First example of the ribbed-functionalized iron(II) clathrochelate with six pendante *closo*-borate substituents*

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The nucleophilic substitution of the reactive chlorine atoms of the *n*-butylboron-capped hexachlorine-containing clathrochelate precursor with the thiol-terminated *closo*-decaborate $(PPh_4)_2[B_{10}H_9OCH_2CH_2OCH_2CH_2SH]$ in the presence of triethylamine afforded the *closo*-decaborate-containing clathrochelate dodecaanion $[Fe\{[(B_{10}H_9OCH_2CH_2OCH_2CH_2S)_2Gm]_3(BBu^n)_2\}]^{12-}$, which was isolated in the form of its tetraphenylphosphonium and sodium salts. The complexes obtained were characterized using elemental analysis, UV-VIS, ^1H, ^{11}B, and $^{13}C\{^1H\}$ NMR, and IR spectroscopies.

Key words: macrocyclic compounds, clathrochelates, iron complexes, *closo*-borates, boron neutron capture therapy.

Up to date, a number of pharmaceuticals have been designed for the boron-neutron capture therapy (BNCT) of cancer. However, most of these compounds do not satisfy the main requirements on the BNCT agents.[1] Higher polyhedral boron hydrides $B_nH_n^{2-}$ ($n = 6—12$) and the functionalized boron clusters are available, chemically stable, and low-toxic compounds. Hence, the derivatives of the decahydro-*closo*-decaborate ($B_{10}H_{10}^{2-}$) and dodecahydro-*closo*-dodecaborate ($B_{12}H_{12}^{2-}$) anions seem to be the most promising compounds for this type of the radiotherapy.[2—4]

Earlier,[5] we have performed a functionalization of the macrobicyclic dichlorine-containing clathrochelate precursor $Fe[Bd_2(Cl_2Gm)(BF)_2]$ (Cl_2Gm^{2-} is dichloroglyoxime dianion) with the amine-terminated *closo*-dodecaborate anion $[B_{12}H_{11}NH_2]^{2-}$ as the nucleophilic agent, which resulted in the formation of the *closo*-dodecaborate-containing clathrochelate dianion $[Fe\{Bd_2[Cl(B_{12}H_{11}NH)Gm](BF)_2\}]^{2-}$. It should be noted that only the monofunctionalized product of the nucleophilic substitution has been formed even in the presence of an excess of the nucleophilic agent. We also have observed that the *closo*-borate mono- and dianions with HO, HS, and H_2N groups attached inherently to the polyhedral framework are the unefficient nucleophilic agents for the functionalization of these clathrochelate precursors. This result can be explained by the steric hindrances induced by repulsion between the bulky negatively charged *closo*-borate substituents in the same ribbed chelate α-dioximate fragment.

Results and Discussion

As it has been found earlier,[6] the alkyl- and arylthiolate anions are the most suitable for the ribbed functionalization of the halogen-containing tris-dioximate clathrochelate precursors by their nucleophilic substitution. In the present study, we performed the nucleophilic substitution of the reactive chlorine atoms of the hexachlorine-containing macrobicyclic complex $Fe[(Cl_2Gm)_3(BBu^n)_2]$ with the spacer-containing *closo*-decaborate fragments using the thiol-terminated *closo*-decaborate dianion. The reaction of this clathrochelate precursor with the dianion $[B_{10}H_9OCH_2CH_2OCH_2CH_2SH]^{2-}$ in acetonitrile in the presence of triethylamine as a strong organic base for the deprotonation of the thiol group afforded the hybrid fully functionalized product, *viz.*, the hexa-*closo*-decaborate iron(II) clathrochelate (Scheme 1). The synthesis of the complex $(PPh_4)_{12}[Fe\{[(RS)_2Gm]_3(BBu^n)_2\}]$ (R is the $CH_2CH_2OCH_2CH_2OB_{10}H_9^{2-}$ dianion) was performed under argon to prevent the oxidation of the resulting *closo*-decaborate-containing thiolate anions to the corresponding disulfide and at low temperature to avoid

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the side composition of the clathrochelate framework in the presence of the strong base. The reaction of this intermediate tetraphenylphosphonium salt of the clathrochelate dodecaanion with $NaBPh_4$ gave the hybrid complex $Na_{12}[Fe\{[(RS)_2Gm]_3(BBu^n)_2\}]$, which was characterized using elemental analysis, UV-VIS, ^1H, ^{11}B, and $^{13}C\{^1H\}$ NMR, and IR spectroscopies. The resulting product demonstrates very high solubility in water, and this allows us to study its biological activity as a precursor of the antiviral and antitumor drug candidaty, in particular, for the BNCT treatment.

