Published in final edited form as:

J Am Chem Soc. 2011 August 3; 133(30): 11508–11511. doi:10.1021/ja205779b.

Boron in Disguise: The Parent “Fused” BN Indole

Eric R. Abbey, Lev N. Zakharov, and Shih-Yuan Liu*

Department of Chemistry, 1253 University of Oregon, Eugene, Oregon 97403-1253, United States

Abstract

“Fused” BN indoles are an emerging class of boron-containing indole mimics, featuring similar geometric structure and electrophilic aromatic substitution reactivity as indoles, however 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- π and π - π interactions).⁵ Indole is the biosynthetic parent to the essential amino acid tryptophan, the neurotransmitters serotonin⁶ and melatonin⁷, the auxin plant hormones,⁸ and remains a prominent structural feature in drug design.⁹ Expansion of the diversity available to indole-based structures through BN/CC isosterism¹⁰ is in part driven by potential therapeutic¹¹ and analytical motives enabled by boron¹² 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 similar reactivity to 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 electrophilic aromatic substitution 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 wish to report the synthesis of the parent *N*-H BN indole **3a**, with an in-depth comparison to its carbonaceous counterpart **1a**.

Corresponding Author: lsy@uoregon.edu.

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>.

Our initial attempts in removing the *N*-*t*-Bu group from **3b** to access the parent **3a** were not successful. We then chose TBS (*t*-butyldimethylsilyl) as an alternative *N*-protecting strategy.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' 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 (**3c**•**Fnap**) of the product **3c** with perfluoronaphthalene **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 an identical unit cell (cell volume 662.42 Å³, space group Pna2(1)) to the similarly disordered indole (**1a**) XRD data.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 CH₂Cl₂, but were unfortunately also disordered. Screening 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 π - π 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 indolepicric 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 is relatively long compared to **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** compared to **1a** is likely the consequence of the larger atomic radius of boron compared to 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 voltammetry 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**, and is consistent with reported observations in BN arenes in comparison to their organic analogs.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 CH₃CN, whereas BN indole's absorption maximum is bathochromically shifted to λ = 293 nm (Figure 2). The fluorescence spectrum of **1a** in CH₃CN 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 **1a** are consistent with a smaller HOMO/LUMO gap in **3a** vs. **1a**. The fluorescence quantum yield of **3a** ($\Phi = 0.08$) is lower than that exhibited by indole **1a** ($\Phi = 0.32$),²⁹ as is the molar absorptivity ($\epsilon = 6400$ vs. $8200 \text{ M}^{-1} \text{ cm}^{-1}$,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 $\text{p}K_{\text{a}}$ of the *N*-H proton in **3a** through a series of ^1H NMR bracketing experiments. Deprotonation of **3a** with potassium hydride in THF-*d*8 occurs cleanly, yielding anion **3d**. By adding one equivalent of a proton source R-H of known $\text{p}K_{\text{a}}$ 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 nine orders of magnitude less acidic than natural indole, with a $\text{p}K_{\text{a}}$ around 30, compared to the literature value of indole at 20.95³¹ (Table 2). Indeed, addition of one equivalent 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 when exposed to ten equivalents of water in DMSO-*d*6 solution for 96 hrs, and benzene-*d*6 solutions of **3a** exposed to pure O_2 at 50 °C also show <5% decomposition over 4 hours by ^1H 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, Grant R01-GM094541). This material is based upon work supported by the National Science Foundation under Award No. DGE-072540 (E.R.A.). We thank Chris Weber for cyclic voltametry measurements and sharing his expertise in electrochemistry.

