

Molecular Complexes of Homologous Alkanedicarboxylic Acids with Isonicotinamide: X-ray Crystal Structures, Hydrogen Bond Synthons, and Melting Point Alternation

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Received March 7, 2003

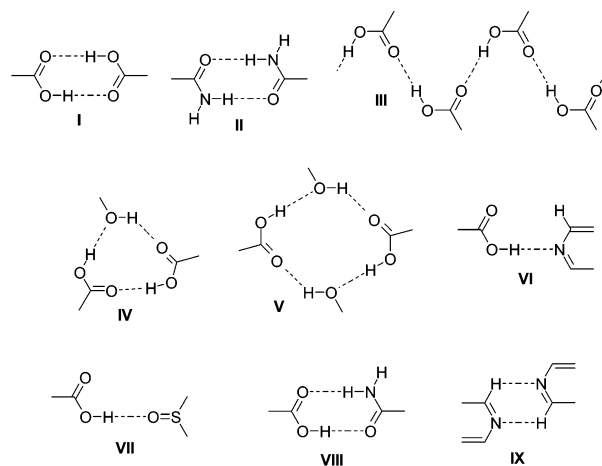
ABSTRACT: Crystallization of α,ω -alkanedicarboxylic acids ($\text{HOOC}-(\text{CH}_2)_{n-2}-\text{COOH}$, $n = 2-6$) with isonicotinamide (IN) is carried out in 1:2 and 1:1 stoichiometry. Five cocrystals of (diacid)·(IN)₂ composition (diacid = oxalic acid, malonic acid, succinic acid, glutaric acid, and adipic acid) are characterized by X-ray diffraction at 153(2) K. Tapes of acid–pyridine $\text{O}-\text{H}\cdots\text{N}$ and amide–amide $\text{N}-\text{H}\cdots\text{O}$ hydrogen bond synthons stabilize these five crystal structures as predicted by the hierarchic model: the best donor (COOH) and best acceptor group (pyridine N) hydrogen bond as acid–pyridine and the second best donor–acceptor group (CONH_2) aggregates as an amide dimer. Glutaric acid and adipic acid cocrystallize in 1:1 stoichiometry also, (diacid)·(IN), with acid–pyridine and acid–amide hydrogen bonds. Synthon energy calculations ($\Delta E_{\text{synthon}}$, RHF/6-31G**) explain the observed hydrogen bond preferences in 1:2 (five examples) and 1:1 (two examples) cocrystals. The acid–pyridine hydrogen bond is favored over the acid–amide dimer for strong carboxylic acids because the difference between $\Delta E_{\text{acid-pyridine}}$ and $\Delta E_{\text{acid-amide}}$ ($-2.21 \text{ kcal mol}^{-1}$) is greater than the difference for weak acids ($-0.77 \text{ kcal mol}^{-1}$), which cocrystallize with both of these hydrogen bond synthons. We suggest $\Delta E_{\text{synthon}}$ as a semiquantitative parameter to rank hydrogen bond preferences and better understand supramolecular organization in the multifunctional acid–IN system. Melting point alternation in five homologous (diacid)·(IN)₂ cocrystals is correlated with changes in crystal density and packing fraction.

Introduction

Hydrogen bonding is the master key in crystal engineering, supramolecular chemistry, and biological recognition.^{1–3} The strong and directional nature of hydrogen bonds is exploited in the organized self-assembly of molecules in solution and the solid state. Carboxylic acids and amides are two commonly used functional groups in crystal engineering because they generally form robust architectures via $\text{O}-\text{H}\cdots\text{O}$ and $\text{N}-\text{H}\cdots\text{O}$ hydrogen-bonded dimers.^{4,5} However, our understanding of the factors that direct hydrogen-bonding motifs when other functional groups are also present in the molecule is still evolving.⁶ The main challenge in carrying out crystal design with multifunctional molecules is that one is unable to predict when a particular functional group (e.g., hydroxyl, halogen, pyridine, ester, amide) will perturb the normal hydrogen bond motif of a given functional group (say COOH). The exercise is further complicated because the way in which the hydrogen bond motif changes in a particular system could subtly depend on the molecular structure.^{6f} Therefore, research on understanding the forces that govern recognition between multifunctional molecules is of fundamental importance in supramolecular chemistry. For the successful implementation of target crystal synthesis, it is necessary to understand the synergy, interplay, and competition between different functional groups during self-assembly.⁷

A current theme in crystal engineering is to use strong and weak hydrogen bonds ($\text{O}-\text{H}\cdots\text{O}$, $\text{O}-\text{H}\cdots\text{N}$, $\text{N}-\text{H}\cdots\text{O}$, $\text{C}-\text{H}\cdots\text{O}$) for building nanoscale architectures

Scheme 1. Hydrogen Bond Synthons Discussed in This Paper

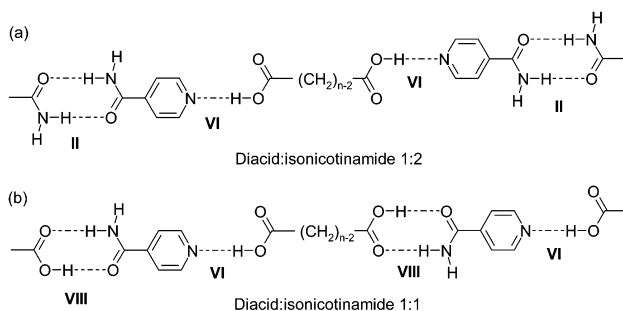


from molecular scaffolds via multipoint recognition supramolecular synthons.⁸ Statistical trends retrieved from the Cambridge Structural Database (CSD)⁹ are a better guide in crystal design than the observed interaction patterns in a subset of structures. For two common bimolecular synthons, carboxylic acid dimer I occurs in 33% crystal structures and amide dimer II is very rare (8%) in the global archive.¹⁰ Apart from homodimer I, carboxylic acids also aggregate via catemer III and hydrated motifs IV and V (Scheme 1). On the other hand, the success rate of carboxylic acid hydrogen bonding with complementary functional groups is much higher: acid–pyridine VI (91%), acid–sulfoxide VII (78%), and acid–amide VIII (78%).¹¹ The synthesis of binary crystals¹² (molecular complexes of two neutral

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Scheme 2^a

^a (a) Acid-pyridine VI and amide-amide II synthons in diacid·(IN)₂ cocrystals ($n = 2-6$). (b) Acid-pyridine VI and acid-amide VIII synthons in diacid·(IN) cocrystals ($n = 5, 6$).

components, cocrystals) mediated via heterosynthons rapidly affords a large number of crystal structures for analysis.

