

Do Polymorphic Compounds Make Good Cocrystallizing Agents? A Structural Case Study that Demonstrates the Importance of Synthons Flexibility

Christer B. Aakeröy,^{*,†} Alicia M. Beatty,[‡] Brian A. Helfrich,[†] and Mark Nieuwenhuyzen[§]

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506,
Department of Chemistry and Biochemistry, University of Notre Dame,
Notre Dame, Indiana 46556 and School of Chemistry, The Queen's University of Belfast,
Belfast BT9 5AG, Northern Ireland

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Ⓜ This paper contains enhanced objects available on the Internet at <http://pubs.acs.org/crystal>.

ABSTRACT: The ability of four polymorphic compounds, isonicotinamide (**1**), 2-amino-3-nitropyridine (**2**), 4-chlorobenzamide (**3**), and maleic hydrazide (**4**), to form molecular cocrystals has been examined in a systematic structural study. Compounds **1–3** participate in a wide variety of binary and ternary (in the case of **1**) cocrystals with aromatic or aliphatic compounds substituted with a multitude of functional groups. However, despite considerable efforts, it has not been possible to form any cocrystals with **4**. The reason for this may be due to the fact that even though there are three known polymorphs of **4**, they all contain the same hydrogen-bonding synthons. In contrast, the polymorphs of **1–3** display considerable synthon flexibility, e.g., different hydrogen bond interactions are present in polymorphs of the same compound. Because **1–3** can form robust synthons in a variety of ways, whereas **4** always engages in the same primary hydrogen bond interactions, it may explain why the former compounds are readily able to accommodate other molecules within the same lattice whereas there are no known cocrystals of **4**.

Introduction

The ability to change key physical properties, e.g., solubility, crystal morphology, mechanical stability, etc., of a specialty chemical while retaining its essential biophysical or molecular activity is of enormous commercial and fundamental interest. Classic examples of how this can be achieved are regularly demonstrated through the conversion of a pharmacologically active molecule into its chloride or nitrate salt.¹ Alternatively, many drugs are manufactured and processed as solvates, normally as a hydrate. Despite the fact that these two avenues can lead to materials that eventually become commercially viable, potentially useful drugs may never reach this point because they fail to meet one or more of the stringent standards required from the point of view of processing, storage, or bioavailability. Recent developments in solid state organic chemistry and crystal engineering² may furnish an alternative approach that can offer better control (and tunability) of fundamental physical properties of specialty chemicals.

If a crystalline material that contains both a pharmaceutically relevant molecule and a structure-directing (but biologically/environmentally passive) component can be rationally assembled through intermolecular synthesis, then the inherent activity of the drug molecule remains intact while the physical properties of the bulk material are modified. The efficient preparation of such cocrystals hinges on an a priori ability to identify reliable and versatile cocrystallizing agents (CAs) without having to resort to endless crystallization experiments.³

A good CA should be able to form intermolecular interactions with the target molecule that are more favorable than the homomeric interactions that exist between target...target or between CA...CA.⁴ The CA must also have the ability to "tolerate" the presence of a different molecular building block within the same crystalline lattice, which makes it seem reasonable to search for CAs among polymorphic compounds.⁵ Polymorphism means that a compound is found in more than one crystalline manifestation, which,⁶ in turn, indicates that such compounds display a degree of structural flexibility. In other words, the multidimensional potential energy surface that describes the thermodynamics governing the molecular recognition processes that eventually leads to crystal growth is likely to be rather shallow with many accessible local energy minima.

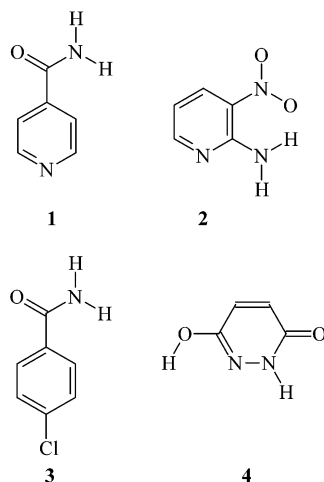
The hypothesis that polymorphic compounds are more likely to form cocrystals than are compounds that never display polymorphism is, at this stage, little more than a notion based upon empirical observations. However, from a practical perspective, it would be extremely useful to have access to reliable guidelines for how we might focus and target a search for reliable CAs for a specific family of compounds. Furthermore, if we encounter cases that do not follow our initial hypothesis, it would be equally important to be able to rationalize the results in the context of intermolecular forces and molecular recognition. To address some of these challenges, we herein report our results from a structural study on three polymorphic compounds, isonicotinamide (**1**), 2-amino-5-nitropyrimidine (**2**), 4-chlorobenzamide (**3**), and maleic hydrazide (**4**) and several cocrystals thereof. The reason for selecting these four compounds (apart from the fact that they are all polymorphic) is that they are all potentially capable of engaging in

[†] Kansas State University.

[‡] University of Notre Dame.

[§] The Queen's University of Belfast.

