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Halogen Bonding of (Iodoethynyl)benzene Derivatives in Solution

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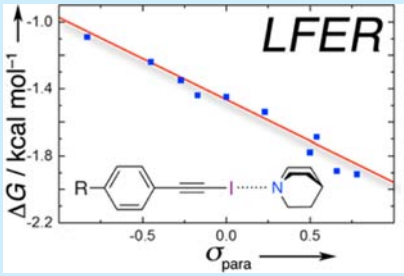
Supporting Information

ABSTRACT: Halogen bonding (XB) between (iodoethynyl)benzene donors and quinuclidine in benzene affords binding free enthalpies (ΔG, 298 K) between −1.1 and −2.4 kcal mol^{-1}, with a strong LFER with the Hammett parameter σ_{para}. The enthalpic driving force is compensated by an unfavorable entropic term. The binding affinity of XB acceptors increases in the order pyridine < C═O < S═O < P═O < quinuclidine. Diverse XB packing motifs are observed in the solid state.

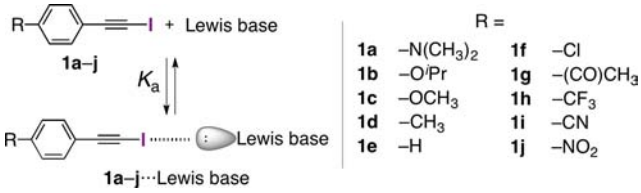


Halogen bonding (XB) is the noncovalent interaction of the electrophilic part of a halogen and a Lewis base. The electron-donating entity, the XB acceptor, binds with its electron lone pair to the electropositive region of the XB donor, corresponding to the σ^* orbital of the C−X bond, often referred to as the σ hole.[1,2] Important geometric boundary conditions for efficient XB are A···X−C angles near 180° and an A···X contact distance below the sum of the van der Waals radii (A = XB acceptor). Halogen bonding has emerged as a reliable motif in supramolecular architectures,[3,4] and in catalysis by C−X activation.[5] The interaction is also abundant in biological complexation.[6,7] Nevertheless, only a limited number of systematic quantitative XB studies in solution have appeared.[8−10] Here, we present a systematic study of halogen bonding by (iodoethynyl)arenes and demonstrate the linear free enthalpy relationship (LFER) of their XB with the Hammett parameter σ_{para}. Binding strengths to different XB acceptors, thermodynamic profiles, and intermolecular solid-state interactions are analyzed.

In 1981, Laurence et al. investigated changes in the IR spectra of Lewis bases in dilute solution in the presence of iodoethynyl derivatives R−C≡C−I with various substituents directly attached to the acetylene.[8] They observed good linear correlations between log K_a (association constant) and the Hammett parameter σ_{para} for the substituent, with the most Lewis acidic organoiodines demonstrating the strongest interactions.[8] Almost 30 years later, Taylor et al. studied the XB properties of perfluorinated iodoarenes and iodoalkanes as XB donors with a set of XB acceptors, using ^{19}F NMR binding titrations in cyclohexane.[9] The scope of XB donors in this study was limited to perfluorinated materials, as fluorine substituents increase the polarization of arene or alkane C−X bonds, creating a more positive σ-hole potential. A modest linear correlation between log K_a and σ_{para} was observed (r^2 = 0.82), although computational modeling predicted a very strong one for fluorinated iodoarenes (*ab initio* study: r^2 = 0.98).[11]

Here, we investigate (iodoethynyl)benzene derivatives as XB donors (Scheme 1) in benzene solution by performing NMR binding titrations with a focus on tuning XB donor strength by distant *para*-substituents on the aromatic ring. Iodoalkynes undergo XB in the solid state with a variety of acceptors,[12] and their XB donor abilities[2a,b] were ranked to be as strong as pentafluoroiodobenzene by solid-state IR investigations.[13] In early work, Goroff et al. observed large solvent-dependent changes in the ^{13}C NMR chemical shift of the signal corresponding to the C(1)-atom in iodoalkynes and demonstrated through computational and experimental studies that this effect resulted directly from XB interactions with the solvents, acting as an XB acceptor.[14] Taking advantage of these interactions, diiodobuta-1,3-diyne was aligned in a designed bis(nitrile)oxalamide XB acceptor matrix and shown to undergo topochemical polymerization to form poly(diiododiacetylene) in a crystal-to-crystal transformation.[15] Iodoethynyl motifs are also present in the lead structure of the commercial antimycotic drug haloprogin,[16a,c] of which the mechanism of action is still unknown.[16b]

