

Unexpected trends in halogen-bond based noncovalent adducts

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Abstract

Unexpected trends in the strengths of halogen-bond based adducts of CY_3I ($Y = F, Cl, Br, I$) with two typical Lewis bases (chloride and trimethylamine) show that the halogen-bond donor strength (Lewis acidity) of a compound $R-X$ is not necessarily increased with higher electronegativity of the (carbon-based) group R .

Halogen bonds (XBs), i.e. non-covalent interactions between electrophilic terminal halogen substituents and Lewis bases, have recently gained increased interest and by now form the basis of various applications in the solid state and in solution. The interaction itself has been known for more than 150 years and was for a long time considered as a special case of a charge-transfer complexation. The most prominent visualization of the electronic origin of XBs is the so-called " σ -hole", i.e. a region of positive electrostatic potential on the electron isodensity surface of the halogen atom X of the halogen-bond donor (i.e. the Lewis acid; cf. Fig. 1). As it was repeatedly shown that the strengths of XB-based adducts correlate linearly to the most positive electrostatic potential on the XB donor (i.e., the magnitude of the σ -hole, $V_{S,max}$), XBs have often been portrayed as predominantly electrostatically driven interactions. It is currently also widely accepted that an XB donor RX with a more electronegative group R will form stronger XBs with Lewis bases.

However, when we performed orientating computations to complement our experimental investigations, we found trends in the strengths of XB-based adducts that run opposite to what would be predicted by the electronegativity trend of the groups attached to the electrophilic halogen atom (and likewise the magnitude of the corresponding σ -hole, $V_{S,max}$). In the following, we will present these cases and rationalize the findings by energy decomposition analyses.

We will focus our discussion on a few select examples featuring CY_3I derivatives ($Y = F, Cl, Br, I$) as representative strong XB donors in complexes with chloride and trimethylamine as typical charged and neutral Lewis bases (Scheme 1). Table 1 shows the relevant data for the

complexes of CY_3I of hydrogen bonds. 12 Another established decomposition scheme, the ESIw method, 13 arrives at the same conclusions (see ESIw).

The NEDA analyses allow the partition of the chemical bond between the XB donor and the Lewis base into few chemical relevant contributions: the electrostatic interaction, the charge transfer and the lone pair repulsion.

The electrostatic term includes the Columbic nuclei–nuclei, nuclei–electron and electron–electron interaction between the two adducts, as well as the effect of the induced polarization exerted by the field of one fragment over the other. This term is usually attractive, i.e. with a negative energy, shown in Table 1. The charge transfer term defines the amount of electrons transferred from one adduct to the other upon formation of the chemical bond. It is also an attractive contribution. The lone pair repulsion term (with the acronym “Core” in Table 1) is a consequence of the Pauli exclusion principle, i.e. same spin electrons cannot occupy the same region of space. This term, as the word defines it, is always positive. Several qualitative trends become apparent:

Firstly, and most significantly, both the electrostatic contribution (Table 1, line 4) and the charge-transfer contribution (line 5) to the overall interaction energy (line 7) increase with less electronegative groups CY_3 , i.e. from $Y = F$ to $Y = I$. Along this trend, the charge-transfer contribution changes by a larger amount than the electrostatic contribution. The magnitude of charge-transfer from the chloride to the XB donor was also analysed by Natural Population Analysis (line 8), 14 which confirms the previous findings. The increased charge transfer for the heavier halogen substituents Y can be explained by the energy levels of the respective $C-I$ σ^* -orbitals of the XB donors CY_3I (Fig. 3). These orbitals become lower in energy and thus more favourable for an interaction with the HOMO of the Lewis base from $Y = F$ to I .

Secondly, the magnitude of the σ -hole of the XB donors examined ($V_{S,max}$, line 1) does not even correlate to the actual electrostatic contribution (line 4). Thus, while Cl_4 features a less positive $V_{S,max}$ than CF_3I , the electrostatic term is more favourable for the former. Clark et al. have previously elegantly shown for hydrogen bonds 15 that the magnitude of the σ -hole changes in the presence of an external electric field (a point charge in that case). Using the same approach by locating a negative point charge of 1.0, along the $C-I$ axis, at the computed equilibrium position of Cl for each given CY_3I-Cl complex, it becomes apparent that although the σ -hole of the isolated Cl_4 is smaller than that of CF_3I , it is the opposite in the presence of an external field due to the higher polarizability of the Cl_4 molecule (Fig. 1), thus explaining the more favourable electrostatic term for the complex of Cl_4 with chloride (see also Table 1 for concrete values of $V_{S,max}$ in the presence of a point charge: $V_{S,max}$ (induced)). However, this inversion of the trend is still mostly qualitative, since the progression of the $V_{S,max}$ (induced) values (lines 2 and 11) is not regular enough to fully explain the trend of the interaction energies.

