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Structural Competition between Hydrogen Bonds and Halogen Bonds

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One of the main difficulties with directed-assembly of specific multicomponent supermolecules or extended architectures arises because such synthetic operations are typically limited to one-pot processes, as the desired products are held together by noncovalent and readily reversible interactions.[1] One way to overcome such restrictions may be to identify hierarchies of intermolecular interactions and then to develop supramolecular synthetic strategies that utilize synthons[2] that can operate side-by-side without interfering with each other. This type of approach has been employed successfully in the construction of ternary cocrystals, where hydrogen bonds of different strengths are responsible for organizing three molecular building blocks into supermolecules in a predictable manner.[3]

However, a strategy that exclusively relies on hydrogen bonds could soon run into problems as it would become increasingly difficult to avoid crossover reactions between multiple hydrogen-bond based synthons that compete with each other in one reaction mixture. Consequently, it may be useful to incorporate halogen bonds, intermolecular interactions where halogen atoms act as electrophiles, into this approach. Halogen bonds have characteristics that parallel those of hydrogen bonds in terms of strength and directionality,[4] and N···I halogen bonds have been employed frequently in supramolecular chemistry.[5] The question is, can we develop effective supramolecular synthetic strategies around a hierarchy of synthons that comprise both hydrogen and halogen bonds?

Herein, we address this question through a series of cocrystallization reactions between a ditopic structural probe molecule, **1**, containing two sites (pyridyl and benzimidazole) that can act as either hydrogen-bond or halogen-bond acceptors. The counterpart will be a molecule containing a weak and a strong hydrogen-bond donor as well as one potential halogen-bond donor (Figure 1).

With two acceptors and three donors, every cocrystal is likely to end up with one donor without a partner allowing the different synthons to be ranked according to relative structural influence.

Molecular electrostatic potential (MEP) calculations[6] were carried out on **1**−**4** to identify the best hydrogen-bond donor/acceptor and second-best donor/acceptor sites; this ranking is based on the assumption that electrostatic interactions dominate conventional hydrogen bonds.[7] The values indicate that the benzimidazole moiety is a better hydrogen-bond acceptor than the pyridine functionality,[8] and the −OH (oxime) site is a better hydrogen-bond donor than the imine −CH moiety. In addition to the examination of three cocrystals, we also obtained crystal structures for **3** and **4**, to compare the structural balance between hydrogen bonds and halogen bonds (−Br vs −I).

The crystal structure of **3** is dominated by a pair of self-complementary O−H···N hydrogen bonds (O···N, 2.855(2) Å)

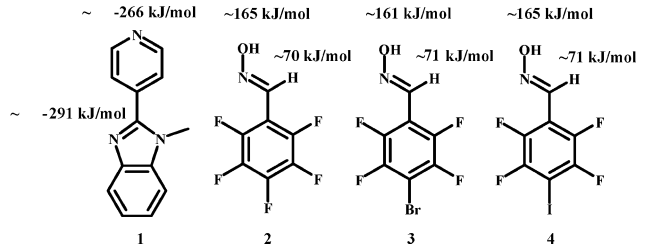

Figure 1. Electrostatic charges for the hydrogen-bond donors/acceptor sites in **1**−**4** based on AM1 calculated MEP's.

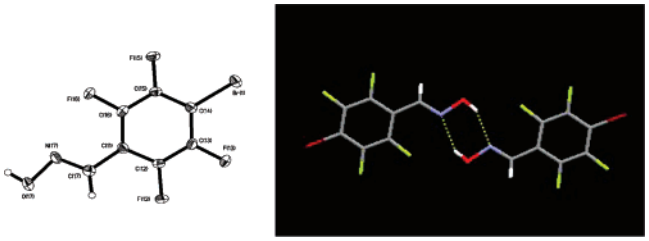

Figure 2. Thermal-ellipsoids plot (50% probability level) of **3** and the oxime···oxime dimer.

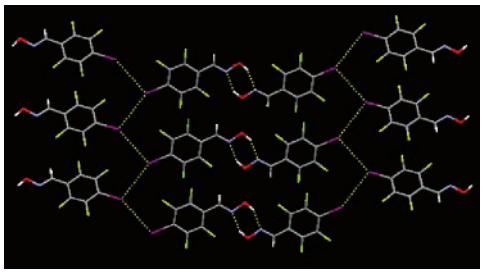

Figure 3. 2-D sheet generated through a combination of self-complementary hydrogen bonds and I···I interactions.

producing a common oxime···oxime dimer. There are, however, no short Br···Br contacts in this structure (Figure 2).

The crystal structure of **4** also contains oxime···oxime dimers formed through symmetry-related O−H···N (O···N, 2.872(4) Å) hydrogen bonds. The dimers are organized into a 2-D sheet through I···I bonds, 3.944 Å, (Figure 3). The two C−I···I angles, 108° and 143°, respectively, indicate that these contacts are due to specific (and attractive) polarization induced type II interactions.[9]

To establish a relative ranking of competing supramolecular synthons, we subsequently prepared three cocrystals **12**−**14**, by allowing **1** to react in a 1:1 stoichiometry with **2**−**4**, respectively.

