Expeditious synthesis of porphyrin–cobaltacarborane conjugates†

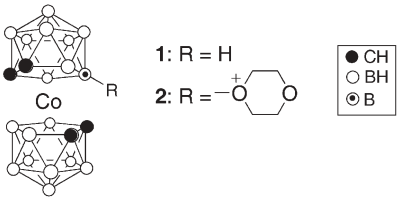
Erhong Hao and M. Graça H. Vicente*

Received (in Corvallis, OR, USA) 11th October 2004, Accepted 7th December 2004
First published as an Advance Article on the web 20th January 2005
DOI: 10.1039/b415649h

Two porphyrin–cobaltacarborane conjugates 5 and 6 were prepared in high yields *via* a nucleophilic ring-opening reaction of 2. These novel boron-rich and fluorescent compounds have potential application as boron delivery agents for the boron neutron capture therapy of tumors.

The selective delivery of large amounts of boron (15–30 μg g^{-1}) to individual tumor cells is crucial for successful boron neutron capture therapy (BNCT) of tumors.[1] Several boron-containing porphyrin derivatives have been synthesized and evaluated as boron delivery agents for BNCT.[2,3] Most of these compounds contain 2 to 4 boron cages per porphyrin platform and only a few are able to deliver therapeutic amounts of boron to tumors with acceptable toxicity.[2–5] Porphyrins of higher boron content could potentially deliver larger amounts of boron to target cells with minimal systemic toxicity. Two porphyrin derivatives bearing eight boron cages linked to the porphyrin ring *via* ester[6] or carbon–carbon bonds[7] have previously been reported. Herein we describe the high yield syntheses of two fluorescent porphyrin–cobaltacarborane conjugates, containing eight dicarbollide cages per porphyrin unit linked *via* ethylene glycol chains.

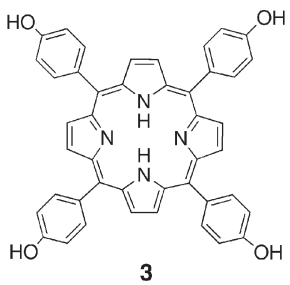
Metallacarboranes belong to the large family of metallocene-type complexes.[8] Among these, the cobaltabisdicarbollide anion $[Co(C_2B_9H_{11})_2]^-$ (**1**) has attracted much attention because of its remarkable stability towards acids, moderate bases, high temperature and to radiation.[9] These properties have made cobaltacarborane **1** and some of its metallo analogues good candidates for medical imaging[9] and radiotherapy.[10] The recent discovery of a high yield synthesis of zwitterionic [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{11}$)][11] (**2**) has opened the door to more efficient routes for the preparation of new mono-substituted cobaltacarborane complexes. Compound **2** has been shown to undergo a dioxane ring-opening reaction in the presence of a variety of nucleophilic reagents, such as fluoride, chloride, and hydroxide anions,[12] imide, cyanide and amines,[13] phenolate[14] and pyrrolyl salts.[15] We have discovered an easy, efficient, high yield synthesis of novel porphyrin–cobaltacarborane conjugates of high boron content *via* the dioxane ring-opening reaction of **2** using porphyrins **3** and **4** as the nucleophilic species.



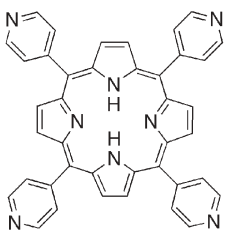
† Electronic supplementary information (ESI) available: Spectroscopic data for compounds **5–7**. See http://www.rsc.org/suppdata/cc/b4/b415649h/

