CRYSTAL GROWTH & DESIGN

ACS Editors' Choice

Article

pubs.acs.org/crystal

Terms of Use

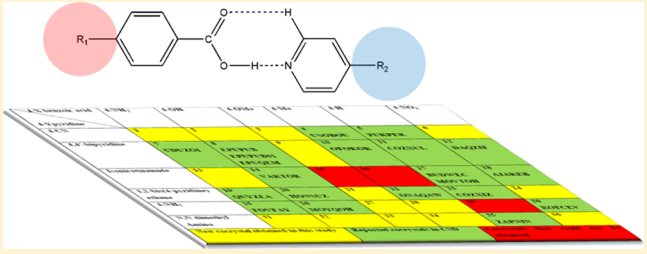
Combinatorial Exploration of the Structural Landscape of Acid–Pyridine Cocrystals

Arijit Mukherjee and Gautam R. Desiraju*

Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, India

Supporting Information

ABSTRACT: The structural landscape of acid–pyridine cocrystals is explored by adopting a combinatorial matrix method with 4-substituted benzoic acids and 4-substituted pyridines. The choice of the system restricts the primary synthon to the robust acid–pyridine entity. This methodology accordingly provides hints toward the formation of secondary synthons. The pK_a rule is validated in the landscape by taking all components of the matrix together and exploring it as a whole. Along with the global features, the exploration of landscapes reveals some local features. Apart from the identification of secondary synthons, it also sheds light on the propensity of hydration in cocrystals, synthon competition, and certain topological similarities. The method described here combines two approaches, namely, database analysis and high throughput crystallography, to extract more information with minimal extra experimental effort.



INTRODUCTION

The rational synthesis[1] of cocrystals has received considerable attention in recent times mainly because of the potential applications of these substances.[2,3] The key to the understanding of the formation of cocrystals lies in the concept of supramolecular synthons. Synthons can be categorized in two different types: *homosynthons* that result from the aggregation of like functionalities and *heterosynthons* which originate from mutual recognition of different molecules. Generally, cocrystals are formed when heterosynthon formation is favored over homosynthon formation. As synthons are kinetic units that encapsulate information during the process of crystallization, it is likely that they are formed initially in solution and are carried over into the final product when classical nucleation theory (CNT) is applicable. Any way of understanding the evolution of synthons in solution would be helpful in the formulation of new design strategies. The image of synthon structures in solution can be obtained directly by spectroscopic techniques and indirectly by crystallographic or computational studies. Spectroscopy, especially vibrational spectroscopy, has been successful in a few cases in the depiction of primary synthon structures in solution and their correlation with the solid state.[4,5] Computational studies, on the other hand, adopt crystal structure prediction (CSP) protocols to explore the crystal energy landscape for a particular system.[6] The energy landscape generally explores the low energy–high density region and provides hints toward the kinetic structural possibilities, which in many cases may be linked to synthon structures. The crystallographic route to access such diverse and robust synthon information would be to see the recurrence of structural patterns. In this context, in analogy with the energy landscape, the concept of structural landscape was introduced.[7,8] The structural landscape explores multiple structural possibilities (which includes synthon possibilities also) by small chemical perturbations, and the recurrence of synthon patterns or other structural features carries with it hints as to the probable kinetics of crystallization.[7] Therefore, any study of the structural landscape needs to define the structural space that is to be investigated, and certain variations in this space are required that can be taken as *structural variables*.

The structural landscapes have been explored for single molecules so far by chemical perturbation,[7,9] but reports on the full exploration of structural landscapes of cocrystals are still limited.[10,11] The structural landscapes of cocrystals differ from those of single molecules in two respects: (i) As the mutual recognition between coformers usually occurs in solution, the probability of polymorphism is reduced in cocrystals, and therefore the structural landscape of cocrystals is expected to give less kinetic information in terms of variability of primary synthons. Instead, it will give a hint to robustness. (ii) Exploration of structural landscapes of cocrystals covers more structural space compared to single components, and the overlap of structural space of individual coformers may not always be mutually exclusive. In other words, the structural landscapes of cocrystals will sample more structural space in terms of secondary synthons as landscapes of cocrystals represent the addition of two (or more) individual landscapes.

To reduce the difficulties of overlap of multiple structural spaces and to reduce the competition between primary synthons, we chose the acid–pyridine synthon as the primary synthon for this study. The acid–pyridine synthon is robust.[12−14] As some

Received: December 12, 2013
Revised: January 27, 2014
Published: February 16, 2014

dx.doi.org/10.1021/cg401851z | *Cryst. Growth Des.* 2014, 14, 1375−1385

recent reports reveal, this synthon is formed in nearly 98% cases when competing hydrogen bond donors/acceptors are absent.[15] In this study, therefore, the exploration of the landscape is done by fixing the primary synthon mostly to acid−pyridine and then varying the 4-substitutions in both benzoic acids and pyridines (Figure 1). It should be noted here that substitution is a very

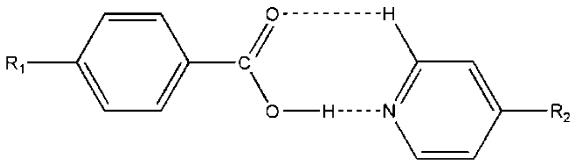


Figure 1. The combinatorial matrix is explored by varying 4-substitutions both in substituted benzoic acids and substituted pyridines.

useful tool in chemical perturbation in structural landscapes.[9,11] This can be done primarily in two ways (i) by keeping the substituents fixed and varying their positions or (ii) by changing the substituents and keeping their relative positions fixed. In this study, we have adopted the second strategy, and the landscape is explored by formation of cocrystals between 4-substituted acids and 4-substituted pyridines. As each cocrystal is considered as a data point in the landscape, this method of exploration of the structural landscape is a combinatorial matrix with 4-substituted benzoic acids representing the columns and 4-substituted pyridines representing the rows.

The method itself offers a combination of Cambridge Structural Database (CSD) analysis and high throughput crystallography[16] and provides a systematic way of acquiring insights from a particular landscape. The advantage that this method provides is that it sheds light on some general issues while taken as a whole, and it also gives hints to the kinetics when one tries to study individual columns/rows. As the primary synthon is already fixed, this method provides hints toward secondary synthons which when interpreted in terms of stages of crystallization can be correlated with the hierarchy of supramolecular organizations.

EXPERIMENTAL SECTION

Preparation of Cocrystals. Appropriate acids and pyridines were ground together in 1:1 molar ratio with the addition of a few drops of MeOH in a mortar. The ground mixture was then dissolved in a set of solvents. Crystals were obtained by solvent evaporation method. The specific crystallization conditions are given below. Because solvents play a role in the organization of coformers in solution, the choice of solvent is likely to affect the structural landscape.

*4-Cyanopyridine−4-Aminobenzoic Acid (**1**).* Block-shaped and pale yellow diffraction quality crystals were obtained from MeOH, EtOH, and iPrOH after three days.

*4-Cyanopyridine−4-Hydroxybenzoic Acid (**2**).* Diffraction quality crystals were obtained from ethanol and iPrOH and MeCN after four days.

*4-Cyanopyridine−4-Methoxybenzoic Acid (**3**).* Diffraction quality crystals were obtained from EtOH after three days.

*4-Cyanopyridine−4-Nitrobenzoic Acid (**6**).* Diffraction quality crystals were obtained from $MeNO_2$ after four days.

*4,4′-Bipyridine−4-Methoxybenzoic Acid (**9**).* Diffraction quality plate like crystals were obtained from $MeNO_2$, EtOAc, and $CHCl_3$ after three days.

*Isonicotinamide−4-Aminobenzoic Acid (**13**).* Diffraction quality platelike crystals were obtained from MeOH and THF after three days.

