Reviews

Cage complexes of transition metals in biochemistry and medicine

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The review presents the following main trends and the perspectives of application of the transition metal clathrochelates in medicine and biochemistry: encapsulation of radioactive metal ion for diagnostics and therapy; imaging agents for MRI; antidotes and prolonged pharmaceuticals; pharmaceuticals for boron neutron capture therapy; antihelminthic and antiparasitic detergents; antioxidants; membrane transport of the metal ions; interaction of the cage metal complexes with nucleic acids and the potential of their self-assembling reactions in immunology and molecular biology (recognition of antibodies, antigens and DNA sites); design of HIV inhibitors for the therapy.

Key words: macrocycles, clathrochelates, radiotherapy, HIV therapy, antioxidants, phenols, membrane transport, *closo*-borates, boron neutron capture therapy, encapsulation, nucleic acids, detergents, magnetic resonance imaging, adamantane and its derivatives.

Introduction

Macrobicyclic cage complexes with encapsulated metal ions (clathrochelates) are representatives of a relatively new class of compounds with unusual chemical, physical, and physicochemical properties. The keen interest of scientists working in several fields of chemistry and biochemistry in these compounds is caused by the unique properties of a metal ion completely encapsulated in the three-dimensional cavity of a macropolycyclic ligand and largely isolated from the external factors.[1]

The availability of these compounds combined with their chemical (kinetic and thermodynamic) and photochemical stabilities, intensive coloration, low toxicity, and the ability to undergo reversible redox reactions and to form ordered molecular structures imply practical use of metal cage complexes as functional materials, dyes, luminescent probes, biologically active compounds, and elec-

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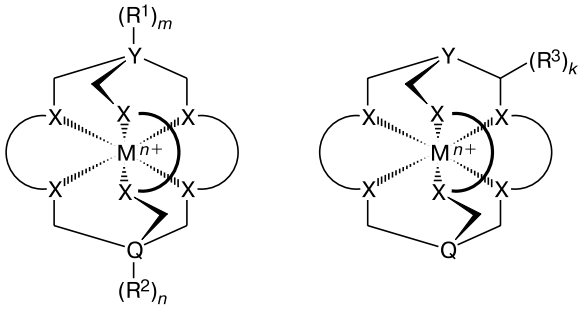
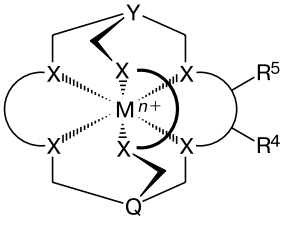
tron carriers in catalytic redox systems. The unique structure of clathrochelates, *i.e.*, the presence of a metal ion completely isolated from the environmental factors, makes them attractive research subjects for photochemistry, magnetochemistry, and electrochemistry. In bioinorganic chemistry, these compounds may be of interest as models of the active sites of enzymes and siderochromes. Clathrochelates are unique rigid cage molecules that are selectively self-assembled from simple precursors under mild conditions. This makes them promising "molecular scaffolds" for the synthesis of polyfunctional and polytopic molecular and supramolecular systems.[2—5]

The chemical variability of metal cage complexes allows both apical (by choosing functional substituents in cross-linking groups)[6,7] and ribbed (by nucleophilic substitution of reactive substituents in the chelating α-dioximate fragments[2,3,8—17]) functionalization.



Apical functionalization



Ribbed functionalization

Y, Q are cross-linking atoms, R^1—R^5 are functionalizing substituents.

In this paper we attempted to highlight the main well-developed and perspective trends in biochemical and medicinal applications of clathrochelates, *i.e.*, cage complexes with encapsulated transition metal ions.

1. Complexes with encapsulated metal ions in the diagnostics and therapy of diseases in humans and animals

The possibility of using clathrochelates in the diagnostics and therapy of many diseases is caused by their unique properties, first of all, the isolation of an encapsulated metal ion from the environmental factors (the solvent, complexation with other ligands, *etc.*), and by their photo- and chemical (kinetic and thermodynamic) stabilities. More opportunities are determined by functionalization of cage complexes, which enables targeted delivery of radiotherapeutic and pharmaceutical agents to the specified target in tissues, organs, or cells of a living organism.

1.1. Encapsulation of radioactive metal ions for radiotherapy and diagnostics

It is well known[18] that radionuclides are widely used in various fields of medicine; the radionuclides and radiopharmaceuticals based on them have been classified according to their application into diagnostic and therapeutic agents. Diagnostic radiopharmaceuticals include, for example, radionuclide compounds used in single-photon emission computer tomography (SPECT). These compounds are γ-emitters with energies approximately 100—200 keV and half-life times ranging from several minutes to several hours.[18] The majority of diagnostic SPECT investigations are carried out with short-lived ^{99m}Tc compounds; this opens up the possibility to scan the organism several times during a short time period without overexposure. This isotope was used to diagnose infectious, ophthalmic, and skin diseases; endocrine and intestinal system diseases; kidney, adrenal gland, and spleen diseases; respiratory, cerebral, spinal chord, and bone marrow diseases; and bone and joint diseases and also to study cardiovascular, blood circulatory, lymphatic, and urogenital systems.[18]

A highly important task for using ^{99m}Tc in medicine and biochemistry is the synthesis of radiopharmaceutical agents. The specificity of action of these agents depends on both the oxidation state of the radioactive labeling ion and the chemical, physicochemical, physical, and pharmacological properties of labeled compounds to which the isotopically is bound. In terms of their biological specificity, radiopharmaceutical agents based on ^{99m}Tc were divided into three main groups:[18] sodium and potassium pertechnetates, technetium(VII) complexes with various organic ligands, and technetium(III) and technetium(IV) coordination compounds. The pertechnetate ion, which is mainly accumulated in human endocrine and lymphatic glands, has a low specificity, is distributed rather evenly in the body, and is mainly excreted over 24 h. Compounds of this ion are used for diagnosis of almost all organs and systems of the living organism. The second group of agents exhibit higher biological specificities and technetium(VII) compounds are used in the micellar form. Compounds of the third group, which demonstrate the highest biological specificity, are complexes of technetium ions in lower oxidation states. It has been suggested to use $^{99m}Tc^{III}$ and $^{99m}Tc^{IV}$ complexes with various types of organic ligands (alcohols, carbohydrates, nucleic acids, nucleoproteins, chelates, and

macrocyclic ligands), which provide isotope chemotaxis into damaged systems of the organism.[18]

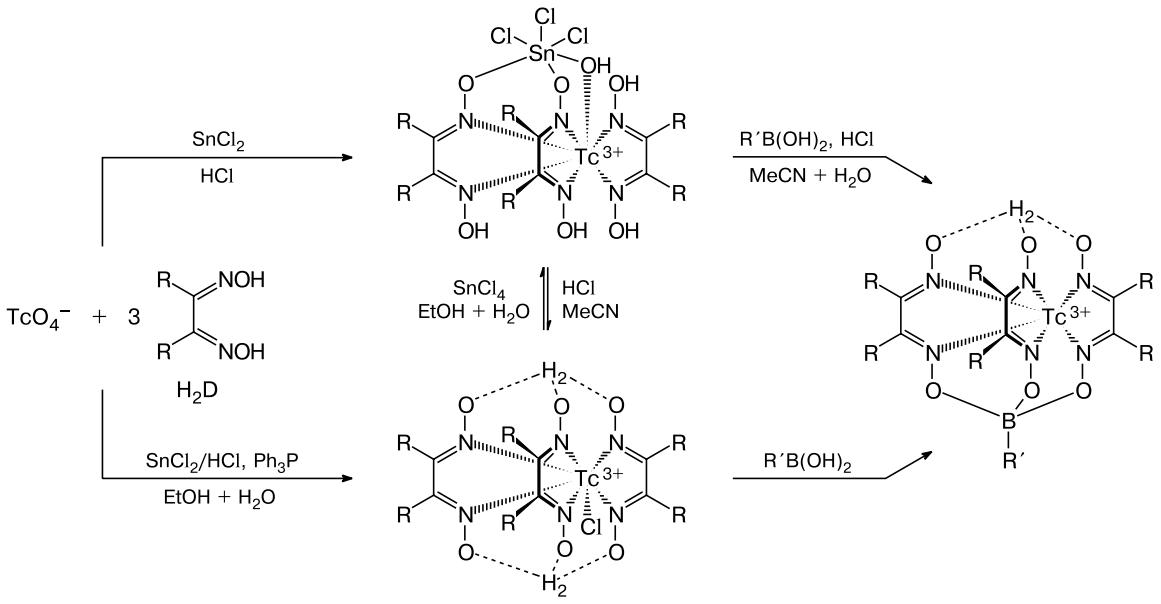
Therefore, it is obvious that the first attempts to encapsulate a radioactive metal ion in order to obtain useful radiotherapeutic agents for clinical practice were undertaken for the $^{99m}Tc^{3+}$ cation (see Refs 19—22). A research group from the National Institutes of Health (USA) made an attempt to obtain cage complexes of this ion with encapsulating tris-diiminate macrobicyclic ligands but failed to encapsulate the technetium(III) ion by the template reaction of α-dioximes and alkylboronic acids: instead of the target technetium(III) clathrochelates, only lacunary compounds with one apical boron-containing group were isolated and structurally characterized.[19,20] Analogous tin-containing compounds were synthesized by reduction of the pertechnetate anion TcO_4^- with tin(II) dichloride in the presence of α-dioximes (Scheme 1).

The reactions of these tin-containing complexes with alkylboronic acids also afforded lacunar semiclathrochelate compounds. Unsuccessful attempts to obtain boron-containing complexes with an encapsulated Tc^{3+} ion in the cavity of the macrobicyclic ligand are caused by the use of a cross-linking agent with an insufficiently large ionic radius of the apical capping atom. Obviously, the self-assembly of cage technetium tris-diiminate complexes requires the use of template cross-linking of aliphatic (acyclic and alicyclic) and aromatic α- or β-dioximes with Lewis acids (*e.g.*, antimony(V) triorganyls, tin(IV) halides, or germanium(IV) perfluorotriorganyls) that have sufficient ionic (Shannon) radius for encapsulation of a big technetium ion, by analogy with the previously obtained iron(II) and cobalt(III) complexes.[1] It is assumed that transmetallation of the apical groups of these compounds may result in polytopic cage technetium complexes with porphyrin- and phthalocyanine-containing apical fragments (Scheme 2).

Cryptands with N- or N,O-donor groups seem to be effective ligands for the targeted delivery of the TcO_4^- anion, as they form inclusion compounds upon encapsulation of the anion in the cavity of the protonated ligand (Fig. 1).

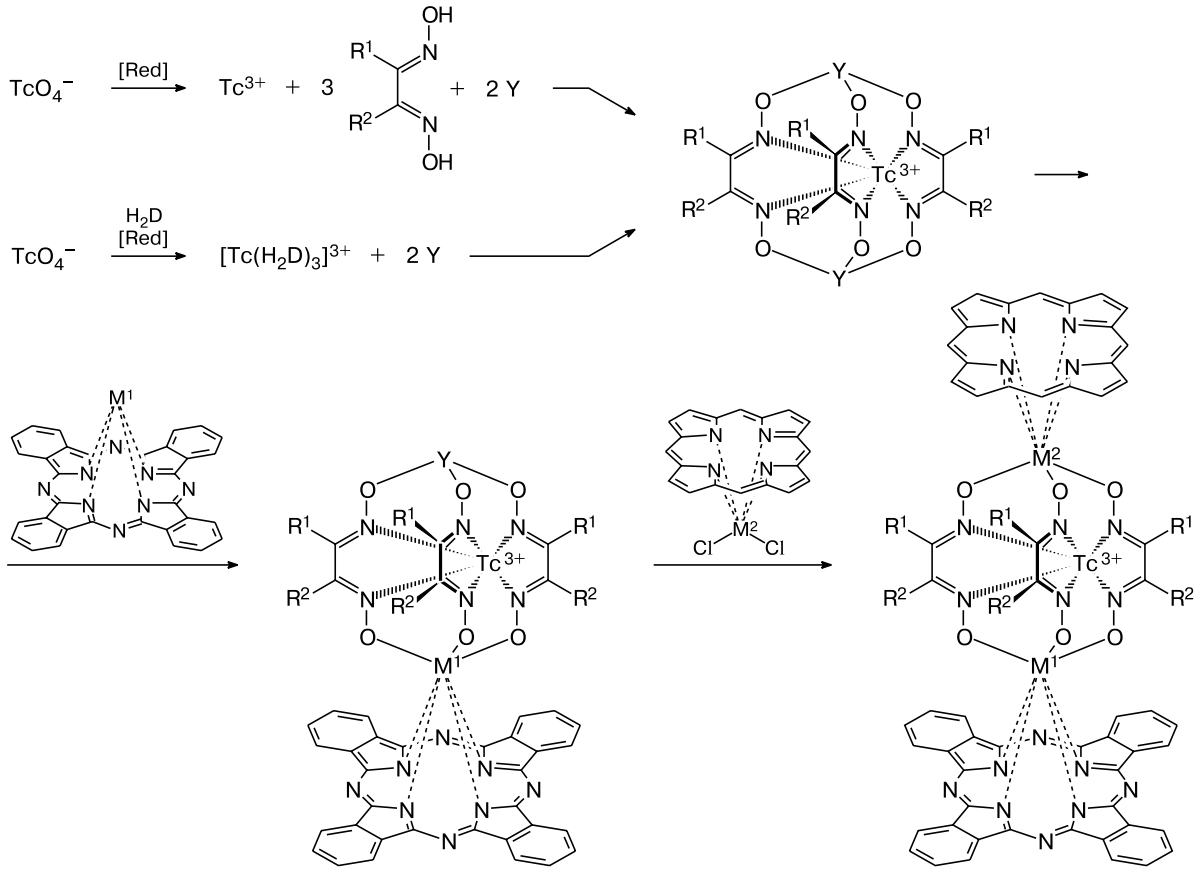
This type of macrobicyclic ligands **1—4** having high affinities to the TcO_4^- ion were synthesized and studied[23] as extractants for ReO_4^- and TcO_4^- anions in comparison with their non-macrocyclic tripodal analogs **9—16**. It was shown that, at different pH values, various protonated forms of macrobicyclic ligands are in equilibrium and it is mainly with the pentaprotonated form of ligand **3**; that the complexes with these ions are formed, but ReO_4^- and TcO_4^- also form complexes with less protonated forms of the ligand. The ReO_4^- anion is encapsulated more efficiently than the perchlorate ion because of better fit (according to X-ray diffraction data) of the former to the size and shape of the cavity of the macrobicyclic ligand and higher polarization of this anion. Study of the competitive complexation of the hexaprotonated form of ligand **3** with perchlorate and perrhenate ions showed that in the $\mathbf{3}\cdot 6H^+—ClO_4^-—ReO_4^-$ system with anions in 1 : 1 to 1 : 6 ratios, only crystals with the encapsulated perrhenate ion were formed. In the case of pyridine-containing ligand **7**, oxo anions are not encapsulated by

Scheme 1



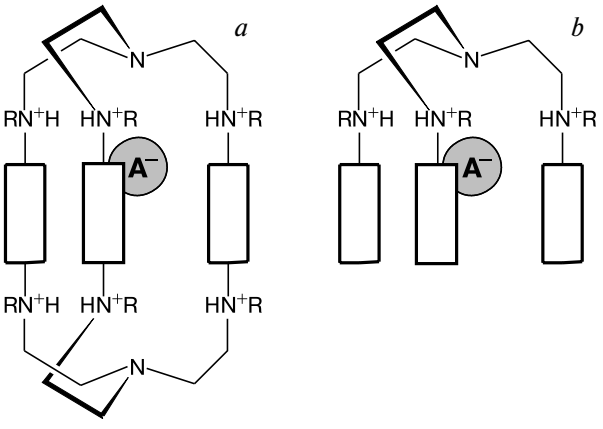
R = Me, (R,R) = $(CH_2)_4$; R′ = Me, OH

Scheme 2



Y = $SnHal_3$, $Ge(CF_3)_3$, $SbEt_3$, $SbPh_3$

D^{2-} is α- or β-dioxime dianion

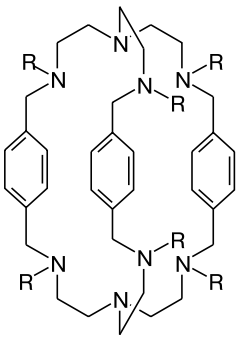


A^- = TcO_4^-, ReO_4^-

Fig. 1. Schematic view of the complexes of anions with macrobicyclic (*a*) and tripodal (*b*) ligands with N-donor groups.

macrobicyclic ligands but the ligand fragments bind three exocyclic perrhenate anions. However, the lack of selectivity of anion binding caused by their molecular recognition by the macrobicyclic cavity has been observed in this case.[23]

The extraction ability of macrobicyclic ligands **1—8** and their nonmacrocyclic analogs **9—16** toward the perrhenate ion and/or pertechnetate ion were studied for the $NaTcO_4$ ($NaReO_4$)—buffer—H_2O—ligand—$CHCl_3$ systems. In all cases, the TcO_4^- anion was extracted somewhat better than ReO_4^-. This result has been attributed to higher lipophilicity of the pertechnetate ion.[23] The extraction ability of polyamine macrobicycles is essentially limited under these conditions and increases in the ligand series **1** < **7** < **4** ≈ **2** < **6** < **8**. In all cases, *N*-methylated ligands have a better extraction ability than their NH-containing analogs. The best extraction ability was found for *N*-methylated macrobicyclic pyridine derivative **8**. Tripodal nonmacrocyclic ligands **9—16** showed significant difference in the extraction behavior: in some cases, their extraction ability was lower, while in other cases, it was higher than that of macrobicyclic ligands. Ligands **9**, **12**, and **15** had extraction abilities similar to those of macrobicyclic ligands. The best extraction ability has been ob-



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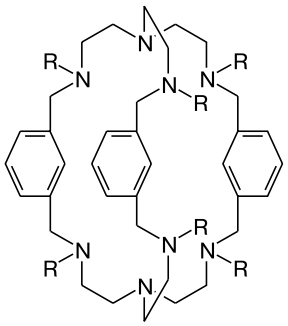
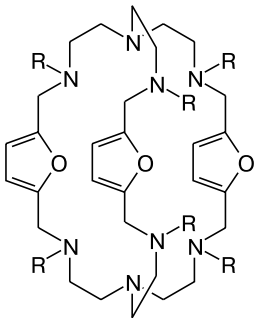
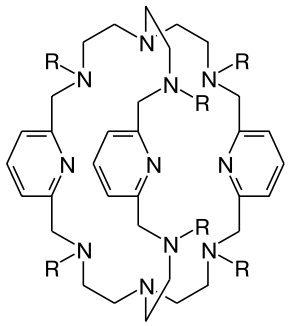


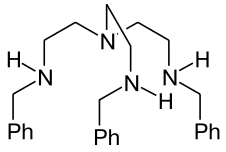
3, **4**



5, **6**



7, **8**



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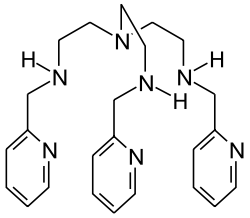

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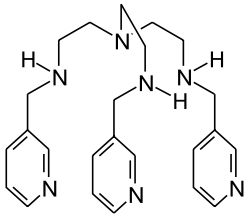

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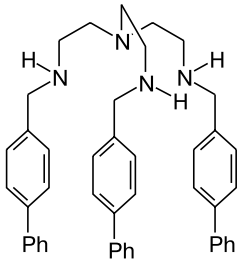

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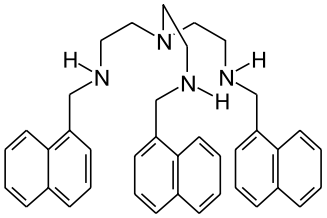

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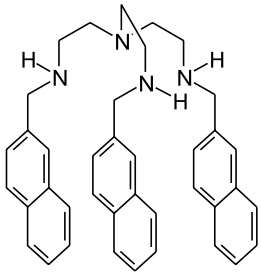

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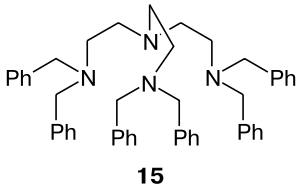

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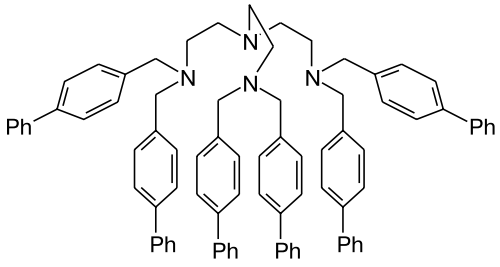

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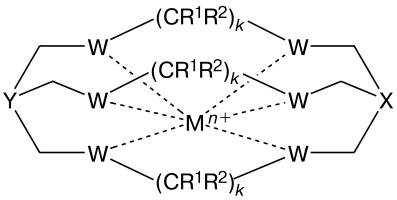
R = H (**1**, **3**, **5**, **7**); Me (**2**, **4**, **6**, **8**)

served for 2-naphthyl-containing ligand **14**, which extracted the pertechnetate ion the best among all the ligands studied. However, ligands **11**, **13**, and **16** demonstrated unefficient transport of tetraoxo-anions into the organic phase.