Scheme 1. Four Polymorphic Molecules Capable of Forming a Variety of Hydrogen-Bonded Synthons^a



^a isoNicotinamide, **1**; 2-amino-3-nitropyridine, **2**; 4-chlorobenzamide, **3**; and maleic hydrazide, **4**.

several well-defined and robust intermolecular hydrogen bond motifs (Scheme 1).^{7,8}

Experimental Section

Crystal Growth and Polymorphism of 1. Upon recrystallization of **1** from nitrobenzene or nitromethane, colorless, rodlike crystals, **1a**, were formed. When **1** was recrystallized from a wide variety of other solvents, e.g., ethanol, water, tetrahydrofuran (THF), dioxane, etc., colorless platelike crystals, **1b**, were obtained. No other crystalline forms have been obtained either by slow evaporation or by liquid/vapor diffusion methods. Sublimation under reduced pressure yields crystals with a structure corresponding to that of **1a**.

Crystal Growth and Polymorphism of 2. Compound **2** is known to exist in three different polymorphic forms. Form I **2a** appears as yellow needles.⁹ Form II **2b** can be obtained by recrystallization from ethanol at ambient temperature (yellow, diamond-like crystals).¹⁰ Form III **2c** was obtained when **2** was recrystallized from ethanol at ambient conditions in the presence of fumaric acid (yellow, thick plates).¹⁰ No other polymorphs have been reported to date.

Crystal Growth and Polymorphism of 4. Compound **4** is known to exist in three different crystalline forms: **4a** (form I) is triclinic,¹¹ **4b** (form II) is monoclinic,¹² and **4c** (form III), another monoclinic structure, can be obtained by slowly cooling a solution of **4** in acetic acid.¹³

Cocrystals of 1.¹⁴ (a) **2-Hexenoic Acid/1 (1:1)**, **11**. Compound **1** (0.050 g; 0.41 mmol) dissolved in ethanol (3 mL) was mixed with 2-hexenoic acid (0.047 g; 0.41 mmol) dissolved in ethanol (3 mL) in a small test tube. After 48 h of slow evaporation at room temperature, colorless, needlelike crystals formed on the side of the test tube (mp 110–112 °C).

(b) **4-Nitrobenzoic Acid/1 (1:1)**, **12**. Compound **1** (0.050 g; 0.41 mmol) dissolved in ethanol (5 mL) was mixed with 4-nitrobenzoic acid (0.068 g; 0.41 mmol) dissolved in ethanol (5 mL) in a small test tube. After 48 h of slow evaporation at room temperature, rectangular, colorless crystals formed on the side of the test tube (mp 181–183 °C).

(c) **3,5-Dinitrobenzoic Acid/1/4-Methylbenzoic Acid (1:1:1)**, **13**. Equimolar quantities of **1** (0.050 g; 0.41 mmol), 3,5-dinitrobenzoic acid (0.086 g; 0.41 mmol), and 4-methylbenzoic acid (0.056 g; 0.41 mmol) were dissolved separately in ethanol (3 mL) and mixed together in a small test tube. After 48 h of slow evaporation at room temperature, pale yellow, irregular prisms were formed on the side of the test tube (mp 141–143 °C).

Cocrystal of 2. (a) 2-Amino-5-nitropyrimidine/2 (1:1), **21**. 2-Amino-5-nitropyrimidine (0.250 g; 1.68 mmol) and **2** (0.254 g; 1.81 mmol) were dissolved together in hot ethanol (50 mL). Slow evaporation at ambient conditions yielded yellow, needlelike crystals that consistently grew in clumps from one point (mp 178–181 °C).

Cocrystals of 3. (a) 3,5-Dinitrobenzoic Acid/3 (1:1), **31**. Compound **3** (0.064 g, 0.41 mmol) and 3,5-dinitrobenzoic acid (0.086 g; 0.41 mmol) were dissolved together in hot methanol (8 mL). Slow evaporation at ambient conditions yielded colorless, platelike crystals (mp 154–156 °C).

(b) **3-Dimethylaminobenzoic Acid/3 (1:1)**, **32**. Compound **3** (0.064 g, 0.41 mmol) and 3-dimethylaminobenzoic acid (0.068 g, 0.41 mmol) were dissolved together in hot ethanol (8 mL). Slow evaporation at ambient conditions yielded pale yellow, irregular prism crystals (mp 118–121 °C).

(c) **Fumaric Acid/3 (1:1)**, **33**. Compound **3** (0.065 g, 0.42 mmol) and fumaric acid (0.024 g, 0.21 mmol) were dissolved together in hot ethanol (8 mL). Slow evaporation at ambient conditions yielded colorless, block crystals (mp 174–178 °C). Crystals of individual components could also be found and were confirmed by single-crystal X-ray diffraction.

Cocrystals of 4. Despite numerous attempts (about 25 different compounds) at forming cocrystals with **4** and a variety of aromatic (including heterocyclic) or aliphatic compounds with different functional groups, e.g., carboxylic acids, amides, oximes, etc., we were only ever able to isolate unreacted starting materials. Crystal growth experiments involved slow evaporation and liquid/vapor diffusion using a range of solvents, e.g., MeOH, EtOH, MeCN, etc. Essentially, **4** was put through the same cycle of experiments as were **1–3**.

