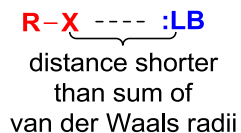


Overview

- Intro to halogen bonding and the concept of the σ hole
- Thermodynamics of halogen bonding interactions
- Halogen bond catalysis
- Potential Applications of halogen bonding

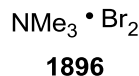
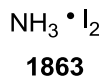
Background

- Proposed IUPAC Definition: “A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity.”



worth: 0 - 10 kcal/mol
comparison: moderate
hydrogen bond

- The halogen is termed the “**halogen bond donor**,” even though it is the *acceptor* of electron density. The Lewis base is called the “**halogen bond acceptor**,” even though it is the donor of electron density.
- First observed in 1863 by Guthrie and later by Norris with amine complexes of dihalides

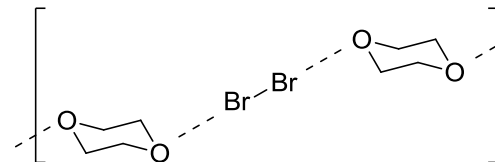


Rissanen, K. *Pure Appl. Chem.* **2013**, 85, 1711.

Guthrie, F. *J. Chem. Soc.* **1863**, 16, 239.

Remsen, I.; Norris, J. *Am. Chem. J.* **1896**, 18, 90.

- The term “halogen bonding” was introduced by Dumas 1976.
- 1969 Nobel Prize: Hassel reports halogen bonding in a crystal structure.



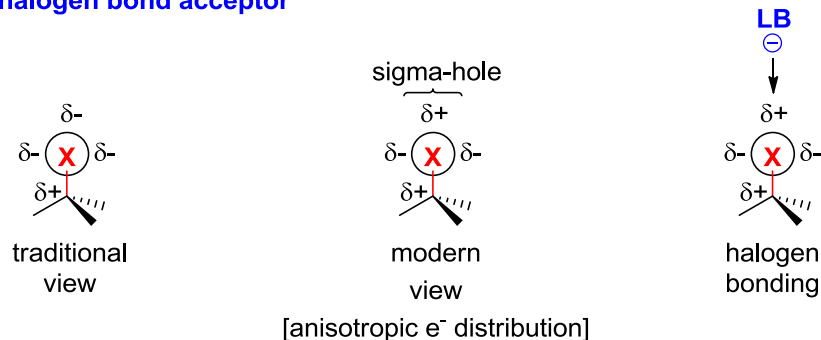
Dumas, J.-M.; Kern, M.; Dubry-Janier, J. L. *Bull. Soc. Chim. Fr.* **1976**, 1785.
Hassel, O. *Science* **1970**, 170, 497.

- Much early work concerned identification of halogen bonding in crystal structures and studying it theoretically.

The σ Hole: A Provocative Picture

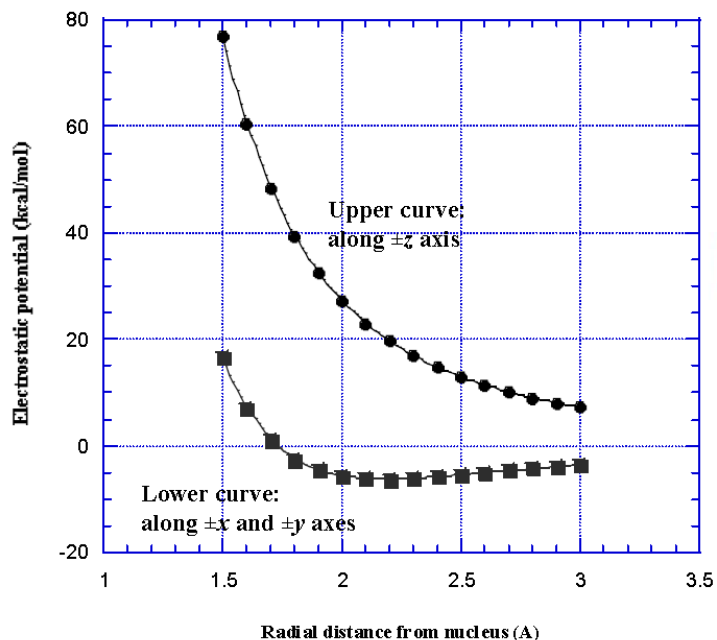
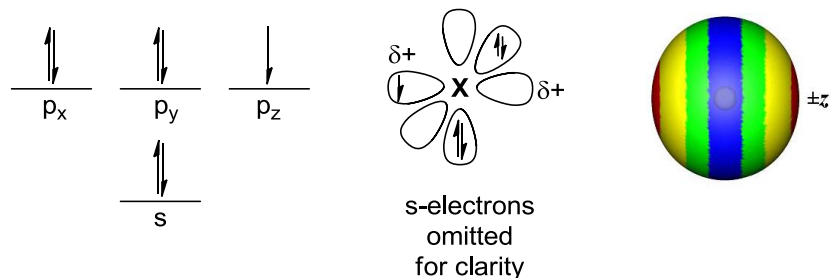
- How do halogens interact with Lewis bases?

halogen bond donor
halogen bond acceptor

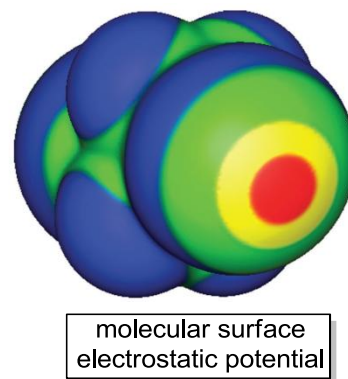
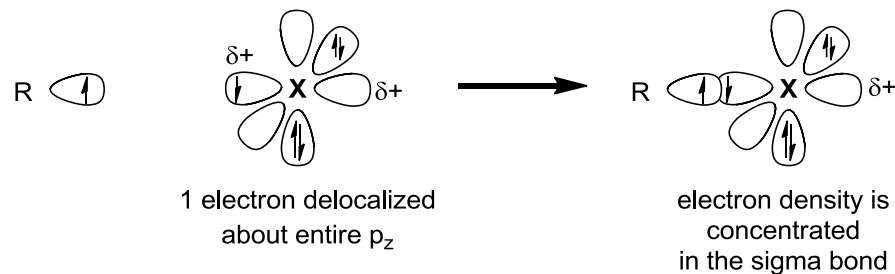


Origin of the σ -hole

- For **atomic halogens**, the p_z orbital is “singly occupied” and imperfectly shields the nucleus’s positive charge along this axis

