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# Iodine(III) derivatives as halogen bonding organocatalysts

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Abstract: Hypervalent iodine(III) derivatives are known as versatile reagents in organic synthesis, but there is only one previous report on their use as Lewis acidic organocatalysts. Herein, we present first strong indications on the crucial role of halogen bonding in this kind of catalyses. To this end, the solvolysis of benzhydryl chloride and the Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone serve as benchmark reactions for halide abstraction and the activation of neutral compounds. Iodolium compounds (cyclic diaryliodonium species) were used as activators or catalysts, and their activity could be markedly reduced or completely switched off by sterically blocking one or two of their electrophilic axes. In comparison with previously established bidentate cationic halogen bond donors, the monodentate organoiodine derivatives used herein are at least similarly active (in the Diels-Alder reaction) or even decidedly more active (in the benzhydryl chloride solvolysis).

Organoiodine compounds feature a rich hypervalent chemistry.<sup>[1]</sup> One example for such species are iodine(III) derivatives,<sup>[2]</sup> which have been established as useful reagents in organic synthesis,<sup>[3]</sup> for example to oxidize functional groups<sup>[4]</sup> or to transfer electrophilic substituents.<sup>[5]</sup> Neutral iodine(III) compounds typically<sup>[6]</sup> possess three substituents in a T-shaped geometry, as exemplified by phenyliodine(III) diacetate. Two of these substituents engage in a three-center-four-electron (3c4e) hypervalent bond. In an apparent contrast, cationic diaryliodonium species feature two substituents at a roughly 90° angle towards each other. However, it is well established that "the overwhelming majority of iodonium salts show a significant secondary bonding between the iodine atom and the anion."[3c] Thus, the iodine center is trivalent in both cases, and the rationalization of the resulting T-shaped geometry is a matter of definition: if one substituent is bound markedly weaker than the others (as in diaryliodonium salts), a "secondary" (noncovalent) interaction may be the most illustrative model (Figure 1 right), otherwise the 3c4e picture is often preferred.



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Figure 1. Left: halogen bonding with monovalent halogen substituents (definition); right: halogen bonding with iodine(III) species; LB = Lewis base.

Both variants may also be viewed as a special case of halogen bonding (XB), i.e. the interaction of Lewis bases with electrophilic halogen substituents.<sup>[7]</sup> So far, XB has mostly<sup>[8]</sup> been considered for monovalent halogen substituents (Figure 1 left), but the IUPAC definition<sup>[9]</sup> explicitly also includes higher substituted halogen centers.

In view of our interest to apply XB in organocatalysis,<sup>[10]</sup> we intended to extent this concept towards the use of iodine(III) compounds as noncovalent Lewis acids. To the best of our knowledge, there is only one prior example of such an application,<sup>[11]</sup> which lacked any mechanistic study.<sup>[12]</sup> Herein, we present two proof-of-principle cases in which the action of XB is clearly demonstrated by a series of comparison experiments.

In this study, we focused on cyclic iodolium salts<sup>[13,14]</sup> (see Figure 2) for two reasons: a) the core structure is more rigid than in the acyclic diaryliodonium species, so the geometry of XB complexes is more predictable and b) as one consequence of this, both electrophilic axes of the iodolium compound may be conveniently blocked by *ortho*-substituents (relative to iodine) on the aromatic rings.

The synthesis of derivatives 1a<sup>[13]</sup>, 2a and 3a<sup>[14]</sup> (Figure 2) proceeded via the reaction of an arylmagnesium bromide with benzene-derived aryne and subsequent quenching with elemental iodine.<sup>[15]</sup> Oxidation of the resulting ortho-iodinated biphenyl with *m*-chloroperoxybenzoic acid and HOTf<sup>[16]</sup> yielded the respective iodolium triflate. The trifluoromethyl substituent of compound 2a allows to easily monitor the stability of this Lewis acid by <sup>19</sup>F-NMR spectroscopy, whereas the methyl substituent of 3a is intended to block one of the two electrophilic axes. Previously unknown derivative 4a features two such substituents and should thus constitute a reference compound devoid of any XB options. It was synthesized by Suzuki-Miyaura crosscoupling of 2,4-dimethyl-6-bromoaniline and (2,4dimethylphenyl)boronic acid (yield: 25 %) followed by iodination (via diazotation and treatment with KI)<sup>[13b]</sup> and final oxidation as described above (yield: 48 % over two steps). Next to the triflate salts, we also prepared variants with noncoordinating BArF4-[17] (1b, 3b, 4b) or more strongly coordinating chloride (1c, 3c) counterions by anion metathesis with NaBAr<sup>4</sup><sub>F</sub> or NaCl.