For some of these macrobicyclic and tripodal ligands, the dependence of the degree of extraction of the ReO_4^- and TcO_4^- anions on pH was studied. In the case of ligands **1**, **2**, and **10**, the highest efficiency has been observed at pH 7—8 where the degree of ligand protonation is insignificant and the ligands are more hydrophobic. Thus, phase transfer is preferred for less charged complexes of the "macrobicycle-anion" type, although they have lower stability constants in aqueous solutions. Despite the lowest lipophilicity in the series of ligands studied, the pyridine-containing compounds demonstrated high

extraction abilities. It is obvious that the extraction properties of these ligands cannot be attributed only to their lipophilicity.[23]

Various types of macrobicyclic ligands with S-, O-, and NH-containing donor groups have been proposed for encapsulation of both the ^{99m}Tc ions in lower oxidation states and a number of other stable or radioactive metal cations, first of all, radioactive copper(II) isotopes $^{64}Cu^{2+}$ and $^{67}Cu^{2+}$ (see Ref. 24). This makes use of not only apical and ribbed functionalizations of the clathrochelate and random selection of donor groups, but also the change in the size of cavity of the clathrochelate framework by varying the structure of the chelate fragment.



M^{n+} are Tc, Ga, In, Co, Re, Fe, Ag, Au, Rh, Pt, Bi, Cr, W, Mo, Ni, V, Pb, Ir, Zn, Cd, Mn, Ru, Pd, Hg, Ti, Tl, Sn, Zr, lanthanide, actinide and their radionuclide ions (in particular, the radionuclides of In, Ga, Fe^{III}, Cu^{II} ($^{64}Cu^{2+}$ and $^{67}Cu^{2+}$), Ti^{IV}, Re and lanthanides)

W = NH, S, O

R^1, R^2 = H, Me, COOH, NO_2, CH_2OH, H_2PO_4, HSO_3, CN, $CONH_2$

R^2 = H, Alk

X, Y = CR^3, N, P, C—Z, where Z is the functionalizing substituent

R^3 = H, Hal, OH, NO_2, NO, NH_2, Alk, Ar, ArAlk, CN, $COOR^4$, $COCOOR^4$, $NHCOCH_2Br$, $NHCOCH{=}CHCOOR^4$

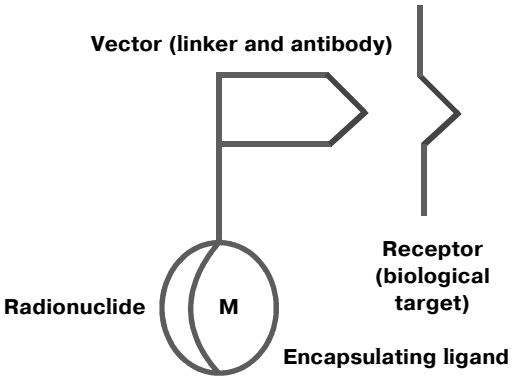
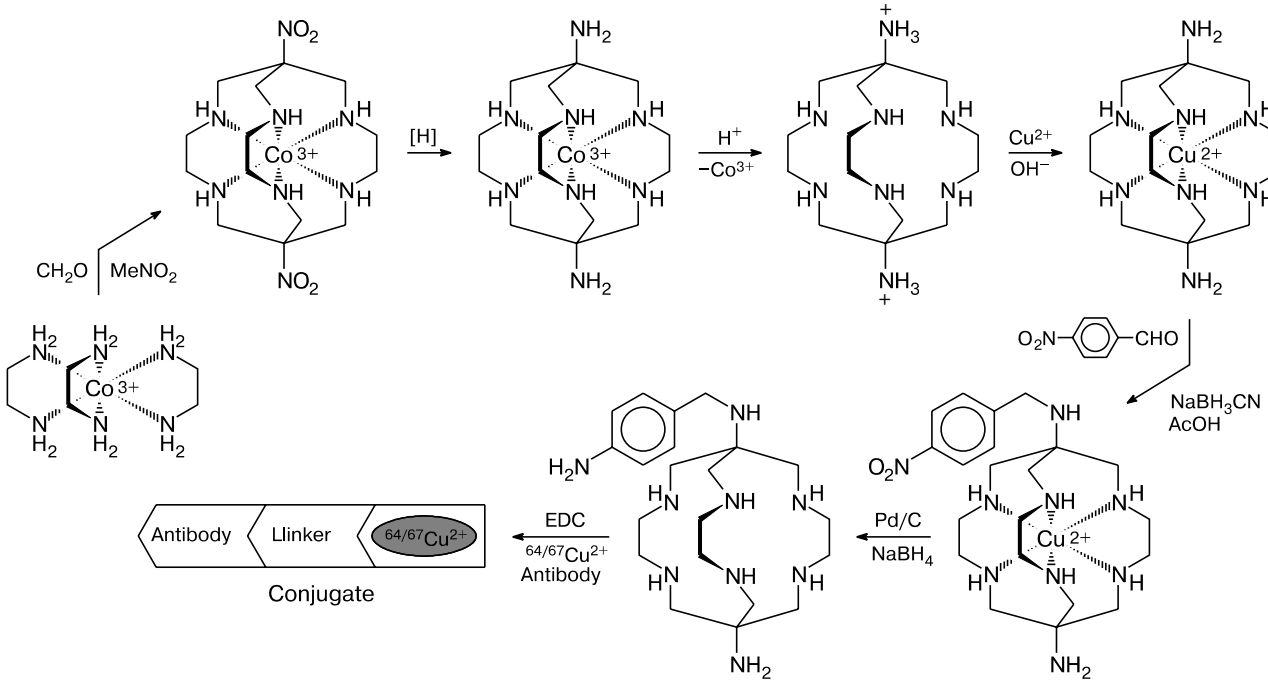


Fig. 2. Use of the conjugate for targeted delivery of an encapsulated radioactive metal ion to a biological target.
Note. Fig. 2 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

The design of apical and ribbed functionalizing substituents serves in this case for implementation of targeted delivery of radiopharmaceutical agents. The functionalization of substituents in macrobicyclic complexes of radioactive metal ions with linker fragments allows binding of these compounds to antibodies, proteins, peptides, oligonucleotides, oligosaccharides, and liposomes using well-know standard procedures with activating and coupling agents and/or enzymatic and immunochemical methods.[24]

The formation of a conjugate (Fig. 2)[25] implies the use of the immune system of an organism as the "locomotive"

Scheme 3

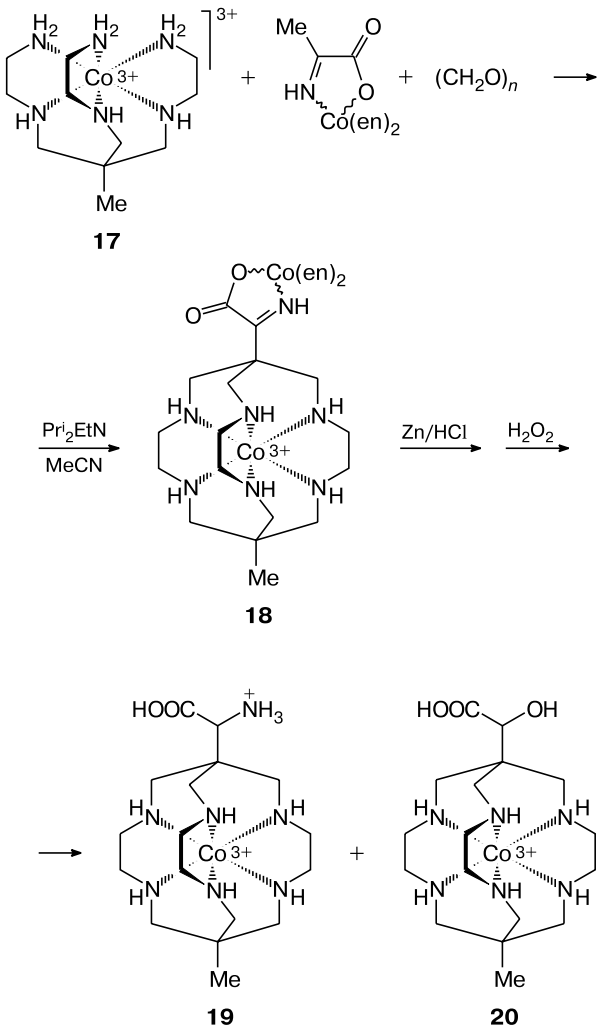


for targeted drug delivery: the radioactive metal ion is encapsulated in the cavity of the macropolycyclic ligand that is recognized by the biological target (receptor) using a vector (linker and antibody).

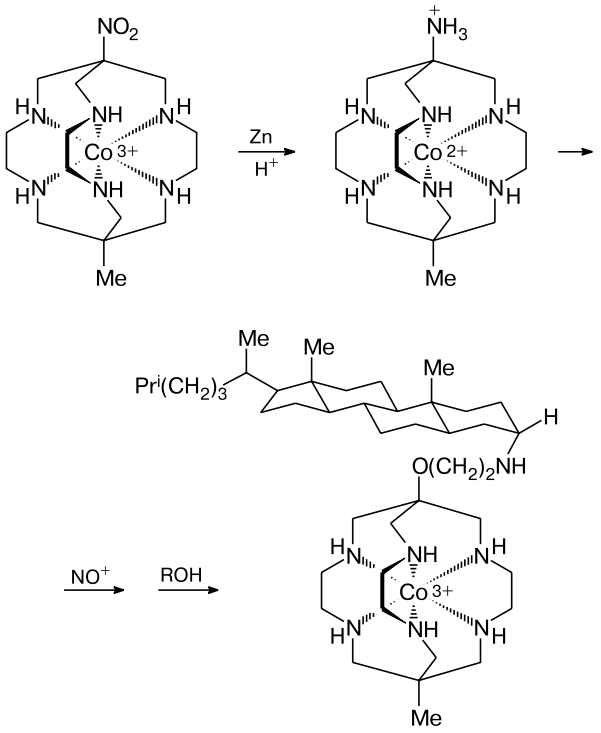
An example of the synthesis of radioactive $^{64}Cu^{2+}$ ion-labeled antibody with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as the coupling agent is shown in Scheme 3.[24]

An uncommon approach for the preparation of polyamine clathrochelates with functionalizing amino and hydroxy carboxylic acid fragments in the apical position has been reported[26] (Scheme 4). The cage complex was synthesized by three-component macrocyclization of the lacunar precursor **17** with cobalt(III) iminopyruvate complex as the methylene active component and formaldehyde. In this unique reaction, cobalt(III) ions play three roles, namely, a template for the synthesis of the sarcophaginate ligand, a protecting group for the imine fragments, and a promoter of the formation of the carbon—carbon bond by increasing the CH-acidity of the coordinated iminopyruvate anion. Transformations of the resulting binuclear clathrochelate **18** afforded macrobicyclic complexes **19** and **20** with glycine and glycolic acid residues, respectively, in the apical positions. These substituents readily form peptides and depsipeptides, being efficient spacers for functionalization and conjugation of clathrochelate complexes. The introduction of a cholestane substituent into a cobalt cage complex by diazotization of amino-substituted clathrochelate in the presence of an appropriate alcohol (Scheme 5)[27] yielded a water-soluble cholestane-containing cobalt(III) complex, which is able to be recognized by cholesterol-containing receptors.

Scheme 4

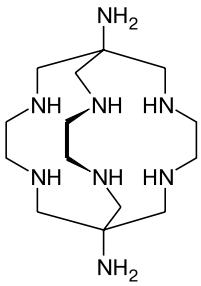


Scheme 5



1.2. Imaging agents for magnetic resonance tomography

Complexes of polyamine cage ligands with paramagnetic Fe^{3+} and Mn^{2+} ions were proposed as imaging agents for magnetic resonance tomography.[27] In particular, it was noted that manganese(II) diaminosarcophaginate $[Mn(diAMsar)]^{2+}$ (with ligand **21**) is a moderate relaxation agent for water protons; however, upon binding of its functionalized derivatives with proteins, the relaxation efficiency markedly increases because of an increase in the rotational and translational correlation times. This allows one to study protein-rich parts of a living organism.[27]



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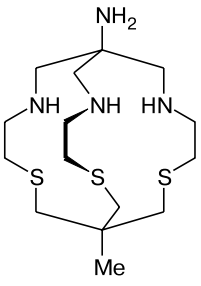

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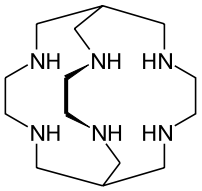

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1.3. Detoxifying biological systems (antidotes) based on macrobicyclic polyamine ligands and prolonged pharmaceuticals

Efficient capture of transition metal ions by macrobicyclic ligands has been used[27] for detoxification of biological systems, in particular, for patients with Wilson´s disease whose liver does not release copper(II) ions. These ions are accumulated in the liver and brain, and this leads to premature death. It is obvious that effective *in vivo* binding of transition metal ions requires the use of coordinatively labile macrobicyclic ligands, in particular, polyamine and polythioamine compounds **21—23**. Copper(II) complexes with these ligands are characterized by kinetic and thermodynamic stability, whereas virtually no complexation of alkali and alkaline-earth metals with these macrobicycles occurs. The results of comparative binding studies of copper(II) and other biologically significant transition metal ions have shown that N_3S_3-sarcophaginate **22** is a more selective ligand for Cu^{2+} ion than its N_6-containing analog **21**. However, the resulting copper(II) complex is kinetically less inert. *In vitro* tests on removing copper ions from the liver cells have been carried out. Ligand **21** is more effective than penicillamine, which is used in the clinical therapy of Wilson´s disease, and macrobicyclic ligand **23**. These results looked very promising from the point of view of using these nontoxic cage ligands for preventing organism intoxication with transition metal ions.[27]

The unique kinetic parameters of the template synthesis and decomposition of cage complexes, which allowed one to control efficiently dissociation of these compounds in various media (in particular, in biological media at physiological pH values) by choosing cross-linking fragments, substituents in them, and substituents in chelating groups,[28—33] make the clathrochelates very promising for prolonged release of therapeutic amounts of an encapsulated metal ion in humans and mammals.

2. Targeted ribbed and apical functionalization of macrobicyclic complexes: closo*-borate- and carborane-containing apically and ribbed functionalized transition metal clathrochelates as promising agents of boron neutron capture therapy of cancer*

Boron neutron capture therapy (BNCT) based on a nuclear reaction of stable ^{10}B isotope with thermal neutrons (0.025 eV) is a method for cancer therapy. The particles formed upon the reaction, *i.e.*, helium nuclei (α-particles), lithium-7 recoil nuclei, and soft γ-photons, have high linear energy loss and a relatively short overall path comparable with cell dimensions (up to 14 μm) in tissues.[34—39] The selective accumulation of the ^{10}B-containing compound in tumor cells resulted in selective radiation effect inducing the necrosis of only these cells (including metastases of any size) without damaging the healthy tissues can be attained at the cellular level. For successful BNCT treatment of a tumor, the boron-containing agent should possess a number of features, one being the ability to be selectively accumulated in malignant tumor cells, thus ensuring targeted delivery of a therapeutic amount of ^{10}B, its optimal distribution in the cells, and the ability to be retained in the cells for a period needed to complete the radiological treatment.[36—40]

The efficiency of BNCT is determined by the site and degree of accumulation of the boron-containing agent in the malignant tissues. The amount of ^{10}B in the tumor may change significantly depending on localization of the agent in the cell; the so-called "factor of compound" is determined by the chemical structure and metabolism of this compound and has an essential influence on the efficiency of the therapy.[40]

As a result, the main requirements to the boron-containing agent for BNCT procedure were formulated:[34—40]

(1) the highest ^{10}B content in the therapeutic form (for the minimum required therapeutic effect, the ^{10}B concentration in the tumor should be equal to 10—30 μg of ^{10}B per g of the tumor cell depending on the agent distribution in the cell; the agent should also be enriched in the minor boron isotope ^{10}B whose natural abundance is ~20%);

(2) rather high solubility of the therapeutic form in water;

(3) low toxicity of the radiopharmaceutical ^{10}B-containing agent (additional intoxication caused by the agent apart from intoxication by the products of its radiolysis may be fatal for the organism);

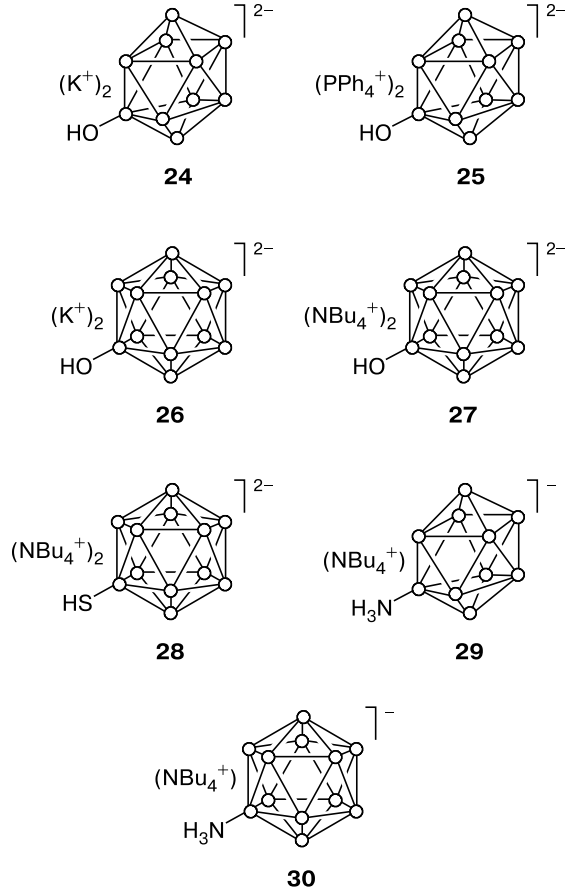
(4) high selectivity of agent accumulation in tumor cells (the efficiency of BNCT increases, while the radiation exposure decreases in the case of targeted delivery of the ^{10}B-containing agent to the tumor cells);

(5) stability of the agent under physiological conditions and metabolism suitable for the therapeutic protocol (to attain the highest therapeutic effect, the boron-containing agent must remain in the tumor cells throughout the whole period of radiological treatment).

