HALOGEN BONDING CATALYSIS

Reported by Nicholas Angello   October 15, 2019

The σ-Hole

Intrinsic to covalent bonding is a polarization of electron density between the bonding atoms. This polarization imparts a degree of *p* character on the bond, such that electron density is increased on the lateral sides of the bond and decreased along the extension of the bond.[1-3] The region of lower electron density following the extension of a bond is termed the "σ-hole." In some cases, particularly with Group 15-17 elements, the existence of this σ-hole leads to an area of overall positive electrostatic potential. This area of positive electrostatic potential affords the possibility of noncovalent, attractive electrostatic interactions with atoms of negative potential. Formally, this constitutes a Lewis acid-Lewis base interaction, with the σ-hole fulfilling the role of the Lewis acid, which is often termed σ-hole

bonding. The positive character of the σ-hole of an atom, and therefore the strength of σ-hole bonding, increases with the overall positive electrostatic potential of the atom. Therefore, increasingly polarizable atoms bonded to electron withdrawing substituents are more effective at σ-hole bonding. Accordingly, this phenomenon strengthens proceeding down the rows of the periodic table.
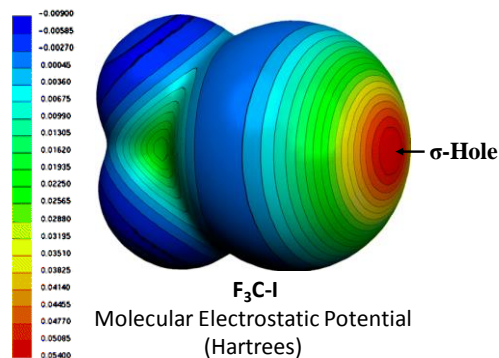

Figure 1. The σ-hole of an Organohalide

The Halogen Bond

Over 200 years ago it was observed that iodine forms encapsulated complexes with plant starch.[4] Later studies isolated halogen-Lewis base adducts of defined stoichiometry;[5] a perplexing result at the time given that halogens are electronegative and electron rich and thus typically behave as nucleophiles. Structural characterization through crystallography elucidated that both atoms of diatomic halogens can bind to Lewis bases and therefore afford nearly linear polymeric adducts. This realization was critical to the development of halogen bonding as a crystal engineering technique and played an important role in Odd Hassel's 1969 Nobel Prize.[6] Following the introduction of the σ-hole concept to explain halogen bonding in 2005,[1] parallels were quickly drawn to hydrogen bonding and it was postulated that catalysis of organic transformations in solution could be mediated by halogen bonds.

Achieved and Desired Reactivity

Initial efforts to effect catalysis using halogen bonding focused on achieving comparable reactivity to hydrogen bonding catalysis through the use of halogen bonds. To this end, halogen bonding catalysts were developed which catalyze selective reductions of heteroarenes and imines, cycloadditions

and cyclization reactions, as well as aldol and conjugate additions.[7] More recent applications employ the characteristic advantages of halogen bonding to accomplish halide abstractions, desilylative couplings, and cationic
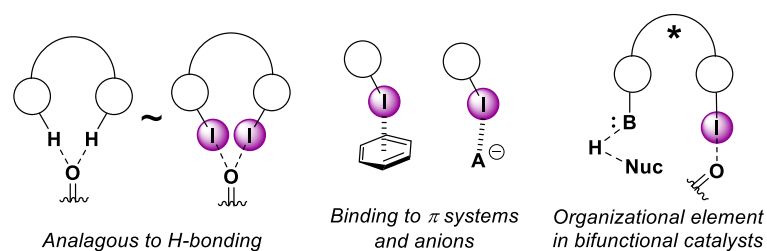

Figure 2. Reactivity of Halogen Bonding Catalysts

polymerizations.[8] Asymmetric transformations using halogen bonding have thus far proven elusive owing to the intrinsically long distance between substrate and chiral catalyst backbone. However, the use of halogen bonding as a secondary interaction in bifunctional catalysts can successfully achieve stereoselection[8] and therefore necessitates serious consideration regardless of the challenge in isolating the effects of halogen bonding.

Catalyst Design and Control Experiments

Despite the extensive historical use of elemental iodine in catalysis, the design of stable halogen bonding
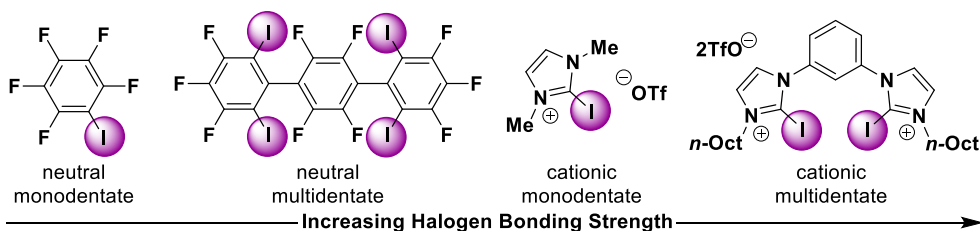

Figure 3. Trends in Halogen Bonding Catalyst Design

catalysts remains challenging owing to the strict directionality requirements and the interaction energies of σ-hole bonding. Accordingly, a weak donor is ineffective, and a strong donor can be a halogenating reagent. Successful scaffolds feature polyfluorinated backbones, imidazoliums, positive charges paired with weakly coordinating anions, and multidentate halogen bonding motifs.[7-8] Extra care must be taken when designing and testing these catalysts to avoid erroneously attributing the reactivity from Brønsted acid catalysis to halogen bonding. Therefore, background reaction, catalyst stability, and the comparative performance of Brønsted acids should be determined.

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