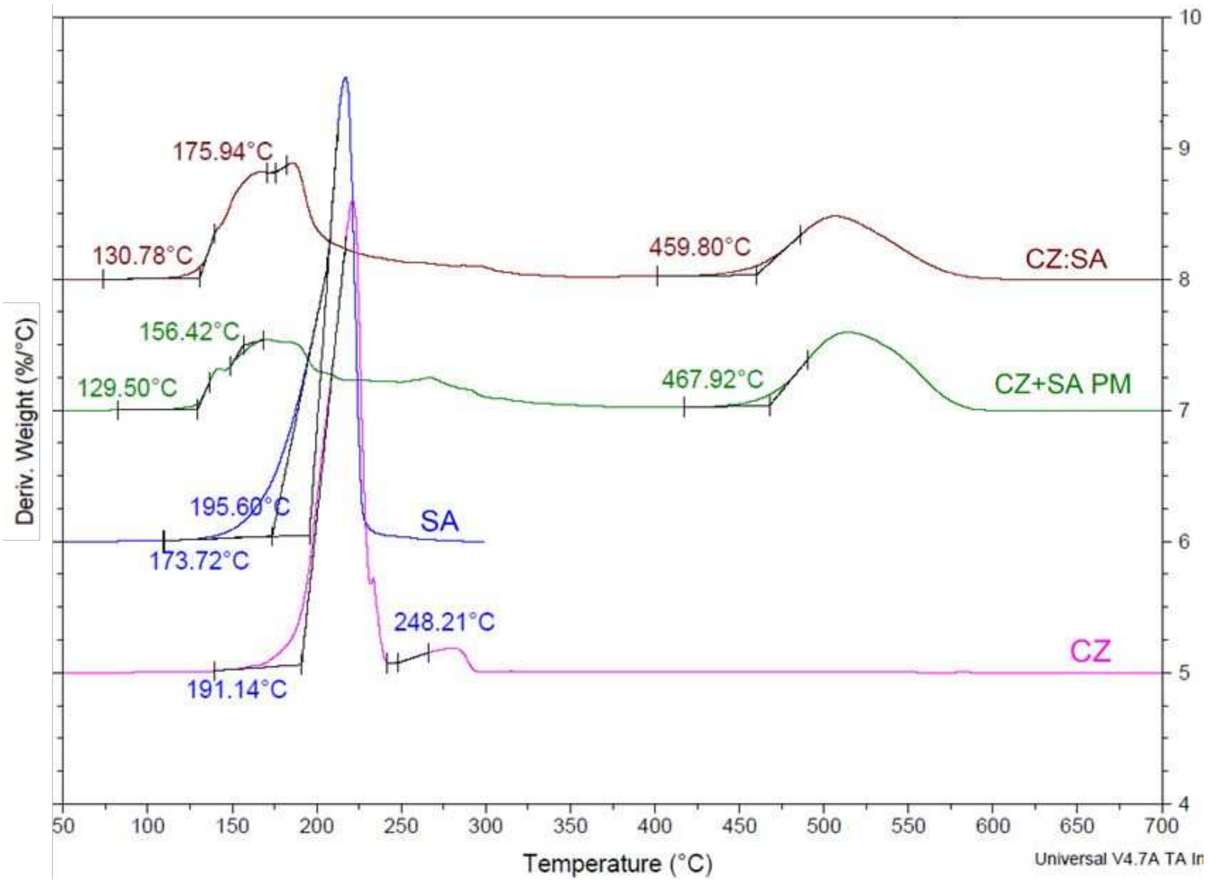

Figure S5: DTA thermograms of CZ:SA cocrystal, related pure compounds and 1:1 physical mixture (PM).

