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Ministry of Higher Education& Scientific Research

Salahaddin University-Erbil(SUE)

College of science

Department of chemistry

Boron chemistry and its application as anti cancer

Research project

submitted to the department of chemistry in partial fulfillment of the requirements for the degree of BSc. in chemistry science.

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Dedication:

I dedicate this report with great love to my family. I would not have succeeded in preparing it without their constant support, especially my parents and I also dedicate it to my supervisor, M.SC Adnan, thanks for his efforts. I dedicate it to the department of Chemistry and to everyone who contributed to my support and help, thank you everyone.

Acknowledgments:

Thanks for Allah for giving me strength and success to complete the work on my research. I also want to express my gratitude to my supervisor, the M.SC. Adnan , for encouraging me and following up on my project step by step, I really appreciate her effort .Thanks to my family for their support, help and motivation. Thanks to the friends who surrounded me with kindness. Tuqa who accompanied me every step of the way, Teba is the source of my positive energy all the time, and the beautiful Amena . Thanks for the Chemistry department and all the academic staff.

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Abstract :-

Boron neutron capture therapy (BNCT) is a biochemically targeted radiotherapy based on the nuclear capture and fission reactions that occur when non-radioactive boron-10, which is a constituent of natural elemental boron, is irradiated with low energy thermal neutrons to yield high linear energy transfer alpha particles and recoiling lithium-7 nuclei. Therefore, BNCT enables the application of a high dose of particle radiation selectively to tumor cells in which boron-10 compound has been accumulated. We applied BNCT using nuclear reactors for 167 cases of malignant brain tumors, including recurrent malignant gliomas, newly diagnosed malignant gliomas, and recurrent high-grade meningiomas from January 2002 to May 2014. Here, we review the principle and history of BNCT. In addition, we introduce fluoride-18-labeled boronophenylalanine positron emission tomography and the clinical results of BNCT for the above-mentioned malignant brain tumors. Finally, we discuss the recent development of accelerators producing epithermal neutron beams. This development could provide an alternative to the current use of specially modified nuclear reactors as a neutron source, and could allow BNCT to be performed in a hospital setting.

Aim of the project:-

The main objective of this research is to properties boron element and it's complexs and their importance in medicinal chemistry. Along with explaining their biological effectiveness against some types of diseases especially cancer ,and explaining of the theory that we will used to treat (BNCT).

1. Introduction:-

Boron the fifth element in the periodic table, is a naturally occurring element. In the environment, boron is combined with oxygen and other elements in compounds called borates. Borates are widely found in nature, and are present in oceans, rocks and soils. There are several commercially important borates, including BA, borax (BX) and the minerals colemanite (COL) and ulexite (UX) . These compounds are widely used in industrial, agricultural, cosmetic, medical settings, household products and a numerous smaller applications. The boron, a trace mineral for plants, animals and humans, has been has been shown to have apparent beneficial effects in humans at intakes commonly found in diets abundant in foods such as fruits and vegetables. Research finding suggest that physiological amounts of supplemental dietary boron (as BA) affect a wide range of metabolic parameters in animals. It probably strengthens the antioxidant defense mechanism by a yet unknown mechanism. Orally administered boron is rapidly and completely absorbed from gastrointestinal tract into the blood stream and plays an important role in improving arthritis, plasma lipid profiles, brain function. A variety of boronated agents with hypolipidemic, anti-inflammatory or anticancer properties is also developed. Moreover, the boron compounds show mineral potential for genotoxicity in bacteria and cultured mammalian cells. Thus, these compounds remain very interesting research topics due to equivocal and relatively unknown useful actions, roles in the treatment of various diseases, and interactions of other element. (Hasan Turkez 2012).

1.1Boron delivery agents for neutron capture therapy of cancer:-

Recent efforts to improve the selectivity of boron delivery agents has involved incorporating them into tumor-targeting moieties, such as unnatural amino acids, polyamines, peptides, proteins, antibodies, nucleosides sugars, porphyrins, liposomes and nanoparticles Among the low molecular weight boron delivery agents are boronated natural amino acids as well as boronated derivatives of other amino acids such as aspartic acid, tyrosine, cysteine, methionine and serine . Boron-containing unnatural amino acids also have been investigated because of their higher metabolic stability compared with the natural ones.(Rolf F Barth2012).

