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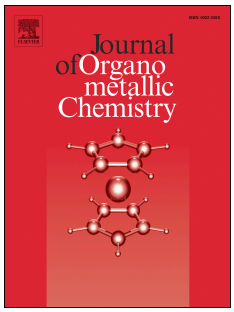

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Natalia I. Shlyakhtina, Alexander V. Safronov, Yulia V. Sevryugina, Satish S. Jalisatgi, M. Frederick Hawthorne

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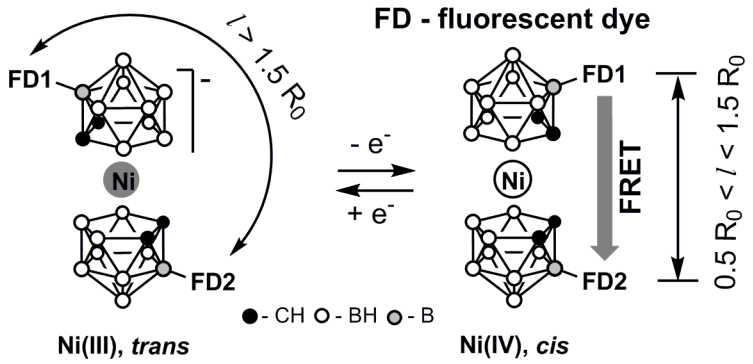
Graphical Abstract Synopsis

The design and synthesis of bis(dicarbollyl)nickel complexes bearing two fluorophore molecules capable of fluorescence resonance energy transfer was performed. The FRET couple with R_0 of approximately 26 Å consisted of tryptophan and BODIPY. The target compounds were prepared via a multistep organic/organometallic synthesis and their fluorescence spectra were studied.



Synthesis, Characterization, and Preliminary Fluorescence Study of a Mixed-ligand Bis(dicarbollyl)nickel Complex Bearing a Tryptophan-BODIPY FRET Couple

Natalia I. Shlyakhtina,[a] Alexander V. Safronov,[a] Yulia V. Sevryugina,[b] Satish S. Jalisatgi,[a] M. Frederick Hawthorne[a,*]

[a]International Institute of Nano and Molecular Medicine, School of Medicine, University of Missouri-Columbia, 1514 Research Park Drive, Columbia, MO 65211, USA.

[b]Department of Chemistry, Texas Christian University, Fort Worth, TX 76129, USA.

*Corresponding author. Fax 1-573-884-6900. E-mail: hawthornem@missouri.edu

Abstract

In continuation of our work on nickelacarborane-based nanomolecular devices, the design and synthesis of a bis(dicarbollyl)nickel complex, in both formal Ni(III) and Ni(IV) oxidation states, bearing two fluorophore molecules capable of fluorescence resonance energy transfer (FRET) was performed. The FRET couple with a small Förster radius (R_0 of 26 Å) consisted of tryptophan and 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY). Each fluorophore was connected to the nickelacarborane core by a rigid linker containing two pairs of alternating ethynyl and *para*-phenylene groups, which created a specific distance (*l*) between the fluorophore molecules depending on the conformation of the nickelacarborane core. The presence (13 Å < *l* < 39 Å) or absence (*l* > 39 Å) of energy transfer in the designed system provides insight into the conformational changes of nickelacarboranes in solution. The target nickelacarboranes were prepared via a multistep organic/organometallic synthesis. The structures and compositions of the intermediates and final products were established by a combination of spectroscopic methods and X-ray structure analysis. A preliminary fluorescence study of the prepared nickelacarboranes was performed.

Keywords: Nickelacarborane; Molecular motor; Synthesis; Fluorescence; BODIPY; FRET.

1. Introduction

Transition metal metallacarborane π-complexes were first discovered in the mid-1960s [1]. Since that time, most of the research in the area has been concentrated on the synthesis of new types of complexes [2] and their application in homogeneous catalysis [3]. However, when the general interest in homogeneous catalysis research began to decline at the end of the 1990s, medicinal applications of transition metal metallacarboranes started to emerge. A number of potent HIV inhibitors [4], nitric oxide

synthase inhibitors [5], new boron neutron capture therapy reagents [6], PET-CT [7] and Raman spectroscopy [8] imaging agents containing metallacarborane complexes of various transition metals were discovered. During the explosive development of nanoscience and nanotechnology in the 2000s, it was postulated that their unique capability of producing complexes with redox-controlled rotational motion might allow some transition metals metallacarboranes to find applications in nanoelectronics and nanomachine engineering [9].

A key step toward the application of metallacarboranes in nanotechnology is the visualization of their controllable conformational interconversion in solutions and, eventually, on a surface. Fluorescence spectroscopy is a very powerful tool permitting such conformational assignments in solution. Among fluorescence spectroscopy techniques, fluorescence resonance energy transfer (FRET) is extensively used in biology for structural and dynamical studies of proteins [10]. FRET occurs between two fluorescent molecules in solution, and its efficiency depends on many parameters. The most important parameter is the degree of overlap of the emission spectrum of the donor and the absorption spectrum of the acceptor. For the energy transfer to occur, the distance l between the donor and acceptor molecules must obey the Förster equation, $0.5\ R_0 < l < 1.5\ R_0$, where R_0 is the Förster radius, the distance at which fluorescence energy transfer occurs with 50% probability. In practice, FRET does not occur at distances of $l > 1.5\ R_0$. Besides for spectral overlap and the appropriate distance, the relative orientations of the fluorophores in space is also very important.

Recently, it was demonstrated that tryptophan and a BODIPY dye derivative, N-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4adiaza-s-indacene-3-yl)methyl iodoacetamide, form a FRET couple with an R_0 value of approximately 26 Å [11]. During the folding study of the two-state protein S6 (from *Thermus thermophilus*), this small value of R_0 allowed the investigators to probe intramolecular distances ranging between 17 and 34 Å with an error of less than 10%. The tryptophan/BODIPY couple appeared to be very attractive for small-molecule FRET measurements, such as conformational assignments in nickelacarboranes. The distances determined for the tryptophan/BODIPY couple within an effective FRET range are easily achievable in metallacarborane chemistry. The conformational changes of the nickelacarborane core during oxidation-reduction processes would provide the necessary distance changes between the dye molecules, and the presence or absence of the FRET effect would theoretically allow for the conformational assignment of the metallacarborane moiety.

Herein, the design, synthesis, characterization, and preliminary fluorescence study of Ni(III) and Ni(IV) nickelacarborane complexes bearing tryptophan/BODIPY FRET couple connected to the metallacarborane core by rigid linkers are reported.

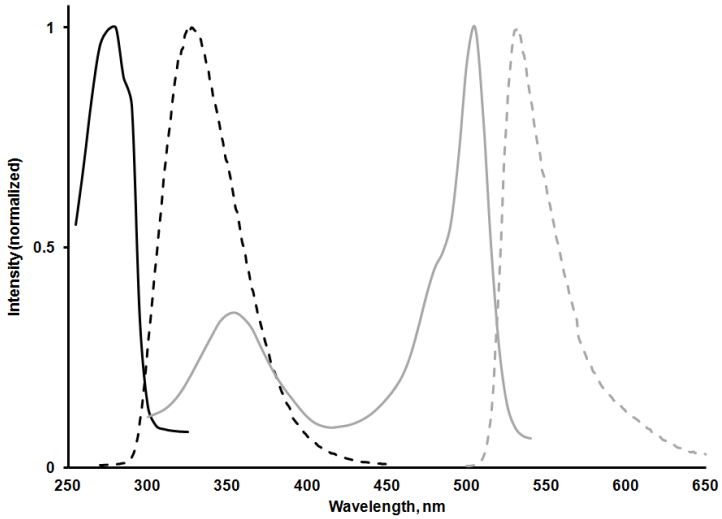
2. Results and discussion

2.1. Design of the target compounds

To facilitate the synthesis of the target products, N-boc-tryptophan and 8-(4′-bromophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene were chosen as the FRET donor and acceptor, respectively. It was decided that the introduction of the tryptophan fluorophore into the molecule could be achieved by an esterification reaction such the amino-group of tryptophan was protected to avoid the formation of any by-products. The introduction of a brominated phenyl ring into the BODIPY molecule was necessary to facilitate attachment of the molecule to the complex via cross-coupling.

To ensure that the fluorescent molecules form a FRET couple with a Förster radius of approximately 26 Å, their absorption and fluorescence behavior was studied. As seen from Figure 1, the spectroscopic behavior of both dye molecules is as expected. N-boc-tryptophan showed absorption and emission maxima at 280 and 326 nm, respectively. The BODIPY dye molecule revealed two absorption maxima at 354 and 505 nm and one emission maximum at 531 nm. The fluorescence band of N-boc-tryptophan shows a significant overlap with the lower wavelength absorption band of 8-(4′-bromophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene. Using the recorded spectra of the compounds and Photochemcad 2.1 software [12], the Förster radius R_0 of this FRET couple in CH_2Cl_2 was calculated to be 25.5 Å, which is very close to the published data [11].

Figure 1. Normalized absorption (solid black line) and fluorescence (dashed black line) spectra of N-boc-tryptophan and absorption (solid grey line) and fluorescence (dashed grey line) spectra of 8-(4′-bromophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (10^{-4} M, CH_2Cl_2, 293 K).



During the design of the complex, four main requirements were formulated for the linkers connecting the dye molecules to the nickelacarborane core:

1) Rigidity. The linkers must provide a constant distance between each carborane cage of the nickelacarborane complex and the fluorescent dye molecule.

2) Length. The length of the linkers must provide a distance of 12 Å < *l* < 38 Å (0.5 R_0 < *l* < 1.5 R_0) between the dye molecules in the *cis* conformation of the nickelacarborane [Ni(IV)] and a distance of at least 38 Å, or more than 1.5 R_0, in the *trans* conformation [Ni(III)].

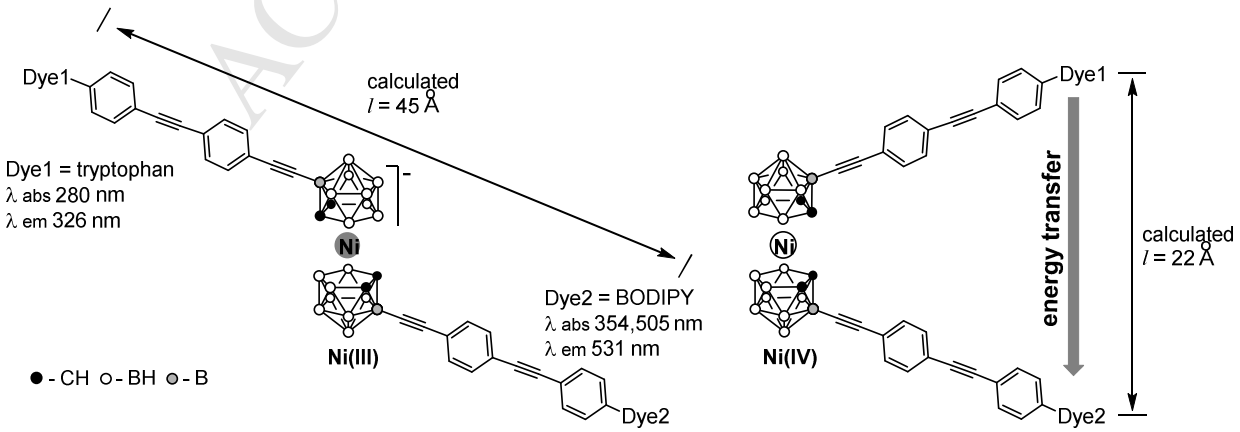
3) Synthesis. The complexes containing the linkers satisfying the two previous conditions must not be extremely difficult to prepare.

