A High-Yielding Supramolecular Reaction

Christer B. Aakeröy,*,[†] Alicia M. Beatty,[‡] and Brian A. Helfrich[†]

*Contribution from the Department of Chemistry, Kansas State University, Manhattan, Kansas
and the Department of Chemistry and Biochemistry, University of Notre Dame,
Notre Dame, Indiana*

Received July 24, 2002

Abstract: The X-ray crystal structure determinations of twelve cocrystals involving *iso*-nicotinamide and a variety of carboxylic acids have revealed a very consistent pattern of hydrogen-bond preferences. The combination of a monocarboxylic acid, an amide, and a pyridine moiety leads, in every case, to discrete "supermolecules" (consisting of two molecules of *iso*-nicotinamide and two molecules of the relevant carboxylic acid) with well-defined and robust connectivity. The two dominant (regularly occurring) supramolecular synthons in these crystal structures are (1) the heteromeric carboxylic acid⋯pyridine hydrogen bond and (2) a self-complementary amide⋯amide hydrogen-bond interaction, both of which prevail in the presence of widely differing chemical functionalities. In four of these cocrystals, a dicarboxylic acid is employed, which alters the structural outcome from discrete entities to infinite assemblies (or to a hexameric complex in a "U-shaped" dicarboxylic acid), which is fully expected since the two primary supramolecular synthons remain intact. This structural study shows that *iso*-nicotinamide is a supramolecular reagent that can produce well-defined supermolecules (containing carboxylic acids) in very high yields.

Introduction

Intermolecular forces are responsible for the extraordinarily specific way in which molecules can interact to form a highly ordered crystalline material.[1] Once positioned within a lattice, the communication between these molecules is also governed by intermolecular interactions and this ensemble of interactions ultimately defines the physical properties and reactivity of any given solid. It should be no surprise then that an improved understanding of noncovalent interactions[2] is an important interdisciplinary research goal.[3] The ability to utilize molecular recognition processes in the construction of supermolecules or extended architectures is particularly important in supramolecular synthesis and crystal engineering, where molecules or ions, not atoms, act as building blocks of new materials, and noncovalent forces are employed as synthetic tools.

Much of the fundamental work in current crystal engineering is geared toward developing reliable supramolecular reactions, where the success and efficiency of a reaction can be judged by the frequency of occurrence of desired intermolecular interactions and connectivities. The probability that a certain motif will appear in a crystalline lattice is, in many ways, a measure of the yield of a supramolecular reaction. Just as a covalent synthetic chemist searches for ways in which a specific reaction can be promoted or prevented, a supramolecular chemist

tries to identify the experimental regime where a supramolecular synthon prevails despite competition from other noncovalent forces.

While it is important to acknowledge that every intermolecular force will have some influence on the outcome of a crystallization process, it is self-evident that some noncovalent forces are more significant than others.[4] To further develop reliable supramolecular reactions based on robust supramolecular synthons,[5] it is therefore essential to determine (whenever possible) the relative influence of, and balance between, competing intermolecular interactions.[6-8] In this context, Etter formulated an empirical guideline regarding the hierarchy of hydrogen-bond interactions,[9] "the best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another"—a consequence of this statement is that the second-best donor will form a hydrogen bond to the second-best acceptor, and so forth. If this idea is coupled with the fact that a few intermolecular interactions can provide a significant part of the lattice energy of a molecular solid,[10] it is reasonable to surmise that directed assembly of multicomponent networks of predictable connectivity may be accomplished with just a few well-chosen supramolecular synthons. In recent years, efforts have been made to identify robust supramolecular synthons, and the reliability of homomeric self-

* Address correspondence to this author. E-mail: aakeroy@ksu.edu.
† Kansas State University.
‡ University of Notre Dame.

(1) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: Amsterdam, 1989.
(2) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48.
(3) Aakeröy, C. B. *Acta Crystallogr.* **1997**, *B53*, 569. Zaworotko, M. J. *Chem. Commun.* **2001**, 1. Nangia, A.; Desiraju, G. R. *Top. Curr. Chem.* **1998**, *198*, 57. Nangia, A.; Desiraju, G. R. *Acta Crystallogr.* **1998**, *A54*, 934.
(4) Lehn, J.-M. *Supramolecular chemistry: concepts and perspectives*; VCH: Weinheim, 1995.
(5) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.
(6) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A.; *Angew. Chem., Int. Ed.* **2001**, *40*, 3240.
(7) Lynch, D. E.; McClenaghan, I. *Acta Crystallogr.* **2001**, *C57*, 830.
(8) Nguyen, T. L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **2001**, *123*, 11057.
(9) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.
(10) Dauber, P.; Hagler, A. T. *Acc. Chem. Res.* **1980**, *13*, 105.

complementary pair-wise hydrogen bonds, for example, carboxylic acid···carboxylic acid, amide···amide, oxime···oxime, and 2-pyridone···2-pyridone, have been established through extensive structural[11] or database studies.[12] Some heteromeric pair-wise interactions are particularly robust, for example, carboxylic acid···pyridine,[13,14] hydroxy···pyridine,[15] and hydroxy···amine,[16] and these heteromeric interactions have allowed for the assembly of a range of binary cocrystals.[17] However, to add more versatility and refinement to crystal engineering, it is necessary to further explore the possibility of "ranking" different supramolecular synthons. Crystal engineering and noncovalent synthesis based on such a dominance hierarchy of intermolecular interactions would set the stage for highly modular design principles that would enable the directed assembly of multicomponent heteromeric structures in high supramolecular yields.

