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Cobaltacarborane functionalized phthalocyanines: Synthesis, photophysical, electrochemical and spectroelectrochemical properties

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ABSTRACT

New tetra-cobaltacarborane modified zinc, cobalt and manganese phthalocyanine complexes have been synthesized via nucleophilic attack of the reference hydroxylated phthalocyanines to the oxonium adduct of cobalt bis(dicarbollide). The compounds were characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{11}B NMR, UV–vis and mass spectroscopic data. Photophysical properties of zinc phthalocyanine **6** suggest that it may have potential application as dual sensitizers in the PDT and BNCT treatment of tumors. The electrochemical, in situ spectroelectrochemical and electrocolorimetric properties of these phthalocyanine conjugates were investigated together with reference phthalocyanines. In the case of electroactive Co- and Mn-phthalocyanine with cobaltacarborane substituents, in addition to ring based reduction, metal based reductions in both phthalocyanine core and cobaltocarborane units have been clearly identified.

1. Introduction

Phthalocyanines have a wide application range such as dyeing, electrophotography, energy transfer, optical data storage, laser technology, etc. [1,2]. In addition to these areas, phthalocyanines are also used in medicinal chemistry [3]. Over the past two decades, the use of phthalocyanines as photosensitizers for photodynamic therapy of cancer (PDT) has gained rising momentum [4]. Phthalocyanine derivatives have stronger absorbances at longer wavelengths compared to porphyrins and most of them are capable of photoinduced singlet oxygen generation. The exciting point of phthalocyanines as photosensitizing agents is having tunable properties with the addition of substituents to the periphery of the macrocycle or axial ligands to the chelated central metal ion.

Additionally, phthalocyanines can be used in boron neutron capture therapy (BNCT) agents when boron containing moieties are introduced [5–17]. BNCT involves the irradiation of ^{10}B-enriched tumors with thermal neutrons, which produces high linear energy transfer particles $^4He^{2+}$ and $^7Li^{3+}$ that are highly cytotoxic [18,19]. In this direction, a novel compound which contains both polyhedral boron derivative and the phthalocyanine macrocycle is considered to be an interesting combination in BNCT and PDT of cancer.

Both methods are binary modalities for the treatment of cancer. There are number of examples of phthalocyanines bearing boron clusters [13–15,20,21]. As they have remarkable chemical-, thermal-, and photo-stabilities, the cobalt bis(dicarbollide) anion $[Co(C_2B_9H_{11})_2]^-$ and its adducts have attracted much attention among the boron clusters [22]. Also, cobalt bis(dicarbollide) substituted phthalocyanines enhance the properties of the compound as it displays a rich chemistry due to the high stability, electrochemistry and ease of functionalization related to cobalt bis(dicarbollide) moieties [22–24].

Herein, we report the synthesis and electrochemical characterization of novel phthalocyanine–cobaltacarborane conjugates with $[3,3'\text{-}Co(8\text{-}C_4H_8O_2\text{-}1,2\text{-}C_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})]$ groups as peripheral substituents. In order to differentiate the metal-centered and ring based oxidation–reduction reactions, a redox inactive metal ion (Zn^{2+}) and two redox active metal ions (Co^{2+} and Mn^{3+}) have been preferred in the inner core. Photophysical, electrochemical and spectroelectrochemical properties for all these compounds are reported and comparisons are made with the nonboronated hydroxyl derivatives.

2. Experimental

2.1. Materials and equipment

IR spectra were measured in the range of 650–4000 cm^{-1} with a PerkinElmer Spectrum One FT-IR (ATR sampling accessory)

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spectrophotometer. UV–vis solution spectra other than those for spectroelectrochemistry were recorded on a Scinco S-3100 spectrophotometer by using 10 mm path length cuvettes at the room temperature. Fluorescence spectra were recorded on a PerkinElmer LS55 fluorescence spectrophotometer using 10 mm path length cuvettes at room temperature. A Rofin Polilight PL400 Forensic Plus light source was used for the irradiation of the samples at 650 nm for qualitative singlet oxygen determination. ^{1}H NMR, ^{13}C NMR and ^{11}B NMR spectra were recorded on Agilent VNMRS 500 MHz. Mass spectra were measured on a Bruker Microflex MALDI-TOF/MS mass spectrometers.

Electrochemical measurements were carried out using a Gamry Reference 600 galvanostat/ potentiostat at 298 K with a glassy carbon working electrode and platinum wires as counter and reference electrodes with 0.1 M $n\text{-Bu}_4\text{NClO}_4$ in DMF and acetonitrile under nitrogen. In situ UV–vis absorption spectra were measured with an Ocean Optics HR2000$^+$ diode array spectrophotometer. For in situ spectroelectrochemical measurements, an optically transparent thin-layer quartz cell of path length 1 mm was employed, in which a Pt gauze electrode, a Pt wire, and a SCE were used for the working, counter, and reference electrodes, respectively.

