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Comparison of pyridyl and pyridyl N-oxide groups as acceptor in hydrogen bonding with carboxylic acid†

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Competition experiments between pyridyl and pyridyl N-oxide groups have been performed to find out which of these two groups is a better acceptor in hydrogen bonding with the carboxylic acid group. 4,4′-bipyridine N-monoxide, a rigid, conjugated, and linear molecule and 4,4′-trimethylenebipyridine N-monoxide, a flexible, non-conjugated between two aryl groups, and bent molecule, have been used to synthesize complexes with some carboxylic acid containing compounds. The study shows that although the occurrence of pyridyl···acid synthon is more than the corresponding pyridyl N-oxide···acid synthon, based on the distance criterion and energy calculation, the pyridyl N-oxide···acid synthon is slightly stronger than the pyridyl···acid synthon. Solubility studies also show that the pyridyl N-oxide compound may be a better choice as a coformer than the corresponding pyridyl derivative to increase the solubility of carboxylic acid containing compounds.

Introduction

Synthons play a very important role in the fields of crystal engineering and pharmaceutical cocrystals.[1] Strong and robust synthons[2] are comparatively more reliable than the weak interactions[3] in the designing strategy of a cocrystal or a desired network. In a given set of functional groups, according to Etter's rule,[4] the strong donating group would prefer strong acceptor and weak donor would prefer weak acceptor. There are several studies on competition experiment for the preferred synthon available in a reacting medium. Aakeröy *et al.* performed some competition experiments to compare the donating ability of hydroxyl and halogen groups (F, Cl and I) in the 1 : 1 cocrystals of 1-methyl-2-(4-pyridyl) benzimidazole with halo substituted oximes.[5] They also have performed similar type of experiments using 3,3′-azobipyridine and 4,4′-azobipyridine, co-crystallized with bi-functional donor molecules containing halogen-bond donor (I or Br) as well as a hydrogen-bond donor (acid, phenol or oxime) on the same backbone to compare hydrogen bond and halogen bonds.[6] Brammer *et al.* performed competition experiments between nucleophiles for the hydrogen bond and halogen bond formation in a series of halopyridinium salts of mixed halide–halometallate anions.[7] Nangia *et al.* observed the synthon competition and cooperation in the molecular salts of hydroxybenzoic acids and aminopyridines.[8] Reddy and co-workers have performed competition experiments between sulfoxy and pyrimidine groups in the course of studying pharmaceutical cocrystals of sulfamethazine.[9] Recently, Jagadeesh and coworkers in their competition experiments, using cytosine–carboxylic acid complexes, found that choice of a synthon in crystal structure determination depends on the strength of the acid coformer and the stoichiometry used for it.[10] In pharmaceutical cocrystal the solubility is an important factor which could be tuned by changing the coformer.[11] Generally, strong hydrogen bond donor or acceptor groups are chosen as coformer to ensure complex formation. Carboxyl, hydroxyl, *etc.* groups are known as strong hydrogen bond donors and pyridyl, pyridyl N-oxide, sulfoxide, are known as strong hydrogen bond acceptors. Pyridyl N-oxide group is not as widely used functional group as the pyridyl group in the formation of complexes with strong hydrogen bond donors.[12] Herein, we have performed a competition experiment between the pyridyl and pyridyl N-oxide groups as an acceptor in hydrogen bonding with the carboxyl group.

Experimental

4,4′-bipyridine (BPY), 4,4′-trimethylenebipyridine, *p*-coumaric acid (PCA), α-cyanoparacoumaric acid (CPCA), *p*-cyanobenzoic acid (PCBA), and *p*-nitrobenzoic acid (PNBA) were purchased from Sigma Aldrich and used as such without further purification.

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p-hydroxybenzoic acid (PHBA) was purchased from Loba Chemie and *m*-chloroperoxybenzoic acid was purchased from Himedia. $CDCl_3$ and mesitylene were purchased from Sigma Aldrich. All other solvents were purchased from S D Fine-chem. ^{1}H NMR spectra were recorded on Bruker 400 MHz instrument.

