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RESEARCH ARTICLE

TRANSITION METALS MEDIATED S-M BONDED LIGANDS; OXOKETENE *GEM*-DITHIOLS INSERTION IN TO Au, Ni, Co, AND Hg. FIRST APPROACH; AND INVESTIGATE THE PRODUCTS AGAINST SOME MICROORGANISMS

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ABSTRACT

The C-S-Metal complexes were synthesized *via* a simple and satisfied method by reaction of ketene *gem*-dithiol with transition metal salts, $NaAuCl_4.2H_2O$, $NiCl_2.6H_2O$, $CoCl_2$ and $HgCl_2$. The products were investigated against some microorganisms e. g. *Bacillus subtilus*, *Staphylococcus* and *Lactococcus*. A satisfactory inhibition was observer especially for gold complex.

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INTRODUCTION

Metal complexes have shown interesting preclinical and clinical results as antitumor drugs, gold complexes have recently gained considerable attention due to their strong antiproliferative potency. Medicinal chemistry of known gold complexes with *in vitro* and *in vivo* tumor growth inhibiting properties. The cell growth inhibiting effects could be related to anti-mitochondrial effects making gold species interesting drug. The spectrum of gold complexes described as antiproliferative compounds comprises a broad variety of different species including many phosphine complexes as well as gold in different oxidation stats (Ott, 2009). Two major drugs based on metals that have no known biological function, Pt(cisplatin) and Au (auranofin), are widely used for the treatment of genitourinary, head and neck tumors, rheumatoid arthritis, lung cancer, ovarian cancer, lymphomas cancer, bladder cancer and cervical cancer respectively, Interest in gold complexes containing S-bonded ligands stems from their potential application in the glass and ceramic industries (Papazian, 1982) and more importantly, in medicine (chrysotherapy) (Papazian and Gold Bull, 1982). Thiolato gold (I) complexes such as the commercial Myocrisin, Allochrysine, Solganol, or Auranofin, are among the most efficient antiarthritic drugs (Lorber and Simon, 1979). In addition, Solganol and Auranofin show *in vitro* inhibitory effects on Human Immunodeficiency Virus 1 (Okada *et al.,* 1993), high cytotoxicity to tumor cells (Simon *et al.,* 1981) and activity against i.p. P388 leukaemia (Mirabelli *et al.,* 1985). In addition, compounds of radioactive metal ions such as 99 mTc complexes of paramagnetic metals such as gold (III) are now in wide-spread use as imaging agents for the diagnosis of disease (Lippard, 1994; Nicolini *et al.,* 2014; National cancer institute, 2014). Gold (I)-based drugs have been used successfully for the treatment of rheumatoid arthritis (RA) for several years. Although the exact mechanism of action of these gold (I) drugs for RA has not been clearly established, the interaction of these compounds with mammalian enzymes has been extensively studied. The interaction of gold (I) compounds with different enzymes and the biochemical mechanism underlying the inhibition of enzymatic activities may have broad medicinal implications for the treatment of

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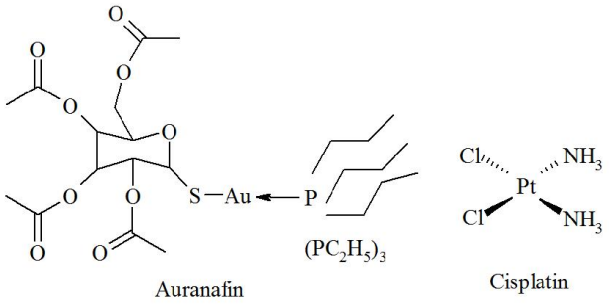
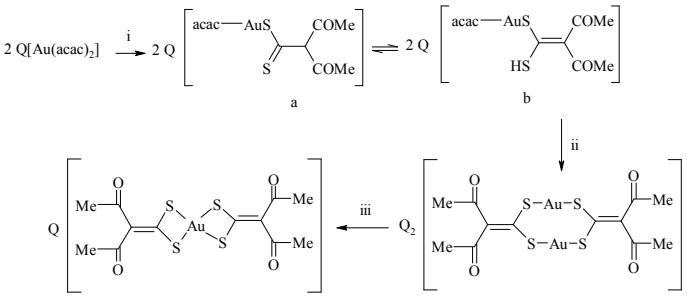
RA (Bhabak *et al.,* 2011). The relatively low toxicity of gold (I) compounds and its liability allows human consumption of drugs formed with this element. Trinuclear and tetranuclear clusters look particularly interesting because of the strong basicity of the gold (I) centers in this molecules (Abdou *et al.,* 2009).



