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Synthesis and structure of the first ribbed-functionalized quinoxaline clathrochelate: design of cage complexes for efficient intercalation into DNA structure*

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Condensation of the dichloride clathrochelate $FeBd_2(Cl_2Gm)(BF)_2$ precursor (Bd^{2-} is the α-benzyl dioxime dianion, Gm is the glyoxime residue) with quinoxaline-2,3-dithiol in the presence of triethylamine afforded the ribbed-functionalized quinoxaline clathrochelate. The structure of this complex was established by X-ray diffraction analysis.

Key words: macrocyclic compounds, clathrochelates, iron(II), X-ray diffraction analysis.

A recent keen interest in tris-α-diazine complexes of rare-earth elements and ruthenium(II), iridium, and rhodium(III) ions, is associated mainly with the fact that these complexes show promise in biochemistry as luminescent probes and reagents for DNA sequencing.[1—3] In most cases, one of the three α-diazine ligands, which are prone to form nonbonded interactions with nucleic bases, including π-stacking interactions, is used for efficient intercalation into DNA structure. The quinoxaline system is one of the most efficient fragments of this type. Earlier, it has been proposed to use polyaromatic substituents in apical fragments for modifications of cage complexes with the aim of achieving efficient intercalation into DNA structure.[4,5] However, we have demonstrated[6,7] that the mutual influence of apical substituents and the encapsulated metal ion is insignificant, whereas substituents in ribbed fragments have a much more substantial effect on the electronic properties and geometry of the cage framework (and, therefore, of the encapsulated metal ion) through a system of conjugated π bonds of the chelate ring.[8—13] We performed functionalization of one of the three ribbed fragments of the iron(II) cage complex for efficient intercalation into DNA structure.

Results and Discussion

The quinoxaline-containing clathrochelate was synthesized by the nucleophilic substitution of the reactive chlorine atoms in one of the ribbed fragments with the corresponding dithiolate dianion (Scheme 1).

The molecular structure of complex **4** is shown in Fig. 1. The symmetry of the clathrochelate framework is nearly D_{3h}. In addition to the threefold symmetry pseudoaxis coinciding with the B(1)...B(2) axis, complex **4** has a symmetry pseudoplane, which is perpendicular to the B(1)...B(2) axis and passes through the midpoints of the C—C bonds in the chelate rings and the encapsulated iron(II) ion. The symmetry of the macrobicyclic framework deviates from D_{3h} because the coordination polyhedron of the iron(II) ion is intermediate between the trigonal prism (TP, the distortion angle φ = 0°) and the trigonal antiprism (TAP, φ = 60°). The N—Fe—N bond angles in the chelate rings are substantially smaller than the value characteristic of the ideal octahedron (90°); these angles are in the range of 77.9—78.3° for the nitrogen atoms of one chelate ring and in the range of 86.1—86.8° for the nitrogen atoms of the different dioximate fragments. The N—Fe—N angles between the

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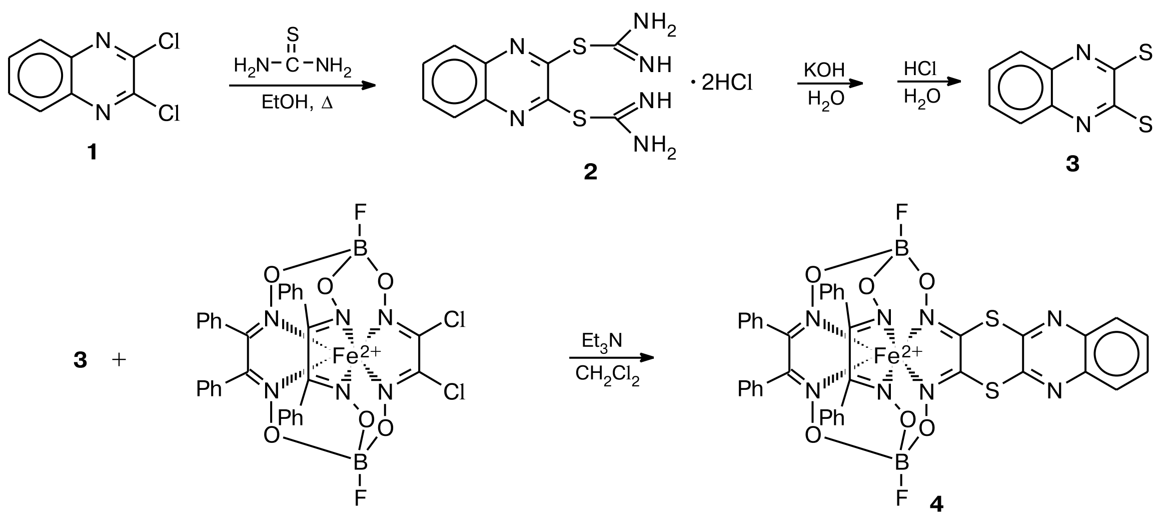
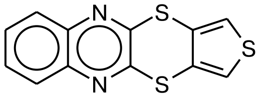
Scheme 1