It should be noted that BNCT is suitable in those cases where no other options for therapy exist (in particular, against skin or brain tumors at the terminal stages).

A number of BNCT agents have been proposed earlier; however, most of these agents have low selectivity, high toxicity, and low stability.[34—40] Therefore, it is necessary to develop a new strategy for the design of BNCT agents.

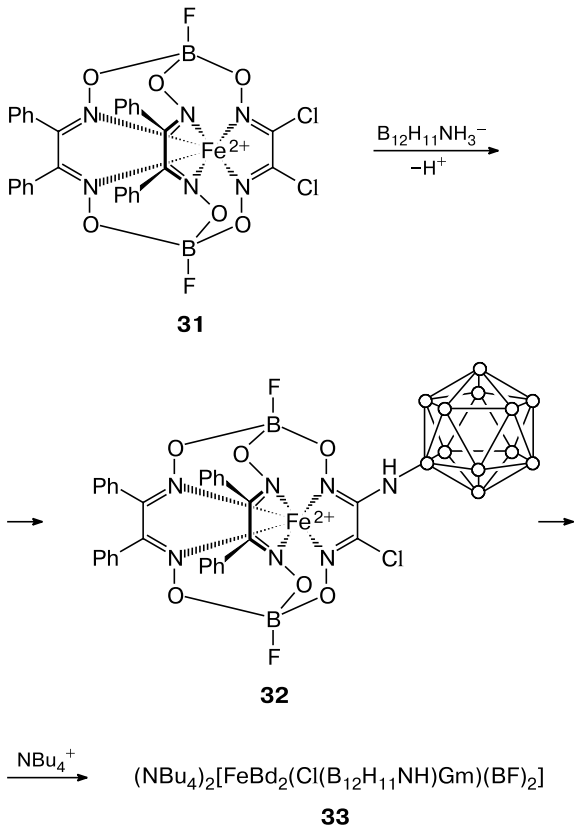
Higher polyhedral boranes $B_nH_n^{2-}$, where $n = 6—12$, are readily available, stable, and low-toxic compounds. Therefore, in recent years, derivatives of decahydro-*closo*-decaborate ($B_{10}H_{10}^{2-}$) and dodecahydro-*closo*-dodecaborate ($B_{12}H_{12}^{2-}$) anions have been recognized as the most promising BNCT agents.[41—64] As noted above, cage complexes with an encapsulated metal ion have been proposed as "molecular scaffolds" for the assembly of polytopic and polyfunctional systems. The majority of this type of molecules are formed by cross-linking with boron-containing apical groups, which increase the percentage of ^{10}B in the complex.



Therefore, an attempt has been undertaken[65] at ribbed functionalization of the clathrochelate iron(II) tris-dioximates with *closo*-deca- and dodecaborate mono- and dianions of different nature (**24**—**30**).

Alkane- and arenethiols are most convenient for ribbed functionalization of clathrochelate iron(II) tris-dioximates through nucleophilic substitution of reactive chlorine atoms in iron(II) mono-, di-, tri-, and hexachloride clathrochelates.[1,2,7—17] However, in the case of thiol-containing *closo*-borate **28**, nucleophilic substitution cannot be performed even in the presence of strong bases (in particular, potassium *tert*-amylate).[65] The hydroxyl-containing *closo*-borate dianion **27** proved to be more reactive, but in this case, too, nucleophilic substitution occurred only partially and in low yield. The use of amino-*closo*-borate **30** and the dichloride clathrochelate precursor $FeBd_2(Cl_2Gm)(BF)_2$ (**31**) in the presence of potassium *tert*-amylate afforded the *closo*-borate-containing clathrochelate dianion $[FeBd_2(Cl(B_{12}H_{11}NH)Gm)(BF)_2]^{2-}$ (**32**), which was isolated as the tetra-*n*-butylammonium salt **33** (Scheme 6)[65].

Scheme 6

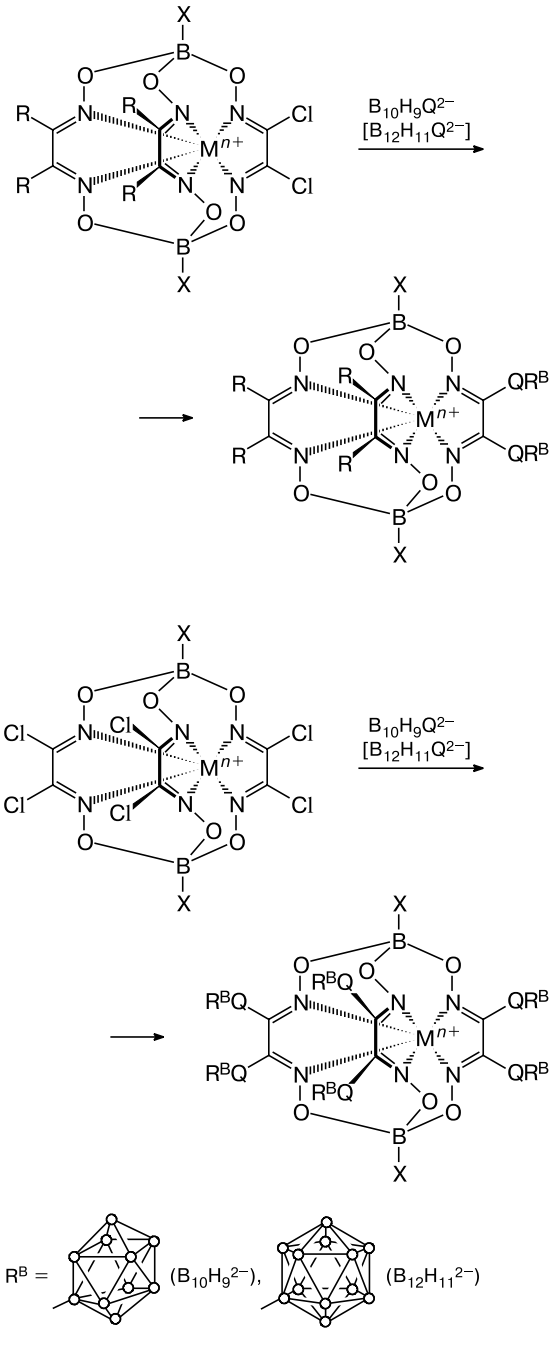


Bd is α-benzyldioxime dianion

Thus, *closo*-borate mono- and dianions with HO, HS, and H_2N groups attached inherently to the boron

cluster proved to be insufficiently reactive functionalizing agents for the synthesis of polytopic cage complexes, because of both the steric hindrance and reduced nucleophilicity of these groups due to the inductive effect of the boron hydride cage. Therefore, it was proposed to carry out nucleophilic substitution using derivatives of *closo*-borate dianions containing aliphatic spacers with terminal HO, HS, and H_2N groups (Scheme 7). This allows one to extend the range of systems for targeted delivery of the clathrochelate molecules by varying the substituents.[41,51,56,63–65] Indeed, the use of spacer-containing functionalized *closo*-borate with a spacer containing a terminal thiol group, the $[B_{10}H_{11}OCH_2CH_2OCH_2CH_2SH]^{2-}$ dianion, gave, for the first time, an iron(II) clathrochelate completely modified by *closo*-borate substituents (Scheme 8).

Scheme 7

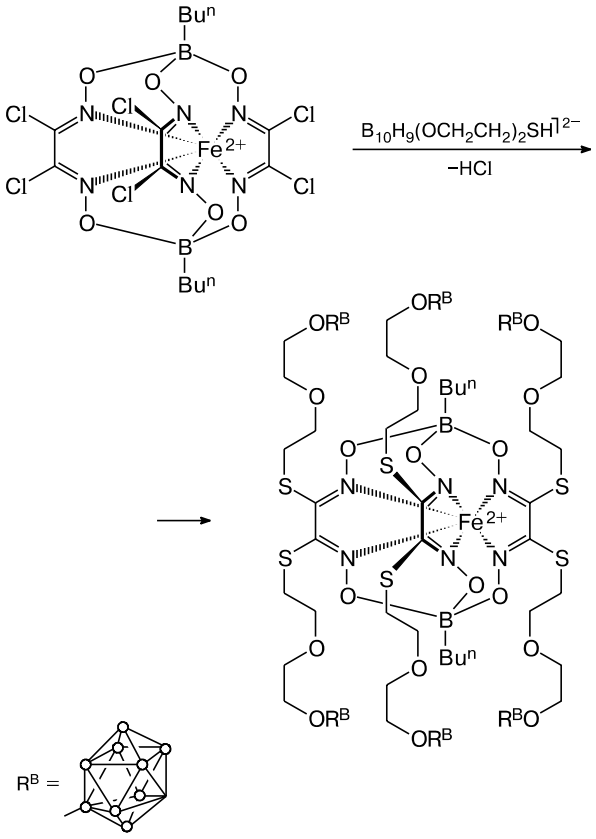


R = Me, Ph, (R,R) = $(CH_2)_n$

M^{n+} = Fe^{2+}, Ru^{2+}, Co^{2+}, Co^{3+}

X is an apical substituent for targeted delivery to a biological target, Q is the spacer

Scheme 8

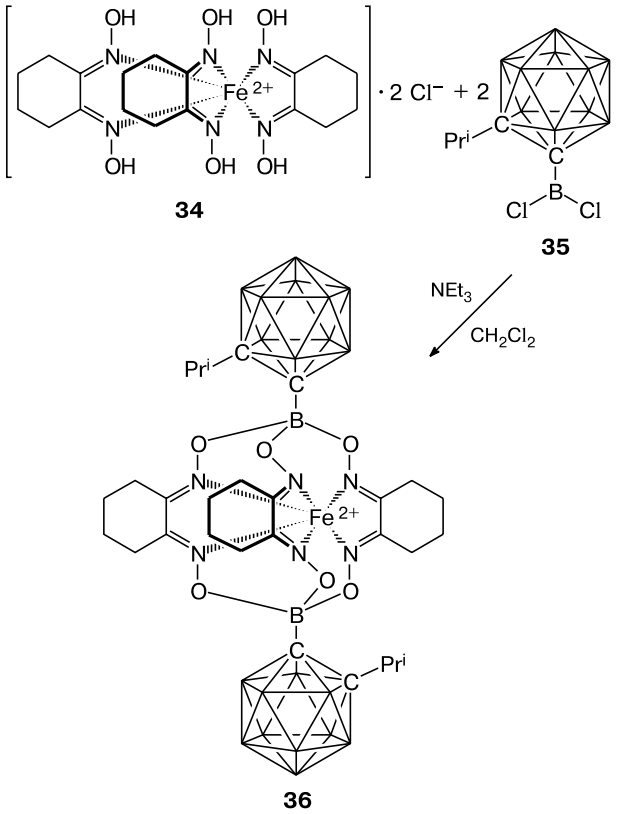


This type of compounds have a suitable 3D geometry and contain 62 or 74 boron atoms within a twelve-charged clathrochelate anion. The hydrophilic, transport, and adsorption properties of these complexes can easily be varied over a broad range by choosing apical substituents and counter-ions and by the formation of inclusion compounds with organic cations, in particular, guanidine- and arginine-containing peptides and betaines. This provides targeted delivery and accumulation of the agent in the cytoplasm or cell membranes, incorporation in liposomes, and binding to antibodies. The presence of an intensive chromophore center (clathrochelate framework) facili-

tates the studies of distribution, migration, and bio- and radiodegradation of these agents.

The first iron(II) clathrochelate with functionalizing apical carboranyl substituents that has been obtained by cross-linking with C-carboranylboronic acid derivative is a representative of a new type of potential BNCT agents based on the clathrochelate complex with an encapsulated transition metal ion.[66] In this case, the Lewis acidity of 1-isopropyl-2-dichloroboryl-1,2-dicarba-*closo*-dodecaborane **35** was used[66] for macrocyclization of iron(II) complex with cyclohexanedione-1,2-dioxime (nioxime) whose derivatives are more stable and more readily formed than complexes of acyclic dioximes.[33] Template condensation of the initial nonmacrocyclic iron(II) *tris*-nioximate **34** and boronate **35** resulted in the formation of carboranylboron-linked iron(II) clathrochelate **36** with apical 1-isopropyl-*o*-carboranyl substituents (Scheme 9).[66]

Scheme 9



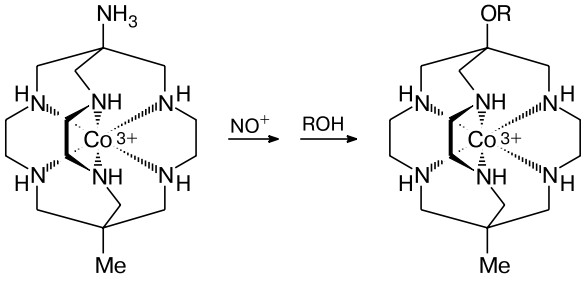
34 **35** **36**

3. Surface- and membrane-active clathrochelates. Lipid transport of metal cage complexes

3.1 Anthelminthic and antiparasitic properties of detergents based on cobalt(III) polyamine cage complexes

A new class of detergents based on cobalt(III) polyamine clathrochelates functionalized with apical long-chain paraffin substituents was synthesized[27,67,68] by alkylation of long-chain alcohols with carbocations formed upon diazotization of aminosarcophaginates (Schemes 10 and 11), reductive alkylation (Schemes 11 and 12), and *N*-alkylation and the C—C bond formation between the apical carbon atom and the long-chain alkyl substituent (Scheme 13).[68] The resulting apically functionalized clathrochelates showed antihelminthic and antiparasitic properties, which are determined, in particular, by the ability of amphiphilic complexes with long-chain alkyl substituents to be incorporated into cell membranes.[27] This functionalization provides the targeted delivery of a cobalt-containing clathrochelate whose antiparasitic actiivity was attributed to its physical properties.[27] The ^{57}Co-labeled polyamine cage complexes were employed to study the biodistribution of both apically functionalized complexes and the original cobalt(III) clathrochelate. The complex with a long-chain hydrocarbon substituent is efficiently sorbed by the gastrointestinal tract surface and remains in the organism for several days, whereas the original clathrochelate with the apical amino group is not accumulated in the organism, but is excreted almost entirely over a period of 24 h. It was also shown[27] that apical substituents determine the resorption of these cage complexes through the wall of the gastrointestinal tract.

Scheme 10



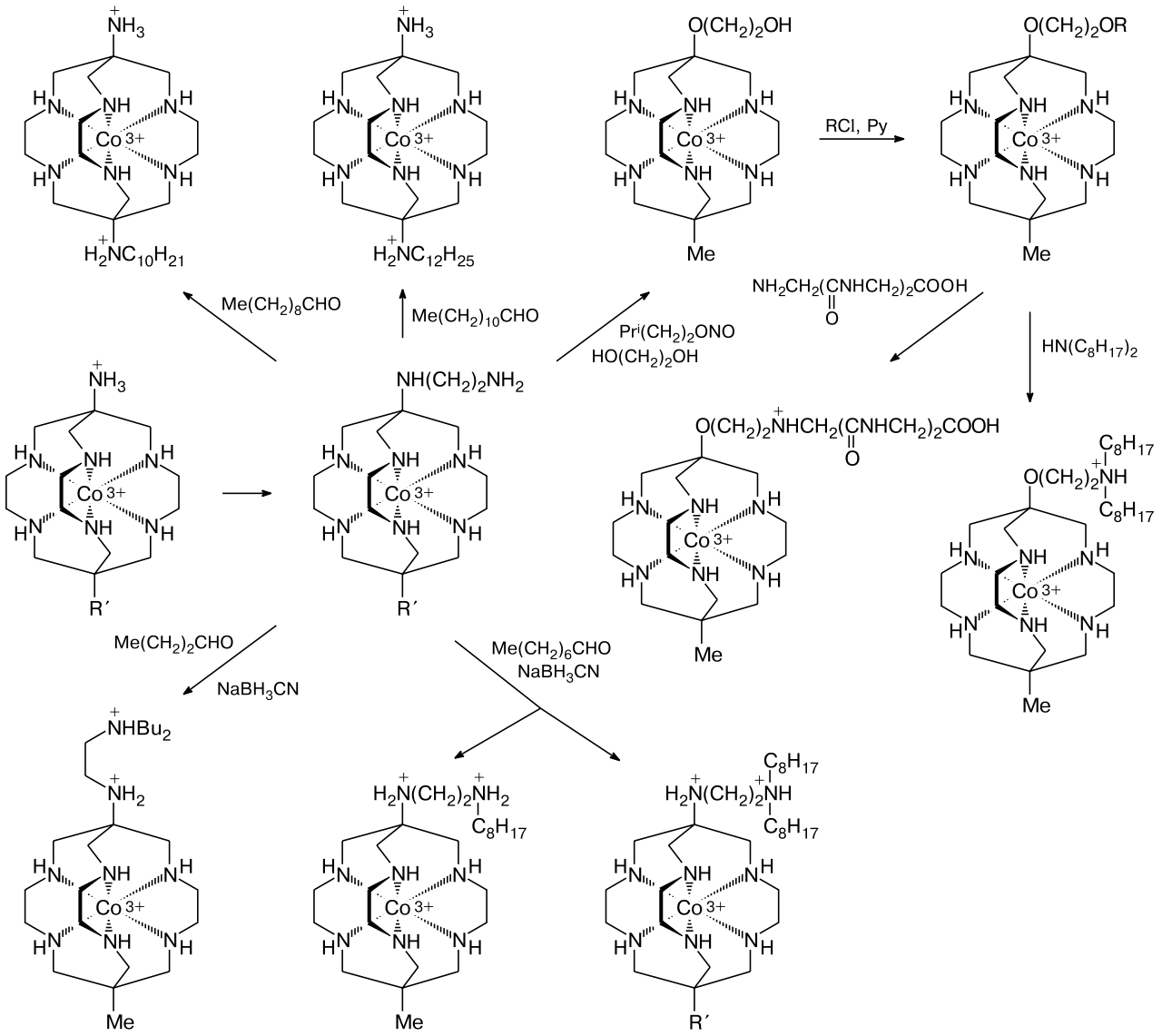
R = Me, Pr^i, $(CH_2)_2OH$, $PhCH_2$, $Ph(CH_2)_2$, *n*-C_6H_{13}, *n*-$C_{10}H_{21}$, *n*-$C_{15}H_{31}$

3.2. Antioxidant activity of iron and cobalt(II) clathrochelates in peroxidation processes

The molecular assembly of polytopic systems containing clathrochelate fragments was used to design novel antioxidants based on sterically hindered phenols. 2,6-Di(*tert*-butyl)phenols are well-known antioxidants widely used in various fields of food industry and pharmaceutics.[69] Their antioxidant activity is determined by stability of the phenoxyl radicals formed upon their oxidation, the redox potential value, and the mechanism and reversibility of the electron transfer.

