Iodine(III)-Based Halogen Bond Donors: Properties and Applications

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This account is dedicated to Prof. Jean Lessard on the occasion of his 85th birthday.
Abstract: Halogen bonding, the non-covalent interaction of Lewis bases with an electron-deficient region of halogen substituents, received increased attention recently. Consequently, the design and evaluation of numerous halogen-containing species as halogen bond donors have been subject to intense research. More recently, organoiodine compounds at the iodine(III) state have been receiving growing attention in the field. Due to their electronic and structural properties, they provide access to unique binding modes. For this reason, our groups have been involved in the development of such compounds, in the quantification of their halogen bonding strength (through the evaluation of their Lewis acidities), as well as in the evaluation of their activities as catalysts in several model reactions. This account will describe these contributions.

Keywords: Halogen bonding, Hypervalent iodine, Lewis acidity, Iodolium, Diaryliodonium

1. Introduction

Iodine, as the largest stable halogen, sets itself apart from its lower homologues in multiple aspects, and two of these special features of organoiodine compounds have recently been combined: the possibility to form strong halogen bonds with Lewis bases and the existence of various stable hypervalent compounds, most importantly iodine(III) derivatives.

These hypervalent iodine (HVI) compounds offer a rich range of structural motifs and reactivities. Iodine(V) derivatives like Dess-Martin’s periodinane 6 (Scheme 1) and iodine(III) variants with oxygen-based ligands (such as PIDA 2 and Koser’s reagent 1, see Scheme 1) have been used for many oxidative transformations, such as carbonyl α-oxidations, phenol dearomatizations, and alkene functionalizations. Cyclic compounds with mixed oxygen- and carbon-based ligands like Togni’s reagents (3 and 4) have found widespread use as synthetic equivalents for synthons like CF₃⁺ (or RC≡C⁺).[12–14]

Iodine(III) compounds with two aryl groups, on the other hand, have extensively been used as electrophilic aryl sources. A large range of nucleophiles can be functionalized in this fashion, either directly or through transition metal intermediates. The diaryliodonium reagents (5, Scheme 1) typically feature a T-shaped geometry in which iodine’s two bonds to aryl groups are complemented by a third interaction with the counterion. The latter is formed in elongation of one aryl-iodine bond and can be of varying strength. The metal-free arylation reactions thus proceed via association, or ligand exchange of the counterion, with a nucleophile, followed by rate-determining reductive elimination to form the arylated product.[16]

While these arylation reactions that are associated with the reductive elimination step are obviously of great synthetic value, in recent years there has been an increasing interest in the initial step, the association, or exchange of the counterion, with other Lewis bases. As we will discuss in more detail below (chapter 2), depending on the strength of the iodine-Lewis base bond, the T-shaped structure may either be viewed as a hypervalent compound or as an halogen-bonded adduct between an iodonium species and the Lewis base.

In general, halogen bonding (the noncovalent interaction of electrophilic halogen substituents with Lewis bases) has also received continually growing attention in several fields of chemistry in the last years, particularly regarding its application in solution-phase. As could be expected from its topological similarity with hydrogen bonding, it shares

![Scheme 1. Common iodine(III) and iodine(V) compounds.](image-url)
several similarities with the latter, but also possesses some peculiar distinctions. This refers, for instance, to the "soft" nature of the interacting atoms and to the very high directionality of the interaction. Strong halogen bond donors (halogen-based Lewis acids) are usually based on iodine and a backbone with electron-withdrawing substituents or positive charge(s).

Up to about 2017, all halogen bond donors that were explicitly designed to act via this interaction were based on iodine(I) derivatives, i.e. terminal halogen substituents. Even though the Lewis acidity of iodine(III) compounds has been known in principle, and despite the specific inclusion of hypervalent species in the official definition of halogen bonding,\cite{18} the rational use of such compounds as Lewis acids was lacking. This has changed in the last few years, and in this account we will provide an overview on the latest development, with a focus on the work of our groups.

First, in chapter 2, we will provide more background on some fundamental issues, including the contributions of electrostatics,\cite{26,27} charge transfer,\cite{28,29} and dispersion to the overall binding energy. Chapter 3 will give a comprehensive overview on the quantification of iodine(III)-based Lewis acidity. The thermodynamic parameters for the binding of weak Lewis bases to a variety of iodine(III) compounds have been determined by now and the influence of structural modifications has been elucidated. The Lewis acidity of organoiodine(III) derivatives also enables them to act as organocatalysts, and this topic will be covered in chapter 4.

2. Fundamental Aspects

2.1. Halogen Bonding: The Electrostatic Model and its Limitations

Halogen bonding has traditionally been considered as a special case of charge-transfer interaction. In the last 15 years, an electrostatic reasoning based on a region of low electron density on the surface of the halogen atom (opposite the σ-bond) has gained much popularity. This also provides a very intuitive explanation for the highly directional binding, compared to hydrogen bonding.\cite{30} Indeed, a number of studies have also found good correlations between the most positive electrostatic potential at the so-called σ-hole\cite{31} of a halogen bond donor and the resulting interaction energy with Lewis bases.\cite{30,32} There are, however, a series of experimental and computational studies which clearly suggest that a purely electrostatic approach cannot satisfactorily predict halogen bonding strength and that other contributions, most notably charge-transfer (for strong bonds) and dispersion (for weak bonds) must also be taken into account. Huber and coworkers, for instance, reported an extensive computational investigation on this issue.\cite{33} They first benchmarked several DFT functionals against CCSD(T)/CBS association energies of five halo-methanes with chloride ion and ammonia. M052X-D3/def2-

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TZVPD gave the closest fit to the reference values and was thus used for the full set of 18 iodine(I) XB donors. By comparing systematically the correlation between complexation energies and various system properties, they confirmed that the maximum electrostatic potential value of the σ-hole did correlate reasonably well ($R^2=0.92$) with complexation energies of ammonia. However, the correlation in the case of chloride adducts was significantly poorer ($R^2=0.76$). In particular, XB donors with complexation energies in the middle of the set did not correlate at all with the electrostatic parameter, while the extrema (strongest and weakest bindings) were predicted relatively well.