Next, X-ray structural analyses were performed to confirm the absence of XB to potential substrates along the blocked electrophilic axes in the singly (**3a-c**) or doubly (**4a-b**) *ortho*-substituted derivatives. While the unhindered parent compound **1** featured XBs along both axes with bromides (Figure 3 left),<sup>[18]</sup> the methyl substituent in **3** indeed blocks one of these axes and thus only one XB is found in the chloride salt (Figure 3 right). Accordingly, despite multiple attempts, no co-crystals of the tetramethylated species **4** with halides could be obtained, confirming that the methyl groups block interactions with these substrates. The interaction parameters of both complexes shown in Figure 3 are typical for XB, i.e. distances below the sum of the van-der-Waals radii<sup>[19]</sup> (3.2 Å vs. 3.83 Å and 3.0 Å vs 3.73 Å) as well as near linear C-I···X angles (approx. 170°).



**Figure 3.** Cutouts of the X-ray structural analyses of the XB complexes of **1** with bromide (left) and **3** with chloride (right). Ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity.

Orientating calorimetric measurements resulted in a binding constant of compound **1a** with tetrabutylammonium (TBA) bromide of approx.  $10^6$  mol/l in acetonitrile, which is higher (by a factor of 2) than the one of our previously employed bidentate (!) XB donor **5a** (Figure 4) under identical conditions.<sup>[20]</sup>



Figure 4. Bidentate XB donors 5a/5b as reference compounds.

Consequently, we decided to use a more challenging variant of our earlier halide abstraction benchmark reaction (the solvolysis of benzhydryl bromide)<sup>[21]</sup> and instead investigated the reaction of benzhydryl chloride **6** to acetamide **7** in wet acetonitrile (Figure 5).

Even after six days, no background reaction was observed without any activator. In contrast, iodolium compounds **1a**, **1b** and **2a** lead to about 80% formation of product in the same time (Figure 5). The BAr<sup>F</sup><sub>4</sub> salt **1b** shows a slightly higher conversion than the triflate salt **1a**, possibly due to the noncoordinating nature of the anion. No additional peaks were observed in the <sup>19</sup>F-NMR spectra of the reactions involving Lewis acid **2a** even

after several weeks, demonstrating the stability of the iodolium compounds under reaction conditions.



Figure 5. Reaction of benzhydryl chloride 5 with one equivalent of various potential activating reagents in wet  $CD_3CN$  (yields according to <sup>1</sup>H-NMR spectroscopy).

In the methylated derivatives **3a** and **3b**, one electrophilic axis is blocked, and thus lower activity is expected. Indeed, only 25-36% yield of product **7** is obtained. In this case, the triflate salt is somewhat more active than the  $BArF_4$  one. Further detailed studies will be required to elucidate the origins of this finding.

Most importantly, compounds **4a** and **4b**, in which both axes are blocked, show no conversion in this benchmark reaction. The overall trend in the relative performance of **1**, **3** and **4** provides a strong indication that XB is the main mode of activation. Other possible reasonings like anion- $\pi$  interactions or counterion effects should be roughly comparable over these Lewis acids and would not be able to explain these drastic differences.

Additional experiments were performed with the corresponding chloride salts **1c** and **3c** as well as with a combination of **1a** and one equivalent TBA chloride (forming **1c** *in situ*). In all cases, no activation was observed, likely because the electrophilic iodine centers were blocked by chloride. It should be noted that the calorimetric titrations of **1a** with chloride (or bromide) yielded a 1:1 complex stoichiometry, indicating that the formation of a 2:1 complex in solution is energetically not favorable.

