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Boron Asymmetry in a BODIPY Derivative

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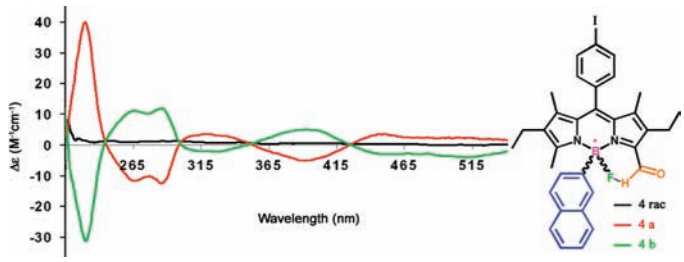
ABSTRACT



A boradiazaindacene (BODIPY) fluorophore with a chirality held on the central boron has been synthesized and the racemate resolved. Dissymetrization of the BODIPY core was obtained by oxidation of the 3-methyl group to the corresponding carboxaldehyde. A hydrogen bond between the aldehyde proton and the fluorine on the boron atom was evidenced by both ^{1}H NMR and X-ray diffraction. Chiral high-performance liquid chromatography as well as circular dichroism confirm the persistence of both enantiomers.

The demand for sophisticated luminophores to be used in modern biological labeling and advanced optoelectronic devices has stimulated chemists to engineer organic dyes with novel fluorescence properties.[1] The boradiazaindacene, BODIPY, family, in particular, has been subject to intense development because of the inherent stability, chemical versatility, high brightness, and exceptional fluorescence properties of these dyes.[2] Advanced applications in various fields such as sensors,[3] energy-transfer cassettes,[4] biological labeling,[5] or photovoltaic devices have been investigated.[6] Chemically, the central core supports postsynthetic functionalization, enabling fine-tuning of the optical and physical properties of the dyes.[2] A significant breakthrough was brought by the replacement of the fluorine of the boron atom by various functional substituents,[7] allowing the generation of energy-transfer cassettes and wires,[8] soft materials,[9] polymers,[10] and water-soluble dyes.[11] The chemistry at boron

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has also made possible both mono- and heterodisubstitution,[12] paving the way to chiral BODIPYs asymmetric at boron. It may be noted here that most known chiral organic fluorophores are based on binaphthol modules and have been used in chiral recognition processes, such as to determine the enantiomeric purity of chiral amines, amino acids, and alcohols.[13]

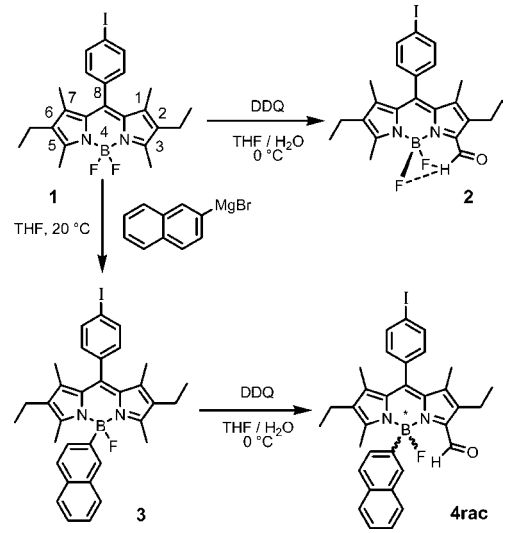
Stable, asymmetric boron complexes are rare, and only a few can be resolved because of facile dissociation/inversion processes.[14] The stability of asymmetric N-donor complexes of boron is related to the strength of the N−B bond.[15] The activation enthalpy for racemization can be correlated to the length of this bond, and thus in the case of a BODIPY, we anticipated that the presence of an N-donor chelate would ensure good stability, inhibiting stereochemical rearrangement and allowing resolution using chiral high-performance liquid chromatography (HPLC).[16]

The few examples of enantiomerically pure BODIPY fluorophores known were obtained by decorating the central core with an asymmetric carbon[17] and not by utilization of the potential asymmetry at boron. Notice that racemic mixtures of boron dipyrrin derivatives[18] and azadipyrromethene dyes have recently been prepared.[19] We present here the first synthesis and resolution of an asymmetric boron B*-BODIPY, with its chirality arising solely from the stereochemistry at boron, and describe the optical properties of both enantiomers.

