



New reagent for attachment of cobaltacarborane clusters to biomolecules

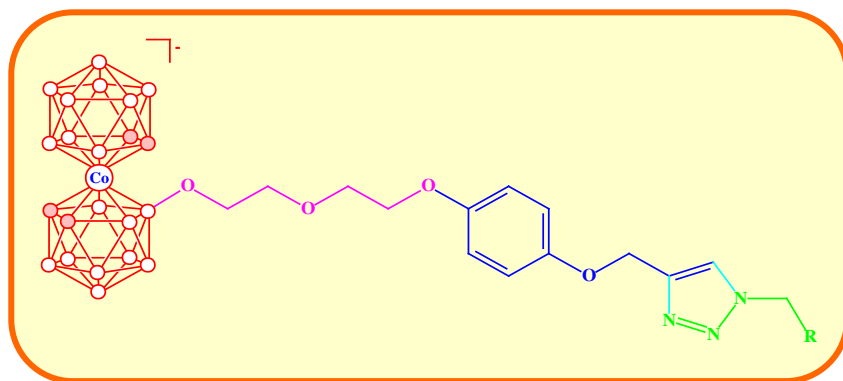
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ABSTRACT



A novel boron reagent for click-labeling biomolecules [8-HC≡CCH₂OC₆H₄O(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] has been prepared by the ring disclosure of the cyclic oxonium derivative of cobalt bis(dicarbollide) with hydroquinone monopropargyl ether. In the presence of Cu(I) catalyst the obtained alkyne reacts with organic azides forming 1,4-derivatives of 1,2,3-triazole as the 1,3-dipolar cycloaddition products. The products obtained were characterized by the methods of multinuclear NMR spectroscopy and mass-spectrometry.

Keywords: Cobalt bis(dicarbollide), Oxonium ring disclosure, Acetylene, 1,3-Dipolar cycloaddition

INTRODUCTION

Boron neutron capture therapy (BNCT) is modern method for cancer treatment based on the reaction of two virtually harmless for health components giving highly toxic products that damage the cancer cell. The method is based on selective accumulation of the non-radioactive ¹⁰B isotope in the cancer cells followed

by their treatment with a flux of thermal neutrons. The short ranges of the two high-LET products of the ¹⁰B(n,α)⁷Li reaction, which are comparable with the cell size, allow to selective destroy tumor cells with the surrounding healthy tissue being virtually unaffected.¹⁻⁵

Nowadays derivatives of cobalt bis(dicarbollide) [3,3'-Co(1,2-C₂B₉H₁₁)₂] attract increased attention for the design of BNCT agents as well as for other medical applications.⁶⁻¹¹ Earlier we proposed a convenient approach to functionalization of cobalt bis(dicarbollide) *via* the ring disclosure of its cyclic oxonium derivative [8-O(CH₂CH₂)₂O-3,3'-Co(1,2-C₂B₉H₁₀)-(1',2'-C₂B₉H₁₁)] (**1**) by various nucleophiles.¹² Over the past years this approach became the main road for synthesis of its organic and bioorganic derivatives.^{13,14} It can be used for both direct boronation of organic and bioorganic molecules and synthesis of various boron-containing labeling reagents for

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indirect boronation through formation of amide, carbamide and thiocarbamide bonds. During the last decade the Cu(I)-catalyzed 1,3-dipolar cycloaddition of azide and alkyne to form 1,4-substituted 1,2,3-triazole, termed click chemistry, was established as an important tool for chemical modification of biomolecules.¹⁵⁻²⁰ The 1,2,3-triazole ring is rigid linking unit that can mimic geometry and electronic properties of a peptide bond without the same susceptibility to hydrolytic cleavage. The alkyne and azide functions are convenient to introduce independently, stable, and do not react with common organic reagents or functional groups that are present in biomolecules. All these factors allow broad application of the click chemistry approach in synthesis of various classes of compounds. Synthesis of cobalt bis(dicarbollide) containing nucleosides,²¹ porphyrins²² and steroids²³ using the click chemistry approach have been reported. The boronation reagents used in these reactions were azide [8-N₃(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] and alkynes [8-HC≡C(CH₂)_nO-(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] (n = 1-3) prepared by the oxonium ring disclosure with azide ion and the corresponding ω-alkyne alcoholates.

