Universitat Autònoma
de Barcelona

ON THE VERGE OF BIOORGANIC AND INORGANIC CHEMISTRY: METALLACARBORANES IN NANOMEDICINE

Adnana Alina Zaulet

TESI DOCTORAL

Programa de Doctorat en Química

Director: Prof. Clara Viñas i Teixidor

Tutor: Josefina Pons Picart

Departament de Química

Facultat de Ciències

2015

Memòria presentada per aspirar al Grau de Doctor per

Adnana Alina Zaulet

Vist i plau

Prof. Clara Viñas i Teixidor **Prof. Josefina Pons Picart**

Bellaterra, 25 de setembre de 2015

MINISTERIO
DE ECONOMÍA
Y COMPETITIVIDAD

CSIC
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

ICMAB
INSTITUT DE CIÈNCIA
DE MATERIALS DE
BARCELONA (ICMAB)

La Professora Clara Viñas i Teixidor, Professora d'Investigació del *Consejo Superior de Investigaciones Científicas* a l'*Institut* de *Ciència de Materials de Barcelona*

CERTIFICA

Que n'ADNANA ALINA ZAULET, llicenciada en Química, ha realizat sota la seva dirección el treball que porta per titol "*On the verge of bioorganic and inorganic chemistry: Metallacarboranes in nanomedicine*" que queda recollit en aquesta memoria per optar al titol de Doctor per la Universitat Autònoma de Barcelona.

I, perquè aixi consti i tingui els efectes corresponents, signa aquest certificat a Bellaterra, a 22 de setembre del 2015.

Prof. Clara Viñas i Teixidor
ICMAB-CSIC

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Aquest treball d'investigació, amb data de defensa del 20 de novembre de 2015, té com a membres del tribunal a:

- President: Prof. Enric Brillas i Coso, Professor Catedràtic del Departament de Química Física d'Universitat, Universitat de Barcelona.

- Secretari: Dr. Lluïs Escriche i Martínez, Professor titular de Química Inorgànica, Universitat Autonòma de Barcelona.

- Vocal: Dra. María Concepción Gimeno Floría, Professora d'investigació, Departamento Instituto de Síntesis Química y Catálisis Homogénea, Universidad de Zaragoza.

Com a membres suplents:

- Suplent 1: Prof. Joan Suades i Ortuño, Professor Catedràtic del Departament de Química Inorgànica, Universitat Autonòma de Barcelona.

- Suplent 2: Dra. Maria Isabel Romero García, Professora titular del Departament de Química, Universitat de Girona.

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Thank you ALL for your friendship and for being there for me: you made me who I am today!

Organització del Manuscrit

D'acord amb la normativa vigent i prèvia acceptació de la Comissió de Doctorat de la Universitat Autònoma de Barcelona, aquesta memòria es presenta com a compendi de publicacions, presentats i acceptats per la Comissió de Doctorat en Química de la UAB, el 27 de abril de 2015. Els treballs inclosos en aquesta memòria són els següents:

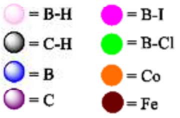
- "Investigations on antimicrobial activity of cobaltabisdicarbollides".Teodora Popova, Adnana Zaulet, Francesc Teixidor, Radostina Alexandrova, Clara Viñas, *J. Organomet. Chem*, **2013**, *747*, 229-234. http://dx.doi.org/10.1016/j.jorganchem.2013.07.006.

- "Lyotropic Lamellar Phase Formed from Monolayered θ-Shaped Carborane-Cage Amphiphiles". Damien Brusselle, Pierre Bauduin, Luc Girard, Adnana Zaulet, Clara Viñas, Francesc Teixidor, Isabelle Ly, Olivier Diat, *Angew. Chem. Int. Ed.*, **2013**, *46*, 125, 12336-12340. DOI: 10.1002/anie.201307357.

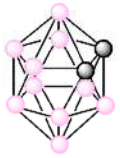
- "COSAN as a molecular imaging platform: synthesis and *''in vivo''* imaging". Kiran B. Gona, Adnana Zaulet, Vanessa Gomez-Vallejo, Francesc Teixidor, Jordi Llop, Clara Viñas, *Chem. Commun.*, **2014**, *50*, 11415-11417. DOI: 10.1039/c4cc05058d.

Compounds list

Starting Compounds



Neutral clusters



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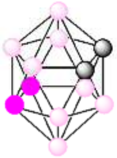
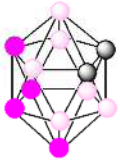
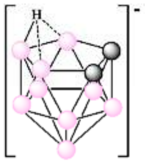


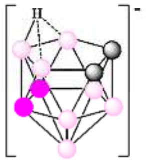
I_2-**1**



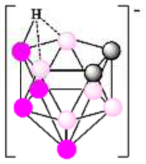
I_4-**1**



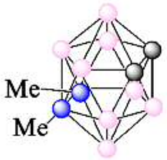
$[\mathbf{2}]^{-}$



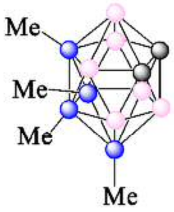
$[\mathrm{I}_2\text{-}\mathbf{2}]^{-}$



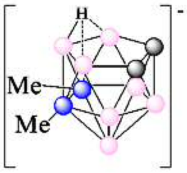
$[\mathrm{I}_4\text{-}\mathbf{2}]^{-}$



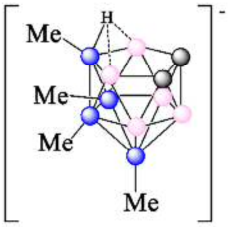
Me_2-**1**



Me_4-**1**

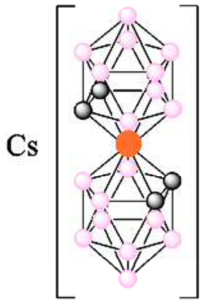


$[\mathrm{Me}_2\text{-}\mathbf{2}]^{-}$

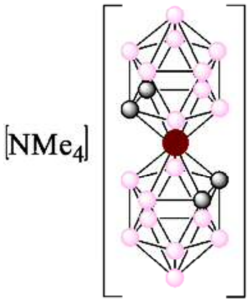


$[\mathrm{Me}_4\text{-}\mathbf{2}]^{-}$

Anionic clusters



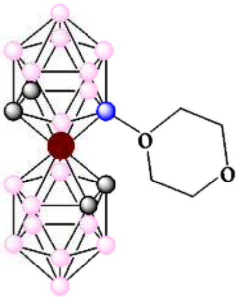
Cs[**3**]



[NMe_4][**4**]

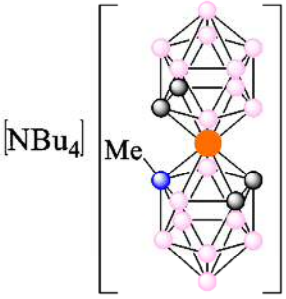
Zwitterionic clusters

5

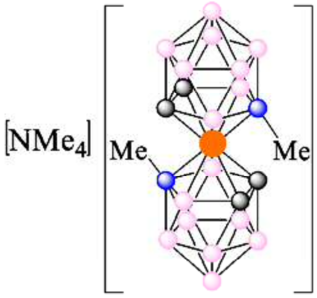


6

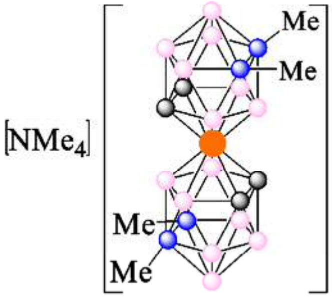
2.1.1. -Anionic methylated cobaltabis(dicarbollide) derivatives