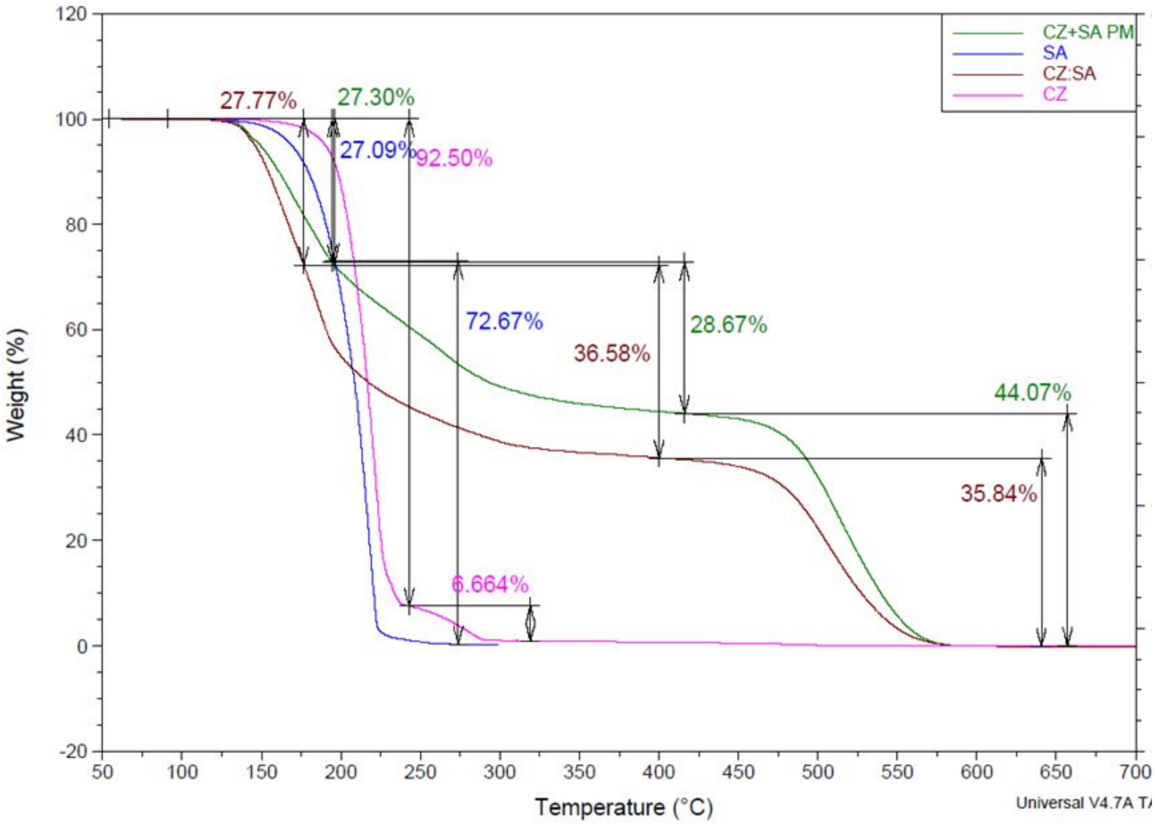

Figure S6: TGA thermograms of CZ:SA cocrystal, related pure compounds and 1:1 physical mixture (PM).