4) Spectroscopic properties. The absorption and fluorescence of the linkers must not interfere with the absorption and fluorescence of the attached dye molecules.

The first two requirements were relatively easy to satisfy. Indeed, alternating *para*-phenylene and ethynyl fragments could provide the linkers with the necessary rigidity. Geometry optimization [13] of the suggested structure with two alternating ethynyl and two *para*-phenylene linkers (Figure 2) showed that the distance between the dye molecules would be approximately 45 Å and 22 Å in the *trans* and *cis* conformations of nickelacarborane, respectively, which lie within the required distance range.

Synthetically, the attachment of such linkers to the carborane cage could be achieved via Pd-catalyzed cross-coupling reactions. In Figure 2, the linkers are positioned on atoms B(6) and B(6′) of the nickelacarborane core because the starting material for this attachment (i.e., 3-iodo-1,2-dicarba-*closo*-dodecaborane) is easily accessible and the symmetry of the products avoids any stereoisomerism-related problems.

Figure 2. Schematic representation of the target nickelacarborane complexes.



Although the synthesis and characterization of oligo- and poly(phenylacetylenes) has been the subject of multiple studies [14], spectroscopic information of lower-molecular-weight species is not readily available. Thus, the decision regarding the applicability of the conjugated (phenylethynyl) linkers in the system under consideration was based on the information available for 1,2-diphenylacetylene. It was demonstrated that this compound's absorption and fluorescence bands appear at approximately 300 nm; however, the fluorescence quantum yield was determined to be 0.003 [15]. Theoretically, if the linkers absorb some of the excitation energy, their contribution to the fluorescence will be minimal.

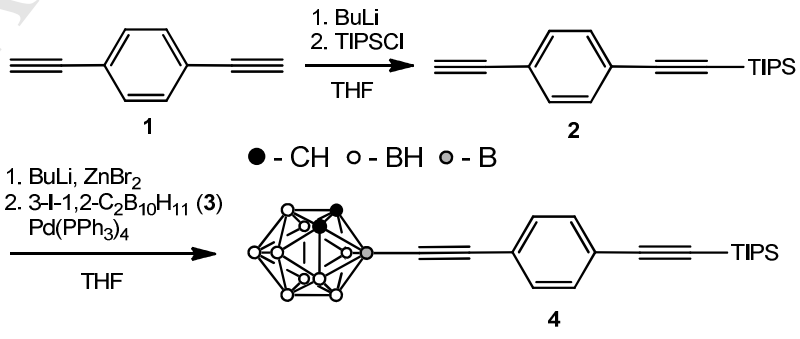
The results of the preliminary spectroscopic studies and calculations were encouraging, and based on these results, the synthesis of the target nickelacarboranes was initiated.

2.2. Synthesis of the target nickelacarboranes

Initially, the preparation of two *nido*-carboranes was envisioned, each bearing a dye molecule attached to the cage through the linker at position B(3). Next, an equimolar mixture of these two compounds would be used in the reaction with $Ni(acac)_2$ in the presence of an appropriate base. This reaction would yield a mixture of three complexes: a mixed-ligand target compound and two symmetrical nickelacarboranes. The separation of the mixed-ligand complex from the by-products was to be achieved chromatographically.

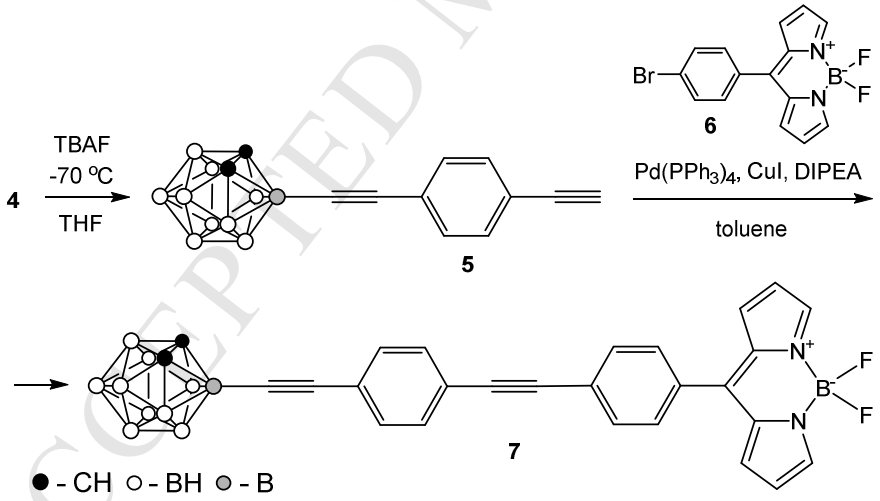
The synthesis of the *closo*-carborane complexes began from the preparation of the mono-protected 1,4-diethynylbenzene **2** (Scheme 1). The organozinc derivative of **2** prepared by deprotonation of the free ethynyl group was cross-coupled with 3-iodo-1,2-dicarba-*closo*-dodecaborane (**3**) in the presence of the $Pd(PPh_3)_4$ catalyst. Compound **4** was isolated in very good yield and characterized by a variety of spectroscopic techniques (see Experimental).

Scheme 1. Synthesis of protected *closo*-carborane **4**.



The protective group was removed using TBAF at -70 °C to avoid deboronation of the carborane cage. The product **5** (Scheme 2) was introduced into a cross-coupling reaction with 8-(4′-bromophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene **6** in the presence of N,N-diisopropylethylamine (DIPEA) and $Pd(PPh_3)_4$ catalyst according to the Sonogashira protocol. Compound **7** was isolated chromatographically and characterized by multinuclear NMR spectroscopy. The ^{1}H NMR spectrum of **7** showed the presence of the *ortho*-carborane fragment (characteristic broad singlet at 3.78 ppm and a broad multiplet in the range 2.9 – 1.6 ppm, which correspond to the cage C–H and B–H resonances, respectively), two *para*-phenylene groups of the linker and the BODIPY fragment. In the ^{11}B NMR spectrum of **7**, a 2:1:1:2:4 pattern in the 0 – (-20) ppm range characteristic of 3-substituted *closo*-*ortho*-carboranes was observed, along with an additional triplet signal at 0.1 ppm ($J_{B–F}$ 28 Hz) from the BF_2-group of the BODIPY. In the $^{19}F\{^{1}H\}$ NMR spectrum of **7**, a characteristic quartet ($J_{F–11B}$ 28 Hz) overlapping with a lower intensity septet ($J_{F–10B}$ 7.5 Hz) was observed at -145 ppm. HRMS data confirmed the composition of the compound.

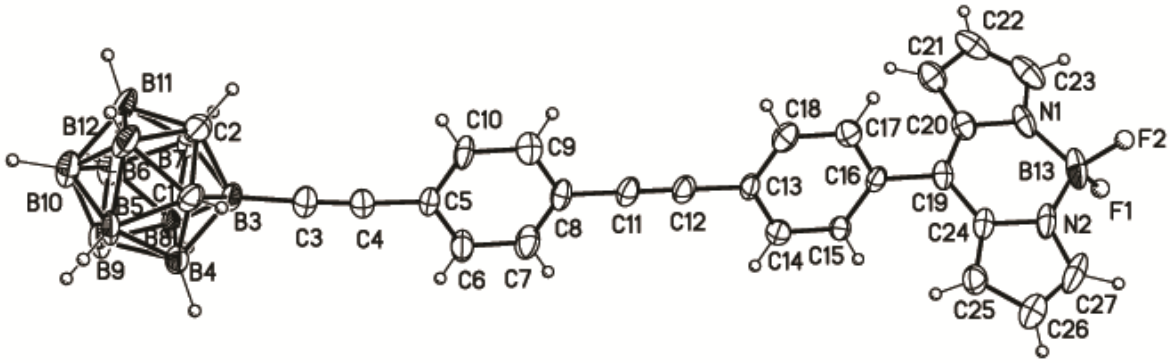
Scheme 2. Synthesis of *closo*-carborane **7**.



We were able to obtain single crystals of **7** and study its structure by X-ray diffraction (Figure 3). The structure of **7** was found to contain a *closo ortho*-carborane fragment substituted at position B(3). The substituent contained two alternating ethynyl and two *para*-phenylene fragments. The *para*-position of the terminal phenyl ring was connected to a BODIPY dye consisting of two pyrrole rings connected through a carbon atom in the α-positions and coordinated to a BF_2-fragment via the nitrogen atoms of the rings. The interatomic distances within the carborane, the linker and the dye were in the normal range. The distance between the substituted cage boron atom B(3) and the boron atom B(13) of the BF_2 fragment

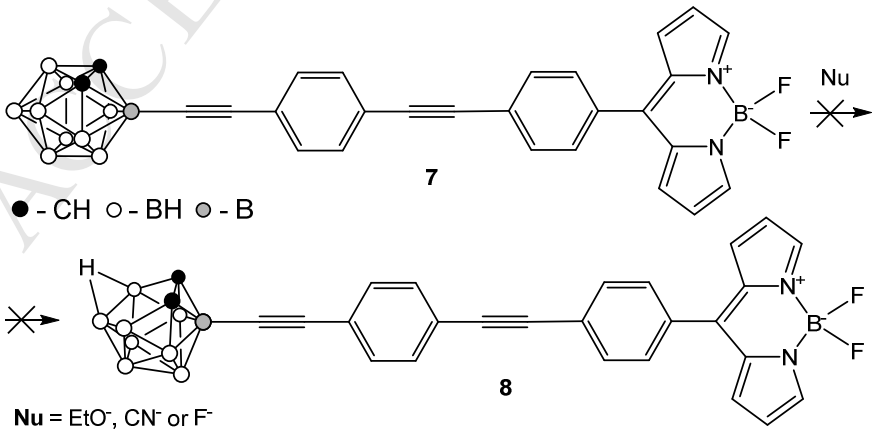
of the dye was determined to range from 18.092 to 18.390 Å for different crystallographically unique units (molecules) of **7**.

Figure 3. ORTEP representation of **7**, drawn at the 40% probability level. Only one of three crystallographically unique molecules is shown.



