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# Polyhedral Boranes for Medical Applications: Current Status and Perspectives

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This review focuses on the current status and perspectives of the application of polyhedral boron hydrides in medicine. The main topics discussed are boron neutron capture therapy for cancer and radionuclide diagnostics and therapy. X-ray contrast diagnostics, antitumor activity of some metal derivatives of carboranes, and drug design including carborane fragments are discussed as well.



## Introduction

The discovery of polyhedral boron hydrides was one of the most important events in the chemistry of the 20th century. Polyhedral boron hydrides are characterized by electron-deficient bonding, meaning that there are too few valence electrons for bonding to be described exclusively in terms of two-centered two-electron bonds. One characteristic of electron-deficient structures is the aggregation of atoms to form unusual three-centered two-electron bonds, which typically result in the formation of trigonal faces and hypercoordination. The establishment of three-centered two-electron bonds made a true revolution in the theory of chemical bonding, and William Lipscomb was awarded the Nobel Prize in 1976 "for his studies on the structure of boranes illuminating problems of chemical bonding".[1] In contrast to the previously known boron hydrides, the polyhedral boron hydrides were shown to be exceptionally stable. Investigation of the properties of these compounds resulted in the conclusion that these compounds have aromatic properties. This was the first example of nonplanar three-dimensional aromatic compounds and resulted in the development of the concept of three-dimensional aromaticity that is generally accepted at present.[2] The high stability of polyhedral boron hydrides opens numerous perspectives to their practical use;[3] boron neutron capture therapy[4] and the carborane-based superacids[5] are, probably, the best known. At the same time, an interest in the practical application of polyhedral boron hydrides provoked active development of their chemistry. Moreover, synthesis of bo-

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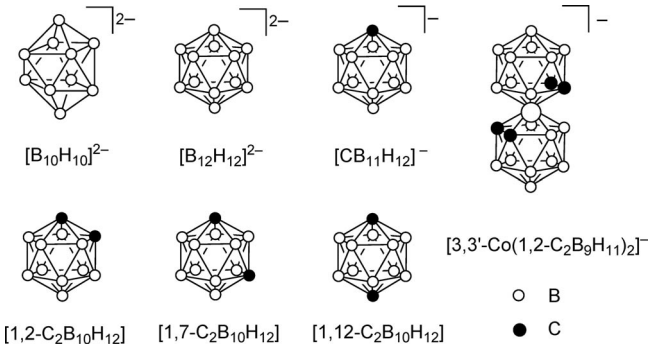
ron compounds for medical applications has been one of the main driving forces for the development of boron hydride chemistry for the last twenty-five years. In this review we survey briefly all fields of medical application of polyhedral boron hydrides, including their current status and perspectives.

## Main Types of Polyhedral Boron Hydrides

All polyhedral boron hydrides proposed for various medical applications (Scheme 1) can be divided in two main groups: neutral and anionic. The first group includes *ortho*-, *meta*-, and *para*-isomers of icosahedral dicarbaboranes [$C_2B_{10}H_{12}$]. All these compounds are highly hydrophobic as a result of the hydridic character of the BH groups, which prevents the formation of classical hydrogen bonds with water. On the other hand, the CH groups in carboranes are weakly acidic, and this makes them available for "normal" organic chemistry.[6] Because of this feature, the carborane cages can be easily functionalized and incorporated into organic structures, and, as result, synthesis of a wide range of various carborane-containing analogues of biomolecules have been described.[7]




Scheme 1. Main types of polyhedral boron hydrides.

Removal of one of the boron atoms adjacent to the two carbon atoms of *ortho*-carborane by action of base results in the formation of anionic 7,8-dicarba-*nido*-undecaborate (*nido*-carborane): [7,8-$C_2B_9H_{12}$]$^-$. This approach is often used to increase the water solubility of carborane-containing biomolecules.[7] Recently, an efficient method for the direct functionalization of the parent *nido*-carborane has been described.[8]

The isoelectronic and isostructural analogue of carboranes, the dodecahydro-*closo*-dodecaborate anion [$B_{12}H_{12}$]$^{2-}$, is a typical representative of anionic polyhedral boron hydrides. Sodium salts of the parent *closo*-dodecaborate and their derivatives have a good solubility in water, which is an important precondition for many medical applications. The sodium salt of the parent anion, $Na_2[B_{12}H_{12}]$, was found to be practically nontoxic with an approximate lethal dose for rats $>$ 7.5 g/kg of body weight, which is roughly comparable to that of sodium chloride.[9] However, functionalization of this purely inorganic system, has been problematic up to recent times, because of the absence of a clear reaction center. At present there are two general approaches to the synthesis of functional derivatives of *closo*-dodecaborate.[10] The first includes the introduction of a primary substituent (-OH, -SH, -$NH_2$) followed by modification of this substituent by using standard methods of organic chemistry.[11–13] The second approach is based on the preparation of cyclic oxonium derivatives of *closo*-dodecaborate followed by ring opening with various nucleophilic reagents.[14] This method is very efficient for the synthesis of derivatives with pendant functional groups connected to the boron cage through flexible spacers of 5–6 atoms and can be successfully applied to other types of polyhedral boron hydrides.[15]

The decahydro-*closo*-decaborate anion, [$B_{10}H_{10}$]$^{2-}$, is another member of the [$B_nH_n$]$^{2-}$ family. The sodium salt of the parent *closo*-decaborate, $Na_2[B_{10}H_{10}]$ (GB-10), is approved for human use by the US Food and Drug Administration. However, the chemistry of *closo*-decaborate is much less studied than that of *closo*-dodecaborate, and despite new research activity in this field,[16–18] to the best of our knowledge only two reports on the medical application of *closo*-decaborate derivatives have appeared for the last years.[19]

The carba-*closo*-dodecaborate anion, [$CB_{11}H_{12}$]$^-$, combines advantages of both its isostructural and isoelectronic analogues, [$C_2B_{10}H_{12}$] and [$B_{12}H_{12}$]$^{2-}$: the good solubility in water as the sodium salt and the presence of a carbon atom available for functionalization by standard methods of organic chemistry.[20] It should be noted that the practical importance of the carba-*closo*-dodecaborate anion was very limited until convenient preparative methods for the parent cluster and their *C*-phenyl derivatives were developed recently.[21] A few examples of the incorporation of [$CB_{11}H_{12}$]$^-$ into various porphyrins have been reported quite recently.[22]

The cobalt bis(dicarbollide) anion, [3,3′-Co(1,2-$C_2B_9H_{11}$)$_2$]$^-$, is another boron moiety that was proposed for use in medicinal chemistry relatively recently. The cobalt atom in this extraordinarily stable complex is held between two $\eta^5$-bonding [$C_2B_9H_{11}$]$^{2-}$ ligands derived from *nido*-carborane.[23] The sodium salt of this metallacarborane cluster demonstrates good solubility in water; however, the anion itself is rather lipophilic, and that could have some advantages in medical applications. The problem related to the synthesis of monosubstituted functional derivatives of cobalt bis(dicarbollide) was solved a few years ago when nucleophilic opening of the 1,4-dioxane oxonium derivative was reported.[24] At present, this approach is widely used for the synthesis of various functional derivatives of cobalt bis(dicarbollide).[15] The other functionalization methods include Pd-catalyzed cross-coupling of the 8-iodo derivative[25] or modification of the 8-amino derivative;[26] however, both of these methods have not found wide synthetic application.

The polyhedral boron hydrides described above are available from commercial sources; however, all are very expensive because of the absence of large-scale industrial production and find practical applications only in some areas where no alternative exists. The use of polyhedral boranes

in some of the fields described below have no alternatives, in other fields the price of modern pharmaceuticals is comparable with the price of boron hydride derivatives, and in some cases the price of boron hydride is negligible in comparison with the price of the drug as a whole.

## Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) is the most widely known medical application of boron hydrides. Boron neutron capture therapy is a binary method for the treatment of cancer, which is based on the nuclear reaction of two essentially nontoxic species, nonradioactive $^{10}B$ and low-energy thermal neutrons. The neutron capture reaction by $^{10}B$ produces an α-particle, $^{4}He^{2+}$, and a $^{7}Li^{3+}$ ion together with 2.4 MeV of kinetic energy and a 480 keV photon. These high-linear-energy transfer ions dissipate their kinetic energy before traveling one cell diameter (5–9 μm) in biological tissues, which gives them the potential for cell-killing with precision. High accumulation and selective delivery of boron into the tumor tissue are the most important requirements to achieve efficient neutron capture therapy of cancer. The most important requirements for the development of boron compounds are: (1) achieving minimal tumor concentrations in the range of 20–35 μg of $^{10}B$ per gram of tumor tissue, (2) selective delivery of the boronated compounds to tumor cells while keeping the boron concentration in the cells of the surrounding normal tissue low to minimize the damage to normal tissue, and (3) sufficiently low toxicity. Ideally, only tumor cells should be destroyed without damage to healthy tissues in the irradiated bulk. The absence of an adverse effect on the surrounding healthy tissues is attributed to the fact that the thermal neutron capture cross-sections of elements present in tissues are 4–7 orders of magnitude smaller than that of the $^{10}B$ isotope (Table 1).

