Tetrahedron Letters
journal homepage: www.elsevier.com/locate/tetlet

Synthesis and chiroptical properties of phenanthrene-fused N_2O-type BODIPYs

Yuki Gobo, Ryota Matsuoka, Yusuke Chiba, Takashi Nakamura, Tatsuya Nabeshima*

Graduate School of Pure and Applied Sciences and Tsukuba Research Center for Energy Materials Science (TREMS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan

ARTICLE INFO

Article history:
Received 30 August 2018
Received in revised form 26 September 2018
Accepted 2 October 2018
Available online

ABSTRACT

A series of phenanthrene-fused N_2O-type boron-dipyrrin complexes (BODIPYs) with various substituents were synthesized. The synthesized BODIPYs show light absorption and emission in the red to near-infrared region due to their extended π-system. Furthermore, the first optical resolution of the N_2O-type BODIPY was achieved using the phenyl-substituted complex. The separated enantiomers are stable to racemization at room temperature, and exhibited a Cotton effect in the deep-red region.

Keywords:
BODIPY
Chirality
Near-infrared fluorescence
Circular dichroism

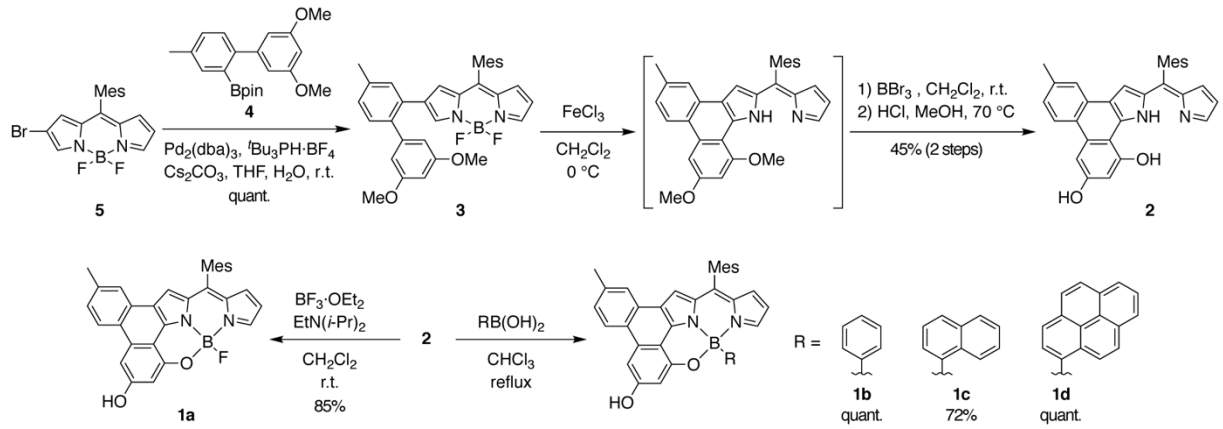
Boron-dipyrrin complexes (BODIPYs) have been used in various research fields as chemosensors,[1] laser dyes,[2,3] photosensitizers,[4–8] and bioimaging reagents[9] because of their strong absorption/emission and high photochemical stability.[10,11] Recently, chiral BODIPYs have attracted more increasing attention due to their significant chiroptical responses such as circular dichroism (CD) and circularly polarized luminescence (CPL).[12–28] These properties are applicable in chiral chromogenic/fluorogenic sensing and chiral responsive optoelectronics.[29–31] In particular, chiral molecules that absorb and emit the light in the red to near-infrared (NIR) region (650–900 nm) can be used as a chiroptical probe in biological systems.[32] However, chiral BODIPYs with absorption/emission in this wavelength region (> 650 nm) are still rare despite their broad utility.[24–28]