Parameters related to charge transfer, such as the energy levels of the LUMO or the molecular orbital that best describe the C–I σ* orbital, predict complexation energies relatively poorly as single parameters. However, they provided better correlation for chloride adducts than for ammonia adducts, while the reverse is true for maximum electrostatic potentials. This supports the hypothesis that the electrostatic and charge transfer contributions change significantly depending on the base. Namely, one would expect to have a more significant charge transfer in the case of chloride adducts, which would explain the poor predictive power of the σ-hole model in this case.

The linear combination of the maximum electrostatic potential and the energy of the LUMO proved to have greater predictive power than any parameter alone. Indeed, by combining these two descriptors with empirically optimized coefficients, correlation coefficients of 0.93 for ammonia adducts and 0.95 for chloride adducts were obtained. From this, it appears clear that multiple physical contributions must contribute to halogen bonding. It should be noted that Politzer and coworkers used a different approach to remedy the shortcomings of the static σ-hole by including polarization effects which were induced by a point charge that was placed at the position of the Lewis base. This, however, requires the computation of the XB complexes and thus cannot act as predictive tool for the Lewis acidity of XB donors.

These overall findings were supported by SAPT analyses performed by Liithi and coworkers. In the acetonitrile adducts of iodine(I) and iodine(III) compounds, the electrostatic term was dominant. However, the covalent contributions to the interaction (charge transfer and induction) were not negligible and became more significant as the iodine became more polarized (e.g. IF or IF$_3$). It could be expected that those contributions would be even more significant with anionic Lewis bases, although that was not modelled in this work.

### 2.2. The Case of Iodine(III) Compounds

Trivalent iodine(III) compounds feature a 3-center-4-electron (3c–4e) bond, which greatly influences their properties. This type of bonding involves two ligands opposite to each other on each side of a central atom (in our case, iodine). According to the Rundle-Pimentel model, the iodine atom interacts constructively with both ligands, via unhybridized $p$ orbitals. The combination of those three $p$ atomic orbitals yields one bonding, one non-bonding and one anti-bonding orbital, of which only the first two are occupied. The electron density of the non-bonding orbital is localized on the ligands, leading to strong electrostatic interactions between the electron-deficient iodine and electron-rich ligands. Furthermore, from a covalency point, each bond has an order of one half and will thus be comparably weak. As such, ligand exchange is relatively facile; in the case of iodine(III) this has been used to generate new compounds from easily obtainable starting materials.

Trivalent iodine(III) compounds form a T shape, in which the two ligands facing each other are involved in the 3c–4e bond, while the third forms a 2 center classical covalent bond with iodine. Depending on the nature of the ligands, isomerization can be facile (e.g. with diaryliodonium adducts) or kinetically inaccessible (e.g. with Togni's trifluoromethylation reagents). This comes from the fact that the nature of the 3c–4e bond is greatly linked to the trans influence of both ligands. In particular, aryl ligands are relatively electron-donating and favor the dissociation of the opposite ligand. This also favors geometries where the two most electronegative ligands are opposite to each other (see crystal structures in the next section). It is thus not surprising that triaryliodine compounds are unstable and lead to various decomposition products. However, diaryliodonium salts and their derivatives are mostly air- and moisture-stable at room temperature, provided that the third ligand (or counter-ion) is weakly coordinating. For example, iodolium azide, cyanide, thiocyanate and sulfinate have been synthesized and characterized by x-ray diffraction spectroscopy. Legault, Mayer and coworkers have also generated and isolated diphenyliodoni um benzoate and 4-nitrophenolate by anion metathesis. These adducts proved to be stable at room temperature, but underwent reductive elimination above that temperature.

When the third ligand is a weakly coordinating Lewis base, it is likely more or less dissociated in solution. In this case, a formal iodonium ion is formed and the salt can be thought of as a halogen bonded adduct, with the iodonium cation being the halogen bond donor and the anion being the Lewis base.

As can be expected, the dissociation of a ligand introduces a new electronic deficiency. As such, cationic iodine(III) compounds of the general form $R_2I^+$ display two zones of low electronic density directly opposite to the two $\sigma$ C–I bonds. It also reduces the overall electronic density around iodine and greatly increases the magnitude of the electrostatic potential maxima. A similar activation of neutral iodine(III) reagents...
can be done by the protonation of a ligand. The iodine atom in such compounds can provide two halogen bonds.

As will be seen in Section 4, most iodine(III)-based halogen bond donors used in catalysis are derivatives of diaryliodonium salts with a weakly complexing counter-ion, to favor access to this free ion. To reach these compounds, many syntheses involve oxidation promoted by strong acids (e.g. triflic acid, tetrafluoroboric acid) in order to have the weakly complexing conjugate base (TfO\(^–\), BF\(_4\)\(^–\)) as counter-ion. Another strategy is to form the diaryliodonium salt with a milder acid (e.g. p-toluenesulfonic acid), then perform a counter-ion exchange. These strategies are necessary in catalysis to avoid inhibiting the catalyst. Section 3 will show concretes example of the drastic influence of the counter-ion on binding affinity.

