CRYSTAL GROWTH & DESIGN

Article

Cite This: Cryst. Growth Des. 2018, 18, 2495−2501

pubs.acs.org/crystal

Elusive Nonsolvated Cocrystals of Aspirin: Two Polymorphs with Bipyridine Discovered with the Assistance of Mechanochemistry

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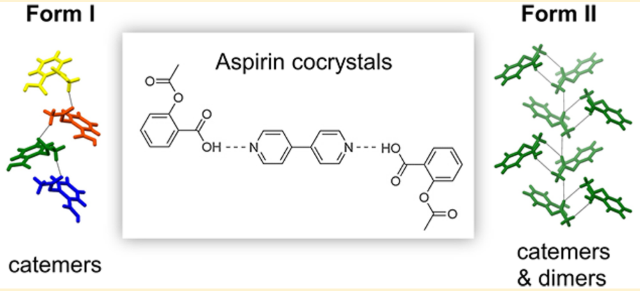


ABSTRACT: We report the discovery two nonsolvated polymorphic cocrystals of acetylsalicylic acid (ASA) and 4,4′-bipyridine (4,4′-bipy) in the form of 2(ASA)·(4,4′-bipy). Form I was discovered through mechanical dry grinding, and Form II was discovered through rapid cooling in ethanol. Both polymorphs consist of three-component hydrogen-bonded assemblies sustained by O−H···N hydrogen bonds. The components of the assemblies adopt an anti-conformation. The polymorphs differ in terms of relative twists of carboxylic acid groups and pyridyl rings. In Form I the ASA molecules are linked by discrete catemeric methyl C−H···O forces of the acetyl substituents, while in Form II the ASA molecules are linked by both infinite methyl C−H···O catemers and centrosymmetric dimers of the acetyl groups. Our results demonstrate the importance of neat mechanical grinding in the discovery and design of pharmaceutical cocrystals and polymorphs.

■ INTRODUCTION

In 2003, Zaworotko and co-workers demonstrated one of the first examples of a pharmaceutical cocrystal in the form of 2(ASA)·(4,4′-bipy)·x(hexane) (where ASA = acetylsalicylic acid, 4,4′-bipy = 4,4′-bipyridine). The solvated cocrystal formed from a mixture of two solvents, namely, diethyl ether and hexane.[1] Pharmaceutical cocrystals have now been developed to represent a class of materials used to directly impact solubility, mechanical properties, and stability, as well as influence the intellectual property of active pharmaceutical ingredients (APIs).[2−6] The formation of cocrystals composed of ASA and 4,4′-bipy has been a subject of subsequent and very recent investigations.[7−9] An early report described an attempt to monitor the cocrystallization of ASA and 4,4′-bipy from a variety of solvents.[7] It was determined that a cocrystallization from ethanol alone results in degradation of ASA into salicylic acid (SA) to generate a polymorph of composition 2(SA)·(4,4′-bipy). In two later reports, it was determined that a cocrystal based on ASA and 4,4′-bipy can be formed by modifying the concentrations of the individual components in ethanol, as well as the crystallization temperature.[8,9] A series of sequential cocrystallizations from ethanol described an isolation of a cocrystal composed of ASA and 4,4′-bipy that was attributed to a chemical reaggregation process. It was also suggested that the generation of cocrystals involving ASA and 4,4′-bipy is possible in the absence of hexane.

