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Polymorphism in cocrystals of urea : 4,4'-bipyridine and salicylic acid : 4,4'-bipyridine

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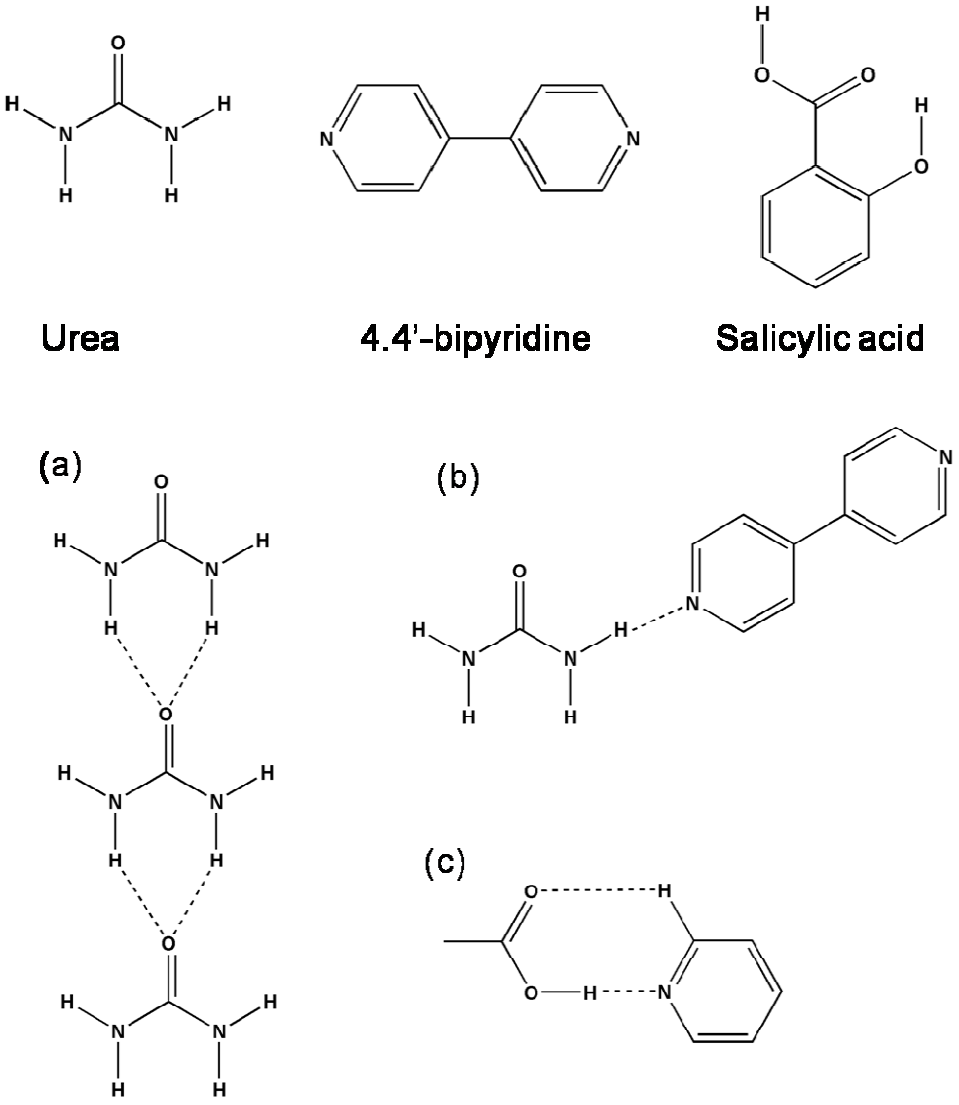
Abstract: Polymorphic cocrystals of urea : 4,4'-bipyridine and salicylic acid : 4,4'-bipyridine were obtained by crystallization from different solvents. The urea tape is a rare phenomenon in cocrystals, but it is consistent in urea : 4,4'-bipyridine polymorphic cocrystals. The polymorph obtained from MeCN has symmetrical N–H···N hydrogen bond distances on either side of urea tape. But the other form obtained from MeOH has unsymmetrical N–H···N hydrogen bonds lengths. In polymorphic cocrystals of salicylic acid : 4,4'-bipyridine, the basic supramolecular synthon acid-pyridine is same but 3D packing is different. Both the polymorphic pairs of cocrystals come under category of packing polymorphs. All polymorphs were characterized by single crystal X-ray diffractometer (SCXRD), PXRD, DSC, FT-IR and HSM. N–H···N and acid-pyridine supramolecular synthons are insulated by FT-IR vibrational spectroscopy.

Introduction

Polymorphism is the arrangement of the same molecule in different ways in different crystal structures leading to different crystal packing.[1] Polymorphism can be seen in cocrystals as well as single component crystals. Cocrystals[2] are crystalline solids that contain at least two different chemical components in the asymmetric unit. If the two chemical components are arranged in different ways in two or more different crystal structures, then they are defined as cocrystal polymorphs.[3] Conformational polymorphism,[4] synthon polymorphism[5] and tautomeric polymorphism[6] are well known in the literature. Different polymorphs are obtained under different crystallization conditions such as different solvents used for crystallization, temperature and pressure. Sometimes, if the energy differences between two or more polymorphs are very small, they may appear concomitantly.[7] In other circumstances, if the compound has multiple polymorphs, it may be exceedingly difficult to reproduce the exact experimental conditions in which some of these were obtained, leading to cases of disappearing polymorphs.[8] Different

polymorphs exhibit different physical properties such as solubility[9], shelf life[10], and bioavailability.[11]

Polymorphs of single component crystals are well known, but in recent times the literature on polymorphic cocrystals has been increasing. At least 114 such systems have been identified so far.[3i] Reports of different types of polymorphs can be seen in the literature. Some examples are as follows: Matzger and coworkers reported two polymorphs of carbamazepine–nicotinamide and carbamazepine–saccharin cocrystals from solvent crystallizations.[12] Bernstein and coworkers synthesized four sets of dimorphic cocrystals by taking different combinations of single component crystals which exhibit polymorphic forms in their native states.[13] Recently, Desiraju and coworkers obtained synthon polymorphism in 2:1 cocrystals of 4-hydroxybenzoic acid : 4,4'-bipyridine. Nangia and coworkers have shown three different synthon variations in celecoxib cocrystals with cyclic amides.[14] Champness showed polymorphism in cyanuric acid and bis(4-pyridyl)ethane.[15] In one polymorph only one type of sheet (AAA) is observed in the arrangement of molecules, while in the other both sheet arrangements (AABAAB) exist. Both polymorphic crystals have N–H···O hydrogen bonds, but the difference is in the hydrogen bond lengths. In general, cocrystals containing urea have either the urea ribbon or the urea tape. Fowler and Lauher showed the urea tape in ureylenedicarboxylic acid and 4,4′-bipyridine cocrystals.[16] Later they also showed urea tape in the urea of glycine and the oxamide of glycine cocrystallized with bipyridines. Nangia *et* al. showed urea tapes in diarylureas via N–H···O as a primary synthon and X···O_2N (X = halogen) interaction providing auxiliary support in the lateral direction.[17] Aitipamula and Tan coworkers published series of papers on cocrystal polymorphs.[3i, 4b, 5c,d] Recently, Kim *et al.* studied crystallization process of salicylic acid : 4,4′-bipyridine cocrystal by Raman spectroscopy.[18] Packing polymorphs have special attention because basic supramolecular synthons and conformations are same but differ only 3-D arrangement. The present paper mainly discusses on binary cocrystal packing polymorphs of urea : 4,4′-bipyridine and salicylic acid : 4,4′-bipyridine. In all cocrystal forms 4,4′-bipyridine is common coformer for the crystallization, see Scheme 1.



