Derivatives of the *closo*-dodecaborate anion and their application in medicine

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The paper presents a comparative analysis of the possibilities and characteristic features of the application of various polyhedral boron compounds, *viz.*, the *closo*-decaborate anion $[B_{10}H_{10}]^{2-}$, the *closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$, the carba-*closo*-dodecaborate anion $[CB_{11}H_{12}]^{-}$, carboranes $C_2B_{10}H_{12}$, and the bis(dicarbollide) complexes $[M(C_2B_9H_{11})_2]^{-}$ (M = Fe, Co, or Ni), in boron neutron capture therapy (BNCT) for cancer. The requirements on compounds used in BNCT are formulated and the advantages of the application of the *closo*-dodecaborate anion are considered. The data on the synthesis of various derivatives of the *closo*-dodecaborate anion, which either already found use in BNCT or are most promising in this field, are summarized. The possibilities of the application of agents derived from the *closo*-dodecaborate anion in medical diagnostics are discussed.

Key words: *closo*-dodecaborate anion, application; boron neutron capture therapy for cancer; radioisotope diagnostics; X-ray imaging diagnostics.

The dodecahydro-*closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ was first synthesized by Hawthorne and Pitochelli in 1960.[1] This synthesis has been the brilliant verification of the results of quantum-chemical calculations performed by Longuet-Higgins and Roberts,[2] who predicted that the icosahedral boron hydride system will be stable only as the double charged $[B_{12}H_{12}]^{2-}$ anion. Not only boron chemists but also physicians waited for the synthesis of the $[B_{12}H_{12}]^{2-}$ anion. The reason is that the concept of an original method for the cancer treatment, *viz.*, boron neutron capture therapy (BNCT), was proposed by Locher[3] as early as 1936 (Scheme 1), and the main requirements of this method were formulated by the early 1960s.

Scheme 1

$$^{10}B + {}^{1}n \rightarrow [^{11}B] \xrightarrow{6\%} {}^{4}He + {}^{7}Li + 2.79\ MeV$$
$$[^{11}B] \xrightarrow{94\%} {}^{4}He + {}^{7}Li + 2.31\ MeV + \gamma\ (0.48\ MeV)$$

Boron neutron capture therapy is based on selective accumulation of the nonradioactive ^{10}B isotope in cancer cells followed by their treatment with the thermal neutron flux. Irradiation affords high-energy fission products, which are characterized by the short effective range in tissue comparable with the cell size. This allows one to selectively destroy tumor cells without affecting the surrounding healthy tissues. In idea, only tumor cells will be destroyed, including very small metastases, without damage of healthy tissues in the irradiated bulk. The absence of a negative effect on the surrounding healthy tissues is attributed to the fact that the thermal neutron capture cross-sections of elements forming tissues are 4—7 orders of magnitude smaller than that of the ^{10}B isotope (Table 1).[4,5]

The resulting particles are equally lethal both for oxygenated and hypoxic cells. Sublethal and potentially lethal damages caused by these particles are not repaired,

Table 1. Thermal neutron capture cross-sections of isotopes characterized by the largest capture cross-sections and cross-sections of isotopes of some physiologically important elements

Isotope	Capture cross-section/barn	Isotope*	Capture cross-section/barn
^{10}B	$3.8 \cdot 10^3$	^{1}H (10.0)	0.33
^{113}Cd	$2.0 \cdot 10^4$	^{12}C (18.0)	$3.4 \cdot 10^{-3}$
^{149}Sm	$4.2 \cdot 10^4$	^{14}N (3.0)	1.8
^{151}Eu	$5.8 \cdot 10^3$	^{16}O (65.0)	$1.8 \cdot 10^{-4}$
^{155}Gd	$6.1 \cdot 10^4$	^{31}P (1.16)	0.18
^{157}Gd	$2.6 \cdot 10^5$	^{32}S (0.20)	0.53

* The average content in tissues (%) is given in parentheses.

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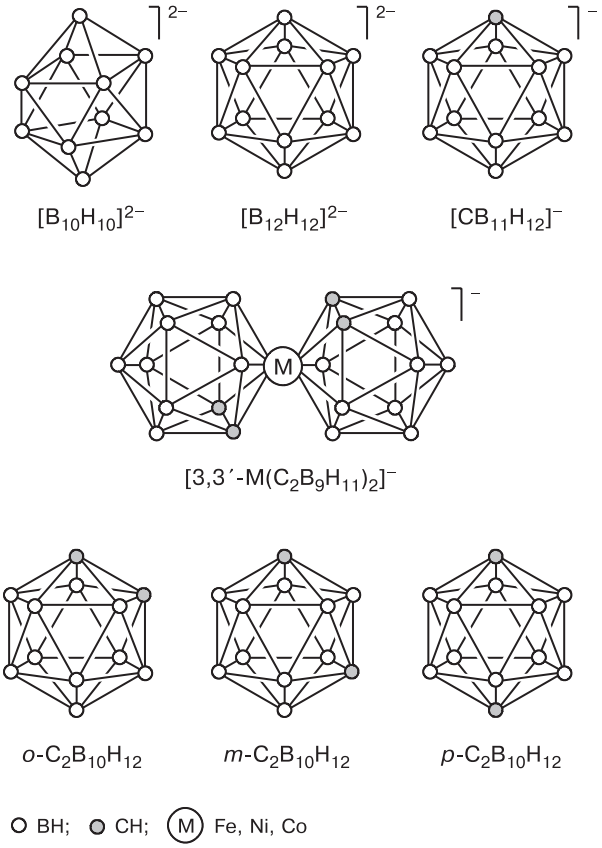
unlike damages caused by photon irradiation. Hence, BNCT is favorable for the treatment of tumors whose cells are characterized by a high level of DNA reparations, in particular, of melanomas or glyoblastomas.

To take advantages of the unique possibilities of BNCT in clinical practice, it is necessary to solve a number of complex chemical, biological, medical, and technical problems. The key step is the synthesis of boron-containing agents. It should be noted that, in spite of the fact that the thermal neutron capture cross-section of the ^{10}B isotope is smaller (see Table 1) than those of some other elements (^{113}Cd, ^{149}Sm, ^{151}Eu, ^{155}Gd, or ^{157}Gd), the ^{10}B isotope is virtually the alternativeless element for neutron capture therapy for cancer because it readily forms stable covalent compounds. At the same time, the synthesis of stable *in vivo* complexes of cadmium and f-elements, which are able to undergo modifications, is presently an intractable problem.

