CRYSTAL GROWTH & DESIGN

Communication

pubs.acs.org/crystal

Crystallization at Solvent Interfaces Enables Access to a Variety of Cocrystal Polymorphs and Hydrates

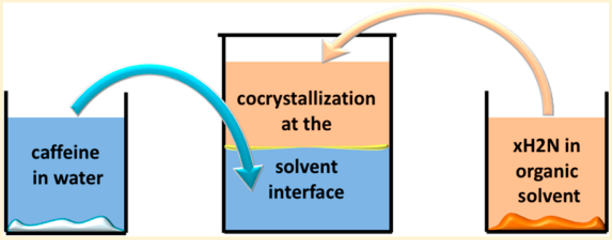
Stefan J. Diez,[§] Mark D. Eddleston,[§] Mihails Arhangelskis,[§] Marie Milbled,[§] Matthias J. Müller,[§] Andrew D. Bond,[§] Dejan-Krešimir Bučar,[*,†] and William Jones[*,§]

[§]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

[†]Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, United Kingdom

Supporting Information

ABSTRACT: A crystal growth technique, interfacial cocrystallization, is demonstrated to be a simple and effective method for preparing multicomponent crystal forms. The technique is based on the generation of a liquid−liquid interface between two immiscible solutions of cocrystal-forming compounds, and its utility is demonstrated through the preparation of polymorphs and hydrates of caffeine cocrystals, involving three different hydroxy-2-naphthoic acids, including the formation of some with unexpected compositions.



INTRODUCTION

Multicomponent crystals are widely utilized for crystal engineering purposes in a variety of settings, including the pharmaceutical industry.[1] Cocrystals, which consist of at least two different types of neutral molecules (coformers) held together by noncovalent interactions (such as hydrogen bonds), play an increasingly important role in drug development owing to their capacity to enhance relevant chemical and physical properties of drug molecules in the solid state[2] (e.g., chemical stability,[3] hygroscopicity,[4] tabletability,[5] or taste[6]). The mounting number of patents and new FDA-approved medicines[7] based on pharmaceutical cocrystals also attest to their potential and usefulness. Cocrystals are, however, prone to polymorphism like all other types of molecular crystals,[8,9] and as a result it is essential to screen thoroughly for polymorphic forms of cocrystals during product development.[10]

To date, various techniques have been developed for the preparation of cocrystals on a laboratory scale,[11−16] with the majority being solvent based (e.g., solvent evaporation and solvent cooling[17,18]). Solvent-based methods avoid partial degradation of drug molecules during cocrystallization, which may occur in the use of thermal methods such as cocrystallization from the melt.[19] A drawback of solution growth, however, is the high risk of precipitating the pure components because of their potentially significant solubility differences,[20] or the undesired formation of solvates.[21] To avoid this issue, methods that employ less or even no liquid solvent (such as grinding,[22] liquid-assisted[11] and polymer-assisted grinding,[23] and slurrying[24]) have been devised and applied.

We applied the approach of crystallization at solvent interfaces to the cocrystallization of phenazine and mesaconic acid in an earlier study, resulting in the generation of a novel monohydrate cocrystal form.[20] Here we report the results of a systematic study that aimed to explore how precipitation at the boundary between two immiscible solutions containing the coformer molecules, a technique referred to as interfacial cocrystallization (IC), is a very effective screening method (Scheme 1).

Recognizing the numerous studies that report the use of solvent interfaces to precipitate or crystallize various organic and inorganic species,[25−29] this study focuses on the preparation of pharmaceutical cocrystals at solvent interfaces and highlights in particular the large number of experimental variations that are possible.