4,4′-bipyridine N-monoxide (BPMO)[13] and 4,4′-bipyridine *N*,*N*′-dioxide (BPDO)[14] were synthesized by following the reported procedures.

Synthesis of 4,4′-trimethylenebipyridine N-monoxide (TBPO)

TBPO was prepared by following a procedure similar to the synthesis of BPMO.[13] 4,4′-trimethylenebipyridine (1 g, 5.05 mmol) was taken in chloroform solvent (20 ml). To this solution, 70% *m*-chloroperbenzoic acid (871.47 mg, 5.05 mmol) in 50 ml chloroform was added and the resulting solution was allowed to stir for three days at room temperature. Additional four more portions of *m*-chloroperbenzoic acid (134.730 mg, 0.78 mmol) each in chloroform (15 ml) were added after every 24 hours and the reaction was allowed to stir for a total of seventeen days. The crude mixture was filtered and solvent was removed in vacuum. TBPO was separated by using column chromatography and was found to be a yellow hygroscopic compound. Yield 62%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.512 (d, J = 5.6 Hz, 2H), 8.142 (d, J = 9 Hz, 2H), 7.101 (d, J = 5.6 Hz, J = 2H), 7.098 (d, J = 9 Hz, 2H), 2.657 (t, J = 7.2 Hz, 2H), 2.637 (t, J = 7.2 Hz, 2H), 1.971 (qn, J = 7.6 Hz, 2H).

Crystallization

TBPO·PNBA. TBPO and PNBA (1 : 1) were dissolved in methanol solvent. Single crystals were formed after two days through slow evaporation of the solvent.

TBPO·PCBA. Equimolar amounts of TBPO and PCBA were dissolved in methanol solvent. Slow evaporation of the solvent after three days resulted in good quality single crystals.

TBPO·PHBA. 1 : 1 mixture of TBPO and PHBA was dissolved in a methanol–mesitylene (2 : 1) solvent mixture. The solution was allowed to evaporate at room temperature and after a period of eight days, single crystals were obtained.

TBPO·CPCA. Single crystals of this system were obtained when a methanolic solution of TBPO and CPCA (1 : 1) was allowed to evaporate at room temperature.

BPMO·PHBA·H_2O. BPMO and PHBA (1 : 1) were dissolved in a 1 : 1 mixture of water and methanol. The solution was allowed to evaporate slowly at room temperature and diffraction quality single crystals were obtained after five days.

BPMO·PHBA. 1 : 1 mixture of BPMO and PHBA was dissolved in ethanol. The solution was allowed to evaporate slowly at room temperature and diffraction quality single crystals were obtained after four days.

BPMO·PCA. Equimolar amounts of BPMO and PCA were dissolved in methanol. The hot solution was allowed to evaporate slowly at room temperature and diffraction quality single crystals were obtained after three days.

BPMO·CPCA. Single crystals of this system were obtained when methanol solution of equimolar amounts of BPMO and CPCA was allowed to evaporate at room temperature.

X-ray crystallography

X-ray crystal data were collected on Xcalibur Eos Oxford Diffraction Ltd. with Mo-K_α radiation (λ = 0.71073 Å). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm were applied.[15] Structure solution and refinement were performed with SHELXS[16] and SHELXL[17] respectively using Olex2-1.1 software package.[18] Hydrogen atoms attached to carbon were placed in calculated position using riding model. All the hydrogen atoms attached to O atoms were refined with O–H = 0.85 Å and where the hydrogen atoms attached to N atoms were refined with N–H = 0.91 Å.

Solubility studies

Preparation of standard solution. For preparing the calibration curve, known concentration of stock solutions were prepared by taking 4.6 mg (0.299 mmol) of BPY and 5.0 mg (0.299 mmol) of PNBA individually and made up to 500 ml using double distilled water, and for BPDO 5.7 mg (0.302 mmol) was taken and dissolved in 1 L of water. Five standard solutions were prepared from each of these stock solutions by taking 1, 3, 5, 7 and 9 ml from these solutions and then made up to 10 ml individually by adding double distilled water and these solutions were used for UV-Visible experiments.