In addition to the selective accumulation in tumor cells, an essential requirement for compounds used in BNCT is that the concentration of the ^{10}B isotope should be equal to ~20—35 μg g^{-1} of the tumor, which provides the required therapeutic effect.[4] The first-generation agents (sodium borates, boric acid, and its derivatives), which were used in clinical trials in 1950s—the early 1960s, did not satisfy the above-mentioned criteria both with respect to selective accumulation in the tumor and the achievement of the desired therapeutic concentration.

The synthesis of stable polyhedral boron hydrides (see below) performed in 1960s gave new impetus to investigation in the area of BNCT. The possibility of modification of polyhedral boron hydrides by the replacement of H atoms with various functional substituents opens up the approach to the synthesis of compounds, which can be selectively accumulated in tumor cells, while the presence of ten or even more B atoms in a single molecule facilitates the attainment of the required therapeutic concentration in the tumor tissue.

Before proceeding to the detailed characterization of the major subject of the paper, *viz.*, the *closo*-dodecaborate anion, let us take a look at its close relatives, which can also be considered as potential starting compounds for the synthesis of BNCT agents. The closest relative, *viz.*, the decahydro-*closo*-decaborate anion $[B_{10}H_{10}]^{2-}$ (see Ref. 6), has the advantages much the same as those of its "elder brother," *viz.*, the *closo*-dodecaborate anion. Thus, it possesses high chemical and hydrolytic stability, high solubility in water in the form of sodium salts, and low toxicity (LD_{50} are 1.0 and 1.025 g kg^{-1} for $Na_2[B_{10}H_{10}]$ [7] and $Na_2[B_{12}H_{12}]$ [8], respectively), *i.e.*, the properties necessary for the design of pharmaceuticals. The chemical properties of the *closo*-decaborate anion are even more diversified because its core is composed of atoms with different coordination numbers. However, the $[B_{10}H_{10}]^{2-}$ anion attracts much less interest as the starting compound for the synthesis of BNCT agents as compared to the $[B_{12}H_{12}]^{2-}$ anion. There are three reasons for this fact. One formal reason is that the $[B_{10}H_{10}]^{2-}$ anion contains the smaller number of B atoms. The second main reason is the lack of preparative procedures for the synthesis of the *closo*-decaborate anion from commercially available ^{10}B-enriched compounds. Thus, the $[B_{10}H_{10}]^{2-}$ anion is generally prepared by the closure of the open boron core of decaborane $B_{10}H_{14}$, whereas the $[B_{12}H_{12}]^{2-}$ anion is produced in greater or lesser amounts in virtually all pyrolysis reactions of boron compounds, including isotopically enriched reagents, under reductive conditions. Besides, there is the historical reason. Thus, the mercapto derivative of the *closo*-dodecaborate anion, *viz.*, $Na_2[B_{12}H_{11}SH]$, quickly found use in clinical practice, which generated increased interest in the synthesis of other compounds based on this anion.



Among other representatives of the family of polyhedral boron hydrides, icosahedral carboranes, *viz.*, 1,2-, 1,7-, and 1,12-dicarba-*closo*-dodecaboranes(12) $C_2B_{10}H_{12}$ have attracted the most attention.[9—11] These compounds are isostructural and isoelectronic analogs of the $[B_{12}H_{12}]^{2-}$ anion and are derived from the latter by the formal replacement of two B atoms with C atoms. As the starting compounds for the synthesis of BNCT agents, icosahedral carboranes have the same drawbacks as the $[B_{10}H_{10}]^{2-}$ anion. In addition, high hydrophobicity of

the carborane cage is often responsible for poor solubility of the resulting compounds in water thus hindering their practical use. At the same time, the introduction of C atoms into the boron cage leads to a radical change in the chemical properties of carboranes as compared to those of the *closo*-dodecaborate anion. Thus, the H atoms bound to these C atoms exhibit pronounced acidic properties. This enables one to use conventional methods of organic chemistry due to which carboranes are particularly attractive for organic chemists engaged in the design of BNCT agents. A large number of carborane-containing analogs of biomolecules have been already synthesized.[12–14] However, the relative ease of procedures for the synthesis of functional derivatives does not compensate for the above-mentioned drawbacks of carborane systems.

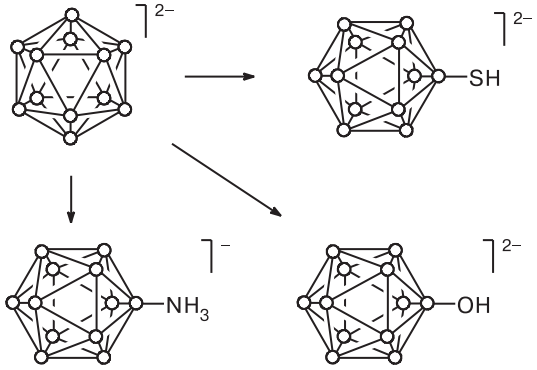
The carba-*closo*-dodecaborate anion $[CB_{11}H_{12}]^-$,[15,16] which is an intermediate between the *closo*-dodecaborate anion $[B_{12}H_{12}]^{2-}$ and carboranes $C_2B_{10}H_{12}$, combines the advantages of these compounds, *viz.*, solubility in water and the ability to undergo the replacement at the C atom. The chief drawback of the $[CB_{11}H_{12}]^-$ anion is an elaborate procedure for its synthesis, which hinders its practical use.

The bis(dicarbollide) complexes of Fe, Ni, and Co of composition $[3,3'\text{-}M(1,2\text{-}C_2B_9H_{11})_2]^-$ (M = Fe, Ni, or Co)[17,18] are characterized by a high boron content and are potential agents for the application in BNCT. However, the synthesis of these complexes is based on the use of *o*-carborane, which hampers their preparation from commercially available ^{10}B-enriched compounds. In addition, procedures for their functionalization[19] are not sufficiently developed.

Following the first-hand view of polyhedral boron hydrides, let us consider the *closo*-dodecaborate anion by itself from the viewpoint of its possible application in BNCT. The apparent advantages of this anion are the large number of B atoms in the structural unit and the numerous procedures available for its synthesis, including those from readily accessible ^{10}B-enriched compounds.[20] Among other advantages of this anion, which are of equal importance for its use in medicine, are its high solubility in water[21] and low toxicity.[8] One more advantage of the $[B_{12}H_{12}]^{2-}$ anion over carboranes, which is not evident at first sight, is the fact the H atoms at the B atoms can be easily replaced with halogen atoms.[22–24] This allows one to introduce a radiohalogen label into the resulting compounds, which significantly facilitates investigation of their distribution in organisms and pharmacokinetic studies.[25]

The chief drawbacks of the *closo*-dodecaborate anion as compared to carboranes is the lack of the reaction center (due to a high, nearly spherical, symmetry of the boron cage) and its high reactivity with respect to electrophilic agents. As a result, mixtures of products with different degrees of substitution are often obtained. However, the synthesis of BNCT agents generally requires the introduction of a single substituent (in the case of carboranes $C_2B_{10}H_{12}$ containing two reaction centers, it is often necessary to introduce blocking protective groups). Hence, the first step involves the introduction of an initial substituent into the *closo*-dodecaborate system. This reaction center can be subsequently modified. The iodine atom as well as the hydroxy, thio, or amino groups can serve as such initial substituents. Preparative procedures for the synthesis of these derivatives have been well developed (Scheme 2).

