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“Triply Activated” Phenyl 3-Iodopropiolates: Halogen-Bond Donors with Remarkable σ-Hole Potentials

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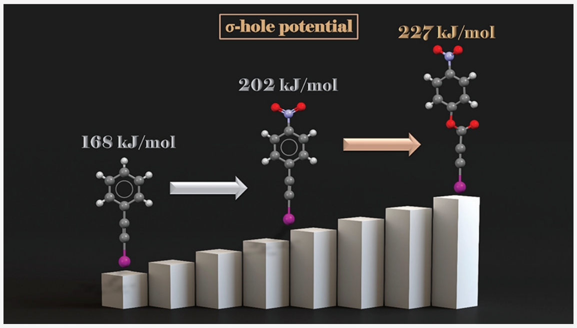
ABSTRACT: The ability of halogen-bond donors to form strong and directional intermolecular interactions remains integral to their prospects of becoming reliable synthetic tools for the bottom-up assembly of functional materials. An activation strategy involving three different electron-withdrawing groups in parallel, was employed in order to develop new halogen-bond donors possessing some of the highest σ-hole potentials reported to date.



The ability to design and assemble functional materials possessing specific supramolecular architectures requires an effective toolkit comprising a range of reliable noncovalent interactions (NCI). While hydrogen bonds have been the most commonly used NCI in supramolecular chemistry,[2] the emergence of versatile σ-hole interactions,[4] primarily halogen bonds,[6] have provided new and exciting opportunities for more complex orthogonal design strategies in the realm of crystal engineering. σ-Hole interactions, resulting from an attraction between an electron-deficient σ-hole on a halogen atom, and an electron-rich region on a Lewis base, can offer high directionality and tunability, which make them well-suited for the directed assembly of desired and robust supramolecular architectures.[7] These properties have provided a foundation for halogen-bond-based structural chemistry with applications in a wide range of fields, fromcatalysis,[8,9] luminescence,[10] nonlinear optics,[11,12] energetics,[13] gels,[14] and polymers,[15] to molecular recognition,[16] self-assembly,[17,18] and drug discovery.[19] The strength of the halogen bond is directly related to the magnitude of the σ-hole, for which molecular electrostatic potentials are frequently used as a yardstick.[20,21] Stronger halogen bonds lead to synthon robustness, which means that we need access to an extensive library of molecules possessing large σ-hole potentials in order to impart supramolecular synthetic reliability.

Several strategies have been described in the literature for designing molecules capable of forming strong halogen bonds. Typically, this is accomplished by “activation” of the halogen-bond donor by adding an electron withdrawing group (EWG) to the molecular backbone, which reduces the electron density at the σ-hole, thereby strengthening the resulting halogen bond.[1] Attaching the halogen atom to a benzene ring through an sp-hybridized carbon atom which further polarizes and enhances the σ-hole is a second strategy that has been employed.[22] There are also a few reports where both an sp-hybridized carbon atom and an EWG have been used together in “doubly-activated” halogen-bond donors.[5,23,24] In the work presented herein, we now describe a class of molecules, combining the electron withdrawing ability of an sp-hybridized carbon atom with two different electron withdrawing moieties in parallel to produce a “triply activated” σ-hole, possessing among the highest σ-hole potentials reported in the literature to date. Scheme 1 illustrates our approach showing how the σ-hole potential on an iodine atom in iodobenzene (95 kJ/mol) can be enhanced systematically by first introducing an sp-hybridized carbon atom (168 kJ/mol), then by adding an electron withdrawing ester group between the C≡C and the aromatic ring (204 kJ/mol), and finally by adding an EWG to the aromatic backbone to give a triply activated halogen-bond donor (227 kJ/mol).