A critical aspect in investigations concerning activation by XB is the risk of hidden activation by acid traces or other impurities, such as traces of Na<sup>+</sup> from the anion metatheses. Both of these issues could be ruled out: firstly, NaBAr<sup>F</sup><sub>4</sub> as potential activator does not lead to any product formation and secondly, the use of

a detectable amount (5 mol-%) of HOTf lead to a measureable but relatively low yield of 16% (which could be suppressed by addition of 5 mol-% of TBACI).

Finally, the performance of the iodolium salts was compared to that of our previous bidentate XB donor **5a**. Under the same reaction conditions, 29% yield of product **7** were obtained. This striking difference between the monodentate iodolium species and the bidentate iodolimidazolium derivative - which is in agreement with the calorimetric measurements - is clearly underlining the strong potential of the iodolium compounds in XB-based halide abstraction reactions.

With this strong activity in hand, we turned our attention towards the more challenging activation of neutral substrates in a catalytic fashion.<sup>[10a]</sup> As test reaction, we chose the prototypical Diels-Alder reaction between cyclopentadiene 9 and methyl vinyl ketone 8 (Figure 6, top).<sup>[22]</sup> In contrast to our previous studies, however, 5 mol-% of catalyst were used instead of 20 mol-%. The same set of iodolium compounds as above was tested as catalysts, and kinetics of the reaction were obtained via <sup>1</sup>H-NMR spectroscopy in CD<sub>2</sub>Cl<sub>2</sub> (Figure 6). After six hours of reaction time. 19% vield of product **10** were observed in the uncatalvzed reaction (endo/exo = 3:1). With iodolium compound **1b** or **3b** as catalysts, quantitative formation of product was achieved in about three hours, and as expected the methylated (singly blocked) variant 3b was less active than the parent compound 1b (endo/exo = 9:1 and 9:1). Our earlier study had shown that BArF<sub>4</sub> salts are decidedly more potent in the activation of carbonyl groups than triflate salts, since the counterion of the latter might compete with the substrate.<sup>[22]</sup> This was also observed for the iodolium catalysts, as triflate salts 1a, 2a and 3a induced markedly less yield of product (23-30% after six hours).<sup>[23]</sup> Just as in the previous test reaction, no additional peaks - indicating decomposition - were observed in the <sup>19</sup>F-NMR spectra of the reaction involving 2a. As expected, both doubly blocked derivatives 4a and 4b were completely inactive in the reaction. Also, no additional product formation was observed when 1a, 1b or 3b were premixed with one equivalent of TBACI. Finally, the possibility of acid formation by slow decomposition was ruled out:[24] after the reactions involving catalysts 1-5 had run for one day, the same amounts of starting materials 8 and 9 were added once more, with virtually identical results of the catalyses (see Table S2 in SI). If traces of acid had slowly formed during the first run, a better performance in the second run would have been expected. All these reference and comparison experiments again clearly point towards XB catalysis by the iodine(III) derivatives.

A direct comparison with the bidentate bis(imidazolium)-based XB donor **5b** (Figure 4) shows a slightly better conversion rate by the latter.<sup>[25]</sup> Still, the relative activation by the monodentate iodolium catalysts is impressive, given that a monodentate iodoimidazolium catalyst had shown very poor performance even as BArF<sub>4</sub> salt in the previous study.<sup>[22]</sup>





Figure 6. Diels-Alder reaction in CD<sub>2</sub>Cl<sub>2</sub>, as followed by <sup>1</sup>H-NMR spectroscopy. Experiments with additional TBACI were carried out with 10 mol% XB donor and 10 mol% TBACI.

To obtain a first insight into the structure of a likely transition state, orientating DFT calculations were performed (for further details see SI). The corresponding transition state involving catalyst **1a** is shown in Figure 7.



