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Cage complexes as a molecular "scaffold" for assembling of polyfunctional and multicentered systems: synthesis of ribbed-functionalized dopamine-containing iron(II) clathrochelate and its properties as a receptor for boric acid

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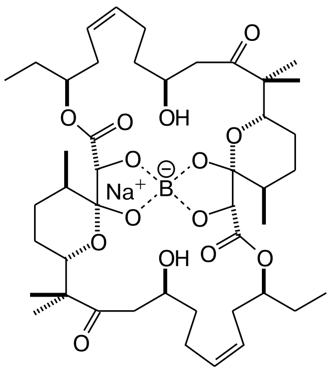
The monoribbed-functionalized clathrochelate with two dopamine residues in one of the three dioximate fragments was synthesized by the reaction of the dichloride clathrochelate $FeBd_2(Cl_2Gm)(BF)_2$ precursor (Bd^{2-} is the α-benzyldioxime anion, and Gm is the glyoxime residue) with PhB-protected dopamine in the presence of Et_3N. The MALDI-TOF mass spectrometry data showed that the complex synthesized is an efficient receptor for boric acid.

Key words: macrocyclic compounds, clathrochelates, iron(II) complexes, boron compounds, molecular recognition.

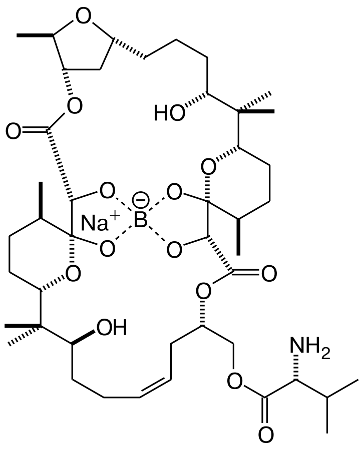
Dopamine is a biogenic amino derivative of pyrocatechol that regulates functions of endocrine glands and transfers nerve impulses. Dopamine stimulates somatotropine secretion, glycolysis, diuresis, and kidney blood circulation. It suppresses prolactin secretion and is widely used in drug therapy of shock and preshock states; cardiac, vascular, and kidney deficiency; hypotension; *etc.* Several natural antibiotics (boromycin, borophycin, and aplasmomycin[1—4]) contain two diol fragments coordinated to the B^{3+} ion to form the central anionic polyhedron O_4B^-.

Boron-containing pseudo-cryptands, *viz.*, derivatives of bis-catecholate diazacrown ethers (Fig. 1), have been proposed[5—8] for selective binding of alkaline metals and ammonium cations. The macrobicyclic tris-catecholate ligands (Fig. 2) and their complexes are analogs of natural siderophores.[9,10]

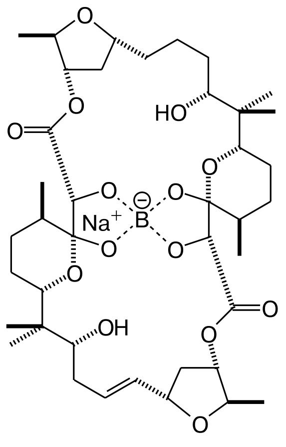
The clathrochelate framework is widely used as a molecular "scaffold" for the synthesis of polynuclear and multicentered systems.[11—23] Clathrochelates with ribbed crown-etheric, quinoxaline, nitroxyl-containing, and aryl- and arylsulfide substituents and their derivatives, in par-



