Orthogonal halogen and hydrogen bonds involving a peptide bond model†

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The peptide bond model N-methylacetamide self-assembles with a range of dihalotetrafluorobenzenes forming co-crystals that all show the occurrence of orthogonal hydrogen and halogen bonds.

Orthogonal self-assembly relies on the use of multiple interaction motifs applied in the same system to drive the assembly of different components. The specific and highly controllable interactions that are used do not influence each other's assembly profile and can be manipulated independently and simultaneously.1

In 2009, P. S. Ho and co-workers2 demonstrated, through a Protein Data Bank (PDB) survey, that in protein–ligand complexes hydrogen (HB) and halogen (XB) bonds3 occur orthogonally, in terms of both their geometric features and their chemical behaviour, when sharing the carbonyl oxygen atom of the peptide bond as a common bond acceptor. Lately, we have demonstrated that HB and XB can successfully be combined in an orthogonal manner to drive the self-assembly of complex and functional supramolecular networks.4 In this latter case, the two interactions did not share the same acceptor partner. Very recently, Bruce et al. successfully reproduced Ho's orthogonal motifs by using N-methylacetamide and N-methylbenzamide as peptide bond models with a selected number of iodinated XB donors.5 However, in their hands N-methylacetamide decomposed to methylacetamide and any attempt to get analogous motifs involving brominated donors failed.

In this communication, we demonstrate in small-molecule self-assembly that HB and XB occur orthogonally on the same acceptor site in a very reliable and consistent manner also when brominated XB donors are used. We chose N-methylacetamide (NMA, 1) as the smallest molecule that mimics the peptide bond (–NH–C==O) and thus the protein backbone.6 NMA effectively self-assembles with a range of dihalotetrafluorobenzenes resulting in co-crystals characterized by XBs occurring orthogonal to the classical HB pattern that characterizes the homomeric assembly of NMA.

Very few examples of engineered orthogonal XB and HB in the context of crystal engineering can be found in the Cambridge Structural Database (CSD),7 one exception being the isonicotinamide–chloroacetic acid co-crystal8 (details about the CSD search are given in the ESI†).

Our goal was to rationally design systems based on the orthogonal HB/XB supramolecular synthons and verify its robustness for use in crystal engineering. For this reason, NMA 1, affording the carbonyl oxygen acceptor site, was co-crystallized with several dihalotetrafluorobenzenes (DXTFBs), the XB donors, 1,2-dibromotetrafluorobenzene (12BrTFB, 2a), 1,3-dibromotetrafluorobenzene (13BrTFB, 2b), 1,4-dibromotetrafluorobenzene (14BrTFB, 2c), 1,2-diiodotetrafluorobenzene (12IITFB, 2d), 1,3-diiodotetrafluorobenzene (13IITFB, 2e), and 1,4-diiodotetrafluorobenzene (14IITFB, 2f). The corresponding complexes 3a–f were obtained (Scheme 1).

We first re-determined the crystal structure of 1 at low temperature by in situ cryo-crystallization using a zone-melting procedure with an optical heating and crystallization device (OHCD).9 This was intended to get rid of static disorder that is found in the previously reported structures of NMA.10 A fully ordered crystal structure of 1 resulted in the Pnma space group. Classical N–H⋯O (1.878(2) Å)11 HBs link NMA molecules into infinite 1D chains running along the a crystallographic axis (Fig. 1). The two interacting groups N–H and C==O are in the trans conformation, mimicking the molecular...
The IR spectra of the co-crystals in 3a–e is involved in the XB with the carbonyl oxygen atom. Differently, in 3f, both of the iodine atoms of 14DITFB are halogen-bonded to the carbonyl oxygens of two NMA molecules belonging to different hydrogen-bonded chains. In all of the six co-crystals, the oxygen atom of NMA is simultaneously involved in short HBs. Special attention during the analysis of the crystal structures has been given to the angle \(\alpha\), which has been defined as the angle between XB and HB, \(\angle X\cdots O-N\) as shown in Scheme 1. These angles in 3a–f vary in the range 77.9–98.5°, thus demonstrating the intrinsic tendency of HB and XB to occur orthogonal to each other when sharing the same sp\(^2\) O atom (Fig. 2).

