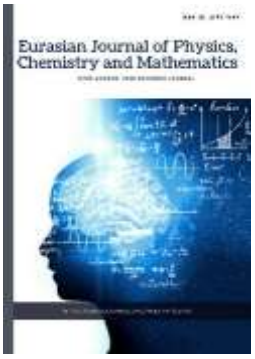

Metal Chelates as Antibacterials and Elemental Analysis of the Ligands

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ABSTRACT

Both the relationship between metal binding and chemotherapy, as well as the complexes formed by metals with one of the drug families, have been the subject of research. There has been substantial progress achieved in this area thanks to the contributions of completing species, in particular chelating compounds. According to the definition of chelating agents, they are required to have two or more electron donor groups that are capable of combining with medallion to create one or more stable ring structures with five or six members. Chelating agents are also required to be able to bind to metal ions. The work done to complete species has been of tremendous assistance to this area of study. There is abundant evidence to support the hypothesis that chelation is the primary mechanism behind the therapeutic benefits of a significant number of medical medicines, both naturally occurring and synthetically produced. Albert has conducted study on the relationship between metal binding and chemotherapy, and he has written a report on the metal complexes that may be discovered in one of the several families of medications. He differentiates between two separate categories of metal binding chemicals that both have a chemotherapeutic effect. Those that are able to function as antibacterial agents by adding a metal in sufficient significant numbers to bring about a rearrangement of bacterial meta boils, and those that are able to function as antidotes in cases of metal poisoning by removing metal ions from the tissue. Both of these types of compounds are known as metalloporphyrins. In order for metals to be effective as antibacterial agents, they need to be injected directly into the blood stream; however, this is not possible since metals are not selective and their toxicity is harmful to the host. This occurs as a result of the manner in which metals are utilised.

Keywords: Metal , Chelates , Antibacterials, Ligands

Introduction

Metal Chelates As Antibacterials:

It is possible to trace back to prehistoric times the illogical use of inorganic substances as medicinal therapies. There has been substantial progress achieved in this area thanks to the contributions of completing species, in particular chelating compounds. According to the definition of chelating agents, they are required to have two or more electron donor groups that are capable of combining with medallion to create one or more stable ring structures with five or six members. Chelating agents are also required to be able to bind to metal ions. The work done to complete species has been of tremendous assistance to this area of study. There is abundant evidence to support the hypothesis that chelation is the primary mechanism behind the therapeutic benefits of a significant number of medical

medicines, both naturally occurring and synthetically produced.

Albert has conducted study on the relationship between metal binding and chemotherapy, and he has written a report on the metal complexes that may be discovered in one of the several families of medications. He differentiates between two separate categories of metal binding chemicals that both have a chemotherapeutic effect. Those that are able to function as antibacterial agents by adding a metal in sufficient significant numbers to bring about a rearrangement of bacterial meta boils, and those that are able to function as antidotes in cases of metal poisoning by removing metal ions from the tissue. Both of these types of compounds are known as metalloporphyrins. Metals cannot be directly injected into the blood stream in order for them to function as antibacterial agents. This is due to the lack of selectivity that metals possess as well as the toxicity that they pose to the host. This is the only way that something like this could be done. To add insult to injury, even more water-soluble metal ions like iron are unable to penetrate past the membranes of bacterial cells and exert their effect. This is an example of how the membranes of bacterial cells prevent metal ions from exerting their influence. It was found to have that 8-hydroxy group. On the other hand, quinoline has the potential to form a complex with the iron that is normally present in the host and then transport that iron across the membranes of bacteria and fungi. This is a unique property that distinguishes it from other antimicrobial agents. Because of this, the complex has the potential to operate as a fungicide as well as an antibacterial agent.

The fact that cobalt is required for the metabolic processes that organisms that create vitamins must go through has also been proposed as an explanation for the antibacterial action of 8-hydroxyquinoline. Another one of the reasons that has been proposed is this one. B_{12}, Additionally, because of the reaction that takes place when this metal is combined with 8-hydroxy quinoline, the metal is rendered unavailable to the body. Albert has reached the conclusion that the action of 8-hydroxy quinoline is not based on the removal of metallic ions but rather on the provision of an excess of anion that is toxic to the organism. He came to this conclusion after conducting research into the mechanism of action of 8-hydroxy quinoline. As a result of his investigation, he arrived at this judgement. The activity poisons the organism with metallic compounds rather than eliminating essential trace metals from the metabolic pathway of the organism. This is because the activity does not work as intended.