Scheme 1. Possible supramolecular synthons in cocrystals (a) urea tape (b) urea-pyridine and (c) acid-pyridine heterosynthons.

Experimental section

Materials

4,4'-bipyridine was procured from Alfa Aesar and urea, salicylic acids and all solvents are obtained from S. D. fine chemicals used as such without further purifications.

Singlecrystal X-ray diffraction

Single crystal X-ray data for all polymorphs were collected on a Rigaku Mercury375/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo-Kα radiation at 150 K and the

data were processed with Rigaku CrystalClear software.[19] Structure solution and refinement were performed using SHELX-97 by WinGXsuite.[20] Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were carried out by the full-matrix least-squares method. The hydrogen atoms attached to carbon atoms were generated using a Riding model and refined isotropically. All H-atoms which are attached to N- and carboxyl O-atoms (O3 in Form IB and O2 Form IIB) were located from difference Fourier maps and these H-atoms were refined isotropically. H-atoms which are attached to O2 in Form IB and O3 in Form IIB were located from Riding model. The crystallographic parameters and final R indices of all the crystal structures are listed in Table **1** and PLATON[21] was used to prepare hydrogen bonding tables. Mercury version 3.3 was used for molecular representations and packing diagrams.

Powder X-ray diffraction (PXRD)

Powder X-ray diffraction data, for urea : 4,4'-bipyridine polymorphic cocrystals, Form IA and Form IIA, were collected on a Philips X'pert Pro X-ray powder diffractometer equipped with an X'cellerator detector. The scan range was $2\theta = 5$ to 40° and step size 0.017

Thermal Analysis

For urea : 4,4'-bipyridine polymorphic cocrystals (Form IA and Form IIA), DSC was performed on a Mettler Toledo DSC 822e module. About 4−6 mg of the sample was placed in crimped but vented aluminum pans of 40 μL, and the temperature range scanned was 30−250 °C at a heating rate of 5 °C/min. The sample was purged by a stream of dry nitrogen flowing at 50 mL/min.

FT-IR Spectroscopy

FT-IR data for all polymorphic cocrystals were collected on a Perkin-Elmer Spectrum Frontier Fourier transform-infrared (FT-IR) spectrometer in the range from 500 to 4000 cm^{-1}.

Hot Stage Microscope (HSM)

For all cocrystals melting point was monitored on a Wagner & Munz (PolyTherm A) hot stage microscope .

Cocrystal preparation

Urea : 4,4'-bipyridine cocrystal polymorph (Form IA) (**1**)

Equimolar quantities of urea and 4,4'-bipyridine were ground together in a mortar with pestle for 10 minutes after adding 2-3 drops of EtOH (solvent drop grinding)[22]. The resulting material was dissolved in 5 ml of MeCN The solution was kept to evaporate for six days. Block shape crystals were obtained. Good quality crystal was selected carefully for single crystal X-ray diffraction. Solvent drop grinding is one of the successful methods for cocrystal synthesis. Solvent used while grinding could be acts as nucleation site for cocrystal formation.

Urea : 4,4'-bipyridine cocrystal polymorph (Form IIA) (**2**)

Equimolar quantities urea and 4,4'-bipyridine were ground together in a mortar with pestle for 10 minutes after adding 2-3 drops of EtOH. The resulting material was dissolved in 5 ml of MeOH The solution was kept to evaporate for three days. Needle type crystals were obtained. Good quality crystal was selected for single crystal X-ray diffraction.

Salicylic acid : 4,4'-bipyridine cocrystal polymorph (Form IB) (**3**)

Equimolar quantities of salicylic acid and 4,4'-bipyridine were ground together in mortar with pestle for 10 minutes after adding 2-3 drops of EtOH. The resulting material was dissolved in 5 ml of MeCN. Good quality single crystal was selected carefully for X-ray diffraction. Here good quality of crystals is also obtained in EtOH, MeOH, acetone, dioxane, THF, and EtOAc.

Salicylic acid : 4,4'-bipyridine cocrystal polymorph (Form IIB) (**4**)

Equimolar quantities of aspirin and 4,4'-bipyridine were ground together in mortar with pestle for 10 minutes after adding 2-3 drops of EtOH. The resulting material was dissolved in 5 ml of MeOH. The solution was kept to evaporate for 3 days, needle type crystals were obtained. Good quality of single crystals was selected carefully for X-ray diffraction. In ordered to obtain crystal for characterization, experiment was repeated several times in 11 different solvents and in different crystallization conditions. Most of the times end up with cocrystal **3.** Form IIB crystals were never obtained.

Results and discussion

Identification of a particular pattern has subtle importance in crystal engineering because certain properties can be designed. The urea tape is rare in urea containing cocrystals. In the Cambridge Structural Database (CSD version 5.35, November 2013) about 194 urea containing cocrystal structures can be seen, among them only five structures contain urea tape.[23] Two consecutive urea tapes can pack parallel or antiparallel depends on crystallographic space group. Urea tape can be seen in polymorphs of urea : 4,4'-bipyridine cocrystals (Form IA and Form IIA). Even though, Form IA and Form IIA have different 3D packing, two dimensional crystal packing mimicking each other. Another set of polymorphic cocrystal are obtained with salicylic acid : 4,4′-bipyridine (Form IB and Form IIB). Both set of cocrystals are discussed under the category of packing polymorphs. 4,4-Bipyridine prone to form organic cocrystals (299 hits in CSD). Among them one system is quartermorph, two are trimorphic and another two are dimorphic cocrystals (Refcodes are given in supporting information); Hence, it was taken as coformer for our polymorphic cocrystals study.

Polymorphic cocrystals

Urea : 4,4'-bipyridine Form IA (1)

The cocrystal takes the space group *C*2/*c*, with half molecule each of urea and 4,4'-bipyridine in the asymmetric unit. Urea and 4,4'-bipyridine are sitting on 2-fold axis and center of inversion respectively. Those molecules are connected by N–H···N (D_1 = 3.047(2) Å) ($D_1 = D_2$) synthons and urea is self associated by the urea tape involving bifurcated N–H···O (D_3 = 2.890(2) Å) synthons at the O-atom. Two urea tapes run in opposite directions (Figure 1).