Thirdly, the repulsive contribution to the overall interaction energy (line 6), i.e. the Pauli repulsion including the lone-pair repulsion of the iodine p orbitals with the Lewis base, partly compensates the trend set by the attractive forces (compare lines 4 and 5), as it increases from $Y = F$ to $Y = I$.

Overall, however, the trend of the interaction energy is dominated by the variations of the attractive contributions. The fact that the complexes of CY_3I with chloride become more favourable towards the heavier halogens is also reflected by a shortening of the corresponding I-Cl interaction distances from $Y = F$ to $Y = I$ (Table 1, line 9).

Parallel to chloride as a Lewis base, we also performed calculations employing trimethylamine as a prototypical neutral nucleophile (see Table 1).¹⁶ All relevant trends described for the chloride complexes are also observed for the adducts with trimethylamine. Since the overall interaction energies are smaller for the trimethylamine complexes, the trends also become more subtle and are in some cases probably within the error of the computational methods. Even so, the trimethylamine complexes once again show that the interaction strength of XB-based adducts cannot easily be predicted by a simple measure (e.g. the electronegativity of the fragment CY_3).

In conclusion, we have presented a series of XB-based adducts which contradict the general consensus that more electronegative (carbon-based) groups R, bound to the electrophilic halogen atom X, will lead to more stable complexes of R-X with Lewis bases.¹⁷ We note that elemental iodine could serve as a further example for this point, as it forms strong XB adducts despite the lack of an electronegative substituent (see e.g. the recent detailed discussions by Laurence et al., Taylor et al., and Zou et al.).¹⁸

In addition, the magnitude of the σ -hole on the relevant halogen atom apparently does not always forecast trends of interaction strengths correctly. Although the σ -hole itself provides a very intuitive visualization of the rather intriguing electron distribution around the halogen atom, the concept behind it might have to be expanded by taking into account quantum chemical effects like charge transfer and the Pauli repulsion. As a direct consequence of these findings, the design of highly potent XB donors R-X may not necessarily rely on the use of very electronegative groups R (e.g. perfluorinated backbones). Instead, highly polarizable groups, or groups that help to stabilize the C-X σ^* -orbital might be more effective for selected cases.

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References

1. (a) Halogen Bonding: Fundamentals and Applications, (Structure and Bonding vol. 126), ed. P. Metrangolo and G. Resnati, Springer, Berlin, 2008; (b) P. Metrangolo, F. Meyer, T. Pilati, G. Resnati and G. Terraneo, *Angew. Chem., Int. Ed.*, 2008, 47, 6114; (c) A. C. Legon, *Phys. Chem. Chem. Phys.*, 2010, 12, 7736.