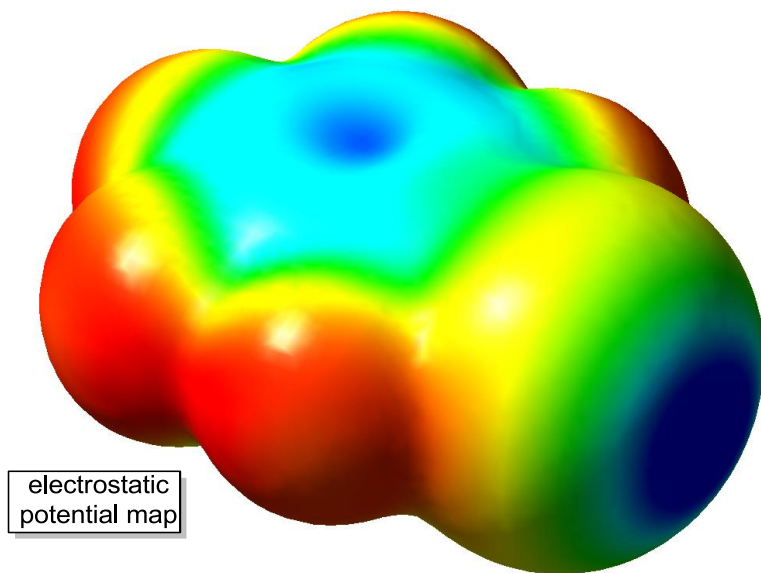
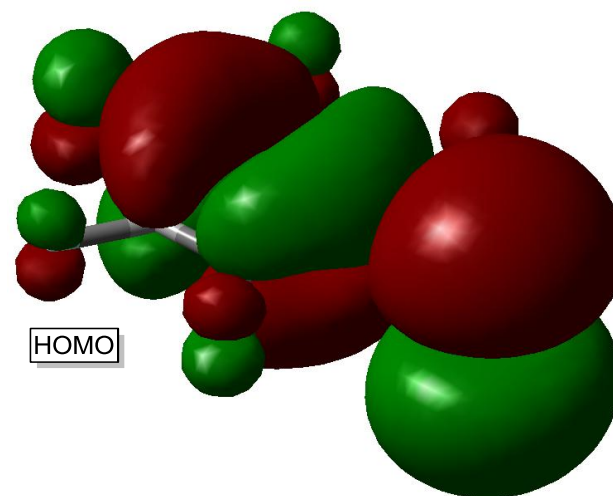
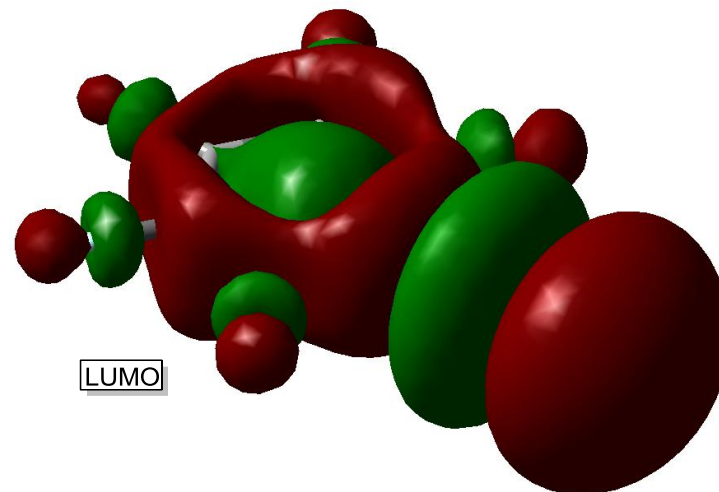
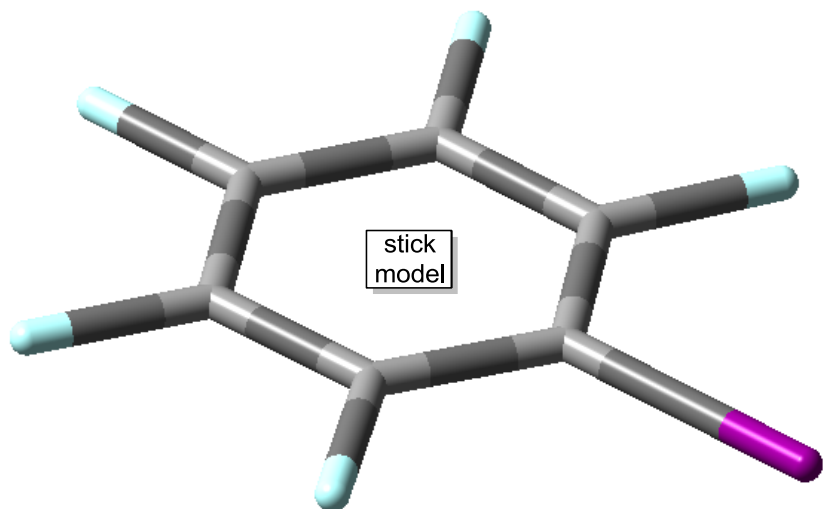


- When a halogen forms a covalent bond, the electron density in its p_z orbital becomes polarized toward the bonding region, diminishing the electron density on the outer region of the p_z lobe.



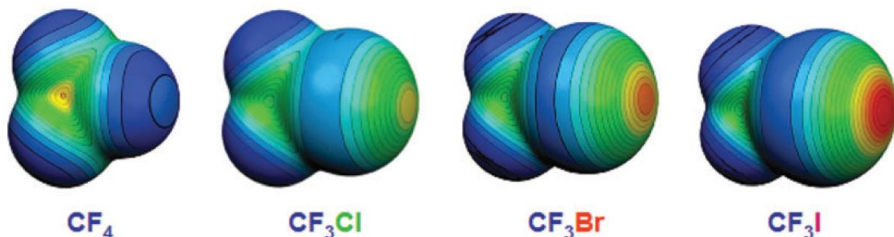
- Interaction of controversy? Some argue that this interaction is simply electrostatic, and is not an interaction with the R-X σ^*
- Computational evidence against LB donation into R-X σ^* is that some interactions cause a strengthening and shortening of the R-X bond
- Likely, halogen bonding arises mainly from electrostatic contributions, but also has charge-transfer and dispersion contributions.

Electrostatic model and the MO model



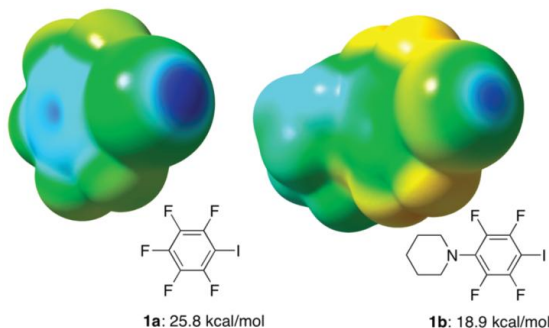
Factors affecting electrostatic potential of the σ hole

- Polarizability of halogen
- Electronegativity of halogen



- As a halogen bond donor: $F \ll Cl < Br < I$

- Electron-withdrawing capability of "R"



- More electron-withdrawing "R" = better halogen bond donor
- Halogen bond ability: $R(sp^3) < R(sp^2)$, $R(sp)$

Terraneo et al. *Chem. Soc. Rev.* **2011**, 40, 2267.
Taylor et al. *J. Am. Chem. Soc.* **2010**, 132, 1646.

Strength of halogen bonding: Brief Overview

- Typical strength of interaction: **0 – 10 kcal/mol**

Classical	Worth (kcal/mol)
ion-ion interactions:	50-70
ion-dipole interactions:	12-50
dipole-dipole interactions:	1-12
hydrogen bonding, strong:	14-28
medium:	3-14
weak:	<3
cation - π :	1-20
π - π :	0-12
van der Waals:	<1
hydrophobic:	solvent dependent

New	New
anion - π :	?
C-H - π :	weak
C-H - anion:	weak
halogen bonding:	0 - 10

- Typically distance of interaction: 20% reduction of van der Waals radii between donor and acceptor

Table 1. Sum of van der Waals Radii between Halogen and Halogen Bond Acceptors in Å

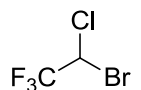
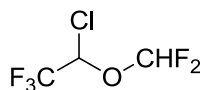
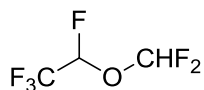
halogen	nitrogen	oxygen	sulfur
fluorine	3.02	2.99	3.27
chlorine	3.30	3.27	3.55
bromine	3.40	3.37	3.65
iodine	3.53	3.50	3.78

Rissanen, K. *Tubulous and Porous Materials via Halogen Bonding*. 2nd International Workshop on Halogen bonding. Milan, Italy, May, 7, 2010.
Narayan et al. *J. Chem. Inf. Model.* **2013**, 53, 2781.

Table 1. Distance dependencies of noncovalent interactions

Noncovalent interaction		Energy dependence on distance
Charge-charge		$1/r$
Charge-dipole		$1/r^2$
Dipole-dipole		$1/r^3$
Charge-induced dipole		$1/r^4$
Dipole-induced dipole		$1/r^5$
Dispersion		$1/r^6$
H-bond		Complicated $\sim 1/r^2$
Steric repulsion		$1/r^{12}$

- Halogen bonding can be competitive with hydrogen bonding
- This interaction has important implications for anesthetics

halothane
[anesthetic]isoflurane
[anesthetic]desflurane
[anesthetic]

Knowles, R.; Jacobsen, E. *PNAS* **2010**, *107*, 20678.
Paolo, T.; Sandorfy, C. *Can. J. Chem.* **1974**, *52*, 3612.

