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PAPER

Co-crystals of caffeine with substituted nitroanilines and nitrobenzoic acids: Structure–mechanical property and thermal studies†

Soumyajit Ghosh and C. Malla Reddy*

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Nine new 1 : 1 co-crystals of caffeine with some halogenated nitroanilines and two nitrobenzoic acids have been synthesized. These new caffeine (CAF) co-crystals, with 4-nitroaniline (4NA), 4-fluoro-3-nitroaniline (4F3NA), 4-chloro-3-nitroaniline (4Cl3NA), 4-iodo-3-nitroaniline (4I3NA), 2-fluro-5-nitroaniline (2F5NA), 2-chloro-5-nitroaniline (2Cl5NA), 2-iodo-4-nitroaniline (2I4NA), 2,4-dinitrobenzoic acid (24DNB), 2-fluoro-5-nitrobenzoic acid (2F5NB), are characterized by single crystal X-ray diffraction, differential scanning calorimetry, thermogravimetric analysis and infrared spectroscopy. The co-crystals adopt a range of structures, namely two-dimensional (2D) flat layer, corrugated layer and 3D interlocked structures. The series of crystals allowed us to establish a structure–mechanical property relationship by using a simple mechanical deformation (qualitative) method. The 2D flat layer crystals (CAF/24DNB, CAF/2Cl5NA and CAF/2I4NA), which have strong *intra*layer and weak *inter*layer interactions show shear deformation behaviour, while those with weak *intra*layer interactions (CAF/4Cl3NA and CAF/4I3NA) show brittle fracture on application of a mechanical stress. The structures with corrugated layers (CAF/2F5NA) or 3D interlocked packing (CAF/NA, CAF/2F5NB and CAF/4F3NA) also show brittle behaviour. We also show the need for a wide initial search, targeting even the least expected synthons, to improve the efficiency of co-crystal screening.

Introduction

Co-crystallization of active pharmaceutical ingredients (APIs) represents a viable means of enhancing the physical properties of a drug substance, particularly when the API is nonionizable for salt formation and the amorphous material is undesired due to its inherent instability.[1] In recent times, co-crystal formation using the crystal engineering[2] approach has been shown to be effective for altering physicochemical properties of APIs such as melting point,[3] solubility,[4] thermal[5] and photostability,[6] as well as mechanical properties.[7] The first and simple step in this process is generally a careful selection of co-formers, targeting some specific supramolecular synthons,[8] and/or with suitable size and shape that match to the target API. In recent studies, the synthon based co-crystal search has been shown to be very efficient.[9] Because this approach helps to quickly narrow down the list of potential co-formers by eliminating the most improbable candidates, thus improving the success rate. However, in this process, one may miss some co-formers that can form the least expected synthons which may have the potential to occur repeatedly in co-crystals with a set of similar co-formers.

Caffeine (CAF), a central nervous system stimulant and a smooth muscle relaxant, is known to exist in two anhydrous polymorphic forms (α, β), a hydrated form and a number of co-crystal and salt forms.[10] The polymorphs display poor stability under higher relative humidities (RHs) due to their conversion into the hydrate form. The hydrate in low RHs loses water to transform into anhydrate form, hence it is also not desired for pharmaceutical applications. The associated poor stabilities of these crystalline forms have sparked research interest in improving the physicochemical properties of caffeine. Among all the caffeine co-crystals (47) reported in the Cambridge Structural Database (version 5.33, update Nov 2011), the majority of co-formers contain carboxylic acid (15), phenolic OH (11) or both the functional groups (15), leaving some exceptions (6) where none of these two groups are present. The carboxylic acids mostly form synthon-1 (Scheme 1) involving caffeine's free aromatic N-atom. While, there are only two cases (Refcodes: SACCAF, VIGVOW) where the co-formers possess sulfanilamide groups that form N–H···N hydrogen bonds (synthon-2, R = C(=O)Me or C(=O)Ar) with caffeine.

With this in mind, to expand the caffeine co-crystal landscape, we made a search using a variety of co-formers by targeting synthons, mostly unexplored previously. In our search, we

Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal, 741252, India. E-mail: cmreddy@iiserkol.ac.in; cmallareddy@gmail.com; Fax: +91-33-25873020; Tel: +91-33-25873118, Ext.No.: 238

† Electronic supplementary information (ESI) available: List of some unsuccessful co-formers used in the co-crystal screening, geometrical parameters of molecules from crystal structures, melting points table, powder X-ray diffraction patterns, infrared spectra, ORTEP diagrams and some optical images of crystals. CCDC reference numbers 860122–860130. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ce06754d

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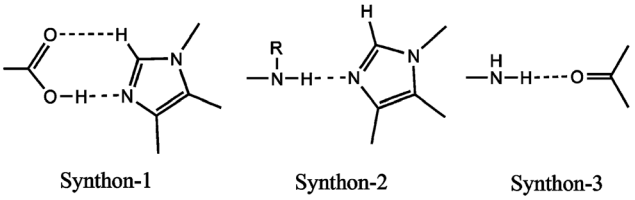
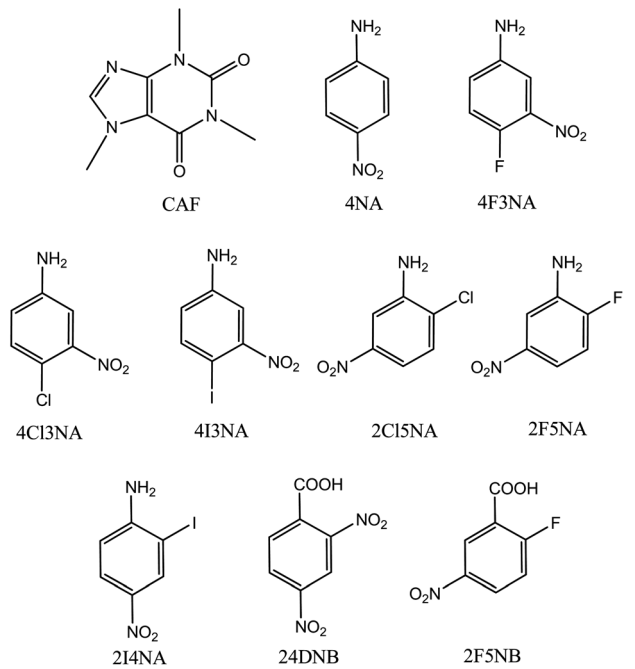


Scheme 1 Synthons between different groups and caffeine.