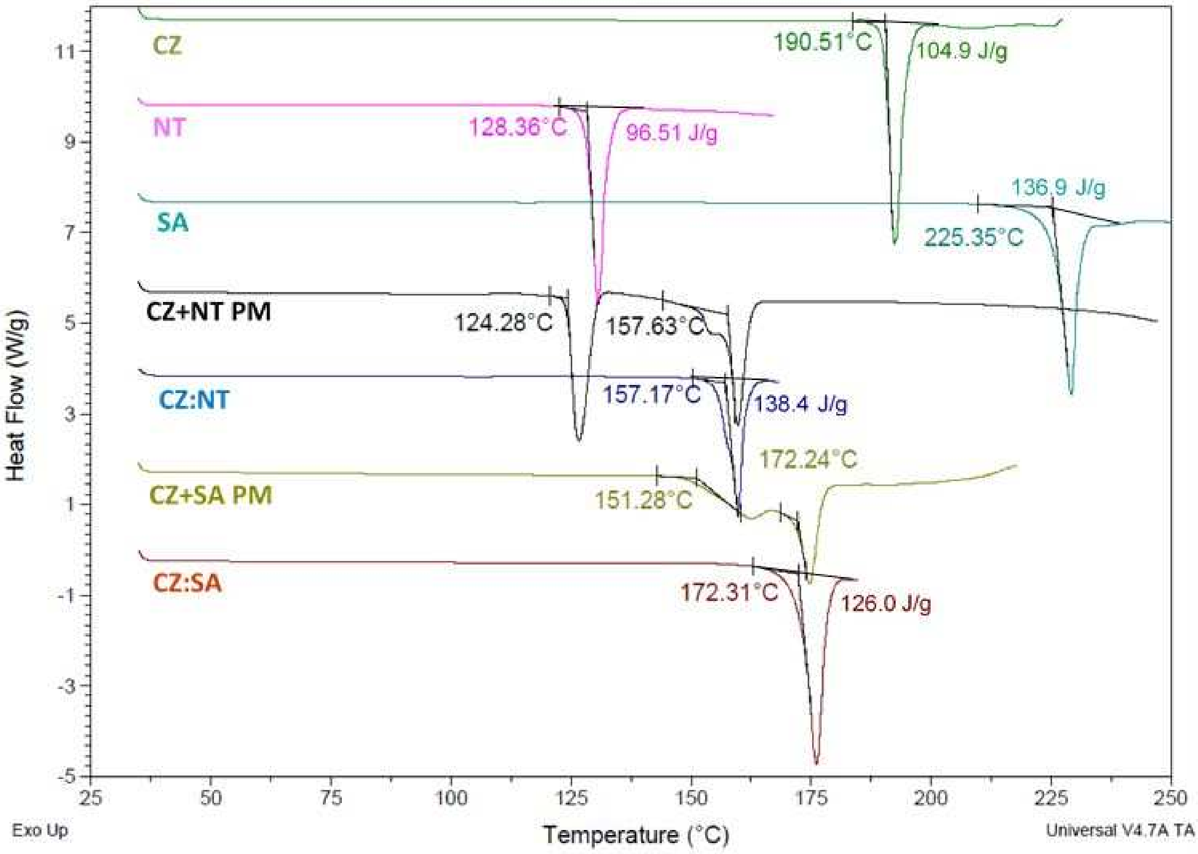

Figure S7: DSC thermograms of CZ:NT and CZ:SA, related pure components and 1:1 physical mixtures (PM).

Table S2: Summary of TGA and DSC data. It includes onset (°C) and weight loss (%).

Compound	DSC			TGA				
	1st Endotherm		2nd Endotherm	1st Step		2nd Step		3rd Step
	Onset °C	Enthalpy J/g	Onset °C	Onset °C	%Weight loss	Onset °C	%Weight loss	Onset °C
CZ	190.5	104.9	NA	191.1	94.4	248.2	NA	NA
NT	128.4	96.5	NA	162.4	99.9	NA	NA	NA
CZ+NT	124.3	NA	157.6	161.1	16.0	181.9	80.5	249.0
CZ:NT	157.2	138.4	NA	151.9	33.4	186.2	62.1	251.0
SA	225.4	136.9	NA	173.7	99.4	NA	NA	NA
CZ+SA	151.3	NA	172.2	129.5	27.3	156.4	28.7	467.9
CZ:SA	172.3	126.0	NA	130.8	27.8	175.9	36.6	458.5

2.2. Sublimation results:

Table S3: Sublimatsion results:

Compound	Residue (R)	Sublimate (S)
CZ	CZ	CZ
NT	NT	NT
SA	SA	SA
CZ+NT	CZ:NT+CZ+NT	NT
CZ+SA	CZ+SA	CZ+SA
CZ:NT	CZ:NT	NT
CZ:SA	CZ:SA	CZ + SA
Physical Mixture (CZ + SA + NT)	CZ:NT + CZ + SA	NT + CZ
CZ:SA + NT	CZ:SA + CZ:NT	NT + CZ + SA