In this contribution we describe synthesis and some reactions of novel click-boronation reagent [8-HC≡CCH₂OC₆H₄O-(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)].

EXPERIMENTAL SECTION

Materials and Methods. Starting materials, [8-O(CH₂CH₂)₂O-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] (**1**) and 4-(prop-2-yn-1-yloxy)phenol, were prepared as described in the literature.^{24,25} All other chemicals were reagent grade and received from standard commercial vendors. Acetonitrile was distilled over CaH₂. The reaction progress was monitored by TLC (Merck F254 silica gel on aluminum plates) and visualized using 0.5% PdCl₂ in 1% HCl in aq. MeOH (1:10). Acros Organics silica gel (0.060-0.200 mm) was used for column chromatography. The ¹H, ¹¹B, ¹¹B{¹H}, and ¹³C NMR spectra were recorded on Bruker Avance-400 spectrometer. ¹H and ¹³C chemical shifts were referenced to SiMe₄, ¹¹B chemical shifts were referenced to BF₃•OEt₂. The negative ion electrospray ionization mass spectra (ESI-MS) were obtained with a microOTOF II instrument (Bruker Daltonics) operating in a mass range of m/z 50-3000.

Synthesis of K[8-HC≡CCH₂OC₆H₄O(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] (2**).** 250 mg (0.61 mmol) of 1,4-dioxane derivative of cobalt bis(dicarbollide) **1**, 90 mg (0.61 mmol) of 1,4-HOC₆H₄OCH₂C≡CH and 800 mg (6.10 mmol) of K₂CO₃ (6.10 mmol) in 30 ml of acetonitrile were heated under reflux for 5 h. The reaction mixture was cooled to room temperature, filtered and concentrated to dryness under reduced pressure. The residue was dissolved in 25 ml of dichloromethane and treated with 25 ml of 2.5 % solution of KOH. The organic layer was separated, washed with water (3 × 30 ml), dried over anhydrous Na₂SO₄ and evaporated *in vacuo*. The crude product was purified by column chromatography on silica using mixture of dichloromethane and acetone (3:2) to obtain 320 mg (87 %) of the orange product. ¹H NMR (acetone-

*d*₆, ppm): 6.93 (4H, m, C₆H₄), 4.72 (2H, d, *J* = 2.4 Hz, OCH₂C≡CH), 4.29 (4H, s, CH_{carb}), 4.09 (2H, t, *J* = 5.0 Hz, C₆H₄OCH₂CH₂O), 3.80 (2H, t, *J* = 5.0 Hz, C₆H₄OCH₂CH₂O), 3.67-3.55 (4H, m, OCH₂CH₂O) 3.04 (1H, t, *J* = 2.4 Hz, OCH₂C≡CH). ¹³C NMR (acetone-*d*₆, ppm): 153.8, 151.9, 115.9, 115.4, 79.2, 75.9, 71.9, 69.4, 68.4, 68.0, 56.0, 54.4, 46.4. ¹¹B NMR (acetone-*d*₆, ppm): 22.9 (1B, s), 3.9 (1B, d), 0.4 (1B, d), -2.4 (1B, d), -4.2 (2B, d), -7.8 (6B, d), -17.2 (2B, d), -20.4 (2B, d), -21.9 (1B, d), -28.3 (1B, d). ESI-MS *m/z* for C₁₇H₃₆B₁₈O₄Co: calcd. 558.3747, found 558.3743 [M].

