Cage complexes as a molecular scaffold for polyfunctional and polytopic systems: synthesis of the first *closo*-borate iron(II) clathrochelate

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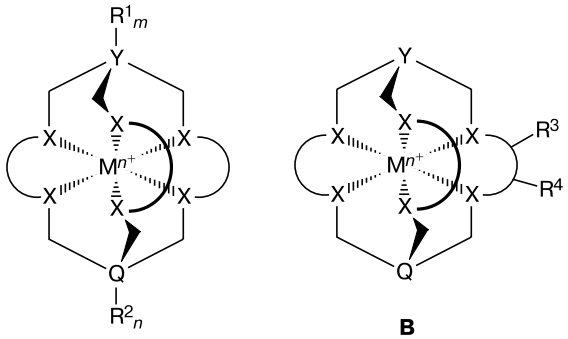
The ribbed functionalization of the clathrochelate iron(II) tris-dioximates as a potential "molecular scaffold" for the synthesis of polyfunctional and polytopic complexes with *closo*-dodecaborate-anion substituents was performed. *closo*-Dodecaborate-substituted clathrochelate $[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}$ (where Bd^{2-} is α-benzyldioxime dianion, Gm is glyoxime residue) dianion was prepared starting from dichloride clathrochelate $FeBd_2(Cl_2Gm)(BF)_2$ precursor with amino-*closo*-dodecaborate $(NBu_4)[B_{12}H_{11}NH_3]$ in the presence of potassium *tert*-amylate. This clathrochelate dianion was isolated as a tetra-*n*-butylammonium salt and characterized using elemental analysis, MALDI-TOF and PD mass, IR, UV—Vis, ^{57}Fe Mössbauer spectra as well as by ^{1}H, ^{11}B and $^{13}C\{^{1}H\}$ NMR spectra.

Key words: macrocyclic compounds, clathrochelates, iron(II) complexes, *closo*-dodecaborates, boron-neutron capture therapy.

The polyhedral boranes derivatives have been studied intensively as potential agents for boron-neutron capture therapy (BNCT)[1] of tumor. This approach is based on the nuclear reaction of the stable isotope ^{10}B with the thermal neutrons. The combination of various properties of the boron-containing agent is necessary for a successful BNCT treatment of the tumor. The key problem is the target and selective delivery of the agent to the tumor cells, which allows one to decrease the dose required for the effective therapeutic treatment and therefore to prevent the intoxication of organism by this agent. In particular, carboran and *closo*-dodecaborate phthalocyanines and porphyrins can be used for target delivery of the BNCT agents.[2] In these cases, the macrocyclic ring plays the role of "molecular scaffold" for the design a the molecule with improved properties (hydrophilic-lipophilic balance, solubility, liposomes affinity, *etc*.).

The cage complexes with an encapsulated metal ion, possessing unique properties,[3] have been proposed as a "molecular scaffold" for the assembling of polytopic and polyfunctional systems.[4—7] In particular, the fuctionalization as apical (by the selection of the functionalizing substituents in capping groups[8,9] (**A**)) and ribbed (by nucleophilic substitution of the reactive chloride substituents in chelating α-dioximate fragments with HO-, HS- and H_2N-containing functionalizing agents[4,5,10—19] (**B**)) has been performed.



Y, Q — cross-linking atoms; X — donors atoms; R^1—R^4 — functionalizing substituents

In this study a ribbed fuctionalization of clathrochelate iron(II) tris-dioximates as a potential "molecular scaffold" for the synthesis of polyfunctional and polytopic mono- and dianione *closo*-borate-containing complexes was performed.

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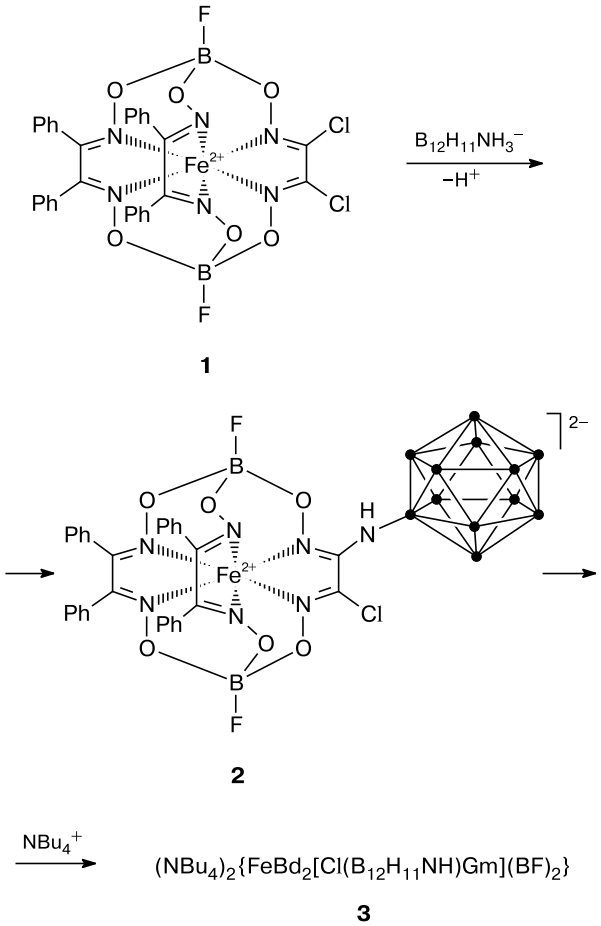
Results and Discussion