**Figure 7.** Transition state obtained by DFT calculations (M06-2X TZVPP). Distances (Å) and angles (°): I-O = 2.65, C-I-O = 167°, H-O = 2.22, C-H-O = 128°. Graphic generated by CYLview.<sup>[26]</sup>

The optimized geometry features a very strong XB between the catalyst and the carbonyl compound with an I-O distance of 2.65 Å (sum of van-der-Waals radii: 3.5 Å). In addition, the oxygen atom also accepts a hydrogen bond from the catalyst (2.22 Å vs. 2.62 Å).<sup>[27]</sup> The corresponding barrier of activation (corrected with the SMD intrinsic solvation model for dichloromethane) is 26.7 kJ/mol. In agreement with the experimental findings, it is

similar to the barrier with catalyst **5a** (26.5 kJ/mol), but markedly lower than uncatalyzed (29.5 kJ/mol).

conclusion, hypervalent iodolium derivatives In were introduced as activators in a halide abstraction reaction and as organocatalysts in a Diels-Alder benchmark reaction. For the first time, strong indications on the crucial importance of halogen bonding on the observed activities could be obtained by multiple comparison experiments. These findings are in line with previous computational studies on the importance of XB in complexes of  $\lambda^3$ -iodanes with nucleophiles.<sup>[11]</sup> Most importantly, by sterically blocking one or two of the electrophilic axes, the Lewis acidity of the iodine(III) compounds could be markedly reduced or switched off. This study thus establishes further class of organoiodine derivatives in XB а organocatalysis. Even though the compounds in these experiments were monodentate, they exhibited comparably strong activity. This relative strength as well as the unique options associated with the two electrophilic axes offer fascinating prospects for the further development of this class of catalysts.

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**Keywords:** hypervalent compounds • noncovalent interactions • halogen bonding • solvolysis • organocatalysis

- a) T. Wirth, *Hypervalent lodine Chemistry*, 1<sup>st</sup> ed., Springer-Verlag, Berlin Heidelberg, **2003**; b) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328; c) T. Dohi, Y. Kita, *Hypervalent lodine*, in *lodine Chemistry and Applications* (ed T. Kaiho), John Wiley & Sons, Inc, Hoboken, NJ. **2014**, *103-157*.
- [2] E. A. Merrit, B. Olofsson, Angew. Chem. Int. Ed. 2009, 48, 9052; E. A. Merrit, B. Olofsson, Angew. Chem. 2009, 121, 9214.
- a) A. P. Antonchick, S. Manna, R. Narayan, *Synlett* **2015**, *26*, 1785; b)
   M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, *49*, 2175; c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108* (12), 5299.
- [4] a) F. V. Singh, T. Wirth, *Chem. Asian. J.* **2014**, *9*, 950; b) R. D. Richardson, T. Wirth, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.
- [5] a) E. A. Merrit, B. Olofsson, Synthesis 2011, 4, 517; b) S. V. Kohlhepp, T. Gulder, Chem. Soc. Rev. 2016, 45, 6270; c) J. Waser, Alkynylation with Hypervalent lodine Reagents, in Hypervalent lodine Chemistry (ed T. Wirth), vol. 373, Springer, 2016, pp. 187-222; d) J. Charpentier, N. Früh, A. Togni, Chem. Rev. 2015, 115, 650; e) K. Kiyokawa, T. Kosaka, T. Kojima, S. Minakata, Angew. Chem. Int. Ed. 2015, 54, 13719.