Single-Crystal X-ray Diffraction. Single crystals were placed in paratone, mounted on a glass pin, and transferred into the cold stream of the diffractometer. Crystal data for **11–13** were collected and integrated using a Bruker SMART 1000 system with graphite monochromated Mo K α ($\lambda = 0.71073$ Å) radiation at 173 K. Crystal data for **21** were collected at 301 K and for **31–33** at 203 K. Crystal data for **1a,b** were collected using a Siemens P4 four circle diffractometer with graphite monochromated Mo K α radiation at ca. 150 K in a dinitrogen stream. Crystal stability was monitored by measuring standard reflections every 100 reflections, and there were no significant variations ($<\pm 1\%$). ψ -Scans were employed for data collection, and Lorentz and polarization corrections were applied. Each of the structures was solved by direct methods, using SHELXS-97 and refined using SHELXL-97. Nonhydrogen atoms were found by successive least-squares refinement on F^2 and refined with anisotropic parameters. All hydrogen atoms, except for those on the methyl group in **13**, were located on the difference map. A riding model with fixed thermal parameters ($[u_{ij} = 1.2U_{ij}(\text{eq})]$ for the atom that the hydrogen atoms are riding) was applied, except for **32**, where the methyl hydrogen atoms were calculated. Crystallographic data for **1a,b**, **11–13**, **21**, and **31–33** can be found in Table 1.

Results

Crystal Structure of 1 (Form I). Form I of **1** is monoclinic with one molecule in the asymmetric unit. The molecular geometry does not display any unexpected behavior, and the amide moiety is slightly twisted out of the plane of the aromatic ring (30.5°) (Figure 1).

The amide moieties in **1a** generate a slight variation on the extended ribbonlike motif, which occurs frequently in primary amides. There is a self-complementary N–H $\cdots$ O head-to-head synthon between adjacent molecules, and neighboring dimers are connected into an infinite assembly through symmetry-related N–H $\cdots$ O hydrogen bonds aligned perpendicular to the long axis of the dimers (Figure 2).

Table 1. Crystallographic Data for 1a,b, 11–13, 21, and 31–33

compd	1a	1b	11	12	13
formula	C ₆ H ₆ N ₂ O	C ₆ H ₆ N ₂ O	C ₁₂ H ₁₆ N ₂ O ₃	C ₁₃ H ₁₁ N ₃ O ₅	C ₂₁ H ₁₈ N ₄ O ₉
FW	122.13	122.13	236.27	289.25	470.39
temp (K)	173(2)	173(2)	173(2)	173(2)	173(2)
cryst syst	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
space group, Z	P2 ₁ /c, 4	P2 ₁ /c, 4	I2/a, 8	I2/a, 8	P $\bar{1}$, 2
a (Å)	10.176(1)	15.735(3)	20.445(4)	20.512(4)	7.763(1)
b (Å)	5.7319(6)	7.998(2)	5.2309(9)	5.1675(6)	8.722(1)
c (Å)	23.008(4)	9.885	23.008(4)	23.694(5)	15.743(2)
α (deg)					93.483(2)
β (deg)	98.042(3)	105.59(2)	96.981(3)	90.66(3)	98.981(3)
γ (deg)					93.913(7)
V (Å ³)	579.5(1)	1198.2(5)	2442.3(7)	2511.3(0)	1047.6(2)
density (g/cm ³)	1.400	1.354	1.285	1.530	1.491
M _(MoKα) (mm ⁻¹)	0.100	0.096	0.093	0.120	0.119
θ range	2.92–27.49	1.34–22.48	1.72–28.04	2.51–26.19	2.61–26.9
range h	–13 to 13	–16 to 16	–26 to 26	–26 to 26	–9 to 10
range k	0 to 7	–8 to 0	–6 to 6	–6 to 5	–11 to 11
range l	–13 to 0	0 to 10	–30 to 30	–30 to 31	–19 to 20
refl collected	1413	1680	8158	8293	7248
ind refl (R _{int})	1334 (0.0164)	1565 (0.0151)	2808 (0.1235)	2759 (0.0544)	2622 (0.0549)
data/restraints/params	1334/0/82	1565/0/163	2808/0/154	2759/0/190	4662/0/307
R/R _w ² (obs data)	0.0395/0.0985	0.0437/0.1185	0.0736/0.1794	0.0432/0.1097	0.0433/0.1052
R/R _w ² (all data)	0.0494/0.1050	0.0528/0.1258	0.1129/0.1969	0.0678/0.1200	0.0839/0.1209
$\Delta\rho_{\max/\min}$ (e Å ⁻³)	0.229/–0.218	0.179/–0.280	0.229/–0.388	0.315/–0.232	0.314/–0.199
compd	21	31	32	33	
formula	C ₉ H ₉ N ₇ O ₄	C ₁₄ H ₁₀ ClN ₃ O ₇	C ₁₆ H ₁₇ ClN ₂ O ₃	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₆	
FW	279.23	367.70	320.77	427.23	
temp (K)	301(2)	203(2)	203(2)	203(2)	
cryst syst	monoclinic	triclinic	triclinic	triclinic	
space group, Z	P2(1)/n, 4	P $\bar{1}$, 2	P $\bar{1}$, 2	P $\bar{1}$, 2	
a (Å)	11.786(3)	7.246(1)	7.173(1)	9.2674(8)	
b (Å)	5.161(1)	8.626(1)	8.369(2)	10.1386(9)	
c (Å)	19.975(5)	13.281(2)	12.997(3)	10.481(1)	
α (deg)		92.566(3)	88.638(4)	86.428(6)	
β (deg)	95.275(5)	101.875(3)	80.875(4)	72.174(6)	
γ (deg)		109.472(3)	77.463(4)	89.506(7)	
V (Å ³)	1210.0(5)	760.0(2)	752.0(3)	935.6(2)	
density (g/cm ³)	1.533	1.607	1.417	1.517	
M _(MoKα) (mm ⁻¹)	0.124	0.298	0.268	0.386	
θ range	1.93–28.36	2.52–28.14	1.59–28.28	2.05–28.25	
range h	–15 to 14	–9 to 9	–9 to 9	–12 to 12	
range k	–6 to 6	–11 to 11	–11 to 10	–13 to 13	
range l	–26 to 26	–16 to 17	–15 to 16	–13 to 13	
refl collected	10 429	5265	5256	6971	
ind refl (R _{int})	2757 (0.1056)	3375 (0.0358)	3371 (0.0309)	4128 (0.0291)	
data/restraints/params	2757/0/182	3375/0/227	3371/0/200	4128/0/254	
R/R _w ² (obs data)	0.0555/0.1433	0.0452/0.1021	0.0545/0.1277	0.0389/0.1003	
R/R _w ² (all data)	0.1112/0.1890	0.0724/0.1141	0.1014/0.1513	0.0546/0.1082	
$\Delta\rho_{\max/\min}$ (e Å ⁻³)	0.221/–0.304	0.301/–0.283	0.287/–0.320	0.361/–0.289	