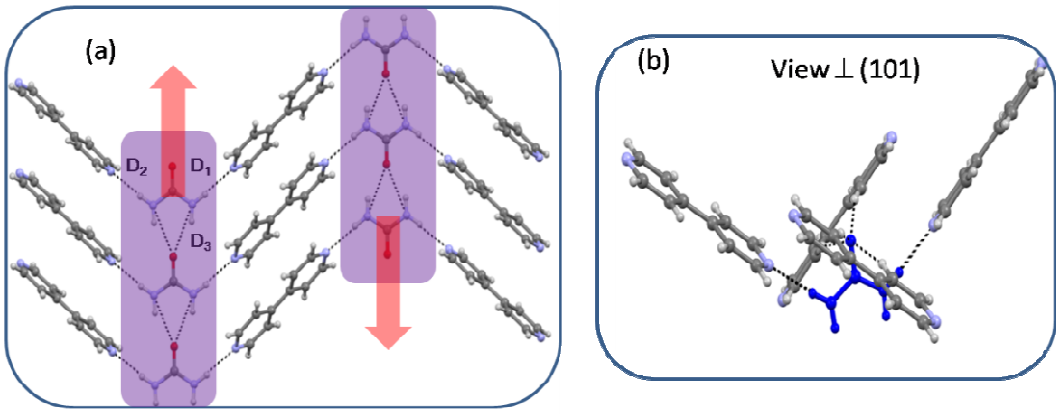


Figure 1. In urea : 4,4'-bipyridine cocrystal Form IA (a) 4,4'-bipyridine molecules are connected symmetrically to urea on either side of urea tape. Notice the urea tapes running antiparallel directions. (b) In 3D packing, urea (blue) is at the center and it is surrounded by four bipyridines- one set of parallel bipyridine is almost orthogonal to another set of parallel bipyridines

Urea and 4,4'-bipyridine cocrystal Form IIA (2)

Form IIA cocrystal has similar two dimensional crystals packing with Form IA and it takes the space group *Pnma*, with half molecule each of urea and 4,4'-bipyridine in the asymmetric unit. All atoms of urea and half of 4,4'-bipyridine molecule are sitting on mirror plane. Urea and 4,4'-bipyridine are connected by two different N–H···N (D_1= 3.024(3) Å, D_2= 3.113(3) Å) ($D_1 \neq D_2$) synthons and urea is self assembled by the urea tape forming bifurcated N–H···O (D_3 = 2.863(2) Å, D_4 = 2.915(3) Å) synthons at the O-atom of urea (Figure 2). Note that $D_1 = D_2$ in Form IA and $D_1 \neq D_2$ in Form IIA. For Form IA and Form IIA, the difference arises due to the arrangement of urea and 4,4'-bipyridine molecules in consecutive planes. In Form IA and Form IIA molecules are packed in ABA′B′ABA′B′ and ABAB fashion respectively.

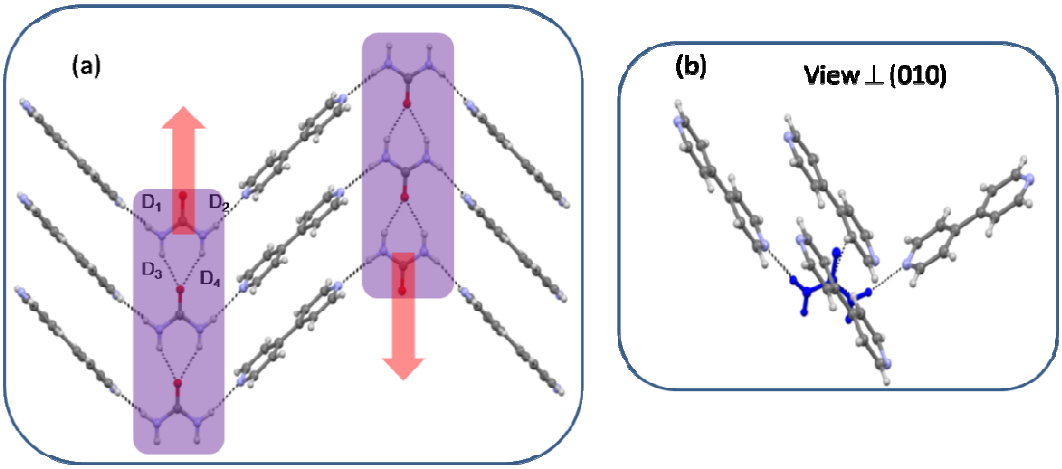


Figure 2. Urea : 4,4'-bipyridine cocrystal Form IIA has similar packing as Form IA. Here 4,4'-bipyridine molecules are connected unsymmetrically on either side of urea tape. Notice urea tapes running in antiparallel directions. (b) In 3-D packing, urea (blue) is at center and among four bipyridine molecules, three bipyridines are parallel and another one bipyridine is almost orthogonal to these three bipyridine.

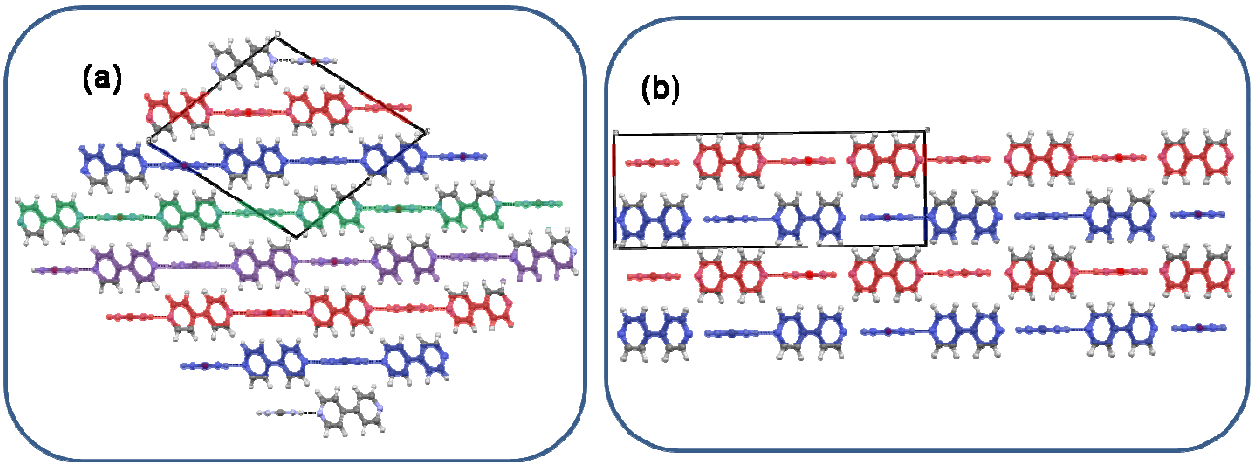


Figure 3. Difference in urea : 4,4'-bipyridine cocrystals packing polymorphs (Form IA and IIA). (a) In Form IA, consecutive planes are arranged in ABA′B′ABA′B′. (b) In Form IIA, consecutive planes are layers are arranged in ABAB.