Herein, we describe a systematic crystallographic study of the competition between three prevalent hydrogen-bonding moieties; carboxylic acid, primary amide, and pyridine. The main reason for choosing these particular moieties is that they are ubiquitous in biochemistry as well as in materials science, and versatile supramolecular synthesis requires assembly strategies that take advantage of (and tolerate) the interplay between common chemical functional groups. The objectives of this particular study are to establish the presence of preferential hydrogen-bond interactions and to determine how a supramolecular reaction is likely to proceed in the presence of all three components. Despite the preponderance of carboxylic acids, amides, and pyridine-based molecules, only a handful of crystal structures that contain all three fragments simultaneously have been reported.[18] The paucity of suitable crystal structures containing all three moieties means that we are not able to establish reliable patterns of behavior based on existing crystallographic data. Hence, the necessary structural data have been

Table 1. Compound Names and Melting Points for **1**–**12**

compound	melting point
cinnamic acid: *iso*-nicotinamide (**1**)	146−148 °C
3-hydroxybenzoic acid: *iso*-nicotinamide (**2**)	144−146 °C
3-*N,N*-dimethylaminobenzoic acid: *iso*-nicotinamide (**3**)	138−140 °C
3,5-bis(trifluoromethyl)benzoic acid: *iso*-nicotinamide (**4**)	160−163 °C
d,l-mandelic acid: *iso*-nicotinamide (**5**)	168−170 °C
chloroacetic acid: *iso*-nicotinamide (**6**)	95−98 °C
fumaric acid monoethyl ester: *iso*-nicotinamide (**7**)	92−95 °C
12-bromododecanoic acid: *iso*-nicotinamide (**8**)	88−90 °C
fumaric acid: 2 *iso*-nicotinamide (**9**)	145−148 °C
succinic acid: 2 *iso*-nicotinamide (**10**)	134−136 °C
4-ketopimelic: 2 *iso*-nicotinamide (**11**)	111−114 °C
thiodiglycolic: 2 *iso*-nicotinamide (**12**)	138−140 °C

obtained through the syntheses and single-crystal structure determinations of cocrystals of *iso*-nicotinamide with a wide range of aromatic and aliphatic carboxylic acids.

Experimental Section

Synthesis. Stoichiometric amounts (one *iso*-nicotinamide per monocarboxylic acid, two *iso*-nicotinamides per dicarboxylic acid) of the two compounds were dissolved in warm ethanol. The solutions were then cooled to room temperature and crystals formed upon slow evaporation (anywhere from hours to days) of the solvent. Melting points for **1**−**12** are given in Table 1.

X-ray Crystallography. Crystalline samples of **1**−**12** were placed in inert oil, mounted on a glass pin, and transferred to the cold gas stream of the diffractometer. Crystal data were collected and integrated using a Bruker SMART 1000 system, with graphite monochromated Mo−Kα ($\lambda = 0.71073$ Å) radiation. The structures were solved by direct methods using SHELXS-97 and refined using SHELXL-97.[19] Non-hydrogen atoms were found by successive full matrix least-squares refinement on F^2 and refined with anisotropic thermal parameters. Hydrogen atom positions were located from difference Fourier maps and a riding model with fixed thermal parameters [$u_{ij} = 1.2U_{ij}$(eq) for the atom to which they are bonded] was used for subsequent refinements. Table 2 provides crystallographic details for **1**−**12**, and the molecular geometries and numbering scheme are shown in Figure 1a−l.

Results

Thermal analyses and X-ray powder diffraction[20] of **1**−**12** revealed that only one new phase was present in each experiment, and single-crystal X-ray diffraction demonstrated that all twelve structures were composed of molecular cocrystals of *iso*-nicotinamide and the relevant acid. The ratio of *iso*-nicotinamide to acid was 1:1 when monocarboxylic acids were employed (**1**−**8**) and 2:1 when dicarboxylic acids were used (**9**−**12**). The structural data, supported by IR spectroscopy, confirmed that no proton transfer had taken place in any of these structures.[21]

(11) Leiserowitz, L. *Acta Crystallogr.* **1976**, *B32*, 775. Leiserowitz, L.; Tuval, M. *Acta Crystallogr.* **1978**, *B34*, 1230. Dunitz, J. D. *Pure Appl. Chem.* **1991**, *63*, 177.

(12) Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G. P.; Taylor, R. *New J. Chem.* **1999**, *1*, 25.

(13) Some examples of crystal structures containing intermolecular carboxylic acid···pyridine hydrogen bonds: Kane, J. J.; Liao, R.-F.; Lauher, J. W.; Fowler, F. W. *J. Am. Chem. Soc.* **1995**, *117*, 12003. Grunert, M.; Howie, R. A.; Kaeding, A.; Imrie, C. T. *J. Mater. Chem.* **1997**, *7*, 211. Vishweshwar, P.; Nangia, A.; Lynch, V. M. *J. Org. Chem.* **2002**, *67*, 556. Palmore, G. T. R.; Luo, T.-J. M.; McBride-Wieser, M. T.; Picciotto, E. A.; Reynoso-Paz, C. M. *Chem. Mater.* **1999**, *11*, 3315. Aakeröy, C. B.; Beatty, A. M.; Tremayne, M.; Rowe, D. M. *Cryst. Growth Des.* **2001**, *1*, 377. Sharma, C. V. K.; Zaworotko, M. J. *Chem. Commun.* **1996**, 2655. Pedireddi, V. R.; Chatterjee, S.; Ranganathan, A. *Tetrahedron* **1998**, *54*, 9457. Amai, M.; Endo, T.; Nagase, H.; Ueda, H.; Nakagaki, M. *Acta Crystallogr.* **1998**, *C54*, 1367.

(14) A search of the CSD (V. 5.23) for structures containing both carboxylic acids and 2,6-unsubstituted pyridine (excluding *N*-alkylpyridines and pyridine-*N*-oxides) resulted in over fifty hits; the overwhelming majority of these structures contain a complementary acid···pyridine hydrogen bond (see Supporting Information).