When all three ligands are of similar strength, the conceptual relation to halogen bonding is different. Here, a noncovalent interaction will be formed at a fourth coordination site of the iodine. The nature of all ligands will influence the strength as well as the direction of this binding. For example, as shown by Lüthi and coworkers, IH\(_3\) displays two local maxima on the molecular electrostatic potential surface (σ-holes), while IF\(_3\) has only one, although broader, when viewing the same isosurface.

Kozuch and coworkers have noted that IF\(_3\) can also adopt an unstable trigonal planar \(D_{3h}\) geometry. In that case, three σ-holes are found opposite to every σ bond. However, in its stable \(C_{2v}\) form, these σ-hole cannot be directly opposite to the σ bonds and instead deviate from some varying angle. The polarity of the ligands thus appears to directly influence this angle by draining the electronic density from the iodine and thus bringing the two σ-holes into a single “non-classical” σ-hole. In this case, a broad zone of low electron density is observed on the other side of the classical 2-centers covalent bond (2cb). Comparison of XF\(_3\) compounds with varying central halogens shows a distinct trend: as the central halogen becomes more polarizable (F to I), the two σ-holes become further split apart. A bidentate ligand such as the formate anion can thus bind in a bifurcated fashion to IF\(_3\). This nicely illustrates the critical role how the ligands can shape the electronic density around iodine(III) and modify its binding properties.

As an example, the acetonitrile adducts of iodine(III) compounds displayed various binding geometries (see Figure 1 for selected examples). While halogen bonding in iodine(I) acetonitrile adducts is very linear (Figure 1, a and c), this is not necessarily the case with all iodine(III) acetonitrile adducts. Only the two most electronically drained iodine(III) centers (as measured by the maximum electrostatic potential) lead to nearly linear complexation modes. N–I–R angles ranging from 152 to 175 degrees, and C–N–I angles from 88 to 116 degrees, were observed in other iodine(III) compounds. It is important to note however that all these compounds are formally neutral.

2.3. Structural Data

The calculated binding modes described above are indeed also found in solid-state structures. We will discuss only a few representative examples for both concepts mentioned above, i.e. halogen bonding based on R\(_2\)I\(^+\) and R\(_3\)I. Diphenyliodonium halides form crystalline dimers which have for example been resolved by Alcock and Countryman (Figure 2). In these structures, each halide binds to both iodine centers with I–X–I...
angles slightly below 90 degrees (86.53 degrees when X=Cl to 88.10 degrees when X=I). This shows precisely the ideal position of the binding sites for this type of compounds.

Many iodine(III) compounds with three strongly coordinated ligands also display secondary halogen bonding in their crystal structures. Phenyliodine(III) diacetate (PIDA, 2) demonstrates the possible secondary bonding of the acetate ligands. While the distances between the carbonyl-oxygen atoms and iodine are significantly longer than for the oxygen atoms involved in the 3c–4e bond (2.8–2.9 Å versus 2.1–2.2 Å, see Figure 3), both distances are much smaller than the sum of the Van der Waals radii (3.56 Å).\(^{[54]}\)

(Dichloroiodo)arenes also display a secondary halogen bonding between molecules in the crystal structure.\(^{[55,56]}\) The distance between the iodine and the chlorine atoms in this interaction is 3.45 Å in absence of substituents on the aromatic ring.\(^{[55]}\) Once again, this is below the sum of the Van der Waals radii (3.79 Å).\(^{[54]}\) The crystal features periodic secondary interactions (see Figure 4). Substituted aromatic rings result in an increased I⋯Cl distance, e.g. up to 3.82 Å with 2,6-bis(3,5-dichloro-2,4,6-trimethylphenyl)benzene.\(^{[56]}\) In this case, the packing present secondary interactions in a dimeric form instead of periodic, due to the greater steric constraints.

As a final example, Koser and coworkers have reported the crystal structure of the adduct between chloride and 1-chloro-1,2-benziodoxol-3-one (Figure 5).\(^{[57]}\) In this structure, chloride binds directly opposite of the C–I bond, in agreement with the computational studies mentioned above.

3. Quantification

In the previous section, we have covered the nature of halogen bonding and its particularities with iodine(III) compounds. Quantum calculations allowed convenient access to interaction energies between Lewis bases and various halogen bond donors. The previously presented crystal structures also evidence the formation of a considerable interaction. This section presents the different works featuring experimental quantifications of that interaction.

3.1. Early Works

In 1998, Ochiai, Okuyama and coworkers studied the reaction of iodonium salts 9 (Scheme 2) with a chloride anion in different conditions. Their kinetic modeling allowed them to find the equilibrium constants for the complexation of chloride anion to the iodonium cations (assuming full dissociation of

![Figure 3. Crystal structure of (diacetoxyiodo)benzene with hydrogens added.\(^{[52]}\)](image)

![Figure 4. Halogen bonding in the crystal structure of (dichloroiodo)benzene with hydrogens added.\(^{[55]}\)](image)

![Figure 5. Halogen bonding in the crystal structure of 1-chloro-1,2-benziodoxolin-3(1H)-one tetra-n-butyammonium chloride with added hydrogens.\(^{[57]}\)](image)

![Scheme 2. Iodonium salts studied by Ochiai, Okuyama and coworkers.\(^{[58]}\)](image)
the tetrafluoroborate counter-ion). They found equilibrium constants of the order of $10^2$–$10^3$ M$^{-1}$.[58]

The authors also considered the binding of a second chloride anion to the neutral chloroiodane. Their measurements suggest that this process occurs, but the equilibrium constant is around three orders of magnitude smaller than for the first complexation ($K_1 = 10^8–10^9$ M$^{-1}$). Similarly, in 2005, Okuyama and coworkers obtained the binding constant of bromide to iodonium salt 10 (Scheme 3).[59]

This compound is proposed to decompose into iodo benzene and vinyl carbocation 11 under medium heat (50–60°C) in polar solvents. The carbocation undergoes further reactions depending on the reaction conditions.

