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Hierarchy of Supramolecular Synthons: Persistent Hydroxyl···Pyridine Hydrogen Bonds in Cocrystals That Contain a Cyano Acceptor

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Abstract: An analysis of the Cambridge Structural Database reveals >99% occurrence of the hydroxyl···pyridine supramolecular heterosynthon in crystal structures that contain hydroxyl and pyridine moieties in the absence of other hydrogen-bonding moieties. The occurrence of the hydroxyl···cyano supramolecular heterosynthon in crystal structures that contain hydroxyl and cyano moieties is ca. 77%. Such high frequencies indicate that these heterosynthons are strongly favored over the competing hydroxyl···hydroxyl supramolecular homosynthon. However, the CSD does not contain enough information to evaluate which supramolecular heterosynthon prevails when only OH, pyridine, and CN moieties are present in a crystal structure. We have addressed the competition between the hydroxyl···pyridine and the hydroxyl···cyano supramolecular heterosynthons by characterizing a series of 17 cocrystals that are composed of cocrystal formers which contain a permutation of OH, pyridine, and CN functional groups. Structural analysis reveals that all cocrystals are sustained by the hydroxyl···pyridine heterosynthon.

Keywords: Cambridge Structural Database; cocrystal; polymorphism in cocrystals; pharmaceutical cocrystal; supramolecular heterosynthon

1. Introduction

Crystal engineering,[1] a term coined by Pepinsky[2] and then implemented by Schmidt,[3] has become synonymous with supramolecular synthesis[4] in the solid state. An important aspect of crystal engineering is that it represents an opportunity to generate new compounds through self-assembly, i.e., without the need to invoke traditional, often multistep, covalent synthesis. Furthermore, the diversity of the physicochemical properties that are associated with crystal engineered materials can be exploited in many areas as exemplified by cocrystals, which have relevance to host−guest chemistry,[5] NLO,[6] organic conductors,[7] photographic materials,[8] pharmaceuticals,[9−17,33] and solid-state organic chemistry.[18]

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The design step of crystal engineering utilizes an empirical knowledge of the noncovalent forces that mediate the formation of supramolecular synthons,[19] which are subsequently exploited to form compounds with well-defined composition, structure, and properties. The understanding of supramolecular synthons, their geometries, and their frequency of occurrence in the presence of other hydrogen-bonding groups is a prerequisite for the rational design and supramolecular synthesis of novel cocrystals and for understanding the structure−function relationships in such compounds. In this context, it should be unsurprising that hydrogen-bonded supramolecular synthons are commonly used in crystal engineering of cocrystals due to their relatively high strength, predictability, ubiquity, and directionality.[20−24] There are two distinct categories: supramolecular homosynthons,[25] which are composed of self-complementary functional groups, as exemplified by the carboxylic acid dimer; and supramolecular heterosynthons,[25,26] which are composed of different but complementary functional groups. For instance, the latter include acid···pyridine,[25,27−32] acid···amide,[11,28,33−36] hydroxyl···amine,[37] and hydroxyl···pyridine[38,39] supramolecular synthons. These studies suggest that some supramolecular heterosynthons are strongly favored over related supramolecular homosynthons.[11,25−39] However, to our knowledge studies that have systematically addressed supramolecular heterosynthons in a competitive environment are rather more limited in scope. Furthermore, while the Cambridge Structural Database (CSD)[40] contains enough information to evaluate the competitiveness of some supramolecular homosynthons vs supramolecular heterosynthons, the prevalence of a particular supramolecular heterosynthon over another can only be addressed empirically when both of the functional groups involved are commonly encountered, e.g., alcohols (or phenols) and ethers. Therefore the hierarchies that exist between competing sets of supramolecular heterosynthons such as hydroxyl···pyridine vs hydroxyl···amine, hydroxyl···pyridine vs hydroxyl···cyano, hydroxyl···amine vs hydroxyl···cyano, etc. remain to be determined. Although it might seem intuitive that the stronger base will win out as the hydrogen bond acceptor in such a competition, the effect of induced polarizability could favor the cyano moiety, and in the absence of sufficient empirical data a systematic study is warranted.

Cocrystals are ideally suited to study competition between different supramolecular heterosynthons.[22] First, most cocrystals are sustained by supramolecular heterosynthons rather than supramolecular homosynthons except for rare examples of cocrystals sustained by, for example, two carboxylic acids[41−43] or two amides.[44] Second, scattering of the competing hydrogen-bonding groups over two or more simple molecules can mitigate steric considerations. Utilizing

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the "cocrystal approach" to delineate the hierarchies of two supramolecular heterosynthons is predicated upon the idea that a cocrystal will result only if the favored supramolecular heterosynthon is formed between the reacting molecules. Conversely, a cocrystal is not expected to form if a dominant supramolecular heterosynthon can occur between the functional groups that exist in only one of the components.

Although we can trace the origin of term "cocrystal" to at least as far back as the 1960s,[45] its usage remains vaguely defined and is currently a subject of debate.[46,47] We[9−11] and others[48] have operated under the assumption that a cocrystal is a multiple component crystal in which all components when pure are solid under ambient conditions. Such compounds have been described using various terms, e.g., *molecular compounds*,[49] *organic molecular compounds*,[50] *addition compounds*,[51] *molecular complexes*,[52] *solid-state complexes*,[53] or *heteromolecular crystals*.[54] Although such compounds are long known, as exemplified by the prototypal cocrystal quinhydrone (1844),[55] cocrystals are not as widely studied as single-component crystals or solvates. For example there are 1,487 hydrogen-bonded molecular cocrystals in the CSD,[56] i.e., only 0.42% of the structures archived in the CSD. On the other hand, there are 45,883 hydrates (ca. 13%) archived in the CSD. Nevertheless, cocrystals are attracting attention in the context of pharmaceuticals[9−17,25,33,57,58] as an alternative to the traditionally accepted crystalline forms (polymorphs, solvates/hydrates, and salts) of APIs,[59] and as media for solid-state (green) synthetic chemistry.[60]

As part of our continuing effort to explore pharmaceutical cocrystals[15] we have decided to investigate cocrystal formers that contain permutations of hydroxyl (OH), aromatic nitrogen (N_{arom}), and cyano (CN) moieties. The cyano moiety is present in a number of APIs, e.g., cimetidine and bicalutamide, and the hydroxyl moiety is one of the most commonly occurring functional groups in biologically active compounds. Bicalutamide (propanamide, *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-(±)), is a nonsteroidal antiandrogen used in the treatment of prostate cancer.[61] From a supramolecular perspective, bicalutamide is a relatively complex molecule due its conformational flexibility and the presence of multiple hydrogen-bonding moieties: hydroxyl (O−H), 2° amine (N−H), carbonyl (C═O), cyano (C≡N), and sulfonyl (O═S═O), Chart 1.

In this contribution we report the X-ray crystal structures of 17 cocrystals and discuss their relevance to understanding the hydrogen-bonding hierarchy among OH, N_{arom}, and CN moieties. We also report the results of failed attempts to form cocrystals which support the observations from the structures of the 17 cocrystals achieved. In addition, we evaluate the viability of solid-state methodologies for preparing these cocrystals, namely, dry grinding, solvent-drop grinding, and melting/cooling procedures. Finally, we address polymorphism in these cocrystals in the context of solvent-drop grinding since this methodology has shown the ability to effect polymorphic transformations.[62,63]

2. Experimental Section

Cocrystal formers that contain permutations of OH, N_{arom}, and CN moieties were used in this study (Chart 1). A series of cocrystallization reactions afforded the following cocrystals: 3-cyanophenol·4-phenylpyridine, **1**; $(3\text{-cyanophenol})_2$·1,2-bis(4-pyridyl)ethane, **2**; $(3\text{-cyanophenol})_2$·*trans*-1,2-bis(4-pyridyl)ethylene, **3**; 3-cyanophenol·*trans*-1,2-bis(4-pyridyl)-ethylene, **4**; 4-cyanophenol·4-phenylpyridine, **5**; $(4\text{-cyanophenol})_2$·4,4′-bipyridine, **6**; $(4\text{-cyanophenol})_2$·1,2-bis(4-pyridyl)-ethane, **7**; $(4\text{-cyanophenol})_2$·*trans*-1,2-bis(4-pyridyl)ethylene, **8**; 4-cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene, form I, **9a**; 4-cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene, form II, **9b**; $(3\text{-cyanopyridine})_2$·4,4′-biphenol, **10**; $(4\text{-cyanopyridine})_2$·resorcinol, **11**; $(4\text{-cyanopyridine})_2$·4,4′-biphenol, form I, **12a**; $(4\text{-cyanopyridine})_2$·4,4′-biphenol, form II, **12b**; $(4\text{-cyanopyridine})_3$·phloroglucinol, **13**; bicalutamide·4,4′-bipyridine, **14**; bicalutamide·*trans*-1,2-bis(4-pyridyl)ethylene, **15**.

Synthesis. All reagents were purchased from Aldrich and used without further purification. Single crystals of compounds **1**−**15** were obtained via slow evaporation of stoichiometric amounts of starting materials in an appropriate solvent, and they were removed from their mother liquors before complete evaporation of the solvent had occurred. The

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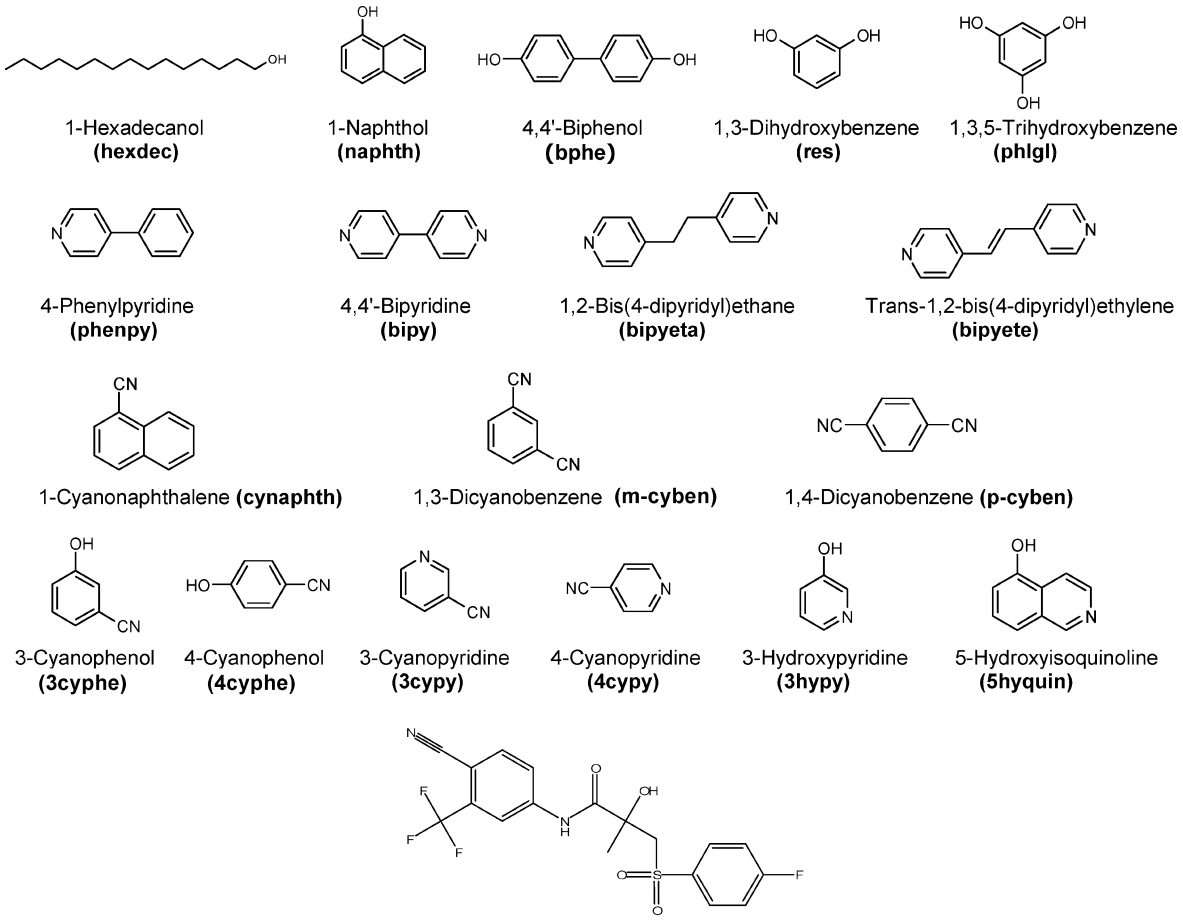
Chart 1. Molecular Structures of Components Used in Cocrystallization Experiments