*vicente@lsu.edu

Compound **2** was obtained, as described in the literature,[16] from the reaction of cobaltacarborane **1** with dioxane in the presence of $BF_3{\cdot}Et_2O$. The conjugation of 5,10,15,20-tetra(4-hydroxyphenyl)-porphyrin **3** with cobaltacarborane **2** was achieved in 85% yield upon activation of the porphyrin hydroxyl groups with either cesium carbonate or potassium carbonate in anhydrous acetone, thus affording conjugate **5** as the cesium or potassium salts. Similarly, the zwitterionic porphyrin conjugate **6** was prepared in 88% yield upon refluxing 5,10,15,20-tetra(4-pyridyl)porphyrin **4** in a 1 : 1 mixture of chloroform and acetonitrile, in the presence of excess of compound **2**. Both reactions were monitored by TLC and ^{1}H-NMR spectroscopy, and the target conjugates **5** (as the Cs or K salt) and **6** were purified by column chromatography on silica gel, using ethyl acetate/acetone mixtures for elution, followed by filtration on a Sephadex LH-20 column using methanol (for **5**) or acetonitrile (for **6**) as eluant. Conjugate **5** was also prepared, although in only 20% yield, from condensation of the new aldehyde **7** with pyrrole, under Lindsey-type conditions (using $BF_3{\cdot}Et_2O$ as the catalyst and DDQ as the oxidizing agent).[17] Aldehyde **7** was prepared in 90% yield from reaction of commercially available 4-hydroxybenzaldehyde with cobaltacarborane **2** in the presence of potassium carbonate.



3



4

Compound **5Cs** (obtained by conjugation in the presence of cesium carbonate) is easily converted into **5K** or **5Na** using an ion-exchange Dowex resin in the K^+ or Na^+ forms, respectively. Conjugates **5Cs**, **5K**, **5Na** and **6** are highly soluble in polar organic solvents, such as acetone, ethyl acetate, acetonitrile, DMF and DMSO. Interestingly, while **5** is also soluble in methanol, compound **6** is not, and the only water soluble conjugates are **5K** and **5Na**.

Compounds **5** and **6** were characterized by HRMS MALDI-TOF, ^{1}H-NMR, ^{13}C-NMR, UV-Vis and fluorescence spectroscopy (see ESI†). Compound **5Na** displays a peak in the MALDI-TOF spectrum at 2415.5407 while **6** shows a peak at 2267.5351. The ^{1}H-NMR spectrum of **5Cs** shows the β-pyrrolic protons as a singlet at 8.94 ppm, two doublets for the phenyl protons at 8.17 and 7.43 ppm, four broad singlets corresponding to the OCH_2 protons at 4.48, 4.37, 4.30 and 4.05 ppm, the

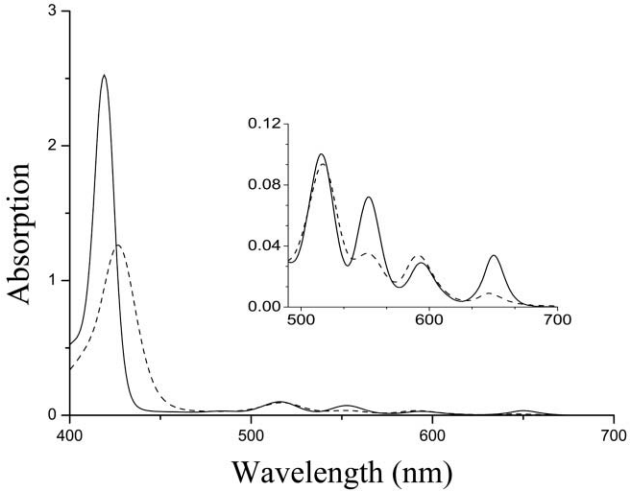


Fig. 1 Optical spectra of porphyrins **5** (full line) and **6** (dashed line) at a concentration of 6×10^{-6} M in acetone solution.

dicarbollide cage CH protons as a singlet at 3.76 ppm and the inner NH protons upfield at −2.70 ppm. The ^{13}C-NMR of **5Cs** characteristically shows six upfield peaks at 73.6, 71.0, 69.9, 69.3, 55.9 and 47.9 ppm corresponding to the OCH_2 and CH carbons, in addition to the aromatic carbons. Porphyrin **6** displays in its ^{1}H-NMR spectrum a singlet at 9.26 ppm for the β-pyrrolic protons, two doublets at 9.80 and 9.15 ppm for the pyridyl protons, four broad singlets at 5.36, 4.43, 4.05 and 4.00 ppm for the OCH_2 protons, the dicarbollide CH protons at 3.85 ppm and the NH protons at −2.89 ppm. The ^{13}C-NMR spectrum of **6** also shows the expected six upfield carbons at 74.0, 70.6, 70.5, 62.9, 53.3 and 47.9 ppm. The UV-Vis spectra of conjugates **5K** and **6** are shown in Fig. 1 and the fluorescence emission spectra in Fig. 2. Both conjugates show five bands in their optical spectra, as do their precursors **3** and **4**, with the Soret band at 419 nm for **5** and 427 nm for **6**. The observed broadening and 15 nm red-shifted Soret band of conjugate **6** as compared with the starting porphyrin **4**, may indicate that this zwitterionic conjugate forms aggregates in solution, even at micromolar concentrations. The fluorescence spectra of **5K** and **6** (Fig. 2) show emissions at 656 and 653 nm, respectively, in acetone solution upon excitation at 512 nm, which indicates that they retain the important fluorescence properties characteristic of porphyrin macrocycles.