Preparation of saturated solution. Individual saturated solutions of BPY (300 mg, 19.20 mmol), PNBA (200 mg, 11.96 mmol), BPDO (500 mg, 26.57 mmol), BPY·PNBA cocrystal (700 mg, 14.27 mmol), and BPDO·PNBA cocrystal (700 mg, 13.40 mmol) were prepared by stirring each of the compounds for 48 hours in 5 ml of double distilled water. The solutions were then filtered and further diluted by adding water as follows to study the UV-Visible spectrum.

PNBA. 1 ml saturated solution was taken and made up to 100 ml.

BPY. 0.5 ml of saturated solution was taken and made up to 100 ml. 30 ml of this solution was further diluted to 100 ml.

BPDO. 0.5 ml of saturated solution was taken and made up to 100 ml. 10 ml of this solution was further diluted to 500 ml.

BPY·PNBA. 0.5 ml saturated solution was taken and made up to 100 ml.

BPDO·PNBA. 0.5 ml saturated solution was taken and made up to 200 ml.

Five solutions were prepared from each of the above mentioned solutions by taking 1, 3, 5, 7 and 9 ml from these solutions and then made up to 10 ml individually by adding double distilled water and these solutions were used for UV-Visible experiments.

Results and discussion

Crystal structures and hydrogen bonds

In this work we have intended to find out which of the two groups, pyridyl or pyridyl N-oxide, is a better hydrogen bond acceptor in their heterosynthons with carboxylic acid group. Competition experiments could be performed by dissolving equimolar quantities of an acid, pyridine and pyridine N-oxide molecules in a suitable solvent to check which synthon is formed in the resulting cocrystal (Table 1).[19] But there could be a drawback in this process. Apart from the synthon stability, the solubility also could play a very important role in the outcome of the crystallization product, which might mislead the conclusion. Therefore, in our experiments we have introduced both of the groups, pyridyl as well as the pyridyl N-oxide, in the same molecule to overcome the solubility difference of the acceptor moieties.

We have chosen two different types of molecules, BPMO, a rigid, conjugated, and linear molecule, and TBPO, a flexible, non-conjugated between the two aryl groups, and bent molecule, for this study (Scheme 1). On the other hand, we have selected some simple compounds, including drugs, which contain a COOH group as hydrogen bond donor (Scheme 1). Then the occurrence of the heterosynthons and bond distances were analyzed to understand the most favourable heterosynthon of the two. Solubility studies using UV absorption experiments on two cocrystals containing these heterosynthons were also performed to investigate whether the idea of replacement of pyridyl entity with the pyridyl N-oxide would give any solubility advantage in pharmaceutical cocrystal research.

