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Facile *meso*-BODIPY Annulation and Selective Sensing of Hypochlorite in Water

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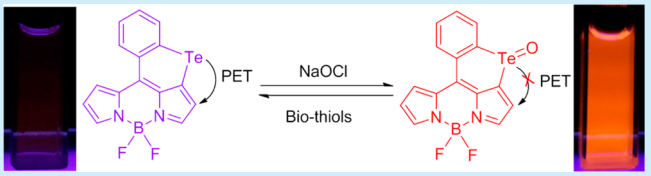
Supporting Information

ABSTRACT: Annulated BODIPY chalcogenide (Se, Te) systems were synthesized from their respective bis(*o*-formylphenyl)dichalcogenide intermediates. The annulated BODIPY selenide product was confirmed by X-ray diffraction. The red-shifted telluride version was found to be sensitive and selective for hypochlorite detection, reversible upon treatment with biothiols.



Organoselenium compounds are of growing importance in medicinal and materials chemistry. Recent inroads into enzymology, medicine, and bioorganic chemistry have profiled heterocyclic selenium-containing compounds that possess biological activity including anti-inflammatory, antitumor, antifungal, and antibacterial properties. Antioxidative and enzymatic properties (e.g., glutathione peroxidase-like activities) are, in many researchers' minds, among the most crucial systems to fully understand.[1−3] A great number of novel heterocycles bearing single or multiple nitrogen, oxygen, sulfur, selenium, or tellurium sites have been investigated over the years; many of these are heterocyclic pharmacophores bearing biological activity.[4] One important challenge for organochalcogen chemists has been to synthesize novel heterocyclic systems. The routes toward ring formation are sometimes complex and poorly accessible. Annulation reactions are vital in synthetic organic chemistry; they hold very modest precedent in polypyrrole chemistry[5] with respect to, e.g., the secondary attachment *ortho* substituent on a *meso* aryl group. However, these reports are few and extend to only O- and N-bridging atoms.[6] Surprisingly, no annulations have yet been reported for BODIPY species to the best of our knowledge, although the BODIPY systems have been widely derivatized and heralded as an extremely versatile platform.

Molecular probes are currently essential in efforts to understand the presence and concentration of analytes such as reactive oxygen species (ROS) in biological systems. These species are thought to play a very important role in diabetes, cancer, and neurodegenerative disease disorders such as Parkinson's and Alzheimer's disease.[7] ROS, often discussed in connection with nitrogen-based RNS analogues, include hydrogen peroxide (H_2O_2), hypochlorite (^-OCl), superoxide ($O_2^{\bullet-}$), hydroxyl radical ($^\bullet OH$), nitric oxide (NO), and peroxynitrite ($ONOO^-$).[8] Specifically, hypochlorous acid (HOCl) is a potential antimicrobial agent that plays a significant role in the immune system. The reaction of hydrogen peroxide with chloride gives rise to endogenous hypochlorous acid, which protects the immune system against the invasion of pathogens. However, excess production of this strong oxidant can also lead to diseases such as lung injury, atherosclerosis, rheumatoid arthritis, and cardiovascular disease.[7] Thus, to understand the role of hypochlorous acid in living systems, it is very important to monitor its concentration in aqueous solutions accurately. Probes for the detection of hypochlorous acid have been reported in the literature,[9] but often do not underscore issues of selectivity, sensitivity, reversibility, water solubility, and low probe molecular weight. Molecular weight in fact revolves around the notion of blood brain barrier passage based on "drug likeness" with guidelines suggesting that low MW values, e.g., <500 are preferred.[9g] Thus, in this work, we are presenting novel annulated BODIPY selenide and telluride systems and *bis*(BODIPY)diselenide systems and chemosensing results.

The synthesis of selenium- and tellurium-containing compounds **2**−**4** is outlined in Scheme 1. Bis(*o*-formylphenyl)-diselenide and bis(*o*-formylphenyl)ditelluride systems (**1**)[10] were treated with excess pyrrole in the presence of a catalytic amount of trifluoroacetic acid (TFA) under nitrogen. Intermediates **2a** and **2b** were isolated and characterized. Bis(BODIPY)diselenide (**3**) was synthesized from dipyrromethane diselenide intermediate (**2a**). The annulated BODIPY selenide (**4a**) was obtained as a secondary product in a reaction that yielded **3** and was purified and isolated in 11% yield. However, the analogous compound of **4a**, annulated BODIPY telluride **4b**, was the only product from reaction with dipyrromethane ditelluride intermediate **2b**.

