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First clathrochelate iron and cobalt(II) tris-dioximates with reactive apical substituents

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ABSTRACT

Direct template macrobicyclization of three 1,2-cyclohexanedione dioxime molecules with monofunctionalized HO-, H_2N- and HOOC-containing phenylboronic acids on Fe^{2+} and Co^{2+} ions as a matrix afforded new macrobicyclic iron and cobalt(II) tris-dioximates with reactive apical substituents. The clathrochelates synthesized has been characterized by spectroscopic methods, X-ray crystallography and cyclic voltammetry.

Cage complexes with encapsulated metal ions (clathrochelates) having high chemical stability and unique physical and physicochemical properties [1] have been widely used as suitable molecular scaffolds and building blocks for the design of materials that meet the criteria for practical use [2–18]. In particular, their functionalization with *closo*-borate-containing ribbed substituents gave some prospective target compounds for boron-neutron capture therapy of cancer [19–21], and that with halogen atoms and thiol-terminated spacer groups afforded very efficient electrocatalysts (including those immobilized on a surface of a working electrode) for hydrogen production [22,23]. Moreover, several clathrochelate iron(II) tris-dioximates have also been tested as transcription inhibitors in the systems of model enzymes (RNA and DNA polymerases, topoisomerase, etc.) and were found [24] to be very efficient inhibitors in the case of T7 RNA polymerase; so they are prospective antiviral and antitumor drug candidates.

The presence of reactive terminal groups in the apical capping fragments of clathrochelates allows varying their properties: these groups help to perform further modification and functionalization of clathrochelates (in particular, for chemical immobilization of the clathrochelate-based electrocatalysts on a surface of element oxide matrices or metallic working electrodes [23]). Thus, protono- and ionogenic groups increase their solubility in water and other biological media for biological studies [25]. Reactive and donor groups can be used to modulate the biological activity of functionalized cage metal complexes using pharmacophore or bio-relevant substituents, in particular, organic cationic, N-donor heterocyclic (including nucleotides), aromatic intercalating and oligopeptide residues. The choice of these groups can be made by using preliminary molecular docking calculations (starting from experimental X-ray and NMR data) optimizing their hydrophobic–hydrophilic balance.

Among the tris-dioximate *d*-metal clathrochelates, the complexes of the alicyclic 1,2-cyclohexanedion dioxime (nioxime, H_2Nx) are the most stable, and much easier to synthesize than the similar acyclic compounds due to the fact that nioxime has a *cis*-conformation both in crystal and in solution [1]. In this paper, we describe the synthesis, structure, and spectral and electrochemical properties of first tris-dioximate iron and cobalt(II) clathrochelates with reactive apical hydroxyl, carboxyl and amino groups. They were obtained in moderate yields by template condensation of nioxime with HO-, H_2N- and HOOC-monofunctionalized phenylboronic acids on a corresponding metal ion as a matrix (Scheme 1) [26]. In the case of 3-aminophenylboronic acid, triethylamine as a strong organic base was added to prevent the protonation of terminal amino groups by H^+ ions formed in the reaction course.

The complexes synthesized were characterized using elemental analysis, MALDI-TOF and ESI mass spectrometry, IR, UV–vis, EPR (in the case of the cobalt(II) complexes), ^1H, ^{11}B and $^{13}C\{^1H\}$ NMR

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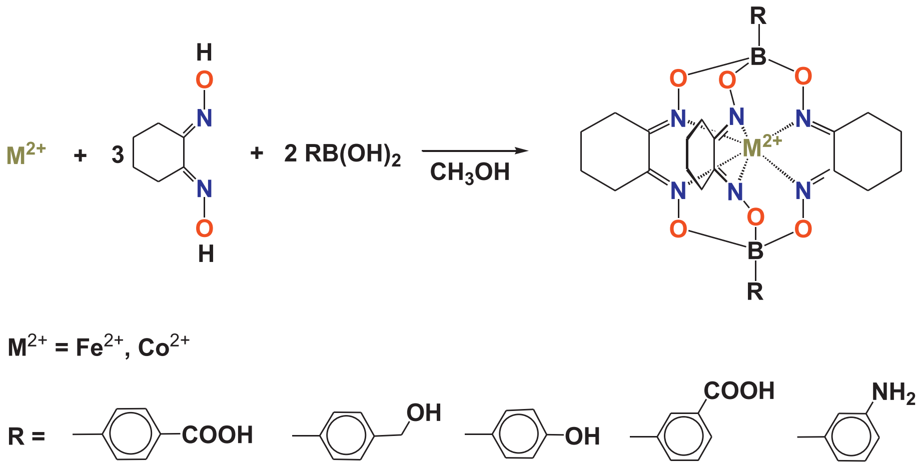

Scheme 1. Template synthesis of the apically functionalized iron and cobalt(II) clathrochelate tris-dioximates.

spectroscopies and X-ray crystallography (in the case of *para*-hydroxymethylphenylboron-capped iron(II) clathrochelate); their electrochemical properties were studied by cyclic voltammetry (CV).

