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Halogen Bonding Organocatalysis Enhanced through Intramolecular Hydrogen Bonds

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Recent results indicate a halogen bond donor is strengthened through direct interaction with a hydrogen bond to the electron-rich belt of the halogen. Here, this *Hydrogen Bond enhanced Halogen Bond* (HBeXB) plays a clear role in a catalyst. Our HBeXB catalyst improves product conversion in a halide abstraction reaction over a traditional halogen bonding derivative.

The axiom, "the whole is greater than the sum of the parts", can be especially true for noncovalent interactions. Biomolecules, like DNA, carbohydrates, and proteins, employ networks of hydrogen bonds that can enhance individual interactions and promote the remarkable function of these molecular machines.[1] To describe these hydrogen bond networks terms such as σ-bond cooperativity, hydrogen bond cooperativity, hydrogen bond-enhanced hydrogen bond and polarization-enhanced hydrogen bond have been invoked.[2] Small molecule studies[3] have refined our understanding of how adjacent hydrogen bonds influence each other, offering insight into the complexities of natural systems. Furthermore, this cooperative[4] noncovalent approach has been used in synthetic molecules to enrich the function of hydrogen bond based anion receptors[5] and organocatalysts[6]. However, studies of how alternative noncovalent interactions (e.g. halogen bond, chalcogen bond) are influenced by proximal hydrogen bonds are lacking. Given the ubiquity of the hydrogen bond, and the growing importance of σ-hole-type interactions,[7] understanding this relationship is of broad importance.

The field of halogen bonding organocatalysis is nascent, yet rapidly developing.[8] The unique characteristics of the halogen bond—the linear directionality and soft halogen donor—have the potential to complement well-established hydrogen bonding analogues. In fact, remarkable progress in halogen bonding organocatalysis has recently been reported, such as outperforming hydrogen bonding catalysts[9] and the first example of an enantioselective halogen bonding catalyst.[10] §

This emerging sector has reinforced the significance of preorganization to elicit superior function of halogen bonding materials. Yet, despite the various methods used to preorganize anion receptors[11] only sterics have been employed to improve the function of halogen bond organocatalysts. Here, inspired by natural and abiotic hydrogen bonding catalysts, we demonstrate another way to preorganize halogen bonding organocatalysts though polarization enhanced noncovalent cooperativity. Specifically we demonstrate that intramolecular hydrogen bonds directed at the electron belt of halogen bond donors can improve catalysis.§§

The importance of understanding how hydrogen bonds influence organohalogens and halogen bond donors is underscored by the significant interest in fluorine containing drugs[12] and the controversy surrounding its role as a hydrogen bond acceptor.[13] In contrast, the study of hydrogen bonding to heavier halogens (chlorine, bromine and iodine) has lagged,[14] despite the fact that over half of launched organohalogen drugs contain these halogens that have the capacity to be halogen bond donors.[15] Recently, it was shown that hydrogen bonding directly to the electronegative belt of the halogen bond donor (the hydrogen bond enhanced halogen bond, HBeXB) can enhance anion recognition as well as protein stability.[16] To this end, our lab developed an HBeXB anion receptor that incorporated two charged iodopyridinium rings flanking a bisethynyl-4-fluoroaniline core (Figure 1, molecule **3**). We found that the amine hydrogen bonds to the surrounding iodine atoms to promote rigidity and produce convergent halogen bond donors—enhancing halide binding by approximately an order of magnitude.[17] We hypothesized that **3** could function as

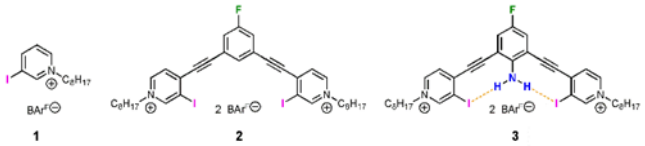

Figure 1 Monodentate halogen bond catalyst **1**, bidentate halogen bond organocatalyst **2** (without intramolecular hydrogen bonds), and hydrogen bond-enhanced halogen bond catalyst **3**. For synthesis of molecules **1** and **2** see ESI. Molecule **3** was synthesized as previously reported.[17]

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an organocatalyst in a halide abstraction reaction (Figure 2) to further demonstrate the utility of the HBeXB.