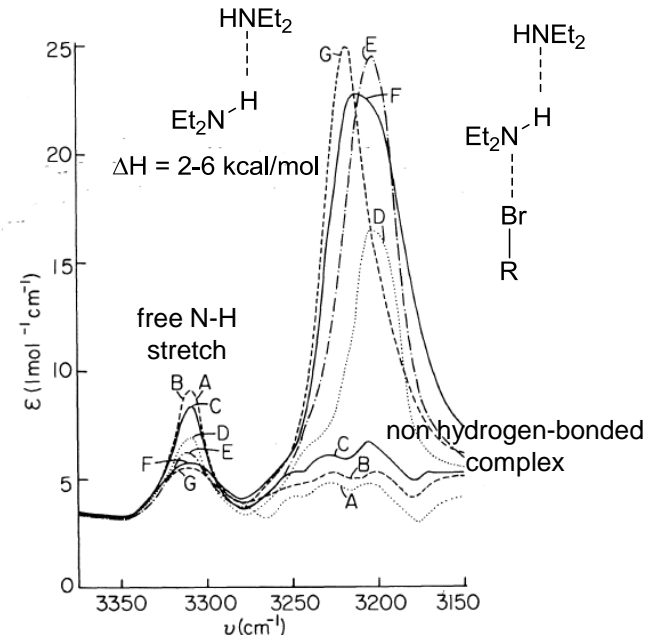
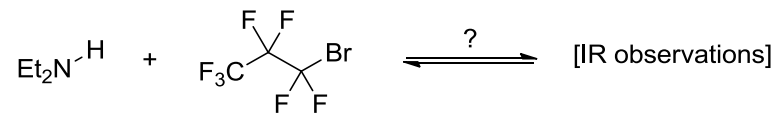
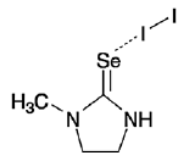


FIG. 1. The i.r. spectra of a 0.6 M solution of diethylamine in a 1:1 mixture of CCl_3F and methylcyclohexane (FM) at -190°C in the presence of variable amounts of $n\text{-C}_3\text{F}_7\text{Br}$. Concentration of $n\text{-C}_3\text{F}_7\text{Br}$: A, 1.04 M; B, 0.87 M; C, 0.62 M; D, 0.42 M; E, 0.32 M; F, 0.08 M; G, 0.

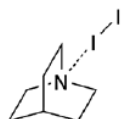
⇒ This is really cool! Halogens may not only increase the efficacy of drugs, but may be *responsible* for the mechanism of action!!!

Strength of halogen bonding: Contributing Factors

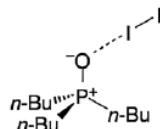
- Nature of the halogen bond acceptor (E_{HOMO} , HSABT, etc.)

Interactions of I_2 :

$K_a = 2.6 \times 10^6 \text{ M}^{-1}$
(UV-vis, CH_2Cl_2)
 $\Delta G = 37 \text{ kJ/mol}$
8.9 kcal/mol



$K_a = 1.6 \times 10^5 \text{ M}^{-1}$
(UV-vis, $n\text{-C}_7\text{H}_{16}$)
 $\Delta G = 30 \text{ kJ/mol}$
7.2 kcal/mol



$K_a = 561 \text{ M}^{-1}$
(UV-vis, C_6H_{12})
 $\Delta G = 16 \text{ kJ/mol}$
3.8 kcal/mol



$K_a = 1.4 \text{ M}^{-1}$
(UV-vis, C_6H_{12})
 $\Delta G = 0.8 \text{ kJ/mol}$
0.2 kcal/mol

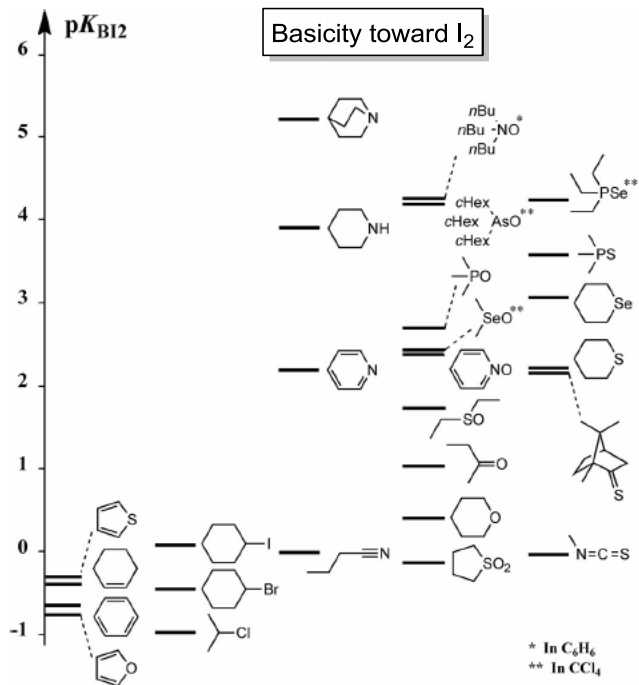
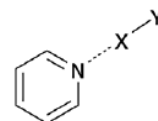
 ΔG (kcal/mol)-8.2
-6.8
-5.5
-4.1
-2.7
-1.4
0
1.4Terraneo et al. *Chem. Soc. Rev.* **2011**, *40*, 2267.Ghomari et al. *Chem. Eur. J.* **2011**, *17*, 10431.

Table 4. Examples of substituent effects increasing or decreasing diiodine basicity.

Substituted base	pK_{BI2}	Parent base	pK_{BI2}	Main substituent effect	$\delta pK_{\text{BI2}}^{(a)}$
4-Me ₂ NC ₅ H ₄ N	3.78	C ₅ H ₅ N	2.22	resonance	+1.56
Cl ₃ PS	-1.39	Me ₃ PS	3.60	field/inductive	-4.99
<i>n</i> BuNH ₂	3.00	NH ₃	1.76	polarisability	+1.24
<i>t</i> Bu ₂ (<i>n</i> Pr)N	1.11	NMe ₃	3.88	steric	-2.77

- Electrostatic potential of σ hole on halogen bond donor

Inorganic XB donors:



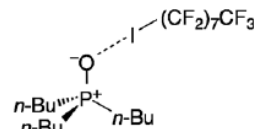
X = I, Y = Cl
 $K_a = 2.3 \times 10^6 \text{ M}^{-1}$
(UV-vis, CCl_4)
 $\Delta G = 31 \text{ kJ/mol}$
7.4 kcal/mol

X = I, Y = Br
 $K_a = 1.2 \times 10^5 \text{ M}^{-1}$
(UV-vis, CCl_4)
 $\Delta G = 24 \text{ kJ/mol}$
5.7 kcal/mol

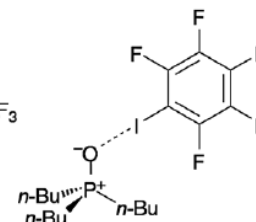
X = I, Y = I
 $K_a = 77 \text{ M}^{-1}$
(UV-vis, CCl_4)
 $\Delta G = 11 \text{ kJ/mol}$
2.6 kcal/mol

X = Br, Y = Br
 $K_a = 9.8 \text{ M}^{-1}$
(UV-vis, CCl_4)
 $\Delta G = 5.7 \text{ kJ/mol}$
1.4 kcal/mol

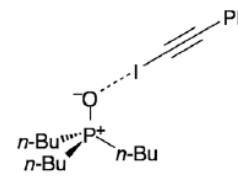
Organic XB donors:



$K_a = 18 \text{ M}^{-1}$
(NMR, C_6H_{12})
 $\Delta G = 7.2 \text{ kJ/mol}$
1.7 kcal/mol

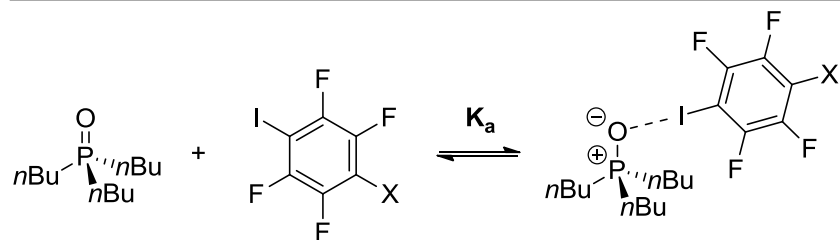


$K_a = 12 \text{ M}^{-1}$
(NMR, C_6H_{12})
 $\Delta G = 6.2 \text{ kJ/mol}$
1.5 kcal/mol



$K_a = 2.4 \text{ M}^{-1}$
(IR, C_6H_6)
 $\Delta G = 2.2 \text{ kJ/mol}$
0.5 kcal/mol

Ghomari et al. *Chem. Eur. J.* **2011**, *17*, 10431
Terraneo et al. *Chem. Soc. Rev.* **2011**, *40*, 2267.
Taylor et al. *J. Am. Chem. Soc.* **2010**, *132*, 1646.



