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Preparation and Synchrotron X−Ray Structure of an Apically- and Ribbed−Functionalized Iron(II) Clathrochelate Decorated with Six Methoxyl and Two Carboxyl Terminal Groups

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Octafunctionalized iron(II) cage complex with six equivalent methoxyl-terminated alkylsulfide ribbed fragments and two terminal carboxyl groups in its apical aromatic substituents was obtained using nucleophilic substitution of an appropriate hexachloroclathrochelate precursor with an anionic derivative of mercaptoacetic acid; generated in situ in the presence of triethylamine, followed by the further esterification reaction of thus obtained product with methanol. The obtained diamagnetic cage complex was characterized using elemental analysis, MALDI-TOF mass spectrometry, UV-Vis and ^{1}H NMR spectra, and by the synchrotron single crystal X-ray diffraction experiment as well.

Keywords: Macrocycles, cage compounds, clathrochelates, iron complexes, ligand reactivity, synchrotron studies.

Получение апикально− и реберно−функционализированного клатрохелата железа(II), содержащего шесть метоксильных и две карбоксильные терминальные группы, и его структура по данным синхротронного рентгенодифракционного эксперимента

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Октафункционализированный клеточный комплекс железа(II) с шестью эквивалентными метоксиалкилсульфидными реберными фрагментами и двумя терминальными карбоксильными группами в его апикальных ароматических заместителях был получен нуклеофильным замещением соответствующего гексахлорклатрохелатного предшественника под действием анионного производного меркаптоуксусной кислоты, генерированного in situ в присутствии триэтиламина и последующей реакцией полученного продукта с метанолом. Полученный диамагнитный клеточный комплекс был охарактеризован с использованием данных элементного анализа, MALDI-TOF масс-спектрометрии, электронного и ^{1}H ЯМР спектров, а также путем синхротронного РСА его монокристалла.

Ключевые слова: Макроциклы, клеточные соединения, клатрохелаты, комплексы железа, реакционная способность лигандов, синхротронные исследования.