Somewhat surprisingly, there are no prominent hydrogen bond interactions involving the pyridine nitrogen atom (Table 2). Although adjacent molecules are positioned tail-to-tail, the rings are not coplanar and the symmetry-related C...N distances are over 3.47 Å (Figure 3).

Crystal Structure of 1 (Form II). Form II of **1** is also monoclinic but with two molecules in the asymmetric unit. As in **1a**, there are no remarkable intra-

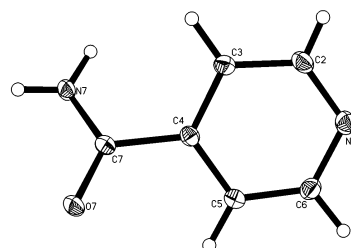


Figure 1. Thermal ellipsoids (30%) and numbering scheme in **1a**.

molecular features in either molecule, and the amide moiety is twisted out of the plane in each molecule (by 25.4 and 24.0°, respectively) (Figure 4).

In **1b**, the dimeric head-to-head motif has been abandoned in favor of an N–H(amide)···N(pyridine),

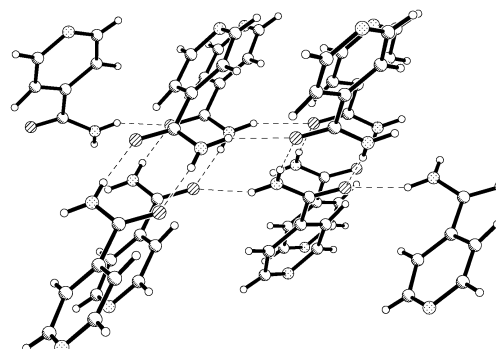


Figure 2. Dominating hydrogen bond interactions in **1a**.

Ⓢ A 3D rotatable image of **1a** in PDB format is available.

Table 2. Hydrogen Bond Geometries^a

Hydrogen Bonds for 1a (Å and °)				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(7)–H(72)···O(7)#1	0.89	2.09	2.9354(14)	157.9
N(7)–H(71)···O(7)#2	0.86	2.08	2.9366(16)	173.5
C(2)–H(2)···N(1)#3	0.88	2.63	3.4275(19)	151.1
C(6)–H(6)···N(1)#4	0.98	2.72	3.4790(19)	135.0

Hydrogen Bonds for 1b (Å and °)				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(7)–H(71)···N(1)#1	0.97	2.02	2.982(3)	171.4
N(7)–H(72)···O(7)#2	0.93	2.01	2.934(2)	170.4
N(17)–H(171)···N(11)#1	0.96	2.02	2.974(3)	168.7
N(17)–H(172)···O(17)#3	0.96	1.99	2.947(3)	174.0

Hydrogen Bonds for 11 (Å and °)			
D–H···A	d(H···A)	d(D···A)	<(DHA)
N(7)–H(72)···O(17)#1	2.09	2.952(2)	163.4
N(7)–H(71)···O(7)#2	2.02	2.8720(19)	169.3
O(18)–H(18)···N(1)	1.67	2.5768(19)	178.2

Hydrogen Bonds for 12 (Å and °)			
D–H···A	d(H···A)	d(D···A)	<(DHA)
N(7)–H(71)···O(7)#1	1.94	2.880(2)	168.0
N(7)–H(72)···O(10)#2	2.02	2.919(3)	160.9
O(11)–H(11)···N(1)	1.66	2.655(3)	169.2

