Hypervalent Iodine(III) Compounds as Biaxial Halogen Bond Donors

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ABSTRACT: “Hypervalent” iodine(III) derivatives have been established as powerful reagents in organic transformations, but so far only a handful of studies have addressed their potential use as halogen-bonding noncovalent Lewis acids. In contrast to “classical” halogen-bond donors based on iodine(I) compounds, iodine(III) salts feature two directional electrophilic axes perpendicular to each other. Herein we present the first systematic investigation on biaxial binding to such Lewis acids in solution. To this end, hindered and unhindered iodolium species were titrated with various substrates, including diesters and diamides, via 1H NMR spectroscopy and isothermal titration calorimetry. Clear evidence for biaxial binding was obtained in two model systems, and the association strengths increased by 2 orders of magnitude. These findings were corroborated by density functional theory calculations (which reproduced the trend well but underestimated the absolute binding constants) and a cocrystal featuring biaxial coordination of a diamide to the unhindered iodolium compound.

INTRODUCTION

The chemistry of hypervalent iodine (HVI) compounds is known for its versatility in organic reactions.1 Iodine(III) species, for instance, are established in a wide range of organic transformations, such as the oxidation of functional groups2 or as transition-metal catalyzed3 or direct3a,4 arylating agents. In the latter case, diaryl iodonium species are often applied. These typically feature a T-shaped structure with the two aryl substituents bound to iodine in a roughly 90° angle and the anion bound via an additional “secondary” bonding.1a This interaction between the iodonium cation and its anion vividly illustrates the electrophilic nature of the iodine center, and the coordination can be seen as a special case of halogen bonding (the noncovalent interaction between electrophilic halogen halogen substituents and Lewis bases).5 Halogen bonding is based on contributions from electrostatics,6 charge transfer,7 and dispersion, and one of its key features is its high linearity, that is, interaction angles of ~180°. Iodine(I)-based Lewis acids have by now been used in various applications, for example, in crystal engineering,8 molecular recognition,9 and catalysis.10

Even though the Lewis acidity of iodine(III) species has implicitly been exploited in countless instances in synthesis, the organoiodine compounds act as reagents in all these cases. The explicit use of iodine(III)-based Lewis acidity, in contrast, has only been studied and applied in very few examples so far: Liu et al. applied diaryl iodonium salts as Lewis acids in a threefold Mannich reaction,11 whereas Legault et al. quantified the Lewis acidity of iodine(III) compounds and compared their strength with other classical Lewis acids.12 Recently, our group reported the use of cyclic iodonium compounds in two benchmark reactions, namely, the solvolysis of benzhydryl chloride with acetonitrile and a classical Diels–Alder reaction.13

In all these cases, however, only one electrophilic axis on the iodine atom has been used to bind to Lewis bases despite the fact that iodine(III) derivatives—in contrast to iodine(I) species—feature two such electrophilic axes in elongation of both R–I bonds (Figure 1).

This has been confirmed by several theoretical studies14 and also by various solid-state structures, as it is well-known that diaryliodonium halides form dimers in which two halides are bound to each iodine(III) center.15 Somewhat surprisingly, to the best of our knowledge, there is currently only one application that is based on the simultaneous use of both electrophilic axes: Ochiai and co-workers used crown ethers to complex to iodine(III) species like ethynyl(phenyl)-λ3-iodanes in order to increase their thermal stability. Crystal structures provided
obtained (Figure 2). However, because of the presence of three or more oxygen atoms on the Lewis bases, there is no ideal match between halogen bond donor and acceptor, and in addition also the reference compounds (like diglyme) likely bind in a two-point fashion. Thus, there is currently no systematic comparison of biaxial versus monoaxial binding and no investigation of their relative strength. Herein, we present such a study, featuring the biaxial binding of a neutral bidentate Lewis base to an iodolium salt, supported by density functional theory (DFT) calculations, $^1$H NMR titrations, isothermal titration calorimetry (ITC) titrations, and X-ray diffraction (XRD) analyses.

RESULTS AND DISCUSSION

Orientating Computational Screening. Iodolium cations were chosen as halogen-bond donors, since they feature a very rigid geometry, which also allows to block one or both electrophilic axes by substituents in $\alpha$-position to the iodine center. In order to identify suitable bidentate Lewis bases that are capable of binding to both electrophilic axes of these donors simultaneously, we performed DFT calculations (M06-2X/def2-TZVP(D)/SMD18, for further details see below). Initially investigated substrates were based on malonic acid derivatives, which bear two carboxyl groups in close proximity (complex 1, Figure 2). The calculations revealed, however, that the distance between the two oxygens is too short, and thus only a single halogen bonding interaction is found. Instead, biaxial binding was found in complexes with isophthalic acid (a single halogen bonding interaction is found. Instead, biaxial binding was found in complexes with isophthalic acid (bottom). Graphics generated with CYLview.