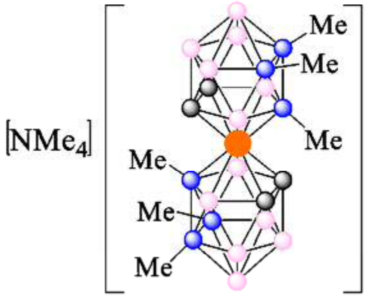
[NBu$_4$][Me-**3**]



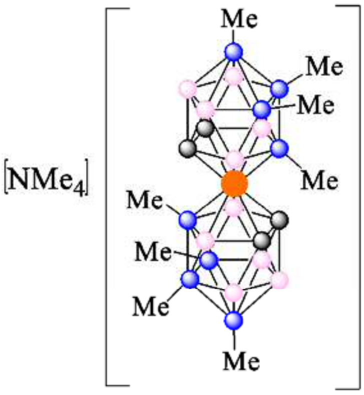
[NMe$_4$][Me$_2$-**3**]



[NMe$_4$][Me$_4$-**3**]



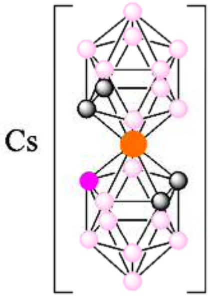
[NMe$_4$][Me$_6$-**3**]



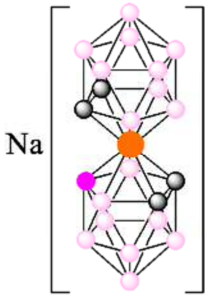
[NMe$_4$][Me$_8$-**3**]

2.1.2.- Anionic halogenated cobaltabis(dicarbollide) derivatives

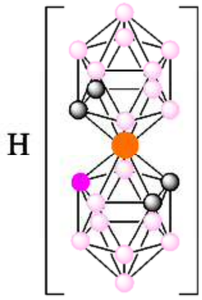
2.1.2.a.- Iodinated derivatives



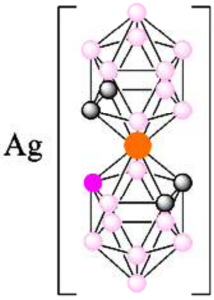
Cs[I-**3**]



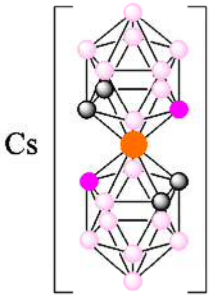
Na[I-**3**]



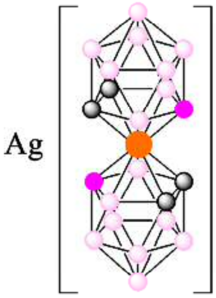
H[I-**3**]



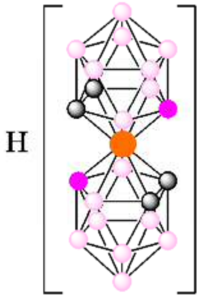
Ag[I-**3**]



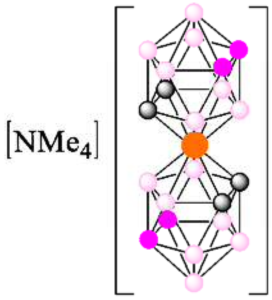
Cs[I$_2$-**3**]



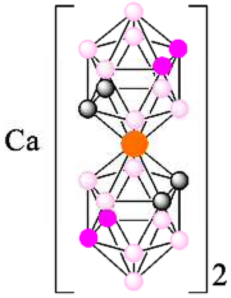
Ag[I$_2$-**3**]



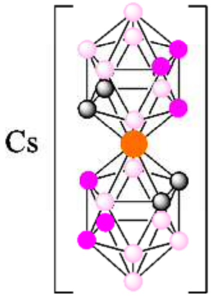
H[I$_2$-**3**]



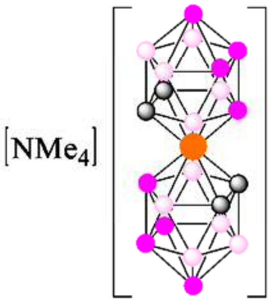
[NMe$_4$][I$_4$-**3**]



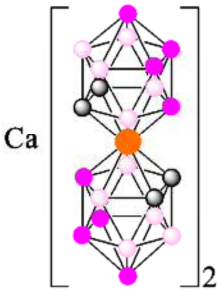
Ca[I$_4$-**3**]$_2$



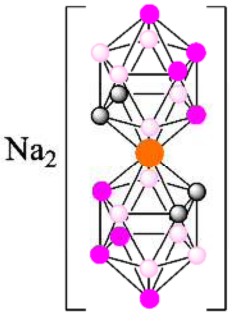
Cs[I$_6$-**3**]



[NMe$_4$][I$_8$-**3**]

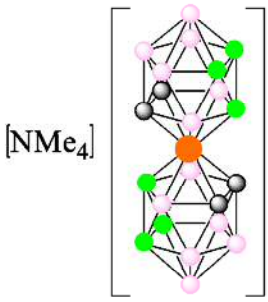


Ca[I$_8$-**3**]$_2$

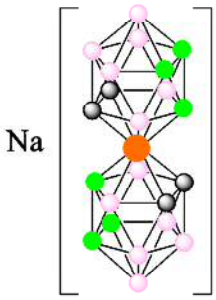


Na$_2$[I$_8$-**3**]

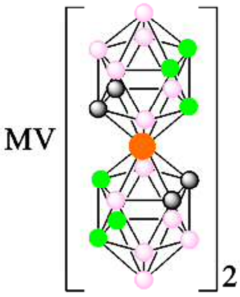
2.1.2.b -Chlorinated derivatives



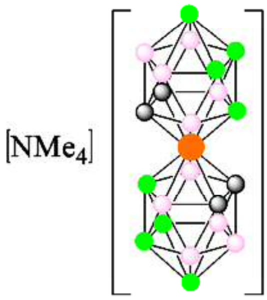
[NMe$_4$][Cl$_6$-**3**]



Na[Cl$_6$-**3**]



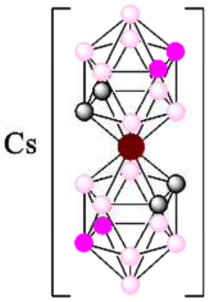
MV[Cl$_6$-**3**]$_2$



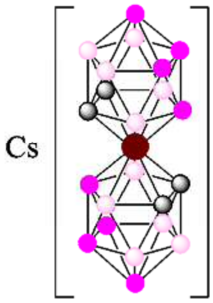
[NMe$_4$][Cl$_8$-**3**]

2.1.3. –Anionic ferrabis(dicarbollide) derivatives

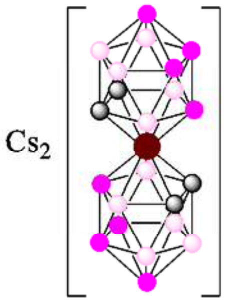
2.1.3.a. – Iodinated derivatives



Cs[I$_4$-**4**]