Borophycin



Boromycin



Aplasmomycin

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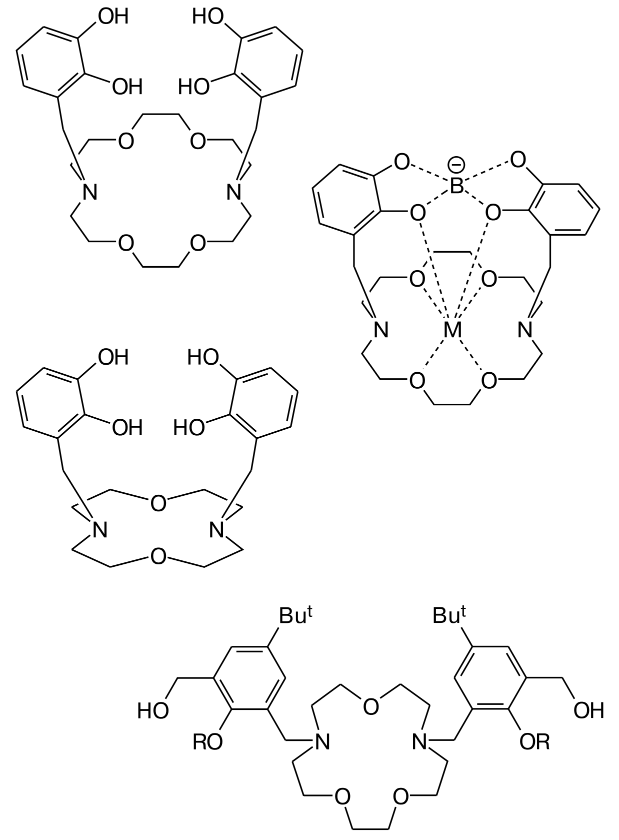


Fig. 1. Bis-catecholate diazacrown ethers and their boron-containing derivatives (pseudo-cryptands).

ticular, complexes with platinum(II) and platinum(IV), have been synthesized[24—26] starting from reactive halide clathrochelate precursors.

In the present study, we describe the synthesis of a clathrochelate with two dopamine substituents in the chelate dioximate fragment. The receptor properties of the complex synthesized for trigonal boron(III) compounds, first of all, boric acid, were studied.

Experimental

The following commercial (Fluka) reagents were used: dopamine hydrochloride (dop•HCl), boric and phenylboronic acids, triethylamine, ion-exchange resin Dowex 50 Wx2 (H^+-form), and tetra-*n*-butylammonium hydroxide (0.8 *M* solution in MeOH). The $FeBd_2(Cl_2Gm)(BF)_2$ complex was prepared as described.[14]

C, H, N elemental analysis was carried out with a Carlo Erba microanalyzer (model 1106). The iron content was determined spectrophotometrically.

MALDI-TOF mass spectra were recorded with a Bruker MALDI-TOF-MS Autoflex time-of-flight mass spectrometer in reflecto-mol mode. The ionization was induced by a UV laser with the wavelength 336 nm. The sample was applied to a nickel plate, and 2,5-dihydroxybenzoic acid was used as a matrix. The accuracy of measurement was ±0.1%.

The IR spectrum (KBr pellets) was recorded with an IR-200 Thermo Nicolet FT spectrometer in the range 400—4000 cm^{-1}.

The UV—Vis spectrum of the solution of the complex in CH_2Cl_2 was recorded on a Perkin—Elmer Lambda 9 spectrophotometer in the range from 230 to 900 nm. The individual Gauss components of this spectrum were calculated using the SPECTRA program.

^1H and ^{13}C NMR spectra of the solution in CD_2Cl_2 were recorded on a Bruker AC-200 FT spectrometer.

The ^{57}Fe Mössbauer spectrum was obtained with a YaGRS-4M spectrometer in constant acceleration mode. The spectrum was collected with a 256-channel 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 chromium matrix was used as the source and always kept at 298 K. The minimal absorption line width in the spectrum of a standard sample of sodium nitroprusside was 0.24 mm s^{-1}.