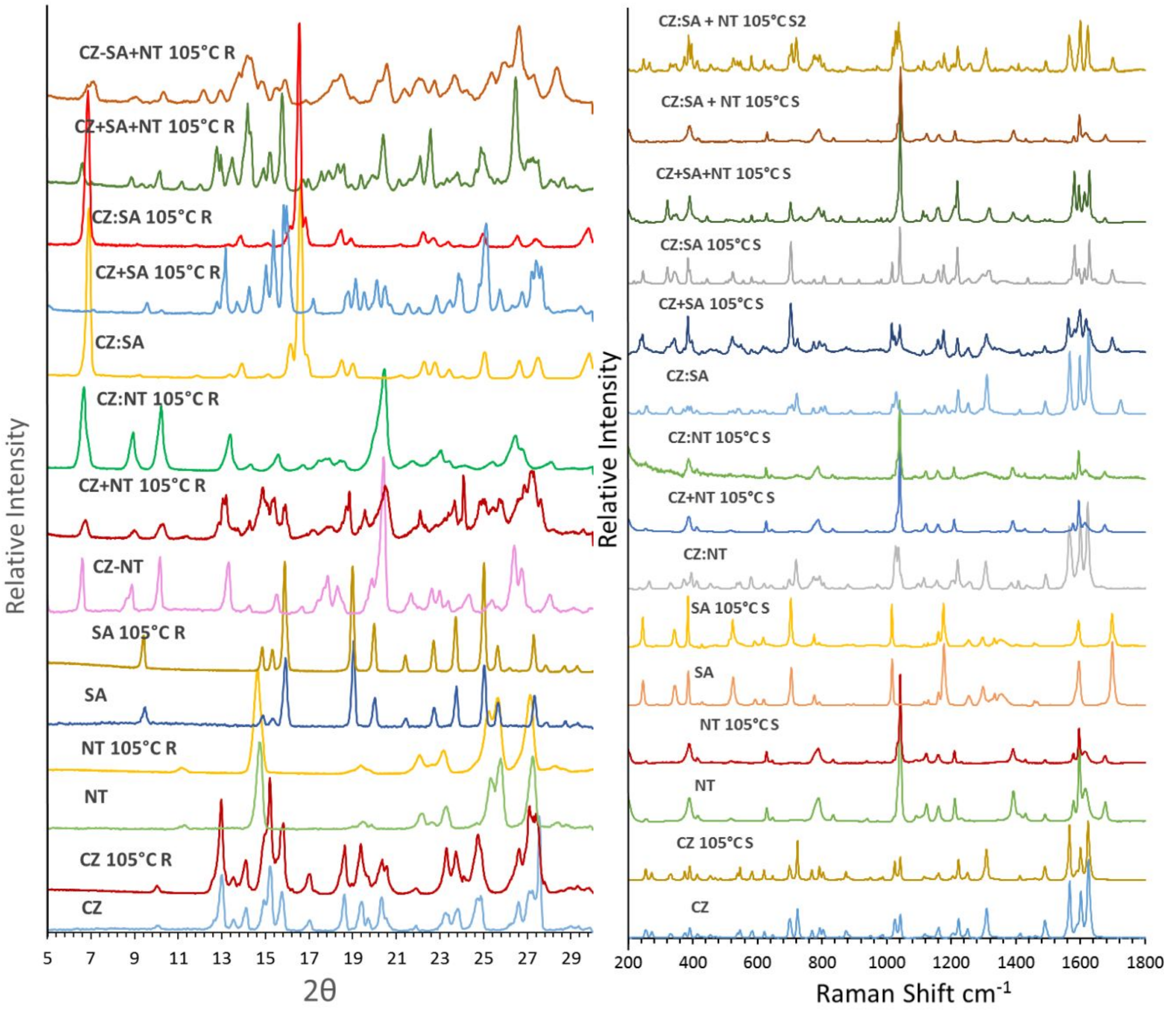

Figure S8: Structural analysis of sublimation experiments outcomes which was performed at 105 °C on pure components, 1:1 CZ+NT and CZ+SA physical mixtures, CZ:NT and CZ:SA cocrystals, and 1:1 stoichiometric mixture of CZ:SA and the competitive coformer NT. Left: PXRD patterns of residuals (R). Right: Raman spectra of sublimates (S).

