

Spectrophotometric determination of anti-hypertensive drug captopril via its quantitative conversion into trithiocarbonate and its complexation with OS(VIII): characterization by elemental analysis, FTIR, NMR, ESR, TGA, DTA and TGA proposed structure of the complex.

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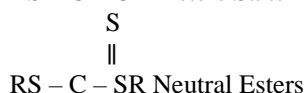
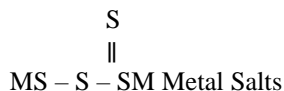
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Abstract: Microdetermination of the trithiocarbonate derivative of the drug captopril as its Os (VIII) complex is achieved spectrophotometrically. λ max 610 nm Beer's law range 6.33×10^{-8} mg to 6.96×10^{-7} mg $\epsilon = 3.74 \times 10^3$ L Mol⁻¹cm⁻¹ metal ligand ratio was confirmed by Job's method and was found to be 1:1. Interference of foreign metal ions was also studied, one ppm of captopril trithiocarbonate could sustain 0.00031 ppm of rathenium trichloride, 0.00022 ppm of nickel sulphate, 0.0003 ppm of zinc sulphate 0.0052 ppm of cobalt nitrate, 0.0002 ppm of copper acetate, palladium chloride, ferric chloride and ferrous ammonium sulfate interfere severely. Characterization of the complex was done by elemental analysis (CHN) which confirms the ascertain the ratio as FTIR spectrum of the complex ascertain the binding, of sulphur atom of trithiocarbonate group, oxygen molecules. No ESR signals is indicative of diamagnetic nature of the complex and covalent nature of the complex. The proton NMR spectrum of the complex further confirms the involvement of sulphur oxygen atoms of trithiocarbonate and carbonyl group respectively with Os(VIII), The TGA of the complex confirm the proposed structure and presence of coordinated and lattice water molecules.

Keywords: FTIR, NMR, ESR, DSC, TGA & DTA.

1. INTRODUCTION

Trithiocarbonate derivatives are of the following general types.



These derivatives exhibit the difunctionality and salts are considered to be a well known class of thiocarbonyl compounds.

Trithiocarbonates are derivatives of thiols, obtained by stirring an equimolar ratio of thiols with carbon disulphide and potassium hydroxide at a temperature below 10°C. The proposed Method employed for the determination of captopril involves its quantitative conversion to TTC at room temperature.

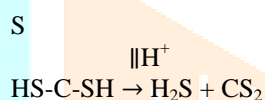
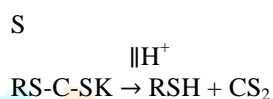
Trithiocarbonic acid exists in the free state or in non- aqueous media, and it differs from carbonic acid in this respect. The free acid gets easily decomposed back to carbon disulphide and hydrogen sulphide.

As compared to trithiocarbonic acid metal salts are more stable. These salts of alkaline earth metal are usually prepared by the interaction of the metal sulphide in aqueous solution with carbon disulphide.



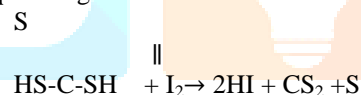
The trithiocarbonates have number of applications, as plant defoliant, lubricating oils, additives, vulcanization, accelerators. Glycol and glycerol trithiocarbonate ester are used to improve wet strength of viscous yarns. Alkylene trithio-carbonate are used for improving plywood adhesives. TTC has relevance to their biological activity as insecticides and therapeutic formulations. Anti-radiation activity against mites²⁻⁴ and in some cases against fungi³ and nematodes⁵ have been shown by some diverse structure of trithiocarbonate.

Alkyl trithiocarbonates form salts with Copper (I) and Zinc (II). Which are well known bird repellants⁶. Trithiocarbonates derived from mercaptoethylamine and 2- mercaptoethylguanidine are reported to have activity as anti radiation drugs. Little attention has been paid to their assay in general and titrimetric determination in particular⁸. Most of the quantitative analysis are based on exploiting the instability of TTC in acidic media where they decompose quantitatively into carbon disulphide and hydrogen sulphide or mercaptans quantitatively⁹.

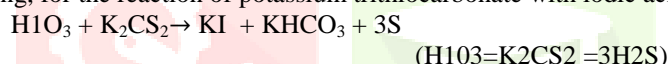


This is one of the most preferred approaches to the quantitative analysis of trithiocarbonate salts.