(15) Huang, K.-S.; Britton, D.; Etter, M. C.; Byrn, S. R. *J. Mater. Chem.* **1997**, *7*, 713. MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 7817.

(16) Ermer, O.; Eling, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 925.

(17) A few examples of binary cocrystals based on principles of molecular recognition are Sarma, J. A. R. P.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1905. Huang, C.; Leiserowitz, L.; Schmidt, G. M. J. *Chem. Soc., Perkin Trans. 2* **1973**, 503. Tamura, C.; Sakurai, N.; Sato, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1473. Pan, F.; Wong, M. S.; Gramlich, V.; Bosshard, C.; Gunter, P. *Chem. Commun.* **1996**, 2. LeFur, Y.; Bagieu-Beucher, M.; Masse, R.; Nicoud, J. F.; Levy, J. P. *Chem. Mater.* **1996**, *8*, 8. Zerkowski, J. A.; MacDonald, J. C.; Whitesides, G. M. *Chem. Mater.* **1997**, *9*, 9. Liao, R.-F.; Lauher, J. W.; Fowler, F. W. *Tetrahedron* **1996**, *52*, 3153. Shan, N.; Bond, A. D.; Jones, W. *Cryst. Eng.* **2002**, *5*, 9. Pedireddi, V. R.; Jones, W.; Chorlton, A. P.; Docherty, R. *Chem. Commun.* **1996**, 997.

(18) Throughout this manuscript we will deal only with molecular species where there have been no proton transfer from acid to pyridine.

(19) Sheldrick, G. M. University of Göttingen,

(20) In all cases, there was a satisfactory match between the experimental powder X-ray diffraction pattern and the simulated pattern on the basis of the single-crystal data. Furthermore, it was not possible to detect any significant amounts of un-reacted *iso*-nicotinamide or carboxylic acid. These observations were supported by DSC measurements, which did not indicate any appreciable amounts of starting materials. A combination of these data suggests that an estimate of crystal yields of **1**−**12** of no less than 90% would be conservative (see Supporting Information for representative examples of DSC and XRD data).

(21) Chloroacetic acid is the strongest carboxylic acid employed in this study (pK_a = 2.7, Kartrum, G.; Vogel, W.; Andrussov, K. *Constants of Organic Acids in Aqueous Solution*; Butterworth: London, 1961), and proton transfer did not take place between *iso*-nicotinamide and any of the twelve acids presented in this study. It is, of course, possible to protonate *iso*-nicotinamide with stronger organic acids (e.g., maleic acid) or with mineral acids but it has not yet been possible to establish the precise conditions for when a salt will be formed in preference to a molecular cocrystal.

Table 2. Data Collection, Structure Solution, and Refinement Parameters for **1**−**12**

compound	1	2	3	4
formula	$C_{30}H_{28}N_4O_6$	$C_{13}H_{12}N_2O_4$	$C_{15}H_{17}N_3O_3$	$C_{15}H_{10}F_6N_2O_3$
MW	270.28	260.25	287.32	380.25
color, habit	colorless, plates	colorless, prisms	colorless, plates	colorless, blocks
crystal system	triclinic	monoclinic	monoclinic	triclinic
space group, Z	$P\text{-}1$, 2	$C2/c$, 8	$C2/c$, 8	$P\text{-}1$, 2
a (Å)	8.4779(8)	22.419(3)	27.360(8)	7.349(3)
b (Å)	10.703(1)	5.1408(6)	5.311(2)	8.748(3)
c (Å)	15184(1)	20.867(3)	20.180(6)	12.555(5)
α (deg)	75.560(2)			81.605(7)
β (deg)	81.882(2)	97.717(2)	101.541(6)	82.488(6)
γ (deg)	82.980(2)			78.004(6)
V (Å^3)	1315.5(2)	2383.1(5)	2872.(1)	776.7(5)
density (g/cm^3)	1.365	1.451	1.329	1.626
temperature (K)	173(2)	173(2)	203(2)	203(2)
X-ray wavelength	0.71073	0.71073	0.71073	0.71073
$M_{(MoK\alpha)}$ (mm^{-1})	0.097	0.110	0.095	0.161
θ range (deg)	1.97−28.28	1.83−28.22	1.52−22.27	1.65−24.01
reflections collected	8842	8091	6222	4161
independent reflections (R_{int})	5641 (0.0176)	2768 (0.0595)	1830 (0.0427)	2438 (0.0349)
$R(F)$, $R_w(F)$	0.0440, 0.0614	0.0418, 0.0667	0.0556, 0.0999	0.0685, 0.1249

compound	5	6	7	8
formula	$C_{19}H_{22}N_4O_7$	$C_8H_9ClN_2O_3$	$C_{12}H_{14}N_2O_5$	$C_{18}H_{29}BrN_2O_3$
MW	418.41	216.62	266.25	401.34
color, habit	colorless, plates	colorless, plates	colorless, needles	colorless, blocks
crystal system	triclinic	monoclinic	monoclinic	triclinic
space group, Z	$P\text{-}1$, 2	$C2/c$, 8	$P2_1/n$,	$P\text{-}1$, 2
a (Å)	6.667(1)	21.031(3)	3.8803(6)	6.783(1)
b (Å)	8.433(2)	5.1179(7)	7.822(1)	8.363(1)
c (Å)	17.964(4)	19.845(3)	42.606(7)	17.949(3)
α (deg)	78.697(4)			98.148(3)
β (deg)	82.533(4)	117.344(2)	91.238(4)	91.846(3)
γ (deg)	88.018(4)			107.580(3)
V (Å^3)	981.9(4)	1897.3(5)	1293.0(4)	957.8(3)
density (g/cm^3)	1.415	1.517	1.368	1.392
temperature (K)	173(2)	203(2)	203(2)	203(2)
X-ray wavelength	0.71073	0.71073	0.71073	0.71073
$M_{(MoK\alpha)}$ (mm^{-1})	0.110	0.385	0.108	2.164
θ range (deg)	1.17−28.34	2.18−28.28	0.96−28.27	1.15−26.39
reflections collected	6729	6279	8273	6219
independent reflections (R_{int})	4355 (0.0180)	2203 (0.0141)	2974 (0.0515)	3910 (0.0218)
$R(F)$, $R_w(F)$	0.0469, 0.0755	0.0350, 0.0440	0.0449, 0.0908	0.0370, 0.0695