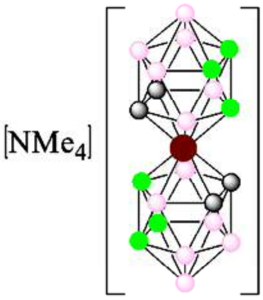


Cs[I$_8$-**4**]

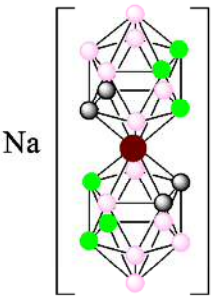


Cs$_2$[I$_8$-**4**]

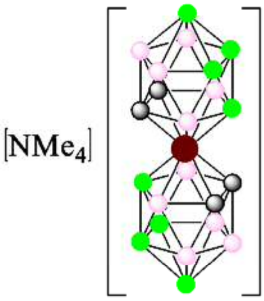
2.1.3.b. – Chlorinated derivatives



[NMe$_4$][Cl$_6$-**4**]

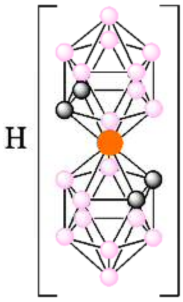


Na[Cl$_6$-**4**]

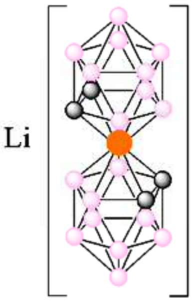


[NMe$_4$][Cl$_8$-**4**]

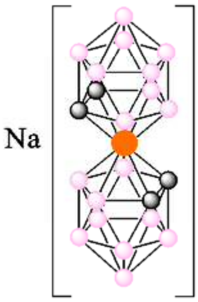
3.1.-Study of different salts of parent $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$ and some of its derivatives



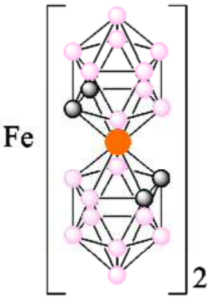
H[**3**]



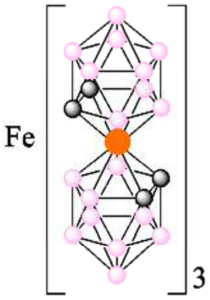
Li[**3**]



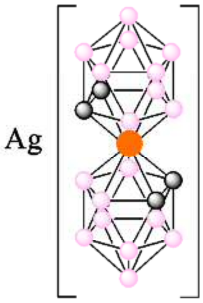
Na[**3**]



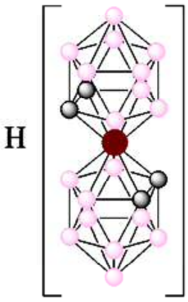
Fe[**3**]$_2$



Fe[**3**]$_3$



Ag[**3**]



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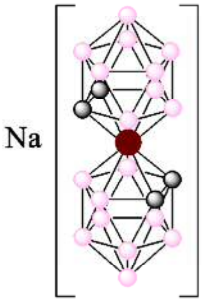

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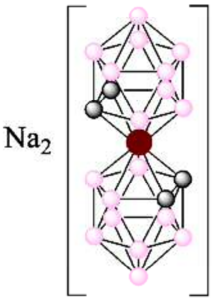
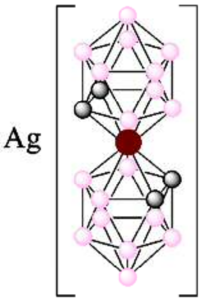
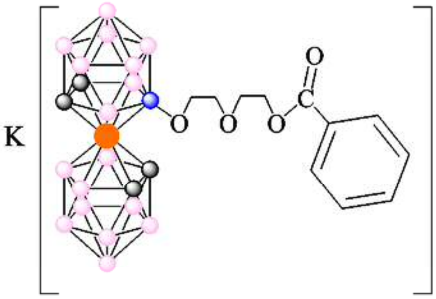


Na$_2$[**4**]

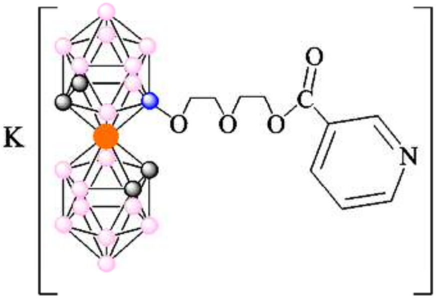


Ag[**4**]

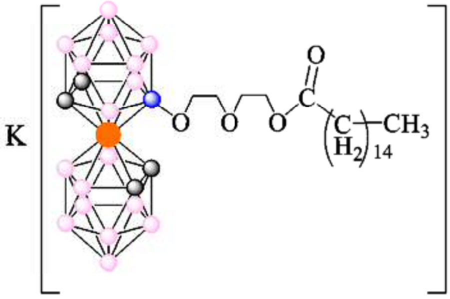
6.1.- Ring-opening reactions of 1,4-dioxane derivative of metallabis(dicarbollide) with biomolecules



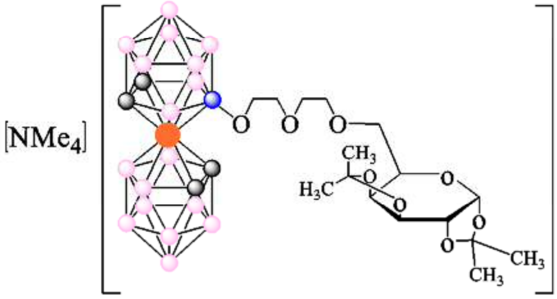
K[**7**]



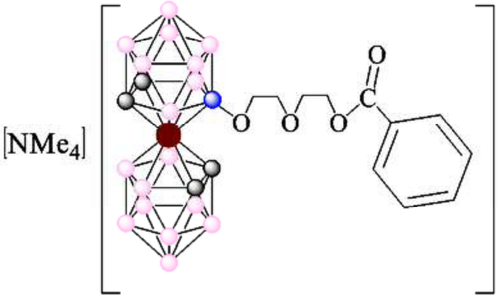
K[**8**]



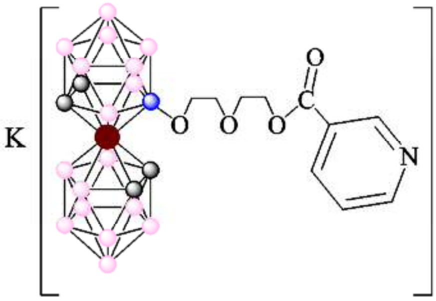
K[**9**]



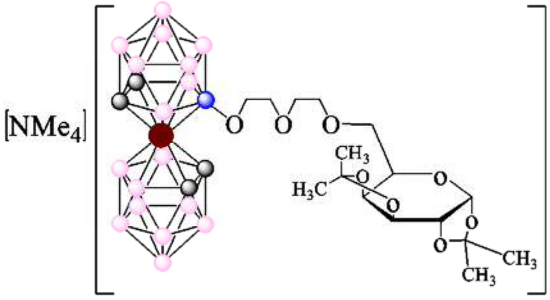
[NMe$_4$][**10**]



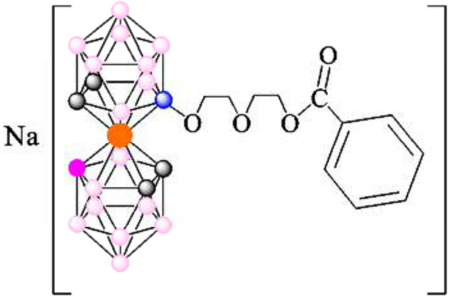
[NMe$_4$][**11**]