Table 1. Influence of the counter-ion on the binding constant of diphenyliodonium salts to 18-crown-6.[60]

| Counter-ion | $K_a$ (M$^{-1}$)[a] |
|-------------|---------------------|
| PF$_6^-$    | $6.65 \times 10^3$  |
| AsF$_6^-$   | $5.84 \times 10^3$  |
| BF$_4^-$    | $1.02 \times 10^3$  |
| ClO$_4^-$   | $8.13 \times 10^3$  |
| TRO         | $2.83 \times 10^3$  |
| BPh$_4^-$   | $1.47 \times 10^3$  |
| Br$^-$      | 0                   |
| I$^-$       | 0                   |

[a] Values obtained by $^1$H NMR titrations in CD$_2$Cl$_2$ at 24°C.

The authors noticed that the addition of a bromide salt considerably slows down this process and leads to vinyl bromide 12 as additional product. They studied the reaction kinetics and, in doing so, determined the equilibrium constants for the single and double complexation of bromide anion to 10. They observed that the equilibrium constant for the first complexation greatly increased when going from methanol ($K_a = 5.0$ M$^{-1}$) to acetonitrile ($K_a = 690$ M$^{-1}$) and chloroform ($K_a = 1600$ M$^{-1}$).

Ochiai and coworkers also formally studied and quantified the interaction between iodine(III) compounds and a Lewis base in 2003.[60] They measured the equilibrium constants between six diaryliodonium salts and 18-crown-6. They measured significant binding constants ($K_a = 10^5–10^6$ M$^{-1}$) and obtained x-ray structures of the adducts (see Figure 6).

The influence of functional groups on the diaryliodonium salts are well represented by Hammett $\sigma$ values. Notably, the correlation between the $\sigma^+$ of para substituents correlates with very well ($R^2 = 0.99$, n = 5) with the logarithm of the binding constants (i.e. the binding free energies). The choice of solvent also significantly influenced the binding constants. As could be expected, the binding constants decreased as the donating ability of the solvent increased. The authors found a good correlation between the logarithm of the binding constants and Gutmann’s donor number of the solvents.[61]

The tetrafluoroborate salts were used for most of the measurements. Although it can be seen as a very poor Lewis base, its influence appears not to be negligible: using hexafluorophosphate or hexafluoroarsenate lead to a six-fold increase of the binding constants (Table 1). Moreover, diphenyliodonium bromide and iodide did not appear to bind to 18-crown-6 at all. This is not surprising, as these counterions are much better Lewis bases.

The same group has also found that this complexation can stabilize reactive cationic iodine(III) compounds. As such, there were able to obtain the crystal structure of PhI(OH)$_2^+$ complexed to crown ether.[62,63] This cation normally decomposes at room temperature within a couple minutes to give a black tar.[62]

Ochiai and coworkers have further reported the binding constants of diphenyliodonium tetrafluoroborate with four nitrogen heteroarenes in 2006.[64] All the studied Lewis bases lead to 1:1 adducts, as evidenced by Job plots. Pyridine 13, 2,2'-bipyridyl 15 and 2,2':6',2''-terpyridine 16 all gave binding constants in the same order of magnitude ($K_a = 2.02 \times 10^3$ to $6.35 \times 10^3$ M$^{-1}$, see Scheme 4). Each additional nitrogen is linked to an increase of the affinity, which would suggest that a multidentate binding is possible. 1,10-Phenan throline 14 was found to be a much stronger ligand, with an affinity constant of $20.0 \times 10^3$ M$^{-1}$. Interestingly, the 1,10-phenanthroline adduct adopts a distorted trigonal bipyramidal geometry (Figure 7) according to a previously measured crystal
This is quite different from the biaxial coordination that could be expected from this ligand. The authors also recorded the crystal structure of the pyridine adduct, which adopted the expected geometry, with the pyridine and tetrafluoroborate anion each binding a site of the iodonium cation.

3.2. Extensive Quantification

In an effort to compare them to widely-used Lewis acids in catalysis, Legault and coworkers have quantified more extensively the Lewis acidity of iodine(III) compounds, starting by a combined experimental and computational work in 2017. In this work, the Lewis acidity of four diaryliodonium salts were determined by $^{31}$P NMR using the Gutmann-Beckett method. Their Lewis acidity was compared to other common Lewis acids.

The method involves using a Lewis base as probe, in this case triethylphosphine oxide (TPO). The chemical shift of the probe is monitored as the amount of Lewis acid is varied. The increasing population of the probe complexed to the Lewis acid causes a displacement of the observed chemical shift. The curve obtained in this fashion can be analysed by curve fitting to find the binding constant. The maximum extent of the chemical shift displacement is indicative of the strength of the Lewis acid. Both the solvent and the counter-ion had a significant influence on the measured Lewis acidities. For example, the binding constant in dichloromethane was nearly four times greater than in acetonitrile for diphenyliodonium hexafluorophosphate. Moreover, the tosylate counter-ion was found to bind significantly to the diphenyliodonium cation, reducing the Lewis acidity of the latter. DFT calculations proved to be adequate to reproduce the experimental results. The Lewis acidities of six additional diaryliodonium ions were predicted with the method. This preliminary scale gave a sense of the Lewis acidity of numerous proposed transient species in iodine(III)-mediated reactions.

