Mendeleev Communications

Mendeleev Commun., 2025, **35**, 673–675

Synthesis of BODIPY derivatives with iodinated cobalt bis(dicarbollide)

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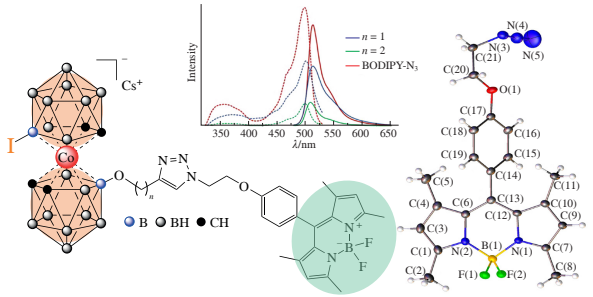
DOI: 10.71267/mencom.7812

The solid-state molecular structure of azido derivative of BODIPY was determined by a single-crystal X-ray diffraction; this compound was subjected to a Cu^{I}-catalyzed azide–alkyne cycloaddition with ethynyl-containing iodine cobalt bis(dicarbollides) to give the corresponding new 1,2,3-triazole conjugates. Their study by absorption–emission spectroscopy showed that the addition of a boron cluster weakened the fluorescence of the starting azido BODIPY.



Keywords: cobalt bis(dicarbollide), BODIPY, alkynes, azides, 'click' reaction, fluorescent labeling, boron neutron capture therapy.

The widespread prevalence of oncological diseases requires scientists to create new effective methods for their treatment and diagnosis. One way to address this problem is fluorescence diagnostics and boron neutron capture therapy (BNCT), which are the examples of simultaneous visualization and treatment. In this case, photosensitizer provides visualization of the tumor, and the boron cluster introduced into tumor cells, upon capture of thermal neutrons in the target cell, generates high-energy particles ^{4}He and ^{7}Li with a short range, which leads to the selective destruction of tumor cells without affecting the surrounding healthy tissue.[1,2]

Among the wide range of polyhedral boron hydrides, cobalt bis(dicarbollide) [3,3′-Co(1,2-$C_2B_9H_{11})_2]^-$ (refs. 3, 4) has proven itself as a promising molecule for use as a boron carrier in BNCT, due to its exceptional stability, good solubility in water in the form of sodium salts[5] and low toxicity both *in vitro*[6,7] and *in vivo*.[6,8] Since cobalt bis(dicarbollide) is amphiphilic,[9] it is able to cross lipid membranes and to accumulate in cells without violating their integrity.[10–12] Currently, various fluorescent labels including 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) and its derivatives are commonly used to label cobalt bis(dicarbollide).[13] The BODIPY derivatives are also used to label *nido*-carborane.[14,15] The BODIPY derivatives are actively developing fluorescent dyes based on a fixed arylmethene structure, which allows for various modifications thereby changing their optical properties, namely, shifting the positions of spectral maxima, increasing the quantum yield of fluorescence, *etc.*[16] Literature data indicate that BODIPY dyes are able to easily penetrate the cell membrane and to accumulate mainly in mitochondria and endoplasmic reticulum,[17] thus, they can accumulate in tumor cells.

The aim of this work was to synthesize fluorescent conjugates of cobalt bis(dicarbollide) with BODIPY using the 'click' cycloaddition methodology. The acetylene derivatives of cobalt bis(dicarbollide) and azido derivative of BODIPY as the starting compounds were used for the 'click'-reaction.

Previously, in our laboratory, 'click'-reactions were used to prepare conjugates of cobalt bis(dicarbollide) with cholesterol[18] and acridine.[19] One approach to the synthesis of cobalt bis(dicarbollide) derivatives is based on the nucleophilic opening of the iodonium derivative [8,8′-μ-I-3,3′-Co(1,2-$C_2B_9H_{10})_2$], in which two dicarbollide ligands are linked *via* the iodine atom.[20–26] Due to its high reactivity, the iodonium bridge is easily opened by the *O*-nucleophiles (*e.g.*, 2-propyn-1-ol and 3-butyn-1-ol) leading to the corresponding acetylene derivatives Cs[8-HC≡CCH_2O-8′-I-3,3′-Co(1,2-$C_2B_9H_{10})_2$] **1a** and Cs[8-HC≡$C(CH_2)_2$O-8′-I-3,3′-Co(1,2-$C_2B_9H_{10})_2$] **1b**,[25] which then by the 'click' reaction with the azido derivative of BODIPY **2** yield fluorescent conjugates of cobalt bis(dicarbollide) as potential BNCT agents. This is a less known method for synthesizing cobalt bis(dicarbollide) derivatives compared to the nucleophilic opening of cyclic oxonium derivatives.[27] At the same time, it allows one to obtain derivatives with a shorter spacer between the metallacarborane cluster and the biologically active part of the molecule, which may be important for its biochemical properties. It should be noted that the presence of the iodine atom allows one to 'fix' the rotation of dicarbollide ligands due to the formation of intramolecular hydrogen bonds C–H···I between the CH groups of one dicarbollide ligand and the halogen atom of another ligand, which leads to the minimization of the dipole moment of the metallacarborane fragment.[28] This facilitates penetration of the compound through lipid membranes and reduces the possibility of its non-specific interactions with various cell components.[29,30]