The ^1H NMR spectrum of **4a** revealed seven singly integrating and one doubly integrating signals (Figure S27). These peaks indicated a strikingly different compound type.

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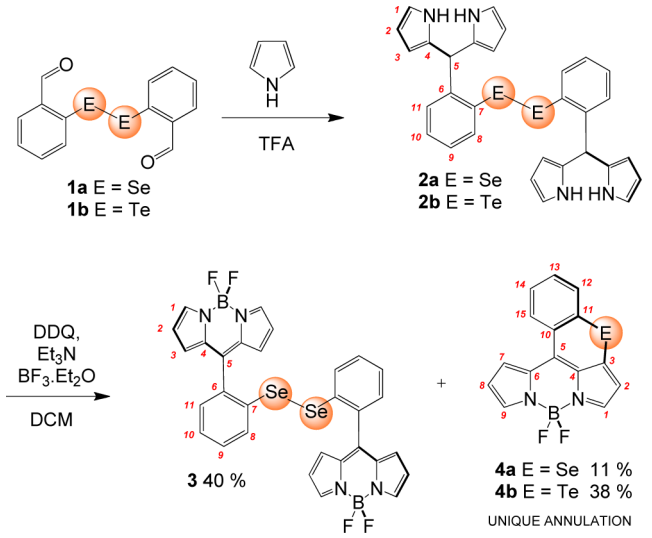
Scheme 1. Reaction Pathway in *Bis*(BODIPY)dichalcogenide (3) Formation and Unexpected Annulated Products 4a and 4b



The mass spectral value (SI) obtained approximated in value half of the molecular weight calculated for **3**; an annulated product was thus formulated (**4a**), and X-ray structural data was acquired (Figure 1), confirming the unexpected and unique

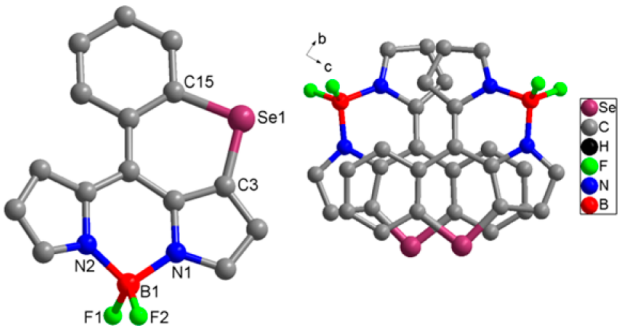
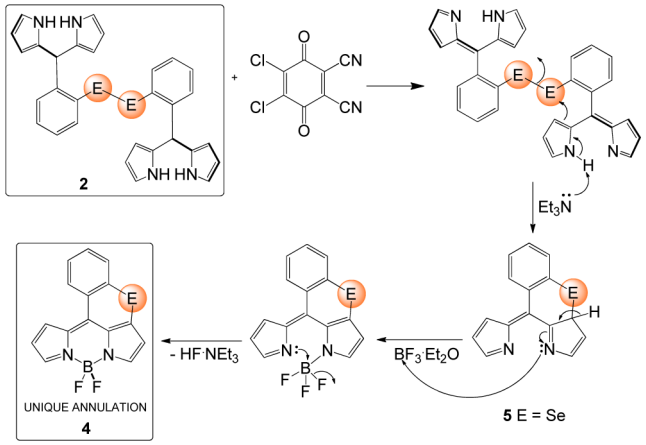


Figure 1. Molecular structure of compound **4a** (CCDC #955225). Cell lengths (Å) a = 7.3600(15), b = 10.043(2), c = 17.403(4); Cell angles (°) α = 85.74(3), β = 89.65(3), γ = 89.41(3); Space group = P-1; System = Triclinic; Selected bond lengths (Å) and angles (°): Se1−C15 1.884(4), Se1−C3 1.849(4), N1−B1 1.532(5), N2−B1 1.538(6), F1−B1 1.396(5), C15−Se1−C3 97.8(2), N2−B1−N1 105.1(3), and F1−B1−F2 109.3(3). Hydrogen atoms are omitted for clarity.

structure of **4a**. Analogously, compound **4b** showed nine aromatic signals in the ^{1}H NMR spectrum (Figure S36). The mass spectrum showed $[M+Na]^+$ peaks with the expected isotopic pattern.