Synthesis of K[8-C₆H₅CH₂N₃C₂HCH₂OC₆H₄O-(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] (3**).** 200 mg (0.34 mmol) of alkyne **2**, 46 μl (50 mg, 0.37 mmol) of benzyl azide, 70 mg (0.04 mmol) of CuI and 3 drops of triethylamine in 25 ml of acetonitrile were heated under reflux for 30 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in 40 ml of dichloromethane and washed with 3×25 ml of water. The organic layer was separated, dried over Na₂SO₄ and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica with dichloromethane followed by a mixture of dichloromethane and acetone (2:3) as eluents to obtain 190 mg (81 %) of the orange product. ¹H NMR (acetone-*d*₆, ppm): 8.05 (1H, s, CH_{triaz}), 7.38 (5H, m, C₆H₅), 6.95 (2H, d, *J* = 2.4 Hz, C₆H₄), 6.89 (2H, d, *J* = 2.4 Hz, C₆H₄), 5.65 (2H, s, C₂H₂N₃CH₂C₆H₅), 5.12 (2H, s, C₆H₄OCH₂C₂H₂N₃), 4.31 (4H, s, CH_{carb}), 4.08 (2H, t, *J* = 5.0 Hz, C₆H₄OCH₂CH₂O), 3.80 (2H, t, *J* = 5.0 Hz, C₆H₄OCH₂CH₂O), 3.68-3.55 (4H, m, OCH₂CH₂O). ¹³C NMR (acetone-*d*₆, ppm): 153.5, 152.7, 144.1, 136.1, 128.8, 128.3, 128.0, 123.7, 115.8, 115.6, 72.0, 69.5, 68.4, 68.1, 62.1, 54.2, 53.4, 46.5. ¹¹B NMR (acetone-*d*₆, ppm): 22.9 (1B, s), 3.8 (1B, d), 0.3 (1B, d), -2.5 (1B, d), -4.2 (2B, d), -7.7 (6B, d), -17.5 (2B, d), -20.5 (2B, d), -22.0 (1B, d), -28.6 (1B, d). ESI-MS *m/z* for C₂₄H₄₃B₁₈O₄N₃Co: calcd. 691.4391, found 691.4384 [M].

Synthesis of K[8-CH₃OOCCH₂N₃C₂HCH₂OC₆H₄O-(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] (4**).** 0.20 g (0.34 mmol) of alkyne **2**, 40 mg (0.34 mmol) of methyl azidoacetate, 0.07 g (0.04 mmol) of CuI and 3 drops of triethylamine in 25 ml of acetonitrile were heated under reflux for 30 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in 40 ml of dichloromethane and washed with 3×25 ml of water. The organic layer was separated, dried over Na₂SO₄ and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica with dichloromethane followed by a mixture of dichloromethane and acetone (2:3) as eluents to obtain 180 mg (79 %) of the orange product. ¹H NMR (acetone-*d*₆, ppm): 8.12 (1H, s, CH_{triaz}), 6.96 (2H, d, *J* = 9.2 Hz, C₆H₄), 6.92 (2H, d, *J* = 9.2 Hz, C₆H₄), 5.39 (2H, s, C₂H₂N₃CH₂COOCH₃), 5.17 (2H, s, C₆H₄OCH₂C₂H₂N₃), 4.29 (4H, s, CH_{carb}), 4.09 (2H, t, *J* = 4.9 Hz, C₆H₄OCH₂CH₂O), 3.80 (2H, t, *J* = 4.9 Hz, C₆H₄OCH₂CH₂O), 3.78 (3H, s, COOCH₃), 3.66-3.55 (4H, m, OCH₂CH₂O). ¹¹B NMR (acetone-*d*₆, ppm): 22.9 (1B, s), 3.9 (1B, d), 0.5 (1B, d), -2.4 (1B, d), -4.3 (2B, d), -

7.8 (6B, d), -17.3 (2B, d), -20.4 (2B, d), -21.9 (1B, d), -28.5 (1B, d). ESI-MS m/z for $C_{20}H_{41}B_{18}O_6N_3Co$: calc. 673.4131, found 673.4132 [M]⁺.

RESULTS AND DISCUSSION

The oxonium ring disclosure in [8-O(CH₂CH₂)₂O-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] (**1**) with phenolate ions is rather mild and convenient method of boronation of organic molecules. It was used earlier for synthesis of cobalt bis(dicarbollide) based tyrosine,²⁶ porphyrins,²⁷⁻²⁹ phthalocyanines,³⁰⁻³² calix[4]arenes,³³⁻³⁵ resorc[4]arenes³³ and dendrimers.³⁶

In this contribution 4-(prop-2-yn-1-yloxy)phenol that can be easily prepared by monoalkylation of hydroquinone with propargyl bromide²⁵ was used as the phenolate ion source. Its reaction with **1** in the presence of K₂CO₃ in refluxing acetonitrile gave the goal alkyne **2** isolated in 87 % yield (Figure 1).