A 1 : 1 cocrystallization of the TBPO with PNBA and PCBA molecules resulted into the 1 : 2 cocrystals of the TBPO·PNBA acid ($P\bar{1}$) and TBPO·PCBA acid ($P2_1/c$) systems. The carboxylic groups are hydrogen bonded to both of the acceptors of the TBPO molecule (Fig. 1a, b). The strong hydrogen bond accepting nature of the pyridyl and pyridyl N-oxide groups and due to decrease in selectivity owing to the presence of strong electron withdrawing groups (nitro or cyano) in the acid molecule, the resultant complex ratio is 1 : 2 rather than the intended 1 : 1 product. Hence no preference, based on the occurrence of the synthons, could be observed in these two experiments. Therefore, we have introduced an electron donating protic functional group (OH) in the acid molecule, expecting that it would increase the selectivity by decreasing the acidity of the carboxylic acid group as well as being relatively a weaker donor it would satisfy the weaker acceptor through hydrogen bond formation. Both of the 1 : 1 complex of TBPO·PHBA and 1 : 2 complex of TBPO·CPCA crystallize in $P\bar{1}$ space group. The carboxylic acid groups of the PHBA and the CPCA in these complexes prefer hydrogen bonding with the pyridyl group, while the phenolic O–H groups form hydrogen bonds with the pyridyl N-oxide group of the TBPO molecule (Fig. 1c, d). Similar results were also observed in the cocrystals of these two molecules with BPMO (Fig. 1e, f). These two 1 : 1 complexes of BPMO·PHBA and BPMO·CPCA crystallize in $P\bar{1}$ and *Cc* space groups respectively. It is worth to mention here that the BPMO·CPCA acid crystal lattice is noncentrosymmetric and made of closely parallel hydrogen bonded chains of the highly polar coformers. Therefore, it is expected to show a good second harmonic generation (SHG) property. On the other hand, a reverse trend has been observed in the cocrystals of the BPMO·PHBA·H_2O ($P\bar{1}$, 1 : 1 : 1) and BPMO·PCA ($P\bar{2}_1/n$, 1 : 1) systems. Where, the carboxylic acid groups prefer the pyridyl N-oxide group over the pyridyl group of the BPMO molecule (Fig. 1g, h). Hence, there are four carboxyl···N-oxide synthons and six carboxyl···pyridine synthons in these eight complexes reported here. Therefore, the occurrence of the carboxyl···pyridine synthons is higher than the carboxyl···N-oxide synthons. On the other hand, the average O···O bond distance (2.561 Å) in the carboxyl···N-oxide synthons is much shorter (by 0.479 Å) than the van der Waals sum of the oxygens (3.04 Å) compared to the average O···N bond distance (2.633 Å) in the carboxyl···pyridine synthons which is shorter only by 0.437 Å than the van der Waals sum (3.07 Å) of the oxygen and nitrogen atoms. Hydrogen bond distances are given in Table 2.

Energy calculation

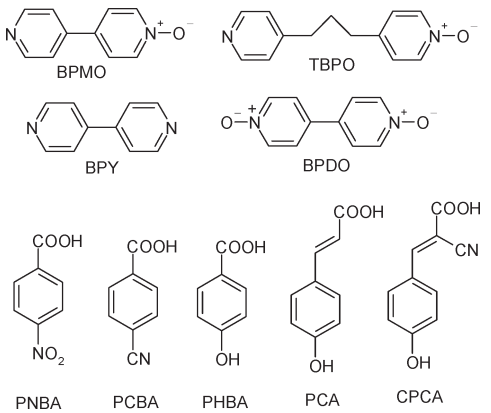
We also have performed theoretical energy calculation on these two synthons. Geometry optimization of individual molecules and their corresponding hydrogen bonded complexes were performed using M06-2X[20] density functional. M06-2X is shown to be accurate in computing hydrogen bonding interactions with the mean unsigned error (MUE) less than 1 kcal mol^{-1}.[20] Harmonic vibrational frequencies were computed and were used for applying zero-point vibrational energy correction. The DFT calculations using Gaussian-09[21] package with M06-2X/6-31+G(d,p) level of theory shows that after considering the BSSE and ZPE corrections, the carboxyl···N-oxide synthon between the benzoic acid and pyridine N-oxide (−13.47 kcal mol^{-1}) is slightly more stable than the carboxyl···pyridine synthon between benzoic acid and pyridine molecules (−11.84 kcal mol^{-1}). According to the independent studies by Berthelot[22] and Nangia,[23] the pyridine N-oxide group is shown to be a better hydrogen bond acceptor than the pyridyl N when the donor group is phenolic OH or carboxamide respectively.