Besides the usual peroxide bomb oxidation method that converts organic and inorganic forms of sulphur to sulphate ion, there are several other methods which oxidise to a lesser degree. Thus iodine has been found to oxidize trithiocarbonic acid and its alkali metal salts accordingly to the equation given below¹⁰⁻¹⁴.



Johri and Singh¹⁵ also studied the oxidative determination of potassium trithiocarbonate, using KIO_3 in HCl or free HIO_3 in aqueous solution. The stoichiometry of oxidation is not the same for the two oxidation systems. That of the latter is the most interesting, for the reaction of potassium trithiocarbonate with iodic acid is such that the three sulphur atoms undergo oxidation.



This is attributed to two factors. First, the reaction between potassium thiocarbonate and iodic acid is direct, unlike that between hydrochloric acid and potassium iodate. Thiocarbonic acid is first liberated from potassium thiocarbonate in presence of HCl as an intermediate step before its interaction with iodate is possible because iodic acid is weaker than hydrochloric acid. The reaction with trithiocarbonate is gradual, thus permitting all the three atoms of sulphur to undergo oxidation. Trithiocarbonate esters constitute a moderately important class of organic sulphur compounds.

For the determination of microamount of osmium, sulphonic acid¹⁶ is proposed as a reagent. It forms a stable dark violet complex with 1:2 metal ligand ratio. The optimum pH range is 1.8-3.5 and maximum absorbance occurs at 490nm, with sensitivity of $0.02 \mu\text{g}/\text{cm}^2$ and $0.01 \mu\text{g}/\text{cm}^2$.

m-Aminobenzoic¹⁷ acid has been proposed for the spectrophotometric determination of Os(VIII) forming stable purple coloured complex with the reagent, ($\lambda_{\text{max}} = 500\text{nm}$), Beer's law range upto 8 ppm of Osmium(VIII), sensitivity $0.012 \mu\text{g}/\text{cm}^2$.

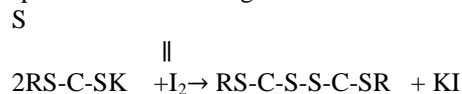
The composition and stability of the complexes of osmium and seleno-urea were studied by Pilipento and Seredo.¹⁸ Seleno-urea first reduces osmium to the tetravalent state, then forms an intensely coloured blue-green complex. The complex has an osmium seleno-urea ratio of 1:8 metal ligand. The colour appears when the eighth molecule of seleno-urea has been added. The intermediate product of the osmium reduction is also intensely coloured and absorbs in the ultraviolet and visible regions.

Dithio-oxamide (rubeanic acid) was applied by Wawlzayezek and Nijakowska¹⁹ to determine osmium in the range 8-15 ppm of osmium as the octavalent oxide. The optimum pH was 6-7 and full colour development was achieved after allowing, it to stand for 1 hour.

For the range of determination from 8 to 24 ppm of osmium, Majumdar and Savariar²⁰ used Tiron, the disodium salt of 1, 2-hydroxy-benzene-3, 5-disulphonate. The reagent produces a reddish violet coloured constituent with a 1:1 mole ratio of osmium to reagent and with a sensitivity of $0.033 \mu\text{g}/\text{cm}^2$. Full and stable colour development was achieved by heating for 15 minutes at pH 4.9-5.5. Maximum absorbance occurs at 470nm. Associated platinum and base metals cause interference).

High performance liquid chromatography has been applied for the separation of several metal ions as their dithiocarbonate complexes. Wana, et al²¹ reported a method for the separation of Co(III), Cr(II), Cu(II), Fe(II), Ni(II), Pd(II), Pt(II), Se(IV), and Te(IV) as their dithiocarbonates (DDC) complexes. Separation can be achieved using ACN-H₂O (70:30) as a mobile phase.

Various reagents like bromine monochloride²², N-iodosuccinimide²³, N-chlorosuccinimide²⁴ have been applied for further determination of sodium or potassium salts of organic derivatives of trithiocarbonic acid in aqueous as well as in non aqueous media.



To control a variety of pests²⁵, dithiocarbamates and their metal derivatives are used as agricultural fungicides on foliage and fruit and also as antioxidants and industrial applications as vulcanization accelerators and floating agents^{26,27}.

In analytical chemistry chelating resins have been gaining importance owing to their potential to remove transition metal ions from dilute solutions²⁸⁻³⁰. This capability is further increased by synthesizing their corresponding dithiocarbamates and trithiocarbonates³¹.