References

1. For a leading reference, see: Shih C, Museth AK, Abrahamsson M, Blanco-Rodriguez AM, Di Bilio AJ, Sudhamsu J, Crane BR, Ronayne KL, Towrie M, Vlcek A Jr, Richards JH, Winkler JR, Gray HB. *Science*. 2008; 320:1760–1762. [PubMed: 18583608]
2. For an overview of protein radicals in enzyme catalysis, see: Stubbe J, van der Donk WA. *Chem Rev*. 1998; 98:705–762. [PubMed: 11848913]
3. For an overview, see: Callis PR. *Methods Enzymol*. 1997; 278:113–150. [PubMed: 9170312]
4. Lippitz M, Erker W, Decker H, van Holde KE, Basche T. *Proc Nat Acad Sci USA*. 2002; 99:2772–2777. [PubMed: 11880629]
5. (a) Dougherty DAC. *J Nutr*. 2007; 137:1504S–1508S. [PubMed: 17513416] (b) Dougherty DA. *J Org Chem*. 2008; 73:3667–3673. [PubMed: 18412391] (c) Burley SK, Petsko GA. *Science*. 1985; 229:23–28. [PubMed: 3892686]
6. Fernstrom JD. *Physiol Rev*. 1983; 63:484–546. [PubMed: 6132421]
7. (a) Klein DC, Berg GR, Weller J, Glinsmann W. *Science*. 1970; 167:1738–1740. [PubMed: 4313580] (b) Arendt J. *J Biol Rhythms*. 2005; 20:291–303. [PubMed: 16077149]
8. (a) Radwanski ER, Last RL. *Plant Cell*. 1995; 7:921–934. [PubMed: 7640526] (b) Tan X, Calderon-Villalobos LI, Sharon M, Zheng C, Robinson CV, Estelle M, Zheng N. *Nature*. 2007; 446:640–645. [PubMed: 17410169]
9. Humphrey GR, Kueth JT. *Chem Rev*. 2005; 106:2875–2911. [PubMed: 16836303]
10. For an overview of BN/CC isosterism, see: (a) Bosdet MJD, Piers WE. *Can J Chem*. 2009; 87:8–29. (b) Liu Z, Marder TB. *Angew Chem Int Ed*. 2008; 47:242–244.
11. (a) Zhou HB, Nettles KW, Bruning JB, Kim Y, Joachimiak A, Sharma S, Carlson KE, Stossi F, Katzenellenbogen BS, Greene GL, Katzenellenbogen JA. *Chem Biol*. 2007; 14:659–669. [PubMed: 17584613] (b) Ito H, Yumura K, Saigo K. *Org Lett*. 2010; 12:3386–3389. [PubMed: 20586441] (c) Soloway AH, Zhuo JC, Rong FG, Lunato AJ, Ives DH, Barth RF, Anisuzzaman AKM, Barth CD, Barnum BA. *J Organomet Chem*. 1999; 581:150–155.
12. (a) Probst TU. *Fresenius J Anal Chem*. 1999; 364:391–403. (b) Bendel P. *NMR Biomed*. 2005; 18:74–82. [PubMed: 15770608]
13. For pioneering work in this area, see: (a) Ulmschneider D, Goubeau J. *Chem Ber*. 1957; 90:2733–2738. (b) Goubeau J, Schneider H. *Liebigs Ann Chem*. 1964; 675:1–9.
14. For an overview of 1,3,2-benzodiazaborolines, see: Weber L. *Coord Chem Rev*. 2008; 252:1–31.
15. For leading references on 1,2-dihydro-1,2-azaborine chemistry, see: (a) Pan J, Kampf JW, Ashe AJ. *Org Lett*. 2007; 9:679–681. [PubMed: 17249680] (b) Marwitz AJ, Abbey ER, Jenkins JT, Zakharov LN, Liu SY. *Org Lett*. 2007; 9:4905–4908. [PubMed: 17944483] (c) Abbey ER, Zakharov LN, Liu SY. *J Am Chem Soc*. 2008; 130:7250–7252. [PubMed: 18479099] (d) Campbell PG, Abbey ER, Neiner D, Grant DJ, Dixon DA, Liu SY. *J Am Chem Soc*. 2010; 132:18048–18050. [PubMed: 21141893] (e) Daly AM, Tanjaroon C, Marwitz AJ, Liu SY, Kukolich SG. *J Am Chem Soc*. 2010; 132:5501–5506. [PubMed: 20349985] (f) Liu L, Marwitz AJ, Matthews BW, Liu SY. *Angew Chem Int Ed Engl*. 2009; 48:6817–6819. [PubMed: 19688806]
16. Abbey ER, Zakharov LN, Liu SY. *J Am Chem Soc*. 2010; 132:16340–16342. [PubMed: 21043508]
17. For leading references, see: (a) Sun H, Greathouse DV, Andersen OS, Koeppel RE II. *J Biol Chem*. 2008; 283:22233–22243. [PubMed: 18550546] (b) Chauhan N, Thackray SJ, Rafice SA, Eaton G, Lee M, Efimov I, Basran J, Jenkins PR, Mowat CG, Chapman SK, Raven EL. *J Am Chem Soc*. 2009; 131:4186–4187. [PubMed: 19275153]
18. The TBS group has been shown to be a viable N-protecting group in 1,2-dihydro-1,2-azaborine chemistry, see: Marwitz AJ, Matus MH, Zakharov LN, Dixon DA, Liu SY. *Angew Chem Int Ed*. 2009; 48:973–977.
19. (a) Correspondence concerning X-ray crystallography should be directed to Lev Zakharov. E-mail: lev@uoregon.edu. Reductive de-fluorination with Pd is precedent but not well studied. For leading references, see: (b) Narumi T, Tomita K, Inokuchi E, Kobayashi K, Oishi S, Ohno H, Fujii N. *Org Lett*. 2007; 9:3465–3468. [PubMed: 17655320] (c) Torrens H. *Coord Chem Rev*. 2005; 249:1957–1985.