The incorporation of a metal ion in a phenol-containing molecule is known[70] to be an efficient way for stabiliz-

Scheme 11



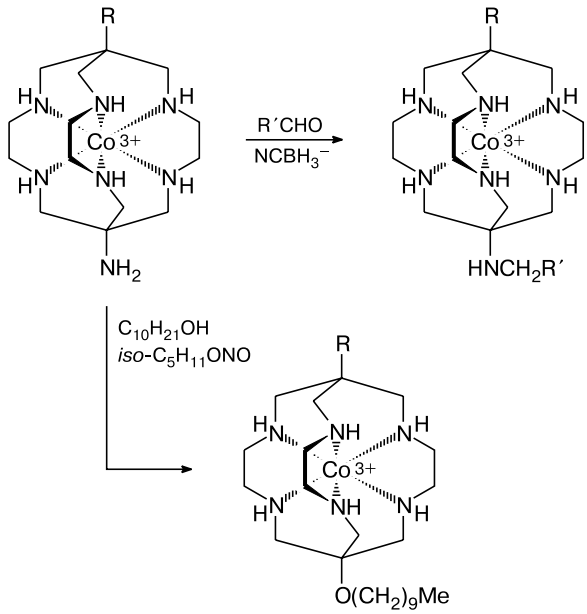
R = Ms or Ts, R′ = Me or NH_2

ing the phenoxyl radical formed upon its oxidation (Scheme 14). The effect of the metal ion on the physicochemical characteristics of radical reaction products is determined by two main factors, namely, steric factor (an increase in the structural rigidity of the molecule and steric hidrance of the reactive radical centers) and electronic factor (a decrease in the spin density on the radical fragment as a result of delocalization of the unpaired electron within the common electronic system of the complex).

In addition, the central metal ions in these complexes can initiate oxidation (in particular, through coordination of molecular oxygen and catalysis of hydroperoxide homolysis).[71]

Comparative study of the antioxidant activity was carried out for macrocyclic square bipyramidal iron(II) and cobalt(III) bis-dioximates and cage macrobicyclic iron(II) and cobalt(II) tris-dioximates.[72] Two series of macrocyclic and macrobicyclic iron and cobalt α-dioximates differing in the molecular geometry and the number of 2,6-di(*tert*-butyl)phenol substituents in them were prepared. Specifically, the macrocyclic iron and cobalt bis-dioximates, $FeD_2(BF_2)_2Py_2$ and $CoD_2(BF_2)_2PyCl$, where D^{2-} is the methyl[3,5-di(*tert*-butyl)-4-hydroxyphenyl]glyoxime dianion, contained two fragments of this type, whereas the molecules of cage iron and cobalt trisdioximates contained one or six sterically hindered phenolic groups.

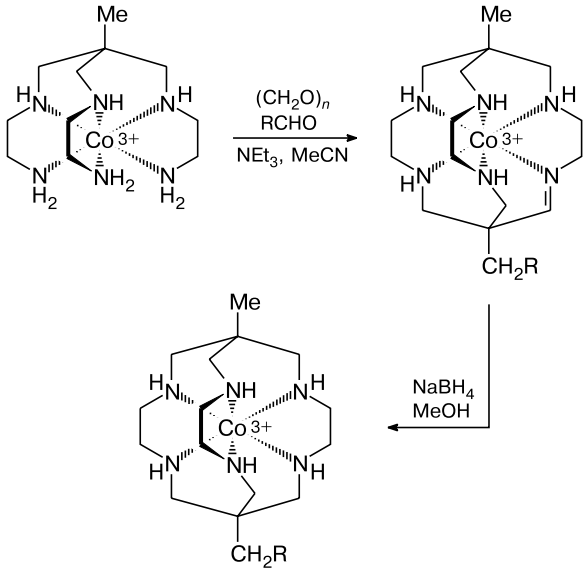
Scheme 12



R = Me, NH_2

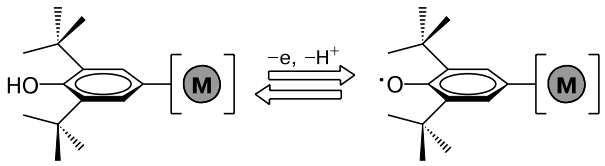
R´ = n-$C_9H_{19}CH_2N(C_8H_{17}{}^n)_2$

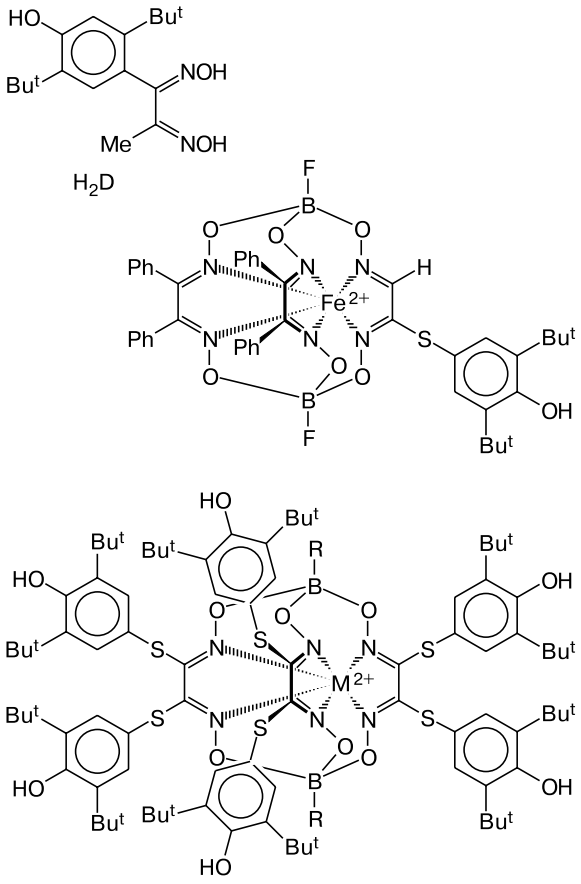
Scheme 13



CH_2R = $(CH_2)_7Me$, $(CH_2)_{11}Me$, $(CH_2)_{15}Me$

Scheme 14





M^{2+} = Fe^{2+}, Co^{2+}, R = Ph

M^{2+} = Fe^{2+}, R = Bu^n

(*Z*)-Octadec-9-enoic (oleic) acid was chosen as the substrate as a model of autoxidation of lipids by molecular oxygen. The liquid-phase oxidation of oleic acid is a radical chain process[73] giving hydroperoxides as the primary products, which then decompose to yield oxidative destruction products (mainly, carbonyl compounds).

The macrocyclic cobalt(III) bis-dioximate $CoD_2(BF)_2PyCl$ fairly high initiates with activity in the oxidation of oleic acid. The effect of the cobalt(II) cage complex is the opposite, namely, the macrobicyclic complex inhibits this reaction. It was also shown that the iron(II) tris-dioximate clathrochelate exhibits a much higher antioxidant activity than bis-dioximate macrocycles.

Thus, encapsulation of the metal ion in macrobicyclic iron(II) tris-dioximate results in inhibition of accumulation of hydroperoxides and their decomposition products. The most pronounced antioxidant properties were observed for the complexes containing six 2,6-di(*tert*-butyl)phenol residues.

The level of peroxidation of unsaturated fatty acids was measured based on accumulation of carbonyl compounds formed upon hydroperoxide decomposition; the

content of carbonyl compounds was determined by spectrophotometry based on the reaction with thiobarbituric acid (TBA).[72] The measured concentrations of TBA-positive products (the percentage with respect to the control experiment in the absence of an inhibitor) also confirmed that clathrochelate iron(II) tris-dioximates with six sterically hindered phenolic substituents have the highest antioxidant activity, whereas macrocyclic phenol-containing iron(II) and cobalt(III) bis-dioximates do not show a considerable effect on the rate of formation of TBA-positive reaction products.

The effect of macrobicyclic phenol-containing iron and cobalt(II) tris-dioximates on the lipid peroxidation was studied *in vitro* using liver homogenates from Wistar line laboratory rats. The relative amounts of the TBA-positive oxidation products were determined in the presence of either equimolar amounts of these clathrochelate complexes or 2,6-di(*tert*-butyl)-4-methylphenol (ionol), an antioxidant widely used in food industry. It was found that ionol has no considerable influence on the lipid peroxidation in rat liver homogenates, whereas macrobicyclic iron and cobalt(II) complexes markedly inhibit the oxidation, the best antioxidant activity being observed for clathrochelate iron(II) tris-dioximates.[72]

The high antioxidant activity of the clathrochelate iron and cobalt tris-dioximates compared to their macrocyclic bis-dioximate analogs is attributable to the possibility of incorporating additional antioxidant phenolic groups into the molecules of macrobicyclic complexes (Figs 3 and 4). The encapsulated metal ion provides high stability of the phenoxyl radicals formed, and the steric hindrance of the metal ion encapsulated in the cavity of the macrobicyclic clathrochelate tris-dioximate ligand prevents its involvement in dioxygen coordination and activation. In addition, the efficiency of inhibition of oxidation processes in the cells is determined by inclusion of clathrochelates with lipophilic peripheral substituents into the lipid bilayer of the cell membrane (Fig. 5).

3.3. Membrane transport of metal cations: the formation of the second (hydrophobic) shell of an encapsulated metal ion

As noted above, the apical functionalization of clathrochelates affects mainly the physical and physicochemical properties of these complexes. The substituents in the ribbed fragments have much greater both steric and electronic effects on the structure and properties of clathrochelate framework (and, therefore, the metal ion encapsulated by the macrobicyclic ligand). The presence of branched bulky hydrocarbon substituents (in particular, diamonoid hydrocarbon derivatives) creates steric hindrance in the periphery of the molecule, which gives rise to a hydrophobic shell. The physical and physicochemical properties of the obtained clathrochelates with the second hydrophobic shell resemle those of diamonoid hydrocarbons, which suggests, first of all, a promising application for membrane transport of encapsulated metal ions. As noted in Section 1, complexes with an encapsulated metal cation (in particular, radioactive ion) can be used as radiopharmaceutical and pharmaceutical agents for diagnostics and therapy. Meanwhile, some derivatives of diamonoid hydrocarbons (in particular, adamantane)

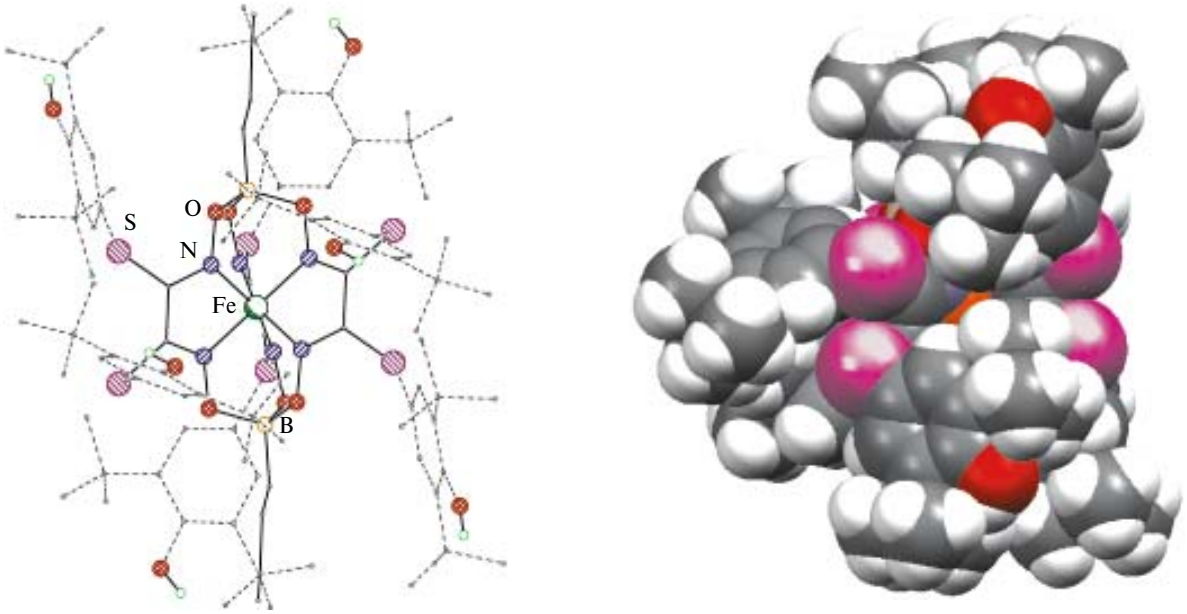


Fig. 3. General view of the iron(II) hexaphenolic clathrochelate.
Note. Fig. 3 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

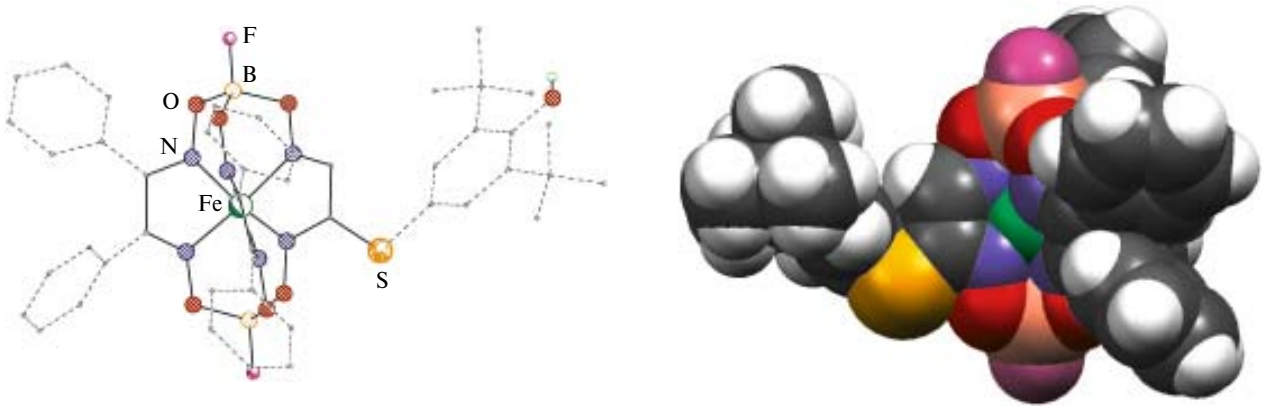


Fig. 4. General view of the iron(II) monophenolic clathrochelate.
Note. Fig. 4 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

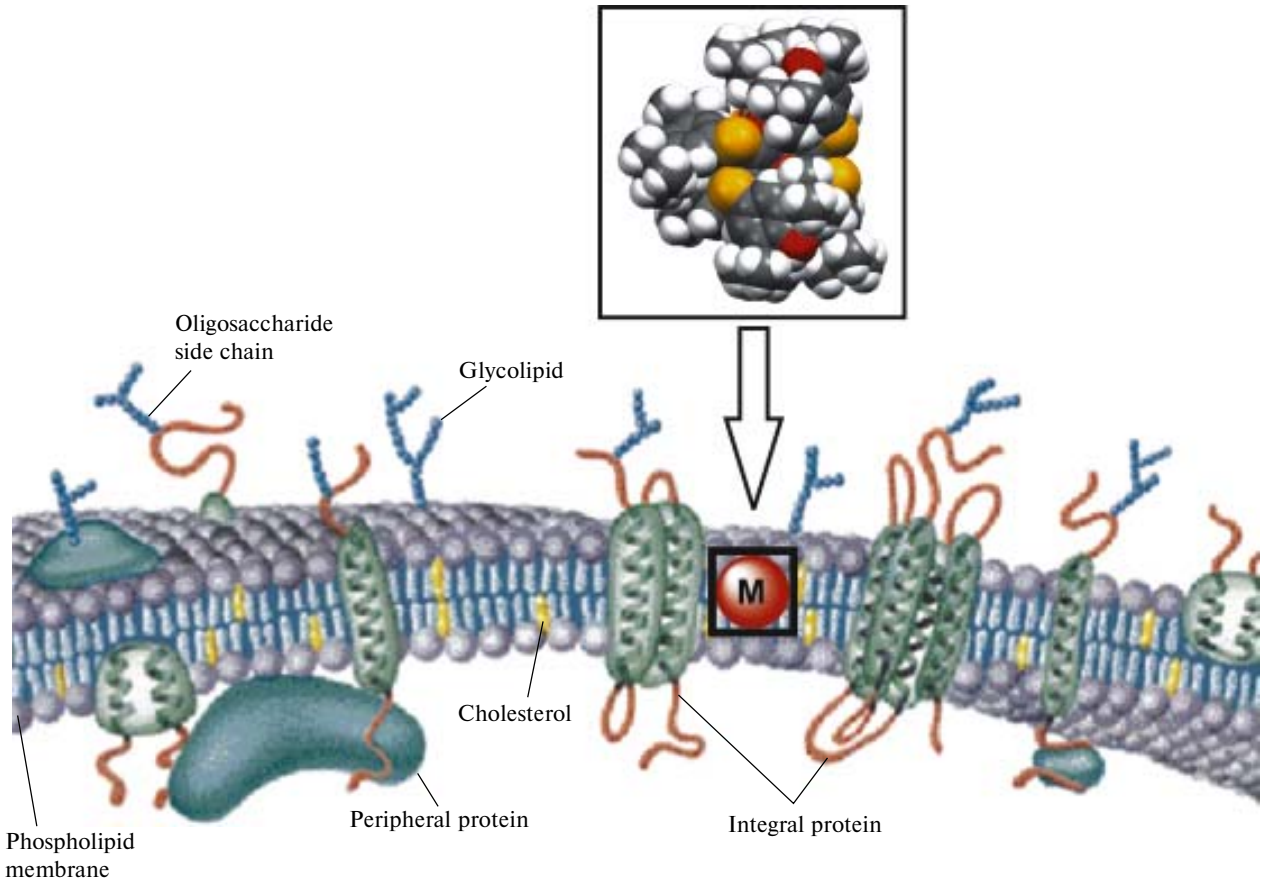


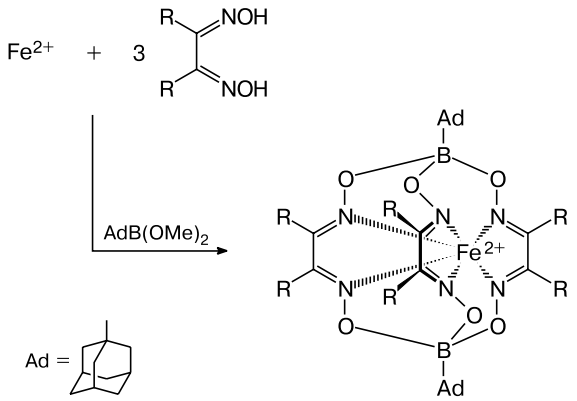
Fig. 5. Incorporation of the clathrochelate complex into the lipid bilayer of a cell membrane.
Note. Fig. 5 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

are well-know efficient pharmaceuticals (*e.g.*, remantadine). Therefore, tris-dioximate iron(II) clathrochelates with apical or ribbed adamantyl substituents and complexes with both types of adamantyl substituents were synthesized.[74]

