Halogen Bonding

Gabrielle Lovett
MacMillan Group Meeting
June 6, 2019
Introduction to the Halogen Bond

**Traditional View**

Electronegative halogens possess higher $e^-$ density, e.g., CF$_4$.

**σ-Hole View**

Region of lower $e^-$ density along the $R$–$X$ axis, e.g., CF$_3$Br.

Outline

- Introduction to Halogen Bonding
  - definition
  - origin of halogen bonding
    - electrostatics
    - charge transfer
    - dispersion and polarization

- Applications
  - crystal engineering and supramolecular chemistry
  - halogen bonds in biological settings
  - medicinal chemistry and rational drug design
  - catalysis
Halogen Bonding Before “The Halogen Bond”

- Reports of I$_2$ complexed with Lewis bases as early as 1814:
  
  \[ \text{I} \cdots \text{I} \cdots \text{NH}_3 \]

- Early 20\textsuperscript{th} century: I$_2$ in many organic solvents turns different colors forming DA complexes

- X-ray crystallographic studies in the 1950’s identifying “halogen-atom bridges”

  \[ \text{Br} \cdots \text{Br} \cdots \text{O(CH}_2\text{CH}_2)_2\text{O} \]

- Intermolecular distances shorter than sum of van der Waals radii

- Highly directional interaction: bond angle close to 180\degree

- Early 2000’s: development of concept of “\sigma\text{-holes}” to explain observed phenomena

Kleinberg, J.; Davidson, A. W.; Chem. Rev. 1948, 42, 601.
Definition of Halogen Bonding

“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” - IUPAC, 2013

**electrophilic region**

\[
R^+X \cdots Y
\]

**nucleophilic region**

X: halogen \quad Y: lone pair or \(\pi\)-system

**what is the origin of this seemingly counterintuitive interaction?**

**electrostatic component: \(\sigma\)-hole**

\[
R^+X \cdots Y
\]

**charge-transfer component**

\[
R^- [XY]^+
\]

R–X: “halogen-bond donor”

Y: “halogen-bond acceptor”
Electrostatic Component: the $\sigma$-Hole

The lobe of $p_z$ orbital opposite the C–X $\sigma$ bond becomes depopulated, leading to electron deficient hole

$\sigma$-hole increases with increasing X-atom polarizability ($F < Cl < Br < I$)

The size and magnitude of the $\sigma$-hole (generally) correlate with the strength of the halogen bond

Halogen Bonding and the σ-Hole

**tunability:** varying strength of XB donor and acceptor

- **XB donor ability of X atom**
  - I > Br > Cl > F

- **hybridization of C of the C–X bond**
  - C(sp) > C(sp²) > C(sp³)

- **EWG on atom the XB donor is bound to**
  - e.g., –CN, –NO₂, protonated heteroarene

**highly directional:** Y enters along the σ-bond axis (σ-hole)

when Y = π-system, the symmetry axis of the π-system lies along σ-bond axis

The Charge Transfer Component

XB has long been attributed to charge-transfer, motivated by UV-Vis studies.

XB directionality attributed to donation into $\sigma^*$ of the R–X bond: $n \rightarrow \sigma^*$

Experimental and computational data suggest the important role of CT in XB.

- lengthening of C–X bond
- HOMO/LUMO overlap (not always site of $\sigma$-hole)

Mulliken, R. S. J. Am. Chem. Soc. 1950, 72, 600.
Dispersion and Polarization

calculated electrostatic potential: CH$_3$Cl

purple indicates *negative* potential

no σ-hole for CH$_3$Cl!

but halogen bonded complexes with CH$_3$Cl with formaldehyde have been predicted...

*as CH$_3$Cl interacts with formaldehyde*

*electron densities of each are polarized*

now σ-hole for CH$_3$Cl is predicted

important to recognize dispersion and polarization for an accurate interpretation


XB in Crystal Engineering and Supramolecular Chemistry

layered crystal structure of solid Cl₂

“windmill” self-assembled C₆Br₆

anion organic networks
molecular recognition
materials science
chiral resolution

For review on this area: Chem. Rev. 2015, 115, 7118.
Naturally Occurring Bioactive XB Systems

Naturally Occurring XB Donors

Thyroid Hormone T3

Thyroid Hormone T4

numerous I⋯O contacts play important role in thyroid hormone recognition

XB formed between T4 and transporter protein transthyretin (TTR)

Recognition of T3 by human thyroid hormone receptor

**Early Examples of XB in Biological Systems**

**IDD594**

human aldose reductase (AR) inhibitor

- replacing Br with Cl led to decrease in IC$_{50}$ from 500 to 1300 nM
- XB promoted specificity over aldehyde reductase (where Thr113 is a bulkier Tyr)

**DNA Holliday Junction: HB vs. XB**

thymine  →  5-bromouracil

XB is 5 kcal/mol stronger!


