Constructing, deconstructing, and reconstructing ternary supermolecules†‡

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A hypothesis-driven protocol comprising precise and predictable molecular recognition events based upon an electrostatic view of competing hydrogen-bond interactions is proposed and subsequently employed in the construction of ternary co-crystals.

The design,[1] construction,[2] properties[3] and even the definition[4] of molecular co-crystals have received considerable attention recently. This intense interest can be explained in part because co-crystallization reactions offer unique opportunities for examining the balance between and structural influence of intermolecular interactions. However, co-crystals may also be of considerable practical and economic importance, notably to the pharmaceutical industry.[5] Despite a wealth of publications detailing new co-crystals,[6] very few of them describe examples composed of three or more different molecular building blocks assembled using precise and well-defined supramolecular synthons;[7] bringing three different molecular species into one crystalline lattice without making or breaking covalent bonds, is still exceedingly difficult.

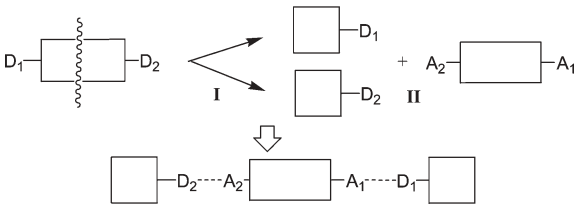
Herein, we provide a hypothesis-driven protocol for the construction of ternary supermolecules and co-crystals where stoichiometry and primary intermolecular interactions can be readily rationalized. Our approach is based upon three complementary steps:

I. Allow a series of ditopic molecules equipped with two different hydrogen-bond acceptors to react with a molecule containing two different hydrogen-bond donor moieties. Use structural data for the resulting binary 1 : 1 co-crystals to establish intermolecular pattern preferences.

II. Once complementary hydrogen-bond interactions can be ranked according to frequency of occurrence, use covalent synthesis to deconstruct one of the ditopic compounds into mono-functional components (**I**).

III. Combine a ditopic ligand (with two hydrogen-bond acceptors) and two different hydrogen-bond donors in the deliberate synthesis of a specific ternary co-crystal (**II**), Scheme 1.

This approach requires a library of ditopic supramolecular reagents that contain either two different hydrogen-bond donors or two different hydrogen-bond acceptors that can be ranked according to relative hydrogen-bonding capability.



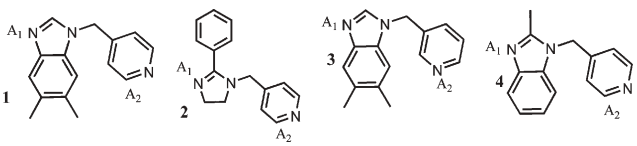
Scheme 1 Protocol for deconstructing and reconstructing ternary co-crystals. D_1 and D_2 = hydrogen-bond donors, A_1 and A_2 = hydrogen-bond acceptors.

Recently we demonstrated how ditopic hydrogen-bond acceptors based on pyridyl/benzimidazole can act as a hub for the assembly of ternary co-crystals in combination with two carboxylic acids of different strengths.[8] The stronger acid (based upon pK_a-values) binds to the best hydrogen-bond acceptor (the more basic N-heterocycle) whereas the weaker acid binds to the second-best acceptor site. The use of pK_a values for identifying the better hydrogen-bond donor can work *within* a family of compounds,[9] but such data offers no reliable information when comparing hydrogen-bond donor/acceptor strength for different functional groups.[10] Instead, Hunter has shown how calculated molecular electrostatic potential (MEP) surfaces can be employed for assigning (and ranking) the relative hydrogen-bond donor/acceptor strengths across a wide range of chemical functionalities.[11] The calculations can be performed at a relatively low level of theory (AM1), which makes this a versatile and readily accessible tool.

In order to test our hypothesis we employed four asymmetric ditopic hydrogen-bond acceptors, (**1–4**), Scheme 2 and two asymmetric ditopic hydrogen-bond donors, **5–6**, Scheme 3.