To gain a much deeper understanding of the behavior of these new halogen bond donors, Legault, Mayer and coworkers reported in 2020 the binding constants for the association of 17 diaryliodonium salts with 11 Lewis bases. The study was a challenge as it relied on numerous titration methods. Direct determination of the binding constants of the chloride and triflate anions was possible using conductivity measurements. Dilute solutions of diaryliodonium triflate salts, and anionic Lewis bases (as tetrabutylammonium salts) displayed a linear increase of the conductivity with concentration. However, this was not the case of the resulting Ar$_2$ILB adducts, as they did not completely dissociate into ions. This principle was hence used as method of determining the quantity of free ions, and thus the association constants. At higher concentrations (> 2 mM), the association of the triflate anion to the diphenyliodonium cation stops being negligible. Indeed, the deviation between the predicted conductivities (based on measurements with concentrations below 0.25 mM) and the experimental conductivities becomes larger than 15 %. When diphenyliodonium hexafluorophosphate was used, the deviation was less than 5 % at 2 mM. This provided important insight on the concentration range required for rigorous measurements using alternative titration experiments.

Isothermal titration calorimetry (ITC) was then used on a subset of the diaryliodonium salts and Lewis bases. The method provided additional information on the binding stoichiometry. This work found a 1 to 1 binding of all Lewis bases to the diaryliodonium salts in the studied concentration range. The method could not however be used for the whole range of Lewis bases studied. Photometric titrations were thus considered.
When the colored 4-nitrophenolate ($\lambda_{\text{max}}$ 430 nm) was used as Lewis base, the association constants could be determined by direct photometric titration of the latter. It was discovered that addition of diaryliodonium salts to a solution of the phenolate led to a significant hypsochromic shift due to the formation of the adduct. Mathematical modelling of the titration process enabled the measurement of free and bound 4-nitrophenolate species in solution from measured absorbance.

To greatly extend the range of Lewis bases studied, an alternative photometric titration method had to be developed, since the diaryliodonium salts do not present characteristic UV/Vis absorbances. A cross-titration method relying on the benzhydrylium ions reported by the Mayr group was thus developed.\(^{[69,70]}\) These ions are colored in solution and their binding constants with an extensive set of Lewis bases has been determined. By assuming reversible association to both the benzhydrylium and diaryliodonium ions, a thermodynamic cycle could be defined and exploited to obtain the binding constants with the diaryliodonium ions. Based on the previously developed Lewis basicity scale,\(^{[69,71,72]}\) the authors were then able to isolate representative Lewis acidity parameters for the diaryliodonium salts. These parameters allow the prediction of association constants within a factor of 3 for almost all pairs of diaryliodonium salts and Lewis bases. The only exception occurred when the steric effects became significant. The advantage of this new cross-titration method is the range of measurable binding constants: $K_a$ values from $10^2$ to $10^8 \text{M}^{-1}$ have been determined. This extensive range is accessible by changing the reference benzhydrylium ion. One could envision extending the concept to other Lewis acids.

The method was also applied to measure the Lewis acidities of cyclic diaryliodonium salts (i.e. dibenzo[b,d]iodolium salts). Interestingly, there were found to possess Lewis acidities around two orders of magnitude greater than their corresponding acyclic diaryliodonium analogs.

Further investigation of the thermodynamic of binding was performed, through decomposition of the free energies into their enthalpic and entropic contributions. Chloride, bromide and iodide all displayed very similar binding enthalpies ($-9.7 \text{kJ/mol}$ to $-11.2 \text{kJ/mol}$), although the entropic contribution varied much more ($-10.6 \text{kJ/mol}$ to $-17.1 \text{kJ/mol}$). This appears to indicate solvation effect. Moreover, the complexation entropy of chloride with different diaryliodonium salts varied significantly. Interestingly, quinuclidine was the only measured compound to have a negative binding entropy. While its binding enthalpy is extremely favorable ($-50.6 \text{kJ/mol}$), the entropic term causes quinuclidine to have a moderate binding free energy ($-13.6 \text{kJ/mol}$). This illustrates the stark difference between neutral and anionic Lewis bases. This could come from a number of physical phenomena, such as solvent organisation around the Lewis base or ion pairing effects. In particular, the triflate counter-ion was shown to bind weakly to the diaryliodonium salts. The coulombic repulsion between anionic Lewis bases and this counter-ion likely influences the complexation entropy. This ion-pairing phenomenon is currently under investigation.

### 3.3. Biaxial Complexation

As discussed earlier, diaryliodonium salts with non-complexing counter-ions have two binding sites approximately 90 degrees from each other. As such, most Lewis bases do not have the geometrical requirements to bind both sites at once. In the case of cyclic diaryliodonium salts (e.g. iodolium salts), substituents near the binding positions can effectively block a binding axis completely (see Figure 8). It is important to note that due to the highly directional nature of halogen bonding, this biaxial complexation results in a mostly square planar geometry at the iodonium center.

