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# ADVANCES AT THE INTERFACE OF POLYHEDRAL BORANE CHEMISTRY AND MEDICINE

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# ADVANCES AT THE INTERFACE OF POLYHEDRAL BORANE CHEMISTRY AND MEDICINE

#### M. FREDERICK HAWTHORNE

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I first met Gordon during the autumn of 1960 when we were both located at Harvard. Gordon was an Assistant Professor of Inorganic Chemistry while I was on temporary appointment as a Visiting Lecturer teaching Paul Bartlett's graduate course on organic chemistry. My stay at Harvard was made possible by a leave of absence from the Rohm and Haas Company, Redstone Arsenal Research Division. Gordon's research at the time was concerned with the study of the NMR phenomena associated with the acid-base complexes of boranes and Lewis bases. He was just beginning to enter the emerging field of modern organometallic chemistry. My interests at that time, and since, were centered upon the exploratory chemistry of the larger boranes, polyhedral borane anions and the carboranes. I had not yet discovered metallacarborane chemistry, an event of 1965. Both Gordon and I interacted scientifically with Bill Lipscomb during our time at Harvard. This was a truly exciting era since Lipscomb was developing his bonding theory for boranes and rapidly determining the structures of a variety of borane derivatives made available by the research community. Early in 1961 I returned to my industrial position and in 1962 I became a Professor of Chemistry at the University of California, Riverside. Gordon returned to England as a Professor of Inorganic Chemistry at Queen Mary College, the University of London. Later, Gordon became a Professor of

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Inorganic Chemistry at the University of Bristol with astounding success.

Throughout the years Gordon has always provided me with invitations to participate in important scientific meetings and lectures in Britain. The first instance in which Gordon entertained me occurred in 1963 when he arranged my appointment as a special lecturer at the University of London and several other universities. The number of invitations which Gordon has extended to me over the years is too large to recall, but I shall always be grateful for his friendship and help extended to me in the earliest part of my career. Consequently, I am extremely grateful for the opportunity to attend this meeting in Waco and to interact with my old friend, Gordon Stone. I wish him well even though he insists upon drawing dicarbollide-containing structures "upside-down"!

Keywords: carboranes, closomers, metallacarboranes, polyhedral boranes

#### POLYHEDRAL BORANE AND CARBORANE CHEMISTRY

Since the late 1950s the chemistry of boranes has been on a new track. The original borane chemistry (Borane Chemistry of the First Kind) was immensely amplified and made nearly unrecognizable by the discovery of extremely stable polyhedral ions and molecules based upon Archimedean structures and having formal connections to B<sub>n</sub>H<sub>n</sub><sup>2-</sup> species by substitution of cage BH groups by heteroatom-containing vertices chiefly comprised of CH and metallic elements from throughout the periodic table. These are conveniently grouped in Borane Chemistry of the Second Kind. In addition to these generalities, it is also obvious that boron and carbon bear a special relationship to each other as neighbors in the periodic table. Approximately, one might expect the catenation properties of carbon chemistry to be reflected in the chemistry of boron and this qualitative expectation is met by the ubiquitous appearance of polyhedral borane chemistry. Consequently much of what my research has entailed beyond the discovery stage has been aimed at the utilization of second kind borane chemistry in advancing the medical arts and materials science.

Scheme 1 summarizes the field of organoborane chemistry as I see it at the moment, while Scheme 2 lists unique functions of borane of the second kind.

#### The First Kind

- Comprised of small boranes and their reactions.
- Most useful as reagents in organic syntheses.
- · Analogous to aliphatic organic species.
- · Designed reactivity.

#### The Second Kind

- Based upon the organic and organometallic derivatives of polyhedral borane and carborane structures.
- Analogous to aromatic organic species.
- Structural scope is second only to that of organic chemistry.
- Designed function.

Scheme 1. Two kinds of organoborane chemistries. (Figure appears in color online.)