Table 1. Thermal neutron capture cross-sections of isotopes characterized by the largest capture cross-sections and cross-sections of isotopes of the most abundant elements in human tissues.

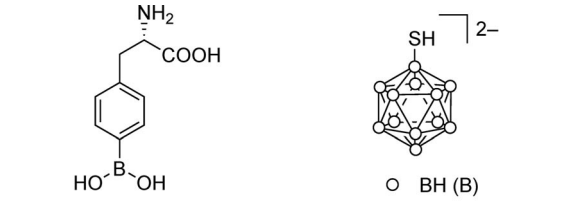
| Isotope | Capture cross-section (barn) | Isotope | Capture cross-section (barn) | Average content in tissues |
|---|---|---|---|---|
| $^{10}B$ | $3.8\times10^{3}$ | $^{1}H$ | 0.33 | (10.0%) |
| $^{113}Cd$ | $2.0\times10^{4}$ | $^{12}C$ | $3.4\times10^{-3}$ | (18.0%) |
| $^{149}Sm$ | $4.2\times10^{4}$ | $^{14}N$ | 1.8 | (3.0%) |
| $^{151}Eu$ | $5.8\times10^{3}$ | $^{16}O$ | $1.8\times10^{-4}$ | (65.0%) |
| $^{155}Gd$ | $6.1\times10^{4}$ | $^{31}P$ | 0.18 | (1.16%) |
| $^{157}Gd$ | $2.6\times10^{5}$ | $^{32}S$ | 0.53 | (0.20%) |

Despite the fact that the thermal neutron capture cross-section of the $^{10}B$ isotope is smaller (see Table 1) than those of other elements ($^{113}Cd$, $^{149}Sm$, $^{151}Eu$, $^{155}Gd$, or $^{157}Gd$), at present the $^{10}B$ isotope is virtually the only nucleus used for neutron capture therapy of cancer, because it readily forms stable covalent compounds.

Since BNCT is based on the nuclear properties of the $^{10}B$ isotope, BNCT agents can be based on non-polyhedral boron compounds. Moreover, one of the clinically used BNCT agents, L-*p*-dihydroxyborylphenylalanine, contains only one boron atom. The question that arises is why should expensive polyhedral boron hydrides be used for the synthesis of BNCT agents? There are at least three reasons: (1) the number of boron atoms in one molecule: a compound that incorporates boron clusters containing ten or more boron atoms, in principle, allows delivery of at least ten times more boron atoms by using the same tumor-targeting vector, (2) the extremely high stability of boron clusters, and (3) their rather low toxicity.

The main target of BNCT has been brain tumors – high-grade gliomas and specifically glioblastoma multiform (> 300 patients treated), which are extremely resistant to all current forms of therapy, including surgery, chemotherapy, radiotherapy, immunotherapy, and gene therapy.[27] Metastatic melanomas, which cannot be treated by either surgical excision or stereotactic radiosurgery, are other candidates for the BNCT treatment.[28] The use of BNCT for treatment of head and neck recurrent tumors (squamous cell carcinomas, sarcomas, parotid tumor)[29] and adenocarcinoma of the colon that has metastasized to the liver[30] have been reported recently.

The two boron compounds that have been extensively used in clinical trials with BNCT are L-*p*-dihydroxyborylphenylalanine (BPA) and disodium mercaptoundecahydro-*closo*-dodecaborate (BSH) (Scheme 2). In some cases, the effectiveness of the treatment can be improved by combining BPA and BSH or BPA and GB-10. It should be noted that current BNCT agents were developed more than 30 years ago[10b,31,32] and are far from ideal.




L-*para*-boronophenylalanine (BPA) sodium mercaptododecaborate (BSH)

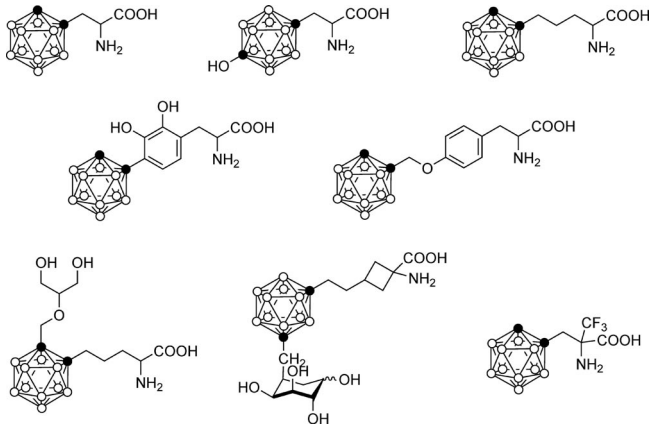
Scheme 2. Clinically used BNCT agents.

Therapeutic treatment of brain cancers such as gliomas is a very serious problem because of the necessity of transporting therapeutic agents across the blood–brain barrier (BBB). It is estimated that more than 98% of all small-molecular-weight drugs and practically 100% of large-molecular-weight drugs developed for central nervous system disorders do not cross the BBB. A very restricted number of lipophilic small molecules (MW < 400 Da) cross the BBB by free diffusion. All the other molecules do not cross the BBB at all or they are transported across the BBB by catalyzed transport, owing to specific interactions between the therapeutic agent and certain BBB transport systems.[33] It was shown that BSH does not penetrate either the BBB or the cellular membrane and therefore passively accumulates in the intracellular space of the bulk tumor, i.e. where

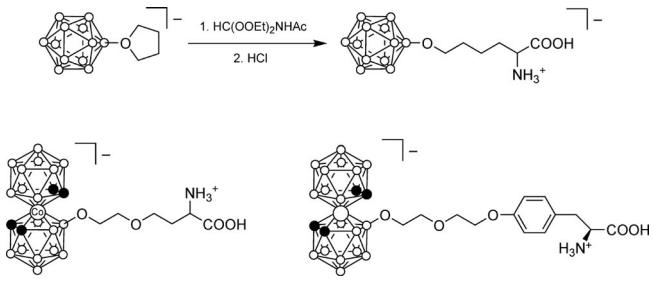
  

the BBB is disrupted, whereas BPA is actively transported across the BBB and the cellular membranes and into the tumor cells.[34]

The BBB transporters can be divided into three groups: carrier-mediated transporters, active efflux transporters, and receptor-mediated transporters. The carrier-mediated and active efflux transporters generally transport small molecules, whereas endogenous large molecules enter the brain from blood via receptor-mediated transport. The carrier-mediated transporters include the Glut1 glucose carrier, the MCT1 monocarboxylic acid carrier, the LAT1 or CAT1 amino acid carriers, and the CNT2 purine nucleoside carrier. Generally, these systems are responsible for the transport of nutrients in the blood-to-brain direction.[35] Since the vascular density in the brain is very high, once molecules have penetrated the BBB, they are distributed rapidly in the whole brain tissue. Nutrients provide both building blocks and the energy supply to drive the cell metabolism and synthesize the necessary cellular components. In contrast with normal cells, tumor cells have an elevated requirement for certain constituents necessary for cell replication (amino acids, nucleic acid precursors, carbohydrates, etc.). Thus, the limiting factor in the treatment of brain cancers is the delivery of therapeutic agents to the brain across the BBB. That is why the most widespread chemical effort has been related to the design and synthesis of boron-containing cellular building blocks.



Scheme 3. Carborane-containing amino acids.




Scheme 4. Anionic boron-containing amino acids.