Scheme 2



Another problem associated with derivatives of the *closo*-dodecaborate anion is their low lipophilicity, which does not allow these compounds to overcome intracellular and membrane barriers. For example, it is known that sodium mercapto-*closo*-dodecaborate $Na_2[B_{12}H_{11}SH]$ cannot penetrate through the blood-brain barrier located at the interface between the blood channel and central nervous system. However, one would expect that the introduction of various lipophilic substituents into the *closo*-dodecaborate anion will facilitate its penetration through biological membranes. At the same time, a series of approaches are being developed to the selective delivery of boron-containing agents to brain tumors, such as the hyperosmotic modification or biochemical opening of the blood-brain barrier, electropermeabilization, and the direct intracerebral injection of pharmaceuticals.[26]

Following the consideration of the main advantages and drawbacks of the *closo*-dodecaborate anion, let us cover the syntheses of pharmaceuticals based on this anion. Sodium mercapto-*closo*-dodecaborate, which is presently used in clinical practice, belongs to the second-generation BNCT agents and does not exhibit high selectivity of accumulation.[5] It should also be noted that the mechanism of its accumulation in tumors remains unclear in spite of the numerous studies devoted to this problem. Because of this, investigations are being carried out on the directed synthesis of third-generation

BNCT agents based on compounds capable of being selectively accumulated in tumors. The spectrum of compounds, which can be potentially used as BNCT agents, is rather wide and includes low-molecular-weight compounds, such as porphyrins, phthalocyanines, cyclic thioureas, phosphates, phosphonates, depressants of the central nervous system (promazines, hydantoins, and barbiturates), compounds capable of binding DNA (alkylating agents, DNA intercalators, and polyamines), cellular building blocks (amino acids and short peptides, precursors of nucleic acids, lipids, and phospholipids), as well as more complex biomolecules with higher molecular weights, such as monoclonal and bispecific antibodies, growth factors, hormones, lipoproteins, liposomes, *etc*.

Taking into account a wide variety of compounds, which can be used as BNCT agents, let us formulate the major approaches to the synthesis of these compounds derived from the *closo*-dodecaborate anion. As mentioned above, to avoid the formation of oligomeric and polymeric associates of different types, the *closo*-dodecaborate anion must, as a rule, contain a single substituent (except for the syntheses of bis-intercalators or oligomeric fragments of a finite length). Another limitation is associated with the bulkiness of the *closo*-dodecaborate fragment and its charge. To avoid the undesirable steric and electronic consequences of the introduction of such a substituent for the binding of the biologically active (address) portion of the drug to the receptor in the tumor, the *closo*-dodecaborate fragment must, as a rule, be located at the periphery of the molecule and be bound to the active site of the molecule through a chain containing from three to five atoms. Generally, the initial substituent serves as a fragment of this chain. Hence, it seems reasonable to classify procedures for the synthesis of BNCT agents according to the type of the initially introduced substituent. We will now look at the principal properties of the initial derivatives of the *closo*-dodecaborate anion and the pathways of their transformations into various functional derivatives, which can be used for the synthesis of BNCT agents of various types.

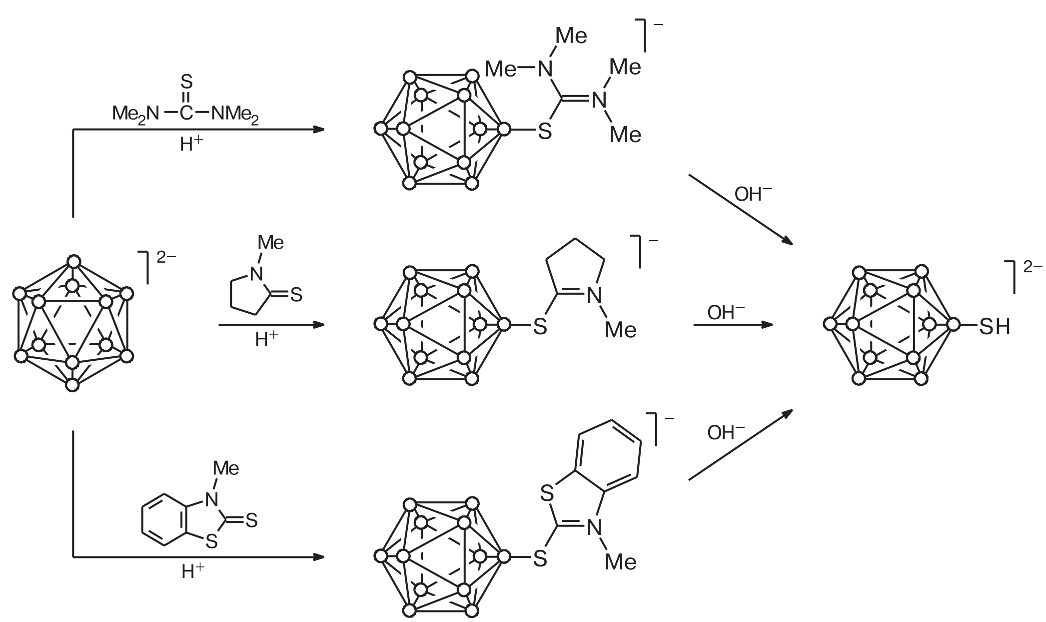
Derivatives with the boron—sulfur bond. Of polyhedral boron hydrides, only the mercapto-*closo*-dodecaborate anion $[B_{12}H_{11}SH]^{2-}$ found use in clinical practice. Therefore, procedures for its synthesis attract considerable interest. The mercapto-*closo*-dodecaborate anion was first prepared by the direct reaction of the acidic form of the *closo*-dodecaborate anion with H_2S under pressure.[27] However, this reaction affords a mixture of mono- and dimercapto derivatives as well as hydroxy derivatives of the *closo*-dodecaborate anion, which are difficult to separate.[28]

Later on,[28—31] more convenient procedures were developed for the synthesis of the monomercapto derivative. These procedures involve the reactions of the $[B_{12}H_{12}]^{2-}$ anion with different thioamides in an acidic medium followed by alkaline hydrolysis of the intermediates and are used for the routine preparation of the *closo*-dodecaborate anion (Scheme 3).