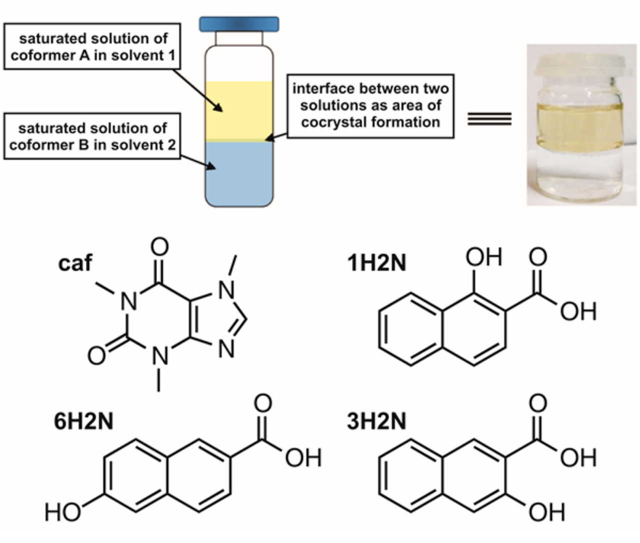
Using caffeine (**caf**) and hydroxy-2-naphthoic acids (**xH2Ns**) as model compounds, we show that IC enables fast access to a variety of polymorphs, hydrates of pharmaceutical cocrystals, as well as cocrystal forms with atypical stoichiometric ratios. We further demonstrate how the chemical nature of the solvents, solution concentrations, various cocrystallization rates, and the surrounding ambient temperatures affect the crystallization outcome. We also highlight several key advantages of the IC approach, namely, the ability to screen multiple potential coformers simultaneously in a single experiment by using solutions containing several possible coformers, as well as the ability to access a broad variety of crystal forms without the knowledge of solubility phase diagrams.

The studied compounds have previously been investigated in the context of crystal engineering and pharmaceutical cocrystals;[30−34] **caf** is a widely known central nervous system stimulant, while **xH2Ns** are pharmaceutically active ingredients known to exhibit higher activity than salicylate in the treatment of stress-mediated diseases.[35] The three hydroxy-2-naphthoic acids, namely, 1-hydroxy-2-naphthoic acid (**1H2N**), 3-hydroxy-

Received: January 19, 2018
Revised: April 9, 2018
Published: April 30, 2018

DOI: 10.1021/acs.cgd.8b00114
Cryst. Growth Des. XXXX, XXX, XXX−XXX

Scheme 1. Representation of an Interfacial Cocrystallization Experiment Whereby Two Saturated Solutions of Coformers in Immiscible Solvents Are Prepared Separately and Then Combined (Providing an Interface at Which Cocrystallization Can Occur) (Top); and Molecular Structures of caf, 1H2N, 3H2N, and 6H2N (Bottom)



2-naphthoic acid (**3H2N**), and 6-hydroxy-2-naphthoic acid (**6H2N**), differ significantly in the geometry of their potential hydrogen-bonding interactions (Scheme 1), and therefore in their solubility and cocrystallization performance.

The **caf:xH2N** cocrystals were initially investigated using more traditional solution-based methods by Bučar et al.,[30] who identified and structurally characterized one cocrystal form for each system, each having a 1:1 stoichiometry (Cambridge Structural Database (CSD) reference codes: KIGKIV, KIGKOB, KIGKUH; henceforth referred to for each case as form **I**).[30] In the study reported here, we pursued the interfacial cocrystallizations of **caf** with the same three **xH2Ns**. The reactions involved the layering of two solutions: one being a saturated solution of caffeine in water (a reasonably good solvent for **caf**), and the second being a nearly saturated solution of **xH2N** in an organic solvent that is immiscible with water (see SI) and in which the solubility of the acid is high, while the solubility of **caf** is low (e.g., noncyclic ethers, aliphatic alcohols, and acetic acid esters). Whereas there is no driving force for crystallization to occur because of the low amount of both coformers simultaneously present in either phase, layering the two solutions allows a cocrystal to precipitate at the interface (Scheme 1) owing to its lower free energy. A coformer concentration gradient at the interface then facilitates slow incorporation of coformer molecules from both sides of the interface to the growing cocrystal. In almost every example reported below, crystals suitable for single crystal X-ray studies were obtained.

■ RESULTS AND DISCUSSION

1. Effects of Solvent Choice on Cocrystal Composition and Polymorphic Form. *1.1. caf:6H2N Cocrystal.* Initial studies focusing on the **caf:6H2N** system yielded a range of cocrystals of various stoichiometries, as well as new polymorphs and hydrates (Table 1), thus demonstrating the high efficacy of IC in cocrystal screening. Specifically, we were able to reproduce the 1:1 (**caf**)·(**6H2N**) cocrystal, initially reported by Bučar et al. (form **I**; space group $P\bar{1}$, $Z' = 1$) (Figure 1a), but we also obtained an additional new polymorph of this cocrystal, namely, form **II** (see SI document). Form **II** crystallizes in space group $P2_1/c$ and its structure is based on discrete 2:2 supramolecular **caf:6H2N** assemblies, wherein the **6H2N** molecules form dimers through O−H···O hydrogen bonds via an $R_2^2(8)$ synthon. The **caf** molecules are disordered over two positions and are bound to the hydroxyl group of **6H2N** through either an O−H···O hydrogen or an O−H···N hydrogen bond via a $D(2)$ synthon (Figure 1b).