A mechanism for the formation of **4a** and **4b** is proposed in Scheme 2. Compound **2** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by treatment of triethylamine to give compound **5**, which was isolated and confirmed by ^{1}H NMR spectroscopy in the case of the selenium analogue (Figure S46). These standard conditions were introduced by Dolphin et al. and Lindsey et al.[11a,b] Finally, $BF_3{\cdot}Et_2O$ was added to give compound **4**. The formation of the product involves E−E bond cleavage and Se−C/Te−C bond formation. The reaction was also monitored by TLC, which showed a crisp new spot after addition of each reagent (Figure S50).

Scheme 2. Plausible Mechanism for the Formation of Annulated Product 4



As per our knowledge, the annulated BODIPY selenide and BODIPY telluride (**4a** and **4b**) are the first examples of selenium and tellurium that exists directly attached, to a pyrrole ring in, e.g., meso porphyrin or BODIPY chemistry. Also, it is the first such report of a system that involves direct and facile formation of such a group. Importantly, due to the geometrical effect imparted by annulation, the aryl group becomes more coplanar (14° torsion angle) with the BODIPY body.

The molecular structure of **4a** is depicted in Figure 1 with parameters found in Table S1. The divalent selenium atom (C15−Se1−C3) forms an angle of 97.8(2)°. The C−Se bond lengths (Se1−C15 1.884(4) and Se1−C3 1.849(4) Å) are shorter than those expected for a single bond, indicating partial C═Se double bond character. Molecule **4a**, including its aryl group and BODIPY body, is largely planar, with a [C4−C5−C10−C15] torsion angle of 14.2°.

Compounds **3**, **4a**, and **4b** (probes) were then screened with ROS (e.g., $O_2^{\bullet-}$, H_2O_2, ^{t}BuOOH, $^-$OCl, $^\bullet$OH, and ^{t}BuO$^\bullet$). The spectroscopic properties of the probes were determined under physiological conditions in water−ethanol (v/v = 99/1, 0.1 M PBS, pH 7.5). In this assay, 3 mL samples of probe solutions (**3**, **4a**, and **4b**) were treated with 7 equiv of ROS (in water). When the sensing ability of the probes was tested with various ROS, *bis*(BODIPY)diselenide **3** did not show any fluorescence with ROS. Both annulated BODIPY probes (**4a** and **4b**) showed selective detection of hypochlorite; however, the annulated telluride species **4b** showed an extremely fast response together with high sensitivity (62-fold) bearing a strong red fluorescence (Figure 2a). This is in contrast with the annulated BODIPY selenide **4a** (10-fold; Figure S57). Upon addition of hypochlorite (6.6 μM) to a solution of **4b**, the fluorescence quantum yield (Φ_F) increased from 0.06 to 0.23.

In particular, a steady increase in fluorescence intensity was observed, effected by even additions of hypochlorite concentration (Figure 2b), and the detection limit was found to be 3.7 μM. Equilibration became even clearer with further experimentation. In terms of kinetics, tellurium oxidation is extremely fast for probe **4b**; it was thus difficult to obtain meaningful time-dependent fluorescence data involving a steady increase in emission intensity under this normal protocol. To work around this, hypochlorite was added to the probe solution a short time (2.5 min) after spectral collection began; this sharp "turn-on" event emphasized the