Solubility study

The main aim of the solubility study in this case was to compare the solubility of the acid in acid·pyridine and acid·pyridine N-oxide complexes. We prepared 1 : 2 complexes of PNBA with BPY and BPDO.[24] In both the complexes the acid group forms heterosynthons with pyridine or pyridine N-oxide hydrogen bond acceptor. The usual way to find out the concentration of a compound in a saturated solution using Lambert–Beers law is by calculating the extinction coefficient (ε) of the compound from the absorption *vs.* concentration plots of some solutions with known concentration of the compound (standard solutions) and then by measuring

Table 1 Crystallographic table

	TBPO·PNBA	TBPO·PCBA	TBPO·PHBA	TBPO·CPCA	BPMO·PHBA	BPMO·CPCA	BPMO·PHBA·H_2O	BPMO·PCA
Formula	$C_{13}H_{14}N_2O{\cdot}2(C_7H_5NO_4)$	$C_{13}H_{14}N_2O{\cdot}2(C_8H_5NO_2)$	$C_{13}H_{14}N_2O{\cdot}C_7H_6O_3$	$C_{13}H_{14}N_2O{\cdot}2(C_{10}H_7NO_3)$	$C_{10}H_8N_2O{\cdot}C_7H_6O_3$	$C_{10}H_8N_2O{\cdot}C_{10}H_7NO_3$	$C_{10}H_8N_2O{\cdot}C_7H_6O_3{\cdot}H_2O$	$C_{10}H_8N_2O{\cdot}C_9H_8O_3$
M_r	548.50	508.52	352.38	592.59	310.30	361.35	328.32	336.34
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Triclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	Cc	$P\bar{1}$	$P2_1/n$
a (Å)	7.3410(5)	15.3106(11)	6.2766(9)	7.3004(9)	6.4902(17)	13.3286(4)	6.8052(4)	7.6894(5)
b (Å)	7.4478(4)	11.2938(7)	7.8957(13)	10.1353(13)	7.288(2)	10.7445(3)	9.9004(7)	19.3400(10)
c (Å)	24.440(3)	14.6971(7)	17.992(3)	20.884(2)	16.056(3)	12.3344(4)	12.1414(10)	10.6910(6)
α (°)	96.237(7)	90.00	100.669(13)	99.943(9)	88.34(2)	90.00	111.542(7)	90.00
β (°)	90.714(7)	99.163(6)	93.653(12)	90.989(9)	78.438(19)	102.018(3)	93.418(6)	101.843(5)
γ (°)	103.836(5)	90.00	95.958(13)	108.782(12)	73.56(3)	90.00	98.055(6)	90.00
V (Å^3)	1288.74(18)	2508.9(3)	868.3(2)	1436.6(3)	713.3(3)	1727.68(9)	747.87(10)	1556.05(15)
Crystal size (mm)	0.40·0.35·0.31	0.45·0.28·0.22	0.42·0.34·0.31	0.50·0.21·0.08	0.40·0.27·0.24	0.55·0.44·0.40	0.52·0.41·0.40	0.43·0.35·0.31
T (K)	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)
Z	2	1	2	2	2	4	2	4
F(000)	572	1064	372	620	324	752	344	704
μ(mm^{-1})	0.108	0.094	0.095	0.098	0.105	0.099	0.109	0.102
Ref. collected/ unique	4533/1977	4428/2265	3067/1585	5039/2577	2514/1015	3124/2917	2624/2231	2725/1818
Parameters	369	347	243	414	216	252	233	234
Final R indices [$I > 2\sigma(I)$]	0.0569	0.0551	0.0728	0.1181	0.0616	0.0338	0.0379	0.0462
R indices (all data)	0.1421	0.1584	0.2071	0.3593	0.1693	0.0883	0.1003	0.1104
Goodness of fit on F_2	0.972	0.997	0.995	1.061	0.972	1.035	1.061	1.036



Scheme 1 Compounds used in the complex formation in this study.

the absorption of the saturated solution.[25] Unfortunately, the absorbance of the acid and the co-former in each of these two complexes were overlapping (Fig. 2) and hence solubility of the acid in the saturated solutions could not be determined by the usual way, *i.e.* from the absorption at λ_{max} of the saturated solutions. There are some experimental techniques *e.g.* NMR, HPLC, *etc.* used to find out the concentration of a component in saturated solution in these cases.[26] But these methods involve expensive equipment, hazardous solvents *etc.* Here, we have used a simple and less expensive method, explained below, to resolve the overlapping problem.