## Boronated Amino Acids

Interest in the development of carborane-containing amino acids arose soon after the first carboranes were synthesized, and *o*-carboranylalanine was one of the earliest described carborane-based analogues of biomolecules. It was first synthesized, as the racemic mixture, independently by Brattsev[36] and Zakharkin.[37] Subsequently, other methods of its synthesis in high yield,[38–40] as well as the stereoselective synthesis of the L-isomer,[41] have been proposed. More recently, several more useful stereoselective syntheses of the L- and D-isomers have been developed.[42–44] A number of carborane-containing amino acids, including the *p*-carborane analogue of tyrosine,[45] carborane derivatives of 1-amino-cyclobutanecarboxylic acid,[46] and α-trifluoromethyl-*o*-carboranylalanine[47] (Scheme 3) have been synthesized. Synthesis and use of carborane-containing amino acids have been reviewed recently.[48]

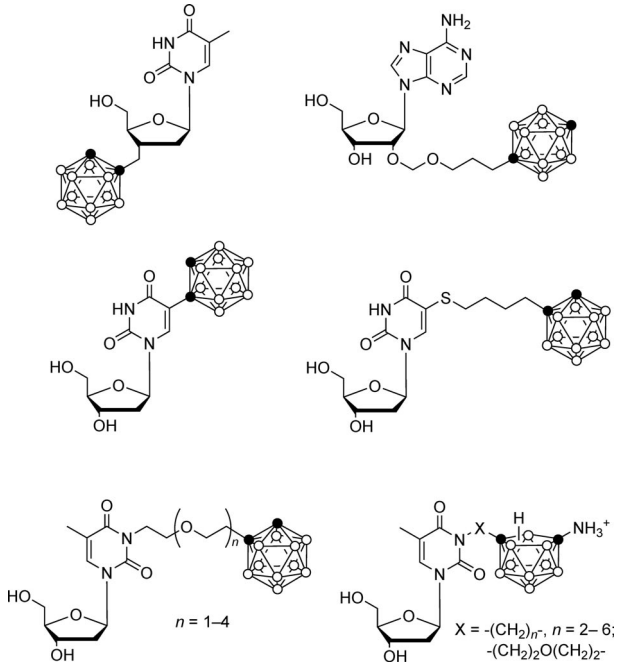
As a result of the high hydrophobicity of the carborane cluster, most carborane-containing amino acids are insoluble in water. An introduction of different types of hydrophilic groups, as well as transformation of the *closo*-carborane cage to the *nido*-carborane cage, were proposed to increase the water solubility of carborane-based amino acids. Amino acids based on anionic boron hydrides were prepared by nucleophilic ring-opening of their cyclic oxonium derivatives[14a,24] (Scheme 4). More recently, this approach has been applied to the synthesis of boron-containing amino acids derived from lysine and tyrosine.[49]

## Boronated Nucleosides and Nucleotides

Boron-containing nucleosides are considered to be promising candidates for BNCT, because of their potential to be retained in rapidly dividing tumor cells after 5′-monophosphorylation by phosphorylating enzymes, thymidine kinase 1 and deoxycytidine kinase. Thymidine kinase 1 is pyrimidine-specific, phosphorylating thymidine and 2′-deoxyuridine, whereas deoxycytidine kinase has a broad substrate specificity, phosphorylating 2′-deoxycytidine, 2′-deoxyadenosine, and 2′-deoxyguanosine. Cellular efflux of such 5′-monophosphates would be retarded because of the negatively charged phosphate moiety. The design strategy for BNCT nucleoside prodrugs should focus on structures which enter tumor cells either by passive diffusion or via nucleoside membrane transporters and are selectively trapped intracellularly as anabolically and catabolically stable nontoxic 5′-monophosphates and/or 5′-diphosphates.[50]

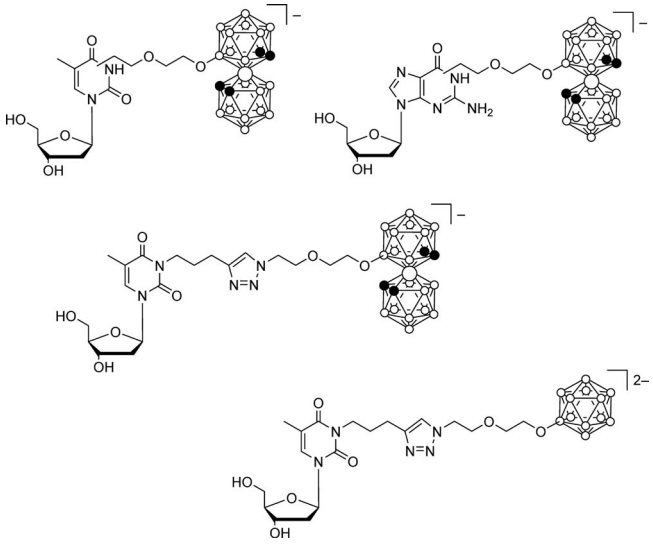
Syntheses and results of biological studies on carborane-containing nucleosides have been reviewed several times in the last ten years.[50–56] On the basis of the results of phosphoryl transfer assays of a few series of carborane-containing nucleosides, a three-dimensional quantitative structure–activity relationship has been developed.[57] Structures of some carborane-containing nucleosides synthesized are presented in Scheme 5.




Scheme 5. Carborane-containing nucleosides.

Syntheses of a number of boron-containing nucleosides prepared by reaction of the 1,4-dioxane derivative of cobalt bis(dicarbollide) with the canonical nucleosides thymidine, 2′-*O*-deoxycytidine, 2′-*O*-deoxyadenosine, and 2′-*O*-deoxyguanosine have been described.[58,59] Syntheses of ferra bis(dicarbollide)-[59] and *closo*-dodecaborate-based[60] nucleosides were reported as well. Structures of some of these nucleosides are presented in Scheme 6.



Scheme 6. Cobalt bis(dicarbollide)- and *closo*-dodecaborate-based nucleosides.

## Boron-Containing Peptides and Antibodies

Receptor-mediated BBB transporters can transport large molecules. In addition, receptor-specific peptide-mimetic monoclonal antibodies (mAbs) can bind specific BBB receptors to trigger receptor-mediated transport across the brain capillary endothelium. Endogenous peptides or peptide-mimetic mAbs may act as molecular Trojan horses and ferry any attached drug across the BBB.[61] That is why development of receptor-mediated tumor-selective drugs has always been in the mainstream of the BNCT-related boron chemistry. High-molecular-weight delivery agents usually contain a boron cluster linked through a hydrolytically stable bond to a tumor-targeting moiety, such as monoclonal antibodies (mAbs) or low-molecular-weight receptor-targeting ligands. Examples of these include Tyr3-octreotate to target the somatostatin (SST) receptor[62,63] and the epidermal growth factor (EGF) or the mAb cetuximab (IMC-C225) to target the EGF receptor or its mutant isoform EGFRvIII, which are over-expressed in a variety of malignant tumors.[64]

The use of antibodies to deliver boron to tumor cells was suggested in the 1960s. The initial investigations of boron conjugation chemistry with model protein substrates such as bovine serum albumin and human γ-globulin started nearly simultaneously in several laboratories in the 1970s. The studies focused on the type of boron compounds that were to be used, the linkages that would be required, and the effect of such a covalent attachment and its boron moiety on the physiochemical properties of the conjugate formed. The results of these early studies were surveyed in Hawthorne's review.[4a] However, some fundamental strategic problems arose soon after the first boron-containing conjugates were obtained. The minimum number of boron atoms which must be attached to each receptor-targeted biomolecule to achieve the necessary therapeutic dose $10^9$ boron atoms per cell is $10^9/R$ where $R$ is the average effective number of receptor sites available on each targeted cell. It was estimated that the boronated antibody molecule must contain $10^3$ $^{10}$B atoms (ca. 100 boron cages) to provide the necessary therapeutic boron concentration in the tumor.[65] The question is: could that number of boron cages be introduced to the antibody molecule with retention of its conformational and targeting specificity? It was demonstrated that the introduction of approximately 1300 $^{10}$B atoms per molecule of 17–1A Mab monoclonal antibody with *N*-succinimidyl 3-(2-undecahydro-*closo*-dodecaboranyldithio)propionate, $[B_{12}H_{11}SS(CH_2)_2COO\{N(CO)_2(CH_2)_2\}]^{2-}$, resulted in the loss of 90% of its immunoreactivity.[66] This result indicates that attaching 100 functional groups on the antibody molecule apparently results in the loss of its targeting specificity. It means that minimum modification of the antibody molecule is needed for retention of its immunoreactivity. Thus, there are two requirements for preparing boron-containing antibodies for BNCT: (1) synthesis of boronated macromolecules containing up to 100 boron cages, and (2) development of a linkage technology to attach such structures to antibodies.

The initial approach included the use of a preformed macromolecule containing a large number of functional groups to which the boron polyhedron could be covalently attached. The first macromolecule that has been used as a

platform for delivering boron compounds was polylysine, a polymer having multiple reactive amino groups. The protein-binding polyhedral boron derivative, isocyanato-*closo*-dodecaborate, $[B_{12}H_{11}NCO]^{2-}$, was linked to polylysine and subsequently to the anti-B16 melanoma mAb IB16–6.[67] The bioconjugate had an average of 2700 boron atoms per molecule and retained 58% of the native antibody immunoreactivity. Other bioconjugates prepared by this method had more 1000 boron atoms per molecule of antibody and retained 40–90% of the immunoreactivity. Using site-specific linkage of boronated polylysine to the carbohydrate moieties of the anti-TSH antibody resulted in a bioconjugate that had approximately 6000 boron atoms with retention of its immunoreactivity.[68] One of the limitations of this approach is that the polymer itself is not a discrete and homogeneous entity and that heterogeneity is markedly increased as a result of boronation, since the number of boron groups attached to each polymeric molecule could vary.