2.Applications:-

Since 1857, boron has been known to be present in plants. Reports byWarington1 in 1923 and Sommer and Lipman in 1926 resulted in the acceptance of boron as an essential nutrient for plants because it was necessary to complete the life cycle. Interestingly, over 80 years have past and a clearly defined biochemical function has not been identified for boron in the reproductive process of plants. Boron does have a structural role in plant cell walls, thus, boron is a constant constituent of foods of plant origin. In the 1870s, it was discovered that sodium borate and boric acid could be used to preserve foods. For about the next 50 years, borate addition was considered one of the best methods for preserving or extending the palatability of foods such as meat and dairy products. Boron had a vital role as a preservative in preventing food crises during both World War I and II. Boron apparently was considered relatively non-toxic because no deaths were attributed to using boron as a preservative.

BNCT is based on the nuclear capture and fission reactions that occur when boron-10 (10B), which is a nonradioactive constituent of natural elemental boron, is irradiated with low-energy thermal neutrons to yield high linear energy transfer (LET) alpha particles (4He) and recoiling lithium-7 (7Li) nuclei(Sheng MH-C, 2001).

2.1 Boron Neutron Capture Therapy for Malignant Brain Tumors:-

The BNCT in theory provides a way to selectively destroy malignant cells and spare normal cells. BNCT requires two components, i.e., a neutron and a boron-carrier. Sir James Chadwick discovered neutron in 1932 and was awarded the 1935 Nobel Prize in Physics for his discovery.A mere 4 years later, Locher introduced the concept of BNCT. there are only two boron delivery agents in clinical use: the polyhedral boron anion, sodium mercaptoundecahydro-closo-dodecaborate (Na_2 B_{12} H_{11} SH), commonly known as sodium borocaptate (BSH), and the boron-containing amino acid (L)-4-dihydroxyborylphenylalanine, known as boronophenylalanine (BPA). Structural diagrams of both compounds are shown in Fig. 1. (Barth RF 2005).

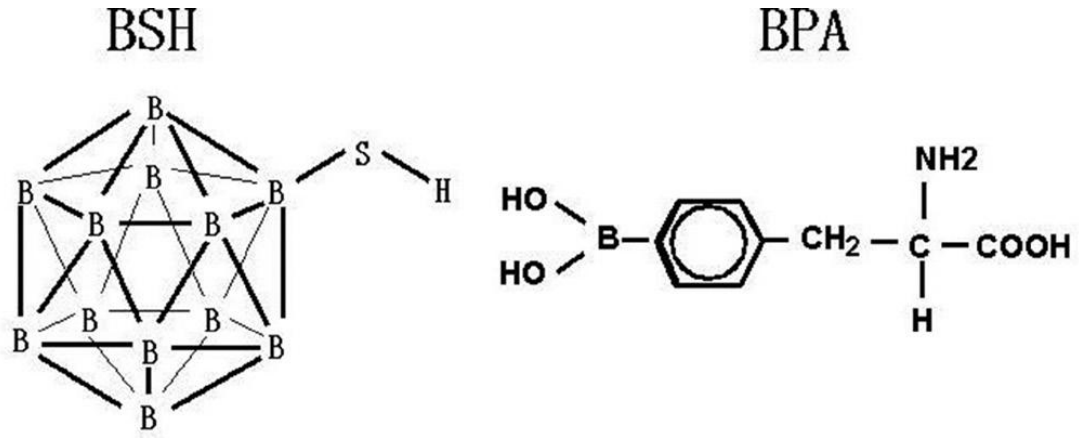
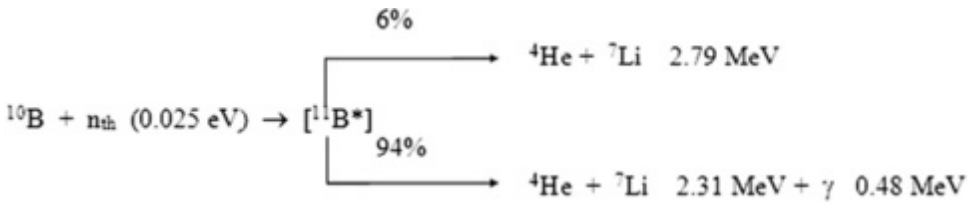


Figure 1:
Structural diagrams of sodium borocaptate (BSH) and boronophenylalanine (BPA). BSH is a macro-molecule. BPA is boronated-phenylalanine, one of the essential amino acid.