*1,2-Bis-(4-pyridyl)-ethane−4-Methoxybenzoic Acid (**21**).* Diffraction quality crystals were obtained from EtOAc after three days.

*1,2-Bis-(4-pyridyl)-ethane−4-Nitrobenzoic Acid (**24**).* Diffraction quality platelike crystals were obtained from EtOH after four days.

*4-Aminopyridine−4-Methoxybenzoic Acid (**27**).* Diffraction quality crystals were obtained from MeOH after three days.

*4-Aminopyridine−4-Methylbenzoic Acid (**28**).* Diffraction quality crystals were obtained from EtOAc and $CHCl_3$ after three days.

*4-N,N′-Dimethylaminopyridine−4-Aminobenzoic Acid (**31**).* Diffraction quality crystals were obtained from 1,4-dioxane after four days.

*4-N,N′-Dimethylaminopyridine−4-Hydroxybenzoic Acid (**32**).* Diffraction quality crystals were obtained from iPrOH after four days.

*4-N,N′-Dimethylaminopyridine−4-Methoxybenzoic Acid (**33**).* Diffraction quality crystals were obtained from $CHCl_3$ after three days.

*4-N,N′-Dimethylaminopyridine−4-Methylbenzoic Acid (**34-I**).* Diffraction quality crystals were obtained from MeCN after three days.

*4-N,N′-dimethylaminopyridine−4-methylbenzoic acid (**34-II**).* Diffraction quality crystals were obtained from acetone and THF after three days.

*4-N,N′-Dimethylaminopyridine−Benzoic Acid (**35**).* Diffraction quality crystals were obtained from MeOH after four days.

*4-N,N′-Dimethylaminopyridine−4-Nitrobenzoic Acid (**36**).* Diffraction quality crystals were obtained from THF and EtOAc after four days.

Techniques. *Single Crystal X-ray Diffraction.* X-ray Data were collected on a Rigaku Mercury 375R/MCCD (XtaLABmini) diffractometer with a graphite monochromator using Mo Kα radiation (λ = 0.7 A∀), attached with a Rigaku low-temperature gas spray cooler. The data were processed with the Rigaku CrystalClear software.[17] Structure solution and refinement were carried out using SHELX97[18]

Table 1. Matrix Method for the Family of Cocrystals Obtained between 4-Substituted Acids and 4-Substituted Pyridines

4-Ypyridine \ 4-X benzoic acid	4-NH_2	4-OH	4-OMe	4-Me	4-H	4-NO_2
4-CN	1	2	3	4 USOBOU	5 PUKPER	6
4,4'-bipyridine	7 UDUZOI	8 EPUPUB EPUPUB01 EPUQEM	9	10 OFOKOK	11 COZXUL	12 DAQZIF
Isonicotinamide	13	14 VAKTOR	15	16	17 BUDWEC MOVTOH	18 AJAKEB
1,2-bis(4-pyridine) ethane	19 QUYZEA	20 HONSUZ	21	22 ONAQAW	23 COZXIZ	24
4-NH_2	25 FOVFAY	26 MOYQOH	27	28	29	30 ROFCEV
N,N dimethyl Amino	31	32	33	34	35 ZAPNIN	36

New cocrystal obtained in this study | Reported cocrystals in CSD | Cocrystals that could not be obtained

dx.doi.org/10.1021/cg401851z | Cryst. Growth Des. 2014, 14, 1375−1385

incorporated in the WinGXsuite.[19] All the non-hydrogen atoms were refined anisotropically, whereas all the hydrogen atoms were refined isotropically. Aromatic hydrogen atoms were fixed on carbon atoms based on riding model. Acidic hydrogens were located from the Fourier map.

Database Studies. CSD searches were performed[20] with all the bases and acid included in the matrix by imposing the criteria that three-dimensional coordinates should be determined and the search restricted only to organic molecules.

RESULTS

Combinatorial Matrix Method. The combinatorial matrix method intends to maximize the available information content from a given landscape. Specifically, it is also important to observe what happens when two coformers are varied simultaneously in a systematic way. High throughput, by its definition, indicates a way by which a minimal experimental setup produces a greater output. In this context, the combinatorial matrix method is introduced. This method explores local features and points towards secondary synthons, topological similarity, and on the other hand it can shed light on crystallization mechanism as well as long-standing issues such as salt versus cocrystal formation. The matrix discussed in this paper is given below (Table 1).

Database Studies. Besides exploring global and local features, the matrix method also combines database and experimental results in a rational way. In this work, 17 out of 36 matrix elements are taken from the CSD.

Database Studies for Column (Pyridine) Elements. (i) 4-Cyanopyridine. A CSD search for the cocrystals of 4-cyanopyridine with 4-substituted benzoic acids gave two hits. Both the cocrystals are included in the matrix: USOBOU (4-methyl benzoic acid) and PUKPER (benzoic acid).

(ii) 4,4′-Bipyridine. A CSD search on the cocrystals of 4,4′-bipyridine with 4-substituted benzoic acids with acid-pyridine synthon resulted in 34 hits. Another search for salts with the carboxylate···pyridinium synthon did not give any hit. This shows the preference of 4,4′-bipyridine for the formation of cocrystals over salts when cocrystallized with various 4-substituted benzoic acid coformers. The cocrystals that are included in the matrix are COZXUL (benzoic acid), DAQZIF (4-nitrobenzoic acid), OFOKOK (4-methylbenzoic acid), EPUPUB, EPUPUB01, EPUQEM (4-hydroxybenzoic acid), and UDUZOI (4-aminobenzoic acid). Among these cocrystals, noteworthy is the 1:2 cocrystal of 4,4′-bipyridine with 4-hydroxybenzoic acid.[21] This system shows synthon polymorphism, which is very rare and involves deep-rooted changes in primary synthon formation.

(iii) Isonicotinamide. The CSD search on isonicotinamide cocrystals with 4-substituted benzoic acids gives seven hits (ASAXUN and ASAXUN01 are the same crystal form and therefore only ASAXUN is considered). Among these seven hits, five are binary cocrystals, whereas the other two are ternary. Isonicotinamide is a very good and a good supramolecular reagent especially when the formation of a ternary cocrystal is involved. Among the five binary systems, the acid−pyridine heterosynthon is formed in three cases (AJAKEB, ASAXUN, BUDWEC), whereas VAKTOR shows the presence of the acid··· amide synthon. MOVTOH being a 2:1 cocrystal of benzoic acid and isonicotinamide shows the presence of both synthons. Therefore, it may be assumed that in a 1:1 situation acid··· pyridine is preferred over acid···amide with the exception of VAKTOR which is a cocrystal with 4-hydroxybenzoic acid. (It should be noted that the acidity of the phenolic −OH group in this compound is very high, resulting in various unusual features, e.g., synthon polymorphism.) Among these five binary systems, VAKTOR, AJAKEB, and BUDWEC (and also MOVTOH) are the components of the matrix.

(iv) 1,2-Bis(4-pyridyl) Ethane. 1,2-Bis(4-pyridyl) ethane forms five cocrystals with 4-substituted benzoic acids (barring HONSUZ01 which is same structure with HONSUZ and YAKVUC which is a ternary system that encapsulates *N*,*N*′-dimethylformamide). Among the five cocrystal systems, four are 1:1 cocrystals, whereas one cocrystal was found that shows 1:2 composition (HONSUZ). All five complexes are cocrystals in nature.

(v) 4-Aminopyridine. A search with 4-aminopyridininium cation with 4-substituted carboxylate anion generated 31 hits. Among these 31 hits, 13 contain water. It forms three salts with 4-substituted benzoate anions (FOVFAY, MOYQOH, ROFCEV). Among these three salts, two are hydrated (FOVFAY and MOYQOH), and all three salts are the components of the matrix.