Insertion reactions of CS_2 into transition-metal are known to produce dithioformiato, dithiocarboxylato, dithiocarbamato, phosphinodithiocarboxylato, trithio- or perthiocarbonato, or chlorodithioformiato complexes, respectively (Pandey, 1996). The removal of organosulfur compounds from fossil fuels represents one of the largest-scale industrial processes catalyzed by transition metals today (Topsøe, *et al.,* 1996). Metal-molecular interface as bond state information is indispensable to control molecular devices and sensors using bio-molecules. Recently a formation of strong chemical bond between sulfur and gold was found, and it has been used for the immobilization of sulfur-terminated organic molecules on gold substrate as an anchor (Schreiber, 2002; Ulman, 1996; Poirier and Pylant, 1996). For instance, thiols (R-SH) on gold surface are the Prototypical self-assembled monolayers (SAMs) system in which Au-S covalent bonding anchors the molecules to the surface. As to the bio-molecules, proteins or artificial peptides have been shown to bind to gold surfaces through sulfur atoms (Chi *et al.,* 2000; Bass *et al.,* 2002). It has been found that L-cysteine dimerizes with another molecule on Au surface forming strong chemical bond with gold (Kühnle *et al.,* 2002).

In this study, for the first time we report the Au-S interface bond state between oxoketene *gem*-dithiol and gold surface. Ketene dithioacetals are of current interest because the double carbon-carbon bond, they present is amenable to both nucleophilic and electrophilic attack (Wang and Huang, 1990). On the other hand, the interest in ketene dithioacetals with electron-withdrawing substituents stems from some of their physical properties as push-pull polarized ethylenes. Thus, the effect of chiral substituents or hydrogen bonding on second-order non-linearity, the free energy of activation for rotation around the carbon-carbon double bond (Schreiber, 2002; Kühnle *et al.,* 2002), or the influence of the double bond twisting on the position of the IR stretching band (Lippard, 1994) or on the photoionization energy have been studied (Taylor and Ronald, 1977; Mohanalingam *et al.,* 1996; Sandström and Sjöstrand, 1978; Smith and Taylor, 1979).

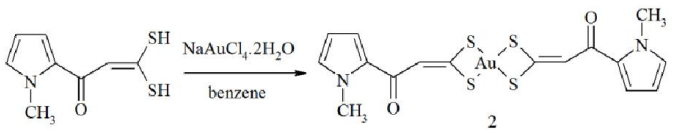
Metal complexes have shown interesting preclinical and clinical results as antitumor drugs and platinum compounds are well established in current cancer chemotherapy. However, the platinum based treatment of tumoral diseases is massively hampered by severe side effects and resistance development. Consequently, the development of novel metallodrugs with a pharmacological profile different from that of the platinum drugs is in the focus of modern medicinal chemistry and drug design. Among the non-platinum antitumor drugs, gold complexes have recently gained considerable attention due to their strong antiproliferative potency. In many cases the cell growth inhibiting effects could be related to anti-mitochondrial effects making gold species interesting drug candidates with a mode of action different from that of the platinum agents. The spectrum of gold complexes described as antiproliferative compounds comprises a broad variety of different species including many phosphine complexes as well as gold in different oxidation states (Ott, 2009). In a similar reaction of gold with dithiocarbamates, It is appears that the gold insertion was postulated to be in many forms (José Vicente *et al.,* 1997). Gold coordinate with thiols to form one to four oxidation state as shows.



Q = $[N(PPh_3)_2]$, acac = acetylacetonate. Reagents and conditions: i, CS_2 (excess) in acetone, 1 h, room temp; ii, -2Hacac; iii, + Cl_2IPh-PhI-Q$[AuCl_2]$, CH_2Cl_2, 45 min, room temp.

