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Boron in Disguise: The Parent "Fused" BN Indole

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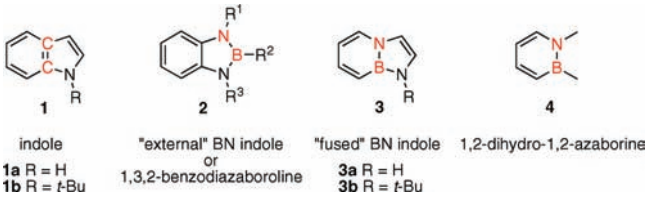
Supporting Information

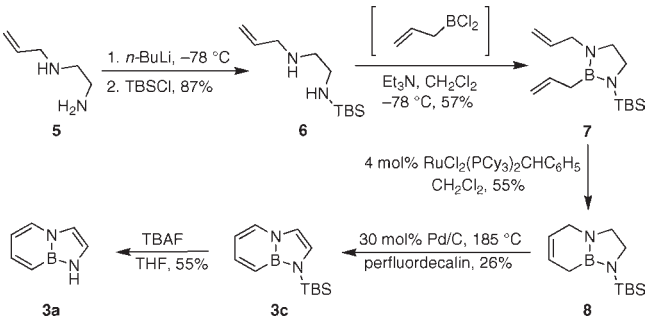
ABSTRACT: "Fused" BN indoles are an emerging class of boron-containing indole mimics, featuring geometric structure and electophilic aromatic substitution reactivity similar to those of indoles but exhibiting distinct electronic structure, leading to unique optoelectronic properties. Herein we report the synthesis of the parent *N*-H BN indole and provide a head-to-head comparison of the structural features, pK_a values, and optoelectronic properties of this hybrid organic/inorganic indole with the classic natural indole.

Indole (**1a**) is a heterocycle of great importance to biological systems. Within proteins, the redox-active indole side chain of tryptophan is one of the primary charge carriers involved in electron transfer.[1,2] The optical properties of indole make tryptophan one of the principal intrinsic fluorophores in protein fluorescence analysis.[3,4] The electron-rich aromatic indole core in tryptophan is also responsible for tryptophan's ability to participate in a wide range of inter- and intramolecular interactions (e.g., cation$-\pi$ and $\pi-\pi$ interactions).[5] Indole is the biosynthetic parent to the essential amino acid tryptophan, the neurotransmitters serotonin[6] and melatonin,[7] and the auxin plant hormones,[8] and it remains a prominent structural feature in drug design.[9] Expansion of the diversity available to indole-based structures through BN/CC isosterism[10] is in part driven by potential therapeutic[11] and analytical motives enabled by boron[12] and has produced the phenylenediamine family of 1,3,2-benzodiazaborolines **2** ("external" BN indoles)[13,14] and the recently reported "fused" BN indoles **3**, containing the 1,2-dihydro-1,2-azaborine (**4**)[15] core.



Our group recently found that the "fused" BN indole **3b** displays reactivity similar to that of indole **1b** in electrophilic aromatic substitution (EAS) reactions.[16] This is in contrast to the family of 1,3,2-benzodiazaborolines **2**, which have not been shown to undergo EAS reactions at the five-membered ring. While *N*-*t*-Bu-BN indole **3b** closely mimics indole's chemistry at the C2−C3 bond, it does not contain a free *N*-H fragment, an important feature in the biochemistry of indole and its derivatives.[17] We now report the synthesis of the parent *N*-H BN indole **3a**, with an in-depth comparison to its carbonaceous counterpart **1a**.

