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Synthesis and properties of cobaltacarborane-functionalized Zn(II)-phthalocyanines

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ABSTRACT

The syntheses of two new A_3B-type Zn(II)-phthalocyanines (Zn-Pcs) containing either one or two cobaltacarborane residues are reported, and the X-ray structure of a key phthalonitrile precursor is presented. The Zn-Pcs are highly soluble and exist as monomers in polar organic solvents.

Boron neutron capture therapy (BNCT) and photodynamic therapy (PDT) are both binary modalities for the treatment of cancer. BNCT[1,2] involves the irradiation of ^{10}B-rich tumors with low-energy neutrons, which produces high linear energy transfer particles $^4He^{2+}$ and $^7Li^{3+}$ that are highly cytotoxic. On the other hand, PDT[3,4] produces reactive oxygen species, mainly $^1O_2$, from the activation of a tumor-localized photosensitizer with red light. Photofrin and Visudyne are two porphyrin derivatives, FDA-approved for the PDT treatment of various cancers, and the age-related macular degeneration, respectively.[5] Two clinically approved boron-containing drugs, BSH and BPA, have been used in the US, Europe, and Japan for the treatment of high-grade gliomas, melanomas, and head and neck tumors.[6] One advantage of BNCT over PDT is that thermal and epithermal neutrons can penetrate much deeper through tissue (up to about 7 cm) than can light, and for this reason BNCT has been used in the treatment of deep-seated tumors such as glioblastomas. One of the main challenges in BNCT is that a high concentration of ^{10}B nuclei is required for effective tumor cell killing (~20 μg ^{10}B/g tumor). Several porphyrins and derivatives containing borane moieties have been synthesized and evaluated as boron delivery agents for BNCT, and also as dual BNCT/PDT sensitizers.[7,8] Boron-containing Pcs are particularly promising for dual application in BNCT and PDT because of their strong absorptions in the near-IR where light penetration through tissue is substantially increased compared with visible light.[9,10] However, only a few examples of boronated Pcs have been reported to date,[10–14] probably as a consequence of their poor solubility in most solvents which makes their synthesis and purification difficult. We have previously reported a high yielding synthesis of cobaltacarborane-functionalized porphyrins, via a nucleophilic ring opening reaction of zwitterionic 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$).[15–18] Herein, we report for the first time the synthesis and characterization of two A_3B-type Zn(II)-Pcs containing cobaltacarborane residues, that are highly soluble in polar organic solvents.

The synthetic route to Pcs **1** and **2** from commercially available 2,6-dihydroxyphthalonitrile **3** is shown in Scheme 1. The 2,6-dihydroxyphthalonitrile **3** was mono-methylated using methyl iodide in DMF,[17] to produce phthalonitrile **4** in 50% yield. The molecular structure of **4** as the crystalline monohydrate was determined[19] at low temperature, and is shown in Figure 1. The molecule is nearly planar, with all nonhydrogen atoms except the methyl C having a mean deviation of 0.007 Å from coplanarity. The methyl carbon atom is twisted 0.055(3) Å out of this plane, forming a C–C–O–C torsion angle of −3.3(3)°. The OH group donates an essentially linear hydrogen bond of O···O distance 2.582(3) Å to the water molecule, and the water molecule donates slightly longer hydrogen bonds, 2.898(4) and 2.917(3) Å, respectively, to nitrile N and OH on adjacent molecules.

In the presence of an excess of zwitterionic 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)[20] and anhydrous potassium carbonate in either acetone (in the case of **3**) or in a mixture of acetone/chloroform 5:1 (in the case of **4**), cobaltacarborane-substituted phthalonitriles **5** and **6** were obtained, in 96 and 92% yield, respectively.[21]

Cyclotetramerization of phthalonitriles **5** and **6** in quinoline at 220 °C for 1 h, in the presence of Zn(II) acetate and a 40-fold excess

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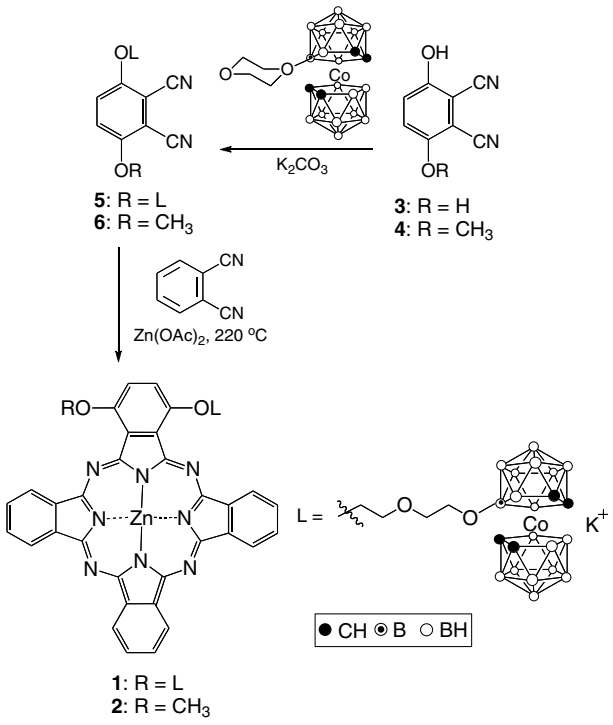