Two chelating resins containing trithiocarbonates and dithiocarbamate groups from commercially available cross linked chloromethylated polystyrene³² and their use for the extraction of lead(II), Copper(II), Nickel(II) and Cobalt(II), was studied. The absorptive capacity of trithiocarbonate and dithiocarbonate resin with respect to Copper(II) was 8.5 and 4.4 $\mu\text{g/g}$ of dry resin at pH 6.0.

Several inert metal complexes including $[\text{Fe}(\text{CN})_6]^{3-}$ ³³ oxidise dithiocarbamates. The metal complexes employed in this study usually act as one electron outer sphere oxidantes owing to their facile reduction and relative inertness towards ligand substitution.

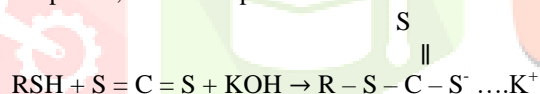
Various methods have been reported for the determination of dithiocarbamates by the carbon disulphide evolution technique³⁴⁻³⁶. Spectrophotometric methods have also been reported for the determination of dithiocarbamates³⁷⁻⁴¹.

Spectrophotometric⁴² method for the determination of sodium dimethyl dithiocarbamate, tetramethyl thiuram disulphide, zinc dimethyl dithiocarbamate, N-methyl piperazinecarbodithiolate, and potassium morpholine-4-carbodithiolate based on extraction of their selenium complexes into chloroform, measured at 430nm against reagent blank. The method is sensitive and can be used for the determination of dithiocarbamates in commercial samples.

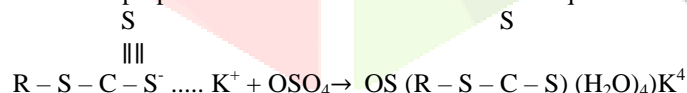
Various techniques were also used for the quantitative estimation of dithiocarbamates and trithiocarbonates. Gudeva⁴³ reported identification and determination of some thioureas and dithiocarbamates by precipitation and paper chromatography. The method involves the treatment of solution of dithiocarbamates in benzene with ethenolic cupric chloride, which gives brown color.

Sodium diethyl dithiocarbamate is used in cancer chemotherapy^{44,45} to reverse the side effects of cisplatin, i.e renal toxicity. This reagent is also a potential drug of Wilson's disease which is characterised by excess deposition of copper in liver and brain. Sodium diethyl dithiocarbamate acts as chelating, agent to remove excess amount of copper.

Fourier transform infra-red spectroscopy, electron spin resonance, nuclear magnetic resonance spectroscopy studies can be applied for characterization of trithio carbonates at 2500 cm^{-1} characteristic band of thiol is obtained in FTIR⁴⁶ spectrum and this band disappears when they are converted to trithiocarbonate. Thiols are diamagnetic in nature hence they do not exhibit ESR spectrum, but its trithiocarbonate is paramagnetic. In NMR spectrum chemical shift (δ) for suiphydryl group at 1:5 ppm from TMS peak⁴⁷, this peak also disappears in the NMR spectrum of a trithiocarbonate. All these evidence thus confirm the formation of trithiocarbonates of corresponding sulphhydryl compound, thiol. The present method involved the reaction as follows.



The TTC of captopril thus formed has been determined quantitatively following the reaction given below.



The product is 1:1 ratio of Os(VIII) and TTC of captopril. Thus by determining captopril TTC determination of captopril is possible by simple calculation.

The method thus formed could be made applicable to a variety of ideas for assay of these functions, medicine, adhesive, anti-radiation drug etc.

The method evolved is accurate to 1% and does not need pre-separate step. The results were almost reproduced in a variety of matrices.

This method of determination of captopril TTC by Os(VIII) has successfully been transformed into determination of Osmium tetroxide by using captopril as an analytical reagent.

2. EXPERIMENTAL

2.1 Instruments:

Toshiwal V.V. 2000 chemito spectrophotometer was used for all the spectrophotometric observation at Bose Memorial Research Lab, Govt. Science College, Jabalpur.

The FTIR spectra was recorded in Nicolet FTIR spectrophotometer in the range 4000-400 cm^{-1} using KBr. Pellets at RSIC, IIT, Powai, Mumbai

The ESR spectra were recorded in Varian 300 MHz. spectrometer using in the scan range of 3000 gauss. Tetracyanoethylene was used as marker at RSIC, IIT Powai, Mumbai.