X	K_a (M^{-1})	ΔG (kcal/mol)
F	12	1.47
$\xi-C\equiv C-Ph$	5.6	1.02
Ph	3.9	0.81
OMe	3.3	0.71
$N(CH_2)_5$	1.3	0.16

- If you need to find a complexation constant, check out the supporting info of *Chem. Eur. J.* **2011**, *17*, 10431. It has ~800 complexation constants for I_2 with ~800 bases:

Organic Halogen-bond donors : $I(CF_2)_5CF_3$ in CCl_4 and C_6H_6 at 25 °C					
Base	pK_{BI_2}	Solvent	$pK_{BI(CF_2)_5CF_3}$	Solvent	$pK_{BI(CF_2)_5CF_3}$
Tri-n-Butylphosphane oxide	2.75	CCl_4	0.6	C_6H_6	0.7
Quinuclidine	5.22	CCl_4	1.2	C_6H_6	1.6
Diazabicyclooctane	4.69	CCl_4	0.7	C_6H_6	1.2
Piperidine	3.85	CCl_4	0.7	C_6H_6	0.9
n-Hexylamine	3.00	CCl_4	-0.2	C_6H_6	0.3
Diethylamine	3.73	CCl_4	0.1	C_6H_6	0.6
Triethylamine	3.67	CCl_4	0.3	C_6H_6	0.3
Pyridine	2.22	CCl_4	-0.1	C_6H_6	0.0

Ghomari et al. *Chem. Eur. J.* **2011**, *17*, 10431
Taylor et al. *J. Am. Chem. Soc.* **2010**, *132*, 1646.

- Denticity of halogen bond donors

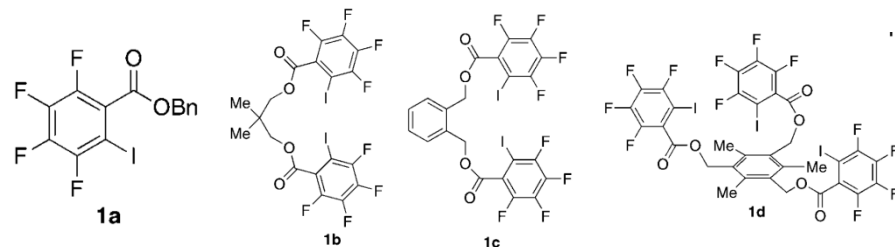
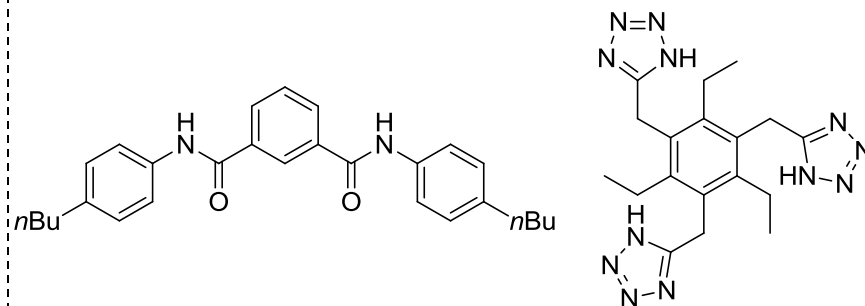


Table 1: Binding constants of **1a-d** with $nBu_4N^+X^-$ (acetone, 295 K).

Entry	Halogen-bond donor	X^-	K_a [M^{-1}] ^[a]
1	1a	Cl^-	70
2	1b	Cl^-	1.1×10^3
3	1c	Cl^-	1.8×10^3
4	1d	Cl^-	1.9×10^4

hydrogen bond donor comparisons?



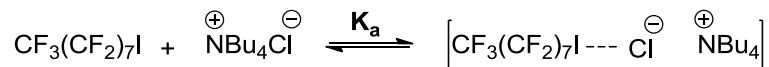
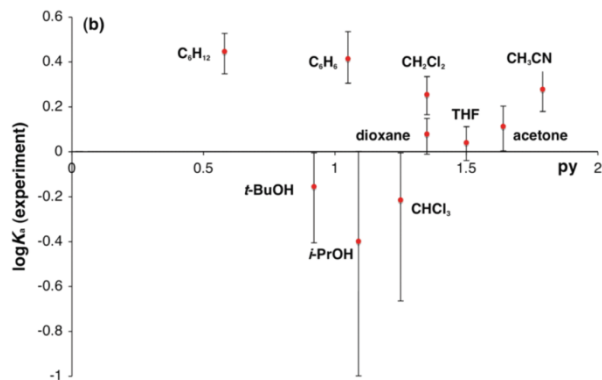
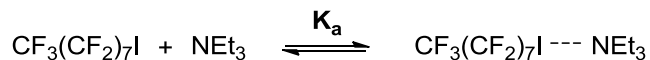
$K_a(Cl^-, DCM) = 6.1 \times 10^4 M^{-1}$
 $\Delta G = -6.4$ kcal/mol

$K_a(Cl^-, CH_3CN) = 1.1 \times 10^7 M^{-1}$
 $K_a(Cl^-, CHCl_3/MeOH) = 1.9 \times 10^3 M^{-1}$

Taylor et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 1674.
Crabtree et al. *J. Am. Chem. Soc.* **1997**, *119*, 2325.
Hof et al. *Org. Lett.* **2008**, *10*, 4653.

- Solvent Effects

"It just depends." -Bob Grubbs" -Bob Waymouth

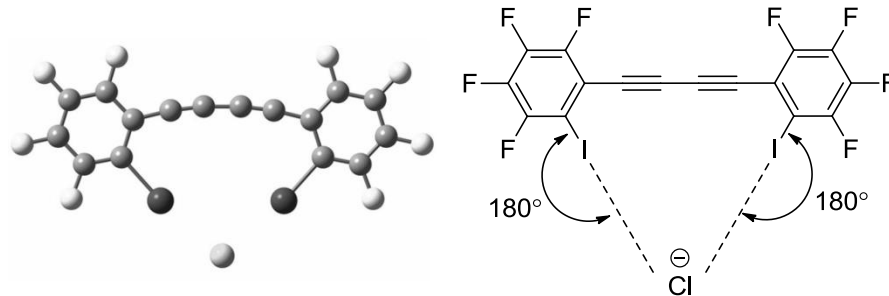


XB donor	Solvent	K_a [M ⁻¹] ^[a]
C ₈ F ₁₇ I	acetone	2.2×10^3
C ₈ F ₁₇ I	acetonitrile	1.3×10^2
C ₈ F ₁₇ I	dimethylsulfoxide	3.2×10^1
C ₈ F ₁₇ I	dichloromethane	3.1×10^1

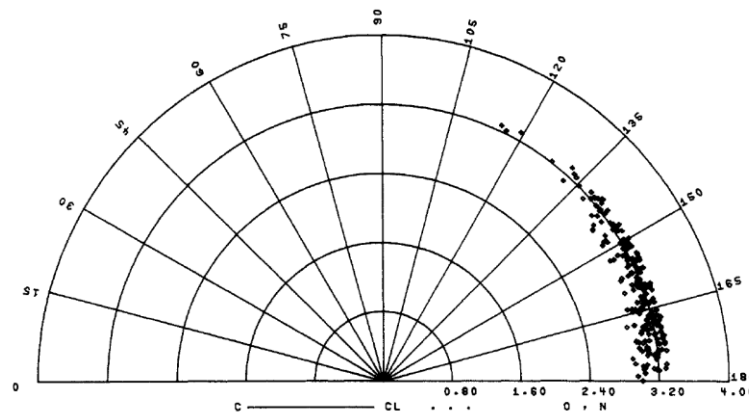
Taylor et al. *Chem. Eur. J.* **2013**, *19*, 2050.
Taylor et al. *J. Am. Chem. Soc.* **2010**, *132*, 1646.

Directionality of halogen bonding

- Halogen bonding is **highly directional**, rigorously preferring a 180° geometry between halogen bond donor and acceptor