2.2 Current Status of Boron Neutron Capture Therapy of High Grade Gliomas and Recurrent Head and Neck Cancer:-

Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when boron-10, which is a non-radioactive constituent of natural elemental boron, is irradiated with low energy (0.025 eV) thermal neutrons. This results in the production of high linear energy transfer (LET) alpha particles (4He) and recoiling lithium-7 (7Li) nuclei, as shown below



In order to be successful, a sufficient amount of 10B must be selectively delivered to all tumor cells (~ 20 μg/g weight or ~109 atoms/cell), and enough thermal neutrons must be absorbed to cause lethal damage from the 10B (n,α)7Li capture reaction.(Rolf of Barth 2018).

2.3 Boron Neutron Capture Therapy of Cancer, Current Status and Future Prospects:-

General requirements. The development of boron delivery agents for BNCT began f50 years ago and is an ongoing and difficult task of the highest priority. The most important requirements for a successful boron delivery agent are as follows:
(a)low systemic toxicity and normal tissue uptake with high tumor. (b) tumor concentrations of f20 Ag 10B/g tumor. (c) rapid clearance from blood and normal tissues and persistence in tumor during BNCT.

However, it should be noted that at this time no single boron delivery agent fulfills all of these criteria. With the development of new chemical synthetic techniques and increased knowledge of the biological and biochemical requirements needed for an effective agent and their modes of delivery, several promising new boronnagents have emerged. The major challenge in their development has been the requirement for selective tumor targeting to achieve boron concentrations sufficient to deliver therapeutic doses of radiation to the tumor with mineral normal tissue toxicity. (Rolf of Barth 2005).

3.Compounds:-

The boron-containing compounds epitomize a new class for medicinal chemists to use in their drug designs. Carboranes are a class of organometallic compounds containing carbon (C), boron (B), and hydrogen (H) and are the most widely studied boron compounds in medicinal chemistry.

3.1 Boron Chemistry for Medical Applications:-

Carborane clusters and polyhedral boranes are characterized by delocalized electron deficient bonding, meaning that there are too few valence electrons for bonding to be described exclusively in terms of 2-center-2-electron (2c2e) pair bonds . One characteristic of electron deficient structures is the aggregation of atoms to form 3-center-2-electron (3c2e) bonds. The best-known types of polyhedral boron compounds which are most often used in medicinal chemistry are icosahedral dicarbadodecarboranes (C2B10H12), in which two CH units replaced the two BH vertices. Carboranes have a highly delocalized electron hydrophobic surface, and are reflected to be inorganic benzenes or three-dimensional aromatic compounds . The carborane occupied almost 50% greater space than that of the rotating phenyl group. The carboranes are found in three isomeric forms due to the position of two carbon atoms within the cage as shown in Figure 1 The carborane system has the ability to enter in the substitution reaction at both boron and carbon atoms without degradation of the carborane cage. This is considered to be one of the most important features of this system for participation in various types of substitution reactions. (Ali, Fayze,2020).

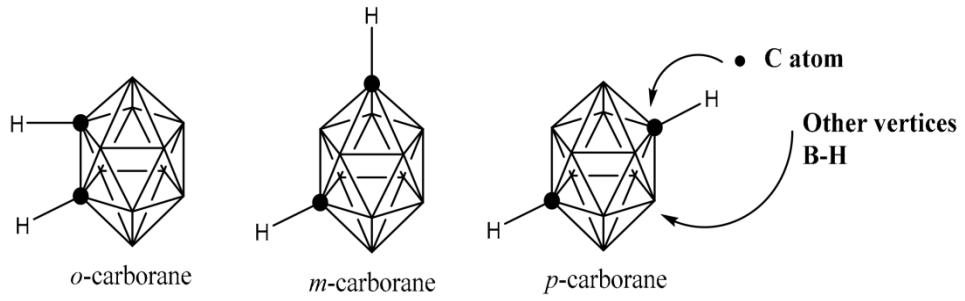
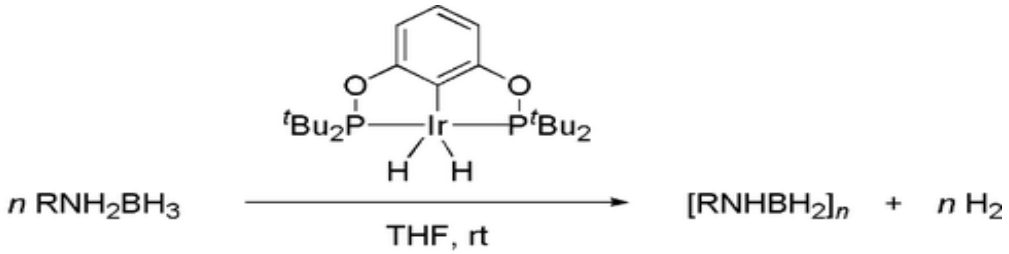


