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Utilization of BODIPY-Based Redox Events to Manipulate the Lewis Acidity of Fluorescent Boranes

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This report describes the implementation of a 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) dye into the ligand framework of a borane. The redox-active nature of the BODIPY dye is utilized to generate a family of molecular boranes that are capable of exhibiting tunable Lewis acidities through BODIPY-based redox events.

Boranes are widely used in organic transformations. Although boranes are a common choice for a Lewis acid to promote a chemical transformation, the fact that a boron center does not exhibit redox activity limits the scope of these reagents. For example, $B(C_6F_5)_3$ is a strong Lewis acid that is widely used in frustrated Lewis pair chemistry,[1-3] but the lack of reactivity at the boron center renders the small molecule adducts of $B(C_6F_5)_3$ and $^tBu_3P$ inert to further reactivity.[4]

One approach to introduce redox capabilities into a main group scaffold is through the incorporation of a fluorescent dye.[5] Fluorescent dyes are attractive substrates for introducing redox capabilities, as they are capable of reversible redox chemistry.[6] One molecular dye that has received recent attention is the metal-free 4,4-difluoro-4-bora-3a,4adiaza-s-indacene (BODIPY) dye.[7] The BODIPY scaffold is attractive as it exists in a metal free motif and has been widely employed as a fluorescent dye,[8] in photodynamic therapy,[9] and as a sensor for molecules such as cyanide,[10] nitric oxide,[11] carbon dioxide,[12] and heavy metals.[13] BODIPY dyes are also capable of reversible electrochemistry.[14]

BODIPY dyes are also attractive from a synthetic standpoint, as they can be readily appended to donor atoms and functionalized.[8] For example, incorporation of a methylthio group or a halogen into the BODIPY skeleton allows for nucleophilic substitution at that position. This reactivity can be employed in the synthesis of BODIPY dyes containing donor groups that can be appended to Lewis acids.[5]

In this manuscript, we describe how the incorporation of two BODIPY scaffolds can be utilized to control the Lewis acidity of a boron center. We also discuss how the incorporation of a BODIPY fragment introduces two redox events that are BODIPY-based. We have shown that the incorporation of BODIPY fragments greatly reduces the electron density at a donor atom,[15] suggesting that the BODIPY fragments appended to donor atoms could be utilized in the generation of Lewis acids. We hypothesized that the introduction of BODIPY fragments into a Lewis acid scaffold could introduce redox activity into main group elements that are not capable of redox chemistry, allowing for manipulation of the Lewis acidity of the borane through BODIPY-based redox events.

Treatment of dipotassium *N,N'*-bis-BODIPY-ethylenediamide or dipotassium (±)-*N,N'*-bis-BODIPY-cyclohexane-1,2-diamide, generated from the addition of $KN(SiMe_3)_2$ to the respective *N,N'*-bis-BODIPY-diamine,[5] with one equivalent of $PhBCl_2$ in CH_2Cl_2 resulted in orange colored solutions that fluoresced a screamin' green[16] color under UV light (Figure 1). Isolation of the boron-containing products resulted in a scarlet colored solid in 91 and 58% yield for the

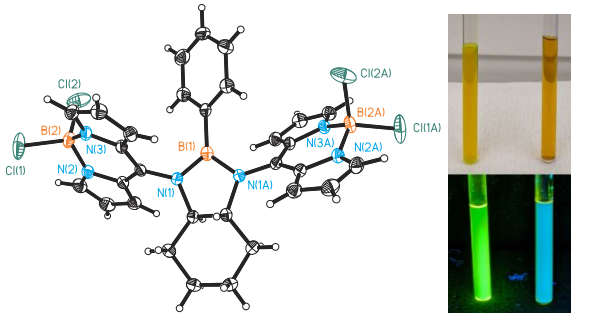

Figure 1. Molecular structure of **2Cl$_4$**. Thermal ellipsoids are drawn at 50% probability. Pictures of **2** in $CDCl_3$ (left) and CD_3CN (right) under (top) lab light and (bottom) UV light.

