Chapter 3
Supramolecular Assembly and Solid State Chemistry

Christer B. Aakeröy and Manomi D. Perera

Abstract The deceptively simple act of molecular recognition is the result of a balancing act between a variety of intermolecular interactions. Through the use of structural chemistry, interpreted against a background of calculated molecular electrostatic potential surfaces it is possible to identify binding preferences supramolecular patterns of behavior of discrete molecular species. The outcome is robust supramolecular synthetic strategies based on tunable site-specific intermolecular interactions that facilitate the preparation of co-crystals and specific solid-state motifs via selective and hierarchical self-assembly.

Keywords Hydrogen bonds • Halogen bonds • Co-crystals • Molecular recognition • Intermolecular interactions • Synthons

3.1 Introduction

Effective and successful synthetic crystal engineering demands an ability to organize and connect discrete molecular or ionic blocks into desired solid-state architectures with well-defined topologies and metrics. Such endeavors rely on relatively weak and reversible intermolecular interactions that facilitate the preparation of co-crystals and heteromeric constructions through selective and hierarchical self-assembly. This type of synthesis requires reliable structural information regarding the relative importance of the most commonly used non-covalent synthetic tools; hydrogen bonds and halogen bonds.

The most recent attempt [1] at defining hydrogen bonding arrives almost a century after Latimer and Rodebush proposed the concept of hydrogen bonding [2]. The dominant contribution in most hydrogen-bond interactions is the electrostatic component, but the hydrogen bond is partially covalent in nature, [3, 4] and induction and dispersion, in addition to induced covalency and exchange correlation from short range repulsion, all contribute to the complexity of this chemical

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bond [5, 6]. Crystallographic data have been used to characterize hydrogen bonding although it is difficult to decide upon definitive hydrogen bond distances [7, 8] or energies, [9, 10] as parameters for a definition and instead the linearity of a hydrogen bond has been identified as the "discriminative attribute" [11]. Spectroscopic studies reveal that hydrogen bonds frequently result in a red-shift of X-H bands in the IR [12, 13] and a down-field shift in NMR [14] However, alternative interpretations remain as to whether these methods produce consistent changes in response to hydrogen-bond interactions [15, 16].

Halogen bonding was highlighted as a viable non-covalent interaction by Hassel, [17] and it has recently received considerable attention from the crystal engineering community and beyond [18]. The halogen bond (XB) shows fundamental similarities to the hydrogen bond, and it has been debated in ways that are reminiscent of the way in which hydrogen bonding has been described. This attention to halogen bonding is understandable given its documented importance in supramolecular synthesis, materials chemistry, biological systems and drug design [19, 20]. Halogen bond strength and effectiveness are also "tunable" through a variety of covalent modifications [21, 22]. Electron-withdrawing groups in suitable locations facilitate redistribution of electron density thereby making the halogen atom more electropositive and thus a more effective halogen-bond donor. However, electrostatic forces are not exclusively responsible for the power of halogen bonds and dispersion and induction also play a role, [23] which means that the debate about the nature of different halogen-bond interactions is very similar to that which has accompanied the hydrogen bond. While accurate energies and geometries can be determined by calculations many methods are expensive and often difficult for large halogen-bonding complexes [24, 25].

The question is how do we now develop strategies that effectively utilize the synthetic possibilities that these two interactions offer without having to resort to chance or to some supramolecular combinatorial approach [26–30]? One way of getting some answers may be through systematic structural studies where relatively simple custom-designed probe molecules, equipped with potentially competing hydrogen- and halogen-bond donor sites, are introduced to a series of molecules decorated with varying accessible acceptor sites. By examining the structural outcome of a sufficient number of experiments, it may be possible to begin to identify some of the finer details in the structural landscape that surrounds competing (or complementary) hydrogen- and halogen bonds [30–33].

3.2 Hydrogen-Bond Directed Assembly of Co-crystals

To develop supramolecular synthetic strategies based on hydrogen bonding, we must identify a series of chemical functional groups that display reliable binding preferences [34]. The molecular recognition preferences of these groups can then be explored systematically in order to establish a hierarchy of hydrogen-bond preferences [35].