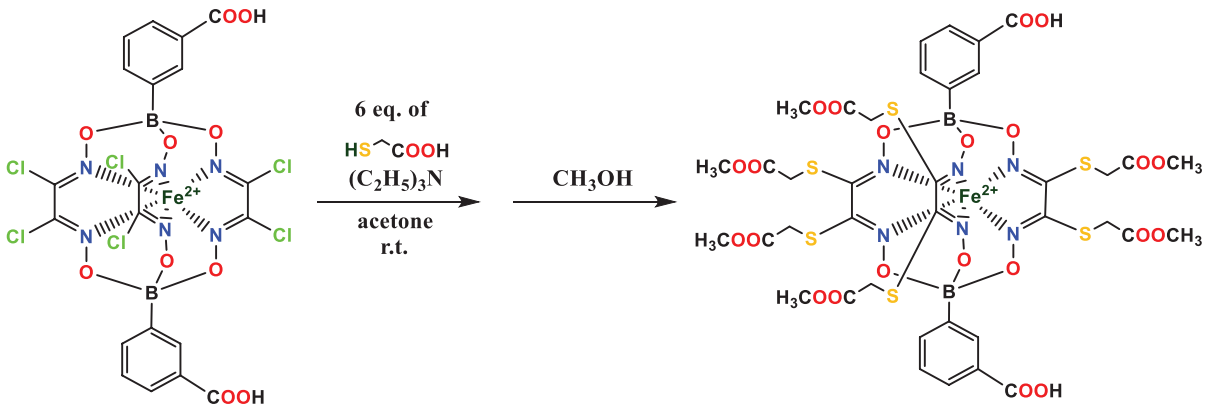
Macropolycyclic cage metal complexes (clathrochelates[1]) are the three-dimensional, chemically robust and easy-to-modify molecular scaffolds (platforms), which seem to be prospective for the direct molecular design and efficient synthesis of various biologically active compounds and molecular optical probes.[2] Their interactions with biomolecules have been extensively studied,[3–9] revealing the iron(II) mono- and bis-clathrochelates to be the efficient submicromolar and low micromolar inhibitors in the transcription systems of T7 RNA,[3] and Taq DNA[4] polymerases, respectively. Highest *in vitro* inhibitory activity in the transcription systems of these polymerases has been observed for cage iron(II) complexes containg functionalizing ribbed carboxyl-terminated arylsulfide substituents in the α-dioximate chelate fragment(s) of a macrobicyclic framework. The same carboxyl-terminated arylsulfide iron(II) mono- and bis-clathrochelates are also reported[5,6] to be able to affect the protein–protein interactions in amyloid self-aggregation. It was shown,[5,6] that both the kinetics of fibril formation and the morphology of protein fibrils formed by insulin and lysozyme, have been affected by the presence of these cage metal complexes. The formation of supramolecular complexes between the iron(II) clathrochelates and transport serum albumins has been observed.[7] An ability of the inherently CD-silent cage molecules to give an induced circular dichroism (ICD) output in the visible range upon such an assembling is reported[8] for the first time. Such clathrochelate-based ICD response is explained[8] by the existence of an initial clathrochelate framework as an equilibrium of enantiomers with trigonal prismatically (TP)-distorted and trigonal antiprismatically (TAP)-distorted optically active conformations (Δ- and Λ-conformations, respectively). Binding of a designed clathrochelate guest to the asymmetric binding site of a given protein macromolecule as a host leads to a selective fixation (and thus accumulation) of one of these enantiomers and, therefore, in formation of the intensive clathrochelate-based ICD signals in the visible and near UV-ranges. An ability of the hexacarboxyphenylsulfide iron(II) cage complexes to discriminate between the proteins of similar structures (*i.e.*, human and bovine serum albumins) by their ICD outputs is reported.[9] The interactions between a complete set of the monoribbed-functionalized iron(II) clathrochelates with two equivalent or non-equivalent carboxyl-terminated arylsulfide groups in the same chelate α-dioximate fragment and a series of globular proteins, such as bovine and human serum albumins, lysozyme, beta-lactoglobulin, trypsin and insulin have been studied.[10] Among the tested iron(II) clathrochelates and bis-clathrochelates, those with terminal biorelevant polar and H–bond donor (in particular, carboxyl) groups, have been recognized as most efficient bioeffectors and/or optical molecular probes. Indeed, the presence of terminal H–bond donor carboxyl groups in their molecules as the guests suggests an ability to form the strong hydrogen bonds with appropriate biological macromolecules and/or their supramolecular assemblies as the hosts. The effect of such host–guest binding can be taken into account using the derivatives of these cage compounds, the molecules of which do not contain the above terminal H–bond donor group(s) (first of all, due to a formation of their methyl esters). Indeed, methyl group is least bulky in a row of alkyl homologs and it causes the minimal steric clashes within the cavities of biomacromolecules and/or their supramolecular aggregates. Such methoxyl-containing macrobicyclic derivatives, the terminal biorelevante carboxyl groups of which are protected by a formation of their alkyl esters, did not formed the stable supramolecular assemblies with globular proteins.[8,11] The synthetic pathway for preparation of a series of the methyl ester-terminated macrobicyclic iron(II) complexes, which are appropriate reference compounds in biochemical and biological testings of their parent carboxyl-terminated cage complexes, have been elaborated.[11] As follows from the single crystal X-ray diffraction data, a structural disordering of their functionalizing ribbed substituents in the corresponding X-rayed crystals has been observed and explained[11] by the absence of strong H–bonded supramolecular assemblies, characteristic of their carboxyl-terminated clathrochelate analogs. Such the absence of these intermolecular interactions, as well as that of the substantial sterical clashes hampering a rotation around the single C–S bonds, caused the different orientations of the functionalizing methoxyl-terminated arylsulfide substituents at a cage framework in their X-rayed crystals. So, they are prospective reference cage compounds for biological and spectral (including fluorescent and CD) studies.[11] In the present stage, we aimed to obtain an apically- and ribbed-functionalized iron(II) clathrochelate, the terminal carboxyl groups of which are protected *via* their esterification (*i.e.,* a formation of eight ester $COOCH_3$-fragments): its molecule seems to be not able to form the strong intermolecular and intramolecular O–H…X hydrogen bonds.