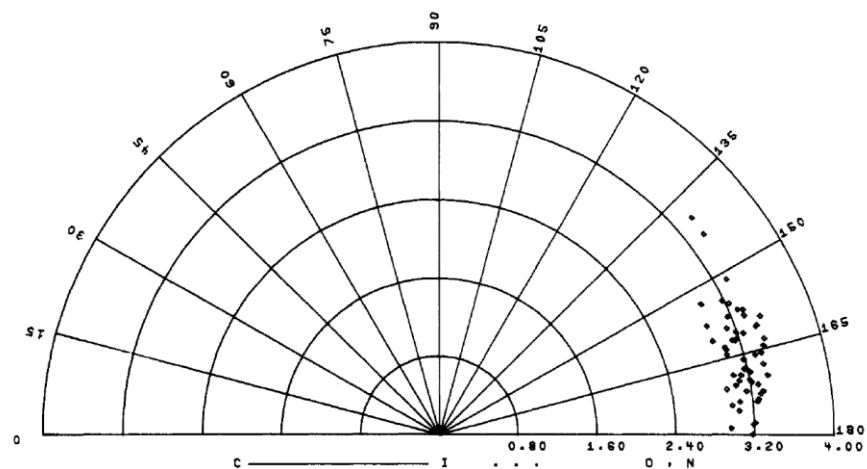
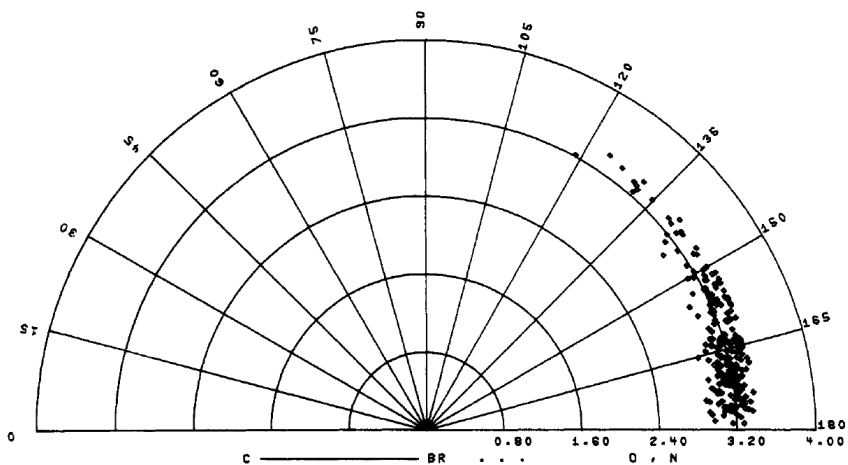


- Complex interactions in binding pockets can cause deviation from this linear geometry



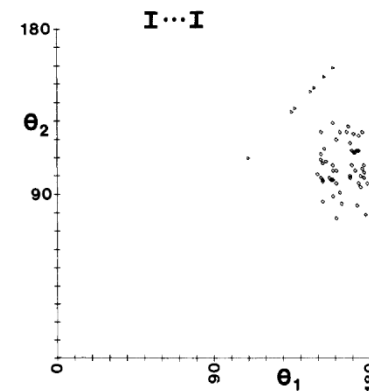
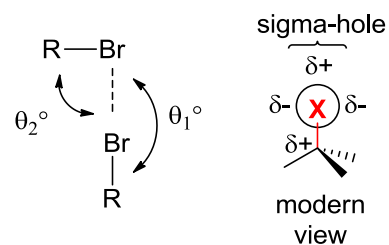
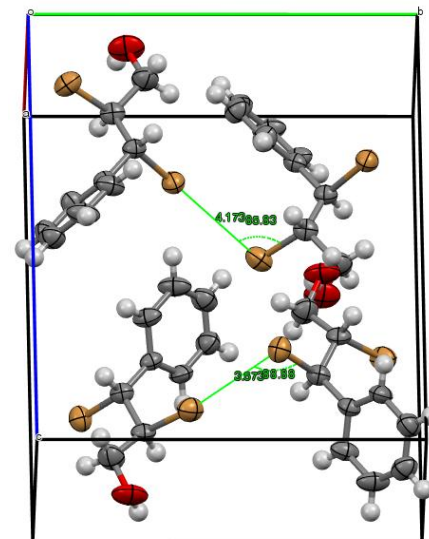
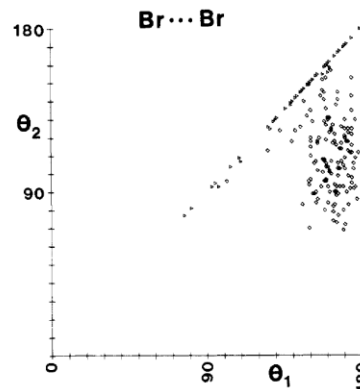
Murray-Rust et al. *J. Am. Chem. Soc.* **1986**, *108*, 4308.
Taylor et al. *Chem. Eur. J.* **2013**, *19*, 2050.

Directionality of halogen bonding



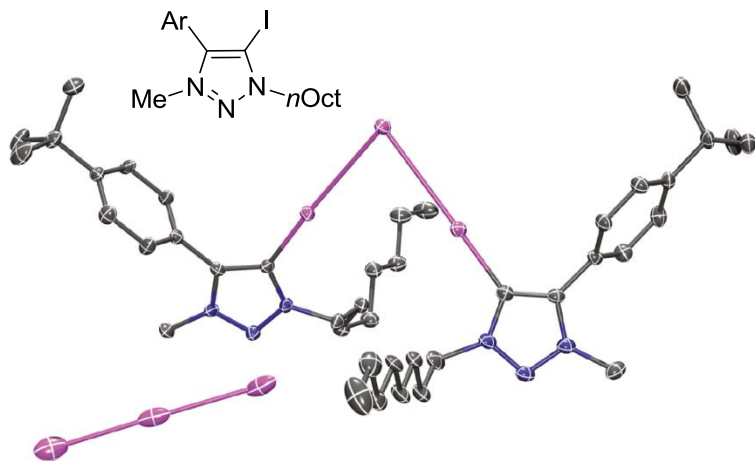
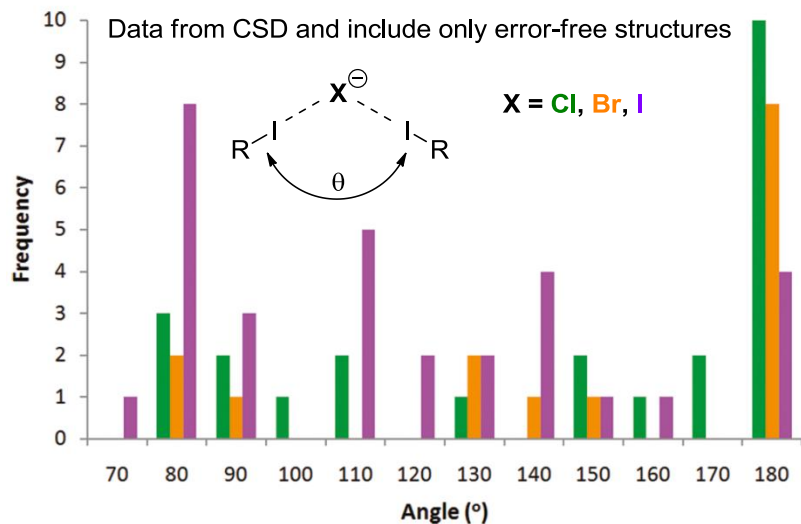
Murray-Rust et al. *J. Am. Chem. Soc.* **1986**, *108*, 4308.

- Halogen bonding can even occur with Lewis bases as weak as neutral halogens.



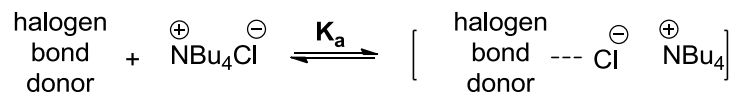
Murray-Rust et al. *J. Am. Chem. Soc.* **1986**, *108*, 4308.
Burns-lab-best-lab JACS+++, #1

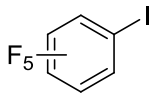
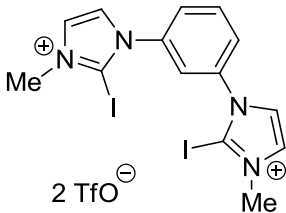
- Directionality in the case of bidentate halogen bond donors



Beer et al. *Cryst. Growth Des.* **2011**, *11*, 4565.

Enthalpy and entropy of halogen bonding

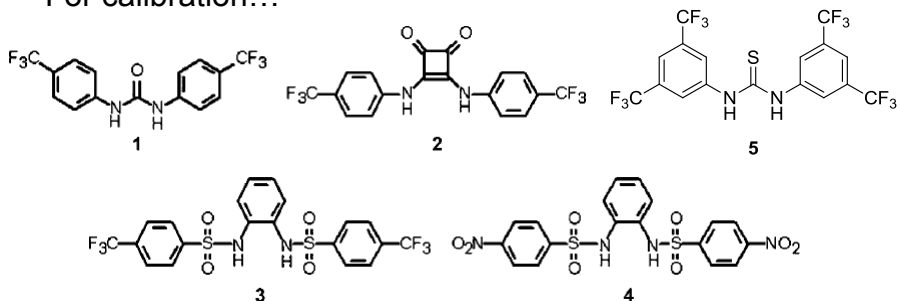


Donor	ΔG (kcal/mol)	ΔH (kcal/mol)	$T\Delta S$ (kcal/molK)
	-2.9	-2.7	0.5
$\text{CF}_3(\text{CF}_2)_7\text{I}$	-4.5	-3.0	1.4
		$\Delta\Delta H$	$T\Delta\Delta S$
		-0.3 kcal/mol	0.9 kcal/mol
	-7.9	-3.2	4.7
2 TfO ⁻			

- Binding event is entropically favored
- Favorability attributed to desolvation of donor
- Entropy can be dominant factor in ΔG
- Entropic favorability is not easily predicted

Taylor et al. *Chem. Eur. J.* **2013**, *19*, 2050.
 Huber et al. *J. Am. Chem. Soc.* **2012**, *134*, 8507.
 Schmidtchen et al. *Chem. Eur. J.* **2011**, *17*, 5972.

