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Synthesis of a cycloimide bacteriochlorin *p* conjugate with the *closo*-dodecaborate anion

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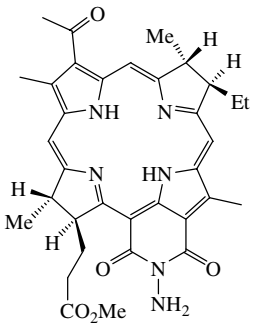
A new derivative of natural bacteriochlorophyll *a*, namely, a cycloimide bacteriochlorin *p* conjugate with the *closo*-dodecaborate anion, was prepared.

Photodynamic therapy[1] and boron neutron capture therapy[2–4] are promising methods for treating tumors. Both methods are based on the accumulation of special compounds in a tumor, which will subsequently acquire enhanced toxicity causing degradation of cancer cells after specific physical effects (irradiation with light or thermal neutrons). Thus, the synthesis of porphyrins and phthalocyanines based on boron polyhedra is of particular interest.

Porphyrin-type compounds are used as photodynamic agents. Their efficiency depends on the nature of light used to irradiate the tumor. The longer the wavelength, the deeper the light penetration into a tissue or tumor. Porphyrin and phthalocyanine derivatives containing fragments of polyhedral boron hydrides were synthesised.[5–9] However, conjugates of the *closo*-dodecaborate anion with bacteriochlorins are not reported to date. The latter have a therapeutic absorption band at 770–840 nm, which provides light penetration into a tissue by 15–20 mm compared to 3–4 mm for porphyrins.[1] Conversely, *closo*-dodecaborate derivatives are colourless compounds which do not possess specific affinity toward malignant neoplasms, but they contain boron atoms, which can capture thermal neutrons and generate α-particles, which will degrade the tumor.

Here, we describe the synthesis of a cycloimide bacteriochlorin *p* conjugate with the 12-vertex $[B_{12}H_{12}]^{2-}$ anion. The synthesis was carried out using *N*-aminocycloimide bacteriochlorin *p* (**1**) as a starting material. The synthesis and reactivity of **1** were reported previously.[10]



1

In order to introduce the boron-containing fragment to the bacteriochlorin macrocycle, carboxylic acid **4**, a derivative of the *closo*-dodecaborate anion, was synthesised (Scheme 1).†

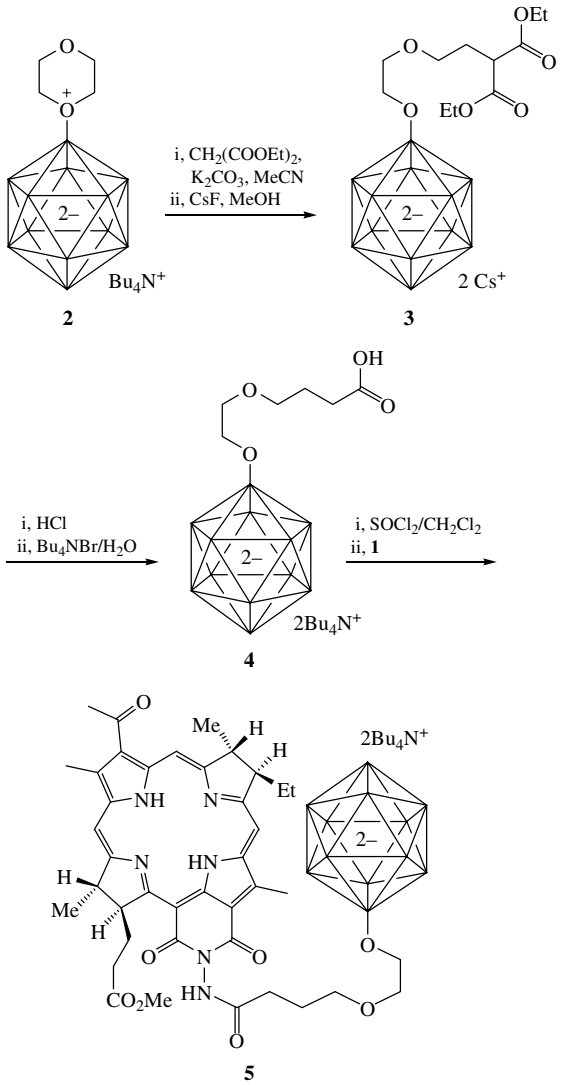
Previously,[11] it was found that the oxonium derivatives of $[B_{12}H_{12}]^{2-}$ react with nucleophiles. β,β-Dicarbonyl compounds or their analogues can be used as such nucleophiles. In this study, dioxonium derivative **2** was introduced in the reaction with diethyl malonate. This resulted at first in a diester tetrabutylammonium salt, which was converted *in situ* to cesium salt **3** to obtain a water-soluble derivative for the next step. Com-pound **3** was characterised by ^{1}H, ^{11}B and ^{13}C NMR spectra and elemental analysis. In the ^{11}B NMR spectrum, there are four signals with a ratio typical of a monosubstituted B_{12} system. The signal of the substituted boron atom at δ 5.6 ppm is shifted upfield by ~3 ppm compared to starting material **2** at δ

