“Anti-Electrostatic” Halogen Bonding

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Abstract: Halogen bonding (XB) is often described as being driven predominantly by electrostatics, and thus adducts between anionic XB donors (halogen-based Lewis acids) and anions seem counterintuitive. Such “anti-electrostatic” XBs have been predicted theoretically, but there are currently no experimental examples based on organic XB donors. Herein, we report the synthesis of two negatively charged organoiodine derivatives, which were subsequently investigated towards their ability to form “anti-electrostatic” XBs with anions. Even though the electrostatic potential is universally negative across the surface of both compounds, DFT calculations indicate kinetic stabilization of their halide complexes in the gas phase and particularly in solution. Experimentally, self-association of the anionic XB donor was observed in solid-state structures, resulting in dimers, trimers and infinite chains. In addition, co-crystals with halides were obtained which featured XB adducts between two or even three anions. The bond-lengths of all observed interactions are 14-21% shorter than sum of the van-der-Waals radii.

In recent years, halogen bonding (XB),[11] the noncovalent interaction between electrophilic halogen substituents and Lewis bases (LB), has found widespread use in many fields of chemistry, including crystal engineering,[2] anion recognition,[3] and organocatalysis.[4] The somewhat counterintuitive attraction between the seemingly electron-rich halogen substituent and Lewis bases was originally described by Mulliken[5] as a form of n→σ∗-type orbital interaction.[6] Later, an electrostatic model became very popular, which is based on the “σ-hole”,[8] a region of positive electrostatic potential at the elongation of the R···X bond (X = halogen). Sometimes, the interaction has even been described as “electrostatically-driven”.[6] Consequently, XB donors (halogen-based Lewis acids) are typically either neutral[9] or cationic,[11] and the latter bind particularly strongly to anionic Lewis bases due to charge assistance.[12] On the other hand, the coordination of such substrates with anionic XB donors does not seem sensible based on an electrostatic reasoning. It is noteworthy that for other interactions, a growing number of experimental evidence for adducts between ions of like charge was reported, e.g. for guanidinium ions in water,[13] biomolecules like oligopeptides,[14] metastable colloidal crystallites[15] or ionic liquids with weakly coordinating counterions.[16] In the latter example, cationic imidazolium species form clusters which are stabilized by cooperative hydrogen bonds (HB). The latter is another type of interaction that is considered to be primarily electrostatic in nature,[22] but for which n→σ∗ orbital interactions are often also non-negligible.[21] This was demonstrated vividly in a study by Weinhold and Klein[22] on cation-cation and anion-anion complexes that showed unusual kinetic stability, thereby challenging the seemingly generally accepted electrostatic of HBs. This first report of so-called anti-electrostatic hydrogen bonds (AEHB) was followed by numerous theoretical studies[23,24] as well as experimental evidence.[18-19,25]

For halogen bonding, first theoretical studies on anti-electrostatic XB (AEXB)[26,27] appeared only very recently. The only experimental systems that could be considered to contain AEXBs are polyhalides like [Cl···I-I-Cl]3–, which form linear XB adducts in crystal structures if the terminal halides are coordinated by further interactions.[28] However, it is debatable whether these complexes feature direct anion-anion interaction or if not a better description would be the interaction of two anions with the same neutral XB donor (I2). To the best of our knowledge, there are no further examples for AEXBs, and especially no examples with organic XB donors. Herein, we present anionic iodo-cyclopropenium and iodoimidazole derivatives that show various forms of self-association as well as co-crystal formation with halides in the solid state and thus allow first experimental realizations of AEXBs.

In the context of work directed at other goals, we became interested in iodinated bis(dicyanomethyldicyclopropenium) derivative 1 (Scheme 1) and it became soon apparent that this type of compound is an ideal starting point to study AEXBs. First, DFT calculations were performed at the M06-2X/def2-TZVP level.[29] The thus-obtained electrostatic potential on the surface of anion 1 shows that the negative charge is distributed over the whole molecule and that no region of positive electrostatic potential can be found (see Figure 1, right), even though there is a region of less negative electrostatic potential in elongation of the C-I bond.