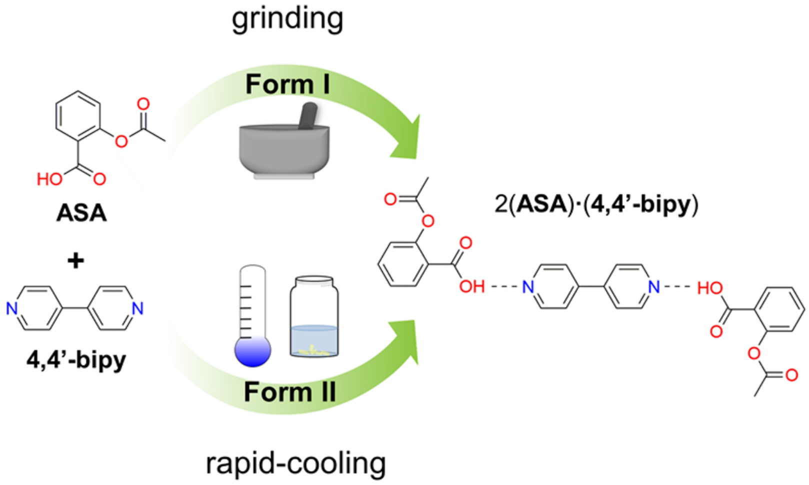
The discovery, characterization, and isolation of single- and multicomponent crystalline forms of organic materials (e.g., pharmaceutics) are of paramount importance for both fundamental research and industrial applications. A challenge presented with studies of crystallization processes, and particularly that of organic compounds, is polymorphism.[10,11] The prediction of polymorphic forms relies on understanding subtle differences in energy related to packing and/or conformation.[12−14] In this sense, mechanochemistry has been a promising avenue for discovering new pharmaceutical solid forms, both as cocrystals and polymorphs.[15−18] ASA itself has four polymorphic forms, the reported single crystal structures of which differ mainly in terms of intermolecular C−H···O forces.[19−22] Specifically, Form I generates centrosymmetric dimers, while Forms II and IV generate catemers. Form III is stable only at high pressures, and a structure has not been reported.[22] Challenges associated with studying polymorphism can also be compounded by reactivity properties of a molecular component (e.g., degradation).[23] ASA itself degrades via hydrolysis in the presence of moisture (i.e., relative humidity) and heat, where the shelf life can vary depending on the formulation.[24−26] The process of cocrystallization has, thus, recently been used to confront problems of reactivity of component molecules in the solid state.[27,28] Specifically, Vangala and co-workers have shown that cocrystals of the antibiotic nitrofurantoin and 4-hydroxybenzoic acid improve stability of an API susceptible to degradation as a solid. Suryanarayanan and co-workers, on the other hand, have described how decomposition of ASA in a solid tablet with carbamazepine affords an unintended cocrystal of SA.[29] Given the difficulties and challenges above, it is, perhaps, not surprising that only a handful of cocrystals with ASA with have been reported.[19,20,30−37]

Herein, we report the isolation and characterization of two nonsolvated cocrystal forms of ASA and 4,4′-bipy in the form of 2(ASA)·(4,4′-bipy) (Scheme 1). Our initial discovery of one of the two forms was achieved by dry grinding of the two neat

Received: January 18, 2018
Published: March 8, 2018

DOI: 10.1021/acs.cgd.8b00104

Scheme 1. Generation of Two Polymorphs of 2(ASA)·(4,4′-bipy)



