A cocrystallisation-based strategy to construct isostructural solids†

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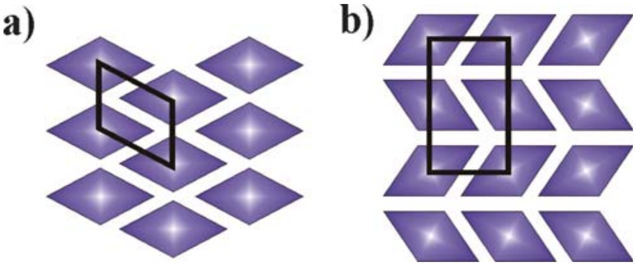
Cocrystallisation provides a means for dissimilar functional groups to become structurally equivalent, *i.e.* adopt similar structural roles in the solid. We describe a strategy to systematically construct sets of isostructural solids by using this cocrystallisation-induced structural equivalence. The strategy utilises cocrystallisation to combine different types of structurally equivalent functionalities in the solid state and enlarge an already existing set of isostructural cocrystals from two to four members. Halogen-bonded cocrystals of acridine (**acr**) and phenazine (**phen**) with iodopentafluorobenzene (**ipb**) form a pair of isostructural solids related by cocrystallisation-induced structural equivalence of aromatic CH and N groups. Structural equivalence of halogen-bonded Br and I groups allowed the replacement of **ipb** in these cocrystals with its bromo analogue, bromopentafluorobenzene (**bpb**), without disturbing the cocrystal architecture. Consequently, combining structurally equivalent groups allowed the construction of a set of four solids based on the same supramolecular blueprint.

Introduction

The ability to control the solid-state assembly of molecules into crystalline solids is of considerable technological importance,[1] especially for the design and synthesis of functional solid materials.[2] In that context, extensive effort has been dedicated to the study of polymorphism, the phenomenon of identical molecular species occupying different crystalline arrangements (Scheme 1).[3] The interest of materials scientists in polymorphism is largely inspired by the importance of this phenomenon for the pharmaceutical industry.[4,5]

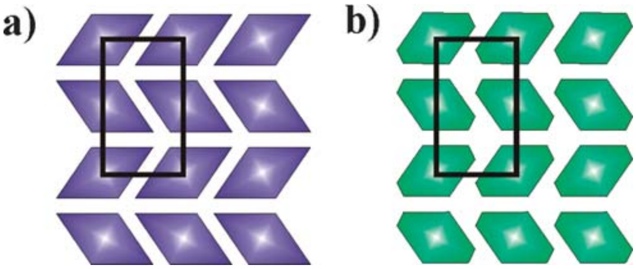
In contrast, much less attention has been given to the study of the opposite phenomenon, isostructurality, that addresses different molecular species occupying the same (or very similar) crystalline arrangements (Scheme 2).[6]

The apparent lack of interest of materials scientists for isostructural solids is somewhat surprising, since the control of isostructurality could, in principle, provide an attractive opportunity to construct materials of different properties following a common structural blueprint. This lack of attention is most likely caused by the rare occurence of this phenomenon.[7] Additionally, sets of isostructural compounds rarely include more than two members.[8] The rarity results from the close packing of molecules in crystalline solids, and is linked to the observation that minor changes in molecular structure often result in significant changes in crystal structure.[9] The sensitivity of crystal packing to molecular structure suggests that isostructurality could be difficult to achieve in single-component solids.



Scheme 1 Comparison of two polymorphic structures, consisting of different arrangements of identical building blocks. The difference between the two structures is demonstrated by different unit cell shapes.

However, the same arguments suggest that isostructurality could be more common in multi-component crystals (*i.e.* cocrystals[10]).[11–13] In these materials, the significance of structural changes made to one molecular component could be "buffered" by the remaining, unchanged components. In that way, the crystal structure of a cocrystal could be more tolerant to changes in molecular structure of its components than a



Scheme 2 Comparison of two isostructural structures consisting of different building blocks in an identical arrangement. The similarity of the two structures is demonstrated by identical unit cell shape.