The following requirements were envisaged as necessary to obtain a stable B* chiral BODIPY: (i) lateral differentiation of the dipyrromethene core; (ii) introduction of a polar group suitable for intramolecular association with a BF unit; (iii) use of polyaromatic residues causing moderate steric congestion around the boron atom and facilitating chromatographic resolution on a chiral solid phase.

To obtain an unsymmetrical dipyrromethene ligand bound to B, a selective dichlorodicyanoquinone (DDQ) oxidation of the methyl group in the substitution position 3 of dye **1** was used to give the corresponding aldehyde **2** (Scheme 1).[20] Interestingly, the proton signal of the aldehyde at δ 10.39 ppm appears as a triplet because of coupling with the two fluoride atoms (J_{HF} = 1.9 Hz). This pronounced through-space coupling is confirmed by the ^{13}C NMR peak of the formyl group (triplet at 186.1 ppm, J_{CF} = 3.3 Hz). Full confirmation of the nature of **2** was obtained from the X-ray crystal structure (Figure 1). The structure was solved under space group *C*2/*c*, although the apparent 2-fold symmetry of the molecule is the result of 1:1 disorder of the oxygen substituent over two sites on carbon atoms located on the C3 and C5 positions of dipyrromethene. In the boraphenyldipyrromethene unit, 18 atoms are *quasi*-coplanar with a root-mean-square deviation of 0.038 Å. The molecules lie in sheets, parallel to the (101) plane, formed by antiparallel linear arrays involving head-to-tail halogen bonding (F···I) laterally connected by CH···O bonds. Between sheets, an overlap in the projection of the pyrrole units brings several carbon atoms into ~3.5 Å contact distances.

Scheme 1. Synthesis of the B*-BODIPY Racemate



The iodophenyl group lies essentially orthogonal to the BODIPY platform (dihedral angle of ca. 80°) probably to minimize interactions with the adjacent methyl groups, though possibly also because of intersheet F···aromatic interactions. The formyl residue lies in the same plane as the BODIPY core, with a maximum deviation of 7.1(3)°.

After several heterodisubstituted E-BODIPY (E = ethynyl) derivatives were investigated,[7] attention was focused on the monoaryl-substituted compound obtained by the reaction at

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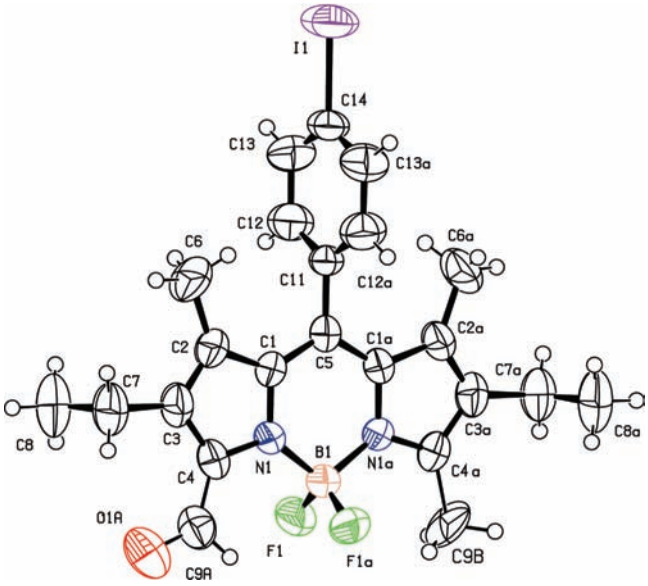

Figure 1. ORTEP view of compound **2**. Displacement ellipsoids are drawn at the 30% probability level. Selected distances (Å): C4−N1 1.354(20); N1−B1 1.543(18); B1−F1 1.385(16).

low temperature of naphthylmagnesium bromide with the symmetrical F-BODIPY **1** (Scheme 1). The BODIPY core of dye **3** was then rendered unsymmetrical by selective oxidation with DDQ previously developed for compound **2**, leading to the aldehyde $\mathbf{4}_{\mathbf{rac}}$ as a racemic mixture. Again, through-space coupling of the formyl proton to fluorine, as seen for **2**, was apparent in the ^{1}H NMR spectra (Figure 2).

