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ARTICLE TYPE

A robust two-dimensional hydrogen-bonded network for the predictable assembly of ternary co-crystals

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Consideration of the geometrical features of the functional groups present in furosemide has enabled a systematic approach to be adopted for the synthesis of a series of ternary co-crystals, containing a robust asymmetric two-dimensional network, and with predictable structural features.

Co-crystals of active pharmaceutical ingredients (APIs) are currently of great interest to the pharmaceutical industry as they afford scope for tuning the physical properties of a drug, offer reproducible control over composition and eliminate the need for solvents, of which there is a limited number that meet with regulatory approval, inherent in solvate-screening. It has also been suggested¹ that co-crystals may be less prone to polymorphism than the constituent API. This has implications for Intellectual Property (IP) in developing APIs into suitable solid dosage form; polymorphism lying behind the majority of legal actions associated with IP in the pharmaceutical industry. The search for new co-crystals of APIs would be greatly accelerated if a rational approach to the prediction of crystal packing arrangements, based solely on the structure of molecular components, could be adopted. However, this remains one of the foremost challenges in organic crystal engineering.² Current efforts in molecular crystal engineering focus on targeting and reproducing a particular supramolecular synthon.³ While this approach has been extremely successful, little or no control can be achieved over the crystal-packing characteristics of ancillary functional groups in the molecules. This is due to the absence of reliable structural paradigms involving supramolecular synthons.

Here, we demonstrate how the identification of a neutral asymmetric two-dimensional hydrogen-bonded network leads to a new family of ternary crystals of the API furosemide (4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid) in the presence of the co-crystal former 4,4'-bipyridine, through the inclusion of a third component. The ternary systems have been created following consideration of the geometry and dimensionality of the preferred hydrogen-bonding interactions of carboxylic acid, sulphonamide and pyridyl moieties leading to co-crystals with predictable crystal symmetry and structural features.

All of the co-crystals described were initially synthesized by a process of liquid-assisted grinding.⁴ Crystallization of the resulting polycrystalline products to yield single crystals suitable for structure solution was subsequently carried out from solution. Details are provided in the ESI†.

Furosemide is a loop diuretic used in the treatment of oedema and arterial hypertension. The molecular structure of furosemide contains both a carboxylic acid and a sulphonamide functional group. The pseudo-tetrahedral-shaped sulphonamide group, in comparison to the planar carboxylic acid group, provides additional dimensionality for hydrogen bonding interactions.⁵ The ability of the planar carboxylic acid group to form a two-dimensional acid-pyridine supramolecular heterosynthon has been previously exploited in co-crystal formation.⁶

Furosemide (fus) readily forms a co-crystal [(fus)₁-(bipy)_{0.5}] (1) with 4,4'-bipyridyl (bipy) from a fus:bipy mixture of molar ratio 1:0.5. The structure of (1) contains an acid-pyridine supramolecular heterosynthon, with the bipyridyl molecule located at an inversion center. The sulphonamide donors and the carboxylic acid acceptors of furosemide participate in N(2)-H(2)···O(1) and N(3)-H(1)···O(1) hydrogen bonding interactions to form a host network of furosemide molecules in which bipyridyl molecules occupy guest positions (Fig. 1).

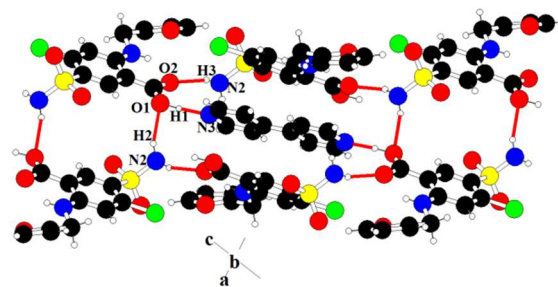


Fig. 1 Packing arrangement in co-crystal (1) viewed along [010].

Considering the ditopic hydrogen-bond acceptor nature of bipyridyl and the ability of the non-planar sulphonamide group of furosemide to participate in multiple hydrogen-bonding interactions, we anticipated binary co-crystal formation at a 1:1 fus:bipy molar composition, through an alternating arrangement of fus and bipy molecules. However, powder X-ray diffraction data of the product of solvent drop grinding of such a mixture revealed the components remain as a physical mixture at this composition⁷ (see the ESI†). This provided the starting point for our investigation of three-component co-crystals containing furosemide and bipyridyl. When a third component, such as dimethyl sulphoxide (DMSO), dimethylformamide (DMF) or methanol (MeOH), was added to the 1:1 furosemide-bipyridyl mixture a series of three-component crystalline phases could be

isolated.