† *N*-Aminocycloimide bacteriochlorine p_6[10] and dioxonium derivative **2**[11] were prepared as previously described.

3: yield 62%, mp 200 °C (decomp.). ^{1}H NMR (400 MHz, D_2O) δ: 4.14 (q, 4H, OC*H*$_2$Me), 3.56 [t, 1H, C*H*(COEt)$_2$], 3.49 (m, 6H, CH_2O), 2.06 (m, 2H, CH_2CH_2CH), 1.17 (t, 6H, OCH_2*Me*), 1.9–0.1 (br. m, 11H, BH). ^{13}C NMR (400 MHz, D_2O/[$^2H_6$]DMSO, 10:1 v/v) δ: 172.7 (CO), 72.1, 69.4, 68.7 (CH_2O), 64.2 (O*C*H$_2$Me), 54.6 [*C*H(COEt)$_2$], 29.7 (CH_2*C*H$_2$CH), 14.8 (OCH_2*Me*). ^{11}B NMR (400 MHz, D_2O) δ: 5.6 [s, 1B, B(1)], –17.2 [d, 5B, B(2–6)], –19.0 [d, 5B, B(7–11)], –24.0 [d, 1B, B(12)]. Calc. for $C_{11}H_{30}B_{12}Cs_2O_6$ (%): C, 20.21; H, 4.62; B, 19.84. Found (%): C, 20.14; H, 4.69; B, 19.76.

4: yield 82%, mp 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.96 (br. s, 1H, OH), 3.72 (t, 2H, CH_2O), 3.47 (t, 2H, CH_2O), 3.33 (t, 2H, CH_2O), 3.11 (m, 16H, NC*H*$_2$CH$_2$CH$_2$Me), 2.21 (t, 2H, C*H*$_2$COOH), 1.67 (m, 2H, C*H*$_2$CH$_2$COOH), 1.53 (m, 16H, NCH$_2$C*H*$_2$CH$_2$Me), 1.27 (m, 16H, NCH$_2$CH$_2$C*H*$_2$Me), 0.89 (t, 24H, NCH$_2$CH$_2$CH$_2$*Me*), 1.9–0.1 (br. m, 11H, BH). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 174.8 (CO), 69.7, 68.7 (CH_2O), 57.9 (N*C*H$_2$CH$_2$Me), 30.8 (*C*H$_2$COOH), 25.1 (*C*H$_2$CH$_2$COOH), 23.5 (NCH$_2$*C*H$_2$CH$_2$Me), 19.6 (NCH$_2$CH$_2$*C*H$_2$Me), 13.9 (NCH$_2$CH$_2$CH$_2$*Me*). ^{11}B NMR (400 MHz, $CDCl_3$) δ: 5.4 [s, 1B, B(1)], –16.2 [d, 10B, B(2–11)], –20.2 [d, 1B, B(12)]. Calc. for $C_{38}H_{94}B_{12}N_2O_4$ (%): C, 59.05; H, 12.26; N, 3.62; B, 16.78. Found (%): C, 58.95; H, 12.14; N, 3.68; B, 16.65.