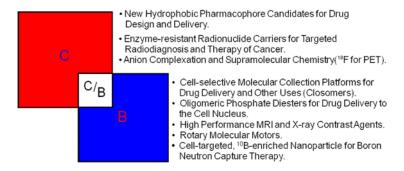
Examples of molecular building blocks utilized in this work are explained in Schemes 3 and 4 in which the icosahedron and Archimedean bicapped anti-prism are the models for structural design of the most commonly used borane components.

#### **BORON NEUTRON CAPTURE THERAPY (BNCT)**

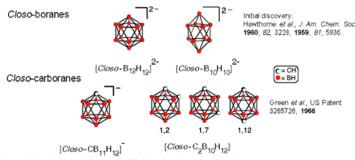
Scheme 5 illustrates the rudiments of the BNCT method for cancer therapy. This highly selective and effective method has been studied since 1954 when neutrons became available for peaceful purposes.

### Designed Function

Fusion of Borane, Organic and Metal Cluster Chemistries



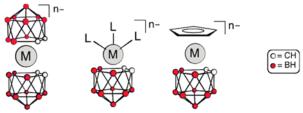
Scheme 2. Unique functions of boranes of the second kind. (Figure appears in color online.)



- Aromatic icosahedral species contain 26 delocalized cage-bonding electrons.
- Derivatives are formed by the substitution of hydrogen at BH and CH vertices or by substitution of B by elements other than carbon.
- Extensively substitution icosahedral scaffolds demonstrate variable molecular size including nanoscale, ionic charge, organofunctionalities, hydrophobicity, electronic and magnetic properties.
- Multiple organofunctionalization provides novel structures having unique applications in biomedicine and materials science.

Scheme 3. Aromatic *closo*-borane and -carborane construction modules. (Figure appears in color online.)

The basis of the method is the high nuclear capture cross-section for  $^{10}$ B (ca 4000 Barns) compared to other light elementals that comprise living tissue ( $10^5-10^4$  smaller). The reason BNCT is not available today is due to: (a) poor selection of cancer target for validation (Glioblastoma Multiforme, GBM), an incurable brain cancer; (b) the inability of agent synthesis to be carried through to evaluation of efficacy; and (c) the high cellular concentration of  $^{10}$ B required for targeting tumors ( $10^{-3}$  to  $10^{-4}$  M). My recent move to the University of Missouri, Columbia,



Hawthorne et al., J. Am. Chem. Soc. 1965, 87, 3987.

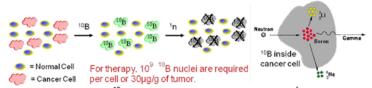
M = Transition, main group, lanthanide and actinide metals in a variety of formal oxidation states.

- A huge number of structures are available having a variety of cage geometries, with and without carbon vertices, as well as variable numbers and types of metal centers and substituents.
- Excellent chemical, thermal and photochemical stabilities; redox and magnetic properties; variety of sizes, shapes and hydrophobicities.

Scheme 4. Metallacarborane construction modules. (Figure appears in color online.)

$$^{10}B + ^{1}n \longrightarrow ^{7}Li^{3+} + ^{4}He^{2+} + \gamma + 2.4 MeV$$

- Neutron X- section of <sup>10</sup>B is about 10<sup>4</sup> to 10<sup>5</sup> larger than that of all other light elements.
- The <sup>7</sup>Li<sup>3+</sup> and <sup>4</sup>He<sup>2+</sup> ions have short trajectories in tissue and create ionization damage in cancer cells, notably DNA double-strand breaking.
- Boron-10 is selectively delivered to cancer cells by various means (targeting tumor cells with liposomes and related nanoparticles using the Enhanced Permeability and Retention effect).

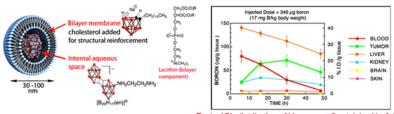


High concentration of <sup>10</sup>B is required in the tumor volume (10<sup>-4</sup>M)

Scheme 5. Boron neutron capture therapy of cancer. (Figure appears in color online.)

with its 10 MW nuclear reactor, a new neutron beam and the establishment of an institute (International Institute of Nano and Molecular Medicine), which, for the first time, brings together chemistry, medicine, and nuclear capability in one location, will allow us to establish a renaissance of BNCT research, which is based upon less demanding tumor models than GBM and at the same time utilizes targeted nanoparticle delivery of <sup>10</sup>B to tumor cells. Scheme 6 illustrates the preliminary biodistribution data obtained using liposomes as nano delivery vehicles. Research at Missouri will soon begin.