N_2O_2 BODIPYs, in which the boron atom is chelated by a 3,5-*ortho*-phenoxy substituted dipyrrin, exhibit distinct chiroptical responses because of their helical conformation stabilized by the tetrahedral geometry around the boron center.[25,28] Their absorption and emission are significantly red-shifted, probably because the intramolecular N_2O_2-chelation decreases the dihedral angle between the phenoxy rings and the dipyrrin moiety.[25,28,33–35] The N_2O-type derivatives have also been reported to show absorption and emission in the red to NIR regions.[36–40] The phenoxy ring of the N_2O-type BODIPYs are more coplanar with the dipyrrin moiety compared to the N_2O_2 BODIPYs.[38,39] This structural feature is suitable for further π-extension of the BODIPY structure by aromatic ring-fusion, which has often been employed for the creation of NIR absorbing/emitting BODIPYs.[41–43] In addition, a substituent can be introduced to the boron center of N_2O-type BODIPYs to tune their physical and chemical properties.[37,39] The substituent also contributes to the generation of a chiral boron center in the N_2O-type BODIPYs, which would be utilized for chiral recognition or for chiroptical responses. We now report a series of phenanthrene-fused N_2O-type BODIPYs **1a**–**1d** that show light absorption/emission in the red to NIR region. The N_2O-type BODIPY **1b** was optically resolved for the first time, and the separated enantiomers exhibit a Cotton effect in the red to NIR region.

The ring-fused N_2O-type BODIPYs **1a**–**1d** were synthesized as shown in Scheme 1. An unsymmetrically substituted BODIPY **3** was prepared quantitatively by the Suzuki-Miyaura cross coupling reaction bewteen the 2-bromo-BODIPY **5**[44] and a biaryl boronic acid **4**.[45] The oxidative annulation of BODIPY **3** and elimination of the BF_2 moiety was conducted together using anhydrous $FeCl_3$ at 0 °C to give an α-fused dipyrrin as an intermediate, which was treated with BBr_3 to produce the demethylated N_2O-type dipyrrin ligand **2** in 45% yield in two steps. The complexation of **2** with $BF_3{\cdot}Et_2O$ in the presence of a base produced the F-appended BODIPY **1a**, while the reaction of **2** with various boronic acids in chloroform gave the corresponding aryl-substituted BODIPYs **1b**–**1d**. The obtained compounds **1a**–**1d** were characterized by ^{1}H NMR, ^{11}B NMR, ^{13}C NMR, 2D NMR (^{1}H–^{1}H COSY, HSQC, HMBC), and HR ESI-mass spectroscopies (Figures S1–S12).

The optical properties of the ring-fused N_2O-type BODIPYs **1a**–**1d** were investigated by UV-vis and fluorescence spectroscopies (Figure 1 and Table 1). **1a**–**1d** showed an intense

* Corresponding author. Tel.: +81-29-853-4507; fax: +81-29-853-4507; e-mail: nabesima@chem.tsukuba.ac.jp



Scheme 1. Synthesis of ring-fused N_2O-type BODIPYs **1a**–**1d**.

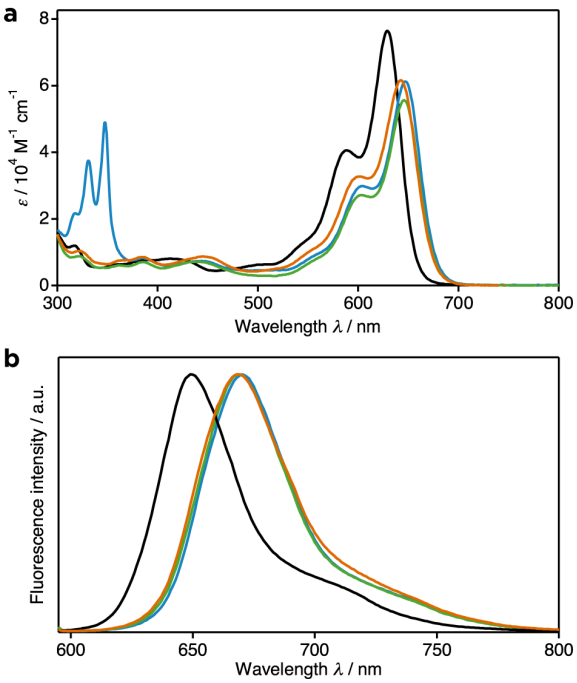


Figure 1. (a) Absorption and (b) emission spectra of ring-fused N_2O-type BODIPYs: **1a** (black), **1b** (orange), **1c** (green), **1d** (blue) ($CHCl_3$, 298 K, [**1a**, **1b**, **1c**] = 5.0 μM, [**1d**] = 5.4 μM).