Salicylic acid and 4,4′-bipyridine cocrystal Form IB (3)

Form IB (3) has, 4,4′-bipyridine, same coformer as earlier crystal structures. The cocrystal takes space group *P*1, one molecule of salicylic acid and a half of 4,4'-bipyridine present in asymmetric unit. Salicylic acid and 4,4′-bipyridine molecules are connected by O–H···N (D_1 = 2.614(3) Å) synthons (Figure 4). Trimers (two of salicylic acid and one of 4,4′-bipyridine) in 2-D are connected by C–H···O (D_2 = 3.384(4) Å) hydrogen bonds and molecules are further connected 3-D by π-π stacking (D_3 = 3.219(4) Å).

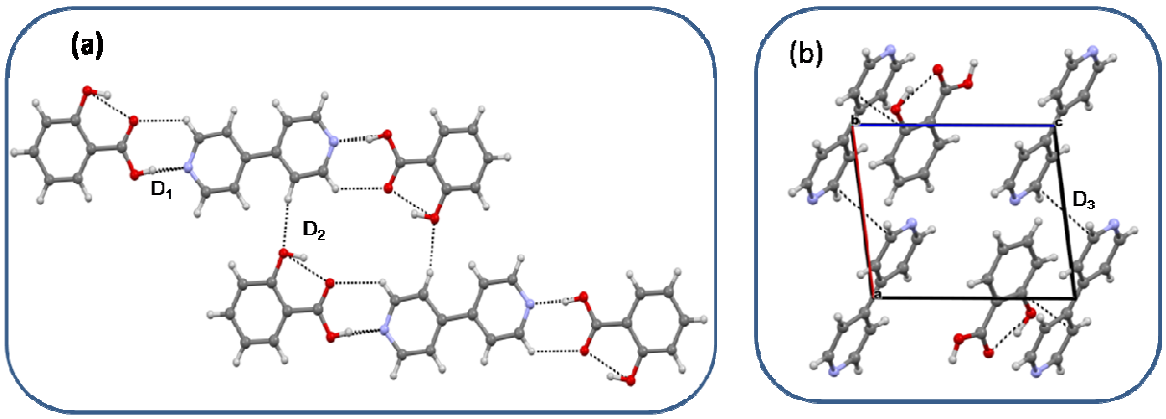


Figure 4. (a) In Form IB cocrystal polymorph, molecules are associated together by O–H···N supramolecular synthons and C–H···O hydrogen bonds. (b) Unit cell of salicylic acid : 4,4′-bipyridine cocrystal in Form IB.

Salicylic acid : 4,4′-bipyridine cocrystal Form IIB (4)

The basic strong hydrogen bonded supramolecular synthons in Form IIB (4) are similar to Form IB (3). The cocrystal takes the space group $P2_1/c$, with one molecule of salicylic acid and a half of 4,4'-bipyridine in the asymmetric unit. Salicylic acid and 4,4′-bipyridine are connected by O–H··· N (D_1 = 2.581(3) Å) hydrogen bond (Figure 5). Crystal packing is further stabilized by weak bifurcated C–H···O (D_2 = 3.393(4) Å, D_3 = 3.414(4) Å) hydrogen bonds (Figure 5).

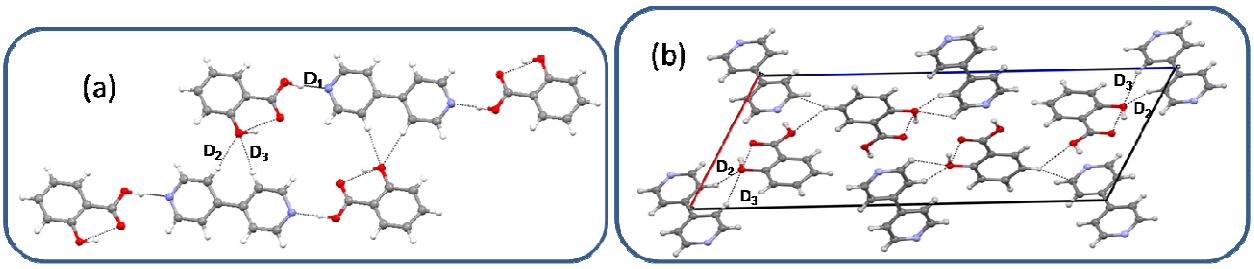


Figure 5. In Form IIB cocrystal polymorph, molecules are connected together by O–H···N supramolecular synthons and bifurcated C–H···O hydrogen bonds. (b) Unit cell of salicylic acid : 4,4′-bipyridine cocrystal in Form IIB.

Packing polymorphism in cocrystals

By careful observation of Form IA and Form IIA, the urea tape is common to both the cases. The basic difference is the lengths of the N–H···N hydrogen bonds present on either side of carbonyl group of urea. The other two N–H hydrogen bond donors of urea are bonded to the N-atom of 4,4'-bipyridine. The robust design of molecular recognition between strong donor and strong acceptor is fulfilled. Crystal structure analysis demonstrates that solvent used for crystallization can change the geometric arrangement of molecules. Form IA has N–H···N synthons present on either side of urea tape and different bond lengths and bond angles (D_1=3.113(3) Å, D_2= 3.024(3) Å and θ is 169(2)º, 172(2)º), but in the crystal of Form IIA the interaction lengths and angles are same (symmetrical) on either side of urea (D = 3.047(2) Å, and θ is 175(2)º) (Table 2). Polymorphic cocrystals Form IB and Form IIB have stabilized by intermolecular hydrogen bonds (O–H···N and C–H···O) and intramolecular hydrogen bonds O–H···O. The two forms are considered to be packing polymorphs. Trimers in Form IIB slides more compare to Form IB (supporting information, Figure S1). In Form IB, the trimers are parallel whereas in Form IIB, they are perpendicular to each other (Figure S2). Even after several attempts, Form IIB was never obtained again under the same and/or different experimental conditions.

Table 1. Crystallographic data and structure refinement parameters.

	1	**2**	**3**	**4**
	(Form IA)	(Form IIA)	(Form IB)	(Form IIB)
Formula	$(CH_4N_2O)\cdot(C_{10}H_8N_2)$	$(CH_4N_2O)\cdot(C_{10}H_8N_2)$	$2(C_7H_6O_3)\cdot(C_{10}H_8N_2)$	$2(C_7H_6O_3)\cdot(C_{10}H_8N_2)$
Formula weight	216.25	216.25	432.42	432.42
Crystal System	Monoclinic	Orthorhombic	Triclinic	Monoclinic
Space group	*C*2/*c*	*Pnma*	*P*1	$P2_1/c$
a (Å)	14.999(3)	25.070(4)	7.860(8)	9.920(9)
b (Å)	4.6030(9)	9.1849(15)	8.308(8)	4.919(4)
c (Å)	16.068(3)	4.5943(8)	8.547(8)	23.046(18)
α (°)	90	90	87.812(14)	90
β (°)	108.53(3)	90	82.149(3)	114.28(3)
γ (°)	90	90	65.900(14)	90
V (Å^3)	1051.8(4)	1057.9(3)	504.6(9)	1025.1(15)
Z	4	4	1	2
ρ_{calc} *(gcm^{-3})*	1.366	1.358	1.423	1.401
F(000)	456	456	226	452
μ(mm^{-1})	0.093	0.093	0.104	0.102
Temp(K)	150	150	150	150
Total ref.	5213	9326	5358	10989
Unique ref.	1195	1274	2291	2348
Observed ref. (I > 2σ(I))	1066	1019	2045	1930
R	0.0408	0.0513	0.0442	0.0582
wR2	0.1566	0.1380	0.1228	0.1660
S	1.254	1.141	1.077	1.060
CCDC No.	984585	984586	984587	984588