Table 1. Solvents Used in Combination with Water to Crystallize Various caf:xH2N Cocrystal Forms

xH2N	organic solvent	cocrystal form obtained
6H2N	ButOAC	1:1, form **I**
	EtOAc	1:1, form **II**
	DIPE[a]	1:1, form **III**
	DIPE/xylene[a]	1:1, form **IV**
	ButOAC	1:1, monohydrate
	DIPE	2:1
	2-butanone[a]	2:3, monohydrate
1H2N	EtOAC	1:1, form **I**
	DIPE	1:1, form **II**
3H2N	EtOAC	1:1, form **I**
	DIPE	1:1, form **II**

[a]Supersaturated solution.

Further IC experiments led to the discovery of a third anhydrous cocrystal form, namely, the 2:1 (**caf**)$_2$·(**6H2N**) cocrystal (see SI). The crystal structure of this material is based on discrete three-component **caf:6H2N** assemblies. In the assembly, one **caf** molecule is bound to **6H2N** through an O−H···N hydrogen bond via an $R_2^2(7)$ synthon, while the second **caf** molecule is disordered over two positions and bound to naphthoic acid through an O−H···N or O−H···O hydrogen bond (depending on the **caf** orientation) via a $D(2)$ synthon (Figure 1d).

Notably, two hydrated **caf:6H2N** cocrystal forms were discovered: the 1:1:1 (**caf**)·(**6H2N**)·(H_2O) and the 2:3:1 (**caf**)$_2$·(**6H2N**)$_3$·(H_2O) cocrystal monohydrate.[36] The crystal structure of the (**caf**)·(**6H2N**)·(H_2O) cocrystal monohydrate is based on two-dimensional flat hydrogen-bonded layers. Within the layers, **caf** and disordered **6H2N** molecules are connected by O−H···N hydrogen bonds via $R_2^2(7)$ synthons. The **caf:6H2N** molecular pairs are further linked through water molecules by O−H···O hydrogen bonds through $D(2)$ synthons (Figure 1e). Structural analyses of the (**caf**)$_2$·(**6H2N**)$_3$·(H_2O) monohydrate revealed that its structure is based on interpenetrated three-dimensional **caf:6H2N**:H_2O assemblies. In these structures, **caf** and **6H2N** are linked into molecular chains that are sustained by O−H···N and O−H···O hydrogen bonds via $R_2^2(7)$ and $D(2)$ synthons. The one-dimensional structure is extended into three dimensions by a disordered pair of **6H2N**:H_2O molecules (Figure 1f).

It should be noted that it was not possible to obtain reproducibly phase-pure samples of the previously reported anhydrous 1:1 cocrystal (form **I**) using nearly saturated solutions of the coformers. This form was initially only observed 3 days after harvesting all (**caf**)·(**6H2N**)·(H_2O) crystals at the solvent interface, when a second crop of large single crystals of form **I** emerged.

The mechanisms leading to the formation of the large variety of **caf:6H2N** cocrystal forms are not understood at this time.[37]