Scheme 2 Chemical structures of the compounds used in this study.

employed co-formers with functional groups such as $–NH_2$, $–CONH_2$, –CHO, –OR as well as *aza*-aromatics (see ESI, Scheme S1†) which have the potential to bind to the caffeine free N-atom or form π-stacking interactions.[11–13] The other criterion we followed in co-formers was similar size and shape (flat) to match the caffeine molecule. Our initial screening studies led us to identify anilines as potential candidates for forming co-crystals with caffeine. We further searched by employing several commercially available halogenated nitroanilines, and then extended to halogenated nitrobenzoic acids to successfully obtain a series of co-crystals (Scheme 2). The co-crystals adopt a variety of crystal structures, including 2D flat layers, corrugated layers and 3D interlocked structures. We took advantage of the structural variations to study the structure–mechanical property relationship in the series.[14]

Experimental section

Materials

Caffeine and all co-crystal formers were purchased from Sigma-Aldrich. Commercially available solvents were used as received without further purification.

Single crystal preparation

Caffeine and co-crystal former in a definite stoichiometric ratio (1 : 1) were subjected to grinding with an addition of a few drops of methanol solvent using an agate mortar and pestle for about 15 min. After grinding, the mixture was transferred to a 10 mL conical flask followed by addition of methanol. The suspension was heated until a clear solution was obtained. The resulting mixture was boiled for 10 min before being filtered into a fresh conical flask. The filtrate was left to evaporate slowly at ambient conditions. Co-crystal screening was also carried out from other solvents such as ethyl acetate, ethanol, acetonitrile, *etc.* In some cases, co-crystals were obtained, but generally the yields were not as good as compared to that from methanol, as confirmed by powder X-ray diffraction. The single crystals suitable for X-ray diffraction studies were obtained from methanol solution in 4 to 6 days. For CAF/24DNB co-crystal, acetonitrile was used instead of methanol, as this yielded better quality single crystals for XRD studies.

NMR

^{1}H nuclear magnetic resonance (NMR) analysis of single crystals (2 to 3) was performed on a JEOL 400 MHz NMR in $CDCl_3$ at 25 °C to confirm the API to co-former ratio.

Powder X-ray diffraction (PXRD)

The PXRD patterns were collected on a Rigaku SmartLab with a Cu-Kα radiation (1.540 Å). The tube voltage and amperage were set at 40 kV and 50 mA respectively. Each sample was scanned between 10 and 90° 2θ with a step size of 0.02°. The instrument was previously calibrated using a silicon standard.

Single crystal X-ray diffraction (SCXRD)

Co-crystals of caffeine were individually mounted on a glass pip. Intensity data were collected on a Bruker KAPPA APEX II CCD Duo system with graphite-monochromatic Mo-Kα radiation (λ = 0.71073 Å) at 293 K for all the co-crystals, except CAF/4F3NA, CAF/4Cl3NA and CAF/2Cl5NA, which were collected at 100 K. Data reduction was performed using Bruker SAINT software.[15] Crystal structures were solved by direct methods using SHELXL-97 and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for non H-atoms using SHELXL-97. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained riding positions. Hydrogen atoms associated with oxygen and nitrogen atoms were included in the located positions. Crystallographic data and structure refinement parameters are included in Table 1. Structure graphics shown in the figures were created using the X-Seed software package version 2.0.[16]

Melting point

Melting points of co-crystals and the individual co-formers were measured using a digital melting point apparatus, SECOR INDIA.

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Table 1 Crystallographic data and structure refinement parameters of CAF co-crystals

	CAF/NA	CAF/4F3NA	CAF/4Cl3NA	CAF/4I3NA	CAF/2F5NA	CAF/2Cl5NA	CAF/2I4NA	CAF/24DNB	CAF/2F5NB
Chemical Formula	$C_8H_{10}N_4O_2$,$C_6H_6N_2O_2$	$C_8H_{10}N_4O_2$,$C_6H_5FN_2O_2$	$C_8H_{10}N_4O_2$,$C_6H_5ClN_2O_2$	$C_8H_{10}N_4O_2$, $C_6H_5IN_2O_2$	$C_8H_{10}N_4O_2$, $C_6H_5FN_2O_2$	$C_8H_{10}N_4O_2$,$C_6H_5ClN_2O_2$	$C_8H_{10}N_4O_2$,$C_6H_5IN_2O_2$	$C_8H_{10}N_4O_2$, $C_7H_4N_2O_6$	$C_8H_{10}N_4O_2$, $C_7H_4FNO_4$
Formula weight	332.33	350.32	366.77	458.22	350.32	366.77	458.22	406.32	379.31
Cryst syst.	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$Pna2_1$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P-1$	$P2_1/c$
a/Å	10.5157(7)	15.8624(19)	7.7950(6)	8.0323(5)	5.8784(5)	13.585(6)	8.1283(5)	8.5624(4)	12.5652(6)
b/Å	10.7574(7)	13.5643(15)	13.5627(9)	13.7265(8)	33.258(3)	13.9085(6)	13.8659(7)	11.8197(6)	8.1475(4)
c/Å	13.6464(10)	7.3360(9)	14.9920(10)	15.3774(9)	8.0008(7)	17.5266(8)	14.9447(8)	18.7587(10)	16.5266(8)
α (°)	90	90	90	90	90	90	90	88.2690(10)	90
β (°)	100.1790(10)	90	95.6570(10)	93.5480(10)	92.806(2)	104.8920(10)	97.473(3)	77.0890(10)	93.688(2)
γ (°)	90	90	90	90	90	90	90	72.2120(10)	90
Vol/Å^3	1519.41(18)	1578.4(3)	1577.25(19)	1692.19(18)	1562.3(2)	3200.4(2)	1670.05(16)	1760.53(15)	1688.41(14)
D_c/g cm^{-3}	1.453	1.474	1.545	1.799	1.489	1.522	1.822	1.533	1.492
μ/mm^{-1}	0.110	0.119	0.278	1.926	0.120	0.274	1.952	0.127	0.125
θ range (°)	1.97–27.0	1.98–27.0	2.63–26.98	1.99–27.0	2.62–27.0	1.89–27.0	2.01–26.99	1.81–27.0	2.47–27.0
Z	4	4	4	4	4	8	4	4	4
Range h	−13 to + 13	−20 to + 20	−9 to + 6	−10 to + 10	−7 to + 7	−17 to + 17	−10 to + 10	−10 to + 10	−15 to + 16
Range k	−13 to + 13	−17 to + 17	−17 to + 17	−17 to + 17	−40 to + 42	−11 to + 17	−17 to + 17	−15 to + 15	−10 to + 10
Range l	−17 to + 17	−9 to + 2	−17 to + 19	−19 to + 19	−10 to + 9	−22 to + 22	−19 to + 18	−23 to + 23	−9 to + 20
Reflns collected	23085	7079	13582	13862	12814	26368	41560	28334	14412
Independent reflns	3326	2053	3420	3697	3384	6933	3644	7644	3678
Obsd reflns	2798	1704	3181	3227	2911	6332	2992	5914	2902
T/K	296(2)	100(2)	100(2)	296(2)	296(2)	100(2)	296(2)	296(2)	296(2)
R_1	0.0401	0.0429	0.033	0.0256	0.0588	0.0298	0.0443	0.0558	0.0457
wR_2	0.1192	0.1106	0.0936	0.0649	0.1406	0.0805	0.1015	0.1464	0.1274
GOF	1.054	1.080	1.035	1.073	1.134	1.067	1.208	1.030	1.026
CCDC No.	860127	860125	860124	860123	860129	860126	860122	860128	860130

Differential scanning calorimetry (DSC)

DSC was conducted on a Mettler-Toledo DSI1 STAR^e instrument. Accurately weighed samples (2–3 mg) were placed in hermetically sealed aluminium crucibles (40 μL) and scanned from 30 °C to 300 °C at a heating rate of 5 °C min^{-1} under a dry nitrogen atmosphere (flow rate 80 mL min^{-1}). The data were managed by STAR^e software.