Figure 2:
Structure of carborane due to the attachment of carbon at di_erent sites.

3.2 Iridium-Catalyzed Dehydrogenation of Substituted Amine Boranes: kinetics, Thermodynamics, and Implication for Hydrogen Storage

Dehydrogenation of amine boranes is catalyzed efficiently by the iridium pincer complex (κ^3 -1,3-(OP^t Bu_2)$_2$ C_6H_3)Ir($H)_2$. With $CH_3NH_2BH_3$ (MeAB) and with AB/MeAB mixtures (AB) NH3BH3), the rapid release of 1 equiv of H2 is observed to yield soluble oligomeric products at rates similar to those previously reported for the dehydrogenation of AB catalyzed by 1. ΔH for the dehydrogenation of AB, MeAB, and AB/MeAB mixtures has been determined by calorimetry. The experimental heats of reaction are compared to results from computational studies.(Denny,M.C,2006).



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4.complexes:-

4.1 *Pseudo*-*S*6 Complex Cations of a Hexakis-*N*-methylformamide Nickel(II) Complex:-

The nickel(II) complex [Ni(NMF)6](BPh4)2 [NMF = *N*-methylformamide] [hexakis(*N*-methylformamide-*kO*)nickel(II) bis(tetraphenylborate)] was prepared, and characterized by a single-crystal X-ray method. (fig.3)(Miyatak,2020).

