

# Organic and Inorganic Chemistry 2018: Application of Halogen Bonding to Organocatalysis: A Theoretical Perspective - Richard M W Wong- National University of Singapore

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The strong, specific, and directional halogen bond (XB) is an ideal supramolecular synthon in crystal engineering, as well as rational catalyst and drug design. These attributes attracted strong growing interest in halogen bonding in the past decade and led to a wide range of applications in materials, biological, and catalysis applications. Recently, various research groups exploited the XB mode of activation in designing halogen-based Lewis acids in effecting organic transformation, and there is continual growth in this promising area. In addition to the rapid advancements in methodology development, computational investigations are well suited for mechanistic understanding, rational XB catalyst design, and the study of intermediates that are unstable when observed experimentally. In this review, we highlight recent computational studies of XB organocatalytic reactions, which provide valuable insights into the XB mode of activation, competing reaction pathways, effects of solvent and counter ions, and design of novel XB catalysts.

## Introduction:

Halogen bonding attracted growing interest in recent years, due to its wide range of applications as highly directional motifs in supramolecular chemistry, crystal engineering, materials science, organocatalysis, and drug design [1]. Halogen bond (XB) is defined by the International Union of Pure and Applied Chemistry (IUPAC) as “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” [2]. Essentially, the halogen atom serves as an electron-deficient moiety (XB-donor) to interact with a nucleophilic region of a Lewis base (XB-acceptor) to form a halogen bond (Figure 1). Since XB interaction features high directionality, it has excellent molecular recognition ability.

The  $\sigma$ -hole concept of Politzer et al. [3,4] represents the most widely accepted model to explain the origin of the halogen bond. In this model, the halogen atom is characterized by anisotropic distribution of electron density with a localized region of positive electrostatic potential (ESP) along the extension of the R–X bond (Figure 1). This model readily accounts for the close contact between halogen and nucleophile (Nu), as well as the linearity of the R–X...Nu angle.

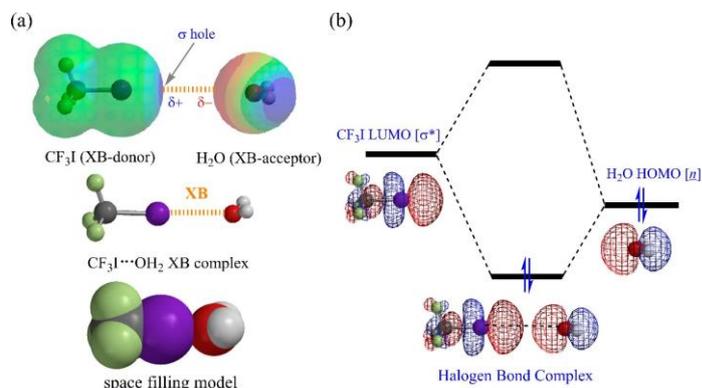


Figure 1. (a) Electrostatic ( $\sigma$ -hole) and (b) molecular orbital models of halogen bond (XB) formation. The formation of an XB complex between  $\text{CF}_3\text{I}$  (XB-donor) and  $\text{H}_2\text{O}$  (XB-acceptor) is used as an illustration.

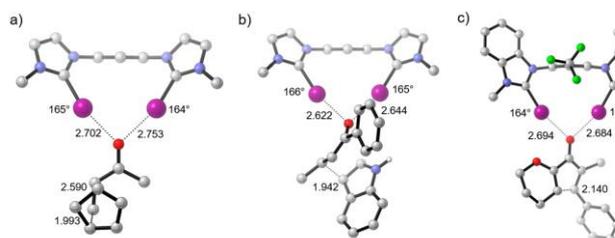
## Computational Methods for XB Organocatalysis

Over the past decade, a large number of computational studies were reported for halogen-bonded systems and various XB applications. One of the most accurate quantum chemical methods is CCSD(T), coupled cluster with single, double, and perturbative triple excitations [35]. Unfortunately, it is expensive and not practical for normal application studies. Thus, it is mainly used for benchmarking purposes for small halogen-bonded systems [36–39]. Density functional theory (DFT) methods are popular alternatives because they provide sufficient accuracy with significantly lower computational expense.

## Transition State and Binding XB Complex Studies

Along with the experimental development of halogen bond catalysis, computational studies are playing an increasingly important role in establishing XB catalysis. For many catalyzed reactions reported by Huber et al., calculations of catalyzed transition states (TSs) or binding complexes were often performed to further support the hypothesized XB catalysis pathway (Figure 2) [23,52–56]. For the investigated halogen bond catalysts, especially those of bidentate and tridentate nature, calculated structures helped chemists to gain important insights, e.g., the number of halogen bonds formed and XB-acceptor atoms involved, XB interaction distances, and structural changes upon binding. These important structural insights are difficult to obtain through experimental means.