Dendrimers are one of the most attractive polymers used as boron carriers as a result of their well-defined structure and large number of reactive terminal groups. Initially, second- and fourth-generation polyamidoamino (PAMAM) dendrimers, which have 12 and 48 reactive terminal amino groups, respectively, were treated with the isocyanato derivative of the *closo*-decaborate anion, $[Me_3NB_{10}H_8NCO]^-$. The boronated dendrimer was then linked to mAb IB16–6 directed against the murine B16 melanoma.[69] More recently, the fifth-generation PAMAM dendrimer was boronated with the same polyhedral borane anion and linked to the anti-EGFR mAb cutuximab or the EGFRvIII specific mAb L8A4. The resulting bioconjugate contained ca. 1100 boron atoms per molecule and was found to retain the native antibody immunoreactivity.[70]

Besides monoclonal antibodies, boronated PAMAM dendrimers can be targeted to tumors by using the epidermal growth factor,[71,72] vascular endothelial growth factor,[73] and folic acid, a vitamin that is transported into cells by folate-receptor-mediated endocytosis.[74]

Synthesis of other boronated dendrimers[75,76] and dendrimer-like structures[77,78] that could potentially be used as boron delivery agents for BNCT were reported. Other types of polymers that could be used as boron carriers include dextrans, glucose polymers consisting mainly of a linear α-1,6-glucosidic linkage with some degree of branching by a 1,3-linkage. Several examples of $[B_{12}H_{11}SH]^{2-}$ coupling to modified dextran derivatives have been described.[79–81]

Two different approaches were proposed for tumor targeting of boronated polymers: the streptavidin-biotin strategy[82] and bispecific antibodies.[69b,83] Both methods were considered in detail in the earlier review.[4b]

### Boron-Containing Low-Density Lipoproteins and Liposomes

Another approach directed to selective delivery of therapeutics into tumors is the use of nanocontainers, such as low-density lipoproteins (LDL) or liposomes. One of the observed differences between tumor cells and their normal counterparts is the rate of the metabolism of low-density lipoproteins (LDLs). The LDL vesicle comprises a phospholipid/cholesterol shell with a diameter of approximately 15–20 nm, filled with cholesteryl and glyceryl esters of long-chain alkyl carboxylic acids. This difference is based on the increased need that tumor cells possess for cholesterol in order to facilitate new membrane formation. The overexpression of the LDL receptors on the tumor cell membrane is responsible for its LDL accretion. This provides a basis for cellular differentiation and the targeting of tumor cells with boron if cholesteryl esters of the LDL core are replaced with a boron species that would simulate cholesterol in its physiochemical properties. This concept was proposed by Kahl in the early 1990s. The initial compounds synthesized were esters of carborane carboxylic acid with various fatty acid alcohols.[84] Later, some other derivatives of cholesterol were synthesized,[85,86] and LDLs were proposed as tumor delivery agents for carborane-containing porphyrins.[87]

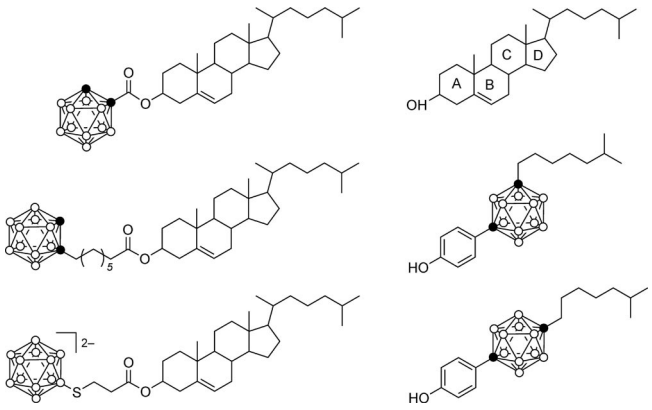
While LDLs are natural lipoproteins with a proclivity for those tumor cells in which the receptors for these vesicles are overexpressed, liposomes can be considered as related synthetic vesicles. They consist of a phospholipid bilayer that forms a spherical shell surrounding an aqueous core. Modification of the liposomal surface by PEGylation or attachment of antibodies or receptor ligands will increase their circulation time and improve their selective targeting. Design strategies for boron-containing liposomes for BNCT focus on both nontargeted and tumor-targeted formulations.[64] The latter includes liposomes conjugated to transferrin,[88] EGF,[89] antibodies,[90] vascular endothelial growth factor,[91] α(v)-integrin-specific arginine-glycine-aspartate peptides,[92] and folic acid.[93]

There are two general approaches to the construction of boron-containing liposomes: encapsulation of boron compounds in the aqueous core of the liposome, and incorporation of boron-containing lipids in the liposome bilayer. Most of the liposomes designed for BNCT were based on the encapsulation of boron compounds such as BSH and BPA, anionic polyhedral boron hydrides with or without simple substitution patterns, various carborane derivatives (amines, polyamines, acridines, carbohydrates, etc.) in the aqueous core of the liposome.[94–98] Problems arising by the encapsulation of these compounds into liposomes are low encapsulation efficiency, changes in the physical-chemical behavior of liposomes, and boron leakage upon storage and in contact with serum. Many of the problems encountered in the encapsulation approach can be avoided by using the second approach.

Phospholipids are common lipid bilayer components of liposomes, and they have been proven to be effective anchors for boron compounds in the form of single-[93a,99] or dual-chain *nido*-carborane[88c,100,101] or *closo*-dodecaborate[102,103] phospholipid mimetics. Cholesterol is another major component of the mammalian cell membrane and most liposomal formulations. Therefore, the development of carborane-[85,86] and *closo*-dodecaborate-[104] containing derivatives of cholesterol is potentially an effective ap-

proach for delivery of boron to cancer cells via both liposomes and LDL. More recently, a novel strategy for the design and synthesis of carboranyl cholesterol mimics has been proposed. In these mimics, both the B and C rings of cholesterol were replaced with a carborane cluster (Scheme 7). The novel carboranyl cholesterol mimics are excellent lipid bilayer components for the construction of nontargeted and receptor-targeted boronated liposomes for BNCT of cancer.[91]

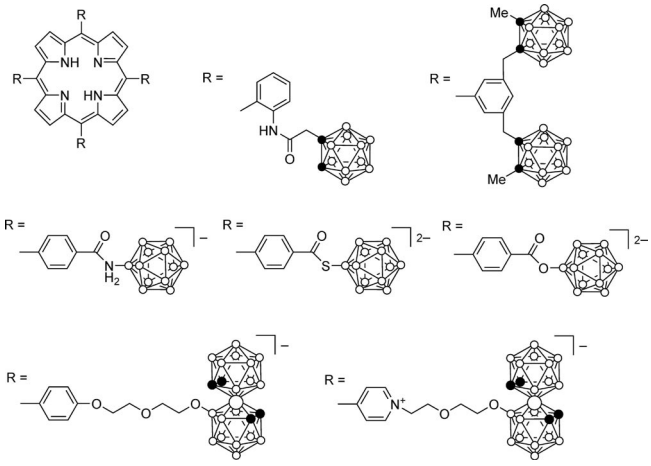


Scheme 7. Boron-containing analogues of cholesterol.

## Boronated Porphyrins and Phthalocyanines

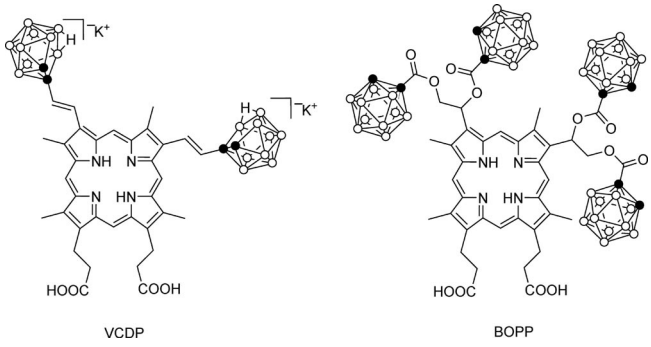
Photodynamic therapy (PDT) has become a clinically established bimodal cancer therapy whereby superficial tumors loaded with a photosensitizing porphyrin or related macrocycle are irradiated with red laser light to form an excited triplet state which reacts with molecular oxygen and other substrates to generate highly cytotoxic species (e.g. singlet oxygen, superoxide anions, hydroxyl radicals) that cause irreversible destruction of tumor cells.[105] At present, approximately ten clinical photosensitizers based on a porphyrin (Photofrin®, Visudyne®, Levulan®, Metvix®, Antrin®, Foscan®, LS11, Photochlor) or phthalocyanine (Photosens®) platform are commercially available,[106] and many others are currently being evaluated in animal models for the treatment of certain cancers and other diseases. It was reported that the LDL receptor-mediated pathway plays a key role in the delivery of porphyrins to tumor cells.[107] This caused interest in the synthesis of boronated porphyrins as possible BNCT agents and BNCT/PDT dual sensitizers.