(vi) 4-N,N′-Dimethylaminopyridine. A CSD search on the cocrystals show that there are three salts reported with 4-*N*,*N*′-dimethylaminopyridinium cation with 4-substituted benzoates. Among these three salts, FETDEO and ZAPNIN form hydrates, while GUKWAL is anhydrous. It should also be noted that in GUKWAL, the coformer is a terephthalate anion that shows the presence of an excess number of oxygens. The search made with 4-*N*,*N*′-dimethylaminopyridinium with neutral 4-substituted acids did not give any hit.

Database Studies for Row (Acid) Elements. (i) 4-Aminobenzoic Acid. 4-Aminobenzoic acid searched with 4-substituted pyridines gave eight hits (barring UDUZOI01 which is identical with UDUZOI). Among these eight hits, three are solvated (GOLHOF, KOMQOT, LATDIV). Among the five cocrystals without solvent, four (OCATUH, QUYJEA, UDUZOI, VUJNEO) are of 1:1 composition and except VUJNEO, and others show the presence of an additional amino $-NH_2\cdots O{=}C$. In VUJNEO and RILZIF (with 1:2 composition), both amine $-NH_2$ and carboxylic −OH participate in hydrogen bonding with pyridine nitrogen. Two matrix elements are included in these eight hits (UDUZOI, QUYJEA). Apart from these eight hits, there is a report of a salt hydrate, FOVFAY, which is also included in the matrix.

(ii) 4-Hydroxybenzoic Acid. A CSD search generated 15 hits for the cocrystals made by 4-hydroxybenzoic acid with 4-substituted pyridines (barring HONVUC01 which is identical with HONVUC). Notably, the presence of synthon polymorphs with 4,4′-bipyridine is seen. The structures although mostly dictated by acid−pyridine heterosynthons show the occurrence of phenolic $-OHPPPN_{pyr}$ interactions. This indicates the similar acidity of acidic and phenolic group of this compound. It also produces two salts: MOYQOH and LESYIT. MOYQOH is a salt hydrate with 4-aminopyridinium ion and therefore is a matrix element.

(iii) 4-Methoxybenzoic Acid. There is no report of cocrystals or salts of 4-methoxybenzoic acid with the 4-substituted pyridines.

(iv) 4-Methylbenzoic Acid. 4-Methylbenzoic acid forms five cocrystals with 4-substituted pyridines. Among these, three are elements of the matrix: OFOKOK (4,4′-bipyridine), ONAQAW (1,2-bis(4-pyridine) ethane), and USOBOU (4-cyanopyridine). The acid participates in a ternary cocrystal AJAKIF (with isonicotinamide and 3,5-dinitrobenzoic acid) and a cocrystal hydrate (ZAQMIP). There is no report of a salt for 4-methylbenzoic acid.

dx.doi.org/10.1021/cg401851z | *Cryst. Growth Des.* 2014, 14, 1375−1385

Table 2. Crystallographic Information Table for Cocrystals Studied in the Combinatorial Matrix

name	1	2	3	6	9
formula	$C_7H_7NO_2$, $C_6H_4N_2$	$C_7H_6O_3$, $C_6H_4N_2$	$C_8H_8O_3$, $C_6H_4N_2$	$C_7H_5NO_4$, $C_6H_4N_2$	$C_{10}H_8N_2$, $2(C_8H_8O_3)$
molecular weight	241.25	242.23	256.26	271.23	460.47
crystal system	monoclinic	monoclinic	triclinic	monoclinic	monoclinic
space group	$C2/c$	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
a (Å)	13.2990(16)	7.279(4)	7.4624(16)	7.4700(7)	9.0486(11)
b (Å)	8.0627(10)	11.601(6)	7.7677(17)	6.7036(6)	10.8727(13)
c (Å)	22.101(3)	13.669(7)	10.981(2)	24.933(2)	23.603(3)
α (°)	90	90	91.289(6)	90	90
β (°)	100.795(7)	100.809(8)	95.146(7)	104.302(7)	98.100(7)
γ (°)	90	90	102.190(7)	90	90
volume (Å^3)	2327.9(5)	1133.8(10)	619.1(2)	1209.85(19)	2299.0(5)
Z	8	4	2	4	4
ρ_{calc} (g/cm^3)	1.377	1.419	1.375	1.489	1.330
$F(000)$	1008	504	268	560	968
μ (Mo Kα) (mm^{-1})	0.096	0.103	0.099	0.114	0.095
temp (K)	150	150	150	150	150
θ range for data collection (°)	3.0, 27.5	3.0, 27.5	3.2, 27.5	3.2, 27.5	3.0, 27.5
R_1	0.0426	0.0485	0.0467	0.0580	0.0514
wR_2	0.1225	0.1161	0.1335	0.1604	0.1293
goodness-of-fit	1.05	1.04	1.04	1.11	1.04
reflns collected	11249	11547	6406	12205	21957
unique reflns	2669	2594	2834	2766	5264
observed reflns	2052	1930	2267	2384	3741
CCDC no.	972671	972672	972991	972673	972674

name	13	21	24	27	28
formula	$2(C_7H_7NO_2)$, $C_6H_6N_2O$	$C_{12}H_{12}N_2$, $2(C_8H_8O_3)$	$C_{12}H_{12}N_2$, $2(C_7H_5NO_4)$	$C_8H_7O_3$, $C_5H_7N_2$	$C_8H_7O_2$, $C_5H_7N_2$, $2(H_2O)$
molecular weight	396.40	488.52	518.48	246.26	266.29
crystal system	monoclinic	triclinic	monoclinic	monoclinic	triclinic
space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a (Å)	17.085(19)	11.481(4)	8.874(5)	10.0131(9)	8.96800
b (Å)	5.193(5)	17.733(5)	6.631(4)	9.7642(8)	9.45100
c (Å)	22.891(16)	18.570(6)	21.677(10)	12.7953(11)	9.63700
α (°)	90	76.543(5)	90	90	108.5300
β (°)	112.28(6)	88.680(6)	110.720(18)	99.809(7)	105.0500
γ (°)	90	81.754(6)	90	90	103.4000
volume (Å^3)	1879.0(3)	3639(2)	1193.1(11)	1232.71(19)	702.458
Z	4	6	2	4	2
ρ_{calc} (g/cm^3)	1.401	1.337	1.443	1.327	1.259
$F(000)$	832	1548	540	520	284
μ (Mo Kα) (mm^{-1})	0.103	0.095	1.443	0.096	0.094
temp (K)	150	150	150	296	150
θ range for data collection (°)	1.3, 27.5	3.0, 27.5	3.2, 27.5	3.2, 27.5	3.6, 27.5
R_1	0.0692	0.0746	0.0410	0.0451	0.0541
wR_2	0.2001	0.2196	0.1021	0.1136	0.1566
goodness-of-fit	1.14	1.04	1.05	1.04	1.03
reflns collected	18795	38329	11822	12766	7452
unique reflns	4284	16596	2728	2818	3219
observed reflns	3058	7718	2261	2095	2550
CCDC no.	972675	972992	972676	972678	972679

name	31	32	33	34-I	34-II
formula	$C_7H_6NO_2$, $C_7H_{11}N_2$, $2(H_2O)$	$C_7H_5O_3$, $C_7H_{11}N_2$	$C_8H_7O_3$, $C_8H_8O_3$, $C_7H_{11}N_2$	$C_8H_7O_2$, $C_7H_{11}N_2$, H_2O	$C_8H_7O_2$, $C_7H_{11}N_2$, $2H_2O$
molecular weight	295.34	260.29	426.46	276.33	293.34
crystal system	triclinic	triclinic	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	Cc	$P2_1/c$
a (Å)	9.3411(16)	7.9027(16)	9.612(2)	6.6469(8)	11.0254(19)
b (Å)	9.6823(17)	9.251(2)	10.0841(2)	12.9935(15)	11.0167(19)
c (Å)	10.1738(17)	9.692(2)	12.239(2)	16.782(2)	16.124(2)
α (°)	67.609(5)	70.636(5)	72.85(4)	90	90
β (°)	67.912(5)	77.528(7)	84.64(6)	94.544(7)	127.876(8)
γ (°)	88.549(6)	79.727(7)	71.17(5)	90	90