![Figure 1](image)

**Figure 1.** Left: Energy profile of the scan of the I···Cl bond distance for the 1 ICl adduct in the gas phase (red) and in acetonitrile (black); right: Electrostatic potential of 1 mapped on the 0.001 electron/Bohr² iso-surface of electronic density. In elongation of the C-I bond, a region of less negative electrostatic potential (Vₓᵧ,z₁ = -80.36 kJ/mol) can be seen (green colour).

To test the ability of anion 1 to act as halogen bonding Lewis acid, halides X (X = Cl and I) were placed in elongation of the C-I bond and energy profiles scanning the C···X distances were obtained (see e.g. Figure 1 left). Both calculations yielded minima corresponding to XB adducts with well depths (i.e., energies of the minima vs. highest energies at longer distances) of -16 kJ/mol (X = I) and -33 kJ/mol (X = Cl). Halogen bonding is indicated by the 1···I (3.5 Å) or 1···Cl (3.0 Å) bond distances, which are
markedly shorter than the sum of the van-der-Waals (vdW) radii[30] (3.96 Å - 3.73 Å) and the high directionality of the interaction (with C-I-X angles of 180°). The overall binding energies (ΔE), enthalpies (ΔH) and Gibbs free enthalpies (ΔG) of the complexes were still markedly positive, however (see Table 1, Entries 1/2 and Table S16). This is not a surprise for a system consisting of two anions in the gas phase and is in line with calculations on anionic systems reported in literature.[24],[27] On the other hand, when calculations were performed in acetonitrile (via the SMD18[31] solvation model), negative binding energies for both iodide and chloride were found (Table 1, Entries 3/4 and Figure 1). The corresponding Gibbs free energies were either very slightly positive (0.6 kJ/mol for 1-I) or even negative (-2.9 kJ/mol for 1-Cl), suggesting that these AEXBs could be stable in solution.

| complex | d_{LB} (Å) | θ_{C-I-X} (°) | well depth | ΔE (kJ/mol) | ΔG (kJ/mol) |
|---------|------------|---------------|------------|-------------|-------------|
| 1       | 3.5        | 180           | -16        | 108         | 117         |
| 2       | 3.0        | 180           | -33        | 87          | 117         |
| 3       | 3.5        | 178           | -23        | -10         | 0.6         |
| 4       | 3.1        | 180           | -26        | -13         | -2.9        |
| 5       | 3.0        | 171           | -24        | 111         | 142         |
| 6       | 3.6        | 157           | -3.0       | 126         | 158         |
| 7       | 3.6        | 176           | -18        | 6.7         | 11          |
| 8       | 3.0        | 176           | -21        | 6.7         | 5.7         |
| 9       | 3.0        | 174           | -13        | 80          | 141         |
| 10      | 3.0        | 171           | -89        | 95          | 152         |
| 11      | 3.1        | 177           | -2.1       | 101         | 154         |
| 12      | 3.0        | 180           | -14        | -14         | 45          |

[a] Calculated with SMD18 using parameters for acetonitrile. [b] This dimeric structure features one XB-contact as found for A···C in the crystal structure of 6a (see Figure 5). [c] A scan for the dimeric structure as found in the crystal structure of 6b (see figure 4) was not possible. In case of 6-6 XB, almost identical energies were obtained when calculations were performed either on the crystal structure geometry or the optimized minimum. Therefore, we used the geometries found in the crystal structure as minimum structure for further optimisation and energy calculation.

Obviously, in the complexes discussed here, various electronic components contribute favourably or unfavourably to the overall interaction energy: Pauli repulsion and electrostatic repulsion (due to the like charges) act against orbital interactions (n→σ*), polarization and dispersion as attractive forces. The electrostatic repulsion will be lowered by counterions (which were not considered in these calculations) as well as by the dielectric environment of polar solvents (and individual interactions by the solvent molecules). In suitable cases like 1···Cl, the attractive forces, taken together, may overcome the repulsive components to form stable XB adducts – as indicated by our calculations.