syntheses of **1**−**13** were also accomplished via dry grinding, solvent-drop grinding, and melting/cooling of the cocrystal formers. **14** and **15** were also obtained via solvent drop grinding while **15** was also obtained via melt/cooling.

Cocrystallization via Grinding. Stoichiometric amounts of the cocrystal formers were ground with a mortar and pestle for ca. 20 min, and the resulting powders were analyzed by diffuse reflectance IR spectroscopy and X-ray powder diffraction.

Cocrystallization via Solvent-Drop Grinding. Stoichiometric amounts of the cocrystal formers were ground with a mortar and pestle for ca. 4 min following addition of the solvent (10 μL per 50 mg of starting materials) from which the single crystals were grown. The resulting powders were analyzed by diffuse reflectance IR spectroscopy and X-ray powder diffraction.

Cocrystallization via Solvent Evaporation. 3-Cyanophenol·4-Phenylpyridine, 1. To 3-cyanophenol (0.015 g, 0.13 mmol) was added 4-phenylpyridine (0.020 g, 0.13 mmol) and 2 mL of 1:1 of an acetone/ethyl acetate solution. Slow evaporation of the solution afforded colorless crystals of **1**, (0.027 g, 0.10 mmol, 77%) mp = 54−57 °C, after 3 days. Grinding was done using a 1:1 ratio, respectively.

(3-Cyanophenol)$_2$·1,2-Bis(4-pyridyl)ethane, 2. 3-Cyanophenol (0.026 g, 0.22 mmol) and 1,2-bis(4-pyridyl)ethane (0.020 g, 0.11 mmol) were dissolved in 2 mL of acetone. After 3 days colorless crystals of **2** (0.035 g, 0.083 mmol, 75%), mp = 106−108 °C, were afforded. Grinding was done using a 2:1 ratio, respectively.

(3-Cyanophenol)$_2$·*trans*-1,2-Bis(4-pyridyl)ethylene, 3. Cocrystallization of the cocrystal formers in a 2:1 molar ratio afforded a 1:1 cocrystal, **4**. However, **3** was obtained using the cocrystal formers in a 4:1 molar ratio. 3-Cyanophenol (0.052 g, 0.44 mmol) and *trans*-1,2-bis(4-pyridyl)ethylene (0.020 g, 0.11 mmol) were dissolved in 2 mL of 1:1 acetone and ethyl acetate. After 2 days colorless crystals of **3** (0.031 g, 0.074 mmol, 67%), mp = 112−114 °C, were obtained. Grinding was done using a 2:1 ratio, respectively.

3-Cyanophenol·*trans*-1,2-Bis(4-pyridyl)ethylene, 4. Cocrystal **4** was obtained using the cocrystal formers in a 2:1 ratio. 3-Cyanophenol (0.026 g, 0.22 mmol) and *trans*-1,2-bis(4-pyridyl)ethylene (0.020 g, 0.11 mmol) were dissolved in 2 mL of ethyl acetate. Colorless crystals of **4** (0.026 g, 0.086 mmol, 79%), mp = 124−125 °C, appeared after 2 days. Cocrystal **4** can also be obtained by using the reagents in 1:1 molar ratio. Grinding was done using a 1:1 ratio of cocrystal formers.

4-Cyanophenol·4-Phenylpyridine, 5. 4-Cyanophenol (0.015 g, 0.13 mmol) and 4-phenylpyridine (0.020 g, 0.13 mmol) were dissolved in 2 mL of chloroform and left to

evaporate slowly at 4 °C. After 4 days colorless crystals of **5** (0.030 g, 0.11 mmol, 85%), mp = 65−66 °C, were harvested. Grinding was done using a 1:1 ratio of cocrystal formers.

(4-Cyanophenol)$_2$·4,4′-bipyridine, 6. 4-Cyanophenol (0.031 g, 0.26 mmol) and 4,4′-bipyridine (0.020 g, 0.13 mmol) were dissolved in 2 mL of methanol, and the solution was left undisturbed to evaporate under ambient conditions. After 12 days yellow needles of **6** (0.042 g, 0.097 mmol, 75%), mp = 143−146 °C, were harvested. Grinding was done using a 2:1 ratio, respectively.

(4-Cyanophenol)$_2$·1,2-Bis(4-pyridyl)ethane, 7. 4-Cyanophenol (0.026 g, 0.22 mmol) and 1,2-bis(4-pyridyl)ethane (0.020 g, 0.11 mmol) were dissolved in 2 mL of methanol. After 8 days colorless crystals of **7** (0.031 g, 0.073 mmol, 67%), mp = 138−139 °C, were obtained. Grinding was done using a 2:1 ratio, respectively.

(4-Cyanophenol)$_2$·*trans*-1,2-Bis(4-pyridyl)ethylene, 8. Cocrystallization of the cocrystal formers in a 2:1 molar ratio afforded two forms of the 1:1 cocrystal (**9a** and **9b**), whereas **8** was obtained using the reagents in a 4:1 molar ratio. 4-Cyanophenol (0.052 mg, 0.44 mmol) and 1,2-bis(4-pyridyl)ethylene (0.020 mg, 0.11 mmol) were dissolved in 2 mL of acetonitrile. After 2 days colorless crystals, mp = 141−142 °C, were isolated.

Analysis of the single crystals so isolated revealed that **8** crystallizes concomitantly with polymorphic forms of the 1:1 cocrystals **9a** and **9b**. Grinding was done using a 2:1 ratio, respectively.

4-Cyanophenol·*trans*-1,2-Bis(4-pyridyl)ethylene, 9a (Form I) and 9b (Form II). Cocrystals **9** were formed in solution from the cocrystal formers in a 2:1 molar ratio. 4-Cyanophenol (0.026 g, 0.22 mmol) and *trans*-1,2-bis(4-pyridyl)ethylene (0.020 g, 0.11 mmol) were dissolved in 2 mL of methanol. After 14 days colorless crystals, mp = 153−156 °C, were harvested. The single-crystal X-ray analysis revealed the presence of two concomitant polymorphs of 4-cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene (1:1), **9a** and **9b**. Cocrystals of **9** also crystallize concomitantly from solutions containing 4-cyanophenol and *trans*-1,2-bis-(4-pyridyl)ethylene in a 1:1 ratio. Grinding was done using a 1:1 ratio of cocrystal formers for both **9a** and **9b**.

(3-Cyanopyridine)$_2$·4,4′-Biphenol, 10. 3-Cyanopyridine (0.040 g, 0.38 mmol) and 4,4′-biphenol (0.036 g, 0.19 mmol) were dissolved in 2 mL of methanol. After 6 days colorless crystals of **10** (0.052 g, 0.13 mmol, 68%), mp = 250 °C, were isolated. Grinding was done using a 2:1 ratio respectively.

(4-Cyanopyridine)$_2$·Resorcinol, 11. 4-Cyanopyridine (0.040 g, 0.38 mmol) and resorcinol (0.021 g, 0.19 mmol) were dissolved in 2 mL of acetonitrile. The solution was left to evaporate at ambient temperature, and after 8 days colorless crystals of **11** (0.055 g, 0.16 mmol, 84%), mp = 93−94 °C, were harvested. Grinding was done using a 2:1 ratio, respectively.

(4-Cyanopyridine)$_2$·4,4′-Biphenol, 12a (Form I) and 12b (Form II). 4-Cyanopyridine (0.040 g, 0.38 mmol) and 4,4′-biphenol (0.036 g, 0.19 mmol) were dissolved in a 1:1 mixture of methanol and ethyl acetate, and the solution was left to evaporate at ambient conditions. After 4 days, yellow crystals of two distinct morphologies (0.044 g, 0.13 mmol, 67%) were formed. The X-ray single-crystal analysis revealed that the bulk samples consisted of two concomitant polymorphs, **12a** and **12b.** Grinding was done using a 2:1 ratio, respectively.

(4-Cyanopyridine)$_3$·Phloroglucinol, 13. 4-Cyanopyridine (0.041 g, 0.39 mmol) and phloroglucinol (0.016 g, 0.13 mmol) were dissolved in 2 mL of acetone. After 3 days yellow needles of **13** (0.045 g, 0.10 mmol, 77%), mp = 116−117 °C, were isolated. Grinding was done using a 3:1 ratio, respectively.

Bicalutamide·4,4′-Bipyridine, 14. Bicalutamide (0.05 g, 0.115 mmol) and 4,4′-bipyridine (0.018 g, 0.115 mmol) were dissolved in 1 mL of acetone. After 3 days colorless plates were formed, mp = 157−159 °C. Grinding was done using a 1:1 ratio of cocrystal formers.

Bicalutamide·*trans*-1,2-Bis(4-pyridyl)ethylene, 15. Bicalutamide (100 mg, 0.23 mmol) was added to *trans*-1,2-bis(4-pyridyl)ethene (21 mg, 0.115 mmol) in a 2:1 molar ratio. To the solid mixture was added DMSO (0.5 mL), and the solution was left to evaporate at ambient temperature. After 3 days colorless plates were formed, mp =161−163 °C. Grinding was done using a 1:1 ratio of cocrystal formers.

