Design of Boron Carriers for Neutron Capture Therapy

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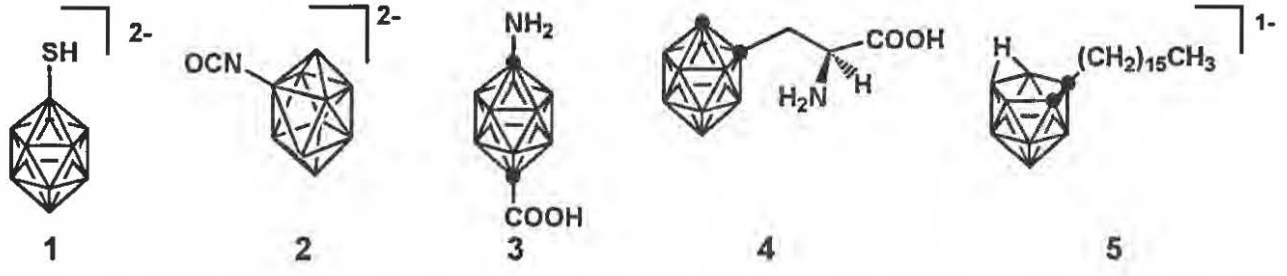
Neutron Capture Therapy (NCT) is a binary method for treating cancer. The first part involves selective uptake of a suitable atom in sufficient concentration by the target cells. The second part involves bombardment of the target tissue with thermal (~0.025 eV) neutrons. Boron-10 is an exceptionally suitable atom for NCT because of its high neutron capture cross-section and the stability of its compounds. The resulting fission fragments (α, ^7Li) kill the cell.[1] The migratory range of these particles is ~10 μm, which is approximately one cell diameter. Therefore, the damage is localized to the targeted cell and its immediate neighbors.

Boron carriers of choice are almost exclusively derivatized cage compounds due to their stability and high boron content. These cages are either modified by simple derivatization or incorporated into biologically relevant molecules such as peptides, nucleotides, lipids and barbiturates. There are two ways to deliver these compounds to tumor cells. The first method is arterial injection of the compound, allowing its polarity and shape to dictate its uptake. Results have been mostly disappointing in this area. Although this route is still being pursued, a more practical method has recently been developed. Liposomes accumulate in tumors in far greater numbers than normal tissue, and therefore are used to either encapsulate boron compounds for delivery or incorporate them as part of the membrane.[1-4]

Closo boranes $B_{10}H_{10}^{2-}$ and $B_{12}H_{12}^{2-}$ have been extensively studied and derivatized as potential BNCT agents.[5-6] The classic example is $B_{12}H_{11}SH^{2-}$ (BSH) **1**, which was first tried in Japan with limited success and is now being reevaluated in Japan, U.S. and Holland. Many BOH analogues have also been synthesized.[7-8] A recent development in this class is the synthesis and promising evaluation of $B_{10}H_{10}NCO^{2-}$ (**2**). It is proposed that **2** binds to proteins by reacting with an amine group on an amino acid to give a $—NH_2C(O)NH–B_{10}H_9$ derivative.[9]

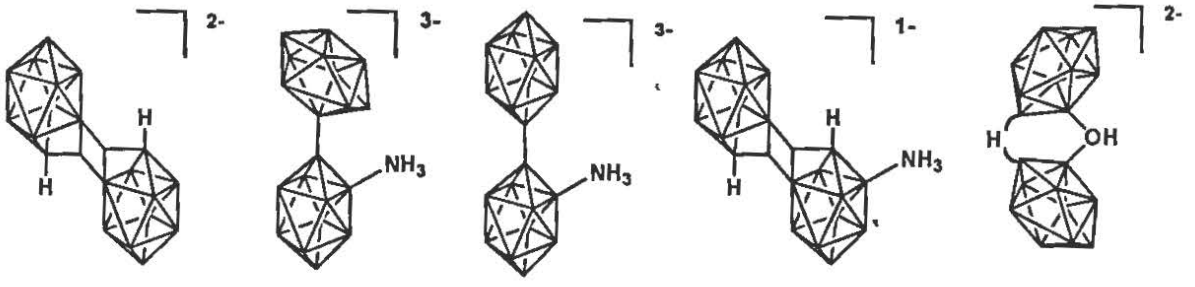


1 2 3 4 5

Carboranes have also been extensively used in BNCT drug design, mainly because they can be easily functionalized. *Closo* carboranes, especially dodecacarborane ($C_2B_{10}H_{12}$) are of particular interest due to their remarkable stablity. One way to achieve this functionalization is by lithiating the carborane carbons followed by reacting with an organic electrophile. Some of derivatives obtained in this fashion include the *p*-aminocarboxycarborane **3** [10] and L-*o*-carboranylalanine **4** [11]; the latter is currently undergoing animal studies. *Nido* carboranes have also been used as potential agents. A notable

example is *nido*-7-hexadecyl-7,8-$C_2B_9H_{11}$ (1-) (**5**), which has been incorporated into the membrane of liposomes with promising results. To synthesize this compound, the acetylide $CH_3(CH_2)_{15}C{\equiv}CH$ adds to *nido* $B_{10}H_{14}$ to give the [*closo*-1-$CH_3(CH_2)_{15}$-$C_2B_9H_{11}$]. This compound then converts to *nido* carborane by reacting with KOH.[4]

Decaborane dimers and their derivatives comprise another approach to BNCT drug design. The 3c-2e bond connecting the two decaborane cages in $[B_{20}H_{18}]^{2-}$ (**6**) can be attacked by a nucleophile.[12] The nucleophilic attack of $NaNH_2$ formed *in situ* by reacting liquid NH_3 and $NaC{\equiv}CH$ converts compound **6** to [*ae*-$B_{20}H_{17}NH_3]^{3-}$ (**7**), a promising BNCT agent.[3] The *ae* denotes that the axial boron on one of the cages is attached to an equatorial boron on the other. The axial-axial compound, [a^2-$B_{20}H_{17}NH_3]^{3-}$ (**8**) can be obtained by treating the *ae* compound first with acid (TFA in CH_3CN) and then with NaOH.[3,12] Hawthorne and co-workers suggest that inside the cell, **7** undergoes a two electron oxidation to form compound $[B_{20}H_{17}NH_3]^{1-}$ (**9**).[3] In support of this proposal, the oxidation potential of both isomers of $[B_{20}H_{17}NH_3]^{3-}$ is >0.5 V lower than $[B_{20}H_{18}]^{2-}$ which is known to undergo oxidation.[3] Inside the cell, **9** could react with intracellular nucleophiles such as amines on a protein. They were not able to synthesize **9** directly by oxidation of **7** because of the extreme instability **9** which reacts further to give other reduced species. The ^{11}B NMR spectra of the product mixtures showed a variety of decaborane dimers with more than one substituent.



6 **7** **8** **9** **10**

Efforts to make new decaborane dimer compounds that are easily derivatized has led to the synthesis and characterization of the first hydride-hydroxy double bridge decaborane dimer, [μ-$B_{20}H_{17}OH]^{2-}$ (**10**). The μ-OH can be easily deprotonated (pKa ~3) to give [μ-$B_{20}H_{17}O]^{3-}$. Heating this deprotonated species in acetonitrile in presence of an alkyl halide (RX) gives [μ-$B_{20}H_{17}OR]^{2-}$ in 90% yield, demonstrating the efficacious functionalization of the hydroxyl oxygen.[13]

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