**Halogen and Hydrogen Bonds in Biological Settings**

<table>
<thead>
<tr>
<th>H–Bond and X–Bond Acceptors</th>
<th>Proteins</th>
<th>Nucleic Acids</th>
<th>Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>peptide bond (O/N/π)</td>
<td>base (O)</td>
<td>(O/N/S)</td>
<td></td>
</tr>
<tr>
<td>side chains (O/O⁻,N/S/π)</td>
<td>phosphoribose (O/O⁻)</td>
<td>X (F, Cl, Br, I)</td>
<td></td>
</tr>
<tr>
<td>solvent (O)</td>
<td>solvent (O)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H– and X– bond donors include biomolecules as well as synthetic molecules (e.g., pharmaceuticals)

**chemical complexity of biological systems leads to diverse set of interactions (less geometrically/structurally defined)**

**Identifying XB in biological settings**

- X–LB distance ≤ sum of van der Waal radii
- angle of approach > 120°

> 700 halogen–protein interactions found


Halogen Bonding in the Protein Data Bank

no significant attractive forces beyond 40° deviation
larger deviations negatively impact I more than Br or Cl

Effects of Angle and Distance on the XB Strength

Trends for $I \cdot O$ contacts between Ar–I and backbone C=O

White space indicates areas of repulsive interactions

Plots to be used as rough guidelines for scaffold, substitution pattern, polarization effects, all may affect binding in the protein.

A Closer Look at I–O Interactions in the PDB

IC$_{50}$ = 15 nM in C26 colon carcinoma cells

intramolecular H-bond stabilizes bioactive conformation
A Closer Look at I–O Interactions in the PDB


highly potent inhibitor: IC$_{50}$ = 2 nM

network of H-bond, π-π, and halogen bond

HIV1-reverse transcriptase inhibitor

**A Closer Look at Interactions with Iodine in the PDB**


**Finding false positive and redundancies**

*ligand facing the shielded region of S*

*not consistent with a true XB*

*indicates multiple signals where methionine bound to identical ligand*
Interactions with Br and Cl in the PDB

Shinada, N. K.; de Brevern, A. G.; Schmidtke, P. J. Med. Chem. 2019, Just Accepted
Approved Drugs Containing Iodine and Bromine

launched drugs containing iodine: ~ 1%

Levothyroxine: thyroid hormone deficiency
Idoxuridine: anti-herpesvirus antiviral
Amiodarone: antiarrhythmic medication

launched drugs containing bromine: ~ 1.5%

Macitentan: pulmonary arterial hypertension
Bromazepam: anti-anxiety agent
Bromfenac: NSAID

~15% of drugs contain at least one chlorine atom

Halogen-Water-Hydrogen Bridges

X atom can interact with both $e^-$ rich and poor sites

H$_2$O for simultaneous XB with diclofenac and HB with cytochrome P$_{450}$ complex

H$_2$O for simultaneous XB with diclofenac and HB with lactoferrin

$XWH$ bridges difficult to exploit in rational design, but importance of XB in stabilizing conformations

Halogen Bonding and Triclosan

FDA in 2017 banned triclosan from “consumer antiseptic washes”

Triclosan interactions with enoyl-acyl protein reductase (ENR)

- XB with C=O of Glyc204 of ENR from *Plasmodium berghei*
- XB with C=O of Ala97 of ENR from *Bacillus anthracis*
- With ENR from *Staphylococcus aureus* with NADPH and triclosan

XB is 3.25 Å and 162.4°
XB is 3.08 Å and 166.2°
2 simultaneous H-bond at 90°

Can exploitation of halogen bonds be used in rational drug design?
Current Challenges for Rational Design of XB

Halogenes in Pharmaceuticals

- Many halogens have been installed in drugs through trial and error, rather than by design
  - increase membrane permeability
  - fill spaces in binding pockets

computational modelling to exploit XB?

Goal: high-throughput virtual screening

- density functional theory (DFT)
  - inadequate description of dispersion forces
- force field approach (e.g., docking)
  - fail to capture anisotropic nature of XB

- semi-empirical methods:
  - often fail to accurately predict XB
- high-level QM calculations
  - accurate, but computationally costly

p53 is inactivated in many cancers (mutation or pathway perturbation)

~1/3 of mutations slightly lower melting temp. → protein unfolds at body temp.