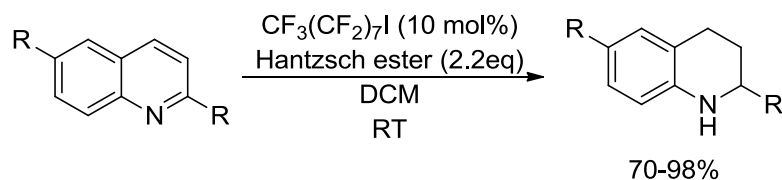
- For calibration...

Some Data of Thermodynamic Nature (in CH₃CN)

Anion	Donor	ΔG (kcal/mol)	ΔH (kcal/mol)	$T\Delta S$ (kcal/molK)
Cl ⁻	1	-5.5	-3.95	2.3
	2	-8.0	-5.76	3.5
	3	-4.8	-3.49	1.1
	4	-5.1	-3.70	1.9
Br ⁻	5	-4.4	-1.63	2.8

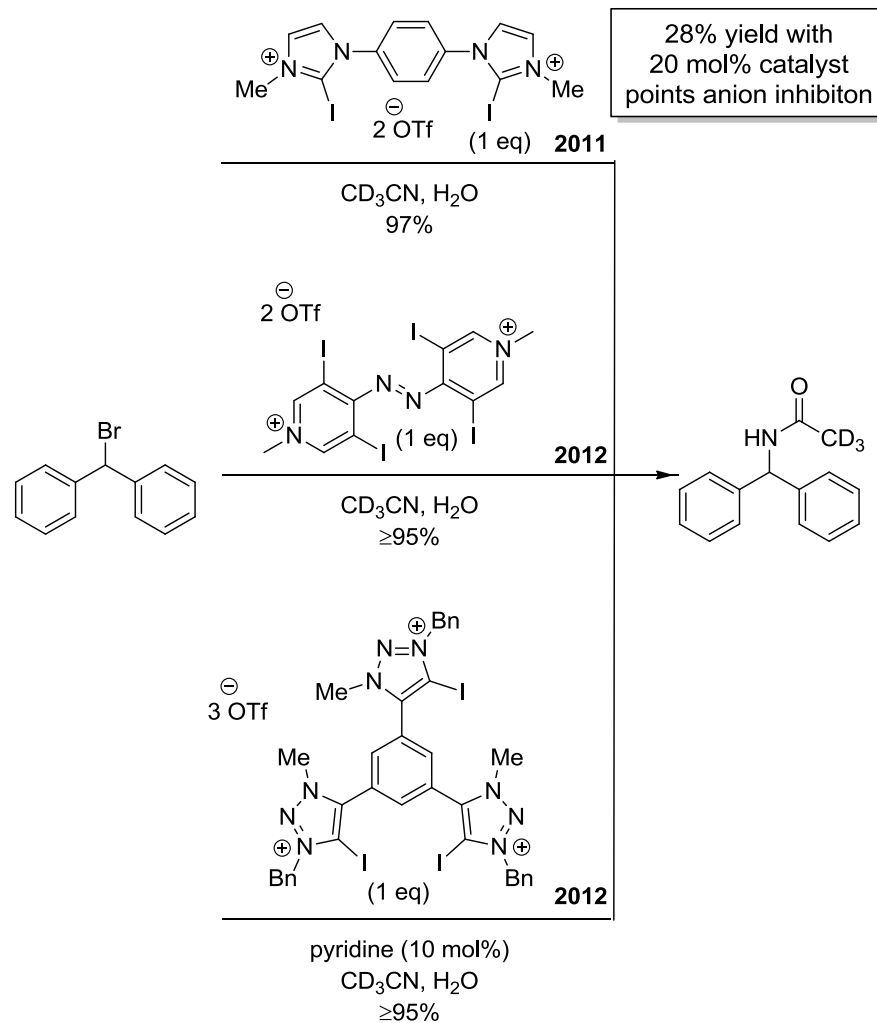
Halogen bond catalysis

- Bolm (2008)



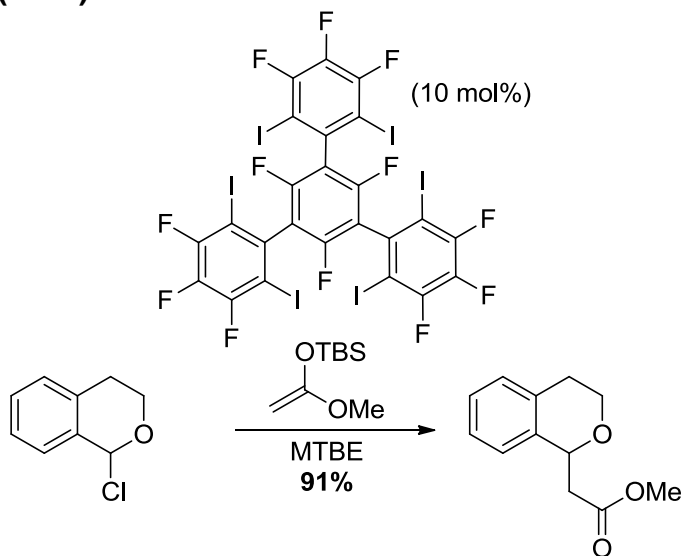
Schmidtchen et al. *Chem. Eur. J.* **2011**, *17*, 5972.
Bolm, C. *Synlett* **2008**, *6*, 900.

- Huber (2011 – 2012)

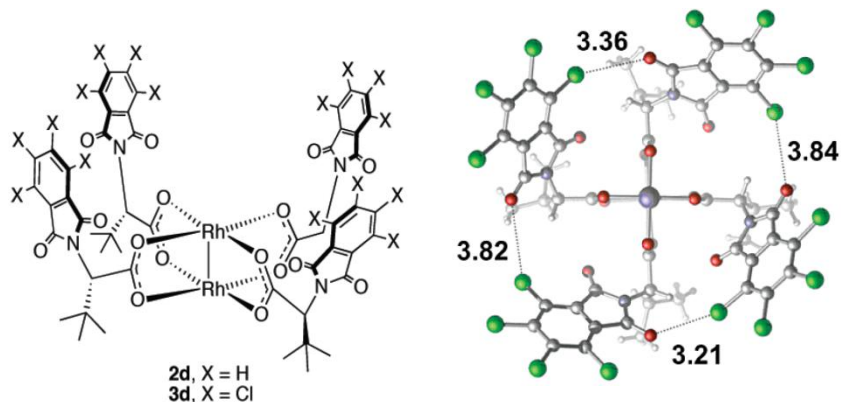


Huber et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 7187.
Huber et al. *Chem. Eur. J.* **2012**, *18*, 1306.
Huber et al. *Chem. Commun.* **2012**, *48*, 9299.

• Huber (2013)



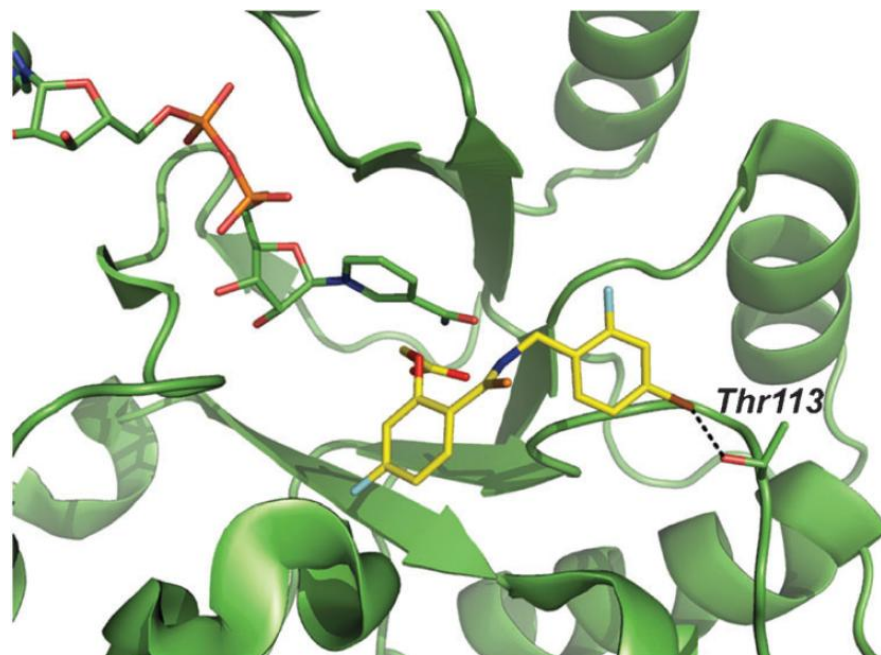
• Charette (2009)



Huber, *Angew. Chem. Int. Ed.* **2013**, *52*, 7028.
Charette et al. *J. Am. Chem. Soc.* **2009**, *131*, 16383.