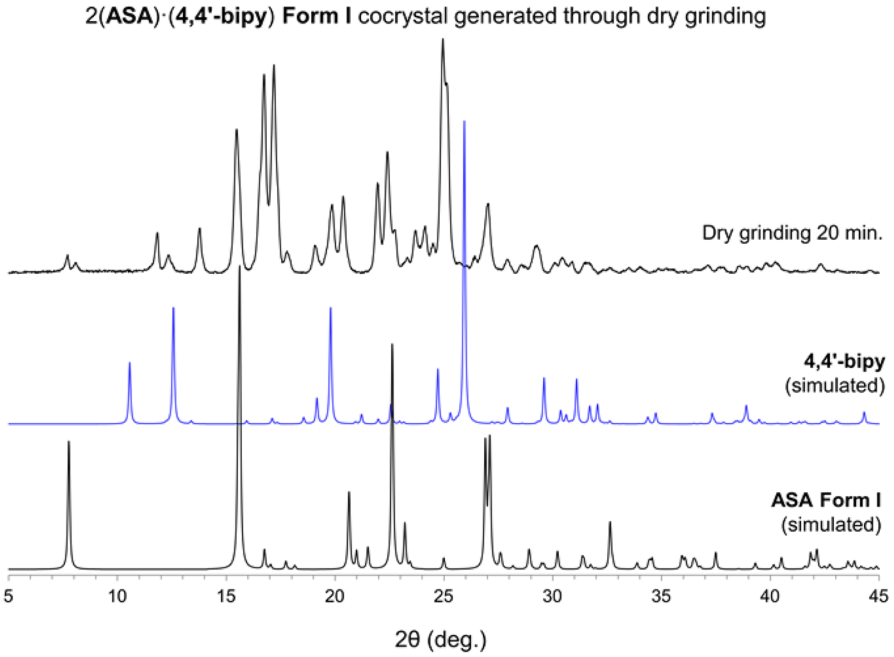


Figure 1. Form I cocrystal generated through dry grinding showing diffractograms of ASA and 4,4′-bipy upon 20 min of dry grinding (top) and comparisons to single components.[43]

components.[38] The corresponding single crystals were generated with minimal exposure to water from diethyl ether to generate 2(ASA)·(4,4′-bipy) Form I. The second polymorph (Form II) was achieved by rapid cooling from ethanol during related studies of solution crystallizations. The main structural differences between the two polymorphs arise owing to (i) rotational flexibility of the carboxylic acid functionality of ASA and the pyridyl moieties of 4,4′-bipy and (ii) acetyl group C−H···O forces between ASA molecules which generate catemers in Form I and both catemers and centrosymmetric dimers in Form II. Collectively, our results demonstrate the utility of employing neat dry grinding to generate new cocrystals and polymorphs of organic solids hitherto unobserved for organic solids. The use of the dry grinding applied is particularly important as related to generating nonsolvated crystal forms of pharmaceutical solids.[15−18]

■ EXPERIMENTAL SECTION

Cocrystal Syntheses. Solvents were purchased from Fischer Scientific. Aspirin (ASA) and 4,4′-bipyridine (4,4′-bipy) as a known dihydrate[39] were purchased from ACROS organics and used as received. For the synthesis of 2(ASA)·(4,4′-bipy) Form I, ASA (54.2 mg, 0.30 mmol) and 4,4′-bipy (23.4 mg, 0.12 mmol) were dissolved separately in minimal boiling diethyl ether. The two solutions were combined and then allowed to cool to room temperature. Slow evaporation of the solution after 24 h yielded colorless plates of 2(ASA)·(4,4′-bipy) Form I suitable for single-crystal X-ray diffraction (SCXRD). For the synthesis of 2(ASA)·(4,4′-bipy) Form II, ASA (125.8 mg, 0.70 mmol) and 4,4′-bipy (108.8 mg, 0.57 mmol) were dissolved separately in absolute ethanol (25 °C). The solution of 4,4′-bipy was then cooled to ca. 0 °C. After being cooled, the solution of ASA was added to the cold solution of 4,4′-bipy. The resulting mixture was immediately stored at ca. 0 °C and left overnight. After 24 h, the resulting precipitate was filtered from the cold solution to yield colorless lath-like crystals of 2(ASA)·(4,4′-bipy) Form II suitable for SCXRD. We note that further cocrystallizations to generate Form II when left undisturbed for up to 2 weeks at ca. 0 °C resulted in the conversion of Form II to Form I.

Grinding Experiments. Crystalline powders of ASA (Form I) (80.5 mg, 0.45 mmol) and 4,4′-bipy (34.9 mg, 0.18 mmol) were mixed with a spatula. The components were then ground together with an agate mortar-and-pestle. The combined and ground solids were each characterized using powder X-ray diffraction (PXRD) in approximate 5 min increments.

Single-Crystal X-ray Diffraction. SCXRD data were measured on a Bruker Neditonius APEX II Kappa diffractometer using Mo Kα radiation (λ = 0.71073 Å) using a graphite monochromator equipped with an Oxford Cryostream low temperature device. Crystals were mounted in Paratone oil on a Mitegen magnetic mount. Lorentz and polarization corrections were applied, and programs from the APEXII package were used for data reduction. Solution and refinement were accomplished by direct methods using ShelXL[40] and ShelXT[41] in Olex2[42] graphical user interface. All non-hydrogen atoms were refined using anisotropic displacement parameters.