Synthesis of 1,8-bis(2-fluorobora)-2,7,9,14,15,20-hexaoxa-3,6,10,13,16,19-hexaaza-4,5,11,12-tetraphenyl-17,18-bis[2-(3,4-dihydroxyphenyl)ethylamino]bicyclo[6.6.6]eicosa-3,5,10,12,16,18-hexaene(2–)iron(2+), $FeBd_2(dop_2Gm)(BF)_2$ (1). Dopamine hydrochloride (0.4 g, 2.1 mmol) and phenylboronic acid (0.28 g, 2.3 mmol) were dissolved in MeOH (10 mL), and the resulting solution was refluxed for 2.5 h. Then MeOH was distilled off from the reaction mixture to a small volume and DMF (1 mL) was added. The reaction mixture was cooled to room temperature and complex $FeBd_2(Cl_2Gm)(BF)_2$ (0.6 g, 0.8 mmol) and DMF (2.5 mL) were added. Then the solution of triethylamine (0.58 mL, 4.2 mmol) in DMF (3 mL) was slowly added dropwise to the stirred reaction mixture. The reaction mixture was stirred for 8 h and left for 48 h. The initial complex was filtered and the filtrate was precipitated with 5% solution of acetic acid and NaCl in water (50 mL). The precipitate was filtered, washed with water, two small portions of MeOH, and dissolved together with phenylboronic acid (50 mg) in acetonitrile (10 mL). The ion-exchange resin Dowex 50Wx2 (H^+-form) (1.2 g) was suspended in water (5 mL) and neutralized with $NaHCO_3$, adding the latter in small portions to neutral pH. The ion-exchange resin was filtered, washed twice with water and acetone, and the filtrate was added to an acetonitrile solution of the complex obtained and phenylboronic acid. The reaction mixture was stirred for 20 min and filtered. The precipitate was washed with acetonitrile, and the combined filtrates were rotary evaporated to dryness. The yield of a mixture of clathrochelate products **1—3** was 0.70 g (76%).

The mixture of clathrochelate products **1—3** (0.7 g, 0.61 mmol) was dissolved in chloroform (8 mL) and glycerol (6 mL) and MeOH (10 mL) were added. The reaction mixture was stirred for 2 h and then washed with NaCl saturated aqueous solution (50 mL). The chloroform extract was separated, and the product was additionally extracted from the aqueous phase with chloroform (2×3 mL). This extract was combined with the first chloroform solution and glycerol (3 mL) and MeOH (6 mL) were added. The reaction mixture was stirred for 1.5 h and washed with NaCl saturated aqueous solution (5×50 mL). The chloroform solution was dried with Na_2SO_4 and filtered, and the filtrate was evaporated to dryness *in vacuo*. The solid residue was washed with hexane, dried *in vacuo*, and reprecipitated from a MeOH solution (10 mL) with water. The precipitate was washed with a MeOH—water (1 : 1) mixture, dried in air, and re-