- [6] A notable exception are iodonium ylides, which are also neutral compounds, but carry only two substituents on the iodine center.
- G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* 2016, *116* (4), 2478.
- [8] a) L. Catalano, G. Cavallo, P. Metrangolo, G. Resnati, *Halogen Bonding in Hypervalent Iodine Compounds*, in *Hypervalent Chemistry. Topics in Current Chemistry* (ed T. Wirth), vol. 373, Springer, Cham 2016, pp. 289-309 b) G. Cavallo, J. S. Murray, P. Politzer, T. Pilati, M. Ursini, G. Resnati, *IUCrJ* 2017, *4*, 411.
- [9] G. R. Desiraju, P.S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati, K. Rissanen, *Pure Appl. Chem.* 2013, *85* (8), 1711.
- a) D. Bulfield, S. M. Huber, *Chem. Eur. J.* 2016, 22 (41), 14434; b) J.-P. Gliese, S. H. Jungbauer, S. M. Huber, *Chem. Commun.* 2017, 53, 12052; c) S. H. Jungbauer, S. M. Huber, *J. Am. Chem. Soc.* 2015, 137, 12110.
- [11] For a related computational study, see: H. Pinto de Magalhães, A. Togni, H. P. Lüthi, J. Org. Chem. 2017, 82, 11799.
- [12] Y. Zhang, J. Han, Z.-J. Liu, RSC Adv. 2015, 5, 25485.
- [13] a) L. Mascarelli, G. Benati, *Gazz. Chim. Ital.* **1908**, *38*, 619; b) J. Collette, D. McGreer, R. Crawford, F. Chubb und R. B. Sandin, *J. Am. Chem. Soc.* **1956**, *78*, 3819; c) R. C. Reynold, C. Fuson, R. L. Albright, *J. Am. Chem. Soc.* **1959**, *81*, 487; d) P. S. Postnikov, O. A. Guselnikova, M. S. Yusubov, A. Yoshimura, V. N. Nemykin, V. V. Zhdankin, *J. Org. Chem.* **2015**, *80*, 5783; e) H. Xie, S. Yang, C. Zhang, M. Ding, M. Liu, J. Guo, F. Zhang, *J. Org. Chem.* **2017**, *82*, 5250.
- [14] D. Hellwinkel, G. Reiff, V. Nykodym, *Liebigs. Ann. Chem.* 1977, 1013.
   [15] H. Tomori, J.M. Fox, S.L. Buchwald, *J. Org. Chem.* 2000, *65*, 5334.
- [16] M. Bielawski, M. Zhu, B. Olofsson, Adv. Synth. Catal. 2007, 349, 2610.
- [17] N. A. Yakelis, R. G. Bergman, *Organometallics* 2005, 24, 3579 and references cited therein.
- [18] The corresponding structure of the chloride salt shows a similar coordination pattern: see reference [8b].
- [19] A. Bondi, J. Phys. Chem. 1964, 68, 441.
- [20] S. M. Walter, F. Kniep, L. Rout, F. P. Schmidtchen, E. Herdtweck, S. M. Huber, J. Am. Chem. Soc. 2012, 134, 8507.
- [21] S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, Angew. Chem. Int. Ed. 2011, 50, 7187.
- [22] S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep, S. M. Huber, Chem. Commun. 2014, 50, 6281.
- [23] Interestingly, the methylated compound 3a is more active than the nonmethylated one (1a) in this reaction, for currently unknown reasons.
- [24] D. von der Heiden, S. Bozkus, M. Klussmann, M. Breugst, J. Org. Chem. 2017, 82, 4037.
- [25] The performance of catalyst **5b** in this study was better than in the originally published work (reference [21]), possibly due to traces of triflate in the originally employed catalyst.
- [26] CYLview, 1.0b; C. Y. Legault, Université de Sherbrooke 2009 (<u>http://www.cylview.org</u>).
- [27] In the crystal structures of Figure 3, only weak contacts between the halide and suitable hydrogen bond donating substituents of the iodolium compounds were found (with distances of at least 95% of the sum of the van-der-Waals radii).

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#### Entry for the Table of Contents (Please choose one layout)

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### COMMUNICATION

Hypervalent iodine(III) compounds are used as activators or organocatalysts in benchmark reactions. By a series of comparison experiments - also involving sterically blocked derivatives - the crucial role of halogen bonding in this kind of catalysis is demonstrated for the first time. The activities of these monodentate Lewis acids match or exceed those of previously used bidentate cationic halogen bond donors.



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lodine(III) derivatives as halogen bonding organocatalysts

Layout 2:

### COMMUNICATION

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