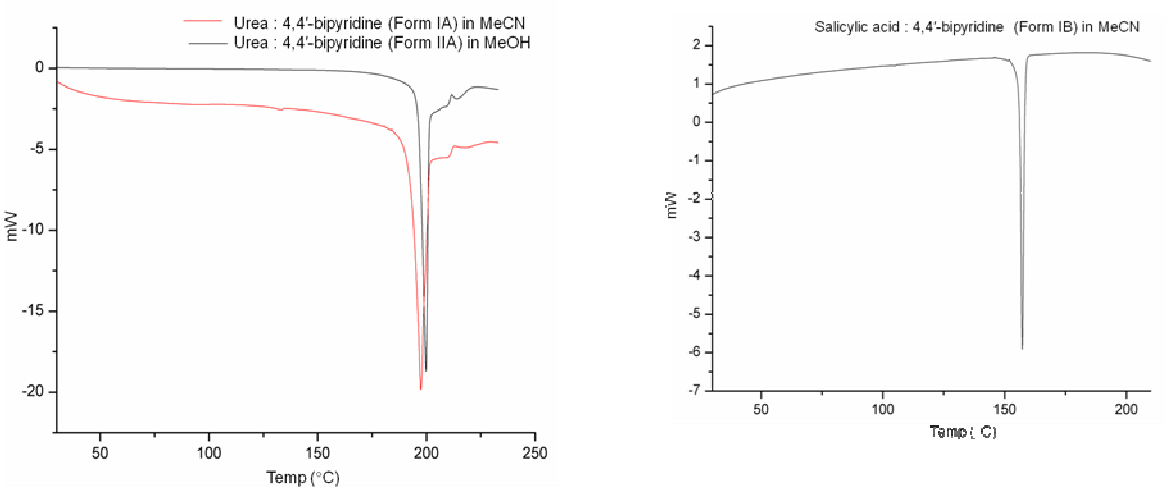
Table 2. Hydrogen bond donor (D) and acceptor (A) geometries for **1, 2, 3** and **4.**

Cocrystal Polymorphs	D−H···A	d(D−H), Å	d(H···A), Å	d(D···A), Å	∠(D−H···A), °
1 Form IA[a]	N(1)–H(5)···N(2)$^{\#1}$	0.88(2)	2.17(2)	3.047(2)	175(2)
	N(1)–H(6)···O(1)$^{\#2}$	0.88(2)	2.08(2)	2.890(2)	151(2)
2 From IIA[b]	N(3)–(3A)···N(2)	0.88(3)	2.25(3)	3.113(3)	169(2)
	N(3) –H(3B)···O(1)$^{\#1}$	0.88(3)	2.14(3)	2.915(3)	147(2)
	N(4)–H(4A)···N(1)$^{\#2}$	0.89(3)	2.14(3)	3.024(3)	172(2)
	N(4)–H(4B)···O(1)$^{\#3}$	0.89(3)	2.06(3)	2.863(2)	150(2)
3 Form IB[c]	O(3)–H(1)···O(1)	0.99(2)	1.66(2)	2.567(3)	151(2)
	O(2)–H(2)···N(1)$^{\#1}$	0.91	1.72	2.614(3)	167
	C(24)–H(5)···O(1)$^{\#2}$	0.95	2.58	3.403(4)	145
	C(5)–H(11)···O(1)$^{\#1}$	0.95	2.55	3.219(4)	128
	C(3)–H(12)···O(3)$^{\#3}$	0.95	2.49	3.384(4)	156
4 Form IIB[d]	O(2)–H(2)···N(2)$^{\#1}$	0.95(2)	1.64(2)	2.581(3)	175(3)
	O(3)–H(3)···O(1)	0.96	1.68	2.571(3)	153
	C(8)–H(8)···O(3)$^{\#2}$	0.95	2.57	3.414(4)	148
	C(9)–H(9)···O(3$^{\#3}$	0.95	2.55	3.393(4)	148

[a]Symmetry operators used to generate hydrogen bonded molecules. #1,3/2-x,3/2-y, 1-z #2, x,-1+y, z. [b]Symmetry operators used to generate hydrogen bonded molecules. #1, x,y,-1+z; #2, -1/2+x,1/2-y,3/2-z; #3, x,y,-1+z.
[c]Symmetry operators used to generate hydrogen bonded molecules. #1,-x,1-y,1-z; #2,1+x,y,z; #3,1+x,1+y,z.
[d]Symmetry operators used to generate hydrogen bonded molecules. #1,1-x,-y,1-z; #2, 2-x,1-y,1-z; #3, x,1+y,z.

DSC of urea : 4,4'-bipyridine polymorphic cocrystals

Presence of polymorphs is confirmed by DSC. Form IA is obtained from MeCN has sharp melting point at 197 °C. Form IIA cocrystals are obtained from MeOH has melting endotherm at 200 °C. Form IIA is more stable than Form IA because it has high melting point. Melting endotherms of different forms (Form IA and IIA) show two independent melting points without transforming to other forms (Figure 6) so, cocrystal Form IA and Form IIA are monotropically related.[24] Melting endotherm for Form IB is 157 °C. Melting point for all cocrystal forms, except Form IIB, is also monitored by HSM (Figure 7).



(a) (b)

Figure 6. DSC of (a) urea : 4,4'-bipyridine polymorphic cocrystals (Form IA and Form IIA) and (b) salicylic acid: 4,4'-bipyridine polymorphic cocrystals (Form IB).

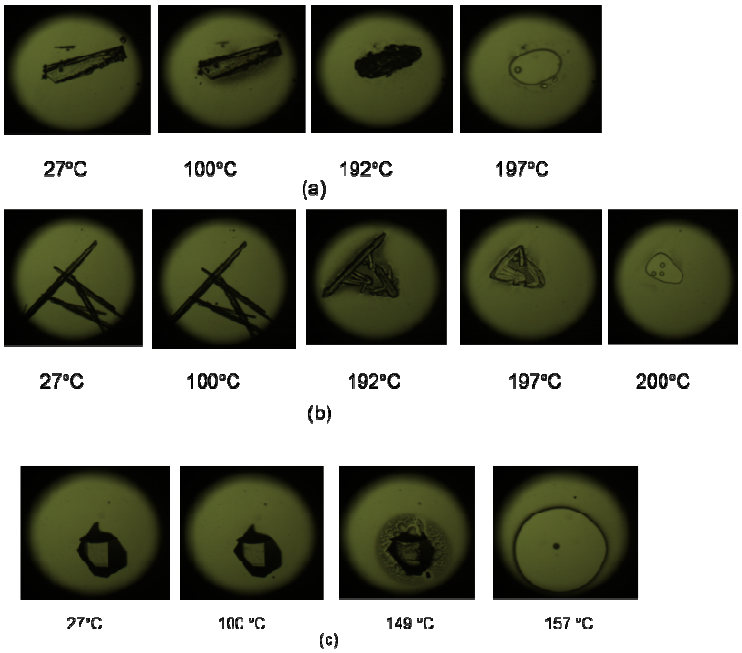


Figure 7. HSM images of urea : 4,4'-bipyridine polymorphic cocrystals (a) Form IA and (b) Form IIA. (c) HSM images of salicylic acid : 4,4'-bipyridine polymorphic cocrystals (Form IB)