5: yield 82%. UV-VIS [$CHCl_3$, λ/nm (relative intensities)]: 370, 423 (Soret), 557 and 838 (1:0.52:0.47:0.66). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (br. s, 1H, NHCO), 9.25 (s, 1H, 10-H), 8.74 (s, 1H, 5-H), 8.65 (s, 1H, 20-H), 5.16 (m, 1H, 17-H), 4.30 (m, 2H, 8-H, 7-H), 4.12 (m, 1H, 8-H), 3.83 (br. m, 6H, OCH_2), 3.70 (s, 3H, 12^1-Me), 3.59 (s, 3H, 17^5-Me), 3.55 (s, 3H, 2^1-Me), 3.31 (m, 16H, N*C*H$_2$CH$_2$CH$_2$Me), 2.89 (m, 2H, 8^1-CH_2), 2.41 (t, 2H, 17^2-CH_2), 2.19 (m, 4H, 17^1-CH_2 + C*H*$_2$CONH), 1.84 (br. m, 8H, 7-Me, 8-Me + C*H*$_2$CH$_2$CONH), 1.67 (m, 16H, NCH$_2$C*H*$_2$CH$_2$Me), 1.49 (m, 16H, NCH$_2$CH$_2$C*H*$_2$Me), 1.13 (t, 3H, 8^2-Me), 1.02 (t, 24H, NCH$_2$CH$_2$CH$_2$*Me*), –0.35 (br. s, 1H, NH), –0.56 (br. s, 1H, NH). ^{11}B NMR (400 MHz, $CDCl_3$) δ: 6.2 [s, 1B, B(1)], –16.5 [d, 5B, B(2–6)], –17.6 [d, 5B, B(7–11)], –22.4 [d, 1B, B(12)].



2 **3** **4** **5**

Scheme 1 Synthesis of conjugate **5**.

9.2 ppm. This is usual for conversion of BO^+ system into B–O, which proves unambiguously the opening of the dioxonium ring. In the ^{13}C NMR spectrum, a signal of the ester CO group at δ 172.7 ppm was observed.

The subsequent acidic hydrolysis of compound **3** followed by decarboxylation led to acid **4** in a high yield. The structure of **4** was confirmed by IR, ^1H, ^{11}B, and ^{13}C NMR spectra, as well as by elemental analysis. In the IR spectrum, absorption bands of the CO group (1726 cm^{-1}) and the B–H groups (2470 cm^{-1}) were observed. The ^{11}B NMR spectrum contains four signals with a ratio of 1:5:5:1, typical of monosubstituted B_{12} polyhedra. In the ^{13}C NMR spectrum, there is a characteristic signal of the carboxyl CO group at δ 174.8 ppm (CO) and signals at δ 30.8 ppm (CH_2COOH) and 25.1 ppm (CH_2CH_2COOH), which confirm the decarboxylation.

Acid **4** was transferred into corresponding acid chloride *in situ*. The latter was introduced into reaction with **1**. The reaction took 4 h, and the formation of the product was monitored by TLC. As a result, conjugate **5** was formed. The structure of the new compound was confirmed by electronic, ^1H and ^{11}B NMR spectra. In the electronic spectrum, a bathochromic shift of the Q band from 832 to 838 nm is observed, which proves the substitution of exocyclic amino group at the nitrogen atom. The ^{11}B NMR spectrum of the compound obtained contains a set of signals characteristic of the monosubstituted *closo*-dodecaborate anion. The ^1H NMR spectrum shows signals typical of both the boron-containing fragment of the molecule (B–H protons) and the bacteriochlorin macrocycle.

Thus, a new conjugate formed by a cycloimide of natural bacteriochlorin *p* and the *closo*-dodecaborate anion, bound *via* a spacer group, was obtained in this study.

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