dx.doi.org/10.1021/cg401851z | Cryst. Growth Des. 2014, 14, 1375−1385

Table 2. continued

name	31	32	33	34-I	34-II
volume (Å^3)	780.8(2)	648.3(2)	1072.9(5)	1444.9(3)	1545.9(5)
Z	2	2	2	4	4
ρ_{calc} (g/cm^3)	1.256	1.333	1.320	1.270	1.260
F(000)	316	276	452	592	628
μ (Mo Kα) (mm^{-1})	0.093	0.095	0.096	0.089	0.092
temp (K)	150	150	150	150	150
θ range for data collection (°)	3.0, 27.5	3.2, 27.5	1.7, 27.5	3.1, 27.5	3.0, 27.5
R_1	0.0515	0.0535	0.0681	0.0395	0.0818
wR_2	0.1593	0.1383	0.2061	0.0942	0.2180
goodness-of-fit	0.98	0.96	1.33	1.06	1.16
reflns collected	8239	6814	11459	7602	15547
unique reflns	3575	2962	4872	3326	3531
observed reflns	2674	1986	2973	2986	2492
CCDC no.	972680	972681	972682	972683	972684

name	35	36
formula	$C_7H_5O_2$, $C_7H_{11}N_2$, H_2O	$C_7H_4NO_4$, $C_7H_{11}N_2$
molecular weight	262.30	289.29
crystal system	monoclinic	monoclinic
space group	$P2_1/c$	Cc
a (Å)	11.470(2)	11.2644(19)
b (Å)	10.6498(19)	11.2611(19)
c (Å)	13.027(2)	21.640(4)
α (°)	90	90
β (°)	121.303(11)	91.271(6)
γ (°)	90	90
volume (Å^3)	1359.7(4)	2744.4(8)
Z	4	8
ρ_{calc} (g/cm^3)	1.281	1.400
F(000)	560	1216
μ (Mo Kα) (mm^{-1})	0.091	0.105
temp (K)	150	150
θ range for data collection (°)	3.1, 27.5	3.2, 27.5
R_1	0.0562	0.0508
wR_2	0.1665	0.1115
goodness-of-fit	1.10	1.07
reflns collected	13801	13210
unique reflns	3111	6202
observed reflns	2011	5152
CCDC no.	972685	972686

(v) Benzoic Acid. There are nine reports of cocrystals of benzoic acids with 4-substituted pyridines. There are four matrix elements among these nine cocrystals: BUDWEC (isonicotinamide), MOVTOH (2:1 with isonicotinamide), COZXIZ (1,2-bis(4-pyridine) ethane), COZXUL (4,4′-bipyridine), and PUKPER (4-cyanopyridine). There are two reports of the formation of salts: IKAJAG and ZAPNIN. ZAPNIN is a salt hydrate with *N*,*N*′-dimethyaminopyridinium ion and is included in the matrix.

(vi) 4-Nitrobenzoic Acid. There are five cocrystals reported in CSD with 4-nitrobenzoic acid and 4-substituted pyridines. Among these, three are constituted with matrix elements: AJAKEB (with isonicotinamide), DAQZIF (with 4,4′-bipyridine), and ROFCEV (with 4-aminopyridinium ion). The interesting feature in ROFCEV is that one 4-nitrobenzoic acid is deprotonated, while the other one is intact.

DISCUSSION

The matrix method offers a unique opportunity of exploring the structural landscape both in terms of global features and local features. Global features are those that take into account the systematic change in the 4-position and therefore reveal an overall property. Local features, on the other hand, can be explored by taking a specific row or a column and then exploring it.

Global Features. *pK_a Rule: Salts versus Cocrystals.* The salt−cocrystal issue poses a major problem in crystal engineering.[22,23] Earlier reports on acid−pyridine cocrystals had revealed that if the pK_a difference between base and acid coformer is greater than 2 or 3 (ΔpK_a = pK_a (protonated base) −pK_a(acid)), salt formation is expected. This rule is called the pK_a rule for the formation of the cocrystals. Nangia et al. showed that negative pK_a differences between acid−base pairs will generally produce cocrystals, but in the region of Δ pK_a between 0 to 3.75, the prediction is difficult as the O−H···N has an intermediate character, while Δ pK_a > 3.75 results in salts.[24] In a recent study, it

dx.doi.org/10.1021/cg401851z | Cryst. Growth Des. 2014, 14, 1375−1385

Table 3. Salt (Orange) and Cocrystal (Blue) Region of the Matrix[a]

4-X benzoic cid / 4-Ypyridine	4-NH_2 pK_a= 4.86±0.10	4-OH pK_a= 4.57±0.10	4-OMe pK_a= 4.47±0.10	4-Me pK_a= 4.37±0.10	4-H pK_a=4.20±0.10	4-NO_2 pK_a= 3.42±0.10
4-CN pK_a= 1.92±0.10	cocrystal	cocrystal	cocrystal	cocrystal	cocrystal	cocrystal
	-2.94	-2.65	-2.55	-2.45	-2.28	-1.5
4,4'-bipyridine pK_a=3.27±0.26	cocrystal	cocrystal	cocrystal	cocrystal	cocrystal	cocrystal
	-1.59	-1.3	-1.2	-1.1	-0.93	-0.15
Isonicotinamide pK_a=3.39±0.26	cocrystal	cocrystal	15	16	cocrystal	cocrystal
	-1.47	-1.18	-1.08	-0.98	-0.81	-0.03
1,2-bis(4-pyridine) ethane pK_a=6.13±0.10	cocrystal	cocrystal	cocrystal	cocrystal	cocrystal	cocrystal
	1.27	1.56	1.66	1.76	1.93	2.71
4-NH_2 pK_a=9.26±0.12	salt-hydrate	salt-hydrate	salt	salt-hydrate	29	salt
	4.4	4.69	4.79	4.89	5.06	5.84
N,N dimethyl Amino pK_a=9.52±0.10	salt-hydrate	salt	salt	salt-hydrate	salt-hydrate	salt
	4.66	4.95	5.05	5.15	5.32	6.1

[a]Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (1994-2013 ACD/Labs).

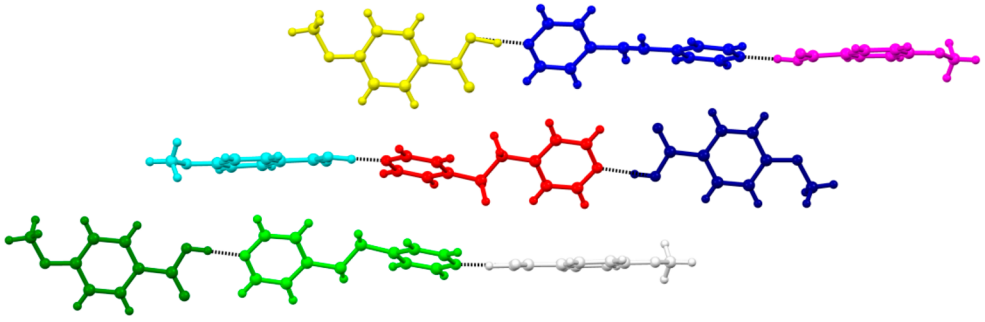


Figure 2. 2:1 cocrystal of 4-methoxybenzoic acid and 1,2-bis(4-pyridine) ethane showing the molecules according to crystallographic symmetry.