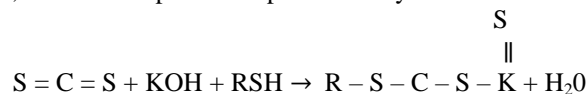
¹HNMR spectra were recorded in Varian - 300 MHz spectrometer using deuterium oxide as solvent at RSIC, IIT, Powai, Mumbai.

Thermal studies, Thermogravimetric analysis(TGA) were carried out in Dupoint thermal analysis system under nitrogen atmosphere from 0°-800°C temperature range at a rate of 20°C/min at RSIC, IIT Mumbai.

2.2 Reagents and Sample:

1. Osmium tetroxide - A standard stock solution of osmium tetroxide was prepared by dissolving 1.00 gm of osmium tetroxide (EMC Electron Microscopy Laboratories Ltd. Bombay) in 100 ml of double distilled water, and standardization of osmium tetroxide solution was done iodometrically, solutions of lower concentration were prepared by diluting aliquots of stock solution.

2. Preparation of Trithiocarbonate : Trithiocarbonate derivatives of captopril was prepared by shaking an equimolar mixture of captopril, carbon disulphide and potassium hydroxide below 10°C according to reaction.



When captopril trithiocarbonate solution was mixed with osmium tetroxide solution, the colour changes from light yellow to dark brown. The λ max for complex is 610nm, whereas the metal to ligand ratio is 1:1.

Effect of pH: The complex is stable at pH=7.0, but its λ max shifts to higher wavelength when pH is decreased.

3. ANALYSIS

Procedure : An aliquote containing 6.330×10^{-8} mg of the trithiocarbonate sample in a 25 ml measuring flask and equivalent amount of 975×10^{-3} M solution of OsO_4 and make up the volume with water. Reference cell is filled with this solution and concentration of the sample is measured by observing the absorbance at 610nm. Concentration of the complex between Osmium tetroxide and trithio carbonate of captopril are calculated from Bougner- Lambert-Beer's Law graph.

Adherence to Beer's Law : Beer's Law is obeyed in the range 6.330×10^{-8} mg to 6.968×10^{-7} . The molar absorptivity or molar extinction coefficient $\epsilon = 3.67 \times 10^3$.

Metal: Ligand Ratio Studies : Mole ratio method and Job's methods of continuous variance was applied. Osmium (VIII) was found to form 1:1 complex with captopril trithiocarbonate.

Effect of Foreign Metal Ions : Interference of foreign metal ions in the proposed method of determination was studied for 1 ppm of captopril trithio carbonate by adding Ru(III), Ni(II), Zn(II), Co(II),Cu(II),which do not cause interference upto 0.00031, 0.00022, 0.0003, 0.0052, 0.0002 respectively, Fe(II), Fe(III) and Pd(II) interferes severely.

Effect of Temperature : At room temperature the complex formation takes place and at higher temperature the trithiocarbonate dissociates fastly.

Stability: The complex is stable upto 4 To 5 days and minimum time required for complex formation is 50 minutes, while wavelength of maximum absorbance max is 610nm.

4. RESULTS AND DISCUSSION

The results of determination of captopril as its trithiocarbonate are summarized in Table-I. This method could be applicable for the determination of drug captopril. The method which is developed for the determination of captopril has been successfully employed for the determination of Osmium (VIII) solution in the range 6.33×10^{-8} mg to 8.96×10^{-7} mg.

The Osmium (VIII) : Captopriltrithiocarbonate complex, is eharacterized by ecrnental analysis as well as spectral anal:, sis. The details are as follows.

4.1 Elemental Analysis :

Results of elemental analysis are summarized in Table III. These are in good agreement with the calculated percentage of various elements present in the complex. These results confirm that M:L ratio in the complex is 1:1.

4.2 FTIR Spectra:

The FTIR spectra of pure captopriltrithiocarbonate and complex of Osmium (VIII) with captopriltrithiocarbonate exhibit the following features:-

An stretching band at 577 cm^{-1} assigned to C-S stretch in pure captopril has been found to be shifted to 850 cm^{-1} in its trithiocarbonate. This confirms the conversion of thiol group to trithiocarbonate group. Complex formation of captopril trithiocarbonate with Osmium (VII), is further confirmed by the shifting of the C-S band to 624 cm^{-1} in its complex.