$^1$H NMR and ITC Titration Experiments. To confirm the formation of these complexes in solution, binding constants of various ketones, esters, and amides to iodolium/BArF$_4$ 4a (Figure 4) in CDCl$_3$ were determined by $^1$H NMR titrations. Figure 3 (top) illustrates the binding event between iodolium/BArF$_4$, 4a and diester 5 with a typical fitting curve of the $^1$H NMR titration (middle) and the relevant $^1$H NMR data set indicating the shifting signals of the $\alpha$-protons (bottom). If compounds like diester 5 would bind in a biaxial manner, stronger complexation should occur compared to electronically similar structures, which cannot coordinate in such a fashion due to geometric constraints. The experimental data are summarized in Figure 4.

Indeed, a comparison of diesters 5 and 7, which only differ in their substitution pattern but are otherwise electronically identical, clearly demonstrates biaxial binding of the former to the iodolium. DFT calculations confirm that only one carbonyl of 7 is bound to the Lewis acid (see Supporting Information). This leads to very marked differences in the measured binding constants: while ortho-diester 5 showed an association strength of $K = 1.0 \times 10^1$ M$^{-1}$, para-diester 7 featured a significantly lower value of $K = 1.7 \times 10^1$ M$^{-1}$. Thus, biaxial adduct formation increases the binding strength by at least 2 orders of magnitude.

To underline the significant relative binding strength of diester 5, an array of further esters and ketones, including $\alpha$-alkyne, $\alpha$-alkene, and cyclic esters/ketones, was also tested. In general, esters 9, 11, and 12 show very similar binding constants of $\sim K = 1.0 \times 10^1$ M$^{-1}$, which is in good agreement with the value found for the monoaxially binding diester 7. Interestingly, these data also indicate that diester 9, which was found to bind in a biaxial fashion in DFT calculations (complex 2, Figure 2), acts as a monodentate Lewis base.

In comparison to the open-chain systems, cyclic ester 16 gave a higher binding constant of $K = 1.0 \times 10^2$ M$^{-1}$, which was also superior to the one of structurally related cyclohexanone (15). Ketones 10 and 13, in contrast, were found to bind stronger ($K = 2.6-4.8 \times 10^2$ M$^{-1}$) than the corresponding open-chain esters. Motivated by these findings, the experiments were expanded toward amides. Their increased Lewis basicity should lead to...
higher binding constants for isostructural motifs. Similar to the esters 5 and 7, we expected a significant difference in binding constants for the corresponding ortho- and para-substituted diamides 6 and 8. Because of stronger binding, the association constant of diamide 6 could be determined via ITC experiments, and a representative measurement is shown in Figure 5. For a related figure that is based on free energies, see the Supporting Information (Figure S38).

binding strength was measured for the complexation of 5 and 6 to 4b with comparable values of $K = 3.5 \times 10^3 \text{ M}^{-1}$ and $K = 3.1 \times 10^3 \text{ M}^{-1}$, respectively. On the other hand, the values for substrates 7 and 8 are similar to the ones with the unhindered system 4a, as expected. Finally, when both electrophilic axes are blocked in derivative 4c, weak and somewhat comparable binding constants are obtained for all substrates ($K = 1.2 - 9.6 \times 10^2 \text{ M}^{-1}$), which are possibly due to $\pi-\pi$ interactions.

**Theoretical Modeling of Binding Energies.** As already indicated above, our experimental studies were accompanied by DFT calculations (using the Gaussian16 software suite, Rev. B.01), which were first performed as described in our previous report on the SMD18 solvation model, the M06-2X/def2-TZVP combination. 23 All geometries were fully optimized with the SMD18 intrinsic solvation model using parameters for chloroform on an ultrafine grid. The identity of minima was confirmed by the absence of imaginary frequencies (except for three cases, for which persistent low-lying imaginary frequencies less than $-50 \text{ cm}^{-1}$ were transformed to positive ones; see the Supporting Information). All frequencies were scaled by 0.9753, as recently recommended for the M06-2X/def2-TZVP(D) combination. 23 Gibbs free energies were computed at 300 K and were corrected to account for the 1 M standard state in solution.