Foye Duvall and her colleague conducted research on the antitubercular activity of metal complexes and chelates of p-amino salicylic acid (P.A.S.). The structure of the copper complex will be discussed in further depth in the following paragraphs. It is a phenolic compound that is open to inspection.

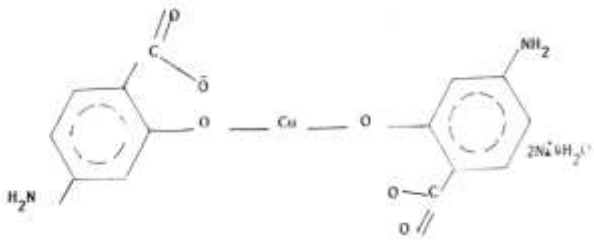


Figure 1: Chelates of p-amino salicylic acid (also known as P.A.S.) for the treatment of tuberculosis

while it is hypothesised that the structure of chelates looks like this:

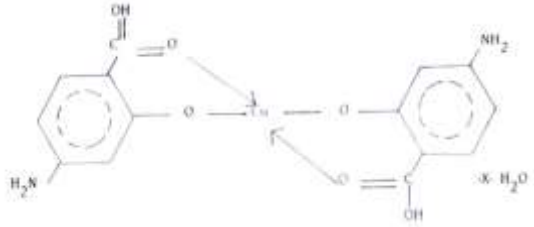


Figure 2: cupric chelate anti tabercular action

The cupric chelate shown significantly higher levels of in vivo anti-tubercular activity when tested on mice in comparison to what the cupric tests indicated for the complex. Both in vivo and in Vitro bidentate complex to be comparable to or superior than PAS alone, and these researchers came to the conclusion that PAS most likely exerts its anti-tuberculous activity as a cupric chelate. [Citation needed] Both in vivo and in Vitro bidentate complex to be comparable to or superior than PAS alone [Citation needed] [Citation needed] [Further citation is required] In comparison to the ionic tubercle bacilli cell complex CompleX, the solubility of the non-ionic chelate is approximately thirty times higher. In addition to this, the non-ionic chelate may be penetrated more easily than the Complex can. It is possible that the nature of the chelate, which is more lipophilic, is the reason why its divalent cations play an essential role in the maintenance of the gram-negative bacteria cell structure. This idea is supported by the observation that lipophilicity is positively correlated with an essential role. When the cations in question are chelated with ethylenediamine tetraacetic acid, the cell surface of an organism like E. coli or P. aeroginosa undergoes a profound transformation into a state of severe disorganisation. This results in a decrease in the bacteria's resistance to antibacterial drugs, the impact of which is dependent on the ability of the agents to penetrate the cell membrane of the pathogen. This causes a decrease in the bacteria's ability to cause disease. On the other hand, the bacteriocidal activity that is exerted on these bacilli is diminished when calcium or magnesium ions are brought to the surface of the cell in an effort to make the cell more robust. This occurs when calcium or magnesium ions are brought to the surface of the cell.

By decreasing the permeability barriers, the use of a combination of antibiotics and chelating agents as a topical treatment has the potential to significantly increase the efficacy of suitable antibiotics in the treatment of a local infection. This is accomplished through the administration of the combination topically. In the field of dermatology, the use of 8-hydroxy quinoline -5- sulfonate, which is water-soluble, is widely implemented for the treatment of bacterial and fungal illnesses. The impact that it has on gram-positive bacteria is caused by the formation of a chelate with appropriate metal ions, such as copper (II), iron (II), and iron (III). It is possible that these metal ions are located within the cell as well as in the media that surrounds the cell.

Procedure for the Synthesis of 2-Chloro-4-Phenylthio-Uracil-6-Phenylpyrimidine: (CpTUpP)

The method developed by Hilbert and Johnson to produce 2 chloro 4 pheny thio uracil and 6 phenyl pyrimidine relies on the reaction that takes place between the RNCS group and 2 chloro 4amino 6 phenyl pyrimidine. This reaction is the foundation for the Hilbert and Johnson methodology. The following is a list of the 1ines that need to be completed in order to create 2 chloro 4 phenyl thio uracil 6 phenyl Pyrimidine (CpTUpP). The synthesis of (CpTUpP) was carried out in a manner that was compliant with the instructions provided in the appropriate body of research.