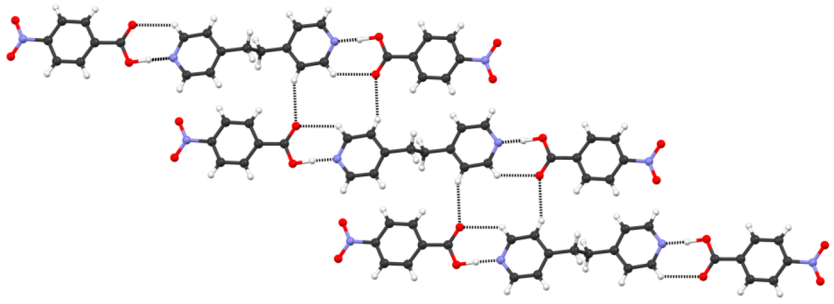


Figure 3. The cocrystal of 4-nitrobenzoic acid and 1,2-bis(4-pyridine) ethane.

is highlighted that if $\Delta\ pK_a < -1$, the cocrystal is expected, whereas in the region $\Delta pK_a > 4$, the salt is more common. In the region $-1 \leq \Delta\ pK_a \geq 4$, a salt−cocrystal exists continuum where the probability of proton transfer increases with increasing ΔpK_a.[25] As the matrix method presents a systematic analysis of cocrystals and salts, it is important to check whether or not the pK_a rule is validated in the matrix elements. An overall analysis of the matrix and thereby a systematic variation of pK_a shows that the earlier trend holds well for the matrix (Table 3).

It is also important to see how the matrix behaves in the salt−cocrystal continuum region. The row of 1,2-bis(4-pyridine) ethane represents this region, and therefore it is necessary to

dx.doi.org/10.1021/cg401851z | Cryst. Growth Des. 2014, 14, 1375−1385

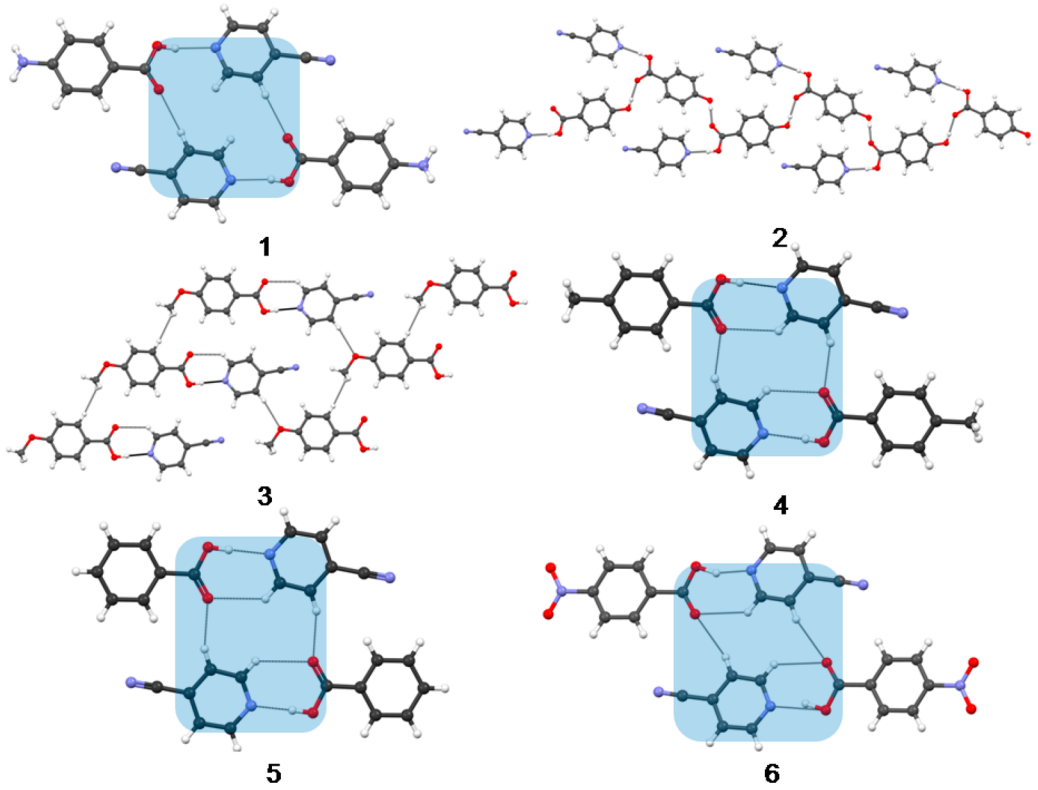


Figure 4. Cocrystals formed by 4-cyanopyridine. Note the tetramer pattern as observed in four cocrystal structures.

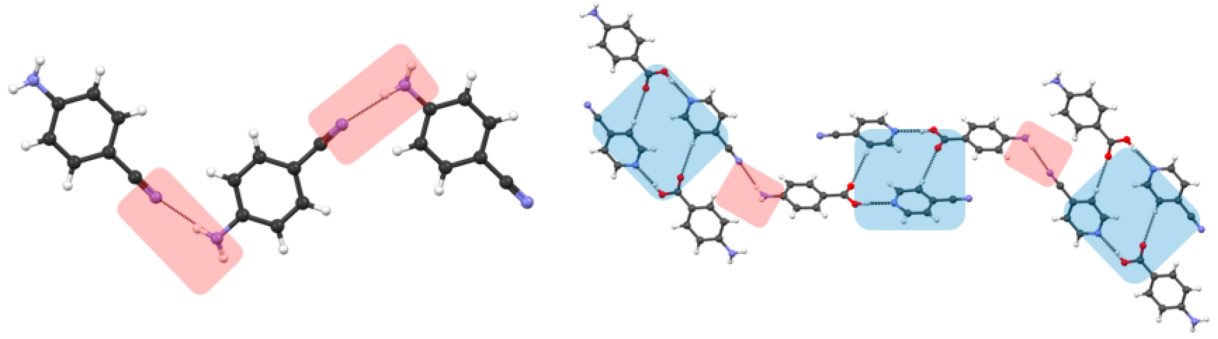


Figure 5. Topological similarity between the cocrystal of 4-aminobenzoic acid and 4-cyanopyridine with 4-cyanoaniline.

inspect this region more closely. There are four crystal structures reported in the literature, and two new structures were obtained in this study. All four structures which are reported in the literature are cocrystals. The two new structures obtained here are also cocrystals. The crystallization of 4-methoxybenzoic acid and 1,2-bis(4-pyridine) ethane cocrystal produces a 2:1 cocrystal with six molecules of 4-methoxybenzoic acid and three molecules of 1,2-bis(4-pyridine) ethane in the asymmetric unit. However, in this cocrystal, the O−H bond length is longer than the standard value hinting at partial proton transfer. The O−H···N distances between acid and pyridine vary between different molecules (Figure 2).

In contrast to this, the cocrystal of 4-nitrobenzoic acid and 1,2-bis(4-pyridine) ethane shows that both the nitrogen atoms of 1,2-bis(4-pyridine) ethane are crystallographically equivalent. However, the O−H···N distance is 1.458 Å, which is much shorter compared to 1.716 Å as observed in the cocrystals between 4-aminobenzoic acid and 1,2-bis(4-pyridyl) ethane. This cocrystal also shows elongation of the O−H length and thereby points to a salt−cocrystal continuum.