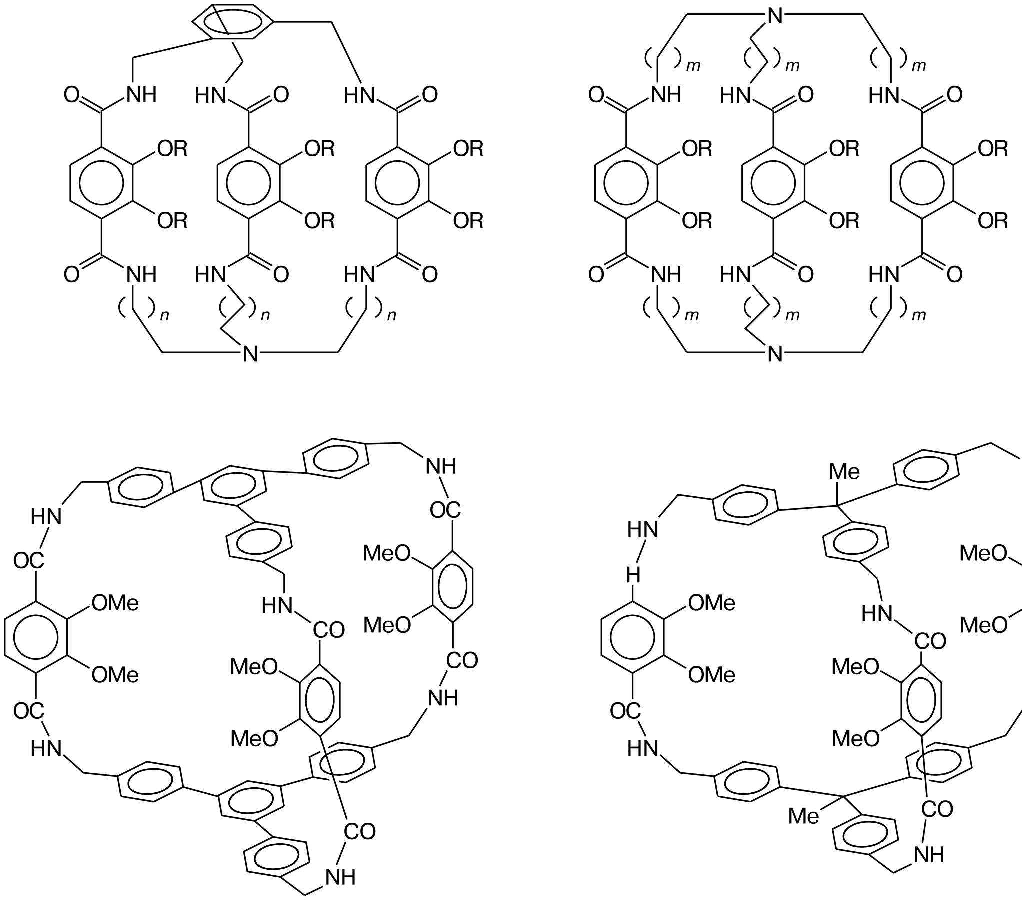


Fig. 2. Macrobicyclic tris-catecholate ligands.

precipitated from an acetonitrile solution with an Et_2O—hexane mixture. The oily precipitate was treated with a hexane—Et_2O (2 : 1) mixture, and the resulting solid product was filtered, washed with Et_2O and hexane, and dried *in vacuo*. The yield of **1** was 0.30 g (38%). Found (%): C, 56.22; H, 4.21; N, 11.33; Fe, 5.70. $C_{46}H_{40}B_2F_2FeN_8O_{10}$. Calculated (%): C, 56.36; H, 4.11; N, 11.43; Fe, 5.70. Mass spectrum, *m/z*: (positive region) 980 $[M]^{\bullet +}$; 1003 $[M + Na^+]^+$; 1019 $[M + K^+]^+$; (negative region) – 979 $[M - H^+]^-$; –1007 $[M \cdot BOH - H^+]^-$; –1032 $[M \cdot 2BOH - H^+]^-$; –1079 $[M \cdot BO \cdot \text{glycerol}]^-$; –1105 $[M \cdot BOH \cdot \text{glycerol}]^-$; –1141 $[M \cdot B \cdot DHB]^-$; –1967 $[2M \cdot B]^-$; –2013 $[2M \cdot BOH - H^+]^-$. ^1H NMR (CD_2Cl_2), δ: 2.53 (4 H, CH_2Ar); 3.45 (4 H, CH_2N); 5.62 (2 H, NH); 6.55 (2 H, Ar, dopamine); 6.73 (4 H, Ar, dopamine); 7.23 (24 H, Ph(Bd) + OH (dopamine)). ^{13}C NMR (CD_2Cl_2), δ: 37.6 (CH_2Ar); 47.2 (CH_2N); 115.9, 117.2, 121.7 (Ar (dopamine)); 128.3 (Ph(Bd)); 129.7 (Ar (dopamine)); 130.2, 130.7 (Ph(Bd)); 143.4, 143.7 (ArOH (dopamine)); 150.6 (NC=N); 157.9 (PhC=N). UV-Vis (CH_2Cl_2), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$/L mol^{-1} cm^{-1}): 232 (29), 265 (11), 283 (12), 299 (9.3), 315 (6.1), 344 (3.6), 375 (3.1), 432 (5.8), 489 (8.6), 521 (9.0), 553 (2.1).