Carboxylic acid-pyridine synthon VI has emerged as a robust and recurring design strategy in crystal engineering.¹³ A modular self-assembly approach to carboxylic acid·isonicotinamide (IN) cocrystals stabilized by acid-pyridine synthon VI and amide-amide dimer II was recently proposed by Aakeröy¹⁴ based on the hydrogen bond hierarchy (ranking) rules formulated by Etter:¹⁵ the best donor (COOH) hydrogen bonds to the best acceptor (pyridine N), and the second best donor and acceptor groups hydrogen bond next (amide dimer). Notwithstanding the synthetic ease of building nanostructures through such a supramolecular synthesis protocol, the factors that control self-assembly in competitive hydrogen bond situations are still not properly understood. For example, different combinations of O-H···O, O-H···N, and N-H···O hydrogen bonds in the carboxylic acid-IN system can result in at least four different synthons (I, II, VI, VIII; Scheme 1) with the preference order acid-pyridine VI > acid-amide VIII > amide-amide II > acid-acid I. However, subtle molecular features, crystallization conditions, and small differences in hydrogen bond energy could alter this hierarchy in favor of one motif or another, particularly between heterosynthons VI and VIII. It is therefore ideal to probe hydrogen bonding in such (almost) isoenergetic synthons in X-ray crystal structures with systematic variation of molecular structure. We have synthesized cocrystals of IN with homologous α,ω -alkanedicarboxylic acids (HOOC-(CH₂) _{$n-2$} -COOH): oxalic acid (OA, $n = 2$), malonic acid (MA, $n = 3$), succinic acid (SA, $n = 4$), glutaric acid (GA, $n = 5$), and adipic acid (AA, $n = 6$). These five acids afford the expected 1:2 complex of diacid and IN stabilized by acid-pyridine VI and amide-amide II hydrogen bonds (Scheme 2a). GA and AA also cocrystallize in 1:1 stoichiometry with acid-pyridine VI and acid-amide hydrogen bond VIII (Scheme 2b).¹⁶ The idea of using symmetrical dicarboxylic acid with chemically equivalent COOH groups is to study supramolecular organization in competitive hydrogen bond situations. We explain through computation of hydrogen bond synthon energy ($\Delta E_{\text{synthon}}$, Spartan, RHF/6-31G**) the formation of 1:2 cocrystals and rationalize why 1:1 cocrystals are isolated in two out of five cases. Melting point alternation in diacid·(IN)₂ cocrystals is correlated with alternation in crystal density and packing fraction.

Results

The molecular complex of the appropriate dicarboxylic acid (HOOC-(CH₂) _{$n-2$} -COOH, $n = 2-6$) and IN was obtained by dissolving the components in 1:2 stoichiometry in suitable solvent(s). Slow evaporation at room temperature gave diffraction quality crystals after a few days. Binary crystals were characterized by Fourier transform infrared, melting point (differential scanning calorimetry; DSC), and X-ray diffraction (XRD) (see Experimental Section). Similarly, 1:1 cocrystals of diacid ($n = 5, 6$) and IN were grown and analyzed. Crystallographic details are summarized in Table 1, and hydrogen bond metrics are listed in Table 2. ORTEP plots of crystal structures are displayed in the Supporting Information.

The crystal structure of OA·(IN)₂ contains half a molecule of OA and one molecule of IN in the monoclinic space group *C2/c* (Table 1). The OA molecule resides on the 2-fold rotation axis in *syn*-planar conformation. The COOH group hydrogen bonds to pyridine N, and carboxamide groups aggregate as a centrosymmetric dimer (O-H···N: 1.58 Å, 2.5636(13) Å, 179.5°; N-H···O: 1.91 Å, 2.9168(13) Å, 173.8°). Linear tapes of synthons VI and II are connected via N-H···O hydrogen bond to acid carbonyl group of inversion-related tapes as shown in Figure 1a (2.00 Å, 3.0079(13) Å, 170.9°). The overall structure is stabilized by numerous C-H···O interactions.¹⁷ The crystal structure of MA·(IN)₂ in the triclinic space group *P1* has three symmetry-independent diacid molecules and six crystallographically unique IN molecules.¹⁸ Symmetry-independent MA and IN molecules constitute the zigzag tape of acid-pyridine and amide-amide hydrogen bonds, which are in turn connected via amide N-H···O hydrogen bonds (Figure 1b). Metrics of hydrogen bonds and C-H···O interactions are in the usual range (Table 2). The crystal structure of SA·(IN)₂ (at 203 K) was published¹⁴ while this work was in its final stages. We present our crystallographic result (at 153 K, Figure 1c) because it is part of the homologous series. The fact that an identical crystal structure of the same complex is obtained in different laboratories means that polymorphism, the existence of the same chemical substance in different crystalline modifications, is not a complication in the present family of compounds. The tape structure in GA·(IN)₂ has two symmetry-independent diacid molecules and four IN molecules (space group *P2₁/n*, Figure 1d). In both diacid molecules, one of the O-H···N hydrogen bonds is shorter than the other contact (O···N: 2.58, 2.66; 2.59, 2.68 Å). AA·(IN)₂ crystallizes in the triclinic space group *P1* with *Z'* of half for diacid and one molecule of IN (Figure 1e).