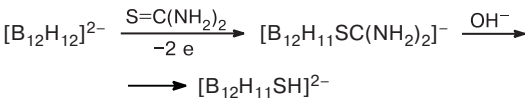
Another convenient method for the synthesis is based on electrochemical oxidation of the *closo*-dodecaborate anion in the presence of thiourea[32] (Scheme 4).

In aqueous solutions, the $[B_{12}H_{11}SH]^{2-}$ anion is readily oxidized with atmospheric oxygen to the

Scheme 3

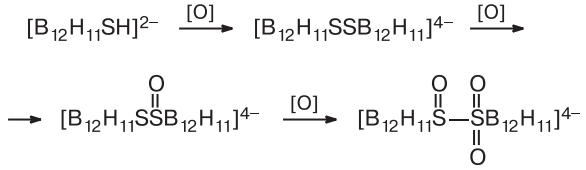


Scheme 4



corresponding disulfide $[B_{12}H_{11}SSB_{12}H_{11}]^{4-}$ (Scheme 5). Deeper oxidation affords thiolthione $[B_{12}H_{11}SS(O)B_{12}H_{11}]^{4-}$ and thionyl sulfone $[B_{12}H_{11}S(O)SO_2B_{12}H_{11}]^{4-}$.[33] Therefore, the preparations of sodium mercapto-*closo*-dodecaborate always contain an impurity of oxidized forms.[34]

Scheme 5

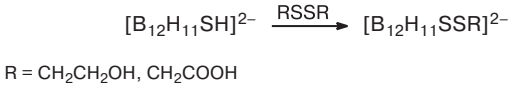


It is assumed that analogous transformations proceed *in vivo* after the injection of the agent. Hence, what particle is responsible for the accumulation of boron in tumor cells remains unclear. Trials on animals demonstrated that the disulfide form is more readily accumulated in tumors than the mercapto form, but it is more toxic.[35,36]

The reactions of the $[B_{12}H_{12}SH]^{2-}$ anion with organic disulfides give rise to the corresponding mixed disulfides[28] (Scheme 6).

This approach was applied to the synthesis of *N*-succinimidyl 3-(*closo*-dodecarboranyldithio)propionate, which is an efficient agent for boronation of proteins. This compound was used for the introduction of up to 1300 boron atoms per molecule of 17-1A monoclonal antibody, which reacts with human carcinoma cells[37] (Scheme 7).

Scheme 6

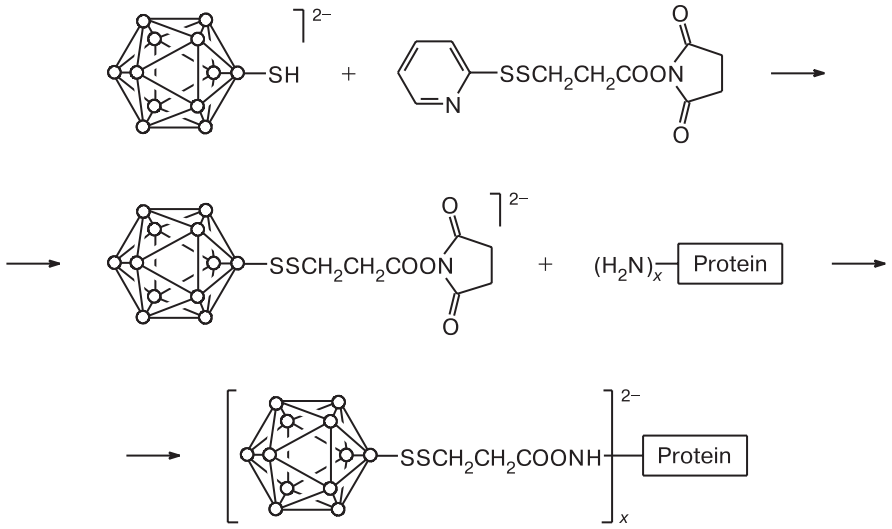


It should be noted that the mercapto-*closo*-dodecaborate anion by itself also can be used for boronation of antibodies through interactions with disulfides bridges of proteins. However, in this case, the efficiency of boronation is an order of magnitude lower, which may be associated with the fact that the disulfide bridges of polypeptides are less accessible due to the formation of a complicated quaternary structure as well as with steric hindrances due to the bulkiness of the *closo*-dodecaborate cage[38] (Scheme 8).

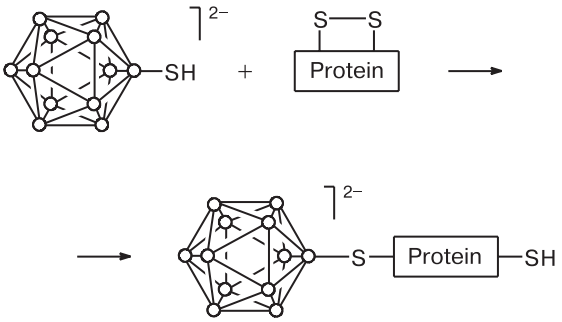
Another procedure, which is used for binding the mercapto-*closo*-dodecaborate anion to various biomolecules, is based on interactions between the $[B_{12}H_{11}SH]^{2-}$ anion and the fragments containing active double bonds, such as the allylic or maleimide groups, which are introduced into the biomolecule beforehand.[39–41]

Alkylation of the mercapto-*closo*-dodecaborate anion generally affords a mixture of mono- and disubstituted products. The depth of the reaction is determined by the ratio between the starting reagents as well as by the steric properties of the alkyl groups that are introduced[42–44] (Scheme 9).