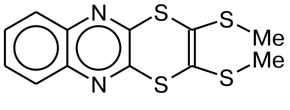
nitrogen atoms in the *trans* positions (150.5—151.8°) also differ substantially from the ideal value (180°). The distortion angle φ of the coordination polyhedron intermediate between TP and TAP is 23.6°. The Fe(1)...B(1) and Fe(1)...B(2) distances have equal values (2.966(3) Å). The B(1)...Fe(1)...B(2) angle is 179.8°.

In all three chelate fragments, the average Fe—N, N—O, C=N, and C—C bond lengths are 1.912, 1.369, 1.305, and 1.449 Å, respectively. The bond angles in these fragments are also virtually identical.

The tricyclic 1,4-dithiino-2,3-quinoxaline system in molecule **4** is nonplanar. The dihedral angles characterizing folding along the S(1)...S(2) and C(8)...C(13) lines are 15.6 and 7.6°, respectively. In quinoxaline-containing structures **5** and **6**, the dihedral angles characterizing folding along the S...S line are substantially larger (47.8 and 37.6°, respectively), whereas the remaining moiety of the molecule is planar.[14]



5



6

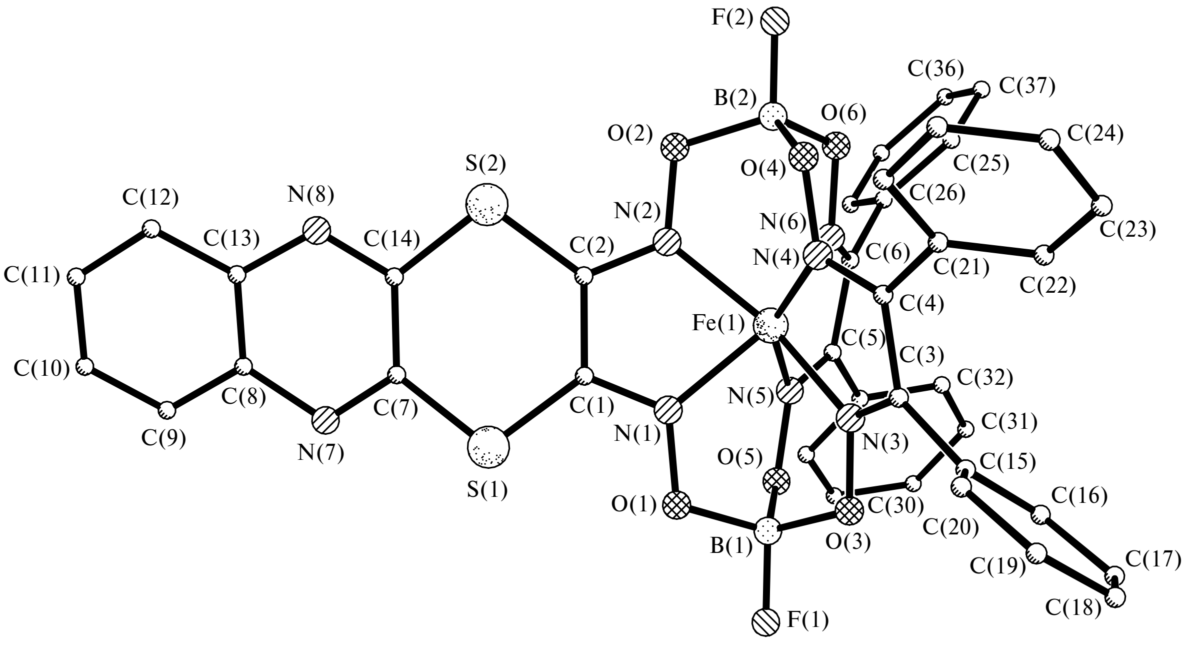


Fig. 1. Molecular structure of clathrochelate **4**.