Hydrogen Bonds for 13 (Å and °)			
D–H···A	d(H···A)	d(D···A)	<(DHA)
N(7)–H(71)···O(27)	1.93	2.886(2)	176.0
N(7)–H(72)···O(17)#1	2.09	2.995(2)	167.9
O(18)–H(18)···N(1)	1.69	2.5479(19)	159.8
O(28)–H(28)···O(7)	1.67	2.6423(18)	168.4

Hydrogen Bonds for 21 (Å and °)				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(2)–H(21)···N(11)	0.88	2.21	3.074(3)	169.8
N(2)–H(22)···O(2)#1	0.82	2.32	2.970(3)	136.3
N(12)–H(121)···N(1)	0.97	1.99	2.958(3)	178.9
N(12)–H(122)···N(13)#2	0.92	2.14	3.057(3)	173.3
N(2)–H(22)···O(2)	0.82	2.11	2.677(3)	126.7

Hydrogen Bonds for 31 (Å and °)				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(7)–H(72)···O(14)#1	0.95	2.31	2.890(2)	118.8
N(7)–H(71)···O(18)	0.97	2.01	2.967(2)	167.0
O(17)–H(17)···O(7)	1.05	1.50	2.531(2)	169.8

Hydrogen Bonds for 32 (Å and °)				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(7)–H(71)···O(18)	0.99	1.98	2.937(3)	164.6
N(7)–H(72)···O(18)#1	0.87	2.22	3.045(3)	156.4
O(17)–H(17)···O(7)	0.91	1.68	2.586(3)	172.9

Hydrogen Bonds for 33 (Å and °)				
D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(7)–H(71)···O(32)	0.88	2.10	2.957(2)	164.3
N(7)–H(72)···O(22)	0.81	2.12	2.930(2)	172.9
N(17)–H(171)···O(22)	0.89	2.08	2.942(2)	164.4
N(17)–H(172)···O(32)#1	0.81	2.23	3.027(2)	168.2
O(21)–H(21)···O(17)	0.85	1.71	2.565(2)	172.7
O(31)–H(31)···O(7)	0.80	1.73	2.518(2)	168.5

^a Symmetry transformations used to generate equivalent atoms. **1a**: #1, $x, -y + 1/2, z - 1/2$; #2, $-x, -y + 1, -z$; #3, $-x + 1, y + 1/2, -z - 1/2$; #4, $-x + 1, -y - 1, -z$. **1b**: #1, $x, y - 1, z$; #2, $x, -y + 1/2, z - 1/2$; #3, $x, -y - 1/2, z - 1/2$. **11**: #1, $-x - 1/2, y + 1, -z + 1$; #2, $-x, -y + 1, -z + 1$. **12**: #1, $-x, -y + 1, -z$; #2, $-x - 1/2, y - 1, -z$. **13**: #1, $x, y - 1, z$. **21**: #1, $-x + 1, -y, -z$; #2, $-x, -y + 2, -z$. **31**: #1, $-x + 1, -y + 4, -z + 1$. **32**: #1, $-x - 2, -y, -z + 1$. **33**: #1, $x + 1, y, z$.

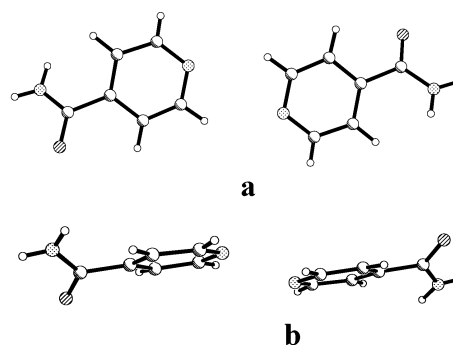


Figure 3. (a) Face-on view of the orientation of adjacent molecules in **1a**. Although the relative positions of the molecules indicate the existence of complementary C–H···N hydrogen bonds, the edge-on view (b) makes this less likely as the rings are not coplanar.

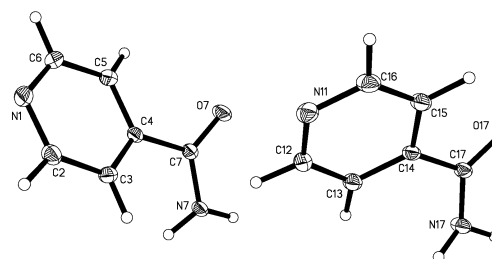


Figure 4. Thermal ellipsoids (30%) and numbering scheme in **1b**.

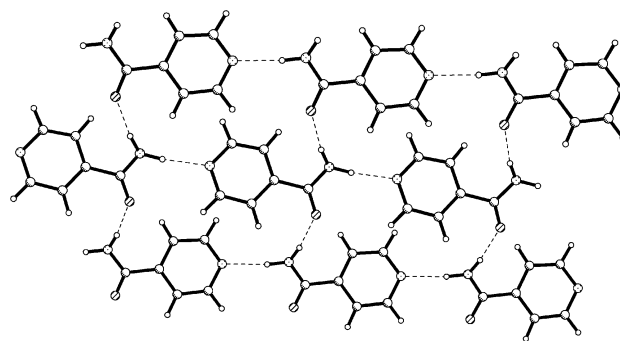


Figure 5. One of the two unique infinite 2D assemblies ribbons in **1b** (both networks have identical connectivity).