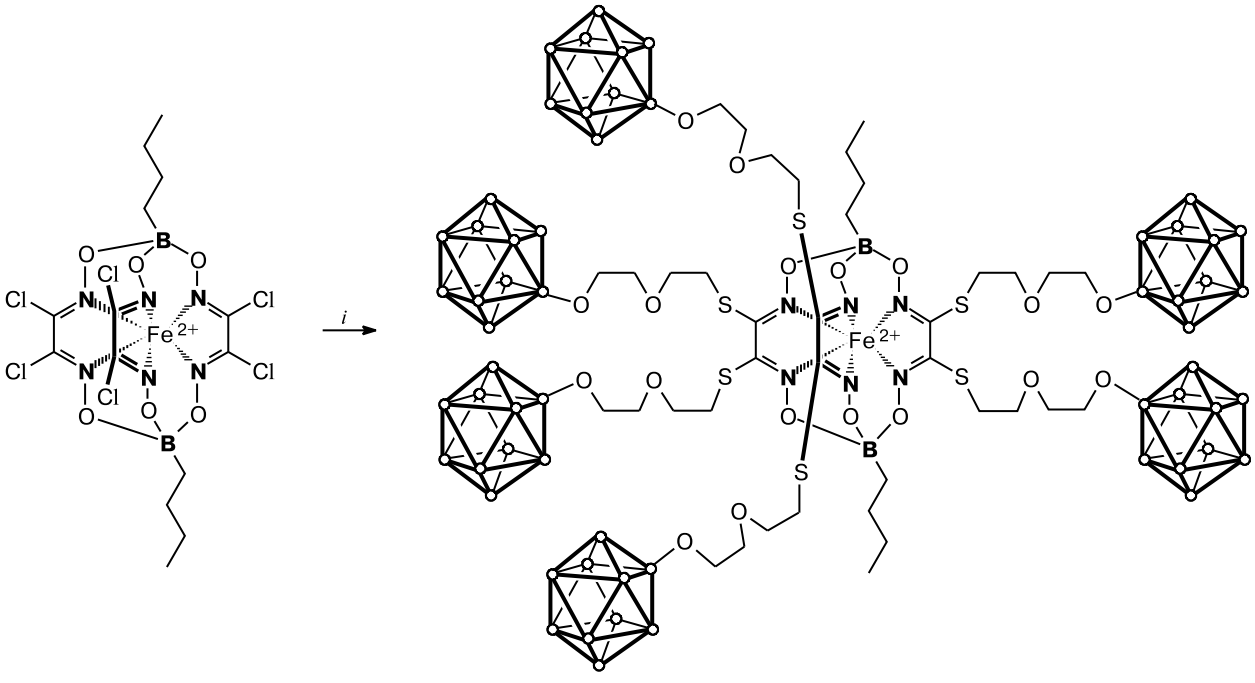
The ^1H and $^{13}C\{^1H\}$ NMR spectra of an acetonitrile solution of the hybrid *closo*-decaboratoclathrochelate $Na_{12}[Fe\{[(RS)_2Gm]_3(BBu^n)_2\}]$ contain the signals of the protons and carbon atoms of the *closo*-decaborate-containing spacer substituents in the ribbed chelate fragments of its clathrochelate framework, as well as the signals of the apical *n*-butyl groups. The number and the position of the signals in these spectra as well as the ratios of their integral intensities in the ^1H NMR spectrum confirmed the composition of the hybrid *closo*-decaboratoclathrochelate obtained and the C_3-symmetry of its molecule (this axis is passing through the apical capping boron atoms and the encapsulated iron(II) ion). The $^{11}B\{^1H\}$ NMR spectrum of this hybrid complex is characteristic of the *closo*-decaborate compounds with the only equatorial substituent in the boron cluster. In the absence of broadband boron—hydrogen spin-spin decoupling, all the signals observed are split into the symmetric doublets, except that for the signals of the low-field boron atom and those of the cross-linking RBO_3 groups.