Huber and coworkers developed carbonyl-based ligands which have the right geometry to occupy both binding sites of cyclic diaryliodonium salts.\(^{[73]}\) A computational screening using DFT allowed them to identify dimethyl isophthalate 18 and diethyl-3,3’-(1,2-phenylene)dipropiolate 19 derivatives as suitable biaxial ligands (see Scheme 5). They thus synthesized ester

![Figure 8. Concept of binding axis blockage as a tool for proving a halogen bonding mediated process.](image)

![Scheme 5. Cyclic diaryliodonium salts used and suitable biaxial Lewis bases identified by computational screening.](image)

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and amide derivatives of these compounds and measured their association constants to cyclic diaryliodonium salts by $^1$H NMR and isothermal titration calorimetry (ITC). Compared to linear analogues, suitable chelating ligands provided binding constants to dibenzo[8,9]iodolium $^{17}$a around two orders of magnitude larger. The chelating binding was also confirmed by the significantly reduced affinity of biaxial ligands for iodolium $^{17}$b, while the affinity with linear (i.e. monodentate) ligands was only slightly affected. Cocrytallization of $^{17}$a with a diamide (using $^{37}$Cl instead of $^{37}$F for better crystallization) gave a crystal suitable for XRD, which confirmed the biaxial binding (see Figure 9).

DFT calculations were further performed to model the complexation phenomenon and try to predict binding free energies. Although the method used had previously given results comparable to CCSD(T)/CBS calculations in the gas phase,$^{[33]}$ mean absolute errors between 1.8 kcal/mol and 3.8 kcal/mol were obtained, depending on the solvation model used and whether Grimme’s vibrational entropy correction$^{[74]}$ was used or not. Surprisingly, this correction was detrimental to the quality of the results both with SMD18$^{[75]}$ (SMD with corrected solvation radii for iodine and bromine) and PCM as solvation models. The SMD18 solvation radii were optimized while applying Grimme’s vibrational entropy correction, which could explain why PCM outperforms SMD18 in this case. The bottom line is that it is not trivial to obtain accurate complexation free energy calculations with iodine(III) species.

4. Applications in Organocatalysis

Beside crystal engineering$^{[76,77]}$ and recognition studies,$^{[19]}$ organocatalysis is by now one of the most important fields in which iodine(I)-based halogen bonding is utilized.$^{[78–80]}$ In the last decade, it has emerged as an interesting alternative to hydrogen bonding, with recent examples showing successful induction of chirality.$^{[81,82]}$ While the first successful XB based organocatalyses employed neutral iodine(I) species with polyfluorinated backbones like $^{20}$ (Scheme 6)$^{[83,84]}$ by now mostly cationic heteroaryl backbones like (benz)imidazolium or triazolium ions are used, as they provide much higher activity.$^{[78–80]}$ The preorganized bidentate cationic donor $^{21}$ is by now the arguably strongest iodine(I) based XB donor (Scheme 6)$^{[85,86]}$

In contrast to the wide range of iodine(I) based organocatalysts, iodine(III) compounds are markedly underrepresented. The fact that diaryliodonium salts have been quantified by Legault and coworkers to be as Lewis acidic as thiourea compounds, popular bidentate H-bond catalysts, gives a first glimpse at their high potential as catalysts.$^{[66]}$

4.1. First Use as Lewis Acid Catalysts

In 2015, the first example of the use of diaryliodonium salts as Lewis acid catalysts has been presented by Han and Liu in a three component Mannich reaction performed under solvent-free conditions (Scheme 7)$^{[87]}$.

Different counter-ions ($^{37}$O$^-$, $^{37}$S$^-$, $^{37}$F$^-$, $^{37}$B$^-$) were compared using simple diphenyliodonium salts and the highest activity was achieved using the corresponding triflate. Furthermore, some tunability was shown leading to the most active catalyst $^{22}$ featuring a pentafluoro phenyl moiety. Also, the authors attempted at the first XB-based application of asymmetric counteranion directed catalysis$^{[88]}$, but only a low enantiomeric excess of 7% was achieved using their strongest diaryliodonium (cation of $^{22}$) as BINOL phosphate salt. Further mechanistic studies on the nature of the activating Lewis acid-base interaction were not performed, and thus a

Figure 9. Crystal structure of $^{17}$a with a $^{37}$Cl$^-$ counter-ion complexed with diamide.$^{[76]}$ The counter-ion is omitted for clarity.

Scheme 6. A typical polyfluorinated multidentate neutral XB donor $^{20}$ and the arguably by now strongest cationic XB donor $^{21}$.

Scheme 7. First examples of iodine(III) salts as Lewis acid catalysts by Han and Liu: A Mannich reaction.$^{[87]}$
halogen-bonding-based mode of activation could not be confirmed in that study. As the reaction was also strongly activated by acids, hidden acid catalysis could not be ruled out. It is worth mentioning that, in parallel to the work of Han and Liu, another group planned on using diaryliodonium salts as Lewis acids to activate the fluorination of arynes. They found out however that in their case the mechanism did not rely on Lewis acidity.\cite{89}

### 4.2. Halogen Bonding as Decisive Interaction

The concept of diaryliodonium salts as Lewis acid catalysts was further examined by Huber and coworkers in 2018, providing clear evidence for a XB-mediated mechanism.\cite{90} In contrast to the work presented in section 4.1, iodolium salts were employed due to their rigid geometry, which allowed a more precise prediction of the XB geometry and a blockage of binding sites by substituents ortho towards the iodine (concept sketched in Figure 8). These cyclic compounds have also been known for their higher stability compared to their acyclic analogues,\cite{91} which is also helpful for mechanistical investigations. As presented in section 3.2, Legault, Mayer and coworkers have clearly demonstrated that they also provide higher Lewis acidity than their acyclic counterparts,\cite{92} they therefore provide numerous advantages for XB catalysis.