However, in the complex of **5** with tetracyanoquinodimethane, this angle is 1.7 and 10.0° in two independent molecules **5**. One of molecules **5** is involved in stronger intermolecular stacking interactions with the tetracyanoquinodimethane molecules compared to another molecule **5**. Therefore, the deviation of this system from planarity reflects the character of intermolecular interactions in the crystal structure and is not characteristic of the tricyclic fragment as such.

It should also be noted that the C—S bond lengths in molecule **4** (1.723—1.738 Å) are, on the average, smaller than those in molecules **5** and **6** (1.75—1.76 Å). The nitrogen atoms in the quinoxaline fragment of the clathrochelate molecule are substantially nonequivalent; the N(7)—C(8) bond length (1.414(3) Å) is larger than the N(8)—C(13) bond length (1.396(3) Å). The C(7)—N(7)—C(8) bond angle (117.1(4)°) is smaller than the C(13)—N(8)—C(14) bond angle (120.8(4)°). This may be associated with vibrations of the C(8)—C(13) benzene ring, as evidenced by the larger thermal parameters of the N(7), N(8), and C(8)—C(13) atoms compared to other atoms.

In the crystal, the adjacent molecules are linked in pairs by the intermolecular S(2)...F(2) contacts (3.24 Å), whose length is close to the sum of the van der Waals radii (3.21 Å).[15] Nevertheless, the "dimers" formed due to these interactions are clearly seen in the crystal of **4** (Fig. 2). In addition, two benzene solvate molecules are also involved in these "dimers". The planes of these benzene molecules are virtually orthogonal to the quinoxaline fragment (the dihedral angle between the planes of the benzene ring and the N(7)—N(8)—C(7)—C(8)—C(13)—C(14) ring is 80.2°). The angle between the C(1s)...C(4s) line of the benzene ring and the N(7)...N(8) line is 21.6°. One of the hydrogen atoms of the benzene ring forms a contact with the N(8) atom, whose length (2.58 Å) corresponds to the sum of the van der Waals radii.[15]

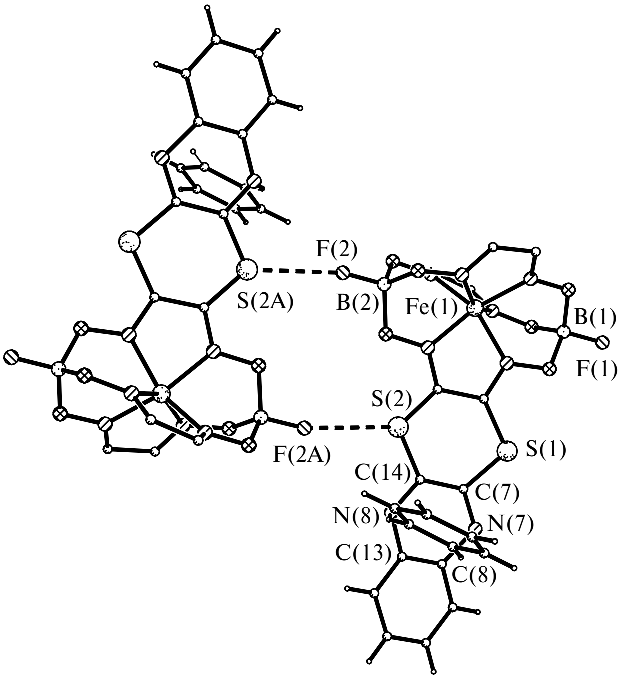


Fig. 2. Formation of "dimers" in the crystal of **4** · 1.5C_6H_6.