Hydrogen bonds can be considered primarily electrostatic attractive forces where the hydrogen bond donor is the positively charged site and the acceptor the negatively charged group. By quantifying this charge we can develop the means for quantifying the expected relative importance of different hydrogen bond donors and acceptors [36]. Simple semi-empirical calculations (AM1) provide molecular electrostatic potential values that can be used as quantitative approximations for the charges on individual donor and acceptor groups.

According to Etter's rules, the best hydrogen bond donor forms a hydrogen bond with the best acceptor and the second best donor binds to the second best acceptor [37]. Therefore we can postulate that the donor with the highest positive molecular electrostatic potential value will preferentially bind to the acceptor with the highest negative molecular electrostatic potential value and the donor with the second highest value will bind to the acceptor with second highest value. In order to test the validity of this hypothesis we focused on five different hydrogen-bond donors, (Fig. 3.1).

To test the binding preferences of cyanooximes, acetyloximes, carboxylic acids, phenols, and amines, a series of asymmetric ditopic donor molecules decorated with a combination of these functional groups were synthesized and characterized, (Fig. 3.2). The molecular electrostatic potential values shown were calculated using semi-empirical methods.

These ligands were co-crystallized with a series of asymmetric ditopic acceptors (see Fig. 3.3 for one example) and suitable crystals obtained (from slow evaporation) were analyzed by single crystal X-ray diffraction.

The crystal structures obtained show that the best donor forms a hydrogen bond to the best acceptor and the second best donor binds to the second best acceptor (ranking based upon the values obtained from molecular electrostatic potential calculations), (Fig. 3.3).

All of the crystal structures obtained in this series display hydrogen-bond (HB) patterns and connectivities that can be rationalized in the context of preferences based on the molecular electrostatic potential calculations. Of course, even though hydrogen bonds have considerable strength and directionality, they are reversible which means that synthon polymorphism [38] and synthon crossover [39] are always possible in synthetic crystal engineering, and solvent effects can also be expected to influence the outcome (much as can be observed in conventional organic synthesis). Therefore, even though exceptions are to be expected, it is still very worthwhile to be able to identify patterns of structural behaviour, because trends clearly provide useful starting points for further studies that can validate or refine early observations.