The ¹H NMR spectrum of compound **2** contains signals of the carborane CH groups at 4.29 ppm and signals of methylene groups of opened 1,4-dioxane ring at 3.55-4.09 ppm as well the characteristic triplet of the acetylene CH group at 3.04 ppm, doublet of the propargyl ether methylene group at 4.72 ppm and signal of aromatic ring protons at 6.93 ppm.

The Cu(I)-catalyzed reactions of 1,3-dipolar cycloaddition of alkyne **2** and benzyl azide and methyl azidoacetate produced the corresponding 1,2,3-triazoles **3** and **4**, isolated in 81 and 79 % yields, respectively (Figure 1). The ¹H NMR spectrum of compound **3** (Figure 2) contains singlet at 8.05 ppm corresponding the formation of the 1,2,3-triazole ring as well as signals of the phenyl group at 7.38 ppm and the benzylic methylene group at 5.65 ppm. At the same time the characteristic triplet of the acetylene CH group disappears and the former doublet of the propargyl ether methylene group transforms to singlet and undergoes the low field shift to 5.12 ppm. The ¹³C NMR spectrum of compound **3** demonstrates the absence of signals corresponding to alkyne fragment at 79.2 and 75.9 and appearance of characteristic signals of the 1,2,3-triazole ring at 144.1 and 123.7 ppm. In the similar way, the ¹H NMR spectrum of compound **4** contains the of the 1,2,3-triazole ring singlet at 8.12 ppm and singlets of methylene groups attached to carbon and nitrogen atoms of the 1,2,3-triazole ring at 5.17 and 5.39 ppm, respectively. The pattern of the all ¹¹B NMR spectra is characteristic for 8-substituted derivatives of cobalt bis(dicarbollide) with the singlet of *O*-substituted boron atom at 22.9 ppm (Figure 2).

CONCLUSION

In conclusion, a novel cobalt bis(dicarbollide) based reagent for labeling biomolecules using click chemistry approach [8-HC≡CCH₂OC₆H₄O(CH₂CH₂O)₂-3,3'-Co(1,2-C₂B₉H₁₀)(1',2'-C₂B₉H₁₁)] was synthesized by the ring disclosure of the 1,4-dioxane derivative of cobalt bis(dicarbollide) with hydroquinone monopropargyl ether. The capability of the obtained alkyne to react with organic azides (benzyl azide,