Table 1
Optical properties of ring-fused N_2O-type BODIPYs **1a**–**1d** ($CHCl_3$, 298 K)

BODIPY	λ_{abs} / nm	ε / 10^4 M^{-1} cm^{-1}	λ_{em} / nm	Φ_F	τ / ns
1a	629	7.6	649	0.35	4.0
1b	643	6.2	669	0.21	3.0
1c	646	5.6	669	0.27	3.5
1d	647	6.1	670	0.24	3.5

absorption band with a maximum at 629, 643, 646, and 647 nm in chloroform, respectively. These bands were assigned by TD-DFT calculations to the $^1\pi$–π^* (HOMO → LUMO) transitions of the N_2O-type BODIPY unit (Table S1). The absorption maxima of **1a**–**1d** are shifted to longer wavelengths by 16–68 nm compared to those of the previously reported N_2O-type BODIPYs.[38,39] These bathochromic shifts indicate the extended π-conjugation in the ring-fused frameworks of **1a**–**1d**. **1d** has another absorption band at 310–370 nm, which was attributed to the π-π^* transition of the pyrenyl moiety. BODIPYs **1a**–**1d** showed a deep-red to NIR fluorescence with moderate fluorescence quantum yields (Φ_F = 0.21–0.35); the fluorescence maximum of **1a** appears at 649 nm, while those of **1b**–**1d** are at 669–670 nm. Excitation of the pyrenyl moiety of **1d** at 350 nm resulted in the emission suppression of the pyrenyl moiety around 380 nm but intense emission from the BODIPY unit instead (Figure S14). This result indicates that energy transfer from the pyrenyl moiety to the BODIPY unit takes place upon excitation.[37,39,46] Fluorescence lifetime studies of **1a**–**1d** revealed that each BODIPY exhibited a first-order decay with a lifetime (τ) of 3–4 nanoseconds (Table 1, Figures S15–18, and Table S2), which is comparable to those of other aryl-fused BODIPYs.[41–43]

In order to understand the structures and optical properties of the ring-fused N_2O-type BODIPYs, DFT and TD-DFT calculations were performed on **1a** and **1b** using the B3LYP functional with the 6-31G* basis set. The geometry optimized structure of the BODIPY skeletons of **1a** and **1b** are almost the same, and each boron center adopts a distorted tetrahedral geometry (Figure 2a). For both complexes, the HOMO and LUMO distribute over the entire conjugated π-system of the N_2O

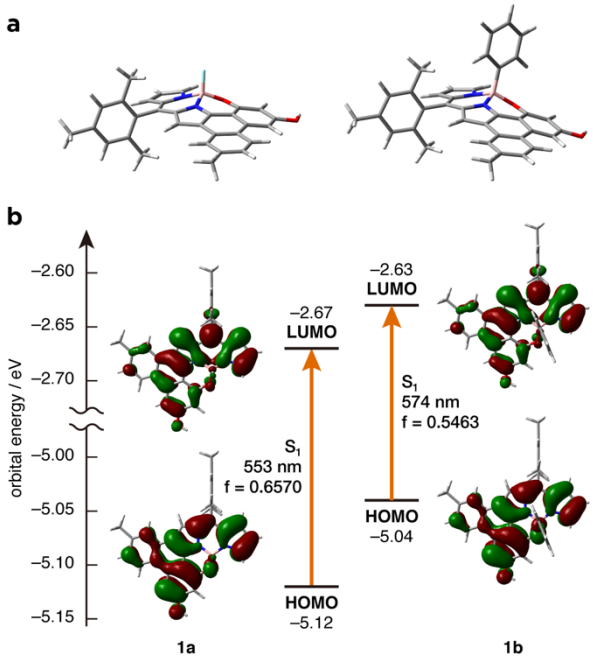


Figure 2. (a) Structures and (b) Kohn-Sham frontier orbitals of **1a** (left) and **1b** (right) obtained by DFT calculations at the B3LYP/6-31G* level. The vertical transition energies of the complexes calculated by the TD-DFT calculations at the same level are also shown in (b).