Overall, these calculations served several purposes: first and foremost, they helped to identify suitable interaction pairs for biaxial binding, as already discussed above (see Figure 2). Second, they test the feasibility of predicting useful binding constants for such kinds of complexes in silico. In our previous study, very good agreement with experimental data was achieved with the above-mentioned protocol and additional corrections for low-frequency entropy issues, as published by Grimme. 25 Such calculations were performed for the complexes of 4a with all substrates 5–17 and for the complexes of 4b and 4c with substrates 5–8 (the most relevant substrates for biaxial coordination). For all Lewis acid/base pairs, alternative modes

![Figure 4. Binding constants of various Lewis bases to XB-Donors 4a–4c. Binding constants were measured via $^1$H NMR titrations in CDCl$_3$ at 300 K or via ITC experiments at 303 K. For a related figure that is based on free energies, see the Supporting Information (Figure S38).](image)

![Figure 5. ITC measurement of the complexation of iodolium/BAr$_3$F$_4$ 4a with diamide 6 in CHCl$_3$ at 304 K.](image)
A more stable conformer (e.g., based on \( \pi \)-stacking) was found. A more stable error for corrected \( \Delta G \) values (calculations vs experiment). Mean absolute errors.

Table 1. Comparison of Experimental and Calculated Gibbs Free Energies \( \Delta G \) of Adduct Formation

| complex | \( \Delta G \) | \( \Delta G \) with SMD | \( \Delta G \) with PCM |
|---------|---------------|---------------------|---------------------|
|         | experimental  | calculated          | calculated          |
| 4a      | 5             | −4.1                | −3.7                | 0.4                 | −2.0                | 2.1                 | 2.1                 | −3.3                | 0.8                 | −2.0                | 2.1                 |
|         | 6             | −6.3                | −9.1                | 2.8                 | −7.6                | 1.3                 | 1.3                 | −6.6                | 0.3                 | −6.7                | 0.4                 |
|         | 7             | −1.7                | 2.3                 | 4.0                 | 4.4                 | 6.1                 | 6.1                 | 1.2\( ^c \)           | 0.5                 | 5.1                 | 6.8                 |
|         | 8             | −4.4                | −1.3\( ^c \)         | 3.1                 | 0.1\( ^c \)         | 4.5                 | 4.5                 | −2.8\( ^b \)          | 1.6                 | −0.7\( ^c \)         | 3.7                 |
|         | 9             | −1.7                | 0.0\( ^c \)          | 1.7                 | 2.8                 | 4.5                 | 4.5                 | 0.4\( ^c \)           | 1.3                 | 3.1\( ^c \)          | 4.8                 |
|         | 10            | −2.0                | 0.7                 | 2.7                 | 2.9                 | 4.9                 | 4.9                 | 0.3                 | 2.3                 | 2.6                 | 4.6                 |
|         | 11            | −1.6                | −1.5                | 0.1                 | 1.1                 | 2.7                 | 2.7                 | 0.4                 | 2.0                 | 2.3                 | 3.9                 |
|         | 12            | −1.4                | 0.1                 | 1.5                 | 2.4                 | 3.8                 | 3.8                 | −0.1                | 1.3                 | 2.4                 | 3.8                 |
|         | 13            | −2.1                | −1.7                | 0.4                 | 0.7                 | 2.8                 | 2.8                 | −2.8                | 0.7                 | 0.5                 | 2.6                 |
|         | 14            | −3.2                | −2.1                | 1.1                 | −0.1                | 3.1                 | 3.1                 | −2.0                | 1.2                 | −0.1                | 3.1                 |
|         | 15            | −2.1                | −0.4                | 1.7                 | 1.9                 | 4.0                 | 4.0                 | 0.2                 | 2.3                 | 2.3                 | 4.4                 |
|         | 16            | −2.8                | −3.3                | 0.5                 | −1.1                | 1.7                 | 1.7                 | −2.1                | 0.7                 | −0.1                | 2.7                 |
|         | 17            | −3.4                | −3.9                | 0.5                 | 0.5                 | 2.0                 | 2.0                 | −3.1                | 0.3                 | −1.2                | 2.2                 |
| 4b      | 5             | −2.1                | −1.3                | 0.8                 | 0.5                 | 2.6                 | 2.6                 | −1.0                | 1.1                 | 0.9                 | 3.0                 |
|         | 6             | −4.8                | −3.6                | 1.2                 | −3.8                | 1.0                 | 1.0                 | −1.7                | 3.1                 | 0.1                 | 4.9                 |
|         | 7             | −1.5                | 2.7                 | 4.2                 | 5.5                 | 7.0                 | 7.0                 | 2.5                 | 4.0                 | 5.6                 | 7.1                 |
|         | 8             | −4.3                | 1.0                 | 5.3                 | 3.0                 | 7.3                 | 7.3                 | 1.7                 | 6.0                 | 3.5                 | 7.8                 |
| 4c      | 5             | −1.1                | 0.2                 | 1.3                 | 0.3\( ^c \)         | 1.4                 | 1.4                 | −1.6\( ^c \)         | 0.5                 | −1.6                | 0.5                 |
|         | 6             | −1.6                | −0.8\( ^c \)         | 0.8                 | −1.0\( ^c \)        | 0.6                 | 0.6                 | −3.0\( ^b \)          | 1.4                 | −3.6                | 2.0                 |
|         | 7             | −0.1                | 7.8                 | 7.9                 | 9.7                 | 9.8                 | 9.8                 | 3.6                 | 3.7                 | 4.3                 | 4.4                 |
|         | 8             | −1.4                | 2.9                 | 4.3                 | 5.1                 | 6.5                 | 6.5                 | 1.4                 | 2.8                 | 4.3                 | 5.7                 |
| MAE\( ^c \) |              | 2.2                 | 3.8                 | 1.8                 | 3.8                 |