In order to synthesise 2-chloro-4-amino-6-phenyl pyrimidine, the Behrend method is utilised.

" While vigorously shaking the flask, 2.55 grammes of analar grade recrystallized 2:4 dichloro-6-phenyl pyrimidine are dissolved in 80 millilitres of ethanolic ammonia. The flask is shaped like a circular bottom. The flask is heated to 50 degrees Celsius for five minutes, which results in the production of a solution

that is transparent and yellow in colour. As a reaction to this proposed remedy, an alcoholic beverage was provided. solution of C_6H_5NCS prepared by dissolving 1.22 gms of analar 8rade C_6H_5NCS Absolute alcohol requires the addition of the component to the liquid at a slow and steady rate while continuously stirring the mixture. The reaction mixture is heated for an hour on a water bath that is also fitted with a reflux condenser. The procedure takes place in a separate container. After it has been vigorously shaken, this step is carried out. After a period of time has passed and it has been left to stand, the end result will be a yellow granular product. The contents of the flask are transferred into a beaker that has a capacity of 250 ml, and then they are let to cool for some time. Following that, it goes through the steps of being dried, filtered, and washed with ethanol. When ethenol is heated, the chemical compound known as CpTUpP is produced as a byproduct of the recrystallization process. The product was put through a series of tests, and the results showed that it is made up of the components 2 chloro, 4 pheny I thio uracil, and 6 phenyl pyrimidine (CpTUpP).

The Synthesis Of 2-Chloro, 4-Bromo, and 6-Phenyl-Thio-Uracil and 6-Phenyl Pyrimidine (Cbptupp):

The two processes that follow are the ones that need to be completed in order to prepare 2, chloro, 4 bromo phenyl thio uracil 6 phenyl pyrimidine.

Preparation of 2-bromo phenyl iso thiocyanate

The preparation of 2-bromophenyl isothiocyanate involves using the approach that has been utilised by previous scientists. A flask with a circular bottom is used to dissolve three grammes of analar grade phenyliso thiocyanate in ten millilitres of water. $CHCl_3$

On the other hand, one may prepare a bromine solution in chlaroform and acetic acid by first dissolving five grammes of bromine in ten millilitres of the chlaroform. This will result in a total volume of ten millilitres of the bromine solution. $CHCl_3$ and 10 millilitres of glacial acetic acid. Now, about this bromine $CHCl_3$ The solution is added to the flask containing the combination of phenylisothiocyanate and methanol one drop at a time while the flask is constantly stirred. $CHCl_3$ On the water bath, the reaction mixture is allowed to reflux for a total of two hours. After allowing the mixture to stand for 15 minutes, a pale yellow precipitate of 2-bromo phenyliso is produced. The thiocyanate is then recovered, the liquid of the flask is filtered, and the precipitate is washed many times with ethanol before being dried. The product is made by recrystallizing hot ethanol at a concentration of 60%. M.P. was determined to be 105 c, and the yield was satisfactory.

The Preparation of 2-Chloro, 6-Bromophenyl-Thio-Uracil-Pyrimidine (CbpTupp)

To dissolve 2.5 grammes of 2-bromo phenylisogms thiocyanate, a round-bottomed flask holding 25 millilitres of ethyl alcohol is needed. The flask also has a round bottom. An alcoholic solution of 2-chloro-4-amino-6-phenyl-pyrimidinone that was prepared before has to be added to this flask. After one hour of heating on a water bath and itting with a reflux condenser, the reaction mixture is ready to be used. The mixture next receives an addition of the Dy that was created by dissolving three grammes of analar grade 2 chloro 4 amino 6 phenyl pyrimidine in twenty-five millilitres of ethyl alcohol. A pale yellow precipitate is created after the solution is concentrated, and then cooled, to bring about the concentration. The product is then dried after being filtered and washed with alcohol at a concentration of sixty percent. Ethanol that has been heated is utilised in the process of re-crystallizing the product. 224 C is the address of the site of M.P. A number of factors are considered, including the critical temperature, melting point, and elemental analysis.