The parameters of the ^{57}Fe Mössbauer spectrum of quinoxaline clathrochelate **4** (the isomer shift is 0.33 mm s^{-1}, the quadrupole splitting is 0.47 mm s^{-1}) are characteristic of low-spin iron(II) complexes with a geometry intermediate between TP and TAP, which is consistent with the above-given X-ray diffraction data. It should be noted that, in spite of the nonequivalence of the dioximate fragments of the molecule, the UV-Vis spectrum of complex **4** shows only one intense Fe*d* → Lπ^* charge-transfer band in visible region, which is indicative of strong conjugation in the clathrochelate moiety.

Experimental

The chemical reagents and the physical methods (used in the present study) were described in detail earlier.[13] The $FeBd_2(Cl_2Gm)(BF)_2$ complex (Bd^{2-} is the α-benzyl dioxime dianion, Gm is the glyoxime residue) was prepared according to a procedure described earlier.[10] 2,3-Dichloroquinoxaline (**1**) was synthesized according to a known procedure.[16]

2,3-Diisothiuronium quinoxaline dihydrochloride (2). A mixture of 2,3-dichloroquinoxaline (**1**) (10.3 g, 52 mmol) and thiourea (8.7 g, 115 mmol) was dissolved/suspended in 95% EtOH (120 mL). The reaction mixture was refluxed for 5 h. The goldish-orange precipitate that formed was filtered off, washed with EtOH (10 mL), and dried. The yield was 11.1 g (61%). ^{1}H NMR (DMSO-d_6), δ: 7.48, 7.57, and 7.72 (all m, 4 H, Ar); 9.85 and 10.00 (both br.s, 6 H, NH). ^{13}C{^{1}H} NMR (DMSO-d_6), δ: 116.5, 126.5, 127.8, 131.0, 131.1, and 134.7 (all Ar); 159.8 and 164.6 (both C=CS); 170.6 (S—C=N).

Quinoxaline-2,3-dithiol (3). A mixture of diisothiuronium dihydrochloride **2** (11.1 g, 40 mmol) was dissolved/suspended in water (40 mL) and a solution of KOH (4.9 g, 90 mmol) in water (20 mL) was added. The orange precipitate that formed was filtered off, washed with water, and suspended in water (5 mL). A saturated aqueous KOH solution was added portionwise to pH ≈ 14 and until the precipitate was completely dissolved. A 1 *M* HCl aqueous solution was added with stirring to the dark-brown solution to pH ≈ 1. The dark-brown precipitate that formed was filtered off, washed with water, and dried *in vacuo*. The yield was 6.6 g (85%). ^{1}H NMR (DMSO-d_6), δ: 7.27 and 7.40 (both s, 4 H, Ar); 14.2 (s, 2 H, SH). ^{13}C{^{1}H} NMR (DMSO-d_6), δ: 115.5, 125.6, 127.8 (Ar); 179.3 (S—C=N).