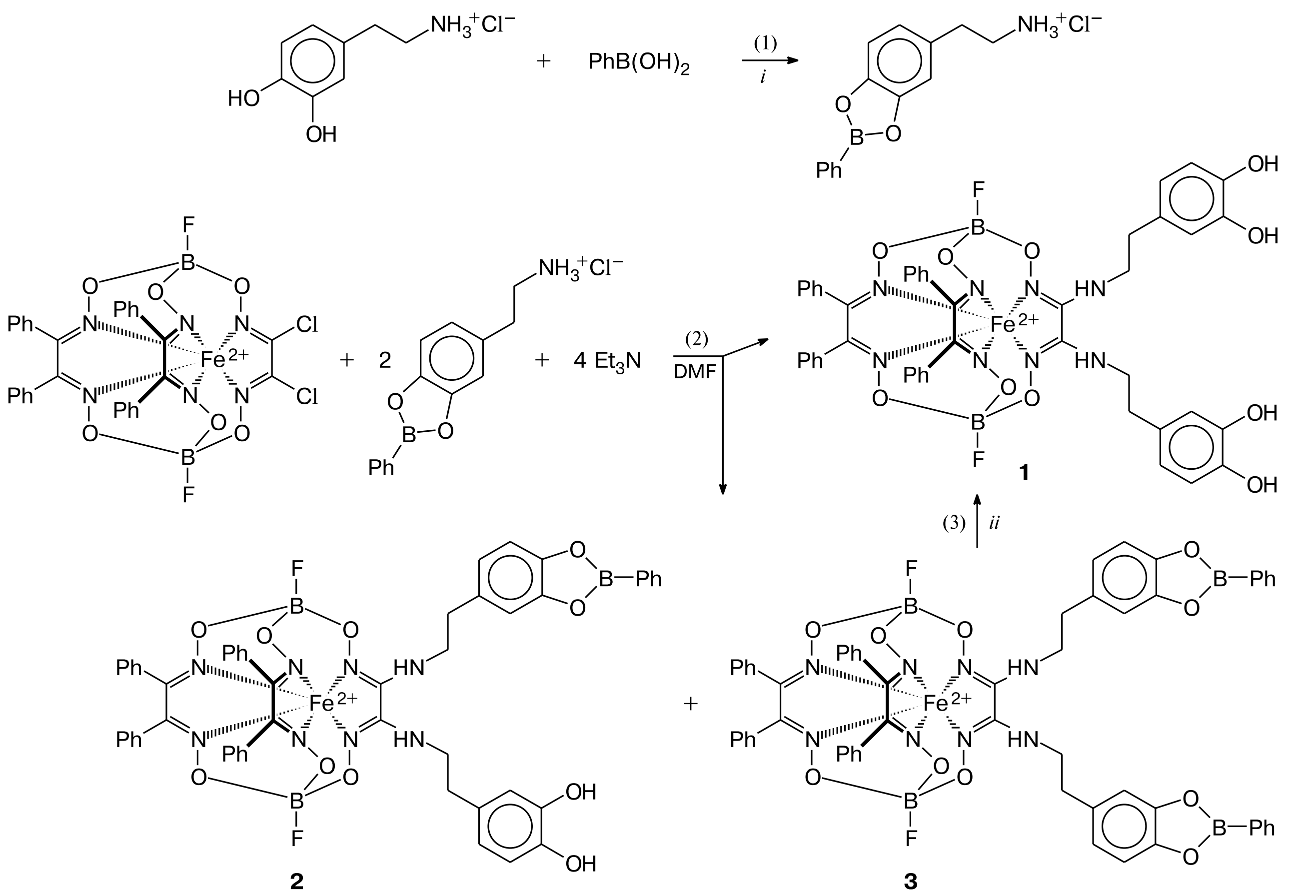
Reaction of complex $FeBd_2(dop_2Gm)(BF)_2$ with H_3BO_3. The initial components were mixed in MeOH (1 mL) and the reaction mixture was left for a week. Then the reaction mixture was filtered and the filtrates were studied by MALDI-TOF mass spectrometry.