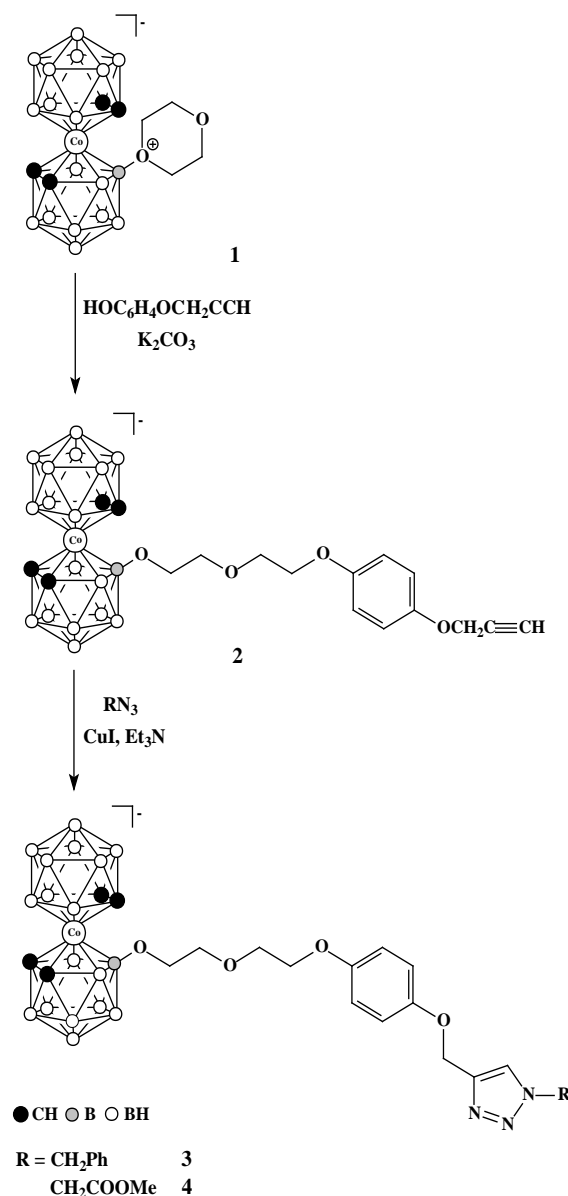


Figure 1. Synthesis of cobalt bis(dicarbollide) based alkyne **2** and 1,2,3-triazoles **3** and **4**.

methyl azidoacetate) under conditions of Cu(I)-catalyzed 1,3-dipolar cycloaddition was demonstrated.