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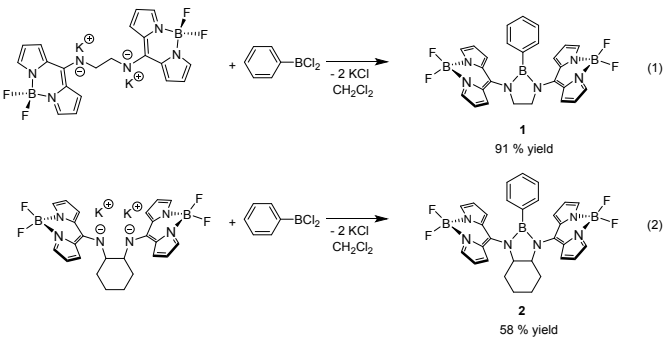
Electronic Supplementary Information (ESI) available: Synthetic methods, multinuclear NMR spectra of **1** and **2**, details of molecular structure analysis, cyclic voltammograms, normalized absorbance and emission spectra, pictures of the addition of reductants and Lewis bases to **1** and **2**, table of computed reduction potentials, free energies for the binding of Lewis bases to **1** and **2**, gas phases energies of all computed structures, molecular orbitals of **1** and **2**, and 3D coordinates of all computed structures. CCDC 2121686 and 2128647. See DOI: 10.1039/x0xx00000x



ethylenediamine and diaminocyclohexane containing boranes, **1** and **2**, respectively (Equations 1 & 2). The resulting boranes were sparingly soluble in most organic solvents (Complex **1**: Toluene: 5 mg/mL, Acetonitrile: 10 mg/mL, Dichloromethane: 10 mg/mL; **2**: Toluene: 8 mg/mL, Acetonitrile: 15 mg/mL, Dichloromethane: 30 mg/mL), exhibiting the best solubility in CH_2Cl_2. Although **1** and **2** were poor (**1**) to moderately (**2**) soluble in most solvents, generation of **(*R,R*)-2** (from (*R,R*)-diaminocyclohexane), resulted in a borane that was soluble in most organic solvents (e.g. arenes and pentane).

The ^{1}H NMR spectrum of **1** exhibited six resonances in the aromatic region, three for the BODIPY groups and three for the phenyl group, in addition to one resonance for the ethylenediamine fragment at 4.42 ppm. Unlike **1**, complex **2** exhibited nine resonances, six BODIPY and three arene, in the aromatic region of the ^{1}H NMR spectrum.

The presence of a three-coordinate boron center and two four-coordinate boron centers in **1** was verified by ^{11}B{^{1}H} NMR spectroscopy,[17-18] where a triplet at 0.45 ppm ($^1J_{BF}$ = 28.5 Hz) and a broad singlet at 35.48 ppm in a 2:1 ratio, respectively, were observed. Similar ^{11}B NMR spectra were observed for **2**, see Supporting Information. The ^{19}F{^{1}H} spectrum of **1** was solvent dependent, where a CD_3CN solution exhibited a single 1:1:1:1 quartet at −145.5 ppm and a broad singlet at −146.5 in $CDCl_3$. The 1 : 1 : 1 : 1 quartets in the ^{19}F NMR spectrum arise from the one bond coupling (~27 Hz) between the fluorine atoms and ^{11}B (I = 3/2), which is 80% abundant. A slight shoulder on the 1 : 1 : 1 : 1 quartet is attributed to coupling between the fluorine atoms and ^{10}B (I = 3, 20% abundant). The introduction of chiral centers in **2**, resulted in a ^{19}F{^{1}H} spectrum exhibiting a 1:1:1:1 quartet of AB quartets with a J_{AB} of 104 Hz (for the $^2J_{FF}$ coupling of the AB quartet), and a 27 Hz one bond coupling between the ^{11}B and fluorine centers, see Supporting Information, Figure S11.

Dissolution of **1** and **2** in $CDCl_3$ resulted in very broad signals in the ^{19}F NMR spectra. If the $CDCl_3$ contained trace water, the ^{19}F signals disappeared within seconds to minutes. The disappearance of the fluorine atoms of the BODIPY dyes were further verified by ^{11}B NMR spectroscopy, where a singlet at 1.82 ppm was observed. These results suggest a Lewis acid catalysed, water promoted, chlorine-fluorine exchange in **1** and **2**, generating **$1Cl_4$** and **$2Cl_4$**, respectively (Figure 1). The exchange only occurred in the boranes, not in the free ligands, and occurred only in chloroform.