It has been noted earlier[15] that the thiol group is most convinient for the ribbed fuctionalization of clathrochelate iron(II) tris-dioximates. The nucleophilic substitution of reactive chlorine atoms of mono-, di, tri-, and hexachloride iron(II) clathrochelates by alkyl- and arylsulfide substituents in the presence of organic and inorganic bases proceeds easily and in high yields.[4,10–17,19] The reaction of chloride clathrochelate precursors with monofunctionalized *closo*-borates in the presence of strong bases (in particular, potassium *tert*-amylate) with an intermediate formation of the corresponding *closo*-borate aniones allowed one to perform the nucleophilic substitution for the amino-containing $B_{12}H_{11}NH_3^-$ anion only. The nucleophilicity of its O- and S-containing analogs is not enough for this process. The reaction of the amino-*closo*-borate $(NBu_4)[B_{12}H_{11}NH_3]$ and dichloride $FeBd_2(Cl_2Gm)(BF)_2$ (**1**, Bd^{2-} is α-benzyldioxime dianion, Gm is the glyoxime residue) precursor in the presence of potassium *tert*-amylate (Scheme 1) led to the *closo*-borate-containing clathrochelate $\{FeBd_2[Cl(B_{12}H_{11}NH)Gm](BF)_2\}^{2-}$ dianion (**2**), which was isolated as individual tetra-*n*-butylammonium salt **3** and characterized using both elemental analysis and instrumental methods.

Scheme 1



1 **2** **3**

The most intense peak (m/z = 1594) in the positive region of the MALDI-TOF mass spectrum of clathrochelate **3** belongs to the cation $\{(NBu_4^+)_3[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}\}^+$ that formed by addition of NBu_4^+ cation to ionic associate **3**. In the negative region of the MALDI-TOF mass spectrum, the peaks of $\{H^+[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}\}^-$ and $\{Na^+[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}\}^-$ monoaniones, but no peaks of $\{(NBu_4^+)[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}\}^-$ monoanione, were observed. The negative region of the plasma desorption (PD) mass spectrum of **3** is the same: the only peak belonging to the $\{H^+[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}\}^-$ anion is observed. No peaks in the positive region of the PD mass spectrum were detected.

The ^1H, ^{11}B, and $^{13}C\{^1H\}$ NMR spectra of CD_3CN and CD_2Cl_2 solutions of **3** confirmed the composition and symmetry of the complex under study: the ratio of integral intensities of the superposition of ^1H NMR signals of the *closo*-borate substituent and tetra-*n*-butylammonium cation and ^1H NMR signals of Ph-substituents agree with the proposed composition. The splitting of ^{13}C NMR signal of azomethine fragment PhC=N in two components gives evidence of the absence of the symmetry plane passing through the middles of C—C bonds in the dioximate fragments and the encapsulated iron(II) ion. Moreover, the ^{13}C NMR signal of the azomethine fragment ClC=N at δ ~130 remains unchanged and the ^{13}C NMR signal of the azomethine fragment NC=N at δ ~150 appears. The ratio of integral intensities of ^{11}B NMR signals of the tetrahedral capping boron atoms of O_3BF-groups at δ 4.3 (relative to $BF_3 \cdot OEt_2$) and the superposition of ^{11}B NMR signals of the *closo*-dodecaborate $B_{12}H_{11}$ fragment boron atoms at δ −3.0 and −15 is close to 1 : 6. This fact confirms the formation of the mono-*closo*-borate complex. At the same time nonequivalence of the apical boron atoms is not seen clearly because of significant half-width of lines in the ^{11}B NMR spectra and long distance between the ribbed substituents and these boron atoms.

Alongside the C=N, N—O, B—O, and B—F stretching vibrations of the clathrochelate fragment, the IR spectrum of complex **3** also contains the strong ν(B—H) bands of the *closo*-dodecaborate substituent.

UV—Vis spectrum of CH_2Cl_2 solution of clathrochelate **3** in the visible region contains four bands of nearly equal intensity, which were assighed to the charge transfer Fed → Lπ* ($\varepsilon \approx (1—4) \cdot 10^3$ L mol^{-1} cm^{-1}) bands. Their maxima (λ_{max} = 440—560 nm) have a longwave shift compared to the spectrum of the initial dichloride complex (λ_{max} = 428, 489 nm). The similar longwave shift

has been observed in the UV—Vis spectrum of the C_2-symmetric diamine $FeBd_2[(BuNH)_2Gm](BF)_2$ complex (λ_{max} ≐ 432, 506 nm).[16] The double set of bands in the UV—Vis spectrum of clathrochelate **3** can be due to the absence of symmetry elements in this molecule and the nonequivalence of various donor oxime groups.