With these promising calculations in hand, we synthesized XB donor 1 starting from inner salt 2, which was first reported by Fukunaga and is known to react with nucleophiles under release of triethylamine.[32] Since the direct conversion to the iodinated species failed using iodide as nucleophile, the corresponding H-analogue 3 (Scheme 1) was chosen as precursor. This compound was already reported by Seitz et al. who described an eight-step synthesis with an overall yield of about 5%. [34]

Aiming for a more efficient synthesis, we reacted starting material 2 with sodium borohydride to form the desired anion of 3 as water-soluble sodium salt. Cation exchange from sodium to the organic cation tris(dimethylamino)cyclopentenium (TDA)[35] increases the solubility of the anion in organic solvents, and intermediate 3 was obtained in 63% yield. Iodination of the latter was performed with 1,3-diiodo-5,5-dimethylhydantoin (4) in DCM over two hours.[36] Product 1, which was isolated in 81% yield, was crystallised from DCM/diethyl ether or DCM/cyclopentane. Single crystal analysis[37] confirmed the formation of the desired XB donor (Figure 2).

A closer inspection of the crystal structure revealed short contacts between the iodine substituents of one molecule and the nitrogen atoms of a second molecule (Figure 3), which represents the first AEXB between two organic molecules in the solid state. The interaction features a bond length of d_{XB} = 2.97 Å (16% shorter than the sum of the vdW radii (3.53 Å)[30]) and shows the characteristic high directionality of XBs with angles of
4C$_{11}$N = 178.8°. The AEXBs result in infinite chains of XB donor 1, and the counterions are positioned alongside these chains (see Figures S24 and S26).

Inspired by these results, we wondered whether the anionic bis(dicyanomethyldicyclopropenium substituent (L) can be incorporated into other systems to obtain further AEXBs and 2-iodimidazole (5) seemed to be a promising core structure for this purpose. Therefore, calculations similar to the ones mentioned above were performed on the imidazolyl-substituted anion 6 (Scheme 1). In this case, the negative charge is also distributed over the entire molecule and the region of least negative electrostatic potential (ψ-hole) on iodine is even more negative (-127.9 kJ/mol) than in compound 1. Scans of the C-I···X (X = Cl, I) distances yielded similar energy profiles as obtained for 1···X (compare Figure 1). While the gas phase data for the complex 6···Cl is mostly in line with the results of 1···X (Table 1, Entry 5), a less stable adduct was found for adduct 6···I (Entry 6), which is evident by the comparatively small well depth (-3.0 kJ/mol) and the deviation from linearity (157°). In acetonitrile, both adducts showed similar well depths and geometric parameters (Entries 7/8) as 1···X (Entries 3/4), with linear arrangements and higher kinetic stability (well depths of -18 to -21 kJ/mol). In contrast to the complexes with 1, however, the binding energies and Gibb’s free energies are predicted to be positive.

The synthesis of imidazolyl derivative 6 was achieved in a straightforward manner by deprotonation of 2-iodimidazole (5) with lithium disopropylamide (LDA) and subsequent reaction with inner salt 2. To obtain a well soluble compound, organic counterions were then introduced leading to TDA salt 6a and tetrabutylammonium (NBu$_4$) salt 6b in 62% and 66% overall yield. Single crystals for both salts 6a and 6b could be grown in DCM/diethyl ether and X-ray structural analyses revealed that in both cases, short contacts (XBs) between iodine substituents and nitrogen atoms either from cyano groups or the imidazole are found. However, depending on the counterion, two different patterns are observed. Figure 4 shows the symmetric dimers 6···6XB which exist in the crystal structure of the tetrabutylammonium salt 6b. The halogen bonds feature a longer interaction distance (d$_{NB}$ = 3.03 Å) and a less linear angle ($\angle_{C.IN}$ = 172.76°) compared to the AEXBs observed with XB donor 1 (Figure 3). The imidazole and cyclopropenium rings in one molecule are not coplanar but are slightly twisted by about 15°. In addition to the strong XB, weak HBs to the counterions are detected (d$_{HN}$ = 2.78 and 2.72 Å, d$_{vdW}$ radii = 2.80 and 2.65 Å), so that each dimer is surrounded by eight tetrabutylammonium ions (see figure S28).