Interestingly, while in 1 and 3f the N–H⋯O HB occurs perfectly in the carbonyl plane, in the structures of 3a–e it assumes an out-of-plane arrangement deviating from the carbonyl plane by angles in the range 36.19°–72.57°. The orthogonal XB occurs in an out-of-plane arrangement in all of the structures 3a–f, with the largest deviations in 3c and 3f where the positive \(\sigma\)-holes\(^\text{13}\) of bromine and iodine atoms enter the oxygen atom approximately in the equatorial region; the corresponding angles are 62.91° in 3c and 99.41° in 3f (see the ESI,† Fig. S4). Similar out-of-plane X⋯O interactions have been recently noted in protein–ligand complexes.\(^\text{14}\)

The IR spectra of the co-crystals 3a–f essentially contain modified vibrations of both the corresponding starting compounds and the observed band shifts may give an indication of how much the orthogonal HB and XB perturb the electron...
orthogonal synthon, which occurs in 100% supramolecular yield\(^\dagger\) of the attempted co-crystals. The two interactions are also chemically orthogonal as the XB formation does not alter the 1D and hydrogen-bonded \(\beta\)-sheet mimetic chains typical of the homomeric assembly of \(N\)-methylacetamide. A PDB survey performed by Ho et al. showed that hydrogen and halogen bonds are orthogonal, both in terms of their geometric alignments and their chemical behaviour, when sharing the carbonyl oxygen atom of a peptide bond. Our results demonstrate that this feature is not a peculiarity occurring only when biomacromolecules are involved,\(^3\) but it is a general feature of the two interactions and is probably inherent to their intrinsic chemical nature. The reported results pave the way to a new design concept in orthogonal self-assembly and crystal engineering and may also have important implications in other fields such as materials processing. As far as this field is concerned, amyloid and silk fibers are examples of ordered nanomaterials and both feature robust \(\beta\)-sheet elements. The manipulation of the self-assembly and structural complexity of these nanomaterials during processing is still far from being completely understood.\(^1\) An approach based on the orthogonal interaction of \(\beta\)-sheets with halogen-bond donor mesogens may be particularly valuable.\(^1\) Current studies in our laboratory are addressing this issue and the results will be reported elsewhere.

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Notes and references

\(^\dagger\) Single-crystal X-ray diffraction data for 1 and 3a-f were recorded using Mo-K\(\alpha\) radiation on a Bruker KAPPA APEX II diffractometer. Data were collected in \(\omega\) and \(\varphi\) scan with a scan width of 0.5. The data were reduced with empirical absorption corrections. Structures were solved by direct methods using SHELXL.\(^\dagger\) The molecular diagrams shown were generated using Mercury 3.3.\(^\dagger\) The non-hydrogen atoms are refined anisotropically and hydrogen atoms are positioned geometrically for 3a-d. All crystallographic details are listed in Table S2 and intermolecular interactions are listed in Table S3 in the ESI.\(^\dagger\)

6 NMA has been widely used as a model for peptide and protein folding studies, which resulted in various spectroscopic and

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**Fig. 2** Partial crystal packing showing how infinite 1D chains (horizontally positioned) formed by NMA via N–H⋯O HBs further interact with 14DITFB via Br⋯O XBs in 3c (top) and I⋯O XBs in 3f (bottom). The disorder on the NMA molecule is omitted for clarity.
theoretical investigations. In spite of its biological relevance, however, very few structural studies of NMA are known. The CSD, in fact, contains only three co-crystal structures of NMA with relevant organic compounds forming different hydrogen-bonded motifs (refcodes: IBOXOO, ANOPUP, ITYRMA10).

7 CSD search (ConQuest Version 1.15, 2013).
20 Mercury 3.3 is a software program for crystal structure visualization, exploration, and analysis, which is acopyright work of the Cambridge Crystallographic Data Centre (CCDC) and its licensors. Also see C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, J. Appl. Crystallogr., 2008, 41, 466.