Upon isolation of 1:2 cocrystals for five homologous dicarboxylic acids with IN, we posed the question: Is it possible for COOH groups of the α,ω -alkanedicarboxylic acid to hydrogen bond via acid-pyridine and acid-amide synthons in the same crystal? Our experiment with 1:1 cocrystallization was successful with two out of five diacids tried, GA and AA. In the 1:1 complex of GA·IN and AA·IN (both in *P2₁/c*), one molecule of each component is present in the asymmetric unit. What is of note in the 1:1 cocrystal is that the identical COOH group of diacid hydrogen bonds via different synthons, acid-pyridine VI and acid-amide VIII (Figure 2).

Table 1. Crystallographic Data and Structure Refinement Parameters (CCDC Deposit Nos. 199970–199976)

compound	OA·(IN) ₂	MA·(IN) ₂	SA·(IN) ₂	GA·(IN) ₂	AA·(IN) ₂	GA·IN	AA·IN
empirical formula	(C ₂ H ₂ O ₄) _{0.5} · (C ₆ H ₆ N ₂ O)	(C ₃ H ₄ O ₄) ₃ · (C ₆ H ₆ N ₂ O) ₆	(C ₄ H ₆ O ₄) _{0.5} · (C ₆ H ₆ N ₂ O)	(C ₅ H ₈ O ₄) ₂ · (C ₆ H ₆ N ₂ O) ₄	(C ₆ H ₁₀ O ₄) _{0.5} · (C ₆ H ₆ N ₂ O)	(C ₅ H ₈ O ₄)· (C ₆ H ₆ N ₂ O)	(C ₆ H ₁₀ O ₄)· (C ₆ H ₆ N ₂ O)
formula wt	167.15	1044.95	181.17	752.74	195.20	254.24	268.27
crystal system	monoclinic	triclinic	triclinic	monoclinic	triclinic	monoclinic	monoclinic
space group	C2/c	P1̄	P1̄	P2 ₁ /n	P1̄	P2 ₁ /c	P2 ₁ /c
<i>a</i> (Å)	11.7466(2)	11.9420(2)	6.8198(2)	14.0439(2)	5.2522(1)	9.8980(3)	13.6429(4)
<i>b</i> (Å)	10.0164(2)	14.8580(2)	7.0650(2)	10.9859(1)	9.1180(2)	16.7520(6)	9.6159(2)
<i>c</i> (Å)	12.1967(2)	15.6820(2)	9.0971(3)	23.0238(4)	10.4487(3)	7.3150(5)	9.8215(2)
α (°)	90.0	65.6990(6)	80.509(1)	90.0	104.473(1)	90.0	90.0
β (°)	102.395(1)	85.5740(6)	77.614(1)	97.5560(5)	103.477(1)	95.479(2)	97.562(1)
γ (°)	90.0	67.3070(6)	72.838(1)	90.0	100.811(1)	90.0	90.0
<i>Z</i>	8	2	2	4	2	4	4
volume (Å ³)	1401.60(4)	2328.62(6)	406.62(2)	3521.4(12)	454.824(19)	1207.37(10)	1277.26(5)
<i>D</i> _{calc} (g cm ^{−3})	1.584	1.490	1.480	1.420	1.425	1.399	1.395
μ (mm ^{−1})	0.126	0.117	0.115	0.109	0.109	0.112	0.110
<i>2θ</i> (°)	5.96–54.96	5.82–54.94	6.08–54.98	5.82–54.96	5.82–54.96	5.82–54.96	5.82–54.96
range <i>h</i>	−15 to 15	−15 to 15	−8 to 7	−18 to 18	−6 to 6	−12 to 12	−17 to 17
range <i>k</i>	−12 to 12	−15 to 19	−9 to 8	−14 to 12	−10 to 11	−21 to 18	−10 to 12
range <i>l</i>	−15 to 15	−20 to 20	−11 to 11	−29 to 29	−10 to 13	−9 to 9	−12 to 12
reflns collected	2980	16180	2738	13721	3003	4619	4705
unique reflns	1596	10660	1818	7966	2012	2710	2803
observed reflns	1428	6898	1565	5020	1582	1966	2235
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)] ^a	0.0329	0.0463	0.0348	0.0439	0.0393	0.0392	0.0394
<i>wR</i> ₂ (all)	0.0916	0.1017	0.0880	0.0990	0.0946	0.0900	0.1091
goodness-of-fit	1.064	1.031	1.048	0.982	1.052	1.049	1.060
<i>C</i> _k * (%) ^b	77.1	73.1	74.1	71.8	73.0	70.3	71.6

^a *R*₁, crystallographic reliability index. ^b *C*_k*, Packing fraction calculated with PLATON.**Table 2. Geometrical Parameters of Hydrogen Bonds**

