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Combining halogen bonds and hydrogen bonds in the modular assembly of heteromeric infinite 1-D chains†

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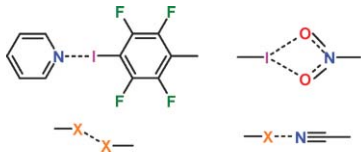
Hydrogen bonds and halogen bonds operate in concert in the directed assembly of infinite 1-D chains in binary co-crystals of iodine *iso*-nicotinamide (2 : 2), 1 and tetrafluorodiiodobenzene *iso*-nicotinamide (1 : 2) 2.

Ten years ago, Desiraju and co-workers[1] presented a succinct study that served to highlight the important analogies between crystal engineering and conventional covalent synthesis. The practical ramifications of many such efforts have, collectively, provided a solid foundation for the directed assembly of molecular solids using the robust principles of molecular recognition. The ability to combine a range of different synthons[2] within one and the same supramolecular reaction process has provided more refined tools for the construction of both discrete and extended heteromeric molecular architectures of considerable complexity. The rational synthesis of co-crystals is of considerable importance, partly because of the fundamental interest in molecular recognition-driven assembly processes,[3] and partly because of the potential applications of co-crystals in many areas of functional solids and speciality chemicals, notably pharmaceuticals.[4]

One of the main challenges facing supramolecular synthesis[5] stems from the fact that the reactants need to be held together by reversible intermolecular interactions, which, essentially, limits most supramolecular assembly processes to one-pot reactions. A possible solution to the problem of making a one-pot synthesis "sequential" may be to devise modular assembly processes based on a hierarchy of intermolecular interactions.[6] So far, hydrogen bonds of different strengths have been employed in the deliberate design of binary and ternary co-crystals,[7] but many other synthons, like the ones based on halogen atoms, could, in principle, be brought together simultaneously in a single reaction (Scheme 1).

In this Communication, we wish to report the crystal structures of two binary co-crystals assembled with the aid of two different intermolecular interactions, hydrogen bonds and halogen bonds, that have been combined in the successful assembly of a supramolecular structure of desired connectivity.

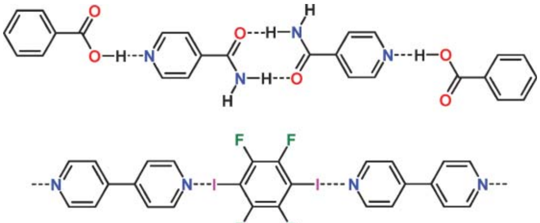


Scheme 1 Examples of supramolecular synthons based on interactions involving halogen atoms (X = Cl, Br, I).

The term halogen bond is used[8] for describing any non-covalent interaction that involves halogen atoms acting as electrophilic species. These interactions are undoubtedly both commonplace and versatile.[9] The strengths of these interactions correlate well with acidity scales and provide additional opportunities for further developing supramolecular synthetic strategies based on a modular view of intermolecular interactions.

The starting point is *iso*-nicotinamide, a bifunctional polymorphic compound that has become a near-classic co-crystallizing agent,[10] readily forming co-crystals with a variety of compounds in high supramolecular yield.[11] The fact that the two polymorphic forms of *iso*-nicotinamide display fundamentally different connectivities (synthon flexibility)[12] means that it displays considerable structural latitude and is not "locked" into a single type of crystalline lattice or packing mode. When these factors are coupled with favourable solubility in a range of solvents, *iso*-nicotinamide becomes a natural participant in solvent-based co-crystallization reactions.

It is well known that *iso*-nicotinamide readily forms tetrameric supermolecules in co-crystals with monocarboxylic acids through a combination of acid···py and amide···amide hydrogen bonds (Scheme 2, top), whereas if the monoacid is replaced with a diacid, a chain is the most likely outcome. Similarly, various examples are reported[13] where tetrafluorodiiodobenzene, in combination with suitable dipyridyl derivatives, form infinite chains through I···N-heterocycle halogen bonds (Scheme 2, bottom). Infinite chains are also formed when diiodine interacts with weak ditopic Lewis bases



Scheme 2 Top: Typical tetramer in a binary 2 : 2 acid–*iso*-nicotinamide co-crystals. Bottom: An infinite chain in bipy–tetrafluorodiiodobenzene.