The IR spectrum of the sodium salt of the *closo*-decaborate iron(II) clathrochelate contains, along with the bands of the C=N, N—O, and B—O stretching vibraitons of the clathrochelate framework, the highly intensive bands of the B—H stretching and B—B—H bending vibrations characteristic of the *closo*-decaborate-containing ribbed substituent.[7]

The UV-VIS spectrum of methanol solution of the hybrid complex contains two highly intensive bands ($\varepsilon \approx 5 \cdot 10^3$ mol^{-1} L cm^{-1}) in the visible range assigned to the charge transfer Fe$d \rightarrow$Lπ^*, with the substantially long-wave-shifted maxima (by approximately 55 nm) in comparison with the spectrum of its hexachlorine-containing clathrochelate precursor.[6] The UV range of its spectrum contains three bands from 220 to 300 nm assigned to one π,π^* transitions in the highly π-conjugated α-dioximate chelate fragments of the macrobicyclic framework.

The electrochemical characteristics of the hybrid *closo*-decaborate iron(II) clathrochelate obtained were studied by cyclic voltammetry (CV). All the peaks observed in its cyclic voltammograms is characteristic of the diffusion-controlled current processes. Two waves in the anodic ranges is observed: first of them is a partially reversible multielectron wave at $E_p = 400$ mV (Fig. 1) whereas second weak one appears at $E_p = 1150$ mV (in the case

Scheme 1



i. $[B_{10}H_{11}OCH_2CH_2OCH_2CH_2SH]^{2-}$, NEt_3, MeCN.

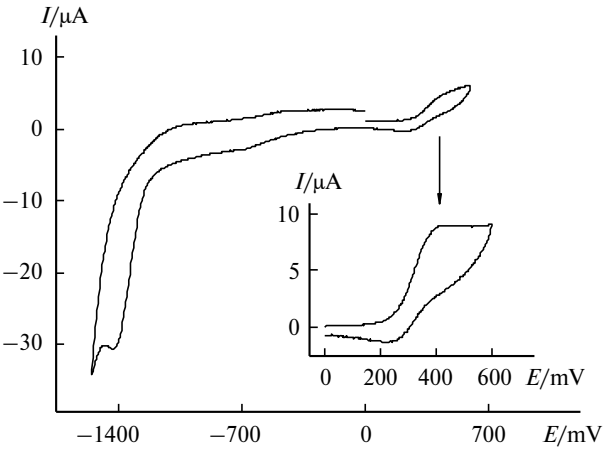


Fig. 1. Cyclic voltammogram (CV) of an acetonitrile solution of the hybird complex $Na_{12}[Fe\{[(B_{10}H_9OCH_2CH_2OCH_2CH_2S)_2Gm]_3(BBu^n)_2\}]$ with a potential scan to 600 mV; the inset shows a fragment of the anodic branch of the CV curve from 0 to 600 mV (the concentration of the clathrochelate was 1 mmol L^{-1}, 200 mV s^{-1}, Pt, *versus* Ag/AgCl/KCl).

of the potential scan ring up to 2000 mV). This CV pattern is explained by the one-electron oxidation of six decaborate dianions at the potential of the first wave, which is responsible for the multielectron character of this process. The shift of the oxidation potentials of the decaborate dianiones compared with those earlier-reported in the studies[8,9] may be explained by a formation of the ionic associates of the clathrochelate dodecaanion with sodium ions in acetonitrile solution. The second oxidation wave may be associated as with the $Fe^{2+/3+}$ redox process on the encapsulated metal ion as with the subsequent oxidation of the products resulted from the oxidation at the first potential.

The cathodic range of this CV for the iron(II) *closo*-borateclathrochelate obtained contains a multielectron wave at $E_p = -1500$ mV assigned to the reduction of the *closo*-borate fragments of their ribbed substituents.

The parameters of the ^{57}Fe Mössbauer spectrum of the clathrochelate $(PPh_4)_{12}[Fe\{[(B_{10}H_9OCH_2CH_2OCH_2CH_2S)_2Gm]_3(BBu^n)_2\}]$ (the isomeric shift (IS) is 0.36 mm s^{-1} and the quadrupole splitting (QS) is 0.53 mm s^{-1}) are characteristic of the low-spin iron(II) complexes possess a geometry intermediate between a trigonal prism (the distortion angle $\varphi = 0°$) and a trigonal antiprism ($\varphi = 60°$). Based on the QS value and a concept of the partial quadrupole splitting,[10] we deduced the distortion angle of the N_6-coordination polyhedron of an encapsulated iron(II) ion (approximately 25°).