Scheme 7



Scheme 8



Scheme 9

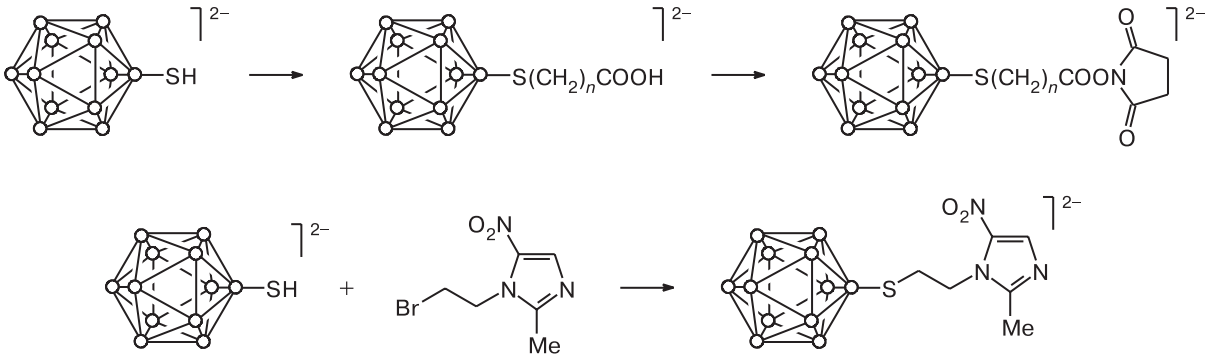
$$[B_{12}H_{11}SH]^{2-} \xrightarrow{RX} [B_{12}H_{11}SR]^{2-} + [B_{12}H_{11}SR_2]^{-}$$

This approach was used for the synthesis of boron-containing acids[45] and nitroimidazoles[46] (Scheme 10) as well as for the preparation of more complex molecules, such as boron-containing porphyrins[43,44] and sugars.[44,47]

The selective synthesis of monoalkyl derivatives can be performed with the use of the cyanoethyl protective group.[42] This procedure also allows one to introduce two different substituents and was used in the synthesis of bifunctional derivatives **A** and **B**. The latter are potential building blocks for the preparation of oligomers based on phosphate esters[48,49] (Scheme 11).

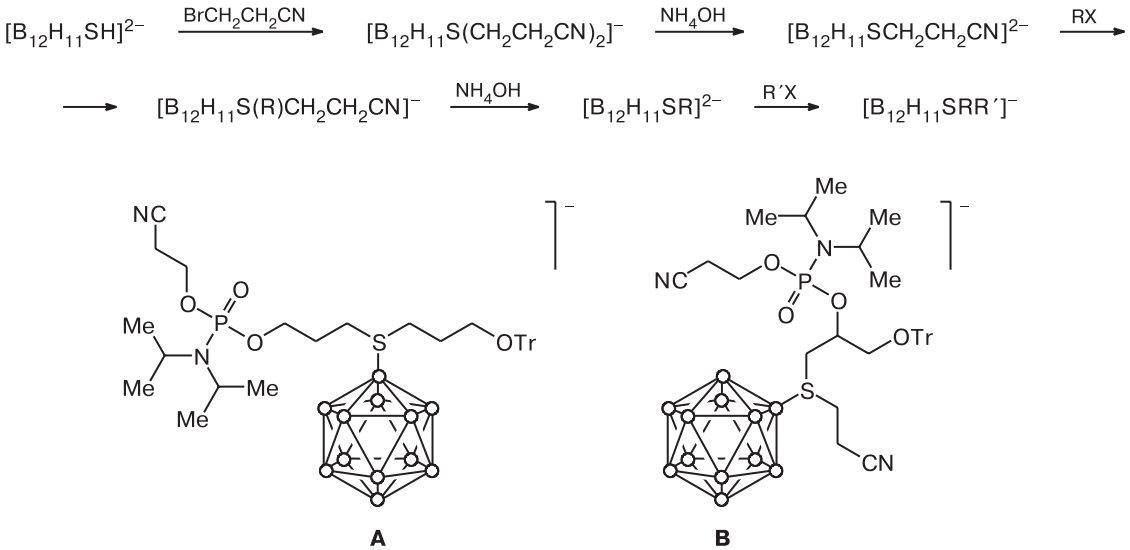
Another approach to the synthesis of functional derivatives involves partial demethylation of dimethylsulfonium derivatives of the *closo*-dodecaborate anion with potassium phthalimide or sodium ethylthiolate followed by treatment of the resulting methyl sulfides with the corresponding haloalkanes.[50,51] Dimethyl sulfide de-

Scheme 10



n = 1, 2

Scheme 11



rivatives can be prepared bypassing mercapto derivatives with the use of pyrolysis of the dimethyl sulfide—borane complex,[52—54] its reaction with decarborane(14),[52] or the reaction of the *closo*-dodecaborate anion with DMSO in the presence of acid[50,55] (Scheme 12).

Scheme 12

$$Me_2S\cdot BH_3 \longrightarrow [B_{12}H_{11}SMe_2]^- + [1,2\text{-, }1,7\text{-, and }1,12\text{-}B_{12}H_{10}(SMe_2)_2]$$

$$B_{10}H_{14} + Me_2S\cdot BH_3 \longrightarrow [B_{12}H_{11}SMe_2]^- + [B_{12}H_{10}(SMe_2)_2]$$

$$[B_{12}H_{12}]^{2-} \xrightarrow[H^+]{DMSO} [B_{12}H_{11}SMe_2]^- \xrightarrow[H^+]{DMSO} [B_{12}H_{10}(SMe_2)_2]$$

$$[Me_2SB_{12}H_{10}SMe_2] \longrightarrow [Me_2SB_{12}H_{10}SMe]^- \longrightarrow [Me_2SB_{12}H_{10}S(Me)R]$$

R = $CH_2C_6H_4$-3-COOH, $CH_2C_6H_4$-4-NO_2, $CH_2C_6H_4$-4-$NHCOCF_3$

Unfortunately, this approach was applied only to the synthesis of neutral disubstituted sulfonium derivatives whose hydrophobic nature hinders their practical use.

The thiocyanato-*closo*-dodecaborate $[B_{12}H_{11}SCN]^{2-}$ anion is another promising BNCT agent. This anion was prepared by the reaction of the *closo*-dodecaborate anion with $(SCN)_2$ in CH_2Cl_2 [56,57] or its electrochemical oxidation in the presence of the thiocyanate ion[58] (Scheme 13).

Scheme 13

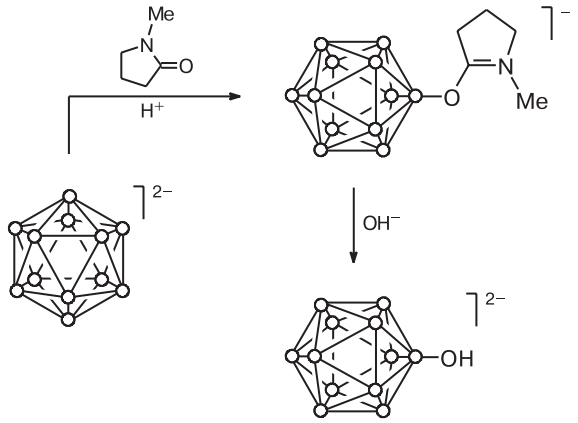
$$[B_{12}H_{12}]^{2-} \xrightarrow{(SCN)_2} [B_{12}H_{11}SCN]^{2-}$$

$$[B_{12}H_{12}]^{2-} \xrightarrow[-2\ e]{SCN^-} [B_{12}H_{11}SCN]^{2-}$$

In a number of toxic and pharmacological characteristics, this compound is superior to the mercapto-*closo*-dodecaborate anion, which is presently used in clinical practice.[59,60]

Derivatives with the boron—oxygen bond. Although the hydroxy-*closo*-dodecaborate anion $[B_{12}H_{11}OH]^{2-}$ was first prepared[27,61] in the middle 1960s, its chemical properties remained almost unknown until recently. The synthesis of *closo*-dodecaborate esters of phosphorous acids was the only example.[62] The situation changed only in recent years due, primarily, to the development of a convenient preparative procedure for the synthesis of the $[B_{12}H_{11}OH]^{2-}$ anion[63] (Scheme 14).