A saturated solution of the PNBA·BPY complex was diluted to five different concentrations and their absorptions were plotted against wavelength. Similarly, five standard solutions were prepared from each of the individual compounds and absorption *vs.* wavelength was plotted. Then two wavelengths, λ_1 (260 nm) and λ_2 (274 nm), were selected at which absorptions *vs.* concentration plots for the two individual compounds solutions as well as the saturated cocrystal solution show good linear fittings. Two extinction coefficients, ε_1' and ε_2' have been calculated at these two wavelengths, λ_1 and λ_2, respectively from the absorption *vs.* concentration plots of standard solutions of PNBA. Similarly, two extinction coefficients, ε_1'' and ε_2'' have been calculated at those two wavelengths, λ_1 and λ_2, from the plots of standard solutions of BPY. Then absorptions, A_1 and A_2 have been measured from the linear absorption *vs.* concentration plots for the saturated solution of the PNBA·BPY complex at λ_1 and λ_2 respectively. Solving two linear equations (eqn (1) and (2)) produces the values of the concentrations of PNBA (c') and BPY (c'') in the particular diluted solutions prepared from the saturated solution of the complex.

$$A_1 = \varepsilon_1' c' + \varepsilon_1'' c'' \text{ at } \lambda_1 \text{ nm} \ldots \quad (1)$$

$$A_2 = \varepsilon_2' c' + \varepsilon_2'' c'' \text{ at } \lambda_2 \text{ nm} \ldots \quad (2)$$

In a similar way, the concentrations of PNBA and BPDO in the saturated solution of the 1 : 2 complex of PNBA·BPDO have been calculated at 293 nm and 298 nm. Calculation

