Synthesis of *closo*-monocarbon carborane-substituted natural porphyrins

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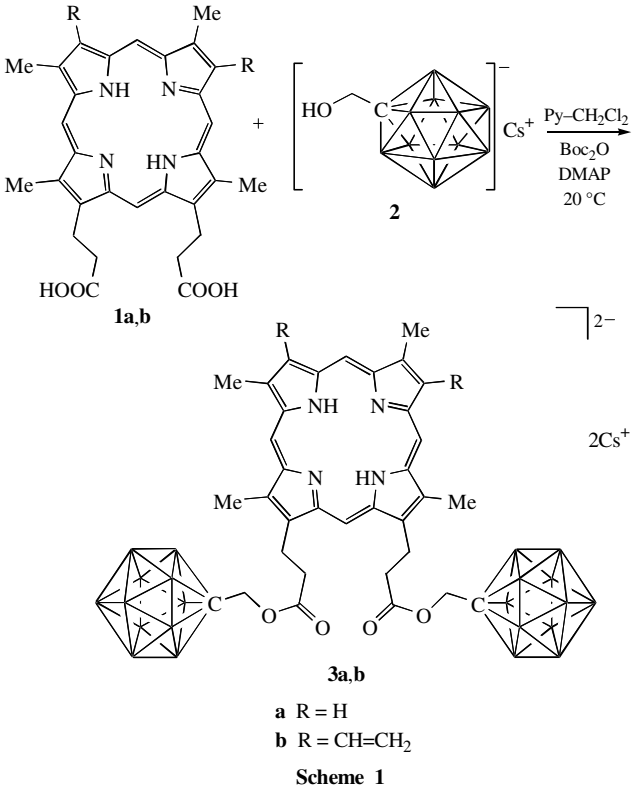
Previously unknown 1,3,5,8-tetramethyl-6,7-di[2′-(*closo*-monocarbon carborane-1′′-yl caesium)methoxycarbonylethyl]porphyrin and 1,3,5,8-tetramethyl-2,4-divinyl-6,7-di[2′-(*closo*-monocarbon carborane-1′′-yl caesium)methoxycarbonylethyl]porphyrin were synthesised in the reactions of deuteroporphyrin IX and protoporphyrin IX, respectively, with (1-hydroxymethyl-*closo*-monocarbon carborane)caesium.

Currently, considerable attention is paid to the synthesis of carboranyl-substituted heterocycles for the use as pharmaceuticals for the boron neutron-capture therapy (BNCT) of cancer.[1] Among these compounds are carboranylporphyrins, which were synthesised more than two decades ago.[2] Interest in the synthesis of boronated porphyrins is caused by the ability of these compounds to accumulate selectively and to persist in tumour cells for a long time.

Previously,[3–5] we described the syntheses of carboranyl-substituted porphyrins, in which the carborane polyhedron is bound to the porphyrin ring through the boron atom of carborane, which allows further functionalization at carbon atoms of the carborane polyhedron in order to decrease the lipophilicity of carborane substituents.

Current progress in the carborane chemistry provides an opportunity to prepare new functionalised organic derivatives of monocarbon carborane,[6] which are convenient synthons for the synthesis of a new type of monocarbon carborane-substituted porphyrins for BCNT.

This work is devoted to the synthesis of novel monocarbon carborane-substituted porphyrins. Using natural deuteroporphyrin IX **1a**, protoporphyrin IX **1b** and (1-hydroxymethyl-*closo*-monocarbon carborane)caesium **2**, we obtained anionic monocarbon carborane derivatives of deuteroporphyrin IX **3a** and protoporphyrin IX **3b**, in which the *closo*-monocarbon carborane substituent is bound to the carboxylic groups of porphyrins **1a**,**b** through the carbon atom of the *closo*-monocarbon carborane polyhedron (Scheme 1).†



Scheme 1

The reactions were performed in a methylene chloride–pyridine (1:1) mixture. Upon activation of carboxylic groups of porphyrins **1a**,**b** with di-*tert*-butylpyrocarbonate (Boc_2O) in the 1:2 ratio, compounds **3a** and **3b** were obtained as dark claret substances in 52 and 50% yields, respectively. Note that, although they are salts, compounds **3a** and **3b** are, nevertheless, poorly soluble in hydroxy-containing solvents. At the same time, they are readily soluble in THF, DMSO, DMF, MeCN and C_5H_5N. It is believed that the use of Na^+, K^+ or lipophilic organic cations instead of the Cs^+ cation increases the water solubility of these compounds. The structures of **3a** and **3b** were confirmed by mass spectrometry and electronic absorption, IR and ^1H NMR spectroscopy.‡

† *General procedure for the synthesis of porphyrins* **3a**,**b**. To a solution of porphyrin **1a** or **1b** (0.196 mmol) in a mixture of 5 ml C_5H_5N and 5 ml CH_2Cl_2, Boc_2O (0.22 mmol) was added, and the mixture was stirred for 10 min at 0 °C. Then, compound **2** (0.392 mmol) and 4-dimethylaminopyridine (15 mg) were added, and the mixtiure was stirred for 1 h at 20 °C. The reaction was monitored by TLC [Silufol plates, $CHCl_3$–MeOH (9:1) as an eluent]. After completion of the reaction, the solvents were removed *in vacuo*, $CHCl_3$ (5 ml) was added to the residue, and crystals of precipitated porphyrins **3a** or **3b** precipitated were filtered off. Recrystallisation from a DMSO–water mixture gave porphyrins **3a** and **3b** in 52 and 50% yields, respectively.