Scheme 14

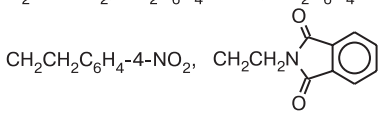


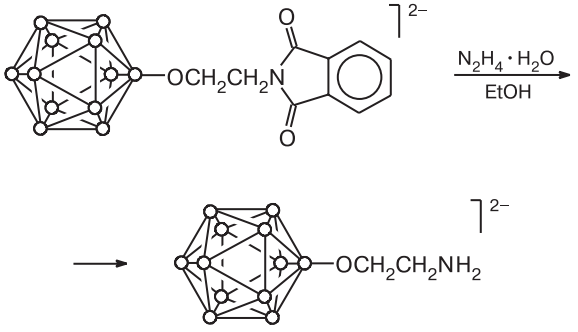
Unlike the mercapto derivative, its hydroxy analog demonstrates a weak acidic character, and alkylation of the latter compound requires an excess of a base. At the same time, alkylation of the $[B_{12}H_{11}OH]^{2-}$ anion does not afford dialkyl oxonium derivatives.[64] A series of alkoxy derivatives of the *closo*-dodecaborate anion containing functional groups were prepared by the reactions of the $[B_{12}H_{11}OH]^{2-}$ anion with different alkyl and benzyl halides[65,66] (Scheme 15).

Scheme 15

$$[B_{12}H_{11}OH]^{2-} \xrightarrow[K_2CO_3,\ Me_2CO]{RX} [B_{12}H_{11}OR]^{2-}$$

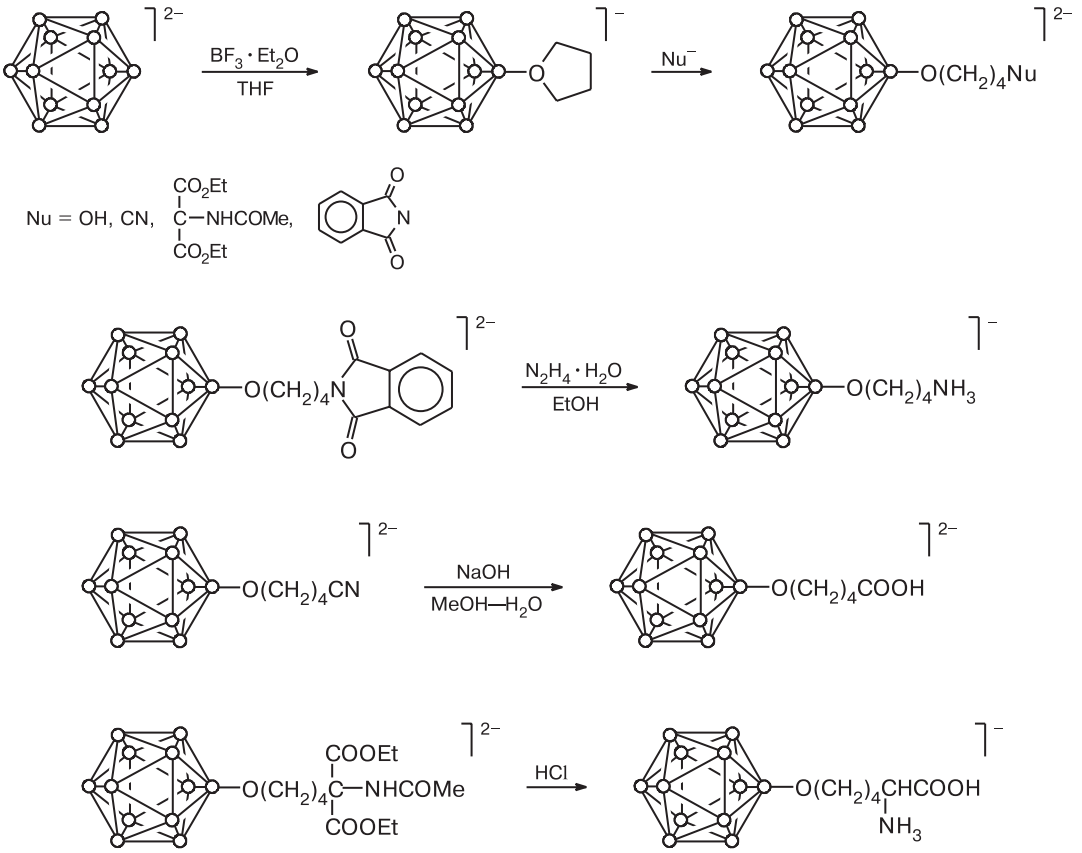
R = $CH_2CH{=}CH_2$, $CH_2C_6H_4$-4-CN, $CH_2C_6H_4$-4-NO_2,





Another interesting method for the synthesis of alkoxy derivatives of the *closo*-dodecaborate anion involves the reaction of the $[B_{12}H_{12}]^{2-}$ anion with $BF_3\cdot Et_2O$ in THF followed by the ring opening in the resulting tetra-

Scheme 16



methylene oxonium derivative $[B_{12}H_{11}O(CH_2)_4]^-$ under the action of nucleophilic agents. This procedure was used for the preparation of various functional derivatives of the *closo*-dodecaborate anion. In these reactions, the nearly optimum distance between the boron cage and the functional fragment was achieved[66,67] (Scheme 16).

Derivatives with the boron—nitrogen bond. Until recently, the chemistry of derivatives of the *closo*-dodecaborate anion with the boron—nitrogen bond, like that of derivatives with the boron—oxygen bond, remains almost unknown. The amino derivative of the *closo*-dodecaborate anion was prepared in high yield by the reaction of the $[B_{12}H_{12}]^{2-}$ anion with hydroxylamine-*O*-sulfonic acid[68,69] (Scheme 17).