Cocrystallization via Melting/Cooling. Stoichiometric amounts of the cocrystal formers were heated until melting, and the mixture was left to stand at ambient conditions. The resulting products were analyzed by IR spectroscopy and X-ray powder diffraction. Cocrystals **12**, **13**, and **14** could not obtained by this procedure. Presumably **12** and **13** were unsuccessful due to decomposition of 4,4′-biphenol and sublimation of phloroglucinol upon heating.

Polymorph Screen. Cocrystals **1**−**15** were subjected to a preliminary polymorph screen using solvent-drop grinding (as described above) with seven solvents that exhibit a wide range of polarity: cyclohexane, toluene, chloroform, ethyl acetate, methanol, dimethyl sulfoxide (DMSO), and water. A summary of the results obtained from solution crystallization, dry grinding, solvent-drop grinding, and melting/cooling is presented in Table 1.

Attempts to obtain 3-cyanopyridine·1-hexadecanol and 4-cyanopyridine·1-hexadecanol using solvent evaporation, grinding, solvent-drop grinding, and melting/cooling were unsuccessful; the IR spectra and PXRD patterns revealed a mixture of cocrystal formers. Mixtures of cocrystal formers were also afforded following solvent evaporation, dry grinding, solvent-drop grinding, and melting/cooling during attempts to obtain the following cocrystals: 3-hydroxypyridine·1-cyanonaphthalene, (3-hydroxypyridine)$_2$·1,3-dicyanobenzene, (3-hydroxypyridine)$_2$·1,4-dicyanobenzene, 5-hydroxyisoquinoline·1-cyanonaphthalene, (5-hydroxyisoquinoline)$_2$·1,3-dicyanobenzene, and (5-hydroxyisoquinoline)$_2$·1,4-dicyanobenzene.

Cocrystallization experiments utilizing solvent evaporation, grinding, solvent-drop grinding, and melting/cooling that involved stoichiometric amounts of the pairs 3-cyanopyridine

Table 1. Results Obtained from Solution Crystallization, Grinding, Solvent-Drop Grinding, and Melting Experiments

cocrystal no.	solution	grinding	solvent-drop grinding	melting	no. of polymorphs determined
1	**1**	**1**	**1**	**1**	one
2	**2**	**2**	**2**	**2**	one
3	**3**	**3**, **4**	**3**	**3**, **4**	one
4	**4**	**3**, **4**	**3**, **4**	**3**, **4**	one
5	**5**	**5**	**5**	**5**	one
6	**6**	**6**	**6**	**6**	one
7	**7**	**7**	**7**	**7**	one
8	**8**, **9a**, **9b**	**8**, **9a**, **9b**	**8**, **9a**, **9b**	**8**, **9a**, **9b**	one
9	**9a**, **9b**	**8**, **9a**, **9b**	**8**, **9a**, **9b**	**8**, **9a**, **9b**	two
10	**10**	**10**	**10**	**10**	one
11	**11**	**11**	**11**	**11**	one
12	12a, 12b	**12b**	**12b**	n/a	two
13	**13**	**13**	**13**	n/a	one
14	**14**	n/a	**14**	n/a	one
15	**15**	n/a	**15**	**15**	one

and 1-naphthol, 3-cyanopyridine and resorcinol, 3-cyanopyridine and phloroglucinol, and 4-cyanopyridine and 1-naphthol resulted in products that are liquid under ambient conditions and were not pursued further.

Cocrystals were characterized by infrared spectroscopy using a Nicolet Avatar 320 FTIR instrument. The purity of bulk samples was confirmed by X-ray powder diffraction. Cocrystals **1**, **5**, **6**, **8**, **10**, and **12** were analyzed on a Rigaku Miniflex diffractometer using Cu Kα radiation ($\lambda = 1.54056$ Å), 30 kV, 15 mA. The data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/min. Compounds **2**−**4**, **7**, **9**, **11**, **13**, **14**, and **15** were analyzed on Bruker AXS D8 discover X-ray diffractometer equipped with GADDS (General Area Diffraction Detection System), a Bruker AXS HI-STAR area detector at a distance of 15.05 cm as per system calibration, a copper source, automated *x*-*y*-*z* stage, and 0.5 mm collimator. Data were collected over a 2.1−37.0° 2θ range at a step size of 0.02° 2θ. Melting points of compounds **1**−**11**, **13**, **14**, and **15** were determined on a MEL-TEMP apparatus, and they are summarized in Table 2. Differential scanning calorimetry was conducted on a TA Instruments DSC 2920.

Single-Crystal X-ray Data Collection and Structure Determinations. Cocrystals **1**−**15** were examined under a microscope, and suitable single crystals were selected for further study. Data were collected on a Bruker AXS SMART APEX CCD diffractometer with monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) connected to a KRYO-FLEX low-temperature device. Data for **2**, **3**, **6**, **7**, and **10** were collected at 100 K. Data for **1**, **4**, **5**, **8**, **9**, and **11**−**15** were collected at 298 K. Lattice parameters were determined from least-squares analysis, and reflection data were integrated using the program SAINT. Lorentz and polarization corrections were applied for diffracted reflections. In addition, the data of all compounds except one (**13**) was corrected for absorption using SADABS.[64] Structures were solved by direct methods and refined by full matrix least-squares based on F^2 using SHELXTL.[65] All non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms bonded to carbon atoms were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times U_q of the atoms to which they were attached. The O-bonded protons were located from a Fourier difference map and refined isotropically with thermal parameters based upon the corresponding O atom ($U(H) = 1.2U_q(O)$). Crystallographic data for **1**−**15** are presented in Table 3, and selected hydrogen bond distances are listed in Table 4.

Table 2. Comparison of Melting Points of Cocrystals **1**−**15** and the Starting Components

cocrystal no.	mp of cocrystal [°C]	mp of component 1 [°C]	mp of component 2 [°C]
1	54−57	81−82 (**3cyphe**)	68−71 (**phenpy**)
2	106−108	81−82 (**3cyphe**)	110−112 (**bipyeta**)
3	112−114	81−82 (**3cyphe**)	150−153 (**bipyete**)
4	124−125	81−82 (**3cyphe**)	150−153 (**bipyete**)
5	65−66	110−113 (**4cyphe**)	68−71 (**phenpy**)
6	143−146	110−113 (**4cyphe**)	110−114 (**bipy**)
7	138−139	110−113 (**4cyphe**)	110−112 (**bipyeta**)
8	141−142	110−113 (**4cyphe**)	150−153 (**bipyete**)
9a	153−156	110−113 (**4cyphe**)	150−153 (**bipyete**)
9b	153−156	110−113 (**4cyphe**)	150−153 (**bipyete**)
10	250 (dec)	49−50 (**3cypy**)	283 (**bphe**)
11	93−94	76−79 (**4cypy**)	109−111 (**res**)
12a		76−79 (**4cypy**)	283 (**bphe**)
12b		76−79 (**4cypy)**	283 (**bphe**)
13	116−117	76−79 (**4cypy**)	216 (**phlgl**)
14	157−159	191−193 (bicalutamide)	110−114 (**bipy**)
15	161−163	191−193 (bicalutamide)	150−153 (**bipyete**)

3. Results and Discussion

3.1. CSD Analysis.[66] There are three hydrogen-bonded supramolecular synthons that might be expected when OH, N_{arom}, and CN groups are present in the same crystal structure: the hydroxyl···pyridine supramolecular heterosynthon, **I**; the hydroxyl···cyano supramolecular heterosynthon, **II**; and the hydroxyl···hydroxyl supramolecular homosynthon, **III** (Chart 2). **I** is well established and has been exploited in the context of crystal engineering.[38,39,67] A CSD analysis reveals that in 136 structures containing only OH and N_{arom} (i.e., no other hydrogen-bonding moieties) 135

(64) *SADABS* [Area-Detector Absorption Correction]; Siemens Industrial Automation, Inc.: Madison, WI, 1996.

(65) Sheldrick, G. M. *SHELXTL*; University of Göttingen: Göttingen, Germany, 1997.

(66) CSD, August 2006 release. Search parameters: organics only, 3D coordinates determined, $R < 7.5\%$. All statistics presented in this section relate to OH Narom and CN moieties and their engagament in forming synthons I, II, and III in the absence of other functional groups.

(67) Biradha, K.; Zaworotko, M. J. *J. Am. Chem. Soc.* **1998**, *120* (25), 6431−6432.

Table 3. Crystallographic Data and Structure Refinement Parameters for Cocrystals **1**−**15**

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
chem formula	$C_7H_5NO\cdot C_{11}H_9N$	$(C_7H_5NO)_2\cdot C_{12}H_{12}N_2$	$(C_7H_5NO)_2\cdot C_{12}H_{10}N_2$	$C_7H_5NO\cdot C_{12}H_{10}N_2$	$C_7H_5NO\cdot C_{11}H_9N$	$(C_7H_5NO)_2\cdot C_{10}H_8N_2$	$(C_7H_5NO)_2\cdot C_{12}H_{12}N_2$	$(C_7H_5NO)_2\cdot C_{12}H_{10}N_2$
fw	274.31	422.48	420.46	301.34	274.31	394.42	422.48	420.46
cryst syst	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/n$	$C2/c$	$C2/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
a (Å)	9.90(1)	13.223(3)	16.542(2)	18.715(8)	26.22(1)	3.848(2)	11.195(3)	14.660(3)
b (Å)	21.65(3)	6.197(1)	7.506(1)	7.228(3)	7.481(5)	8.755(4)	7.335(2)	4.110(1)
c (Å)	7.590(9)	14.630(3)	18.709(2)	23.208(9)	19.41(1)	14.364(6)	13.530(4)	18.290(4)
α ((deg)	90	90	90	90	90	96.647(7)	90	90
β ((deg)	112.14(2)	113.661(3)	106.763(2)	90.48(1)	128.31(1)	94.498(8)	99.456(7)	90.74(3)
γ (deg)	90	90	90	90	90	95.474(7)	90	90
vol (Å^3)	1508(3)	1098.1(4)	2224.2(4)	3139(2)	2987(3)	476.6(4)	1095.9(6)	1101.9(4)
D_{calc} (g cm^{-3})	1.208	1.278	1.256	1.275	1.220	1.374	1.280	1.267
Z	4	2	4	8	8	1	2	2
θ range	1.88−24.99	1.68−26.73	1.95−25.00	1.75−24.99	1.98−25.00	1.43−26.37	1.84−25.00	2.61−23.35
Nref/Npara	2607/191	2314/145	3798/290	2748/208	2585/190	1888/136	1818/145	1565/145
T (K)	298	100	298	100	298	100	100	298
R_1	0.0558	0.0597	0.0504	0.0688	0.0630	0.0659	0.0672	0.0502
wR_2	0.1461	0.1550	0.1501	0.1492	0.1759	0.1926	0.1752	0.1307
GOF	0.924	1.103	1.069	1.002	0.805	1.042	1.044	0.814
abs coeff	0.076	0.083	0.082	0.081	0.077	0.090	0.083	0.083