Scheme 1. Synthesis of Parent BN Indole 3a



Our initial attempts at removing the *N*-*t*-Bu group from **3b** to access the parent **3a** were not successful. We then chose *tert*-butyldimethylsilyl (TBS) as an alternative *N*-protecting group.[18] Thus, treatment of *N*-allylethylenediamine (**5**) with *n*-BuLi followed by quenching with TBSCl provided **6** in 87% yield (Scheme 1). Condensation of diamine **6** with *in situ*-generated allylboron dichloride afforded heterocycle **7** in 57% yield. Subsequent ring-closing metathesis with Grubbs's first-generation catalyst provided the bicyclic product **8**. Oxidative dehydrogenation of **8** with a catalytic amount of Pd/C in perfluorodecalin furnished the fully aromatic *N*-TBS BN indole **3c**. We found perfluorodecalin to be a more convenient solvent than decane that was used in the synthesis of **3b**, because the product can be isolated via biphasic extraction with cold THF. Interestingly, X-ray diffraction (XRD) studies of crystals isolated from the crude reaction mixture revealed an almost parallel (3.7°) π-complex of the product **3c** with perfluoronaphthalene **Fnap** (**3c**·**Fnap**, Table 1), with an interplanar distance of 3.524 Å.[19] Silica gel chromatography allowed isolation of clean **3c**. Deprotection of the *N*-TBS group of **3c** with TBAF afforded the target parent BN indole **3a** in 55% yield. To the best of our knowledge, BN indole **3a** is the only example of a natural product isostere (i.e., isoelectronic and isostructural to a natural product (e.g., indole)) containing an sp^2-type BN bond pair.[20,21]

With **3a** in hand, we began characterization of the structural, optical, and physical features of the new heterocycle. X-ray-quality crystals of **3a** had a disordered structure, with a unit cell (cell volume 662.42 Å^3, space group *Pna*2(1)) identical to that of the similarly disordered indole **1a**.[22] Given our fortuitous discovery of the crystalline π-complex **3c**·**Fnap**, we attempted co-crystallization of the parent **3a** with perfluoronaphthalene. X-ray-quality crystals of **3a**·**Fnap** were obtained through slow evaporation from CH_2Cl_2 but unfortunately were also disordered. Screening

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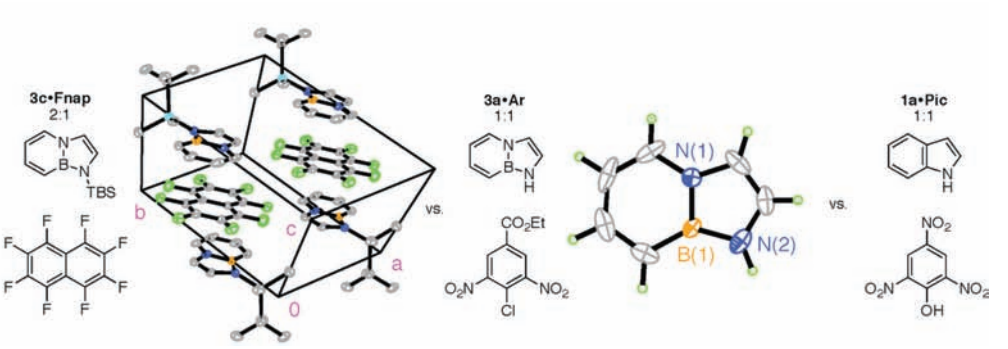
Table 1. Bond Length Comparison: π-Complexes of BN Indoles and Indole

Bond	Complex 3c•Fnap	3a•Ar	1a•Pic
1	1.444(8)	1.417(7)	1.401(7)
2	1.408(7)	1.369(8)	1.354(9)
3	1.304(9)	1.339(9)	1.304(9)
4	1.403(8)	**1.402(7)**	**1.468(9)**
5	1.349(8)	1.367(7)	1.36(1)
6	1.384(10)	1.357(10)	1.42(1)
7	1.392(11)	1.395(11)	1.37(1)
8	1.343(9)	1.361(10)	1.361(9)
9	1.525(9)	**1.487(8)**	**1.378(7)**
Bridgehead	1.442(8)	1.423(7)	1.392(7)