With this strategy, we developed our target library (Figure 1) consisting of the doubly activated unsubstituted parent

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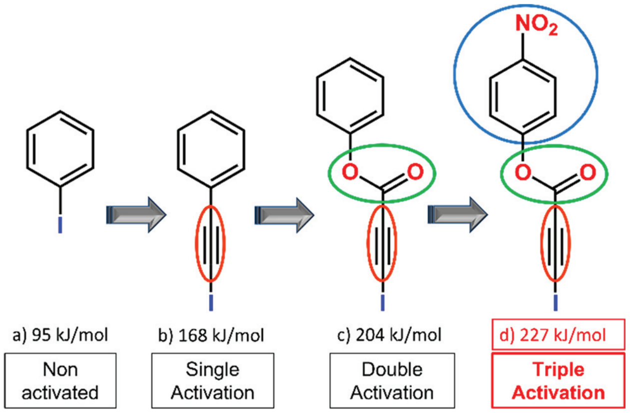
Scheme 1. (a−d) Strategy Employed in Creating Triply Activated XB Donors, Showing the σ-hole Potentials on the Iodine Atom Computed Using DFT at the B3LYP/6-311++G** Level of Theory at iso = 0.002



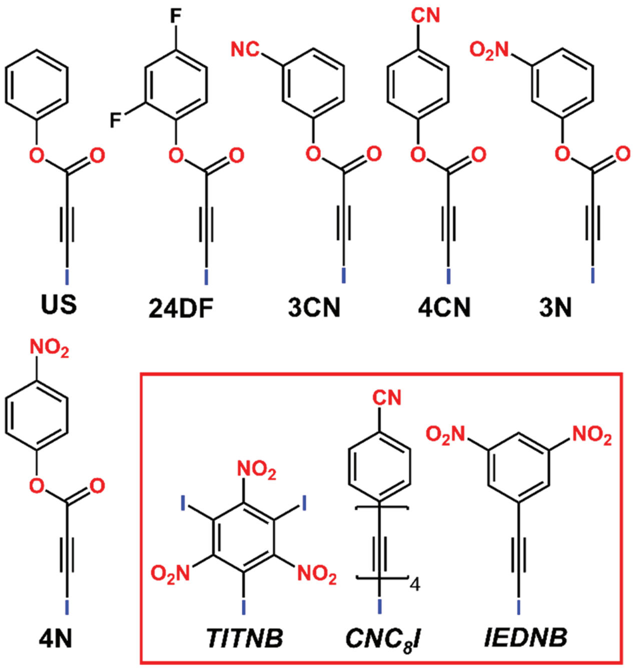


Figure 1. Library of target molecules explored in this study, along with the benchmark molecules (red box) from literature **TITNB**,[1] **CNC$_8$I**,[3] and **IEDNB**.[5]

molecule (**US**) as a benchmark, along with five triply activated esters: 2,4-difluoro (**24DF**), 3-cyano (**3CN**), 4-cyano (**4CN**), 3-nitro (**3N**), and 4-nitro (**4N**). The σ-hole potential of 227 kJ/mol for **4N** far exceeds those reported for other strong halogen-bond donors such as 1,3,5-triiodo-2,4,6-trinitrobenzene (**TITNB**, 207.0 kJ/mol),[1] or doubly activated 4-(iodoocta-1,3,5,7-tetrayn-1-yl)benzonitrile (**CNC$_8$I**, 208.4 kJ/mol),[3,24] and 1-(iodoethynyl)-3,5-dinitrobenzene (**IEDNB**, 217.7 kJ/mol).[5] These known molecules have also been included as benchmark comparisons.

In order to assess the effect of different EWGs on the σ-hole of the iodine atom, molecular electrostatic potential surface maps were generated for all molecules at the B3LYP/6-311++G** level of theory at iso = 0.002 (Figure 2). As expected, the doubly activated **US** has the lowest σ-hole potential, and **4N** has the highest. The cyano (**3CN**, **4CN**) and nitro (**3N**,