DOI: 10.1021/acs.cgd.8b00114
Cryst. Growth Des. XXXX, XXX, XXX−XXX

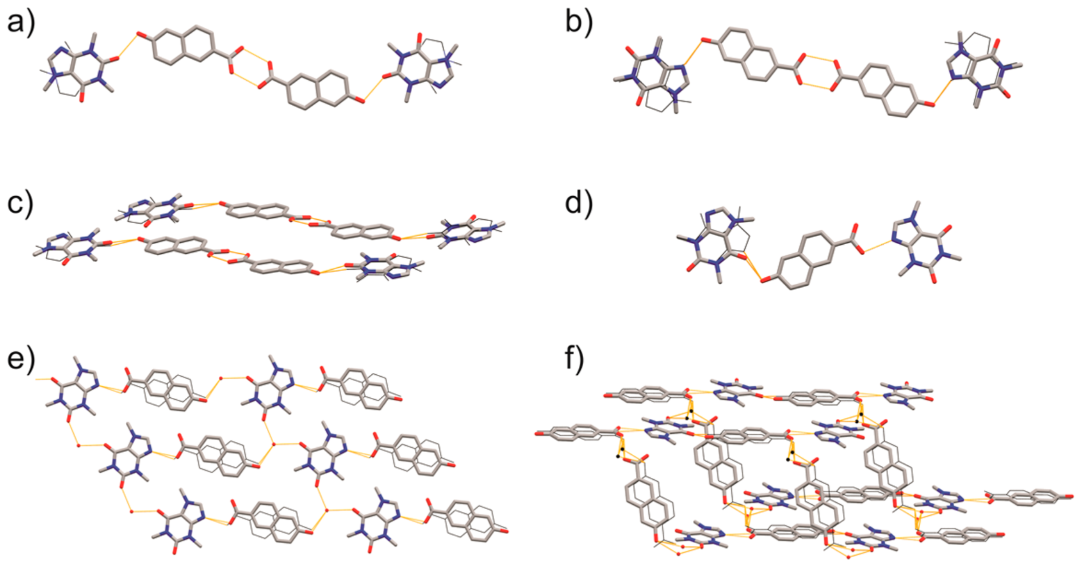


Figure 1. Supramolecular **caf:6H2N** assemblies in the crystal structures of (a) anhydrous (**caf**)·(**6H2N**), form **I**; (b) anhydrous (**caf**)·(**6H2N**), form **II**; (c) anhydrous (**caf**)·(**6H2N**), form **III**; (d) anhydrous $(\textbf{caf})_2\cdot(\textbf{6H2N})$; (e) (**caf**)·(**6H2N**)·(H_2O) monohydrate; (f) $(\textbf{caf})_2\cdot(\textbf{6H2N})_3\cdot(H_2O)$ monohydrate. Minor occupation sites (up to 50%) of disordered molecules are shown using the "wireframe" display style. Hydrogen atoms are omitted to enhance clarity.

We do, however, speculate that access to the crystal form with a different atypical stoichiometry may be attributed to solubility effects. In particular, we believe that a change from a 2:1 to 1:1 coformer ratio is likely to be related to the higher solubility of **6H2N** in butyl acetate compared to diisopropyl ether, leading to a higher concentration of **6H2N** at the interface.

1.2. caf:1H2N and caf:3H2N Cocrystals. The substantial variety of discovered **caf:6H2N** cocrystal forms prompted us to extend our studies to the **caf:1H2N** and **caf:3H2N** cocrystal systems. A more limited set of experiments soon led not only to the preparation of the previously known cocrystal phases (Figure 2a,b), but also to the discovery of a new polymorph of (**caf**)·(**1H2N**) and (**caf**)·(**3H2N**), referred to as form **II** (Table 1 and SI). Form **II** of (**caf**)·(**1H2N**) crystallizes in space group $P2_1/n$ with three **caf:1H2N** pairs in the asymmetric unit (Z' = 3). Each of the pairs is held together by O−H···N hydrogen bonds through $R_2^2(7)$ synthons, whereby the **1H2N** hydroxyl groups are engaged in intramolecular O−H···O hydrogen bonds by a $S(6)$ synthon (Figure 2a). Form **II** of (**caf**)·(**3H2N**) crystallizes in space group $P2_1/n$ with one molecule of **caf** and **3H2N** in the asymmetric unit (Z' = 1). The cocrystal components are also held together by O−H···N and O−H···O hydrogen bonds through $R_2^2(7)$ and $S(6)$ synthons (Figure 2b).

It was also established that, in the cases of the **caf:1H2N** and **caf:3H2N** cocrystal systems, a change in polymorphic form of the product was achieved by varying the interface conditions, as shown in Table 1.

Specifically, the use of more polar solvents favored in both cases the crystallization of form **I**. That solvent properties can influence the polymorphic outcome of IC processes is not unexpected,[9] as it mirrors what has been widely reported for conventional solution crystallizations. With specific regard to cocrystal polymorphism, however, it should be noted that problems associated with the precipitation of individual coformers during conventional solution crystallization experiments[20] are minimized.