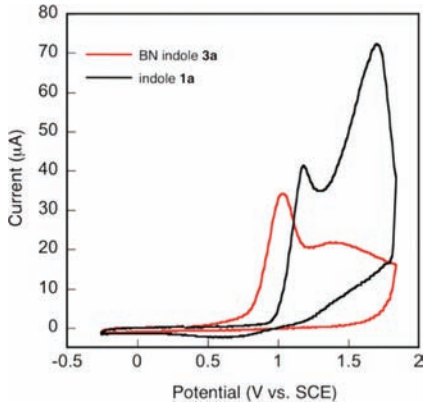
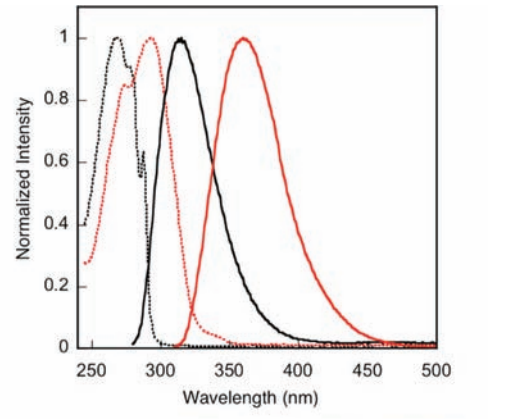


Figure 1. Cyclic voltammograms of BN indole **3a** and indole **1a** (0.08 M TBAOTf in CH_3CN at glassy carbon electrode; scan rate, 50 mV/s).



	λ_{abs}	λ_{em}	ε (M^{-1} cm^{-1})	Φ (CH_3CN)	Stokes Shift (cm^{-1})
BN indole **3a**	293	360	6400	0.083 +/- 0.011	6350
indole **1a**	268	315	8200[a]	0.32[b]	5570

Figure 2. Normalized absorption (dotted line) and emission (solid line) spectra of BN indole **3a** (red) and indole **1a** (black) and photophysical data for **3a** and **1a** in CH_3CN. [a]Literature value, see ref 30. [b]Literature value, see ref 29.

other electron-deficient aromatics, we successfully obtained a non-disordered XRD structure by complexation with ethyl 4-chloro-3,5-dinitrobenzoate (**Ar**). The orange 1:1 complex **3a·Ar** shows evidence of $\pi-\pi$ stacking in the solid state, with an interplanar distance of 3.268 Å and an almost parallel (1.2°) relationship. These structural features are consistent with a charge-transfer complex, and the interplanar distance is slightly shorter than the range of spacings found in the indole−picric acid π-complex **1a·Pic**[23] and other related structures (3.3−3.5 Å).[24] A qualitative comparison of the parent "fused" BN indole complex **3a·Ar** with **1a·Pic** reveals striking similarities.[25] However, Bond 4 in **3a** is relatively short and Bond 9 relatively long compared to those in **1a** (Table 1). A shorter Bond 4 in BN indole **3a** vs **1a** is consistent with a smaller atomic radius of nitrogen versus carbon.[26] A longer Bond 9 in **3a** vs **1a** is likely the consequence of the larger atomic radius of boron versus carbon.[26] All three structures are highly planar, with bond lengths consistent with aromatic delocalization. All three indoles exhibit a relatively short C(2)−C(3) bond length (Bond 3), which shows significant double bond character and is responsible for much of indole's unique chemistry.

Cyclic voltametry reveals some of the electronic differences between heterocycles **1a** and **3a**. BN indole **3a** has an irreversible oxidation wave, peaking at 1.04 V, compared to 1.18 V measured for indole **1a** vs SCE (Figure 1). Both oxidations are irreversible and show evidence of polymerization at the electrode, consistent with previously reported CV measurements of indole.[27] The lower oxidation potential measured for **3a** is consistent with a higher energy HOMO and more electron-rich character of **3a** compared to indole **1a**; it is also consistent with reported observations on BN arenes in comparison to their organic analogues.[28]