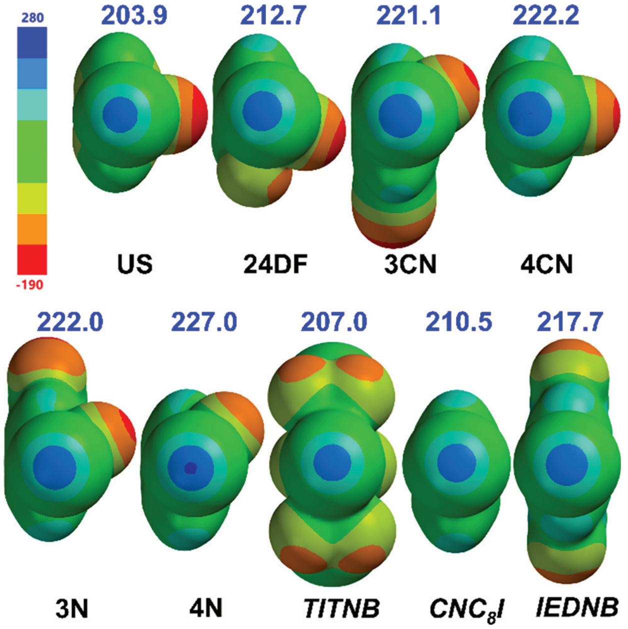


Figure 2. MEP surfaces computed at the B3LYP/6-311++G** level of theory at iso = 0.002 showing the σ-hole potential (top, in kJ/mol) on the iodine atoms of targets and benchmark compounds **TITNB**,[1] **CNC$_8$I**,[3] and **IEDNB**[5] explored in this study.

4N) targets have a higher σ-hole potential than all of the benchmark molecules. Cyano-substituted positional isomers **3CN** and **4CN** seem to have a negligible positional influence on the σ-hole potential, whereas this effect is much more enhanced with nitro substituents, where para-substituted **4N** has a σ-hole potential 5 kJ/mol higher than its meta-substituted positional isomer **3N**. Overall, the σ-hole potential observed on the iodine atoms increase in the order **US** > **TITNB** > **CNC$_8$I** > **24DF** > **IEDNB** > **3CN** > **3N** > **4CN** > **4N**.

In order to assess if the σ-hole potential translates into halogen-bond strength, counterpoise (CP) corrected interaction energy (IE) calculations were carried out on all targets and ammonia as a model acceptor, at the MP2/6-311++G** level of theory. The resulting I···NH$_3$ halogen-bond distances and the associated % reduction in their combined van der Waals radii[25] are summarized in Table 1.

Table 1. σ-Hole Potential Computed at B3LYP/6-311++G** at iso = 0.002 and Counterpoise Corrected Interaction Energies and Halogen-Bond Distances for Dimers with Ammonia Computed at MP2/6-311++G**

	σ-hole potential	interaction energy	calculated XB distance	
target	kJ/mol	kJ/mol	Å	% vdW reduction
US	203.9	−22.9	3.0	14.3
24DF	212.7	−23.8	3.0	14.6
3CN	221.1	−24.5	3.0	14.8
4CN	222.2	−24.6	3.0	14.8
3N	222.0	−24.6	3.0	14.8
4N	227.0	−24.8	3.0	14.9
TITNB[1]	207.0	−27.2	2.9	16.9
CNC$_8$I[3]	210.5	−23.3	3.0	14.5
IEDNB[5]	217.7	−24.0	3.0	14.6

The results show that **US**, which has the smallest σ-hole potential, has the lowest IE with ammonia at −22.87 kJ/mol, while **4N** with the highest σ-hole potential has the highest IE with ammonia at −24.78 kJ/mol. While **TITNB** shows an unusually large computed IE compared to its σ-hole potential, a feature previously observed when it was compared to **IEDNB**,[1] all the other targets and benchmark molecules follow the trend of a higher σ-hole potential resulting in a stronger interaction with ammonia (Figure 3), as reflected by its computed XB distance and % vdW reduction, Table 1.

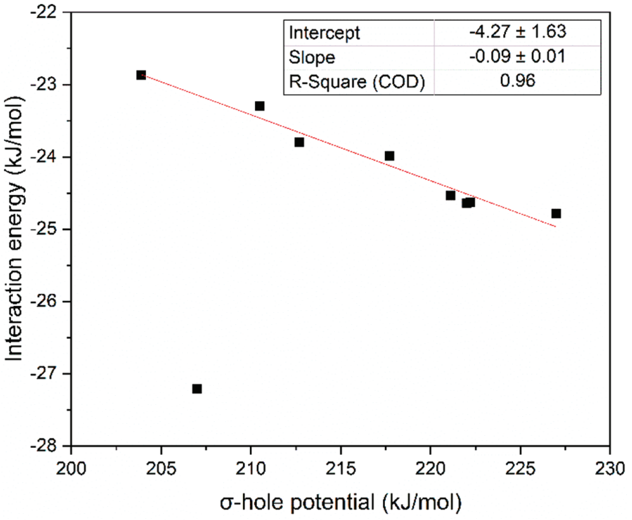
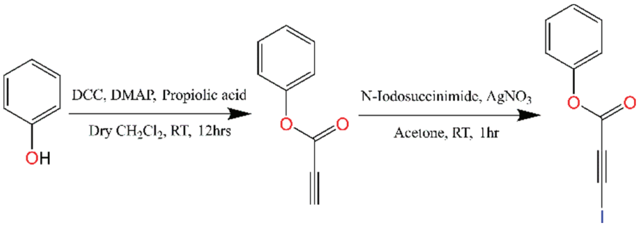