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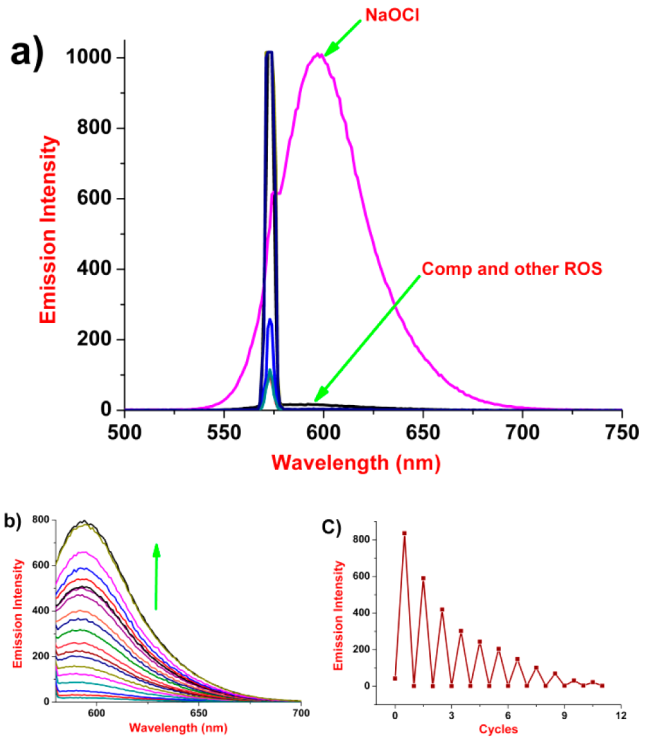

Figure 2. (a) Emission spectra of probe **4b** (45×10^{-6} M, water–ethanol: v/v = 99/1, 0.1 M PBS, pH 7.5) with ROS ($O_2^{\bullet-}$, H_2O_2, ^tBuOOH, ^-OCl, $^\bullet OH$, and $^tBuO^\bullet$) (333 μM in water, 7 equiv) incubated for 5 min at rt. (b) Emission spectra of probe **4b** (45×10^{-6} M, water–ethanol: v/v = 99/1, 0.1 M PBS, pH 7.5) with increasing concentration of ^-OCl (3.3–63.3 μM in water) incubated for 5 min at rt. (c) Reversibility cycles of probe **4b** (45×10^{-6} M, water–ethanol: v/v = 99/1, 0.1 M PBS, pH 7.5) with hypochlorite and glutathione (GSH).

velocity and saturation in the probe/analyte reaction that gives rise to fluorescence (Figure S53).

In order to understand the cycling capacity of probe **4b**, the solution of probe **4b**, oxidized with hypochlorite, was treated with glutathione, *N*-acetyl-L-cysteine, homocysteine, and L-cysteine, well-known reducing biothiols, to determine whether the tellurium oxide species **4b═O** could revert to its original reduced state (**4b**). The results obtained showed a quenching of fluorescence intensity after the addition of biothiols (Figure S54), and again a fluorescence increase with addition of hypochlorite. This process can be cycled with GSH (~10 redox cycles) (Figure 2c) with **4b** to demonstrate the reversibility of ROS probing. This may be useful in monitoring the dynamic variations of hypochlorite in living systems. However, in the case of probe **4a** the reversibility reaction with biothiols was found to be slow compared to that for probe **4b** (Figure S58).

Finally, to understand the chemical and photomechanisms involved in the fluorescence "turn-on" event, probe **4b** was treated with NaOCl and the mass spectrum was recorded. The mass spectrometry showed the isotopic pattern $(M+Na)^+$ for the oxidized product in the spectrum (Figures S48 and S49). This proposed that the ability for the photoinduced electron transfer (PET) from the phenyl tellurium group to the BODIPY moiety is blocked. This PET mechanism is supported by HOMO–LUMO level analysis of the probe **4b** and its oxidized form (**4b═O**) through DFT theoretical calculations (see SI, Figure S60 and accompanying text). The elaborated PET mechanism has been discussed previously in the literature.[9]

In conclusion, the first examples of BODIPY annulation were discovered. A plausible mechanism for product formation involves discrete *E*–*E* bond cleavage and *E*–C bond formation steps. The X-ray structure of the annulated BODIPY selenide was obtained. The annulated BODIPY telluride was highly sensitive and selective (detection limit 3.7 μM and 62-fold) for hypochlorite. A red-shifted detection (λ_{ex} = 597 nm) is provided which can be acquired under physiologically relevant conditions (water–ethanol: v/v = 99/1, 0.1 M PBS, pH 7.5). Also, the tellurium probe showed reversibility with biothiols. In the future, this annulated BODIPY telluride probe can be used in living neuronal cells for the detection of hypochlorite. The bis(BODIPY)diselenide was also synthesized and characterized and did not show any activity with ROS.

■ ASSOCIATED CONTENT

Supporting Information

Methods, experimental procedures, additional spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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