

Complementary halogen and hydrogen bonding: sulfur···iodine interactions and thioamide ribbons†

Hadi D. Arman,^a Rebecca L. Gieseck,^b Timothy W. Hanks^b and William T. Pennington^{*a}

Received (in Austin, TX, USA) 9th December 2009, Accepted 13th January 2010

First published as an Advance Article on the web 12th February 2010

DOI: 10.1039/b925710a

Complementary halogen bonding and hydrogen bonding coexist in co-crystals of organoiodines with molecules containing the thioamide functionality. Thiourea-organiodine co-crystals are shown to exhibit a remarkably reliable synthon with complementary N–H···S ribbons and S···I interactions.

Interest in halogen bonding (X-bonding)¹ has increased dramatically over the past few years, and this interaction is now an accepted and useful tool for the rational design of pharmaceuticals, novel solids, and functional materials. The importance of halogen bonding in biological systems is also being increasingly recognized.²

Almost all of the reports involving halogen bonding with organohalogens thus far have involved either nitrogen or oxygen as the X-bond acceptor (e[−] pair donor).³ This focus is not surprising given the much larger number of known structures with short contact distances to halogens for nitrogen and oxygen than for other potential X-bonding acceptor atoms.^{4†}

Nitrogen and oxygen Lewis bases serve as excellent acceptors for both hydrogen and halogen bonding, and numerous reports comparing the strength and occurrence of these two interactions have appeared.⁵ Competition between these two interactions is counterproductive for effective crystal engineering applications, where the construction of supramolecular assemblies often depends on the use of diverse and selective synthons.⁶ Coexistence of the two interactions within a given crystal has been reported,⁷ but only recently has a systematic approach to combining them, based on a hierarchy of potential H-bonding and X-bonding interactions, been proposed.⁸ This approach is similar to the very successful use of hydrogen bonds of varying strengths for the construction of binary and ternary co-crystals.⁹

Our interest is focused on the use of organoiodines as halogen bond donors, as the more polarizable iodine atom forms much stronger X-bonding interactions.¹⁰ Many of the X-bonded co-crystals involving heavier acceptors with organoiodines were reported in the 1950's and 60's by Hassel and coworkers.¹¹ There has been more recent interest in S···I interactions in conducting solids based on tetrathiafulvalenes and related compounds.¹² Only two other papers focused on

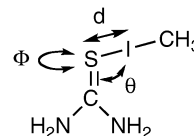
these interactions have appeared in the current decade, our previous paper reporting halogen bonding between organoiodines and the antithyroid drug, methylmercaptoimidazole,¹³ and a paper reporting the structural similarity of halogen bonding acceptors based on nitrogen, oxygen, and sulfur electron donors.¹⁴

In this communication we describe an alternate to crystal engineering based on competitive H-/X-bonding by employing sulfur as an acceptor for *both* H- and X-bonds, in a complementary fashion.

In order to explore the angular sensitivity of the sulfur–iodine bond, we examined a simple model system of thiourea and iodomethane. DFT calculations with the M052X functional and aug-cc-pVTZ basis set were used to fully optimize the structures of the two isolated components. These were then brought together so that the iodine atom was directly between the sulfur and the methyl carbon. The sulfur···iodine distance (*d*), C–S–I bond angle (*θ*) and the N–C–S···I torsional angle (*Φ*) were then systematically varied (Scheme 1). Single point energy calculations were performed at regular intervals and illustrative results are reported in Fig. 1. As has been previously reported, this approach tends to overestimate the halogen bond distance.¹⁵

The thiourea sulfur is anisotropic, with a ring of high negative electrostatic potential normal to the C=S bond and an area of positive potential opposite the carbon. As with the dihalides, the in-plane orientation (*Φ* = 0°) results in the strongest halogen bond. The interaction energy was found to be at a minimum at a bond angle *θ* of 100° in this orientation, but this angle decreased as the iodomethane was moved towards a perpendicular orientation. Presumably steric interactions with the amide protons force the methyl iodine away from the area of maximum electron density in the planar conformation. The energy of the halogen bond is also relatively insensitive to the S···I distance, changing less than 2 kJ mol^{−1} over 0.5 Å or more in most cases.

While increasing the bond angle and the torsional angle decreases halogen bond strength, the energy surface is relatively shallow, allowing for a significant interaction to take place over a broad range of angles and bond distances. This is quite different from the situation with nitrogen halogen bond acceptors, where the interaction is highly directional.