cocrystal	H-bond	<i>d</i> (Å) ^a	<i>D</i> (Å)	θ (°)	H-bond	<i>d</i> (Å) ^a	<i>D</i> (Å)	θ (°)
OA·(IN) ₂	O—H···N	1.58	2.5636(13)	179.5	C—H···O	2.43	3.2853(14)	134.9
	N—H···O	1.91	2.9168(13)	173.8	C—H···O	2.48	3.3055(13)	131.6
	N—H···O	2.00	3.0079(13)	170.9	C—H···O	2.60	3.5317(14)	143.8
	C—H···O	2.38	3.2109(13)	132.2				
MA·(IN) ₂	O—H···N	1.57	2.5475(18)	168.4	N—H···O	1.91	2.9095(18)	168.4
	O—H···N	1.57	2.5517(18)	175.9	N—H···O	1.92	2.9115(18)	167.1
	O—H···N	1.57	2.5523(20)	172.2	N—H···O	1.91	2.9190(20)	175.6
	O—H···N	1.57	2.5545(18)	173.2	N—H···O	1.92	2.9119(18)	166.5
	O—H···N	1.59	2.5642(18)	171.9	N—H···O	1.95	2.9630(20)	177.3
	N ⁺ —H···O [−]	1.55	2.5559(18)	171.2	N—H···O	1.97	2.9820(20)	175.7
	N—H···O	1.86	2.8538(18)	167.9	N—H···O	1.99	2.9644(18)	161.9
	N—H···O	1.86	2.8740(20)	175.6	C—H···O	2.17	3.2382(18)	166.0
	N—H···O	1.89	2.8697(18)	161.7	C—H···O	2.19	3.2549(18)	166.8
	N—H···O	1.89	2.8990(20)	178.2	C—H···O	2.21	3.2843(18)	168.7
	N—H···O	1.89	2.9030(20)	175.1	C—H···O	2.24	3.2877(19)	161.4
	O—H···N	1.65	2.6149(14)	165.6	C—H···O	2.66	3.4368(16)	127.8
SA·(IN) ₂	N—H···O	1.91	2.9211(13)	177.8	C—H···O	2.69	3.4356(15)	125.1
	N—H···O	1.97	2.9487(14)	162.5	C—H···O	2.70	3.6053(16)	141.0
	C—H···O	2.55	3.4897(15)	144.5				
	O—H···N	1.61	2.5822(18)	168.7	N—H···O	1.98	2.9789(19)	168.3
GA·(IN) ₂	O—H···N	1.63	2.5957(17)	166.0	N—H···O	1.99	2.9952(18)	170.1
	O—H···N	1.68	2.6684(17)	177.2	N—H···O	2.09	3.0725(19)	162.4
	O—H···N	1.70	2.6818(17)	174.0	N—H···O	2.11	3.0871(19)	161.6
	N—H···O	1.83	2.8341(19)	174.0	C—H···O	2.22	3.2820(20)	165.1
	N—H···O	1.84	2.8510(19)	174.6	C—H···O	2.27	3.3280(20)	163.1
	N—H···O	1.91	2.9149(19)	174.2	C—H···O	2.36	3.3570(20)	151.9
	N—H···O	1.95	2.9607(19)	173.3	C—H···O	2.37	3.3710(20)	152.9
	O—H···N	1.64	2.6179(15)	170.0	C—H···O	2.39	3.4304(19)	161.1
AA·(IN) ₂	N—H···O	1.87	2.8794(15)	178.1	C—H···O	2.46	3.4508(18)	150.6
	N—H···O	2.04	3.0275(16)	164.6	C—H···O	2.54	3.5401(19)	153.4
	C—H···O	2.35	3.4299(19)	172.1	C—H···O	2.65	3.2665(17)	115.1
	O—H···O	1.64	2.6047(14)	165.4	C—H···O	2.41	3.4844(17)	172.3
GA·IN	O—H···N	1.77	2.6710(15)	150.9	C—H···O	2.41	3.4509(17)	160.5
	N—H···O	1.85	2.8360(16)	163.5	C—H···O	2.45	3.2228(17)	127.3
	N—H···O	1.90	2.9109(17)	173.4				
	O—H···O	1.66	2.6323(15)	167.3	C—H···O	2.43	3.4375(17)	154.2
AA·IN	O—H···N	1.65	2.6301(15)	170.6	C—H···O	2.45	3.4318(19)	149.8
	N—H···O	1.91	2.9055(17)	167.6	C—H···O	2.47	3.2452(16)	127.3
	N—H···O	1.96	2.9616(16)	170.5				

^a O—H, N—H, and C—H distances are neutron-normalized.

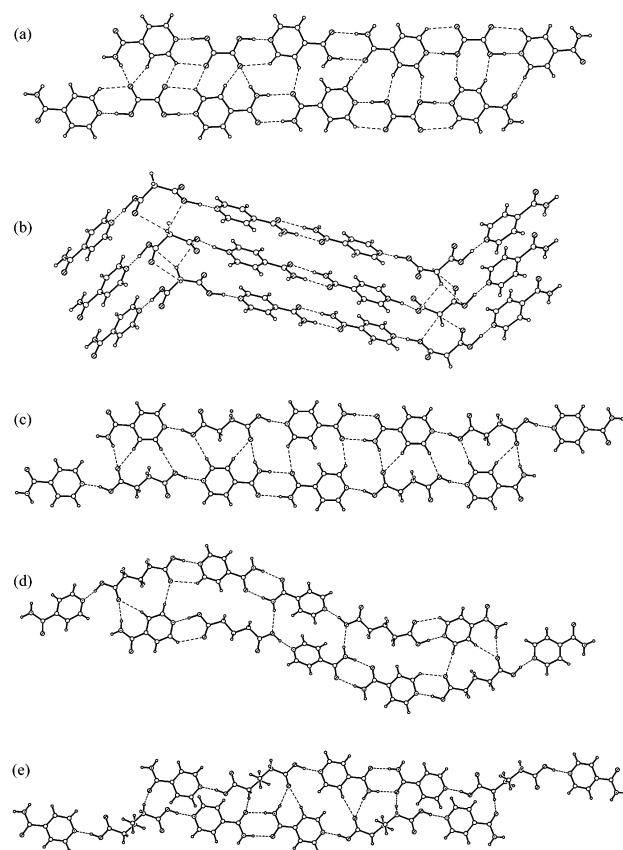


Figure 1. Hydrogen-bonded tapes of diacid and IN molecules assembled via synthons VI and II and N—H···O and C—H···O interactions between the tapes. (a) OA·(IN)₂, (b) MA·(IN)₂, (c) SA·(IN)₂, (d) GA·(IN)₂, and (e) AA·(IN)₂. The central carbon atoms of AA are not clearly visible in (e) because it is present in a folded conformation (Figure 3). Hydrogen bonds are shown as dash lines in this and subsequent figures.