- Normal cell-targeting methods using antibodies or cell-targeting peptides cannot deliver the required number of <sup>10</sup>B nuclei per cell; cell receptors are saturated at therapeutic concentration(10<sup>-4</sup> M).
- Small unilamellar liposomes (30-120 nm diameter) are most promising since they are self-targeting to cancer cell
  interior and/or endothelial cells in tumor vascular supply.

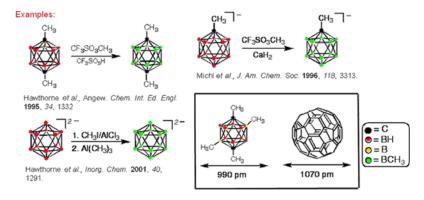


Typical Liposome Constituents and Structure.

Typical Biodistribution of Liposomes Containing Na<sub>3</sub>[a<sup>2</sup>-B<sub>20</sub>H<sub>17</sub>(en)] and Na[C<sub>2</sub>B<sub>9</sub>H<sub>11</sub>(CH<sub>2</sub>)<sub>15</sub>CH<sub>3</sub>] in BALB/c Mice Bearing EMT6 Tumors.

Scheme 6. Boron-containing liposomes as nanoparticle delivery vehicles. (Figure appears in color online.)

Methylation places a hydrophobic shell around cage structures, increasing hydrophobicity and chemical stability

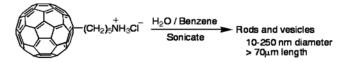


Scheme 7. Permethylation of icosahedral borane derivatives. (Figure appears in color online.)

#### HYDROPHILIC CARBORANE SURROGATES FOR C<sub>60</sub>

The near spherical shape of the icosahedron and the ready availability of the carboranes suggested that the decoration of the carborane surface with methyl groups would increase the effective size of the carborane cage to near that of  $C_{60}$ . Scheme 7 describes this approach and points out the similarity in size of the fully methylated carborane and the  $C_{60}$  molecules.

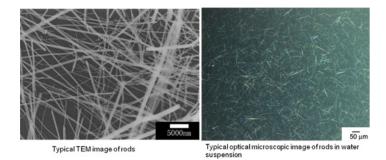
In order to test this hypothesis we carried out the comparison of the  $C_{60}$  chemistry of Tour and that of a similar carborane derivative.



Tour et al., Angew. Chem. Int. Ed. Eng. 1999, 38, 2403.



Scheme 8. Self-assembly of rod structures. (Figure appears in color online.)



Scheme 9. TEM and optical images of self-assembled rods. (Figure appears in color online.)

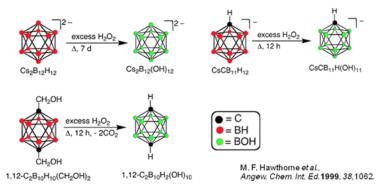
Scheme 8 describes this approach and Scheme 9 presents TEM and optical images of the resulting self-assembled rod product.

This result strongly emphasizes the size and reactivity similarity of the two polyhedral structures.

#### HYDROPHILIC HYDROXYLATED POLYHEDRAL BORANES

Having amply demonstrated the ability to enhance the hydrophilicity of the icosahedral carborane by permethylation of all vertices, it became a challenge to obtain a perhydroxylated species having enhanced hydrophilicity and an array of functional BOH vertices. Scheme 10 illustrates the use of hot 30% H<sub>2</sub>O<sub>2</sub> to accomplish the hydroxylation of BH vertices in a

Hydroxylation of BH vertices produces very stable hydrophilic species having easily derivatized BOH functions. These derivatives are known as "closomers".



Scheme 10. Perhydroxylation of icosahedral borane and carborane derivatives. (Figure appears in color online.)

 Extensive substitution of a closo-polyhedral borane or carborane surface by precisely defined moieties forms closomers.