Results and Discussion

The standard method of synthesis of ribbed-functionalized tris-dioximates is based on nucleophilic substitution of the reactive chlorine atoms in the initial halide clathrochelate complexes with the corresponding nucleophilic agent. However, the reaction of dichloride $FeBd_2(Cl_2Gm)(BF)_2$ clathrochelate with dop • HCl in the presence of a base afforded a mixture of the products, because the dopamine molecule is a biphilic nucleophilic agent and can undergo nucleophilic substitution reactions with both the amino and hydroxyl groups of the pyrocatechol fragment. Therefore, for selective reaction with the amino group only, the HO groups of the pyrocatechol fragments should be protected. We attempted to protect these groups using dimethylsulfate, *n*-butylboronic acid, trimethylborate, and phenylboronic acid. The best results were obtained in the case of phenylboronic acid; other protectants either reacted incompletely with dopamine or dissociated during nucleophilic substitution to form by-products.

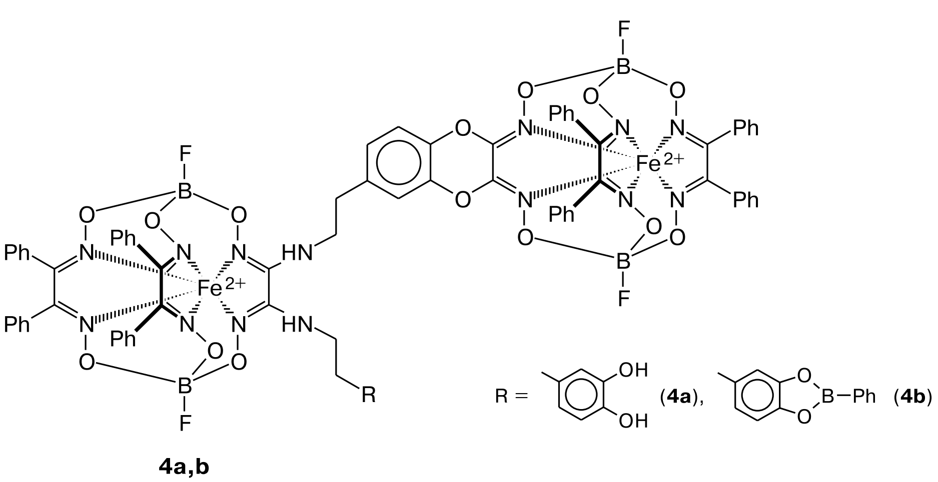
$FeBd_2(dop_2Gm)(BF)_2$ clathrochelate was synthesized according to Scheme 1. The MALDI-TOF mass spectra

Scheme 1



Reagents and conditions: *i*. MeOH, reflux, 2.5 h; *ii*. $CH_2OHCHOHCH_2OH$ (excess), $CHCl_3$/MeOH.

of a mixture of clathrochelate products **1—3**, which was prepared in stage (2), in the positive spectral region exhibits peaks with *m/z* 980, 1066, and 1152 and the intensity ratio 2 : 3 : 2. They correspond to the $[FeBd_2(dop_2Gm)(BF)_2]^{\bullet +}$, $[FeBd_2((PhBdop)(dop)Gm)(BF)_2]^{\bullet +}$, and $[FeBd_2((PhBdop)_2Gm)(BF)_2]^{\bullet +}$ molecular ions. The most intensive peaks in the negative spectral region (*m/z* −979, −1065, and −1151) correspond to the deprotonated complexes with the same structure. Considerably (by 10 times) less intensive peaks (*m/z* 1654, 1740, and −1739) in the spectrum correspond to the clathrochelate by-products of this reaction **4a,b**. A mix-