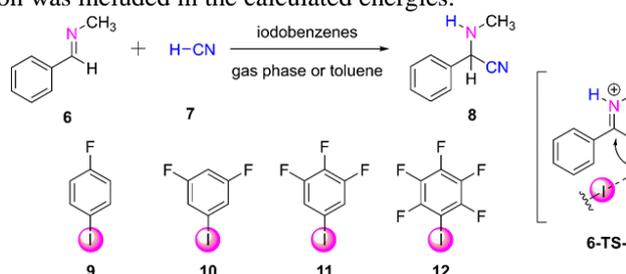
Figure 2. Calculated transition states for halogen bond-catalyzed (a) Diels–Alder cycloaddition [52],



b) Michael addition of indole to trans-crotonophenone [53], and (c) Nazarov cyclization reaction [54]. XB distances are in Å and A–I···B angles are in degrees. Hydrogen atoms are omitted for clarity

### Computational Study of XB-Catalyzed Hydrocyanation of Imines

Hydrocyanation of imines is an important reaction to synthesize amino acids [67]. Recently, Heinz et al. reported a computational investigation of feasibility of the reaction being catalyzed by neutral fluoriodobenzene catalysts 9–12 (Scheme 2) [68]. The DFT method BP86 [69], together with the def2-TZVP basis set for all atoms and ecp-28-mdf pseudopotential for iodine, was used. Both gas- and solution-phase energies were computed. In the latter case, the conductor-like screening model (COSMO) polarizable continuum model (PCM) was employed to study the solvent effect of the calculated gas-phase structures, with toluene used as a solvent. Zero-point energy correction was included in the calculated energies.



### Computational Design of Neutral XB Catalysts

In 2016, our group reported a computational study of an *in silico* designed tridentate halogen bond catalyst, with due consideration of reaction free energies and reaction kinetics [71]. All the calculations were performed using the M06-2X functional. For geometry optimizations, a small basis set, 6-31G(d) for non-iodine atoms and aug-cc-pVTZ for iodine, referred to as the SMALL basis set, was used, while, for single-point energy calculations, a large one, 6-311+G(d,p) for non-iodine atoms and aug-cc-pVTZ for iodine, referred to as the BIG basis set, was used. Reported relative free energies correspond to the M06-2X/BIG//M06-2X/SMALL level of theory at 298.15 K.

### I<sub>2</sub> as an XB Catalyst in Organic Reactions

In recent years, much effort was devoted to computational and experimental studies of the mechanism of I<sub>2</sub>-catalyzed reactions. By far, the most comprehensive

computational mechanistic study was carried out by the Breugst group [81], who investigated the mechanism of four different organic transformations apparently catalyzed by molecular iodine at the B2PLYP-D3/aug-cc-pVTZ/IEFPCM//M06-2X-D3/6-311+G(d,p)/IEFPCM level, with the aug-cc-pVTZ-pp basis set for iodine atoms.

### I<sub>2</sub>-Catalyzed iso-Nazarov Cyclization of Conjugated Dienals

The XB-catalyzed Nazarov cyclization attracted much attention recently [54,83,84]. Breugst and co-workers reported a combined experimental and computational study of I<sub>2</sub>-catalyzed Nazarov cyclization [84]. Based on their results of kinetic studies, i.e., the reaction being first order in I<sub>2</sub>, and the reaction barrier, as well as comparative control studies, the authors could rule out the Brønsted acid pathway in favor of the XB pathway. Their calculated activation barrier of the XB pathway (84 kJ/mol) is in close agreement with the experimental determined value ( $\Delta G^\ddagger_{298} = 86.8$  kJ/mol). The reaction profile and transition state structure.

### Dihalogen-Catalyzed Michael Addition Reactions

By far, the majority of computational and experimental studies of XB catalysis focused on the element iodine. In 2019, Bickelhaupt and co-workers reported a comprehensive computational study of aza-Michael addition of pyrrolidine to methyl acrylate catalyzed by dihalogen molecules (X<sub>2</sub>), namely, F<sub>2</sub>, Cl<sub>2</sub>, Br<sub>2</sub> and I<sub>2</sub> [49]. All geometries were optimized and characterized at the M06-2X/def2-TZVP level. Scalar relativistic effects were accounted for using the zeroth-order regular approximation (ZORA) [85,86]. DLPNO-CCSD(T) calculations were performed using the def2-TZVP basis set on M06-2X/def2-TZVP geometries.

### XB in Metal Acetate-Catalyzed Halolactonization

The above examples are computational studies of neutral XB-catalyzed reactions. There are many literature reports of halogenation reactions where, prior to the halogenation step, halogen bonds are formed between some Lewis base and the halogenation agents [88–90]. Such XBs are transient in nature, as the X–A (X is the halogen and A is some heteroatom) bonds are cleaved in TSs. Recently, Arai and co-workers reported a metal acetate-catalyzed asymmetric halolactonization, where halogen bonding interaction was proposed as a key secondary interaction in the transition state [91]. Experimentally, the authors found that molecular iodine has a significant impact on the acceleration of the reaction.

### Summary and Outlook

Halogen bonding is now established clearly as a reliable noncovalent motif in organocatalysis. We witnessed a continued progress in the application of XB to organocatalysis in recent years. Although computational mechanistic studies of reactions catalyzed by halogen-containing catalysts are still very few, there seems to now be sufficient computational evidence in support of the possibility of XB activation in organocatalysis. Calculated TS structures reported in the literature showed that the catalysts employed can activate

substrates through interaction at the halogen site, with features characteristic of a typical halogen bond, e.g., close to linear binding angle and less than the sum of van der Waals radii binding distance. Various energy decomposition analyses of the strength of XB binding seem to indicate that it could be strong enough to attain a lowering of the reaction free energy barrier.