Two approaches have been used for the synthesis of these compounds – condensation of boron-containing building blocks, on the one hand, and attachment of boron cages to natural or synthetic porphyrins and phthalocyanines, on the other hand. The first carborane-containing porphyrins were reported by Haushalter and Rudolph in 1978,[108] and this field is under extensive development.[109–112] Most of the prepared carborane-containing porphyrins are based on the *meso*-tetraphenylporphyrin skeleton and contain from one to eight *closo*- or *nido*-carborane cages. Besides carborane-based porphyrins, syntheses of *meso*-tetraarylporphyphyrins containing carba-*closo*-dodecaborate,[22a] *closo*-dodecaborate,[113] and cobalt bis(dicarbollide)[114] moieties were reported (Scheme 8).



Scheme 8. Boron-containing porphyrins.

A number of carboranyl porphyrins have been obtained on the basis of natural porphyrin derivatives such as deuteroporphyrin IX and hematoporphyrin IX, and two of them, VCDP and BOPP (Scheme 9), have been extensively studied in animals. BOPP was reported to have a tumor/normal brain ratio from 13:1 to 400:1 for different glioma models.[115,116] High boron levels in tumors (> 60 μg $^{10}$B/g tumor) were achieved in these animal studies. However, data obtained from a human Phase I clinical trial showed that intravenous injection of BOPP does not deliver therapeutic concentrations of boron to the tumors of glioblastoma patients, and dose escalation is prevented by the toxicity of this compound. Nevertheless, BOPP has shown some promise as an effective PDT photosensitizer.[117–119] More recently, it was demonstrated that convention-enhanced delivery of BOPP significantly enhances the boron concentration in tumors and produces very favorable tumor/brain and tumor/blood ratios.[120]

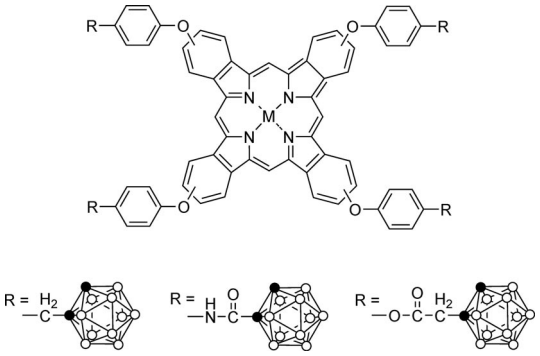


Scheme 9. VCDP and BOPP carborane-containing porphyrins.

More recently, syntheses of anionic boron hydride derivatives of the naturally occurring porphyrin systems pyropheophorbide *a*,[121] chlorine e6,[22b–22c,122] and bacteriochlorin *p*[123] have been reported.

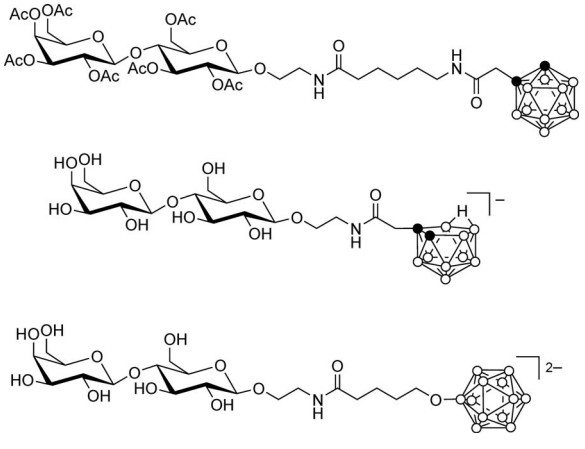
Synthesis of phthalocyanines based on boron hydride has been developed much less. After the first paper reviewed this field,[109] only a few reports have been published[124–128] (Scheme 10).



Scheme 10. Boron-containing phthalocyanines.

### Boron-Containing Carbohydrates

Synthesis of the first carborane-containing carbohydrates was described more than 25 years ago as a way of compensating for the hydrophobicity of the carborane cage and to enhance the water solubility of carborane biomolecules.[129–131] Currently, much more attention is paid to using carbohydrates as tumor-targeting agents. This form of biomolecular recognition involves binding of a carbohydrate to a lectin receptor. Endogenous lectins are found on surfaces of many normal and malignant cells and are involved in various biological functions, acting as specific receptors and/or mediating endocytosis of specific glycoconjugates. This feature has stimulated some interest in carbohydrate-mediated delivery (glycotargeting) of drugs to cells expressing the corresponding lectins.[132] Transformation of a normal cell to a tumor cell often results in a change in the lectin composition of the cell surface and is usually accompanied by over-expression of certain lectins. Attachment of a boron moiety to an oligosaccharide ligand of the lectin will lead to the preparation of boron-containing neoglycoconjugates, which can be used for targeted delivery of boron to the tumor tissues. Syntheses of various boron-containing conjugates have been reported by several research groups[133–137] and reviewed very recently.[138] Some examples of lactose conjugates with various polyhedral boron hydrides are presented in Scheme 11.



Scheme 11. Boron-containing lactoses.

## Boron Neutron Capture Synovectomy

Rheumatoid arthritis is an autoimmune disease characterized by recurrent swollen, inflamed, and painful joints. It afflicts approximately 1% of the US population. Since the cause of rheumatoid arthritis is unknown, patients are treated symptomatically. Anti-inflammatory drugs are effective in approximately 90% of all patients. In the remaining 10%, the inflammation in one or more joints will not respond to drugs, and a more severe approach is taken. In the USA, the only option is surgical synovectomy, a costly and painful procedure followed by extensive physical therapy and rehabilitation. Symptomatic relief lasts roughly 2–5 years, since the cause of rheumatoid arthritis has not been addressed. Radionuclide synovectomy using beta-particle emitters injected directly into the joint is routinely used in Europe and elsewhere and brings about the same symptomatic relief, for the same fraction of patients, and for the same length of time as surgery. Radionuclide synovectomy is less costly, less painful, and requires no rehabilitation time relative to surgery. It is, however, not approved for routine clinical use in the USA because of concerns regarding healthy tissue irradiation caused by leakage of the beta-emitter away from the joint.

Boron Neutron Capture Synovectomy (BNCS) was proposed as a way of carrying out radiation synovectomy without the concern regarding the leakage of a radioactive substance. A $^{10}$B-labeled compound injected into the joint space would be followed by local irradiation with a beam of low-energy neutrons. The experimental parameters required for the successful implementation of BNCS as a treatment modality for rheumatoid arthritis have been determined.[139] The boron neutron capture reaction could be used to selectively ablate arthritic tissue, without causing damage to other tissue and/organs, so long as highly selective and efficient boron delivery vehicles could be developed.[140–142]

## Radionuclide Diagnostics and Therapy

Initially, the labeling of polyhedral boranes with radionuclides was performed with the aim of studying the biodistribution and pharmacokinetics of boron compounds for BNCT.[143] For in vivo imaging of boron compounds, radiolabeled derivatives are of particular interest, since their biodistribution can be easily monitored by using single-photon emission computed tomography (SPECT) and positron emission tomography (PET), depending on the radionuclide employed. In many cases, radiolabeling gives detailed infor-

mation about boron pharmacokinetics that can be used to generate improved patient treatment protocols, for example, by providing information about the required dosage of tumor-seeking boron conjugates and the optimal treatment time.

Another important field is the use of boron clusters as pendant groups for attachment of radionuclides to tumor-seeking biomolecules for targeted radionuclide therapy. The principle of this mode of treatment is based on selective delivery of radionuclides to cancer cells. Due to the very high cytotoxicity of radionuclides, the use of a highly tumor-specific transport system is required. The targeting vectors used in radionuclide diagnostics and therapy are of protein nature. These may be monoclonal antibodies directed toward tumor-specific antigens or regulatory peptides binding to receptors over-expressed on or by malignant cells. The important advantage of targeted radionuclide therapy over boron neutron capture therapy is that the therapeutic concentration of radionuclides in the tumor are, as a rule, a few orders of magnitude less than the therapeutic concentration required for BNCT. As a consequence, less modification of the tumor-seeking molecule is required, which prevents loss of tumor specificity.

## Polyhedral Boron Hydrides As Carriers of Radiohalogen Labels

The most common procedures employed for radiolabeling proteins are radiohalogenations and labeling with radioactive metal ions. Halogen radioisotopes are especially attractive, since they share many chemical properties and possess a variety of half-lives and decay modes (Table 2), which enables optimization of half-life and emitted radiation, depending on the biomedical problem to be solved. Radiohalogens used in nuclear medicine today fall into two main categories: those useful in imaging applications and those useful in therapy applications. At the same time; radiohalogens for imaging applications could be divided into two groups – those for SPECT and PET.[144] Today, nuclear medicine imaging is carried out with highly sophisticated SPECT instruments available in most hospitals worldwide. Another imaging modality, PET, is being used clinically, but is not as widely available.