2.3. Hot Stage Polarized-Light Microscopy:

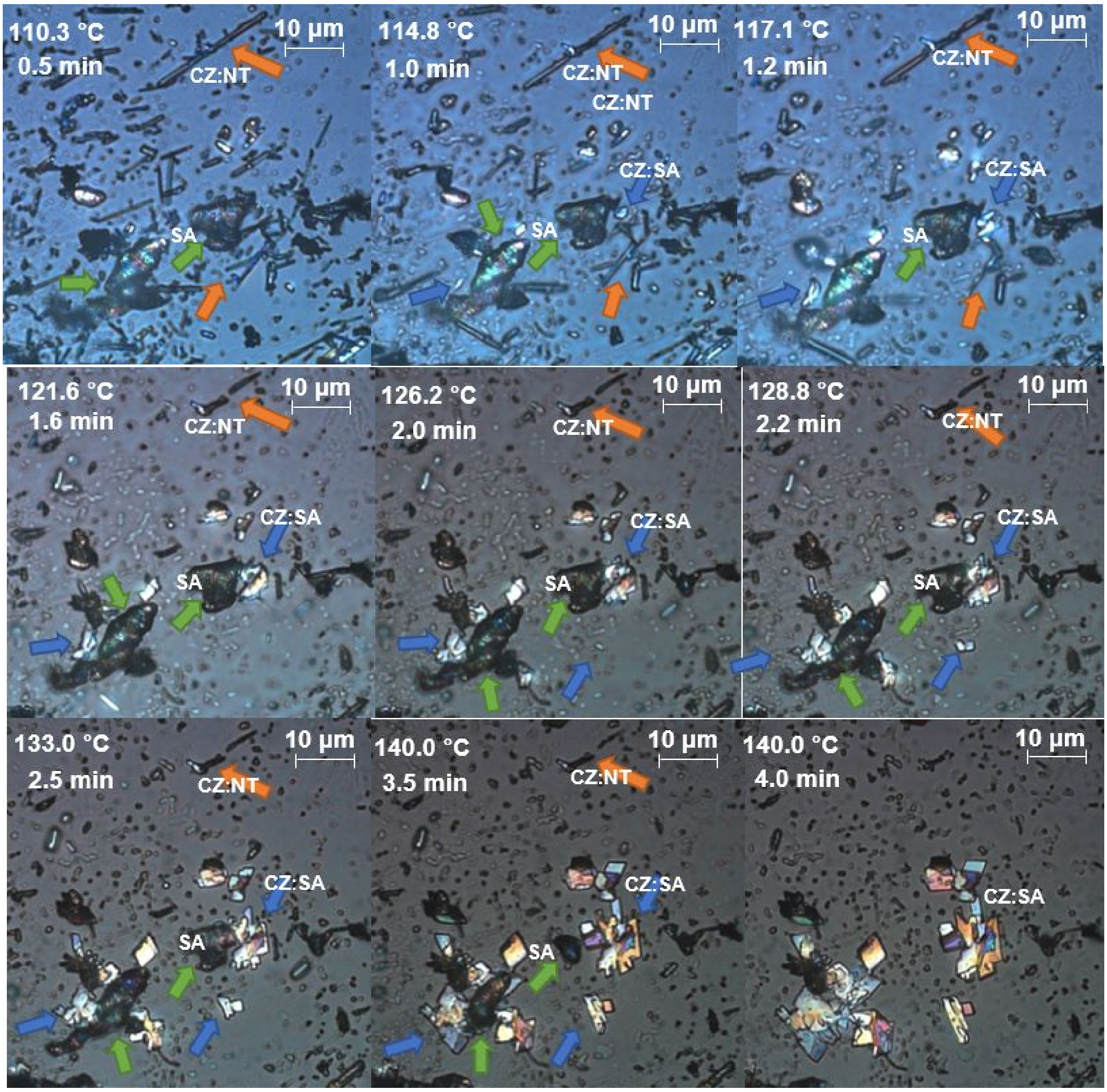

Figure S9: Hot stage polarized optical microscope image of CZ:NT (orange arrows) destabilization is presence of SA (green arrows) and formation of CZ:SA (blue arrows). The reaction started immediately after 0.5 minutes at 113.0 °C where CZ:SA crystals started to grow while both CZ:NT and SA crystals decreased in size until disappearing completely after 4 minutes at 140.0 °C. A video is also available separately as supporting data.