Local Features of the Matrix. *Analysis of the Rows or Columns: Secondary Synthon Information. Cocrystals of 4-Cyanopyridine.* The formation of the acid···pyridine synthon does not need the presence of a center of symmetry. However, cocrystals of 4-cyanopyridine generally show the presence of a synthon which is centrosymmetric because of the interaction between acidic aromatic C−H and carbonyl C═O. The centrosymmetric tetramer is observed for **1**, **4**, **5**, **6**, but **2** and **3** differ from these four cocrystals. The different synthon in **2** can be attributed to the high acidity of phenolic−OH group, whereas **3** is sustained through an alternative choice of C−H···O. Therefore, the probability of the formation of a tetramer centrosymmetric synthon is high unless there is an excess of strong donor/acceptor groups which do not participate in the formation of primary synthons.

The recurrence of secondary synthons in similar structures (**1**, **4**, **5**, and **6**) indicates the robustness of secondary synthons and

dx.doi.org/10.1021/cg401851z | *Cryst. Growth Des.* 2014, 14, 1375−1385

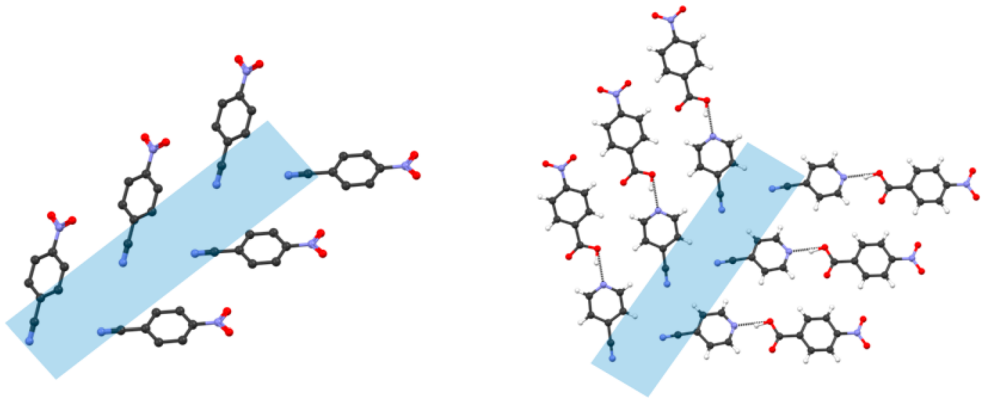


Figure 6. Topological similarity as observed between 4-cyanobenzene and PUKPER.

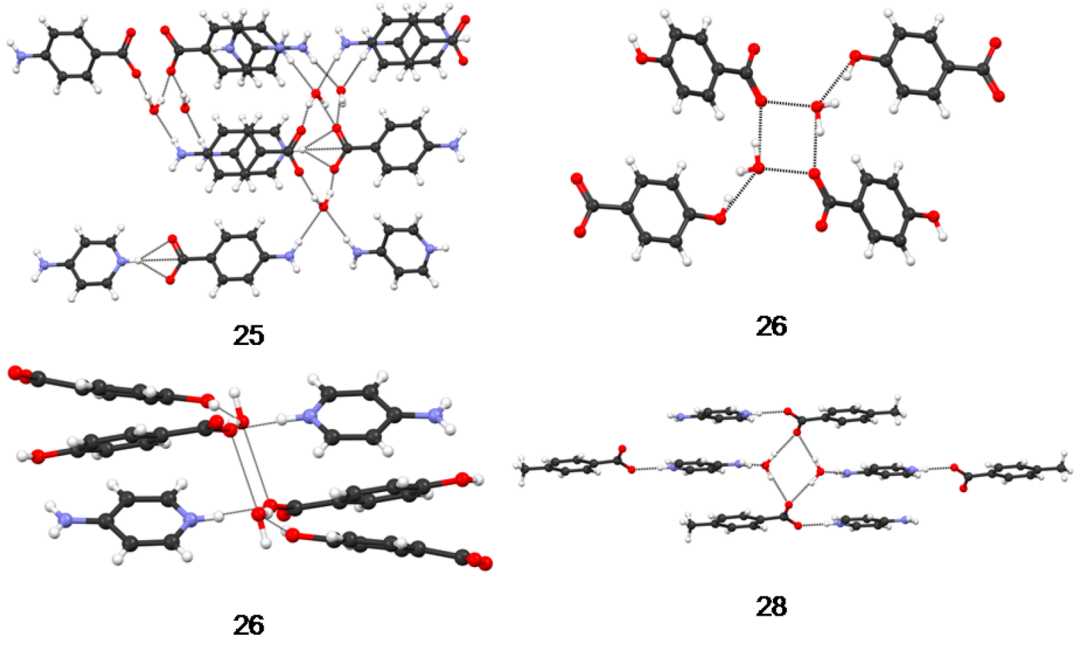


Figure 7. Hydrated multicomponent crystal structures of 4-aminopyridine.

possibly hints at their existence in solution. On the other hand, it is observed that there are two cases (**2** and **3**) where secondary synthons differ but primary synthons still exist. This observation could possibly linked with a hierarchy that, in solution, molecules recognize each other first through primary interactions and then by secondary interactions.

This is an example as to how local features of the matrix can be employed in crystal design. If this particular row is considered (because formation of tetramer restricts the choice for acidic C═O to take part in interactions), the acid···pyridine heterosynthon can be considered as the *genotype*, whereas 4-substituents to the acid and pyridine rings can be considered as *phenotypes*. Once the genotype is fixed, one can get an idea about the secondary association by varying the phenotypes. The change in phenotype organization results in topological similarity between two completely different classes of compounds. All this tries to utilize the modular properties that are inherent to supramolecular synthons.

Topological Similarity. This *genotype*−*phenotype* distinction becomes evident when one looks for topological similarity. The formation of a tetramer synthon restricts the primary synthons to pack in an antiparallel fashion in the tetramer and also makes the acid···pyridine group partially inert in terms of structure directing capability. Hence, a topological similarity is observed between the cocrystal of 4-aminobenzoic acid and 4-cyanopyridine with 4-cyanoaniline.

A similar type of topological similarity is observed between PUKPER and 4-nitrobenzonitrile. This topological similarity indicates the fact that the actual role of phenotypes can be realized once the flexibility of the acid−pyridine synthon can be blocked by formation of some modular synthons.

Propensity of Hydration in Cocrystals. A intriguing question in crystal engineering pertains to the predictability of the occurrence of hydrates.[26−31] It is observed in the past that formation of hydrates is difficult to predict.[32] It was also observed that the synthon patterns in hydrate structures are also unpredictable. While synthon polymorphism is a rare phenomenon in cocrystals, hydrate structures show diverse synthon possibilities. To this end, to add more complexity to the the landscape, 4-NH_2 pyridine and 4-*N*,*N*′-dimethylaminopyridine were chosen as row elements to create a donor/acceptor imbalance. In this matrix, it was observed that formation of hydrate is more probable for the cocrystals and salts of 4-aminopyridine and 4-*N*,*N*′-dimethylaminopyridine. Among the