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† Electronic supplementary information (ESI) available: Fig. 5, and the syntheses of **1** and **2**. See DOI: 10.1039/b707458a.

(*e.g.* phenazine and pyrazine),[14] while trimers are formed with strong Lewis bases such as dipyridyls,[15] as the charge transfer from nitrogen to one iodine atom prevents the other iodine atom from acting as a Lewis acid.

Iodo···py bonds can be of considerable strength (13 and 6 kcal mol^{-1} when I_2 and iodofluorocarbons are involved, respectively)[15] and frequently prevail over hydrogen bonding in controlling supramolecular assembly processes.[16] By using *iso*-nicotinamide, a strong Lewis base, we intended to replace the N–H···N(py) hydrogen bond, which is present in both polymorphs of *iso*-nicotinamide, with an I···N interaction; the latter synthon would play the same structural role as the acid···py interaction, leaving the amide moiety no option but to form a homomeric amide···amide motif. As iodine atoms are poor hydrogen bond acceptors, it seemed unlikely that amide···I interactions would disrupt any of the intended synthons.

The crystal structure determination of **1**‡ reveals that the lattice contains the two molecular components in a 1 : 1 ratio (Fig. 1). The primary intermolecular interaction responsible for the formation of the heteromeric co-crystal is a strong N···I_2 halogen bond (approx. 13 kcal mol^{-1},[15]). Similar to related structures,[14] the interaction is as short as 2.442 Å, corresponding to a 31% reduction of the sum of the van der Waals radii for N and I.[15–17] The fact that the pyridine nitrogen atom is now blocked leads to the formation of a self-complementary amide···amide interaction (Table 1). These tetramers are subsequently organized into infinite chains as a result of short I···I interactions (type I halogen–halogen contacts),[18] with a good interpenetration of the van der Waals radii (corresponding to an 8% reduction of the sum of the van der Waals radii for two I atoms)[17] (Fig. 2). The N···I–I and I–I···I angles are 178° and 170°, respectively. As a probable consequence of the strong n → σ* character of the halogen bond,[19] the covalent I–I bond is significantly elongated (2.79 Å) compared to the distance observed in elemental iodine (2.72 Å).[20] Since the pyridine moiety can form strong donor–acceptor bonds with I_2, it is possible that the polarization of I_2 has reduced the Lewis acidity of the second iodine atom, thus making it incapable of forming a direct I···N bond with a second py moiety.[15]

Surprisingly, there are no interchain amide···amide hydrogen bonds. Instead, the amide anti proton is directed towards an iodine atom. In fact, the infinite chains are parallel and coupled by anti-parallel dipole–dipole (or π–π) interactions between pyridine (*x*, *y*, *z* and 2 − *x*, 3 − *y*, 1 − *z*) rings, with centroid distances of *ca.* 3.58 Å (C3···C5 *ca.* 3.36 Å) (see Fig. 5 in ESI†). This geometry may have been adopted because it is likely to lead to a denser crystal landscape with respect to the empty space generated among the iodine atoms, should the chains be in registry.

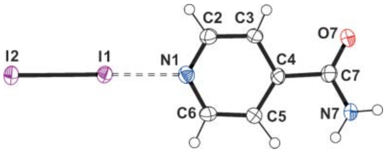

Fig. 1 Thermal ellipsoid (set at 50% probability) view of the two molecular building blocks in the crystal structure of **1**.