20. The parent compound of the family of 1,3,2-benzodiazaborolines **2** (belonging to the C_{2v} point group) is not isosym-metric with indole **1a** and “fused” BN indole **3a** (both belonging to the C_s point group).
21. For examples of natural product isosteres bearing an sp^3 -type BN bond pair, see: (a) Spielvogel BF, Wojnowich L, Das MK, McPhail AT, Hargrave KD. *J Am Chem Soc.* 1976; 98:5702–5703. [PubMed: 956573] (b) Spielvogel BF, Das MK, McPhail AT, Onan KD, Hall IH. *J Am Chem Soc.* 1980; 102:6344–6346.
22. Roychowdhury P, Basak BS. *Acta Crystallogr Sect B: Struct Sci.* 1975; 31:1559–1563.
23. Saminathan K, Sivakumar K. *Acta Crystallogr Sect E: Struct Rep Online.* 2006; 63:o236–o238.
24. Gartland GL, Freeman GR, Bugg CE. *Acta Cryst.* 1974; B30:1841–1849.
25. Although the structure **3a•Ar** is non-disordered, due to the relatively high standard deviations in bond length values, only a qualitative comparison of structures is made.
26. Pyykkö P, Atsumi M. *Chem Eur J.* 2009; 15:12770–12779.
27. (a) Tourillon G, Garnier F. *J Electroanal Chem Interfacial Electrochem.* 1982; 135:173–178.(b) Keech PG, Chartrand MMG, Bunce NJ. *J Electroanal Chem.* 2002; 534:75–78.
28. Taniguchi T, Yamaguchi T. *Organometallics.* 2010; 29:5732–5735.
29. Tatischeff I, Klein R. *Photochem and Photobiol.* 1975; 22:221–229.
30. Muranaka A, Yasuike S, Liu CY, Kurita J, Kakusawa N, Tsuchiya T, Okuda M, Kobayashi N, Matsumoto Y, Yoshida K, Hashizumi D, Uchiyama M. *J Phys Chem A.* 2009; 113:464–473. [PubMed: 19099440]
31. Bordwell FG. *Acc Chem Res.* 1988; 21:456–463.
32. Lamm AN, Liu SY. *Mol BioSyst.* 2009; 5:1303–1305. [PubMed: 19823745]

Figure 1.
Cyclic voltammograms of BN indole **3a** and indole **1a** (0.08 M TBAOTf in CH₃CN at glassy carbon electrode; scan rate: 50 mV/s).

	λ_{abs}	λ_{em}	ϵ ($\text{M}^{-1} \text{cm}^{-1}$)	Φ (CH_3CN)	Stokes Shift (cm^{-1})
BN indole 3a	293	360	6400	0.083 $\pm$ 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 photo-physical data for **3a** and **1a** in CH_3CN . ^a Literature value, see reference 30. ^b Literature value, see reference 29.

Scheme 1.
Synthesis of Parent BN Indole **3a**

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

Table 2pK_a Bracketing Experiments for **3a**

R-H	pK _a (DMSO) ^a	deprotonated by 3d
indole	20.95	yes
Ph ₂ NH	25	yes
PhCCH	28.8	yes
Ph ₃ CH	30.6	trace
CH ₃ CN	31.3	no

^a taken from Bordwell pK_a table, reference 31.