$[3,3'\text{-Co}(8\text{-C}_4\text{H}_8\text{O}_2\text{-}1,2\text{-C}_2\text{B}_9\text{H}_{10})(1',2\ \text{-C}_2\text{B}_9\text{H}_{11})]$ was synthesized according to a described method [25]. Phthalonitrile **1** and phthalocyanines **2** and **3** were synthesized with some modifications in the literature [13,26].

2.2. Synthesis

2.2.1. 4-(4-hydroxyphenoxy)-phthalonitrile (1) [13]

A mixture of hydroquinone (4 g, 36.1 mmol), potassium carbonate (15 g, 108.3 mmol), and dry DMSO (60 mL) was stirred at room temperature for 20 min. 4-Nitrophthalonitrile (2.5 g, 14.5 mmol) was then added and the reaction mixture was stirred at 100 °C for 8 h. After cooling to room temperature, the reaction mixture was poured into HCl solution (1 M 300 mL). The precipitate was then filtered, washed with water, and redissolved in diethylether. The resulting solution was washed with water until the aqueous phase became neutral. After extraction organic phase was dried on sodium sulfate. Diethylether was evaporated and the solid was recrystallized from methanol. Yield: 79%.(2.7 g). FT-IR υ_{max} (cm^{-1}): 3380 (O—H), 3080 (Ar—CH), 2238 ($C{\equiv}N$), 1245 (O—C). ^{1}H NMR (500 MHz, acetone-d$_6$): δ ppm 8.58 (br s, H, OH), 8.01 (d, H, Ar—H), 7.54 (d, H, Ar—H), 7.37 (dd, H, Ar—H), 7.06 (m, 2H, Ar—H), 6.98 (m, 2H, Ar—H). ^{13}C NMR (500 MHz, acetone-d$_6$): δ ppm 162.74, 146.27, 135.86, 121.93, 121.30, 121.06, 117.22, 116.80, 115.58, 115.14, 108.07.

2.2.2. Tetra-(4-hydroxyphenoxy)-phthalocyanine (2)

Lithium (367 mg, 53 mmol) in 1-pentanol (30 mL) was heated at 100 °C until all of the metal was dissolved. After cooling to room temperature, **1** (1 g, 4.23 mmol) was then added and the reaction mixture was stirred at 150 °C for 2.5 h. The reaction mass was then poured into 250 mL ice–water mixture with the addition of acetic acid. In this mixture, the lithium phthalocyanine formed was converted into metal free phthalocyanine. The precipitate was filtered off and the crude product was treated with diethylether, dichloromethane, hexane and then dried under reduced pressure. The crude products were further purified using column chromatography on silica gel with acetone to give a green solid. Yield: 61% (610 mg). FT-IR υ_{max} (cm^{-1}): 3293 (N—H), 3200 (O—H), 3031 (Ar—CH). UV–vis (DMF): λ_{max}/nm: 330, 612, 674. ^{1}H NMR (500 MHz, acetone-d$_6$): δ ppm 8.59 (s, 4H, OH), 7.13–6.43 (m, 28H, Ar—H), −7.70 (s, 2H, N—H). MALDI-TOF, (m/z) calcd.: 946.25; found: 947.27 [M + H]$^+$.

2.2.3. Tetra-(4-hydroxyphenoxy)-phthalocyaninato metal derivatives (3–5)

A mixture of **2** (210 mg, 0.22 mmol), 0.67 mmol anhydrous metal salt (zinc acetate 122 mg, cobalt chloride 86 mg or manganese chloride 83 mg) and dry DMF (10 mL) was refluxed for 2 h under a nitrogen atmosphere. After cooling to room temperature, the suspension was poured into 150 mL ice–water mixture. After that, precipitated solid was filtered off. The precipitate was washed subsequently with hot water, chloroform, hexane and diethyl ether and then dried under reduced pressure.

Tetra-(4-hydroxyphenoxy)-phthalocyaninato zinc **(3)** Yield: 80% (180 mg). FT-IR υ_{max} (cm^{-1}): 3300 (O—H), 3065-3027 (Ar—H). UV–vis (DMF): λ_{max}/nm: 355, 610, 677. ^{1}H NMR (500 MHz, dimethyl sulfoxide-d$_6$): δ ppm 9.59 (s, 4H, OH), 8.97–8.88 (m, 4H, Ar—H), 8.39 (m, 4H, Ar—H), 7.71–7.66 (m, 4H, Ar—H), 7.38–7.31 (m, 8H, Ar—H), 7.07–7.03 (m, 8H, Ar—H), MALDI-TOF, (m/z) calcd.: 1008.16; found: 1011.31 [M + 3H]$^+$.