	9a	**9b**	**10**	**11**	**12a**	**12b**	**13**	**14**	**15**
chem formula	$C_7H_5NO\cdot C_{12}H_{10}N_2$	$C_7H_5NO\cdot C_{12}H_{10}N_2$	$(C_6H_4N_2)_2\cdot C_{12}H_{10}O_2$	$(C_6H_4N_2)_2\cdot C_6H_6O_2$	$(C_6H_4N_2)_2\cdot C_{12}H_{10}O_2$	$(C_6H_4N_2)_2\cdot C_{12}H_{10}O_2$	$(C_6H_4N_2)_3\cdot C_6H_6O_3$	$C_{18}H_{14}F_4N_2O_4S\cdot C_{10}H_8N_2$	$C_{18}H_{14}F_4N_2O_4S\cdot C_{12}H_{10}N_2$
fw	301.34	301.34	394.42	318.33	394.42	394.42	438.44	586.56	612.59
cryst syst	monoclinic	triclinic	monoclinic	triclinic	monoclinic	monoclinic	triclinic	triclinic	triclinic
space group	Cc	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$C2/c$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	18.719(8)	7.616(2)	20.866(6)	9.171(4)	39.87(2)	12.787(2)	7.889(3)	8.298(2)	8.274(3)
b (Å)	7.602(3)	10.003(3)	7.437(2)	9.941(5)	7.586(5)	7.2838(9)	8.156(3)	11.434(3)	10.172(3)
c (Å)	22.09(1)	22.497(6)	6.766(2)	10.265(5)	6.915(2)	44.445(6)	19.673(7)	15.299(4)	18.601(7)
α (deg)	90	87.342(5)	90	95.674(8)	90	90	83.866(7)	74.506(4)	87.521(7)
β (deg)	90.762(9)	81.024(6)	98.142(5)	94.987(8)	91.97(2)	90.895	85.627(6)	75.852(5)	78.256(6)
γ (deg)	90	69.737(6)	90	114.784(8)	90	90	63.512(5)	79.963(4)	71.067(7)
vol (Å^3)	3144(2)	1588.1(8)	1039.4(5)	836(7)	2090(2)	4139.1(9)	1125.9(6)	1347.0(6)	1449.4(9)
D_{calc} (g cm^{-3})	1.273	1.260	1.260	1.263	1.253	1.266	1.293	1.446	1.404
Z	8	4	2	2	4	8	2	1	2
θ range	2.18−27.00	0.92−22.50	0.99−26.73	2.01−24.99	1.02−25.09	0.92−25.00	1.04−25.00	2.55−24.08	1.12−26.73
Nref/Npara	5352/417	4046/415	2181/136	2875/217	1830/136	7284/541	3915/298	4680/370	5985/388
T (K)	298	298	100	298	298	298	298	298	298
R_1	0.0505	0.0502	0.0685	0.0506	0.0682	0.0510	0.0586	0.0724	0.0554
wR_2	0.1390	0.1291	0.1747	0.1397	0.2121	0.1654	0.1676	0.1639	0.1290
GOF	1.058	0.791	1.082	1.058	0.875	0.812	0.938	0.786	1.028
abs coeff	0.081	0.080	0.083	0.086	0.082	0.083	0.089	0.190	0.180
CSD Refcode					TEHNAW	TEHNAW01			

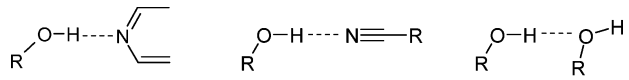
structures exhibit **I** and 37 exhibit **III**, suggesting that **I** is favored over **III**.[68] On the other hand, the occurrence of supramolecular heterosynthon **II** in the 74 crystal structures that contain only OH and CN is ca. 77% (vs 23% for **III**), Table 5. However, there are only three entries archived in the CSD that possess all three moieties (OH, N_{arom}, and CN) in the absence of competing hydrogen-bonding moieties, thereby precluding a meaningful statistical evaluation using CSD data. Thus, the hierarchy between **I**, **II**, and **III** has to be assessed using additional experimental results. The cocrystals reported herein facilitate determination of the relative hierarchy of **I**−**III**, and as will become clear, the results reported herein suggest that heterosynthon **I** is sustained even in the presence of a CN group. These results

(68) There are 197 crystal structures that contain only OH and Narom moieties and no other hydrogen-bonding groups. After manual elimination of structures sustained by intramolecular OH···Narom hydrogen bonds, the set was reduced to 136 structures. In 135 (99%) entries the supramolecular heterosynthon **I** was observed. In one entry, REPPEH, **I** is absent due to a steric hindrance of the Narom moiety. The 27% (37 entries) of OH···OH homosynthon occurrence is due to the presence of multiple OH moieties.

Table 4. Geometrical Parameters of Intermolecular Interactions for Cocrystals **1**−**15**

	hydrogen bond	*d* (Å)	*D* (Å)	*θ* (deg)
1	O−H···N	1.63	2.708(3)	168.9
2	O−H···N	1.77	2.691(2)	176.3
3	O−H···N	1.69	2.727(2)	173.3
	O−H···N	1.75	2.729(2)	173.6
4	O−H···N	1.64	2.663(3)	165.6
5	O−H···N	1.60	2.695(4)	175.7
6	O−H···N	1.84	2.718(3)	175.4
7	O−H···N	1.80	2.698(4)	175.5
8	O−H···N	1.74	2.714(4)	159.5
9a	O−H···N	1.73	2.721(3)	160.9
	O−H···N	1.72	2.669(4)	161.3
9b	O−H···N	1.52	2.689(4)	164.9
	O−H···N	1.52	2.717(4)	172.0
10	O−H···N	1.77	2.765(3)	166.3
11	O−H···N	1.96	2.856(2)	169.9
	O−H···N	1.86	2.763(2)	175.0
12a	O−H···N	1.80	2.733(4)	174.1
12b	O−H···N	1.72	2.838(3)	173.7
	O−H···N	1.69	2.766(3)	164.2
	O−H···N	1.56	2.693(3)	163.2
	O−H···N	1.79	2.789(4)	172.3
13	O−H···N	1.84	2.784(3)	161.6
	O−H···N	1.77	2.721(4)	167.7
	O−H···N	1.77	2.795(3)	176.0
14	O−H···N	1.68	2.759(5)	163.1
	O−H···N	2.04	2.574(4)	110.7
	N−H···N	2.55	3.499(7)	157.4
15	O−H···N	1.93	2.811(3)	157.5
	N−H···O	2.19	2.671(3)	111.9
	N−H···N	2.25	3.119(3)	157.7

Chart 2. Supramolecular Synthons That Can Be Formed When OH, N_{arom}, and CN Moieties Are Present in a Crystal Structure



I **II** **III**

are to be expected based on the basicity of the H-bond acceptors but have not been confirmed in the literature by any comprehensive study.

3.2. Description of Crystal Structures of Cocrystals 1−15. Herein we report the crystal structures of 17 cocrystals that contain OH, N_{arom}, and CN functional groups. We selected cocrystal formers possessing permutations of OH, N_{arom}, and/or CN moieties that are (a) sterically accessible, (b) not involved in intramolecular interactions, and (c) free of other competing hydrogen bond donors and acceptors. The OH, N_{arom}, and CN moieties were dispersed among pairs of cocrystal formers and were cocrystallized in three sets: OH/CN with N_{arom}, N_{arom}/CN with OH, and OH/N_{arom} with CN. The resulting cocrystals were characterized through the following techniques: melting point, differential scanning calorimetry, infrared spectrometry, powder and single-crystal X-ray diffraction. The crystal structures of 17 cocrystals were analyzed in the context of the hierarchy of **I**, **II**, and **III**.

Phenols and pyridines can form neutral cocrystals or organic salts depending on their acidity and basicity, respectively, and it has been suggested that proton transfer will occur if the ΔpK_a is greater than 2.95.[6] The ΔpK_a values in cocrystals **1**−**15**, which range from −1.66 to −8.22 (Table 6), are relatively low. O−H···N supramolecular heterosynthons in these compounds would therefore be expected to be neutral rather than ionic. The neutral or ionic nature of heterosynthon **I** in **1**−**15** was addressed by spectroscopy, proton location in the difference Fourier map, and structural parameters of ancillary groups, namely, the C−N−C angle in the pyridine moieties and C−O bond lengths in the phenolic moieties. The C−N−C angle in pyridines is known to be sensitive to protonation, and its cationic form exhibits higher values (ca. 121°) than that of the corresponding neutral molecules (ca. 116°).[69] Histograms of carbon−oxygen bond lengths in neutral and ionic hydroxyl moieties were generated using the CSD and are presented in Figure 1 (only good quality crystal structures: ordered, error free, nonpolymeric with 3D coordinates determined, and $R < 7.5\%$). The 13,110 crystal structures that contain neutral aliphatic hydroxyl moieties exhibit an average C−OH bond length of 1.42(3) Å while the 4,126 structures that contain neutral aromatic hydroxyl moieties exhibit an average C−OH bond length of 1.36(3) Å. There are 350 crystal structures that contain aliphatic deprotonated hydroxyl moieties which exhibit an average $C-O^-$ bond length of 1.24(3) Å while there are 485 crystal structures that contain aromatic deprotonated hydroxyl moieties that exhibit an average $C-O^-$ bond length of 1.27(3) Å. The average $C-O^-$ bond length previously reported in such structures is 1.27(4) Å.[70]

3-Cyanophenol·4-Phenylpyridine, 1. The crystal structure of **1** (Figure 2A), reveals the presence of discrete 1:1 supramolecular adducts sustained by O−H···N supramolecular heterosynthon **I**, i.e. the **D** graph set.[22,71] In addition to IR spectroscopic evidence, the neutral nature of **I** is supported by the observed structural parameters. The

(69) Boenigk, D.; Mootz, D. *J. Am. Chem. Soc.* **1988**, *110* (7), 2135−2139.

(70) To distinguish neutral C−OH from ionic $C-O^-$, specific restrictions on the oxygen atoms were applied during the CSD searches. For neutral C−OH bond, the presence of the hydrogen atom bonded to oxygen atom was acquired, the oxygen atom was defined to be uncharged, and the number of bonded atoms was set to 2. In the case of ionic $C-O^-$ bond, the charge of the oxygen was set to −1 and the number of bonded atoms was set to 1.

(71) Etter, M. C.; MacDonald, J. C.; Bernstein, J. *Acta Crystallogr., Sect. B: Struct. Sci.* **1990**, *B46*, 256−262.

(72) MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2000**, *122* (32), 7817−7818.

(73) CSD search for the distance distribution of the NH···Narom interaction (organics, 3D coordinates determined, and $R < 7.5\%$) afforded 420 entries that occur within a range of 2.75−3.30 Å, with the average of 3.0(1) Å.

