Synthesis and X-Ray Structure of the Monofunctionalized Amide–Terminated Phenylsulfide Iron(II) Clathrochelates

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Dedicated to Academician Aslan Yu. Tsivadze on the occasion of his 75th Birthday

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The monoamide-terminated cage complexes FeBd 2((X-R(+)-PhCH(CH3)NHOCC6H4S)GmH)(BF)2 (where Bd 2– is α-benzyldioxime dianion, Gm is glyoxime residue, X is ortho- or meta-, or para-substituent) were obtained using one-pot two-step synthetic procedure that includes (i) the reaction of its monocarboxyl-terminated clathrochelate precursor with 1,1’-carbonyldiimidazole (CDI), giving the corresponding azaheterocycle-terminated intermediate, and (ii) its cleavage with R(+)-phenylethylamine leading to the target iron(II) clathrochelate with terminal optically active amide group. The complexes obtained were characterized using elemental analysis, MALDI-TOF mass-spectrometry, IR, UV-Vis, 1H and 13C{1H} NMR spectra, and by single crystal X-ray diffraction (for a meta-substituted constitutional isomer). The number, position and integral intensities of the signals in their 1H NMR spectra confirmed the composition of the macrobicyclic molecules. The number of the signals in their 13C NMR spectra suggests the absence of the C2 symmetry axes passing through the middles of the chelate C–C bonds and of the symmetry plane also passing through these points and the encapsulated iron(II) ion as well. As follows from X-ray diffraction data, the encapsulated iron(II) ion in the molecule FeBd 2((meta-R(+)-PhCH(CH3)NHOCC6H4S)GmH)(BF)2 is situated in the centre of its FeN 6-coordination polyhedron with Fe–N distances falling in the range 1.8904(4)–1.9404(7) Å. This polyhedron possesses the geometry intermediate between a trigonal prism and a trigonal antiprism with the average distortion angle φ of 24.2°; its height h is equal to 2.34 Å and the average bite (chelate) angle α is approximately 78.2°. The terminal PhCH(CH3)NH group of the above clathrochelate molecule is equiprobably disordered over two sites with opposite orientation of its methyl and phenyl substituents; the N–H...F-bonded clathrochelate dimers are formed in its X-rayed crystal.

Keywords: Macrocycles, clathrochelates, cage complexes, iron complexes, ligand reactivity.

Introduction

Tris-dioximate metal clathrochelates[1,2] are the threedimensional macrobicyclic complexes with an encapsulated metal ion, possessing the specific geometry of their MN 6-coordination polyhedra that is intermediate between a trigonal prism (TP, the distortion angle j=0°) and a trigonal antiprism (TAP, j=60°). Due to such TP–TAP-distorted geometry, these polyhedra have no inversion centre and possess an inherent chirality. On the other hand, an equiprobability of their left(Δ)- and right(Δ)-handed distortions, and a rapid transition between them cause the absence of an optical activity of these cage complexes. Hence, a selective fixation of one of these C 3-distorted conformations may result in an appearance of a CD signal in their spectra in the range of the visible metal-to-ligand charge transfer (MLCT) bands (400–600 nm). Indeed, we have recently found[3] an ability of the above quasiaromatic polyzaozomethine complexes to give a CD response upon their supramolecular interactions with or covalent binding to the chiral inductors, such as biomacromolecules, or low-molecular optically active compounds, respectively. To observe an effect of the low-molecular chiral inductor, the CD spectra of the dicarboxyphenylsulfide iron(II) clathrochelates upon their covalent binding to R(+)-1-phenylethylamine, giving the corresponding diamide-functionalized cage complexes, have been measured.[3] In this paper, we report the synthesis, X-ray structure and spectral characteristics of their monofunctionalized macrobicyclic analogs, the molecules of which bear the single optically active amide group and, therefore, are prospective optically active compounds and CD probes for biomacromolecules.
Синтез и рентгеновская структура монофункционализированных
fenilсульфидных клатрохелатов железа(II) с терминальной
амидо-групой

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Посвящается академику А.Ю. Цивадзе по случаю его 75-летнего юбилея