^{57}Fe Mössbauer parameters of clathrochelate **3** (isomeric shift is 0.33 mm s^{-1}, quadrupole splitting is 0.58 mm s^{-1}) are characteristic of the low-spin iron(II) complex with the geometry intermediate between a trigonal prism (distortion angle φ = 0°) and a trigonal antiprism (distortion angle φ = 60°). Taking into account the QS value, the distortion angle φ in molecule **3** is close to 25°.

Thus, *closo*-borate mono- and dianiones with inherent HO, HS, and H_2N groups are inefficient functionalizing agents for the synthesis of polytopic cage complexes. This fact is attributed evidently to both sterical hindrance caused by the repulsion of bulky *closo*-borate substituents and a decrease in the nucleophilicity of the reactive groups due to electron-withdrawing character of *closo*-borate framework. Therefore, it seems to be prospective to use aliphatic spacer-containing *closo*-borates anions with the terminal HO-, HS- and H_2N- groups in nucleophilic substitution reactions.

Experimental

The starting materials and measurements were described in detail earlier.[5,15,17,19] The complex $FeBd_2(Cl_2Gm)(BF)_2$ [16] and the *closo*-borate HO-, HS-, and H_2N-containing mono- and dianions[21—23] were preparared as described earlier. Potassium *tert*-amylate was prepared from equimolar amounts of metallic potassium and *tert*-amyl alcohol in THF.

Di(tetra-*n*-butylamino)(2+)(1,8-bis(2-fluorobora)-2,7,9,14,15,20-hexaoxa-3,6,10,13,16,19-hexaaza-4,5,11,12-tetraphenyl-17-chloro-18-dodeca-*closo*-boratobicyclo[6.6.6]eicosa-3,5,10,12,16,18-hexaene(4−)iron(2+). The complex $FeBd_2(Cl_2Gm)(BF)_2$ (0.06 g, 0.8 mmol) and an excess of $(NBu_4)[B_{12}H_{11}NH_3]$ (0.8 g, 2 mmol) were suspended in DMF (20 mL) and 2 *M* solution of potassium *tert*-amylate in THF (1 mL) was added. The reaction mixture was stirred for 6 h and then precipitated with 1 *M* NBu_4Cl aqueous solution (20 mL). The dark-red precipitate obtained was filtered, washed with water, 50% aqueous MeOH and Et_2O and dried *in vacuo*. The solid was fractionally reprecipitated from a saturated acetonitrile solution with diethyl ether. The precipitates obtained were washed with Et_2O and hexane and dried *in vacuo*. The first two fractions were contaminated with by-products, while the following two fractions contained the pure product. Yield 0.37 g (34%). Found (%): C, 54.88; H, 7.60; B, 11.08; Cl, 2.75; Fe, 3.99; N, 9.18. $C_{62}H_{104}B_{14}ClF_2FeN_9O_6$. Calculated (%): C, 55.06; H, 7.77; B, 11.19; Cl, 2.62; Fe, 4.13; N, 9.32. MS (PD), *m/z* (negative region): −869 $[M - 2\ NBu_4^+ + H^+]^+$. MS (MALDI-TOF), *m/z* (positive region): 1593 $[M + NBu_4^+]^+$; *m/z* (negative range): −869 $[M - 2\ NBu_4^+ + H^+]^-$; −891 $[M - 2\ NBu_4^+ + Na^+]^-$. ^{1}H NMR ($CD_2Cl_2$), δ: 0.60—2.00 (m, 11 H, $B_{12}H_{11}$); 0.86 (m, 24 H, Me); 1.30, 1.45 (both m, each 16 H, CH_2); 2.99 (m, 16 H, NCH_2); 7.21 (m, 20 H, Ph). ^{13}C {^{1}H} NMR (CD_2Cl_2), δ: 13.6 (Me); 19.8, 24.1 (both CH_2); 50.2 (NCH_2); 127.9 (Ph); 129.0 (ClC=N); 129.7, 130.7 (both Ph); 153.8 (NC=N); 155.5, 156.7 (both PhC=N). ^{11}B NMR (CD_3CN, relative $BF_3 \cdot OEt_2$), δ: −15.00, −3.0 (m, 12 B, $B_{12}H_{11}$); 4.3 (m, 2 B, BF). IR (KBr), ν/cm^{-1}: 2482 (ν(B—H)); 1107 (δ(B—B—H)); 694 (δ(B—B—B)); 1510 (ν(ClC=N)); 1597 (ν(PhC=N) + δ(NC=N) + δ(N—H)); 903, 322, 941, 1053 (ν(N—O)); 1192 (δ(B—O) + ν(B—F)). UV—Vis (CH_2Cl_2), λ_{max}/nm (ε · 10^{-3}/L mol^{-1} cm^{-1}): 245 (14), 281 (5.2), 305 (4.1), 339 (2.1), 383 (2.2), 441 (3.3), 482 (3.5), 518 (3.9), 560 (1.5).

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