New boron-containing bacteriochlorin *p* cycloimide conjugate*

M. A. Grin,[a]★ R. A. Titeev,[a] O. M. Bakieva,[a,b] D. I. Brittal,[a] I. A. Lobanova,[b] I. B. Sivaev,[b]★ V. I. Bregadze,[b] and A. F. Mironov[a]

[a]*M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, 86 prosp. Vernadskogo, 119571 Moscow, Russian Federation. E-mail: michael_grin@mail.ru*

[b]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. E-mail: sivaev@ineos.ac.ru*

A conjugate of the bacteriochlorophyll *a* derivative with the cobalt bis(dicarbollide) anion $[3,3'\text{-Co}(1,2\text{-}C_2B_9H_{11})_2]^-$ was synthesized.

Key words: bacteriochlorin *p*, cobalt bis(dicarbollide), conjugate, synthesis.

Photodynamic therapy (PDT)[1,2] and boron neutron capture therapy (BNCT)[3—5] occupy a special place among new methods of cancer treatment. These methods are binary cancer therapies, in which two separately administered non-toxic agents (a photosensitizer or a boron compound, on the one hand, and laser radiation or a thermal (slow) neutron flux, on the other hand) interact in target cells and generate cytotoxic compounds, such as reactive oxygen species or high-energy short-range helium and lithium nuclei.

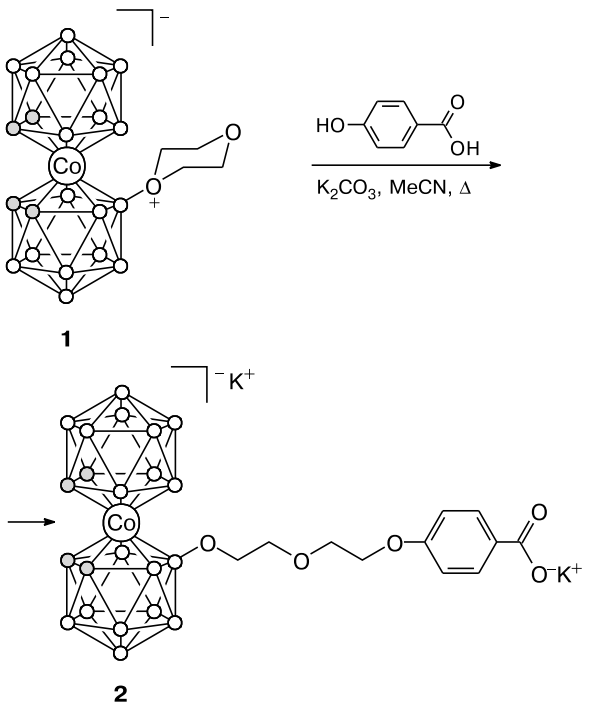
Since tetrapyrrole compounds have a unique property of being selectively accumulated in tumor tissues,[6] they have attracted attention as agents for both the targeted delivery of boron clusters to tumor cells and the combined PDT—BNCT therapy, which would undoubtedly enhance the efficiency of antitumor therapy.[7—9] From this point of view, bacteriochlorin-based photosensitizers with intense near-IR absorption are of particular interest because they allow the use of laser beam penetration into deep malignant tissues.[10,11]

Earlier,[12] we have reported the synthesis of the bacteriochlorin *p* cycloimide conjugate with the *closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$. The cobalt bis(dicarbollide) anion $[3,3'\text{-Co}(1,2\text{-}C_2B_9H_{11})_2]^-$ is another boron cluster promising for BNCT. An obvious advantages of the latter compound are a lower charge and a larger number of boron atoms.[13] The synthesis of boron-containing amino acids,[14] nucleosides,[15] and porphyrins[16] based on cobalt bis(dicarbollide) was documented.

In the present study, we synthesized the bacteriochlorin *p* *N*-aminocycloimide conjugate with cobalt bis(dicarbollide). Earlier, it has been shown[17] that the primary amino group in the *N*-aminocycloimide is reactive and can be used for condensation with aliphatic and aromatic acid chlorides.