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С использованием двухстадийной синтетической процедуры без выделения интермедиата методики были получены моноамидные комплексы FeBd2-X-R(+)-PhCH(CH3)NHOOC-6H4S)(GmH)(BF)2 (где Bd – дианион α-бензилдиксамид, Gm – глиоксимид, X – орто-, мета- или пара-заместитель). Процедура включает: (1) реакцию исходного клатрохелата с терминальной карбоксильной группой с 1,1’-карбонилдимидазолом, приводящую к соответствующему интермедиату с азагетероциклической группой; (2) её расщепление под действием R(+)-фенилэтиламина, приводящее к целевому клатрохелату железа(II) с терминальной оптически активной амидной группой. Полученные комплексы были охарактеризованы методом элементного анализа, MALDI-TOF масс-спектрометрии, ИК, ЭСП, 1H и 13C ЯМР-спектроскопии и рентгеноструктурного анализа (для мета-замещенного конституционного изомера). Количество, положение и интегральные интенсивности сигналов в 1H ЯМР спектрах подтвердили состав макробициклических молекул. Число сигналов в 13C ЯМР спектрах указывает на отсутствие осей С, симметрии, проходящих через середины хелатных связей C–C, а также плоскости симметрии, проходящей через эти же точки и инкапсулированный ион железа(II). По данным РСА, инкапсулированный ион железа(II) в молекуле FeBd2-X-R(+)-PhCH(CH3)NHOOC-6H4S)(GmH)(BF)2, находится в центре его FeN6-координационного полиэдра с расстояниями Fe–N в диапазоне 1.8904(4) – 1.9404(7) Å. Этот полиэдр имеет геометрию, промежуточную между трёхугольной призмой и трёхугольной антипризмой с средним углом искажения φ равным 24.2°; его высота h составляет 2.34 Å, а средний хелатный угол α приблизительно равен 78.2°. Терминальная PhCH(CH3)N группа этой клатрохелатной молекулы равноэнергетично разупорядочена по двум положениям с противоположной ориентацией её метильного и фенильного заместителей; в кристалле обнаружено образование N–H...F-связанных клатрохелатных димеров.

Ключевые слова: Макроциклы, клатрохелаты, клеточные комплексы, комплексы железа, реакционная способность лиганда.

Experimental

The reagents used, sorbents, organic bases and solvents were obtained commercially (Sigma–Aldrich®). The monocarboxyl-containing clathrochelate precursors FeBd2-X-HOOC-6H4S)(GmH)(BF)2 (where Bd – α-benzylidoxime dianion, Gm is glyoxime residue, X is ortho- or meta-, or para-substituent) were prepared as described in.[4]

1H, 13C{1H} and 2D NMR spectra were recorded from CD2Cl2 solutions with a Bruker Avance 600 spectrometer. The measurements were done using the residual signals of CD2Cl2: 1H 5.32 ppm (CD2Cl2), 13C 54.00 ppm.

Analytical data (C, H, N contents) were obtained with a Carlo Erba model 1106 microanalyzer.

MALDI-TOF mass spectra of the monofunctionalized clathrochelates were recorded with and without the matrix using a MALDI-TOF-MS Bruker Autoflex II (Bruker Daltonics) mass spectrometer in reflecto-mol mode. The ionization was induced by UV-laser with wavelength 337 nm. The samples were applied to a nickel plate, 2,5-dihydroxybenzoic acid was used as the matrix. The accuracy of measurements was 0.1 %.

UV-Vis spectra of their solutions in dichloromethane were recorded in the range 230–800 nm with a Varian Cary 50 spectrophotometer. The individual Gaussian components of these spectra were calculated using the Fityk program.[5]