Besides the unfinished iodolium 17a as $\text{TiO}^-$, $\text{BAR}^-$, and Cl$^-$ salts, the CF$_3$ substituted analog 29bOTf was also employed in this study. In addition, they included two variants with one or two methyl groups on the ortho-positions towards the iodine (17b and 17c), which block one or both halogen bonding axes, respectively (Scheme 8). Correspondingly, derivative 17b showed in a chloride co-crystal only an interaction on the side near the unfunctionalized ring, and a halide co-crystal of the two-side methylated analogue 17c was not obtainable. Due to the high directionality of halogen bonding an ortho methyl group is therefore sufficient to block a XB binding site in the rigid iodolium system as proposed in Figure 8. The iodolium salts 17 and 29 were utilized in classical halogen bonding benchmark reactions, working via a halide abstraction or the activation of a carbonyl compound (Scheme 8).

The Ritter-type solvolysis of benzhydryl halides in wet acetonitrile has been presented by the same group as the first example of a C–X activation by halogen bonding.\cite{93} It is typically employed using stoichiometric amounts of XB donors, as the liberated halide binds strongly to the donor and diminishes its activity. The reaction has also been proven to be robust against hidden acid catalysis. In this case, instead of the usual benzhydryl bromide, the more challenging chlorinated analogue 27 was used (Scheme 8a). As expected, iodolium chloride salts were inactive in this reaction, while $\text{TiO}^-$ and $\text{BAR}^-$ salts had measurable and equivalent activities. Accessibility to the XB sites was also explored, as the fully blocked donor 17c showed no activity, and the partially-blocked derivative 17b provided reduced activity. These results clearly point to a halogen bonding-mediated mechanism, as anion–π interactions or counterion effects should not be affected in such a fashion. Hidden Na$^+$ and acid catalysis was also ruled out by control experiments. Interestingly, the non-blocked iodolium salts 17a and 29 were found to be much more active activators compared to the cationic iodine(I) based XB donor 30 in this reaction, even though they activate the substrate through a single XB.

These iodolium salts were found to be proficient catalysts for the activation of methyl vinyl ketone (31) in a Diels-Alder reaction with cyclopentadiene (32) (Scheme 8b). This reaction had previously been used in the first example of the catalytic activation of a carbonyl compound by halogen bonding.\cite{94} As usual, weakly coordinating anions such as $\text{BAR}^-$ are required to activate carbonyl compounds effectively. An activity profile similar to the results obtained in the previous halide abstraction study was observed, although the bidentate iodine (I)-based XB donor 30 was in this case slightly superior. It is interesting to note that these iodine(III) XB donors provide this level of activity without the requirement for chelation. These results provide a first glimpse at the broad potential of iodine(III) XB donors. From these results it could be assumed that iodine(III)-based XB donors seem to be better fitting...
towards halide abstractions than carbonyl activation. The need for stoichiometric amounts of these XB donor, due to strong halide anion coordination, is a disadvantage in these processes, however, and should be kept in mind for future developments.

4.3. Further Use as Halide Abstractors

Since 2020, the use of iodine(III)-based XB donors in organocatalysis seems to gain a foothold in the community and several new examples were published.

The groups of Huber, Kirsch and Legault reported the activation of a gold chlorine bond using XB donors. A catalytic amount of (PPh₃)AuCl was used in combination with the same amount of XB donor. Iodolium salts 17a, 17b, and 17c, as well as the strongest cationic bidentate iodine(I) based XB donor 21 were studied. As expected, weakly coordinating anions like BArF⁻ were again required in the case of iodine(III) XB donors to observe activity. These compounds act as stoichiometric activators of the gold complex, but they are used in a catalytic amounts with respect to the substrate. The effect of these donors were evaluated in two Au(I)-catalyzed cyclization reactions, as depicted in Scheme 9.

The role of halogen bonding in the mechanism could again be supported using the sterically constrained iodonium salts.

Furthermore, ³¹P NMR investigations strongly support the activation of the Au(I)-Cl bond.

Another application of diaryliodonium salts as halide abstractors was presented by Aoshima and coworkers in the catalysis of a living cationic polymerization. Herein, a cationogen is formed by the reaction of an olefinic monomer, triflic acid and tetrabutylammonium iodide. The polymerization is initiated by halide abstraction using a XB donor (Scheme 10). Interestingly, while iodine(I) based XB donors have also been used in such a reaction a few years ago diaryliodonium salts actually have a long history as photocacids of polymerization. The use of the latter as Lewis acid in such a transformation was however never explored. Therein, they used several different diaryliodonium triflate and hexafluorophosphate salts 42 for the polymerization of different vinyl ether and styrene derivatives. Their system allowed highly controlled and living polymerization. Control experiments indicated that the XB-based Lewis acidity is indeed the mode of action.

In the context of halide abstraction, the Ritter-type solvolysis (Scheme 8a) was further utilized as a benchmark by two groups (Scheme 11). In their publication on the synthesis and application of iodolopyrazolium salts, Nachtsheim and coworkers focused on their use as synthetic intermediates, but also shortly investigated their XB donor potential. Under slightly modified conditions (preparative instead of NMR experiments), they tested their compound 43 against the typical iodolium 17aOTf in the solvolysis of benzhydryl chloride and bromide and reported a significant increase in activity. Shortly thereafter, Huber and coworkers published their investigation on the tunability of cyclic diaryliodonium salts using the Ritter-type solvolysis of α-methylbenzyl bromide as a benchmark reaction. In a direct comparison, the simple iodolium derivative 17aOTf was found to be superior in terms of XB-based activity compared to the equivalent, unfunctionalized, six-membered iodininium counterpart 45a, which was basically inactive. This difference was also underlined by ITC experiments, as 45a provided an equilibrium constant approximately fifty times lower than 17aOTf for the binding of...
bromide in acetonitrile. Two additional analogues (44 and 45b) were also studied. The iodoxinium derivative 45b showed higher activity than iodolium 17aOTf, despite its six-membered core structure. The polyfluorinated iodolium 44 surpassed all tested donors by far, which was also reflected by its binding constant towards bromide in acetonitrile, which is approximately eight times higher than the one of its unfunctionalized counterpart as well as of the strongest bidentate iodine(I) based XB donor 21 (as triflate salt).