Tetra-(4-hydroxyphenoxy)-phthalocyaninato cobalt **(4)** Yield: 85% (190 mg). FT-IR υ_{max} (cm^{-1}): 3270 (O—H), 3063–3023 (Ar—H). UV–vis (DMF): λ_{max}/nm: 323, 609, 665. Elemental analyses calcd. (%) for $C_{56}H_{32}CoN_8O_8$: C 67.00, H 3.21, N 11.16; found C 66.78, H 3.28, N 10.98. MALDI-TOF, (m/z) calcd.: 1003.17; found: 1004.29 [M + H]$^+$.

Tetra-(4-hydroxyphenoxy)-phthalocyaninato manganese(III) chloride **(5)** Yield: 65% (150 mg) FT-IR υ_{max} (cm^{-1}): 3270 (O—H), 3060–3025 (Ar—H). UV–vis (DMF): λ_{max}/nm: 372, 499, 727. Elemental analyses calcd. (%) for $C_{56}H_{32}ClMnN_8O_8$: C 64.97, H 3.12, N 10.82; found C 65.18, H 3.07, N 10.58. MALDI-TOF, (m/z) calcd.: 999.17; found: 998.62 [M − Cl]$^+$.

2.2.4. Tetra cobalt bis(dicarbollide) substituted phthalocyanine derivatives (6–8)

A mixture of $[8\text{-O}(\text{CH}_2\text{CH}_2)_2\text{O-}3,3'\text{-Co}(1,2\text{-C}_2\text{B}_9\text{H}_{10})(1',2'\text{-C}_2\text{B}_9\text{H}_{11})]$ (54 mg, 0.13 mmol), 0.03 mmol phthalocyanine (**3** 30 mg, **4** 30 mg or **5** 31 mg), potassium carbonate (165 mg, 1.2 mmol), and dry acetone (20 mL) was heated under reflux for 24 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered and evaporated under reduced pressure. The crude products were further purified using column chromatography on silica using a mixture of dichloromethane and acetone 2:1.

Tetra cobalt bis(dicarbollide) substituted zinc phthalocyanine **(6)** Yield: 82% (68 mg) FT-IR υ_{max} (cm^{-1}): 3046 (Ar—H), 2931–2872 (C—H), 2536 (B—H). UV–vis (DMF): λ_{max}/nm: 314, 355, 610, 667. ^{1}H NMR (500 MHz, acetone-d$_6$): δ ppm 9.39 (m, 4H, Ar—H), 8.90 (m, 4H, Ar—H), 7.80 (m, 4H, Ar—H), 7.39-7.11 (m, 16H, Ar—H), 4.29 (m, 24H, Ar—OCH$_2$ + CH*carb*), 3,95–3.53 (m, 24H, CH$_2$). ^{11}B NMR (500 MHz, acetone-d$_6$): δ ppm 23.0 (1B), 4.1 (1B), 0.5 (1B), −2.4 (1B), −4.2 (2B), −7.3 (2B), −8.2 (4B), −17.2 (2B), −20.4 (2B), −21.9 (1B), −28.3 (1B). Elemental analyses calcd. (%) for $C_{88}H_{144}B_{72}Co_4K_4N_8O_{16}Zn$: C 37.67, H 5.17, N 3.99%; found C 38.12, H 5.03, N 3.91%.

Tetra cobalt bis(dicarbollide) substituted cobalt phthalocyanine **(7)** Yield: 77% (64 mg). FT-IR υ_{max} (cm^{-1}): 3044 (Ar—H), 2933–2874 (C—H), 2536 (B—H). UV–vis (DMF): λ_{max}/nm: 314, 609, 666. ^{11}B NMR (500 MHz, acetone-d$_6$): δ ppm 23.5 (1B), 4.7 (1B), 0.5 (1B), −2.3 (1B), −4.3 (2B), −7.1 (2B), −7.8 (4B), −17.1 (2B), −20.2 (2B), −21.8 (1B), −28.4 (1B). Elemental analyses calcd. (%) for $C_{88}H_{144}B_{72}Co_5K_4N_8O_{16}$: C 37.76, H 5.18, N 4.00; found C 38.09, H 5.21, N 4.07%.

Tetra cobalt bis(dicarbollide) substituted manganese chloride phthalocyanine **(8)** Yield: 66% (55 mg). FT-IR υ_{max} (cm^{-1}): 3050 (Ar—H), 2930–2874 (C—H), 2535 (B—H). UV–vis (DMF): λ_{max}/nm: 315, 372, 498, 728. ^{11}B NMR (500 MHz, acetone-d$_6$): δ ppm 23.1 (1B), 3.8 (1B), 0.6 (1B), −2.4 (1B), −4.2 (2B), −7.3 (2B), −8.1 (4B), −17.2 (2B), −20.4 (2B), −21.9 (1B), −28.1 (1B). Elemental analyses