Alicyclic and acyclic iron(II) α-dioximate clathrochelates with apical adamantyl substituents were synthesized by direct template reaction on the Fe^{2+} ion as the template (Scheme 15).[74] The adamantylborate hexachloride clathrochelate, a derivative of weakly donating

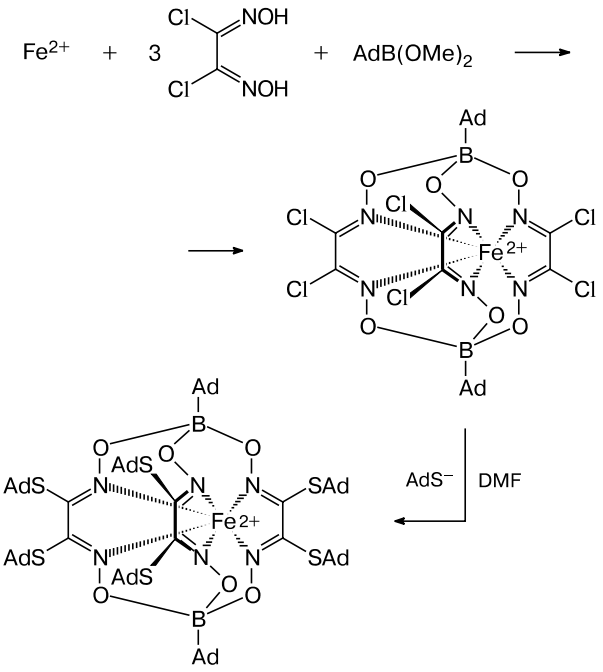
dichloroglyoxime, was also obtained in high yield (Scheme 16). The following nucleophilic substitution of six reactive chlorine atoms on treatment with the adamantanethiolate anion took place only under drastic conditions (prolonged heating in a solvent with a high donor number (DMF) in the presence of a strong base, potassium *tert*-amylate). This gave octaadamantyl complex in relatively low yield. Probably, the formation of the octaadamantyl complex is hampered by steric hindrance caused by the accumulation of bulky adamantyl substituents. Conversely, in the case of phenylborate hexachloride precursor, nucleophilic substitution with adamantanethiolate anion proceeded much more readily and gave the target product in high yield (Scheme 17, Fig. 6).[74]

Scheme 15

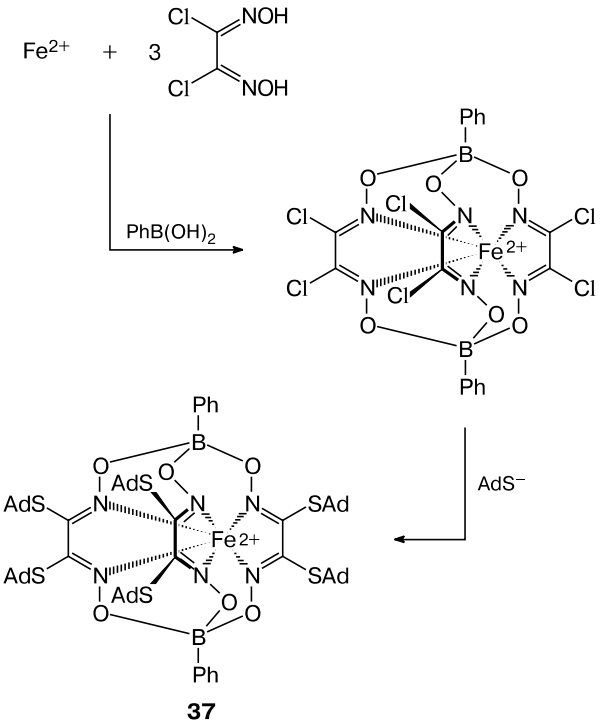


R = Me, Ph; (R,R) = $(CH_2)_4$, $(CH_2)_6$

Scheme 16



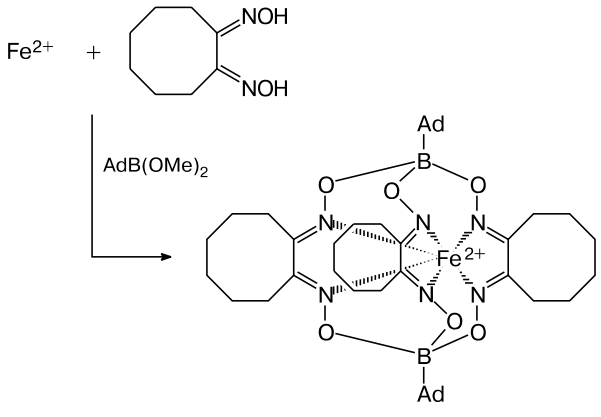
Scheme 17



37

Analysis of the the shape of molecules and crystal packings for adamantyl-containing clathrochelates **37—39** (Schemes 17—19, Fig. 6—8)[74] showed that the formation of their crystal lattices is mainly governed by the dispersion van der Waals interactions between the hydrophobic peripheral parts of the molecule and depends primarily on the overall geometry of the molecule,

Scheme 18



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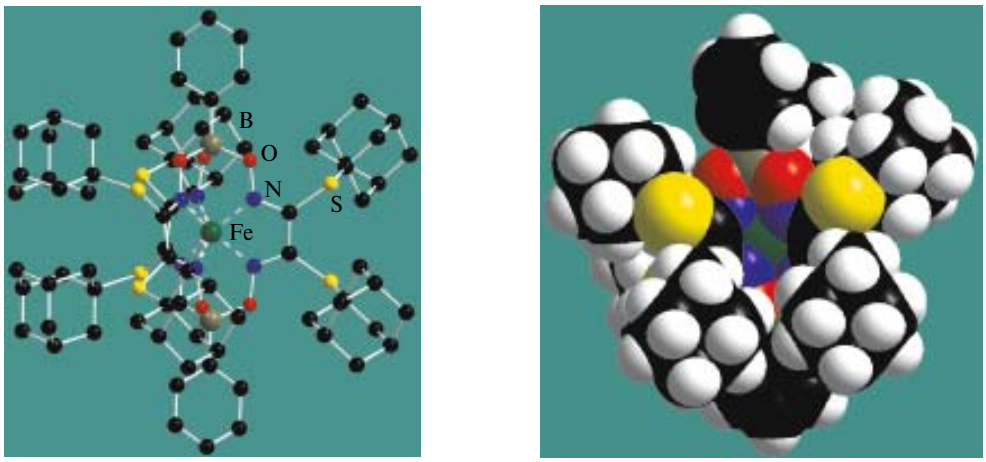


Fig. 6. General view of molecule **37**.
Note. Fig. 6 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

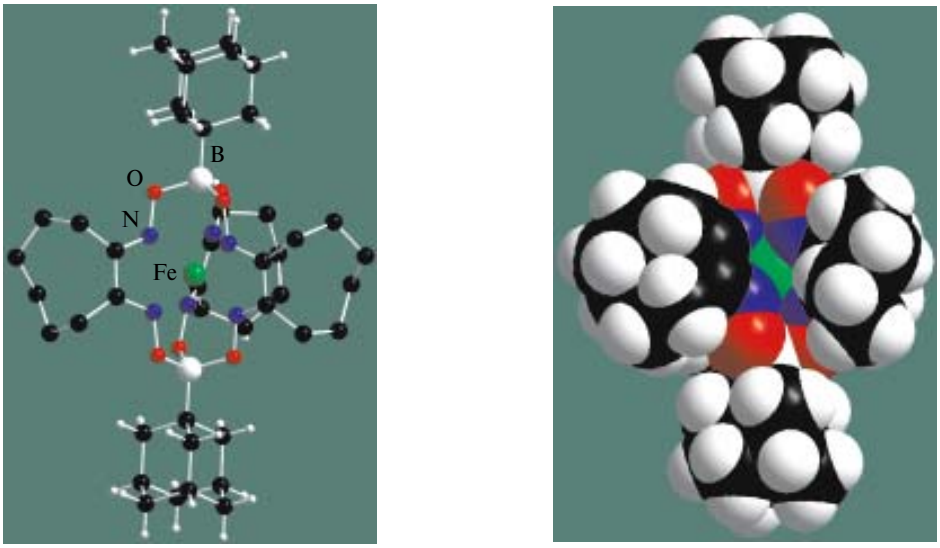


Fig. 7. General view of molecule **38**.
Note. Fig. 7 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

which is determined by the size and the conformational lability of the substituents. The ellipsoidal molecules of adamantyl-containing clathrochelates possess a "whirligig" configuration: the boron atoms with their substituents occupy the apical positions, whereas the chelate rings with substituents form the central belt (toroid) (see Fig. 6—8). In the absence of polar terminal substituents, van der Waals interactions play the main role in the crystal packing of these molecules. Their crystals usually contain various types of cavities that might be occupied by the solvate molecules, while the molecules of adamantyl-containing complexes are arranged in layers whose hydrophobic surface is formed by apical and ribbed substituents.

Thus, the ribbed modification of clathrochelates with diamonoid hydrocarbons allows one to isolate the encapsulated metal ion not only from chemical factors but also from other types of interaction (in particular, dipolar) by creating a shell of densely packed diamonoid hydrocarbons. These compounds are promising as optical and magnetic probes for the investigation of biphilic and hydrophobic interactions in cell membranes, micelles, and liposomes and as specific substrates for hydrophobic receptors (see Section 5).

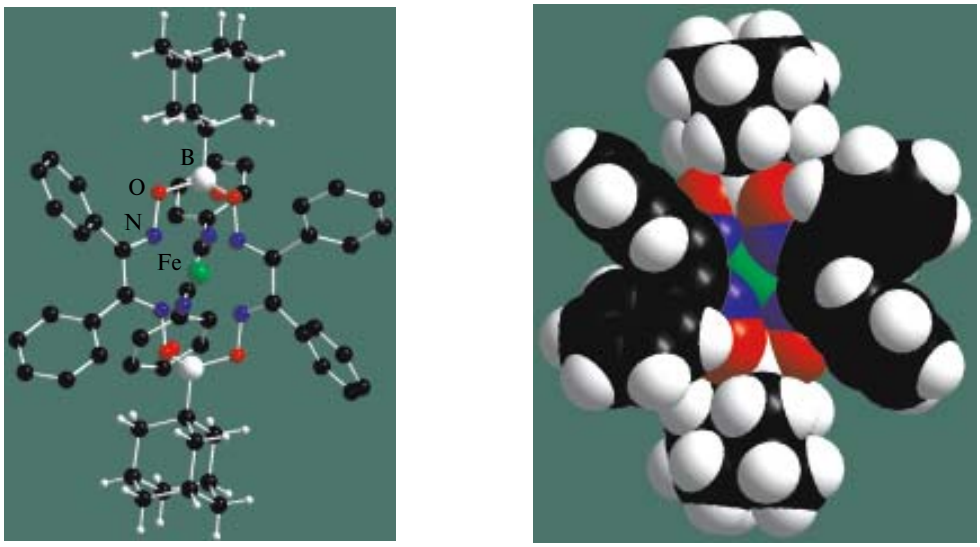
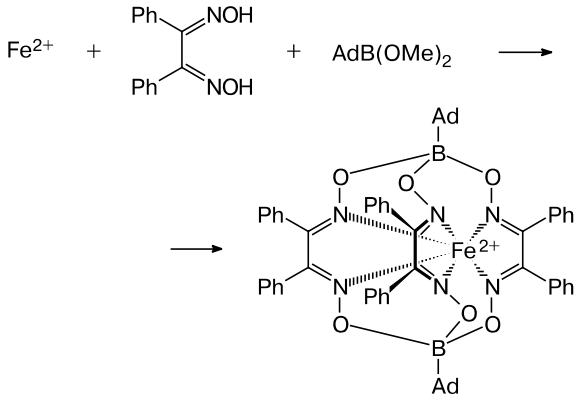


Fig. 8. General view of molecule **39**.
Note. Fig. 8 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

Scheme 19



39

4. Interactions of metal cage complexes with nucleic acids. Self-assembly of clathrochelates in immunology and molecular biology; possibility of using self-assembly of cage complexes for mimicking ligases, and the use of clathrochelates as linkers

In many cases, the synthesis of tris-dioximate iron clathrochelates proceeds very readily under mild, nearly physiological conditions and can be described as a three-component self-assembly of three α-dioxime molecules, iron(II) ion, and two boric or organoboronic acid molecules to give a neutral, stable, and kinetically very inert clathrochelate molecule. The only stable product is removed from the reaction mixture and is inert in further transformations under mild (and in some cases, also under drastic) conditions.

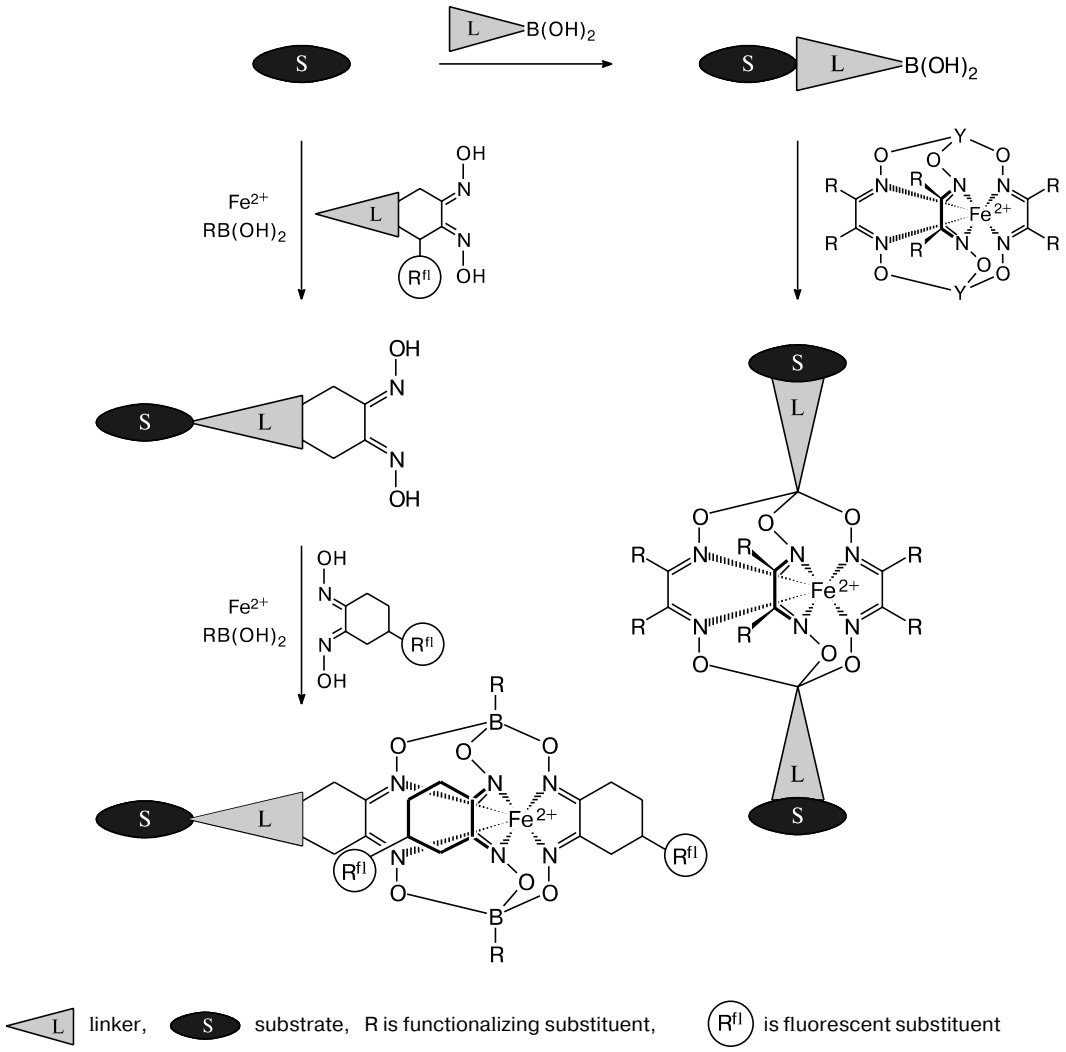
This absolutely unique reaction, resulting in the formation of a big molecule with a low polarity from simple nontoxic abiogenic polar precursors, has no analogy in natural systems. The use of this reaction opens up prospects for the design of linker systems, which can be obtained under specific conditions without overlapping with biogenic processes.

It is also noteworthy that iron tris-dioximate clathrochelate complexes are intensively colored in the visible region of the spectrum with absorption peaks at 400—500 nm ($\varepsilon \approx 10^4$ mol^{-1} L cm^{-1}) and have clear-cut redox characteristics, namely, one-electron oxidation waves over a broad range, from 400 to 1400 mV, the potentials of which are determined by ribbed functionalization.

At nearly neutral pH, the self-assembly reaction of clathrochelate has the first order with respect to boric or boronic acid and the iron(II) ion and the third order with respect to α-dioxime.[28—33] This reaction can be used as a linker reaction for binding the substrates modified by boronic or α-dioximate fragments or their combination when the other components (iron(II) ion, organoboronic acid or α-dioxime) are present in the system. It is important that the formation of the clathrochelate bridging fragment, whose stability is comparable with a covalent bond stability, between the boronic linkers according to Scheme 20 does not affect other functional fragments (amino, thiol, and carboxy groups). This system can be used for immobilization and affinity binding of macromolecules, antibodies, and enzymes, substrate linking to the active sites of these enzymes, and fluorescence probes.