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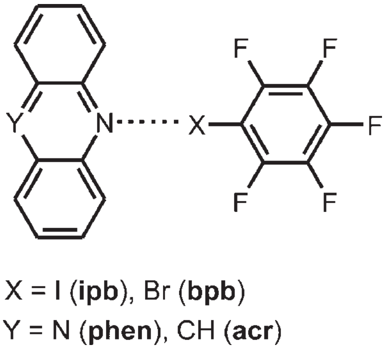
single-component solid. This is supported by crystal structures of lattice inclusion compounds, which can contain guest molecules of different sizes and shapes, without significantly disturbing the host lattice.[14] Our group,[15] and others,[16,17] have recently demonstrated the occurrence of isostructurality among two-component (binary) cocrystals. Indeed, isostructurality of binary cocrystals was observed even in cases where the exchangeable cocrystal components were involved in extensive hydrogen-[18] or halogen-bonding[19] networks.[15,20] In one case, exceptional isostructurality was observed, that involved seven halogen-bonded cocrystals.[15] The underlying reason for the observed isostructurality was the structural equivalence[15,20,21] of functional groups in the different cocrystal constituents, *i.e.* the ability of different substituents to adopt the same structural role. Cocrystal components involving such structurally equivalent functional groups are expected to be exchangeable without significantly altering the overall structure of the cocrystal.

In the context of single-component molecular solids, structural equivalence of chloro and methyl substituents has been recognised as the reason for isostructurality of pairs of compounds bearing these substituents.[22] We have recently explored the structural similarity of chloro and methyl groups in the context of cocrystals based on infinite hydrogen-bonded networks,[23] while Thalladi and co-workers[17] demonstrated the use of chloro/methyl structural similarity to construct pairs of isostructural cocrystals with different thermal properties. Structural equivalence of aromatic CH and N groups in multi-component cocrystals was demonstrated by Boese and co-workers,[24] as well as Babu and Nangia.[25] In the context of halogen-bonded cocrystals, it has been recently demonstrated that Br and I substituents become structurally equivalent when participating in halogen bonding.[20]

We now describe how different structural equivalences can be combined in cocrystals to allow the systematic construction of large sets of isostructural solids. We demonstrate the use of this approach by constructing an extended set of isostructural cocrystals involving acridine (**acr**)[26] or phenazine (**phen**) as halogen bond acceptors and iodopentafluorobenzene (**ipb**) or bromopentafluorobenzene (**bpb**) as halogen bond donors (Scheme 3). All the cocrystals are based on discrete halogen-bonded assemblies that could be constructed by mechanochemical grinding, as well as cocrystallisation from solution.[27]



Scheme 3 General structure of a halogen-bonded assembly constructed using either **acr** or **phen** as the halogen bond acceptor and **ipb** or **bpb** as the donor.

X-Ray powder diffraction (XRPD) was used to establish isostructurality between the cocrystals, and single-crystal X-ray diffraction was used to subsequently analyse their crystal structures.

Experimental

Mechanochemical synthesis of cocrystals

A mixture of 1.0 mmol of the halogen bond acceptor (178 mg **phen** or 179 mg **acr**) and 1.0 mmol of the donor (294 mg 133 μL **ipb** or 247 mg, 125 μL **bpb**) was placed in a 10 mL volume stainless steel grinding jar, along with two stainless steel grinding balls of 7 mm diameter. The mixture was then ground for 30 min in a Retsch MM200 grinder mill operating at a frequency of 30 Hz. The cocrystals were quantitatively obtained as a yellow (in case of (**phen**)·(**ipb**), (**acr**)·(**ipb**) cocrystals) or brown powders (in case of (**phen**)·(**bpb**) and (**acr**)·(**bpb**) cocrystals).

Synthesis of single crystals

Single crystals of (**phen**)·(**ipb**) were obtained by slow evaporation of a solution of 180 mg **phen** and 294 mg **ipb** in nitromethane (2 mL). Single crystals of (**acr**)·(**ipb**) and (**acr**)·(**bpb**) were obtained by slow evaporation of a nitromethane solution containing 179 mg **acr** and either 294 mg of **ipb** or 247 mg of **bpb** in 2 or 1 mL of solvent, respectively.