Ⓜ A 3D rotatable image of **1b** in PDB format is available.

head-to-tail, interaction and a catemeric N–H···O hydrogen bond; the direction of the catemer is almost perpendicular with respect to the chain generated by the amide···pyridine interaction (each asymmetric molecule gives rise to an independent assembly but with identical hydrogen bond connectivity) (Figure 5). We have not observed any phase changes between polymorphs even after an extended period of time (several years).

Crystal Structure of 2-Hexeneoic Acid/1 (1:1), 11. The crystal structure of **11** contains one molecule of the carboxylic acid and one molecule of **1**. These two building blocks are connected into a tetrameric supermolecule constructed from a dimeric, head-to-head amide···amide interaction plus two symmetry equivalent acid···pyridine interactions (Figure 6). The anti amide hydrogen atom forms a hydrogen bond with the

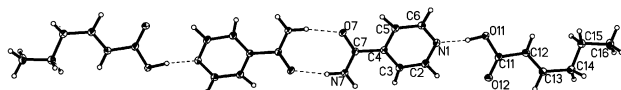


Figure 6. Thermal ellipsoids (30%) and numbering scheme in **11**.

Ⓜ A 3D rotatable image in PDB format is available.

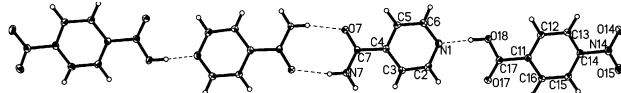


Figure 7. Thermal ellipsoids (30%) and numbering scheme in **12**.

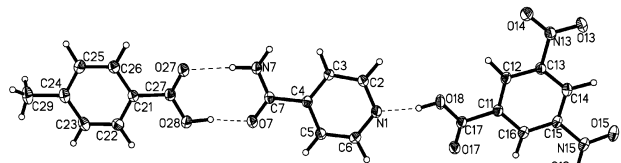


Figure 8. Thermal ellipsoids (30%), numbering scheme, and the complete ternary supermolecule in **13**.

Ⓜ A 3D rotatable image in PDB format is available.

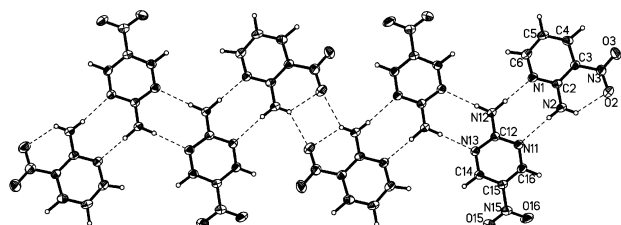


Figure 9. Extended hydrogen-bonded 1D network in **21**.

Ⓜ A 3D rotatable image in PDB format is available.

carbonyl group of an adjacent carboxylic acid. There are no other notable hydrogen bonds in **11** (Table 2).

Crystal Structure of 4-Nitrobenzoic Acid/1 (1:1), 12. The crystal structure of **12** contains one molecule of the carboxylic acid and one molecule of **1**. As is the case in **11**, the two components are connected into a tetrameric supermolecule constructed from a dimeric, head-to-head amide...amide interaction plus a pair of symmetry equivalent acid...pyridine interactions (Figure 7). The anti amide hydrogen atom forms a hydrogen bond with the carbonyl group of an adjacent carboxylic acid. There are no other notable hydrogen bonds in **12**.

Crystal Structure of 3,5-Dinitrobenzoic Acid/1/4-Methylbenzoic Acid (1:1:1), 13. The crystal structure of **13** is a 1:1:1 ternary cocrystal that contains a three component supermolecule with the expected connectivity. The stronger acid ($pK_a = 2.8$)¹⁵ interacts with the pyridine nitrogen atom, and the weaker acid ($pK_a = 4.4$)¹⁵ competes successfully for the amide moiety and forms a heteromeric hydrogen-bonded motif (Figure 8). This motif is consistent with that reported for several other ternary cocrystals of **1** and two carboxylic acids of different strength.¹⁶

Crystal Structure of 2/2-Amino-5-nitropyrimidine (1:1), 21. The asymmetric unit of **21** contains one molecule of each component. Near linear, symmetry-related, N—H...N hydrogen bond interactions connect

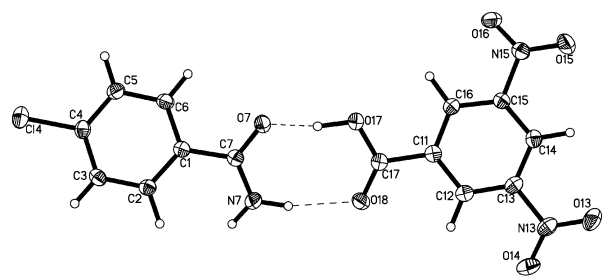


Figure 10. Thermal ellipsoids (30%) and numbering scheme in **31**.

Ⓜ A 3D rotatable image in PDB format is available.