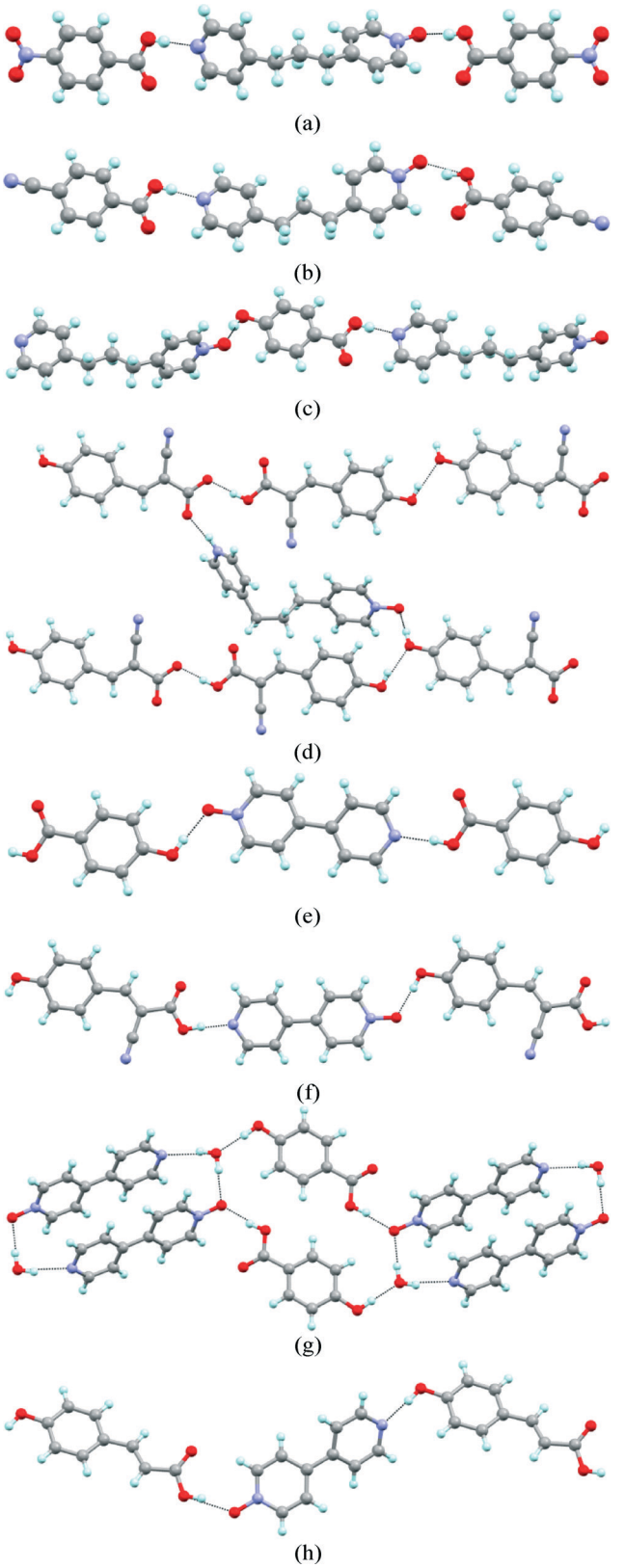


Fig. 1 Hydrogen bond interactions in (a) TBPO·PNBA, (b) TBPO·PCBA, (c) TBPOP·PHBA, (d) TBPO·CPCA, (e) BPMO·PHBA, (f) BPMO·CPCA, (g) BPMO·PHBA·H_2O, and (h) BPMO·PCA.

Table 2 Hydrogen bond parameters

	Hydrogen bonds	d/Å	D/Å	θ/°
TBPO·PNBA	O1–H1···O5	1.67(3)	2.528(3)	172(3)
	O1–H1···N2	2.55(3)	3.364(4)	159(2)
	O6–H6···N3	1.77(4)	2.624(5)	176(4)
TBPO·PCBA	O1–H1···O5	1.55(2)	2.531(3)	155(1)
	O1–H1···N4	2.51(2)	3.543(3)	174(1)
	O3–H3A···N3	1.76(2)	2.620(3)	173(3)
TBPO·PHBA	O1–H1···N1	1.79(3)	2.644(4)	176(2)
	O3–H3···O4	1.86(3)	2.676(4)	159(3)
TBPO·CPCA	O1–H1···O5	1.62(3)	2.491(5)	175(8)
	N3–H3···O4	1.80(6)	2.687(6)	166(7)
	O3–H3B···O6	1.90(4)	2.716(7)	162(8)
	O6–H6A···O7	1.66(7)	2.494(7)	167(9)
	O6–H6A···N4	2.54(8)	3.281(7)	146(7)
BPMO·PHBA	O1–H1···N1	1.76(3)	2.620(4)	175(3)
	O3–H3···O4	1.75(2)	2.596(4)	175(2)
BPMO·CPCA	O1–H1···N1	1.66(2)	2.574(2)	174(2)
	O3–H3···O4	1.76(2)	2.611(2)	175(2)
BPMO·PHBA·H_2O	O1–H1···O4	1.75(2)	2.624(2)	169(2)
	O3–H3···O5	1.80(2)	2.668(2)	172(2)
	O5–H5A···O4	1.88(2)	2.752(2)	175(2)
	O5–H5B···N1	2.00(2)	2.834(2)	166(2)
BPMO·PCA	O1–H1···O4	1.74(2)	2.570(2)	165(3)
	O3–H3···N1	1.83(2)	2.689(2)	175(2)

shows that the concentration of the acid in its saturated solution is 2.3×10^{-3} M, whereas it is 3.4×10^{-3} M and 4.1×10^{-3} M in the PNBA·BPY and PNBA·BPDO complexes respectively. On the other hand, the solubility of BPY in its saturated solution is 3.3×10^{-2} M and that in the PNBA·BPY complex is 8.1×10^{-3} M. Similarly, the solubility of BPDO in its saturated solution is 2.4×10^{-1} M, but that in the saturated solution of the PNBA·BPDO complex is 8.8×10^{-3} M. A comparison of the concentrations of the acid in its saturated solution and in the saturated solutions of the two complexes suggests that solubility of PNBA increases by ~1.5 times in the PNBA·BPY complex and by ~1.8 times in the PNBA·BPDO complex. It has been noticed that owing to the higher polarity, the BPDO compound is ~7 times more soluble than BPY. Therefore, the ability of BPDO to retain the acid compound in solution is more than that of BPY.