A promising application of clathrochelate linkers is mimicking of ligases and binding of nucleotide sequences

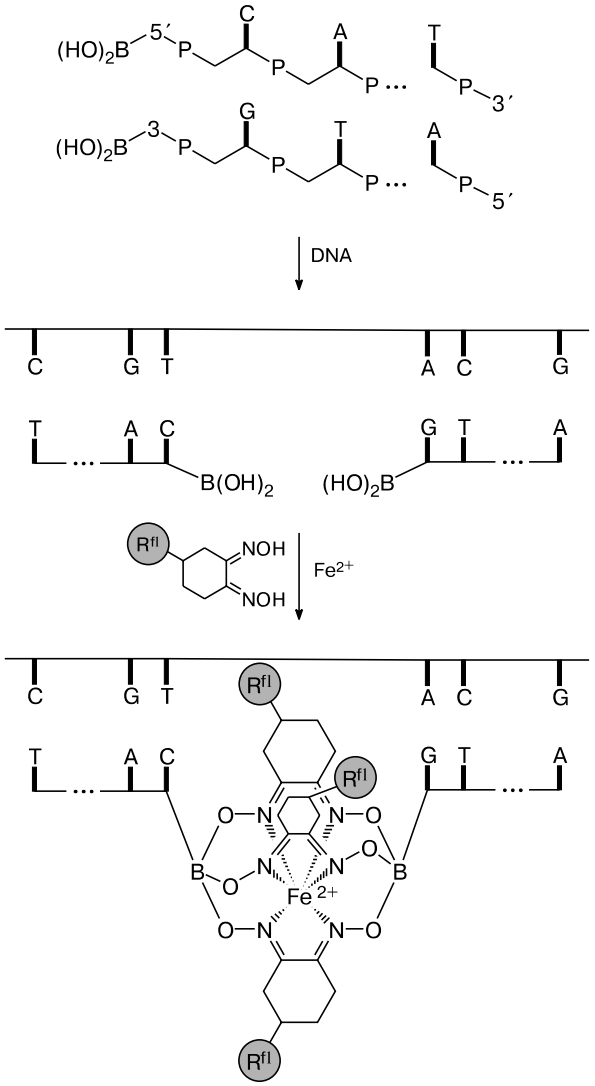
Scheme 20



to a single-stranded DNA template. The matching of oligonucleotide sequences to single-stranded DNA brings the reaction sites (boronic acids, Scheme 21) or α-dioxime fragments (Scheme 22) closer to each other; in view of the self-assembly kinetics, this should results in highly selective binding of oligonucleotide sequences by the clathrochelate linker. It is also significant that the binding process is controlled by a third component (iron(II) ion, α-dioxime, and organoboronic acid) and is an irreversible nonequilibrium process. By selecting the concentrations of reacting components, it is possible to reach an effective reaction only in the presence of complementary interaction of modified oligonucleotides with single-stranded nucleic acid. Clathrochelate linker is formed only in the presence of a third component (the third α-dioxime molecule or two boronic acid molecules, which may be functionalized by fluorescent substituents). Thus, this self-assembly reaction can be used in fluorescence testing systems (probes).

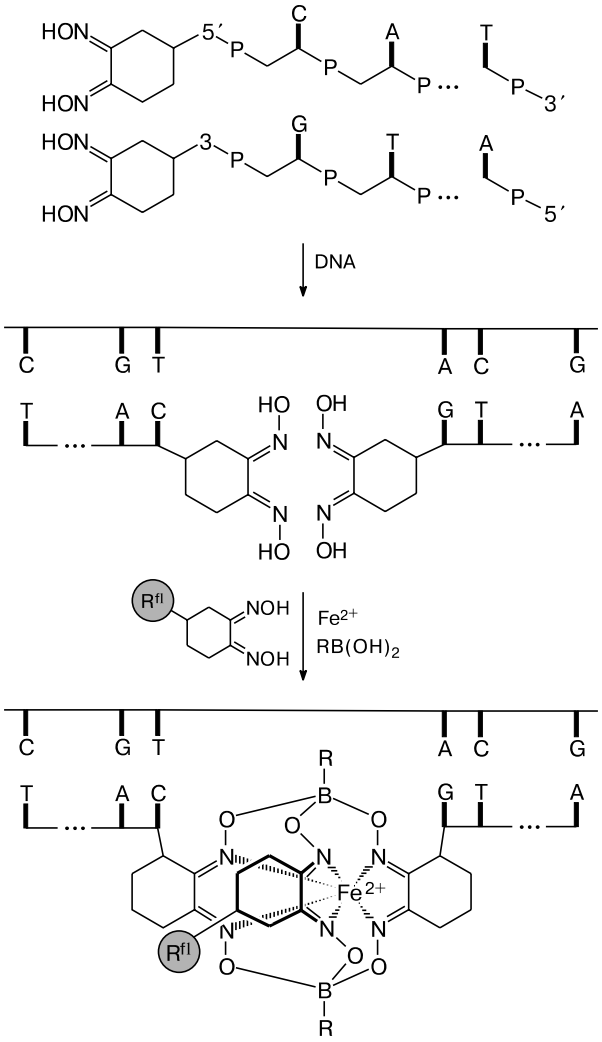
Macrobicyclic cobalt(II) polyamine complexes with apical groups functionalized with polycyclic aromatic substituents were synthesized[75,76] as a new type of DNA intercalators. It was assumed that these systems would demonstrate a synergistic effect in DNA binding both through intercalation of planar apical fragments and through electrostatic interaction of the cationic macrobicyclic complex with the DNA polyanion. Two main approahes have been used for the synthesis: reductive alkylation of aminosarcophaginates or their homologs with anthracene-9-carbaldehyde (Scheme 23) and the Mannich macrobicyclization of lacunary complexes on treatment with formaldehyde and aryl methyl ketones as

Scheme 21



A is adenine, C is cytosine, G is guanine, T is thymine;
R^{fl} is fluorescent substituent.

Scheme 22



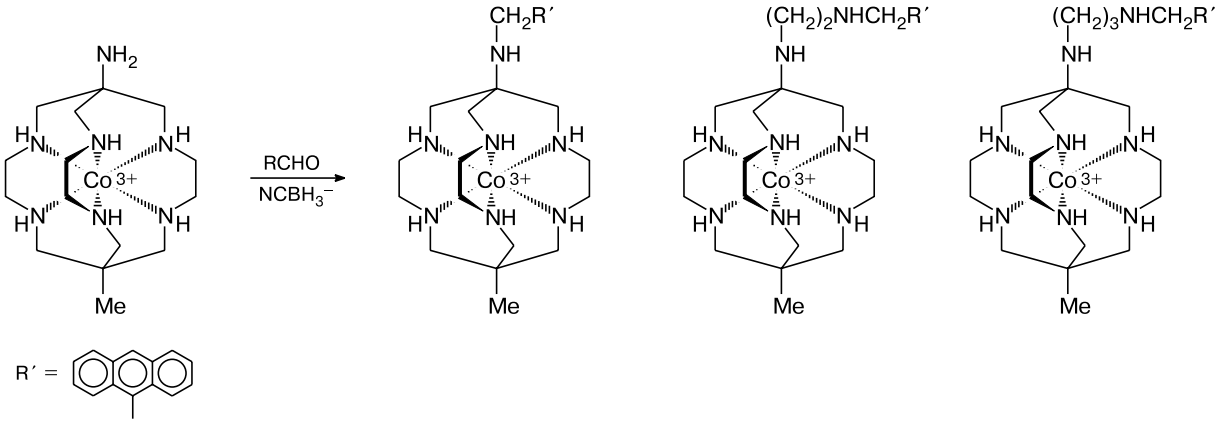
A is adenine, C is cytosine, G is guanine, T is thymine;
R^{fl} is fluorescent substituent.

compounds with active methylene groups (Scheme 24). The intermediate highly electrophilic methyleneimine cations react with the methylene component (aryl methyl ketone) along two pathways to give either symmetrical sarcophaginates with aryl ketone apical substituents upon threefold alkylation of the ketone (1 : 3 : 1 type condensation) or unsaturated aryl-substituted sarcophaginate with an apical substituent in the side chain upon twofold alkylation and intramolecular cyclization (1 : 2 : 1 type condensation), see Scheme 24.

In all cases, except for 9-acetylanthracene, the reaction yielded both C_3-symmetric amine clathrochelates with an apical aromatic substituent and imino sarcophaginates with substituents in the methylene fragment.[75,76] In the case of 9-acetylanthracene, only C_3-symmetric clathrochelate with an aromatic substituent at the apical carbon atom is formed because of steric hindrance. Both types of compounds (except for the anthraquinone complex) were reduced with $NaBH_4$ in aqueous solutions. The nitrophenylsarcophaginate was also reduced with metallic tin in dilute HCl to give an aminophenylclathrochelate ligand derivative, which is capable of subsequent formation of conjugates with antibodies (see Section 1.1).[24]

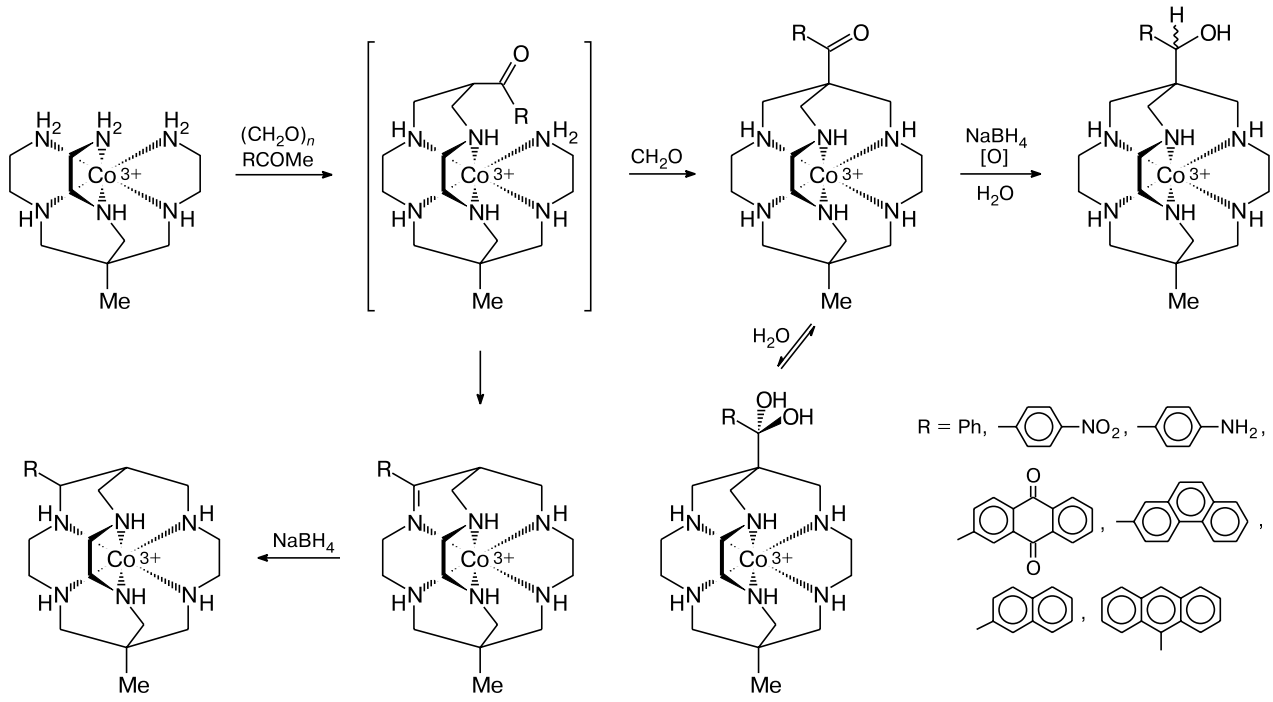
The hybrid functionalized cobalt clathrochelates have physical and physicochemical properties that differ essentially from those of the starting compounds. In particular, the anthracenyl-containing complex, unlike anthracene, is fairly soluble in water and can be intercalated in the DNA structure (Fig. 9). An additional stability of the intercalate is caused by the electrostatic interac-

Scheme 23



RCHO is anthracene-9-carbaldehyde

Scheme 24



tion of the terminal anionic phosphate groups of DNA and the clathrochelate trication. Indeed, spectrophotometric titration showed the presence of intercalative binding between nucleotide DNA pairs and the apical anthracenyl-containing substituent in the cobalt(III) cage complex (the calculated binding constant is approximately 10^5 mol cm^{-3}).[27] The anthracene, phenanthrene, and anthraquinone cobalt(III) clathrochelates shown in Scheme 24 bind to DNA in this intercalative manner.

Moreover, reductive alkylation (Scheme 25) afforded trinuclear nonacationic cobalt(III) tris-sarcophaginate able to cleave DNA upon photochemical UV excitation by charge transfer from the clathrochelate ligand to the encapsulated cobalt(III) ion. This generates a Co^{2+} ion and the cage ligand radical cation, which is a strong oxidant and can cleave DNA. However, in the authors´ opinion,[27] this trinuclear tris-clathrochelate has not intercalated into the DNA structure but forms an ionic associate as a nine-charged cation, being oriented along the DNA major groove.

The binding of these cage complexes to DNA is not regiospecific; specific binding to the target DNA fragments requires additional functionalization of this type of molecules with oligopeptides, oligonucleotides, or polyamines.[27]

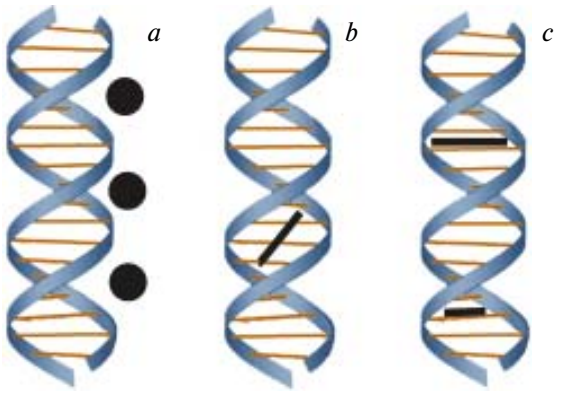
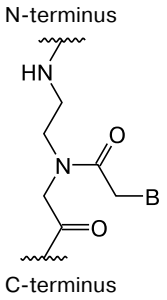


Fig. 9. Modes of clathrochelate binding to DNA fragments:[27] (*a*) electrostatic binding, (*b*) binding to the DNA grooves, (*c*) intercalation into the DNA structure.
Note. Fig. 9 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

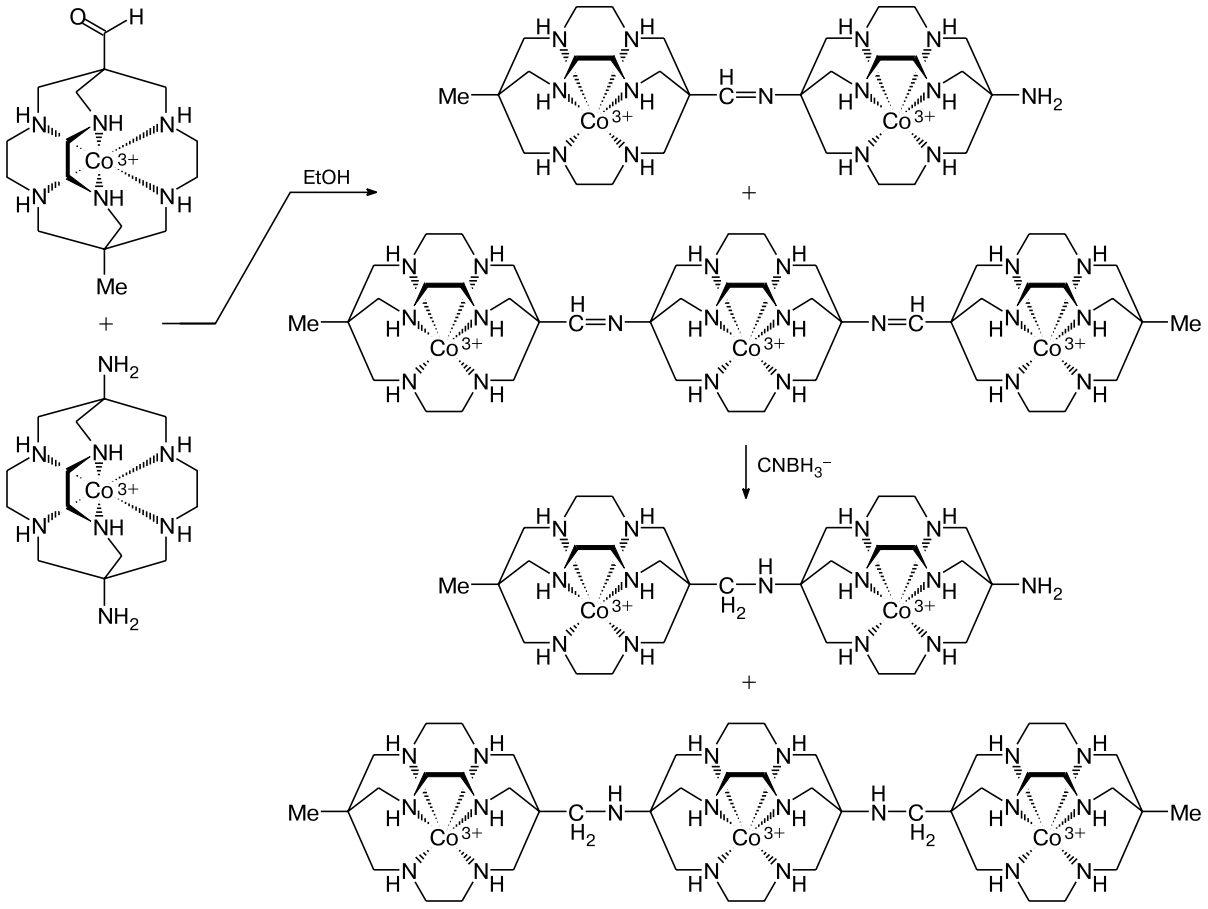
Ruthenium(II) polyazomethine complexes with unique photophysical properties were used for selective cleavage of nucleic acids.[77—81] Tris-dioximate ruthenium(II) clathrochelates with ribbed fragments functionalized for effective binding to specified DNA sites (Scheme 26) were obtained as potential agents for the cleavage (sequencing) of nucleic acid chains through photoexcitation of the encapsulated Ru^{2+} ion (see Ref. 12).