We also determined the absorption and emission properties of BN indole **3a** in direct comparison to indole **1a** (Figure 2). Indole's absorbance maximum was found at λ = 268 nm in CH_3CN, whereas BN indole's absoption maximum is bathochromically shifted to λ = 293 nm (Figure 2). The fluorescence spectrum of **1a** in CH_3CN showed an emission peak at λ_{em} = 315 nm. In contrast, BN indole's λ_{em} appears at 360 nm. Thus, BN indole **3a** displays a larger Stokes shift (6350 cm^{-1}) than its carbonaceous counterpart **1a** (5570 cm^{-1}). The red-shifted absorbance and emission bands of **3a** in comparison to those of **1a** are consistent with a smaller HOMO−LUMO gap in **3a** vs **1a**. The fluorescence quantum yield of **3a** (Φ = 0.08) is lower than that exhibited by indole **1a** (Φ = 0.32),[29] as is the molar absorptivity (ε = 6400 vs 8200 M^{-1} cm^{-1},[30] respectively).

The *N*-H functionality is a critical component of indole-containing biomolecules.[17] While we previously established that *N*-*t*-Bu-BN indole **3b** displays the same regioselectivity as indole in EAS reactions,[16] the chemistry of the *N*-H of BN indole **3a** remained unexplored. We sought to estimate the pK_a of the *N*-H proton in **3a** through a series of ^{1}H NMR bracketing experiments.

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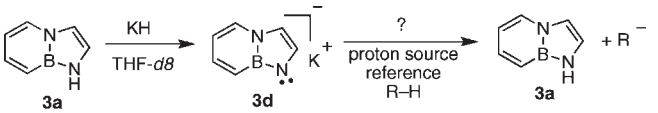
Table 2. pK_a Bracketing Experiments for 3a



R-H	pK_a (DMSO)[a]	deprotonated by **3d**
indole	20.95	yes
Ph_2NH	25	yes
PhCCH	28.8	yes
Ph_3CH	30.6	trace
CH_3CN	31.3	no

[a] taken from Bordwell pK_a table, reference 31.

Deprotonation of **3a** with potassium hydride in THF-d_8 occurs cleanly, yielding anion **3d**. By adding 1 equiv of a proton source R—H of known pK_a to a solution of anion **3d**, we were able to observe whether the reference compound was deprotonated, indicating the relative acidity of **3a** vs the reference. This bracketing strategy demonstrated that the *N*-H proton of BN indole is roughly 9 orders of magnitude less acidic than natural indole, with a pK_a around 30, compared to the literature value of indole of pK_a = 20.95[31] (Table 2). Indeed, addition of 1 equiv of indole **1a** to anion **3d** cleanly yields the starting BN indole **3a**. Conversely, as a control experiment, we determined that the deprotonated indole anion does not remove the *N*-H proton of **3a**. The significantly decreased acidity of the *N*-H proton in **3a** may be due to inductive effects exerted by the neighboring boron atom.

We also investigated the water and air stability of BN indole **3a**. Using the previously reported methods for measuring the air and water stability of 1,2-azaborines,[32] we found that **3a** was significantly more resistant to degradation than any monocyclic 1,2-azaborine measured. BN indole **3a** shows <5% degradation after being exposed to 10 equiv of water in DMSO-d_6 solution for 96 h, and benzene-d_6 solutions of **3a** exposed to pure O_2 at 50 °C also show <5% decomposition over 4 h by ^{1}H NMR compared to internal standards.

In summary, we prepared the parent molecule of the family of "fused" BN indole heterocycles **3** and characterized its structure, optoelectronic properties, and acid—base reactivity in direct comparison to its natural indole counterpart **1a**. Single-crystal structural analysis showed that the geometric structures of **3a** and **1a** are very similar, with some differences associated with the BN/CC isosterism. Electrochemical and photophysical studies of **3a** in comparison to **1a** are consistent with a higher-lying HOMO and a smaller HOMO—LUMO gap in **3a** than **1a**. We also determined that the *N*-H proton in **3a** is significantly less acidic than that of indole **1a**. "Fused" BN indoles are emerging as boron-containing mimics of the classic indole motif. Our work should open new avenues for potential applications of "fused" BN indole derivatives in biomedical research.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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