The azido derivative of BODIPY **2** was obtained by the condensation of 4-(2′-azidoethoxy)benzaldehyde with 2,4-dimethylpyrrole in the presence of trifluoroacetic acid, followed by oxidation and complexation with $BF_3 \cdot Et_2O$.[31] The solid-state structure of azido derivative of BODIPY **2** was determined by a single-crystal X-ray diffraction study

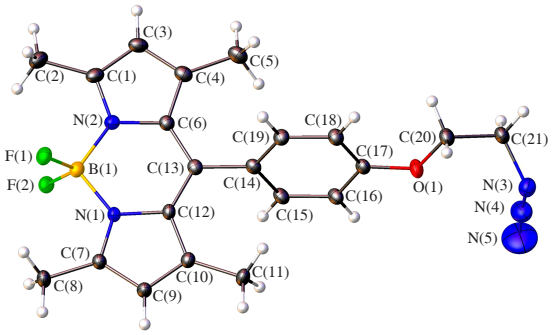
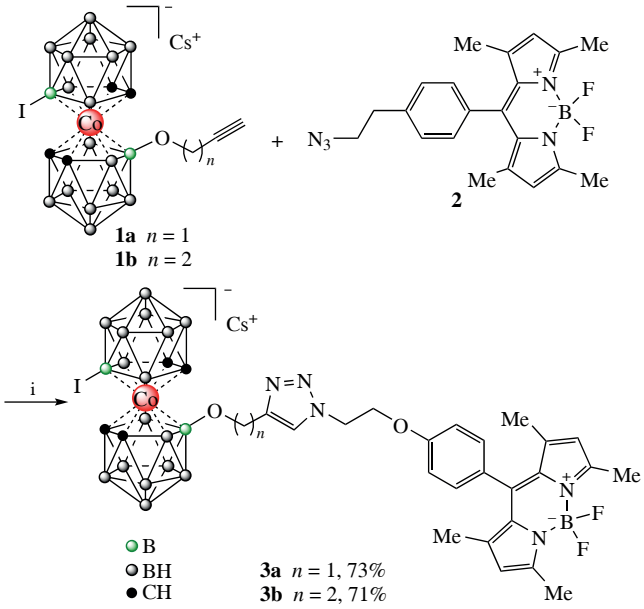


Figure 1 Solid-state structure of azido derivative of BODIPY **2**. Ellipsoids are shown at the 50% probability level. For selected bond lengths and angles, see Online Supplementary Materials.

(Figure 1).† Molecular conformation of **2** is expected and resembles that of *meso*-phenyl BODIPY[32,33] and its *para*-ethoxy derivatives:[33] the phenyl ring is rotated against the bis-pyrrole central fragment on 72.8(1)°. In the crystal, molecules **2** form centrosymmetric dimers by means of C–H···O interactions [C···O 3.547(2) Å]; the dimers are bound into infinite layers stabilized by C–H···F H-bonds [C···F 3.311(2) and 3.381(2) Å]. For the packing details, see Online Supplementary Materials (Figures S21–S23).

The copper(I)-catalyzed 1,3-dipolar [3+2]-cycloaddition reactions of alkynes **1a**,**b** with azido derivative of BODIPY **2** in the presence of diisopropylethylamine (DIPEA) and CuI upon refluxing in ethanol proceed within 2 h to form the corresponding 1,2,3-triazoles **3a** and **3b** in 73 and 71% yields, respectively (Scheme 1). The use of the catalyst CuI in this process provides the reaction's regioselectivity giving 1,4-substituted triazole as the only products. It should be noted that the reactant conversion is close to quantitative since we observed complete disappearance of the starting materials within 2 h. The conjugates **3a** and **3b** were characterized by ^{1}H, ^{11}B, ^{19}F, and ^{13}C NMR spectroscopy, IR spectroscopy, and high-resolution mass spectrometry.