A halide abstraction reaction between bromodiphenylmethane (BrDPM) and 1-methylindole (Figure 2) was chosen to test whether HBeXBing improves catalytic function over a strictly halogen bonding organocatalyst. The reaction produces 3-benzhydryl-1-methyl-1*H*-indole product (**A**) and a side product (1-methylindole dimer, (**B**), which is catalyzed by the production of hydrobromic acid (HBr) during

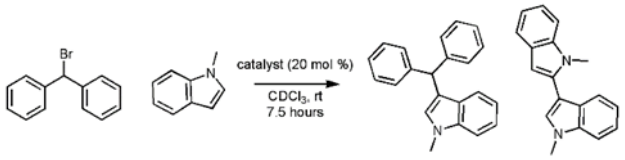

Figure 2 The halide abstraction reaction used to test how the interplay between hydrogen and halogen bonding influences catalysis. The 1-methylindole nucleophile reacts with the bromodiphenylmethane (BrDPM) electrophile producing **A**. The 1-methylindole dimer **B** is formed as a side product in the reaction.

the reaction).[18] To study the formation of **A**, the reaction was carried out using excess 1-methylindole (see ESI). Several control reactions described below established the baseline reactivity and suitability of the system to evaluate HBeXB organocatalysis, as opposed to reaction activation of similar reactions that necessitate stoichiometric amounts of halogen bond donor.[8] The background reaction (no catalyst) afforded only 12% of **A** (Table 1, entry 1). To ensure that HBr did not catalyze the production of **A**, the reaction was tested in the presence of 20 mol% HBr in acetic acid (Table 1, entry 2). In this case, minimal amounts of **A** were formed (6% yield), indicating that HBr does not catalyze the production of **A**.‖ Halogen bond induced catalysis was established using a monodentate 3-iodopyridinium derivative (**1**). After 7.5 hours, 29% of product **A** (Table 1, entry 3) was produced in the presence of 20 mol% of **1**, an approximate 2-fold increase in product formation over the background reaction (entry 1). Taken together, these results confirmed that this reaction is appropriate to evaluate HBeXB organocatalysis.

As expected, bidentate halogen bond donor **2** improved catalysis producing a 41% yield (Table 1, entry 4), which is nearly 3-fold greater than the uncatalyzed reaction (entry 1). Despite being conformationally flexible (*vide infra*), **2** produced **A** in greater yield than monodentate halogen bond catalyst **1** (29%). However, the modest yield of the bidentate catalyst suggested that performance could be improved by noncovalent cooperativity and preorganization of the HBeXBs found in **3**.

To establish whether hydrogen bonding directly to halogen bond donors is a viable strategy to improve catalytic performance, organocatalyst **3** was evaluated and the yield of **A** increased to 71% after 7.5 hours (Figure 3; Table 1, entry 5). The HBeXB catalyst **3** nearly doubled the amount of **A** compared to the nonhydrogen bonding bidentate halogen bond catalyst **2**. Catalyst **3** also had an initial rate constant (k_{rel}) that was more than double that of **2** (see ESI table S1). ^{13}C NMR provided further evidence of the role of halogen bonding in **3**. Adding five equivalents of BrDPM provided a 0.42 ppm downfield shift of

Table 1 Results from halide abstraction reaction

Entry #	Catalyst	Catalyst Equivalents	Yield (%)[a]
1	—	—	12
2	HBr in acetic acid	0.2	6
3	**1**	0.2	29
4	**2**	0.2	41
5	**3**	0.2	71
6	4-fluoroaniline	0.2	13
7	Iodine	0.2	33
8	$TBA^+ BArF^-$	0.2	29

Table 1 Results from the halide abstraction reaction (Figure 2) conducted in the presence of various Lewis acid catalysts: average (from triplicate data) yield of product (**A**) after 7.5[a] hours ($CDCl_3$, rt, dark). [a] Product yield determined by ^{1}H-NMR spectroscopy (cf. See ESI).

the ^{13}C signal that corresponds to the C-I (Figure S13). The downfield shift correlates with halogen bonding in solution and provides additional evidence of the halogen bonding in this system.[19] Together, these data suggest that the HBeXB is a functional molecular design that engenders the improved catalysis demonstrated here.

To ensure the improved catalytic activity of **3** was not due to direct hydrogen bonding between the amine and the substrate, the reaction was also screened in the presence of 4-fluoroaniline (Table 1, entry 6).** In this case, only 13% of **A** was produced, which is nearly identical to the uncatalyzed reaction (12% product). Thus, we conclude the amine alone has no catalytic function in this reaction. Rather, the noncovalent synergy afforded by the interaction of hydrogen bonds with the electronegative belt of the halogen bond donors is crucial for improving catalytic function. A proto derivative of **3** (**H3**) produced similar yields to **2** (see ESI Table S2). Conceivably the pyridinium CH hydrogen bond donors of **H3** catalyst could be binding BrDPM in a multidentate manner facilitating reaction conversion. In fact, a previous study highlights that bromide binding of the non-fluorinated **2** and the **H3** are comparable (K_{11} values of 4690 M^{-1} and 2110 M^{-1} *see reference 17*).