Table 1 Relevant intermolecular interactions for **1**

A–H/I···D	$d_{H/I\cdots D}$/Å	$d_{A\cdots D}$/Å	$\angle_{DH/IA}$/°
N(7)–H(7A)···O(7)[a]	2.07	2.927(5)	173.8
N(7)–H(7B)···I(1)[b]	3.25	3.985(4)	145.1
N(7)–H(7B)···I(2)[b]	3.25	3.788(4)	110.6
C(6)–H(6)···I(2)[c]	3.18	3.945(5)	129.8
I(2)–I(1)···N(1)	2.442(4)	—	178.07(9)
I1–I2···I2[d]	3.6314(7)	—	170.00(2)

[a] 1 − *x*, −*y*, −*z*. [b] −*x*, −*y*, 1 − *z*. [c] *x*, *y*, −1 + *z*. [d] −1 − *x*, 1 − *y*, 3 − *z*.

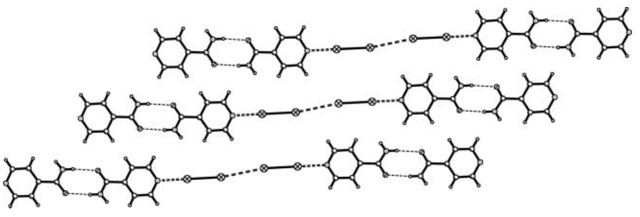

Fig. 2 The infinite 1-D chains in the crystal structure of **1**.

The structure determination of **2**‡ reveals the presence of a 1 : 2 tetrafluorodiiodobenzene–*iso*-nicotinamide co-crystal (Fig. 3). Again, the driving force for the formation of the co-crystal is a strong classic N···I halogen bond, with an N···I bond distance equal to 2.859 Å (corresponding to a 19% reduction of the sum of the van der Waals radii for N and I)[17] and an N···I–C angle of 179.04°. The amide moieties on *iso*-nicotinamide form a self-complementary head-to-head motif, and this time the anti proton provides a means of linking neighbouring chains into an infinite layer through an amide ribbon (Fig. 4).

The infinite 1-D ladder seen in **2** is very similar to what has been observed in several *iso*-nicotinamide–carboxylic acid co-crystals.[10,11] There are also several short F···H contacts (Table 2) but no sign of π···π interactions.

In this study, we have demonstrated how strong directional halogen and hydrogen bonds can be combined in a reliable strategy for the assembly of binary co-crystals.[21] Our strategy employs a py···I bond for the assembly of the co-crystal, whereas the amide···amide dimeric synthon is responsible for propagating

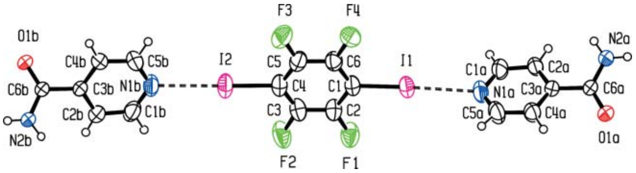

Fig. 3 Thermal ellipsoid (set at 50% probability) view of the two molecular fragments in the crystal structure of **2**.

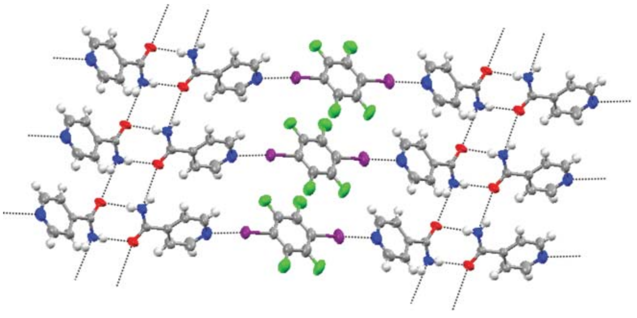

Fig. 4 Horizontal 1-D chains in the structure of **2**. Note the similarity with **1**, with one diiodotetrafluorobenzene molecule substituting for two I_2 molecules.