Scheme 1 Parameters varied in DFT calculations.

^a Department of Chemistry, Clemson University, Clemson, SC, USA.
E-mail: billp@clemson.edu; Fax: +1 864-656-6613;
Tel: +1 864-656-4200

^b Department of Chemistry, Furman University, Greenville, SC, USA.
E-mail: tim.hanks@furman.edu; Fax: +1 864-294-3559;
Tel: +1 864-294-3373

† CCDC 724588, 724589 and 724667. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b925710a

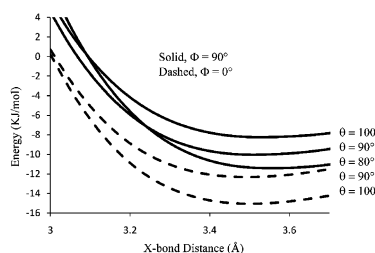


Fig. 1 Interaction energy dependence on X-bond length and angles.

Co-crystals of thiourea and derivatives with three different organoiodines are reported: thiourea-1,4-diiodotetrafluorobenzene (1/1), co-crystal **1**; ethylenethiourea-tetraiodoethylene (2/3), co-crystal **2**; mercaptobenz-imidazole-1,2-diiodotetrafluorobenzene (1/1), co-crystal **3**.[§] In all three co-crystals N–H···S hydrogen bonding, and S···I halogen bonding occur in a complementary fashion.

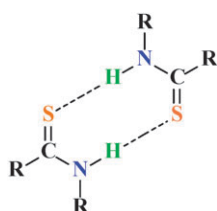
Thioamides having an *E*-configuration about the C–N bond reliably form a dimer with an eight-membered $R_2^2(8)$ ring (Scheme 2).¹⁶ The majority of these dimeric rings (92%) are planar or nearly planar, with only a few having dihedral angles in the ranges, 10–30° and 55–85°.⁴

The thiourea moieties in **1–3** each form infinite ribbons of these $R_2^2(8)$ rings, as is shown for **1** in Fig. 2a. The N···S hydrogen bonding distances for the co-crystals, given in Table 1, are within expected ranges.

In addition to N–H···S hydrogen bonding, the sulfur atoms in **1–3** also act as halogen bond acceptors, with either one (**3**), two (**1**) or four (**2**) interactions. From Table 1, it can be seen that all of these interactions are significantly shorter than the *vdw* sum for sulfur and iodine (1.80(S) + 1.98(I) = 3.78 Å).¹⁷

In **1**, the 1,4-F₄DIB donors bridge N–H···S ribbons into layers (Fig. 2a). The I···S···I angles in (**1**) are 144.33(6)° and 149.88(6)° for the two crystallographically unique, but chemically equivalent sulfur atoms. The interactions are roughly orthogonal to the ribbon plane with I···S–C–N dihedral angles ranging from 66.6(6)° to 97.7(6)°.

In **2**, the *cis*-iodine atoms of a TIE molecule span alternating sulfur atoms of a given ribbon. Iodine atoms *geminal* to the S···I–C=C–I···S spans interact with a neighboring ribbon to form layers of doubly X-bridged ribbons parallel to the *b*-axis. These layers are singly bridged parallel to the *c*-axis by weaker halogen bonds involving a second TIE donor (Fig. 2b) to form a network. I···S···I angles range from 71.63(3)° to 126.57(4)°. The stronger S···I interactions form I···S–C–N dihedral angles that average 48(1)°, but the dihedral angle between the best plane through this donor and the acceptor molecule is 88.87(7)°. The weaker contacts are nearly orthogonal to the acceptor plane with I···S–C–N dihedral angles of 90.3(5)° and 95.2(7)°.



Scheme 2 Thioamide $R_2^2(8)$ dimer.

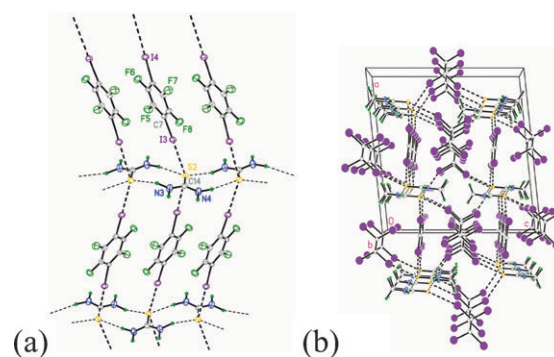


Fig. 2 (a) Layered structure of **1** consisting of N–H···S bridged by 1,4-F₄DIB halogen bonded acceptors. (b) Doubly-bridged layers of **2** crosslinked by a second TIE to form a network.