Resolution of $\mathbf{4}_{\mathbf{rac}}$ was achieved by HPLC using a Chiralcel-OD column and a mixture of hexane/isopropyl alcohol as the mobile phase.[21] The enantiomers **4a** and **4b** were separated by 1.3 min in the elution sequence. As expected, they have identical NMR (Figure 2) and mass and optical spectra. Interestingly, repeated chromatography of the separated enantiomers gave single peaks for both, illustrating the stability of the B center toward inversion even under exposure to full daylight.

The unsymmetrical nature of the BODIPY core is apparent in the doubling of signals in the aliphatic region. The asymmetry at B, associated with the apparently slow rotation of the iodophenyl unit, is reflected in the AA′BB′ multiplets observed for the iodophenyl protons. The asymmetry at B is also reflected in the diastereotopicity observed for the

(21) **Experimental Procedure for HPLC Separation**. Analytical and preparative resolutions of $\mathbf{4}_{\mathbf{rac}}$ were performed on Chiralcel-OD (Daicel) columns. The analytical separations employed an isocratic eluent of 10%/90% isopropyl alcohol/heptane and a flow of 1 mL/min with UV detection at 277 nm on a 250 × 4.6 mm column. HPLC system: Waters, Alliance pump 2696, UV detector 2996, running under *Empower* software (Waters). The preparative separations used a 250 × 10 mm column, eluent 5%/95% isopropyl alcohol/heptane, a flow of 4.7 mL/min, and UV detection at 277 nm. HPLC system: Pump Delta prep 4000, UV 486, manual injection of 1.5−2 mL. The racemic precursor was solubilized in the eluent, filtered, and then injected (3−4 mg/injection). Each fraction was monitored by analytical HPLC, and mixed fractions were collected and reinjected. A total of 17 mg of $\mathbf{4}_{\mathbf{rac}}$ was purified in six injections, giving 6.2 mg of **4a** and 5.8 mg of **4b**.