Scheme 1. Synthesis of carboranyl-Pcs **1** and **2**.

of phthalonitrile gave Zn(II)-Pcs **1** and **2** in 15 and 12% yields, respectively.[22] The cobaltacarborane residues were found to survive the above reaction conditions, while they were unstable under lithium- or DBU-catalyzed high temperature condensations, often used in Pc synthesis. The use of a 40-fold excess of phthalonitrile resulted in the production of only one soluble Pc, the target A_3B-type carboranyl-Pc, along with the insoluble A_4-type Pc, which was readily removed by filtration. The crude highly soluble A_3B-type Pcs **1** and **2** were further purified on Sephadex LH-20 (elution with acetone) and by reverse phase HPLC. The functionalization of a pre-formed hydroxyl-Pc with cobaltacarborane residues via the direct ring-opening reaction of zwitterionic 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$), as we have previously reported for porphyrins,[15–18] was also unsuccessful in the case of Pcs due to the limited solubility of the hydroxyl-Pc precursor.

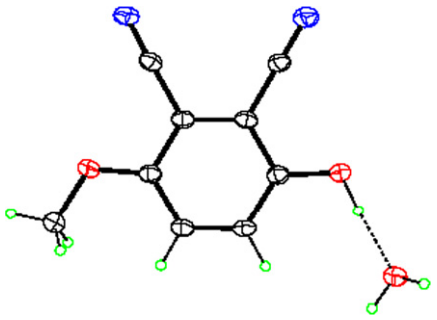

Figure 1. Molecular structure of phthalonitrile 4 as the monohydrate, illustrating hydrogen bonding with the solvent.

Zn(II)-Pcs **1** and **2** are highly soluble in polar organic solvents such as acetone, methanol, DMSO, DMF and THF, and are partially soluble in water. The ^{1}H NMR spectra of Pcs **1** and **2** in DMF-*d* characteristically show the Pc macrocycle protons on the three identical isoindole subunits in the downfield region between 8 and 10 ppm and the cobaltacarborane-substituted isoindole protons in the 7–8 ppm region.[22] As expected, the aliphatic CH_2 protons on the short PEG chains and the dicarbollide CH appear between 3 and 5 ppm. The DEPT spectrum of Pc **1** in Figure 2 clearly shows the dicarbollide CH carbons at 54.15 and 47.24 ppm, while the aliphatic CH_2 carbons appear between 69 and 73 ppm. Furthermore, the ^{13}C NMR spectra of Pcs **1** and **2** show the expected six carbon peaks between 73 and 47 ppm, and in addition, for Pc **2**, the OCH_3 carbon at 57.49 ppm.

The mass spectra (ESI) of the mono-negative molecular ions of Pcs **1** and **2** appear at *m/z* 1430.7214 ($[M-2K+H]^-$) and 1033.4076 ($[M-K]^-$), respectively, and show characteristic isotopic peak patterns due to the presence of the boron atoms. A trace amount of the demethylated byproduct of Pc **2** was observed in the mass spectrum at *m/z* 1019.3934, after the high temperature macrocyclization. Since its separation from Pc **2** was difficult, re-methylation in the presence of excess CH_3I was performed after the macrocyclization step. This reaction was followed by MS-ESI until complete disappearance of the byproduct peak.

The absorption spectra of carboranyl-Pcs **1** and **2** in acetone, DMF, DMSO and methanol show characteristic strong