Thermogravimetric analysis (TGA)

TGA was performed on a Mettler-Toledo TGA/SDTA 851^e instrument. Approximately 10–15 mg of the sample was added to an aluminium crucible and heated from 30 to 350 °C at a rate of 10 °C min^{-1} under continuous nitrogen purge.

IR spectroscopy

Transmission infrared spectra of the solids were obtained using a Fourier–transform infrared spectrometer (Shimadzu). KBr samples (2 mg in 20 mg of KBr) were prepared and 10 scans were collected at 4 cm^{-1} resolution for each sample. The spectra were measured over the range of 4000–400 cm^{-1}.

Results and discussion

Caffeine/4-nitroaniline

Caffeine (CAF) and 4-nitroaniline (4NA) co-crystallize from methanol solution in the monoclinic space group $P2_1/c$. The asymmetric unit contains one molecule of each component. In the structure, each molecule interacts *via* multiple hydrogen bonds (H-bonds) that lead to a three dimensionally (3D) interlocked structure. Each caffeine molecule is connected with neighbouring 4NA molecules *via* N–H···O=C (*d*/Å, *θ*/°: 2.16(2) Å, 165(2)°; synthon-3) and N–H···N (2.32(2) Å, 174(2)°) interactions (synthon-2, R = H; Scheme 1), and with neighbouring caffeine molecule *via* C–H···O=C (2.229(19) Å, 157.4(16)°) interaction (Fig. 1).

Caffeine/4-fluoro-3-nitroaniline

Caffeine and 4-fluoro-3-nitroaniline (4F3NA) co-crystallize from methanol solvent in the orthorhombic space group $Pna2_1$. The asymmetric unit contains one molecule of each component. Two carbonyl groups of each caffeine molecule are involved in two intermolecular N–H···O=C (2.13 Å, 156°; 2.04 Å, 164°) interactions (synthons-3, Scheme 1) with the amino groups of two adjacent 4F3NA molecules, leading to the formation of two zigzag molecular tapes parallel to (011) and (0–11) planes that have an intersecting angle of nearly 50° between them (Fig. 2).[17] Molecules from similar tapes stack down along the *c*-axis to optimize the π···π interactions.[18]

Caffeine/4-chloro-3-nitroaniline

Caffeine and 4-chloro-3-nitroaniline (4Cl3NA) co-crystallize from methanol solution in the monoclinic space group $P2_1/c$. The

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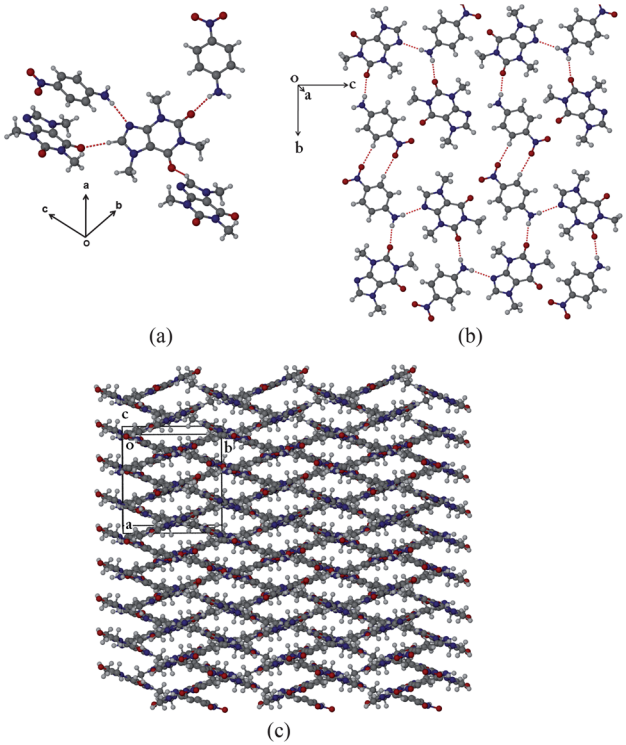

Fig. 1 Caffeine/4-nitroaniline co-crystal. (a) Interaction of each CAF molecule with two 4NA and two CAF molecules *via* intermolecular H-bonds. (b) Crystal packing view along *a*-axis. Note that the molecules shown are not in the same plane. (c) Crystal packing view along *c*-axis to show the 3D interlocked structure in the co-crystal.

asymmetric unit contains one molecule of each component. Two carbonyl groups of each caffeine molecule are involved in two intermolecular N–H···O=C (2.098(18) Å, 168.4(16)°; 2.11(2) Å, 162(2)°) interactions with the amino groups of two adjacent 4Cl3NA molecules that lead to the formation of 2D planar sheets parallel to (101) (Fig. 3). In addition, there is a weak C–H···O hydrogen bond (2.50 Å, 151°) in the two component supramolecular assembly. The Cl-atom from 4Cl3NA is not involved in any significant intermolecular interaction, hence it is merely a spectator in the layer formation. The arrangement of caffeine (A) and co-former (B), 4Cl3NA, within the sheet may be shown as in Fig. 3b. Two perpendicular tapes[19] of ABAB type may be identified within a layer. The sheets stack antiparallel to optimize π···π interactions where the molecules of type A and B stack one over the other with some offset. The separation between the two consecutive layers is 3.016 Å.

Caffeine/4-iodo-3-nitroaniline

Caffeine and 4-iodo-3-nitroaniline (4I3NA) co-crystallize from methanol solution in the monoclinic space group $P2_1/c$. The co-crystal is isostructural to CAF/4Cl3NA. However, the longer C–I bond in 4I3NA allows the iodo-group to reach to the nitro-group of adjacent 4I3NA for forming the C–I···O (3.412 Å, 174.4°) halogen bond (Fig. 4).