Goal: bind molecules to protein to stabilize the folded state

mutant Y220C
“cancer hotspot” (75,000 cases/yr)

halogen enriched fragment library (HEFLibs)

quantum chemical calculations

exploit XB for lead discovery
calculations suggest potential for strong I-O contact with L145

promising lead via thermal shift assay and NMR

$K_D = 184 \, \mu M$

Rational Design in Drug Discovery

Goals:
extend ligand into subsite 1 and 2
increase melting temperature
decrease $K_D$

---

![Rational Design in Drug Discovery](image)

Goals:
extend ligand into subsite 1 and 2
increase melting temperature
decrease $K_D$

---

$K_D = 184 \mu M$
$\Delta T_m (K) = 0.55$

$K_D = 104 \mu M$
$\Delta T_m (K) = 0.97$

$K_D = 87 \mu M$
$\Delta T_m (K) = 1.10$

Rational Design in Drug Discovery

\[ K_D = 247 \mu M \]
\[ \Delta T_m (K) = 0.31 \]

\[ K_D = 247 \mu M \]
\[ \Delta T_m (K) = 0.31 \]

\[ K_D = 1040 \mu M \]
\[ \Delta T_m (K) = 0.03 \]

\[ K_D = 4900 \mu M \]
\[ \Delta T_m (K) = -0.05 \]

decreasing strength of halogen bond

up to 20-fold loss in binding affinity

Rational Design in Drug Discovery

\[ K_D = 104 \ \mu M \]
\[ \Delta T_m (K) = 0.97 \]

extend into subsite 2 using I not involved in XB

\[ K_D = 9.7 \ \mu M \]
\[ \Delta T_m (K) = 3.61 \]

similar properties as above

Rational Design in Drug Discovery

testing the apoptotic effects in human gastric cancer cell lines NUGC-3

Rational Design in Drug Discovery

testing the apoptotic effects in human gastric cancer cell lines NUGC-3

dose-dependent onset of apoptosis in more strongly bound cases

both molecules showed cytotoxic effects at 50 and 100 µM

Halogenation of Drugs: Pros and Cons

prevalence of halogens in pharmaceuticals

Pros for halogen installation:
- improve selectivity and affinity (XB)
- increase ADME properties (F/Cl)
- increase metabolic stability (F/Cl)

Cons for halogen installation:
- synthesis of drugs with Ar–Br/I
- addition of MW, lipophilicity with “heavy” atoms
- metabolic and toxicity issues (Ar-I)

σ-Hole Interactions Beyond the Halogens

σ-hole interactions similarly found in chalcogen and pnicogen series

Calculated electrostatic potential of SCl$_2$ (2 σ-holes)

Calculated electrostatic potential of As(CN)$_3$ (3 σ-holes)

Similar trends for magnitude of the σ-hole as XB:

- less electronegative
- more polarizable
- larger σ-holes

As with F, unlikely to see σ-holes on C, N, or O

Halogen Bonding and Catalysis

“the lipophilic hydrogen bond”

substrate activation
halide binding

examples of bidentate XB donor catalysts

Halogen Bonding and Catalysis

\[ \text{Br} \quad \xrightarrow{\text{XB catalyst}} \quad \text{XB catalyst} \quad \xrightarrow{\text{CD}_3\text{Me, H}_2\text{O}} \quad \text{HN} \cdot \text{CD}_3 \]

**Catalyst**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>XB cat</td>
<td>97%</td>
</tr>
<tr>
<td>none</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

Halogen Bonding and Catalysis

Substrate activation via halogen bond donor catalyst

XB Catalysts for Lewis Acid Activation

**Aza-Diels-Alder**

![Chemical structure](image1)

**Org. Lett. 2015, 17, 318.**

**Quinoline and Imine Reduction**

![Chemical structure](image2)

**Org. Lett. 2014, 16, 3244.**

**C–C bond formation with neutral XB cat**

![Chemical structure](image3)

**J. Am. Chem. Soc. 2015, 137, 12110.**
**Intramolecular Hydrogen Bonding and Asymmetric Catalysis**

- **Equation:**
  
  PMP-\(\text{NO}_2\)-PMP + \(\text{Ph}\)-allyl \(\xrightarrow{\text{cat (0.1 mol\%)} \Es{}_{2}O, -50 ^\circ C}\) \(\xrightarrow{\text{80\% yield}}\)

  - **93\% e.e., >20:1 d.r.**

- **Images:**
  - **XB leads to rigid “all-up” structure**
  - **H in place of Cl on catalyst**
    - low e.e.’s (<5%)

- **Cl⋯O XB induces the catalyst conformation assumed to be responsible for asymmetric induction**