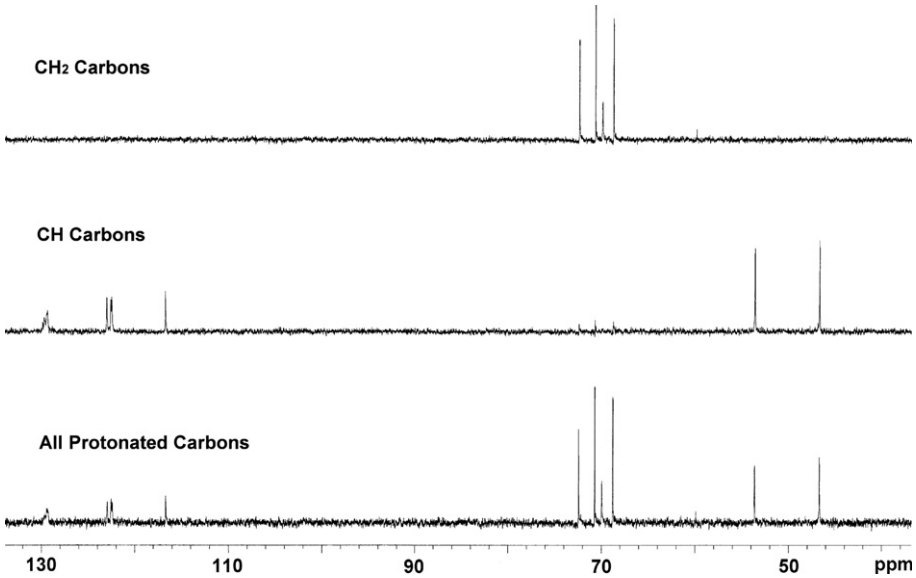

Figure 2. DEPT spectrum of Pc **1** in DMF-*d* (DMF: 34.9, 29.7 ppm).

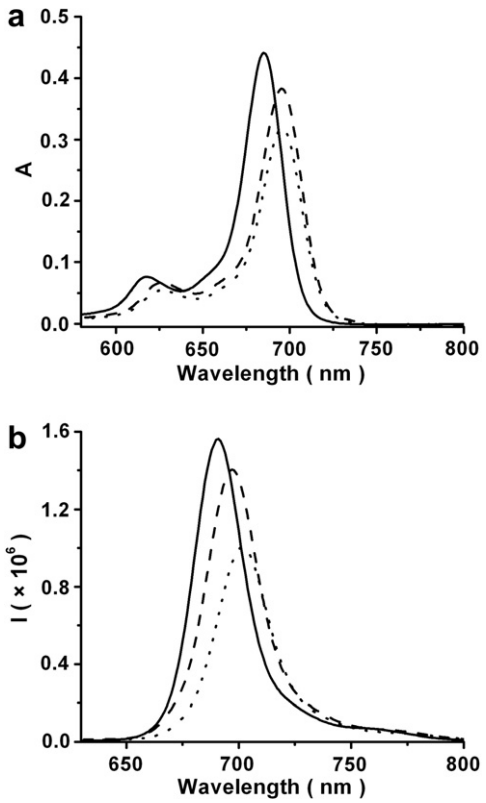

Figure 3. (a) Absorption spectra of carboranyl-Pc **1** at 2.8 μM in acetone (solid line), in DMF (dash line) and in DMSO (dot line); (b) emission spectra of Pc **1** at 300 nM in acetone (solid line), in DMF (dash line) and in DMSO (dot line).

($\varepsilon > 10^5$ L mol^{-1} cm^{-1}) and sharp Q bands that strictly follow the Lambert-Beer law. Interestingly, the λ_{max} for the Q band of Pc **1** was found to be 686 nm in acetone, whereas it was 695 nm in DMF and DMSO, as shown in Figure 3a. Such solvatochromic shifts have been previously observed for carborane-containing aryl ethers.[23] Similarly, the fluorescence emission spectra of Pc **1** (Fig. 3b) showed λ_{max} peaks at 692 nm in acetone, 697 nm in DMF, and 702 nm in DMSO, and fluorescence quantum yields (using ZnPc in 1-chloronaphthalene as standard)[24] in the 0.11–0.13 range. Pc **2** also showed similar absorption and emission characteristics, with 6–12 nm red-shifted bands in DMF and DMSO compared with those in acetone, and quantum yields in the range 0.10–0.14 in these solvents. Both Pcs **1** and **2** showed relatively large Stoke's shifts (6–8 nm) in methanol, acetone and DMSO, but smaller values (2 nm) in DMF.

In summary, we have synthesized two new A_3B-type cobalta-carborane-containing Zn(II)-Pcs **1** and **2** in 12–15% yields. The X-ray structure of a key intermediate is presented. The optimized reaction conditions use a 40-fold excess of phthalonitrile over a carboranyl-functionalized phthalonitrile (**5** or **6**) and take advantage of the easy separation of the target A_3B-type Pcs from the insoluble (unsubstituted) A_4-type Pc. Pcs **1** and **2** are highly soluble in polar solvents such as methanol, acetone, DMF and DMSO, their absorption and emission properties are solvent-dependent, and have ~0.1 fluorescence quantum yields. Their properties suggest that they may have potential application as dual sensitizers in the PDT and BNCT treatment of tumors.