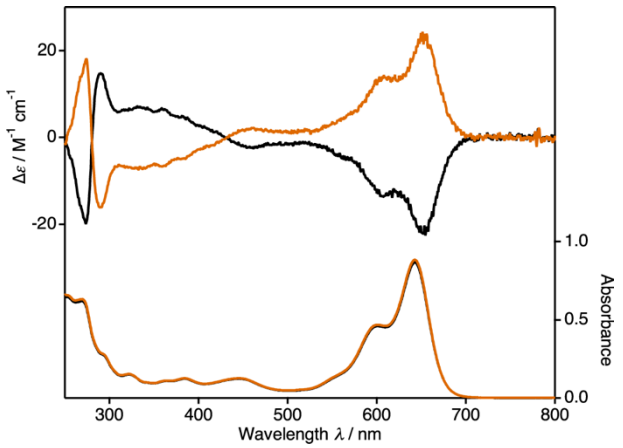


Figure 3. CD spectra (top) and UV-Vis spectra (bottom) of (*S*)-**1b** (black line) and (*R*)-**1b** (orange line). Conditions: $CHCl_3$, 16.7 μM, 298 K, l = 1 cm.

BODIPY units (Figure 2b). The F substituent has only a slight contribution to the HOMO and LUMO of **1a**; on the other hand, the phenyl substituent of **1b** has a significant contribution to the HOMO of **1b** (Figure S13). This contribution presumably resulted in the smaller calculated HOMO-LUMO gap and $S_0 \rightarrow S_1$ excitation energy in **1b** compared to **1a** (Figure 2 and table S1). The calculated results are qualitatively consistent with the observed optial properties of **1a** and **1b**.

Based on the molecular structures obtained by the DFT calculations, the N_2O BODIPYs **1a**–**1d** should be chiral with a boron stereocenter. Therefore, we performed the optical resolution of **1b** using chiral HPLC (Daicel IA, $CHCl_3$/hexane = 1:1) (Figure S19). Each enantiomer of **1b** was successfully separated and analyzed by CD and UV-Vis spectroscopies (Figure 3). The entire CD spectra of the separated enantiomers, (*S*)-**1b** and (*R*)-**1b**, gave a clear mirror image with a maximum around 655 nm. The absolute configuration of each enantiomer was suggested by the sign of the Cotton effect of each CD spectrum and TD-DFT calculations, in which (*S*)-**1b** exhibited a negative Cotton effect in the red region (Table S1). A thermal stability study revealed that (*S*)-**1b** retained almost 100% and 72 ± 3% of its CD intensity after being stored at 50 ºC and 100 ºC for 24 h in toluene, respectively (Figures S20, S21). These results indicate that the chiral inversion of (*S*)-**1b** is negligible at room temperature.

To the best of our knowledge, this is the first example of the enantiopure chiral N_2O-type BODIPYs, although previous reports have suggested the inherent chirality of the N_2O-type BODIPYs.[36] **1a**–**1d** have an unsubstituted pyrrol ring in the BODIPY structure, which can be further modified either by π-conjugated fragments to extend the π-conjugation or by hydrophilic fragments to increase the solubility in water.

In summary, we synthesized a series of phenanthrene-fused N_2O-type BODIPYs **1a**–**1d** appended by various substituents. **1a**–**1d** showed strong absorption in the red region and fluorescence in the deep-red to NIR region due to their extended π-conjugation. The enantiomers of **1b** were successfully separated by chiral HPLC, and exhibited a Cotton effect around 655 nm. This study contributes to the design and development of novel NIR absorbing/emitting chiral BODIPYs for applications such as bioimaging and chiral sensing.

Acknowledgments

This work was supported by Grant-in-Aid for Scientific Research (B) (JSPS KAKENHI grant number JP18H01959), Grant-in-Aid for Scientific Research on Innovative Areas (JSPS KAKENHI grant numbers JP15H00723 (Element Block), JP15H00914 (Stimuli-responsive Chemical Species), and JP17H05351 (Coordination Asymmetry)), and the Mitsubishi Foundation.