1,20-Difluoro-23,24,29,30-tetraphenyl-2,19,21,26,27,32-hexaoxa-5,16-dithia-3,7,14,18,22,25,28,31-octaaza-1,20-diborapentacyclo[18.6.6.0^{4,17}.0^{6,15}.0^{8,13}]dotriaconta-3,6,8(13),9,11,14,17,22,24,28,30-undecaene(2−)iron(2+) (4). A solution of the clathrochelate $FeBd_2(Cl_2Gm)(BF)_2$ precursor (0.75 g, 1 mmol) in CH_2Cl_2 (30 mL) and a solution of quinoxaline-2,3-dithiol (**3**) (0.18 g, 1.1 mmol) and Et_3N (0.3 mL, 2.2 mmol) in a 3 : 2 1,4-dioxane—DMF mixture (50 mL) were added dropwise with vigorous stirring at an equivalent rate to CH_2Cl_2 (100 mL) at ~20 °C for 3 h. The reaction mixture was stirred at ~20 °C for 30 h. Then a solution of quinoxaline-2,3-dithiol (**3**) (0.09 g, 0.55 mmol) and Et_3N (0.15 mL, 1.1 mmol) in a 3 : 2 1,4-dioxane—DMF mixture (60 mL) was added dropwise and the reaction mixture was stirred at 50 °C for 4 h. The precipitate that formed was filtered off and the filtrate was washed successively with water (2×100 mL), a saturated citric acid aqueous solution (2×50 mL), a saturated aqueous Na_2CO_3 solution (2×50 mL), and water (2×100 mL). The organic phase was dried with $MgSO_4$ and then concentrated to dryness *in vacuo*. The solid residue was washed with hexane, dissolved in CH_2Cl_2, and separated by chromatography on SPH-300 silica gel (Chemapol) (CH_2Cl_2 as the eluent), two main fraction being collected. Based on the ^1H and $^{13}C\{^1H\}$ NMR spectroscopic data, the more mobile yellow-orange fraction was identified as the starting dichlorideFeBd$_2$(Cl$_2$Gm)(BF)$_2$ complex , whereas the less mobile red fraction was characterized as the target quinoxaline clathrochelate **4**. The yield of **4** was 0.25 g (29%). Found (%): C, 52.59; H, 2.86; N, 12.87; Fe, 6.35. $C_{38}H_{24}N_8O_6B_2S_2F_2Fe$. Calculated (%): C, 52.56; H, 2.77; N, 12.91; Fe, 6.43. MS, *m/z* 868 $[M]^{+\bullet}$. ^1H NMR (CD_2Cl_2), δ: 7.27 (br.s, 20 H, Ph); 7.68 and 7.85 (both m, 2 H each, Ar). ^{13}C NMR $\{^1H\}$ (CD_2Cl_2), δ: 128.3, 129.2, 130.6, and 130.8 (all Ph); 131.7, 140.1, and 140.6 (all Ar); 144.9 (S—C=N); 157.3 (Ph—C=N). IR (KBr), ν/cm^{-1}: 1544 (S—C=N); 1578 (Ph—C=N); 922, 1066, 1083 (N—O); 1217 (m, ν(B—O) + ν(B—F)). UV-Vis spectrum (CH_2Cl_2): λ_{max}/nm ($\varepsilon \cdot 10^{-3}$/L mol^{-1} cm^{-1}): 270 (19), 292 (15), 338 (45), 403 (4.9), 484 (25).

X-ray diffraction study. Red platelet-like crystals of **4**$\cdot$1.5 C_6H_6 suitable for X-ray diffraction study were grown by by slow evaporation of a saturated solution of this clathrochelate in a 3 : 1 benzene—isooctane mixture. For the crystals of this solvate: $C_{47}H_{33}B_2F_2FeN_8O_6S_2$, M = 985.40, triclinic system, at 120 K a = 10.337(2) Å, b = 13.277(2) Å, c = 16.343(3) Å, α = 95.087(4)°, β = 90.218(4)°, γ = 105.052(4)°, V = 2156.6(6) Å^3, space group $P\bar{1}$, Z = 2, d_{calc} = 1.517 g cm^{-3}. A total of 24067 reflections were measured on a Bruker AXS SMART 1000 diffractometer equipped with a CCD detector at 120 K (λ-Mo-Kα, graphite monochromator, $2\theta_{max}$ = 58.14°) from a single crystal of dimensions 0.2×0.4×0.6 mm^3. Merging of equivalent reflections gave 11338 independent reflections (R_{int} = 0.0393), which were used for the structure solution and refinement. The absorption correction (μ = 5.18 mm^{-1}) was applied using the SADABS program[17] (T_{max} and T_{min} are 0.862 and 0.518, respectively). The structure was solved by direct methods. All nonhydrogen atoms were located from difference electron density syntheses and refined anisotropically against F^2_{hkl}. All hydrogen atoms were placed in geometrically calculated positions and refined using the riding model with U(H) = 1.2 U(C), where U(C) are the equivalent thermal parameters of the carbon atoms to which the corresponding H atoms are bound. The final reliability factors are R_1 = 0.0621 (calculated based on F_{hkl} for 7221 reflections with $I > 2\sigma(I)$), wR_2 = 0.1430 (calculated based on F^2_{hkl} for all 4295 reflections), GOOF = 1.093, 613 parameters were refined.

All calculations were carried out using the SHELXTL PLUS 5 program package.[18] The atomic coordinates were deposited with the Cambridge Structural Database.

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