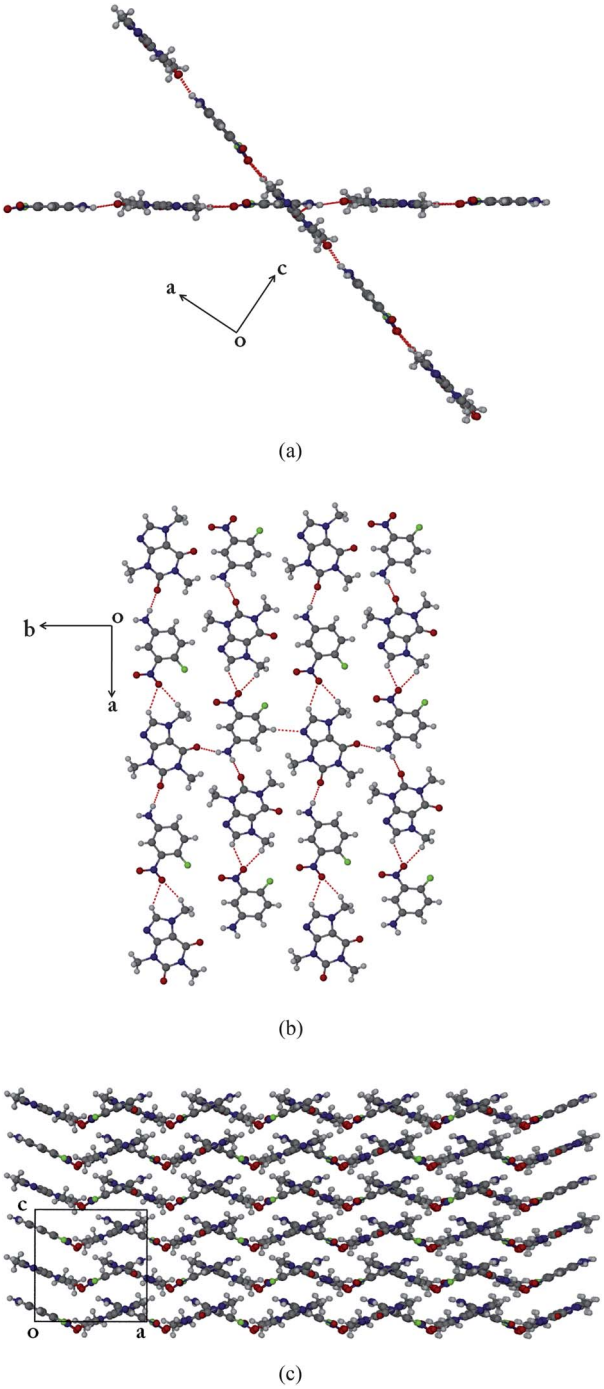

Fig. 2 Caffeine/4-fluoro-3-nitroaniline. (a) Side view (along *b*-axis) and (b) top view (down *c*-axis) of the antiparallel tapes in the structure. (c) 3D interlocking of the antiparallel tapes that are stacked down along the *c*-axis.

Caffeine/2-fluoro-5-nitroaniline

Caffeine and 2-fluoro-5-nitroaniline (2F5NA) co-crystallize from methanol solution in the monoclinic space group $P2_1/c$ with one molecule of each component in the asymmetric unit. In this case also the two carbonyl groups of the caffeine molecule are involved in two intermolecular N–H···O=C (2.06(3) Å, 164(3)°; 2.24(3) Å, 166(3)°) interactions with amino groups of two

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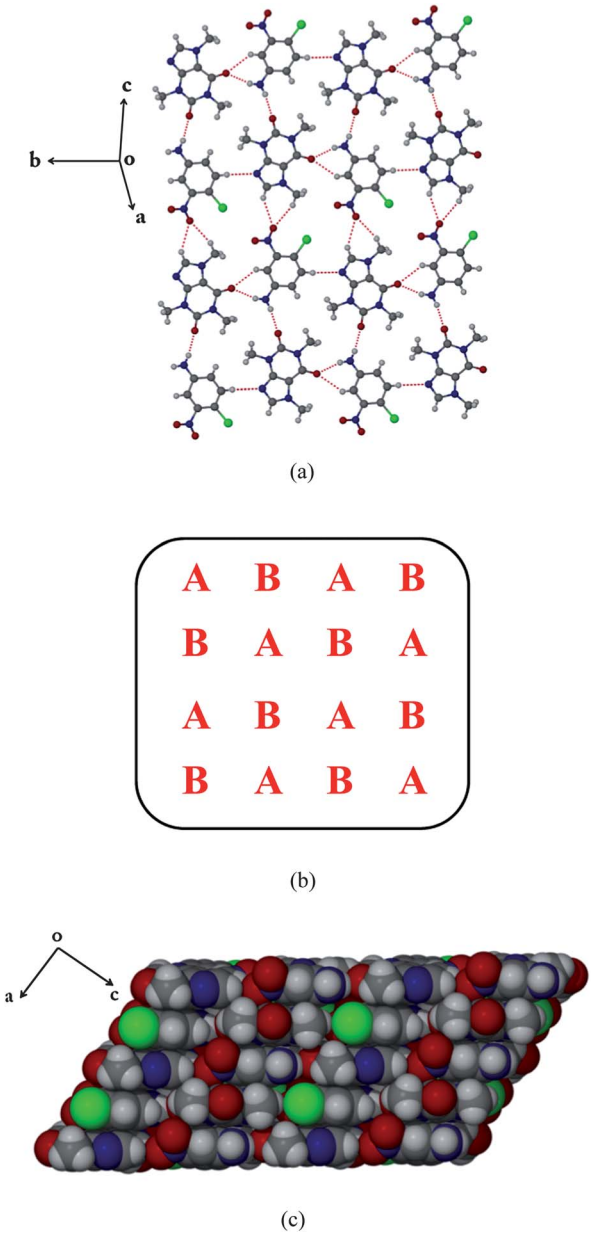

Fig. 3 Caffeine/4-chloro-3-nitroaniline. (a) 2D sheet formed by two component assembly. (b) Representation of perpendicular ABAB type tapes formed by CAF (A) and 4Cl3NA (B) molecules, within a 2D sheet. (c) Stacking of the 2D sheets in an antiparallel fashion.

adjacent 2F5NA molecules, leading to the formation of 2D sheets (Fig. 5). But interestingly, in this case the 2D sheets have a wave-like corrugation. The arrangement of caffeine (A) and co-former (B), 2F5NA, within the 2D sheet may be shown as perpendicular ABAB type tapes (Fig. 3b). The sheets stack along the *b*-axis to optimize the π···π interactions (Fig. 5b). The distance between the two consecutive layers is 3.391 Å.