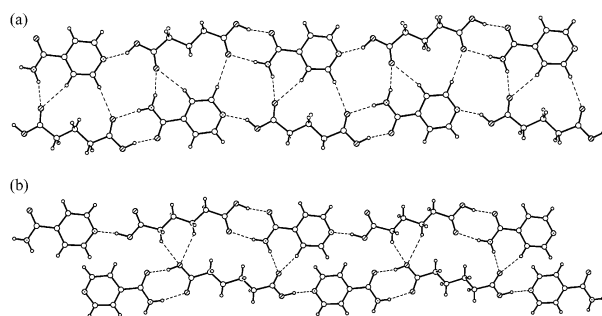


Figure 2. Hydrogen-bonded tapes of diacid and IN molecules assembled via synthons VI and VIII and N—H···O and C—H···O interactions between the tapes. (a) GA·IN and (b) AA·IN.

Discussion

Structural Analysis. Crystal structures of diacid·IN 1:2 complexes presented in this paper have predictable tapes of synthons VI and II. While there are differences in the way these hydrogen-bonded tapes aggregate as layers and then stack to form the three-dimensional crystal, these details are specific to each structure and therefore not discussed. We highlight only those structural features that deal with an unusual molecular conformation or facilitate our understanding of the variable stoichiometry in these cocrystals.

OA usually exists in the anti conformation in its crystal structure and also in many molecular complexes. The anti conformation is more stable than the syn conformation by $<0.5 \text{ kcal mol}^{-1}$.¹⁹ OA is present in the syn-planar conformation in OA·(IN)₂. There are three occurrences of syn conformation in the literature,²⁰ and all of these are cocrystals of OA. The first occurrence of syn-OA in the solid state was reported by Leiserowitz^{20a} in the 1:1 complex with acetamide (space group *A2/a*, $Z' = 2$ molecules of each component). The less stable syn conformation of OA in OA·(IN)₂ is stabilized by O—H···N and C—H···O hydrogen bonds of synthon VI together with a N—H···O hydrogen bond from CONH₂ (Table 2, Figure 1a). Salient bond angles and torsion angles of syn-planar COOH groups of OA are listed in Table 3. The syn-planar conformation of OA in its complex with IN is the most planar among published examples, with a O=C—C=O torsion angle of $0.13(15)^\circ$ as compared to 2.1° in OA·(acetamide). A molecule like OA can reside either on the inversion center (anti conformation) or on the 2-fold rotation axis (syn conformation) in a space group like *C2/c*, *A2/a*. Generally, diacids occupy the inversion center special position in a near planar anti orientation of C=O groups in the crystal. However, if the diacid occupies the 2-fold rotation axis, the syn C=O groups are usually inclined.²¹ The present case is unique in that OA occupies the 2-fold axis special position in a perfect syn-planar conformation. We believe that the C=O groups can be in close proximity (O···O 2.76 Å) despite the severe lone-pair repulsion because the oxygen atoms are engaged in extensive hydrogen bonding and this minimizes their mutual repulsion.

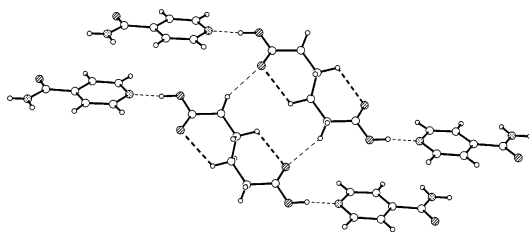
The MA·(IN)₂ cocrystal structure has three symmetry-independent MA molecules and six unique IN molecules. The crystallographic-independent MA molecules have different bond angles and torsion angles (Supporting Information), i.e., they adopt different conformations in the crystal. The phenomenon of multiple molecules in the asymmetric unit ($Z' > 1$) continues to interest crystallographers and structural chemists.²² Database analyses have been carried out to understand high Z' structures, but the exact reasons are still not fully understood. We note that O—H···N hydrogen bonds in symmetry-independent occurrences of synthon VI are short (strong) with a typical O···N distance of ca. 2.55 Å (Table 2). Crystallization of multiple conformations of a molecule from solution to the solid state is common in structures stabilized by strong hydrogen bonds (e.g., alcohols).

GA and AA cocrystals were obtained with 1:2 and 1:1 composition. The three molecules of GA, two in the 1:2 crystal and one in the 1:1 crystal, have a syn orientation (O=C—C=O = 4.5, 6.1, 2.5°). There are many occurrences of the syn conformer of GA in the CSD. AA is present in the extended zigzag conformation in AA·IN but in the folded S-shaped conformation in AA·(IN)₂. The S-shaped conformation is stabilized by an intramolecular C—H···O hydrogen bond (2.65 Å, 115.1°) in a six member ring (Figure 3).²³ The folded conformation is more stable than the extended, zigzag conformation by $0.63 \text{ kcal mol}^{-1}$, as calculated in Cerius² using the Dreiding force field.

GA·IN and AA·IN cocrystals (1:1) have tapes of acid-pyridine VI and acid-amide VIII synthons connected

Table 3. Conformation of OA in OA·(IN)₂ and Some Structures in the CSD

	<i>anti-planar</i>		<i>syn-planar</i>		
	OA·(IN) ₂ ^a (this paper)	OXLACM ^a (ref 20a)	COGREV ^a (ref 20b)	FUNCUM ^{a,b} (ref 20c)	OXALAC05 ^c (ref 27)
	bond length (Å)				
C(1)–C(2)	1.5601(14)	1.529(7)	1.534	1.539	1.542
C(2)=O(3)	1.2172(13)	1.212(6)	1.199	1.189	1.218
				1.195	
C(2)=O(4)	1.2923(13)	1.298(6)	1.298	1.304	1.303
O(4)···O(5)	2.621	2.590	2.574	2.573	
O(3)···O(6)	2.763	2.728	2.754	2.768	
	bond/torsion angle (°)				
C(1)–C(2)=O(3)	119.61(9)	119.6(5)	120.248	120.796	122.07
				121.136	
C(1)–C(2)–O(4)	114.24(9)	114.1(4)	113.169	113.251	110.89
				113.362	
O(3)=C(2)–O(4)	126.14(10)	126.2(5)	126.581	125.947	127.04
				125.482	
O(3)=C(2)–C(1)=O(6)	0.13(15)	2.1	13.81	5.621	180.0