Figure 3. Plot of σ-hole potentials for target and benchmark molecules explored in this study versus their CP corrected IEs with a model acceptor ammonia. The TITNB outlier is excluded from the line of best fit. IE computed at MP2/6-311++G** and σ-hole potential computed at B3LYP/6-311G++G** at iso = 0.002.

All the targets in this study were synthesized using modified versions of previously reported procedures (Scheme 2).[26,27]

Scheme 2. Pathway Used to Synthesize Targets



The first step involves a Steglich esterification,[28] where the corresponding phenol is first dissolved in dry CH_2Cl_2 and cooled in ice, to which propiolic acid is first added, followed by a mixture of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) dissolved in dry CH_2Cl_2 and stirred at room temperature (RT) to give the corresponding phenyl propiolate intermediate. This is then reacted with N-iodosuccinimide (NIS) in the presence of a catalytic amount of $AgNO_3$ in acetone at RT to give the corresponding phenyl 3-iodopropiolate. Detailed synthetic procedures and characterization data are outlined in the Supporting Information.

Before the crystal structures of the targets are examined, it is informative to consider which intermolecular interactions are possible and plausible. Each compound brings a single halogen-bond donor, the triply activated iodine atom, but there are multiple options for acceptor sites. First, the carbonyl oxygen atom of the ester group, which is common to all targets, can act as a XB acceptor, but there is possible competition from the EWGs present on the aromatic ring, −CN, or $-NO_2$, respectively, in four of the targets (**3CN**, **4CN**, **3N**, **4N**). In addition to these directional halogen bonds, it is expected that $\pi-\pi$ stacking would also be present in all six crystal structures.

In the crystal structure of the double-activated **US**, which has only one major bond donor and accepting sites, the expected I···O=C XB is observed, 2.856(2) Å with a 173.13(8)° C−I···O XB bond angle (Figure 4, Table 2). The addition of two fluorine atoms to the aromatic backbone, **24DF**, increases the σ-hole potential but does not add any competing XB acceptors. Consequently, the main XB is an I···O=C; 2.891(2) Å and 173.51(11)°.

The addition of cyano (**3CN**, **4CN**) and nitro (**3N**, **4N**) groups to the molecular backbone brings potential competitors to the C=O acceptor, and in the crystal structure of **3CN**, the main interaction involves a halogen bond to the C≡N moiety, r(I···N) 2.998(3) Å and θ(C−I···N) 171.76(10)°. The same XB is found in the structure of **4CN**, r(I···N) 2.890(7) Å and θ(C−I···N) 171.6(3)°.

In the crystal structure of **3N**, there is a bifurcated I···O/O XB to both oxygen atoms of the nitro group, r(I···O(14)) 3.355(3) Å and θ(C−I···O(14)) 142.87(9)° and r(I···O(15)) 3.059(3) Å and θ(C−I···O(15)), 174.21(9)° respectively. This suggests that a "supramolecular chelating effect" associated with two weaker interactions to the nitro group is preferred to a single interaction with the C=O moiety of the ester group. In contrast, in the crystal structure of the **4N** target, which displayed the largest positive σ-hole potential, there is a single I···O XB to one oxygen atom of the nitro group, r(I···O) 2.918(4) Å and θ(C−I···O) 178.05(18)°. The % vdW reductions in these XBs are given in Table 2, but they do not correlate with the changing σ-hole potential, which may be explained by the fact that the XB acceptor moieties are different across this series, spanning from C=O to −CN and $-NO_2$.