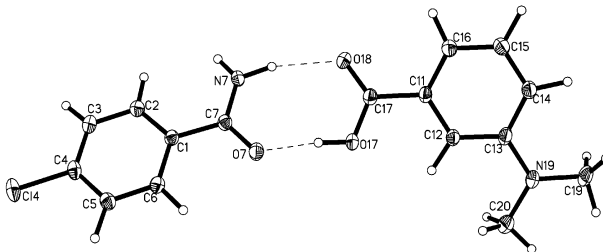


Figure 11. Thermal ellipsoids (30%) and numbering scheme in **32**.

Ⓜ A 3D rotatable image in PDB format is available.

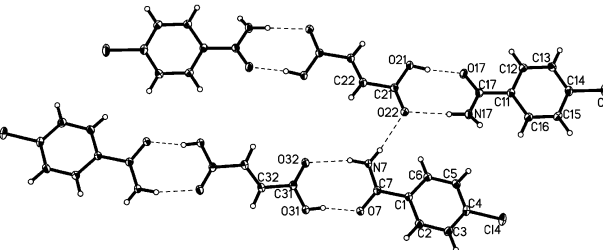


Figure 12. Thermal ellipsoids (30%) and numbering scheme in **33**.

Ⓜ A 3D rotatable image in PDB format is available.

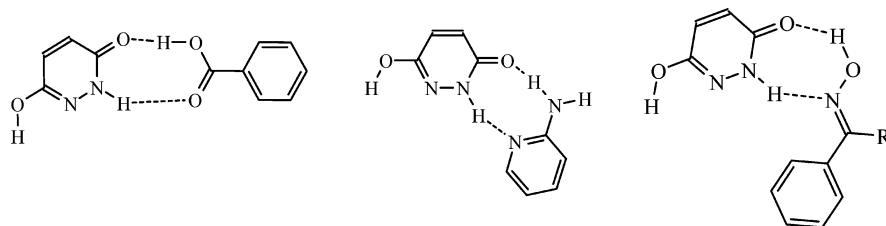
neighboring molecules into tetrameric (A...B...B...A) assemblies. Adjacent tetramers are linked into infinite chains via symmetry-related N—H...O hydrogen bonds (Figure 9).

Crystal Structure of 3,5-Dinitrobenzoic Acid/3 (1:1), 31. The asymmetric unit of **31** consists of one molecule of each component connected by an acid/amide heterodimer (Figure 10). The anti amide hydrogen atom forms a hydrogen bond with a nitro moiety from an adjacent acid molecule. The binary supermolecules form extended stacks with adjacent heterodimer oriented in an antiparallel fashion.

Crystal Structure of 3-Dimethylaminobenzoic Acid/3 (1:1), 32. The asymmetric unit of **32** consists of one molecule of each component connected by an acid/amide heterodimer (Figure 11). The anti amide hydrogen atom forms a hydrogen bond with the carbonyl of an adjacent acid molecule. The acid and amide molecules stack separately as AAAA and BBBB, such that each individual molecular dipole is canceled by the dipole of the molecule above or below it.

Crystal Structure of Fumaric Acid/3 (1:2), 33. The asymmetric unit of **33** consists of two molecules of the

Scheme 2. Three Examples of Known Synthons that Could Facilitate the Formation of Cocrystals Involving **4**



amide and two inequivalent halves of the acid forming two different acid/amide heterodimers (Figure 12). The anti amide hydrogen atoms form a hydrogen bond with a carbonyl of an adjacent acid molecule. The three component ($A \cdots B \cdots A$) heterodimer stacks in an alternating pattern of ABAABA.

Discussion

We have shown that cocrystals can readily be formed from both **2**, **1**, and **3** with a variety of aliphatic and aromatic carboxylic acids. This is in agreement with the suggestion that polymorphs make good CAs (provided that solubility differences are not too large). However, we have been completely unsuccessful in forming any kind of cocrystals with **4**, despite the fact that it exists by itself in three different crystalline forms. We have tried a range of crystallization techniques as well as an extensive series of molecular compounds that in principle, can form effective complementary hydrogen bond interactions with a 2-pyridone moiety (e.g., carboxylic acids, 2-aminopyridines, 2-aminopyrimidines, oximes, etc.) (Scheme 2).

The failure to produce any cocrystals with **4** obviously casts doubts on the notion that polymorphic compounds make good CAs unless there is a significant structural difference in the polymorphic behavior of **1–4**. We decided to take a closer look at all the polymorphs **1a,b**, **2a–c**, **3a–c**, and **4a–c** in an attempt to uncover possible reasons for the unwillingness of **4** to participate in molecular cocrystals. Previous work on polymorphs containing extensive hydrogen-bonded networks has demonstrated that even very complex intermolecular interactions and subtle structural differences are readily identified and categorized through a systematic use of graph-set notation.¹⁷ Consequently, a graph-set analysis was applied to the hydrogen bond patterns displayed by **1a,b**, **2a–c**, and **3a–c**. The two polymorphs of isonicotinamide, **1a** and **1b**, display very different intermolecular connectivities. In **1a**, there is a “classic” amide...amide head-to-head interaction as well as the commonly occurring $N-H \cdots O$ link between adjacent dimers resulting in a $C(4)R_2^2(8)$ notation for the primary hydrogen bonds in this polymorph. However, the primary intermolecular forces in **1b** are significantly different as there is a catemeric amide...amide hydrogen bond, $C(4)$, as well as an amide...pyridine interaction, $C(7)$. A similar classification of the three polymorphs of **2** reveals that the expected intramolecular amine...nitro hydrogen bond is present in all three forms. In addition, **2b** and **2c** have identical intermolecular connectivities and the primary hydrogen bond motifs are thus described with the same graph-set notation, $R_2^2(12)R_2^2(8)S(6)$. In **2a**, however, there are infi-