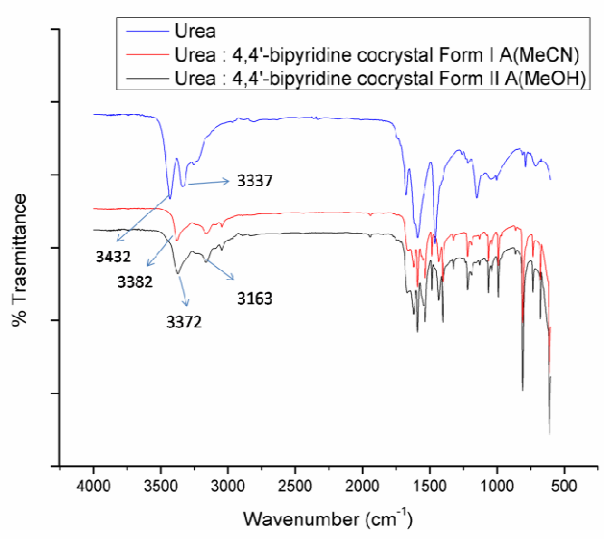
IR Spectroscopy:

IR spectroscopy has substantial importance in identifying supramolecular synthons[25] and different patterns in crystals structures.[26] Recently, Tothadi *et al.* identified acid···amide dimer

synthons using IR spectroscopy.[27] In present study, by comparing N–H asymmetric and symmetric frequencies of single component urea (3432 and 3337 cm^{-1}) with Form IA and Form IIA bathochromic shift is observed. It is a characteristic property of cocrystal formation. (Figure 8a). Form IIA asymmetric frequency is higher than Form IA so that cocrystals forms can be distinguished by IR spectroscopy (Table 3). Urea tape formed by single component urea, N–H···O hydrogen bond, is compared with N–H···O hydrogen bond in Form IA and IIA. In polymorphic cocrystals N–H···O hydrogen bond lengths are shorter than single component urea which is indication of strong hydrogen bond formation in cocrystal. This is evident from IR frequencies. When IR spectra of 4,4′-bipyridine and salicylic acid compared with Form IB a new marker band appeared at 2600-1800 cm^{-1} is characteristic of acid-pyridine synthon[27] (Figure 8b).

Table 3. Symmetric and asymmetric stretching band positions of polymorphic cocrystals.

	Name of the compound	N–H Asymmetric (cm^{-1})	N–H Symmetric (cm^{-1})
	Urea	3432	3337
1	Urea : 4,4'-bipyridine (Form IA)	3382	3163
2	Urea : 4,4'-bipyridine (Form IIA)	3372	3163



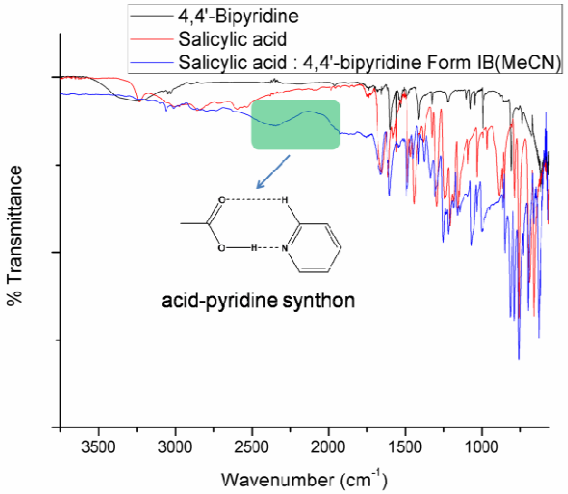
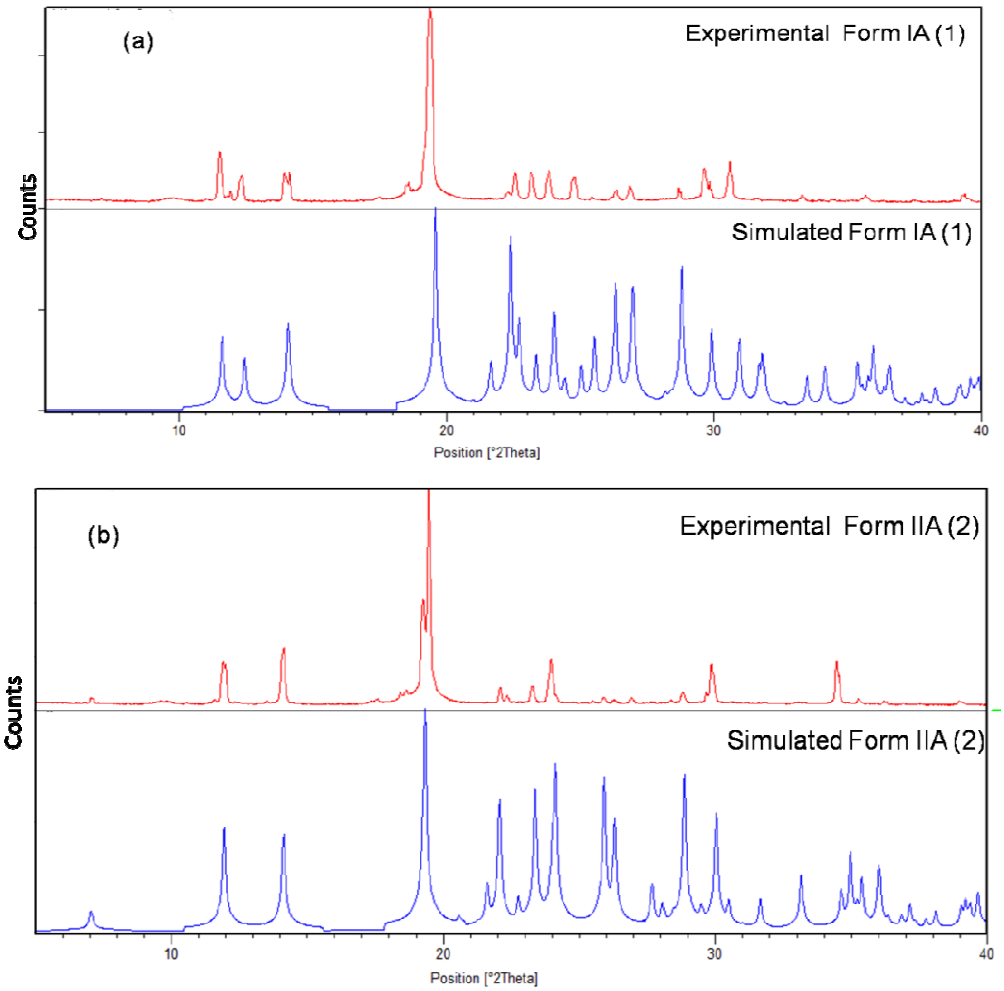


Figure 8. IR spectra (a) urea and polymorphic cocrystals of urea : 4,4'-bipyridine Form IA and Form IIA. (b) Polymorphic cocrystal of salicylic acid : 4,4′-bipyridine Form IB shows marker band of acid-pyridine synthon.