Acknowledgements

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19. *Phthalonitrile* **4**: $C_9H_6N_2O_2{\cdot}H_2O$, M_r = 192.17, monoclinic space group $P2_1$, a = 3.749 (3), b = 6.935 (5), c = 17.204 (14) Å, β = 91.00 (3)°, V = 447.2 (6) Å^3, Z = 2, D_x = 1.427 Mg m^{-3}, Mo Kα radiation, λ = 0.71073 Å, T = 90 K, μ = 0.11 mm^{-1}, θ_{max} = 30.1°, colorless plate 0.32 × 0.23 × 0.02 mm, Nonius KappaCCD diffractometer, 5342 measured reflections, 1407 independent, 1065 with $I > 2\sigma(I)$, R_{int} = 0.035, R = 0.046, $wR(F^2)$ = 0.118 for 137 refined parameters and 1407 data, CCDC 682543.
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21. *Selected spectroscopic data for carboranylphthalonitriles:* **5**, ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.62 (br, 2H, Ar-H), 4.34 (t, J = 5.0 Hz, 4H, OCH_2), 4.22 (br, 8H, OCH_2), 3.86 (t, J = 5.0 Hz, 4H, OCH_2), 3.59 (s, 8H, CH), 3.00–1.50 (br, 34H, BH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 156.31, 121.20, 114.04, 105.00 (Ar-C, CN), 72.99, 70.84, 69.98, 69.27 (OCH_2), 54.91, 47.20 (CH). HRMS-ESI: m/z 489.8393 $[M-2K]^{2-}$, calcd for $[C_{24}H_{60}B_{36}Co_2N_2O_6]^{2-}$ 489.8374. **6**, ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.68 (d, J = 9.5 Hz, 1H, Ar-H), 7.56 (d, J = 9.5 Hz, 1H, Ar-H), 4.34 (t, J = 4.7 Hz, 2H, OCH_2), 4.24 (br, 4H, OCH_2), 3.99 (s, 3H, OCH_3), 3.84 (t, J = 4.7 Hz, 2H, OCH_2), 3.57 (s, 4H, CH), 3.00–1.50 (br, 17H, BH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 156.84, 156.34, 121.69, 119.49, 114.03, 105.33, 104.40 (Ar-C, CN), 73.10, 71.06, 70.21, 69.35 (OCH_2), 57.45 (OCH_3), 55.06, 47.26 (CH). HRMS-ESI: m/z 584.3677 $[M-K]^-$, calcd for $[C_{17}H_{34}B_{18}CoN_2O_4]^-$ 584.3653.
22. *Selected spectroscopic data for carboranyl-Pcs:* **1**, ^{1}H NMR (DMF-d, 250 MHz): δ *9.55–9.45* (m, 6H, Ar-H), 8.34–8.26 (m, 6H, Ar-H), 7.81 (br, 2H, Ar-H), 5.03–4.99 (m, 4H, OCH_2), 4.54–4.50 (m, 4H, OCH_2), 4.39 (s, 4H, CH), 4.36 (s, 4H, CH), 4.08 (t, J = 5.2 Hz, 4H, OCH_2), 3.98 (t, J = 5.2 Hz, 4H, OCH_2), 3.00–1.50 (br, 34H, BH). ^{13}C NMR (DMF-d, 63 MHz): δ 154.26, 154.12, 153.98, 153.77, 151.57, 139.67, 139.21, 130.13, 129.79, 123.46, 123.03, 122.93, 117.12 (Ar-C), 72.98, 71.27, 70.49, 69.34 (OCH_2), 54.15, 47.24 (CH). HRMS-ESI: m/z 1430.7214 $[M-2K+H]^-$, calcd for $[C_{48}H_{73}B_{36}Co_2N_8O_6Zn]^-$ 1430.7214. UV–vis (acetone): λ_{max} (log ε) 686 (5.36), 618 (4.62). **2**, ^{1}H NMR (DMF-d, 400 MHz): δ 9.35 (br, 6H, Ar-H), 8.23–8.22 (m, 6H, Ar-H), 7.61 (br, 2H, Ar-H), 4.96 (br, 2H, OCH_2), 4.60 (s, 3H, OCH_3), 4.49 (t, J = 4.7 Hz, 2H, OCH_2), 4.41 (s, 2H, CH), 4.37 (s, 2H, CH), 4.06 (t, J = 5.4 Hz, 2H, OCH_2), 3.97 (t, J = 5.4 Hz, 2H, OCH_2), 3.00–1.50 (br, 17H, BH). ^{13}C NMR (DMF-d, 100 MHz): δ 154.08, 153.78, 153.65, 152.26, 151.07, 139.25, 139.05, 130.11, 129.90, 129.77, 123.37, 122.95, 117.09, 115.21 (Ar-C), 72.98, 71.21, 70.42, 69.39 (OCH_2), 57.49 (OCH_3), 54.27, 47.27 (CH). HRMS-ESI: m/z 1033.4076 $[M-K]^-$, calcd for $[C_{41}H_{46}B_{18}CoN_8O_4Zn]^-$ 1033.4071. UV–vis (acetone): λ_{max} (log ε) 684 (5.26), 618 (4.49).
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