Table 5. CSD Statistics Related to Supramolecular Synthons That Occur in Structures Containing Only OH, N_{arom}, and CN

moieties present in a structure	no. of structures	supramolecular synthon	structures with synthon	D···A Å]	mean (σ) [Å]
OH and N_{arom}	136	O−H···N	135 (99%)	2.50−3.00	2.77(8)
		O−H···O	37 (27%)		
OH and CN	74	O−H···NC	57 (77%)	2.70−3.20	2.9(1)
		O−H···O	17 (23%)		
OH, N_{arom}, and CN	3	O−H···O	0		
		O−H···N	3		
		O−H···NC	0		

Table 6. pK_a and ΔpK_a Values for the Components of Cocrystals **1**−**15**

cocrystal no.	cocrystal composition	pK_a[a] phenol	pK_a[a] base	ΔpK_a[b]
1	3-cyanophenol·4-phenylpyridine	8.58	5.44	−3.14
2	(3-cyanophenol)$_2$·1,2-bis(4-pyridyl)ethane	8.58	6.13	−2.54
3	3-cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene	8.58	5.50	−3.08
4	(3-cyanophenol)$_2$·*trans*-1,2-bis(4-pyridyl)ethylene	8.58	5.50	−3.08
5	4-cyanophenol·4-phenylpyridine	7.79	5.44	−2.35
6	(4-cyanophenol)$_2$·4,4′-bipyridine	7.79	3.27	−4.52
7	(4-cyanophenol)$_2$·1,2-bis(4-pyridyl)ethane	7.79	6.13	−1.66
8	(4-cyanophenol)$_2$·*trans*-1,2-bis(4-pyridyl)ethylene	7.79	5.50	−2.29
9	4-cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene	7.79	5.50	−2.29
10	(3-cyanopyridine)$_2$·4,4′-biphenol	9.74	1.78	−7.96
11	(4-cyanopyridine)$_2$·resorcinol	9.45	1.92	−7.53
12	(4-cyanopyridine)$_2$·4,4′-biphenol	9.74	1.92	−7.82
13	(4-cyanopyridine)$_3$·phloroglucinol	9.06	1.92	−7.14
14	bicalutamide·4,4′-bipyridine	11.49	3.27	−8.22
15	bicalutamide·*trans*-1,2-bis(4-pyridyl)ethylene	11.49	5.50	−5.99

[a] The listed pK_a values were obtained from SciFinder Scholar. Only the pK_a1 value was used for ΔpK_a calculations. [b] ΔpK_a = pK_a (conjugated acid of the base) − pK_a (phenol).

O−H···N hydrogen bond distance (*D*: 2.708(3) Å) is within the expected range for hydroxyl···pyridine interactions (Table 5).[38,39,72]

(3-Cyanophenol)$_2$·1,2-Bis(4-pyridyl)ethane, 2. The crystal structure of **2** reveals centrosymmetric 2:1 adducts sustained by supramolecular heterosynthon **I** (*D*: 2.691(2) Å). The C−O distance is 1.352(2) Å, and the C−N−C angle within the pyridine ring is 116.6(2)°, indicating a neutral O−H···N hydrogen bond. Adjacent adducts interact via weak C−H···N forces that sustain 1D zigzag chains. Translation related chains are connected via weak C−H···N interaction along the *b*-axis, thereby forming supramolecular sheets (Figure 2B).

(3-Cyanophenol)$_2$·*trans*-1,2-Bis(4-pyridyl)ethylene, 3. The asymmetric unit of **3** consists of two **3cyphe** molecules and one **bipyete** molecule. The components form noncentrosymmetric supramolecular adducts sustained by **I** (D_1, 2.727(2) Å; D_2, 2.729(2) Å). Adjacent supramolecular adducts are stabilized by face-to-face stacking occurring between the aromatic moieties of **3cyphe** and **bipyete** molecules. Such molecular assembly affords columnar alignment of the 2:1 adducts parallel to the *b*-axis. These molecular columns are further interconnected by weak C−H···N interactions thereby forming supramolecular sheets (Figure 2C).

3-Cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene, 4, consists of 1:1 supramolecular adducts sustained by **I** (*D*: 2.663(3) Å, Figure 2D). The inversion related dimers are stabilized by $\pi-\pi$ stacking parallel to the *b*-axis between **bipyete** molecules with interplanar separations of ca. 3.44 Å. Such alignment of the two ethylene sites satisfies the topochemical principle[5] and perhaps makes the system suitable for [2 + 2] photodimerization.[18] Furthermore, it should be pointed out that the 1:1 stoichiometry of the components in **4** is somewhat unexpected, considering that the ratio of hydrogen bond acceptor:donor (in this case N_{arom}:OH) between the two components is 2:1. While the O−H moieties of **3cyphe** are utilized in a strong O−H···N_{arom} hydrogen bond, only one of the two N_{arom} sites of **bipyete** acts as an O−H···N_{arom} acceptor.

4-Cyanophenol·4-phenylpyridine, **5**, is composed of 1:1 discrete supramolecular adducts sustained by **I** (*D*: 2.695(4) Å). In **5** the **phenpy** is nonplanar, as was observed in **1**, with a torsion angle of 33.6°. Adjacent columns of 1:1 adducts are connected by centrosymmetric C−H···N dimers thereby generating supramolecular sheets (Figure 3A).

(4-Cyanophenol)$_2$·4,4′-Bipyridine, 6. The crystal structure of **6** reveals the presence of 2:1 centrosymmetric supramolecular adducts sustained by **I** (*D*: 2.718(3) Å). The **bipy** molecules are flat and stack along the *a*-axis with an

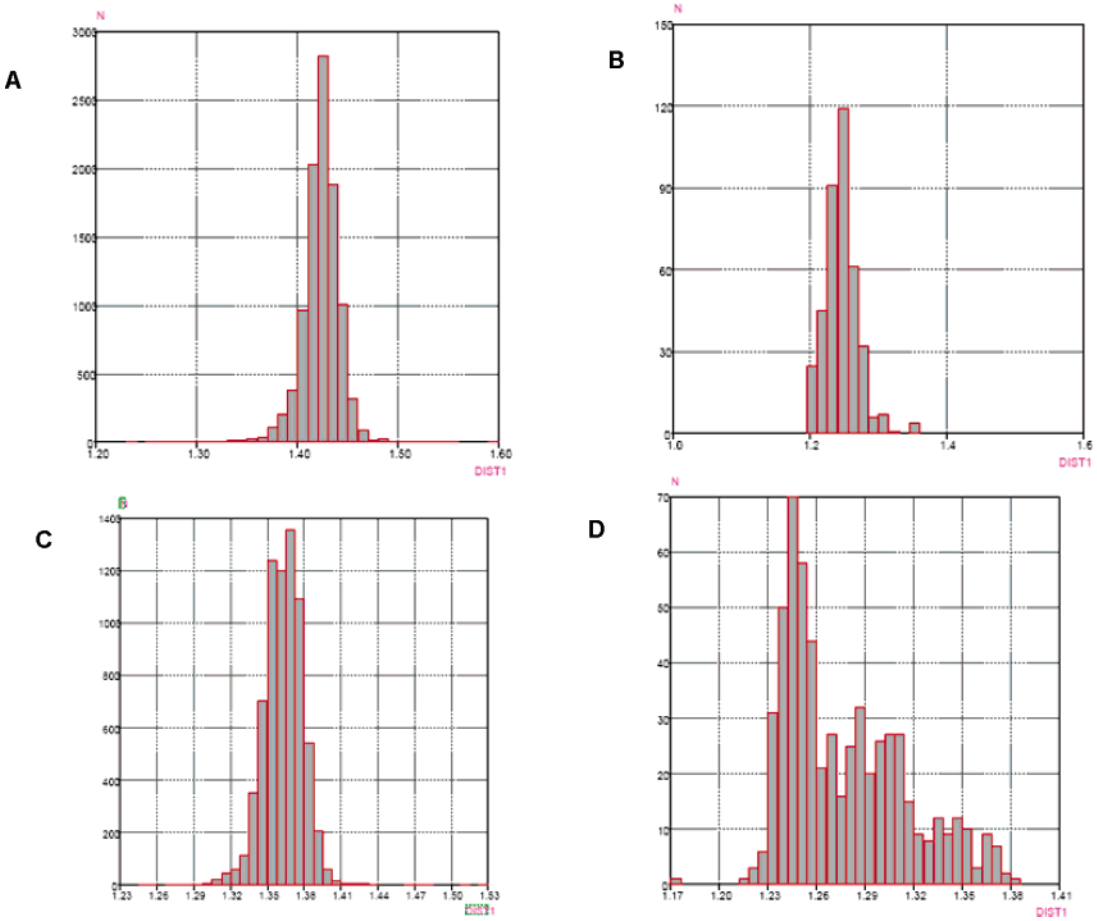


Figure 1. Histograms representing the distribution of carbon−oxygen bond lengths in (A) neutral aliphatic hydroxyl moieties, (B) deprotonated aliphatic hydroxyl moieties, (C) neutral aromatic hydroxyl moieties, and (D) deprotonated aromatic hydroxyl moieties.

interplanar separation of ca. 3.59 Å. The packing of supramolecular adducts is further extended into sheets through centrosymmetric C−H···N dimers formed between neighboring **4cyphe** molecules (Figure 3B).

(4-Cyanophenol)$_2$·1,2-Bis(4-pyridyl)ethane, 7. In the crystal structure of **7**, there exist 2:1 supramolecular adducts that are sustained by supramolecular heterosynthon **I** (*D*: 2.698(4) Å) (Figure 3C). These adducts interact via C−H···O dimers along the *c*-axis, thereby forming 1D chains that are subsequently interconnected via weak C−H···N bonds, thereby generating supramolecular sheets.

(4-Cyanophenol)$_2$·*trans*-1,2-Bis(4-pyridyl)ethylene, 8. The crystal structure of **8** is reminiscent of **6**. It is composed of 2:1 centrosymmetric supramolecular adducts sustained by **I** (*D*: 2.714(4) Å). These adducts are stabilized by $\pi-\pi$ interactions (3.66 Å) parallel to the *b*-axis and further extend into supramolecular sheets through centrosymmetric C−H···N dimers that occur between neighboring **4cyphe** molecules (Figure 4A).