Unfortunately, attempts to synthesize *nido*-carborane **8** from *closo*-carborane **7** in satisfactory yields were unsuccessful (Scheme 3). Standard methods [16] such as the use of NaOH/EtOH or TBAF/THF led to the decomposition of the BODIPY fragment. Attempts to use other systems, such as NaCN/EtOH, KF(dry)/18-crown-6/DCM, KF(wet)/18-crown-6/DCM, CsF/TBABr/DCM, or Deoxo-Fluor/DCM, were unsuccessful and resulted in only trace amounts of the target *nido*-carborane **8**.

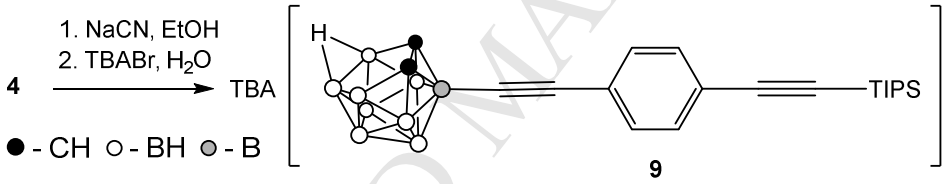
Scheme 3. Synthesis of *nido*-carborane **8**.



Based on the obtained results, the synthetic approach was modified slightly. Instead of constructing the target nickelacarborane from the *nido*-carborane compounds bearing fluorescent dyes with subsequent separation of the nickelacarborane mixture, the revised approach involved first preparing and isolating the mixed ligand nickelacarborane complex bearing modified linkers and then attaching the dye molecules at the end of the process.

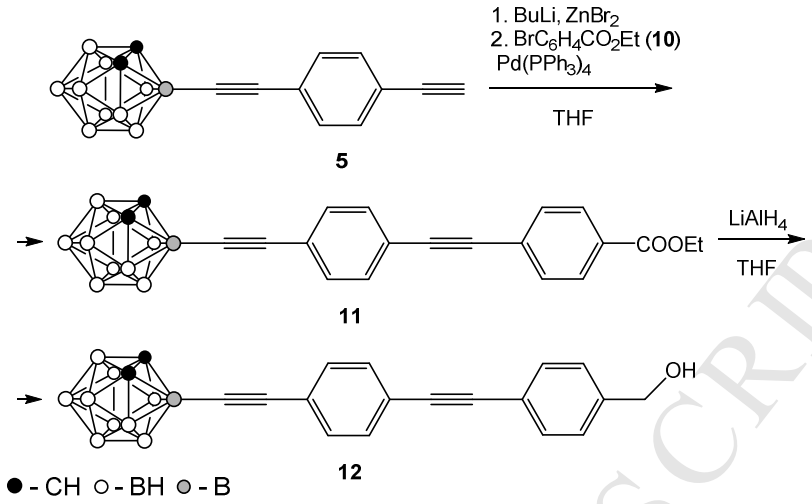
The first *nido*-carborane was prepared by deboronation of the *closo*-carborane **4** in mild conditions [17] to avoid TIPS-deprotection (Scheme 4). Similar to the spectra of **4**, the ^{1}H NMR and ^{13}C{^{1}H} spectra of compound **9** contained characteristic signals of the TIPS group (see Experimental). The ^{11}B NMR spectrum of **9** contained characteristic *nido*-carborane 2:2:1:2:1:1 intensity pattern in the range 0 – (-40) ppm as well as a unique non-splitting resonance at -18.2 ppm, which corresponds to the substituted boron atom B(3). HRMS data confirmed the suggested composition of **9**.

Scheme 4. Synthesis of *nido*-carborane **9**.



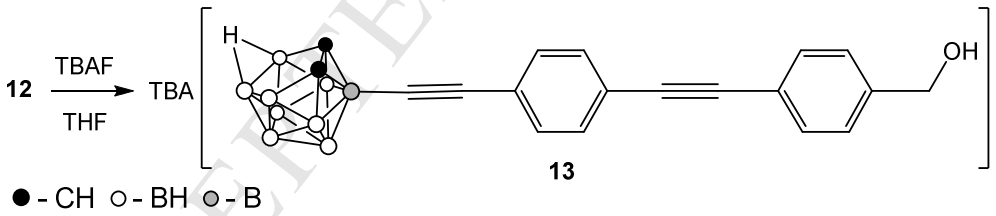
For the preparation of the second *nido*-carborane, the *closo*-carborane **5** containing a terminal acetylene functionality was introduced into a cross-coupling reaction with ethyl 4-bromobenzoate (**10**) to produce *closo*-carborane **11** (Scheme 5). $LiAlH_4$ in THF reduced the ester group in the latter compound with the formation of the corresponding benzyl alcohol in the target *closo*-carborane **12**. In the ^{1}H NMR spectrum of **12**, three groups of signals were observed. The *ortho*-carborane fragment revealed a characteristic broad singlet at 3.76 ppm and a broad multiplet in the range 2.9 – 1.7 ppm corresponding to the cage C–H and B–H resonances, respectively. The signals of the linker were observed in the aromatic region as two pairs of doublets of the two *para*-phenylene groups. The benzyl alcohol showed two signals at 4.73 and 1.69 ppm from the benzyl CH_2-group and OH-group, respectively. The ^{11}B NMR spectrum revealed a standard 2:1:1:3:3 signal pattern for 3-substituted *ortho*-carboranes with a non-splitting resonance of the substituted boron atom B(3) at -11.2 ppm. HRMS data confirmed the suggested composition of **12**.

Scheme 5. Synthesis of *closo*-carborane **12**.



Closo-carborane **12** was deboronated under standard conditions using TBAF in THF at reflux temperature, and the product **13** was isolated in excellent yield by water treatment of the evaporated reaction mixture and filtration of the precipitate (Scheme 6). Product **13** was characterized based on multinuclear NMR spectroscopy and HRMS data (see Experimental).

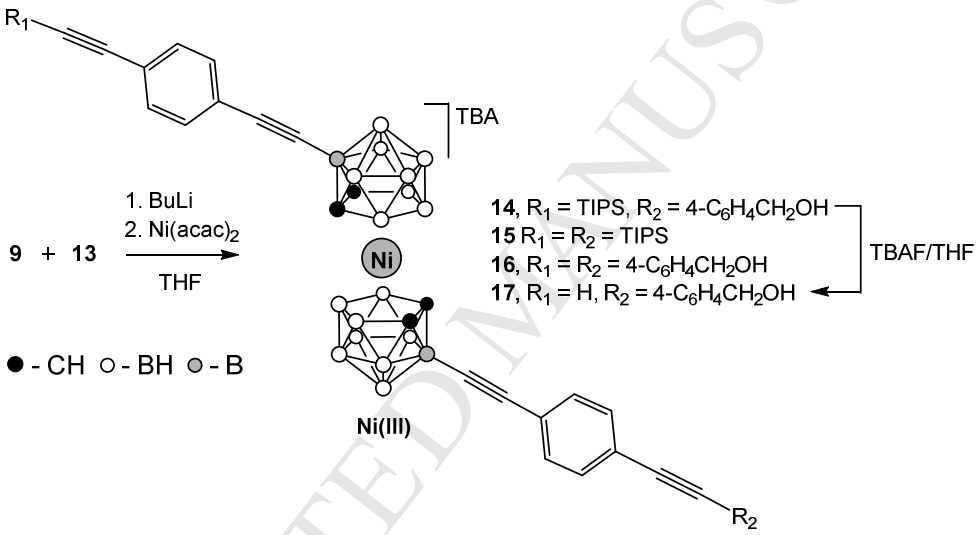
Scheme 6. Synthesis of *nido*-carborane **13**.



The synthesis of the mixed-ligand Ni(III) nickelacarborane **14** was achieved by the reaction of the equimolar mixture of the tetrabutylammonium salts of *nido*-carboranes **9** and **13** with excess butyllithium and then with $Ni(acac)_2$ in THF (Scheme 7). The separation of nickelacarborane mixtures can often be very difficult and generally results in poor yields of the individual compounds. However, the presence of the hydroxyl group facilitated the separation process for the mixture of complexes **14–16**. After addition of butyllithium, the hydroxyl group is deprotonated along with *nido*-carborane anions. After the addition of $Ni(acac)_2$, all three complexes initially form dianionic Ni(II) compounds. Therefore, complex **14** exists in the reaction mixture as a trianion and complexes **15** and **16** as a di- and tetra-anions, respectively. The charge of these species determines their solubility in THF: complex **15** appeared to be the most soluble

and complex **16** the least soluble, whereas complex **14** had limited solubility. Removing the supernatant from the heterogeneous reaction mixture and then washing the precipitate with a small amount of anhydrous THF achieved the initial separation. The supernatant and the THF wash contained complex **15** and a small amount of complex **14**, whereas the precipitate contained only complexes **14** and **16**. After air oxidation and methanol quenching, pairs of complexes were separated chromatographically without complications. In the next step, compound **14** was deprotected by TBAF in THF to form the paramagnetic Ni(III) complex **17** in excellent yield (Scheme 7).

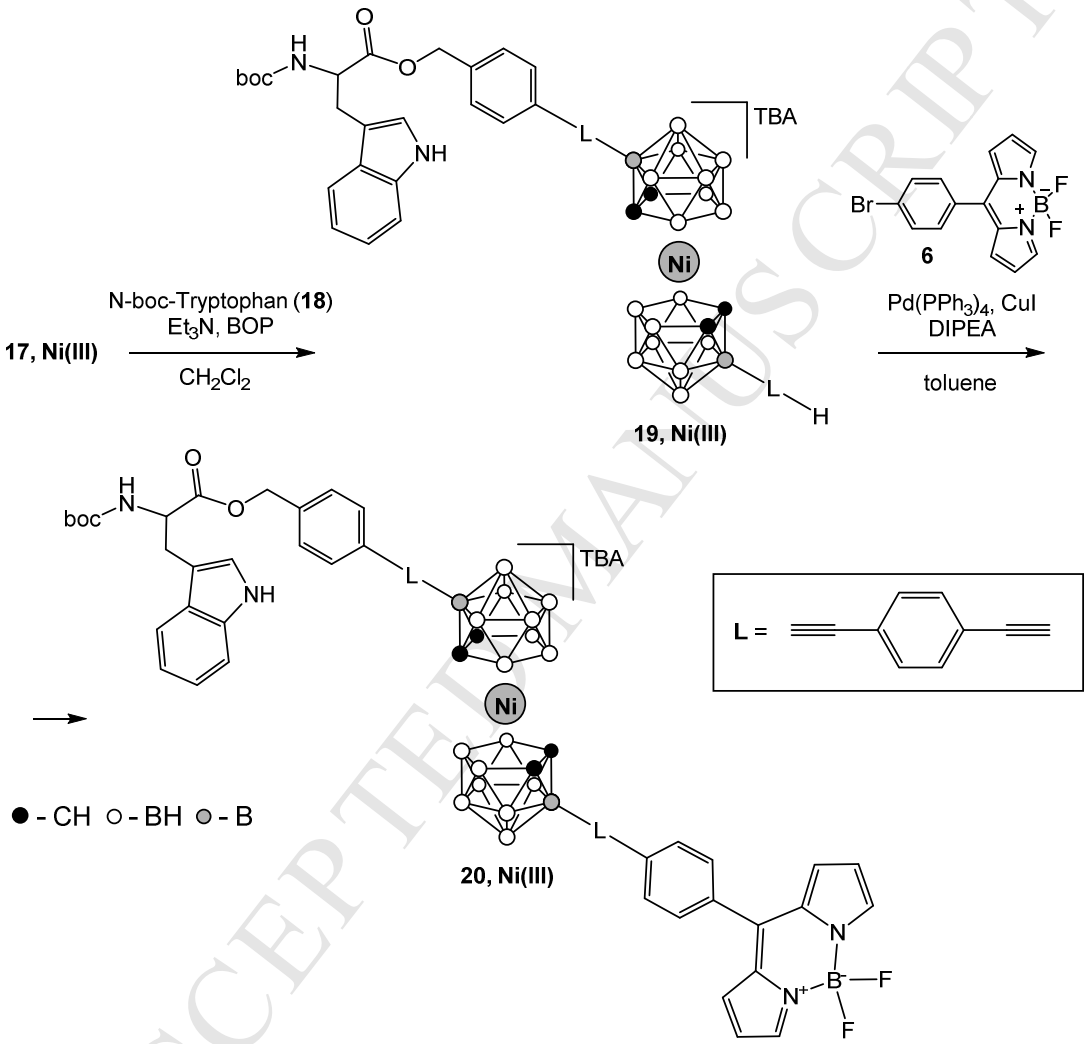
Scheme 7. Synthesis of mixed-ligand nickelacarboranes.