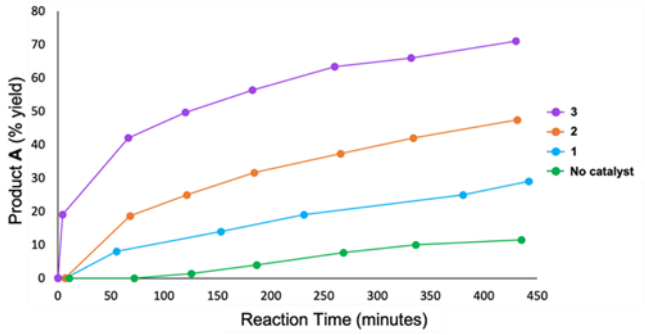

Figure 3 Yield versus time profile of the halide abstraction reaction in the presence of various catalysts and controls (cf. Table 1).

Other control reactions were considered to rule out possible effects of trace iodine or anion catalysis. While there was no indication of catalyst decomposition during the reaction screens (NMR), a control reaction using 20 mol% of molecular iodine was conducted. Iodine produced only 33% of **A** (Table 1, entry 7) indicating that trace amounts of molecular iodine are not the

active catalyst in the reaction. The reaction conducted in the presence of tetra-*N*-butylammonium (TBA) tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr^F) produced only 29% of **A**, (Table 1, entry 8) providing evidence that BAr^F is not the active catalyst. These controls also illustrate that the halogen bond donors in **1**, **2**, and **3** are key to the catalytic activity.

Overall, the HBeXBs of **3** are hypothesized to offer two advantages—molecular preorganization and halogen bond augmentation. To gain insight into how each HBeXB component enhances the catalytic activity of **3**, gas-phase density functional theory (DFT) computations were conducted on the methylated derivatives (without anions, for simplicity), comparing HBeXB catalyst **3Me** and catalyst **2Me** (no HBeXB).

Halide abstraction reactions similar to the one studied herein proceed via S_N1 or S_N2 pathways.[8b] In either mechanism, halogen bonding to the bromine would increase the reactivity of the electrophile.† To assess halogen bond augmentation, we computed DFT complexation energies for the catalyst with bromomethane (BrM)—a surrogate for BrDPM to enable simpler computations (ESI) The complexation energy of **2Me**•BrM was 7.94 kcal/mol while **3Me**•BrM (with HBeXB) was 8.84 kcal/mol. We attribute the 0.91kcal/mol difference in interaction energies to further polarization of the iodine atoms by the hydrogen bond, enhancing the halogen bonds **3Me**. We postulate that a stronger interaction of **3Me** with BrDPM contributes to the improved catalysis.¶¶

Single point energy calculations were carried out on the three planar conformations (Figure S15) of **3Me** and **2Me** to understand whether the HBeXB of **3** confers the preorganized binding conformation compared to **2**. The bidentate binding conformation of **3Me** was more stable than the W conformation by 1.44 kcal/mol. In contrast, the nonconvergent W conformation was the most stable for **2Me**, with the bidentate conformation being the least stable by 0.70 kcal/mol. A relaxed scan alkyne driver study was run on **2Me** and **3Me** and further differences in conformational stability were observed (Figure S14). Notably, the rotational barrier of the amine containing **3Me** was 1.92kcal/mol higher than **2Me**—a greater than 3-fold increase (ESI). The theoretical data suggest that the HBeXBs of **3** preorganize the catalyst and allow it to interact with BrDPM in a bidentate mode more often. We hypothesize that this difference in preorganization is a key factor in the catalytic activity of **3**.

Triflate salts of **2Me** and **3Me** provide further evidence of preorganization in the solid-state. Two X-ray structures of **2Me•2OTf**$^-$—lacking the preorganizing amine—adopt the W conformation (Figure S16). One structure crystalized in the $P\bar{1}$ space group with one molecule of **2Me•2OTf**$^-$ in the asymmetric unit resulting in two unique halogen bond contacts with oxygen atoms of triflate anions (3.130(3) Å (R_{IO}=0.88), 165.09(10)° and 3.181(2) Å (R_{IO}=0.90), 160.37(10)). The W conformation is also found in an orthorhombic polymorph (*Pbcn*) of **2Me•2OTf**. Only half of **2Me•2OTf**$^-$ is present in the asymmetric unit, dictating a single unique halogen bond contact with an oxygen atom of the triflate anion with a distance and angle of 2.889(4) Å (R_{IO}=0.82), 168.69(16)°. In contrast, a previously reported crystal structure of **3Me•2OTf**$^-$ highlights both the bidentate (3.195(10) Å, 172.7(3)˚ and 3.280(9) Å, 148.4(2)˚ (R_{IO} = 0.90 and 0.93, respectively) and monodentate S conformation (2.908(8) Å, 175.91(18)˚ (R_{IO}=0.82) and 3.089(6) Å, 168.1(2)˚ (R_{IO}=0.87) (50/50 disorder)).[17] The bias for these conformations, over the W conformation observed with the two **2Me•2OTf**$^-$ structures, further highlights the importance of the amine in preorganizing the organocatalyst.