Scheme 17

$$[B_{12}H_{12}]^{2-} \xrightarrow{NH_2OSO_3H} [B_{12}H_{11}NH_3]^-$$

Alkylation of the amino-*closo*-dodecaborate anion generally affords a mixture of derivatives with different degrees of substitution[69,70] (Scheme 18).

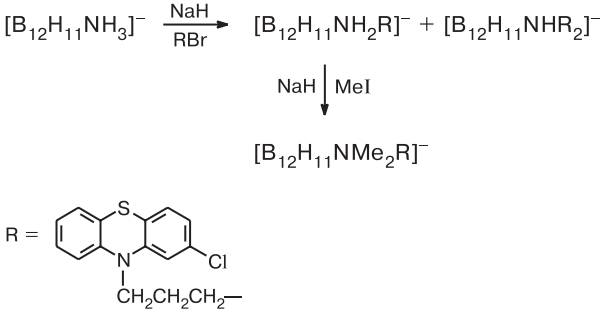
The reactions with the use of an excess of an alkylating agent give rise to compounds with the maximum possible degree of substitution, which depends on the steric properties of the substituents introduced.

Scheme 18

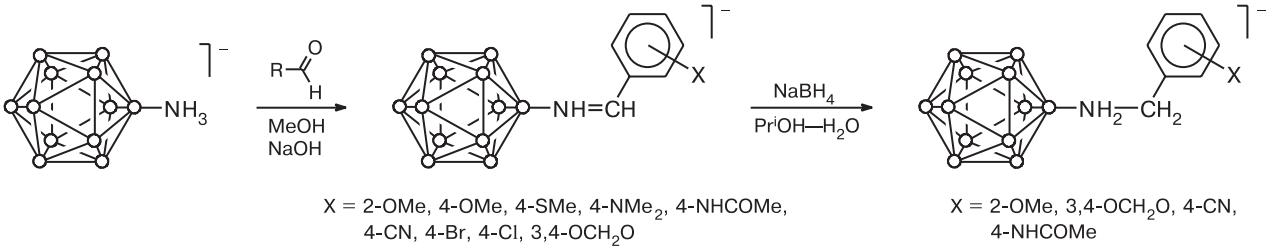
$$[B_{12}H_{11}NH_3]^- \xrightarrow{RX} [B_{12}H_{11}NH_2R]^- + [B_{12}H_{11}NHR_2]^- + [B_{12}H_{11}NR_3]^-$$

An attempt to use this procedure for the synthesis of boron-containing phenothiazines led to the formation of a mixture of mono- and disubstituted products even when

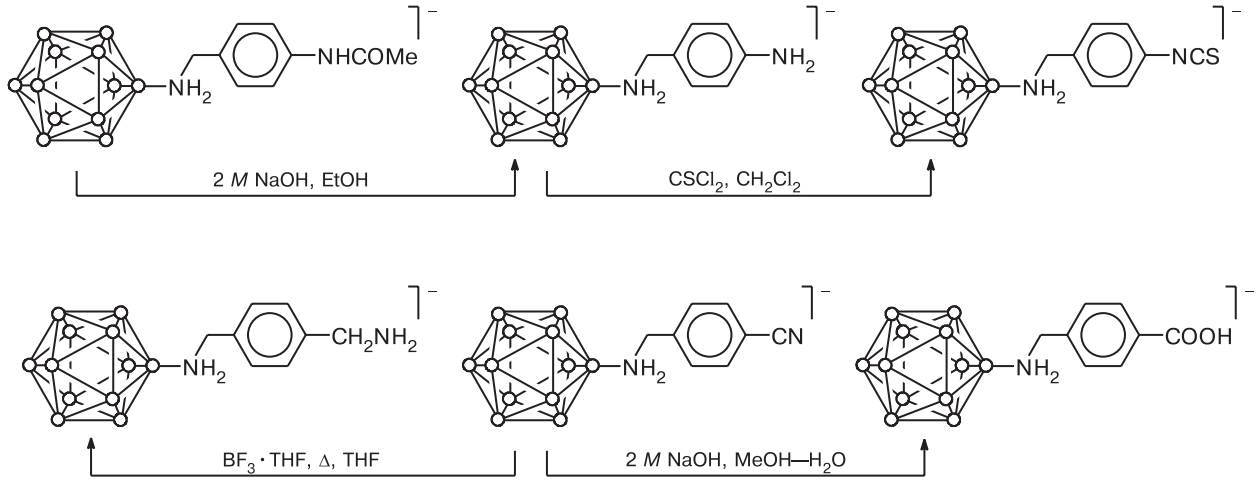
Scheme 19



Scheme 20



Scheme 21



the alkylating agent was taken in a deficient amount. The resulting products were separated by crystallization[71] (Scheme 19).

The use of this procedure in the synthesis of boron-containing phthalocyanines proved to be more fruitful.[72,73]

The synthesis of monoalkylamino derivatives of the *closo*-dodecaborate anion through Schiff´s bases generated in the reactions of $[B_{12}H_{11}NH_3]^-$ with aldehydes holds promise[74—76] (Scheme 20).

This approach was used in the synthesis of a series of functional derivatives of the *closo*-dodecaborate anion[74—76] (Scheme 21).

The reactions of the amino-*closo*-dodecaborate anion with acyl chlorides afforded the corresponding amides[70] (Scheme 22).

Scheme 22

$$[B_{12}H_{11}NH_3]^- \xrightarrow[\text{NaH, THF}]{\text{RCOCl}} [B_{12}H_{11}NH_2COR]^-$$

A series of amide derivatives were prepared by the reactions of the *closo*-dodecaborate anion with nitriles in the presence of *p*-toluenesulfonic acid[77—79] (Scheme 23).

Scheme 23

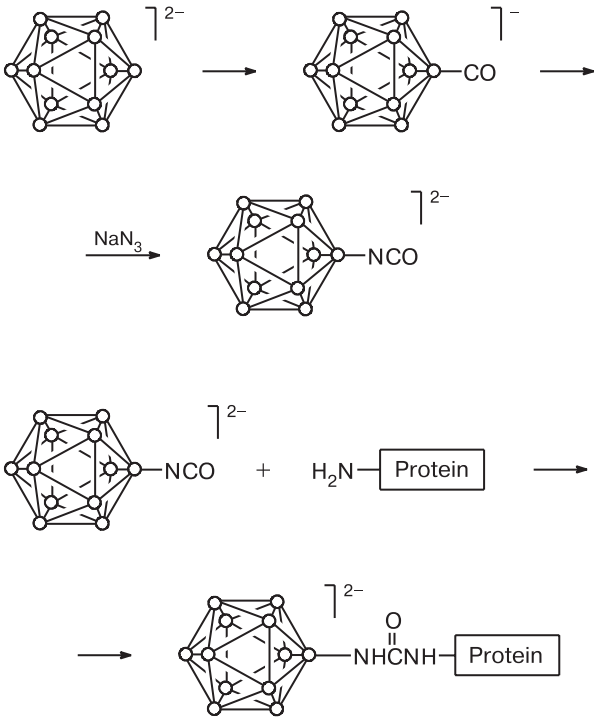
$$[B_{12}H_{12}]^{2-} \xrightarrow[H^+]{\text{RCN}} [B_{12}H_{11}NCR]^- \xrightarrow{H_2O} [B_{12}H_{11}NH_2COR]^-$$