Scheme 1. Halogen Bonding of *para*-Substituted (Iodoethynyl)benzene Derivatives with Lewis Bases



By varying the *para*-substituent, remote from the iodine atom (Scheme 1), we assumed that the environment at the XB

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binding site remains unchanged in the different complexes formed. XB donors **1a–j** and **2** were synthesized following published procedures (see Supporting Information (SI) for synthetic procedures)[17] and are air-stable for days. Quinuclidine was selected as a Lewis base because of its very high XB acceptor abilities.[18]

Binding constants were determined by NMR titrations conducted in C_6D_6 (see SI for details). XB binding energies could be determined for the entire scope of *para*-substituents with σ_{para} ranging from −0.83 to +0.78 (Table 1). Experimental parameters (temperature, solvent, concentrations, XB acceptor batch, spectrometer) were strictly maintained to be constant to allow for precise comparison of data. K_a values (Table 1) range from 6.3 ± 0.6 M^{-1} for the dimethylamino (DMA)-substituted XB donor to 25 ± 8 M^{-1} for the nitro-substituted one. For comparison, the highest XB strength was measured for **2** as the donor, showing K_a values of 60 ± 3 M^{-1} in C_6D_6 and 117 M^{-1} in cyclohexane. Remarkably, even DMA- or isopropoxy-substituted substrates showed measurable association strength despite unfavorable donor effects.

Table 1. Association Constants K_a and Binding Free Enthalpy ΔG for XB Complexes of (Iodoethynyl)benzenes 1a–j and 2 with Quinuclidine in C_6D_6 at 298 K

compd	R	σ_{para}	$K_a{}^a/M^{-1}$	ΔG^b/kcal mol^{-1}
1a	$(CH_3)_2N-$	−0.83	6.3 ± 0.6	−1.1 ± 0.1
1b	*i*PrO−	−0.45	8.1 ± 0.8	−1.2 ± 0.1
1c	CH_3O-	−0.27	9.8 ± 1.5	−1.3 ± 0.1
1d	CH_3-	−0.17	11 ± 3	−1.4 ± 0.2
1e	H−	0	12 ± 2	−1.5 ± 0.1
1f	Cl−	0.23	14 ± 1	−1.5 ± 0.0(3)
1g	CH_3CO-	0.50	20 ± 3	−1.8 ± 0.1
1h	F_3C-	0.54	17 ± 4	−1.7 ± 0.1
1i	NC−	0.66	25 ± 7	−1.9 ± 0.2
1j	O_2N-	0.78	25 ± 8	−1.9 ± 0.2
2	$C_6F_5-C{\equiv}CI$	−[c]	60 ± 3	−2.4 ± 0.0(3)
2	$C_6F_5-C{\equiv}CI$	−[c]	117[d]	−2.8

[a]Determined at 298 K in C_6D_6 by nonlinear least-squares curve fitting of ^{1}H NMR binding titration data to a 1:1 binding isotherm following the *ortho*-protons of the (iodoethynyl)benzene and both CH_2 groups of quinuclidine. See SI for full details. [b]Calculated from averaged K_a. [c]No substituent parameter available for comparison. [d]Association constant determined from $^{19}F_{ortho}$ NMR chemical shift in cyclohexane at 298 K (assumed error ∼20%).

The binding free enthalpies ΔG and substituent parameters σ_{para} are in good linear correlation (Figure 1, r^2 = 0.97; for further details of data analysis, see SI). This correlation confirms that the *para*-substituent is in electronic communication with the iodoethynyl group through the aromatic system. Compared to the variation of the direct acetylenic substituent R in R−C≡C−I in the study by Laurence et al., which gave comparably good linear correlations,[8b] the influence of the *para*-substituent at the aromatic ring is significant. It demonstrates that substituent effects of even distant conjugated groups influence the σ-hole potential substantially, resulting in a remarkable span in binding free enthalpy $\Delta(\Delta G)$ = 0.8 ± 0.2 kcal mol^{-1}. A comparison to the results by Taylor et al. shows that (iodoethynyl)arenes follow a more linear trend than tetrafluoroiodoarenes when the 4-substituent is varied.[9] A lower degree of linear correlation between ΔG and the Hammett parameter σ_{meta} was observed (Figure S55).