The maxima/minima on the AM1-based MEPs for **1–8** are listed in Table 1.[12]

We now begin to construct co-crystals with the assumption that the hydrogen bonds in this system are primarily electrostatic in nature. Consequently, by applying the best donor/best acceptor, second-best donor/second-best acceptor rationale, in the context of the calculated charges in these molecules, we can postulate which molecular recognition events will most likely appear in the resulting crystal structures.



Scheme 2

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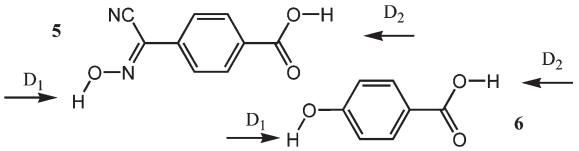
† CCDC 647757–647758 and 652592–652593. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b707518a
‡ Electronic supplementary information (ESI) available: Synthesis of supramolecular reagents. See DOI: 10.1039/b707518a



Scheme 3

Table 1 Calculated MEPs for **1–8** (in kJ mol^{-1})

Molecule	MEP for A_1	MEP for A_2
1	−299	−274
2	−311	−271
3	−301	−255
4	−299	−269
Molecule	**MEP for D_1**	**MEP for D_2**
5	+190	+152
6	+197	+136
Phenylcyanooxime, **7**	+171	—
Pentamethylbenzoic acid, **8**	+129	—

First, we examined the outcome of co-crystallization reactions between **1–4** and **6–7**. The combination of **1** (with benzimidazole and pyridine) and **5** (comprising cyanoxime and a carboxylic acid) produced crystals, **15**, suitable for single-crystal X-ray diffraction. Both cyanoximes[13] and carboxylic acids are known to be effective co-crystallizing agents,[14] but the MEPs indicate that the oxime moiety is the best hydrogen-bond donor, which should make it bind preferentially to the more basic benzimidazole site on **1**.

The primary intermolecular interactions in the structure of the binary 1 : 1 co-crystal **15** are shown in Fig. 1.

The two primary recognition events take place as expected, (based upon an electrostatic argument), and comprise two different O–H···N hydrogen bonds; O48···N13, 2.603(3) Å (oxime···benzimidazole), O41···N31, 2.612(3) Å (acid···pyridine).

The second suitable crystalline sample came from the reaction between **2** and **6**. The relative strengths of the two hydrogen-bond donors/hydrogen-bond acceptors on **6** are indicated by the MEP's in Table 1. This ranking is also consistent with established pK_{HB} values.[10,15]

The primary recognition events take place as expected, Fig. 2, and comprise two hydrogen bonds; O44 (phenol)···N13 (imidazole) 2.659(3) Å and O41 (acid)···N21 (pyridine) Å 2.693(2) Å.

The two structures obtained so far do support our initial hypothesis, but it is conceivable that the carboxylic acid is, in fact, determining the connectivity in both **15** and **26** by preferentially binding (and outcompeting the other donors) to the pyridine moiety. We therefore needed to find out how a single oxime moiety would behave (in the absence of a competing donor) when faced with a ditopic molecule such as **1–4**.

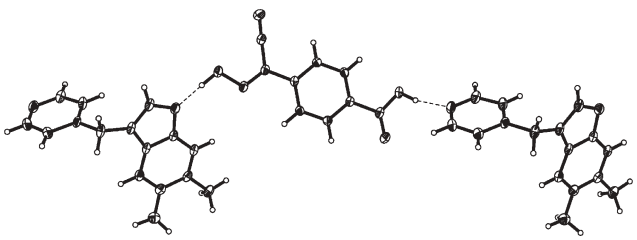


Fig. 1 In **15**, the best hydrogen-bond donor (oxime), binds to the best acceptor, while the second-best donor (carboxylic acid) interacts with the second-best acceptor.