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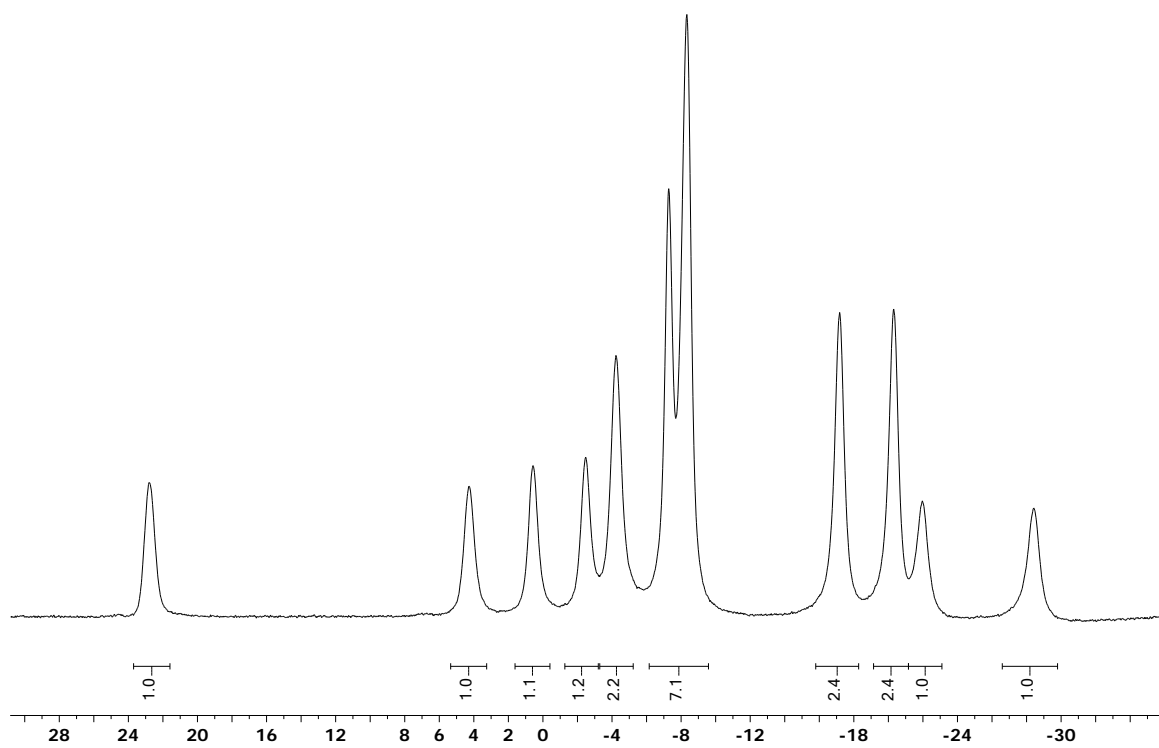
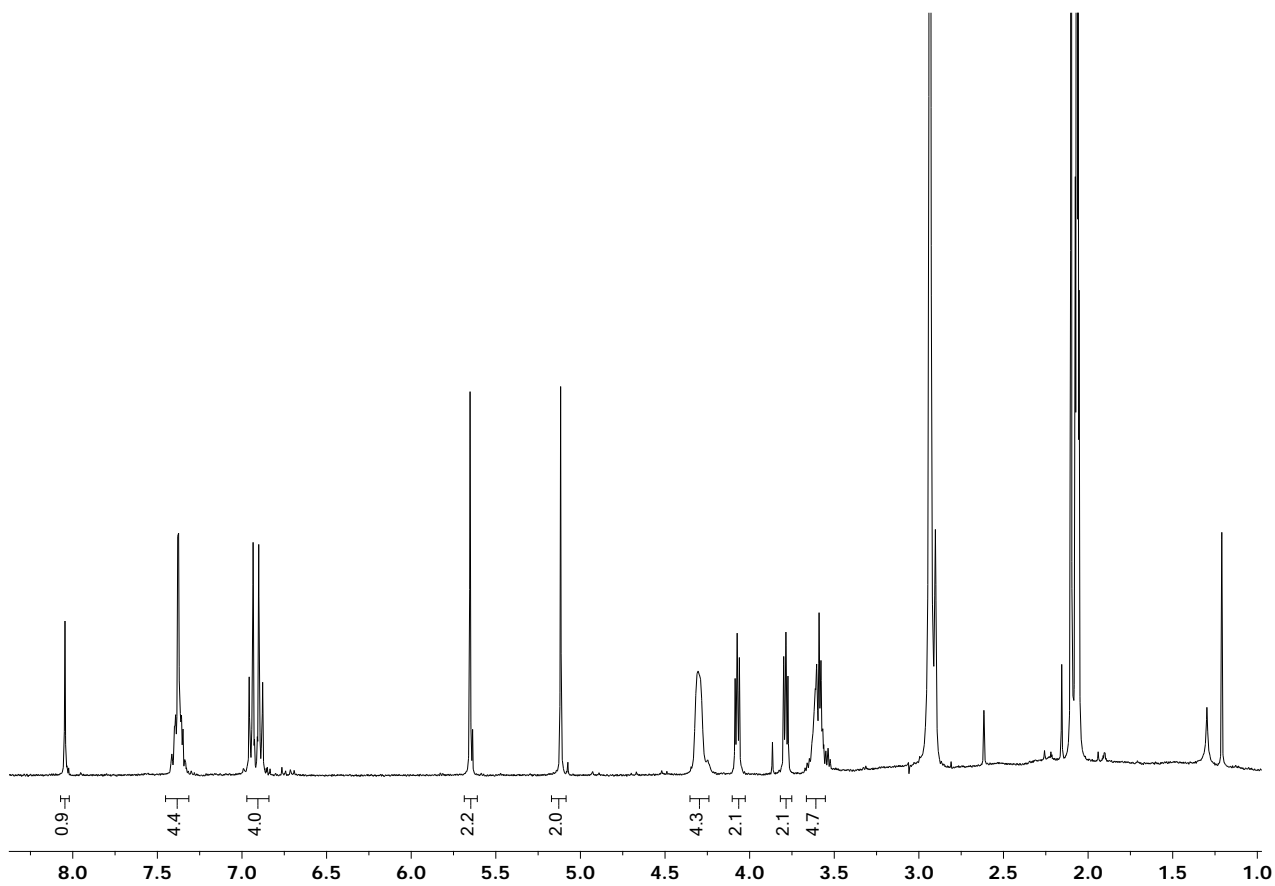


Figure 2. ^1H and $^{11}\text{B}\{^1\text{H}\}$ NMR spectra of $\text{K}[8\text{-C}_6\text{H}_5\text{CH}_2\text{N}_3\text{C}_2\text{HCH}_2\text{OC}_6\text{H}_4\text{O}-(\text{CH}_2\text{CH}_2\text{O})_2\text{-3,3'-Co}(1,2\text{-C}_2\text{B}_9\text{H}_{10})\text{-}(1',2'\text{-C}_2\text{B}_9\text{H}_{11})]$ in acetone- d_6

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