The interaction of a number of ribbed-functionalized clathrochelates with a spacer substituent containing a terminal amino group with peptidonucleic acids (PNA), which are DNA analogs with the *N*-(2-aminoethyl)glycine fragment instead of the sugar-phosphate backbone, was also studied.[82]

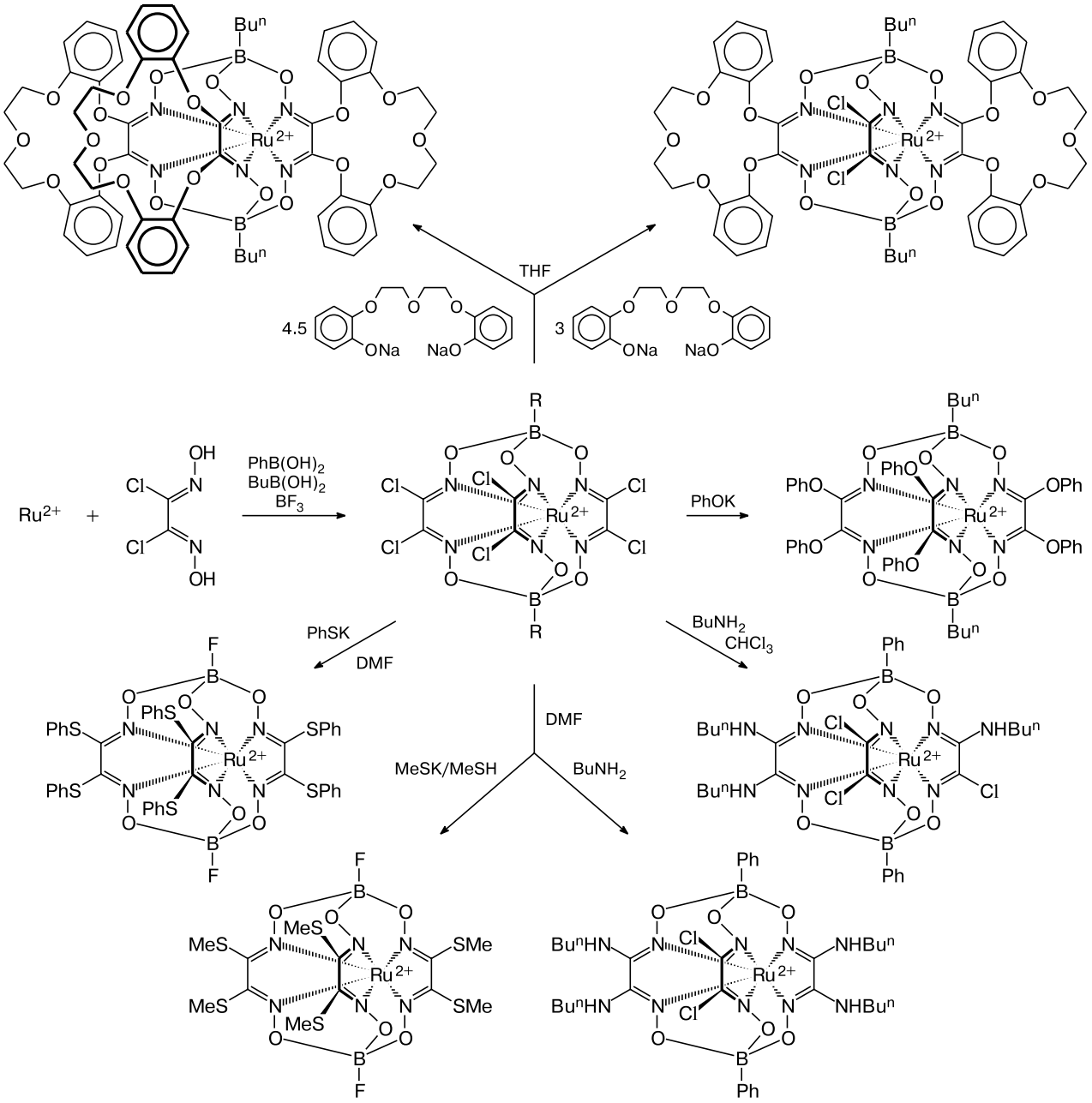


B is the nucleic base.

Scheme 25

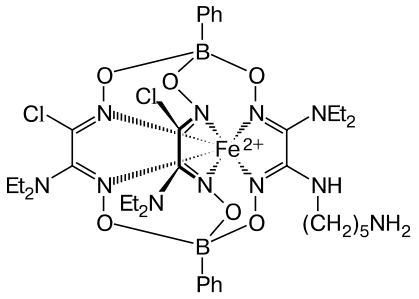


Scheme 26



The advantages of PNA over DNA include higher chemical stability and the capability of specific oligonucleotide binding. Therefore, PNA are used for analysis of nucleic acids and in control of gene expression *in vitro* and, in some cases, also *in vivo*. Conjugation of metal complexes to the PNA terminal sites allowed one to change their optical and electronic properties, to immobilize them chemically on the surface, and to control the binding properties of PNA to DNA, and also in metal ion-catalyzed reactions on DNA templates.

Synthetic routes were developed to both previously unknown α-dioxime—PNA conjugates (*C*- or *N*-terminally modified) and multistranded (because of formation of stable d-metal bis- and tris-α-dioximates) complexes of these conjugates with metal ions in solutions.[82]



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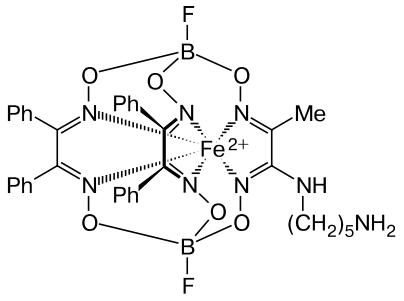


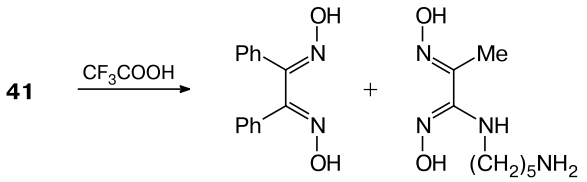
41

These multistranded PNA can be used as building blocks for nanostructures *via* their self-assembly in the presence of complementary oligonucleotides.

Conjugation of α-dioxime to PNA requires protection of the oxime groups, because of side acylation during the PNA synthesis, in particular, monomer coupling, or during acylation with acetic anhydride at the final stage (capping). Therefore, α-dioximes were protected by previously synthesized cage complexes with an encapsulated metal ion.[82] In the clathrochelate complexes, the donor nitrogen atom of dioximate chelate fragment was protected by coordination to the Fe^{2+} ion, while the oxime oxygen atom was protected through covalent binding to the apical tetrahedral boron atom. The linker fragment with the terminal amino group serves for binding of these complexes to PNA.

Clathrochelates **40** and **41** are fully cleaved in the trifluoroacetic acid—*m*-cresol system over a period of approximately 4 min to give free α-dioximes (Scheme 27). No degradation products of these α-dioximes were found in the reaction mixture after 90 min. Thus, the dioximate fragments in the clathrochelate—PNA conjugates can be fully deprotected without side reactions during standard cleavage—PNA deprotection procedure. Moreover, clathrochelates **40** and **41** are stable in the presence of piperidine (under conditions of cleavage of the fluorenylmethoxycarbonyl *N*-protecting group) and in the acetic anhydride—lutidine system (the capping step in the PNA synthesis). This favorably distinguishes the proposed protection scheme[82] from that based on acylation of oximes, which are only partially deprotected in trifluoroacetic acid and are highly sensitive toward of nucleophiles.

Scheme 27



Compounds **40** and **41** can be attached to the *N*-terminal PNA sites. The final PNA cleavage from the polymeric matrix and deprotection gave the target α-dioxime—PNA conjugates in high yields (Scheme 28).

The α-dioxime—PNA conjugates may contain the lysine residue as the spacer (see Scheme 28).

Thus, an efficient and versatile method for conjugation to α-dioximes with *N*- and *C*-terminal PNA sites using clathrochelate complexes as the initial α-dioxime-containing compounds has been developed.[82]

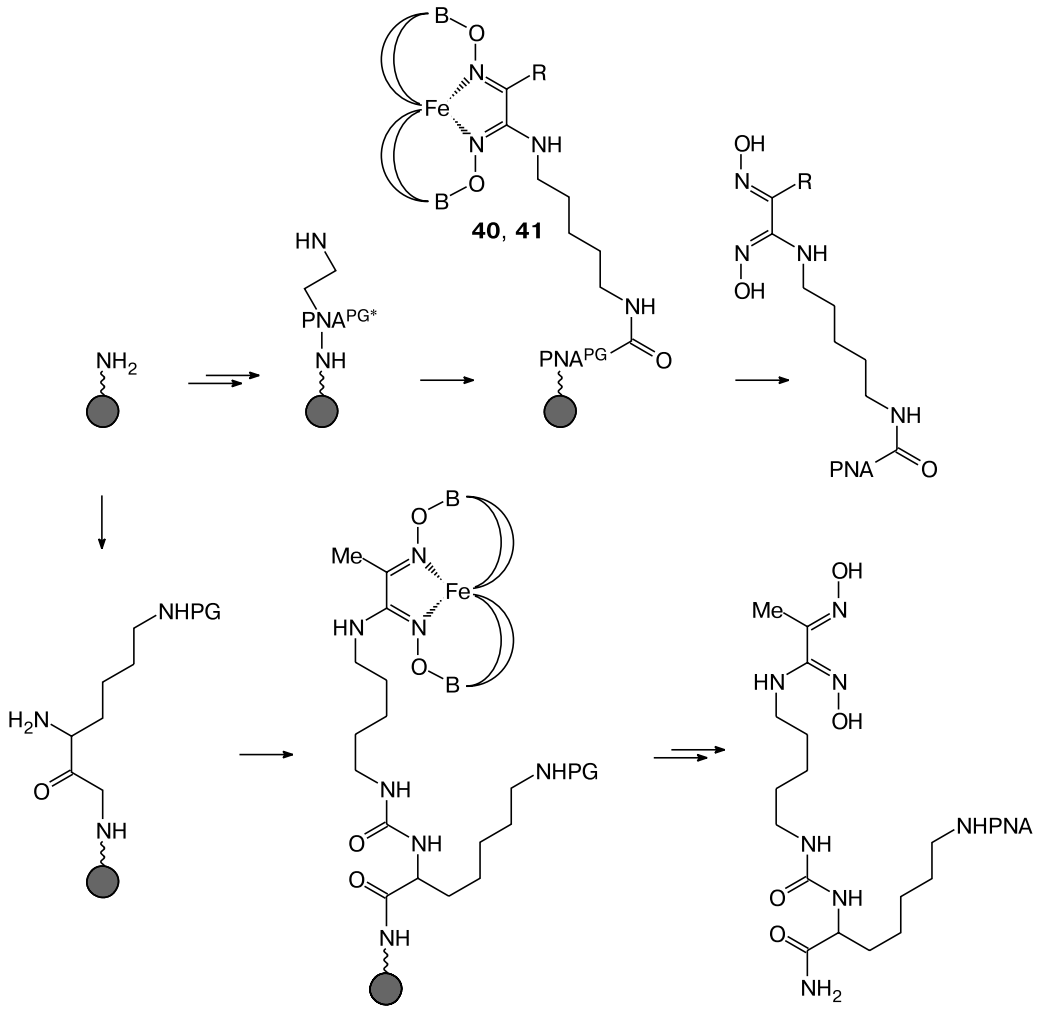
5. The use of specific molecular shape of metal cage complexes: design of viral inhibitors and analogy with fullerene-based inhibitors used in HIV therapy

Currently, the drug therapy of AIDS implies the suppression of one or several key stages of the life cycle of human immunodeficiency virus (HIV) by chemical compounds. Three key enzymes of the virus, namely, reverse transcriptase, integrase, and protease are known to be the prime targets for drugs.

The first two proteins are responsible for cell infection with the virus by reverse transcription of HIV RNA (reverse transcriptase) and integration of the resulting viral DNA in the host cell genome (integrase). The third protein (protease) accomplishes the post-translational processing of the viral polyproteins by splitting them into relatively short proteins. HIV protease inhibitors are efficient drugs for therapy of HIV-infected patients, and the development of novel types of available drugs for inhibiting the HIV protease is a key problem in the AIDS therapy.

HIV protease is a homodimer containing two identical 99 amino acid subunits.[83] The major role in enzyme functioning is played by two aspartic acid fragments located at the center of a hydrophobic cavity, which has a cylindrical shape and a sufficient size for accommodating six substrate amino acids. Other structural elements are two flexible β-hairpins confining the protein active site. Conformational changes in these moieties result in the protein switching from the state with "half-open" to the state with "closed" active site (Fig. 10).

Scheme 28



● Polymeric carrier, PG are protecting groups, PNA is peptidonucleic acid

R = NEt_2, Me

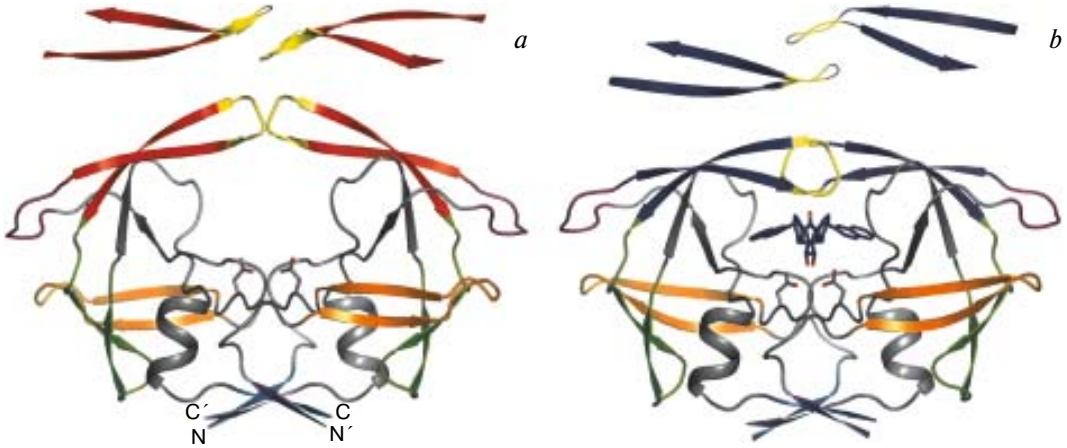
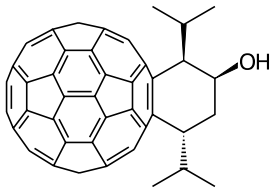


Fig. 10. Structure of HIV protease with the active site semi-open (*a*) and closed (*b*) upon inhibitor binding.[83]
Note. Fig. 10 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

Two types of HIV protease inhibitors were discovered: compounds preventing the assembly of the homodimeric protein from subunits and compounds targeting the active site. Using theoretical simulation of the enzyme—substrate interactions based on X-ray diffraction and NMR structural data, the target activity was predicted for a number of compounds. An interesting finding was the inhibition of HIV protease by C_{60} fullerene derivatives (see Ref. 84). Since the diameter of the HIV protease active site shaped as an oblong cylinder is approximately 10 Å, which corresponds to the C_{60} fullerene diameter, and the hydrophobic surface of the cavity containing the active site should promote a substantial additional van der Waals interaction with hydrophobic fullerene derivatives, it has been suggested that these compounds could be used to prepare HIV protease inhibitors.[85] Some of the C_{60} derivatives with essential structural complementarity to the active site cavity[85] have been synthesized and their low inhibition activity has been detected.[86] The inhibition constants for C_{60} derivatives were too low compared to those of drugs that are currently used in clinical practice. Therefore,[87] the structures of substituted fullerene molecule with higher enzyme affinity have been modeled using the fact that the substrate binding site is not a perfect cylinder but has an elliptical cross-section. Therefore, additional nonpolar substituents have been introduced into the inhibitor molecule in attempt to increase the efficiency of hydrophobic contacts. As a result of theoretical modeling,[87] C_{60} fullerene derivatives with predicted enzyme—substrate binding constant higher than those of known fullerene-based inhibitors have been designed. Two compounds **42** and **43** having the highest predicted binding constants were synthesized; they showed a 50 times higher *in vitro* activity than their known analogs.[87] The surface area of hydrophobic interaction, which is a theoretical criterion for estimating the possible binding constant, found for these compounds is comparable to those typical of HIV protease inhibitors used in clinical practice. Nevertheless, the practical use of the synthesized compounds in drug therapy is impossible, because of their hydrophobic properties.



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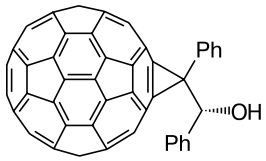

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A task to functionalize C_{60} fullerene derivatives with polar groups trying to increase their solubility in water and, simultaneously, to retain the hydrophobicity of the major part of the molecule to ensure a high binding constant has been solved in recent studies.[88,89] Cationic C_{60} fullerene derivatives with fairly high water solubility and a high HIV protease inhibition constant were designed and then synthesized. It was also shown that the presence of the positively charged fragment near the fullerene core increases the target activity, while the introduction of long-chain hydrophilic groups increases the cytotoxicity.

Theoretical analysis of structural rearrangements in the HIV protease active site upon binding of an inhibitor led to the following conclusions.[90] A special role in this process is played by two flexible β-hairpins (flaps) restricting the access to the substrate binding site. It was shown that binding of an effective inhibitor (in particular, a C_{60} fullerene derivative) can result in closure of the active site by the mobile flaps, structural rearrangements in the local environment of the bound inhibitor, and expelling of water molecules from the cavity containing the catalytic fragments of aspartic acid, which additionally increases the inhibitor binding constant.[90]

The results of these studies suggest a new idea, namely, the use of clathrochelate complexes as protease inhibitors. Probably, the ellipsoidal shape of their molecules allows one to inhibit the HIV protease active site with a cylindrical cavity more efficiently than the spherical functionalized fullerene molecules. The simulation using X-ray diffraction data for iron, ruthenium(II), and cobalt(II,III) cage complexes and also for some C_{60} fullerene derivatives has shown that a number of clathrochelates (in particular, those with adamantyl substituents in the apical positions, see Section 3.3.) has the same van der Waals volume as these fullerenes (~500—600 $Å^3$).

It is obvious that ribbed and apical functionalization of clathrochelate molecules aimed at efficient recognition of HIV protease active site can be accomplished much more easily than the synthesis of appropriate fullerene derivatives.

6. Conclusion

The chemical features of cage metal-centered structures determine the unique scope of their medicinal and biological applications. Cage complexes have unusual combinations of properties caused by the unique geometry of the macrobicycle, the presence of an encapsulated metal ion isolated inside the molecule, and unlimited opportunities for modification and functionalization of the periphery of these molecules, which are determined by various combinations of ribbed and apical groups. A number of cage complexes are formed spontaneously from simple, readily available precursors upon highly specific reactions, which may be defined as self-assembling processes in terms of supramolecular chemistry. The procedures based on the synthetic techniques of coordination and supramolecular chemistry make these unique compounds synthetically available. The useful properties

of cage complexes found previously, studied currently, and expected in the future determine their enormous potential in medicinal and biological studies and in practical medicine.