In summary, in this work, we have explored a new "triple activation" strategy, where combining three different EWGs in parallel to activate a halogen atom resulted in targets with exceptional σ-hole potentials that are among the highest observed to date in the literature. Even higher than molecules like **CNC_8I**[24] which combine multiple of the same EWGs (four C≡C in succession) but result in a lower σ-hole potential. All the triply activated targets showed a comparable or higher % reduction in the XB vdW radii with equal or more linear XB angles when matched against the three literature benchmark molecules. This strategy also produced compounds possessing excellent thermal stability compared to **TITNB**[29] and **CNC_8I**[24] owing to the versatility of varying the nature and position of the three different EWGs. An excellent correlation between increasing σ-hole potentials and increasing IE with ammonia was obtained, confirming that calculated σ-hole potentials can be used as a suitable guideline for estimating the resulting halogen-bond strengths of yet to be synthesized halogen-bond donors. This "triple activation" can be broadly applied to any σ-hole interaction and provides a versatile tool to a chemist designing functional materials to dial-in desired properties toward a wide range of applications. In the next phase of this project, we will cocrystallize these targets with different

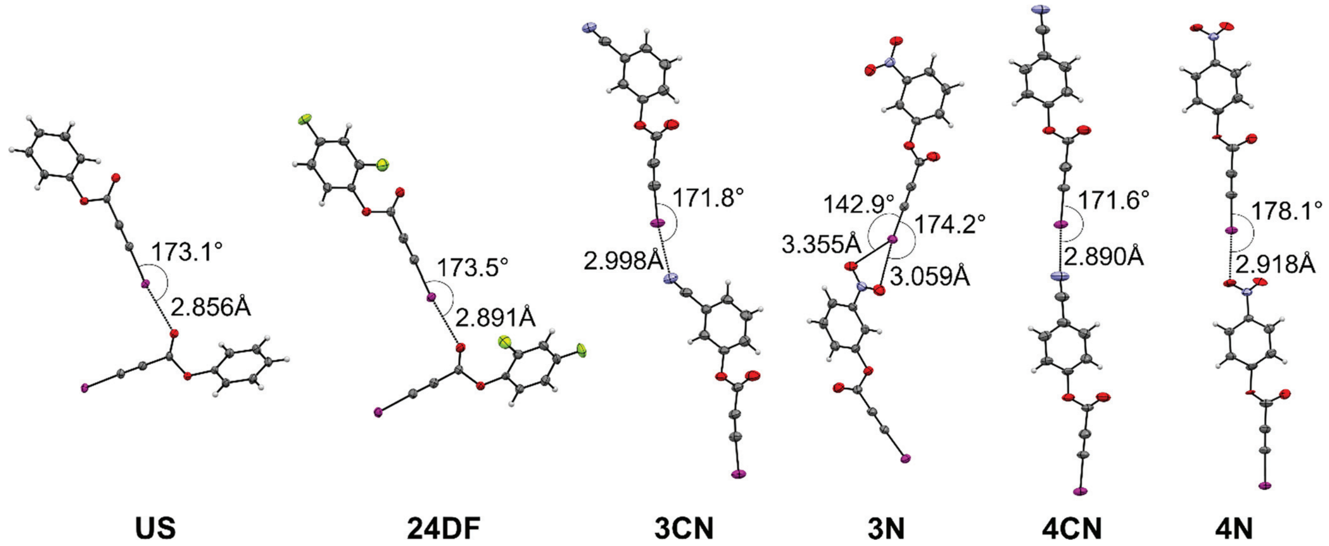


Figure 4. Primary halogen bonds in the crystal structures of five "triply activated" XB donors. The unsubstituted parent (**US**) is included for comparison.

Table 2. σ-Hole Potential Computed at B3LYP/6-311++G at iso = 0.002 and XB Distances and Angles from Crystal Structures**

	σ-hole potential	experimental XB distance		XB angle
target	kJ/mol	Å	% vdW reduction	°
US	203.9	2.86	18.4	173.1
24DF	212.7	2.89	17.4	173.5
3CN	221.1	3.00	15.1	171.8
4CN	222.2	2.89	18.1	171.6
3N	222.0	3.06	12.6	174.2
		3.36	4.1	142.9
4N	227.0	2.92	16.6	178.1
TITNB[1]	207.0	3.14	10.3	165.5
CNC$_8$I[3]	210.5	2.89	18.2	178.5
IEDNB[5]	217.7	3.06	12.6	168.2

coformers, in order to establish their effectiveness and reliability in crystal engineering and supramolecular synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.1c01450.

Synthetic procedures, theoretical calculations, spectral data, and crystallographic information table (PDF)

Accession Codes

CCDC 2121642−2121646 and 2121648 (**US**, **24DF**, **3CN**, **4CN**, **3N**, and **4N**) contain the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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