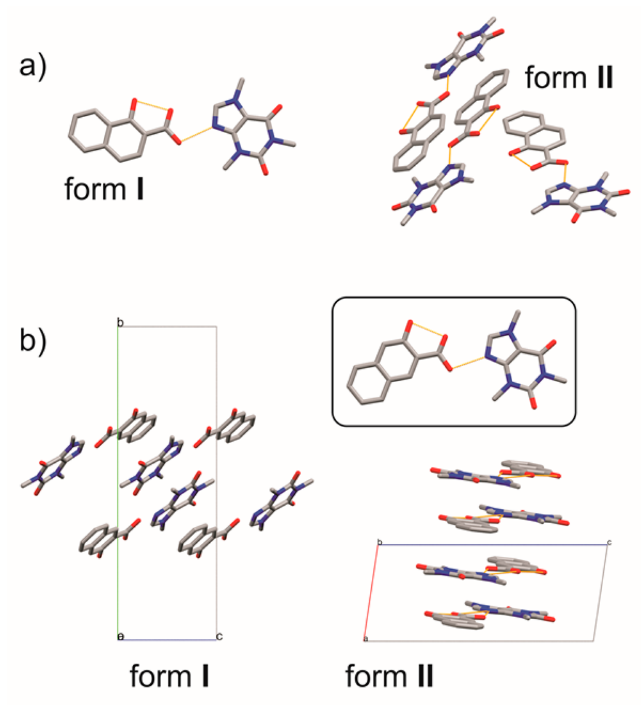


Figure 2. (a) Crystallographically independent **caf:1H2N** assemblies in the (**caf**)·(**1H2N**) cocrystal forms **I** and **II**. (b) Supramolecular **caf:3H2N** assembly found in the crystal structures of (**caf**)·(**3H2N**) forms **I** and **II** (highlighted in the rounded rectangle) and crystal packing diagrams of (**caf**)·(**3H2N**) forms **I** and **II**. Hydrogen atoms are omitted to enhance clarity.

2. Effects of Solution Concentrations on Polymorphic Outcome for the caf:6H2N Cocrystal. In an attempt to facilitate the growth of single crystals during the IC experiments, we resorted to the layering of supersaturated solutions of the cocrystal components. Such an approach has not only led to the formation of crystals suitable for single crystal X-ray diffraction studies, but also enabled, to our

DOI: 10.1021/acs.cgd.8b00114
Cryst. Growth Des. XXXX, XXX, XXX−XXX

surprise, the appearance of new polymorphs. In particular, two new polymorphs of the **caf:6H2N** cocrystal were discovered, namely, forms **III** and **IV** (see SI). These two forms, however, appeared only occasionally and single crystals suitable for structural analyses could be produced only in the case of form **III**.[38]

Crystallographic analyses revealed that form **III** crystallizes in space group $P2_1/c$ with three molecules of both **caf** and **6H2N** in the asymmetric unit ($Z' = 3$). The crystal structure is based on two crystallographically independent types of 2:2 **caf:6H2N** assemblies similar to those seen in forms **I** and **II**. One is centrosymmetric with disordered **6H2N** and ordered **caf** molecules that are held together by O−H···O hydrogen bonds through $R_2^2(8)$ and $D(2)$ synthons. The second assembly is noncentrosymmetric and also based on disordered **caf** and ordered **6H2N** molecules, which are sustained by the same types of hydrogen bonds and synthons as those in the first assembly type (Figure 1c).

It was also observed that the use of supersaturated solutions of **caf** and **6H2N** (using polar solvents) regularely leads to the crystallization of form **I** of the **caf:6H2N** cocrystal, which could not be reliably achieved with the use of nearly saturated solutions (see Table 1 and SI).

3. Effects of Temperature on Cocrystallization Kinetics and Polymorphic form. Saturated solutions of **caf** in water and of the three **xH2N**s in DIPE were prepared, layered, and left for crystallization at a range of different temperatures to monitor the influence of the crystallization rate on the outcome of interfacial cocrystallization. Observations from the resulting IC experiments are summarized in Table 2.