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References

1. Y. Z. Voloshin, N. A. Kostromina, and R. Krämer, *Clathrochelates: Synthesis, Structure and Properties*, Elsevier, Amsterdam, 2002.
2. Y. Z. Voloshin, O. A. Varzatskii, T. E. Kron, V. K. Belsky, V. E. Zavodnik, and A. V. Palchik, *Inorg. Chem.*, 2000, **39**, 1907.
3. A. B. Burdukov, E. G. Boguslavskii, V. A. Reznikov, N. V. Pervukhina, M. A. Vershinin, Ya. Z. Voloshin, O. A. Varzatskii, and Yu. N. Bubnov, *Izv. Akad. Nauk. Ser. Khim.*, 2005, 1097 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1125].
4. Y. Z. Voloshin, O. A. Varzatskii, S. V. Korobko, V. Y. Chernii, S. V. Volkov, L. A. Tomachynski, V. I. Pehn´o, M. Y. Antipin, and Z. A. Starikova, *Inorg. Chem.*, 2005, **44**, 822.
5. Y. Z. Voloshin, O. A. Varzatskii, S. V. Korobko, M. Y. Antipin, I. I. Vorontsov, K. A. Lyssenko, D. I. Kochubey, S. G. Nikitenko, and N. G. Strizhakova, *Inorg. Chim. Acta*, 2004, **357**, 3187.
6. Y. Z. Voloshin, O. A. Varzatskii, A. I. Stash, V. K. Belsky, Y. N. Bubnov, I. I. Vorontsov, K. A. Potekhin, M. Y. Antipin, and E. V. Polshin, *Polyhedron*, 2001, **20**, 2721.
7. Ya. Z. Voloshin, O. A. Varzatskii, I. I. Vorontsov, M. Yu. Antipin, A. Yu. Lebedev, A. S. Belov, and A. V. Pal´chik, *Izv. Akad. Nauk. Ser. Khim.*, 2003, 1469 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 1552].
8. Y. Z. Voloshin, O. A. Varzatskii, A. V. Palchik, I. I. Vorontsov, M. Y. Antipin, and E. G. Lebed, *Inorg. Chim. Acta*, 2005, **358**, 131.
9. Y. Z. Voloshin, O. A. Varzatskii, A. V. Palchik, Z. A. Starikova, M. Y. Antipin, E. G. Lebed, and Y. N. Bubnov, *Inorg. Chim. Acta*, 2006, **359**, 553.
10. Y. Z. Voloshin, O. A. Varzatskii, A. V. Palchik, A. I. Stash, and V. K. Belsky, *New J. Chem.*, 1999, **23**, 355.
11. Y. Z. Voloshin, O. A. Varzatskii, A. V. Palchik, N. G. Strizhakova, I. I. Vorontsov, M. Y. Antipin, D. I. Kochubey, and B. N. Novgorodov, *New J. Chem.*, 2003, **27**, 1148.
12. Y. Z. Voloshin, O. A. Varzatskii, T. E. Kron, V. K. Belsky, V. E. Zavodnik, N. G. Strizhakova, V. A. Nadtochenko, and V. A. Smirnov, *Dalton Trans.*, 2002, 1203.
13. Ya. Z. Voloshin, O. A. Varzatskii, I. I. Vorontsov, M. Yu. Antipin, A. Yu. Lebedev, A. S. Belov, and N. G. Strizhakova, *Izv. Akad. Nauk. Ser. Khim.*, 2004, 92 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 92].
14. Y. Z. Voloshin, V. E. Zavodnik, O. A. Varzatskii, V. K. Belsky, A. V. Palchik, N. G. Strizhakova, I. I. Vorontsov, and M. Y. Antipin, *Dalton Trans.*, 2002, 1193.
15. Ya. Z. Voloshin, A. S. Belov, A. Yu. Lebedev, O. A. Varzatskii, M. Yu. Antipin, Z. A. Starikova, and T. E. Kron, *Izv. Akad. Nauk. Ser. Khim.*, 2004, 1171 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 218].
16. Y. Z. Voloshin, V. E. Zavodnik, O. A. Varzatskii, V. K. Belsky, I. I. Vorontsov, and M. Y. Antipin, *Inorg. Chim. Acta*, 2001, **321**, 116.
17. Ya. Z. Voloshin, O. A. Varzatskii, Z. A. Starikova, M. Yu. Antipin, A. Yu. Lebedev, and A. S. Belov, *Izv. Akad. Nauk. Ser. Khim.*, 2004, **53**, 1439 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1496].
18. N. N. Popova, I. G. Tananaev, S. I. Rovnyi, B. F. Myasoedov, *Usp. Khim.*, 2003, **72**, 115 [*Russ. Chem. Rev.*, 2003, **72** (Engl. Transl.)].
19. E. N. Treher, J. Gougoutas, M. Malley, A. D. Nunn, and S. E. Unger, *J. Labelled Compd. Radiopharm.*, 1986, **23**, 1118.
20. E. N. Treher, L. C. Francesconi, J. Z. Gougoutas, M. M. Maley, and A. D. Nunn, *Inorg. Chem.*, 1989, **28**, 3411.
21. K. E. Linder, M. Malley, J. Gougoutas, S. Unger, and A. D. Nunn, *J. Labelled Compd. Radiopharm.*, 1989, **26**, 54.
22. K. E. Linder, M. F. Malley, J. Z. Gougoutas, S. E. Unger, and A. D. Nunn, *Inorg. Chem.*, 1990, **29**, 2428.
23. D. Farrell, Kar. Gloe, Ker. Gloe, G. Goretzki, V. McKee, J. Nelson, M. Nieuwenhuyzen, I. Pal, H. Stephan, R. M. Town, and K. Wichmann, *Dalton Trans.*, 2003, 1961.
24. S. V. Smith, J. M. Harrowfield, N. M. Di Bartolo, and A. M. Sargeson, *Cryptate Compounds and Methods for Diagnosis and Therapy*, PCT Int. Appl. WO 00 40, 585 (Cl. C07D487/08) Publ. 13.07.2000.
25. T. A. Kaden, *Dalton Trans.*, 2006, 3617.
26. B. Korybut-Daszkiewicz, R. M. Hartshorn, and A. M. Sargeson, *Chem. Commun.*, 1989, 1375.
27. A. M. Sargeson, *Coord. Chem. Rev.*, 1996, **151**, 89.
28. Ya. Z. Voloshin and A. Yu. Nazarenko, *Dokl. Akad. Nauk Ukr. SSR, Ser. B* [*Rep. Ukr. Acad. Sci., Ser. B*], 1985, 34 (in Russian).
29. Ya. Z. Voloshin, N. A. Kostromina, and A. Yu. Nazarenko, *Zh. Obshch. Khim.*, 1990, **60**, 1481 [*J. Gen. Chem. USSR*, 1990, **60** (Engl. Transl.)].
30. Ya. Z. Voloshin, Yu. G. Noskov, M. I. Terekhova, and T. E. Kron, *Ukr. Khim. Zh.* [*Ukr. Chem. J.*], 1993, **59**, 231 (in Russian).
31. Ya. Z. Voloshin and Yu. G. Noskov, *Ukr. Khim. Zh.* [*Ukr. Chem. J.*], 1993, **59**, 347 (in Russian).
32. Y. Z. Voloshin, Y. G. Noskov, M. I. Terekhova, and T. E. Kron, *Polish J. Chem.*, 1996, **70**, 1229.
33. Y. Z. Voloshin, M. I. Terekhova, Y. G. Noskov, V. E. Zavodnik, and V. K. Belsky, *Anales de Qunmica Int. Ed.*, 1998, **94**, 142.
34. M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950.
35. *Boron-Neutron Capture Therapy for Tumor*, Ed. H. Hatanaka, Nisimura, Tokyo, 1986.

36. A. H. Soloway, W. Tjarks, B. A. Barnum, F. -G. Rong, R. F. Barth, I. M. Codogni, and J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
37. M. F. Hawthorne and A. Maderna, *Chem. Rev.*, 1999, **99**, 3421.
38. J. F. Valliant, K. J. Guenther, and A. S. King, *Coord. Chem. Rev.*, 2002, **232**, 173.
39. Y. Endo, T. Iijima, Y. Yamakoshi, H. Fukasawa, C. Miyaura, M. Inada, A. Kubo, and A. Itai, *Chem. Biol.*, 2001, **8**, 341.
40. R. A. Spryshkova, Dr. Sci. (Med.) Thesis, Blokhin Research Center of Oncology, Russian Academy of Medical Sciences, Moscow, 1999 (in Russian).
41. K. Yu. Zhizhin, E. A. Malinina, V. N. Mustyatsa, L. V. Goeva, O. O. Vovk, I. N. Polyakova, and N. T. Kuznetsov, *Koord. Khim.*, 2001, **27**, 613 [*Russ. J. Coord. Chem.*, 2001, **27** (Engl. Transl.)].
42. K. Yu. Zhizhin, E. A. Malinina, L. V. Goeva, V. N. Mustyatsa, I. N. Polyakova, and N. T. Kuznetsov, *Koord. Khim.*, 2001, **27**, 619 [*Russ. J. Coord. Chem.*, 2001, **27** (Engl. Transl.)].
43. V. N. Mustyatsa, K. Yu. Zhizhin, E. A. Malinina, L. V. Goeva, N. A. Votinova, and N. T. Kuznetsov, *Koord. Khim.*, 2001, **27**, 622 [*Russ. J. Coord. Chem.*, 2001, **27** (Engl. Transl.)].
44. K. Yu. Zhizhin, L. V. Goeva, N. A. Votinova, and N. T. Kuznetsov, *Koord. Khim.*, 2001, **27**, 625 [*Russ. J. Coord. Chem.*, 2001, **27** (Engl. Transl.)].
45. K. Yu. Zhizhin, L. V. Goeva, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2002, **47**, 396 [*Russ. J. Inorg. Chem.*, 2002, **47** (Engl. Transl.)].
46. K. Yu. Zhizhin and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2002, **47**, 401 [*Russ. J. Inorg. Chem.*, 2002, **47** (Engl. Transl.)].
47. K. Yu. Zhizhin, E. A. Malinina, M. V. Lisovskii, I. N. Polyakova, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2002, **47**, 1279 [*Russ. J. Inorg. Chem.*, 2002, **47** (Engl. Transl.)].
48. K. Yu. Zhizhin, V. N. Mustyatsa, E. Yu. Matveev, N. A. Votinova, I. N. Polyakova, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2003, **48**, 671 [*Russ. J. Inorg. Chem.*, 2003, **48** (Engl. Transl.)].
49. K. Y. Zhizhin, V. N. Mustyatsa, I. V. Polyakova, M. V. Lisovskii, and N. T. Kuznetsov, *Abstr. Int. Conf. «Boron Chemistry at the Beginning of XXI Century»*, Moscow, 2003, 147.
50. E. A. Malinina, I. N. Polyakova, K. Y. Zhizhin, V. V. Drozdova, L. V. Goeva, and N. T. Kuznetsov, *Abstr. Int. Conf. "Boron Chemistry at the Beginning of XXI Century"*, Moscow, 2003, 136.
51. K. Y. Zhizhin, V. N. Mustyatsa, N. A. Votinova, I. N. Polyakova, E. Y. Matveev, and N. T. Kuznetsov, *Abstr. Int. Conf. "Boron Chemistry at the Beginning of XXI Century"*, 2003, 151.
52. K. Yu. Zhizhin, V. N. Mustyatsa, E. A. Malinina, L. V. Goeva, I. N. Polyakova, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2004, **49**, 221 [*Russ. J. Inorg. Chem.*, 2004, **49** (Engl. Transl.)].
53. L. I. Ochertyanova, V. N. Mustyatsa, O. N. Belousova, K. Yu. Zhizhin, and N. T. Kuznetsov, *Neorg. Materialy* [*Inorg. Materials*], 2004, **40**, 188 (in Russian).
54. M. V. Lisovskii, N. V. Plyavnik, G. A. Serebrennikova, E. A. Malinina, K. Yu. Zhizhin, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2005, **50**, 33 [*Russ. J. Inorg. Chem.*, 2005, **50** (Engl. Transl.)].
55. K. Yu. Zhizhin, V. N. Mustyatsa, E. A. Malinina, I. N. Polyakova, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2005, **50**, 243 [*Russ. J. Inorg. Chem.*, 2005, **50** (Engl. Transl.)].
56. K. Yu. Zhizhin, E. A. Malinina, E. Yu. Matveev, and N. T. Kuznetsov, *Abstrs. Int. Conf. "KLASTERY-2006"* ("CLUSTERS-2006"), Astrakhan´, 2006, OYS20 (in Russian).
57. V. V. Drozdova, M. V. Lisovskii, I. N. Polyakova, K. Yu. Zhizhin, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2006, **51**, 1651 [*Russ. J. Inorg. Chem.*, 2006, **51** (Engl. Transl.)].
58. K. Yu. Zhizhin, V. N. Mustyatsa, E. A. Malinina, I. N. Polyakova, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2005, **50**, 33 [*Russ. J. Inorg. Chem.*, 2005, **50** (Engl. Transl.)].
59. K. Yu. Zhizhin, V. N. Mustyatsa, E. A. Malinina, E. Yu. Matveev, L. V. Goeva, I. N. Polyakova, and N. T. Kuznetsov, *Zh. Neorg. Khim.*, 2005, **50**, 243 [*Russ. J. Inorg. Chem.*, 2005, **50** (Engl. Transl.)].
60. E. Yu. Koldaeva, E. Yu. Grigor´eva, K. Yu. Zhizhin, and N. T. Kuznetsov, *Ross. Bioterapevt. Zh.* [*Russ. Biotherapeut. J.*], 2005, **4**, 24 (in Russian).
61. A. S. Mas´ko, E. Yu. Koldaeva, E. Yu. Grigor´eva, S. A. Petrov, K. Yu. Zhizhin, and N. T. Kuznetsov, *Ross. Bioterapeut. Zh.* [*Russ. Biotherapevt. J.*], 2005, **4**, 95 (in Russian).
62. E. Yu. Grigor´eva, E. Yu. Koldaeva, M. G. Naidenov, Yu. S. Stukalov, A. S. Mas´ko, M. V. Lisovskii, K. Yu. Zhizhin, N. T. Kuznetsov, and G. I. Borisov, *Ross. Bioterap. Zh.* [*Russ. Biotherap. J.*], 2007, **6**, 82 (in Russian).
63. M. V. Lisovskii, A. P. Zhdanov, K. Yu. Zhizhin, and N. T. Kuznetsov, *Ross. Bioterap. Zh.* [*Russ. Biotherap. J.*], 2007, **6**, 48 (in Russian).
64. N. T. Kuznetsov, *Russ. J. Inorg. Chem.*, 2002, **47**, Suppl. 1, S68.
65. Ya. Z. Voloshin, O. A. Varzatskii, K. Yu. Zhizhin, N. T. Kuznetsov, and Yu. N. Bubnov, *Izv. Akad. Nauk. Ser. Khim.*, 2006, 21 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 122].
66. S. Y. Erdyakov, Y. Z. Voloshin, E. G. Lebed, I. G. Makarenko, Y. N. Bubnov, and M. E. Gurskii, *Mendeleev. Commun.*, 2007, No. 5.
67. C. A. Behm, P. F. L. Boreham, I. I. Greaser, B. Korybut-Daszkiewicz, D. J. Maddalena, A. M. Sargeson, and G. M. Snowdon, *Austral. J. Chem.*, 1995, **48**, 1009.
68. C. A. Behm, I. I. Creaser, B. Korybut-Daskiewicz, R. J. Geue, A. M. Sargeson, and G. W. Walker, *Chem. Commun.*, 1993, 1844.
69. V. A. Roginskii, *Phenol´nye antioxidanty: reaktsionnaya sposobnost´ i effektivnost´* [*Phenolic Antioxidants: Reactivity and Efficiency*], Nauka, Moscow, 1988 (in Russian).
70. E. R. Milaeva, *Izv. Akad. Nauk. Ser. Khim.*, 2001, 549 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 573].
71. E. R. Milaeva, *Ross. Khim. Zh.*, 2004, 20 [*Mendeleev Chem. J.*, 2004 (Engl. Transl.)].
72. D. B. Shpakovskii, E. R. Milaeva, A. V. Fionov, A. V. Dolganov, T. V. Magdesieva, A. S. Belov, and Ya. Z. Voloshin, *Abstrs. Int. Conf. "KLASTERY-2006"* ("CLUSTERS-2006"), Astrakhan´, 2006, P90 (in Russian).
73. N. M. Emanuel´, E. T. Denisov, and Z. K. Maizus, *Tsepnye reaktsii okisleniya hydrocarbonov v zhidkoi faze* [*Chain Oxidation of Hydrocarbons in the Liquid Phase*], Nauka, Moscow, 1965 (in Russian).

74. Y. Z. Voloshin, O. A. Varzatskii, A. S. Belov, A. Y. Lebedev, I. S. Makarov, M. E. Gurskii, M. Y. Antipin, Z. A. Starikova, and Y. N. Bubnov, *Inorg. Chim. Acta*, 2007, **360**, 1543.
75. R. J. Geue, B. Korybut-Daszkiewicz, and A. M. Sargeson, *Chem. Commun*., 1996, 1569.
76. P. M. Angus, A. M. T. Bygott, R. J. Geue, B. Korybut-Daszkiewicz, A. W. H. Mau, A. M. Sargeson, M. M. Sheil, and A. C. Willis, *Chem. Eur. J*., 1997, **3**, 1283.
77. K. E. Erkkila, D. T. Odom, and J. K. Barton, *Chem. Rev*., 1999, **99**, 2777.
78. I. V. Yang and H. H. Thorp, *Inorg. Chem*., 2000, **39**, 4969.
79. E. D. A. Stemp and J. K. Barton, *Inorg. Chem*., 2000, **39**, 3868.
80. S. I. Khan, A. E. Beilstein, M. Sykora, G. D. Smith, X. Hu, and M. W. Grinstaff, *Inorg. Chem*., 1999, **38**, 3922.
81. D. Z. M. Coggan, I. S. Haworth, P. J. Bates, A. Robinson, and A. Rodger, *Inorg. Chem*., 1999, **38**, 4486.
82. A. Mokhir, R. Krdmer, Y. Z. Voloshin, and O. A. Varzatskii, *Bioorg. Med. Chem. Lett*., 2004, **14**, 2927.
83. V. Hornak, A. Okur, R. C. Rizzo, and C. Simmerling, *Proc. Natl. Acad. Sci. USA*, 2006, **103**, 915.
84. R. F. Schinazi, R. Sijbesma, G. Srdanov, C. L. Hill, and F. Wudl, *Antimicrob Agents Chemother*., 1993, **37**, 1707.
85. S. H. Friedman, D. L. DeCamp, R. P. Sijbesma, G. Srdanov, F. Wudl, and G. L. Kenyon, *J. Am. Chem. Soc*., 1993, **115**, 6506.
86. R. Sijbesma, G. Srdanov, F. Wudl, J. A. Castoro, C. Wilkins, S. H. Friedman, D. L. DeCamp, and G. L. Kenyon, *J. Am. Chem. Soc*., 1993, **115**, 6510.
87. S. H. Friedman, P. S. Ganapathi, Y. Rubin, and G. L. Kenyon, *J. Med. Chem*., 1998, **41**, 2424.
88. S. Marchesan, T. Da Ros, G. Spalluto, J. Balzarini, and M. Prato, *Bioorg. Med. Chem. Lett*., 2005, **15**, 3615.
89. S. Bosi, T. Da Ros, G. Spalluto, J. Balzarini, and M. Prato, *Bioorg. Med. Chem. Lett*., 2003, **13**, 4437.
90. Z. Zhu, D. I. Schuster, and M. E. Tuckerman, *Biochemistry*, 2003, **42**, 1326.

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