2. Selected recent reviews: (a) K. Rissanen, *CrystEngComm*, 2008, 10, 1107; (b) L. Brammer, G. M. Espallargas and S. Libri, *CrystEngComm*, 2008, 10, 1712; (c) M. Fourmigué, *Curr. Opin. Solid State Mater. Sci.*, 2009, 13, 36; (d) G. Cavallo, P. Metrangolo, T. Pilati, G. Resnati, M. Sansotera and G. Terraneo, *Chem. Soc. Rev.*, 2010, 39, 3772.
3. Review: (a) M. Erdélyi, *Chem. Soc. Rev.*, 2012, 41, 3547; selected examples: (b) M. G. Sarwar, B. Dragisic, S. Sagoo and M. S. Taylor, *Angew. Chem., Int. Ed.*, 2010, 49, 1674; (c) N. L. Kilah, M. D. Wise, C. J. Serpell, A. L. Thompson, N. G. White, K. E. Christensen and P. D. Beer, *J. Am. Chem. Soc.*, 2010, 132, 11893.
4. (a) F. Guthrie, *J. Chem. Soc.*, 1863, 16, 239; (b) I. Remsen and J. F. Norris, *Am. Chem. J.*, 1896, 18, 90.
5. See, for example: (a) O. Hassel, *Science*, 1970, 170, 497; (b) O. Hassel, *Angew. Chem., Int. Ed. Engl.*, 1970, 82, 821; (c) H. A. Bent, *Chem. Rev.*, 1968, 68, 587; (d) A. E. Reed, F. Weinhold, R. Weiss and J. Macheleid, *J. Phys. Chem. A*, 1985, 89, 2688; (e) N. Ramasubbu, R. Parthasarathy and P. Murray-Rust, *J. Am. Chem. Soc.*, 1986, 108, 4308; (f) A. Karpfen, *Theor. Chem. Acc.*, 2003, 110, 1.
6. (a) T. Clark, M. Hennemann, J. Murray and P. Politzer, *J. Mol. Model.*, 2007, 13, 291; (b) P. Politzer, P. Lane, M. C. Concha, Y. Ma and J. S. Murray, *J. Mol. Model.*, 2007, 13, 305.
7. 'Shown' in this case (and others mentioned later) refers to computational studies, see, for example: (a) K. E. Riley, J. S. Murray, M. C. Concha, P. Hobza and P. Politzer, *J. Chem. Theory Comput.*, 2009, 5, 155; (b) Z. P. Shields, J. S. Murray and P. Politzer, *Int. J. Quantum Chem.*, 2010, 110, 2823; (c) P. Politzer, J. S. Murray and T. Clark, *Phys. Chem. Chem. Phys.*, 2010, 12, 7748; (d) K. E. Riley, J. S. Murray, J. Fanfrlík, J. Řezáč, R. J. Solá, M. C. Concha, F. M. Ramos and P. Politzer, *J. Mol. Model.*, 2011, 17, 3309. For a study relating actual experimental thermodynamics of binding to $V_{S,max}$ calculations, see M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras and M. S. Taylor, *J. Am. Chem. Soc.*, 2010, 132, 1646.
8. (a) S. M. Walter, F. Kniep, E. Herdtweck and S. M. Huber, *Angew. Chem., Int. Ed.*, 2011, 50, 7181; (b) F. Kniep, S. M. Walter, E. Herdtweck and S. M. Huber, *Chem.–Eur. J.*, 2012, 18, 1306.
9. A. L. Allred, *J. Inorg. Nucl. Chem.*, 1961, 17, 215.
10. For previous energy decomposition analyses of halogen bond complexes, see, for example: (a) K. E. Riley and P. Hobza, *J. Chem. Theory Comput.*, 2008, 4, 232; (b) M. Palusiak, *THEO-CHEM*, 2010, 945, 89; (c) L. P. Wolters and F. M. Bickelhaupt, *ChemistryOpen*, 2012, 1, 96.
11. (a) E. D. Glandening, *J. Phys. Chem. A*, 2005, 109, 11936; (b) E. D. Glandening, *J. Am. Chem. Soc.*, 1996, 118, 2473; (c) G. K. Schenter and E. D. Glandening, *J. Phys. Chem.*, 2000, 100, 17152; (d) E. D. Glandening and E. Streitwieser Jr., *J. Chem. Phys.*, 1994, 100, 2900.
12. S. J. Grabowski, *Chem. Rev.*, 2011, 111, 2597.
13. T. Ziegler and A. Rauk, *Inorg. Chem.*, 1979, 18, 1558.
14. (a) J. P. Foster and F. Weinhold, *J. Am. Chem. Soc.*, 1980, 102, 7211; (b) A. E. Reed and F. Weinhold, *J. Chem. Phys.*, 1983, 78, 4066; (c) A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.*, 1985, 83, 735.
15. M. Hennemann, J. S. Murray, P. Politzer, K. E. Riley and T. Clark, *J. Mol. Model.*, 2012, 18, 2461.
16. The complexes of CF_3I with amines have previously been studied in the gas phase (see e.g. S. L. Stephens, N. R. Walker and A. C. Legon, *Phys. Chem. Chem. Phys.*, 2011, 13, 20736) and

computationally (see e.g. G. Valerio, G. Raos, S. V. Meille, P. Metrangolo and G. Resnati, *J. Phys. Chem. A*, 2000, 104, 1617).

17. A similar trend has been observed for the related hydrogen-bond donors CY_3H ($Y = F, Cl$) and CH_3Y ($Y = F, Cl, Br$) by experimental (see e.g. J. W. Larson and T. B. McMahon, *J. Am. Chem. Soc.*, 1984, 106, 517) and computational analyses (see e.g. E. S. Kryachko and T. Zeegers-Huyskens, *J. Phys. Chem. A*, 2002, 106, 6832 and L. Pedzisa and B. P. Hay, *J. Org. Chem.*, 2009, 74, 2554 as well as references cited therein).