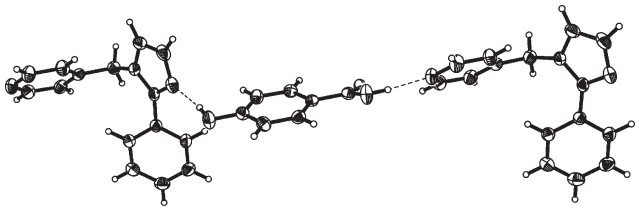


Fig. 2 In **26**, the best hydrogen-bond donor (phenol), binds to the best acceptor, while the second-best donor (carboxylic acid) interacts with the second-best acceptor.

The co-crystallization of 4-bromocyanophenyloxime, **9**, and **3** produced suitable crystals, **39**, Fig. 3, where the oxime moiety interacts with the benzimidazole moiety (O47···N13 2.6100(15) Å).

We now have support, from three different crystal structures,[16] that a binding preference and hierarchy of intermolecular interactions based upon simple MEPs can be employed as the basis for a versatile supramolecular synthetic strategy. In order to prepare a ternary co-crystal, a ditopic hydrogen-bond donor was deconstructed into separate fragments, that were subsequently allowed to react, in a 1 : 1 : 1 ratio, with the ditopic hydrogen-bond acceptor **4**. Phenylcyanooxime, **7**, ranks as a better hydrogen-bond donor, than pentamethylbenzoic acid,[17] **8**, and the structural outcome is shown in Fig. 4.

The construction of the primary supermolecule in **478** is achieved *via* two O–H···N hydrogen bonds. The cyanooxime binds to the benzimidazole moiety (O37···N13, 2.6396(19) Å), and the carboxylic acid interacts with the pyridine site (O51···N21,

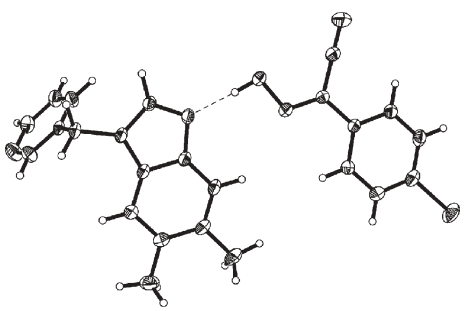


Fig. 3 The only hydrogen-bond donor in **39** binds to the acceptor with the largest MEP, the imidazole moiety, thus confirming the best-donor/best-acceptor premise.

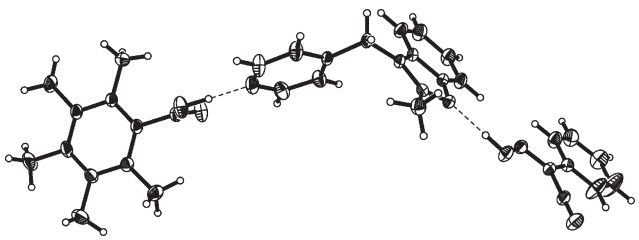


Fig. 4 Ternary supermolecule in the crystal structure of **478** shows that the best donor (oxime), binds to the best acceptor, and the second-best donor (carboxylic acid), binding to the second-best acceptor.

2.622(2) Å). The connectivity in this supermolecule mirrors the intermolecular behavior observed in **15**, and can again be rationalized using an electrostatic argument based upon calculated molecular electrostatic potentials.

The deceptively simple act of molecular recognition is achieved by balancing a range of relatively weak non-covalent, forces and to determine the reliability and limitations of the synthetic protocol presented here, a large number of reactions need to be examined in a systematic manner. The simplicity of the synthetic principles employed herein, should make it relatively easy to modify the nature of the different building blocks in order to maximize the supramolecular yield, and by translating molecular function into predictable intermolecular recognition, it may be possible to develop much more versatile supramolecular synthetic pathways for materials design and biological mimics.

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16 We are seeking more structural data to get better statistics in order to test our hypothesis and the limitations of this approach.

17 We were unable to obtain suitable crystals with benzoic acid, **4**, and **7**, but the MEP for **8** is comparable with that of benzoic acid (134 kJ mol^{-1}), so the experiment still provides a valid test of the initial hypothesis.