Table 2. Radiohalogens used in imaging and therapy.

| Nuclide | Half-life | Mode of decay | Possible application |
|---|---|---|---|
| $^{18}$F | 1.8 h | $\beta^+$ | PET imaging |
| $^{75}$Br | 1.6 h | $\beta^+$ | PET imaging |
| $^{76}$Br | 16 h | $\beta^+$ | PET imaging |
| $^{77}$Br | 2.4 d | electron capture | SPECT imaging |
| $^{80m}$Br | 4.4 h | Auger $e^-$ | therapy |
| $^{82}$Br | 35.3 h | $\beta^-$ | therapy |
| $^{123}$I | 13.2 h | electron capture | SPECT imaging |
| $^{124}$I | 4.2 d | $\beta^+$ | PET imaging |
| $^{125}$I | 59.4 d | electron capture | therapy |
| $^{131}$I | 8.0 d | $\beta^-$ | therapy |
| $^{211}$At | 7.2 h | Auger $e^-$ | therapy |

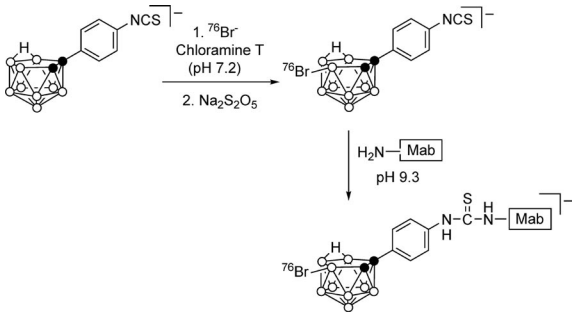
Thus, specific targeting of halogen radionuclides is a promising approach to improve diagnosis and treatment of tumors. A problem in using radiohalogens for labeling tumor-targeting proteins and peptides is that the commonly used radiohalogenation methods provide labels, which, after internalization and lysosomal digestion, rapidly "leak" from malignant cells as radiohalogenated degradation products. The main reason for such leakage is free diffusion of the radiometabolites through lysosomal and cellular membranes.[145] Dehalogenases and peptidases have been considered as enzyme systems responsible for the dehalogenation of radiohalogenated proteins in vivo. This results in increased accumulation of the radioiodide in the thyroid, whereas the radiobromide anion is not excreted but remains distributed in the extracellular space, decreasing the contrast of the image. If the radiometabolite cannot penetrate the cellular membrane, it will be trapped intracellularly until its excretion by exocytosis. Since exocytosis is relatively slow in comparison with diffusion, the cellular retention and, consequently, the tumor accumulation of the radionuclide are improved. This resulted in a new concept in which cellular retention can be improved by placing a radiohalogen label on a structure that cannot penetrate the cellular membrane and remain trapped inside the cell.

Polyhedral borane anions were found to be reasonable linkers for the attachment of radiohalogens to tumor-targeting proteins and peptides. For such applications, the following features of these compounds are important: (1) the high strength of the boron–halogen bonds (higher than those in their carbon–halogen counterparts); (2) the absence of enzymatic systems for cleavage of the boron–halogen bond, due to the very exogenous nature of such compounds; and (3) the negative charges of polyhedral borane anions, which may improve intracellular retention of bound radiohalogens without elevated uptake by the kidneys.

Radionuclide targeting by using polyhedral borane anions as pendant groups can, in many cases, utilize compounds which have been developed for use as boron carriers in BNCT. Functional groups which enable boron hydride coupling with tumor-seeking molecules are amino acids [-CH($NH_2$)COOH], amines (-$NH_2$), acids (COOH), isocyanates (-NCO), and isothiocyanates (-NCS). A number of derivatives containing these functionalities were prepared earlier.[4] The use of polyhedral boron hydrides as carriers of radiohalogen labels has been reviewed recently.[146] Therefore, here we will describe only some of the most characteristic examples as well new results reported in the last years.

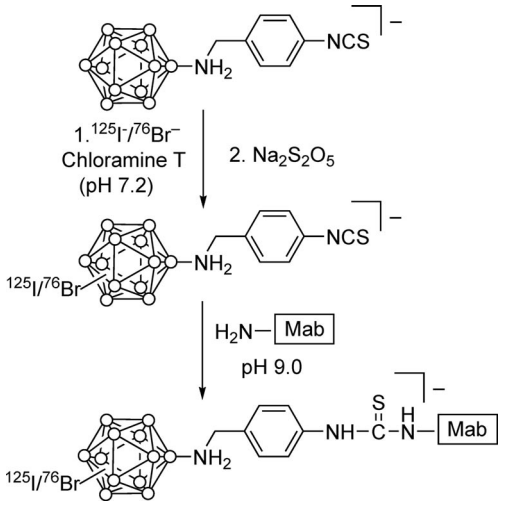
One example is a *p*-isothiocyanatophenyl derivative of *nido*-carborane, [7-(4-$SCNC_6H_4$)-7,8-$C_2B_9H_{11}$]$^-$, synthesized earlier for coupling with anticarcinoembryonic antigen IgG for BNCT.[147] This compound was labeled with the positron-emitting nuclide $^{76}$Br and coupled to anti-HER2 antibody trastuzumab used for the therapy of breast cancer. The label was found to be stable in vitro under physiological and denaturing conditions, and retention of immunoreactivity of trastuzumab after labeling was demonstrated in a cell binding test (Scheme 12).[148]




Scheme 12. Labeling of antibodies with $^{76}$Br-brominated [7-(4-$SCNC_6H_4$)-7,8-$C_2B_9H_{11}$]$^-$.

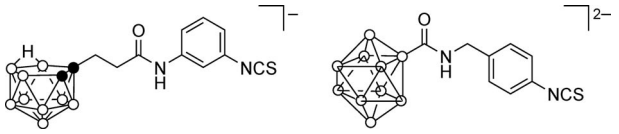
Similarly, the isothiocyanate derivative of the *closo*-dodecaborate anion, $[B_{12}H_{11}NH_2CH_2C_6H_4$-4-NCS]$^-$, prepared previously for a BNCT project,[13a] was used for radiolabeling of proteins. This compound was labeled with $^{125}$I and coupled to anti-HER2/neu humanized antibody trastuzumab[149] (Scheme 13). The study of the biodistribution of a radioconjugate prepared in mice revealed decreased radioactivity uptake by the thyroid in comparison with the directly radiolabeled antibody. Effective targeting of a head and neck squamous cell carcinoma xenograft model by using the chimeric monoclonal antibody cMAb U36 radioiodinated with a *closo*-dodecaborate linker was demonstrated.[150,151] The labeling of the isothiocyanate derivative with $^{76}$Br followed by coupling to anti-HER2/neu humanized antibody trastuzumab was also described (Scheme 13).[152] A comparative study of conventional pendant groups for radiohalogen labeling and those based on the *nido*-carborane and *closo*-dodecaborate isocyanates demonstrated that the last one has improved intracellular retention in vitro in comparison with the other labeling methods.[153] At the same time, the use of the isocyanate derivative for labeling low-molecular-weight polypeptides




Scheme 13. Labeling of antibodies with $^{125}$I-iodinated and $^{76}$Br-brominated $[B_{12}H_{11}NH_2CH_2C_6H_4$-4-NCS]$^-$.

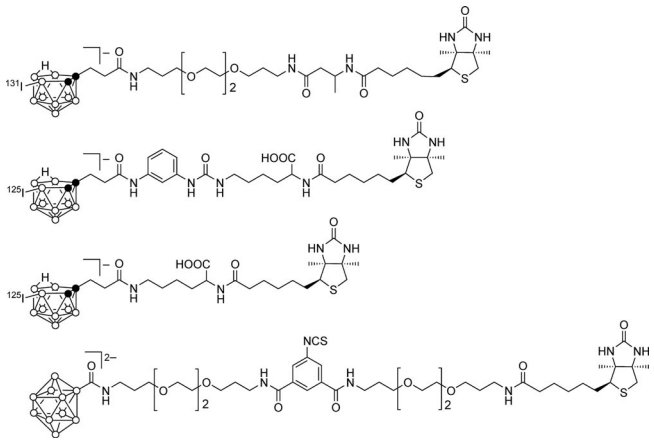
such as Affibody ZHER2:342 was found to be noneffective.[154]

$^{131}$I-labeling of protein conjugates with isothiocyanate derivatives of the 7,8-dicarba-*nido*-undecaborate and *closo*-decaborate anions have been reported (Scheme 14).[19a]




Scheme 14. Anionic boron hydride isothiocyanates.