X-Ray diffraction experiments

X-Ray powder diffraction patterns were obtained using a Philips X'Pert Pro diffractometer equipped with an X'celerator RTMS detector, using Ni-filtered Cu-Kα radiation. Single-crystal X-ray diffraction data for (**phen**)·(**ipb**), (**acr**)·(**ipb**) and (**acr**)·(**bpb**) were collected on a Nonius Kappa CCD diffractometer equipped with a graphite monochromator and an Oxford Cryosystems cryostream, using Mo-Kα radiation. Crystal structure solution from single-crystal diffraction data was performed using the SHELXL[28] set of programs provided with the WinGX suite.[29] An anisotropic model was used for all non-hydrogen atoms during the refinement. Hydrogen atoms were placed in idealised positions with respect to associated carbon atoms and were included in the refinement using the riding model.

Results

Isostructurality of (acr)·(ipb) and (phen)·(ipb) cocrystals

Both (**phen**)·(**ipb**) and (**acr**)·(**ipb**) cocrystals could be readily obtained by cocrystallisation from solution, as well as by grinding together **phen** or **acr** with **ipb**. The XRPD patterns for (**phen**)·(**ipb**) and (**acr**)·(**ipb**) cocrystals (Fig. 1) obtained *via* grinding were almost identical, revealing the isostructurality of the two cocrystals.

Crystal structure analysis (Table 1) of the single crystals of (**phen**)·(**ipb**) grown from solution revealed the formation of two-component assemblies. In the assemblies, molecules of **phen** and **ipb** are held through a single N···I halogen bond (N···I separation: 2.92 Å),[19,20] that involves only one of the two nitrogen atoms in each **phen** molecule (Fig. 2(a)). Crystal structure determination of solution-grown (**acr**)·(**ipb**) single

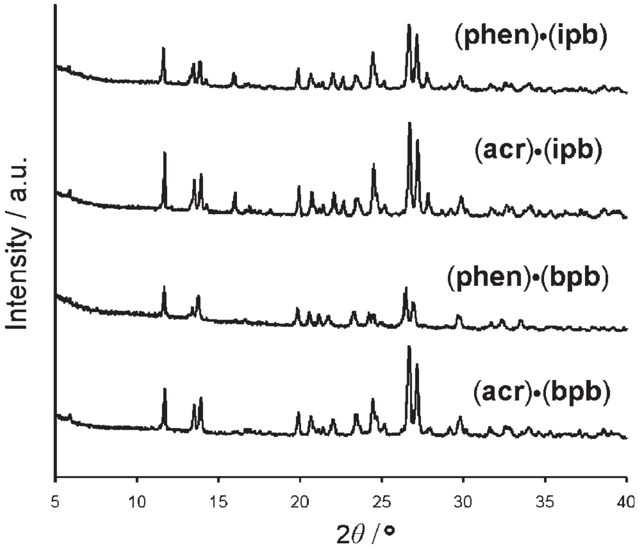


Fig. 1 XRPD patterns of mechanochemically constructed cocrystals.

crystals revealed crystallographic parameters that resembled those measured for **(phen)**·**(ipb)** (Table 1). The assemblies from the two cocrystals have almost identical structures (Fig. 2(b)): the interplanar angle between the two constituents in the assembly changes from 41.0° in **(phen)**·**(ipb)** to 42.0° in **(acr)**·**(ipb)**. The XRPD patterns simulated for the single-crystal structure of both cocrystals coincided with XRPD patterns measured for the cocrystals synthesized by grinding.

The cocrystals (acr)·(bpb) and (phen)·(bpb)

The isostructurality of **(phen)**·**(ipb)** and **(acr)**·**(ipb)** inspired us to attempt expanding this particular set of isostructural cocrystals using the previously demonstrated structural equivalence of I and Br donors in halogen bonding.[20] Cocrystals of either **acr** or **phen** with **bpb** were readily obtained by grinding together of the appropriate components. Cocrystal of **(acr)**·**(bpb)** was also obtained as diffraction-quality single crystals by growth from solution. Crystal structure analysis confirmed that **(acr)**·**(bpb)** was isostructural to **(acr)**·**(ipb)** and **(phen)**·**(ipb)** (Table 1) and consisted of two-component assemblies that highly resembled those found in **(acr)**·**(ipb)** (Fig. 3). Notably, the angle between the best planes drawn through the aromatic moieties of the halogen bond donor and acceptor is only slightly smaller (40.6°) in **(acr)**·**(bpb)** than in **(acr)**·**(ipb)**