\( ^a \)Absolute error (calculation vs experiment). \( ^b \) \( \Delta G \) including low-frequency entropy corrections by Grimme. \( ^c \) A more stable conformer (e.g., based on \( \pi \)-stacking) was found. Mean absolute errors.
estimation of the free energy of complexation in most instances) and the general difficulty of assessing partition function contributions from low-frequency modes associated with relatively weak nonbonded interactions between molecules when those modes are well-described neither as vibrations nor as internal rotations.

**Cocrystallization Experiments.** To corroborate our findings in solution, cocrystallization experiments were also performed by slow evaporation of water and dioxane. Indeed, a biaxial mode of binding was found in the cocrystal of iodolium $4a$/BaCl$_4$ (which was used instead of BaF$_2$ as better crystallization) and diamide 6 (Figure 6, left). Both oxygens of the diamide are bound to one electrophilic axis of the same iodine center, respectively. The interaction parameters of the complex are typical for halogen bonding, with distances below the sum of the van der Waals radii$^{21}$ (2.7 and 2.8 Å vs 3.5 Å) as well as nearly linear C–I···O angles (ca. 177°). The minimum structure calculated with DFT (Figure 6, right) features very similar geometrical data (with almost similar bond distances of 2.77 Å and bond angles of 168°). In both structures, diamide 6 forms an angle of ∼70° to the plane of the iodolium. Thus, while the prediction of absolute energies still seems to be quite challenging for DFT, the structures obtained by such calculations may serve as a very good model for the complex geometries.

**Analysis of the Noncovalent Interactions.** Finally, the nature of the interaction between the halogen-bond donors and the neutral substrates was analyzed by various quantum-chemical approaches. The key question was whether the main interaction could indeed be described as halogen bonding or whether these associations were simply based on unspecific binding of Lewis basic centers to cations. Obviously, several experimental observations already clearly point toward halogen bonding: the highly linear C–I···O interaction angles in the crystal structure of 4 · 6 (Figure 6) are a typical feature of this interaction, and the fact that complex formation can be strongly suppressed by a blockade of the electrophilic axes associated with halogen bonding further corroborates this. Nevertheless, detailed computational analyses were performed for the complexes exhibiting clear biaxial coordination, that is, the adducts of unsubstituted iodolium compound 4a with diester 5 and diamide 6. In both cases, the anion of 4a was omitted in the calculations.

First, natural bond orbital (NBO) analyses$^{27}$ were performed to obtain an orbital-based description of the adduct formation (for further details see Supporting Information). The arguably first theoretical description of halogen bonding by Mulliken$^{28}$ was based on the interaction between a lone pair of the Lewis base with the antibonding orbital of the element–halogen bond. This $\text{n} \rightarrow \sigma^*$ interaction was also identified by NBO second-order perturbation analyses as the key component of intermolecular contact: in the complex 4a · 5, the orbital interactions between oxygen lone pairs of 5 and the C–I $\sigma^*$ orbitals of 4a were found to be the predominant contribution to the binding, with estimated interaction energies of 2.7 kcal/mol (for sp-hybridized oxygen orbitals on 5) and 1.4 kcal/mol (for p-hybridized oxygen orbitals on 5; see Supporting Information). No other intermolecular interaction exceeded 1 kcal/mol. Completely analogous results were obtained for the complex of 4a with 6. Here, the corresponding estimated contributions amounted to 5.1 and 2.6 kcal/mol, respectively, and again no other relevant orbital interactions were found. While the energies just mentioned follow the trend in binding strength observed experimentally, their absolute value should probably not be overinterpreted. Still, the NBO analysis clearly confirms halogen bonding as the dominating force for adduct formation.