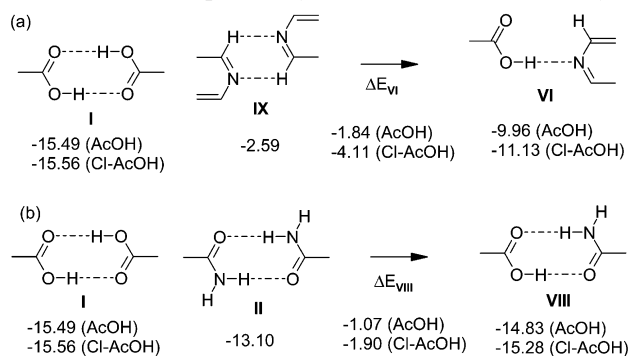
^a *syn*-Planar conformation in cocrystal. ^b Full molecule in asymmetric unit. ^c *anti*-Planar conformation in pure OA.**Figure 3.** Folded S-conformer of AA in AA·(IN)₂. The intramolecular C–H···O hydrogen bond is shown with bold dash lines.

via N–H···O and C–H···O hydrogen bonds (Figure 2). Dicarboxylic acids (e.g., SA, fumaric acid)¹⁴ hydrogen bond with the pyridine acceptor of IN in a symmetrical motif (1:2 cocrystal). It is possible that hydrogen bonding of one COOH will slightly alter the acidity of second COOH (e.g., in cocrystal of OA),^{20a} in effect differentiating between the two donor groups. However, such inductive effects will fall off over a long range in GA and AA. Second, the change in stoichiometry may not be due to orientation of donor groups^{13h} because 1:1 cocrystals are obtained with both even and odd member diacids. In the 1:1 cocrystal, the same COOH donor groups hydrogen bond with the best acceptor (pyridine N) and second best acceptor (CONH₂) via synthons VI and VIII. The reasons for alternative crystallization pathways are discussed next.

Synthon Energy and Database Analysis. Hydrogen bond synthon energies were calculated in Spartan using the RHF 6-31G** basis set. To cover dicarboxylic acids with different strengths in the present series (Table 4),²⁴ chloroacetic acid and acetic acid were taken to represent strong and weak acids, respectively. A reason for selecting Cl–AcOH is that it is a strong acid that hydrogen bonds with IN in a neutral cocrystal without transfer of proton. Computed synthon energies on model complexes AcOH·pyridine, AcOH·CH₃CONH₂, Cl–AcOH·pyridine, and Cl–AcOH·CH₃CONH₂ (Scheme 3) are used for further discussion of hydrogen bonding

Table 4. pK_a (First Step) of Carboxylic Acids^a

acid	pK _a	acid	pK _a
OA	1.23	AA	4.43
MA	2.83	acetic acid	4.75
SA	4.16	chloroacetic acid	2.85
GA	4.31		

^a Ref 24.**Scheme 3.** Energy of Hydrogen Bond Synthons Calculated in Spartan (RHF/6-31G**, kcal mol^{−1})^a

^a E_{synthon} refers to the energy of the hydrogen bond motif and $\Delta E_{\text{synthon}}$ is the stabilization of heterosynthon as compared to homodimers. (a) CH₃COOH·pyridine, ClCH₂COOH·pyridine. (b) CH₃COOH·CH₃CONH₂, ClCH₂COOH·CH₃CONH₂.

in the diacid·IN system. E_{synthon} is the energy of the hydrogen bond motif and $\Delta E_{\text{synthon}}$ is the energy difference between the heterosynthon and the constituent homosynthons. $\Delta E_{\text{synthon}}$ calculations for VI and VIII show that acid–pyridine and acid–amide heterosynthon is favored over the constituent homosynthons for both Cl–AcOH and AcOH but to different extents. ΔE_{VI} and ΔE_{VIII} for complex with Cl–AcOH are quite different (−4.11, −1.90 kcal mol^{−1}), but the energy difference for AcOH is small (−1.84, −1.07 kcal mol^{−1}). Heterosynthon VI is generally favored when COOH, pyridine, and CONH₂ groups compete for hydrogen bonding ($\Delta E_{\text{VI}} < \Delta E_{\text{VIII}}$). For strong carboxylic acids, VI is always formed

in preference to VIII ($\Delta E_{VI} - \Delta E_{VIII} = -2.21$ kcal mol⁻¹, Cl-AcOH), but for weak acids, the selectivity is moderate ($\Delta E_{VI} - \Delta E_{VIII} = -0.77$ kcal mol⁻¹, AcOH). We assume that entropy (kinetic factors) is equally important in these recognition events because they are bimolecular synthons and so differences in enthalpy are an indication of free energy differences. If a product heterosynthon is more stable relative to starting homosynthons, then it is more likely to be formed. That such an assumption is reasonable in the present family of crystal structures is validated by CSD statistics. In the subdatabase of 63 organic crystal structures containing COOH, pyridine (C=N-C), and CONH functional groups, the acid-pyridine hydrogen bond is present in 39 hits as compared to only five hits for acid-amide when O...O and O...N distances within the van der Waals sum were considered.