Caffeine/2-chloro-5-nitroaniline

Caffeine and 2-chloro-5-nitroaniline (2Cl5NA) co-crystallize from methanol solution in the monoclinic space group $P2_1/c$. The asymmetric unit contains two molecules of each component

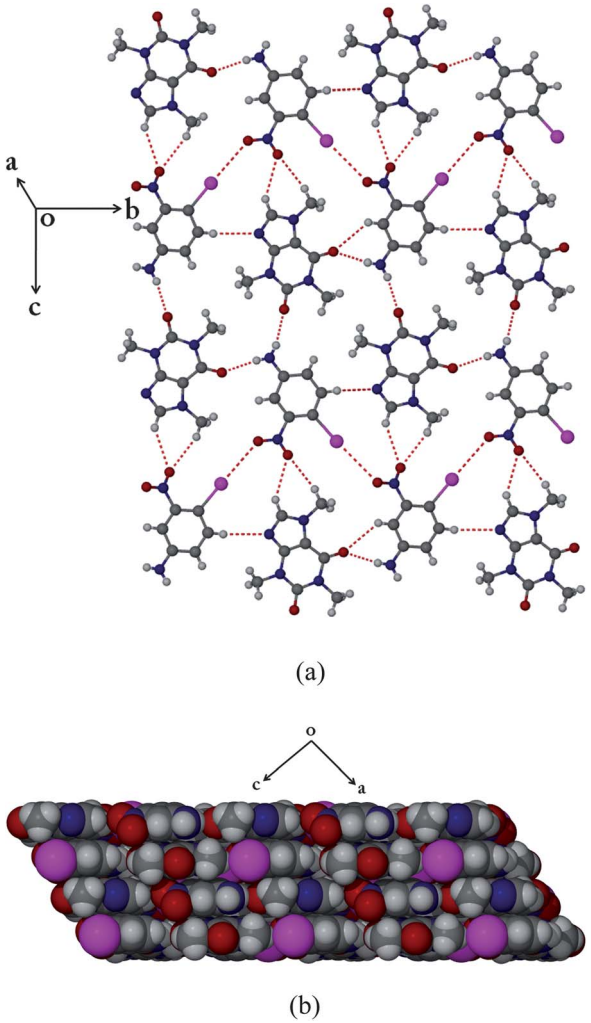

Fig. 4 Caffeine/4-iodo-3-nitroaniline. (a) Top view of the 2D sheet parallel to (101). (b) Stacking of the 2D sheets.

($Z' = 2$). Two carbonyl groups of each caffeine molecule are involved in intermolecular N–H···O (2.04(18) Å, 168.7(16)°) with the amino group and C–H···O (2.37(3) Å, 153°) interactions between caffeine molecules that lead to the formation of 2D wave-like corrugated sheets. There is a weak Cl···$O_{(nitro)}$ (3.211 Å, 143.43°) interaction connecting two 2Cl5NA molecules. The arrangement of the caffeine (A) and co-former (B), 2Cl5NA, within the sheet is completely different in this case (Fig. 6). The perpendicular tapes within the layers are ABAB and AAAA/BBBB types.[19] The sheets stack along [10–5] to optimize the π···π interactions,[18] with an interplanar distance of 3.331 Å.

Caffeine/2-iodo-4-nitroaniline

Caffeine and 2-iodo-4-nitroaniline (2I4NA) co-crystallize in the monoclinic space group $P2_1/n$ with $Z' = 1$. Each caffeine molecule interacts with neighbouring caffeine and 2I4NA molecules *via* a strong C–I···N (3.03 Å, 170.66°) halogen bond and some other supporting weak interactions (Fig. 7). Interestingly both nitro and amino groups from 2I4NA are aligned in the same plane, face to face (Fig. 7a). The arrangement of caffeine (A) and

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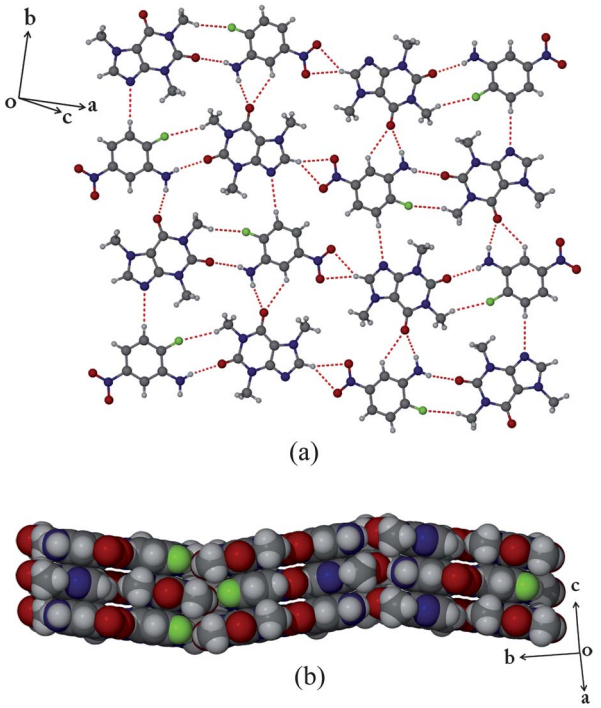

Fig. 5 Caffeine/2-fluoro-5-nitroaniline. (a) Top view of the wave like 2D layer parallel to (−102). (b) Stacking of the 2D wave-like sheets.

co-former (B), 2I4NA, within the sheet may be shown as in Fig. 7b. Three types of tapes may be identified within the layer, AAAA, BBBB and ABAB. The latter is zigzag and perpendicular to the former two, which are parallel to each other. The sheets stack along [10−3] to optimize the π···π interactions.

Caffeine/2,4-dinitrobenzoic acid

Caffeine and 2,4-dinitrobenzoic acid (24DNB) co-crystallize from acetonitrile solution in the triclinic space group $P-1$, with two molecules of each component ($Z' = 2$) in the asymmetric unit. The constituent molecules form an interesting flat layer structure in this case. Four molecules of CAF and four molecules of 24DNB form tetramers *via* multiple C–H···O hydrogen bonds (Fig. 8) with an angle >140° at the donor groups. This indicates their significance when considering the angle criteria for the bond strengths.[20] Each caffeine molecule interacts with two neighbouring caffeine molecules, *via* C–H···O (2.43(2) Å, 145(2)°; 2.41(2) Å, 141.7(19)°), and two 24DNB molecules, *via* O–H···N (1.82(4) Å, 173°; synthon-1), to form AABB type perpendicular tapes. The 24DNB molecules form C–H···O interactions among them. As a result, within the 2D sheet, the four caffeine and four 24DNB molecules, each form a square type tetramer as shown in Fig. 8b.