¡Biology!

- Disclaimer: I am not a biologist. The goal of this section is to distract you with pretty pictures so as to make you think I am one.
- IDD594 (an aldose reductase inhibitor)
 - Aldose reductase reduces glucose to sorbitol, causing accumulation of excess sorbitol from diabetic hyperglycemia
 - Br – O (2.97 Å, 152.8°) [Normal: 3.37 Å, 12%]



Terraneo et al. *Chem. Soc. Rev.* **2011**, *40*, 2267.

- Halothane (anesthetic; a WHO essential medicine)
 - Ferritin is a protein that releases iron to synthesize heme and other iron cofactors
 - (*S*)-halothane binds twice as strongly as (*R*)
 - Br – O (3.10 Å, 144.9°) [Normal: 3.37 Å, 8%]

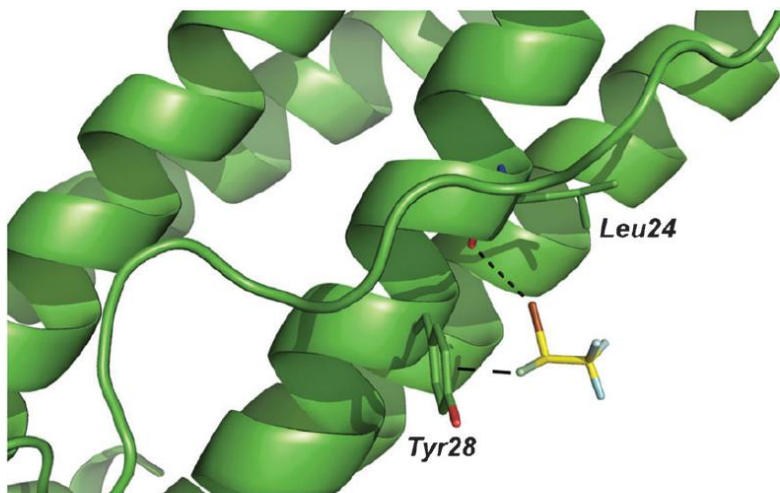


Fig. 6 Halothane makes two simultaneous halogen bonds with ferritin. The bromine atom (depicted in brown) interacts with the main chain oxygen of Leu24, while the chlorine atom (shown in pale green) forms a halogen- π contact with the ring of Tyr28 (PDB code: 1XZ1).

Terraneo et al. *Chem. Soc. Rev.* **2011**, *40*, 2267.

- Triclosan (microbiocide commonly in toothpaste and soap)
 - Inhibits enoyl-acyl carrier protein reductase (enzyme involved in fatty acid chain growth)
 - Cl – O (3.08 Å, 166.2°) [Normal: 3.27 Å, 6%]

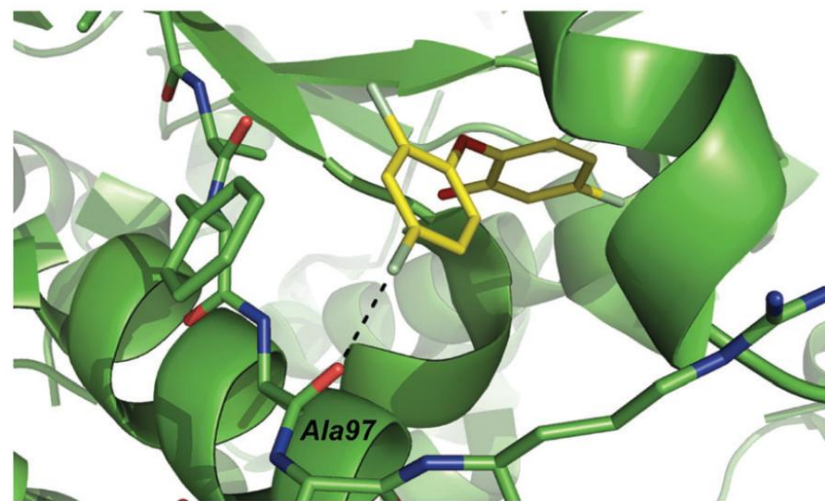
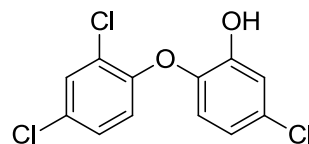


Fig. 8 The Cl(15) atom of triclosan (depicted in pale green) forms a halogen bond with the carbonyl oxygen of the Ala97 residue of the enoyl-acyl carrier protein reductase from *Bacillus anthracis* (PDB code: 2QIO).



Terraneo et al. *Chem. Soc. Rev.* **2011**, *40*, 2267.

- hcatL inhibitors (catabolism of collagen and elastin)

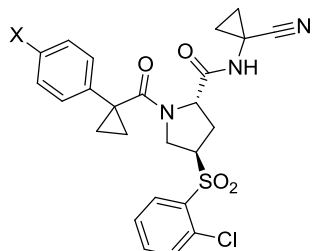


Table 4 Geometric parameters in the crystal structures of analogues **20–25** with hcatL

Compound	X	Angle (°)		Distance (Å)	
		C–X···O	X···O–C	X···O	IC ₅₀ (μM)
20	Me	157	156	3.6	0.13
21	CF ₃	169	150	3.6	0.095
22	F	145	165	4.5	0.34
23	Cl	171	147	3.0	0.022
24	Br	176	146	3.1	0.012
25	I	175	145	3.1	0.0065

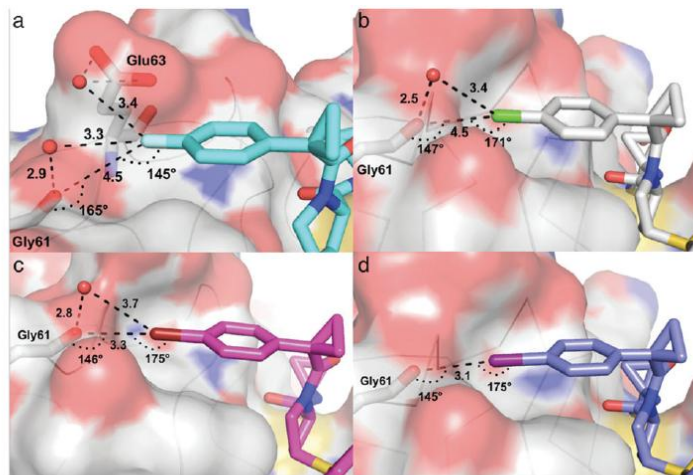


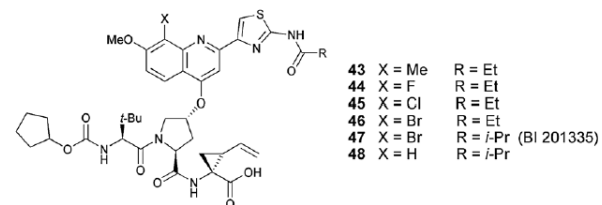
Fig. 14 Inhibitor binding to hcatL showing relevant angles and distances for (a) **22**, X = F; (b) **23**, X = Cl; (c) **24**, X = Br; (d) **25**, X = I.

Taylor et al. *Chem. Soc. Rev.* **2013**, *42*, 1667.