Table 2 Relevant intermolecular interactions for **2**

A–H/I···D	$d_{\mathrm{H/I\cdots D}}$/Å	$d_{\mathrm{A\cdots D}}$/Å	$\angle_{\mathrm{DH/IA}}$/°
N(2A)–H(2NA)···O(1B)[a,b]	2.09(3)	2.904(3)	171(4)
N(2B)–H(2NB)···O(1A)[a,c]	2.20(2)	2.994(3)	172(3)
N(2A)–H(1NA)···O(1A)[a,d]	2.28(2)	3.035(3)	153(4)
N(2B)–H(1NB)···O(1B)[a,e]	2.14(2)	2.898(3)	156(3)
C(1)–I(1)···N(1A)	2.858(3)	—	177.75(10)
C(4)–I(2)···N(1B)	2.859(3)	—	179.04(12)
C(2A)–H(2NA)···F(1)[a,f]	2.46(4)	3.432(4)	165(3)
C(4B)–H(4B)···F(4)[g]	2.46(3)	3.328(4)	159(3)

[a] N–H distances refined with restraints (see ESI). [b] $x, 1 + y, z$. [c] $-1 + x, -1 + y, -1 + z$. [d] $x, -1 + y, z$. [e] $1 + x, 1 + y, 1 + z$. [f] $-x, ½ + y, ½ - z$. [g] $1 - x, 2 - y, 1 - z$.

the inherent geometry in the resulting supermolecules into infinite 1-D chains. We are currently exploring how halogen and hydrogen bonds can be interchanged and utilized for the synthesis of more complex heteromeric molecular architectures.

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Notes and references

‡ *Crystal data for* **1**: $C_6H_6N_2O\cdot I_2$, M = 375.93 amu, triclinic, space group P-1, a = 7.6928(10), b = 7.7411(10), c = 8.1841(11) Å, α = 80.734(2), β = 72.131(2), γ = 85.702(2)°, V = 457.64(10) Å^3, Z = 2, D_c = 2.728 g cm^{-3}, μ(Mo-K$_\alpha$) = 6.820 mm^{-1}, crystal size 0.25 × 0.15 × 0.10 mm, F(000) = 340. Data were collected at 203(2) K on a Bruker SMART 1000 diffractometer. A total of 3221 reflections ($2.64 < \theta < 28.91$) were processed, of which 2051 were unique (R_{int} = 0.0571) and 1668 significant with $I > 2\sigma(I)$. Structure solution and refinement were carried out with the SHELXL-97 software package, release 97-2. Final residuals for $I > 2\sigma(I)$ were R_1 = 0.028 and wR_2 = 0.0676 (GOF = 1.041). Largest diffraction peak and hole = 1.069 and −1.088 e Å^{-3}. CCDC 647524.

Crystal data for **2**: $2(C_6H_6N_2O)\cdot C_6F_4I_2$, M = 646.12 amu, monoclinic, space group $P2_1/c$, a = 20.247(3), b = 5.0710(9), c = 21.279(3) Å, β = 106.911(6)°, V = 2090.3(6) Å^3, Z = 4, D_c = 2.053 g cm^{-3}, μ(Mo-K$_\alpha$) = 3.066 mm^{-1}, crystal size 0.42 × 0.14 × 0.04 mm, F(000) = 1224. Data were collected at 297(2) K on a Bruker SMART 1000 diffractometer. A total of 58508 reflections ($1.97 < \theta < 31.34$) were processed, of which 6507 were unique (R_{int} = 0.0279) and 5096 significant with $I > 2\sigma(I)$. Structure solution and refinement were carried out with the SHELXL-97 software package, release 97-2. Final residuals for $I > 2\sigma(I)$ were R_1 = 0.0320 and wR_2 = 0.0813 (GOF = 1.028). Largest diffraction peak and hole = 1.10 and −0.74 e Å^{-3}. CCDC 647525. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b707458a

1 V. R. Thalladi, B. S. Goud, V. J. Hoy, F. H. Allen, J. A. K. Howard and G. R. Desiraju, *Chem. Commun.*, 1996, 401.

2 G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.

3 (*a*) C. B. Aakeröy, J. Desper and J. F. Urbina, *Chem. Commun.*, 2005, 2820; (*b*) J. Pansanel, A. Jouaiti, S. Ferlay, M. W. Hosseini, J. Planeix and N. Kyritsakas, *New J. Chem.*, 2006, **30**, 683; (*c*) J. D. Wuest, *Chem. Commun.*, 2005, 5830.