The octafunctionalized iron(II) cage complex $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ (where *Gm* is glyoxime residue) with six equivalent methoxyl-terminated carboxyalkylsulfide ribbed fragments and two terminal carboxyl groups in its apical aromatic substituents was obtained by Scheme 1 under mild reaction conditions (in acetone as a solvent at room temperature) using nucleophilic substitution of an appropriate hexachloroclathrochelate precursor $Fe(Cl_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ with an anionic derivative of mercaptoacetic acid; this *S*-nucleophilic monoanion was generated *in situ* in the presence of triethylamine as an organic base. The further esterification reaction of thus obtained product methanol unexpectedly gave[§] the above apically- and ribbed-functionalized cage complex.

This diamagnetic iron(II) cage compound was characterized using elemental analysis, MALDI-TOF/MS mass spectrometry, UV-Vis and ^{1}H NMR spectra and by the synchrotron single crystal X-ray diffraction experiment as well.[#]

The most intensive peaks in the positive range of its mass spectrum (Figure 1) belong to the corresponding molecular ion and its monocationic assemblies with Na^+ and K^+ ions.

Deconvolution of a solution UV-Vis spectrum of the complex $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ (Figure 2) into its Gaussian components[14] gave in the visible and near UV ranges the two less ($\varepsilon_s \sim 1 \div 2\cdot10^3$ mol·L·cm^{-1}) and one more ($\varepsilon \sim 20\cdot10^3$ mol·L·cm^{-1}) intense metal-to-ligand charge transfer Fe(*d*) → L(π^*) bands with maxima at approximately 390, 420 and 490 nm. Six bands assigned to the π–π* transitions in its quasiaromatic macrobicyclic



Scheme 1. Preparation of a titled cage iron(II) complex.