R = Me, CH=CH$_2$, CH$_2$CN

The isocyanato-*closo*-dodecaborate anion $[B_{12}H_{11}NCO]^{2-}$, which was prepared by the reaction of the carbonyl derivative $[B_{12}H_{11}CO]^-$ with NaN_3, is another promising derivative. This anion was used for the synthesis of boron-containing proteins[80] (Scheme 24).

The key step in the synthesis of the $[B_{12}H_{11}NCO]^{2-}$ anion involves the introduction of the carbonyl group. Initially, the carbonyl derivative $[B_{12}H_{11}CO]^-$ was prepared by the reaction of the acidic form of the $[B_{12}H_{12}]^{2-}$ anion with CO in the presence of $Co_2(CO)_8$ as the catalyst at a pressure of 1000 atm at 130 °C.[81] Recently, a procedure was developed for the synthesis of the $[B_{12}H_{11}CO]^-$ anion by the reaction of the *closo*-dodecaborate anion with oxalyl chloride in CH_2Cl_2 at room temperature,[82] which opens up considerable possibilities for the preparation of the isocyanato-*closo*-dodecaborate anion under standard laboratory conditions.

Scheme 24



In addition to the use in boron neutron capture therapy for cancer, the application of derivatives of the *closo*-dodecaborate anion containing a radiohalogen label in radiodiagnostics looks very promisings. As mentioned above, the H atoms in the $[B_{12}H_{12}]^{2-}$ anion can be readily replaced by halogen atoms.[22—24] Recently, halogenation of various substituted derivatives of the *closo*-dodecaborate anion have also been studied.[69,83,84] The introduction of a radiohalogen label essentially facilitates investigation of the biodistribution of agents based on the *closo*-dodecaborate anion and the study of their pharmacokinetics.[25] Recently, this approach was used in studies of the pharmacokinetics of the ^{131}I-labeled thiocyanato-*closo*-dodecaborate anion ^{131}I-$[B_{12}H_{11}SCN]^{2-}$.[85,86]

Radioactive halogen isotopes play an important role in nuclear medicine. The ^{123}I isotope is widely used in gamma-scintillography and single photon emission computerized tomography. The ^{131}I isotope is one of the main radionuclides used in radiotherapy. The ^{18}F, ^{75}Br, ^{76}Br, and ^{124}I isotopes are widely used in positron emission tomography. It is believed that the ^{211}At isotope is one of the most promising therapeutic nuclides and will find application in the immediate future. These facts make it possible to use derivatives of the *closo*-dodecaborate anion synthesized for BNCT in radioimmunodiagnostics and radioimmunotherapy. The important advantage of the *closo*-dodecaborate anion as a carrier of a radiohalogen label over the conventionally used organic fragments, such as tyrosine, is the obvious absence of enzymatic systems capable of abstracting the halogen atom from the boron cage.

The requirements on agents for radioimmunodiagnostics and radioimmunotherapy are essentially different from those imposed on BNCT agents. Thus, the former agents must show high selectivity of accumulation in tumor tissue, which is associated with the possibility of total body irradiation, and a lower therapeutic concentration in the tumor. High selectivity of the delivery of boron compounds containing a radiohalogen label is achieved by their binding to biomolecules capable of being selectively accumulated in tumor tissues, whereas a substantially lower therapeutic concentration makes it possible to use radioconjugates with a lower boron content than that required for BNCT with retention of their immunoreactivity.

The labeling of the *closo*-dodecaborate anion and bioconjugates derived from this anion with the bromine [87] and iodine [87—89] radioisotopes was studied in detail. The conditions favorable for the selective introduction of the radiohalogen label into the *closo*-dodecaborate cage or the tyrosine fragments of polypeptides were found and the pharmacokinetics of the resulting compounds was investigated. Recently,[90—92] it has been demonstrated that the ^{125}I-labeled 4-isothiocyanatobenzylamino derivative of the *closo*-dodecaborate anion, *viz.*, ^{125}I-$[4\text{-}SCNC_6H_4CH_2NH_2B_{12}H_{11}]^-$, can be used for protein labeling. Labeling of the $[B_{12}H_{12}]^{2-}$ anion with astatine-211 was also examined.[93—95]

X-ray contrasting imaging is another potential field of application of derivatives of the *closo*-dodecaborate anion.[96] This method still comprises the majority of all radiological diagnostic procedures done on a worldwide basis in spite of the fact that NMR and ultrasonic imaging techniques are being vigorously developed. Today, iodinated X-ray contrasting agents are used in about 20 million procedures annually in the USA, mainly, in computing tomography and angiography. The sales of these agents in the USA exceeded $550 million in 1997.[97]

Current clinically used iodinated X-ray contrasting agents are derived from iodobenzenes. Most of these compounds contain three iodine atoms, which alternate with other substituents introduced to improve water solubility and decrease toxicity of these pharmaceuticals. It is known that an increase in the iodine content in X-ray imaging agents from 28.7 to 37.5% leads to a twofold increase in contrast at particular irradiation energies. In this respect, the *closo*-dodecaborate anion, which is characterized by high solubility and in which up to 12 hydrogen atoms can be replaced with iodine atoms,[22] would be expected to serve as the starting compound for the preparation of a new generation of X-ray contrasting agents containing 65—85% of I.[98,99]

In conclusion, mention should be made of boron neutron capture synovectomy, which shows promise in treating rheumatic arthritis. This method is based on the above-considered reaction of the ^{10}B isotope with thermal neutrons. One would expect that this technique will compete with the presently used surgical and radiation methods, which are based on the insertion of α-radiating nuclides into the damaged area, and even will replace these methods in the future.[100]

To summarize, derivatives of polyhedral boron hydrides, in particular, the *closo*-dodecaborate anion, possess a high potential for their use in medicine. The compounds of this type can find use in various areas of medicine realizing the strategy of the multigoal synthesis. Hence, many compounds synthesized for BNCT could be suitable for radioimmunodiagnostics and radioimmunotherapy or boron neutron capture synovectomy and vice versa.

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