X-ray quality crystals of **$2Cl_4$** were generated by the diffusion of pentane into a chloroform solution of **$2Cl_4$**. Crystallographic analysis revealed the presence of one three- and two four-coordinate boron centers and chlorine (instead of fluorine) atoms on the BODIPY fragments. The BODIPY fragments were highly planar, exhibiting only a 11° deviation from planarity. Upon further examination of the molecular structure, the protons in the 1-positions of each of the BODIPY fragments were found to reside about 2.9 Å above and below the three-coordinate boron center, indicating a weak B-H interaction. A similar interaction is observed in trimesitylborane.[19] Although this B-H interaction is observed in the solid state, only six proton resonances are observed in the aromatic region of the ^{1}H NMR spectrum of **1** (three corresponding to BODIPY and three corresponding to the phenyl substituent), suggesting that the B-H interaction does not exist in solution (see Supporting Information). However, nine proton resonances are observed in the aromatic region of the ^{1}H NMR spectrum of **2** and **$2Cl_4$** (six corresponding to BODIPY and three corresponding to the phenyl substituent), indicating a stronger B-H interaction (see Supporting Information). Attempts at crystallization of **1** or **2** resulted in crystals that weakly diffracted (**1**, see supporting information) or twinned crystals that were not solvable (**2**).

Examination of the photophysical properties of **1** and **2** revealed absorbances at 411 and 417 nm and emissions at 485 and 531 nm, respectively (Table 1). The absorbances and emission for **1** and **2** are red shifted when compared to the free ligands.[5] Analysis of the quantum yield resulted in a value that was up to five times higher than the free ligands. [5]

Table 1. Photophysical properties of **1** and **2** in CH_2Cl_2.

Complex	λ_{abs} (nm)	λ_{ems} (nm)	ϕ
1	334, 411, 488	485	0.58
2	331, 417, 506	531	0.36

The electrochemical analysis of **1** in CH_2Cl_2 revealed two reversible reductions at −1.21 and −1.56 V, a quasireversible reduction at −1.97 V, and two irreversible oxidations at 0.38 and 0.91 V (Figure 2). Electrochemical analysis of **2** in CH_2Cl_2 revealed three reversible reductions at −1.33, −1.60 and −1.85 and three irreversible oxidations at 0.38, 1.24, and 1.48 V vs. Cp_2Fe/Cp_2Fe^+ (Supporting Information, Figure S32). For **1** and **2** the first two reduction events are attributed to BODIPY-based redox events (see below) and the third reduction is attributed to the reduction of the central borane.

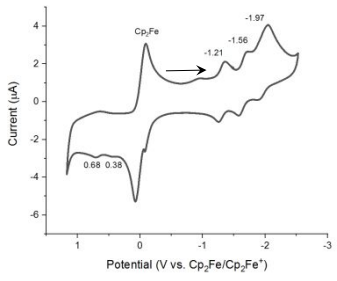
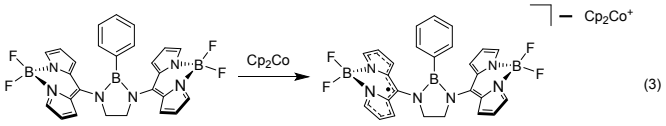


Figure 2. Cyclic voltammogram of **1** in CH_2Cl_2. Scan rate = 100 mV/s, electrolyte = $Bu_4NB(C_6F_5)_4$.

The presence of two reversible reductions suggest that **1** is capable of accepting two electrons. In an attempt to isolate a reduced product, 0.95 equivalents of cobaltocene ($E° = -1.33$ V)[20] were added to **1** (Equation 3), resulting in a chestnut colored solution. ^{1}H NMR analysis showed the presence of a paramagnetic borane containing product. EPR analysis of the reaction products revealed the presence of an unpaired electron with a g-value of 1.9940 (Figure 3), suggesting the presence of an organic radical where the radical is located on a BODIPY fragment.[15] The chestnut colored solution did not fluoresce in the presence of UV light.