4 (*a*) Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2004, 1889; (*b*) P. Vishweshwar, J. A. McMahon, J. A. Bis and M. J. Zaworotko, *J. Pharm. Sci.*, 2006, **95**, 499.

5 (*a*) C. B. Aakeröy, *Acta Crystallogr., Sect. B: Struct. Sci.*, 1997, **53**, 569; (*b*) B. Moulton and M. J. Zaworotko, *Chem. Rev.*, 2001, **101**, 1629; (*c*) G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565; (*d*) M. W. Hosseini, *CrystEngComm*, 2004, **6**, 318; (*e*) L. R. MacGillivray, *CrystEngComm*, 2004, **6**, 77; (*f*) L. Brammer, *Chem. Soc. Rev.*, 2004, **33**, 476; (*g*) C. B. Aakeröy and A. M. Beatty, *Aust. J. Chem.*, 2001, **54**, 409; (*h*) J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, 1995; (*i*) D. L. Caulder and K. N. Raymond, *Acc. Chem. Res.*, 1999, **32**, 975; (*j*) D. N. Reinhoudt and M. Crego-Calama, *Science*, 2002, **295**, 2403; (*k*) J.-M. Lehn, *Science*, 2002, **295**, 2400; (*l*) D. Braga, G. Desiraju, J. S. Miller, A. Joel, A. G. Orpen and S. L. Price, *CrystEngComm*, 2002, **4**, 500; (*m*) D. Braga, L. Maini, M. Polito and F. Grepioni, *Struct. Bonding*, 2004, **111**, 1; (*n*) G. Lewis and A. G. Orpen, *Chem. Commun.*, 1998, 1873; (*o*) L. J. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem., Int. Ed.*, 2001, **40**, 2382.

6 C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *Angew. Chem., Int. Ed.*, 2001, **40**, 3240. To date, more than ten ternary co-crystals based around *iso*-nicotinamide or nicotinamide with two different carboxylic acids are known. In each case, the stronger acid binds to the pyridine moiety and the weaker acid binds to the amide functionality.

7 (*a*) S. Shan, E. Batchelor and W. Jones, *Tetrahedron Lett.*, 2002, **43**, 8721; (*b*) R. D. Bailey Walsh, M. W. Bradner, S. Fleischman, L. A. Morales, B. Moulton, N. Rodriguez-Hornedo and M. J. Zaworotko, *Chem. Commun.*, 2003, 186; (*c*) L. R. MacGillivray, J. L. Reid and J. A. Ripmeester, *J. Am. Chem. Soc.*, 2000, **122**, 7817; (*d*) P. Vishweshwar, R. Thaimattam, M. Jaskolski and G. R. Desiraju, *Chem. Commun.*, 2002, 1830; (*e*) J. A. Zerkowski, J. C. MacDonald and G. M. Whitesides, *Chem. Mater.*, 1997, **9**, 1933; (*f*) J. J. Kane, R.-F. Liao, J. W. Lauher and F. W. Fowler, *J. Am. Chem. Soc.*, 1995, **117**, 12003; (*g*) J.-M. Lehn, M. Mascal, A. DeCian and J. Fischer, *J. Chem. Soc., Chem. Commun.*, 1990, 479; (*h*) Ö. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2004, 1889; (*i*) G. R. Desiraju and J. A. R. P. Sarma, *J. Chem. Soc., Chem. Commun.*, 1983, 45; (*j*) C. Huang, L. Leiserowitz and G. M. Schmidt, *J. Chem. Soc., Perkin Trans. 2*, 1973, 503; (*k*) F. Pan, W. S. Wong, V. Gramlich, C. Bosshard and P. Gunter, *Chem. Commun.*, 1996, 2; (*l*) V. R. Pedireddi, W. Jones, A. P. Chorlton and R. Docherty, *Chem. Commun.*, 1996, 997; (*m*) P. Vishweshwar, A. Nangia and V. M. Lynch, *J. Org. Chem.*, 2002, **67**, 556; (*n*) S. H. Dale, M. R. J. Elsegood, M. Hemmings and A. L. Wilkinson, *CrystEngComm*, 2004, **6**, 207; (*o*) J. F. Remenar, S. L. Morisette, M. L. Peterson, B. Moulton, J. M. MacPhee, H. R. Guzman and Ö. Almarsson, *J. Am. Chem. Soc.*, 2003, **125**, 8456; (*p*) C. B. Aakeröy and J. Salmon, *CrystEngComm*, 2005, **7**, 439.