Crystallization from DMSO led to the isolation of single crystals of $[(\text{fus})_1\text{-(bipy)}_1\text{-(DMSO)}_1]$ (**2**) after 3 days. Structural analysis by single crystal X-ray diffraction reveals the presence of DMSO molecules in the crystal structure. DMSO acts as a conventional hydrogen bond acceptor through the sulphoxide group which is involved in $\text{O}(6)\cdots\text{H}(7)\text{-N}(1)$ interactions with the N-H group of the sulphonamide group of furosemide (Fig. 2). In addition, the furosemide molecules participate in hydrogen bonding with the pyridyl groups through $\text{O}(1)\text{-H}(1)\cdots\text{N}(4)$ and $\text{N}(1)\text{-H}(6)\cdots\text{N}(3)$ interactions. The hydrogen bonding between furosemide and the other components is in accordance with the principle of hierarchy, proposed by Etter.⁸ In addition, a methyl group of DMSO participates in a weak $\text{C}(24)\text{-H}(28)\cdots\text{O}(4)$ interaction with the sulphone group of furosemide to form an asymmetric two-dimensional network as shown in Fig. 2.

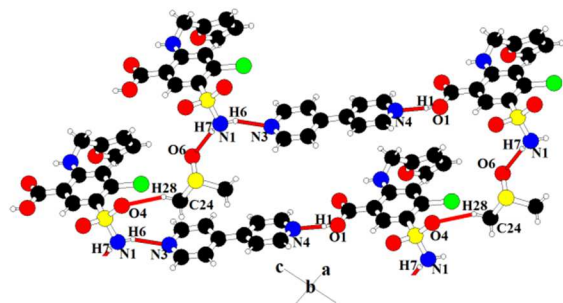


Fig. 2 Two-dimensional hydrogen-bonding network observed in co-crystal (**2**), viewed along [010].

Utilisation of methanol as the crystallization medium resulted in co-crystals subsequently identified as $[(\text{fus})_1\text{-(bipy)}_1\text{-(MeOH)}_1]$ (**3**). Analogous to co-crystal (**2**), the carboxylic O-H and the *syn* (with respect to chlorine) N-H donors of furosemide are preferentially hydrogen bonded to the pyridyl nitrogen of bipyridyl through $\text{O}(1)\text{-H}(1)\cdots\text{N}(4)$ and $\text{N}(1)\text{-H}(6)\cdots\text{N}(3)$ interactions (Fig. 3). These furosemide-bipyridyl aggregates are linked by the third component, in this case methanol, through $\text{N}(1)\text{-H}(7)\cdots\text{O}(6)$ and $\text{O}(6)\text{-H}(25)\cdots\text{O}(3)$ interactions extending infinitely along the crystallographic *a* axis (Scheme 1). The three components assemble to form a two-dimensional network of hydrogen bonding interactions as shown in Scheme 1. Although crystallisation of the polycrystalline product arising from synthesis in the presence of DMF (**4**) was not successful, refined lattice parameters derived from powder diffraction data for (**4**) compare well with those obtained for the single-crystal study of (**3**), providing strong support for the presence of the same two-dimensional hydrogen-bonded network in (**4**).

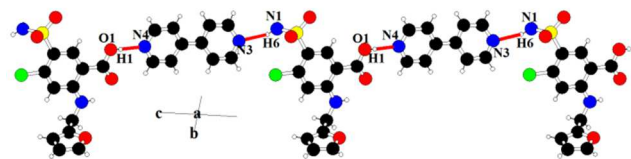
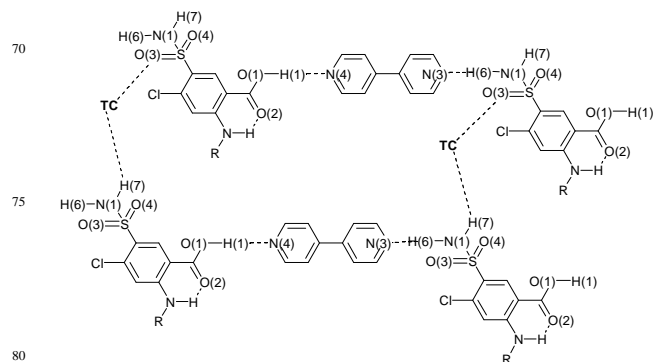


Fig. 3 Columnar arrangement between furosemide and bipyridyl common to all ternary co-crystals (**2**)–(**10**), viewed along [100].

In co-crystals (**2**) and (**3**), the furosemide-bipyridyl columns are assembled into stacks along the *a* crystallographic axis, in a head-to-tail fashion such that the phenyl moieties of furosemide

interact with one of the pyridine ring of 4,4'-bipyridyl (ESI†). The aromatic rings are not parallel but, as is usual for such systems,⁹ are slipped in an offset face-to-face/center-to-edge stacking arrangement with a slip angle of *ca.* 45.6° and 23.4° respectively for (**2**) and (**3**). Arene-arene interactions of this type are known to serve as robust supramolecular synthons¹⁰ and are abundant in chemical and biological systems.¹¹

Reasoning that the methyl groups of methanol in (**3**) help to stabilise an asymmetric two-dimensional hydrogen bonding network but otherwise participate only in van der Waals' interactions, we anticipated that co-crystals containing the same fus-bipy motif should also form with other aliphatic alcohols. Therefore, ethanol, 2-propanol, 1-butanol were tested as ternary components in solvent drop-grinding experiments. In each case, new polycrystalline phases resulted, whose powder X-ray diffraction patterns differed from those of either the reactants or any known binary phases. Moreover, powder diffraction patterns of the polycrystalline materials of each of these products could be indexed on the basis of an analogous unit cell to that of co-crystal (**3**). Refined lattice parameters for materials derived from liquid assisted grinding in ethanol (**5**), 2-propanol (**6**) and 1-butanol (**7**) (Table 1) are in good agreement with expectations from the lattice parameters determined for single-crystals of (**2**) and (**3**). This is consistent with the third component playing a similar role in acting as a bridge between the fus-bipy aggregates in this series of materials, in each case, with the three components being stabilized by the two-dimensional hydrogen-bonded network.