(3)

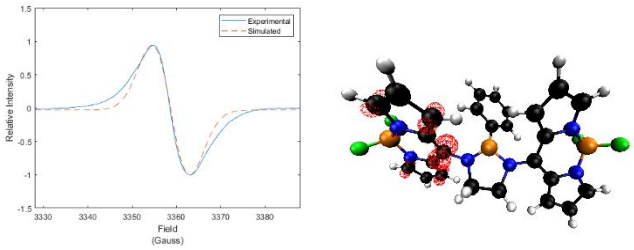
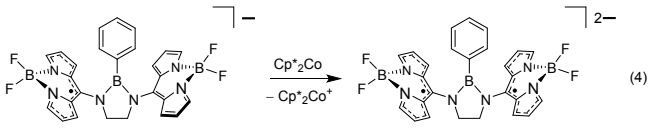


Figure 3. (Left) EPR spectrum of **[1]$^{\bullet-}$** in THF at 90 K. (Right) Unpaired spin density plot of **[1]$^{\bullet-}$**. The positive and negative regions of spin density are shown as red and yellow mesh, respectively. Isovalue = 0.01 e$^-$/a.u. Level of theory: M06-2X/6-31g(d,p). C = black, N = blue, B = orange, F = green, and H = white.

To confirm that the radical of **[1]$^{\bullet-}$** resides on only one of the BODIPY fragments, density functional theory (DFT) calculations were performed. An unpaired spin density plot verified the assignment of the unpaired electron on a single BODIPY dye, where about 92% of the total unpaired spin density resided on a single BODIPY dye (Figure 3). About 4% of the unpaired spin density (2 % each) resided on each the central boron center and the other BODIPY dye. Of the unpaired spin density that resided on a single BODIPY dye, 30% of the unpaired spin density resided on the 8-position, 10% resided on each of the 1,7-positions, and 7 % resided on each of the 3,5-positions (Figure 3). DFT analysis of **[2]$^{\bullet-}$**, showed a similar distribution of unpaired spin density to **[1]$^{\bullet-}$** (see Supporting Information, Figure S47).

To investigate the nature of the BODIPY containing borane upon the addition of two electrons, **[1]$^{\bullet-}$** was treated with an equivalent of Cp^*_2Co (where Cp* = pentamethylcyclopentadienide) ($E° = -1.94$ V)[20] resulting in a brown solution that did not emit (Equation 4) (Figure S42). ^{1}H NMR analysis revealed that all peaks had disappeared, suggesting the presence of a diradical (triplet ground state) instead of a diamagnetic product (singlet ground state). EPR analysis revealed the presence of a singlet with a g-value of 1.9977, which is of similar magnitude to **[1]$^{\bullet-}$.** The presence of a singlet suggests that the diradical is BODIPY-based as opposed to a borane-based radical, which would exhibit ^{11}B hyperfine splitting.[21]



(4)

To further investigate the diradical location for **[1]$^{\bullet\bullet2-}$**, the unpaired spin density plot for **[1]$^{\bullet\bullet2-}$** was computed using DFT. Computational analysis revealed that the unpaired spin density of the triplet state (25 kcal/mol more stable than the singlet state), resides on both BODIPY dyes, with almost no electron density (1.5 %) residing on the central boron center (Figure 4). An unpaired spin density plot of **[1]$^{\bullet\bullet2-}$** exhibited about 30% of the unpaired spin density on each of the 8-positions and about 10 % in each of the 1,7-positions of the BODIPY dyes (Figure 4). DFT analysis of **[2]$^{\bullet\bullet2-}$**, showed a similar distribution of unpaired spin density to **[1]$^{\bullet\bullet2-}$** (see Supporting Information, Figure S46).

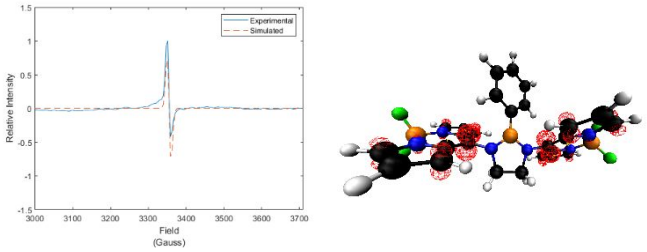


Figure 4. (Left) EPR spectrum of **[1]$^{\bullet\bullet2-}$** in THF at 5 K. (Right) Unpaired spin density plot of **[1]$^{\bullet\bullet2-}$**. The positive and negative regions of spin density are shown as red and yellow mesh, respectively. Isovalue = 0.01 e$^-$/a.u. Level of theory: M06-2X/6-31g(d,p). C = black, N = blue, B = orange, F = green, and H = white.