‡ Electronic absorption spectra were recorded on a Varian MAT 731 instrument. IR spectra were recorded on a UR-20 spectrometer as KBr pellets. ^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer at 400.13 MHz in [$^2H_6$]DMSO with TMS as a standard.

1,3,5,8-Tetramethyl-6,7-di[2′-(closo-*monocarbon carborane-1′′-yl caesium)methoxycarbonylethyl]porphyrin* **3a**: yield 52%. ^1H NMR, δ: 10.82 (s, 1H, *meso*-H), 10.31 (s, 1H, *meso*-H), 10.27 (s, 2H, *meso*-H), 9.33 (s, 1H, β-pyrrole), 9.32 (s, 1H, β-pyrrole), 4.35 (s, 4H, OCH_2), 3.76 (s, 6H, Me), 3.73 (s, 6H, Me), 3.60 (m, 4H, CH_2CH_2CO), 2.92 (m, 4H, CH_2CH_2CO), –4.06 (br. s, 2H, NH). MS, *m*/*z*: 1086.45 (M^+). Electronic spectrum, λ_{max}/nm ($\varepsilon\times10^{-3}$) (DMSO): 399.4 (43.71), 496.8 (9.66), 528.4 (5.97), 564.8 (4.78), 618.8 (2.5). IR (ν/cm^{-1}): 3320 (NH), 2527 (BH), 1723 (C=O). Found (%): C, 37.93; H, 4.86; N, 5.27. Calc. for $C_{34}H_{54}B_{22}Cs_2N_4O_4$ (%): C, 37.58; H, 4.97; N, 5.16.

1,3,5,8-Tetramethyl-2,4-divinyl-6,7-di[2′-(closo-*monocarbon carborane-1′′-yl caesium)methoxycarbonylethyl]porphyrin* **3b**: yield 50%. ^1H NMR, δ: 10.22 (s, 1H, *meso*-H), 10.12 (s, 2H, *meso*-H), 10.09 (s, 1H, *meso*-H), 8.42 (br. s, 1H, C*H*=CH_2), 6.40 (d, 1H, =CH*H*, $^3J_{trans}$ 17.2 Hz), 6.19 (d, 1H, =C*H*H, $^3J_{cis}$ 10.4 Hz), 4.29 (s, 4H, OCH_2), 3.56 (m, 4H, CH_2CH_2CO), 3.08 (m, 4H, CH_2CH_2CO), 2.50 (s, 12H, Me), –4.23 (br. s, 1H, NH), –4.30 (br. s, 1H, NH). MS, *m*/*z*: 1138.53 (M^+). Electronic spectrum, λ_{max}/nm ($\varepsilon\times10^{-3}$) (DMSO): 397.8 (65.40), 495.6 (11.85), 527.6 (6.92), 563.8 (5.57), 617.8 (2.09). IR (ν/cm^{-1}): 3327 (NH), 2532 (BH), 1714 (C=O), 1657 (C=C). Found (%): C, 40.37; H, 4.98; N, 5.07. Calc. for $C_{38}H_{58}B_{22}Cs_2N_4O_4$ (%): C, 40.09; H, 5.10; N, 4.92.

Thus, the anionic nature of the compounds synthesised, as well as the effect of the cation, makes them more promising than the currently known carboranyl-substituted porphyrins for the preparation of water-soluble pharmaceuticals for BNCT.

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References

1 A. 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 R. C. Hausholter and R. W. Rudolph, *J. Am. Chem. Soc*., 1978, **100**, 4628.
3 R. P. Evstigneeva, V. N. Luzgina, V. A. Ol'shevskaya and L. I. Zakharkin, *Dokl. Ross. Akad. Nauk*, 1997, **357**, 637 (*Dokl. Chem*., 1997, **357**, 299).
4 L. I. Zakharkin, V. A. Ol'shevskaya, R. P. Evstigneeva, V. N. Luzgina, L. E. Vinogradova and P. V. Petrovskii, *Izv. Akad. Nauk, Ser. Khim*., 1998, 347 (*Russ. Chem. Bull*., 1998, **47**, 340).
5 L. I. Zakharkin, V. A. Ol'shevskaya, S. Yu. Panfilova, P. V. Petrovskii, V. N. Luzgina and R. P. Evstigneeva, *Izv. Akad. Nauk, Ser. Khim*., 1999, 2337 (*Russ. Chem. Bull*., 1999, **48**, 2312).
6 L. I. Zakharkin, V. A. Ol'shevskaya, P. V. Petrovskii and J. H. Morris, *Mendeleev Commun*., 2000, 71.

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