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IUPAC definition of the halogen bond

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Halogen atoms in organic compounds typically can be found at the periphery of molecules. For this reason, they are ideally positioned to be involved in intermolecular interactions. In fact, thanks to the large number of halogenated drugs and inhibitors, interactions involving halogen atoms are frequently observed in protein-ligand complexes. Halogens also occur naturally in biological systems. The best-known examples of this are probably the iodinated thyroid hormones, such as thyroxine. The crystal structure of the transport protein transthyretin complexed with thyroxine showed multiple iodine to carbonyl oxygen contacts involved in hormone binding [1].

It is well-known that the electron density around the halogen nucleus is highly anisotropic so that halogens can serve both as electron-acceptors and donors. While it could acknowledged that the terminology used to name noncovalent interactions given by halogen atoms has to be as unifying as possible, this has always to be done in keeping with the electrophile/nucleophile role the halogen atom plays.

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. A typical halogen bond may be denoted by the three dots in R–X···Y. R–X is the halogen bond donor, X is any halogen atom with an electrophilic (electron poor) region, and R is a group covalently bound to X. In some cases, X may be covalently bound to more than one group. It may also form more than one halogen bond. Y is the halogen bond acceptor and is typically a molecular entity possessing at least one nucleophilic (electron rich) region (e.g., a lone pair, or a pi system) [2].

The definition itself sheds light on the nature of XB, which possesses numerous similarities with the hydrogen bond, wherein hydrogen functions as the acceptor of electron density.

However, the use of the term halogen bond has to be limited to those interactions wherein halogens function as acceptors of electron density. Its use also to address interactions in which halogen atoms functions as electron-donors is conceptually misleading and contrasts with the clear tendency, well-documented in the literature, to name such R–H···Y interactions differently (i.e., hydrogen bonds) [3].

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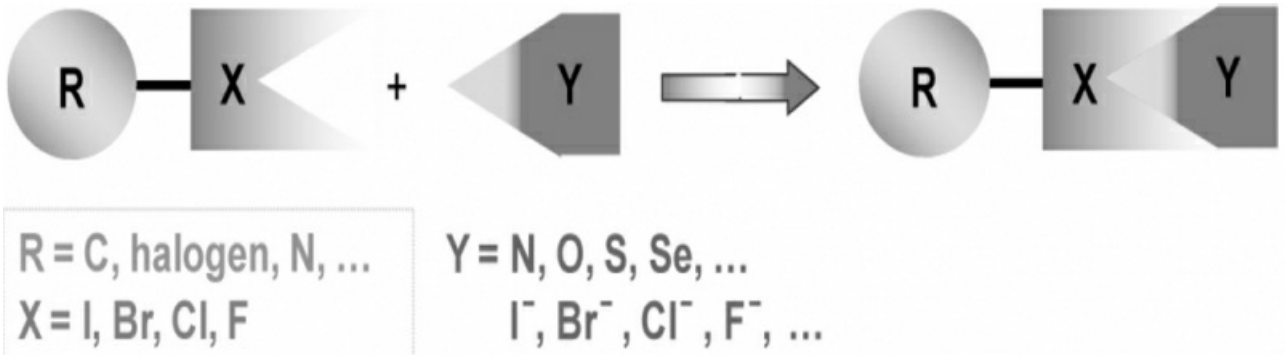

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