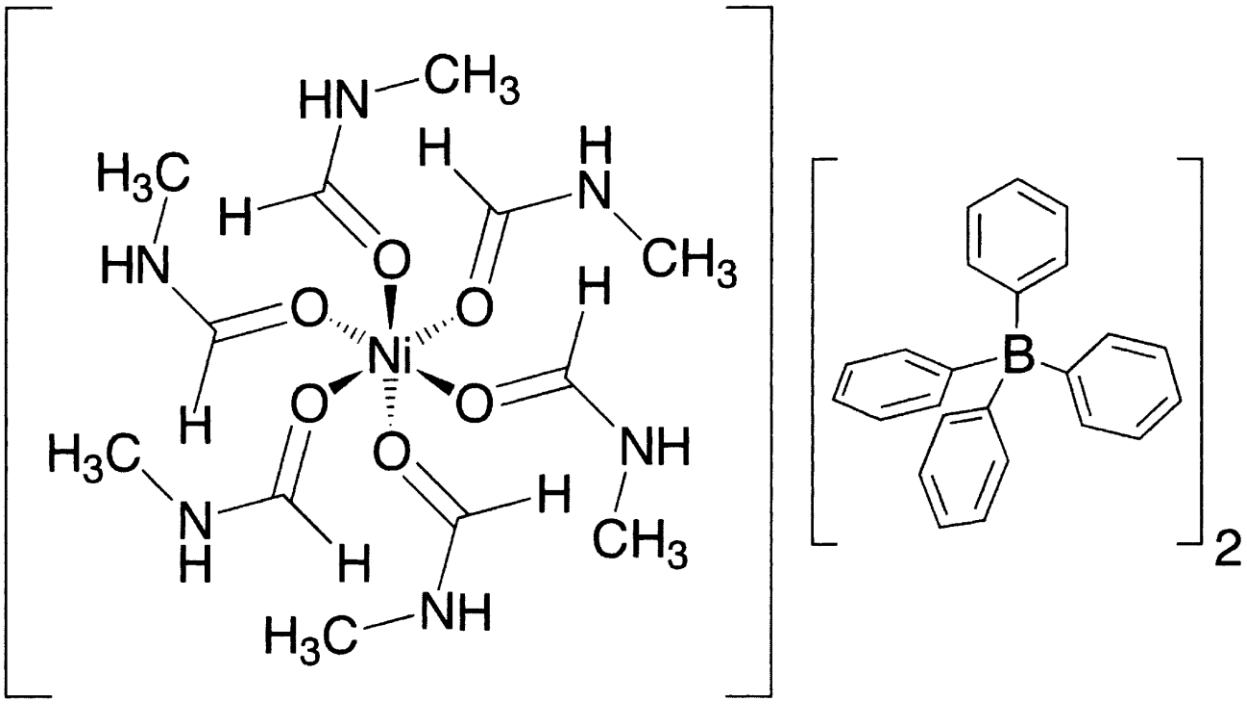
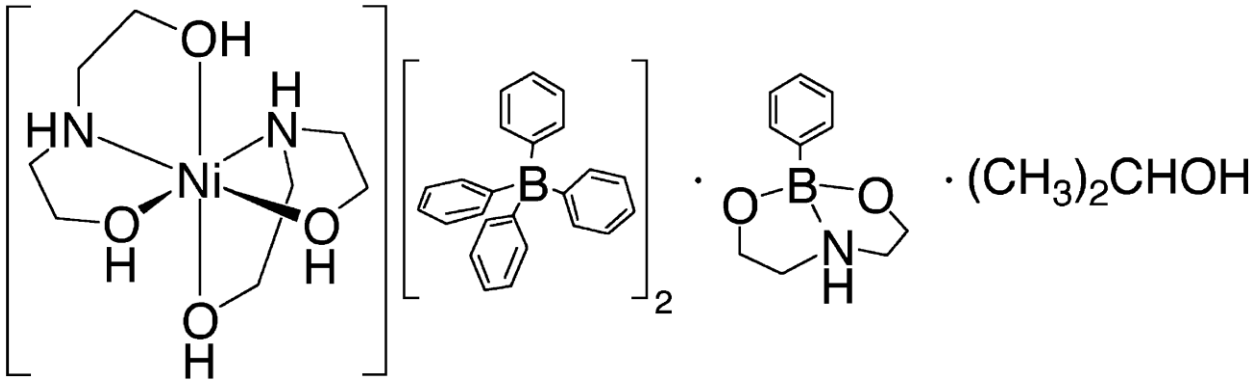


Figure 3 :
Chemical structure of $[Ni(NMF)_6](BPh_4)_2$.

4.2 Structure of Bis(2,2¢-iminodiethanol-*N*,*O*,*O*¢)-Nickel(II) Hydrogen-Bonded to an Organoboron Coordination Complex:-

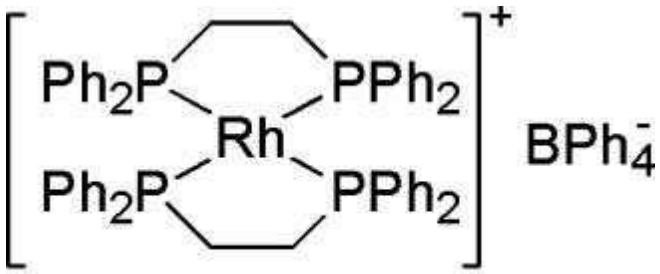
The nickel(II) complex $[Ni\{H_2(ide)\}_2](BPh_4)_2 \cdot BPh(ide) \cdot (CH_3)_2CHOH$ (H_2(ide) = 2,2¢-iminodiethanol) was prepared, and characterized by a single-crystal X-ray method.(fig.4)(M,J.Hossain.2002).



Figures 4 :
Chemical structure of $[Ni\{H_2(ide)\}_2](BPh_4)_2 \cdot BPh(ide) \cdot (CH_3)_2CHOH$.