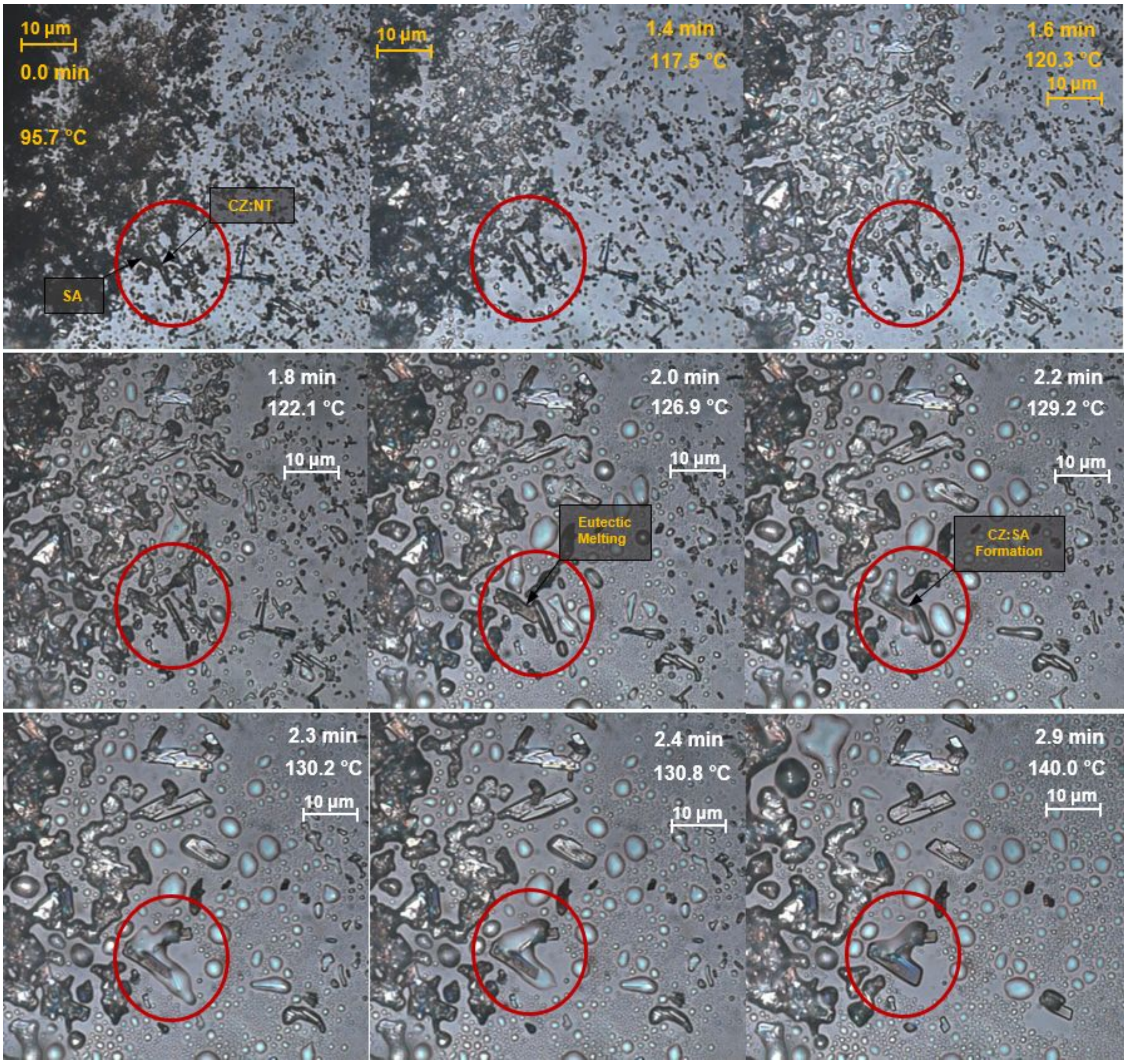

Figure S10: Hot stage polarized optical microscope images of CZ:NT+SA mixture showing formation of eutectic melt and subsequent formation of CZ:SA. The reaction started around 124.0 °C and was completed within few minutes at 140.0 °C. A video is also available separately as supporting data.

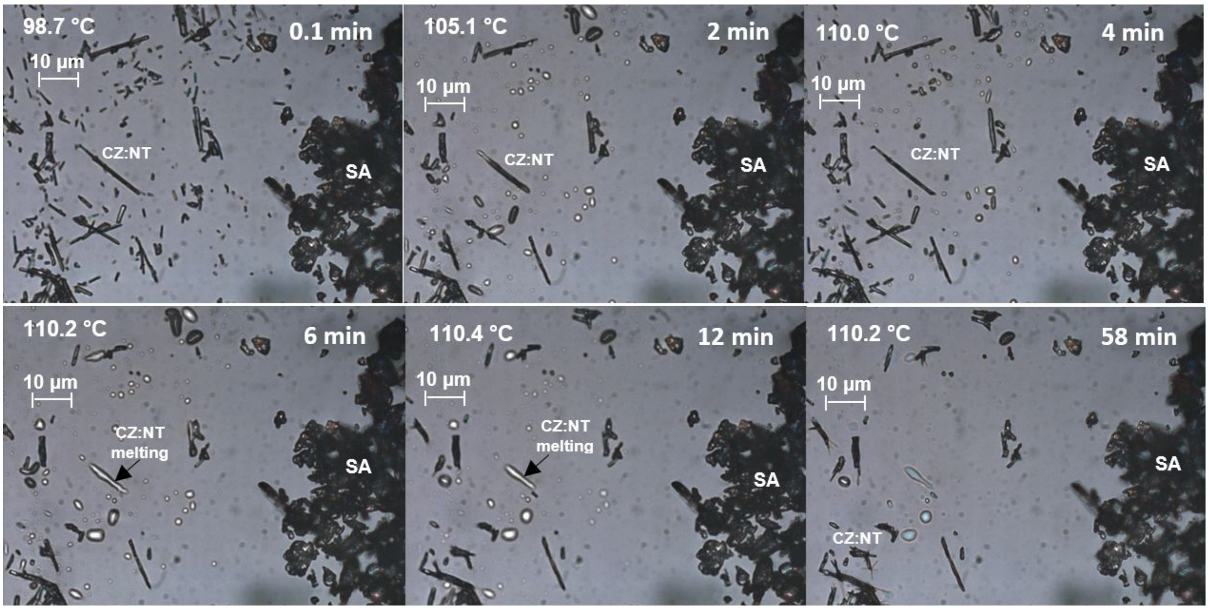

Figure S11: Hot stage microscopy images of CZ:NT and SA placed on a glass slide with no contact. Only partial melting of CZ:NT cocrystal at 110 C was observed and no formation of CZ:SA cocrystal even after 38 minutes. This show that reactants have to be in contact to each other so eutectic formation occurs, thus the transformation to CZ:SA. A video is also available separately as supporting data.