Synthesis

General procedure for preparation of the monoamide-terminated clathrochelates FeBd2-X-R(+)-PhCH(CH3)NHOOC-6H4S)(GmH)(BF)2 (where X is ortho- or meta-, or para-substituent). The corresponding monocarboxyphenylsulfide clathrochelate FeBd2-X-HOOC-6H4S)(GmH)(BF)2 (0.08 g, 0.1 mmol) was dissolved in dry DMSO (2 ml) under argon and a solution of CDI (0.033 g, 0.22 mmol) in DMSO (0.4 ml) was added under the intensive stirring. The reac-
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The reaction mixture was stirred at 50 °C for 40 min, then it was cooled to 20 °C, degassed from CO₂ impurities with argon and R(+)-1-phenylethylamine (0.036 g, 0.3 mmol) was added. The reaction mixture was stirred at r.t. for 1 h and precipitated with 2 % aqueous hydrochloric acid (25 ml). The precipitate was filtered off, washed with water and extracted with dichloromethane. The extract was precipitated with hexane, giving the crude product with a purity of approximately 90 %. This product was flash-chromatographically separated on silica gel (elucent: dichloromethane – iso-propanol 99:1 mixture) and three eluates were obtained. The second eluate was collected and evaporated to dryness. The solid residue was extracted with dichloromethane and the extract was precipitated with hexane. The precipitate was filtered off, washed with hexane and dried in vacuo.

**FeBd ((para-R(-)-PhCH(CH₃)NHOCC₆H₄S)GmH)BF₆**

Yield: 0.06 g (67 %). Found (%): C 57.66, H 3.74, N 10.33. Calculated for C₃₂H₂₄N₄FeBF₆O₂ (positive range) 933 [M⁺] (100), 956 [M+Na⁺] (20), 972 [M+K⁺] (50). UV-Vis (CH₂Cl₂) λmax nm (ε 10⁻³ mol⁻¹ cm⁻¹): 228 (35), 264 (1.8), 284 (2.2), 297 (1.7), 362 (1.2), 452 (5.5), 474 (18). δ ppm: 22.27 (s, CH₃), 50.34 (s, CH), 125.77, 126.70, 128.02, 128.57, 143.55 (s, CH), 149.13 (s, CH), 156.86, 157.25 (two s, PhC=N), 165.11 (C=O). Yields: 0.06 g (67 %). Found (%): C 57.66, H 3.63, N 10.30. Calculated for C₃₃H₂₅N₅FeBF₆O₂: C 57.91, H 3.78, N 10.50 MS (MALDI-TOF) m/z (I, %): 933 [M⁺] (100), 956 [M+Na⁺] (20), 972 [M+K⁺] (50). UV-Vis (CH₂Cl₂) δ ppm: 1.60 (d, 3H, CH₃), 5.28 (m, 1H, CH), 6.47 (d, 1H, NH), 7.36 (m, 26H, Ph + NC6H5), 7.80 (m, 2H, SAR), 7.89 (m, 2H, SAR).

**FeBd ((meta-R(-)-PhCH(CH₃)NHOCC₆H₄S)GmH)BF₆**

Yield: 0.06 g (67 %). Found (%): C 57.63, H 3.63, N 10.30. Calculated for C₃₂H₂₄N₄FeBF₆O₂ (positive range) 933 [M⁺] (100), 956 [M+Na⁺] (20), 972 [M+K⁺] (50). UV-Vis (CH₂Cl₂) δ ppm: 1.59 (d, 3H, CH₃), 5.28 (m, 1H, CH), 6.47 (d, 1H, NH), 7.34 (m, 26H, Ph + NC6H5), 7.61 (m, 1H, SAR), 7.88 (m, 1H, SAR), 7.91 (m, 1H, SAR), 8.19 (s, 1H, SAR), 13.06 (s, 1H, SAR). δ ppm: 22.26 (s, CH₃), 50.19 (s, CH), 125.77, 126.70, 128.02, 128.57, 143.55 (s, CH), 149.13 (s, CH), 156.86, 157.25 (two s, PhD, 165.11 (C=O).

**Results and Discussion**

The monoamide-terminated cage complexes FeBd ((meta-R(-)-PhCH(CH₃)NHOCC₆H₄S)GmH)BF₆ were obtained by Scheme 1 using one-pot two-step synthetic procedure that includes (i) the reaction of its monocarboxyl-terminated clathrochelate precursor with CDI, giving the corresponding azaheterocyclic-terminated intermediate, and (ii) its cleavage with R⁺(+)phenylethylamine leading to the target iron(II) clathrochelate with terminal optically active amide group.