A medium band at 1600 cm^{-1} in trithiocarbonate of the drug captopril assigned to O-C-N band is increased in its Osmium (VIII) complex at 1647.5 cm^{-1} this confirming the involvement of carbonyl group in bonding with Osmium (VIII).

The lattice water in the complex is confirmed by a broad band at 3389.0 cm^{-1} .

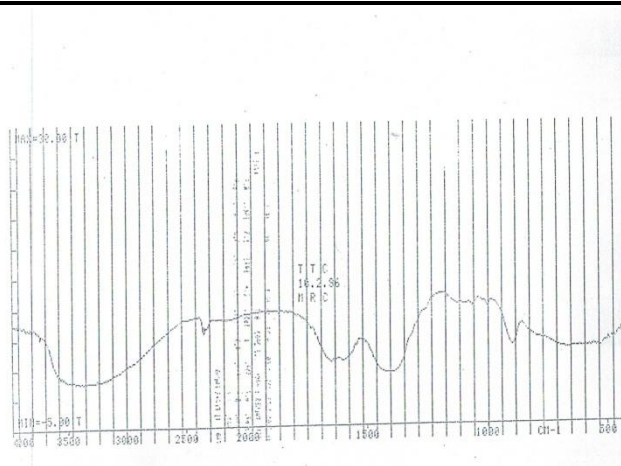


Fig. 1 (a) : FTIR Spectrum of CAPTOPRIL TRITHICARBONATE COMPLEX

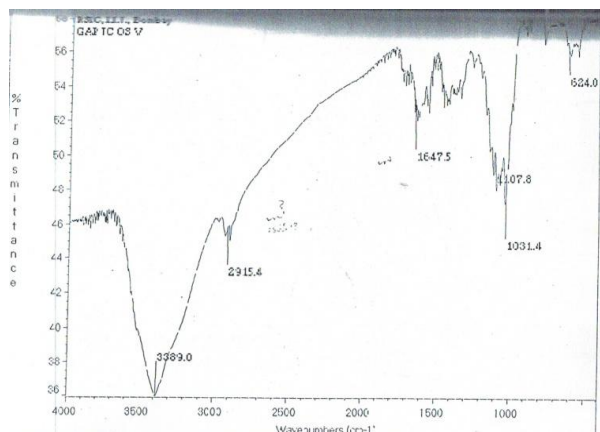


Fig. 1 (b) : FTIR SPECTRUM OF Os (VIII) : CAPTOPRIL TRITHICARBONATE COMPLEX

4.3 ¹H NMR Spectra:

¹H NMR spectrum of each, the trithiocarbonate of the drug captopril and its complex with Osmium (VIII), exhibit the following NMR signals. The chemical shift (δ) at 4.0 ppm attributed to λ CH in the FLNⁱ.va spectrum of trithiocarbonate of captopril is shifted to 4.78 in its Osmium (VIII) complex confirming the involvement of carbonyl group in bonding with Os (VIII).

Appearance of a triplet at 3.6 ppm in TTC of captopril due to S – CH₂ proton show downfield shift to 3.8 ppm in its Os(VIII) complex, suggests M-L binding of Osmium (VIII) to sulphur atom of the drug. signals at 4.4, 4.6, 4.7, 5.2 ppm confirms the water molecule present in the complex.



Fig. 2(a) : PROTON NMR SPECTRUM OF Os (VIII) : CAPTOPRILTRITHICARBONATE COMPLEX

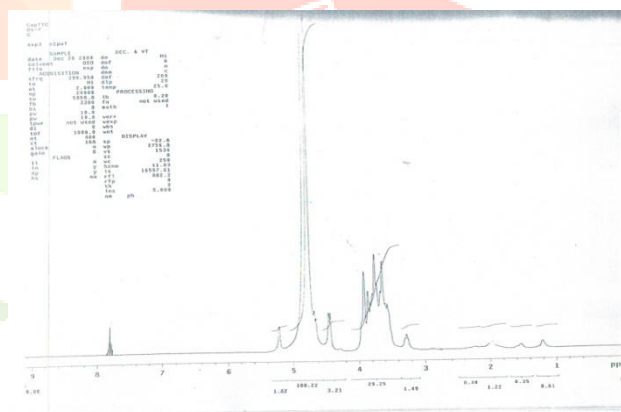


Fig. 2 (b) : PROTON NMR SPECTRUM OF Os (VIII) : CAPTOPRIL TRITHICARBONATE COMPLEX

4.4 ESR Spectra :

Captopril doesn't give any ESR signal since it is diamagnetic in nature but its trithiocarbonate gives an ESR signals at 1400 gauss at liquid nitrogen temperature which indicates paramagnetism.