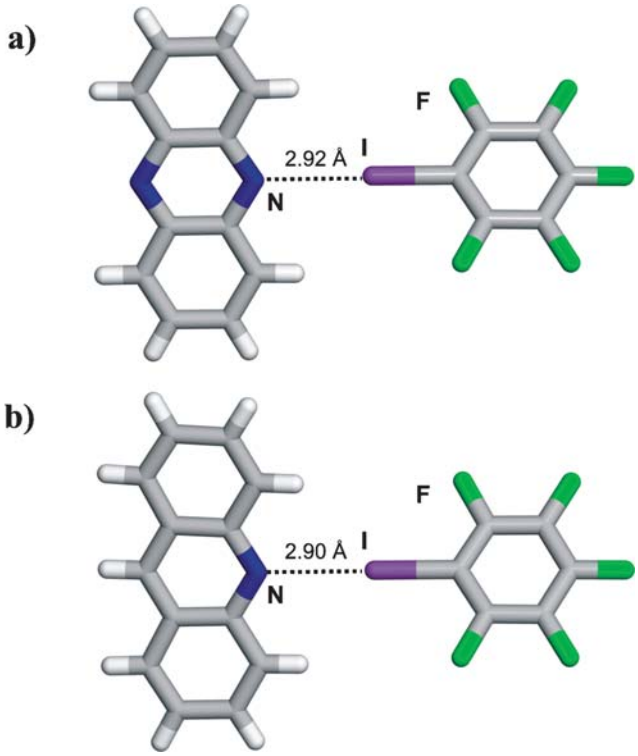


Fig. 2 Wireframe representations of finite halogen-bonded assemblies in the crystal structures of: (a) **(phen)**·**(ipb)** and (b) **(acr)**·**(ipb)**.

Table 1 General and crystallographic parameters for synthesized halogen-bonded cocrystals

Cocrystal	**(phen)**·**(ipb)**	**(acr)**·**(ipb)**	**(acr)**·**(bpb)**
Formula	$C_{18}H_8F_5N_2I$	$C_{19}H_9F_5NI$	$C_{19}H_9F_5BrN$
M_r	474.2	473.2	426.2
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a/Å	16.8943(3)	16.9525(3)	17.0193(7)
b/Å	7.2299(1)	7.2187(2)	7.2045(2)
c/Å	14.9051(2)	14.9464(3)	14.7399(3)
β/°	116.080(1)	116.246(1)	116.535(1)
V/Å^3	1635.20(4)	1640.49(6)	1616.96(9)
Z	4	4	4
D_c/g cm^{-3}	1.926	1.916	1.751
Crystal size/mm	0.12 × 0.14 × 0.16	0.18 × 0.23 × 0.23	0.10 × 0.23 × 0.28
μ/mm^{-1}	2.015	2.007	1.858
θ-range/°	3.7–31.5	3.7–31.5	2.7–30.0
No. reflections: total/unique/observed	18 302/5436/4686[a]	10 457/5306/4746[a]	13 041/4669/3627[a]
No. refinement parameters	235	235	235
R_1 (observed reflections)	0.026	0.024	0.037
wR_2 (all reflections)	0.059	0.059	0.100
S	1.078	1.027	0.995
$\Delta\rho_{\text{min, max}}$/e Å^{-3}	−0.96, 0.43	−1.09, 0.65	−0.76, 0.54

[a] Reflections with $I \geq 4\sigma(I)$ were considered as observed.

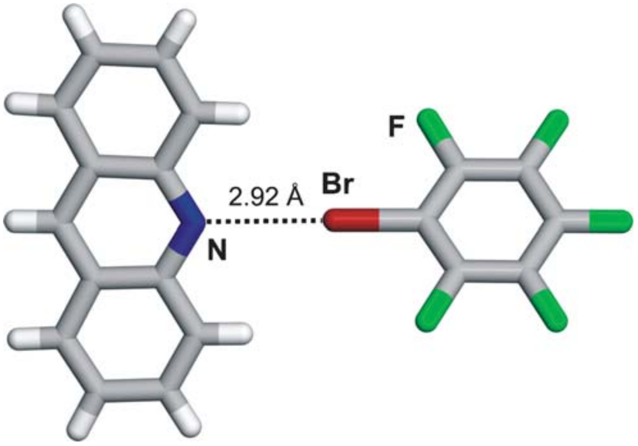


Fig. 3 A wireframe representation of a single halogen-bonded molecular assembly in the crystal structure of (**acr**)·(**bpb**).