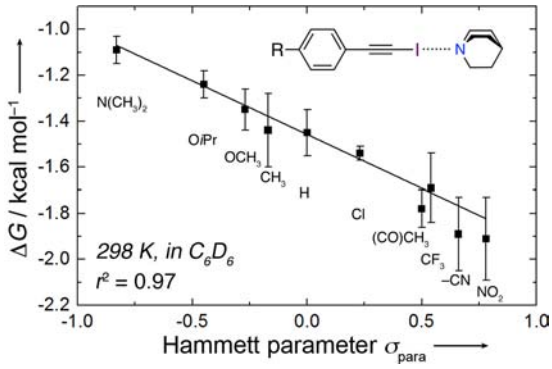
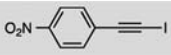
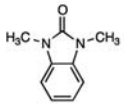


Figure 1. Correlation between binding free enthalpies ΔG and Hammett parameters σ_{para} of different *para*-substituted (iodoethynyl)-benzenes **1a–j** with quinuclidine in C_6D_6 at 298 K.

We found that the observation of the chemical shifts of multiple NMR nuclei provides a good understanding of secondary influences, apart from the direct XB association. In this regard, we determined binding constants from at least two independent titrations, whereas the substrates were titrated in both direction: (1) addition of the XB donor to a constant concentration of XB acceptor, and (2) *vice versa*, which exhibited significant differences in binding constants (see SI for detailed analysis and discussion regarding that issue).

We subsequently explored the variation of the XB acceptors. Exploiting the iodoalkynes with the strongest XB donor abilities, we were able to monitor and quantify the halogen bonding interaction with weaker acceptor molecules, such as *tert*-amides (Table 2). Among the oxygen-bearing acceptors, the earlier reported order of decreasing binding strength of PO > SO > CO is obeyed.[18] Amide and urea carbonyl acceptors are the weakest among all studied examples. Our results are in

Table 2. Association Constants K_a (M^{-1}) of Representative XB Acceptors with 1j and Pentafluoroiodobenzene

		C_6F_5I
XB acceptor	$K_a{}^a$ / M^{-1}	$K_a{}^b$ / M^{-1}
	1.0	–
	1.3	–
	1.7	–
$(nBu)_2SO$	3.0	2.0 ± 0.4
$(nBu)_3PO$	8.4	12 ± 2.5
pyridine	0.8	–
Et_3N	1.9	1.3 ± 0.2
quinuclidine	16[c]	20 ± 4

[a]Association constant in C_6D_6 at 298 K; errors of 20% are generally assumed. [b]Association constant in cyclohexane at 298 K; values taken from ref 9. [c]For comparison, this value derives from the ^{1}H NMR chemical shift for H_{ortho} of the XB donor, in contrast to the value reported in Table 1.

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good agreement with the earlier study of related acceptors interacting with C_6F_5I as the XB donor (Table 2).[9]

Thermodynamic quantities for selected XB complexes were determined by van't Hoff analysis of variable-temperature ^{1}H NMR titration data. The association between quinuclidine and iodoalkynes is promoted by a favorable negative enthalpic term ΔH, partially compensated by an unfavorable negative entropic term $T\Delta S$ (Figure 2). Interestingly, when the aryl substituent is

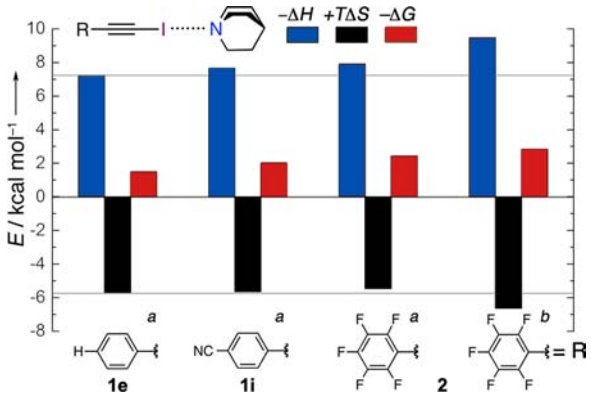

Figure 2. Thermodynamic parameters of halogen bonding between aryl-substituted iodoethynyls and quinuclidine, derived from van't Hoff analyses (see SI for details). $T\Delta S$ is calculated at 298 K. Gray solid lines as reference for $T\Delta S$ and $-\Delta H$ values of **1e**···quinuclidine. [a]In C_6D_6. [b]In C_6H_{12}.