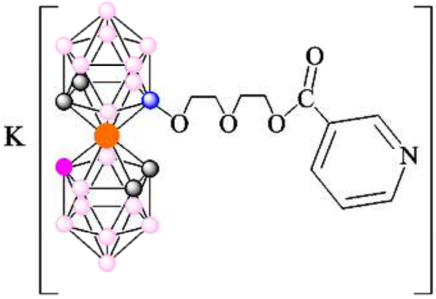
K[**12**]



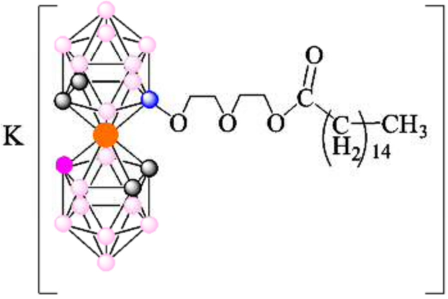
[NMe$_4$][**13**]



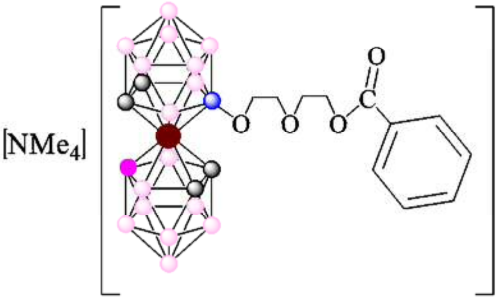
Na[I-**7**]



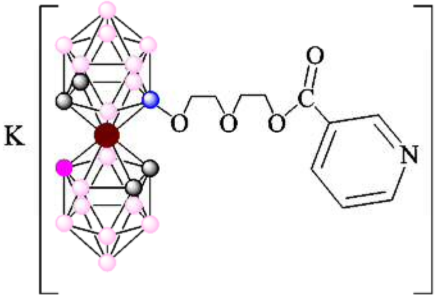
K[I-**8**]



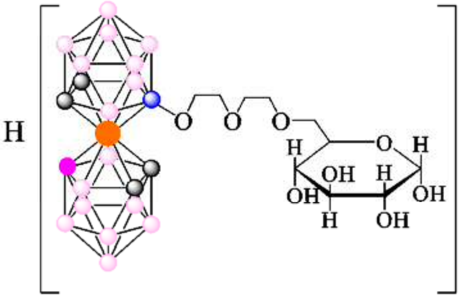
K[I-**9**]



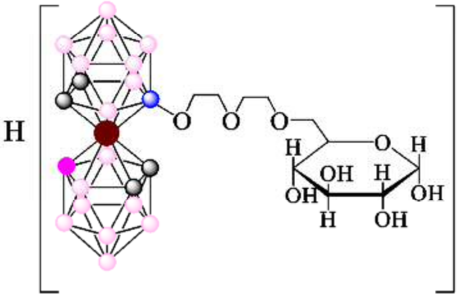
$[NMe_4]$[I-**11**]



K[I-**12**]



H[I-**14**]



H[I-**15**]

Abbreviations

Me:	methyl group
C_c:	carbon atom belonging to the carborane cluster
H_{bridge}:	hydrogen atom bounded to a boron atom from the open face
***o*-carborane**:	*ortho*-carborane
acetone-d^6 (CH_3COCH_3)	deuterated acetone
D_2O:	deuterated water
aq.:	aqueous
eq.:	equivalent
***n*-BuLi**:	*n*-buthyllithium
THF:	tetrahydrofurane
Et_2O:	diethyl ether
SO_2Cl_2:	Sulfuryl chloride
MV:	Methyl viologen
BNCT:	Boron Neutron Capture Therapy
PET:	Positron Emission Tomography
CT:	Computerized Tomography
SPECT:	Single Photon Emission Computerized Tomography
NPs:	Nanoparticles
DSSC$_S$:	Dye Sensitized Solar Cells
IR:	InfraRed
NMR:	Nuclear Magnetic Resonance
MALDI-TOF-MS:	Matrix Assisted Laser Desorption Ionization-Time of Flight–Mass Spectrometry

TGA: ThermoGravimetric Analisys

DSC: Differential Scanning Calorimetry

TEM: Transmission Electron Microscopy

Cryo-TEM: Cryogenic Transmission electron microscopy

DLS: Dynamic Light Scattering

SLS: Static Light Scattering

SWAXS: Small and Wide-angle X-ray Scattering

SEM: Scanning Electron Microscopy

Jsc: Short-circuit current density

Voc: Open Circuit Voltage

m/ z: mass/ charge

PEG: polyethyleneglicol

ca.: circa

δ (ppm): chemical shifts in parts per million

J(A,B): coupling constant between A and B nuclei separated by n bond
TMS: TetraMethylSilane

Summary of the thesis

The research presented in this thesis describes the synthesis and characterization of anionic metallabis(dicarbollide) derivatives and the posterior applications.

The first section of the thesis is focused on the synthesis and characterization of methylated cobaltabis(dicarbollide) derivatives. The alkylation reaction has been successfully accomplished by cross-coupling reaction between the B-I vertex and Grignard reagent in the presence of $[PdCl_2(PPh_3)_2]$ as catalyst and CuI as cocatalyst.

The redox potential determination and modulation of differently substituted metallacarboranes is a matter of interest in our group. So, an efficient synthetic pathway to obtain chlorinated metallabis(dicarbollide) derivatives has been successfully developed and the posterior study of electrochemical properties of the compounds has been accomplished. The $E_{1/2}$ (M^{III}/M^{II}, M=Co, Fe) for B-halogenated and B-methylated metallabis(dicarbollide) anions were experimentally determined by Cyclic Voltammetry indicating that each halogen atom (Cl or I) produces an opposite and larger effect than each alkyl moiety. Based on their $E_{1/2}$ potential, selected compounds have been tested as electrolytes in the DSSC devices.

An important achievement reported in this thesis was the isolation of different calcium, silver and iron salts of cobaltabis(dicarbollide) $[\mathbf{3}]^-$ and its iodinated derivatives. The possible application of such highly iodinated anionic molecules as radiopaque contrast agent for X-ray diagnosting imaging, required the synthesis and characterization of $Ca[I_4\text{-}\mathbf{3}]_2$ and $Ca[I_8\text{-}\mathbf{3}]_2$. Silver set of cobaltabis(dicarbollide) derivatives have been used as precursor to prepare the corresponding Fe(II) and Fe(III) salts that can form magnetic nanoparticles.

The ability of single metallacarboranes to self-assembly and aggregate in aqueous solutions has been demonstrated in the last few years. More recently, it has been proven that minor changes in the molecular structure of $[\mathbf{3}]^-$ provoke major modifications in the solution behavior. The substitution of two B-H by two B-I in the structure of $[\mathbf{3}]^-$ leads to a lamellae lyotropic phase at high concentration, while vesicles are formed at small concentration (1-9mM). We prepared, isolated and characterized a set of different salts of the parent cobaltabis(dicarbollide) and some of its derivatives

and we studied by $^{1}H\{^{11}B\}$-NMR and $^{11}B\{^{1}H\}$-NMR in D_2O their behavior at different concentrations.