The number and the position of signals in ^1H and $^{13}C\{^1H\}$ NMR spectra of the iron and cobalt(II) clathrochelates synthesized, together with the ratios of their integral intensities in the ^1H NMR spectra confirmed the composition of their macrobicyclic molecules as well as their C_3-symmetry. In the case of the cobalt(II) complexes, the paramagnetic broadening has prevented an observation of the signals of the carbon nuclei being in close proximity to the encapsulated paramagnetic metal ion.

Glassy EPR spectra of these cobalt complexes at 60 K (see SM, Fig. S1) are characteristic of the low-spin cobalt(II) clathrochelates with Jahn–Teller distortion [15]. Both *g*- and hyperfine tensors are rhombic, and the spectra contain well-resolved eight-line splittings in the downfield region caused by hyperfine interactions with the ^{59}Co nucleus ($I_{Co} = 7/2$).

The positive range of ESI mass-spectra for most of the iron(II) complexes contains three intensive peaks assigned to their ionic associates with H^+, Na^+ and K^+ cations. In the spectrum of the cobalt(II) clathrochelate CoNx$_3$(B(*meta*-C_6H_4COOH))$_2$, the peak of the molecular ion $[M]^{+\bullet}$ is the most intensive. The spectra of other clathrochelates synthesized also contain the peaks assigned to the cationic species that resulted from the detachment of either one apical substituent at the capping boron atom (for the FeNx$_3$(B(*meta*-$C_6H_4NH_2$))$_2$ complex), or one apical capping moiety with the formation of semiclathrochelate species (for the clathrochelates CoNx$_3$(B(*meta*-C_6H_4COOH))$_2$ and FeNx$_3$(B(*para*-C_6H_4OH))$_2$). For all these species, the experimental isotopic distribution is in a good agreement with the calculated model. In the negative range of these spectra no peaks of any anionic macrobicycles or their derivatives were found.

The X-ray molecular structure of the clathrochelate FeNx$_3$(B(*para*-$C_6H_4CH_2OH$))$_2$ is shown in Fig. 1; its main geometrical parameters are listed in Table S1 (see SM) together with the data for some other macrobicyclic tris-nioximates. The geometry of its FeN_6-coordination polyhedron is intermediate between a trigonal prism (the distortion angle $\varphi = 0°$) and a trigonal antiprism ($\varphi = 60°$), and the averaged φ value (approximately 21.0°) is characteristic of the boron-capped iron(II) tris-nioximates. The rigidity of the $N{=}C{-}C{=}N$ chelate fragments (with deviation angles ranging from 6 to 9°) causes the bite angle α (half of the chelate $N-Fe-N$ angle) and the heights *h* of their coordination polyhedra (39° and 2.35 Å, respectively) to persist. The average $Fe-N$ distance (approximately 1.905 Å) is also characteristic for these iron(II) clathrochelate (Table S1); an encapsulated iron(II) ion is situated in the center of the coordination polyhedron, so all the $Fe-N$ bond lengths are almost equal except for the elongated $Fe(1)-N(5)$ bond (1.918(2) Å) with the α-dioximate chelate ribbed fragment that forms the strong hydrogen bonds $O7-H7W\cdots O8$ and $O8-H8W\cdots O5$ with $r_i\,(O\cdots O) = 2.801(3)$ and 2.967(3) Å and the $O-H-O$ angles equal to 176 and 174°, respectively. As a result, in this crystal the infinite H-bonded chains of the clathrochelate molecules are observed (Fig. 2).

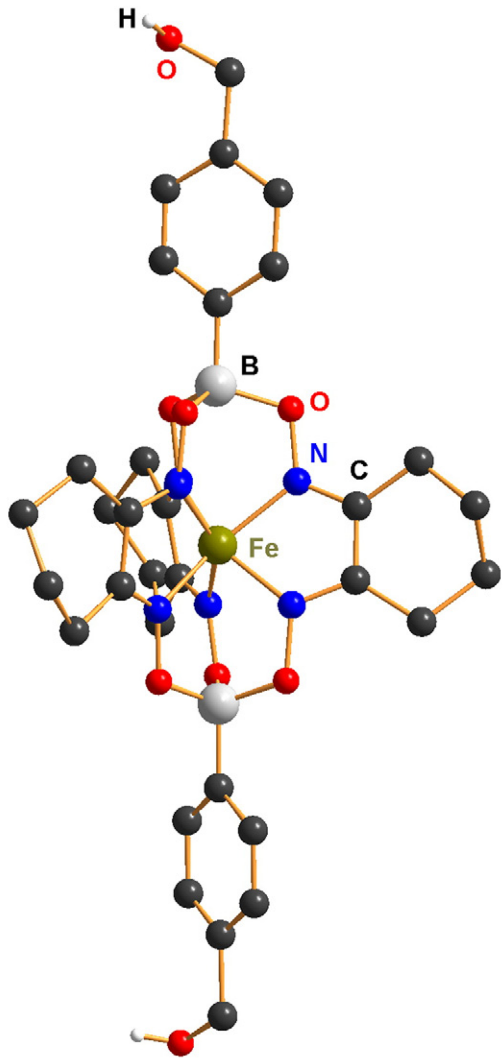

Fig. 1. General view of the clathrochelate FeNx$_3$(B(*para*-$C_6H_4CH_2OH$))$_2$. Hydrogen atoms except for those of the OH groups are omitted for clarity.