| compound	9	10	11	12
formula	$C_8H_8N_2O_3$	$C_8H_9N_2O_3$	$C_{14}H_{14}N_2O_4$	$C_{16}H_{18}N_4O_6S$
MW	180.16	181.17	274.27	394.40
color, habit	colorless, rods	colorless, rods	colorless, plates	colorless, prisms
crystal system	triclinic	triclinic	monoclinic	monoclinic
space grooup, Z	$P\text{-}1$, 2	$P\text{-}1$, 2	$P2(1)/c$, 4	$P2(1)/c$, 4
a (Å)	6.8062(9)	6.8317(7)	5.2275(9)	8.912(2)
b (Å)	7.0018(6)	7.0624(6)	27.857(5)	13.628(3)
c (Å)	8.9692(5)	9.0970(9)	9.245(2)	15.266(3)
α (deg)	80.745(6)	80.495(7)		
β (deg)	78.314(6)	77.573(6)	99.678(3)	105.301(4)
γ (deg)	73.474(9)	72.777(8)		
V (Å^3)	398.85(7)	406.98(7)	1327.2(4)	1788.4(6)
density (g/cm^3)	1.500	1.478	1.373	1.465
temperature (K)	203(2)	203(2)	173(2)	203(2)
X-ray wavelength	0.71073	0.71073	0.71073	0.71073
$M_{(MoK\alpha)}$ (mm^{-1})	0.117	0.115	0.102	0.224
θ range (deg)	2.33−25.00	2.31−24.99	1.46−28.22	2.04−24.78
reflections collected	1780	1818	9180	9802
independent reflections (R_{int})	1394 (0.0073)	1427 (0.0273)	3044 (0.0588)	3057 (0.0491)
$R(F)$, $R_w(F)$	0.0325, 0.0860	0.0397, 0.0535	0.0527, 0.1065	0.0448, 0.0931

Since the primary intermolecular interactions were the same throughout **1**−**12**, the descriptive part of the twelve crystal structures will be relatively limited.[22]

All eight structures that involve monocarboxylic acids, **1**−**8**, contain a "supermolecule"[23] constructed from two molecules of the carboxylic acid and two molecules of *iso*-nicotinamide,

Figure 1a−h. This tetrameric supermolecule is held together by two robust supramolecular synthons, a carboxylic acid⋯ pyridine interaction, and a self-complementary amide⋯amide pair-wise hydrogen bond (in each case the carboxylic acid adopts a syn conformation). An N⋯H−O hydrogen bond between a

(22) Furthermore, since the aim of this study is the intermolecular interactions, specific details of the intramolecular geometries (which were all within expected values) will not be discussed. For information about hydrogen-bond geometries, see Supporting Information.