On complexation of captopril TTC with Os (VIII), again no esr signal is obtained which confirms the diamagnetic the nature of the Os(VIII). Captopril trithio carbonate complex.

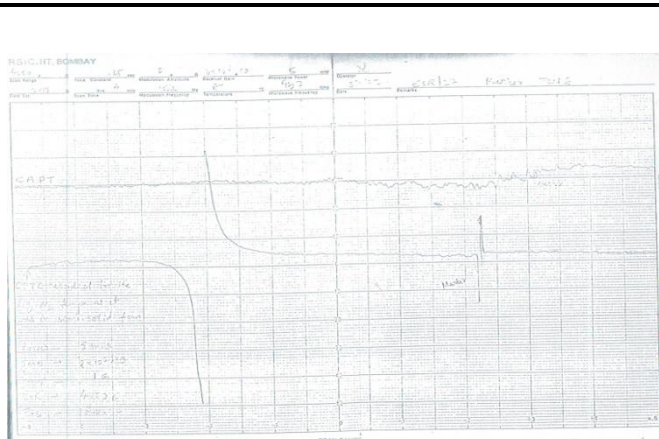


Fig. 3(a) :ESR SPECTRUM OF Os (VIII) : CAPTOPRIL TRITHIOCARBONATE COMPLEX

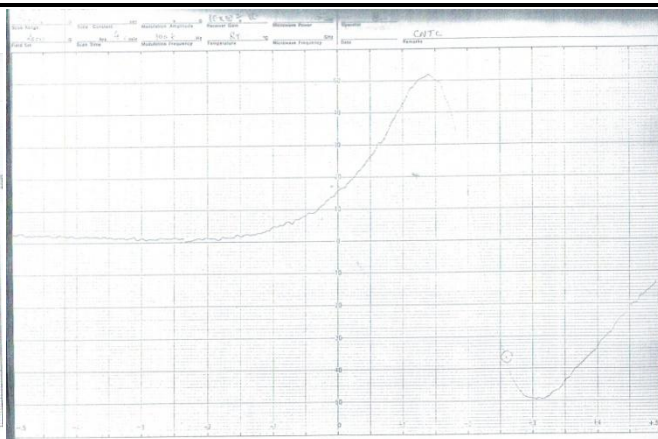


Fig. 3(b) : ESR SPECTRUM OF Os (VIII) : CAPTOPRIL TRITHIOCARBONATE COMPLEX

4.5 Thermal Studies :

Thermogravimetric Analysis (TGA): Thermogravimetric data based on thermogr, am of Os (VII) : captopril to thio carbonate complex exhibit following features :

Weight loss at 169.76°C from 100% to 97.82%, at 272.40°C from 97.82% to 89% at 354.8°C weight loss from 80% to 78% confirms the removal of four coordinated water molecule from the Os(VIII) : Captopril tri thiocarbonate. There is no weight loss after 395.24°C a constant weight is maintained with the increase of temperature at 15°C/min till 800°C which confirms the breaking of captopril trithio carbonate moiety from the complex takes place above 800°C.