Another important goal was the ring opening reaction of the zwitterionic metallabis(dicarbollide) derivatives with biomolecules, such as vitamins, fatty acids and sugars *via* a nucleophilic reaction. The iodination reaction of this biomolecules with natural I_2 was successfully performed in good yields. We have designed new bio-functional metallabis(dicarbollide) derivatives which contain two different reactive sites: a suitable iodinated moiety ready to be radiolabeled and a PEG branch that can carry the vector. Injectable solutions of chemically and radiochemically pure compounds have been obtained after the radiolabelling reactions with either ^{125}I or ^{124}I via palladium catalyzed isotopic exchange reaction. *In vivo* Positron Emission Tomography (PET) biodistribution studies were performed on healthy mice and also in tumor model.

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INTRODUCTION

INTRODUCTION

1.1.- Generalities of icosahedral Boranes, dicarbaboranes and metallacarboranes

Boron and carbon are the elements that have the property to build molecules of unlimited size by covalent self-bonding. In this way, boron produces polyhedral clusters that have been developed for over 50 years. Boron clusters (Figure 1.1) display many particular characteristics that do not find parallel in their organic counterparts.

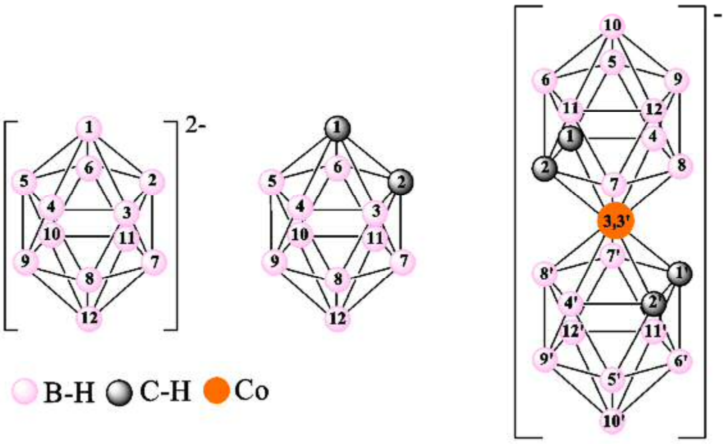


Figure 1.1. Icosahedral heteroboranes with their vertex numbering: dianionic *closo* $[B_{12}H_{12}]^{2-}$ borane, neutral *closo* *o*-$C_2B_{10}H_{12}$ carborane and metallacarboranes [3,3'-$M(1,2-C_2B_9H_{11})_2]^-$, M= Co(III).

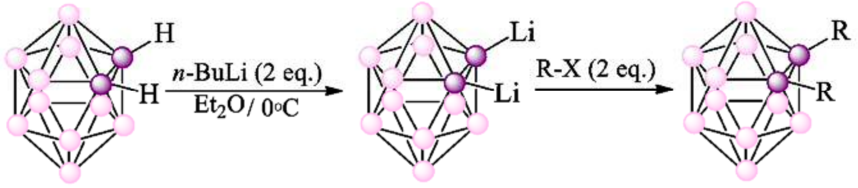
1.1.1.- Boranes

The polyhedral *closo* $[B_{12}H_{12}]^{2-}$ borane is a robust icosahedral cluster stabilized by three-dimensional delocalization of thirteen bonding electron pairs.[1] This charge-delocalized ion $[B_{12}H_{12}]^{2-}$ may be considered the parent aromatic species that serves borane chemistry as benzene serves organic chemistry.[2] Isoelectronic substitution of one or two B-H vertices in *closo* $[B_{12}H_{12}]^{2-}$ by C-H provides the aromatic derivatives *closo* $[1-CB_{11}H_{12}]^-$ and *closo* $C_2B_{10}H_{12}$.[3] The high stability of the ion $[B_{12}H_{12}]^{2-}$ to strong bases, strong acids and oxidizing agents is unique for boron hydride structures. However, the anions react smoothly with certain reagents, particularly electrophilic species, to give stable derivatives in which hydrogen atoms are replaced by the attacking group.[4]

1.1.2.- Carboranes and metallacarboranes

Largely, the twelve-vertex *closo* $C_2B_{10}H_{12}$ icosahedral carboranes have been the most widely studied. The three known isomers, in which the carbon atoms occupy *ortho*- (1,2), *meta*- (1,7), or *para*- (1,12) vertices are white solids that rank among the most stable molecular compounds known. Figure 1.1 displays the *ortho*-dicarborane isomer.

The unique stabilities and geometrical properties of the isomeric *closo* $C_2B_{10}H_{12}$ carboranes suggested these species as building blocks for stereo precise structural platforms of novel reaction centers having properties that cannot be achieved with organic hydrocarbon compounds. Each one of the three isomeric *closo* $C_2B_{10}H_{12}$ carboranes has the potential for the incorporation of a large number of substituents. These species have two moderately acidic CH vertices that are deprotonated with strong bases and subsequently can be functionalized using electrophilic reagents (Scheme 1.1).

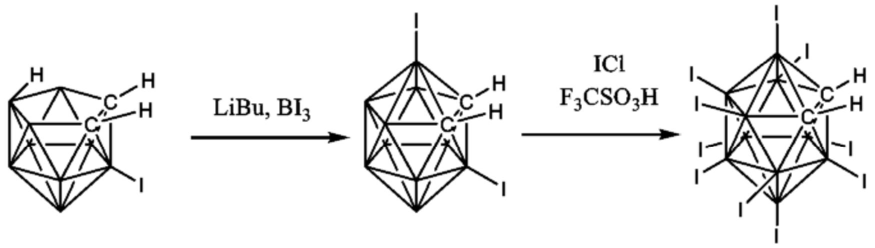


Scheme 1.1. Substitution of C-H vertexes with various functional groups.

The chemistry of boron-substituted carboranes is less developed than that of the carbon-substituted analogues because of the higher difficulty of introducing functional groups at the boron atoms of the carborane cage. The 10 BH vertices present in each of the icosahedral carborane isomers have electrophilic substitution chemistry in many ways reminiscent of arenes.2 Thus, most reactions that occur at the boron vertices do not affect the carbon vertices and *vice versa*. The rigid three-dimensional icosahedra hold substituents in well-defined spatial relationships and most transformations maintain the integrity of the underlying geometry.

Electrophilic iodination and methylation of 1,2-*closo*-$C_2B_{10}H_{12}$ under strong acid catalysis affords 4,5,7,8,9,10,11,12-I_8-1,2-*closo*-$C_2B_{10}H_4$, 4,5,7,8,9,10,11,12-$(CH_3)_8$-1,2-*closo*-$C_2B_{10}H_4$ derivatives depending on the experimental conditions.[5,6] By using the electrophilic procedures named above, it is possible to derivatize all *o*-carborane cluster positions except B(3)/B(6), because these boron atoms that are adjacent to both cluster carbons, are not susceptible to electrophilic substitution. Nine equal substituents, 3,4,5,7,8,9,10,11,12-R_9-1,2-*closo*-$C_2B_{10}H_3$, (R= I, CH_3) on *o*-carborane were obtained in yields 94% and 98%, respectively, from 3-R-1,2-*closo*-$C_2B_{10}H_{11}$ (R= CH_3, I)[7] by a combined nucleophilic-electrophilic reaction sequence.[8]