(23) The term supermolecule used here indicates a discrete 0-dimensional species composed of molecular building blocks, assembled via directional noncovalent forces. Thus, ternary systems formed by ionic interactions (salts) or by incorporation of solvent molecules within a lattice (e.g., clathrates, heterosolvates, or inclusion compounds) are distinctly different from the supermolecules that we discuss in this paper.
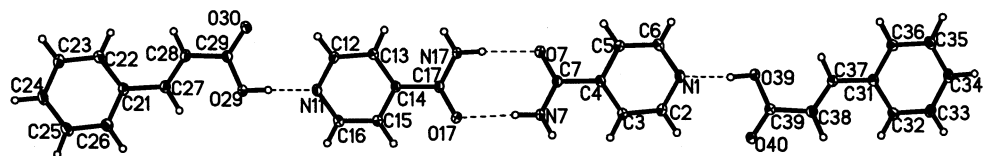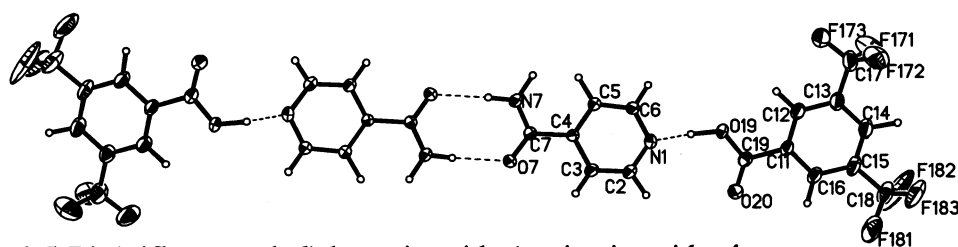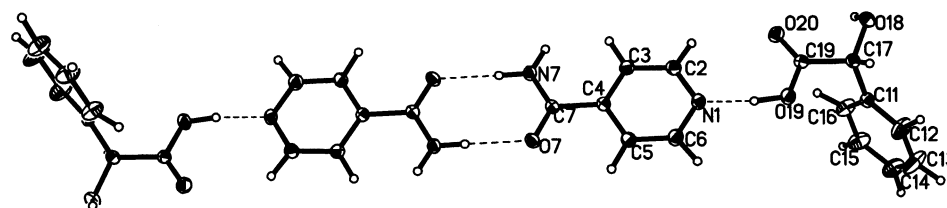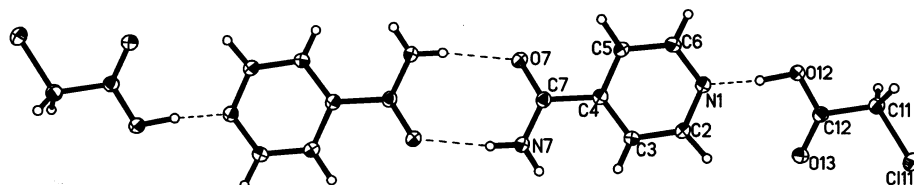
a.   Cinnamic acid : isonicotinamide, **1**
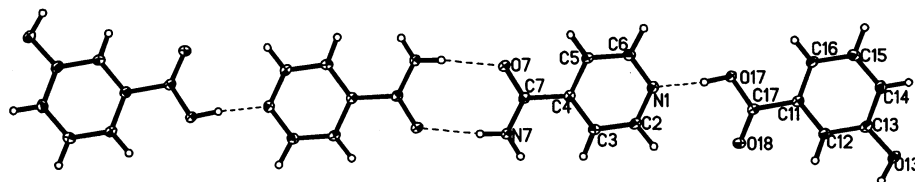
b.   3-Hydroxybenzoic acid : *iso*nicotinamide, **2**
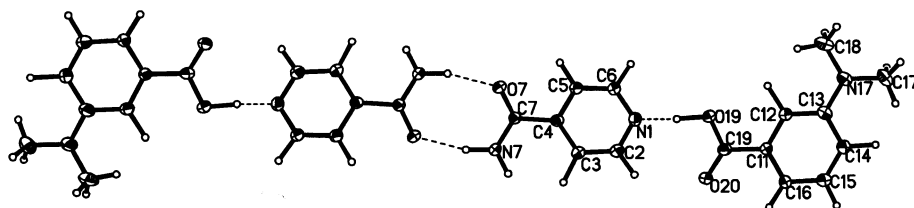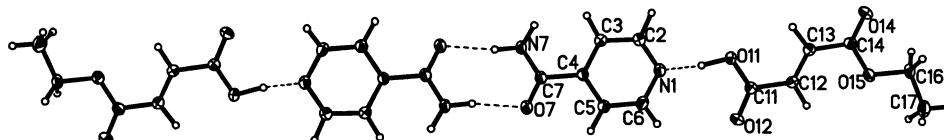

c.   3-N,N-dimethylaminobenzoic acid : *iso*nicotinamide, **3**

d.   3,5-Bis(trifluoromethyl)-benzoic acid : *iso*nicotinamide, **4**

e.   *d,l-* Mandelic acid : *iso*nicotinamide, **5**

f.   Chloroacetic acid : *iso*nicotinamide, **6**

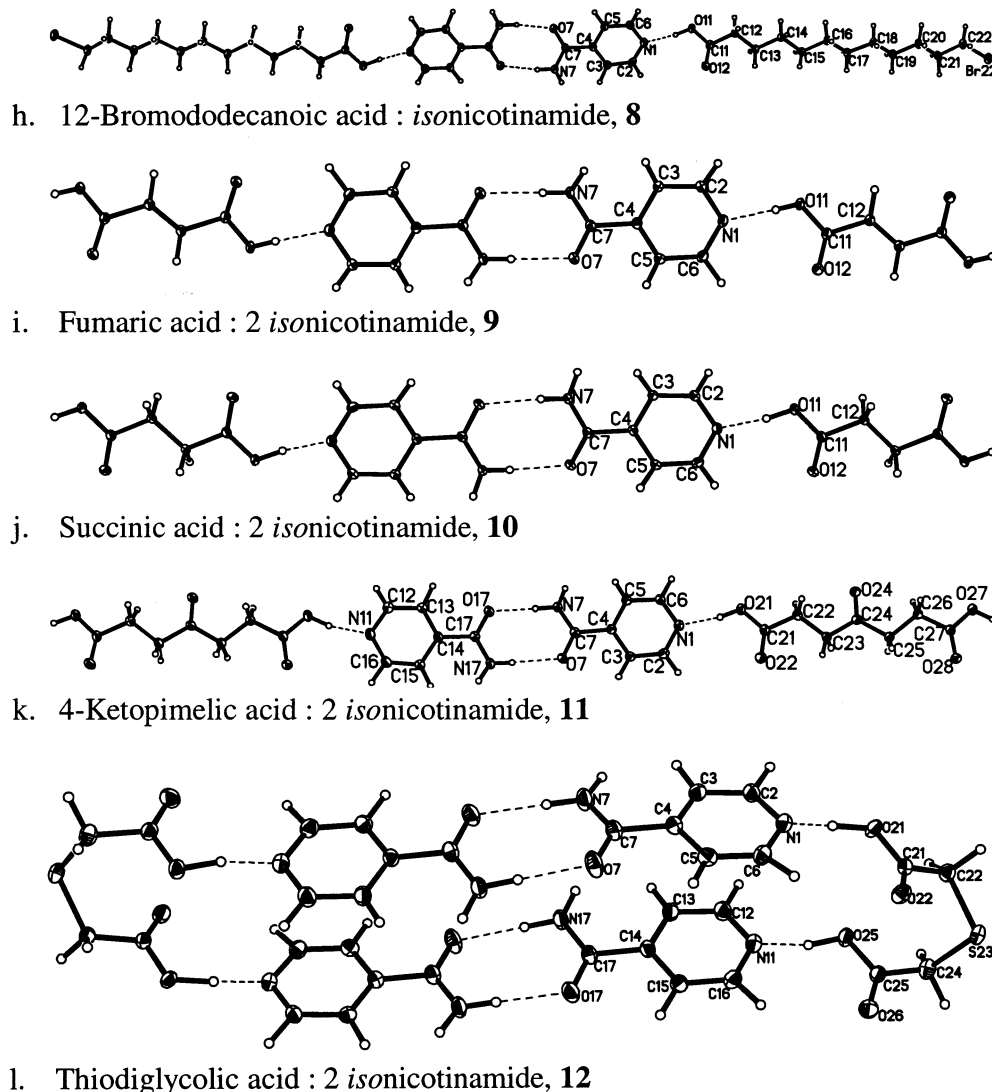g.   Fumaric acid monoethyl ester: *iso*nicotinamide, **7**