The optical properties of azido derivative of BODIPY **2** and its conjugates with cobalt bis(dicarbollide) **3a**,**b** in acetone solution were studied. The luminescence spectra showed that for the azido derivative **2** the absorption maximum was observed at λ_{abs} = 498 nm, whereas for conjugates **3a** and **3b** they are observed at λ_{abs} = 500 nm. The emission maxima are at λ_{em} = 514 nm for both compound **2** and conjugate **3a**, and at λ_{em} = 508 nm for conjugate **3b** (Figure 2). Due to the flexible spacer between the fluorescent core of BODIPY and the boron cluster, only minor changes in the absorption and emission maxima occur when the length of the spacer is changed by one



Scheme 1 *Reagents and conditions*: i, DIPEA, CuI, EtOH, 70 °C, 2 h.

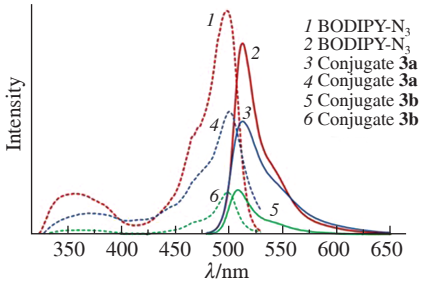


Figure 2 Absorption spectra (dashed lines) and emission spectra (solid lines) of compounds **2** and **3a**,**b** in acetone ($c = 10^{-6}$ M). The excitation wavelength for recording emission spectra is 475 nm.

methylene unit. It can therefore be assumed that they do not depend on the length and structure of the linker through which the boron cluster is attached to the BODIPY fragment. It should be noted that the fluorescence intensities of the conjugates **3a**,**b** are significantly weaker than that of compound **2**, while the fluorescence intensity of conjugate **3a** with short spacer is stronger than that of its analog **3b** with the longer spacer. Probably, it may indicate quenching of the BODIPY fluorescence due to its interaction with the metallacarborane fragment.

In conclusion, the solid-state structure of the azido derivative of BODIPY was determined by a single-crystal X-ray diffraction study. Its Cu^{I}-catalyzed azide–alkyne cycloadditions with acetylene derivatives of cobalt bis(dicarbollide) were studied. As a result, fluorescent conjugates were thus obtained with yields exceeding 70%. It was found that the attachment of the bis(dicarbollide) fragment leads to a significant decrease in the BODIPY luminescence intensity, and this decrease is enhanced with increasing the spacer length, which may indicate fluorescence quenching due to the intramolecular interactions of the metallacarborane cluster with the BODIPY fragment. The results obtained create prerequisites for further research in the field of design of BNCT agents with the BODIPY fluorescent label.

Synthesis and characterization of the compounds described in this study were supported by The Russian Science Foundation (grant no. 24-73-10090). The NMR spectroscopic data were obtained using the equipment of the Center for Molecular Structure Studies at the A. N. Nesmeyanov Institute of

† *Crystal data for* **2**. At 100 K: $C_{21}H_{22}BF_2N_5O$ (M = 409.24), monoclinic, space group $P2_1/c$, a = 12.7585(7), b = 10.4668(6) and c = 15.9235(9) Å, β = 110.823(2)°, V = 1987.5(2) Å^3, μ(MoKα) = 0.10 mm^{-1}, F(000) = 856. Intensities of 31949 reflections were measured with a Bruker Quest diffractometer (MoKα-radiation, graphite monochromator, ω-scans, $2\theta < 61°$) equipped with a Photon-II area-detector at the facilities of the JRC PMR IGIC RAS. The intensity data were integrated and corrected for absorption and decay using SADABS.[34] 5834 independent reflections (R_{int} = 0.0527) were used in further refinement. The structure was solved by dual space methods using SHELXT[35] and refined using SHELXL-2018[36] by full-matrix least squares against F^2 with imposing the anisotropic approximation on non-hydrogen atoms. The hydrogen atoms positions were calculated and refined using the riding model. For **2**, the refinement converged to wR_2 = 0.1276 and GOF = 1.059 for all independent reflections [R_1 = 0.0463 was calculated against F for 4373 observed reflections with $I > 2\sigma(I)$].

CCDC 2446319 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

Organoelement Compounds operating with financial support from the Ministry of Science and Higher Education of the Russian Federation. I. V. Ananyev is grateful to the support of the structural and theoretical study by the Ministry of Science and Higher Education of the Russian Federation as part of the State Assignment of the N. S. Kurnakov Institute of General and Inorganic Chemistry of the Russian Academy of Sciences (1021071612866-5-1.4.7).

The authors express their gratitude to Dr. Alexey A. Titov (Laboratory of Metal Hydrides, A. N. Nesmeyanov Institute of Organoelement Compounds) for recording the luminescence spectra of the compounds described.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7812.

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Received: 28th April 2025; Com. 25/7812