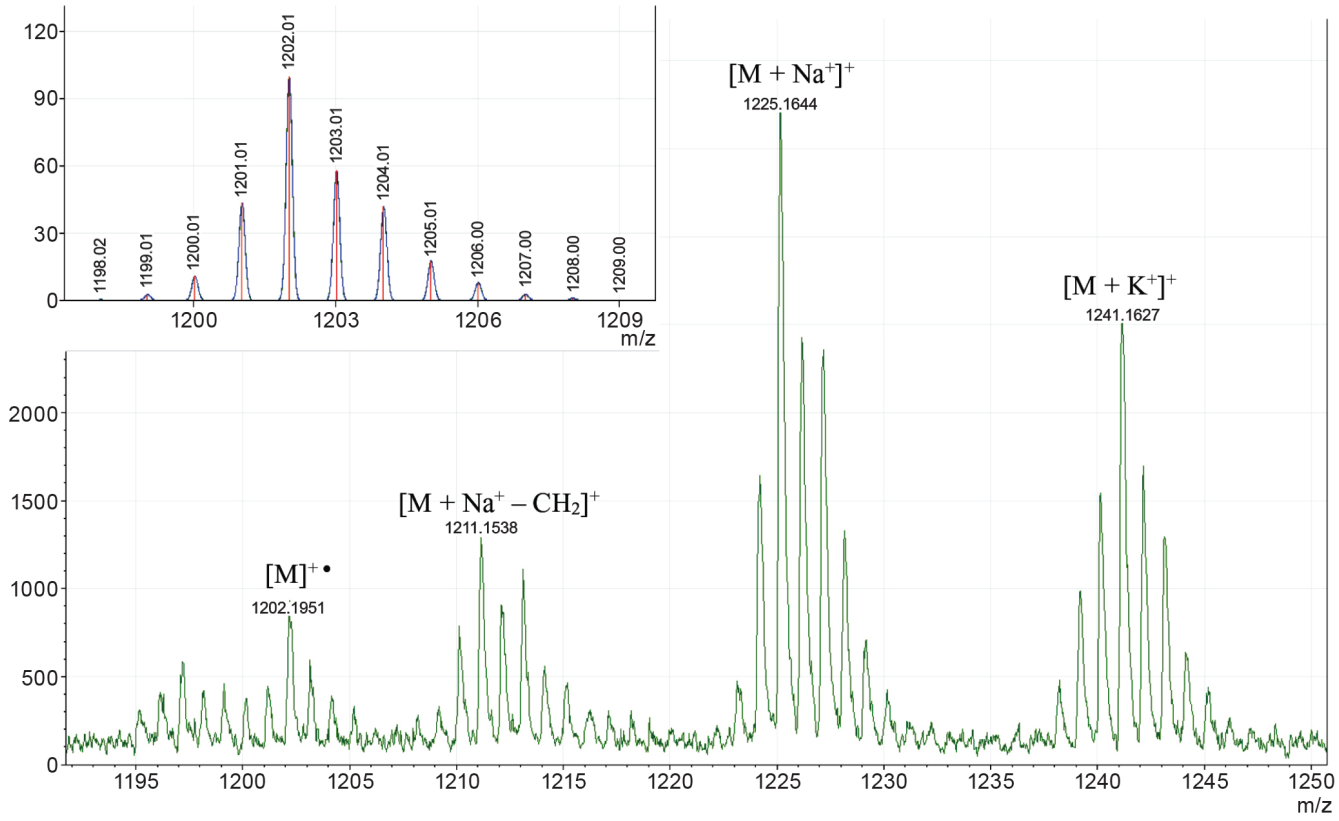


Figure 1. Fragment of the MALDI-TOF mass spectrum of $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$. Inset: the calculated isotope distribution in its molecular ion.

tris-α-dioximate framework, and in the apical aromatic substituents at this framework as well, are observed in the UV range from approximately 230 to 340 nm.

Its ^{1}H NMR spectrum (Figure 3) contains the signals of protons of both the ribbed methoxyl-terminated carboxyalkylsulfide substituents in the α-dioximate chelate fragments of an encapsulating ligand and those of the carboxyl-terminated aromatic groups at the capping boron atoms. The number and position of these signals, as well as the ratio of their integral intensities, confirmed the composition and the molecular C_3-symmetry of the macrobicyclic complex $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$.

Molecular structure of this clathrochelate is shown in Figure 4; main geometrical parameters of its cage framework, as well as those of its hexaalkylsulfide analogs with known X-ray structures[15,16] are complied in Table 1. Average Fe–N distance in the molecule $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ is slightly greater, as compared with those in the ribbed-functionalized hexaalkylsilfide complexes $Fe((n\text{-}C_4H_9S)_2Gm)_3(BC_6H_5)_2$[15] and $Fe((CH_3S)_2Gm)_3(BC_6H_5)_2$.[16]

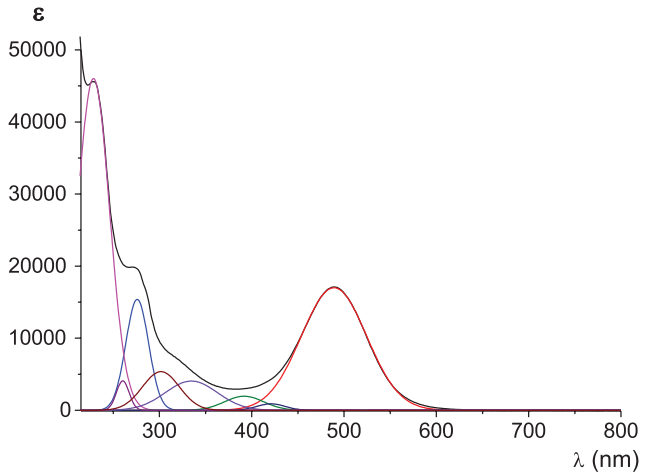


Figure 2. UV-Vis spectrum of a methanol solution of $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ and its deconvolution into the Gaussian components.

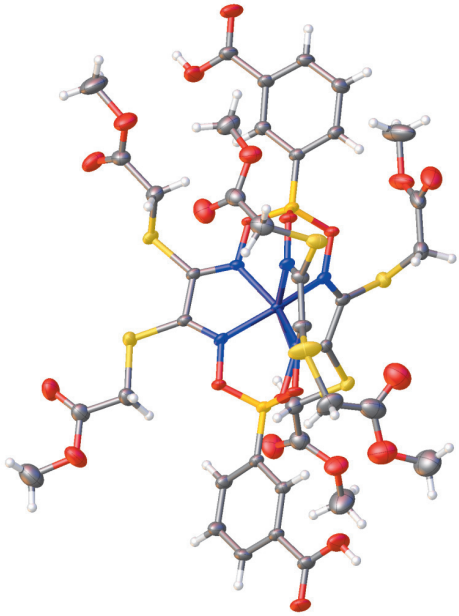


Figure 4. General view of the dicarboxyl-terminated clathrochelate molecule $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ in representations of its atoms with thermal ellipsoids (given with p = 50 %).