18. (a) C. Laurence, J. Graton, M. Berthelot and M. J. El Ghomari, *Chem.–Eur. J.*, 2011, 17, 10431; (b) M. J. Chudzinski and M. S. Taylor, *J. Org. Chem.*, 2012, 77, 3483; (c) J.-W. Zou, Y.-J. Jiang, M. Guo, G.-X. Hu, B. Zhang, H.-C. Liu and Q.-S. Yu, *Chem.–Eur. J.*, 2005, 11, 740.

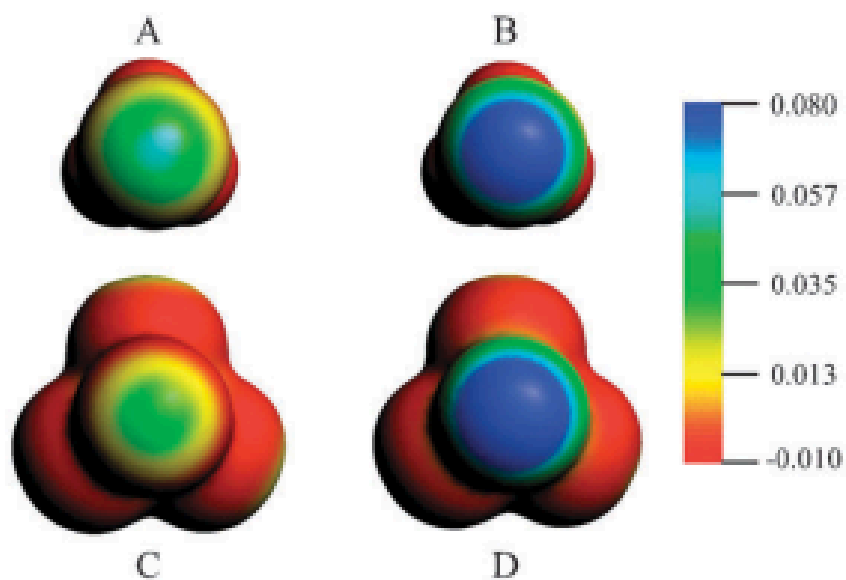
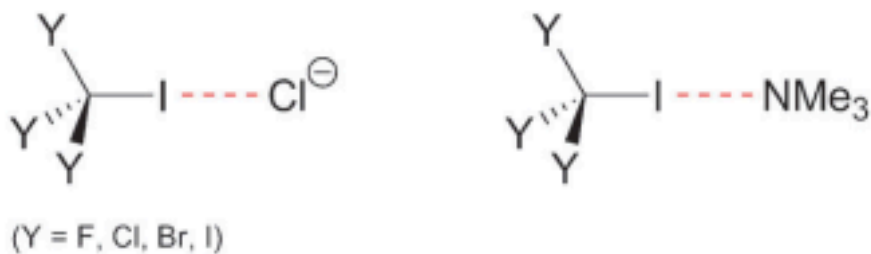


Fig. 1 Electrostatic potentials mapped on the electron isodensity surface of CF_3I (A) and Cl_4 (C) at the same contour value of 0.001 electron per Bohr^3 . The red color shows the most negative potential, while the blue color represents the most positive one. The σ -holes of CF_3I (B) and Cl_4 (D) in the presence of a 1.0 point charge are also depicted. Energies are expressed in a.u.



Scheme 1. XB-based adducts considered in this study.