To acylate the amino group, we synthesized the carboxy derivative of cobalt bis(dicarbollide). For this purpose, we used a known procedure based on the dioxane-ring opening in the cobalt bis(dicarbollide) dioxane com-

Scheme 1



1

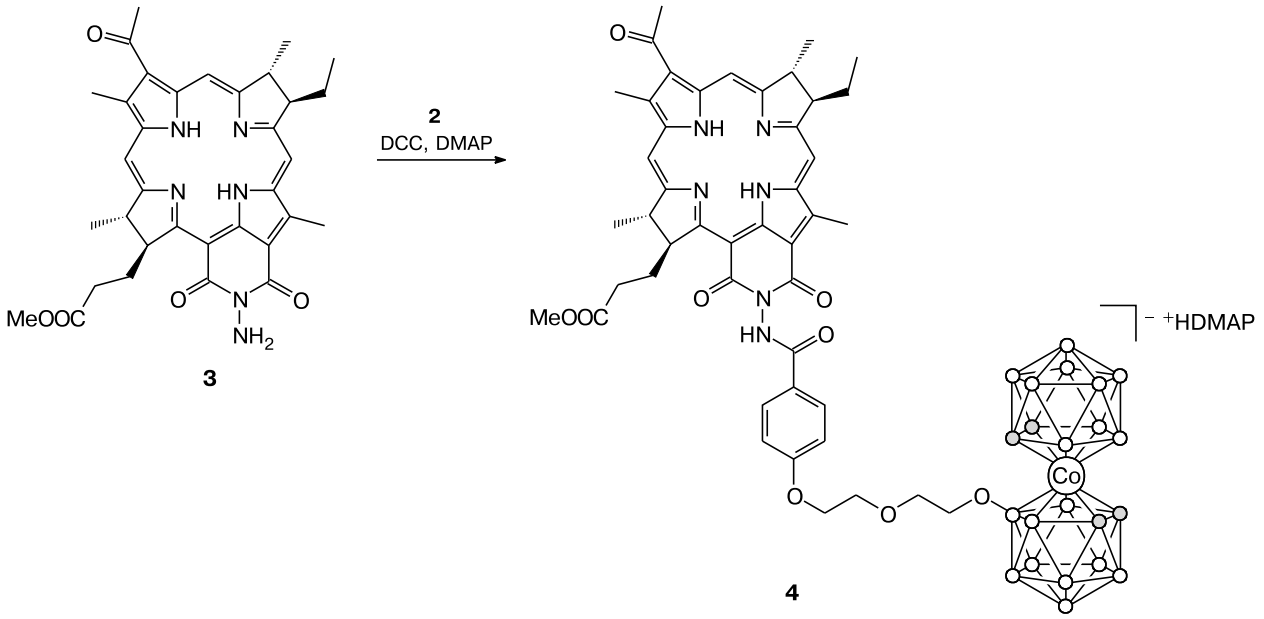
2

* Dedicated to Academician B. A. Trofimov on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2188—2190, October, 2008.

1066-5285/08/5710-2230 © 2008 Springer Science+Business Media, Inc.

Scheme 2



plex (complex **1**) by various nucleophiles giving rise to derivatives where the boron cage and the functional group are linked through the diethylene glycol fragment as a hydrophilic spacer.[14,16a,18] The dioxane-ring opening in the complex with the 7,8-dicarba-*nido*-undecaborate anion by the *p*-hydroxybenzoic acid-based carboxylate phenoxide dianion was used for the synthesis of boron-containing acids.[19]

The reaction of compound **1** with *p*-hydroxybenzoic acid in acetonitrile in the presence of K_2CO_3 under reflux produced the potassium salt of the corresponding acid **2** in virtually quantitative yield (Scheme 1).

The condensation of bacteriochlorin *p* *N*-aminocycloimide **3** with boron-containing acid **2** was performed with the use of dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine (Scheme 2). The conjugate was obtained as the 4-dimethylaminopyridinium salt. It was isolated by preparative TLC and characterized by ^{1}H NMR, UV, and IR spectroscopy.

Boron-containing conjugate **4** retains attractive spectral characteristics of the starting *N*-aminocycloimide **3** (λ_{max} = 830 nm) and, at the same time, contains a large number of boron atoms, due to which this compounds is promising as a photosensitizer for the combined photodynamic therapy and boron neutron capture therapy.

Experimental

The ^{1}H, ^{13}C, and ^{11}B NMR spectra were measured on a Bruker-Avance-400 spectrometer (400.13, 100.61, and 128.38 MHz, respectively). The IR and UV spectra were recorded on a Bruker EQUINOX 55 spectrometer and a Jasco 7800 spectrophotometer, respectively. Dioxane derivative **1** and bacteriochlorin p_6 methyl ester 13,15-(*N*-aminocycloimide) **3** were prepared according to known procedures.[20,21] The TLC analysis was carried out on silica gel plates.