In the final step, the heterodisubstituted nickelacarborane **17** was functionalized by the two components of the FRET couple. First, N-boc-tryptophan (**18**) was esterified by the benzyl alcohol group of **17** under mild conditions using BOP (Castro's reagent) in the presence of triethylamine in dichloromethane in 76% yield (Scheme 8). Second, the isolated and purified complex **19** was introduced into the cross-coupling reaction with 8-(4′-bromophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene **6** in the presence of $Pd(PPh_3)_4$ catalyst according to the Sonogashira protocol. Although compound **20** is paramagnetic, it was characterized by multinuclear NMR spectroscopy and HRMS. In the ^{1}H NMR spectrum of **20**, all signals from linkers and dyes were observed except for the two pairs of protons of the phenyl rings closest to the metallacarborane core. Assignment of the signals in the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **20** was based on the ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC spectra (see Experimental). In the ^{11}B NMR spectrum of **20**, along with a set of very broad resonances of *nido*-carboranes in the range 20 – (-60) ppm, a characteristic triplet resonance of the BF_2-group was observed at 0.1 ppm. A quartet resonance

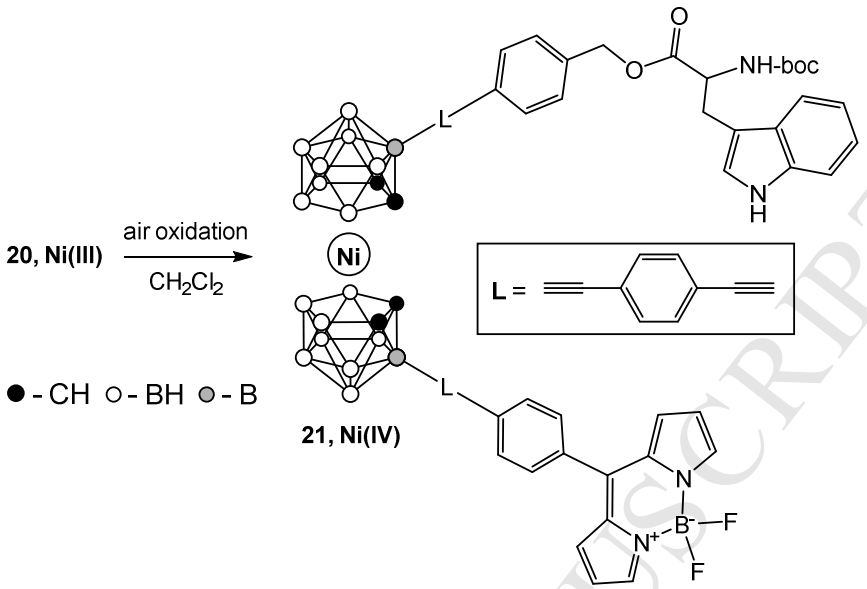
at -145.2 ppm ($J_{F–B}$ 28 Hz) was also observed in the $^{19}F\{^{1}H\}$ spectrum of **20**. The composition of the compounds was also confirmed by the HRMS data.

Scheme 8. Synthesis of the target Ni(III) nickelacarborane **20**.



Oxidation of nickelacarboranes from formal Ni(III) to Ni(IV) oxidation states is usually achieved by the treatment of the former with ferric chloride in polar organic solvents, such as acetonitrile or methanol [18]. However, all attempts to quantitatively oxidize complex **20** by ferric chloride led to its decomposition. Good yields of **21** were achieved by air oxidation of solutions of **20** in dichloromethane (Scheme 9) with subsequent chromatographic purification of the product **21** (see Experimental).

Scheme 9. Synthesis of the target Ni(IV) nickelacarborane **21**.

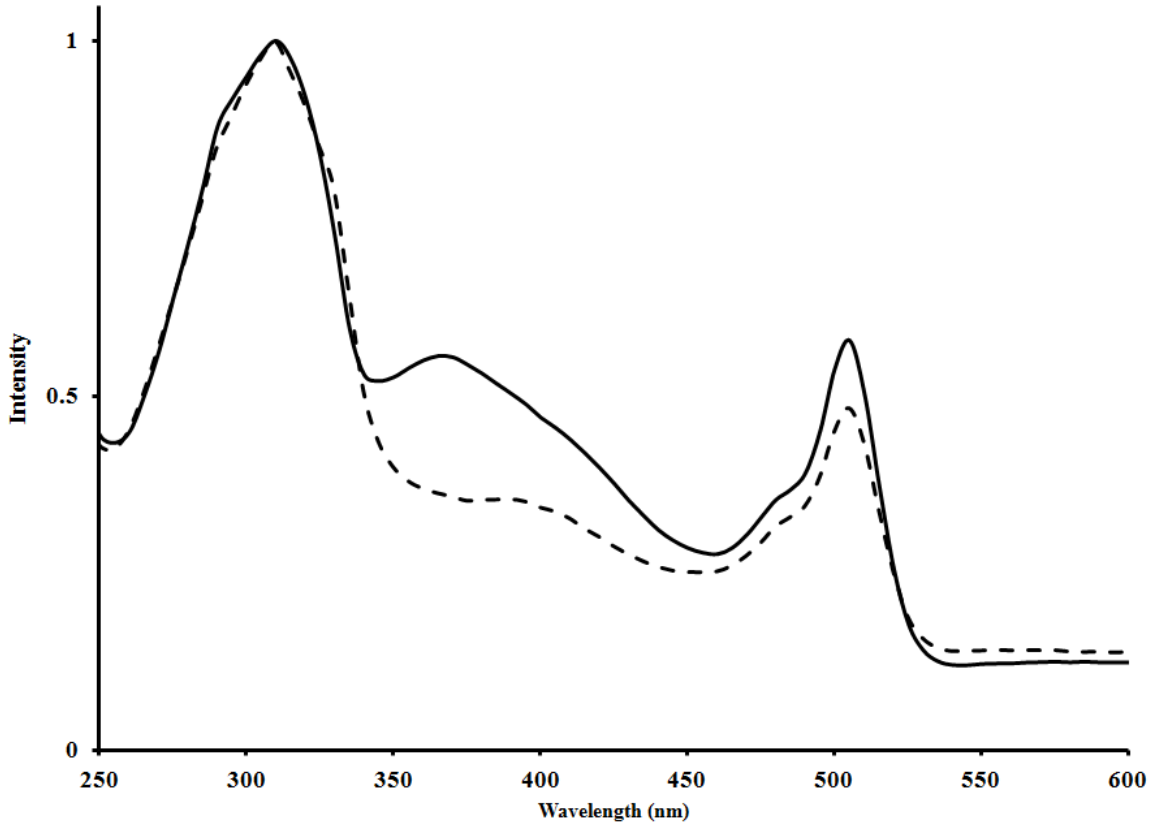


The NMR spectra of **20** and **21** differ only slightly. For example, all resonances from the *para*-phenylene fragments of the linkers were observed in the normal range for aromatic protons (7 – 8 ppm) in the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **21**. Additionally, both the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of **21** lacked signals corresponding to the TBA counter ion. In the ^{11}B NMR spectrum, resonances of **21** were observed in a more compact manner; for the Ni(IV) compounds, these resonances were found in the characteristic range 20 – (-20) ppm. The chemical shifts and $^{11}B–^{19}F$ spin coupling constants of the signals corresponding to the BF_2-fragment persisted both in the ^{11}B and $^{19}F\{^{1}H\}$ NMR spectra of **21** (see Experimental). HRMS data for **21** clearly confirmed the suggested composition of the compound.

*2.3. Preliminary fluorescence study of the nickelacarboranes **20** and **21***

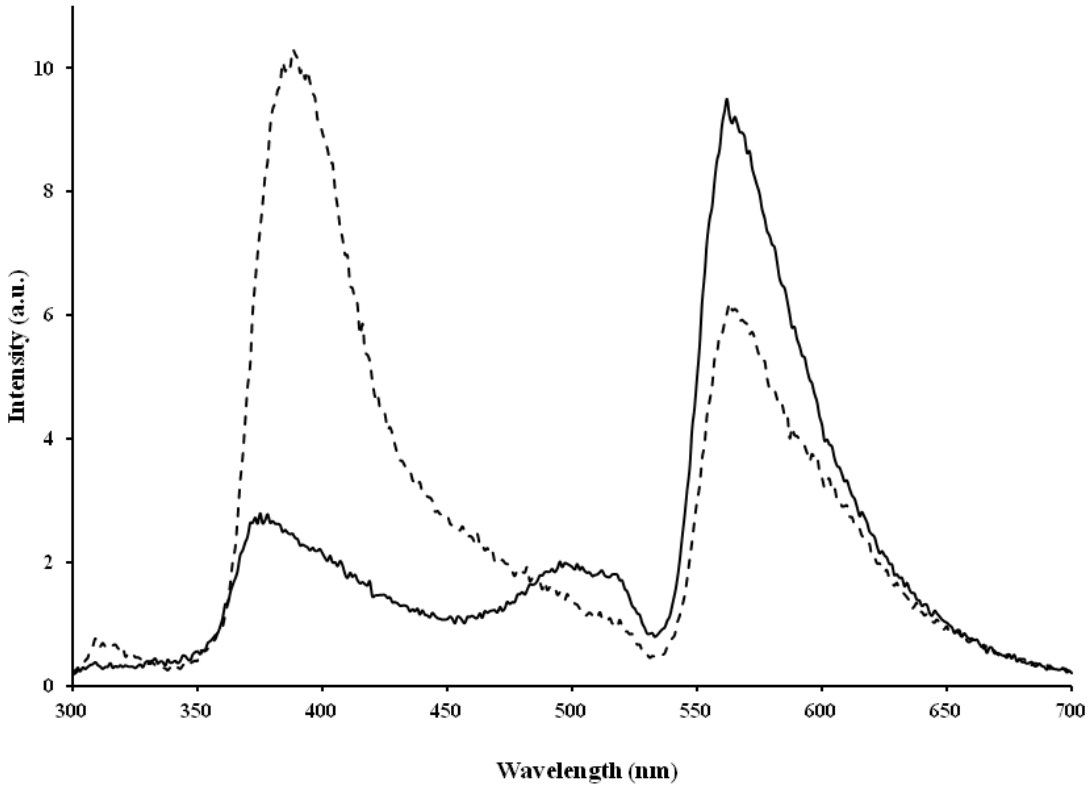
The absorption and fluorescence spectra of complexes **20** and **21** were studied. Figure 4 shows the absorption spectra of complexes **20** and **21** in CH_2Cl_2 at room temperature. The spectra reveal characteristic absorption bands for all parts of the molecules. The broad band centered at approximately 300 nm corresponds to the absorption of tryptophan and the linker in the case of compound **20** and tryptophan, the linker, and the Ni(IV) nickelacarborane core in case of compound **21**. A broad band in the 350 – 400 nm region corresponds to the first absorption of BODIPY in the case of **21** and BODIPY and the Ni(III) nickelacarborane core in the case of **20**. Both spectra show a band at approximately 500 nm, which corresponds to the second absorption of BODIPY.