Powder X-ray Diffraction. PXRD data were collected on a Bruker D-8 ADVANCE X-ray diffractometer using Cu Kα radiation (λ = 1.54056 Å) and a LynxEye detector. Samples were collected from 5° to 45° 2θ (count time: 1 s. per step, step size: 0.02° for Form I and step size: 0.1° for Form II). Millimeter-sized crystals were ground into powders with an agate mortar-and-pestle and mounted on glass slides.

RESULTS AND DISCUSSION

Cocrystallization by Dry Mechanochemistry. The original report describing a cocrystallization of ASA and 4,4′-bipy employed a solvent/antisolvent technique involving diethyl ether/hexane.[1] The outcome was 2(ASA)·(4,4′-bipy)·*x*(hexane), a cocrystal solvate wherein hexane is occluded in cavities generated by packing of three-component hydrogen-bonded assemblies of ASA and 4,4′-bipy. Our goal was to generate a nonsolvated cocrystal of ASA and 4,4′-bipy.[5] In order to circumvent the formation of a solid that integrates hexane, we performed cocrystallization experiments in the absence of excess solvent through neat dry grinding.

Specifically, dry grinding of ASA and 4,4′-bipy in a 2:1 molar ratio resulted in a white powder. In contrast to the single components, the powder tended to adhere to the surfaces of the mortar-and-pestle. Upon grinding the mixture for ca. 20 min, PXRD data revealed the formation of a prominent new phase (Figure 1). The phase was characterized by the presence of diffraction peaks at 16.8°, 17.2°, and 25.0° in 2θ. We note that a PXRD diffractogram collected just prior to grinding the components was consistent with the presence of a physical mixture of ASA and 4,4′-bipy.

Crystal Structures of Polymorphs. *2(ASA)·(4,4′-bipy) Form I.* We managed to grow single crystals of nonsolvated 2(ASA)·(4,4′-bipy) denoted Form I using diethyl ether alone as a solvent. While each component is sparingly soluble in diethyl ether, a cocrystallization to afford single crystals was readily achieved at millimolar concentrations. Single crystals of Form I were, thus, obtained by separately dissolving ASA (2 mol. equiv) and 4,4′-bipy (1 mol. equiv) in minimal boiling diethyl ether. The solutions were combined, and the solvent was allowed to evaporate overnight to obtain colorless blade-like crystals suitable for SCXRD. The solid Form I was then characterized by SCXRD. We note that a simulated PXRD pattern of the structure solution matches the powder diffractogram obtained upon 20 min of dry grinding.

The components of Form I crystallize in the triclinic space group $P\bar{1}$ (Figure 2, Table 1). The asymmetric unit consists of six crystallographically unique molecules; in particular, four full molecules of ASA (ASA1a, ASA1b, ASA2a, and ASA2b) and two full molecules of 4,4′-bipy (bipy1 and bipy2). Similar to the reported solvated cocrystal,[1] the molecules self-assemble to form three-component hydrogen-bonded assemblies (assembly 1 and 2) with each sustained by two O−H···N hydrogen bonds (Table 2). Intermolecular C−H···O forces also serve to hold the components together (C···O distances, C−H···O angle:

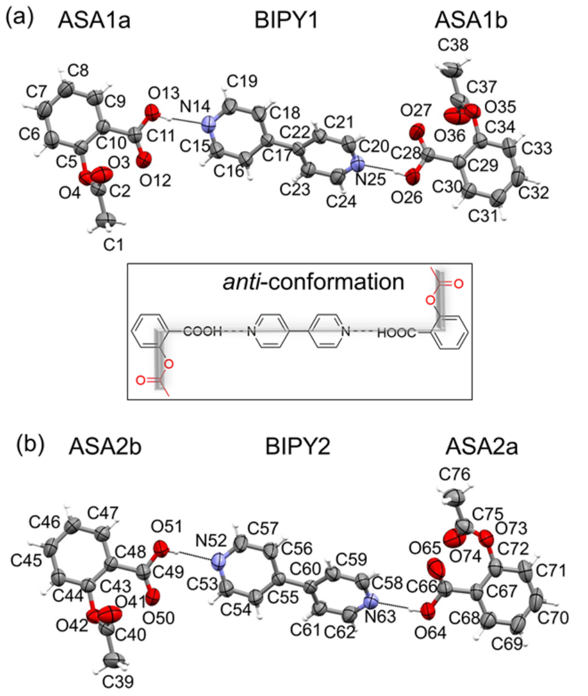


Figure 2. X-ray structure 2(ASA)·(4,4′-bipy) Form I: (a) assembly 1 and (b) assembly 2 (ORTEP view at 50% probability). Inset: Schematic of anti-conformation.