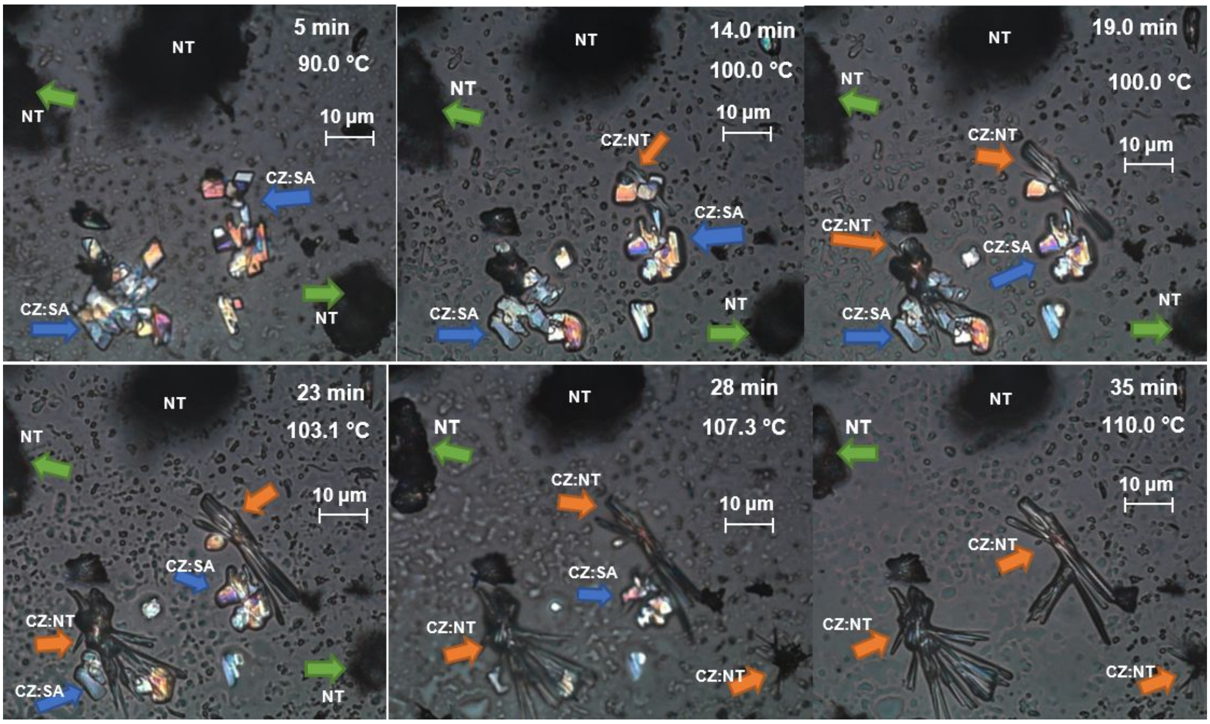

Figure S12: Hot stage polarized optical microscope image of CZ:SA (blue arrows) destabilization is presence of NT (green arrows) and formation of CZ:NT (orange arrows). CZ:NT needle shaped crystals started to grow slowly on CZ:SA crystals after 14 minutes at 100 °C. NT crystals are clearly seen with no contact with CZ:SA. Also, CZ:NT shows crystal growth on NT at later stages and with less extent compared to growth on CZ:SA. The reaction was completed after 35 minutes at 110 °C. A video is also available separately as supporting data.