Figure 4. Absorption spectra of complexes **20** (solid line) and **21** (dashed line) in CH_2Cl_2 (1×10^{-5} M, 293 K).



Although the absorption band of tryptophan cannot be clearly distinguished in the spectra of **20** and **21**, the absorption wavelength of free tryptophan at 280 nm was chosen for the fluorescence study. The fluorescence spectra of complexes **20** and **21** are shown in Figure 5. In the emission spectrum of the formal Ni(III) complex **20**, the intense BODIPY fluorescence band was centered at 532 nm. Two additional bands were present in the spectrum: a lower intensity band at 345 nm, which was interpreted as the residual fluorescence of tryptophan, and a broad emission in the range 450 – 500 nm, which was difficult to assign. The emission spectrum of the Ni(IV) complex **21** showed only two bands. The more intense band centered at 359 nm can also be assigned as the residual fluorescence of tryptophan, and the band at 532 nm is assigned to BODIPY. The presence of the BODIPY emission band at 532 nm in the spectra of both complexes can only be explained by fluorescent resonance energy transfer in solution for both the Ni(III) and Ni(IV) compounds of the studied system.

Figure 5. Fluorescence spectra of complexes **20** (solid line) and **21** (dashed line) in CH_2Cl_2 (7.5×10^{-5} M, 293 K, λ_{ex} 280 nm).



Two possible explanations for the observed emission spectra can be suggested. First, the Ni(III) compound **20** may exist in solution mostly as an intermediate *gauche* conformation between the *cis* and *trans* conformations. Recently, it was demonstrated [19] that bis(dicarbollyl) complexes of Ni(III) bearing massive substituents in positions B(6) and B(6′) exist in acetonitrile solutions at room temperature as almost equimolar mixtures of *trans* and *gauche* conformers. If the same is true for the solution of **20**, then the distance between the components of the FRET couple could be less than 38 Å, which would result in fluorescent resonance energy transfer between the fluorophores. Second, energy transfer between the fluorophores in the Ni(III) compound may occur through the linkers and the nickelacarborane core. A similar energy transfer was previously observed in a bichromophoric complex containing two different iridium-based fluorescent dyes connected to the cage carbon atoms of *para*-carborane through 1,4-diethynylbenzene linkers [20]. This type of energy transfer could theoretically occur for the Ni(IV) complex **21** if it competes with the FRET process.

Although conclusions regarding the conformations of the nickelacarborane core cannot be drawn directly from the preliminary spectroscopic study of complexes **20** and **21**, the prepared nickelacarborane

complexes appear to be very attractive for further fluorescence studies using various solvents and temperatures and as a subject of molecular orbital calculations. The system design can also be varied to study the effect of the nature of the linkers and metal on the spectroscopic behavior of the compounds.

3. Conclusions

Two bichromophoric nickelacarborane complexes containing a tryptophan/BODIPY FRET couple attached to a metallacarborane core by rigid linkers were modeled. The compounds were successfully prepared via a multistep organic/organometallic synthesis and characterized by various analytical techniques. The initial spectroscopic study showed that fluorescent resonance energy transfer occurs for both Ni(III) and Ni(IV) compounds, hindering their unambiguous conformational assignment.

4. Experimental

4.1. Materials

All reactions were performed in an argon atmosphere using standard Schlenk-line and glove-box techniques. Triisopropylsilyl chloride (TIPSCl), 1,4-diethynylbenzene, anhydrous $ZnBr_2$, *n*-butyllithium (BuLi, 2.5 M solution in hexane), copper(I) iodide (CuI), nickel acetylacetonate [$Ni(acac)_2$], di-*tert*-butyl dicarbonate (Boc_2O), sodium cyanide (NaCN), tetrabutylammonium bromide (TBABr), lithium aluminum hydride ($LiAlH_4$), triethylamine (Et_3N), *N*,*N*-diisopropylethylamine (DIPEA) were purchased from Aldrich and used as received. (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) was purchased from Fluka. Potassium carbonate (K_2CO_3) and sodium hydroxide (NaOH) were purchased from Fisher. Ethyl 4-bromobenzoate, L(-)-tryptophan, boron trifluoride etherate ($BF_3 \cdot Et_2O$) were purchased from Acros Organics and used as received. Tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] was purchased from Strem Chemicals. Tetrabutylammonium fluoride (TBAF) was purchased from TCI America as a 1 M solution in THF.

Tetrahydrofuran (THF) was distilled in an argon atmosphere from sodium benzophenone ketyl before use. Dichloromethane (CH_2Cl_2), toluene, triethylamine, and DIPEA were distilled in an argon atmosphere over CaH_2 prior to use. Column chromatography was performed in air using Sorbtech silica gel (60 Å, 63–200 μm). Thin-layer chromatography was performed on Merck pre-coated glass plates (silica 60 F254) using a palladium stain solution for spot development.

((4-Ethynylphenyl)ethynyl)triisopropylsilane (**2**) was prepared according to a previously published procedure [21]. 3-Iodo-1,2-dicarba-*closo*-dodecaborane (**3**) was prepared according to a previously published procedure [22] and azeotropically dried with benzene prior to use. 8-(4′-Bromophenyl)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene **6** was prepared according to a previously

published procedure [23]. N-boc-Tryptophan was also prepared according to a previously published procedure [24].

4.2. Physical measurements

The ^{1}H, ^{11}B, $^{11}B\{^{1}H\}$, and ^{13}C NMR spectra and all 2D NMR spectra were recorded on Bruker Avance-400 and Avance-500 NMR spectrometers. ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were referenced to the residual solvent peak. Boron NMR spectra were referenced to 15% $BF_3{\cdot}Et_2O$ in $CDCl_3$ set as 0 ppm. Fluorine NMR spectra were referenced to $CFCl_3$ set as 0 ppm. Chemical shifts are reported in ppm and coupling constants in Hz. Mass spectra were obtained on an ABI QSTAR and Mariner Biospectrometry Workstation by PerSeptive Biosystems. IR spectra, UV-Vis spectra, and fluorescence spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer, Varian Cary 50 UV-Vis spectrophotometer, and Varian Cary Eclipse fluorescence spectrophotometer, respectively. Melting points were measured in sealed capillaries using an SRS OptiMelt apparatus.

4.3. Descriptions of syntheses and compound characterization

*4.3.1. Synthesis of closo-carborane **4***

To a cooled (-70 °C) solution of **2** (0.355 g, 1.25 mmol) in 5 mL of THF was added 0.5 mL (0.2 mmol) of 2.5 M BuLi in hexane, and the reaction mixture was stirred at -70 °C for 30 min. A solution of anhydrous $ZnBr_2$ (0.324 g, 1.44 mmol) in 2 mL of THF was added to the reaction mixture, and the mixture was then stirred at room temperature for 15 min. Next, a solution of **3** (0.260 g, 0.96 mmol) and $Pd(PPh_3)_4$ (55.0 mg, 4.8×10^{-5}mol) in 3 mL of THF was added to the reaction mixture, and the resulting solution was kept at reflux temperature for 20 h. The reaction mixture was quenched with water and extracted with EtOAc (3×5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Purification of the product was achieved by flash chromatography in hexane to give **4** (0.278 g, 79%) as a pale-yellow glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 4H, C_6H_4), 3.76 (br s, 2H, C_{cb}–H), 2.94–1.53 (m, 9H, B–H), 1.13 (br s+m, 21H, TIPS). ^{11}B NMR (128 MHz, $CDCl_3$): δ -2.6 (d, *J* 151, 2B), -8.7 (d, *J* 159, 1B), -11.4 (1B), -12.7 (d, *J* 159, 3B), -13.5 (3B). $^{13}C\{^{1}H\}$ (100 MHz, $CDCl_3$): δ 132.35, 132.32, 124.8, 121.8, 106.6, 94.1, 57.6 (C_{cb}–H), 19.0 (TIPS), 11.7 (TIPS). HRMS (TIS–): *m*/*z* 424.4505 $[M]^-$ (calcd for $C_{21}H_{36}B_{10}Si$ 424.3589). R_f = 0.25 (hexanes–EtOAc, 5:1). IR (KBr, cm^{-1}): 3071 (C_{cb}–H), 2938, 2890, 2863 (C–H), 2604 (br. BH), 2197, 2154 (C≡C).

*4.3.2. Synthesis of closo-carborane **5***

To a solution of **4** (0.500 g, 1.17 mmol) in 10 mL of THF was added 1 M TBAF in THF (1.17 mL, 1.17 mmol) at -70 °C. The reaction mixture was allowed to warm to room temperature for 30 min, and then 20 mL of water was added. The reaction mixture was extracted with ether (3×10 mL). Combined ethereal layers were dried over Na_2SO_4 and evaporated. The residue was treated by column chromatography using an EtOAc/hexane mixture (10:90) as the eluent. After evaporation and drying in vacuum, compound **5** was obtained as a light-brown solid (0.301 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.42 (m, 4H, C_6H_4), 3.76 (br s, 2H, C_{cb}–H), 3.19 (s, 1H, ≡C–H), 2.80–1.75 (m, 9H, B–H). ^{11}B NMR (160 MHz, $CDCl_3$): δ -2.4 (d, *J* 149, 2B), -8.5 (d, *J* 152, 1B), -11.1 [s, 1B, B(3)], -12.5 (d, *J* 167, 2B), -13.5 (d, 4B). ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 132.45, 132.44, 123.4, 122.5, 83.2, 79.9, 57.5 (C_{cb}–H). HRMS (APCI–): *m*/*z* 268.2034 $[M]^-$ (calcd for $C_{12}H_{16}B_{10}$ 268.2256). m.p. 126–128 °C. R_f = 0.50 (hexanes–EtOAc, 10:1). IR (KBr, cm^{-1}): 3285 (≡C–H), 3065 (C_{cb}–H), 2922 (C–H), 2652, 2611, 2581, 2572, 2558 (B–H), 2194, 2101 (C≡C).