To determine the Lewis acidity of **1** and **2** as a function of redox state, the Gutmann-Beckett Lewis acidity test was attempted.[22] The addition of triethylphosphine oxide to **1** resulted in an insoluble precipitate and only free triethylphosphine oxide in the ^{31}P NMR spectrum. In contrast, the addition of triethylphosphine oxide to **2** resulted in two phosphine resonances, a major resonance at 53.1 ppm and a minor one at 83.5 ppm. Using the major resonance, a Lewis acidity similar to BEt_3 can be estimated.[23] Due to problems with solubility and unclear results employing the Gutmann-Beckett method, the Lewis acidity of **1** and **2** were estimated through the computational determination of the hydride acceptor ability of the Lewis acid.[23] Using this approach, **1** (ΔG_{H-} = −48 kcal/mol) was estimated to exhibit a Lewis acidity similar to BH_3 and **2** (ΔG_{H-} = −55 kcal/mol) was estimated to exhibit a Lewis acidity similar to $BPh(C_6F_5)_2$.[23] Whereas **1** and **2** are capable of BODIPY-based reductions, reduction of the BODIPY fragments were computed to reduce the Lewis acidity of the boron center of **1** and **2** by about 30 kcal/mol for each redox event (Table 2). These results suggest that **1** and **2** can act as redox-tunable Lewis acids.

Being that BODIPY-based redox events can alter the Lewis acidity of a borane, we hypothesized that the redox character

Table 2. Computed hydride acceptor ability of **1** and **2**, before and after BODIPY-based redox events.

Complex	Hydride Acceptor Ability (kcal/mol)
1	−47.9
[1]$^{\bullet-}$	−24.0
[1]$^{\bullet\bullet 2-}$	+4.6
2	−54.5
[2]$^{\bullet-}$	−21.5
[2]$^{\bullet\bullet 2-}$	−0.2

of the pendant BODIPY dyes could be utilized to reversibly bind Lewis bases. Initial studies employed **2** and examined the addition of alkyl ammonium salts of F^-, Cl^-, and Br^-. Interestingly, only F^- coordinated to **2**, which was evident by a rapid loss of color and disappearance of fluorescence under UV light (see Supporting Information). ^{11}B NMR analysis revealed the presence of a multiplet and a triplet in a 1:2 ratio, with the multiplet corresponding to the coordination of fluoride to the central borane. Attempts to bind neutral Lewis bases (e.g. MeCN, pyridine, or PMe_3) to **2**, were unsuccessful. Electrochemical experiments of **2** in pyridine revealed irreversible reduction events at -1.71 and -2.20 V, which were shifted cathodically about 400 mV from **2**, suggesting that pyridine weakly coordinates to the borane, and dissociates upon reduction (see Supporting Information, Figure S33). Electrochemical experiments of **2** in MeCN revealed irreversible reduction events at -1.19 and -1.47 V, suggesting that MeCN also weakly coordinates to the borane and dissociates upon reduction (see Supporting Information, Figure S34). Addition of a fluoride source (Bu_4NF) during the electrochemical reduction of **2** in MeCN resulted in more difficult reductions by 400 mV, -1.61 and -1.84 V (Figure S35).

To determine whether the inability to bind PMe_3, MeCN, Br^-, and Cl^- to **2** is due to steric bulk or weak Lewis acidity at **2**, we examined the binding affinity for F^-, Cl^-, and Br^- to BEt_3 and found that the BEt_3 exhibited a weaker binding affinity for F^-, but a stronger binding affinity for Cl^- and Br^-, suggesting that the binding of Lewis bases to **2** is largely affected by the steric bulk of **2**, see Supporting Information. Based on this result, we measured the steric bulk surrounding the central borane of **1** and **2**. Using the method we have previously described for measuring the cone angles of boranes, we estimate the cone angles of **1** and **2** to be 261° and 287°, respectively.[24] As expected, these values are too big to allow for the coordination of PMe_3 (θ = 118°) or other Lewis bases with a cone angle > 100°.

These results show that the reduction of a BODIPY fragment can alter the Lewis acidity of an appended borane by 15-30 kcal/mol per redox event. The reported redox switchable Lewis acidity presents a new approach towards controlling the strength and reactivity of Lewis acids. The incorporation of BODIPY dyes into molecular scaffolds to control the reactivity of Lewis acids is a topic of interest in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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