#	CY ₃ I-Cl ⁻	Y = F	Y = Cl	Y = Br	Y = I
1	$V_{S,max}$	28.5	27.4	26.6	25.5
2	$V_{S,max}$ (induced)	92.4	100.2	99.7	102.1
3	$\Delta E_{int}(MP2)$	-29.3	-33.5	-35.6	-37.0
NEDA					
4	Electrostatic	-67.7	-76.7	-79.4	-80.6
5	Charge-transfer	-64.5	-85.1	-89.8	-95.6
6	Core	97.3	121.5	126.5	132.3
7	$\Delta E_{int}(DFT)$	-34.9	-40.2	-42.7	-43.9
8	NPA charge transfer	0.29	0.37	0.40	0.43
9	Dist I-Cl DFT(MP2)	2.77(2.80)	2.69(2.70)	2.67(2.67)	2.65(2.64)
#	CY ₃ I-NMe ₃	Y = F	Y = Cl	Y = Br	Y = I
10	$V_{S,max}$	28.5	27.4	26.6	25.5
11	$V_{S,max}$ (induced)	50.8	50.2	49.2	47.4
12	$\Delta E_{int}(MP2)$	-11.0	-13.4	-14.2	-14.6
NEDA					
13	Electrostatic	-28.1	-36.7	-36.6	-37.7
14	Charge-transfer	-27.5	-37.9	-38.1	-39.4
15	Core	47.1	64.3	63.8	66.2
16	$\Delta E_{int}(DFT)$	-8.5	-10.3	-10.9	-10.9
17	NPA charge transfer	0.10	0.15	0.16	0.17
18	Dist I-N DFT(MP2)	2.77(2.76) ^a	2.66(2.64)	2.67(2.61)	2.66(2.59)

^a 2.77 Å from experiment, see Legon *et al.*¹⁶

Table 1. Computed data for the complexes of CY₃I with chloride and trimethylamine. Distances are in Å. Energies are in kcal mol⁻¹.

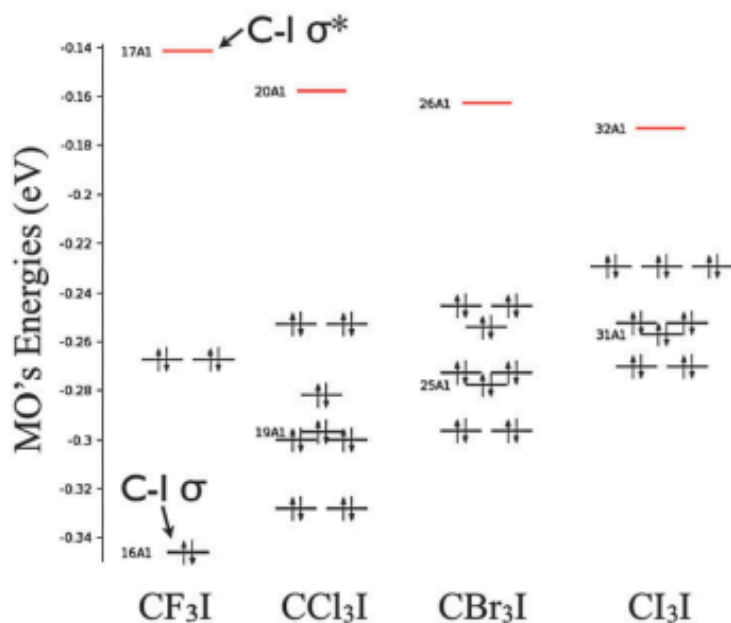


Fig. 3. Energy levels for the CY₃I molecules, as obtained by the DFT calculations (see supporting information; σ* orbitals in red).

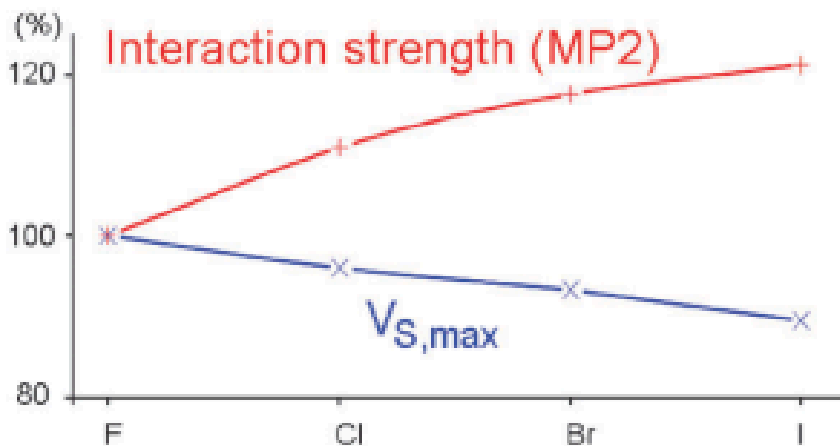


Fig. 2. Absolute value of the computed interaction strength DE_{int} (MP2) for the CY₃I-Cl (Y = F, Cl, Br, I) halogen bond vs. $V_{S,max}$ for CY₃I, each relative to CF₃I(Cl), set at 100%. The lines serve only illustrative purposes.