Caffeine/2-fluoro-5-nitrobenzoic acid

Caffeine and 2-fluoro-5-nitrobenzoic acid (2F5NB) co-crystallize from methanol solution in the monoclinic space group $P2_1/c$ with one molecule of each co-former in the asymmetric unit. The two molecular components interact *via* the strong O–H···N (1.67(4) Å, 175(3)°; synthon-1) hydrogen bond. Two carbonyl groups of each caffeine molecule are involved in the two intermolecular C–H···O

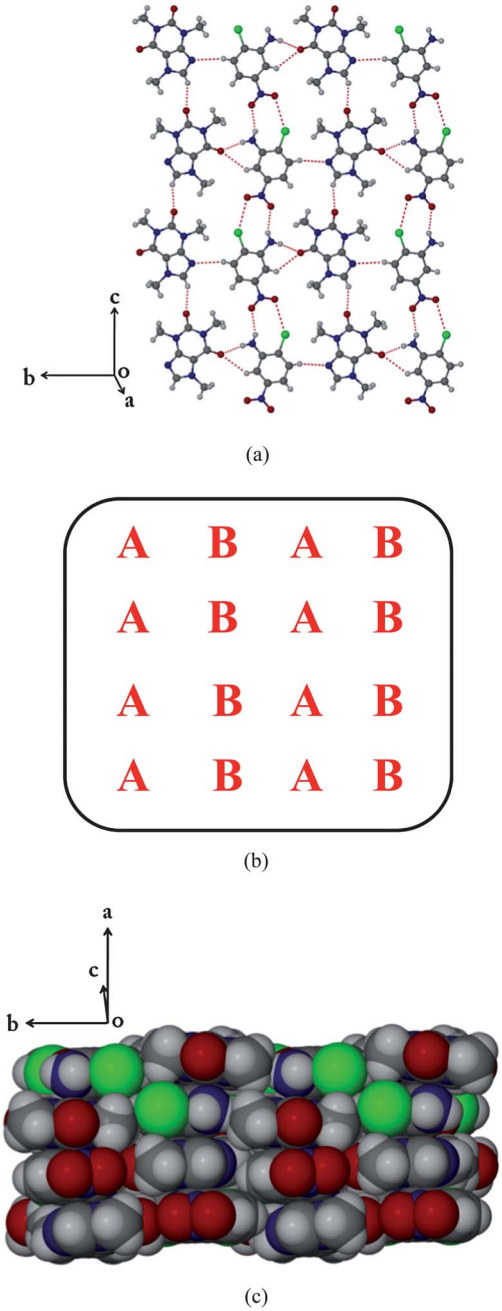

Fig. 6 Caffeine/2-chloro-5-nitroaniline (1 : 1) co-crystal. (a) 2D layer formation by involving caffeine and 2Cl5NA molecules. (b) Schematic representation of the perpendicular tapes, ABAB and AAAA/BBBB type in the 2D layers. (c) Side view of the stacked layers.

interactions, one each with neighbouring caffeine and 2F5NB molecules, leading to molecular tapes which run parallel to (110) or (1$\bar{1}$0) planes with an intersecting angle of nearly 30° (Fig. 9a). This leads to 3D interlocked packing of the molecules (Fig. 9b).

Mechanical properties

Mechanical properties of molecular crystals strongly depend on the features of underlying crystal packing.[7] Based on the mechanical behaviour the molecular crystals are classified into

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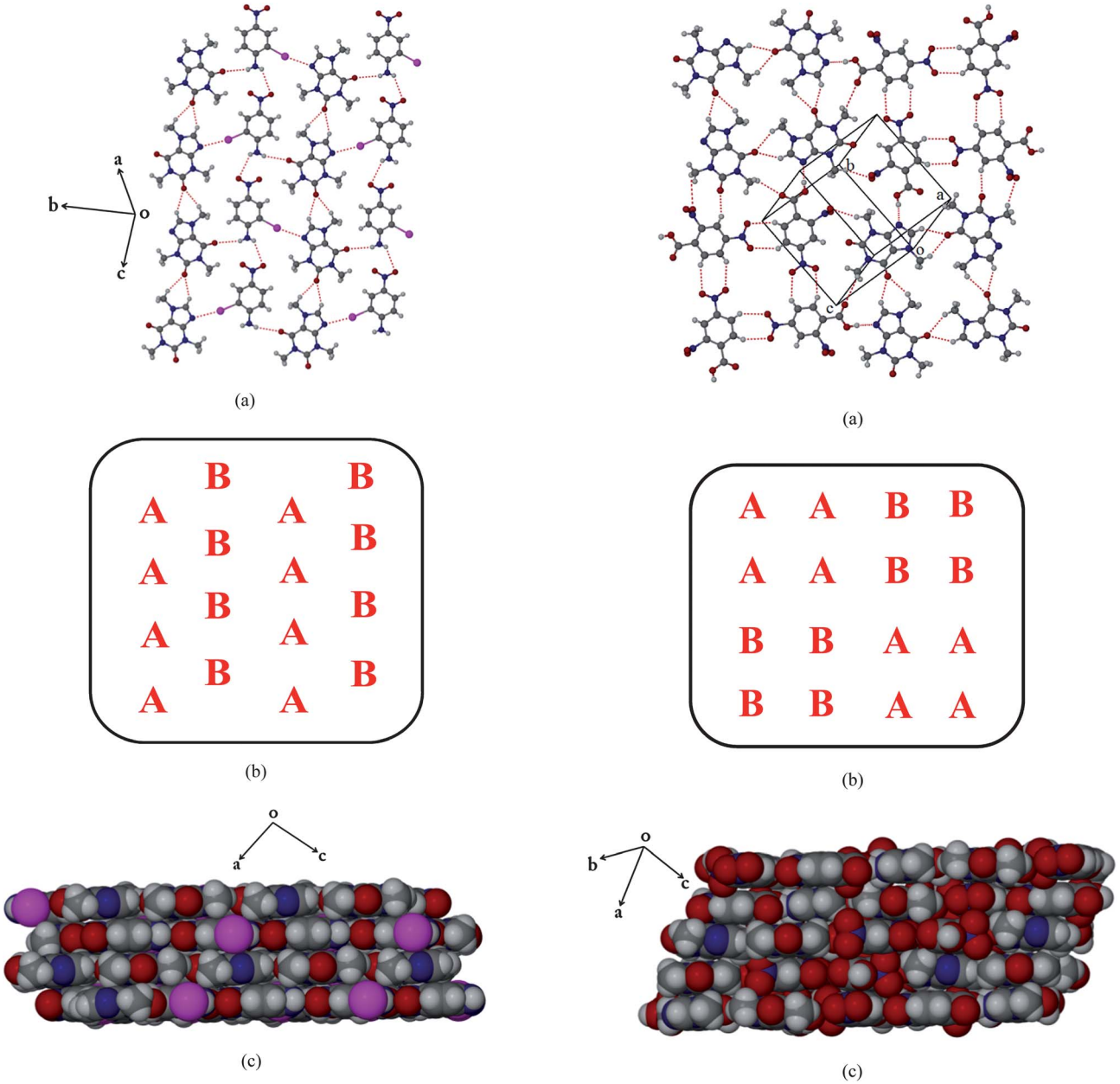

Fig. 7 Caffeine/2-iodo-4-nitroaniline (1 : 1) co-crystal. (a) 2D sheet formed by two component assembly. (b) Molecular tapes, AAAA, BBBB and zigzag ABAB. (c) Offset stacking of molecular sheets.