References and notes

1. Boens, N.; Leen, V.; Dehaen, W. *Chem. Soc. Rev.* **2012**, *41*, 1130–1172.
2. Ortiz, M. J.; Garcia-Moreno, I.; Agarrabeitia, A. R.; Duran-Sampedro, G.; Costela, A.; Sastre, R.; López Arbeloa, F.; Bañuelos Prieto, J.; López Arbeloa, I. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7804–7811.
3. Benstead, M.; Mehl, G. H.; Boyle, R. W. *Tetrahedron* **2011**, *67*, 3573–3601.
4. Awuah, S. G.; You, Y. *RSC Adv.* **2012**, *2*, 11169–11183.
5. Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Chung, L. Y.; Burgess, K. *Chem. Soc. Rev.* **2013**, *42*, 77–88.
6. Bessette, A.; Hanan, G. S. *Chem. Soc. Rev.* **2014**, *43*, 3342–3405.
7. Singh, S. P.; Gayathri, T. *Eur. J. Org. Chem.* **2014**, 4689–4707.
8. Zhao, J.; Xu, K.; Yang, W.; Wang, Z.; Zhong, F. *Chem. Soc. Rev.* **2015**, *44*, 8904–8939.
9. Ni, Y.; Wu, J. *Org. Biomol. Chem.* **2014**, *12*, 3774–3791.
10. Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891–4932.
11. Lu, H.; Mack, J.; Yang, Y.; Shen, Z. *Chem. Soc. Rev.* **2014**, *43*, 4778–4823.
12. Gossauer, A.; Fehr, F.; Nydegger, F.; Stöckli-Evans, H. *J. Am. Chem. Soc.* **1997**, *119*, 1599–1608.
13. Beer, G.; Niederalt, C.; Grimme, S.; Daub, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3252–3255.
14. Beer, G.; Rurack, K.; Daub, J. *Chem. Commun.* **2001**, 1138–1139.
15. Gossauer, A.; Nydegger, F.; Kiss, T.; Sleziak, R.; Stoeckli-Evans, H. *J. Am. Chem. Soc.* **2004**, *126*, 1772–1780.
16. Móczár, I.; Huszthy, P.; Maidics, Z.; Kádár, M.; Tóth, K. *Tetrahedron* **2009**, *65*, 8250–8258.
17. Haefele, A.; Zedde, C.; Retailleau, P.; Ulrich, G.; Ziessel, R. *Org. Lett.* **2010**, *12*, 1672–1675.
18. Nagai, A.; Kokado, K.; Miyake, J.; Chujo, Y. *Polym. J.* **2010**, *42*, 37–42.
19. Wu, Y.; Mao, X.; Ma, X.; Huang, X.; Cheng, Y.; Zhu, C. *Macromol. Chem. Phys.* **2012**, *213*, 2238–2245.
20. Kolemen, S.; Cakmak, Y.; Kostereli, Z.; Akkaya, E. U. *Org. Lett.* **2014**, *16*, 660–663.
21. Bruhn, T.; Pescitelli, G.; Jurinovich, S.; Schaumlöffel, A.; Witterauf, F.; Ahrens, J.; Bröring, M.; Bringmann, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 14592–14595.
22. Lerrick, R. I.; Winstanley, T. P. L.; Haggerty, K.; Wills, C.; Clegg, W.; Harrington, R. W.; Bultinck, P.; Herrebout, W.; Benniston, A. C.; Hall, M. J. *Chem. Commun.* **2014**, *50*, 4714–4716.
23. Sánchez-Carnerero, E. M.; Moreno, F.; Maroto, B. L.; Agarrabeitia, A. R.; Ortiz, M. J.; Vo, B. G.; Muller, G.; Moya, S. de la *J. Am. Chem. Soc.* **2014**, *136*, 3346–3349.
24. Zhang, L.; Zhao, L.; Wang, K.; Jiang, J. *Dye. Pigment.* **2016**, *134*, 427–433.
25. Alnoman, R. B.; Rihn, S.; O'Connor, D. C.; Black, F. A.; Costello, B.; Waddell, P. G.; Clegg, W.; Peacock, R. D.; Herrebout, W.; Knight, J. G.; Hall, M. J. *Chem. Eur. J.* **2016**, *22*, 93–96.
26. Gobo, Y.; Yamamura, M.; Nakamura, T.; Nabeshima, T. *Org. Lett.* **2016**, *18*, 2719–2721.
27. Zinna, F.; Bruhn, T.; Guido, C. A.; Ahrens, J.; Bröring, M.; Di Bari, L.; Pescitelli, G. *Chem. Eur. J.* **2016**, *22*, 16089–16098.
28. (a) Saikawa, M.; Nakamura, T.; Uchida, J.; Yamamura, M.; Nabeshima, T. *Chem. Commun.* **2016**, *52*, 10727–10730; (b) Saikawa, M.; Nakamura, T.; Uchida, J.; Yamamura, M.; Nabeshima, T. *Chem. Commun.* **2018**, *54*, 10379–10380.
29. Maeda, H.; Bando, Y.; Shimomura, K.; Yamada, I.; Naito, M.; Nobusawa, K.; Tsumatori, H.; Kawai, T. *J. Am. Chem. Soc.* **2011**, *133*, 9266–9269.
30. Tedsana, W.; Tuntulani, T.; Ngeontae, W. *Anal. Chim. Acta* **2015**, *867*, 1–8.
31. Yang, Y.; da Costa, R. C.; Fuchter, M. J.; Campbell, A. J. *Nat. Photonics* **2013**, *7*, 634–638.