4.3 Bis[bis(diphenylphosphino)ethane]rhodium(I) tetraphenylborate:-

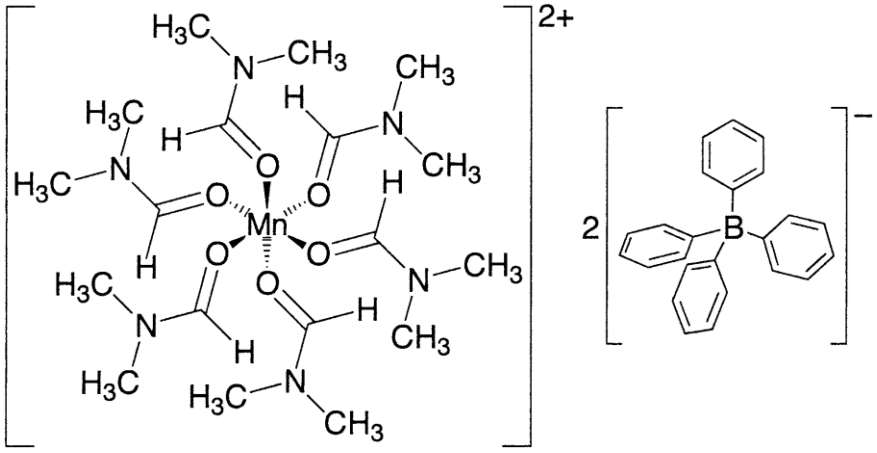
In the title compound, Bis[bis(diphenylphosphino)ethane]rhodium(I) tetraphenylborate both the Rh and the B atom lie on twofold axes of symmetry. Selected geometrical parameters are Rh—P = 2.3076 and 2.3114 A ° , and P—Rh—P = 82.43 and 98.11. (A.Kazama,2008).



(I)

4.4 Synthesis and Crystal Structure of a Trigonally Compressed Hexakis-DMF Manganese(II) Complex:-

The manganese(II) complex [Mn(DMF)6](BPh4)2 [DMF = *N*,*N* dimethylformamide] [hexakis(*N*,*N*-dimethylformamide*kO*) manganese(II) bis(tetraphenylborate)] was prepared, and characterized by a single-crystal X-ray method. (fig.5)(H.Sakiyama 2003).

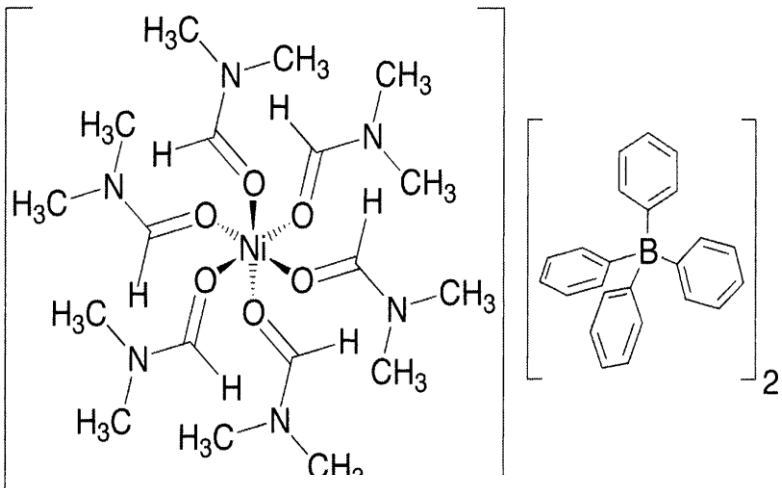


Figures 5:

Chemical structure of $[Mn(DMF)_6](BPh_4)_2$.

4.5 Synthesis and Crystal Structure of a Hexa-DMF Nickel(II) Complex that Belongs to an *S*6 Point Group:-

The nickel(II) complex $[Ni(DMF)_6](BPh_4)_2$ [DMF = *N*,*N*-dimethylformamide] was accidentally formed from $[Ni(bmoen)_2$-$(DMF)](BPh_4)_2 \cdot$DMF [bmoen = bis(2-methoxyethyl)amine] by its decomposition during a recrystallization procedure, which was from a mixture of DMF and 2-propanol (1:1). The obtained crystal was characterized by single-crystal X-ray analysis.(fig6)(H.Sakiyama 1897).