Table 2. Effects of Temperature on Cocrystal Formation

xH2N	10 °C	20 °C	40 °C
1H2N	1:1, form **II**	1:1, form **II**	1:1, form **I** + **II**
	10 min	5 min	<1 min
3H2N	1:1, form **II**	1:1, form **II**	1:1, form **II**
	15 min	8 min	1 min
6H2N	2:1	2:1	2:1
	2 days	1 day	4 h

In general, the higher the temperature at which interfacial cocrystallization is performed, the faster a cocrystal is formed at the interface. For instance, the precipitation of the $(\mathbf{caf})_2\cdot(\mathbf{6H2N})$ cocrystal can be accelerated from 2 days to 4 h by increasing the temperature from 10 to 40 °C. This increase in cocrystallization rate may result from the increased amount of coformer dissolved in solutions at high temperature and/or from increased molecular diffusion rates which facilitate the precipitation process. Accompanying the faster cocrystallization and nucleation processes at higher temperature was a reduction in the particle size of the resulting crystals (see SI Figure S2). Low-temperature interfacial crystallizations were, therefore, found to be most appropriate for the growth of large single crystals suitable for structure determination.

Temperature was also observed to have an influence on the polymorphic outcome (Table 2). With the **caf:1H2N** system, on increasing the crystallization temperature to 40 °C, a mixture of forms **I** and **II** was obtained (rather than pure form **II**, as seen at lower temperatures). We suggest that form **II** is still the form which precipitates at the interface, and the increased temperature merely increases the rate of conversion to the more stable form **I**.[39] This is certainly the case for the **caf:3H2N** system where form **II** precipitates at the interface shortly after layering of the two solutions, but at higher temperature undergoes conversion to form **I** within hours.

4. Effects of Stirring. The effect of high-speed stirring (at 750 rpm) during interfacial cocrystallization was investigated for the three **caf:xH2N** cocrystals using magnetic stir bars (see Table 3). This agitation resulted in the formation of an emulsion of the two immiscible solutions wherein small droplets were created and the curvature of the liquid−liquid interface increased. The crystallization rate of each of the cocrystals increased dramatically as a result. Stirring also led to a change in the polymorphic form which was obtained for the **caf:3H2N** cocrystal, with form **I** rather than form **II** being isolated, and a change in the stoichiometry of the **caf:6H2N** cocrystal form 1:1 to 2:1. The origins of these polymorphic and stoichiometric variations, which could be based on the increased curvature of the interface, or due to the shear introduced to the system by stirring, is still under investigation.

Table 3. Effects of Stirring at Room Temperature on Cocrystal Formation

xH2N	solvent	static conditions	stirred solutions
1H2N	DIPE	1:1, form **II**	1:1, form **II**
3H2N	DIPE	1:1, form **II**	1:1, form **I**
6H2N	DIPE	2:1	1:1, form **I**

5. Competitive Coformer Studies. The potential application of IC to screening for cocrystal formation between a compound of interest and multiple putative coformer molecules in a simultaneous manner was investigated by layering a saturated aqueous solution of caffeine and a solution of DIPE saturated with both **1H2N** and phenazine. Phenazine, in contrast to **1H2N**, does not possess a carboxylic acid group and was, therefore, not expected to form a cocrystal with caffeine. After combining the two solutions, the known **caf:1H2N** cocrystal precipitated at the interface. Phenazine did not crystallize either as a pure phase or as a cocrystal with caffeine, thus demonstrating that cocrystallization of **caf** with a coformer at a solvent interface is not inhibited by the presence of a molecule which does not form a cocrystal.

To investigate a situation where competition between coformer molecules is possible during interfacial cocrystallization a saturated solution of caffeine in water was combined with a solution of DIPE saturated with both **1H2N** and **3H2N** (the overall molar ratio of **caf:1H2N:3H2N** was approximately 1:3:3). PXRD indicated that the resulting precipitate at the solvent interface contained a mixture of (**caf**)·(**1H2N**) form **II** and (**caf**)·(**3H2N**) form **II** (see Figure S1 in SI).

■ SUMMARY AND OUTLOOK

It has been demonstrated that IC is a tunable and efficient technique to produce a range of multicomponent crystal forms. For the three **caf:xH2N** cocrystals investigated in this study, IC yielded at least one new cocrystal form for each system. Furthermore, with appropriate control of temperature, solution concentrations, solvent selection, and the cocrystallization rate, it was possible to grow single crystals at the interface for all three systems.