Further insight was then sought by quantum theory of atoms in molecules (QTAIM)$^{29}$ analyses, which were conducted via Multiwfn$^{30}$ on wfn files generated by Gaussian. In both complexes, four (3/→1) bond critical points (BCPs) were found between halogen-bond donor and substrate. For adduct 4a · 5, these are illustrated, together with the corresponding bond paths, in Figure 7.

The two outer BCPs correspond to hydrogen bonding between oxygen lone pairs of 5 and the $\alpha$-protons of 4a. We note that we had already seen in earlier calculations involving the coordination of a carbonyl group (of a Diels–Alder transition state) to the same iodolium compound 4a that a strong halogen bond between oxygen and iodine is accompanied by a relatively weak hydrogen bond of the oxygen to the nearest iodolium hydrogen. $^{15}$ The two inner BCPs, with density $\rho = -0.14 \times 10^{-11}$ a.u. and Laplacian $\nabla^2 \rho = 0.71 \times 10^{-11}$ a.u., represent halogen bonding. Bond critical points like the ones found here, with relatively small densities $\rho$ and positive Laplacians ($\nabla^2 \rho$), are characteristic for noncovalent intermolecular interactions like hydrogen bonding (and halogen bonding).$^{29,31}$ Virtually identical results were obtained for the complex 4a · 6 (see Supporting Information). The corresponding parameters for the halogen-bonding BCPs are $\rho = -0.20 \times 10^{-11}$ a.u. and $\nabla^2 \rho = 0.84 \times 10^{-11}$ a.u., which are clearly very similar to the ones mentioned above for complex 4a · 5.
In addition, the Multiwfn software was also applied to perform noncovalent interaction (NCI) analyses.\textsuperscript{32} Once again, analogous results were observed for both biaxial adducts. Scatterplots of reduced density gradient (RDG) versus sign($\lambda_2$)\textsuperscript{ρ} yielded spikes of data points with slightly positive RDG and negative sign($\lambda_2$)\textsuperscript{ρ} (see Supporting Information), which indicate attractive intermolecular interactions and are typical for hydrogen bonding and halogen bonding.\textsuperscript{32} The corresponding NCI plots clearly provided evidence for attractive noncovalent interactions between the oxygen atoms of 5 and 6 with the iodine center in 4a (see the bluish surface in Figure 8, which depicts complex 4a \cdot 6, and Supporting Information).

Thus, NBO, QTAIM, and NCI analyses all unambiguously point toward halogen bonding as the key mode of interaction in complexes 4a \cdot 5 and 4a \cdot 6.

\section*{CONCLUSIONS}

The first systematic study on the biaxial coordination of iodine(III)-based Lewis acids with suitable bidentate substrates was presented. This model system was investigated by analyzing the binding constants of a series of Lewis bases to three different iodolium compounds via $^1$H NMR (and in one case ITC) titrations. Biaxial coordination was only achieved in the combination of an unhindered iodolium species with geometrically suitable diesters and diamides. A variation of the bite angle of the latter two substrates, which impedes biaxial binding, led to a reduction in binding strength by 2 orders of magnitude. Subsequent blocking of one or both electrophilic axes on the iodine-based Lewis acids also led to markedly reduced binding constants, even when potentially suitable substrates were used, further corroborating our findings. This trend could also be identified by supporting DFT calculations, but these tend to (sometimes severely) underestimate the binding constants, even when intrinsic solvation models were applied. A crystal structure between a diamide and the unhindered iodolium compound also clearly demonstrated biaxial binding. This study constitutes an important first step toward the rational exploration of the two electrophilic axes in iodine(III)-based Lewis acids, and experiments to utilize this concept in organocatalysis are currently underway.\textsuperscript{33}

\section*{ASSOCIATED CONTENT}

\begin{itemize}
  \item \textbf{Supporting Information}
  
  The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13309.
\end{itemize}
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