*4.3.3. Synthesis of closo-carborane **7***

A mixture of **5** (0.200 g, 0.746 mmol), **6** (0.258 g, 0.746 mmol), CuI (0.007 g, 0.037 mmol), $Pd(PPh_3)_4$ (0.043 g, 0.037 mmol), and DIPEA (0.195 mL, 1.12 mmol) in 10 mL of anhydrous toluene was stirred at 40 °C for 20 h. Next, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and 1 M $NaHSO_4$ (15 mL). The dichloromethane layer was dried over Na_2SO_4 and co-evaporated with 10 mL of silica. Treatment of the reaction mixture by column chromatography using an EtOAc/hexane mixture (15:85) as the eluent gave after evaporation and drying in vacuum compound **7** (0.271 g, 68%) as a deep-red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 2H, BODIPY-pyrrole), 7.66 (d, 2H, *J* 8.2, linker-C_6H_4), 7.58 (d, 2H, *J* 8.4, linker-C_6H_4), 7.52 (d, 2H, *J* 8.6, linker-C_6H_4), 7.50 (d, 2H, *J* 8.6, linker-C_6H_4), 6.93 (d, 2H, *J* 4.1, BODIPY-pyrrole), 6.56 (dd, 2H, J_1 4.3, J_2 1.4, BODIPY-pyrrole), 3.78 (s, 2H, C_{cb}–H), 2.94-1.61 (m, 9H, B–H). ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.12 (t, 1B, $J_{B–F}$ 28, BF_2), -2.6 (d, 2B, *J* 152), -8.5 (d, 1B, *J* 152), -11.1 [s, 1B, B(3)], -12.7 (d, *J* 163, 2B), -13.1 (d, 4B). {^{1}H} (100 MHz, $CDCl_3$): δ 146.4 (BODIPY-pyrrole), 144.5 (linker-C_6H_4), 134.8 (BODIPY-pyrrole), 133.9, 132.4, 131.8, 131.7 (linker-C_6H_4), 131.5 (BODIPY-pyrrole), 130.7, 125.8, 123.7, 122.2 (linker-C_6H_4), 118.8 (BODIPY-pyrrole), 91.6, 90.8 (–C≡C–), 57.4 (C_{cb}–H). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -145.0 (q, $J_{F–B}$ 28). HRMS (ES–): *m*/*z* 533.3600 $[M-H]^-$ (calcd for $C_{27}H_{25}B_{11}F_2N_2$ 534.3082). m.p. 260–262 °C (decomp.). R_f = 0.45 (hexanes–EtOAc, 7:3). IR (KBr, cm^{-1}): 3070 (C_{cb}–H), 2959, 2923, 2852 (C–H), 2596 (B–H), 2197 (C≡C), 1557 (B–F).

*4.3.4. Synthesis of nido-carborane **9***

To a solution of **4** (2.3 g, 5.42 mmol) in 50 mL of EtOH was added NaCN (1.3 g, 27.12 mmol), and the reaction mixture was kept at reflux temperature for 20 h. The solvent was removed under reduced pressure, and the residue was dissolved in 5 mL of water, after which TBABr (2.27 g, 7.05 mmol) was added. The precipitate formed was filtered on a fine-porosity glass filter and washed with water (3×5 mL) and Et_2O (3×5 mL) to give after drying under vacuum over P_2O_5 the product **9** (3.26 g, 92%) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.46–7.43 (m, 2H, C_6H_4), 7.39–7.37 (m, 2H, C_6H_4), 3.49 (m, 8H, TBA), 2.59–(-0.29) (m, 8H, B–H), 1.88 (br m, 10H, C_{cb}–H+TBA), 1.48 (m, 8H, TBA), 1.18 (s+m, 21H, TIPS), 1.02 (t, 12H, ^3J 7.2, TBA), -2.62 (br m, 1H, B–H–B). ^{11}B NMR (128 MHz, acetone-d_6): δ -10.6 (d, J 142, 2B), -16.3 (d, J 139, 2B), -18.2 [s, 1B, B(3)], -21.3 (d, J 151, 2B), -33.7 (br d, J 135, 1B), -36.9 (d, J 144, 1B). ^{13}C{^{1}H} (100 MHz, acetone-d_6): δ 133.3, 133.2, 127.2, 123.5, 108.7, 92.9, 60.2 (TBA), 47.6 (C_{cb}–H), 25.2 (TBA), 21.1 (TBA), 19.7 (TIPS), 14.6 (TBA), 12.8 (TIPS). HRMS (TIS–): m/z 414.3400 $[M+H]^-$ (calcd for $C_{21}H_{35}B_9Si$ 413.3381). IR (KBr, cm^{-1}): 3034 (C_{cb}–H), 2961, 2942, 2866 (C–H), 2523 (B–H), 2153 (C≡C).

*4.3.5. Synthesis of closo-carborane **11***

To a solution of **5** (2.45 g, 9.17 mmol) in 50 mL of THF at -70 °C was added 3.7 mL (9.25 mmol) of 2.5 M BuLi in hexane, and the reaction mixture was stirred at -70 °C for 30 min. Anhydrous $ZnBr_2$ (2.48 g, 11.0 mmol) was dissolved in 20 mL of THF and added dropwise to the reaction mixture at -70 °C. The reaction mixture was stirred at -70 °C for 15 min and then allowed to warm to room temperature. A solution of ethyl 4-bromobenzoate (**10**, 2.73 g, 11.9 mmol) and $Pd(PPh_3)_4$ (0.529 g, 0.450 mmol) in 25 mL of THF was added to the reaction mixture, and the resulting solution was kept at reflux temperature for 24 h. The reaction mixture was quenched with water and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The compound was purified by column chromatography on silica gel using an EtOAc gradient (0→7%) in hexane. After drying in vacuum, compound **11** (2.93 g, 77%) was isolated as a pale-yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 2H, C_6H_4), 7.58 (m, 2H, C_6H_4), 7.51-7.46 (m, 4H, C_6H_4), 4.39 (q, 2H, ^3J 7.2, CH_2-O), 3.76 (br s, 2H, C_{cb}–H), 2.93–1.78 (m, 9H, B–H), 1.40 (t, 3H, ^3J 6.8, CH_3). ^{11}B NMR (128 MHz, $CDCl_3$): δ -2.4 (d, J 157, 2B), -8.6 (d, J 155, 1B), -11.3 [s, 1B, B(3)], -12.6 (d, J 168, 3B), -13.7 (3B). ^{13}C{^{1}H} (100 MHz, $CDCl_3$): δ 166.4 (O–C=O), 132.5, 132.0, 131.8, 130.5, 129.9, 127.7, 124.0, 122.3, 91.8, 91.4, 61.5 (CH_2-O), 57.6 (C_{cb}–H), 14.72 (CH_3). HRMS (APCI-): m/z 416.2234 $[M]^-$ (calcd for $C_{21}H_{24}B_{10}O_2$ 416.2779). m.p. 188–190 °C. R_f = 0.50 (hexanes–EtOAc, 5:1). IR (KBr, cm^{-1}): 3043 (C_{cb}–H), 2980 (C–H), 2591 (B–H), 2195 (C≡C), 1703 (C=O).

*4.3.6. Synthesis of closo-carborane **12***

To a suspension of $LiAlH_4$ (0.32 g, 8.45 mmol) in 100 mL of THF at 0 °C was added a solution of **11** (2.93 g. 7.04 mmol) in 50 mL of THF, and the suspension formed was stirred at room temperature for 1.5 h. The reaction mixture was quenched by water (dropwise, slowly) at 0 °C until gas evolution ceased, and the mixture was then passed through a SiO_2/Na_2SO_4/celite plug. After evaporation, the compound was isolated by column chromatography on silica gel using an EtOAc/hexane mixture (20:80) as the eluent. After evaporation and drying in vacuum, compound **12** (2.51 g, 95%) was obtained as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.44 (m, 6H, C_6H_4), 7.36 (m, 2H, C_6H_4), 4.73 (d, 2H, ^3J 6.0, CH_2Ph), 3.76 (br s, 2H, C_{cb}–H), 2.95–1.70 (m, 9H, B–H), 1.69 (t, 1H, ^3J 6.0, –OH). ^{11}B NMR (128 MHz, $CDCl_3$): δ -2.5 (d, *J* 149, 2B), -8.6 (d, *J* 149, 1B), -11.2 (s, 1B), -12.6 (d, *J* 159, 3B), -13.5 (3B). $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ 141.7, 132.5, 132.1, 131.8, 127.2, 124.6, 122.4, 121.8, 92.1, 89.1, 65.2, 57.6 (C_{cb}–H). HRMS (APCI–): *m*/*z* 374.1841 $[M]^-$ (calcd for $C_{19}H_{22}B_{10}O$ 374.2673). m.p. 188–190 °C. R_f = 0.20 (hexanes–EtOAc, 5:1). IR (KBr, cm^{-1}): 3446 (OH), 3069 (C_{cb}–H), 2960, 2931, 2872 (C–H), 2528 (B–H), 2211 (C≡C).

*4.3.7. Synthesis of nido-carborane **13***

To a solution of **12** (0.500 g, 1.33 mmol) in 4 mL of THF was added 8 mL of a 1 M TBAF in THF (8.00 mmol), and the reaction mixture was kept at reflux temperature for 2 h. The solvent was removed under reduced pressure, and 5 mL of water was added to the residue. The precipitate formed was filtered on a fine-porosity glass filter and washed with water (3×5 mL) and Et_2O (3×5 mL) to give after drying under vacuum over P_2O_5 the product **13** (0.790 g, 97%) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.54 (m, 2H, C_6H_4), 7.50 (m, 2H, C_6H_4), 7.45–7.41 (m, 4H, C_6H_4), 4.69 (s, 2H, Ph–CH_2), 3.49 (m, 8H, TBA), 2.15–0.33 (m, 8H, B–H), 1.93 (br m, 10H, C_{cb}–H+TBA), 1.47 (m, 8H, TBA), 1.02 (t, 12H, ^3J 7.6, TBA), -2.62 (br m, 1H, B–H–B). ^{11}B NMR (128 MHz, acetone-d_6): δ -10.6 (d, *J* 133, 2B), -16.3 (d, *J* 143, 2B), -18.2 [s, 1B, B(3)], -21.3 (d, *J* 154, 2B), -33.7 (br d, 1B), -36.9 (d, *J* 143, 1B). $^{13}C\{^1H\}$ (100 MHz, acetone-d_6): δ 145.0, 133.3, 132.94, 132.90, 128.2, 126.9, 123.6, 123.0, 92.3, 90.2, 64.9, 60.2 (TBA), 47.5 (C_{cb}–H), 25.2 (TBA), 21.1 (TBA), 14.6 (TBA). HRMS (TIS–): *m*/*z* 364.2235 $[M]^-$ (calcd for $C_{19}H_{22}B_9O$ 364.2544). IR (KBr, cm^{-1}): 3446 (OH), 2960, 2931, 2872 (C–H), 2548 (B–H), 2211 (C≡C).