Fig. 8 Caffeine/2,4-dinitrobenzoic acid (1 : 1) co-crystal. (a) 2D layer involving multiple interactions between CAF and 24DNB molecules. (b) Representation of the layer with perpendicular AABB type tapes. (c) Packing of the 2D flat layers.

soft (shearing and bending) and brittle types. Anisotropic crystals with 2D layer packing or with strong and weak (nonspecific) interactions in perpendicular directions are known to show plastic shearing or bending behaviour, respectively. While isotropic crystals with similar interactions in all the dimensions generally show brittle nature. In this series the co-crystals adopt either 2D layer or 3D interlocked packing. Mechanical studies performed on the single crystals, using forceps and needle under a stereomicroscope, revealed that the co-crystals, namely CAF/24DNB, CAF/2Cl5NA and CAF/2I4NA are of the shearing type, while all the others in this series are brittle. Among the shearing type co-crystals, CAF/24DNB was found to be extremely soft and showed smooth shear deformation on application of a mechanical stress parallel to the 2D layers in the crystal (Fig. 10). In this structure the 2D layers are formed *via* strong O–H···N and multiple $_{(Ar)}$C–H···O H-bonds between the molecules (see Fig. 8a). This is consistent with our previously proposed model: the formation of robust layers with weak interlayer interactions is necessary for smooth shearing in 2D layer crystals.[14d,e] 2D layer crystals with comparable interlayer and intralayer interactions do not show such shearing and simply break (*i.e.* shear stress > cleavage stress). Hence, the shearing behaviour in CAF/24DNB is a clear proof for the robustness of intralayer interactions and non-specificity of the interlayer interactions.

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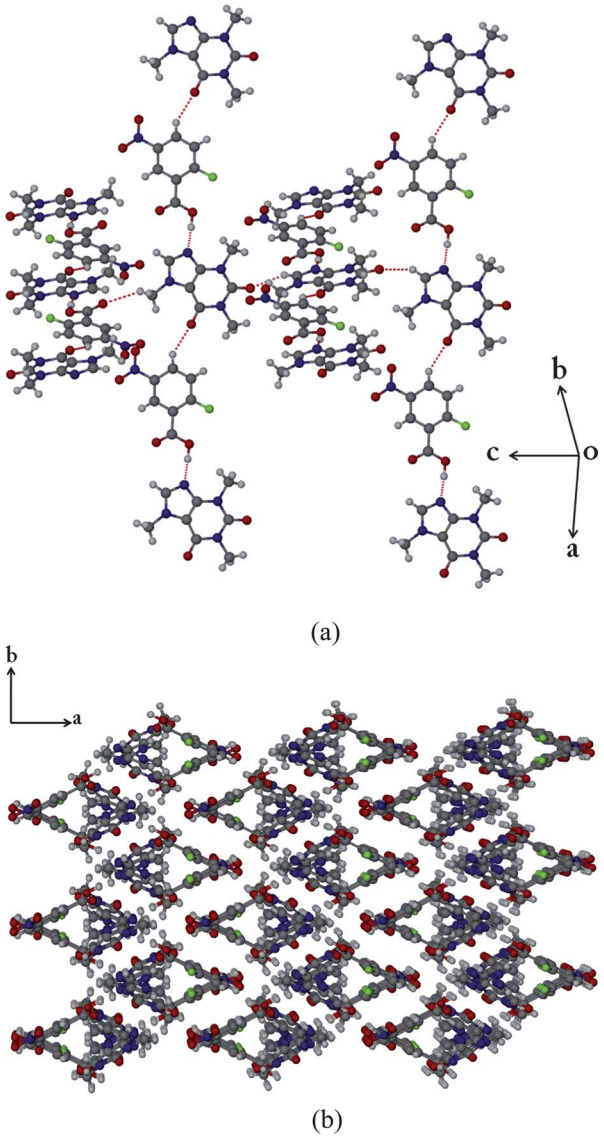

Fig. 9 Caffeine/2-fluoro-5-nitrobenzoic acid (1 : 1) co-crystal. (a) Packing diagram to show the arrangement of perpendicular tapes. (b) 3D interlocked structure of the co-crystal (H-bonds are not shown for clarity).

The other two soft co-crystals, CAF/2Cl5NA and CAF/2I4NA, also show shearing behavior, but also crystal breakage occur easily along the layers (Fig. S20, S21†). Although both the crystals adopt 2D layer packing, in the case of CAF/2Cl5NA, the layers, to a small degree, are wave-like (Fig. 6c), hence possibly lead to easy breakage. Whereas, in the case of CAF/2I4NA, although molecules within the 2D layer form stronger N–H···O and C–I···N bonds, the support from other interactions is not significant, for instance, the aromatic C–H groups from 2I4NA are not engaged at all, while the N–H···O (2.49 Å, 106.17°) hydrogen bond (between NH_2 and NO_2 which are co-planar, face to face) is not robust which is clear from its H-bond matrices (Fig. 7a). Similarly, in case of the two isostructural co-crystals, CAF/4Cl3NA and CAF/4I3NA, which adopt 2D flat layer structures, the aromatic C–H groups are not involved in any hydrogen bonding, hence there is no contribution to the layer strength. Hence these crystals are brittle in nature and do not show any clear sign of shearing. Whereas the co-crystal, CAF/2F5NA has corrugated type layers with significant interlayer interactions, hence is brittle (Fig. 11). The brittle nature in the case of CAF/NA, CAF/2F5NB and CAF/4F3NA is associated with their 3D interlocked structure.

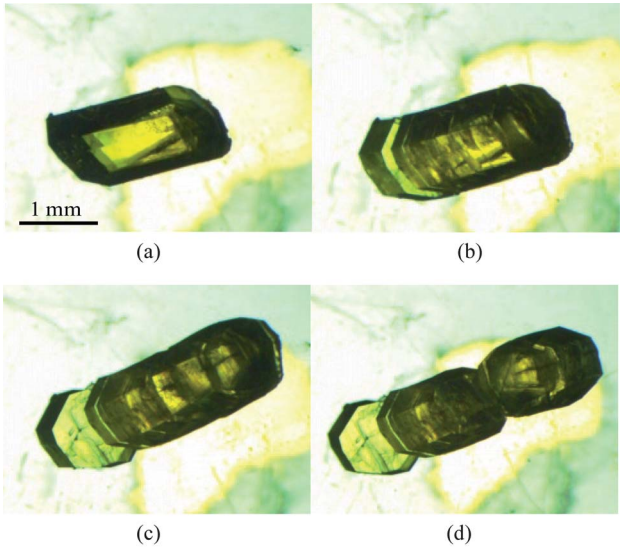

Fig. 10 Shearing in crystals of caffeine/2,4-dinitrobenzoic acid on application of a mechanical stress. (a) Crystal before application of the mechanical stress. (b) To (d) show the stages of crystal shearing. Notice the striations due to shearing and cleavage of crystal layers on application of continuous stress.