8 P. Metrangolo and G. Resnati, *Chem.–Eur. J.*, 2001, **7**, 2511; P. Metrangolo, H. Neukirch, T. Pilati and G. Resnati, *Acc. Chem. Res.*, 2005, **38**, 386; P. Metrangolo, T. Pilati and G. Resnati, *CrystEngComm*, 2006, **8**, 346.

9 G. Marras, P. Metrangolo, F. Meyer, T. Pilati, G. Resnati and A. Vij, *New J. Chem.*, 2006, **30**, 1397; H. Neukirch, E. Guido, R. Liantonio, P. Metrangolo, T. Pilati and G. Resnati, *Chem. Commun.*, 2005, 1534; R. D. Bailey, M. Grabarczyk, T. W. Hanks and W. T. Pennington, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2781.

10 C. B. Aakeröy, J. Desper, E. Elisabeth, B. A. Helfrich, B. Levin and J. F. Urbina, *Z. Kristallogr.*, 2005, **220**, 325; P. Vishweshwar, A. Nangia and V. M. Lynch, *Cryst. Growth Des.*, 2003, **3**, 783; J. A. McMahon, J. A. Bis, P. Vishweshwar, T. R. Shattock, O. L. McLaughlin and M. J. Zaworotko, *Z. Kristallogr.*, 2005, **220**, 340.

11 C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *J. Am. Chem. Soc.*, 2002, **124**, 14425.

12 C. B. Aakeröy, A. M. Beatty, B. A. Helfrich and M. Nieuwenhuyzen, *Cryst. Growth Des.*, 2003, **3**, 159.

13 P. Cardillo, E. Corradi, A. Lunghi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, *Tetrahedron*, 2000, **56**, 5535; M. T. Messina, P. Metrangolo, W. Panzeri, T. Pilati and G. Resnati, *Tetrahedron*, 2001, **57**, 8543; R. Bertani, E. Ghedini, M. Gleria, G. Marras, P. Metrangolo, F. Meyer, T. Pilati and G. Resnati, *CrystEngComm*, 2005, **7**, 511.

14 R. D. Bailey, M. L. Buchanan and W. T. Pennington, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1992, **48**, 2259; T. Uchida and K. Kimura, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1984, **40**, 139.

15 R. D. Bailey, G. W. Drake, M. Grabarczyk, T. W. Hanks, L. L. Hook and W. T. Pennington, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2773; R. Bailey Walsh, C. W. Padgett, P. Metrangolo, G. Resnati, T. W. Hanks and W. T. Pennington, *Cryst. Growth Des.*, 2001, **1**, 165.

16 E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, *Angew. Chem., Int. Ed.*, 2000, **39**, 1782.

17 http://www.webelements.com © 2007 ChemIndustry.com Inc.

18 N. Ramasubbu, R. Parthasarathy and P. Murray-Rust, *J. Am. Chem. Soc.*, 1986, **108**, 4308.

19 S. V. Rosokha, I. S. Neretin, T. Y. Rosokha, J. Hecht and J. K. Kochi, *Heteroat. Chem.*, 2006, **17**, 449.

20 A. Hinchliffe, R. W. Munn, R. G. Pritchard and C. J. Spicer, *J. Mol. Struct.*, 1985, **130**, 93.

21 B. K. Saha, A. Nangia and M. Jaskólski, *CrystEngComm*, 2005, **7**, 355.