h. 12-Bromododecanoic acid : *iso*nicotinamide, **8**

i. Fumaric acid : 2 *iso*nicotinamide, **9**

j. Succinic acid : 2 *iso*nicotinamide, **10**

k. 4-Ketopimelic acid : 2 *iso*nicotinamide, **11**

l. Thiodiglycolic acid : 2 *iso*nicotinamide, **12**

Figure 1. a−l. Molecular geometries, labeling schemes, and primary hydrogen-bond interactions in **1**−**12**.

2,6-unsubstituted pyridine molecule and a carboxylic acid is sometimes accompanied by a stabilizing C−H···O hydrogen bond.[24] However, this interaction does not seem to play an important role in **1**−**12**; neighboring pyridine···carboxylic acid moieties within "supermolecules" in this set of structures frequently deviate from a coplanar arrangement. Furthermore, the C−H...O distances display dramatic variations (H···O, 2.56−3.59 Å; C···O 3.27−3.96 Å), which indicate that the formation (and importance) of the O−H···N hydrogen bond is not necessarily the result of a pair-wise C−H···O/N···H−O supramolecular synthon.

The resulting supermolecules in **1**−**8** exist in two different conformations; a flexibility that is due to the possibility of "rotation" around the two O−H···N hydrogen bonds, Figure 1a−h. Given an overall near-planar geometry of the supermolecules, the carbonyl moieties of the carboxylic acids and the amides (four in total) can be organized in a trans-trans-trans manner (I), Scheme 1a (observed in **1**−**3**, **5**−**6**, **8**, and **11**), or they can be arranged in a cis-trans-cis configuration (II), Scheme 1b (observed in **4**, **7**, **9**−**10**, **12**).

(24) Steiner, T.; Desiraju, G. R. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: New York, 1999.
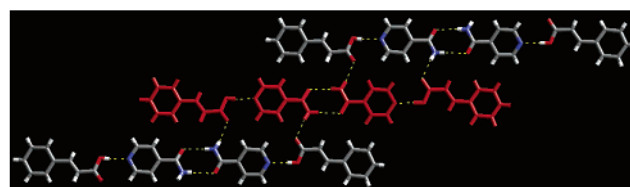
Figure 2. An example of a one-dimensional ribbon in the crystal structure of **1**; the C=O moieties are arranged in trans-trans-trans manner (conformation "I") within each tetrameric supermolecule. One supermolecule highlighted in red.

These conformational differences dictate (or are the result of) the way in which these supermolecules are positioned with respect to each other resulting in supramolecular isomerism.[25] For example, neighboring supermolecules with the (I)-conformation are interconnected via the *anti*-amide proton and a carbonyl oxygen atom resulting in infinite 1-D ribbons, Figure 2, or in a cross-linked 2-D network, Figure 3.

Supermolecules with the alternative conformation (II) also form infinite ribbons through N−H···O hydrogen bonds, but the horizontal displacement of supermolecules in adjacent ribbons is now slightly smaller, Figure 4.

(25) Moulton, B.; Zaworotko, M. J. *Chem. Rev.* **2001**, *101*, 1629.