dx.doi.org/10.1021/cg401851z | *Cryst. Growth Des.* 2014, 14, 1375−1385

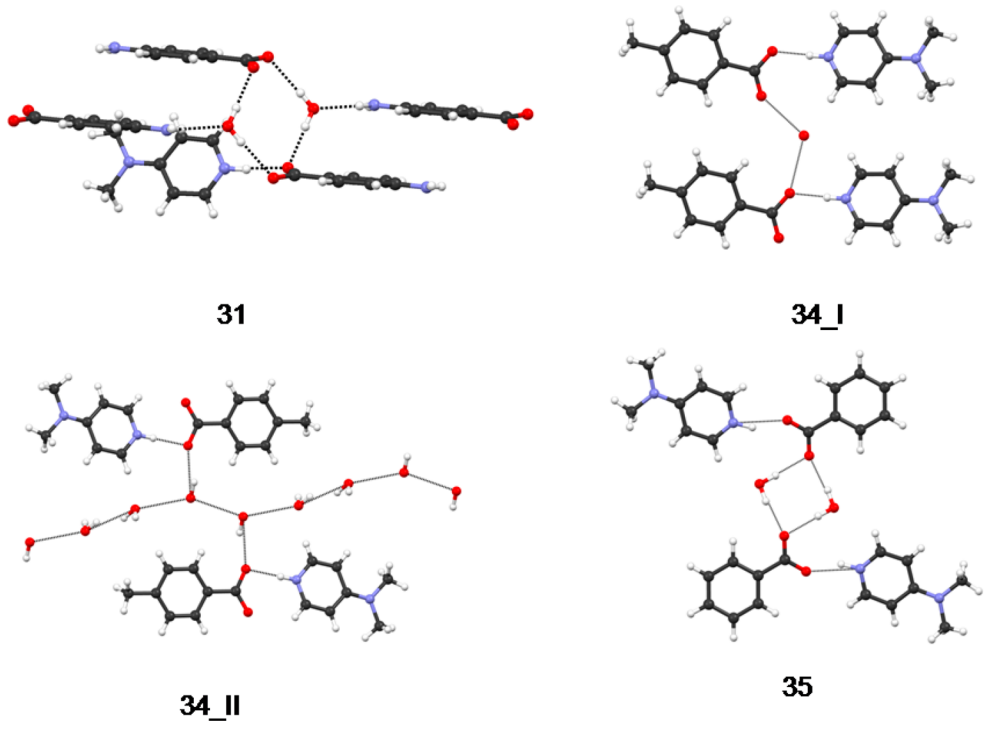


Figure 8. Hydrated multicomponent crystal structures of *N*,*N*′-dimethylaminopyridine.

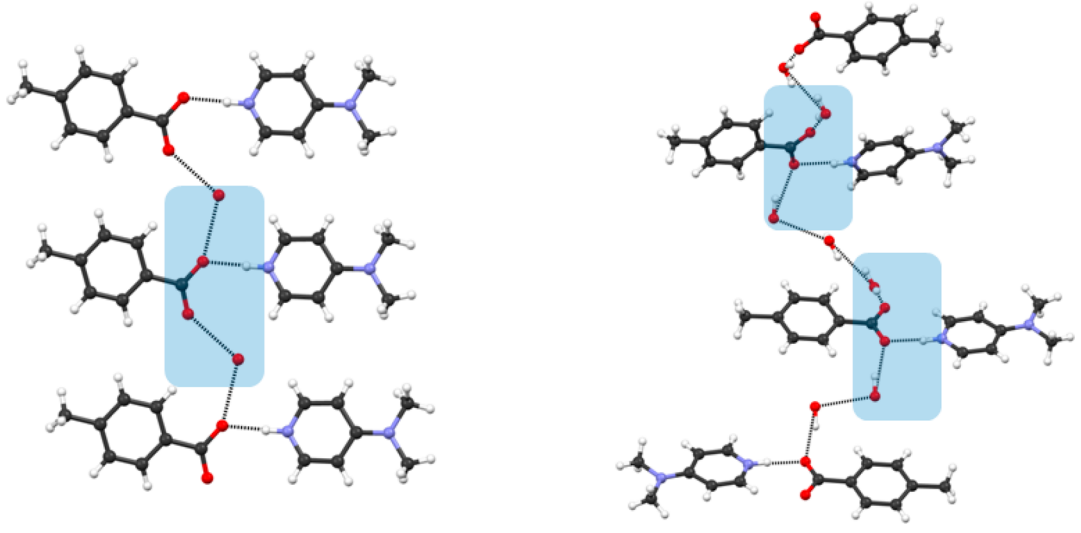


Figure 9. Synthon evolution in two hydrate structures of **34**.

11 matrix elements for which structures are available, six show the occurrence of hydrates. **34** and **35** show the presence of pseudopolymorphs. 4-Aminopyridine forms hydrates when cocrystallized with 4-aminobenzoic acid (**25**), 4-hydroxybenzoic acid (**26**), and 4-methylbenzoic acid (**28**). The analysis of these hydrate structures show that it is the acidic group that mainly participates in hydrate formation. Cocrystals **26** and **28** form tetramer patterns, while **25** forms a hexamer pattern. The difference in the pattern in **25** arises from the fact that both carboxylic oxygens take part in the formation of hydrogen bonding with water molecules.

4-*N*,*N*′-Dimethylaminopyridine gives hydrate structures when cocrystallized with 4-aminobenzoic acid (**31**), 4-methylbenzoic acid (**34**), and benzoic acid (**35**). A hexamer pattern similar to **25** is observed in **31**. The synthon pattern in **35** is also quite similar to the synthon pattern observed in **28**. In **34**, although the synthon pattern is still sustained by the interaction of water with carboxylate group, it is like an infinite chain rather than a closed one. These results show that although hydration is difficult to predict, an idea about the synthon patterns can be obtained from the matrix.

Hydration in Cocrystals: A Crystallization Precursor? Solvates are usually considered as the results of interrupted crystallization[33] events because of the very reason that crystallization is also a way to minimize entropy of the system. Supramolecular synthons are the kinetic units that represent the structures. The success of the synthon concept in crystal engineering may be attributed to the presence of synthons in the solution. Therefore, analyzing the solvate/hydrate structures in terms of supramolecular synthons is expected to provide a hint

dx.doi.org/10.1021/cg401851z | *Cryst. Growth Des.* 2014, 14, 1375−1385

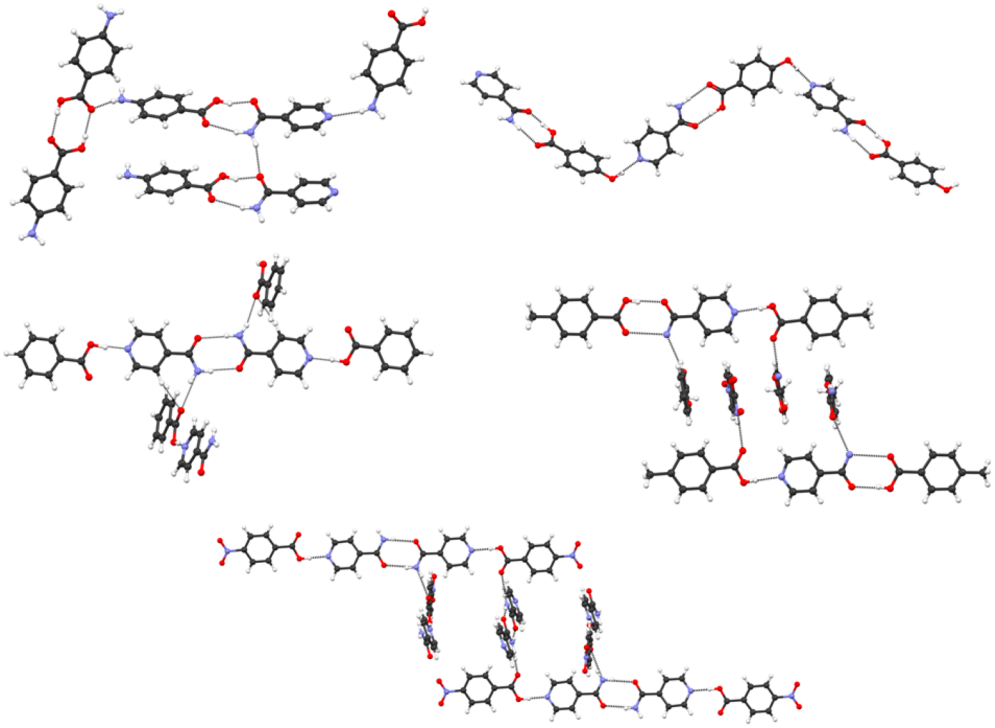


Figure 10. Synthon competition in different isonicotinamide cocrystals.

toward the crystallization mechanisms. Cocrystal **34** is a suitable example to take for this analysis. It shows two pseudopolymorphic hydrates, namely, **34-I**, which is a monohydrate, and **34-II**, which is a dihydrate. The analysis of these two structures shows that the primary repetitive unit is observed in both cases. In the monohydrate, these units are connected to each other, whereas in the dihydrate a water molecule interrupts in between. Therefore, this observation of the presence of similar primary recognition units in both the hydrates and the interruption by water in **34-II** indicates that **34-II** may actually be a crystallization precursor to **34-I**.