Table 1. Crystallographic Parameters for Form I and Form II of 2(ASA)·(4,4′-bipy)

polymorph	Form I	Form II
formula	$C_{28}H_{24}N_2O_8$	$C_{14}H_{12}NO_4$
formula mass	516.49	258.25
crystal system	triclinic	monoclinic
space group	$P\bar{1}$	$P2_1/c$
a (Å)	7.578(3)	16.4916(16)
b (Å)	16.015(5)	6.9636(7)
c (Å)	23.130(8)	11.2713(12)
α (deg)	70.044(5)	90
β (deg)	88.535(5)	95.171(6)
γ (deg)	81.694(5)	90
Z	4	2
V (Å^3)	2610.0(16)	1289.1(2)
ρ_{calcd} (g cm^{-3})	1.314	1.331
T (K)	298	298
μ (mm^{-1})	0.097	0.099
reflections collected	43737	13139
independent reflections	9141	2276
data/restraints/parameters	9141/0/694	2276/0/175
R_{int}	0.0570	0.0522
R_1 ($I > 2\sigma(I)$)	0.0725	0.0489
wR (F^2) ($I > 2\sigma(I)$)	0.1925	0.1028
R_1 (all data)	0.1238	0.1034
wR (F^2) all data	0.2237	0.1254
CCDC no.	1812569	1580354

DOI: 10.1021/acs.cgd.8b00104
Cryst. Growth Des. 2018, 18, 2495−2501

Table 2. O−H···N Hydrogen-Bond Distances and Angles for Polymorphs of 2(ASA)·(4,4′-bipy)

	D···A (Å)	∠D−H···A (deg)
Form I		
O13−H···N14	2.658(4)	170.8(3)
O26−H···N25	2.620(4)	167.3(3)
O51−H···N52	2.650(4)	140.6(3)
O64−H···N63	2.633(4)	164.8(3)
Form II		
O13−H···N14	2.673(1)	176.3(1)

ASA1a: C15···O12, 3.400(5) Å, 125.2(3)°; ASA2a: C53···O50, 3.336(5) Å, 126.4(3)°; twist angles: ASA1a: 11.8°, ASA2a: 13.3°) (Table 3).[31] In the arrangement, the carboxylic acid groups lay generally twisted from the phenyl rings, with the acid group of ASA2b displaying the largest twist (25.1°). The acetoxy group of each ASA molecule lie nearly perpendicular to each phenyl ring, while the two pyridyl rings of each 4,4′-bipy molecule are less twisted (22.6°, 24.5°). As a consequence of the assembly process, the components of Form I adopt an anti-conformation wherein the acetoxy groups of each assembly effectively point away from each other. The anti-conformation contrasts a syn-conformation observed in the originally reported solvated cocrystal.[1]

Table 3. Selected Intra- and Intermolecular Angles for Polymorphs of 2(ASA)·(4,4′-bipy)

	torsion angle (deg)			
molecule	phenyl-acid	acetoxy-phenyl	acid-pyridyl	pyridyl−pyridyl
Form I				
ASA1a	11.8	71.8	14.0	
ASA1b	8.1	81.2	63.6	
ASA2a	13.3	75.8	11.2	
ASA2b	25.1	65.7	22.1	
bipy1				22.6
bipy2				24.5
Form II				
ASA	0.9	76.2	17.5	
bipy				0.3