Perfluorination[9] and perchlorination[9,10] of 1,2-*closo*-$C_2B_{10}H_{12}$ have been obtained however, perbromination has not been accomplished. However, periodination of *o*-carborane, 3,4,5,6,7,8,9,10,11,12-I_{10}-1,2-*closo*-$C_2B_{10}H_2$, was achieved in 73% yield (Scheme 1.2) from 3,6-I_2-1,2-*closo*-$C_2B_{10}H_{10}$[7a] and ICl. For this reaction to succeed, it was taken into account that boron atoms in *o*-carborane are of two types, i.e., those adjacent to both carbon atoms and the remainder. Periodination accentuates the acidity of the carborane and its monoprotic salts are stable in water.[11]

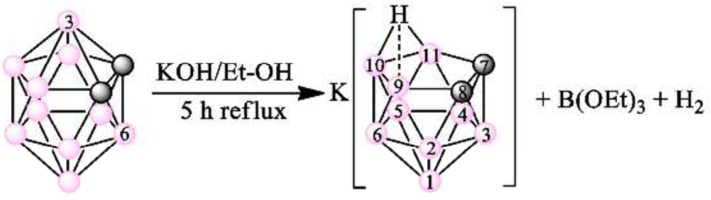


Scheme 1.2. Synthesis of the periodinated *ortho*-carborane.

Following a reported procedure on methylation,[12] treatment of 3,6-$(CH_3)_2$-1,2-*closo*-$C_2B_{10}H_{10}$ with $ICH_3/AlCl_3$ does not produce permethylation of the *o*-carborane cluster, however, 9-$I_{0.707}H_{0.293}$-12-$Cl_{0.566}H_{0.434}$-3,4,5,6,7,8,10,11-$(CH_3)_8$-1,2-*closo*-$C_2B_{10}H_2$, whose ^{11}B-NMR spectrum indicates a mixture of species, was obtained.[13] Suitable colourless crystals indicated that octaboron methyl substitution of the C_2B_{10} icosahedron at positions 3,4,5,6,7,8,10 and 11 had taken place. The remaining positions at B(9) and B(12) are partially occupied by halogen and hydrogen atoms. As in 4,5,7,8,9,10,11,12-$(CH_3)_8$-*closo*-$C_2B_{10}H_4$,5 there are only eight methyl groups on the cluster 9-$I_{0.707}H_{0.293}$-12-$Cl_{0.566}H_{0.434}$-3,4,5,6,7,8,10,11-$(CH_3)_8$-1,2-*closo*-$C_2B_{10}H_2$. It was concluded that boron permethylation in 1,2-*closo*-$C_2B_{10}H_{12}$ is severely hampered due to the –***I*** effect of the methyl group. Theoretical calculations corroborated it.[11b,13]

The *closo ortho*-$C_2B_{10}H_{12}$ goes to partial deboronation under nucleophilic conditions reaction. The nucleophilic attack is produced selectively over one of the boron atoms that are directly bonded to the cluster carbons, because these boron atoms, either B(3) or B(6), are the ones most electronically impoverished (Scheme

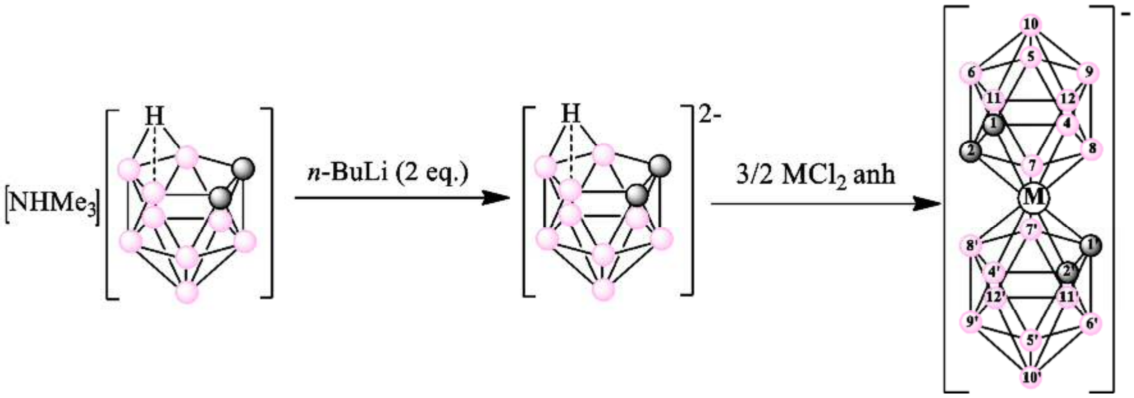
1.3). The partial deboronation reaction leads to the anionic *nido* cluster [7,8-*nido*-$C_2B_9H_{12}$]$^-$. This species has formally lost one B^+ fragment with respect to its *closo* precursor, allowing the formation of a cluster bearing one open pentagonal face, C_2B_3, where its remaining hydrogen is still present; this resultant *nido* cluster is a monoanionic species, as presented in Scheme 1.3. X-ray diffraction studies show that this H_{bridge} is more bonded to B(10) than to B(9) or B(11) and that it maintains itself equidistant to these last two.[14] In the [7,8-*nido*-$C_2B_9H_{11}$]$^{2-}$ ion, the metal may be considered to be η^5-bonded to the open C_2B_3 pentagonal face of an icosahedral fragment, as in the case of the formation of ferrocene from $C_5H_5^-$. In so doing the metal simultaneously completes two icosahedra.[15] In 1965 the first metallacarboranes, [3,3-Fe(1,2-$C_2B_9H_{11}$)$_2$]$^{n-}$ (n = 1, 2), were reported.[15a]



1 **[2]**$^-$

Scheme 1.3. *Ortho*-carborane partial deboronation reaction.

The cobaltabis(dicarbollide) [3,3'-Co(1,2-$C_2B_9H_{11}$)$_2$, [**3**]$^-$, was synthesized in 1965 (Scheme 1.4).[15a] This anion has a great chemical stability, high molecular volume, low nucleophilic character and low charge density because the negative charge is distributed between 45 atoms.[16]

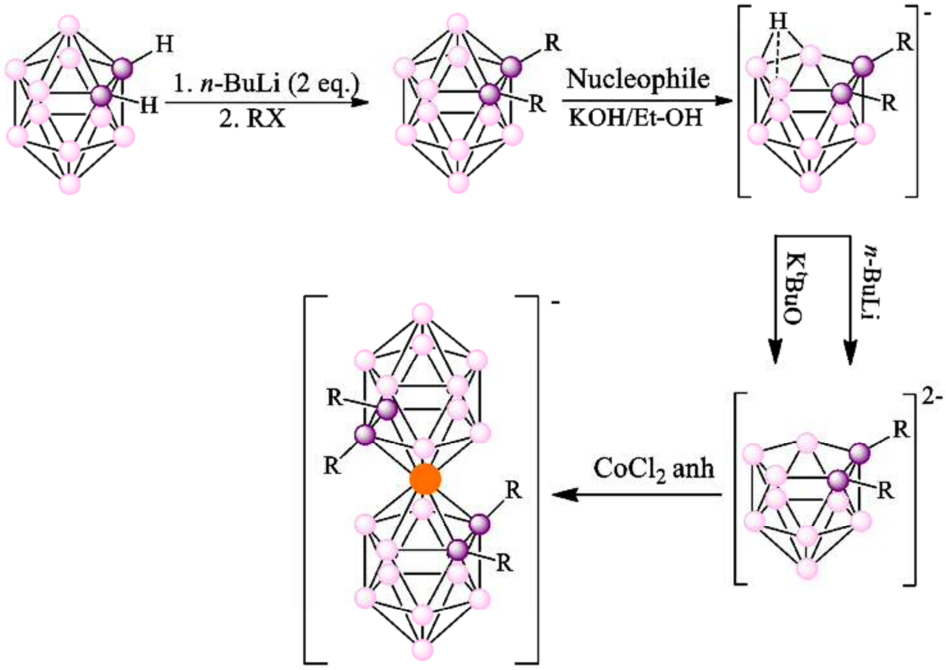


Scheme 1.4. General scheme for the synthesis of cobaltabis(dicarbollide), [**3**]$^-$ and ferrabis(dicarbollide), [**4**]$^-$.