In case of the TDA salt 6a, a trimeric motif is observed, in which the iodine substituent of each XB donor interacts with the imidazole nitrogen atom of another one (Figure 5a). The XB bond distances (d$_{NB}$ = 2.80 to 2.89 Å, 79-81% of the sum of the vdw radii) in these trimers are the shortest ones found in all self-associated crystal structures described herein. Two of the three XB-donors in the trimeric complex lie in the same plane (A and C), whereas the third molecule (B) is tilted out of this plane by about 20° (Figure 5b). In addition to various short contacts of the depicted molecules (Figure 5) to counterions and adjacent...
iodimidazolyl species (see Figure S27 and S34), the XB complex is further stabilised by two weak HBs (Figure 5 a).

All these motifs found in the crystal structure not only demonstrate the feasibility of forming XBs between ions of like charge, but they also exhibit cooperativity, which has been discussed for XB in the literature both theoretically[39] and experimentally. This can probably best be explained from the $\sigma-\sigma^*$ orbital interaction point of view: donation of electron density into the $\sigma^*$ orbital of an XB donor will render its Lewis basic centres (in this case, nitrogen atoms of cyano or imidazole groups) more electron-rich and will thus reinforce their interaction with a second XB-donating moiety. In agreement with the solid state data, this polarization-assisted XBs (PAXBs) are expected to be more pronounced for the trimer (Figure 5) compared to the dimer (Figure 4), as the relevant Lewis basic centres are much closer to the C-1 bond in the former case.

The motifs found in the crystal structures were used for further DFT calculations. For the complexes involving XB donor 6, similar structures to the solid state geometries were obtained (see also Table 1, Entries 9 and 10; $6-6_{XB}$ designates a complex with a single XB). While the structure of a dimer of XB donor 1 in the gas phase deviated significantly from the geometries found in the chain-like motif (Figure 3), calculations in acetonitrile resulted in a linear arrangement of both XB donors and reasonable kinetic stability (Table 1, Entry 12). NCI-plots, visualising non-covalent interactions,[41] of all motifs showed only attractive interactions between the molecules (see Figure S39).

To further investigate the influence of the binding partner on the electrostatic potential of the XB donors, calculations with point charges positioned in elongation of the C-1 bond were performed.[42] Single point charges varying from +1 to -1 at XB-relevant distances vividly illustrated the high polarizability of compound 1, with $V_{S,max}$ values between -266.1 and 154.7 kJ/mol (Table 2). To better simulate a second XB donor like 1 or 6, we also placed the atomic charges (NBO[43] or Mulliken[44] charges) of all the atoms of a binding partner at their respective atomic position in space (to mimic 1-1 or singly/doubly bound 6-6 complexes). As expected, their influence on the electrostatic potential of the investigated XB donor is less pronounced than for single point charges, and in almost all cases $V_{S,max}$ remained negative (Figure 8). Thus, while polarization can significantly decrease the repulsion between the XB donors,[45] this in itself does not seem sufficient to explain XB self-association.

Finally, co-crystals of XB donor 1 with halides were targeted as even more drastic examples of AEXBs: due to their localized negative charge, they seem to be more challenging substrates to coordinate to anionic XB donors. On the other hand, DFT calculations in polar environments had demonstrated the feasibility of adduct formation (Figure 1) and the calculations discussed in the last paragraph indicated that halides would also induce a strong favourable polarization of the XB donor.

Therefore, TDA (X = I, Br, Cl) salts were added in different ratios (1:1, 1:2 and 1:3) to a solution of XB-donor 1 in DCM. As co-solvents cyclopentane and diethyl ether were used, resulting in the formation of several single crystals suitable for XRD measurements. Figures 9 and 10 show the 1:1 and 1:2 co-crystal of TDAI with XB-donor 1.[46] The crystal structure of the 1:1-complex shows one XB contact with an I-I-distance of 3.33 Å, corresponding to only 84% of the sum of vDW radii (or 89% if anion radii according to Pauli[47] are considered for iodide). Additionally, one solvent molecule is incorporated in the crystal structure, which is weakly bound to iodide.