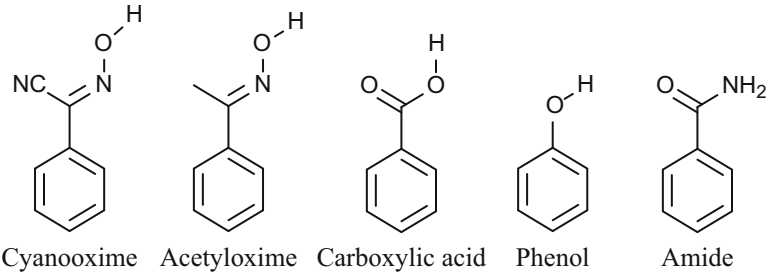

Fig. 3.1 Hydrogen bond donor groups

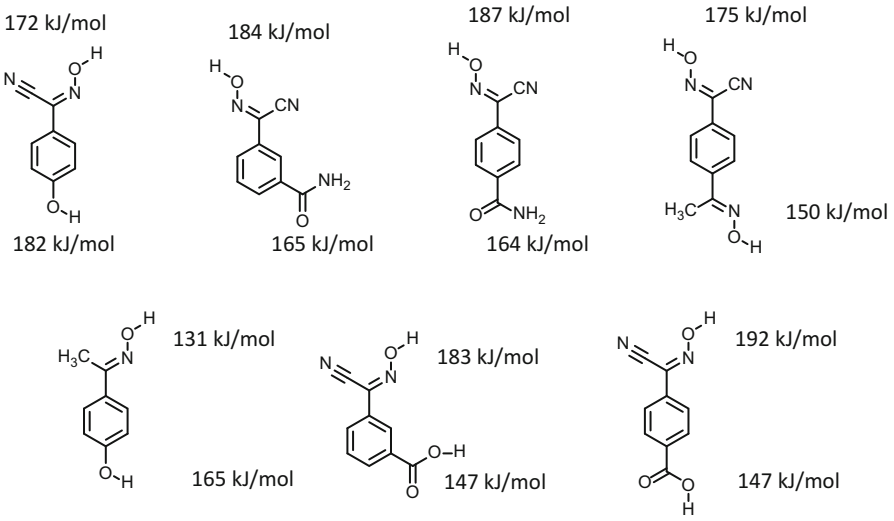

Fig. 3.2 Ditopic hydrogen-bond donors presenting two different donor sites

3.3 Expanding the Scope of Hydrogen-Bond Driven Co-Crystal Synthesis

To provide more support for a supramolecular synthetic strategy informed by calculated electrostatic molecular potential surfaces, we expanded our library of ditopic molecules with two different HB acceptor sites [40]. Our choice of building block was driven by a survey of the Cambridge Structural Database (CSD), [41] which plays a key role in offering extensive and appropriate structural information. In the search of the database, a combination of a carboxylic acid and a 2-aminopyridine based moiety yielded 27 hits whereas a combination of carboxylic acid and pyridine groups gave 202 hits [42]. The purpose of this search was to unambiguously show that carboxylic acids have the capability to bind to both 2-aminopyridine and pyridine based acceptor sites. We subsequently wanted to

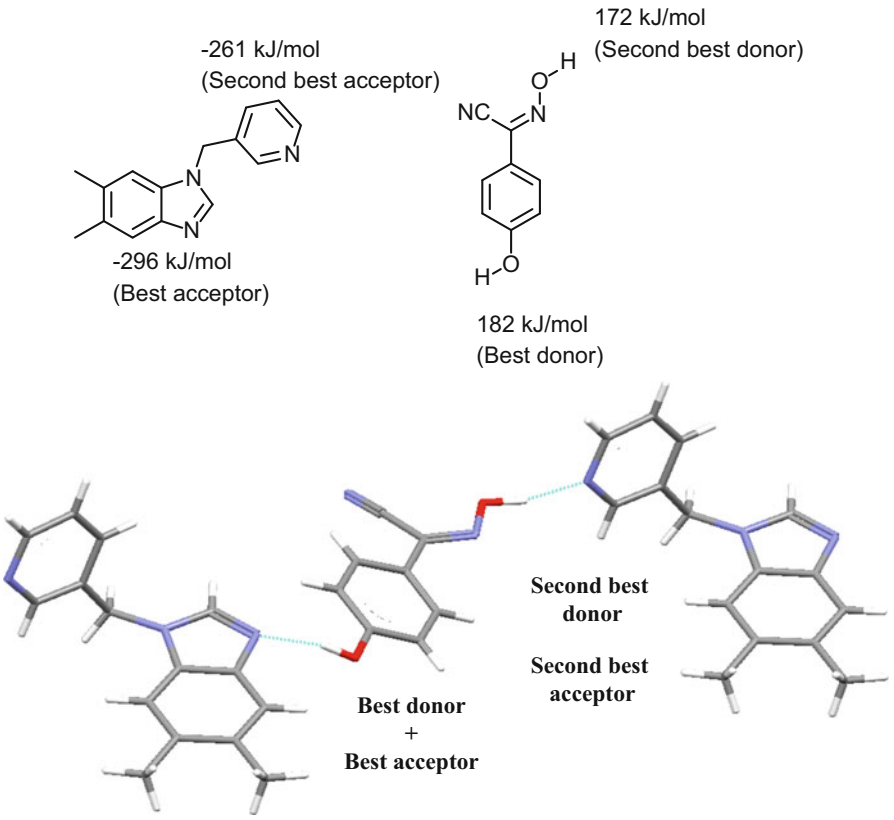

Fig. 3.3 Ranking of hydrogen-bond ability based on electrostatic potential (*top*). The best hydrogen-bond donor selects the best hydrogen-bond acceptor in the crystal structure (*bottom*)

identify any possible preference of carboxylic acids for either of the two binding sites so we chose a target molecular decorated with both functional groups. Aminopyrazine was the natural choice having 2-aminopyridine and a pyridine-type site attached to the same backbone. In order to tune the possible interaction strengths of these sites we modified the aromatic backbone with one or two bromine atoms, respectively, in order to alter the electrostatic potential at the primary hydrogen-bond acceptor site, (Fig. 3.4). We obtained ten crystal structures and 3/10 times the carboxylic acid moiety binds exclusively at the 2-amino end of pyrazine. In the remaining 7/10 there is no pronounced synthon selectivity since the carboxylic acid binds to the 2-amino and the N-4 end of pyrazine at the same time (producing discrete trimers).