Another approach termed "pretargeting", employs biotin (vitamin H) derivatives to deliver therapeutic radionuclides to cancer cells in vivo. In the pretargeting approach, a monoclonal-antibody–streptavidin conjugate (mAb–SAv) is injected and allowed to bind antigens on cancer cells. After a period of time sufficient for adequate tumor targeting (e.g. 24 h), a clearing agent is used to remove excess mAb–ASv conjugate from blood. After an appropriate time (e.g. 1–3 h), the radiolabeled biotin derivative is administered in such a way that it can bind with the pretargeted mAb–SAv on cancer cells as a result of the extraordinarily high biotin–streptavidin affinity. At present, a number of boron-containing derivatives of biotin are synthesized and radioiodinated, and their biodistribution is studied[19a,155] (Scheme 15). The *closo*-decaborate anion was proposed as the best pendant group because of its higher reactivity in halogenation reactions and the possibility of its use for direct radiolabeling of boronated antibody conjugates.[19]

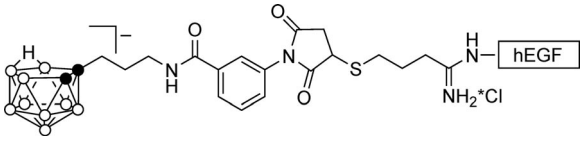



Scheme 15. Radioiodinated boron-containing derivatives of biotin.

The use of polyhedral borane anions as pendant groups for attachment of the α-emitting radionuclide $^{211}$At to tumor-seeking biomolecules is of special interest. The problem is that direct oxidative astatine labeling of proteins gives a very weak astatine–protein bond, which prohibits its application in targeted radionuclide therapy. Study of the *nido*-carborane conjugates with tumor-binding protein human epidermal growth factor hEGF revealed a higher labeling yield (70%) than that obtained by indirect labeling with

*N*-succinimidyl astatobenzoate, whereas in vitro stability is close to the stability hEGF labeled with astatobenzoate (Scheme 16).[156]




Scheme 16. Labeling of hEGF with astatinated *nido*-carborane.

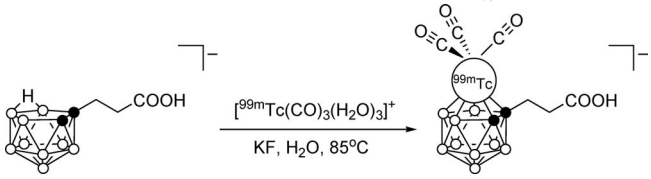
Wilbur and co-workers, concentrating on the use of the *nido*-carborane and *closo*-decaborate derivatives for astatination of biotin, found that *nido*-carborane can be directly labeled in 60–75% yield and the biotin derivatives prepared are more stable to in vivo deastatination than aryl astatine derivatives.[19,155,157]

### Polyhedral Boron Hydrides As Chelators for Radiometals

An alternative approach involves the radiolabeling of proteins that have been covalently modified with metal chelating groups. The ligand systems used for metal complexation include derivatives of EDTA, DTPA, DOTA, TETA, NOTA, etc. It is essential for effective imaging that the radioactive metal ions remain complexed by the protein–chelator conjugate. A particular concern in this regard is the competition for metal binding from serum transferrin, which is known to remove metal ions from chelates in vivo. Of utmost importance is the magnitude of the radionuclide-chelator dissociation rate, which must be minimal. Most desired would be an especially robust chelation system that is promptly excreted along with tightly held radiometal even if the antibody or the chelate-antibody linker molecule suffered catabolic degradation. One possible solution to this problem was proposed by using an extraordinarily stable metallacarborane cluster readily prepared in aqueous solution and bearing organic substituents for conjugation purposes. A pendant arm, such as a carboxylate functional group, can be used to form an amide linkage with biomolecules by established peptide coupling methodology.[158]

$^{99m}$Tc is one of the most widely used radionuclides for nuclear medicine imaging. This is due to the favorable properties of this isotope: the emission of a 140-keV γ-ray with an abundance of 89% and a half-life of 6.0 h.[158–160] The *nido*-carborane cage has been proposed as a pendant group for labeling proteins with $^{99m}$Tc. High-yield preparative methods for the synthesis of $[3,3,3\text{-}(CO)_3\text{-}3,1,2\text{-}MC_2B_9H_{11}]^-$ and $[1\text{-}HOOCCH_2CH_2\text{-}3,3,3\text{-}(CO)_3\text{-}3,1,2\text{-}MC_2B_9H_{10}]^-$ (M = Re, $^{99}$Tc) were developed.[161] More recently, the radiolabeling of the *nido*-carborane derivatives with $^{99m}$Tc in water under weakly basic conditions was described[162–164] (Scheme 17).

The high stability of the radiometallacarborane obtained was demonstrated by its incubation with a 1000-fold excess of cysteine or histidine in phosphate-buffered saline (pH 7.2) solution at 37 °C for 24 h.[162]




Scheme 17. Synthesis of $^{99m}$Tc-labelled metallacarborane.

## Boron Clusters As X-ray Contrast Agents

Another possible medical application of polyhedral boron hydrides is in X-ray contrast imaging. Highly iodinated molecules have application in medicine as X-ray contrast agents due to the opacity of the iodine atoms to low-energy X-rays.[165] Even with the recent phenomenal growth of MRI and ultrasound procedures, X-ray imaging studies remain the workhorse of modern radiology (currently 75–80% of all diagnostic imaging procedures are X-ray-related). Today, iodinated X-ray contrast agents are used in more than 20 million procedures annually in the United States, mainly in computed tomography and angiographic applications. The worldwide market for X-ray contrast media in 2007 was estimated at $4.2 billion.

Current X-ray contrast agents are principally composed of substituted iodinated benzene compounds and their dimers. Most of the iodinated benzene derivatives have three iodine atoms substituted in an alternating fashion with other substituents that are designed to increase water solubility and decrease in vivo toxicity. Although the current radiographic contrast media have been optimized over many years of development, improvements are still being sought. One of the methods of improving contrast agents is to increase the iodine content in the molecules. An increase in the percentage of molecular weight due to iodine in a contrast agent from 28.7 to 37.5% is known to double the contrast of the radiographic image at selected X-ray energies. This fact suggests that chemical moieties other than benzene rings, which can be more highly iodinated, might present new alternatives for contrast agents. Anionic polyhedral boron hydrides can be easily halogenated and have the potential for incorporation of a large number of iodine atoms per molecule (molecules containing 65–85 wt.-% of iodine can be obtained).[166–168]

## Carboranes As Pharmacophores in Drug Design

The exceptional hydrophobic character and the spherical geometry of the carboranes[38,169] might allow them to effectively act as hydrophobic pharmacophores. This approach was first applied when phenylalanine and tyrosine residues in various bioactive peptides and polypeptides were replaced with the *o*-carborane cluster.[38,41,170,171] Later, the synthesis of the carborane analogue of the antiestrogen tamoxifen containing the carborane fragment in place of the A ring phenyl group was reported.[172]

Endo et al. proposed to use carboranes as the cores from which to construct a series of potent estrogen receptor ago-

nists[173,174] and antagonists.[174,175] The rationale behind the design of the agonists was that a hydrophobic carborane cluster could be used in place of the C and D rings of 17β-estradiol, which would play an important role in the binding of the steroid to the estrogen receptors through hydrophobic interactions. Good binding to the receptors and estrogenic activity requires that the appropriate hydrophobic group be located adjacent to a phenolic ring, in addition to having an appropriately positioned H-bonding substituent. As a result, a series of carborane derivatives containing phenolic substituents were prepared. The position of the phenolic OH group, the nature of the substituents at the remaining carborane carbon atom, and the choice of carborane isomer were all varied to obtain structure–activity relationships. One of the carborane compounds prepared was found to be ten times more active than 17β-estradiol in a luciferase reporter gene assay (Figure 1).

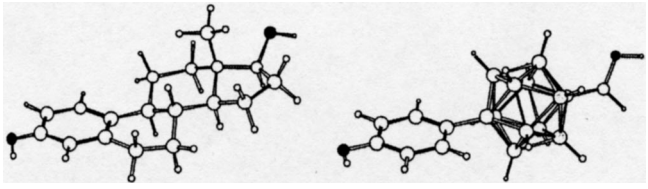
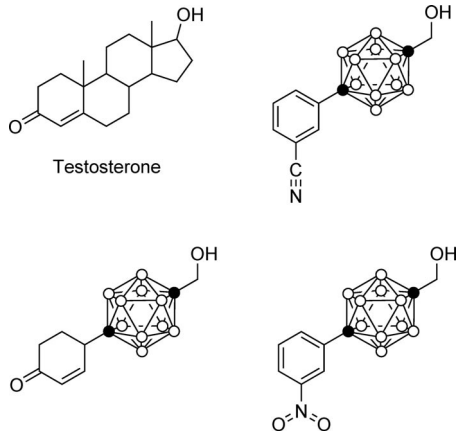


Figure 1. Molecular structures of 17β-estradiol and its *p*-carborane analogue.[173a] Reproduced by permission of the Royal Society of Chemistry.