*4.3.8. Synthesis of mixed-ligand nickelacarborane **14***

A mixture of compounds **9** (0.156 g, 0.230 mmol) and **13** (0.145 g, 0.230 mmol) was azeotropically dried with 50 mL of benzene. After removing the remaining benzene under vacuum, the resulting mixture was dissolved in 50 mL of THF, and 0.29 mL (0.725 mmol) of 2.5 M BuLi in hexane was added at 0°C. After 2 h, a solution of $Ni(acac)_2$ (0.073 g, 0.280 mmol) in 20 mL of THF was added, and the reaction mixture

was stirred at room temperature for 16 h. The supernatant, which contained compound **15** (by MS) almost exclusively, was separated from the reaction mixture via a syringe. The precipitate containing (by MS) a mixture of complexes **14** and **16** was re-dissolved in methanol and co-evaporated with 5 mL of silica. The mixture was treated by column chromatography using a $CHCl_3$ gradient (0→80%) in hexane. After evaporation and drying in vacuum, compound **14** (0.085 g, 33%) was isolated as an orange-brown paramagnetic solid. HRMS (TIS–): *m*/*z* 833.4525 $[M]^-$ (calcd for $C_{40}H_{56}B_{18}NiOSi$ 833.5237). m.p. 228–230 °C. R_f = 0.55 ($CHCl_3$–MeOH, 10:1). IR (KBr, cm^{-1}): 3422 (OH), 2957, 2924, 2864 (C–H), 2553 (B–H), 2260, 2154 (C≡C).

*4.3.9. Synthesis of nickelacarborane **17***

To a solution of **14** (0.121 g, 0.112 mmol) in 2.5 mL of THF was added 0.5 mL of a 1 M TBAF in THF (0.45 mmol), and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). Combined organic extracts were dried over Na_2SO_4 and evaporated to dryness. The residue was washed with hexane (3×3 mL) to remove TIPS fluoride. After drying under vacuum, compound **17** (0.095 g, 92%) was isolated as a brown paramagnetic solid. HRMS (TIS–): *m*/*z* 678.3210 $[M+H]^-$ (calcd for $C_{31}H_{36}B_{18}NiO$ 677.3903). m.p. 215–216 °C (with decomposition). R_f = 0.5 ($CHCl_3$–MeOH, 10:1). IR (KBr, cm^{-1}): 3430 (OH), 3281 (≡C–H), 3037 (C_{cb}–H), 2959, 2924, 2853 (C–H), 2562 (B–H), 2187 (C≡C).

*4.3.10. Synthesis of nickelacarborane **19***

To a mixture of **17** (0.091 g, 0.099 mmol), **18** (0.033 g, 0.108 mmol), and Et_3N (0.015 g, 0.148 mmol) in 4 mL of CH_2Cl_2 was added BOP (0.066 g, 0.148 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 16 h. The reaction mixture was washed with water (6×3 mL), dried over Na_2SO_4, and co-evaporated with 2 mL of silica before being subjected to column chromatography using a $CHCl_3$ gradient (0→100%) in hexane followed by a MeOH gradient (0→5%) in $CHCl_3$. After evaporation and drying in vacuum, compound **19** (0.090 g, 76%) was isolated as a brown paramagnetic solid. HRMS (ESI–): *m*/*z* 964.4032 $[M]^-$ (calcd for $C_{47}H_{54}B_{18}N_2NiO_4$ 964.5224). m.p. 247–249 °C (with decomposition). R_f = 0.35 ($CHCl_3$–MeOH, 10:1). IR (KBr, cm^{-1}): 3425 (NH), 3121 (≡C–H), 3043 (C_{cb}–H), 2961, 2930, 2871 (C–H), 2563 (B–H), 2185 (C≡C).

*4.3.11.Synthesis of nickelacarborane **20***

A mixture of **19** (61.0 mg, 0.050 mmol), **6** (17.5 mg, 0.050 mmol), CuI (0.2 mg, 0.0025 mmol), $Pd(PPh_3)_4$ (28.0 mg, 0.0025 mmol), and DIPEA (0.013 mL, 0.075 mmol) in 3 mL of anhydrous toluene was stirred

at 40 °C for 20 h. Next, the reaction mixture was partitioned between CH_2Cl_2 (15 mL) and 1 M $NaHSO_4$ (3 mL). The dichloromethane layer was dried over Na_2SO_4 and co-evaporated with 1 mL of silica. Treatment of the reaction mixture by column chromatography using a $CHCl_3$ gradient (0→100%) in hexane followed by a MeOH gradient (0→10%) in $CHCl_3$ gave, after evaporation and drying in vacuum, compound **20** (11.4 mg, 15%) as a red solid. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.48 (br s, 2H, linker-C_6H_4), 8.44 (br s, 2H, linker-C_6H_4), 8.18 (br s, 1H, Trp-indole-NH), 7.93 (br s, 2H, BODIPY-pyrrole), 7.67 (d, 2H, *J* 8.4, linker-C_6H_4), 7.61 (d, 2H, *J* 7.9, linker-C_6H_4), 7.55 (d, 1H, *J* 8.0, Trp-C_6H_4), 7.38 (d, 3H, *J* 8.0, linker-C_6H_4+Trp-C_6H_4), 7.28 (d, 2H, *J* 8.0, linker-C_6H_4), 7.20 (t, 1H, *J* 7.5, Trp-C_6H_4), 7.11 (t, 1H, *J* 7.5, Trp-C_6H_4), 7.01 (d, 2H, *J* 3.9, BODIPY-pyrrole), 6.92 (s, 1H, Trp-indole-CH), 6.61 (d, 2H, *J* 3.3, BODIPY-pyrrole), 5.81 (br s, 4H, C_{cb}–H), 5.18 (s, 2H, OCH_2), 5.10 (br s, 1H, Trp-NH-boc), 4.65 (m, 1H, Trp-C<u>H</u>–C=O), 3.29 (d, 2H, *J* 5.7, Trp-CH_2), 3.15 (br m, 8H, TBA), 1.6–0.7 (m, 18H, B-*H*),1.68 (br m, 8H, TBA), 1.49 (br m, 8H, TBA), 1.42 (br s, 9H, *t*-Bu), 1.03 (br s, 12H, TBA). ^{11}B NMR (128 MHz, CD_2Cl_2): δ 11.7, 0.1 (t, $J_{B–F}$ 28, BF_2), -19.3, -51.3. ^{13}C{^{1}H} (100 MHz, CD_2Cl_2): δ 173.2(C=O), 172.8 (C=O), 147.1 (BODIPY-pyrrole), 145.0, 137.4, 137.0, 135.8, 135.1, 134.0, 133.9, 132.3 (BODIPY-pyrrole), 131.0, 128.5, 126.5 (linker-C_6H_4), 123.8, 122.9, 120.3 (Trp-C_6H_4), 119.4 (Trp-C_6H_4+BODIPY-pyrrole), 112.0 (Trp-C_6H_4), 78.4, 78.1, 77.8, 67.0 (OCH_2), 60.6 (TBA), 55.2, 30.50, 28.8 (*t*-Bu), 27.9 (Trp-CH_2), 25.0 (TBA), 20.8 (TBA), 14.4 (TBA). ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ -145.19 (q, $J_{F–B}$ 28, BF_2). HRMS (TIS–): *m*/*z* 1230.4674 $[M]^-$ (calcd for $C_{62}H_{64}B_{19}F_2N_4NiO_4$ 1230.6141). m.p. 245–246 °C (with decomposition). R_f = 0.6 ($CHCl_3$–MeOH, 10:1). IR (KBr, cm^{-1}): 3421 (NH), 3044 (C_{cb}–H), 2960, 2925, 2873, 2853 (C–H), 2563 (B–H), 2213, 2187 (C≡C), 1749, 1739 (C=O), 1558 (B–F).

*4.3.12. Synthesis of nickelacarborane **21***

Compound **21** was isolated with 5.5% yield during the chromatographic separation of compound **20**. Compound **21** was prepared in quantitative yield by air oxidation of a solution of **20** in $CHCl_3$ over 3 days with subsequent isolation of **21** by column chromatography in chloroform. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.18 (br s, 1H, Trp-indole-NH), 7.94 (br s, 1H, BODIPY-pyrrole), 7.70 (d, 2H, *J* 7.7, linker-C_6H_4), 7.65-7.49 (m, 13H), 7.37 (d, 1H, *J* 8.3, Trp-C_6H_4), 7.24 (d, 1H, *J* 8.3, Trp-C_6H_4), 7.19 (t, 1H, *J* 7.6, Trp-C_6H_4), 7.10 (t, 1H, *J* 7.3, Trp-C_6H_4), 6.98 (d, 2H, *J* 4.0, BODIPY-pyrrole), 6.94 (s, 1H, Trp-indole-CH), 6.60 (d, 2H, *J* 3.7, BODIPY-pyrrole), 5.12 (s, 3H, NH-boc, OCH_2), 4.88 (br s, 4H, C_{cb}–H), 4.67 (br m, 1H, CH–C=O), 4.5–0.5 (m, 18H, B-H), 3.30 (br d, 2H, Trp-CH_2), 1.41 (br s, 9H, *t*-Bu). ^{11}B NMR (128 MHz, CD_2Cl_2): δ 18.0, 3.4, 0.1 (t, $J_{B–F}$ 28, BF_2), -6.5, -14.4. ^{13}C{^{1}H} (100 MHz, CD_2Cl_2): δ 172.8, 167.5, 147.1, 145.0, 137.4, 137.0, 135.8, 135.1, 134.0, 133.9, 132.3, 131.0, 128.5, 126.5, 123.8, 122.9, 120.3, 119.5, 119.4, 118.2, 116.5, 112.0, 67.0, 55.2, 55.1, 30.5, 27.9. ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2): δ -

145.1 (q, $J_{F–B}$ 28). HRMS-TIS: *m*/*z* 1231.4337 $[M]^-$ (calcd for $C_{62}H_{64}B_{19}F_2N_4NiO_4$ 1231.6141). m.p. 270–271 °C (with decomposition). R_f = 0.95 ($CHCl_3$–MeOH, 10:1). IR (KBr, cm^{-1}): 3422 (NH), 3043 (C_{cb}–H), 2958, 2927, 2874, 2860 (C–H), 2560 (B–H), 2212, 2189 (C≡C), 1749, 1739 (C=O), 1557 (B–F).