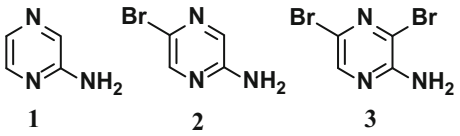

Fig. 3.4 Ditopic supramolecular reagents for probing intermolecular selectivity

3.4 Establishing a Hierarchy of Halogen-Bond (XB) Preferences

Etter's groundbreaking work [43] on the preparation of co-crystals using hydrogen bonds and co-crystallization reactions can be used as probes of the competition between different hydrogen-bonding interactions. Since halogen bonds are also governed to a large extent by electrostatics it is reasonable to expect that they would follow the hierarchy of interactions in a similar manner. To test our hypothesis, we designed and synthesized eight asymmetric ditopic halogen bond donor molecules, (Fig. 3.5), containing two halogen-bond donor sites with slightly different electrostatic potential value. We subsequently allowed these ditopic XB donor molecules to react with a variety of single point XB acceptors, symmetric ditopic acceptors and asymmetric ditopic XB acceptors.

According to molecular electrostatic potential surface calculations, iodine should be a better XB donor site than bromine which should make it bind preferentially to the only available acceptor pyridine site. We obtained two crystal structures, (Fig. 3.6), and in both cases the halogen bonding occurs as anticipated.

3.5 Modular Non-covalent Synthesis with Hydrogen- and Halogen Bonds

In order to refine supramolecular synthesis and to devise more robust synthetic 'reactions', it is necessary to develop supramolecular strategies that can accommodate two or more different non-covalent interactions in such a way that they are unlikely to interfere with each other. A suitable complement to widely studied hydrogen-bond based strategy could be provided by halogen bonds, which are typically formed between activated iodine- or bromine atoms (the halogen-bond donor) and an appropriate halogen-bond acceptor (electron-pair donor) such as an *N*-heterocycle. A potential problem with pairing these two interactions is that any halogen-bond acceptor can also act as a hydrogen-bond acceptor. We hypothesized that if we can choose HB and XB synthons carefully then they can operate in side-by-side in hierarchical fashion in the assembly of co-crystals. We developed a facile one-step strategy to synthesize ditopic XB/HB donor molecules; 2,3,5,6-tetrafluoro-4-halobenzoic acids (halo = iodo or bromo) [44]. We then co-crystallized these donors with the three ditopic acceptors described (Fig. 3.4). Crystal structures for all six reactions (**1**–**3** with the two acids) were obtained and in