The complexes obtained were characterized using elemental analysis, MALDI-TOF mass-spectrometry, IR, UV-Vis, 'H and ^13C{'H} NMR spectra, and by single crystal X-ray diffraction (for one of these clathrochelates). The most intensive peaks in the positive range of their MALDI-TOF mass spectra belong to the corresponding molecular ions. ^1H, ^13C{'H} and 2D NMR spectra, typical of the clathrochelates obtained, are shown in Figures 1–5. The number, position and integral intensities of the signals in their 1H NMR spectra confirmed the composition of the macrobicyclic cluster, and its U(C)N moiety was refined isotropically. Positions of the H(C) atoms were calculated. All hydrogen atoms were included in the refinement using the riding model with Uiso (H)=2/3 Ueq (C). The residual electron density from one highly disordered solvent molecule was treated using SQUEEZE/PLATON program.

### Molecular structure of the complex FeBd ((meta-R(-)-PhCH(CH₃)NHOCC₆H₄S)GmH)BF₆

The molecular structure of the complex FeBd ((meta-R(-)-PhCH(CH₃)NHOCC₆H₄S)GmH)BF₆ was determined using the SQUEEZE/PLATON program. The residual electron density was refined anisotropically using the riding model with Uiso (H)=2/3 Ueq (C). Such coordination polyhedron of the complex FeBd ((meta-R(-)-PhCH(CH₃)NHOCC₆H₄S)GmH)BF₆ possesses the geometry intermediate between a TP and a TAP with the average distortion angle φ of 24.2°. This value is very similar to those for its above monofunctionalized clathrochelate analogs possessing φ from 23.6 to 25.8°. Other geometrical parameters of their clathrochelate frameworks are also very similar: the heights...
Scheme 1. Stepwise preparation of the monofunctionalized amide iron(II) clathrochelates.
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**Figure 1.** $^1\text{H}$ NMR spectrum of the clathrochelate FeBd$_2$(ortho-$R^+$)-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$.

**Figure 2.** $^{13}\text{C}$$^1\text{H}$ NMR spectrum of the clathrochelate FeBd$_2$(ortho-$R^+$)-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$. 
Figure 3. $^{1}H$ – $^{1}H$ COSY NMR spectrum of the complex FeBd$_2$(ortho-$R$+$+$)-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$.

Figure 4. $^{1}H$ – $^{13}C$ HMQC NMR spectrum of the complex FeBd$_2$(ortho-$R$+$+$)-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$. 
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Figure 5. $^1$H – $^{13}$C HMBC NMR spectrum of the clathrochelate FeBd$_2$(ortho-$R^+$-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$.

Figure 6. General view of the molecule FeBd$_2$(meta-$R^+$-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$.

Figure 7. Formation of H-bonded clathrochelate dimer in the crystal FeBd$_2$(meta-$R^+$-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$·CH$_2$Cl$_2$; the corresponding hydrogen bonds are shown with dashed line. The H(C) atoms are omitted for clarity.

$h$ of the FeN$_6$-polyhedra (2.33–2.40 Å) and the bite (chelate) angles $\alpha$ (78.2–78.8°) are characteristic of the fluoroboron-capped iron(II) clathrochelates.$^{[1,2]}$

The terminal PhCH(CH$_3$)NH group of the molecule FeBd$_2$(meta-$R^+$-PhCH(CH$_3$)NHOCC$_6$H$_4$S)GmH)(BF)$_2$ in the above X-rayed crystal is equiprobably disordered over two sites with opposite orientation of its methyl and phenyl groups. Nevertheless, this disorder does not prevent a formation of the corresponding N–H...F-bonded clathrochelate dimers (Figure 7) through the hydrogen bonding between the terminal amide moiety of the single functionalizing ribbed substituent of one of these macrobicyclic molecules and the fluorine apical substituent at a clathrochelate framework of the second molecule of this type on the distance $r$(N...F)=3.0421(8) Å with $\angle$N...H...F=150.4°. Other intermolecular interactions in this crystal include the halogen bonds and weak H-bonding C–H...O and C–H...F interactions.