The three-component hydrogen-bonded assemblies stack along the *b*-axis to generate separate columns comprised of assembly 1 and assembly 2 (Figure 3). Adjacent assemblies interact via a combination of face-to-face and edge-to-face π-forces involving bipy/bipy (centroid−centroid distance (Å): bipy1···bipy1: 3.98, bipy2···bipy 2:3.90) and ASA/bipy molecules (centroid−centroid distance (Å): ASA1a···bipy 1:4.66, ASA1b···bipy 1:4.67, ASA2a···bipy 2:4.73, ASA2b···bipy 2:4.97), respectively (Figure 3a,b). Unique to columns of assembly 1, ASA molecules are linked by alternating phenyl C−H···O forces with the carboxylic acid of ASA1b and the acetyl group of ASA1a (C7···O27 3.527(6) Å, 134(1)°; C32···O3 3.658(6) Å, 153(1)°). In contrast, ASA molecules in columns of assembly 2 are linked by phenyl C−H···O forces with neighboring acetyl groups of ASA molecules (C45···O74 3.575(5) Å, 173(1)°; C70···O41 3.775(6) Å, 139(1)°). Columns stack with neighboring columns perpendicular to the *b*-axis (Figure 3a,b). The two unique three-component structures are linked by discrete catemeric methyl C−H···O forces (Figure 3c) of the acetyl groups along the *b*-axis (C76···O3: 3.630(6) Å, 124(1)°; C1···O41:3.682(6) Å, 145(1)°; C39···O36:3.651(7) Å, 146(1)°) and by aromatic C−H···O forces with the carboxylic acids of ASA molecules (C44···O12: 3.649(6) Å, 160(1)°; C33···O50: 3.627(6) Å, 157(1)°; C71···O27: 3.715(6) Å, 175(1)°). The catemers are present as tetrameric arrays wherein the aceyl groups of adjacent molecules are anti-parallel. The assemblies pack to form an overall herringbone structure (Figure 3d).

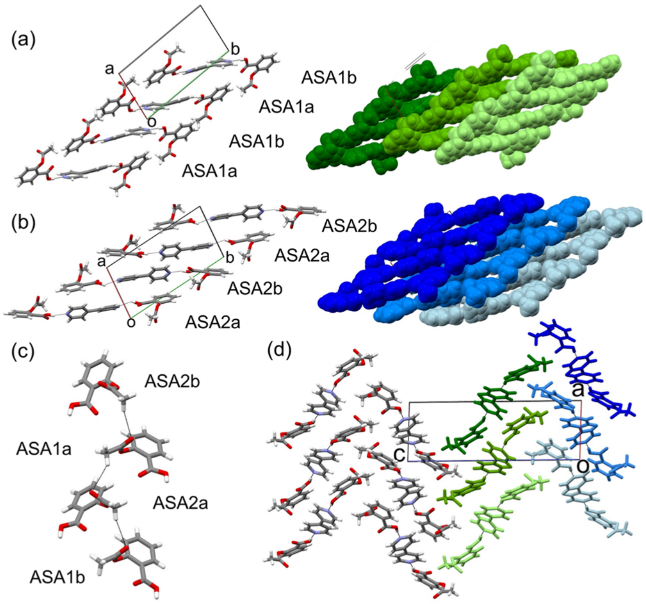


Figure 3. Extended packing of hydrogen-bonded assemblies 2(ASA)·(4,4′-bipy) Form I: (a) assemblies of 1 along the *c*-axis, (b) assemblies of 2 along the *c*-axis, (c) catemers formed by ASA molecules, and (d) herringbone packing of assembly 1 (green) and assembly 2 (blue) along the *b*-axis.

2(ASA)·(4,4′-bipy) Form II. A very recent report describes the generation of cocrystals composed of ASA and 4,4′-bipy formed in ethanol via rapid cooling.[9] Rapid cooling was likely used to avoid degradation ASA in ethanol.[7] In an experiment to generate Form I through rapid cooling in ethanol, we determined the rapid cooling conditions to afford a polymorph of 2(ASA)·(4,4′-bipy) denoted Form II. Form II was, thus, generated by separately dissolving ASA (2 mol. equiv) and 4,4′-bipy (1 mol. equiv) in minimal ethanol (ca. 3 mL total). The two solutions were combined and then immediately cooled to ca. 0 °C. The solution was stored at ca. 0 °C overnight to afford colorless lath-like crystals suitable for SCXRD.