M=Co; [**3**]$^-$
M= Fe; [**4**]$^-$

The derivative chemistry of the cobaltabis(dicarbollide) remains very much unexplored.[17] The fundamental reason is the lack of a comprehensive synthetic strategy leading to these derivatives. As for the $C_2B_{10}H_{12}$ carborane compounds, substitutions may occur on $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$, either on carbon or on boron.

With few exceptions,[18] substitutions on carbon have been achieved only at an early stage of the synthetic process, i.e. on the starting *o*-carborane (Scheme 1.5),[19] but not by direct reaction at the $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$ cage.



Scheme 1.5. General scheme for the substitution of C-H vertexes with diffrent functional groups, follow with the complexation of the coresponding *nido* species.

Substitution at boron vertexes of the anionic $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$ cluster has been achieved under Friedel-Crafts conditions[20] or with strong alkylating agents.[21] Consequently, regioselective substitutions were not possible,[21d] and specific derivatives could be obtained only after careful separations of complex mixtures. Besides these remarkable compounds there are the readily available halogeno derivatives of $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$.[22] In this regard regiospecific synthesis for 8-I and $8,8'\text{-}I_2$[23] have been described. Bregadze in 1992,[24] reported that halogeno derivatives appear to be inert to substitution reactions, however Hawthorne and co-workers shown that starting from $[3,3'\text{-}Co(8,9,12\text{-}I_3\text{-}1,2\text{-}C_2B_9H_8)_2]^-$ it is possible to get hexasubstitution on $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$.[25] This opened up the possibility to get B(8)-C mono substitution from $[8\text{-}I\text{-}3,3'\text{-}Co(1,2\text{-}C_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})]^-$. Starting with $[8\text{-}I\text{-}3,3'\text{-}Co(1,2\text{-}C_2B_9H_{10})(1',2'\text{-}C_2B_9H_{11})]^-$, it has been reported that the B(8)-C cross-coupling reaction is achieved by using several type of B-C cross-coupling reactions: i) by means of

Kumada reaction using a Grignard derivative as the source of the organic group in the presence of [$PdCl_2(PPh_3)_2$] and CuI as catalysts;[21c,26] ii) by Sonogashira coupling using also Pd(II),[27] Cu(I) as catalyst plus a base ($^iPr_2NH$); and iii) B-C_{vinyl} cross-coupling reaction by means of Heck, Negishi or Suzuki-Miyaura reaction conditions using [$PdCl_2(PPh_3)_2$]/CuI in dry DMF with dry 2,6-lutidine as a base at 140 °C.[21c]

The zwitterionic compound [3,3'-Co(8-(C_2H_4O)$_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] was reported for the first time by the reaction of the parent Cs[Co($C_2B_9H_{11}$)$_2$] with H_2SO_4–Me_2SO_4 in 1,4-dioxane in 1996.[28] Compound [3,3'-Co(8-(C_2H_4O)$_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] has been shown to be susceptible to nucleophilic attack on the positively charged oxygen atom resulting in one anionic species formed by the opening of the dioxane ring. Later, the same compound was obtained in a higher yield (94 compared to 45%) by using $BF_3 \cdot OEt_2$ as a Lewis acid that permitted an easier work-up procedure.[29] A great impulse on the synthesis of polyanionic macromolecules incorporating cobaltabis(dicarbollide) was achieved after the most efficient protocol for the synthesis of [3,3'-Co(8-(C_2H_4O)$_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] has been reported.[29,30,31] The latter was covalently bonded to the periphery of scaffolds such as organic aromatic molecules, porphyrins, calixarenes and resorcarenes, among others.

1.2.- Aplications

The currently claimed applications for boron clusters compounds are based either on the unique properties of the molecules or on specific properties of the basic element itself such as: the extreme acidity of acids conjugated to the polyhedral ions combined with a unique hydrophobicity of these anions; the exceptional stability of the polyhedral species due to their aromaticity and the unespected ability to nearly all open-cage clusters to form sandwich metallic complexes.[32]

1.2.1.- Radioimaging

One of the principal challenges in molecular imaging is developing radiotracers which have minimal non-specific biding and thus accumulate only in the area of interest. To achieve preferential localization *in vivo*, the radionuclide is often linked to a targeting vector which can consist of a protein, sugar or molecules that is preferentially retained in the target.[33]

The most commonly employed radioisotopes in current use are halogens, because of their useful chemical properties that simplify incorporation into molecules combined with availability of a wide range of specific radiohalogen isotopes with varying radioactive decay modes and half-lives.

The stability of metallabis(dicarbollide) compounds over a wide range of conditions makes them well-suited as scaffolds for attaching radiolabels and affords an advantage over many radiohalogenated organic molecules such as peptides, which in biological environments tend to undergo cleavage of their weak carbon halogen bonds. As example, the B-I bond dissociation energy (381 (±21) kJ mol^{-1}) is substantially greater than for the C-I bond (209 (±21) kJ mol^{-1}).[11b,34]

The inorganic, boron-based molecule cobaltabis(dicarbollide), [**3**]$^-$, is a stable complex which possess amphiphilic character in water,[35] has the ability to assemble into monolayer vesicles,[36] can cross through synthetic lipid membranes without disrupting membrane integrity[37] and accumulates *in vitro* within living cells.[38] These properties, together with its high boron content, its chemical stability and its solubility in physiologic conditions,[39] turn [**3**]$^-$ into a suitable building block for the preparation of boron carrier drugs. Despite the large variety of [**3**]$^-$ derivatives described in the literature with potential application in BNCT, the transition from bench to bed (even in the preclinical setting) has been only occasionally approached. The main reason behind this fact still remains the lack of techniques able to determine, *in vivo* and on real time, the accumulation of boron in the tumor and surrounding tissue, allowing a candidate-by-candidate screening and prediction of therapeutic efficacy. Positron Emission Tomography (PET) in combination with Computerized Tomography (CT) is a non-invasive and sensitive technique, used to measure the three-dimensional distribution of a radiopharmaceutical administered to a patient or subject. The radioactive decay property that allows the use of radionuclides for imaging is emission of photons with sufficient energy to detect in a device external to the body. Radionuclides that are useful for Single Photon Emission Computerized Tomography (SPECT) imaging emit photons in high abundance and have high enough energy (e.g. >100 keV) to readily escape the body and be detected. In PET imaging, positrons emitted by the radionuclide interact with a negatron (electron) in an annihilation process to produce two coincident 511 keV photons, which are detected simultaneously in a detector ring. An important characteristic is the energy of the emitted positron. The higher its energy the further a positron will travel before the annihilation occurs. A longer distance of positron travel in tissue results in an overall loss of spatial resolution. Another important characteristic of PET is the abundance of the positron emissions since a low abundance requires more radioactivity to be administered.[40]