Powder X-ray diffraction (PXRD): Urea : 4,4′-bipyridine cocrystal polymorphs (Form IA and Form IIA) show different PXRD patterns which is matched with corresponding simulated pattern. Similarly salicylic acid: 4,4'-bipyridine (Form IB) is matched with simulated PXRD pattern (Figure 9).



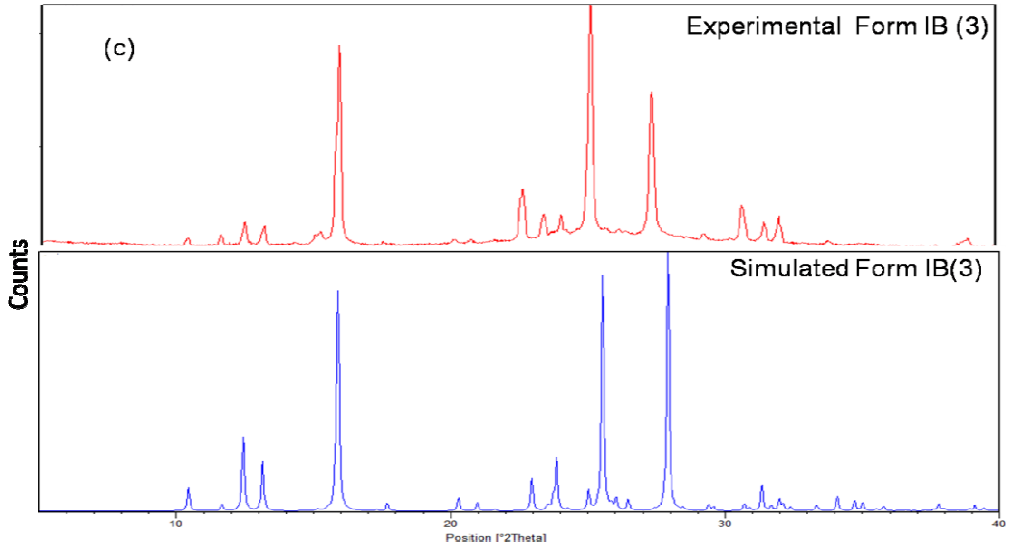


Figure 9. PXRD of polymorphic cocrystals urea : 4,4'-bipyridine (a) Form IA (1) and (b) Form IIA 2) (c) Polymorphic cocrystal of salicylic acid : 4,4′-bipyridine Form IB (3)

Hirshfeld surface area analysis for polymorphic cocrystals

Hirshfeld surface area[28] for the various close intermolecular contacts are drawn for both sets of cocrystals. In Form IA and Form IIA cocrystals the percentage of H···H contribution is more for Form IA (Figure 10). Major difference between two forms are highlighted in circle, it is due to close contacts of all elements inside surface to hydrogen (Figure 11). Here all contacts other than H···H could be collectively responsible for high melting point of Form IIA. It is fact that N–H···O and N–H···N are stronger and more directional interactions than H···H contacts, operate at longer distances. Alternatively, Form IIB has more H···H contribution in salicylic acid : 4,4'-bipyridine than Form IB (Figure 10). Difference between two polymorphs are highlighted in circle, it is because of close contacts of all elements inside surface to hydrogen. Fingerprint plots for polymorphic cocrystals are shown in figure 11.

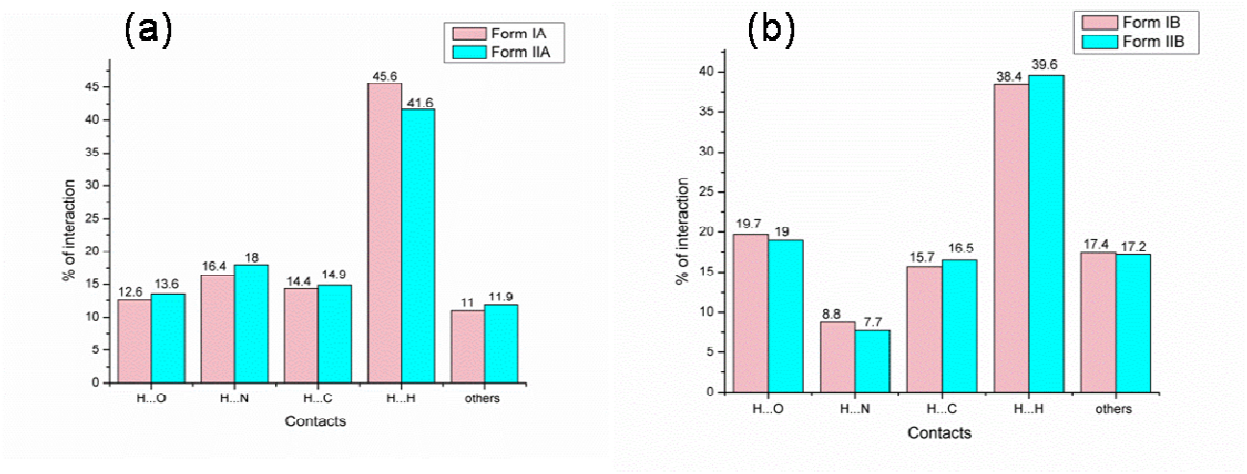
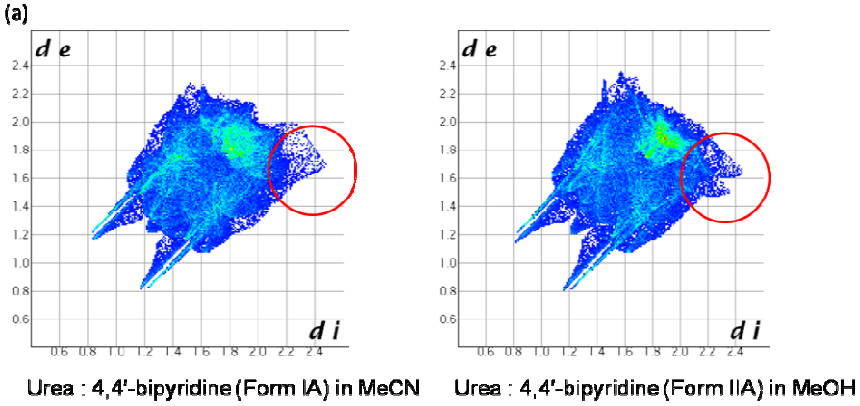
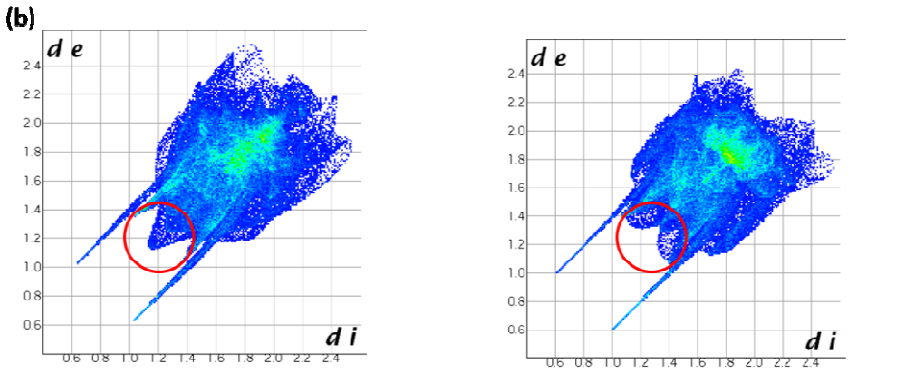