The components of Form II crystallize in the monoclinic space group $P2_1/c$ (Table 1). The asymmetric unit contains one full molecule of ASA and half a molecule of 4,4′-bipy, which lies on an inversion center (Figure 4). Similar to Form I, molecules of Form II self-assemble to form three-component hydrogen-bonded assemblies sustained by two intermolecular O−H···N hydrogen bonds (Table 2). Similar to ASAb of Form I, the

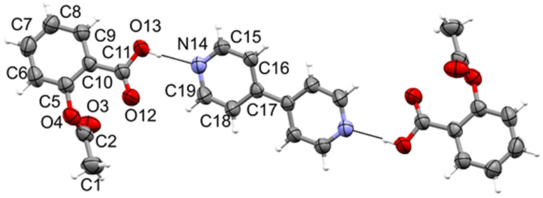


Figure 4. X-ray structure of 2(ASA)·(4,4′-bipy) Form II (ORTEP view at 50% probability).

DOI: 10.1021/acs.cgd.8b00104
Cryst. Growth Des. 2018, 18, 2495−2501

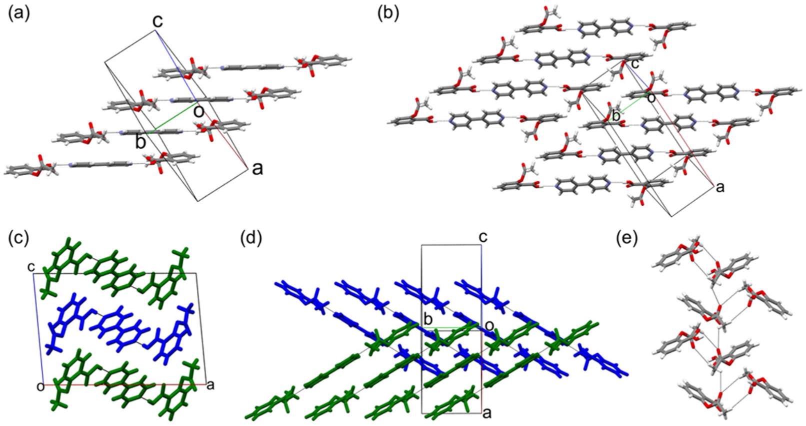


Figure 5. X-ray structure 2(ASA)·(4,4′-bipy) Form II: (a) 1D columns of three-component hydrogen-bonded assemblies, (b) perpendicular to *b*-axis demonstrating centrosymmetric acid dimers, (c) down the *b*-axis with columns of three-component assemblies highlighted in blue and green, (d) perpendicular to *b*-axis of criss-cross sheets with columns highlighted in blue and green, and (e) centrosymmetric dimers and catemers formed by ASA molecules.

carboxylic acid group of ASA is twisted from the pyridyl group of the 4,4′-bipy molecules (17.5°), while the acetoxy groups are nearly perpendicular to each phenyl ring. In contrast to Form I, the carboxylic acid groups are nearly coplanar with the phenyl rings of ASA molecules (0.9°). The two pyridyl rings of 4,4′-bipy in Form II are also nearly coplanar. The components of the three-component assembly also adopt an anti-conformation.

Similar to Form I, the three-component assemblies of Form II stack along the *b*-axis to generate columns (Figure 5). Within the columns, adjacent assemblies interact via face-to-face π-forces involving bipy/bipy (centroid−centroid distance: 4.81 Å) and ASA/bipy molecules (centroid−centroid distance: 4.43 Å) (Figure 5a). Similar to assembly 2 of Form I, assemblies of Form II are linked by phenyl C−H···O forces with neighboring acetyl groups of ASA molecules (C7···O3:3.485(4) Å, 136(1)°). Moreover as opposed to a herringbone arrangement of Form I, the assemblies pack to form sheets where the three-component assemblies are coplanar and linked via centrosymmetric C−H···O dimers of the acetyl substituents of ASA molecules (C1···O3′: 4.046(4) Å, 164(1)°) (Figure 5b,e). Columns of three-component assemblies lie criss-cross with neighboring columns along the *c*-axis linked by catemeric methyl C−H···O forces (C1···O3′: 3.344(4) Å, 122(1)°) in the form of infinite chains and C−H···O forces between 4,4′-bipy and hydroxyl substituents of ASA molecules (C16···O13: 3.267(3) Å, 130(1)°) (Figure 5d−e).