4.4. Towards the Activity of Classical Strong Lewis Acids

The high activity of iodine(III)-based XB donors compared to their non-hypervalent analogues is quite remarkable. In the past, polydentate iodine(I)-based XB donors were required for the efficient activation of several substrates. The iodine(III) species can already activate substrates with a single XB donor site. As a consequence, they are typically smaller than their iodine(I) counterparts, and require shorter synthetic routes. Alternatively, one could then expect even higher catalytic activity of iodine(III) analogues of preorganized bidentate XB donors like 21. Very recently, Huber and coworkers were the first to demonstrate this by utilizing 46, a rigid and therefore highly preorganized bis(iodolium) salt, which clearly can bind Lewis bases in a bidentate fashion.\textsuperscript{[102]} The parent triflate salt was introduced by Yoshikai in 2015, in a different context.\textsuperscript{[103]} Huber and coworkers first tested this catalyst in a typical XB benchmark Michael addition (Scheme 12a), where its activity surpassed 21. The Nitro-Michael reaction between indole derivative 50 and β-nitrostyrene 51 (Scheme 12b) has been shown in the past to be catalyzed by bidentate chalcogen bond donors\textsuperscript{[104]} but not or only very moderately\textsuperscript{[86]} by related iodine (I)-based halogen bond donors. In this case it was modified to a more challenging form employing a lower catalyst loading of 5 mol\% and no excess of the nucleophile. Therein, only catalyst 46 was active, while other reference catalysts (such as 21 and molecular iodine) failed to activate this reaction. In both reactions, the catalyst loading could be lowered to 1 mol\%, while still yielding a reasonable activation. Additionally, a more challenging variant of the Diels-Alder reaction from Scheme 8b, employing 1 eq. of cyclohexadiene instead of 10 eq. of cyclopentadiene (Scheme 12c) was investigated. The presence of 30 mol\% of 46 promoted the reaction; such level of activation is close to the one observed with a strong Lewis acid such as boron trifluoride etherate.

These results demonstrate the extremely high potential for these XB donors in catalysis. Combined with the tunability options described above, a rational design of even stronger XB catalysts is foreseeable.

4.5. Further Activation of Neutral Substrates

In addition to these typical XB model reactions involving neutral substrate activation, the catalysis of Knorr-type reactions between acetylacetone and acyl hydrazides using iodolium 17a was published recently by Bolotin and coworkers (Scheme 13).\textsuperscript{[105]} Therein, it was shown that using 17a salts (as OTf, TFA and NTf\textsubscript{2} salts) provided sufficient activation for the reaction to proceed. In contrast, neutral non-hypervalent XB donors, as well as other iodine(III) compounds such as diphenyliodonium trifluoroacetate failed to promote the reaction. The triflate 17aOTf had the highest activity and was used to optimize the reaction conditions and present a substrate scope. Computational studies as well as \textsuperscript{1}H NMR titrations indicate a XB-mediated mechanism via carbonyl coordination.

While this account is clearly focused on iodine(III)-based XB donors, it is worth to mention that recently the first example of catalysis employing bromine(III) salts was reported: Yoshida and coworkers used a typical Michael reaction similar to the one in Scheme 12a, which was in this case catalyzed by bromolium salts like 58 (Scheme 14).\textsuperscript{[106]}
Several control experiments showed that neither decomposition products like bromine or the corresponding bromobenzyl nor triflic acid, formed by slow hydrolysis of the bromonium salts, were the catalytic active species. The authors also ruled out a radical process. In this study, the authors evaluated the influence of substituting the methyl in 58 by a hydrogen or a trifluoromethyl group, as well as the suitability of different counter-ions (Cl, OTf, BArF). Iodolium triflate 17aOTf was also evaluated in this reaction as a reference catalyst. With the exception of iodolium 17aOTf, all these species were found to be active. Interestingly, 58 turned out to be the strongest catalyst. This is somewhat surprising as the methyl group should decrease the Lewis acidity of the catalyst and a weaker coordinating anion like BArF– should have a positive influence on the reaction outcome. Since these results seem to contradict classical XB theory, this issue should be further investigated. For example, these bromonium salts might activate the substrate through another type of non-covalent interaction, and not via halogen bonding.

5. Conclusion

While hypervalent iodine(III) compounds had been used very successfully as reagents for some time, their application as Lewis acids – and thus halogen bond donors – has only come into focus in the last few years. Solid-state structures of such species had been known for decades, and the Lewis acidity had in principle been demonstrated. A comparative quantification of this phenomenon in solution was, however, only reported in 2017, and based on such fundamental data, first applications in noncovalent organocatalysis have subsequently appeared. In light of the high halogen bonding strength of these compounds (particularly compared to strong iodine(1)-based variants) and of the manifold options to tune the core motifs, many further fascinating developments can be expected in the next years.

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Iodine(III)-based halogen bond donors (halogen-based Lewis acids) have received increasing attention lately. This account provides an overview of the topic and summarizes our studies on Lewis acidity measurements and applications in catalysis.