Figure 10. Percentage contributions to the Hirshfeld surface area for the various close intermolecular contacts in (a) Urea and 4,4'-bipyridine cocrystals Form IA and Form IIA (b) Salicylic acid : 4,4'-bipyridine polymorphic cocrystals Form IB and Form IIB.



Urea : 4,4'-bipyridine (Form IA) in MeCN

Urea : 4,4'-bipyridine (Form IIA) in MeOH



Salicylic acid : 4,4'-bipyridine (Form IB) in MeCN

Salicylic acid : 4,4'-bipyridine (Form IIB) in MeOH

Figure 11. Comparison of the fingerprint plots for polymorphic cocrystals Form IA and Form IIA (b) polymorphic cocrystals of Form IB and Form IIB. Major difference in two set of polymorphs are marked with red circles. Here *di* is the distance from the surface to the nearest atom interior to the surface and *de is* the distance from the surface to the nearest atom exterior to the surface.

Conclusions

Cocrystal polymorphs of urea : 4,4'-bipyridine (Form IA and Form IIA) and salicylic acid : 4,4'-bipyridine (Form IB and Form IIB) have been discussed. Both sets of cocrystals exhibit packing polymorphism. Urea tape and N–H···N hydrogen bonds are the basic supramolecular synthons in urea : 4,4'-bipyridine polymorphic cocrystals. Urea tape is rare in cocrystals of urea that is identified in urea : 4,4'-bipyridine (Form IA and Form IIA) cocrystals. Form IA has a lower melting point (197 °C) than Form IIA (200 °C). Urea band positions in cocrystal polymorphs shows bathochromic shift compare to native urea. Even though cocrystal polymorphs Form IA and Form IIA are obtained with same supramolecular synthons those are well distinguished by IR spectra. Though, the O–H···N and C–H···O hydrogen bonds are the basic supramolecular synthons in the salicylic acid : 4,4'-bipyridine polymorphic cocrystals, 3-D packing is different. All cocrystal polymorphs are obtained with same coformer 4,4'-bipyridine.

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GRAPHICAL ABSTRACT

Polymorphism in cocrystals of urea : 4,4'-bipyridine and salicylic acid : 4,4'-bipyridine

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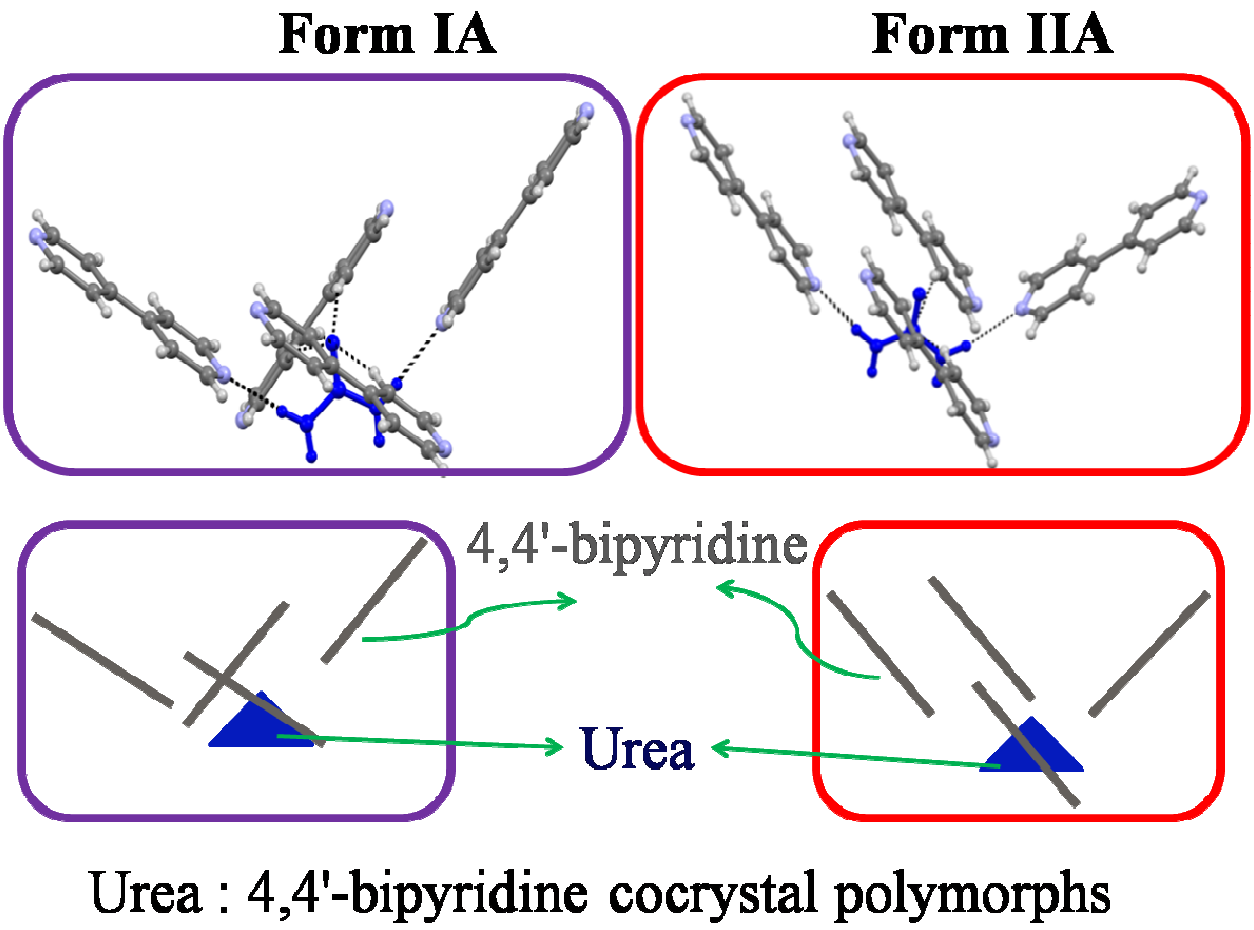

Urea tape is rare in urea cocrystal. Cocrystal packing polymorphs Form IA and Form IIA were obtained selectively in MeCN and MeOH.