Chaitanya G. Dave and his colleagues were able to successfully synthesise pyridopyrimid ines, after which they investigated the antibacterial properties of the compounds. 2-Amino-3-

Cyano -4-(4-chloropheny 1) (4-chloropheny 1) -6-Phenylpyridine in combination with 2-Amino-2-Acetylpyridine -3-carboxamido-4- (4-chloro phenyl) The interaction between this chemical and a variety of isothiocyanates results in the formation of 6-phenylpyrimidine as a byproduct. -7- cyanates, 4-imino -3-substituted -5-(4-chlorop heny1) phenyl Pyrido 12,3-dj pyrimidin -2(TH)- thiones and 2- thioxo pyrimidins -3-s-5-(4-chloropheny 1) pyrimidins (4-chloropheny 1) -7- phenyl Pyrido [2,3-d] In every instance, pyrimidin -4(3H)-ones were produced without any problems. Later on, methylation resulted in the development of 2-methyl mercapto derivatives, which, following a reaction with either moropholine or piperidine, resulted in the formation of 2-N-(morpholino/piperidino)-3-s-5- (4-chloropheny1) phenyl ones with a seven. Some of the chemicals that belong to the Pyrido 12,3-d] Pyrimidine-4 (3H) family have been investigated to see whether or not they contain antibacterial characteristics.

Diethyl maleate has been shown to react in the following ways, according to research conducted by S. El. Bahaie, A.F.EL. Farargy, and M. M. Hamad: The process of forming diethyl 2-(2-arylviny1) -4,5-dimethyl thiopyrano (2,3-d] pyrimidine When 5-acetyl-4-mercaptopyrimid ines are present, the formation of 6,7-dicar boxylate takes place. Following examination of the spectrum data, it has been concluded that the thiopyrano [2,3-d] pyrimidine is the most suitable structural configuration for the product in question.

By combining 2-hydrazinopyrimidine with a variety of N-chloro acetylated amines, M.K. Jani, N.K. Undavia, and P.B. 98 Trivedi"o were able to synthesise a number of 2-(N'-aryl carbamoy l methy1) Some hydrazino-4-hydroxy-6-methyl pyrimidines. After that, scientists put these chemicals through a series of tests to see whether or not they have any antibacterial qualities.

To this moment, however, there has been no attempt made to either synthesise substituted or unsubstituted aryl pyrimidine metal chelates or explore the biological effect of any of these forms. Neither of these things has been done. The author is now working on synthesising 6-aryl pyrimidine tio-urea metal chelates and researching the effect these compounds have on bacteriology.

Objectives Of The Study

1. To study on metal chelates as antibacterials:
2. To study on preparation of 2-bromo phenyl iso thiocyanate

Research Method

The Synthesis of Metal Chelates Comprised of Bivalent Elements Such As CU(11), CD(I1), NI(II), CO(II), MN, And Others (II)

In a process that takes place at temperatures ranging from 50 to 70 degrees Celsius, aqueous solutions of metal salts are mixed with aqueous solutions of ligands. The resultant iron alcohol crystals were recrystallized after being filtered and washed with distilled water to remove impurities. The precipitate of metal chelates occurred very immediately after the process began.

Experimental

A ligand that had been dissolved in water at a concentration of 0.1 M and a solution of metal salts at 0.1 M were mixed in a process that took place at a temperature that ranged from 50 to 70 degrees Celsius. In a method that is comparable, a 0.1 M diltilled water solution of (CpTUpP), (CbpTUpP), and (CNpTUpP) was prepared, and then the metal salt solutions were added to the solution drop by drop with the appropriate ligand while the combination was heated and being stirred continually. The pvalue never deviated from the range of 8-9 at any point. The precipitates that were created are now ready to use after undergoing digestion for fifteen minutes on a water bath. The metal chelates were dried in an air oven after being put through a filter, cleaned with water and alcohol, and then wiped clean with alcohol. In the processes involving Mn(l) and Cd(II), the chlorides of the metals are used. Metal nitrates are used while working with cobalt(III), whilst metal sulphates are utilised when working with copper(II) and nickel (II).