Because the chromophoric FeN$_6$-centers of the obtained macrobicyclic iron(II) $tris$-dioximates, the constitutional isomers, are almost the same, their solution UV-Vis spectra in the visible range are very similar. Their decomposition on the Gaussian components gave a more intensive ($\varepsilon$~2⋅10$^4$ mol$^{-1}$·cm$^{-1}$) band with maximum at approximately
475 nm and a less intensive (ε~(5–9) 10^3 mol−1·l·cm−1) band at approximately 450 nm assigned to the metal-to-ligand Fed→Lp* charge transfer. The bands in the UV range of these spectra were assigned to p–p* transitions in the α-benzildioximate chelate fragments of their macrobicyclic ligands, and to those of the same nature in the arylsulfide ribbed moiety and in the terminal R(+) -phenylethylamine group as well.

Conclusions

Thus, for the first time, we prepared the iron(II) cage complexes with terminal optically active group and characterized them using various spectral techniques and by single crystal X-ray diffraction. These clathrochelates can be regarded as prospective chiroptical CD-active probes for protein structures (in particular, for sensing of their conformational changes).

Acknowledgements. The synthesis of cage complexes was supported by the Russian Science Foundation (grant 16-13-10475). The spectral characterizations were performed with a financial support of the EU Research and Innovation Staff Exchange (RISE) (H2020-MSCA-RISE-2017, Project 778245 ‘CLATHROPROBES’). XRD experiment was performed at the unique scientific facility Kurchatov Synchrotron Radiation Source supported by the Ministry of Education and Science of the Russian Federation (project code RFMEFI61917X0007). Y.Z.V. and A.S.B. thank RFBR (grants 15-03-07509 and 17-03-00587) for the financial support. The contribution of the Center for molecule composition studies of INEOS RAS is also gratefully acknowledged. MALDI-TOF mass spectrometric measurements were performed using an equipment of CKP FMI IPCE RAS.

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Received 22.11.2017
Accepted 10.12.2017

Table 1. Main geometrical parameters of a macrobicyclic cage framework in the fluoroboron-capped monofunctionalized iron(II) clathrochelates.

| Parameter | FeBd₂((meta-R(+)-PhCH(CH₃)NOHCC₆H₄S)GmH(BF)₂[10] | FeBd₂((CH₃S)GmH(BF)₂[12] | FeBd₂((HSCH₂CH₂S)GmH(BF)₂[10] | FeBd₂(PiSGmH(BF)₂[11] |
|-----------|----------------------------------|----------------|------------------|------------------|
| Fe–N (Å)  | 1.8904(4) – 1.9404(7) av. 1.926  | 1.900(3) – 1.916(3) av. 1.908  | 1.891(4) – 1.912(4) av. 1.899  | 1.907(4) – 1.926(4) av. 1.912  |
| B–O (Å)  | 1.4789(4) – 1.5115(5) av. 1.494  | 1.475(5) – 1.516(4) av. 1.491  | 1.465(5) – 1.495(5) av. 1.481  | 1.492(5) – 1.518(5) av. 1.508  |
| N–O (Å)  | 1.3697(3) – 1.382(5) av. 1.372  | 1.363(5) – 1.382(5) av. 1.372  | 1.366(6) – 1.378(5) av. 1.371  | 1.352(4) – 1.376(4) av. 1.366  |
| C=N (Å)  | 1.3078(4) – 1.312(3) av. 1.315  | 1.312(3) – 1.339(4) av. 1.323  | 1.284(5) – 1.321(6) av. 1.310  | 1.301(5) – 1.321(5) av. 1.312  |
| C–C (Å)  | 1.4410(4) – 1.477(3) av. 1.457  | 1.436(6) – 1.454(6) av. 1.444  | 1.418(7) – 1.466(6) av. 1.448  | 1.412(6) – 1.461(6) av. 1.439  |
| N=C–C=N (°) | 8.022(4) – 9.786(5) av. 8.9    | 5.3(4) – 9.8(5) av. 8.1    | 5.6(6) – 12.5(6) av. 9.0    | 7.9(6) – 11.6(6) av. 9.6    |
| j (°)    | 24.2  | 24.7  | 25.3  | 23.9  |
| α (°)    | 78.2  | 78.8  | 78.8  | 78.2  |
| h(Å)     | 2.34  | 2.33  | 2.40  | 2.33  |