Scheme 1. The Two Conformations (A) **I** and (B) **II** Present in **1**−**8**. **I** Results in Either (C) One-Dimensional Chains or (E) Two-Dimensional Networks. **II** Leads to (D) One-Dimensional Chains
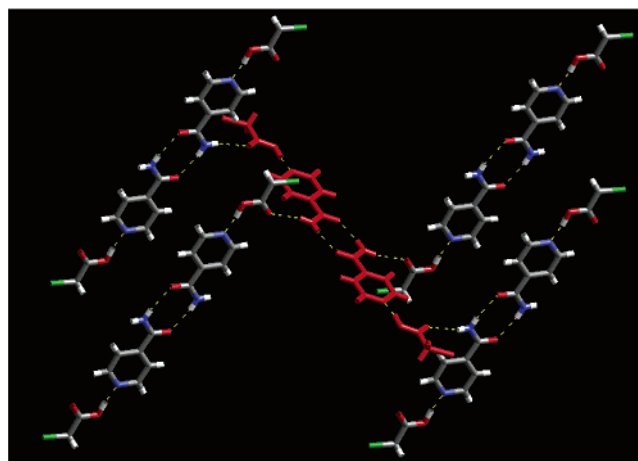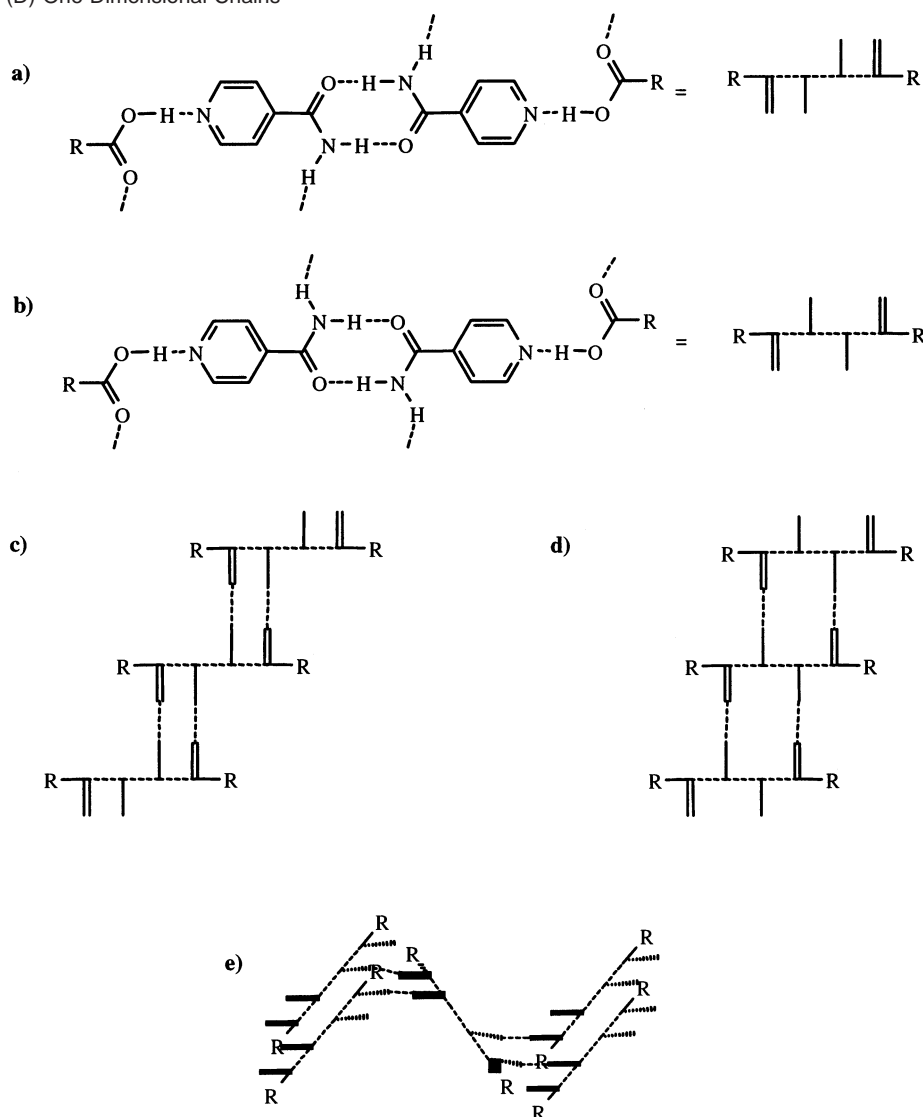

Figure 3. An example of a cross-linked network as observed in the crystal structure of **6** (conformation "I"). One supermolecule highlighted in red.

Figure 4. An example of a two-dimensional sheet as found in the crystal structure of **7**. The C=O moieties are positioned in a cis-trans-cis manner, conformation "II". Part of one infinite chain highlighted in red.

In the reactions between dicarboxylic acids and *iso*-nicotinamide, the results are again molecular cocrystals but this time in a ratio of two molecules of *iso*-nicotinamide for every dicarboxylic acid, Figure 1i−l. All four of these structures,
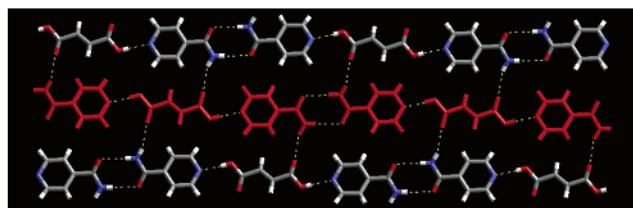
9−**12**, contain the same primary supramolecular synthons as were observed in **1**−**8**; each dicarboxylic acid forms two expected acid•••pyridine hydrogen bonds, and neighboring *iso*-nicotinamide molecules are connected via homomeric self-complementary amide•••amide interactions. The fact that the three dicarboxylic acids in **9**−**11** are ditopic means that the resulting dominating supramolecular motifs in these structures are infinite 1-D chains instead of discrete 0-dimensional entities. In **12**, which does contain a dicarboxylic acid, the primary structural motif is a hexameric supermolecule, which is a result of the observed "U-conformation" of thiodiglycolic acid—the
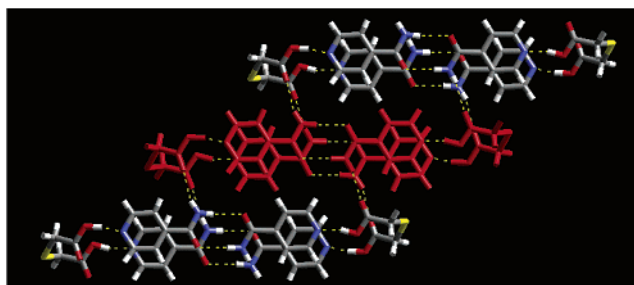
Figure 5. A one-dimensional ribbon composed of hexameric supermolecules (one of the supermolecules highlighted in red) observed in **12**.
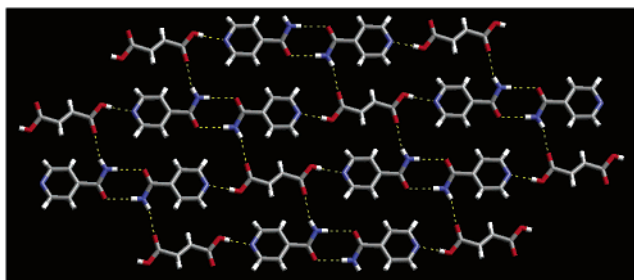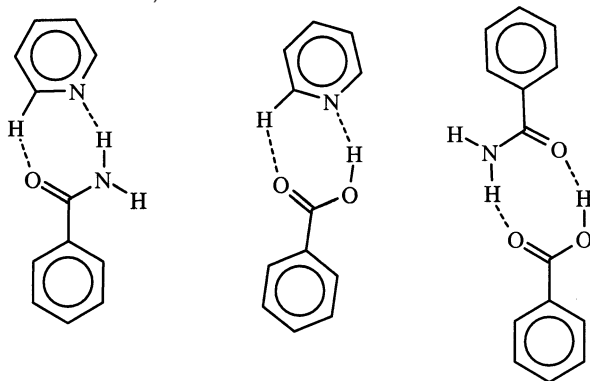

Figure 6. The two-dimensional sheet observed in the crystal structure of **9**; C=O moieties in conformation "II".