The variation of $\Delta E_{synthon}$ with donor acidity may be explained as follows. Acid-pyridine recognition VI has a single hydrogen bond (O-H...N) with auxiliary contribution (occasionally) from a weak C-H...O interaction. The energy of synthon VI decreases for weak carboxylic acids (compare E_{VI} for Cl-AcOH and AcOH, Scheme 3), and this is also reflected in the lengthening of the O-H...N hydrogen bond in 1:2 cocrystals (Table 2, O...N (Å): OA, 2.56; AA, 2.62). However, because numerous directional (long range) and isotropic (short range) forces determine the geometry of a particular interaction in the crystal, a regular increase in the O...N distance with increasing pK_a is not observed in the series. In acid-amide VIII, as the O-H...O bond lengthens, the N-H...O interaction becomes shorter (because C=O is a better acceptor) and hence the synthon energy is not so sensitive to donor strength²⁵ (compare E_{VIII} for Cl-AcOH and AcOH, Scheme 3). The difference in $\Delta E_{synthon}$ for VI and VIII diminishes for weak acid because VI becomes weaker but the energy of VIII is largely invariant.

Finally, we note that success in cocrystallization depends not only on the choice of complementary molecules but also on many other critical factors such as similar solubility, size match, solvent, and temperature. Hence, the cocrystals isolated in our experiments represent only a subset of possible combinations. Several attempts to identify a 1:1 cocrystal of OA, MA, and SA gave 1:2 stoichiometry even when diacid was used in excess.²⁶ Results reported in this paper were confirmed in multiple experiments. We are carrying out crystallization under different solvent/temperature conditions and with mechanical grinding to discover other forms and stoichiometry. Our attempts to correlate calculated lattice energies of crystals (Mimimixer, Cerius²) were thwarted because the space group, number of symmetry-independent molecules, and molecular conformation change from structure to structure.

Melting Point Alternation. The observed melting point (by DSC) and density, the packing fraction (from X-ray structure) in diacid·(IN)₂ cocrystals, and the corresponding pure α,ω -alkanedicarboxylic acids²⁷ are displayed in Figure 4. Melting point alternation in pure diacids is explained through differences in molecular conformation and packing motifs: even diacids close pack in a parallelogram shape with no voids whereas odd diacids adopt less stable conformations and pack

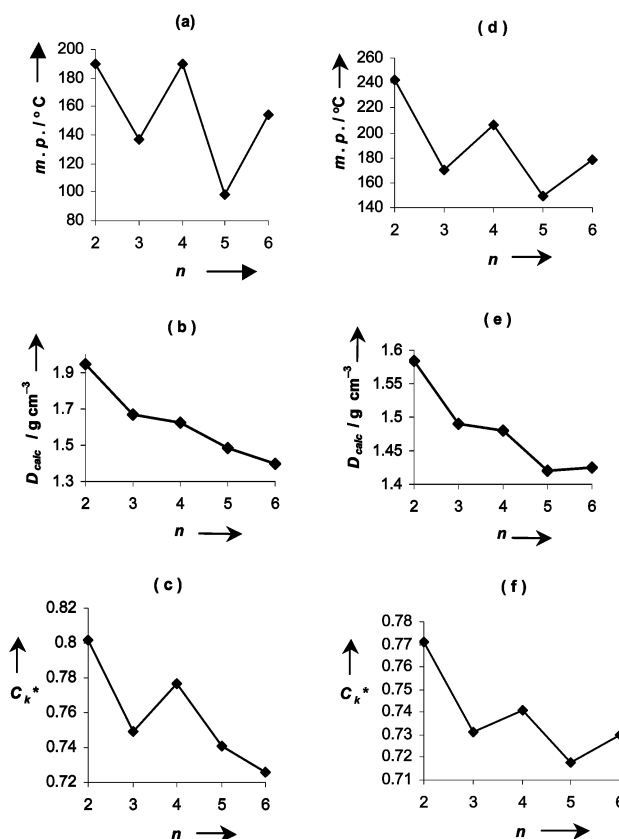


Figure 4. Melting point (a), crystal density (b), and packing fraction (c) for α,ω -alkanedicarboxylic acids using data taken from ref 27. Melting point (d), crystal density (e), and packing fraction (f) for diacid·(IN)₂ cocrystals. Note that melting point alternation in cocrystals correlates with D_{calc} and C_k^* values.

Table 5. Melting Point of Aliphatic Dicarboxylic Acids and Their 1:2 Cocrystals with IN, Diacid·(IN)₂

dicarboxylic acid	mp (°) of diacid ^a	mp (°) of cocrystal
OA	190	243
MA	137	170
SA	193	206
GA	98	149
AA	155	178

^a Ref 27.

as trapezoids with small voids. Cocrystals have higher melting points than the corresponding pure diacids (Table 5) because strong hydrogen bonds and efficient close packing stabilize the structures of molecular complexes. The T_m values of cocrystals with $n = 2-6$ carbon atoms show an alternation of even series having a higher melting point than odd members. Both D_{calc} and C_k^* alternate in these cocrystals, although the correlation is somewhat superior with packing fraction. Inasmuch as enthalpy factors determine the melting point, D_{calc} (or C_k^*) is correlated with T_m of the crystal. Our results together with data on (acid)₂·(pyrazine)²⁸ cocrystals suggest that melting point alternation is a property of the pure carboxylic acids as well as their crystalline complexes.

Conclusions

We have analyzed carboxylic acid-IN crystal structures in a family of homologous α,ω -alkanedicarboxylic

acids to better understand competition and interplay between acid–pyridine and acid–amide hydrogen bond synthons. Five cocrystals of diacid·IN with 1:2 stoichiometry are isolated and characterized by XRD. Hydrogen bonding in these five structures obeys hierarchy rules. Furthermore, two cocrystals with 1:1 composition are characterized in which hydrogen bonding does not follow from the best donor–best acceptor order. The reason for an alternative crystallization pathway in acid–IN complexes is explained by a combination of synthon energy and structural database derived arguments. Acid–pyridine synthon is favored over acid–amide for strong carboxylic acid, but the preference is marginal for weak acid. That there are no formal rules for predicting crystal structures with competing supramolecular organization was noted very recently in the same journal.^{6f} We make a beginning toward understanding hydrogen bond preferences in multifunctional systems with a semiquantitative synthon energy-based approach. The observed melting point alternation in diacid·(IN)₂ cocrystals is correlated with a change in crystal density and packing fraction.