Table 1 Hydrogen and halogen bonding distances (Å) and angles (°) for **1–3**

	1	2	3
N···S	3.442(7) 3.427(7) 3.444(7) 3.489(7)	3.320(7) 3.317(6)	3.380(5) 3.371(5)
S···I	3.3480(19) 3.4036(19) 3.2867(19) 3.2812(19)	3.3736(14) 3.4983(14) 3.6465(15) 3.6563(15)	3.309(2)
C–I···S	176.8(2) 171.0(2) 179.2(2) 179.6(2)	172.31(16) 169.04(17) 158.79(15) 149.97(16)	173.5(2)
C–S···I	91.3(2) 84.6(2) 88.7(2) 86.7(2)	92.76(17) 93.96(18) 160.07(17) 123.33(17)	119.2(3)

Only one of the two iodine atoms of 1,2-diiodotetrafluorobenzene participates in S···I halogen bonding in **3**, so there is no extension of the dimensionality of the structure beyond the N–H···S ribbons (Fig. 3). The S···I interaction is nearly orthogonal to the acceptor ribbon, with an I···S–C–N dihedral angle of 80.2(7)°. The ribbons stack face-to-face parallel to the *c*-axis, with an interplanar separation of 3.474(9) Å, and the pendant donor molecules interdigitate with interplanar spacings of 3.629(15) and 3.762(15) Å.

Previous studies of the interaction between thioureas and I₂ indicate that the halogen bond strength is highly sensitive to the groups adjacent to the thiocarbonyl moiety. The strongest halogen bond acceptors are those in which the adjacent atoms

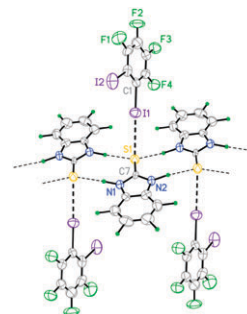


Fig. 3 N–H···S ribbon of **3** with pendant 1,2-F₄DIB acceptors.

are nitrogens, as delocalization of the nitrogen lone pair increases the electron density at the sulfur.¹⁸ In solution, molecular iodine forms 1 : 1 co-crystals with thiourea derivatives and adopts one of two principle geometries. When the nitrogen is bonded to one or two hydrogens, the iodine lies in the N–C–S plane, while bulkier substituents on the nitrogen lead to a halogen bond perpendicular to the plane. Two reasons for this have been proposed. In the case of a primary or secondary nitrogen, the iodine atom that is directly bonded to the sulfur is able to form a hydrogen bond to the thiourea proton. In addition, the HOMO of the thiourea is essentially a sulfur lone pair in a p-orbital. When this proton is replaced by a larger group, hydrogen bonding is no longer possible and steric repulsion forces the iodine perpendicular to the N–C–S plane. Calculations also suggest that the HOMO and HOMO – 1 become very close in energy in these systems.

Our calculations with methyl iodide are consistent with this depiction when it is recognized that the S...I bond is weaker than with the dihalide. Thus, the complementary hydrogen-bonded ribbons are formed without interference, while the halogen bond adjusts to accommodate both the ribbons and crystal packing forces.

In conclusion, the directionality of sulfur-based halogen bonding acceptors is reduced relative to those of second row atoms. For some applications this may be a liability, but the softer nature of this acceptor allows a structural adaptability that can more easily accommodate a variety of guests.¹⁹ This, coupled with the reliability of the thiourea ribbon synthon and the complementarity of the hydrogen and halogen bond acceptor sites, makes this system ideal for crystal design. The systematic study, both structural and theoretical, of the S...I halogen bond is also of biological importance, especially for thyroid chemistry.^{2a,20} Study of this interaction, along with that X-bonds with other heavy atom acceptors is in progress.

Notes and references

† A search of the Cambridge Crystallographic Database for structures with intermolecular contacts <95% *vdw* sum revealed: N...Br 153, N...I 95, O...Br 612, O...I 436, P...Br 1, P...I 1, S...Br 24, S...I 45, Se...I 6.