Potassium 8-{2-[2-(4-carboxyphenoxy)ethoxy]ethoxy}-heneicosahydro-1,1′,2,2′-tetracarba-3-*commo*-cobalta-*closo*-tricosaborate (2).* 4-Hydroxybenzoic acid (0.14 g, 1.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) were added to a solution of compound **1** (0.41 g, 1.0 mmol) in acetonitrile (50 mL). The reaction mixture was refluxed for 5—6 h. The course of the reaction was monitored by TLC in CH_2Cl_2. After cooling to room temperature, the precipitate was filtered off and washed with acetonitrile (10 mL). The filtrate was concentrated to dryness under reduced pressure. The orange product was obtained in a yield of 0.60 g (96%). Found (%): C, 28.18; H, 5.26; B, 31.02. $C_{15}H_{33}B_{18}CoK_2O_5$. Calculated (%): C, 28.82; H, 5.32; B, 31.13. ^{1}H NMR (methanol-d_4), δ: 7.83 (d, 2 H, J = 8.1 Hz); 6.70 (d, 2 H, J = 8 Hz); 4.39 (t, 2 H, J = 4 Hz); 4.12 (s, 4 H); 3.82, 3.71, and 3.64 (all t, 2 H each, J = 4 Hz). ^{13}C NMR (methanol-d_4), δ: 167.4, 166.4, 131.6, 118.2, 116.1, 71.8, 69.0, 68.4, 63.5, 53.5, 46.7. ^{11}B NMR (methanol-d_4), δ: 23.3 (s, 1 B); 5.0, 0.7, and −2.3 (all d, 1 B each); −4.6, −7.2, −6.7, −6.0, −17.2, and −20.3 (all d, 2 B each); −22.0 and −28.5 (both d, 1 B each).

4-Dimethylaminopyridinium 8-{2-[2-(4-*N*- bacteriochlorin p_6 methyl ester 13,15-(cycloimido)carbamoylphenoxy)ethoxy]-ethoxy}heneicosahydro-1,1′,2,2′-tetracarba-3-*commo*-cobalta-*closo*-tricosaborate (4). Trifluoroacetic acid (1 mL) was added to a solution of acid **2** (65 mg, 0.11 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 5 min. The solvent was removed *in vacuo*, the residue was dissolved in dichloromethane (2 mL), and a solution of 4-dimethylaminopyridine (5 mg, 0.04 mmol) and dicyclohexylcarbodiimide

* The names of the compounds are based on the name of substituted cobaltacarborane according to the official nomenclature, heneicosahydro-1,1′,2,2′-tetracarba-3-*commo*-cobalta-*closo*-tricosaborate.

(50 mg, 0.20 mmol) was added. The reaction mixture was stirred for 10 min. Then compound **3** (50 mg, 0.08 mmol) was added and the mixture was stirred for 24 h. The course of the reaction was monitored by TLC in a 5 : 1 chloroform—methanol solvent system (R_f is 0.6 for **3** and 0.2 for **4**). The solvent was removed *in vacuo*, and the product was purified by preparative TLC on silica gel in a chloroform—methanol solvent system with the methanol concentration from 0 to 20%. The yield was 15 mg (12%). ^{1}H NMR ($CDCl_3$), δ: 9.09 (s, 1 H, H(5)); 8.49 (s, 1 H, H(10)); 8.44 (s, 1 H, H(20)); 8.18 (d, 2 H, DMAP, J = 9.5 Hz); 7.68 (d, 2 H, C_6H_4, J = 8.1 Hz); 7.20 (d, 2 H, DMAP, J = 4.4 Hz); 6.67 (d, 2 H, C_6H_4, J = 8 Hz); 4.99 (m, 1 H, H(17)); 4.40 (m, 2 H, H(18) + H(7)); 4.30 (t, 2 H, OCH_2, J = 4 Hz); 4.10 (m, 1 H, H(8)); 4.06 (s, 4 H, CH_{carb}); 3.94 (d, 6 H, DMAP, J = 13 Hz); 3.81 (t, 2 H, OCH_2, J = 4 Hz); 3.74 (s, 3 H, 12-Me); 3.64 and 3.58 (both t, 2 H each, OCH_2, J = 4 Hz); 3.49 (s, 3 H, 17-CH_3); 3.42 (s, 3 H, 2-CH_3); 3.17 (s, 3 H, 3″-CH_3); 2.87 (m, 2 H, 8′-CH_2); 2.47 (m, 2 H, 17″-CH_2); 2.07 (m, 2 H, 17′-CH_2); 1.77 (d, 3 H, 7-CH_3, J = 7.5 Hz); 1.68 (d, 3 H, 18-CH_3, J = 7.2 Hz); 0.88 (t, 3 H, 8″-CH_3, J = 8 Hz); –0.09 and –0.29 (both s, 1 H each, NH). IR (KBr), ν/cm^{-1}: 2559 (B—H). UV ($CHCl_3$), λ_{max}/nm (log ε): 364 (30.5), 417 (12.8), 551 (9.8), 830 (19.6).

This study was financially supported by the Russian Foundation for Basic Research (Project Nos 06-03-32459 and 07-03-00712).