Note Added in Proof

After submitting this paper, we reported the crystal structure of 4-hydroxybenzoic acid·IN that has phenol–pyridine and acid–amide hydrogen bonds and not the expected acid–pyridine and amide–amide synthons. Vishweshwar, P.; Nangia, A.; Lynch, V. M. *CrystEngComm* **2003**, 5, 164–168.

Experimental Section

Crystallization. All chemicals were purchased from Lancaster and used as such for crystallization. The components were well ground and dissolved in appropriate solvents. All crystallization experiments were carried out under near identical conditions and gave recurring results in at least three batches. The melting point was recorded on a Fisher-Johns apparatus and also from the onset temperature of endotherm in DSC.

OA·(IN)₂. OA dihydrate (26 mg, 0.2 mmol) and IN (50 mg, 0.4 mmol) were dissolved in a hot water–ethanol (1:1) mixture. Colorless cubelike crystals were formed after a few days upon evaporation of the solvent; mp 241–243 °C. IR (KBr): 3385, 3161, 1686, 1404, 1236, 1032, 852, 653 cm⁻¹.

MA·(IN)₂. A 1:2 mixture of MA (21 mg, 0.2 mmol) and IN (50 mg, 0.4 mmol) was dissolved in hot ethanol. Needlelike colorless crystals were obtained after a few days; mp 167–170 °C. IR (KBr): 3389, 3178, 1722, 1392, 1153, 1055, 856, 650 cm⁻¹.

SA·(IN)₂. SA (24 mg, 0.2 mmol) was dissolved in hot ethyl acetate–methanol (1:1) together with IN (50 mg, 0.4 mmol). Colorless crystals were formed after 1 week upon evaporation of the solvent; mp 205–206 °C (134–136 °C).¹⁴ IR (KBr): 3395, 3171, 1686, 1413, 1317, 1184, 1063, 1014, 798, 619 cm⁻¹.

GA·(IN)₂. Light brown platelike crystals of the complex were obtained upon crystallization of a 1:2 mixture of GA (27 mg, 0.2 mmol) and IN (50 mg, 0.4 mmol) from hot methanol solution; mp 148–149 °C. IR (KBr): 3410, 3175, 1682, 1556, 1418, 1387, 1283, 1182, 1016, 852, 642 cm⁻¹.

AA·(IN)₂. A powdered mixture of AA (30 mg, 0.2 mmol) and IN (50 mg, 0.4 mmol) was dissolved in hot methanol. Needle-shaped crystals were obtained after a few days; mp 177–178 °C. IR (KBr): 3399, 3158, 2957, 1686, 1410, 1258, 1016, 852, 804, 754, 644 cm⁻¹.

GA·IN. A 1:1 mixture of GA (54 mg, 0.4 mmol) and IN (50 mg, 0.4 mmol) was dissolved in hot methanol. Light brown crystals were collected after a few days; mp 134–135 °C. IR

(KBr): 3391, 3194, 1701, 1589, 1545, 1414, 1281, 1186, 1065, 1005, 883, 858, 756, 638 cm⁻¹.

AA·IN. AA (60 mg, 0.4 mmol) and IN (50 mg, 0.4 mmol) were dissolved in hot methanol. Needle-shaped crystals were formed after a few days; mp 163–165 °C. IR (KBr): 3354, 3169, 2932, 1705, 1601, 1555, 1501, 1466, 1412, 1269, 1186, 1063, 1016, 941, 854 cm⁻¹.

XRD. Reflections were collected on Nonius Kappa CCD diffractometer at 153(2) K with incident X-ray radiation Mo Kα (λ = 0.71073 Å). The crystals were cooled with an Oxford Cryosystem device attached to a CCD machine. Data reductions were performed using DENZO-SMN.²⁹ Structures were solved by direct methods using the SHELXS-97 program and refined by full-matrix least-squares refinement on F² with anisotropic displacement parameters for the non-H-atoms using SHELXL-97.³⁰ The function, Σw(|F_o|² - |F_c|²), was minimized, where w = 1/[(σ(F_o))² + (0.0415*P)² + (0.9360*P)] and P = (|F_o|² + 2|F_c|²)/3. Equations for calculating R(F), R_w(F²), and the goodness of fit, S, are given below. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are taken from the International Tables for X-ray Crystallography. Geometrical analysis was carried out in PLATON³¹ on a Silicon Graphics Octane2 workstation. Details of cell parameters, data collection, and structure refinement are summarized in Table 1. Hydrogen bond metrics are listed in Table 2.

$$R_w(F^2) = \{\sum w(|F_o|^2 - |F_c|^2)^2 / \sum w(|F_o|^4)\}^{1/2}$$

where w is the weight given to each reflection.

$$R(F) = \sum (|F_o| - |F_c|) / \sum |F_o|$$

for reflections with F_o > 4Σ(F_o) and

$$S = [\sum w(|F_o|^2 - |F_c|^2)^2 / (n - p)]^{1/2}$$

where n is the number of reflections and p is the number of refined parameters.

Computations. Hydrogen bond energy was calculated in the RHF 6-31G** basis set with Spartan³² on a Pentium PC. The crystal lattice energy was calculated in Cerius²³³ with Dreiding force field on an Octane2 workstation.

Crystallography Database. The CSD,^{9a} ConQuest version 1.4 (April 2002 update), operating on a Pentium PC was used for statistical analysis. Searches were carried out on organic crystal structures with standard distance and angle cutoff criteria.^{9b}

DSC. DSC was recorded on a Perkin-Elmer DSC4 at a scan rate of 10° min⁻¹.

Acknowledgment. A.N. thanks the CSIR (01/1738/02/EMR-II) for research funding. The UPE program of UGC supports UoH. P.V. thanks the CSIR for a fellowship. V.M.L. thanks the NSF (CHE-9807702) for funding.

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

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CG034037H