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Short communication

Intramolecular self-alkylation reaction of an iron(II) dichloroclathrochelate caused cyclization–demethylation in its chelate ribbed fragment

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ABSTRACT

Nucleophilic substitution of an iron(II) dichloroclathrochelate precursor $FeBd_2(Cl_2Gm)(BF)_2$ (where Bd^{2-} and Gm are α-benzildioxime dianion and glyoxime residue, respectively) with 3-dimethylaminopropylamine unexpectedly afforded the macrobicyclic product of an intramolecular cyclization followed by a demethylation reaction with elimination of CH_3Cl. The molecular structure of this clathrochelate was unambiguously confirmed both in solution and in solid state using multinuclear NMR spectroscopy and by single crystal X-ray diffraction, respectively.

Clathrochelate molecules with pendant substituents containing reactive terminal HO-, H_2N- and HS-groups [1–5], and those with donor (in particular, pyridyl [6–9]) apical groups have been widely used for modification of various materials (in particular, *via* their covalent immobilization on a surface of the working electrodes), and for the synthesis of polyclathrochelate metallomacrocycles and coordination cages as well. This allowed to elaborate new types of molecular switches [2], electrocatalysts for hydrogen evolution reaction [3], the mediators of electron transfer and clathrochelate-modified gold electrodes for amperometric determination of hydrogen peroxide [4]. An unexpected result has been observed in an attempt [1] to obtain an iron(II) bis-clathrochelate by Scheme 1 using nucleophilic substitution of a monochloroclathrochelate precursor $FeBd_2(HGmCl)(BF)_2$ with generated *in situ* anionic derivative of a thiol-terminated cage compound $FeBd_2(H(HSCH_2CH_2S)Gm)(BF)_2$ as *S*-nucleophile. In this case, an iron(II) macrobicyclic complex with inherent HS-group in one of its three α-dioximate ribbed fragments has been isolated as a major product of such a reaction. The detailed study suggested that a clathrochelate $FeBd_2(H(HSCH_2CH_2S)Gm)(BF)_2$ underwent the intramolecular elimination of ethylene sulfide (thiirane) under basic conditions to yield a macrobicyclic product $FeBd_2(HGmSH)(BF)_2$; plausible mechanism of this self-dealkylation process, "the dragon biting its own tail", is also shown in Scheme 1.

When we attempted [5] to synthesize a S_6-thiacrown ether cage complex using a stepwise procedure, by condensation of a dithiol-terminated clathrochelate $FeBd_2((HS(CH_2CH_2S)_2)_2Gm)(BF)_2$ with 1,2-diiodoethane in the presence of Cs_2CO_3 in DMF, this reaction unexpectedly gave S_3-thiacrown ether complex $FeBd_2(S_3\text{-}CwGm)(BF)_2$ as a major macrobicyclic product. It was shown that the deprotonated thiolate group of an initial cage complex attacks the adjacent thiol-terminated alkylsulfide substituent in a *vic*-position of the same ribbed α-dioximate fragment, thus giving the nine-membered S_3-cyclic fragment as a result of the dealkylation reaction by Scheme 2. Moreover, in a series of alkylsulfide clathrochelates, an unusual demethylation of a bis-methylsulfide iron(II) clathrochelate $FeBd_2((CH_3S)_2Gm)(BF)_2$ has been observed as a result of its reaction with $PtCl_4^{2-}$ dianion by Scheme 3, giving the polynuclear platinum(II) bis-cage complexes of the corresponding dithiolate macrobicyclic ligand. Their multicentered molecules are stabilized by formation of the highly stable five-membered PtS_2C_2 chelate cycles [5].

Recently we reported [10] that the electrophilic iron(II) hexachloroclathrochelates with reactive ribbed chlorine substituents are able to alkylate HS-containing compounds (in particular, glutathione, GSH) within a cell. As a result, they showed a high cytotoxicity against