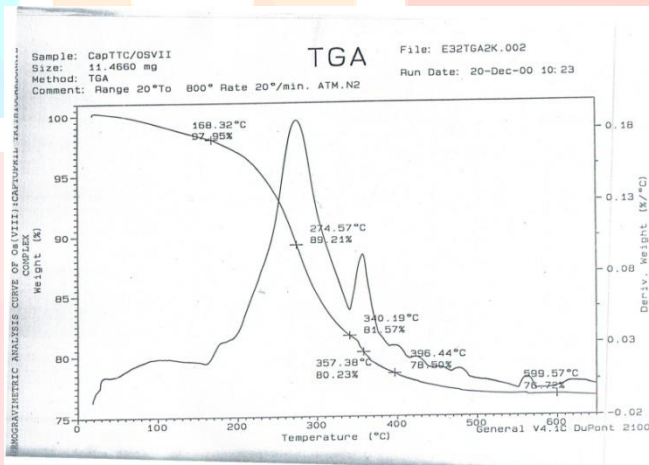


Fig. 4 : TGA SPECTRUM OF Os (VIII) :CAPTOPRIL TRITHIOCARBONATE COMPLEX

MICRODETERMINATION

ROPYL] L-PROLINE TRI-THIO

CARBONATE AS ITS OSMIUM (VIII) COMPLEX

S.No.	Amount of Captopril tri thio carbonate taken (mg).	Amount of Captopril tri thio carbonate found (mg).	% Error	Standard Deviation	Coefficient of Variance
1	6.330x10 ⁻⁸	6.335x10 ⁻⁸	7.89x10 ⁻²	110x10 ⁻²	1.500x10 ⁻¹
2	12.672x10 ⁻⁸	12.670x10 ⁻⁸	1.578x10 ⁻²	1.4x10 ⁻¹⁰	1.120x10 ⁻¹
3	1.900x10 ⁻⁷	1.982x10 ⁻⁷	4.137	1.732x10 ⁻¹⁰	2.731x10 ⁻¹
4	2.534x10 ⁻⁷	2.540x10 ⁻⁷	2.362x10 ⁻¹	2.006x10 ⁻¹⁰	3.154x10 ⁻¹
5	3.167x10 ⁻⁷	3.167x10 ⁻⁷	0.000	2.236x10 ⁻¹⁰	3.526x10 ⁻¹
6	3.809x10 ⁻⁷	3.809x10 ⁻⁷	0.000	2.449x10 ⁻¹⁰	3.862x10 ⁻¹
7	4.434x10 ⁻⁷	4.434x10 ⁻⁷	0.000	2.645x10 ⁻¹⁰	4.171x10 ⁻¹
8	5.068x10 ⁻⁷	5.068x10 ⁻⁷	0.000	2.828x10 ⁻¹⁰	4.459x10 ⁻¹
9	5.704x10 ⁻⁷	5.707x10 ⁻⁷	5.256x10 ⁻²	3.207x10 ⁻¹⁰	5.057x10 ⁻¹
10	6.335x10 ⁻⁷	6.338x10 ⁻⁷	4.733x10 ⁻²	3.162x10 ⁻¹⁰	4.986x10 ⁻¹
11	6.968x10 ⁻⁷	6.969x10 ⁻⁷	1.434x10 ⁻²	3.316x10 ⁻¹⁰	5.229x10 ⁻¹

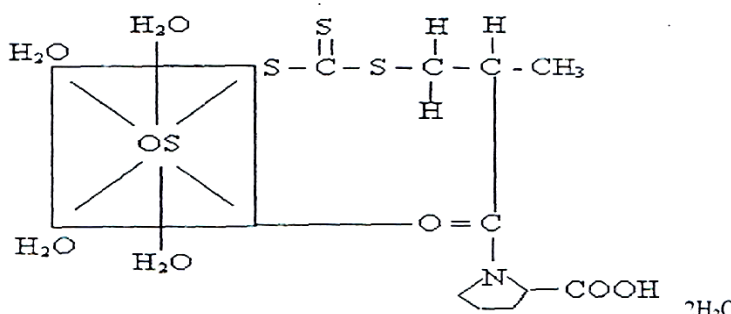
TABLE-II
INTERFERENCE OF FOREIGN METAL IONS ON OS(VIII): CAPTOPRIL TRI THIO CARBONATE COMPLEX

S.No.	Interference	Sample: Interference ppm	% Recovery
1	Ruthenium Trichloride	1: 0.00031	98%
2	Nickel Sulphate	1: 0.00022	99%
3	Zinc Sulphate	1: 0.0003	97%
4	Cobalt Nitrate	1: 0.0052	99%
5	Copper Acetate	1: 0.0002	-
6	Palladium Chloride	Interferes severely	98%
7	Ferric Chloride	Interferes severely	-
8	Ferrous amn. Sulphate	Interferes severely	-

TABLE-III
ELEMENTAL ANALYSIS (CHV.) ESTIMATION OF OS(VIII): CAPTOPRIL TRI THOI CARBONATE COMPLEX

	Calculated	Found
%C	10.45	8.42
%H	1.72	1.54
%N	1.2	1.33

PROPOSED STRUCTURE OF OS (VIII) : CAPTORIL TRI – THIO – CARBONATE COMPLEX



5. ACKNOWLEDGMENT

Govt. Science College, Jabalpur. RSIC,IIT, powai, Mumbai.

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