§ *Crystallographic data for 1*: CH₄N₂S·C₆F₄I₂, *M* = 477.98, monoclinic, *P*2₁/*n* (#14), *a* = 11.6519(18), *b* = 8.6561(14), *c* = 23.639(4) Å, β = 91.057(6)°, *V* = 2383.8(7) Å³, *Z* = 8, *D_c* = 2.66 g cm^{−3}, μ (Mo K α) = 5.477 mm^{−1}, colorless needle crystal, 0.05 × 0.10 × 0.28 mm, *F*(000) = 1744. Data collection at 163(2) K on a Rigaku Mercury/AFC8 diffractometer yielded 20 285 reflections (2.51 < θ < 26.37°) of which 4863 were unique (*R*_{int} = 0.056) and 4098 were observed (*I* > 2 σ (*I*)). Structure solution and refinement were performed with SHELXTL (version 6.10). Final residuals: *R*₁ = 0.0505, *wR*₂ = 0.0934, *R*₁ (all data) = 0.0645, *wR*₂ (all data) = 0.0979, *S* = 1.189. Crystals grown by slow evaporation of acetonitrile solution. Elemental, calculated (observed): %C 17.59 (17.71); %H 0.84 (0.84); 5.86 (6.56). CCDC 724588. *Crystallographic data for 2*: (C₃H₆N₂S)₂·(C₂I₄)₃, *M* = 1799.18, monoclinic, *C*2/*c* (#15), *a* = 19.504(2), *b* = 8.2442(9), *c* = 20.428(3) Å, β = 96.487(9)°, *V* = 3263.7(7) Å³, *Z* = 4, *D_c* = 3.66 g cm^{−3}, μ (Mo K α) = 11.53 mm^{−1}, colorless platelet crystal, 0.03 × 0.11 × 0.14 mm, *F*(000) = 3120. Data collection at 163(2) K on a Rigaku Mercury/AFC8 diffractometer yielded 13 808 reflections (2.74 < θ < 26.02°) of which 3191 were unique (*R*_{int} = 0.028) and 3127 were observed (*I* > 2 σ (*I*)). Structure solution and refinement were performed with SHELXTL (version 6.10). Final residuals: *R*₁ = 0.0285, *wR*₂ = 0.0568, *R*₁ (all data) = 0.0294, *wR*₂ (all data) = 0.0572, *S* = 1.090. Crystals grown by slow evaporation of ethanol–chloroform (50 : 50) solution. Elemental, calculated (observed): %C 8.01 (8.75); %H 0.67 (0.70); 3.11 (3.14). CCDC 724667.

Crystallographic data for 3: C₇H₆N₂S·C₆F₄I₂, *M* = 552.06, triclinic, *P*1 (#2), *a* = 8.2368(14), *b* = 8.5594(15), *c* = 12.643(3) Å, α = 88.742(17)°, β = 85.274(16)°, γ = 66.509(10)°, *V* = 814.6(3) Å³, *Z* = 2, *D_c* = 2.25 g cm^{−3}, μ (Mo K α) = 4.024 mm^{−1}, colorless platelet crystal, 0.02 × 0.10 × 0.12 mm, *F*(000) = 512. Data collection at 293(2) K on a Rigaku Mercury/AFC8 diffractometer yielded 7873 reflections (3.04 < θ < 26.37°) of which 3288 were unique (*R*_{int} = 0.065) and 1938 were observed (*I* > 2 σ (*I*)). Structure solution and refinement were performed with SHELXTL (version 6.10). Final residuals: *R*₁ = 0.0516, *wR*₂ = 0.0772, *R*₁ (all data) = 0.1053, *wR*₂ (all data) = 0.0884, *S* = 0.969. Crystals grown by slow evaporation of methylene chloride solution. Elemental, calculated (observed): %C 15.23 (15.37); %H 1.10 (0.96); 5.07 (5.14). CCDC 724589.