4-Cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene (Figure 4B), **9**, exhibits two concomitant[74] polymorphs: monoclinic form I (**9a**) and triclinic form II (**9b**). The asymmetric unit of **9a** consists of two **4cyphe** molecules and two **bipyete** molecules. Interestingly, the assembly of the two components results in two distinct supramolecular entities. The first is a noncentrosymmetric 2:1 adduct of (**4cyphe**)$_2$·**bipyete** sustained by **I** (D_1, 2.721(3) Å; D_2, 2.669(4) Å). The second is a non-hydrogen-bonded **bipyete** that is sandwiched by the 2:1 adducts. The free and hydrogen-bonded **bipyete** molecules alternate through $\pi-\pi$ stacking parallel to the *b*-axis. The stacking involves face-to-face aromatic interactions with interplanar separations of ca. 3.61 Å, which makes the unsaturated moieties of **bipyete** oriented in a manner that should facilitate photodimerization.[18]

The asymmetric unit of **9b** also consists of two **4cyphe** molecules and two **bipyete** molecules. However, unlike **9a**, the components form two crystallographically independent 1:1 supramolecular adducts sustained by **I** (D_1, 2.689(4) Å; D_2, 2.717(4) Å). The 1:1 adducts stack in face-to-face fashion along the *a*-axis, and the distance between the adjacent **bipyete** molecules is ca. 3.48 Å. The columns of the stacked adducts expand into supramolecular sheets through centrosymmetric C−H···N dimers formed between adjacent

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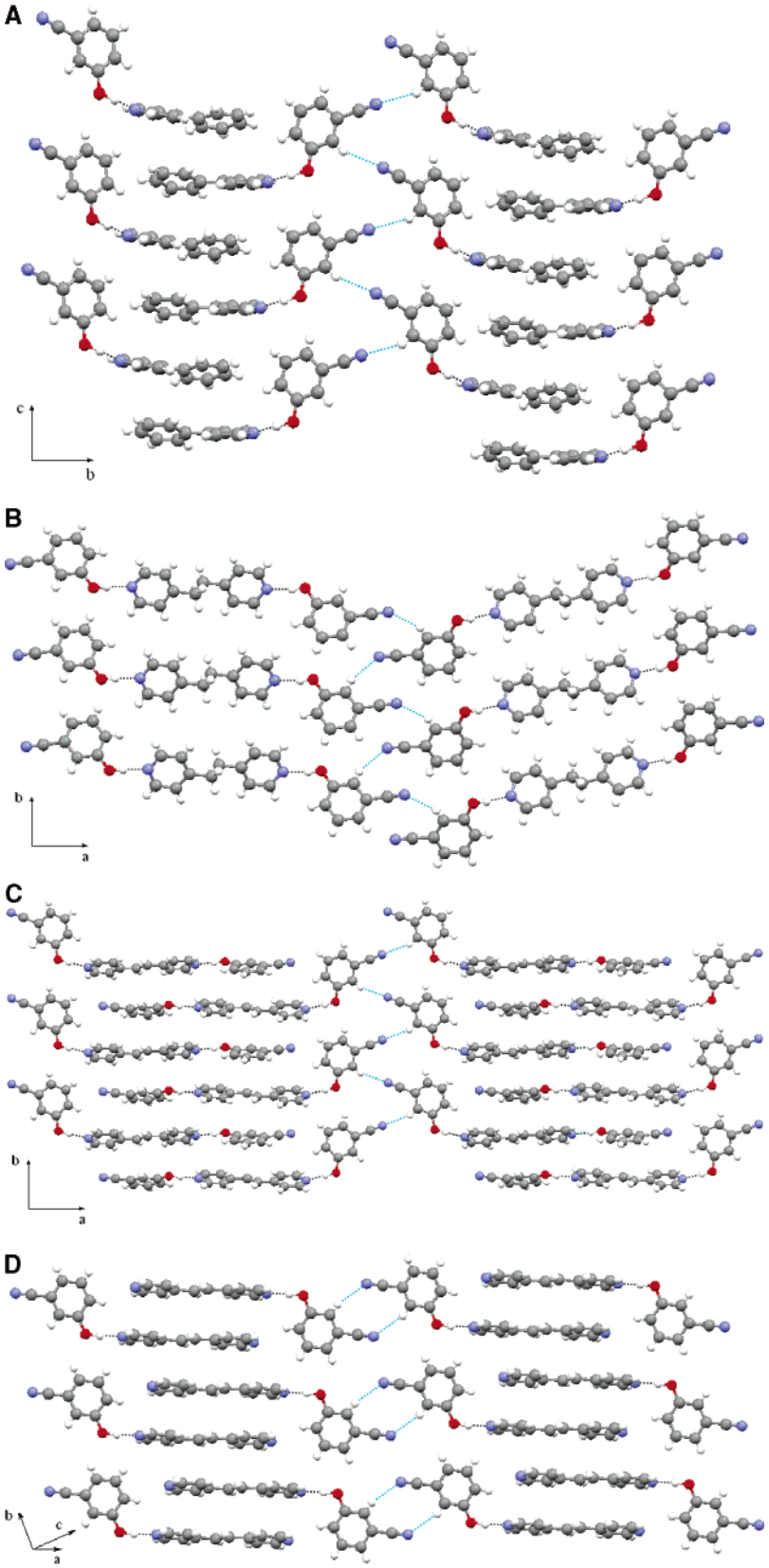

Figure 2. Illustrations of the crystal packing in cocrystals composed of 3-cyanophenols and pyridines. (A) 3-Cyanophenol·4-phenylpyridine, **1**: 1:1 supramolecular adducts in a columnar arrangement parallel to the *c*-axis. (B) (3-Cyanophenol)$_2$·1,2-bis-(4-pyridyl)ethane, **2**: centrosymmetric 2:1 adducts that form supramolecular sheets. (C) (3-Cyanophenol)$_2$·*trans*-1,2-bis(4-pyridyl)ethylene, **3**: 2:1 noncentrosymmetric supramolecular adducts engage in face-to-face stacking with adjacent adducts. (D) 3-Cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene, **4**: 1:1 centrosymmetric supramolecular adducts sustained by **I**.

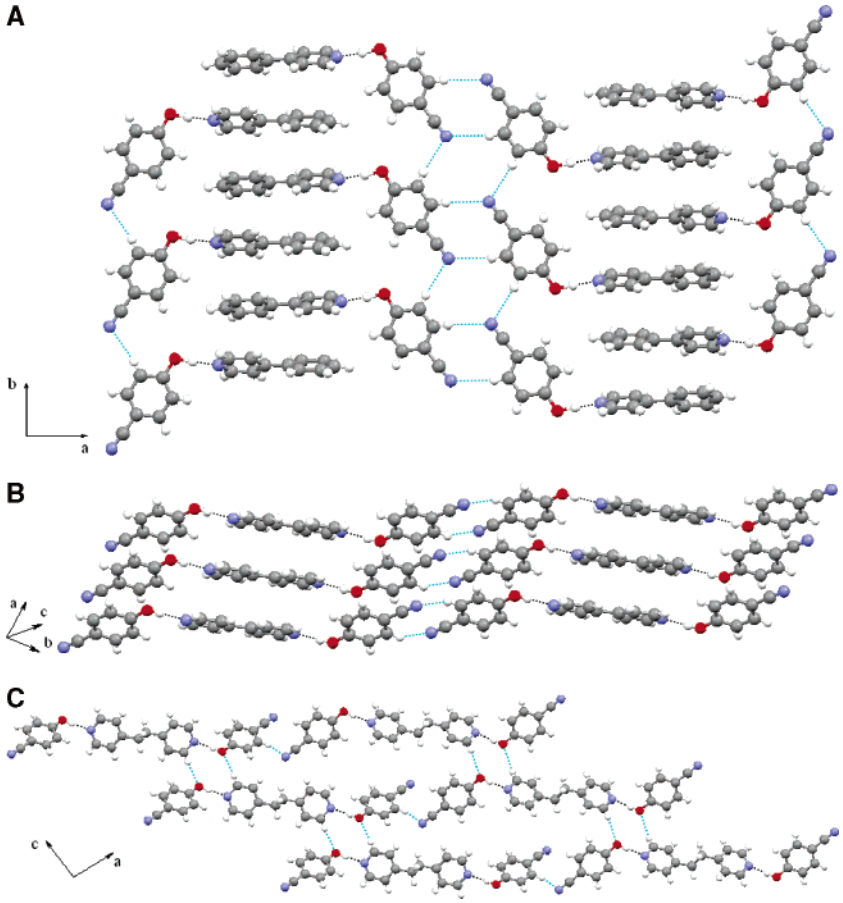

Figure 3. Illustrations of the crystal packing in cocrystals composed of 4-cyanophenols and pyridines. (A) 4-Cyanophenol·4-phenylpyridine, **5**: 1:1 supramolecular adducts sustained by **I** that pack as sheets. (B) (4-Cyanophenol)$_2$·4,4′-bipyridine, **6**: 2:1 centrosymmetric supramolecular adducts sustained by **I** that extend into sheets. (C) (4-Cyanophenol)$_2$·1,2-bis(4-pyridyl)ethane, **7**: 2:1 supramolecular adducts that are sustained by **I**.

4cyphe molecules (Figure 4C). The similarity of crystal packing in **9a** and **9b** manifests itself in the simulated powder diffraction patterns (see Supporting Information).

(3-Cyanopyridine)$_2$·4,4′-Biphenol, 10. In the crystal structure of **10**, a 2:1 centrosymmetric supramolecular adduct is observed, and it is sustained by **I** (*D*: 2.765(3) Å). The C−O distance is 1.381(3) Å, and the C−N−C angle of the hydrogen-bonded **3cypy** ring is 117.79(2)°, suggesting that these are neutral O−H···N hydrogen bonds. (Figure 5A).

(4-Cyanopyridine)$_2$·Resorcinol, 11. The components of **11** assemble in such a manner that they form 2:1 discrete adducts sustained by **I** (D_1, 2.856(2) Å; D_2, 2.763(2) Å). These discrete 2:1 entities are extended into 1D chains via weak C−H···O and C−H···N interactions along the *c*-axis. The translation related 1D chains are then packed side by side through weak C−H···O interactions to form supramolecular sheets (Figure 5B).

(4-Cyanopyridine)$_2$·4,4′-Biphenol, 12. As communicated recently,[75] **12** exhibits two monoclinic polymorphs, form I (**12a**) and form II (**12b**). The asymmetric unit of **12a** consists of half a **bphe** molecule and one **4cypy** molecule which form 2:1 centrosymmetric supramolecular adducts sustained by **I** (*D*: 2.733(4) Å). The 2:1 adducts are connected through C−H···N dimers that generate 1D chains. The packing is further stabilized by C−H···O and C−H···N interaction between chains which are aligned side by side parallel to the *b*-axis (Figure 5C).

The asymmetric unit of **12b** consists of four **4cypy** molecules and two **bphe** molecules. The **bphe** molecules are nonplanar and form two crystallographically independent 2:1 adducts with **4cypy** which are sustained by **I** (D_1, 2.693-(3) Å; D_2, 2.789(4) Å; D_3, 2.838(3) Å; D_4, 2.766(3) Å). The adjacent 2:1 adducts are connected via noncentrosymmetric C−H···N dimers forming 1D chains. The adjacent chains are packed side by side along the *a*-axis, thereby generating a 2D corrugated sheet (Figure 5D).

(4-Cyanopyridine)$_3$·phloroglucinol, **13**, consists of discrete 3:1 entities sustained by **I** (D_1, 2.721(4) Å; D_2, 2.784-(3) Å; D_3, 2.795(3) Å) (Figure 5E). In this structure, rather than adopting 3-fold geometry,[67] the **phlgl** molecules exhibit convergent orientations, thereby allowing two of the **4cypy** molecules to interact via face-to-face stacking (ca. 3.84 Å).