- BI 201335 (NS3-NS4A protease inhibitor of hepatitis C)

- In phase III clinic trials for hepatitis C infection
- Br – O (3.0 Å, 169°) [Normal: 3.27 Å, 11%]

Table 5 Structure–activity relationships for hepatitis virus C protease inhibitors **43–48**



43	X = Me	R = Et
44	X = F	R = Et
45	X = Cl	R = Et
46	X = Br	R = Et
47	X = Br	R = <i>i</i> -Pr (BI 201335)
48	X = H	R = <i>i</i> -Pr

Compound	X	IC ₅₀ ^a (nM)	EC ₅₀ ^b (nM)	K _i ^c (nM)
43	Me	10 ± 2	17 ± 8	—
44	F	7 ± 2	36 ± 10	—
45	Cl	7 ± 2	11 ± 2	—
46	Br	7 ± 2	5 ± 2	—
47	Br	3 ± 1	3 ± 1	0.53 ± 0.05
48	H	—	—	1.89 ± 0.06

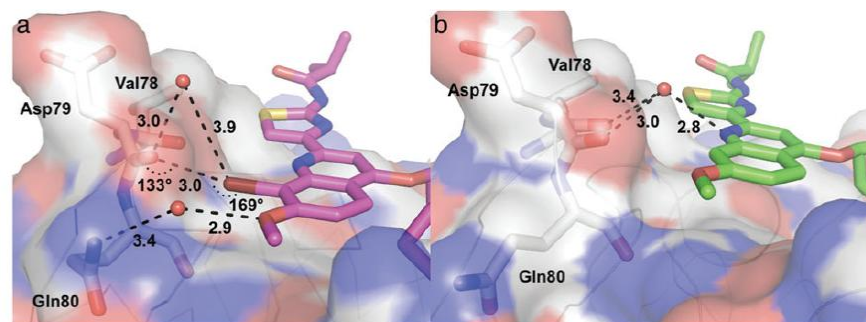


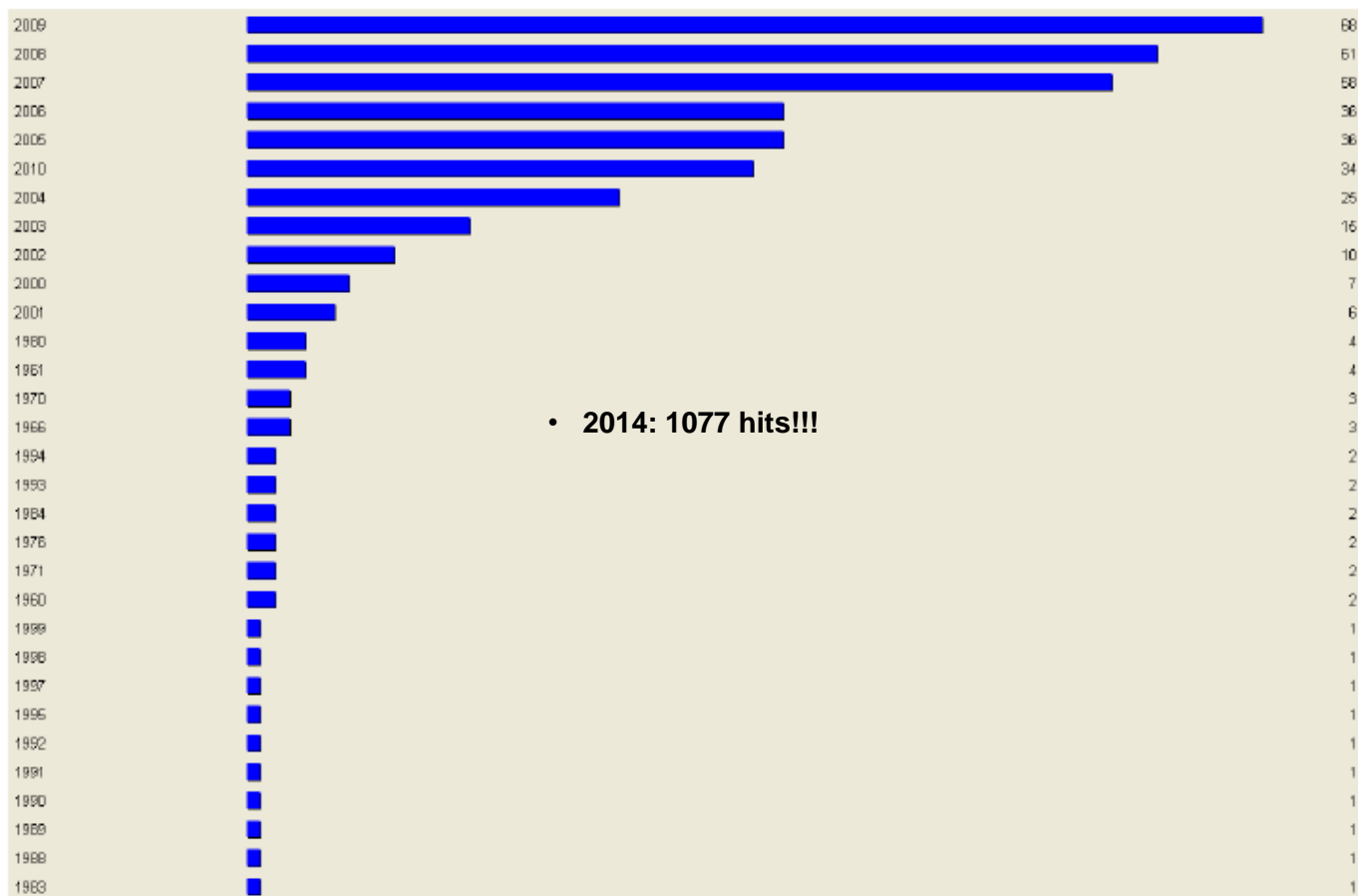
Fig. 15 Inhibitor binding to NS3-NS4A protease for (a) **47** (BI 201335) and (b) **48** (desbromo analog), showing quinoline portion only. Distances, angles and select residues are labelled.

Taylor et al. *Chem. Soc. Rev.* **2013**, *42*, 1667.

What can halogen bonding bring to the table?

- The field is blowing up but progress, especially in chemical catalysis, lags behind.

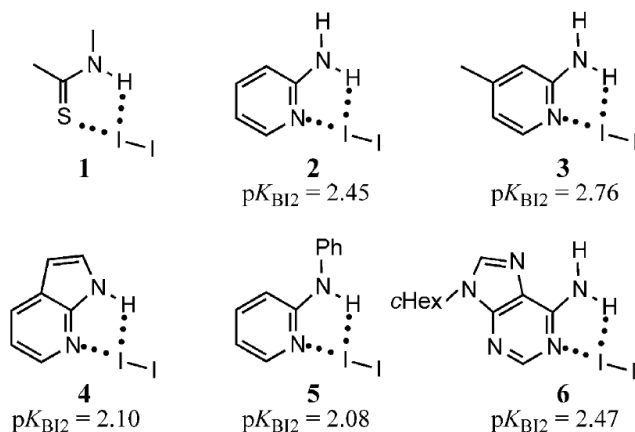
Hits 1983 - 2009 (Sci Finder, CAS) for “Halogen bonding”



Extensions & some considerations

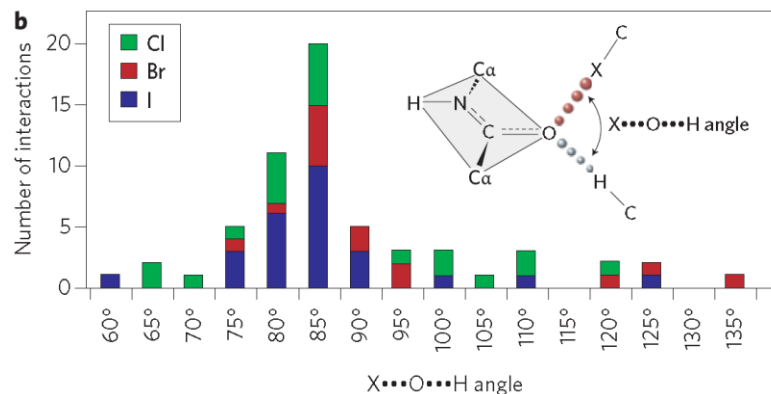
- What can halogen bonds do that hydrogen bonds cannot?
 - specificity in anion binding
 - stability to strong base (asymmetric ketone additions?)
 - biological stability
 - macrostructure of materials
 - amphoteric behavior

Tandem hydrogen bonding can provide 1.2 kcal/mol of additional stabilization



Scheme 2. Hydrogen-bond-assisted halogen bonds.

- Halogens in medicine
 - The protein databank (2008): 1000 protein structures contained halogenated ligands, 154 exhibited halogen bonding
 - so far, halogen bonding interactions have been realized “after-the-fact” in crystal structures, and often not deliberately used as design elements
 - orthogonal point of contact in drugs



- Can halogens do things that other structural features could not (anion transport across lipid membranes, aesthetic properties, etc?)
 - Not only binding affinity, but activity of a drug
- What role can enantioenriched halogenated drugs play?

Extensions & some considerations

- What role can enantioenriched halogenated drugs play?