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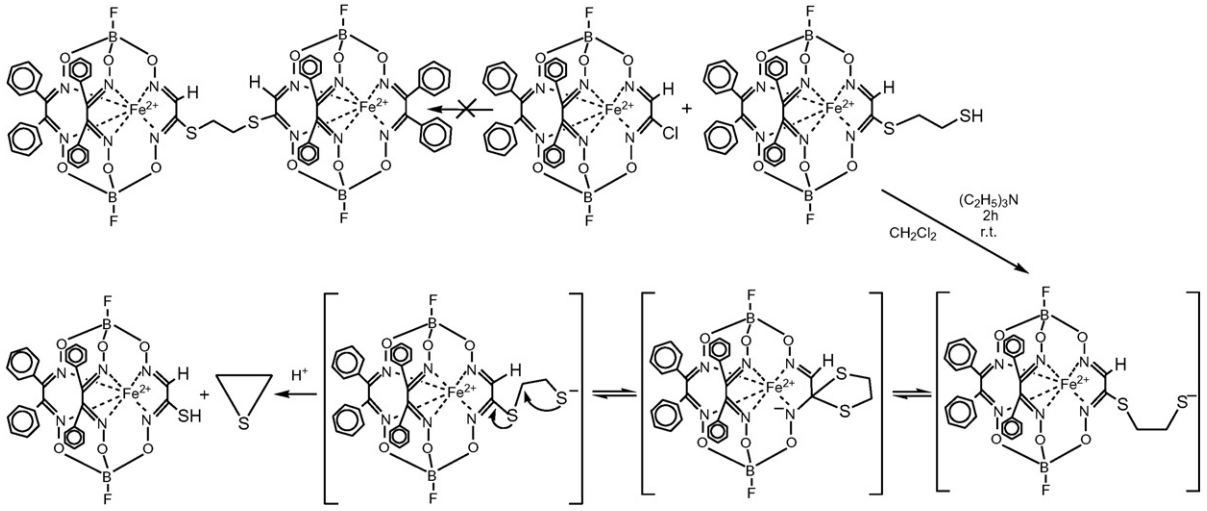
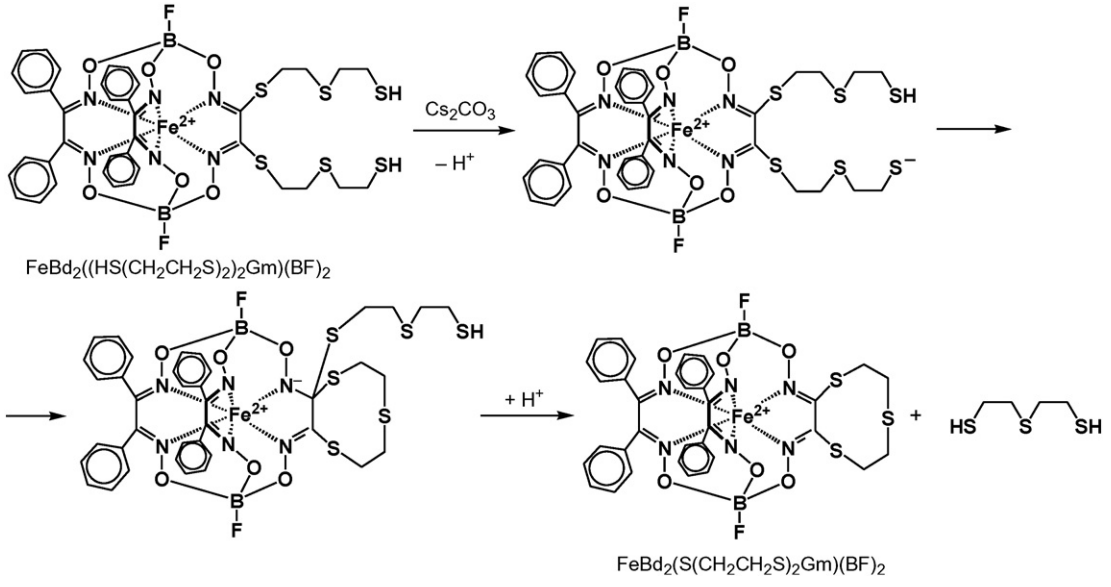


Scheme 1. Self-dealkylation reaction of the thiol-terminated alkylsulfide ribbed substituent at macrobicyclic framework and its plausible pathway [1].

human promyelocytic leukemia cells. Such toxicity has been explained by the ability of these cage metal compounds to increase the intracellular oxidative stress. Based on *in vitro* studies, two processes have been suggested [10] to be responsible for this effect: (1) an alkylation of GSH, and (2) a direct generation of reactive oxygen species by partially alkylated electrophilic clathrochelates. Such a high selective activity suggests that these macrobicyclic complexes are prospective compounds for a search of potent anticancer prodrugs and, therefore, the design and synthesis of such electrophilic macrobicyclic complexes is undoubtedly important task.

Trying to obtain the monoribbed-functionalized iron(II) cage complexes with biogenic terminal amino groups, targeting the DNA structure, as a potent transcription inhibitors (topological drugs [11]), we found that nucleophilic substitution of a dichloroclathrochelate precursor $FeBd_2(Cl_2Gm)(BF)_2$ with 3-dimethylaminopropylamine by Scheme 4 [12] unexpectedly gave the mixture of clathrochelate products, mainly a macrobicyclic complex $FeBd_2((CH_3N(CH_2)_3NH)Gm)(BF)_2$. The latter clathrochelate resulted from an intramolecular cyclization followed by a demethylation reaction *via* elimination of CH_3Cl as most probable second product of this reaction and its molecular structure was unambiguously confirmed both in solution and in solid state using multinuclear NMR spectroscopy [12] and by single crystal X-ray diffraction [13], respectively. At the same time, we failed to obtain the macrobicyclic complex with two terminal *tert*-amino groups under various reaction conditions: in all cases the main product was a cyclic derivative $FeBd_2((CH_3N(CH_2)_3NH)Gm)(BF)_2$. Our attempts to use other solvents and to increase the concentration of this *N*-nucleophile gave either an inseparable mixture of the clathrochelate products or resulted in the complete destruction of a cage framework.

The number and position of the signals in solution ^1H and $^{13}C\{^1H\}$ NMR spectra of a diamagnetic monoribbed-functionalized iron(II) clathrochelate $FeBd_2((CH_3N(CH_2)_3NH)Gm)(BF)_2$ as well as the ratios of the integral intensities of protons of the chelate α-benzildioximate fragments and those of the functionalizing ribbed substituent in its ^1H NMR spectrum confirmed the composition and symmetry of a macrobicyclic molecule $FeBd_2((CH_3N(CH_2)_3NH)Gm)(BF)_2$, thus allowing to deduce its structure. In particular, this molecule does not have a symmetry plane passing through the middles of its chelate C—C bonds and an encapsulated iron(II) ion as well, and it contains



Scheme 2. Dealkylation reaction in a *vic*-position of the same ribbed chelate fragment of a clathrochelate molecule and its plausible pathway [5].