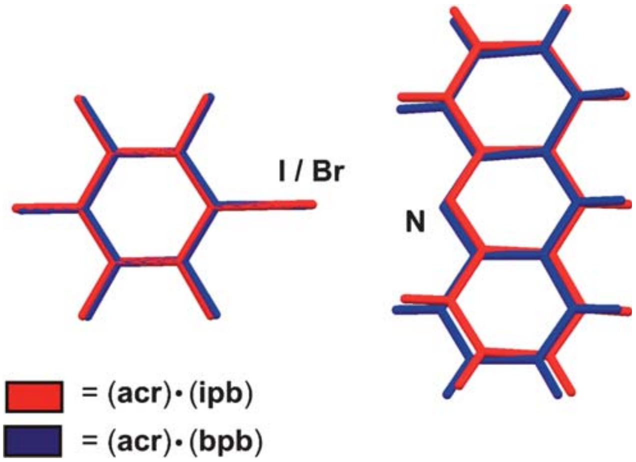


Fig. 4 An overlay of (**acr**)·(**bpb**) and (**acr**)·(**ipb**) solid-state assemblies.

(Fig. 4). The comparison of XRPD patterns indicated that the two cocrystals are isostructural with each other, as well as to their **ipb** analogues (Fig. 1). Also, the halogen bond distance in (**acr**)·(**bpb**) (N···Br, 2.92 Å) is very similar to that observed in the cocrystal with **ipb**.

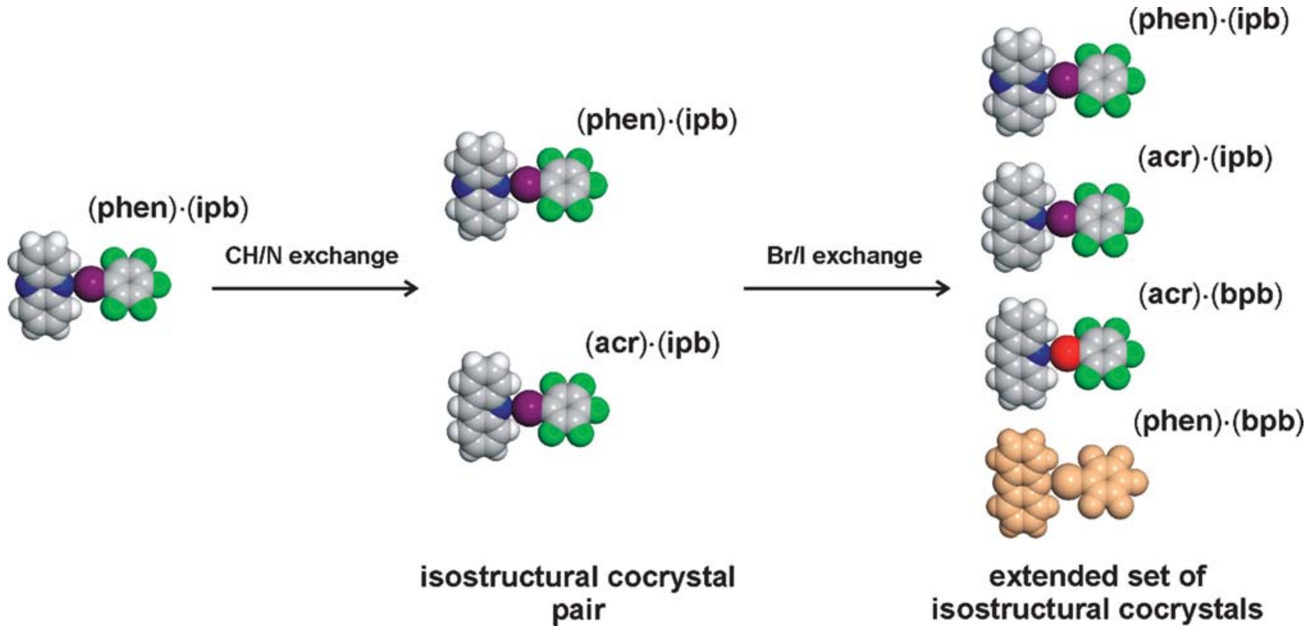
The XRPD pattern simulated for the single crystal of (**acr**)·(**bpb**) closely resembled the measured pattern for the product obtained by grinding **acr** and **bpb**, suggesting that the products of solution-phase and mechanochemical synthesis were identical. The cocrystal of **phen** and **bpb** could not be characterised *via* single-crystal X-ray structure analysis, since cocrystallisation from solution provided crystalline material of inadequate quality for the diffraction experiment. Nevertheless, the XRPD pattern of solution-grown cocrystals was very similar to that of (**acr**)·(**bpb**) obtained by grinding.