The elemental analyses as well as the colours of the metal chelates with the ligand (CpTUpP),

(CbpTUpP), and are included in Table No. 1. (CNpTUpP).

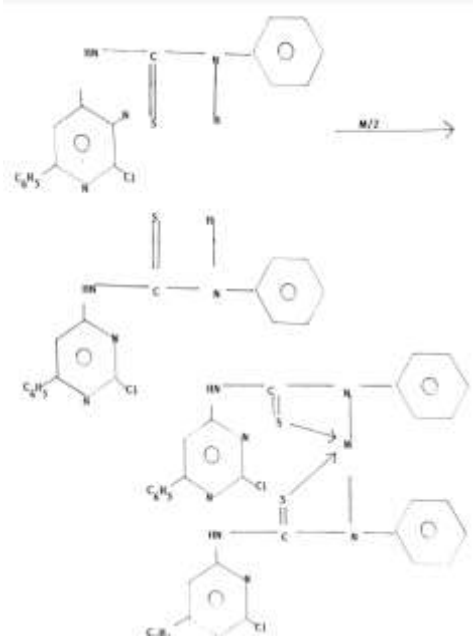
In spite of the fact that the M.P. could not be calculated with any level of accuracy, the temperatures were found to be higher than 225 degrees Celsius.

The element Mn(II), Cu(II), Ni(II), Co(II), or Cd can stand in for any of the following when referring to the composition of the metal chelates, which are designated by the symbol ML (II)

LH = (i) $C_{17}H_{13}N_4SCl$

(ii) $C_{17}H_{12}N_4SClBr$

(iii) $C_{17}H_{12}N_5O_2SCl$



Data Analysis

A method for the preparation of the trivalent metal methyl chelates of Fel1I), Cr(UI), Bi(III), and Al is shown here (III)

At temperatures ranging from 50 to 70 degrees Celsius, solutions of the metal salts in distillate water and solutions of the ligands in distillate water were both permitted to undergo a reaction. The metal precipitates of the chelates were produced when the mixture was filtered, washed, and then re-crystallized from the alcohol. After that, these precipitates were put to use in the production of the chelates.

0.1 M solutions of the metal equivalent salts were generated in distilled water, and then the solutions of the ligands (CpTUpP), (CbpTUp P), and (CNpTUpP) were mixed at a temperature ranging from 50–70 °C in a drop-by-drop fashion while being swirled frequently. Between the numbers 8 and 9, the value of p was kept unchanged. The precipitates that developed as a result of the metal chelates were digested on a water bath for ten to fifteen minutes. After that, the precipitates were filtered and washed with distilled water and alcohol. The procedure is finished up with an extensive chelation followed by drying in an air oven.

Metal chlorides were utilised in the production of Fe(III), whilst sulphates were utilised in the production of Cr(1II) and Al(T), and nitrates were utilised in the production of Bi (III).

The elemental analysis as well as the colour of the metal chelates with the ligands (CplTUpP), (CbpTUpP), and are provided in Table No2 (CNpTUpP).

It was found that none of the metal chelates are soluble in water, alcohol, dioxane, acetic acid, or the vast majority of the organic solvents that are typically put to use. In acetone and benzene, respectively, they exhibit a low degree of solubility. Before anything else, every single one of the metal chelates needs to be filtered through a sintered glass crusible filter.

The processes that were just explained may also be utilised to generate the metal chelates

of another isomer known as 4-chloro-2-amino-6-phenyl-pyrimidine. This isomer is referred to by its full chemical name.

Table No-2 the molecule, composition, melting point, percentage yield, and elemental analysis of the ligands (CpTUpP), (CbpTUpP), and AND (CNpTUpP)

Compound	Composition	M.P.	% Yeild	% C		% H		% N		% S		% Cl		% Br		% O	
				Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Fd	Cal	Fd
CpTUpP	$C_{17}H_{13}N_4SCl$	251	75	59.91	59.93	3.82	3.80	16.45	16.47	9.40	9.45	10.43	10.36	-	-	-	-
CbpTUpP	$C_{17}H_{12}N_4SClBr$	224	80	48.62	48.60	2.86	2.89	13.35	13.34	7.63	7.60	8.46	8.48	19.07	19.08	-	-
CNpTUpP	$C_{17}H_{12}N_5O_2SCl$	235	80	55.81	55.82	3.28	3.28	19.15	19.13	8.76	8.77	9.71	9.71	-	-	8.76	8.7