Intramolecular hydrogen bonding to halogen bond donors represents a new and compelling method to preorganize molecular structure and enhance catalytic activity. A benchmark halide abstraction reaction was used to study different halogen bonding catalysts and explore the enhanced activity of the HBeXB derivative. All halogen bonding compounds herein function as catalysts however, intramolecular hydrogen bonds to the halogen bond donors significantly increased the amount of product produced. Control studies illustrated that the amine was inconsequential to catalytic activity on its own, confirming its primary role as an intramolecular hydrogen bond donor in **3**. Theoretical analysis of **2Me**•BrDPM and **3Me**•BrDPM showed the HBeXB derivative (**3Me**) produced a more favorable complexation energy while conformational analysis of the methylated catalysts suggested favorable preorganization in HBeXB catalyst **3**. This preorganization was also supported by solid-state studies that highlighted that **3Me** adopts the bidentate halogen bonding conformation more often. Altogether, these results showcase those weak noncovalent interactions can enhance organocatalytic reactivity. This emerging strategy is likely to have developments beyond organocatalysis in fields such as bioengineering and halogenated drug-design.

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"There are no conflicts to declare".

Notes and references

§ Others have achieved enantioselectivity but those have been with catalysts that employ halogen bonds with other directional noncovalent interactions (e.g. hydrogen bonds) or with proximal Lewis basic sites. A recent review of asymmetric catalysis with halogen bond contributions are found here Kaasik, M.; Kanger, T. *Front. Chem.* **2020**, *8*, 958

§§ A paper was recently published that included a possible hydrogen bond enhanced halogen bonding catalyst (Kaasik, M.; Martonova, J.; Erkman, K.; Metsala, A. Jarving, I.; Kanger, *Chem. Sci.*, **2021**, *12*, 7561). However, it was not clear from this study that the improved catalytic performance was due to the

halogen bond donor simultaneously accepting a hydrogen bond. Here, we offer a simple system to identify the influence of the HBeXB on catalysis.

‖ To eliminate the 1-methylindole dimer (**B**), we initially ran reaction screens in the presence of base. Unfortunately, no single base was compatible with all the catalysts. Under the conditions, some bases were ineffective at quenching the acid (Cs_2CO_3, K_2CO_3) while others led to decomposition of **2** (pyridine, TEA, proton sponge, DBU, DIPEA) and **3** (pyridine, TEA, DBU, proton sponge, 2,6-bis(tert-butyl)pyridine (BTBP)). Nevertheless, **3** consistently led to a greater yield of product (**A**), regardless of the base that was used. Additional details are in the ESI.

**No side products were observed in the NMR spectra from the amine acting as a nucleophile.

† If the reaction proceeds via S_N1 mechanism the stronger halogen bonds and bidentate interaction with the BrDPM would encourage the formation of an ion-pair intermediate. In contrast, if the reaction proceeds via S_N2 the stronger halogen bonds and bidentate interaction would stabilize the partial negative charge that is built up in the transition state of the S_N2 reaction and/or weaken the C–Br bond in the BrDPM to help facilitate the S_N2 reaction with the 1-methylindole. See Bulfield, D.; Huber, S. M. *Chem. Eur. J.* **2016**, *22* (41), 14434–14450 for discussion of halide abstractions (S_N1 vs S_N2) facilitated by halogen bond donors. An example of a hydrogen bond catalyst abstracting bromide from diarylbromomethanes via an S_N1 pathway can be found Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132* (27), 9286–9288

¶¶ We suspect in this case that stronger noncovalent interactions contribute to improved catalytic performance. For example, pnictogen, chalcogen and halogen bonds were shown to catalyse a chloride abstraction reaction and that stronger noncovalent interactions correlated with improved catalytic activity (Benz, S.; Poblador-Bahamonde, A.I.; Lows-Der, N.; Matile, S. Angew. Chem. Int. Ed. 2018, 57, 5408 –5412).

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