The geometry of their FeN_6-coordination polyhedra is intermediate between an ideal trigonal prism (TP, the distortion angle φ = 0°) and an ideal trigonal antiprism (TAP, φ = 60°). Values of the C–C and C=N bond leghts in the molecule

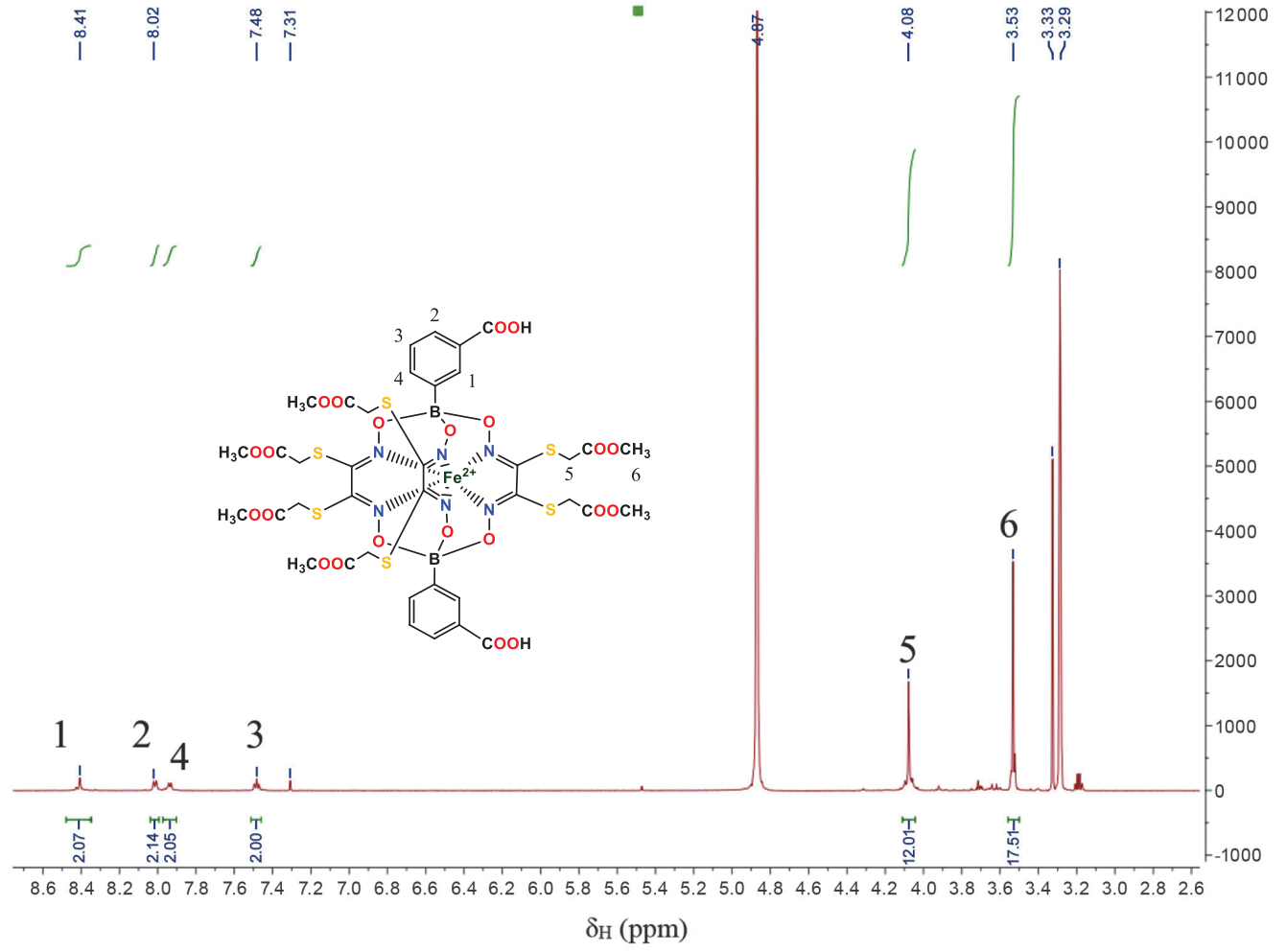


Figure 3. ^{1}H NMR spectrum of the clathrochelate $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ in CD_3OD.