Interfacial cocrystallization can be applied to screen quickly and simultaneously for cocrystal formation between a drug molecule and several potential coformer molecules in one crystallization vessel. We have also demonstrated that a

DOI: 10.1021/acs.cgd.8b00114
Cryst. Growth Des. XXXX, XXX, XXX−XXX

cocrystal will readily form at the interface of two immiscible solvents, despite the direct interactions and competition of coformers within the organic solution. The great variety of identified **caf:xH2N** cocrystal forms obtained, as well as its convenience, establishes the merit of this crystallization method in the context of cocrystal screening and materials discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.8b00114.

Specifics concerning the synthesis of the crystal forms and their crystallographic and microscopic analysis (PDF)

Accession Codes

CCDC 1053238 and 1583501–1583507 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.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: d.bucar@ucl.ac.uk.

*E-mail: wj10@cam.ac.uk.

ORCID

Mihails Arhangelskis: 0000-0003-1150-3108

Andrew D. Bond: 0000-0002-1744-0489

Dejan-Krešimir Bučar: 0000-0001-6393-276X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr J. E. Davies for the collection of single crystal X-ray diffraction data. The EPSRC is thanked for funding. D.K.B. gratefully acknowledges University College London for support through a UCL Excellence Fellowship.

■ ABBREVIATIONS

EtOAc, ethyl acetate; BuOAc, *n*-butyl acetate; DIPE, diisopropyl ether

■ REFERENCES

(1) Morissette, S. L.; Almarsson, Ö.; Peterson, M. L.; Remenar, J. F.; Read, M. J.; Lemmo, A. V.; Ellis, S.; Cima, M. J.; Gardner, C. R. *Adv. Drug Delivery Rev.* **2004**, *56*, 275–300.

(2) Schultheiss, N.; Newman, A. *Cryst. Growth Des.* **2009**, *9*, 2950–2967.

(3) Vangala, V. R.; Chow, P. S.; Tan, R. B. H. *Cryst. Growth Des.* **2012**, *12*, 5925–5938.

(4) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2005**, *5*, 1013–1021.

(5) Sun, C. C.; Hou, H. *Cryst. Growth Des.* **2008**, *8*, 1575–1579.

(6) Maeno, Y.; Fukami, T.; Kawahata, M.; Yamaguchi, K.; Tagami, T.; Ozeki, T.; Suzuki, T.; Tomono, K. *Int. J. Pharm.* **2014**, *473*, 179–186.

(7) Duggirala, N. K.; Perry, M. L.; Almarsson, O.; Zaworotko, M. J. *Chem. Commun.* **2016**, *52*, 640–655.

(8) Aitipamula, S.; Chow, P. S.; Tan, R. B. H. *CrystEngComm* **2014**, *16*, 3451–3465.

(9) Corpinot, M. K.; Stratford, S. A.; Arhangelskis, M.; Anka-Lufford, J.; Halasz, I.; Judas, N.; Jones, W.; Bučar, D.-K. *CrystEngComm* **2016**, *18*, 5434–5439.

(10) Bučar, D.-K.; Lancaster, R. W.; Bernstein, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 6972–6993.

(11) Friščić, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7546–7550.

(12) Lu, E.; Rodriguez-Hornedo, N.; Suryanarayanan, R. *CrystEngComm* **2008**, *10*, 665–668.

(13) Trask, A. V.; Jones, W. Crystal Engineering of Organic Cocrystals by the Solid-State Grinding Approach. In *Organic Solid State Reactions*, Toda, F., Ed.; Springer: Berlin, Heidelberg, 2005; pp 41–70.

(14) Zhang, G. G. Z.; Henry, R. F.; Borchardt, T. B.; Lou, X. *J. Pharm. Sci.* *96*, 990–995.

(15) Bučar, D.-K.; MacGillivray, L. R. *J. Am. Chem. Soc.* **2007**, *129*, 32–33.

(16) Bučar, D.-K.; Henry, R. F.; Lou, X.; Borchardt, T. B.; Zhang, G. G. Z. *Chem. Commun.* **2007**, 525–527.10.1039/B611749J

(17) Rodríguez-Hornedo, N.; Nehm, S. J.; Seefeldt, K. F.; Pagán-Torres, Y.; Falkiewicz, C. J. *Mol. Pharmaceutics* **2006**, *3*, 362–367.