4.4. Crystal structure determination

X-ray quality crystals of compound **7** were obtained by slow evaporation of its CH_2Cl_2 solution. Data collection for **7** was performed at –100 °C on a Bruker SMART 1000 CCD area detector system using the ω scan technique with Mo Kα radiation (λ = 0.71073 Å) from a graphite monochromator. The APEX II [25] and SAINT [26] software packages were used for data collection and data integration. The data were corrected for absorption effects using the SADABS empirical method [27]. The structures were solved and refined using the Bruker SHELXTL [28] software package. All of the non-hydrogen atoms were refined with anisotropic thermal parameters except those in the disordered diazaindacene moiety and one of the phenyl groups. All of the hydrogen atoms in **7** were included at geometrically idealized positions. The crystallographic data and the details of the data collection and structure refinement are provided in Table 1.

Table 1. Crystallographic details for **7.**

compound	**7**
empirical formula	$C_{27}H_{25}B_{11}F_2N_2$
Fw	534.40
crystal size (mm^3)	$0.14 \times 0.08 \times 0.06$
crystal system	triclinic
space group	*P*1
a (Å)	10.132(2)
b (Å)	15.079(3)
c (Å)	29.558(6)
α (deg)	76.433(3)
β (deg)	85.249(3)
γ (deg)	81.123(3)
V ($Å^3$)	4331.9(15)
Z	6
T (K)	173(2)

λ (Å)	0.71073
d_{calc} (g·cm^{-3})	1.229
μ (mm^{-1})	0.075
θ_{max} (deg)	23.26
unique data	36940
observed data [$I > 2\sigma(I)$]	4351
parameters	1114
GOF[a] on F^2	0.951
$R1$[b], $wR2$[c] [$I > 2\sigma(I)$]	0.0796, 0.1620
$R1$[b], $wR2$[c] (all data)	0.2439, 0.2326
$\Delta\rho_{max,min}$ (e·A^{-3})	0.360, –0.322
T_{min}/T_{max}	0.990 /0.996

[a] GOF = $[\Sigma[w(F_o^2 - F_c^2)^2]/(N_{obs} - N_{params})]^{1/2}$.

[b] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [c] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

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6. Appendix A. Supplementary data

CCDC 1051561 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7. References

[1] M. F. Hawthorne, T. Andrews, Carborane analogs of cobalticinium ion, Chem. Commun. (1965) 443-444.

[2] See, for example: (a) C. Vinas, J. Llop, F. Teixidor, R. Kivekäs, R. Sillanpää, Restricted rotation in unbridged sandwich complexes: rotational behavior of *closo*-[Co(η^5-NC_4H_4)($C_2B_9H_{11}$)] derivatives, Chem. Eur. J. 11 (2005) 1933-1941; (b) Rosario Núñez, O. Tutusaus, F. Teixidor, C. Viñas, R. Sillanpää, R. Kivekäs, Highly stable neutral and positively charged dicarbollide sandwich complexes, Chem. Eur. J. 11 (2005) 5637-5647, and references therein.

[3] O. Tutusaus, S. Delfosse, A. Demonceau, A. F. Noels, C. Viñas, F. Teixidor, Kharasch addition catalyzed by half-sandwich ruthenium complexes. Enhanced activity of ruthenacarboranes *Tet. Lett.* **2003**, *44*, 8421-8425 and references therein.

[4] P. Cígler, M. Kožíšek, P. Řezáčová, J. Brynda, Z. Otwinowski, J. Pokorná, J. Plešek, B. Grüner, L. Dolečková-Marešová, M. Máša, J. Sedláček, J. Bodem, H.-G. Kräusslich, V. Král, J. Konvalinka, From nonpeptide toward noncarbon protease inhibitors: Metallacarboranes as specific and potent inhibitors of HIV protease, Proc. Natl. Acad. Sci. USA 102 (2005) 15395-15399.

[5] R. Kaplánek, P. Martásek, B. Grüner, S. Panda, J. Rak, B. S. S. Masters, V. Král, L. J. Roman, Nitric oxide synthases activation and inhibition by metallacarborane-cluster-based isoform-specific affectors, J. Med. Chem. 55 (2012) 9541-9548.

[6] M. Białek-Pietras, A. B. Olejniczak, S. Tachikawa, H. Nakamura, Z. J. Leśnikowski, Towards new boron carriers for boron neutron capture therapy: Metallacarboranes bearing cobalt, iron and chromium and their cholesterol conjugates, Bioorg. Med. Chem. 21 (2013) 1136-1142.

[7] K. B. Gona, A. Zaulet, V. Gómez-Vallejo, F. Teixidor, J. Llop, C. Viñas, COSAN as a molecular imaging platform: synthesis and "in vivo" imaging, *Chem. Commun.* 50 (2014) 11415-11417.

[8] M. Tarrés, E. Canetta, C. Viñas, F. Teixidor, A. J. Harwood, Imaging in living cells using νB–H Raman spectroscopy: monitoring COSAN uptake, *Chem. Commun.* 50 (2014) 3370-3372

[9] (a) M. F. Hawthorne, J. I. Zink, J. M. Skelton, M. J. Bayer, C. Liu, E. Livshits, R. Baer, D. Neuhauser, Electrical or photocontrol of the rotary motion of a metallacarborane, Science 303 (2004) 1849-1851. (b) M. F. Hawthorne, B. M. Ramachandran, R. D. Kennedy, C. B. Knobler, Approaches to rotary molecular motors, Pure. Appl. Chem. 78 (2006) 1299-1304.

[10] See for example: (a) J. R. Lakowicz, Principles of fluorescence spectroscopy, third ed., Springer, 2006. (b) P. Wu, L. Brand, Resonance energy transfer: methods and applications, Anal. Biochem. 218 (1994) 1-13.

[11] M. Olofsson, S. Kalinin, J. Zdunek, M. Oliveberd, L. B.-A. Johansson, Tryptophan–BODIPY: a versatile donor–acceptor pair for probing generic changes of intraprotein distances, Phys. Chem. Chem. Phys. 8 (2006) 3130-3140.

[12] J. M. Dixon, M. Taniguchi, J. S. Lindsey, PhotochemCAD 2: A refined program with accompanying spectral data bases for photochemical calculations, Photochem. Photobiol. 81 (2005) 212-213.

[13] HyperChem Pro 8 (www.hyper.com) was used for building the molecules and performing geometry optimization (MM+ force field with Polak-Ribiere geometry optimization algorithm).

[14] For example: (a) S. Misumi, Alternant Conjugate Systems. I. Syntheses and Properties of Polytolans, Bulletin of the Chemical Society of Japan 34 (1961) 1827-1832. (b) C.-C. Han, A. Balasubramanian, Highly fluorescent mono-substituted poly(arylacetylene)s containing tolane chromophores, J. Polym. Sci., Part A: Polym. Chem. 46 (2008) 5483-5498, and references therein.

[15] Camilla Fenante, Uwe Kensy, Bernhard Dick, Does Diphenylacetylene (Tolan) Fluoresce from Its Second Excited Singlet State? Semiempirical MO calculations and fluorescence quantum yield measurements, J. Phys. Chem. 97 (1993) 13457-13463.

[16] (a) M. F. Hawthorne, D. C. Young, P. M. Garrett, D. A. Owen, S. G. Schwerin, F. N. Tebbe, P. A. Wegner, The preparation and characterization of the (3)-1,2- and (3)-1,7-dicarbadodecahydroundecaborate (-1) ions, J. Am. Chem. Soc. 90 (1968) 862-868. (b) M. A. Fox, W. R. Gill, P. L. Herbertson, J. A. H. MacBride, K. Wade, H. M. Colquhoun, Deboronation of C-substituted *ortho*- and *meta-closo*-carboranes using "wet" fluoride ion solutions, Polyhedron 15 (1996) 565-571. (c) J. Yoo, J.-W. Hwang, Y. Do, Facile and mild deboronation of *o*-carboranes using cesium fluoride, Inorg. Chem. 40 (2001) 568-570.

[17] L. Ma, J. Hamdi, F. Wong, M. F. Hawthorne, Closomers of high boron content: synthesis, characterization, and potential application as unimolecular nanoparticle delivery vehicles for boron neutron capture therapy, Inorg. Chem. 45 (2006) 278-285.

[18] M. F. Hawthorne, D. C. Young, T. D. Andrews, D. V. Howe, R. L. Pilling, A. D. Pitts, M. Reintjes, L. F. Warren, Jr., P. A. Wegner, π-Dicarbollyl derivatives of the transition metals. Metallocene analogs, J. Am. Chem. Soc. 90 (1968) 879-896.

[19] A. V. Safronov, N. I. Shlyakhtina, T. A. Everett, M. R. VanGordon, Y. V. Sevryugina, S. S. Jalisatgi, M. F. Hawthorne, Direct observation of bis(dicarbollyl)nickel conformers in solution by fluorescence spectroscopy: an approach to redox-controlled metallacarborane molecular motors, Inorg. Chem. 53 (2014) 10045-10053.

[20] M. T. Indelli, T. Bura, R. Ziessel, *p*-Carborane-bridged bipyridine ligands for energy transfer between two iridium centers, Inorg. Chem. 52 (2013) 2918-2926.

[21] K. Onitsuka, M. Fujimoto, H. Kitajima, H. Ohshiro, F. Takei, S. Takahashi, Convergent synthesis of platinum-acetylide dendrimers, Chem. Eur. J. 10 (2004) 6433-6446.

[22] A. V. Safronov, M.F. Hawthorne, Novel synthesis of 3-iodo-*ortho*-carborane, Inorg. Chim. Acta 375 (2011) 308-310.

[23] R. Hu, C. F. A. Gómez-Durán, J. W. Y. Lam, J. L. Belmonte-Vázquez, C. Deng, S. Chen, R. Ye, E. Peña-Cabrera, Y. Zhong, K. S. Wong, B. Z. Tang, Synthesis, solvatochromism,

aggregation-induced emission and cell imaging of tetraphenylethene-containing BODIPY derivatives with large Stokes shifts, Chem. Commun. 48 (2012) 10099–10101.

[24] T. W.Greene, P. G. M. Wuts, Protective groups in organic synthesis, third ed., John Wiley & Sons, 1999.

[25] Bruker, Apex 2 v APEX 2010.7; Bruker AXS Inc.: Madison, WI, 2010.

[26] Bruker, SAINT v 7.68A; Bruker AXS Inc.: Madison, WI, 2009.

[27] Sheldrick, G. M. SADABS 2008/1; Gottingen, 2008.

[28] Sheldrick, G. M. SHELXTL, v 2008/4; Bruker AXS, Inc.: Madison, WI, 2008.

Highlights

- Design of a bichromophoric nickelacarborane for the conformational assignment of the nickelacarborane core by means of fluorescence spectroscopy.
- Multistep organic/organometallic synthesis and characterization of both Ni(III) and Ni(IV) nickelacarboranes bearing tryptophan/BODIPY FRET couple.
- Possible energy transfer through the nickelacarborane core revealed during the preliminary fluorescence study.