Scheme 2. Three Heteromeric Interactions Involving Pyridine, Carboxylic Acid, and Primary Carboxamide (All of Which Are Found in the CSD)

six components are held together by two amide···amide and four acid···pyridine interactions, Figure 1l. Neighboring supermolecules are connected into infinite ribbons, Figure 5.

As was the case with the supermolecules in **1**−**8**, two different conformations of the infinite chains can be envisaged (with respect to the relative orientations of the C=O bonds) and one example of how the infinite chains are interconnected into 2-D sheets through N−H···O hydrogen bonds is shown in Figure 6.

Discussion

In theory, an attempted cocrystallization of a carboxylic acid, an amide, and a pyridine-based molecule could result in a plethora of intermolecular interactions and products, in particular since these three moieties are known to form a variety of different heteromeric, Scheme 2, and homomeric, Scheme 3, supramolecular synthons.

However, the supramolecular reaction between *iso*-nicotinamide and a variety of aromatic/aliphatic mono- and dicarboxylic acids does, in fact, proceed in high yield. We have obtained twelve molecular cocrystals containing discrete supermolecules

Scheme 3. Three Homomeric Interactions Involving Pyridine, Carboxylic Acid, and Primary Carboxamide (All of Which Are Found in the CSD)
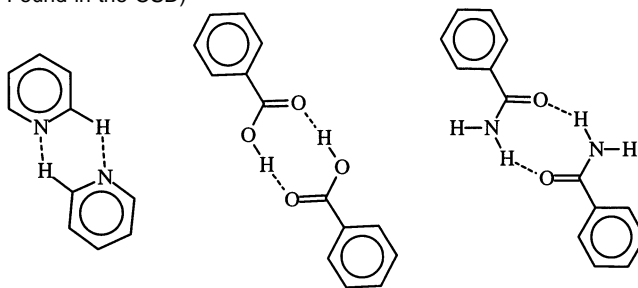
(**1**−**8**, **12**) or infinite architectures (**9**−**11**) that are all constructed from exactly the same primary supramolecular synthons (a) an acid···pyridine interaction and (b) a self-complementary amide···amide pair of hydrogen bonds.

Reaction conditions have not been varied significantly (in each case the reagents were introduced in a consistent manner; one equivalent of *iso*-nicotinamide per carboxylic acid moiety), but the chemical, geometric, and structural nature of the different acids employed in this study cover a significant range. As a consequence, the resulting supermolecules vary widely in shape, size, and functionalization. The tetrameric supermolecule containing chloroacetic acid (a very short aliphatic carboxylic acid) is 24 Å long (from Cl to Cl) whereas the 12-bromododecanoic analogue, **8**, is 50 Å long (from Br to Br). Likewise, the supermolecules in **2**, **4**, and **7** (which are all about the same length, 35 Å), contain −OH, −CF$_3$, and −OC(=O)CH$_3$ substituents, respectively. Furthermore, this supramolecular reaction can be carried out with aliphatic (seven structures) as well as with aromatic (five structures) carboxylic acids. Since these materials contain very different supermolecules, it is not surprising that physical properties vary significantly. For example, an examination of the melting points of **1**−**12** shows that three compounds, **6**−**8**, are much lower melting than the remaining members in this study. A possible reason for this may be the fact that since these three cocrystals contain aliphatic monocarboxylic acids, they are unable to participate in stabilizing π...π interactions and they also cannot form infinite architectures held together by strong hydrogen bonds. The remaining cocrystals, which all melt at temperatures above 110 °C, contain either (a) dicarboxylic acids that generate 1-D extended structures or (b) aromatic carboxylic acids.

Just as different molecules crystallize with a variety of 3-D assembly patterns and crystallographic parameters, the supermolecules in **1**−**12** adopt several different crystal structures. In other words, *iso*-nicotinamide can be viewed as a supramolecular reagent capable of acting upon carboxylic acids in the construction of predictable extended assemblies with well-defined connectivity. The versatility of this reaction is further illustrated by the fact that this reagent is capable of producing either discrete or infinite assemblies.

It is inevitable that certain carboxylic acids in combination with *iso*-nicotinamide will provide exceptions, supramolecular byproducts, compared to the structures observed in this study. However, this does not detract from the importance of *iso*-nicotinamide as a useful supramolecular reagent. Comparisons with organic chemistry are inevitable—very few covalent reactions lead to quantitative yields and most standard organic

substitution or coupling reactions are subject to specific reaction conditions (e.g., absence of certain functional groups). To develop more sophisticated supramolecular chemistry, it is therefore necessary to identify a wide range of supramolecular reagents, each of them with the ability to direct the assembly of families of compounds into predictable networks or super-molecules.

In conclusion, we have shown that a hierarchical view of intermolecular interactions based on structural trends, prob-abilities, and patterns of behavior can support a modular approach to noncovalent assembly thus providing reliable and transferable guidelines for pragmatic supramolecular synthesis.

Supporting Information Available: X-ray crystallographic files (CIF) and representative DSC and powder X-ray diffraction data (experimental and simulated). This material is available and free of charge via the Internet at http://pubs.acs.org.

JA027845Q