Table No 3 Color, elemental analysis of the ligands silver (I), copper (I), and mercury, metal chelates (I)

Metalchelates	Colour	% M		% C		% H		% N		% S		% Cl		% Br		% O	
		Calc	Found	Cal	Fd	Cal	Fd	Cal	Fd	Cal	Fd	Cal	Fd	Cal	Fd	Cal	Fd
$Ag(C_{17}H_{12}N_4SCl)$	Gray	24.13	24.15	45.59	45.60	2.68	2.65	12.51	12.50	7.15	7.13	7.93	7.45	-	-	-	-
$Cu(C_{17}H_{12}N_4SCl)$	Blue	15.75	15.77	50.62	50.60	2.98	2.95	13.90	13.92	7.94	7.95	8.81	8.82	-	-	-	-
$Hg(C_{17}H_{12}N_4SCl)$	Buff	37.53	37.50	37.53	37.50	2.21	2.25	10.30	10.30	5.89	5.90	6.53	6.55	-	-	-	-
$Ag(C_{17}H_{11}N_4SClBr)$	Grey	20.51	20.53	38.75	38.75	2.09	2.10	10.64	10.60	6.08	6.06	6.74	6.75	15.19	15.20	-	-
$Cu(C_{17}H_{11}N_4SClBr)$	Blue	13.17	13.15	42.32	42.35	2.28	2.30	11.62	11.60	6.64	6.62	7.37	7.38	16.60	16.62	-	-
$Hg(C_{17}H_{11}N_4SClBr)$	Buff	32.77	32.75	32.77	32.80	1.77	1.80	8.10	8.12	5.14	5.10	5.70	5.68	12.85	12.86	-	-
$Ag(C_{17}H_{11}N_5O_2SCl)$	Gray	21.93	21.95	41.42	41.40	2.23	2.25	14.21	14.20	6.50	6.51	7.21	7.20	-	-	6.50	6.50
$Cu(C_{17}H_{11}N_5O_2SCl)$	Blue	14.17	14.15	45.54	45.55	2.46	2.45	15.63	15.65	7.14	7.15	7.92	7.90	-	-	7.14	7.15
$Hg(C_{17}H_{11}N_5O_2SCl)$	Buff	34.66	34.65	34.66	34.65	1.87	1.88	11.89	11.90	5.44	5.45	6.03	6.00	-	-	5.44	5.45

Conclusion

Both the relationship between metal binding and chemotherapy, as well as the complexes formed by metals with one of the drug families, have been the subject of research. He differentiates between two separate categories of metal binding chemicals that both have a chemotherapeutic effect. Those that are able to function as antibacterial agents by adding a metal in sufficient significant numbers to bring about a rearrangement of bacterial meta boils, and those that are able to function as antidotes in cases of metal poisoning by removing metal ions from the tissue. Both of these types of compounds are known as metalloporphyrins. Metals cannot be directly injected into the blood stream in order for them to function as antibacterial agents. This is due to the lack of selectivity that metals possess as well as the toxicity that they pose to the host. This is the only way that something like this could be done. To add insult to injury, even more water-soluble metal ions like iron are unable to penetrate past the membranes of bacterial cells and exert their effect. This is an example of how the membranes of bacterial cells prevent metal ions from exerting their influence. However, it is able to transport iron across the membranes of bacteria and fungi by forming a complex with the iron that is normally present in the host and transporting it in that way. that 8-hydroxy quinoline was found to be contained in it has been demonstrated. Because of this, the complex has the potential to operate as a fungicide as well as an antibacterial agent. After a period of time has passed and it has been left to stand, the end result will be a yellow granular product. The contents of the flask are transferred into a beaker that has a capacity of 250 ml, and then they are let to cool for some time. Following that, it goes through the steps of being dried, filtered, and washed with ethanol. When ethenol is heated, the chemical compound known as CpTUpP is produced as a byproduct of the recrystallization process. The product was put through a series of tests, and the results showed that it is made up of the

components 2 chloro, 4 pheny I thio uracil, and 6 phenyl pyrimidine (CpTUpP).

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