Endo et al. prepared and screened a series of carborane-based retinoic acid receptor agonists[176] and antagonists[177] having both amide and amine cores, containing carborane substituents at the 3- and 4-positions of the central aryl group. More recently, syntheses of novel carboranyl testosterone (Scheme 18)[178] and cholesterol (Scheme 7)[91] mimics were reported.




Scheme 18. Carborane-based analogues of testosterone.

Later, carborane analogues of nonsteroidal anti-inflammatory drugs, flufenamic acid, and diflunisal, were synthesized, and some of them were found to be potent inhibitors of transthyretin amyloid formation.[179]

The use of carboranes as pharmacophores in the design of new pharmaceuticals was a subject of several reviews.[7b,7c,180] However, it should be noted that, at the current high cost of carboranes, their practical application as substituents of aromatic rings in drug design does not seem to be achievable today.

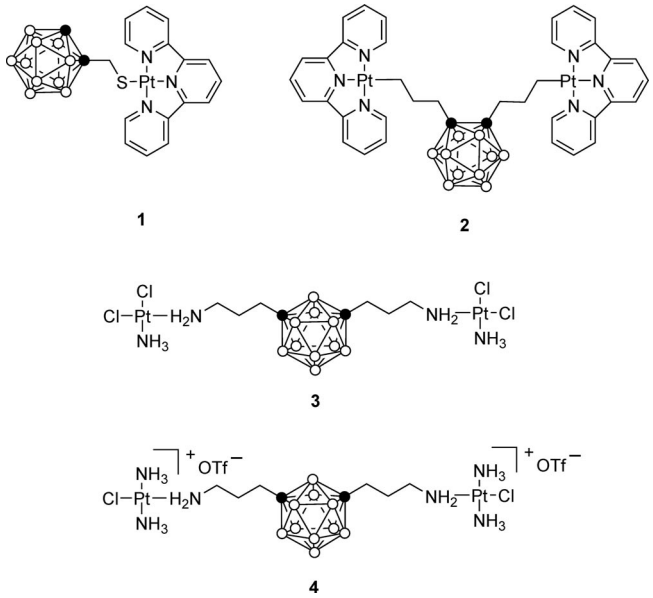
## Carborane-Based Antitumor Agents

Besides the above-described systematic applications of polyhedral boron hydrides in medicine, which are based on certain properties of the boron nucleus or boron clusters as structural elements of drugs, some metal derivatives of carboranes demonstrate rather high antitumor activity themselves. Synthesis and properties of these compounds have been surveyed very recently,[181] and here we will describe only some of the most characteristic platinum and tin derivatives of carboranes.

### Platinum(II) Complexes with Carborane-Containing Ligands

The clinical utility of platinum anticancer agents is well known. One leading anticancer agent, cisplatin, is useful in treating some human cancers but is limited by both its side-effects and the ability of some cancer cells to acquire a resistance to the drug.[182] Therefore, it is desirable to develop a new platinum-based anticancer drug with a broader spectrum of activity, improved clinical efficacy and reduced toxicity, which is better than cisplatin.

A series of platinum(II) complexes containing carborane-based ligands were prepared as DNA metallointercalators for BNCT[183,184] by Rendina et al. (Scheme 19). Some of them were found to have rather high anti-cancer in vitro activity against the L1210 murine leukemia cell line and its




Scheme 19. Structures of some platinum(II) complexes with carborane-containing ligands.

cisplatin-resistant variant (L1210/DDP) as well as against the 2008 human ovarian cancer cell line and its cisplatin-resistant variant (2008/C13) (Table 3).

Table 3. $IC_{50}$ (μM) values for some platinum(II) carborane complexes against selected tumor cell lines.

| Compound | L1210 | L1210/DDP | 2008 | 2008/C13 |
|---|---|---|---|---|
| **1** | 1.6 | 0.9 | 1.7 | 2.1 |
| **2** | 0.9 | 0.8 | – | – |
| **3** | 2.0 | 2.5 | 13 | 13 |
| **4** | 1.1 | 1.4 | 5.5 | 5.6 |
| Cisplatin | 0.5 | 6.9 | 0.6 | 10 |

The relative cytotoxicities of the $Pt^{II}$–carborane complexes are similar in both the cisplatin-sensitive and cisplatin-resistant cell lines. This clearly indicates that the mechanism of cytotoxicity of the $Pt^{II}$–carborane complexes is not affected by the cisplatin resistance mechanism(s). Preliminary in vitro DNA-binding experiments indicate that the complexes are capable of targeting plasmid DNA.

### Organotin Derivatives of Carboranes

Antitumor in vitro activity of many organotin derivatives have been well documented.[185] A number of organotin derivatives of carboranes were synthesized, and the antitumor activity of some of them was determined (Figure 2, Table 4).[186,187]

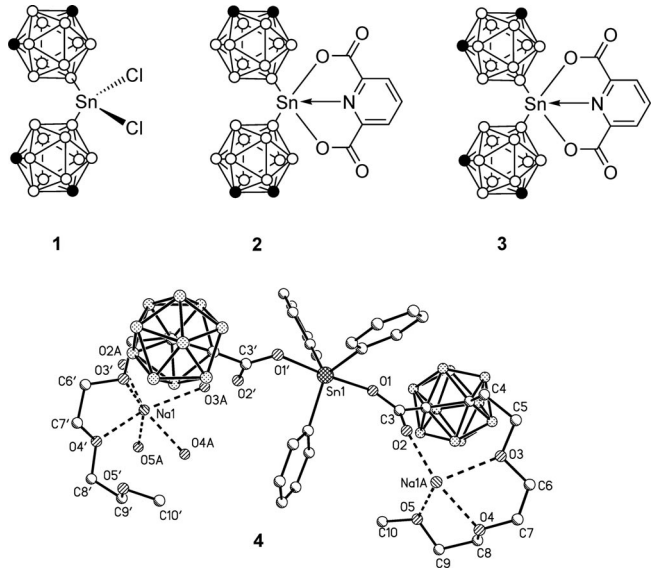



Figure 2. Structures of some organotin derivatives of carboranes.

Table 4. $IC_{50}$ (ng/ml) values for some organotin carboranes against selected tumor cell lines.

| Compound | **1** | **2** | **3** | **4** | Cisplatin | Doxorubicin |
|---|---|---|---|---|---|---|
| MCF-7 | 5 | 10 | 11 | 44 | 800 | 1200 |
| WiDr | 31 | 102 | 45 | 37 | 8 | 20 |

## Metallacarboranes As Inhibitors of HIV Protease

A new application of polyhedral boron hydrides in medicine results from the finding that cobalt bis(dicarbollide) and some its derivatives act as potent and specific inhibitors of HIV-1 protease.[188,189] The structure of the complex of HIV protease with the parent cobalt bis(dicarbollide) was determined by protein crystallography. It was shown that two cobalt bis(dicarbollide) anions bind to the hydrophobic pockets formed by side-chains of HIV protease residues Pro-81, Ile-84, and Val-82 and covered by flap residues Ile-47, Gly-48, and Ile-54.[188] Exo-polyhedral substitution in the parent cobalt bis(dicarbollide) introduces additional noncovalent interactions, leading to the dramatic improvement in inhibition efficacy and selectivity.[190]

Another report describes inhibition of HIV-1 protease by tetraphenylporphyrin–cobalt bis(dicarbollide) conjugates.[191] It should be noted here that specific inhibition of HIV-1 protease by some carborane-containing porphyrins has been reported earlier.[192]

## Conclusions

This paper presents a short survey of current and perspective directions of the application of polyhedral boron hydrides in medicine. Boron neutron capture therapy of cancer remains the main area of research, and regular biennial international conferences on neutron capture therapy are the best evidence of the importance of this field (the latest one, 13th International Congress on Neutron Capture Therapy, was held in November 2008 in Florence, Italy). However, over the past decade, the scope of medicinally centered boron hydride chemistry has expanded to such important fields as radionuclide diagnostics and drug design, including anti-AIDS agents. As recognition of the growing role of the bioorganic/inorganic chemistry of boron, the first ESF Exploratory Workshop on BioBor – Exploring New Opportunities on Boron Chemistry towards Medicine – was held in May 2008 in Lodz (Poland). The role of radionuclide imaging in the application to BNCT was discussed at the International Workshop JRC E&IA "PET for BNCT" in November 2008 in Pisa (Italy). It should be noted that the medical application of boron compounds is one of the most important subjects discussed at regular international and regional conferences on boron chemistry (the latest one, 13th International Conference on Boron Chemistry, was held in September 2008 in Platja d'Aro, Spain).

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