Synthon Competition. Synthon competition is one of the major challenges in crystal engineering.[34−36] When two or more functional groups are present on the molecular periphery they often compete with each other. The insulation is only achieved when there is significant difference in the strength of those functional groups. In the matrix, the isonicotinamide cocrystals show such a type of competition between acid···pyridine and acid···amide heterosynthons. Isonicotinamide forms a 1:2 cocrystal with 4-aminobenzoic acid with the acid···amide synthon. N−H···N is formed between the $-NH_2$ group and pyridine along with an N−H···O. Isonicotinamide forms a 1:1 cocrystal with 4-hydroxybenzoic acid. The acid−amide synthon is formed and the phenolic −OH interacts with pyridine. The crystallization of isonicotinamide with benzoic acid shows two pseudopolymorphic cocrystals. In the 1:1 modification, both acid···pyridine and acid···amide heterosynthons are observed. In the 1:1 cocrystal with 4-nitrobenzoic acid, both acid···amide and acid···pyridine synthons are formed. Therefore, it can be said that on changing the 4-substitution from donor to acceptor groups for the acid coformers, the propensity of formation of acid···pyridine synthon increases.

It is important to note that the synthon polymorphism as observed in matrix element **8** is also a case of synthon competition.[21]

CONCLUSIONS

A combinatorial matrix consisting of 4-substituted benzoic acids and 4-substituted pyridines reveals both local and global features of the course of crystallization, with each row and column representing a part of the landscape for the individual compounds, and therefore it explores the local features of a landscape and the whole matrix representing the global features. From local features, it is possible to get an idea about secondary synthons for that particular structural class. Global features, on the other hand, give an idea about general issues such as the variation of the structures with the relative acidity and basicity of the respective compounds, with connections to issues such as the salt−cocrystal continuum and pK_a dependence of cocrystal formation. This work attempts to combine two regular approaches in crystal engineering, namely, database study and high throughput crystallography, for a particular structural class and tries to extract information about the pathways of crystallization as well as formulation of design strategies for molecular solids. This work proposes the development of a high throughput method for systematic analysis of a structural landscape that provides insight into the analysis of diverse topics. The combinatorial matrix method as proposed in this paper can be extended by further varying the structural variables.

ASSOCIATED CONTENT

Supporting Information

ORTEP diagrams; crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: gautam_desiraju@yahoo.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

A.M. thanks CSIR for a SRF. G.R.D. thanks DST for the award of a J. C. Bose fellowship.

■ REFERENCES

(1) Desiraju, G. R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2311.
(2) Trask, A. V.; Motherwell, W. D. S.; Jones, W. *Int. J. Pharm.* **2006**, *320*, 114.
(3) Almarsson, O.; Zaworotko, M. J. *Chem. Commun.* **2004**, 1889.
(4) Parveen, S.; Davey, R. J.; Dent, G.; Pritchard, R. G. *Chem. Commun.* **2005**, 1531.
(5) Kulkarni, S. A.; McGarrity, E. S.; Meekes, H.; ter Horst, J. H. *Chem. Commun.* **2012**, *48*, 4983.
(6) Price, S. L. *Acc. Chem. Res.* **2008**, *42*, 117.
(7) Mukherjee, A.; Grobelny, P.; Thakur, T. S.; Desiraju, G. R. *Cryst. Growth Des.* **2011**, *11*, 2637.
(8) Tothadi, S.; Desiraju, G. R. *Phil. Trans. R. Soc. A* **2012**, *370*, 2900.
(9) Dubey, R.; Pavan, M. S.; Desiraju, G. R. *Chem. Commun.* **2012**, *48*, 9020.
(10) Dubey, R.; Pavan, M. S.; Guru Row, T. N.; Desiraju, G. R. *IUCrJ* **2014**, *1*, 8−18.
(11) Dubey, R.; Desiraju, G. R. *Chem. Commun.* **2014**, *50*, 1181−1184.
(12) Arora, K. K.; Pedireddi, V. R. *J. Org. Chem.* **2003**, *68*, 9177.
(13) Santra, R.; Biradha, K. *Cryst. Growth Des.* **2009**, *9*, 4969.
(14) Shan, N.; Bond, A. D.; Jones, W. *Cryst. Eng.* **2002**, *5*, 9.
(15) Shattock, T. R.; Arora, K. K.; Vishweshwar, P.; Zaworotko, M. J. *Cryst. Growth Des.* **2008**, *8*, 4533.
(16) Sarma, D.; Ramanujachary, K. V.; Stock, N.; Natarajan, S. *Cryst. Growth Des.* **2011**, *11*, 1357.
(17) *Rigaku Mercury375R/M CCD. Crystal Clear-SM Expert 2.0 rc14*; Rigaku Corporation: Tokyo, J., 2009.
(18) Sheldrick, G. *Acta. Crystallogr. A* **2008**, *64*, 112.
(19) Farrugia, L. *J. Appl. Crystallogr.* **1999**, *32*, 837.
(20) Allen, F. H. *Acta Crystallogr. B* **2002**, *58*, 380.
(21) Mukherjee, A.; Desiraju, G. R. *Chem. Commun.* **2011**, *47*, 4090.
(22) Santra, R.; Ghosh, N.; Biradha, K. *New J. Chem.* **2008**, *32*, 1673.
(23) Aakeröy, C. B.; Fasulo, M. E.; Desper, J. *Mol. Pharmaceutics* **2007**, *4*, 317.
(24) Bhogala, B. R.; Basavoju, S.; Nangia, A. *CrystEngComm* **2005**, *7*, 551.
(25) Cruz-Cabeza, A. J. *CrystEngComm* **2012**, *14*, 6362.
(26) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1991**, 426.
(27) Varughese, S.; Desiraju, G. R. *Cryst. Growth Des.* **2010**, *10*, 4184.
(28) Baur, W. *Acta Crystallogr.* **1965**, *19*, 909.
(29) Chidambaram, R. *J. Chem. Phys.* **1962**, *36*, 2361.
(30) Görbitz, C. H.; Hersleth, H.-P. *Acta Crystallogr. B* **2000**, *56*, 526.
(31) Yadav, V. N.; Gorbitz, C. H. *CrystEngComm* **2013**, *15*, 439.
(32) Clarke, H. D.; Arora, K. K.; Bass, H.; Kavuru, P.; Ong, T. T.; Pujari, T.; Wojtas, L.; Zaworotko, M. J. *Cryst. Growth Des.* **2010**, *10*, 2152.
(33) Biradha, K.; Edwards, R. E.; Foulds, G. J.; Robinson, W. T.; Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1705.
(34) Shan, N.; Batchelor, E.; Jones, W. *Tetrahedron Lett.* **2002**, *43*, 8721.
(35) Sarma, B.; Nath, N. K.; Bhogala, B. R.; Nangia, A. *Cryst. Growth Des.* **2009**, *9*, 1546.
(36) Grossel, M. C.; Dwyer, A. N.; Hursthouse, M. B.; Orton, J. B. *CrystEngComm* **2006**, *8*, 123.