In summary, we have described an expeditious and high yielding synthetic route to new porphyrin–cobaltacarborane conjugates of high boron content. These porphyrin conjugates show absorption and emission spectra characteristic of porphyrin-type compounds.

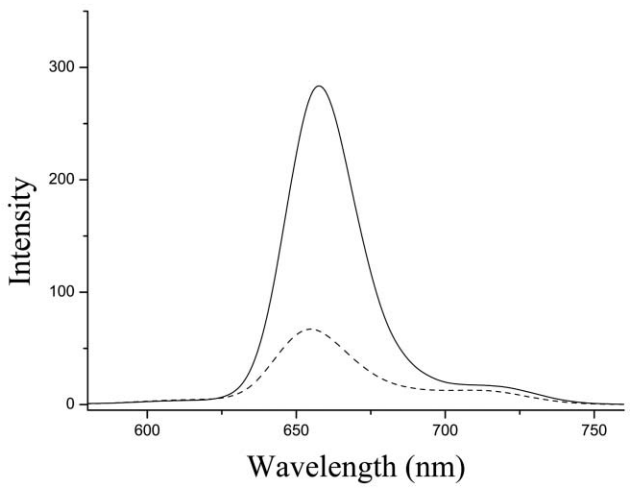
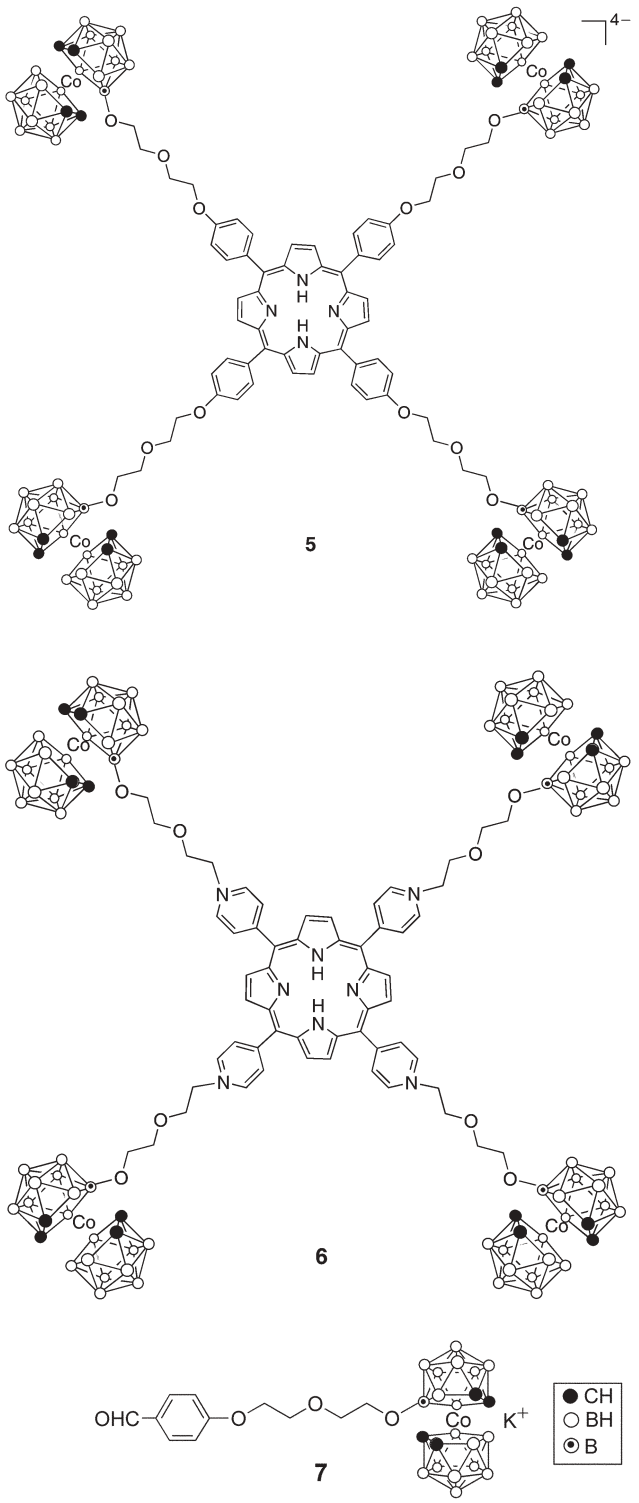