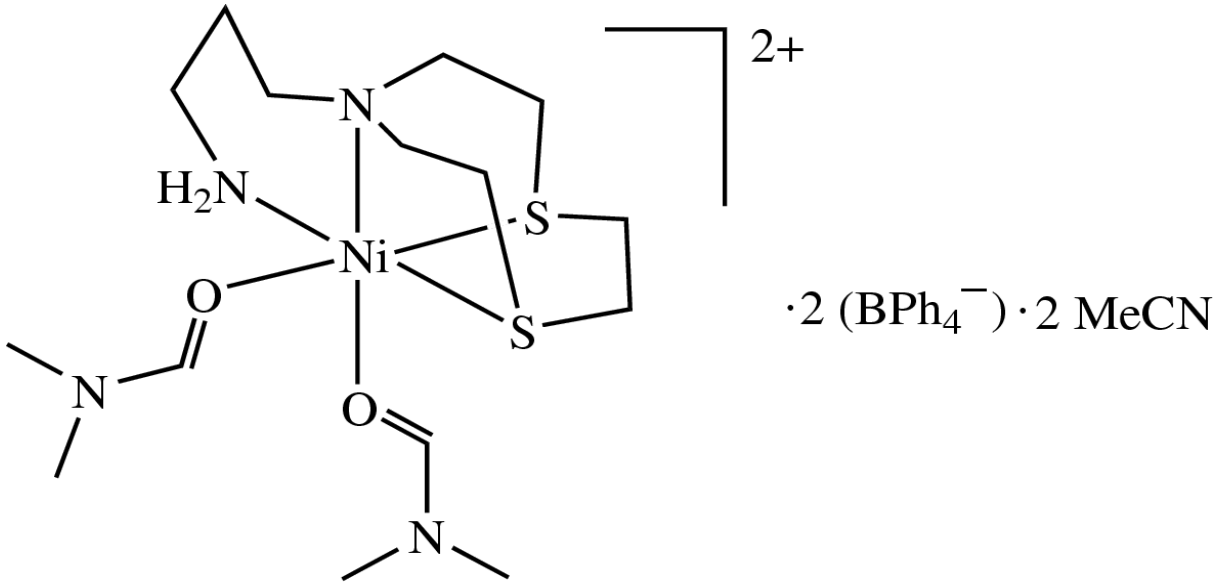


Figures6:

Chemical structure of [Ni(DMF)6](BPh4)2.

4.6 [1-(3-Aminopropyl)-4,7-dithia-1-azacyclononane-k^4 N,N',S,S']bis (dimethylformamide-jO)nickel(II) bis(tetraphenylborate) acetonitrile disolvate:-

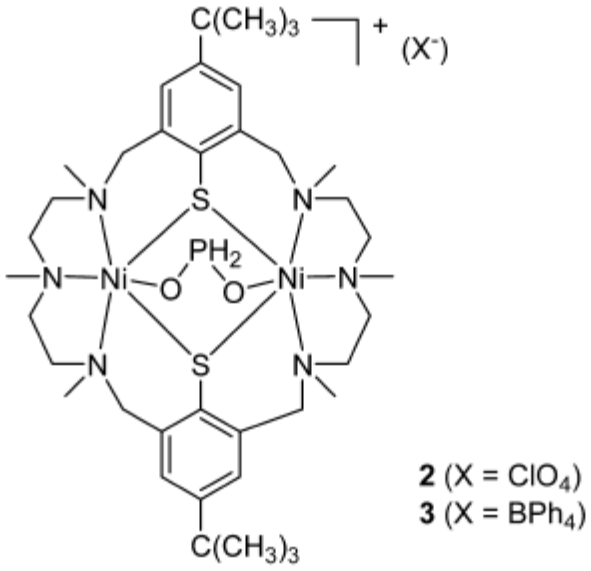
In the title complex, [Ni(C3H7NO)2(C9H20N2S2)](C24H20B)2. 2CH3CN, the metal centre has a distorted octahedral environment, with four coordination sites occupied by two N- and two S-donor atoms from a 3-aminopropyl pendant arm derivative of the nine-membered macrocycle 1-aza-4,7-dithiacyclononane, and the remaining two positions by two mutually cis dimethylformamide ligands. (S.J.Retting and J.Trotter,1975).