32. Heffern, M. C.; Matosziuk, L. M.; Meade, T. J. *Chem. Rev.* **2014**, *114*, 4496–4539.
33. Kim, H.; Burghart, A.; Welch, M. B.; Reibenspies, J.; Burgess, K. *Chem. Commun.* **1999**, 1889–1890.
34. Loudet, A.; Bandichhor, R.; Burgess, K.; Palma, A.; McDonnell, S. O.; Hall, M. J.; O'Shea, D. F. *Org. Lett.* **2008**, *10*, 4771–4774.
35. Tomimori, Y.; Okujima, T.; Yano, T.; Mori, S.; Ono, N.; Yamada, H.; Uno, H. *Tetrahedron* **2011**, *67*, 3187–3193.
36. Ikeda, C.; Maruyama, T.; Nabeshima, T. *Tetrahedron Lett.* **2009**, *50*, 3349–3351.
37. Yamamura, M.; Yazaki, S.; Seki, M.; Matsui, Y.; Ikeda, H.; Nabeshima, T. *Org. Biomol. Chem.* **2015**, *13*, 2574–2581.
38. Sirbu, D.; Benniston, A. C.; Harriman, A. *Org. Lett.* **2017**, *19*, 1626–1629.
39. Chen, N.; Zhang, W.; Chen, S.; Wu, Q.; Yu, C.; Wei, Y.; Xu, Y.; Hao, E.; Jiao, L. *Org. Lett.* **2017**, *19*, 2026–2029.
40. Liu, Y.; Niu, L.-Y.; Liu, X.-L.; Chen, P.-Z.; Yao, Y.-S.; Chen, Y.-Z.; Yang, Q.-Z. *Chem. Eur. J.* **2018**, *24*, 13549–13555.
41. Okujima, T.; Tomimori, Y.; Nakamura, J.; Yamada, H.; Uno, H.; Ono, N. *Tetrahedron* **2010**, *66*, 6895–6900.
42. Sarma, T.; Panda, P. K.; Setsune, J. *Chem. Commun.* **2013**, *49*, 9806–9808.
43. Zhou, Z.; Zhou, J.; Gai, L.; Yuan, A.; Shen, Z. *Chem. Commun.* **2017**, *53*, 6621–6624.
44. Hayashi, Y.; Yamaguchi, S.; Cha, W. Y.; Kim, D.; Shinokubo, H. *Org. Lett.* **2011**, *13*, 2992–2995.
45. Richards, G. J.; Gobo, Y.; Yamamura, M.; Nabeshima, T. *New J. Chem.* **2015**, *39*, 5886–5889.
46. Burghart, A.; Thoresen, L. H.; Chen, J.; Burgess, K.; Bergström, F.; Johansson, L. B.-Å. *Chem. Commun.* **2000**, 2203–2204.

Supplementary Material

Supplementary data (Detailed synthetic procedures, characterization data, DFT calculations, and photophysical measurements) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet. 2018.10.003.