Bicalutamide·4,4′-bipyridine, **14**, reveals discrete 2:2 centrosymmetric supramolecular adducts sustained by the targeted heterosynthon **I** (O−H···N$_{arom}$) and the N−H···N$_{arom}$

(75) Bis, J. A.; Vishweshar, P.; Middleton, R.; Zaworotko, M. J. *Cryst. Growth Des.* **2006**, *6* (4), 1048−1053.

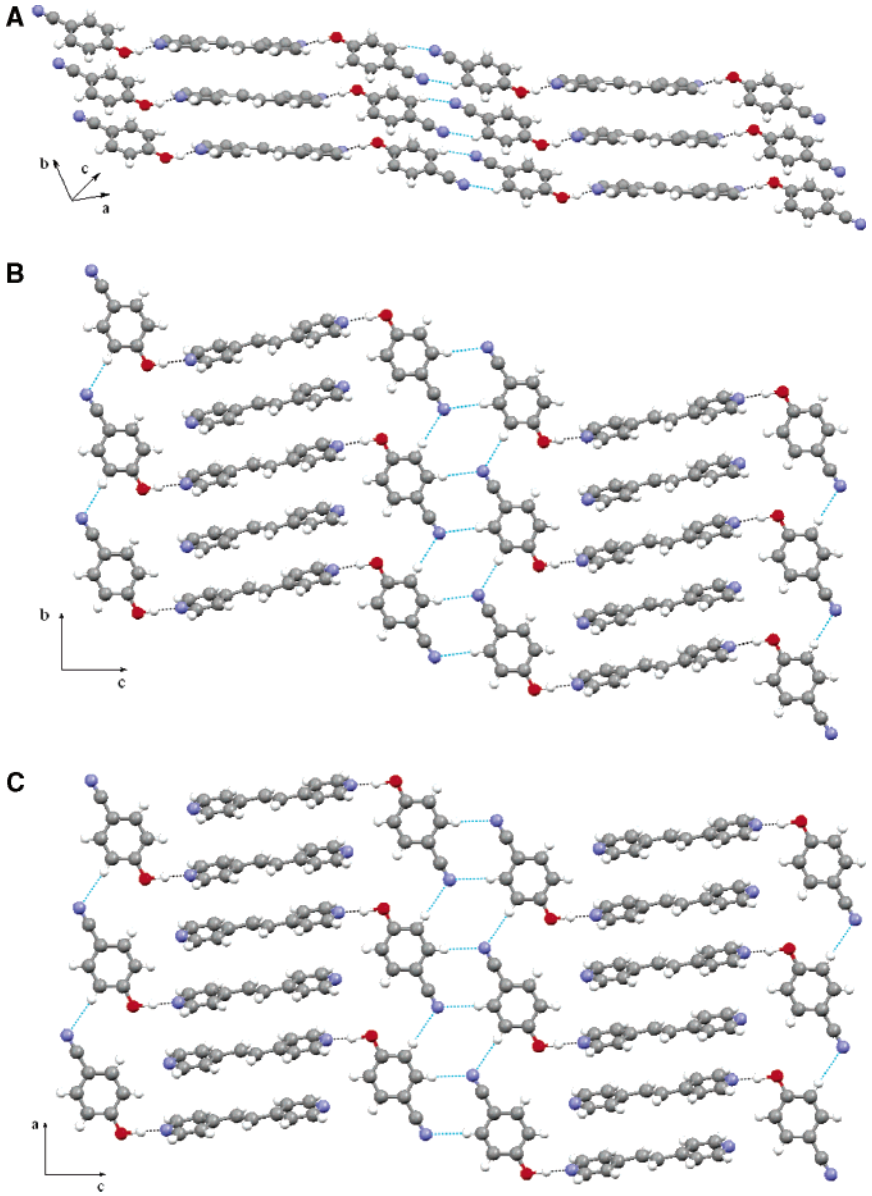

Figure 4. Illustrations of the crystal packing in cocrystals composed of 4-cyanophenol and *trans*-1,2-bis(4-pyridyl)ethylene. (A) (4-Cyanophenol)$_2$·*trans*-1,2-bis(4-pyridyl)ethylene, **8**: 2:1 centrosymmetric supramolecular adducts sustained by **I**. (B) 4-Cyanophenol·*trans*-1,2-bis(4-pyridyl)ethylene, **9a** (form I): noncentrosymmetric 2:1 supramolecular adducts sustained by **I** that engage in $\pi-\pi$ interactions with *trans*-1,2-bis(4-pyridyl)ethylene molecules. (C) **9b** (form II): 1:1 supramolecular adducts sustained by **I** that stack in face-to-face fashion parallel to the *a*-axis.

heterosynthon. The O−H···N$_{arom}$ hydrogen bond distance is 2.759(5) Å, which corresponds to the average length of **I**, Figure 6. The distance of the second hydrogen bond, N−H···N$_{arom}$, is 3.499(7) Å, which is relatively long in the context of N−H···N$_{arom}$ interactions.[73] Each bicalutamide molecule has both ends folded over one another, creating a horseshoe-like structure similar to that seen in form 1 of pure bicalutamide.[76]

Bicalutamide·*trans*-1,2-bis(4-pyridyl)ethylene, **15**, is similar to **14**. The bicalutamide and **bipyete** molecules interact via heterosynthon **I** (*D*: 2.811(3) Å). The adjacent aggregates are related by a center of inversion and form 2:2 supramolecular adducts via N−H···N$_{arom}$ bonds (*D*: 3.119-(3)Å). $\pi-\pi$ stacking occurrs between the **bipyete** molecules (ca. 3.76 Å, Figure 7) along the *a*-axis, thereby forming 1D columns of 2:2 adducts. The columns are related by translation and interconnected by weak C−H···N≡C interactions, which affords layers of stacks.

In summary, the crystal structures reported herein reveal that supramolecular heterosynthon **I** persists in all 17 cocrystals and therefore **I** is unaffected by the presence of a CN moiety. This observation strongly suggests that the O−H···N hydrogen bond, **I**, is favored over the competing O−H···NC hydrogen bond, **II**. Such a conclusion is also supported by the failed cocrystallizations, i.e., attempts to

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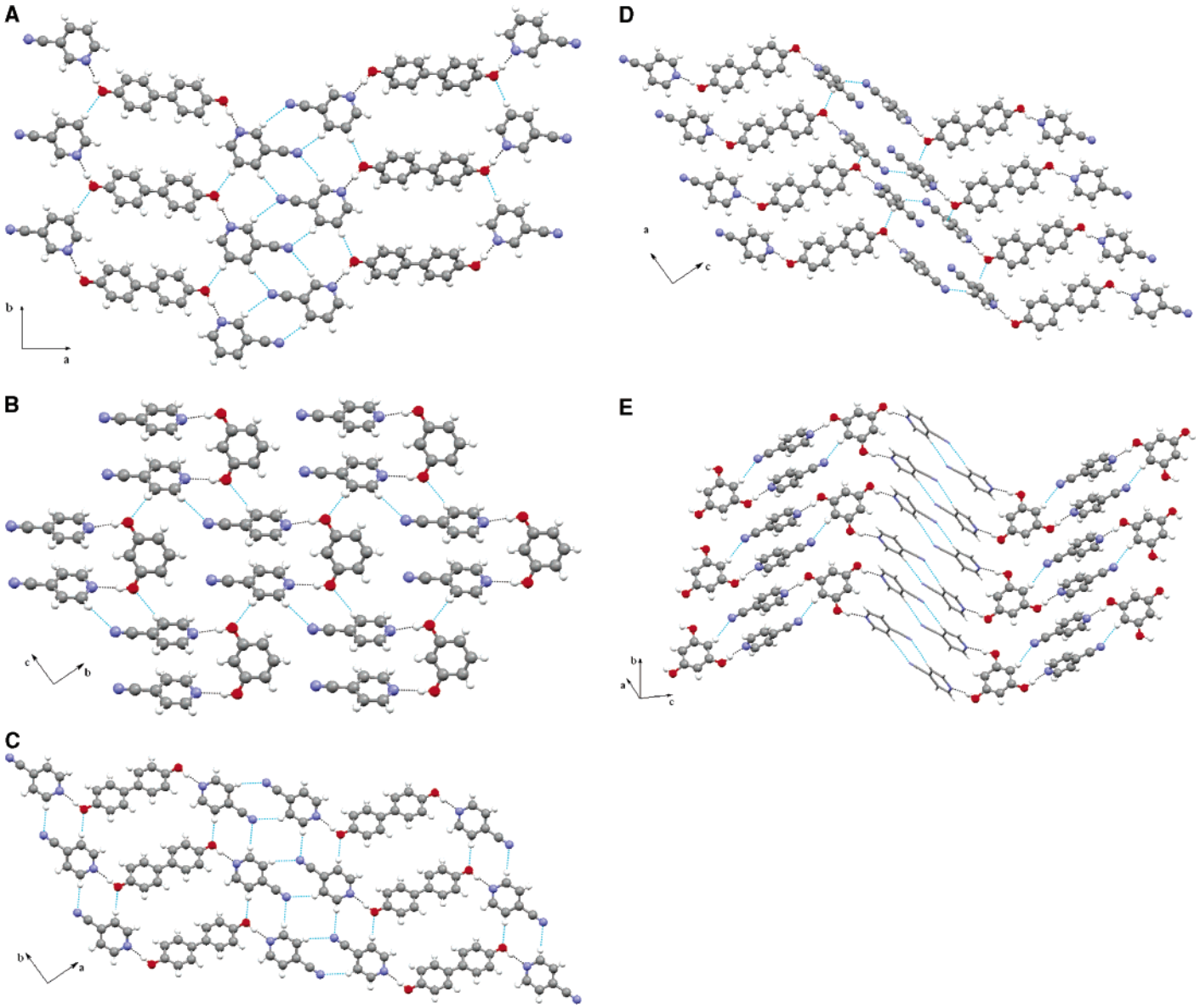

Figure 5. Illustrations of the crystal packing in cocrystals composed of cyanopyridines and phenols: (A) (3-Cyanopyridine)$_2$·4,4′-biphenol, **10**: 2:1 centrosymmetric adducts sustained by **I**. (B) (4-Cyanopyridine)$_2$·resorcinol, **11**: 2:1 adducts sustained by **I** extended into 1D chains via weak C−H···O and C−H···N interactions. (C) (4-Cyanopyridine)$_2$·4,4′-biphenol, **12a** (form I): 2:1 centrosymmetric adducts sustained by **I** connected through C−H···N dimers that thereby generate chains. (D) **12b** (form II): 2:1 adducts sustained by **I** and connected via noncentrosymmetric C−H···N dimers. (E) (4-Cyanopyridine)$_3$·phloroglucinol, **13**: 3:1 supramolecular adducts sustained by **I** with **4cypy** molecules interacting via face-to-face stacking.