Structural Comparison to Pure Forms of ASA. An important precept in crystal engineering is the recognition of structural and packing similarities of constituent molecules. In this context, we note that the ASA molecules in both Forms I and II of 2(ASA)·(4,4′-bipy) share similarities of Forms I, II, and IV polymorphs of pure ASA (Figure 6). Specifically, the ASA molecules of 2(ASA)·(4,4′-bipy) Form I are linked by methyl C−H···O catemers involving the acetyl groups in a tetrameric array. Catemers are also present in both Forms I and II of ASA. In contrast to 2(ASA)·(4,4′-bipy) Form I, the catemers exist as infinite chains, with adjacent ASA molecules also being anti-parallel. The ASA molecules of 2(ASA)·(4,4′-bipy) Form II also interact as catemers in the form of infinite chains with ASA molecules anti-parallel. We note that catemers are also present in Form IV of ASA.[22] The ASA molecules of Form IV, however, adopt a parallel orientation. The centrosymmetric dimers present in 2(ASA)·(4,4′-bipy) Form II are also present in Form I of pure ASA (Figure 6b).

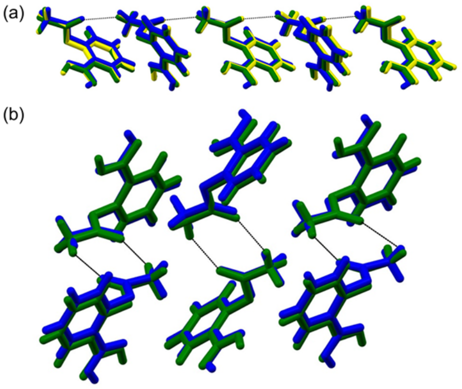


Figure 6. Overlay views involving 2(ASA)·(4,4′-bipy) Form II (blue) demonstrating (a) catemers of cocrystal compared to ASA Form I (green) and ASA Form II (yellow) and (b) dimers of cocrystal compared to ASA Form I (green).[44]

Overlay views show the striking structural similarities of the (i) catemers of 2(ASA)·(4,4′-bipy) Form II and Forms I and II of ASA (Figure 6a) and (ii) dimers of 2(ASA)·(4,4′-bipy) Form II and Form I of ASA (Figure 6a). We note that the importance of the catemers and dimers in the structures of ASA Forms I and II polymorphs has been recently addressed.[45,46] Specifically, the catemers and dimers were described to influence stabilities of the two ASA polymorphs and, in turn, mechanical responses of the crystals. The presence of the dimers and catemers in the cocrystals 2(ASA)·(4,4′-bipy) Forms I and II reflects a degree of persistence in stabilizing the orientation of ASA in solid forms.

■ CONCLUSIONS

In this report, we have described the generation of two polymorphs of nonsolvated 2(ASA)·(4,4′-bipy). Form I was generated in the absence of solvent through neat mechanical grinding, with single crystals being obtained in the absence of hexane. Form II was generated through rapid solvent cooling. The hydrogen-bonded components of the two polymorphs adopt an anti-conformation, which contrasts with the original solvate cocrystal of ASA. We expect our results to have implications in the development of cocrystals containing ASA and related solvated cocrystals, particularly where a need exists to generate nonsolvated forms.

■ ASSOCIATED CONTENT

Accession Codes

CCDC 1580354 and 1812569 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

L.R.M. gratefully acknowledges the National Science Foundation (DMR-1708673) for funding.

■ ABBREVIATIONS

ASA, acetylsalicylic acid; 4,4′-bipy, 4,4′-bipyridine; SA, salicylic acid; PXRD, powder X-ray diffraction; SCXRD, single-crystal X-ray diffraction; API, active pharmaceutical ingredient

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