Table 1. Main geometrical parameters of cage frameworks of the triribbed-functionalized hexaalkylsulfide iron(II) tris-α-dioximate clathrochelates.

Parameter	$Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$	$Fe((n\text{-}C_4H_9S)_2Gm)_3(BC_6H_5)_2$[15]	$Fe((CH_3S)_2Gm)_3(BC_6H_5)_2$[16]
Fe – N (Å)	1.907(4) – 1.945(3)	1.898(6) – 1.922(6)	1.898(4) – 1.917(4)
B – O (Å)	*av.* 1.511	*av.* 1.497	*av.* 1.491
N – O (Å)	*av.* 1.391	*av.* 1.368	*av.* 1.377
C=N (Å)	*av.* 1.327	*av.* 1.309	*av.* 1.298
C – C (Å)	*av.* 1.477	*av.* 1.459	*av.* 1.461
N=C – C=N (°)	*av.* 2.8	*av.* 7.3	*av.* 10.9
φ (°)	25.3	25.6	25.3
α (°)	79.0	78.8	78.6
h (Å)	2.36	2.36	2.32

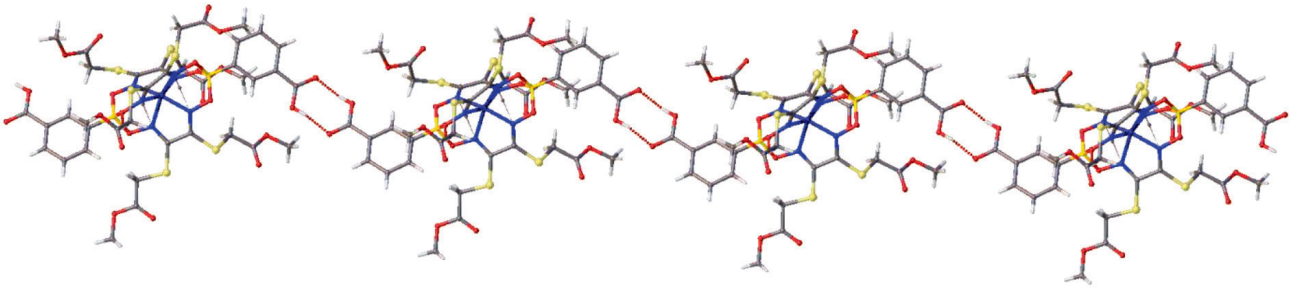


Figure 5. Fragment of H-bonded clathrochelate chains formed in the X-rayed crystal $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$. Hydrogen bonds between their macrobicyclic entities are depicted with dotted lines.

$Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$ are also higher, as compared with those for their above macrobicyclic analogs. The torsion N=C–C=N angles in its apically- and ribbed-functionalized caging ligand are substantially less acute as well, while other geometrical parameters of all their quasiaromatic tris-α-dioximate cage frameworks are almost the same.

Characteristic feature of the crystal structures of carboxylic acid, known from the literature, is a formation of two H-bonds between carboxyl groups of their neighboring molecules. In the crystal $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$, its macrobicyclic entities containing two terminal carboxyl groups in their apical aromatic substituents also form the same hydrogen bonds on the distance *r*(O...O) = 2.660(6) Å with the corresponding O…H…O angle equal to 170.2°. As a result, the infinite H-bonded clathrochelate chains shown in Figure 5 are observed in this X-rayed crystal. Other intermolecular contacts in it are mainly formed by the hydrophobic van der Waals C–H...S and C–H...π interactions.

Thus, we succeeded in preparation and X-ray diffraction characterization of an unusual apically- and ribbed-functionalized iron(II) cage complex, which seems to be a prospective compound from the point of view as its bioactivity (as a cage bioeffector containing the terminal biorelevant carboxyl groups), as a reference clathrochelate guest with protected ribbed substituents.