 Closomers may have several types of substituents, such as branched (dendritic) or linear (oligomeric) chains with functional chain substituents X, Y and Z.

$$\begin{bmatrix} X \\ Y \\ X \\ Y \end{bmatrix}_{12}^{2-} = B$$

$$B_{12} \begin{bmatrix} Y \\ X \\ X \end{bmatrix}_{12}^{2-}$$

Dendritic Closomer

Oligomeric Closomer

 Closomeric structures provide camouflaged, multifunctional modules of variable size, shape, charge, hydrophilicity, etc. designed to accomplish specific functions important to such fields as biomedicine and materials science.

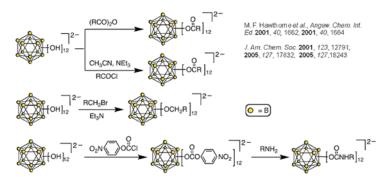
> M. F. Hawthorne et al., Angew. Chem. Int. Ed. 2001, 40, 1662 Angew. Chem. Int. Ed. 2001, 40, 1664

Scheme 11. Closomers represent new motifs in molecular architecture. (Figure appears in color online.)

variety of environments. Most important is the high-yield synthesis of the  $B_{12}(OH)_{17}^{2-}$  ion whose chemistry is still under development.

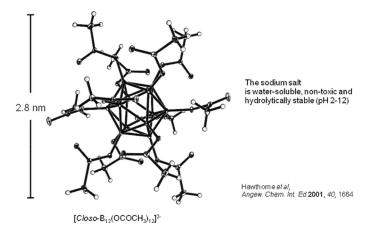
Scheme 11 outlines methods for the utilization of the 12-fold functionality of the  $B_{12}(OH)_{12}^{2-}$  ion, an effective platform for the collection of functional varieties for use in medicine and materials science. Scheme 12 illustrates the versatile reactivity of the icosahedral perhydroxyl closomer.

Schemes 13 and 14 display the structures of the simplest 12-fold acetate ester closomer and the space-filling view of the 12-fold benzyl ether, respectively.



Closomers will have potential applications in nanoscience such as molecular electronics, electrocatalysis, information storage, drug delivery systems, fluorophores and radionuclide carriers etc.

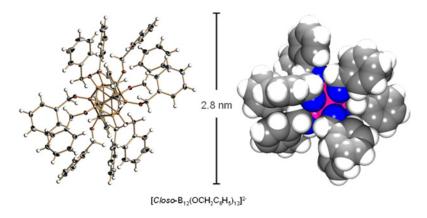
Scheme 12. Synthesis of closomers. (Figure appears in color online.)



Scheme 13. Representative closomer ester structure.

Scheme 15 illustrates the high-yield route for the formation of the 12-fold derivatives such as carbonates. The application of these reactions and reagents to biomedical challenges is obvious.

The ability to target specifically modified closomers (molecular nanoparticles) to bio-sites of interest using bioligands is of great interest and we are pursuing this objective. Scheme 16 displays applications of such systems and ways in which one might proceed.



M. F. Hawthorne et al., Angew. Chem. Int. Ed. 2001, 40, 1662

Scheme 14. Representative closomer ether structure. (Figure appears in color online.)

Other PEG and peptide linkers are also being investigated to enhance the delivery mechanism.

Scheme 15. Closomer conjugates for drug delivery. (Figure appears in color online.)

Scheme 16. Targeted multifunctional nanostructures with diverse applications. (Figure appears in color online.)

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Dr. Peter Kueffer	Dr. Hanbaek Lee	Dr. Ram Pichaandi
Dr. Alok Paital	Mr. Arsen Gulustyan	Mr. Shuo Yang
Mr. Shatadru	Dr. Lixin Ma	Ms. Amanda Dennis
Chakravarty		
Dr. Yulia Sevryugina	Dr. Oscar Tutusaus	Dr. Hairong Li
Mr. Zach Houston		

Lastly, I thank the organizers of the Stone Symposium for the invitation to speak and participate in a celebration of the life of one of England's greatest chemists, my friend, Gordon Stone.