Discussion

Isostructurality and structural equivalence of aromatic CH and N groups

The isostructurality of (**phen**)·(**ipb**) and (**acr**)·(**ipb**) demonstrates the structural equivalence of aromatic CH and N moieties of **acr** and **phen**, respectively. Previous examples of structural equivalence involving CH and N groups include finite hydrogen-bonded assemblies of **acr** and **phen** with 2,2′-dihydroxybiphenyl,[24] and extended hydrogen-bonded frameworks of pyrazine tetracarboxylic acid, pyridinetetracarboxylic acid and pyromellitic acid dihydrates.[25] In contrast, pure **acr** and **phen** in the solid state adopt mutually different crystalline arrangements.

Consequently, the structural equivalence of N and CH moieties is an emergent property of cocrystallisation, and it



Scheme 4 A strategy to build an extended set of isostructural cocrystals through combining structural equivalence of aromatic CH and N groups and of halogen-bonded Br and I groups.

is most likely aided by the discrete nature of the halogen-bonded assemblies that can undergo minor changes in positioning to accommodate small differences in shape of CH and N groups.[30] These changes to positioning are facilitated by the absence of strong interactions to the free nitrogen atom of **phen**: the shortest C–H···N contact involves a C···N separation of 3.73 Å.[30] That structural equivalence of CH and N groups can be achieved by halogen- or hydrogen-bonded[24,25] cocrystallisation suggests that it may be a principle of general use in the design of multicomponent solids.

Expanding the scope of isostructurality

We speculated that the structural equivalence of aromatic CH and N groups, observed in **(phen)**·**(ipb)** and **(acr)**·**(ipb)**, could provide a starting point to rationally construct an extended set of isostructural cocrystals. In particular, we expected that CH/N structural equivalence could be combined with the recently demonstrated cocrystallisation-induced equivalence of Br and I halogen bond donors. Replacement of I with Br in cocrystals of **phen** and **acr**, by using **bpb** as the cocrystal former, would provide an extended set of isostructural cocrystals. However, although structural equivalence of aromatic CH and N functionalities[24,25] and of halogen-bonded Br and I groups in cocrystals have been documented,[15,20] it was not clear whether they would be robust enough to be used simultaneously within a rational strategy to construct isostructural cocrystals (Scheme 4). The mutual isostructurality of synthesized cocrystals demonstrates that CH/N functional group equivalence can be used alongside with the structural equivalence of halogen-bonded Br and I groups in the construction of isostructural solids.

Conclusions

We have demonstrated a cocrystallisation-based strategy for the systematic construction of sets of isostructural solids. In particular, we have utilised the cocrystallisation-induced isostructurality of Br and I halogen bond donors to add additional members to an already existing set of two isostructural cocrystals, based on structural equivalence of CH and N groups. The expanded set of four isostructural cocrystals demonstrates how cocrystal formation can be used to combine different types of structurally equivalent functionalities (*i.e.* Br/I and CH/N groups) in the solid state. We believe that combining different types of structural equivalence may develop into an attractive strategy for the design of isostructural materials. While only three well-established types of structurally equivalent functionalities are currently known (aromatic CH and N groups,[24,25] Cl and CH$_3$ groups[17,22,23] and halogen-bonded I and Br atoms[15,20]), it is likely that more will be observed through further studies of isostructural cocrystals. This expectation is supported by our recent report on cocrystallisation-induced structural equivalence of S, O and NH groups.[15] Presumably, the scope of our strategy for the construction of isostructural materials could be further expanded by forming solid solutions between isostructural cocrystals, as recently illustrated by Thalladi and co-workers.[17] With our interest in the design and synthesis of pharmaceutical materials, we are currently investigating hydrogen bond-driven cocrystallisation as a means of inducing isostructurality.[18]

Acknowledgements

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