(I)

4.7 Stabilization of Hypophosphite in the Binding Pocket of a Dinuclear Macrocyclic Complex: Synthesis, Structure, and Properties of $[Ni_2L(\mu\text{-}O_2PH_2)]BPh_4$ (L = N_6S_2 Donor Ligand):-

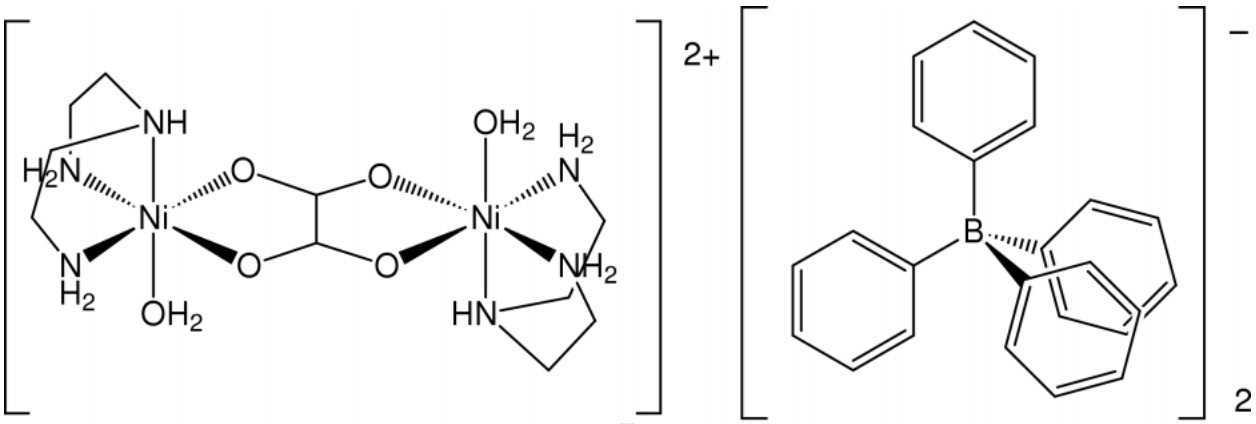
The dinickel(II) complex $[Ni_2L(ClO_4)]ClO_4$.where L2− represents a 24-membered macrocyclic hexaamine-dithiophenolate ligand, reacts with $[nBu_4N]H_2PO_2$ to form the hypophosphito-bridged complex $[Ni_2L(\mu\text{-}O_2PH_2)]+$, which can be isolated as an air-stable perchlorate $[Ni_2L(\mu\text{-}O_2PH_2)]ClO_4$ or tetraphenylborate $[Ni_2L(\mu\text{-}O_2PH_2)]BPh_4$ salt.(fig7)(Berners-Price,S,J,1999).



Figures 7:
Chemical structure of the [Ni2L(μ-O2PH2)]+ complex in the salts 2 and 3.

4.8 μ-Oxalato-k^{4}O^1,O^2:O$^{1'}$,O$^{2'}$ -bis[aqua(diethylene- triamine-K^{3}N)nickel(II)] bis(tetraphenylborate):-

The title compound, $[Ni_2(C_2O_4)(C_4H_{13}N_3)_2(H_2O)_2][B(C_6- H_5)_4]_2$, contains a centrosymmetric dinuclear oxalato±nick- el(II) complex cation in which the oxalate ligand bridges the Ni atoms in a bis-bidentate fashion. The distorted octahedral environment of each Ni atom is completed by the three N atoms of the diethylenetriamine ligand in a fac arrangement, and by one O atom from a water molecule. Tetraphenylborate acts as the counter-anion.(R.Yamaguchi,2014).



(I)

Conclusion :-

BNCT It probably lies in filling a niche for those malignancies, whether primary or recurrent, for which there is no effective therapy. The advantages of BNCT First, it has the ability to selectively deliver a high radiation dose to the tumor with a much lower dose to surrounding normal tissues. This is an important feature that makes BNCT particularly attractive for salvage therapy of patients who have been treated to tolerance with photon irradiation. Second, it has the potential to more effectively target multicentric deposits of tumor than is possible with stereotactic radiosurgery of primary and metastatic brain tumors. Third, although it may be only palliative, it can produce striking clinical responses, as evidenced by the experience of several groups treating patients with recurrent, therapeutically refractory head and neck cancer.

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اقليم كردستان- العراق

وزاره التعليم العالي &والبحث العلمي

جامعه صلاح الدين

كليه العلوم

قسم الكيمياء

كيمياء البورون وتطبيقاته كمضاد للسرطان

مشروع التخرج

مقدم الى قسم الكيمياء كجزء من متطلبات نيل درجة البكالوريوس في علم الكيمياء

اعداد:

مائدة وضاح سعود

باشراف:

م.م عدنان قادر

رمضان-1443 ابريل-2022 نوروز-2722