Scheme 1: Schematic illustration of the two-dimensional network observed in all ternary co-crystals. R=furfuryl, TC=ternary component (DMF; DMSO; MeOH; ethanol; 2-propanol; 1-butanol; ethylene glycol; 1,4-butanediol; hydroquinone). The dotted lines indicate hydrogen bonding interactions.

In all of the ternary co-crystals presented here, the lattice metrics *a*, *c* and the angle between them, β , are principally determined by the dimensions of the asymmetric two-dimensional hydrogen-bonded network, leading to a high degree of consistency in the measured values. In the absence of any significant hydrogen bonding/non-covalent interactions along the *b* axis, this lattice parameter is determined by the long axis of the furosemide molecule, and therefore influenced by the conformational flexibility of furosemide. We tested this hypothesis by investigating ternary systems in which molecules containing a single hydroxyl group are replaced with those containing dihydroxyl-groups. Consideration of the structures of the ternary co-crystals (**2**)–(**7**) leads to the expectation that the three components, crystallising in the space

group $P\bar{1}$, would arrange with the two-dimensional hydrogen-bonded network extending from both ends of a difunctionalised third component. The diols ethylene glycol, 1,4-butanediol and hydroquinone were selected as ternary components. Solvent-drop grinding followed by crystallization produced three ternary co-crystals (**8**), (**9**) and (**10**) with the composition [(fus)₁-(bipy)₁-

diol_{0.5}]. As anticipated, the ternary co-crystals (**8**), (**9**) and (**10**) crystallize in the space group $P\bar{1}$ with retention of the asymmetric two-dimensional network and the stacking interactions between aromatic moieties of furosemide and bipyridyl molecules similar to co-crystals (**2**) and (**3**) (ESI†).

Table-1: Unit cell parameters of all the ternary co-crystals presented here.

3 rd component	<i>a</i> /Å	<i>b</i> /Å	<i>c</i> /Å	α /°	β /°	γ /°	Volume (Å) ³
DMSO (2)	9.7483(4)	10.4805(4)	14.1432(5)	83.747(2)	86.117(2)	65.552(2)	1129.39(9)
Methanol (3)	7.3552(9)	9.3457(11)	18.124(2)	80.525(6)	82.376(6)	75.758(6)	1185.52(2)
DMF (4)	7.452(2)	9.315(5)	18.557(7)	87.16(9)	74.80(1)	76.94(4)	1213.95(3)
Ethanol (5)	7.193(8)	9.780(6)	18.694(2)	89.88(5)	75.50(3)	73.17(1)	1208.96(5)
2-Propanol (6)	7.860(5)	10.001(2)	18.402(4)	76.13(1)	76.56(5)	70.94(2)	1257.41(2)
1-Butanol (7)	7.537(4)	9.374(3)	18.282(2)	81.67(7)	80.54(5)	75.6(3)	1226.57(8)
Ethylene glycol (8)	6.7510(5)	9.5719(6)	18.6178(13)	84.977(4)	89.783(4)	73.488(4)	1146.76(14)
1,4-Butanediol (9)	7.3972(7)	9.3373(8)	18.1141(16)	80.504(4)	82.039(4)	75.173(4)	1186.81(19)
Hydroquinone (10)	6.9302(4)	9.9356(6)	18.6298(11)	83.633(3)	89.624(3)	72.794(3)	1217.34(13)

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In conclusion, we have demonstrated that, consideration of simple geometric principles together with careful selection of components, leads to the identification of a robust asymmetric two-dimensional hydrogen-bonded network, which serves as the prototype for a new family of co-crystals. This has enabled a targeted approach to be adopted in the selection of a ternary component leading to the predictable synthesis of new ternary co-crystals with control over symmetry, gross structural features and lattice metrics that depend on the two-dimensional network. The pseudo-tetrahedral shape of the sulphonamide group and the planar carboxylic acid groups are central to all of the ternary co-crystals synthesised. The study demonstrates that networks that can maintain their dimensionality and integrity when changes occur in the ancillary functional groups, provide a degree of predictability in the crystal packing arrangements in the solid-state. Identification of robust *n*-dimensional networks may therefore offer a means of improving the effectiveness of crystal engineering. To the best of our knowledge this is the first example of a robust neutral asymmetric two-dimensional network involving three components. This network serves as the blueprint for the prediction of the space group and gross structural features in ternary co-crystals. The series of ternary co-crystal presented here also provide insights into the process of crystallization, details of which will be presented in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: [CIF files, Powder X-ray data, NMR, I.R, DTA/TG data]

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