nite hydrogen-bonded ribbons that are described by the following notation, $R_2^2(10)R_2^2(8)S(6)$. The structures of **3a** and **3c** reveal the amide moieties forming the classic amide one-dimensional catemer, $C(4)R_2^2(8)R_4^2(8)$. The difference between the two structures lies in the arrangement of aromatic rings with respect to one another. While the graph-set notation for **3b** is similar to **3a** and **3c**, the larger hydrogen-bonded ring creates a two-dimensional network, $C(4)R_2^2(8)R_4^2(16)$. In contrast, all three polymorphs of **4** contain the same hydrogen-bonded ladders held together by identical synthons; $S(7)R_4^2(14)R_2^2(8)$ (Figure 13).

The fact that these three different polymorphs all contain the same extended networks was also noted in the original paper, “Three Forms of MH(4) Provide a Unique Example of Polymorphic Structures Built of Similar Hydrogen-Bonded Aggregates. The Same Hydrogen-Bonded Supramolecular Aggregates Organize into Different Lattices of Different Symmetries...”.¹³

A detailed structural examination of **1–4** has enabled the identification of significant differences, in terms of molecular recognition patterns, between the different polymorphs that in turn, may provide practical guidelines for distinguishing between (or ranking) candidates that are potentially suitable as CAs. Cocrystals are not necessarily easy to prepare since such heteromeric systems are only likely to appear if the noncovalent forces between different molecules are more favorable than those that exist between molecules in the corre-

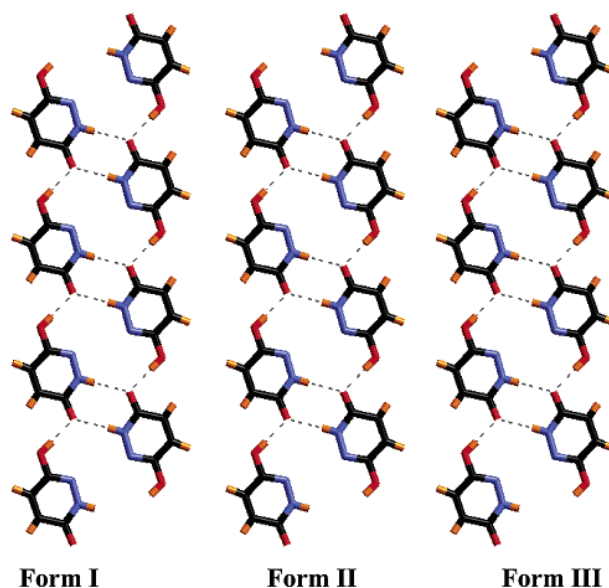


Figure 13. Primary hydrogen bond motifs in the three known polymorphs of **4** display the same connectivity.

sponding homomeric crystals. An important consideration when attempting to prepare cocrystals is to choose a CA that is already known to be polymorphic. Clearly, if a molecular compound exists in several polymorphs, it has demonstrated a structural flexibility and it is not as energetically locked into a single type of crystalline lattice or packing mode. However, as the current study shows, structural flexibility alone is not always enough. It may be equally important to select molecules that can adopt alternative packing patterns as well as display synthron flexibility, an ability to participate in several different robust and well-defined intermolecular interactions that can satisfy the demands of multiple hydrogen bond donors/acceptors on a variety of molecules.

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Note Added After ASAP Posting

An earlier version of this paper posted ASAP on January 28, 2003 contained an incorrect name (2-amino-3-nitropyridine/2) in two paragraphs describing compound **21** in Experimental Section and Results. The corrected name (2-amino-5-nitropyrimidine/2) appears in this version posted February 7, 2003. Links to web-enhanced object files were added March 5, 2003.

Supporting Information Available: X-ray crystallographic files (CIF). This material is available and free of charge via the Internet at <http://pubs.acs.org>.

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- (7) After the initial submission of this manuscript, one reviewer pointed out that **3** (a compound that was not originally part of the study) is also known to be polymorphic (with different hydrogen bond motifs); yet, there are no reported cocrystals or solvates. Because we suggest in this paper that a polymorphic compound displaying synthron flexibility should be a good CA, it seemed that **3** would provide a perfect, independently selected, “test case” for our hypothesis, and it was subsequently included in our study.
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- (14) The three cocrystals **11–13** can also be obtained by manually grinding equimolar mixtures of the relevant components together. The experimental XRD patterns for all solids obtained from grinding match well with the simulated X-ray powder patterns based upon experimental single-crystal data obtained from the corresponding cocrystals prepared from solution.
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