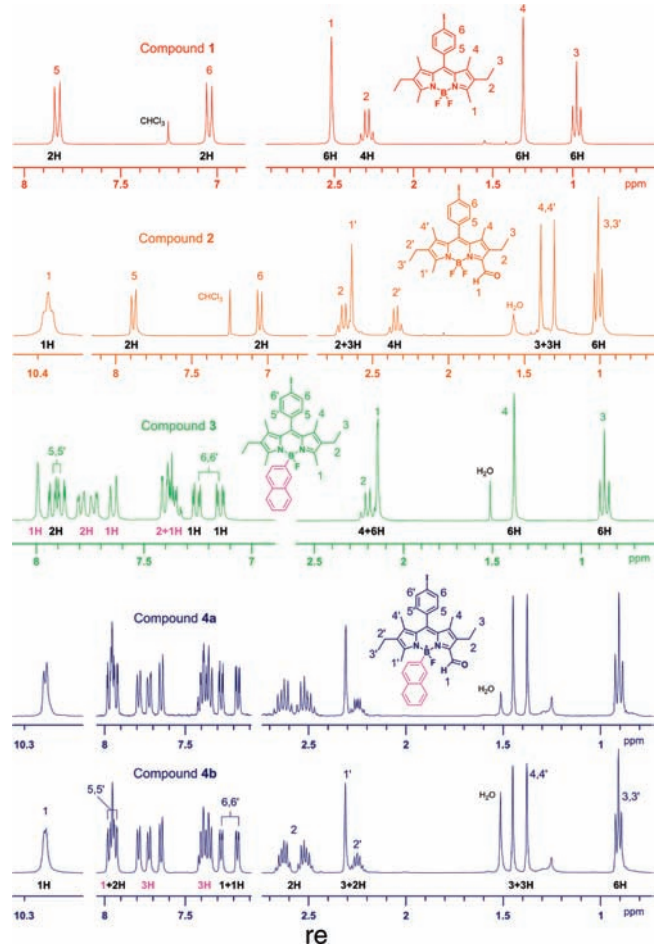

Figure 2. ^{1}H NMR spectra of **1**, **2** ($CDCl_3$, RT), **3**, **4a**, and **4b** (CD_2Cl_2, RT).

methylene protons of the ethyl substituents (Figure 2). A further confirmation of the enantiomeric nature of **4a** and **4b** is the circular dichroic (CD) spectra showing the perfect mirror image of both compounds (Figure 3).

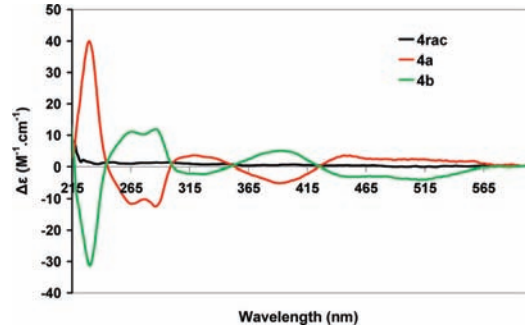

Figure 3. CD spectra of $\mathbf{4}_{\mathbf{rac}}$, **4a**, and **4b** in CH_2Cl_2 at RT.

The absorption spectrum of compound **2** shows a strong absorption at 283 nm attributed to the carbonyl absorption

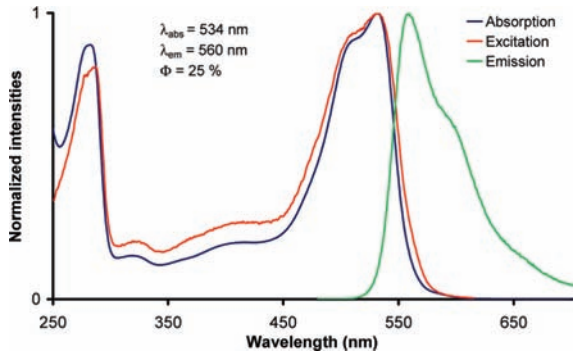

Figure 4. Absorption (blue line), emission (green line), and excitation (red line) spectra of **4a**, in $CHCl_3$ at RT and at a concentration of ca. 1×10^{-6} M.

band (see the Supporting Information). The typical S_0-S_1 transition band found for **1** and **3** at 526 nm with a shoulder at 501 nm is also found for dyes **2**, **4a**, and **4b** but with a hypochromic and slight bathochromic shift of the lower energy band to 534 nm and an enhanced shoulder at 511 nm (Figure 4). This may be due to the strong conjugation of the carbonyl function with the BODIPY π system. The X-ray structure confirms that the aldehyde lies in the same plane as the dipyrromethene core, favoring pronounced orbital overlap. The excited-state lifetime (τ of around 2.50 ns), the radiative rate constant (k_r of about 8×10^7 s^{-1}), and the quantum yield of 25% are all consistent with a singlet-based excited-state manifold in **4a** and **4b**.

In summary, an enantiomerically pure B*-BODIPY was prepared by appropriate substitution on the boron and the dipyrromethene core. Introduction of a formyl substituent on one pyrrole unit both renders the chelate unsymmetrical and stabilizes the configuration at B via hydrogen bonding to the fluoro ligand. Thus, the enantiomers are stable to inversion even in full daylight at room temperature. This first example of a resolved fluorophore with a central chiral boron could serve as a model to build similar reporters with selective recognition groups in the near environment of the chiral center, which could serve for fluorimetric chiral recognition. Further work along these lines is in progress.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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