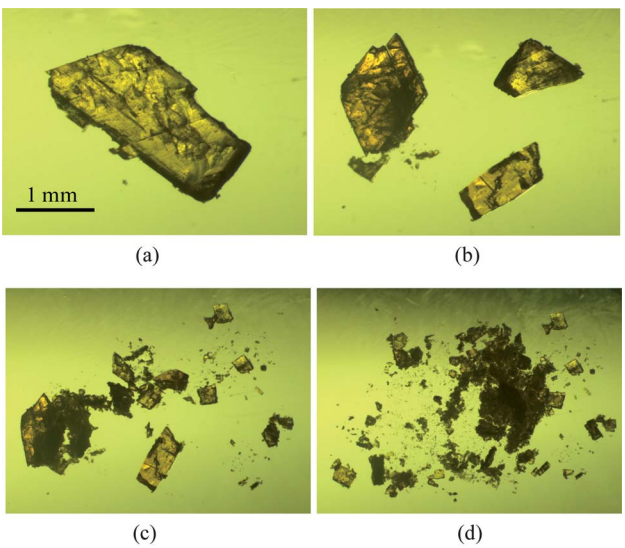

Fig. 11 Brittle crystals of caffeine/2-fluoro-5-nitroaniline on application of a mechanical stress. (a) Crystal before application of the mechanical stress. (b) To (d) show the stages of crystal breakage in the process.

Thermal properties

Detailed DSC and TGA experiments on the co-crystals helped to establish their thermal stabilities with respect to the commercial sample of free caffeine (Form II or β phase). The DSC traces and

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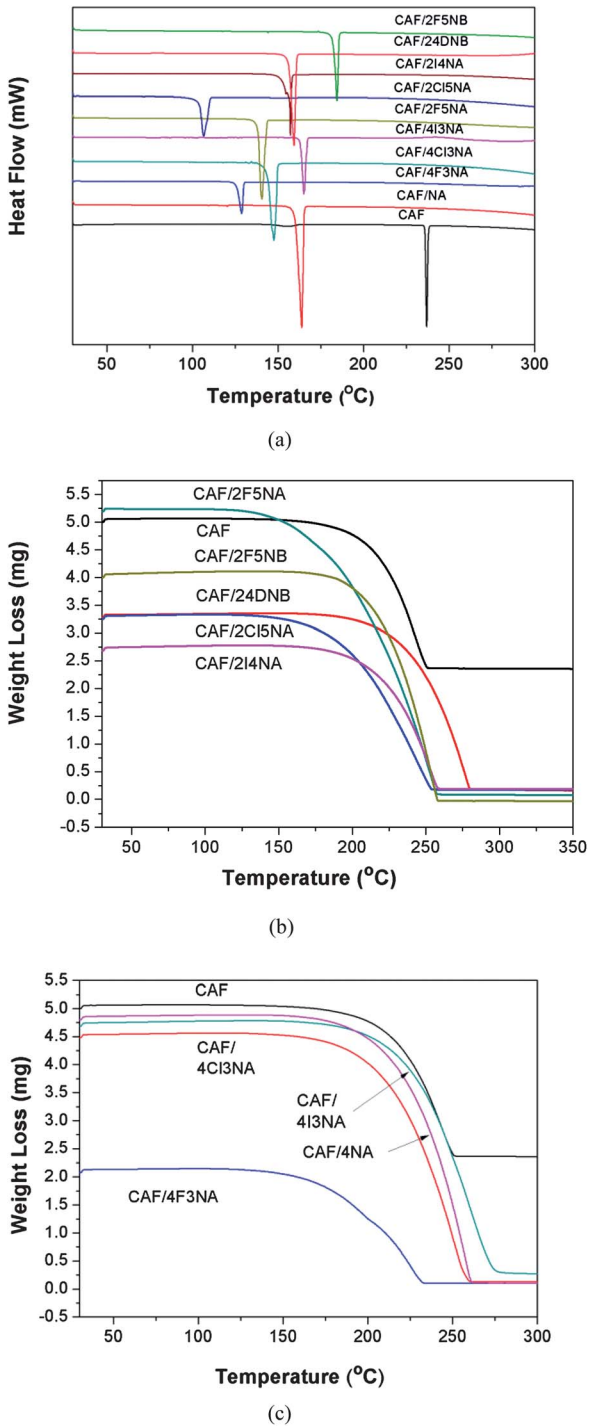

Fig. 12 (a) DSC traces for the co-crystals and the commercial caffeine sample. The endotherms in DSC correspond to the melting of the respective phases. (b) And (c), TGA traces correspond to the decomposition/sublimation of the respective crystalline phases.

thermogravimetric data for all the co-crystals are presented in Fig. 12. The DSC thermograms of all the co-crystals, except CAF/2I4NA, showed a single endothermic transition corresponding to the melting. The melting transition temperature of all the co-crystals was distinct from either of the individual components confirming the formation of a new phase. The thermogram in the case of CAF/2I4NA showed a small additional endotherm at 154 °C, which is very close to the major endotherm at 157 °C. This indicates the presence of an unidentified new phase, which we could not obtain for characterisation by single crystal XRD. DSC plots reveal that the thermal stability of all the co-crystals is lower than that of the commercial caffeine. The least stable among the co-crystals is CAF/2Cl5NA.

Conclusions

In conclusion, the successful formation of co-crystals by the least explored anilines, with caffeine demonstrates the potential of NH_2 group based synthons for achieving new pharmaceutically acceptable co-crystals, for example drug–drug solid forms. Out of the seven CAF/aniline co-crystals in this series, six of them form synthon-3 (strong N–H···O H-bonds), while this is not observed only in the case of CAF/2I4NA. This demonstrates the reliability of the previously unexplored NH_2 group based synthons for synthesizing new caffeine co-crystals. This approach may also be applicable to theophylline and uric acid which also have very similar chemical structures. Interestingly synthon-2 is not seen in any of these co-crystals. Notably, although 4F3NA, 4Cl3NA, 4I3NA are isomeric compounds, only the latter two form the isostructural co-crystals, while we could not synthesize their bromo-analogue. The series of crystals allowed us to establish a structure–mechanical property relationship by using a simple mechanical deformation (qualitative) method. The 2D flat layer crystals (CAF/24DNB, CAF/2Cl5NA and CAF/2I4NA), with robust layers and weak *inter*layer interactions show shear deformation behaviour, while those with comparable *intra*layer and *inter*layer interactions (CAF/4Cl3NA and CAF/4I3NA) showed brittle fracture on application of a mechanical stress. This suggests that the presence of flat 2D layer packing is only a requirement, but not the sufficient condition, *i.e.*, shearing requires relatively stronger intralayer and weaker interlayer interactions. The structures with corrugated layers (CAF/2F5NA) or 3D interlocked packing (CAF/NA, CAF/2F5NB and CAF/4F3NA) show brittle behaviour.

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