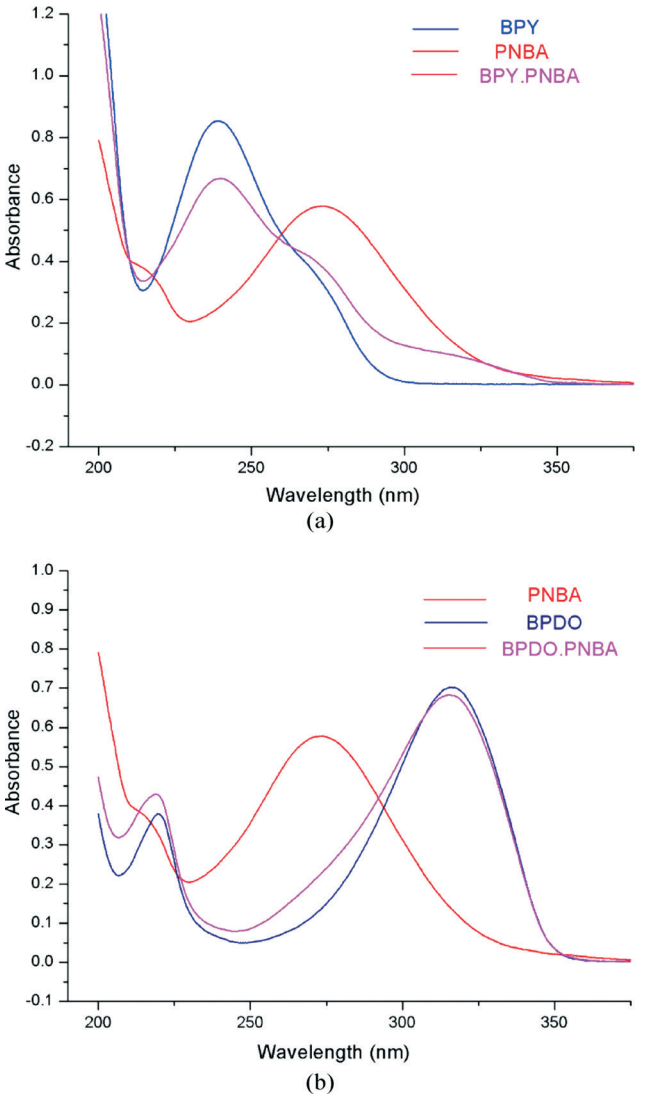


Fig. 2 Absorbance *vs.* wavelength plots for (a) BPY (blue), PNBA (red), BPY·PNBA (magenta) complex and (b) BPDO (blue), PNBA (red), BPDO·PNBA complex (magenta).

Conclusions

In this work we have studied a series of acid···pyridine and acid···pyridine N-oxide complexes. The propensity of occurrence of the acid···pyridine synthon is more than that of acid···pyridine N-oxide synthon, but bond distance analysis shows that the latter is relatively a stronger synthon than the former. Energy calculation also suggests that the acid···pyridine N-oxide is slightly stronger than the acid···pyridine synthon. The higher propensity of the acid···pyridine synthon could be attributed to the salt formation tendency of this particular synthon. The solubility study shows that the acid compound is more soluble in the presence of pyridine N-oxide compared to in the presence of a pyridine compound. The higher solubility of the pyridine N-oxide···acid complex could be due to the much higher solubility of the pyridine N-oxide compound compared to that of the corresponding pyridine compound. This synthon preference and increase in solubility suggest that pyridine N-oxide compound could be a better choice than the pyridine compound in the preparation of pharmaceutical cocrystals with acid compounds.

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Notes and references

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