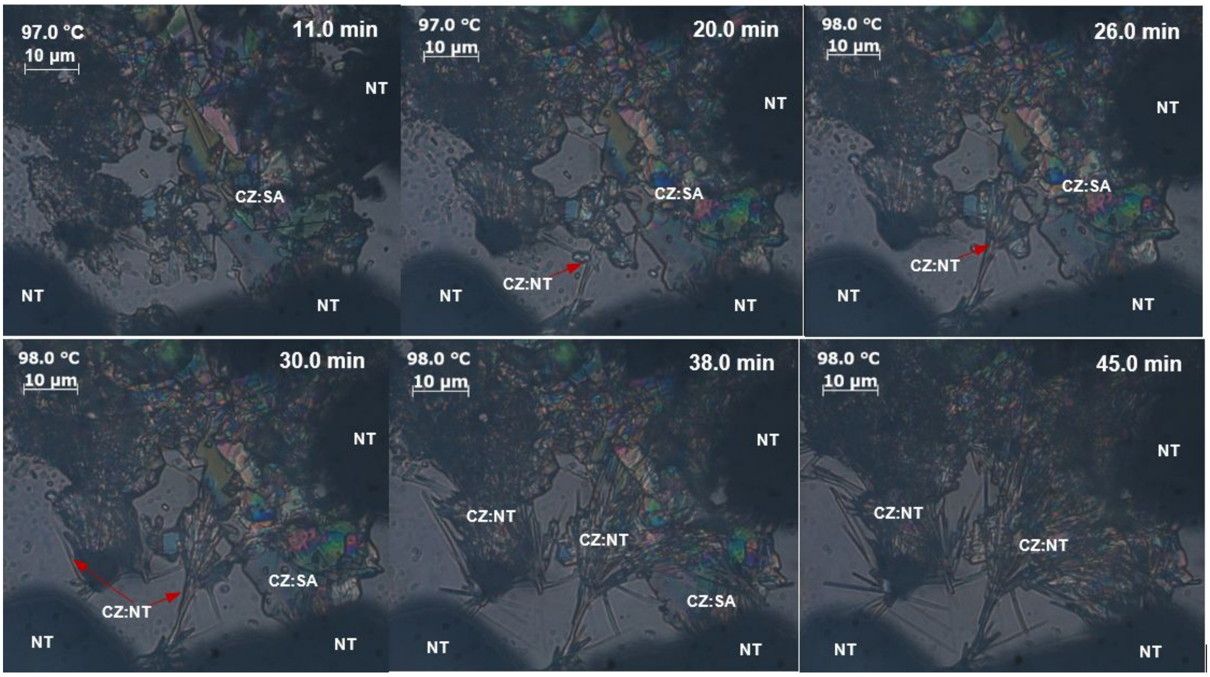

Figure S13: Hot stage polarized optical microscope images of CZ:SA destabilization is presence of NT and with contact to each other. CZ:SA crystal to CZ:NT crystal transformation was observed after ca. 20 minutes at 98.0 °C. The reaction was completed after ca. 45 minutes at 98.0 °C. A video is also available separately as supporting data.

References:

(1) Bannan, T. J.; Booth, A. M.; Jones, B. T.; O 'meara, S.; Barley, M. H.; Riipinen, I.; Percival, C. J.; Topping, D. Measured Saturation Vapor Pressures of Phenolic and Nitro-Aromatic Compounds. *Environ. Sci. Technol* **2017**, *51*, 3922–3928. https://doi.org/10.1021/acs.est.6b06364.

(2) Booth, A. M.; Markus, T.; Mcfiggans, G.; Percival, C. J.; Mcgillen, M. R.; Topping, D. O. Design and Construction of a Simple Knudsen Effusion Mass Spectrometer (KEMS) System for Vapour Pressure Measurements of Low Volatility Organics. *Atmos. Meas. Tech* **2009**, *2*, 355–361. https://doi.org/10.5194/amt-2-355-2009.

(3) Booth, A. M.; Barley, M. H.; Topping, D. O.; Mcfiggans, G.; Garforth, A.; Percival, C. J. Solid State and Sub-Cooled Liquid Vapour Pressures of Substituted Dicarboxylic Acids Using Knudsen Effusion Mass Spectrometry (KEMS) and Differential Scanning Calorimetry. *Atmos. Chem. Phys* **2010**, *10*, 4879–4892. https://doi.org/10.5194/acp-10-4879-2010.

(4) Krieger, U. K.; Siegrist, F.; Marcolli, C.; Emanuelsson, E. U.; Gøbel, F. M.; Bilde, M.; Marsh, A.; Reid, J. P.; Huisman, A. J.; Riipinen, I.; Hyttinen, N.; Myllys, N.; Kurtén, T.; Bannan, T.; Percival, C. J.; Topping, D. A Reference Data Set for Validating Vapor Pressure Measurement Techniques: Homologous Series of Polyethylene Glycols. *Atmos. Meas. Tech* **2018**, *11*, 49–63. https://doi.org/10.5194/amt-11-49-2018.