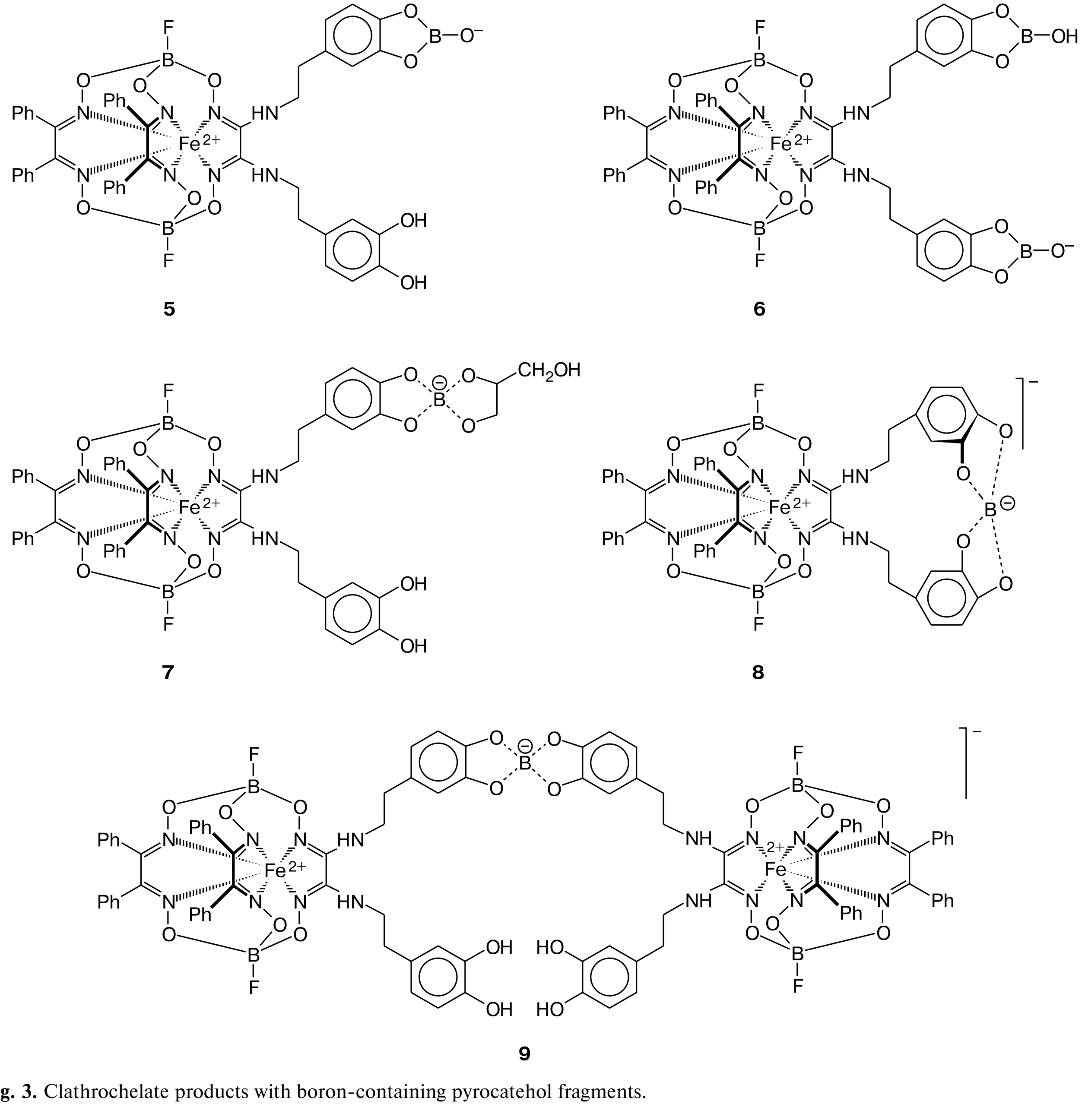
4a,b

ture of the clathrochelate products obtained in stage (2) was not separated and was used in the subsequent stage without additional purification.