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§ *Synthesis of the clathrochelate Fe((*CH_3OOCCH_2S*)*$_2$*Gm)*$_3$*(B-3-*C_6H_4COOH*)*$_2$. Complex $Fe(Cl_2Gm)_3(B3\text{-}C_6H_5COOH)_2$ (0.26 g, 0.33 mmol) was dissolved/suspended in acetone (6 mL) with stirring under argon and a solution of triethylamine (0.20 g, 1.98 mmol) and mercaptoacetic acid (0.18 g, 1.98 mmol) in acetone (6 mL) was added dropwise to the above solution/suspension. The reaction mixture was stirred for 4 h at room temperature and left overnight. The precipitate formed was filtered off and extracted with methanol (60 mL, in four portions). The extract was rotary evaporated and the obtained oily residue was precipitated with 10% aqueous hydrochloric acid (15 mL). The precipitate was filtered off, washed with water and once again extracted with methanol. The obtained extract was evaporated to dryness, washed with diethyl ether and hexane, and then dried *in vacuo*. Yield: 0.19 g (47%). Anal. calc. for $C_{38}H_{40}B_2FeN_6O_{22}S_6 \cdot 2H_2O$: C, 36.85; H, 3.58; N, 6.79. Found (%): C, 37.04; H, 4.02; N, 6.80. MS (MALDI-TOF) *m/z*: 1202 $[M]^+$, 1211 $[M + Na^+ - CH_2]^+$, 1225 $[M + Na^+]^+$, 1241 $[M + K^+]^+$. ^{1}H NMR (CD_3OD) δ ppm: 3.53 (s, 18H, 6COOCH_3), 4.08 (s, 12H, 6S−CH_2−COOCH_3), 7.48 (t, $^3J1_{H-}1_H$ = 7.55 Hz, 2H, 2CH=C*H*−CH), 7.93 (d, $^3J1_{H-}1_H$ = 7.32 Hz, 2H, 2CH=C*H*−C(B)), 8.02 (d, $^3J1_{H-}1_H$ = 7.78 Hz, 2H, 2CH−C*H*=C(COOH)), 8.41 (s, 2H, 2C(B)=C*H*−C(COOH)). UV-Vis (CH_3OH) λ_{max} nm (ε·10^{-3}, mol^{-1}·L·cm^{-1}): 229(46), 260(4.1), 276(15), 302(5.4), 335(4.0), 392(1.9), 421(0.9), 489(17).

X-Ray crystallography. Single crystal of the clathrochelate $Fe((CH_3OOCCH_2S)_2Gm)_3(B\text{-}3\text{-}C_6H_4COOH)_2$, suitable for the synchrotron X-ray experiment, was grown for its saturated solution in acetonitrile – benzene 1:3 mixture. The formed red-plate crystal of the complex $C_{38}H_{40}B_2FeN_6O_{22}S_6$ (M = 1202.59) is triclinic; at 100 K: a = 12.695(3), b = 13.398(3), c = 16.971(3) Å, α = 103.75(3), β = 99.65(3), g = 110.73(3)°, V = 2519.5(11) Å^3, space group P1, Z = 2, $D_{calcd.}$ = 1.585 g·cm^{-3}, μ = 0.920 mm^{-1}. The intensities of 39140 reflections were collected from a single crystal with the dimensions of 0.20×0.15×0.05 mm at the K4.4 station of the Kurchatov Center for Synchrotron Radiation and Nanotechnology in Moscow (Russia) at a wavelength of 0.81182 Å using a MAR CCD 165 detector. Data collection was performed at 100 K using an Oxford CryoJet from Oxford Cryosystems Ltd. Data integration was carried out using the CCP4 software. A multi-scan empirical absorption correction was applied to the data using SCALA. The structure was solved by the direct method and refined by full-matrix least squares method against F^2 of all data, using SHELXL-2014[12] and OLEX2[13] software. Non-hydrogen atoms were found on difference Fourier maps and refined with anisotropic displacement parameters except those for the disordered carbon and oxygen atoms. The positions of hydrogen atoms were calculated and included in refinement in an isotropic approximation by the riding model with the $U_{iso}(H) = 1.5U_{eq}(X)$ for methyl and hydroxyl groups and $1.2U_{eq}(C)$ for other atoms, where $U_{eq}(X)$ are equivalent thermal parameters of the parent atoms. Refinement converged to R_1 = 0.069 (for 8926 observed reflections), wR_2 = 0.157 and GOF = 1.01 (for 10618 independent reflections; R_{int} = 0.057). Crystallographic information file is available from the Cambridge Crystallographic Data Center upon request (https://ccdc.cam.ac.uk/structure, deposition number is 2104917).

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