(18) Sheikh, A. Y.; Rahim, S. A.; Hammond, R. B.; Roberts, K. J. *CrystEngComm* **2009**, *11*, 501–509.

(19) Shah, S.; Maddineni, S.; Lu, J.; Repka, M. A. *Int. J. Pharm.* **2013**, *453*, 233–252.

(20) Eddleston, M. D.; Sivachelvam, S.; Jones, W. *CrystEngComm* **2013**, *15*, 175–181.

(21) Bučar, D.-K.; Filip, S.; Arhangelskis, M.; Lloyd, G. O.; Jones, W. *CrystEngComm* **2013**, *15*, 6289–6291.

(22) Friščić, T.; Jones, W. *Cryst. Growth Des.* **2009**, *9*, 1621–1637.

(23) Hasa, D.; Schneider Rauber, G.; Voinovich, D.; Jones, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 7371–7375.

(24) Bučar, D.-K.; Henry, R. F.; Zhang, G. G. Z.; MacGillivray, L. R. *Cryst. Growth Des.* **2014**, *14*, 5318–5328.

(25) Kadota, K.; Shirakawa, Y.; Matsumoto, I.; Shimosaka, A.; Hidaka, J. *Adv. Powder Technol.* **2007**, *18*, 775–785.

(26) Tanaka, M.; Yamanaka, S.; Shirakawa, Y.; Shimosaka, A.; Hidaka, J. *Adv. Powder Technol.* **2011**, *22*, 125–130.

(27) Douaire, M.; di Bari, V.; Norton, J. E.; Sullo, A.; Lillford, P.; Norton, I. T. *Adv. Colloid Interface Sci.* **2014**, *203*, 1–10.

(28) Yang, H.; Rasmuson, Å. C. *Fluid Phase Equilib.* **2015**, *385*, 120–128.

(29) Dey, K.; Pal, M.; Rout, K. C.; Kunjattu H, S.; Das, A.; Mukherjee, R.; Kharul, U. K.; Banerjee, R. *J. Am. Chem. Soc.* **2017**, *139*, 13083–13091.

(30) Bučar, D.-K.; Henry, R. F.; Lou, X.; Duerst, R. W.; Borchardt, T. B.; MacGillivray, L. R.; Zhang, G. G. Z. *Mol. Pharmaceutics* **2007**, *4*, 339–346.

(31) Bučar, D.-K.; Day, G. M.; Halasz, I.; Zhang, G. G. Z.; Sander, J. R. G.; Reid, D. G.; MacGillivray, L. R.; Duer, M. J.; Jones, W. *Chem. Sci.* **2013**, *4*, 4417–4425.

(32) Madusanka, N.; Eddleston, M. D.; Arhangelskis, M.; Jones, W. *Acta Crystallogr., Sect. B: Struct. Sci., Cryst. Eng. Mater.* **2014**, *70*, 72–80.

(33) Bučar, D.-K.; Henry, R. F.; Duerst, R. W.; Lou, X.; MacGillivray, L. R.; Zhang, G. G. Z. *J. Chem. Crystallogr.* **2010**, *40*, 933–939.

(34) Bučar, D.-K.; Henry, R. F.; Lou, X.; Duerst, R. W.; MacGillivray, L. R.; Zhang, G. G. Z. *Cryst. Growth Des.* **2009**, *9*, 1932–1943.

(35) Jeong, K.-w.; Ku, J.-m.; Park, M.-w.; Park, S.-m.; Yang, J.-e.; Nam, T.-g. *Chem. Pharm. Bull.* **2013**, *61*, 740–746.

(36) The $(\mathbf{caf})_2\cdot(\mathbf{6H2N})_3\cdot(H_2O)$ cocrystal hydrate formed together with a 6H2N hemihydrate. See SI.

(37) Bučar, D.-K. *Cryst. Growth Des.* **2017**, *17*, 2913–2918.

(38) The crystal structure of form **IV** of the (**caf**)·(**6H2N**) cocrystal is under investigation by powder X-ray diffraction and solid-state NMR analyses using a phase-pure sample that was obtained from a melt. The results of these investigations will be published elsewhere.

(39) The relative stability of forms **I** and **II** of (**caf**)·(**1H2N**) was established in competitive slurry experiments.