**Table 2.** Electrostatic potential on the 0.001 electron/Bohr$^2$ isosurface of the electronic density. The distance between point charge and donor is given in Å and the $\sigma$-hole energies ($V_{S,max}$) in kJ/mol.

| charge | d (Å) | $V_{S,max}$ (kJ/mol) |
|--------|------|----------------------|
| +1.0   | 3.5  | -266                 |
| -0.5   | 3.5  | 5.7                  |
| -1.0   | 3.5  | 92                   |
| 1      | 3.0  | 155                  |
| 1      | -1.0 | -16                  |
| 1      | -1.0 | -9.6                 |
| 6      | -    | -128                 |
| 6      | -    | -17                  |
| 6      | -    | -31                  |
| 6      | -    | -45                  |

[a] The optimised structure of the calculation in acetonitrile was used.
[b] A dimer with both XB-donors positioned in one plane featuring one XB contact (see Figure 5) was used as template.
[c] The dimer structure shown in Figure 4 was used as template.

| Figure 8.** Electrostatic potential on the 0.001 au isosurface with and without point charges. The scale ranges from -417 to 0 kJ/mol. |
| Figure 9.** X-ray structural analysis of a 1:1 co-crystal of XB-donor 1 with iodide. $\Delta_-C_1 = 177.5^\circ$. The TDA counterions are omitted. Thermal ellipsoids at 50% probability level. |

Such a weak hydrogen bond is also observed between DCM and iodide in the crystal structure of the 1:2-complex, in which two XB donor molecules coordinate to one iodide. One of these interactions shows almost the same geometric parameters ($\Delta_-C_1 = 178^\circ$; $d_{C-I} = 3.33$ Å) as found in the 1:1-complex. The second contact is slightly longer ($d = 3.41$ Å) and a bit less linear ($\Delta_-C_1 = 172$). Nevertheless, both interactions clearly constitute XBs, and thus this structure represents an XB adduct between three anions! The planes of the three-membered rings are in an
angle of 45° to one another and the angle between the two XBs is $\angle_{AA} = 152°$.

Figure 10. X-ray structural analysis of a 1:2 co-crystal of XB donor 1 with iodide. $\Delta C - C = 172$ and 178°, $\angle_{AA} = 152°$. TDA counter-ions and one DCM molecule, interacting weekly with iodide (see SI), are omitted. Thermal ellipsoids at 50% probability level.

In summary, the first experimental examples of “anti-electrostatic” halogen bonding (particularly with organic halogen bond donors) were reported. Two anionic XB donors based on 1,2-bis(dicyano-methyl)cyclopropenium moieties were synthesized and characterized via solid-state structures, which featured multiple forms of XB-based self-association of the anionic molecules. Even more pronounced examples of such AEXBs were obtained in the form of halide adducts. DFT calculations supported the feasibility of adduct formation in polar environments and illustrated the polarization of the XB donors by the interaction partner (but still predicted entirely negative electrostatic potentials for the self-associated adducts). In our view, all these examples highlight the importance of polarization and n→* orbital interactions for halogen bonding and demonstrate once again[1,24] that a description of this interaction via static n-holes is doomed to fail. These findings may also pave the way towards the utilization of novel classes of (anionic) XB donors, which were so far exclusively based on neutral or cationic compounds.

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N-iodosuccimide can also be used as iodination agent. In this case, the reaction time needs to be increased significantly for full conversion of the starting material. To obtain the target compound in high yields, usage of 4 is recommended.

This motif is known for gold-NHC complexes, see e.g. a) A. Burini, R. Galassi, B. R. Pietroni, J. P. Fackler Jr., R. J. Staples, Chem. Commun. 1998, 95, b) M. A. Rawashdeh-Omary, M. A. Omary, J. P. Fackler, R. Galassi, B. R. Pietroni, A. Burini, J. Am. Chem. Soc. 2001, 123, 9689.

The point charge approach for investigation of polarization in hydrogen bonding was introduced by Clark et al. (M. Hennemann, J. S. Murray, P. Politzer, K. E. Riley, T. Clark, J. Mol. Model. 2012, 48, 7745) and was later used for XB by our group (see [48a]) and others (see e.g. [48b]).

For a co-crystal with chloride/iodide (8:2) see SI.
Two negatively charged organoiodine derivatives were investigated towards their ability to form “anti-electrostatic” halogen bonds (XB) with anions. Even though the electrostatic potential is universally negative across the surface of both compounds, DFT calculations indicate kinetic stabilization of their halide complexes. Experimentally, self-association of the anionic XB donors was observed. Co-crystals with halides were obtained which featured XB adducts between two or even three anions.

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