Radiohalogens used in nuclear medicine today fall into two main categories, those useful in imaging applications and those useful in therapy applications. Radioiodine is the most commonly used radiohalogen and has radionuclides with emissions appropriate for *in vitro* diagnostics [^{125}I], *in vivo* diagnostics [^{124}I (PET)] and *in vivo* therapeutics [^{131}I].[41]

1.2.2.- Boron neutron capture therapy (BNCT)

BNCT is a binary modality for cancer treatment based on the capacity of ^{10}B nuclides to capture low-energy (thermal) neutrons which become ^{11}B atoms in the excited state for a very short time (*ca* 10^{-12} seconds).[42] The excited ^{11}B atoms then fission producing high linear energy transfer particles, $^{4}He^{2+}$ (α-particles) and $^{7}Li^{3+}$, bearing approximately 2.4 MeV of cinetic energy:

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

Both of these particles have a very short range (about one cellular diameter) and cause a significant damage to the cell in which it is contained. Since these α particles travel only about 10μm or less, they selectively destroy cancer cells where the ^{10}B nuclei are localized (Figure 1.2).

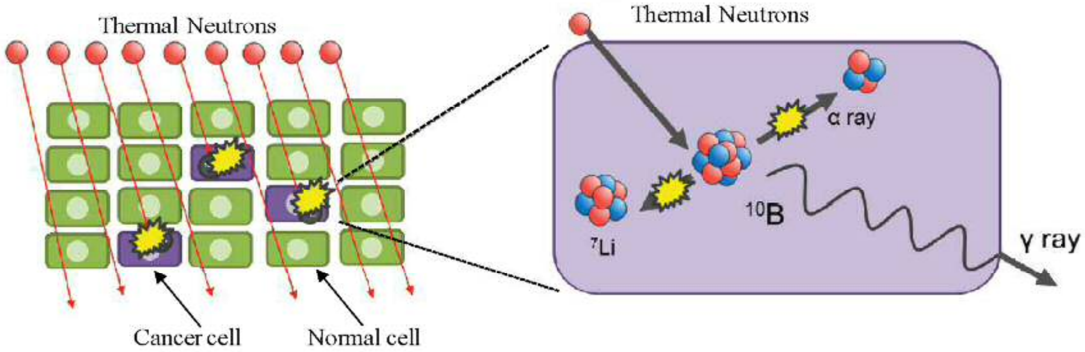


Figure 1.2. Schematic representation of tumor destruction by BNCT.

BNCT could particularly be useful in the treatment of high grade gliomas, malignant melanomas, meningiomas, head and neck tumors and oral cancer.[43] The two approved boron drugs used in BNCT clinical trials for treatment of high-grade gliomas in Europe, Japan and in the United State are disodium-mercapto-*closo*-dodecaborate (BSH) and 4-dihydroxyborylphenylalanine (BPA). It has been estimated that the concentration of ^{10}B necessary for effective BNCT is 15-30 μg of ^{10}B per gram of tumor, depending upon the precise location of the ^{10}B atoms, and the high tumor:blood and tumor:normal tissue boron concentration ratios would significantly increase BNCT effectiveness.[44] In order to achives this required high boron concentration in tumors, the icosahedral carboranes, for example *closo*-*o*-$C_2B_{10}H_{12}$ has been conjugated to dendrimers and various biomolecules including nucleosides, amino acids, phospholipids and porphyrins.[45] A lot of studies have investigated using nanoparticles (NPs) as a boron delivery system. Boron agents can be readily incorporated into nanoparticles via surface adsorption, encapsulation or direct covalent linkage.[46] Nps may accumulate and be utilized to treat glioblastoma and other brain tumors due to the compromised integrity of the BBB.[47] Metallacarboranes, in particular cobaltabis(dicarbollide) anion, $[Co(C_2B_9H_{11})_2]$ have received much interest because of their high boron content and their remarkable stability towards acids, moderate bases, high temperature and radiation.[17a,32,48] These properties make cobaltabis(dicarbollide) a promising agent as a boron-rich carrier for cancer treatment and diagnosis in boron neutron capture therapy (BNCT).[49] For example, Cígler et al, reported that metallacarboranes are highly specific and potent inhibitors of HIV protease.[50]

1.2.3.- Dye sensitized solar cells

Dye sensitized solar cells (DSSCs) have recently been in the focus of attention of researchers due to their relatively high efficiency of solar energy conversion to electric energy in combination with adaptability and low costs. Grätzel was the first in 1991 to propose DSSCs, which generate electric current and imitate the natural photosynthesis process.[51] Initial forms of this technology employed ruthenium(II)-based dyes in conjunction with iodide-based electrolytes to achieve a certified solar-to-electric power conversion efficiency (PCE) of 11.9% under full sun illumination.[52] It is important to use dyes with maximum absorption in the visible range of the light spectrum, which allows to manufacturing elements with high efficiency conversion of solar light into electrical energy. Redox couples, as one of the crucial components of DSSC, have been investigated for many years.

Due to many drawbacks of I^-/I_3^- electrolyte[53] scientists have paid more attention to seeking other alternative electrolyte systems. Due to their reversible electrochemical properties, metal complexes are always promising candidates to replace I^-/I_3^- system in DSSC. Moreover, the redox potential of metal complex can be easily tuned by changing the central metal atoms or/and the ligands. One example, Fe-complex redox couple ferrocene/ferrocenium has achieved the efficiency of 7.5% in DSSC based on iodine-free redox couples under light illumination.[54] Hupp and co-workers[55] developed for the first time the noncorrosive redox shuttle Ni^{III}/Ni^{IV} bis(dicarbollide) complexes modified with electron-donating and electron-withdrawing groups. In addition to a noncorrosive nature, the Ni^{III}/Ni^{IV} bis(dicarbollide) system also has many favorable properties versus other metallocene systems, including fast mass-transport, fast dye regeneration and attractive electron transfer kinetics.[56]

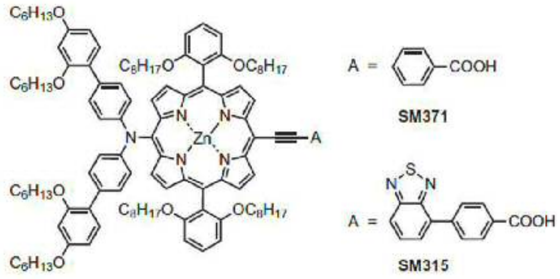


Figure 1.3. Dye structure coded SM371 and SM315. They both feature a porphyrin core and a bulky bis(2’,4’-bis(hexyloxy)-[1,1’-biphenyl]-4-yl)amine donor. Their acceptor groups differs, with SM315 featuring a benzothiadiazole group.

By using cobalt based redox mediators as tris(2,2′-bipyridyl)cobalt(II/III) ($[Co(bpy)_3]^{2+/3+}$ redox shuttle in conjunction with a zinc porphyrin dye as sensitizer, it was achieved a maximum power conversion efficiency of 12.3%. [57]

Figure 1.3 show the dye structure (SM315) that in combination with the redox couple $[Co(bpy)_3]^{2+/3+}$ achived a record of 13% power conversion efficiency. [58] The green dye, SM371 exhibited a performance of 12%.

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