In the positive region, the MALDI-TOF mass spectrum of the $FeBd_2(dop_2Gm)(BF)_2$ clathrochelate synthesized (**1**) contains the intensive peak of the molecular ion and less intensive peaks of its ionic associates with Na^+ and K^+ ions. In the negative spectral region, the MALDI-TOF mass spectrum contains the peak of the deprotonated molecular ion (*m/z* –979) and, in addition, the peaks of admixture clathrochelate products **5—7** (Fig. 3) with the boron-containing pyrocatechol fragments.

The elemental analysis data and ^{1}H, ^{13}C{^{1}H} NMR spectra confirmed the composition, structure, and symmetry of the clathrochelate synthesized (in particular, the ratio of integral intensities of the signals assigned to the aromatic protons of the Ph substituents and pyrocatechol fragment and the aliphatic protons of the spacer fragment in the ^{1}H NMR spectrum, as well as the number and position of the signals in the ^{13}C{^{1}H} NMR spectrum).

The ^{57}Fe Mössbauer parameters for the $FeBd_2(dop_2Gm)(BF)_2$ complex (**1**) (isomeric shift (IS) equal to 0.34, quadrupole splitting (QS) is 0.6 mm s^{-1}) are close to those of the earlier prepared α-benzyl-



5

6

7

8

9

Fig. 3. Clathrochelate products with boron-containing pyrocatehol fragments.

dioximate clathrochelates (ISs equal to 0.34—0.35 and QS are 0.45—0.76 mm s^{-1})[14] and indicate the low-spin state of the encapsulated iron(II) ion and its distorted trigonal-prismatic N_6-environment (distortion angle $\varphi \approx 24—29°$).

The solution UV—Vis spectrum of $FeBd_2(dop_2Gm)(BF)_2$ in CH_2Cl_2 contains four intense bands ($\varepsilon \approx 2—9 \cdot 10^3$ L mol^{-1} cm^{-1}) in visible region caused by the charge transfer Fe$d \rightarrow$ Lπ^*, which is due, in particular, to the absence of symmetry axis C_3 passing in symmetric clathrochelates through the cross-linking atoms and an encapsulated metal ion. For the earlier synthesized monoribbed-functionalized clathrochelate iron(II) bis-α-benzyldioximates, only two bands of close intensity were obtained in the visible region.[14] It is most likely that in the clathrochelate dopamine derivative the charge-transfer bands (as well as a series of the $\pi—\pi^*$-transition bands in the cage polyene ligand) resolved. This resulted in a substantial increase in the number of the bands observed when the deconvolution procedure of UV—Vis spectra was used.

The binding of boric acid by the dopamine-containing clathrochelate synthesized in the presence and absence of a base was studied. The molar ratios of the components in the solutions studied are presented in Table 1.

According to the MALDI-TOF mass spectrometry data, the interaction of $FeBd_2(dop_2Gm)(BF)_2$ with boronic acid was found only for samples *1* and *3* in the absence of the NBu_4OH base. In both cases, the main product was the expected 1 : 1 complex (see Fig. 3, compound **8**). In the negative spectral region the single intense peak with m/z −1141 of the adduct of this complex with the molecule of the matrix (2,6-dihydroxybenzoic acid) was found; no peaks of by-products were observed. Only the spectrum of sample *1* contained a low-intensity peak with m/z −1967 of binuclear product **9**, its tentative structure is shown in Fig. 3.

No peaks (including the peak of the initial complex) were observed in the MALDI-TOF mass spectra of samples *2* and *4* containing the strong NBu_4OH base in a region of ±500—2500.

Thus, this study showed that the ribbed dioximate fragments of the clathrochelate complex with dopamine substituents are efficient receptors of boric acid.

Table 1. Component ratio in the solutions studied by MALDI-TOF mass spectroscopy

Sample number	$FeBd_2(dop_2Gm)(BF)_2$	H_3BO_3	NBu_4OH
1	1	1	—
2	1	1	1
3	1	10	—
4	1	10	10

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