Fig. 2 Fluorescence emission spectra of porphyrins **5** (full line) and **6** (dashed line) at a concentration of 6×10^{-6} M in acetone solution (excitation at 512 nm).



The new conjugates **5** and **6** contain 72 boron atoms per porphyrin platform, are fluorescent and therefore can find application as boron delivery agents for the BNCT of tumors. The biological evaluation of these conjugates is currently under way in our laboratories.

The work described herein was supported by NIH grant CA098902.

Erhong Hao and M. Graça H. Vicente*
Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA. E-mail: vicente@lsu.edu; Fax: 225 578 3458; Tel: 225 578 7405

Notes and references

1 (*a*) M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950; (*b*) H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni and J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
2 M. G. H. Vicente, *Curr. Med. Chem. Anti-Cancer Agents*, 2001, **1**, 175.
3 V. I. Bregadze, I. B. Sivaev, D. Gabel and D. Wöhrle, *J. Porphyrins Phthalocyanines*, 2001, **5**, 767.
4 M. Miura, P. L. Micca, C. D. Fisher, C. R. Gordon, J. C. Heinrichs and D. N. Slatkin, *Br. J. Radiol.*, 1998, **71**, 773.
5 M. G. H. Vicente, A. Wickramasinghe, D. J. Nurco, H. J. H. Wang, M. M. Nawrocky, M. S. Makar and M. Miura, *Bioorg. Med. Chem.*, 2003, **11**, 3101.
6 J. Lee, Y. S. Park, Y. Kim and H. C. Kang, *Bull. Korean Chem. Soc.*, 1999, **20**, 1371.
7 (*a*) M. G. H. Vicente, S. J. Shetty, A. Wickramasinghe and K. M. Smith, *Tetrahedron Lett.*, 2000, **41**, 7623; (*b*) V. Gottumukkala, R. Luguya, F. R. Fronczek and M. G. H. Vicente, *Bioorg. Med. Chem.*, 2005, **13**, in press.
8 M. F. Hawthorne, D. C. Young and P. A. Wegner, *J. Am. Chem. Soc.*, 1965, **87**, 1818.
9 E. Makrlík and P. Vañura, *Talanta*, 1985, **32**, 423.
10 (*a*) M. F. Hawthorne, A. Varadavajan, C. B. Knobler, S. Chakrabarti, R. J. Paxton, B. G. Beatty and F. L. Curtis, *J. Am. Chem. Soc.*, 1990, **112**, 5365; (*b*) M. F. Hawthorne and A. Maderna, *Chem. Rev.*, 1999, **99**, 3421.
11 J. Plesek, S. Hermánek, A. Franken, I. Císarová and C. Nachtigal, *Coll. Czech. Chem. Commun.*, 1997, **62**, 47.
12 T. Peymann, K. Kuck and D. Gabel, *Inorg. Chem.*, 1997, **36**, 5138.
13 I. B. Sivaev, Z. A. Starikova, S. Sjöberg and V. I. Bregadze, *J. Organomet. Chem.*, 2002, **649**, 1.
14 J. Plesek, B. Grüner, S. Hermánek, J. Báca, V. Marecek, J. Jänchenová, A. Lhotsky, K. Holub, P. Selucky, J. Rais, I. Císarová and J. Cáslavsky, *Polyhedron*, 2002, **21**, 975.
15 J. Llop, C. Masalles, C. Viñas, F. Teixidor, R. Sillanpää and R. Kivekäs, *Dalton Trans.*, 2003, 556.
16 F. Teixidor, J. Pedrajas, I. Rojo, C. Viñas, R. Kivekäs, R. Sillanpää, I. Sivaev, V. Bregadze and S. Sjöberg, *Organometallics*, 2003, **22**, 3414.
17 J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney and A. M. Marguerettaz, *J. Org. Chem.*, 1987, **52**, 827.