References

1. R. Bonnett, *Chemical Aspects of Photodynamic Therapy*, Gordon and Breach Sci. Publ., London, 2000.
2. M. G. H. Vicente, *Curr. Med. Chem. Anti-Cancer Agents*, 2001, **1**, 175.
3. M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950.
4. A. H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni, J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
5. I. B. Sivaev, V. I. Bregadze, *Ross. Khim. Zh.*, 2004, **48**, 109 [*Mendeleev Chem. J.*, 2004, **48** (Engl. Transl.)]; V. I. Bregadze, I. B. Sivaev, S. A. Glazun, *Anti-Cancer Agents in Medicinal Chemistry*, 2006, **6**, 75.
6. W. Hausman, *Biochem. Z.*, 1909, **14**, 275.
7. V. I. Bregadze, I. B. Sivaev, D. Gabel, D. Wöhrle, *J. Porphyrins Phthalocyanines*, 2001, **5**, 767.
8. R. P. Evstigneeva, A. V. Zaitsev, V. N. Luzgina, V. A. Ol′shevskaya, A. A. Shtil, *Curr. Med. Chem. Anti-Cancer Agents*, 2003, **3**, 383.
9. M. W. Renner, M. Miura, M. W. Easson, M. G. H. Vicente, *Anti-Cancer Agents Med. Chem.*, 2006, **6**, 145.
10. A. F. Mironov, M. A. Grin, *Vestn. MITKhT* [*Bull. Lomonosov Moscow State Academy of Fine Chemical Technology*], 2006, **1**, 5 (in Russian).
11. M. A. Grin, A. F. Mironov, A. A. Shtil, *Anti-Cancer Agents Med. Chem.*, 2008, **8**, 683.
12. M. A. Grin, A. A. Semioshkin, R. A. Titeev, E. A. Nizhnik, J. N. Grebenyuk, A. F. Mironov, V. I. Bregadze, *Mendeleev Commun.*, 2007, **17**, 14.
13. I. B. Sivaev, V. I. Bregadze, *Collect. Czech. Chem. Commun.*, 1999, **64**, 783.
14. I. B. Sivaev, Z. A. Starikova, S. S. Sjöberg, V. I. Bregadze, *J. Organomet. Chem.*, 2002, **649**, 1.
15. (a) A. B. Olejniczak, J. Plešek, O. Kříž, Z. J. Lesnikowski, *Angew. Chem., Int. Ed.*, 2003, **42**, 5740; (b) Z. J. Lesnikowski, E. Paradowska, A. B. Olejniczak, M. Studzinska, P. Seekamp, U. Schüller, D. Gabel, R. F. Schinazi, J. Plešek, *Bioorg. Med. Chem.*, 2005, **13**, 4168; (c) A. B. Olejniczak, J. Plešek, Z. J. Lesnikowski, *Chem. Eur. J.*, 2007, **13**, 311.
16. (a) E. Hao, M. G. H. Vicente, *Chem. Commun.*, 2005, 1306; (b) E. Hao, T. J. Jensen, B. H. Courtney, M. G. H. Vicente, *Bioconjugate Chem.*, 2005, **16**, 1495; (c) M. Sibrian-Vasquez, E. Hao, T. J. Jensen, M. G. H. Vicente, *Bioconjugate Chem.*, 2006, **17**, 928; (d) E. Hao, M. Sibrian-Vazquez, W. Serem, J. C. Garno, F. R. Fronczek, M. G. H. Vicente, *Chem. Eur. J.*, 2007, **13**, 9035.
17. A. F. Mironov, M. A. Grin, A. G. Tsiprovskii, R. A. Titeev, E. A. Nizhnik, I. S. Lonin, *Mendeleev Commun.*, 2004, **14**, 204.
18. J. Plešek, B. Grüner, S. Heřmanek, J. Bača, V. Mareček, J. Jänchenova, A. Lhotsky, K. Holub, P. Selucky, J. Rais, I. Cisařova, J. Časlavsky, *Polyhedron*, 2002, **21**, 975.
19. M. Yu. Stogniy, E. N. Abramova, I. A. Lobanova, I. B. Sivaev, V. I. Bragin, P. V. Petrovskii, V. N. Tsupreva, O. V. Sorokina, V. I. Bregadze, *Collect. Czech. Chem. Commun.*, 2007, **72**, 1676.
20. F. Teixidor, J. Pedrajas, I. Rojo, C. Viñas, R. Kivekäs, R. Sillanpää, I. B. Sivaev, V. I. Bregadze, S. Sjöberg, *Organometallics*, 2003, **22**, 3414.
21. A. F. Mironov, M. A. Grin, A. G. Tsiprovskii, V. V. Kachala, T. A. Karmakova, A. D. Plyutinskaya, R. I. Yakubovskaya, *J. Porphyrins Phthalocyanines*, 2003, **7**, 725.

Received May 16, 2008;
in revised form July 18, 2008