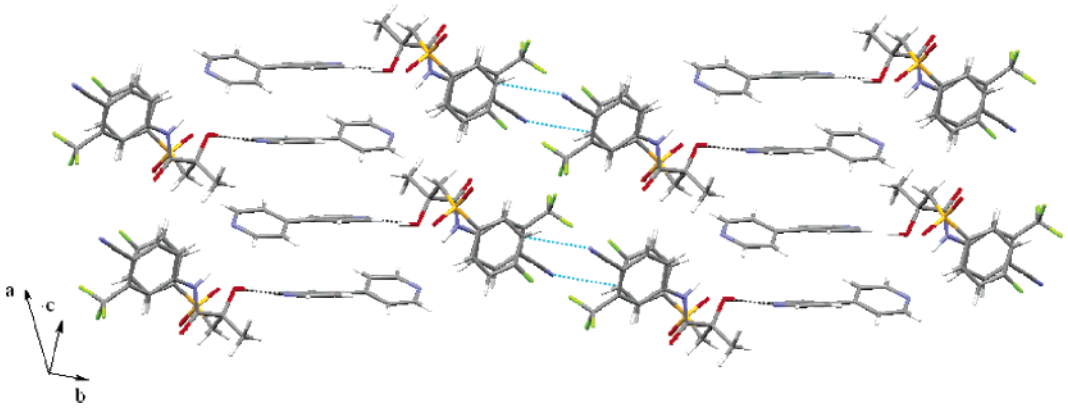

Figure 6. Bicalutamide·4,4′-bipyridine: 2:2 centrosymmetric supramolecular adducts sustained by **I** (O−H···Narom) and N−H···N_{arom} supramolecular heterosynthons.

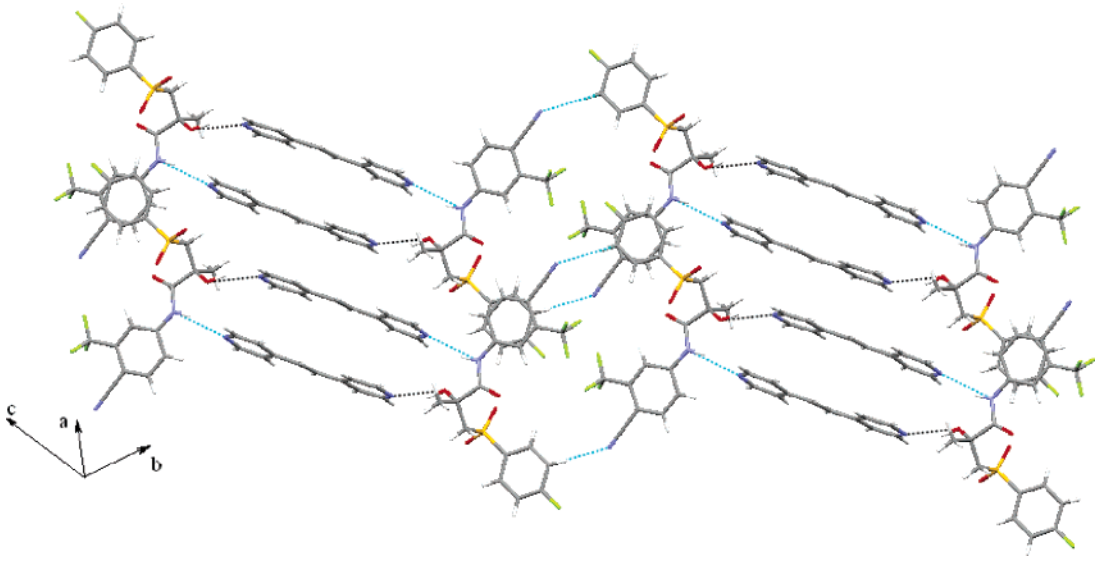

Figure 7. Bicalutamide·*trans*-1,2-bis(4-pyridyl)ethylene: 2:2 supramolecular adducts sustained by N−H···N_{arom} supramolecular heterosynthons and $\pi-\pi$ stacking between the **bipyete** molecules.

cocrystallize **3hypy** and **5hyquin** with CN-containing compounds **cynaphth**, **m-cyben**, and **p-cyben**. These "negative" results can be rationalized because the existence of OH/N_{arom} moieties in the molecular structures of **3hypy** and **5hyquin** facilitates single-component crystals over cocrystals.

The unsuccessful cocrystallizations of **hexdec** with **3cypy** and **4cypy** are most likely associated with the existence of the hydrophobic chain in **hexdec**. Indeed, a CSD analysis of the 135 structures that exhibit **I** (Table 5) reveals that to date there are no examples of cocrystals that are formed between cocrystal formers that contain long chain aliphatic groups.

3.3. Solid-State Methodologies for Preparation of Cocrystals. The 17 cocrystals obtained via solvent evaporation were also investigated in the context of their accessibility via other methods, i.e., dry grinding, solvent-drop grinding (using the same solvent that was used successfully for solvent evaporation except for **14** in which ethyl acetate was used for grinding), and melting/cooling. With regard to the stoichiometry and the crystal form, cocrystals **1**, **2**, **5**, **6**, **7**, **10**, **11**, **13**, and **15** were reproduced cleanly and in high yield using the aforementioned procedures. Cocrystal **14** was only produced with solvent-drop grinding. However, cocrystals **3**, **4**, **8**, and **9**, although also accessible via solid-state approaches, were contaminated by polymorphs, solvates, or cocrystals with different stoichiometry. For instance, 3-cyanophenol and *trans*-1,2-bis(4-pyridyl)ethylene form cocrystals with 2:1 stoichiometry (**3**) and with 1:1 stoichiometry (**4**). Dry grinding or melting/cooling the cocrystal formers in a 2:1 ratio afforded a mixture of **3** and **4**, while solvent-drop grinding of a 1:1 mixture of the cocrystal formers in acetone and ethyl acetate afforded only **3**. Dry grinding, solvent-drop grinding, and melting the cocrystal formers in a 1:1 ratio afforded mixtures of **3** and **4**.

4-Cyanophenol and *trans*-1,2-bis(4-pyridyl)ethylene form three cocrystals: one with 2:1 stoichiometry (**8**), and two polymorphs with 1:1 stoichiometry (form I, **9a**, and form II, **9b**). Dry grinding, solvent-drop grinding, and melting/cooling the cocrystal formers in a 2:1 ratio affords a mixture of **8** and at least one of the 1:1 cocrystals (**9**). Similarly, solid-state experiments involving the cocrystal formers in a 1:1 ratio afforded mixtures of **8** and **9**.

(4cypy)$_2$·bphe (12) was found to exist in two polymorphic forms. While solution crystallization afforded concomitant polymorphs form I (**12a**) and form II (**12b**), both dry and solvent drop grinding experiments resulted exclusively in form II.

3.4. Solvent-Drop Grind Screen for Polymorphs. It has recently been demonstrated that solvent-drop grinding can invoke polymorphic transformations.[60,63,77] A search for other crystal forms of cocrystals **1**−**15** was effected by solvent-drop grinding of cocrystal formers involving seven solvents of different polarity: cyclohexane, toluene, chloroform, ethyl acetate, methanol, DMSO, and water. As determined by IR spectroscopy and PXRD, only one form was isolated for cocrystals **1**-**8**, **10**, **11**, **13**, **14**, and **15**, whereas two polymorphic forms were isolated for cocrystals **9** and **12**. Therefore, this series of solvent-drop grinding experiments tended to mirror the cocrystals that were obtained via slow evaporation. However, there were a few differences. In particular, it was observed that the use of DMSO in solvent-drop grinding can lead to different products. For example, while solvent-drop grinding of a 1:1 ratio of **3cyphe** and **bipyete** with cyclohexane, toluene, chloroform, ethyl acetate, methanol, and water resulted in mixtures of **3** and **4**, it was observed that the DMSO afforded pure **4**. Similarly, solvent-drop grinding of **4cyphe** and **bipyete** in a 2:1 ratio afforded mixtures of **8** and **9** except for DMSO, which afforded **8** exclusively. Furthermore, DMSO solvent-drop grinding of **4cypy** and **bphe** afforded a DMSO solvate of 4,4′-biphenol.

In summary, the utilization of solid-state cocrystallization methods with **1**−**15** indicates that such methods represent viable means for supramolecular synthesis of cocrystals. Although the role of a solvent in the nucleation process is not well understood, it is clear that it leads to variations in which crystal form is isolated. Nevertheless, the results obtained herein suggest that it will be possible in most cases to find experimental conditions under which a specific cocrystal composition will be favored. In the context of cocrystals that exhibit variable stoichiometry or polymorphs, the solvent-drop grinding approach is not only facile and clean, it affords a degree of control over the final product.

4. Conclusions

CSD surveys have indicated that supramolecular heterosynthons **I** and **II** are both favored over the related supramolecular homosynthon **III**. However there is insufficient archival data with respect to the hierarchy of **I**−**III** when OH, N_{arom}, and CN moieties are present in the same crystal structure. The study reported herein utilizes a series of cocrystals to demonstrate that **I** persists even in the presence of a CN moiety. **I** also persists in the polymorphic forms of cocrystals **9** and **12**. This observation is consistent with the supramolecular heterosynthon persistency exhibited by the 11 polymorphic cocrystals that have been structurally characterized and are archived in the CSD.[78] The robustness of **I** was also confirmed by experiments involving solid-state cocrystallization techniques, such as grinding, solvent-drop grinding, and melting. Thus, our data indicates that the relative ranking of the supramolecular synthons is as follows: **I** > **II** > **III**. The hydrogen bond lengths of **I** in all cocrystals correspond to the expected values of a typical O−H···N_{arom} interaction (Table 4), and the structural parameters (C−O lengths and C−N−C angles) of the ancillary groups suggest a neutral character of **I**. The supramolecular chemistry of **I** can also be predicted to a certain extent. Depending on the geometrical distribution and the ratio of the OH and N_{arom} moieties, the formation of **I** leads to 1:1 or 1:2 discrete supramolecular entities, in which CN moieties further extend the discrete structures into 1D chains or 2D sheets sustained by weak C−H···NC interactions.

That cocrystals can be afforded with little or no solvent via solid-state synthesis could be important in the context of green chemistry since cocrystals could be formed between reactive cocrystal formers by solvent-drop grinding. That **I** sustains all 17 cocrystals suggests that **I** is indeed particularly suitable for crystal engineering of new cocrystals involving these moieties. Our findings also provide a perspective on the role that crystal engineering can play in cocrystal design and vice versa. These are relevant issues given the physicochemical implications of cocrystal formation to the pharmaceutical industry where the need to develop a crystal form of an API with optimal solubility and stability is of such great importance.[10,14] In the 1960s McCrone suggested that the number of forms known for a compound is proportional to the time and energy spent in research on that compound.[79] Whereas the generality of this statement in the context of polymorphs is debatable, it seems that cocrystals will be particularly amenable to following "McCrone's rule".

Acknowledgment. We gratefully acknowledge Transform Pharma for financial support of this research.

Supporting Information Available: Crystallographic information (.cif) and DSC, SDG, IR, and PXRD results for **1**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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