Therefore, we found that the functionalized *closo*-decaborate dianion with spacer thiol-terminated substituent is an efficient nucleophilic agent for the synthesis of the hybrid polytopic ribbed-functionalized *closo*-borate clathrochelates. For the first time, the hexasulfide iron(II) clathrochelate fully functionalized (with *closo*-decaborate fragments) was obtained and characterized. This complex is soluble in water and seems to be the promising compound for BNCT treatment.

Experimental

The clathrochelate precursor $Fe[(Cl_2Gm)_3(BBu^n)_2]$ and the initial *closo*-borate-containing thiol were obtained as described previously.[6,11]

Analytical data (C, H, and N contents) were obtained with a Carlo Erba model 1106 microanalyzer. The iron content was determined spectrophotometrically.

The ^{1}H, ^{11}B, and ^{13}C NMR spectra were recorded from CD_2Cl_2 and CD_3CN solutions on Bruker AC-200P and Avance 400 FT spectrometers.

The IR spectra (KBr pellets) in the range of 400—4000 cm^{-1} were recorded with a Perkin—Elmer FT-IR Spectrum BX II spectrophotometer.

The UV-VIS spectra of the solutions of the complexes in CH_3CN were recorded in the range of 200—800 nm with a Perkin—Elmer Lambda 9 spectrophotometer. The individual Gaussian components of these spectra were calculated using the SPECTRA program.

The ^{57}Fe Mössbauer spectrum was obtained with an NP-255 (Hungary) spectrometer with a constant acceleration mode. The spectrum was collected with a 256-multichannel amplitude analyzer. The isomeric shift was measured relative to sodium nitroprusside and an α-Fe foil was used for the velocity scale calibration; ^{57}Co in a rhodium matrix at 298 K was used as the source. The minimal absorption line-width in the spectrum of a standard sample of sodium nitroprusside was 0.24 mm s^{-1}.

Dodeca(sodium)(12+)4,5,11,12,17,18-hexa[2-(2-*closo*-decaboratoxyethoxy)ethylthio]-1,8-dibutyl-2,7,9,14,15,20-hexaoxa-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosa-3,5,10,12,17,19-hexaene-1,8-diborato(14−)iron(2+). The complex $Fe[(Cl_2Gm)_3(BBu^n)_2]$ (0.18 g, 0.3 mmol) and an excess of Ph_4PCl (1.35 g) were dissolved in acetonitrile (7 mL) under argon, and this solution was cooled to −10 °C. Then a solution of $(Ph_4P)_2[B_{10}H_9OCH_2CH_2OCH_2CH_2SH]$ (2 g, 2.2 mmol) and triethylamine (0.31 mL, 2.2 mmol) in acetonitrile (9 mL) cooled to −10 °C was added to the reaction mixture. The reaction mixture was left at 4 °C for 7 days, then stirred at room temperature for 1 h, and evaporated to a half-volume (approximately 8 mL). Then water (50 mL) was added and the oily residue formed was dissolved in dichloromethane (20 mL). The extract formed was washed with water (50 mL), dried with $CaCl_2$, and evaporated to a small volume (approximately 3 mL). Then an excess of hexane was added and the red-orange precipitate formed was filtered off. The precipitate was dissolved in a minimal volume of acetonitrile and its acetonitrile solution was used for the chromatographic separation on silica gel (SPH-300 15-cm column, eluent: CH_2Cl_2—CH_3CN 8 : 5 mixture). The elute, containing the target product, was collected and rotary evaporated to dryness. The resulting oily residue was dried *in vacuo*, washed with diethyl ether and hexane, and again dried *in vacuo*. The yield of the intermediate tetraphenylphosphonium salt $(PPh_4)_{12}[Fe\{[(B_{10}H_9OCH_2CH_2OCH_2CH_2S)_2Gm]_3(BBu^n)_2\}]$ was 0.85 g (50%). Found (%): C, 65.30; H, 6.32; N, 1.02; B, 10.93; Fe, 0.85; S, 3.02. $C_{326}H_{360}N_6B_{62}FeO_{18}P_{12}S_6$. Calculated (%): C, 65.91;