- P. Metrangolo, F. Meyer, T. Pilati, G. Resnati and G. Terraneo, *Angew. Chem., Int. Ed.*, 2008, **47**, 6114, and references therein.
- (a) P. Auffinger, F. A. Hays, E. Westhof and P. S. Ho, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 16789–16794; (b) R. Battistutta, M. Mazzorana, S. Sarno, Z. Kazimierzczuk, G. Zanotti and L. A. Pinna, *Chem. Biol.*, 2005, **12**, 1211–1219; (c) R. M. de Jong, K. H. Kalk, L. Tang, D. B. Janssen and B. W. Dijkstra, *J. Bacteriol.*, 2006, **188**, 4051–4056.
- K. Rissanen, *CrystEngComm*, 2008, **10**, 1107.
- Cambridge Structural Database (version 5.30, May 2009 update): F. H. Allen, *Acta Crystallogr., Sect. B*, 2002, **58**, 380. Surveys were based on a 95% VDW radii cut-off for ordered structures determined from single crystal X-ray analysis (no powder), with 3-D coordinates determined, crystallographic residual *R* < 0.1, and monovalent, neutral XB donors bonded to carbon (*i.e.* organohalogens).
- (a) C. B. Aakeröy, M. Fasulo, N. Schultheiss, J. Desper and C. Moore, *J. Am. Chem. Soc.*, 2007, **129**, 13772; (b) S. Varughese and V. R. Pedireddi, *Chem.–Eur. J.*, 2006, **12**, 1597; (c) E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, *Angew. Chem., Int. Ed.*, 2000, **39**, 1782.
- G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
- (a) S. Sourisseau, N. Louvain, W. Bi, N. Mercier, D. Rondeau, F. Boucher, J. Y. Buzare and C. Legein, *Chem. Mater.*, 2007, **19**, 600; (b) B. K. Saha, A. Nangia and M. Jaskólski, *CrystEngComm*, 2005, **7**, 355; (c) S. Zhu, C. Xing, W. Xu and Z. Li, *Tetrahedron Lett.*, 2004, **45**, 777; (d) S. Zhu, C. Xing, W. Xu, G. Jin and Z. Li, *Cryst. Growth Des.*, 2004, **4**, 53.
- C. B. Aakeröy, J. Desper, B. A. Helfrich, P. Metrangolo, T. Pilati, G. Resnati and A. Stevenazzi, *Chem. Commun.*, 2007, 4236.
- (a) M. C. Etter, *Acc. Chem. Res.*, 1990, **23**, 120; (b) C. B. Aakeröy, N. Schultheiss, J. Desper and C. Moore, *Cryst. Growth Des.*, 2007, **7**, 2324; (c) C. B. Aakeröy and D. B. Salmon, *CrystEngComm*, 2005, **7**, 439.
- T. Messina, P. Metrangolo, W. Panzeri, E. Ragg and G. Resnati, *Tetrahedron Lett.*, 1998, **39**, 9069–9072.
- O. Hassel, *Science*, 1970, **170**, 497, and references therein.
- (a) K. Herve, O. Cador, S. Golhen, K. Costuas, J.-F. Halet, T. Shirahata, T. Muto, T. Imakubo, A. Miyazaki and L. Ouahab, *Chem. Mater.*, 2006, **18**, 790–797; (b) Y. Kosaka, H. M. Yamamoto, A. Nakao, M. Tamura and R. Kato, *J. Am. Chem. Soc.*, 2007, **129**, 3054–3055; (c) T. Imakubo, T. Shirahata, M. Kibune and H. Yoshino, *Eur. J. Inorg. Chem.*, 2007, 4727; (d) L. R. Nassimbeni, M. L. Niven and A. P. Suckling, *Inorg. Chim. Acta*, 1989, **159**, 209; (e) T. Imakubo, H. Sawa and R. Kato, *Chem. Commun.*, 1995, 1097.
- J. I. Jay, C. W. Padgett, R. D. B. Walsh, T. W. Hanks and W. T. Pennington, *Cryst. Growth Des.*, 2001, **1**, 501.
- D. Cinčić, T. Friščić and W. Jones, *Chem.–Eur. J.*, 2008, **14**, 747.
- F. Bigoli, P. Deplano, A. Ienco, C. Mealli, M. L. Mercuri, M. A. Pellinghelli, G. Pintus, G. Saba and E. F. Trogu, *Inorg. Chem.*, 1999, **38**, 5626.
- S. Y. Ho, R. P. A. Bettens, D. Dakternieks, A. Duthie and E. R. T. Tiekink, *CrystEngComm*, 2005, **7**, 682.
- A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
- (a) M. Esseffar, W. Bouab, A. Lamsabhi, J.-L. M. Abboud, R. Notario and M. Yanez, *J. Am. Chem. Soc.*, 2000, **122**, 2300; (b) D. K. Papayannis and A. M. Kosmas, *THEOCHEM*, 2008, **851**, 175.
- K. T. Holman, A. M. Pivovar, J. A. Swift and M. D. Ward, *Acc. Chem. Res.*, 2001, **34**, 107.
- L. Liu, W. A. Baase and B. W. Matthews, *J. Mol. Biol.*, 2009, **385**, 595.