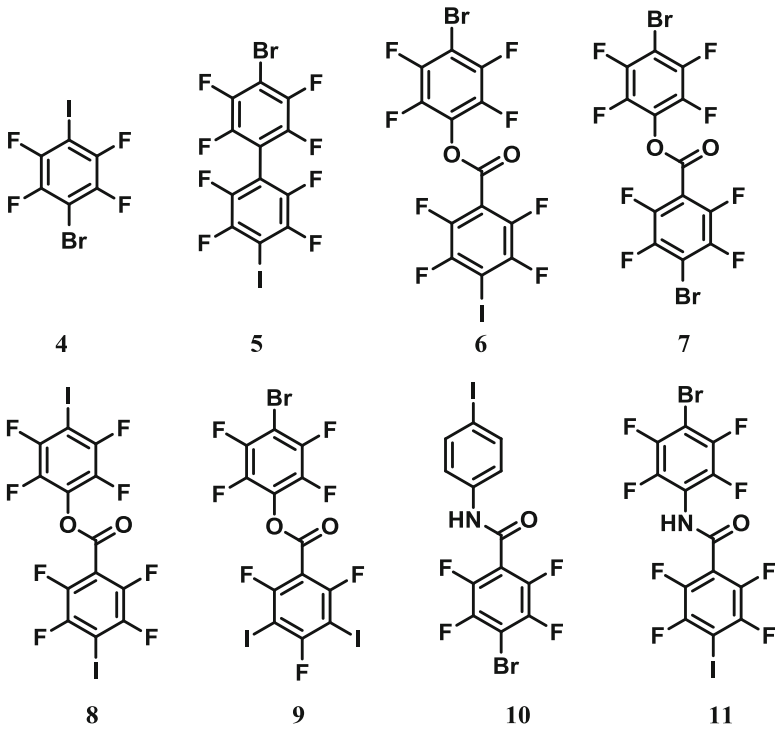

Fig. 3.5 Asymmetric ditopic halogen-bond donors

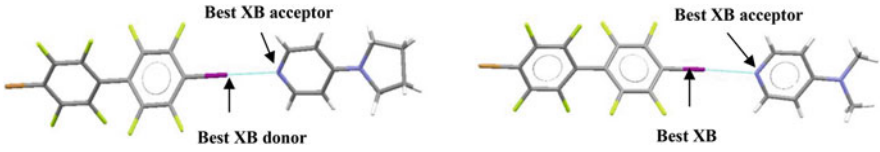

Fig. 3.6 Dimeric supramolecules constructed via hierarchical halogen bonds

each case the supermolecules were constructed via combinations of HB and XB interactions without any interference (Fig. 3.7). Moreover, the role of electrostatic potential in controlling the presence/absence of proton transfer was also emphasized as the acceptor molecule with the highest negative value was capable of abstracting a proton from both acids, leading to two salts and four co-crystals [45].

These results demonstrate how it may be possible to construct complex supramolecular assemblies with a larger number of different molecules (ternary co-crystals are still notoriously difficult to obtain) by combining interactions that can function independently of each other both at the level of molecular recognition, and at the level of overall structural control. In addition, in order to meet specific and well-defined supramolecular challenges it is necessary to employ custom-designed molecules with the appropriate functionalities which lead us to develop

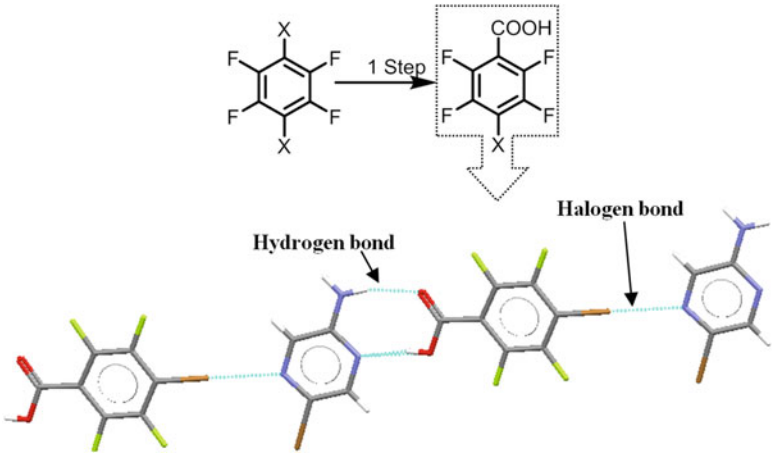

Fig. 3.7 Facile synthesis and supramolecular chemistry of HB/XB-driven multi-tasking tectons

a simple synthetic path to 2,3,5,6-tetrafluoro-4-iodobenzoic acid and 2,3,5,6-tetrafluoro-4-bromobenzoic acid, molecules which combine powerful halogen bond, and halogen bond donors, respectively.

Despite considerable recent interest in the fundamental nature and possible uses of halogen bonds, these interactions and their applications remain substantially underexplored [46]. There are relatively few reports on the logical and deliberate combination of different interactions in supramolecular synthetic and we are currently exploring the improved strategies for the targeted assembly of more complex, multimeric, molecular architectures using an expanded range of reversible intermolecular interactions [47–49].

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