varied from electronically neutral (−Ph) to electron deficient ($-C_6F_5$), the increased gain in binding free enthalpy $-\Delta G$ mostly originates from a more favorable enthalpic term. The positive σ-hole potential becomes enhanced and a stronger halogen bond forms, while the entropic costs are less affected. Furthermore, **2** was found to exhibit a higher association constant in cyclohexane compared to C_6D_6 (Table 1). C_6D_6···C_6F_5CCI quadrupolar interactions and C_6D_6···σ-hole interactions both become perturbed upon halogen bonding. In other words, the XB donor is better solvated in C_6D_6 than in C_6H_{12}, and the resulting desolvation accounts for a more favored entropic term $-T\Delta S$ in C_6D_6. At the same time, loss of σ-hole stabilization by C_6D_6 solvation reduces the overall enthalpic gain, as compared to C_6H_{12}.

In our previous biological study involving the enzyme hcatL,[7] we observed a large gain in protein−ligand affinity even upon formation of halogen bonds between backbone amide C═O and modest XB donors "X−C_6H_4−ligand". It is clear that the entropic costs are paid in this case by the complexation of the large ligand at the active site of hcatL and the full additional enthalpic gains of XB are harvested without much additional loss in entropy.

In the crystalline state, the (iodoethynyl)arenes with additional XB acceptor moieties expectedly exhibit pronounced halogen bonding (Figure 3).[1b,19] Short XB contacts, with I···A distances below the sum of the van der Waals radii and C−I···A angles in the range of 148°−175°, are observed. Thus, XB has a dominant influence on the crystal packing, which is in agreement with the observed solution-phase binding free enthalpies of 1−2 kcal mol^{-1}, well within the range of packing energies previously observed for pairwise aromatic interactions in crystals.[20] Four different XB motifs were found: linear CN···I, bent C═O···I, orthogonal C≡C···I, and a three-center O··I··O halogen bond (see SI for details). Quantum chemical

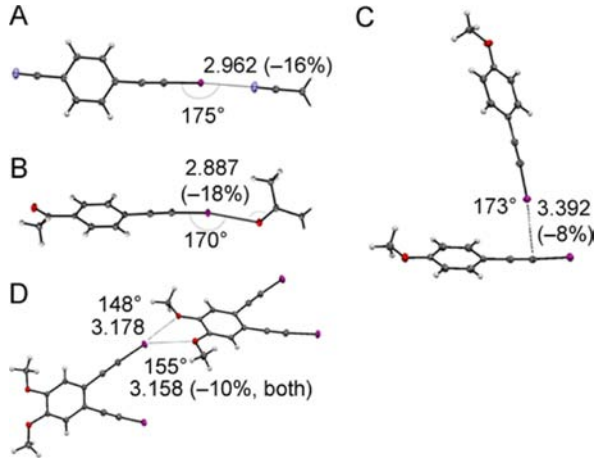

Figure 3. Single crystal X-ray structures of (A) **1i**, (B) **1g**, (C) **1c**, and (D) 4,5-bis(iodoethynyl)-1,2-dimethoxybenzene (**3**). Atomic displacement parameters obtained at 100 K are drawn at 50% probability level. Distances are indicated in Å with the percent of below van der Waals distance in parentheses (for details see SI). Parts of the second molecules in (A) and (B) are omitted for clarity.

investigations and experimental charge density measurements from high-resolution single-crystal X-ray diffraction of these diverse XB motifs are in progress.

In summary, we employed *para*-substituted (iodoethynyl)-benzene derivatives as XB donors and found a strong LFER with σ_{para} in the complexation to the XB acceptor quinuclidine. Binding free enthalpies $-\Delta G$ for 1:1 complexes in C_6D_6 vary between 1.1 (Me_2N−) and 1.9 kcal mol^{-1} (O_2N−). The XB acceptor strength varies in the order pyridine < C═O < S═O < P═O < quinuclidine.[18] Thermodynamic profiles revealed that the enthalpic gain from the established halogen bond is partially compensated by a substantial unfavorable entropic term. Crystal structures showed diverse XB motifs of self-associating (iodoethynyl)benzene derivatives in the solid state. The results demonstrate the versatility of (iodoethynyl)-benzene derivatives as strong XB donors, without the need for aromatic perfluorination, which should make them attractive components in drug design and synthetic supramolecular systems.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, analytical data of synthesized compounds, NMR titration curves, further detailed analysis of binding constant determination, Job plots, X-ray crystal structure data, CIF files, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

§O.D. and D.W. contributed equally.

Notes

The authors declare no competing financial interest.

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