H, 6.11; N, 1.41; B, 11.28; Fe, 0.94; S, 3.24. ^{1}H NMR (CD_2Cl_2), δ: –0.6—1.5 (m, 9 H, $B_{10}H_9$); 0.48 (br.s, 4 H, CH_2B); 0.71 and 1.20 (two br.s, 8 H, $CH_3C\underline{H}_2C\underline{H}_2$); 0.98 (s, 6 H, CH_3); 3.21 (m, 48 H, $OC\underline{H}_2C\underline{H}_2O + CH_2S + OC\underline{H}_2CH_2S$); 7.60 (m, 240 H, Ph). $^{13}C\{^1H\}$ NMR (CD_2Cl_2), δ: 13.9 (s, CH_3); 15.9 (s, CH_2B); 25.6 and 26.0 (two s, $CH_3\underline{C}H_2\underline{C}H_2$); 34.4 (s, CH_2S); 65.5 (s, $O\underline{C}H_2CH_2S$); 69.9 and 76.6 (two s, $O\underline{C}H_2\underline{C}H_2O$); 146.6 (s, C=N); 130.6 (s, *ortho*-C_{Ph}); 134.3 (s, *meta*-C_{Ph}); 135.7 (s, *para*-C_{Ph}). ^{11}B NMR (CD_2Cl_2), δ: –2.4 (B(2), B(10)); –5.4 (B(1)); –6.1 (RBO_3); –24.0 (B(3), B(5), B(6), B(9)); –29.4 (B(7), B(8)); –34.4 (B(4)).

The tetraphenylphosphonium salt $(Ph_4P)_{12}[Fe\{[(B_{10}H_9O\text{-}CH_2CH_2OCH_2CH_2S)_2Gm]_3(BBu^n)_2\}]$ obtained was dissolved under heating in ethanol—1,2-dichloroethane 2 : 1 mixture (150 mL). Then $NaBPh_4$ (0.6 g) was added, and the reaction mixture was cooled to room temperature. The $(Ph_4P)[Ph_4B]$ precipitate formed was filtered off, and the filtrate was evaporated to dryness. The yield of the complex $Na_{12}[Fe\{[(B_{10}H_9OCH_2\text{-}CH_2OCH_2CH_2S)_2Gm]_3(BBu^n)_2\}]$ was 0.25 g (82%). Found (%): C, 21.47; H, 5.89; N, 3.88; Fe, 2.74. $C_{38}H_{120}N_6B_{62}FeNa_{12}O_{18}S_6$. Calculated (%): C, 21.29; H, 5.60; N, 3.92; Fe, 2.61. ^{1}H NMR (CD_3CN), δ: –0.7—1.5 (m, 9 H, $B_{10}H_9$); 0.67 (br.s, 4 H, CH_2B); 0.95 (s, 6 H, CH_3); 1.43 (br.s, 8 H, $CH_3C\underline{H}_2C\underline{H}_2$); 3.33 and 3.55 (two br.s, 24 H, $OC\underline{H}_2C\underline{H}_2O$); 3.40 (br.s, 12 H, CH_2S); 3.71 (br.s, 12 H, $OC\underline{H}_2CH_2S$). $^{13}C\{^1H\}$ NMR (CD_3CN), δ: 13.8 (s, CH_3); 17.1 (s, CH_2B); 25.7 and 26.7 (two s, $CH_3\underline{C}H_2\underline{C}H_2$); 33.48 (s, CH_2S); 69.0 (s, $O\underline{C}H_2CH_2S$); 69.5 and 71.2 (two s, $O\underline{C}H_2\underline{C}H_2O$); 147.7 (s, C=N). ^{11}B NMR (CD_3CN), δ: –2.7 (B(2), B(10)); –5.7 (B(1)); –6.6 (RBO_3); –24.1 (B(3), B(5), B(6), B(9)); –29.8 (B(7), B(8)); –34.3 (B(4)). IR (KBr)/cm^{-1}: 2464 ν(B—H); 1152 δ(B—B—H); 712 δ(B—B—B); 913 *ν*(N—O), 1099m *ν*(B—O), 1579 *ν*(C=N). UV-VIS (CH_3OH), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$ mol^{-1} L cm^{-1}): 226 (42), 267 (8.4), 294 (4.7), 392 (1.9), 489 (4.8), 507 (4.9).

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