In **12** (the 1:1 cocrystal of **1** and **2**), the best hydrogen-bond donor, the oxime moiety, binds to the benzimidazole site, O−H···N (O···N, 2.671(3) Å), which is the best hydrogen-bond acceptor (Figure 4a). Since −F is a very poor halogen-bond donor, the remaining N-heterocycle instead engages with the imine proton C−H···N (C···N, 3.43 Å), leading to an infinite 1-D tape-like motif.

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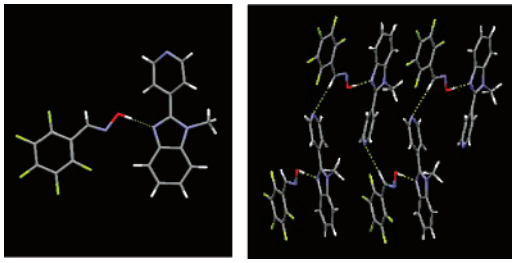

Figure 4. (a) The 1:1 cocrystal of **12**; (b) extended architecture through multiple hydrogen bonds.

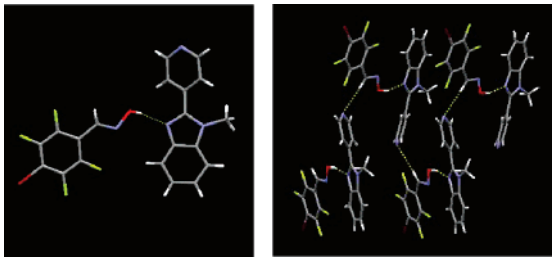

Figure 5. (a) The 1:1 cocrystal of **13**; (b) 1-D chain produced through multiple hydrogen bonds.

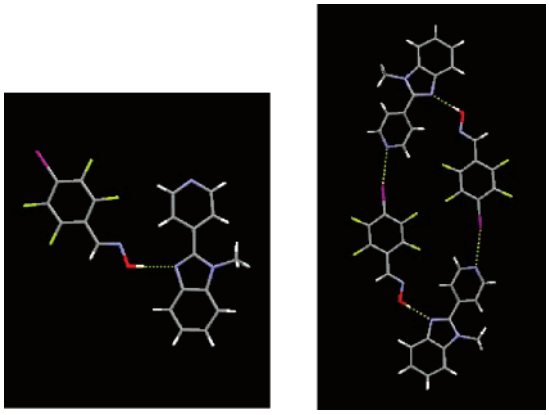

Figure 6. (a) The 1:1 cocrystal of **14**; (b) tetrameric supermolecule constructed through hydrogen bonds and halogen bonds.

In **13** (the 1:1 cocrystal of **1** and **3**) the oxime −OH proton forms a hydrogen bond to the benzimidazole site, (O···N, 2.675(3) Å), as was the case in **12**, which leaves the pyridine moiety free to pick up the imine proton, a significantly weaker hydrogen-bond donor, (C···N, 3.42 Å), resulting in a 1-D extended architecture, (Figure 5a and b).

Although N···Br halogen bonds are known to be of sufficient strength to drive the assembly of molecular cocrystals,[10] the −Br moiety cannot successfully compete with an acidic C−H for the py site in **13**.

In **14** (a 1:1 cocrystal of **1** and **4**) a hydrogen bond is again formed between the −OH oxime and benzimidazole moiety, (O···N, 2.706(6) Å). However, this time the iodo-substituent in **4** ("activated" by four −F substituents), does form a halogen bond, (N···I(1), 2.888 Å; C−I···N, 168°), with the remaining pyridyl group resulting in a four-component supermolecule (Figure 6).

The benzimidazole moiety carries a larger negative MEP than the pyridyl functionality, and in each of the three cocrystals **12**−**14**, the oxime −OH moiety preferentially engages in an O−H···N hydrogen bond with the former, which is in line with the MEP-guided hierarchy. The remaining pyridyl site could have become a participant in either a halogen bond or a hydrogen bond involving an acidic C−H group. In this race for the py group, only the iodo substituent was strong enough to compete successfully with the C−H imine. This structural advantage of N···I bonds over N···Br bonds is also reflected by the fact that the CSD[11] only contains 13 molecular cocrystals assembled through N···Br interactions, whereas there are more than 50 cocrystals constructed using N···I bonds.

This structural study, albeit performed on a relatively small number of compounds, indicates that a good hydrogen-bond donor is likely to be very competitive for a N-heterocyclic moiety, even in the presence of a fluoro-activated organoiodine. The latter group is, however, capable of displacing a less conventional hydrogen-bond donor such as the C−H imine moiety. Furthermore, since C−Br is a significantly weaker Lewis acid than the C−I group, it does not form a halogen bond that can compete with the C−H···N hydrogen bonds in **12** and **13**. The structures presented herein are primarily governed by hydrogen and halogen bonds but the final crystal structure is of course the result of a balance of numerous weak and rather unpredictable interactions (fluorine segregation,[12] however, does not seem to play a discernible role in this series of compounds).

Systematic cocrystallization reactions that probe the balance between, and structural outcome of, a mixture of hydrogen bonds/halogen bonds will undoubtedly assist in developing versatile strategies for the future assembly of discrete supermolecules and heteromeric molecular architectures.

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Supporting Information Available: Detailed experimental procedures for compounds **1**−**4**, along with crystallographic data and CIF files for **3**, **4**, **12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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