RESULTS AND DISCUSSION

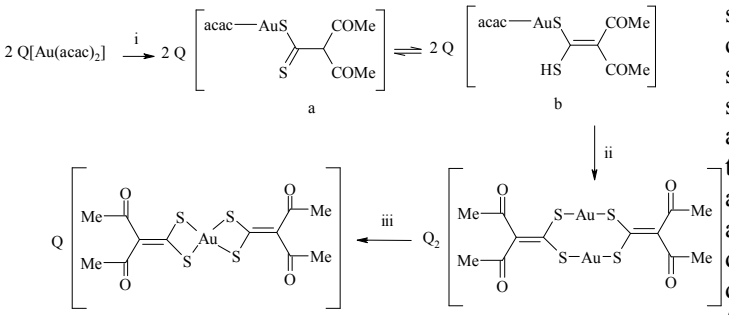
In the present work we have found that, the highly polarized, 3,3- dimercapto-1-(methyl-1-*H*-pyrro-1-2-yl) propen-1-one (1) on reaction with some transition metal halides e.g. aurine sodium chloride $NaAuCl_4$. $2H_2O$, $NiCl_2.6H_2O$, $CoCl_2$ and $HgCl_2$. However, in the case of gold, these reactions have scarcely been studied and the aurine ligand 2 was separated as a binuclear C-S insertion adduct and in the oxidation state (III). In accordance to the obtained spectral measurements structure (2) the formed dimmer is the preferable.



1 2

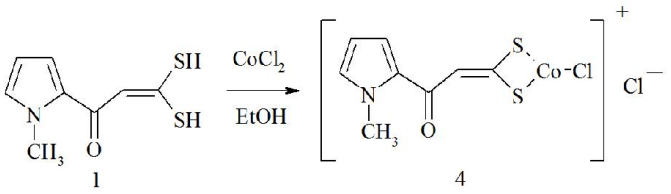
The solid-state IR spectrum of 2 shows two strong bands specific for C=O at 1737 cm^{-1} and 1715 cm^{-1} and a strong band for C=C at 1593 cm^{-1} while the (Au-S) bands could be assigned in the range of 475–430 cm^{-1}; m/e for $C_{16}H_{14}N_2O_2S_4Au$ (592); ^{1}H-NMR spectrum of showed a characteristic signal for N-CH_3 (pyrrol) at δ 3.9 and at 6.1 for CH=C-S –Au and at δ 7.1-7.8 for pyrrole-H. It has been found that nickel complexes with dmit as ligand can be isolated in dianionic (Steimecke *et al.,* 1979), monoanionic (Papavassiliou, 1981), cation-deficient (Papavassiliou, 1982) and neutral (Valade *et al.,* 1985) forms. Dianionic and mono

anionic forms complexes based on dmiot (Ikegawa *et al.,* 1996). Herein, we could prepare nickel complex 3 by the reaction of oxoketene *gem*-dithiol (1) with $NiCl_2 .6H_2O$, in boiling ethanol, but the formation of cation-anion complexes (Anyfantisa *et al.,* 2006; Faulmann *et al.,* 1996; Garnier, 1998; Papavassiliou *et al.,* 1987) competes favorably with the formation of the nickel (II) (Anyfantisa *et al.,* 2006).

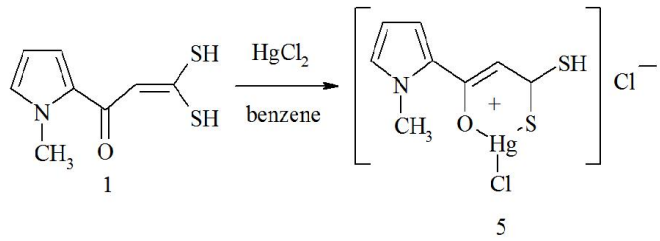


Reaction of (1) with hydrated nickel chloride in boiling ethanol provide binuclear C-S insertion adduct 3 in a satisfactory yield. No intermediate C-S insertion complex of 3 could be detected. ^{1}-H-NMR spectrum under these conditions shows the only nickel-containing product that could be identified was the adduct (3). The structure assignment of (3) is based on the obtained measurement data. MS shows base peak m/e 452 which is the sum of molecular weight of both 2 mols of oxoketene dithiolate (1) and nikel minus 4H. Fragmentation pattern also supported the molecular ion mass m/e for $C_{16}H_{14}N_2O_2S_4Ni$ is (452). ^{1}-H-NMR spectra revealed signals to prove the presence of carbonyl group at 1717 cm^{-1}; ^{1}-H-NMR showed disappearance of a signal for SH, while signals at δ 3.9, δ 6.0-6.1 and at δ 7.0-7.6 characteristic for N-CH_3, CH=C-S-Ni and pyrrole-H respectively. Reaction of 1-norbonyl lithium with the $CoCl_2$/THF in pentane produces, the thermally stable cobalt(IV) tetralkyl (Bower and Tennent, 1972; Byrne *et al.,* 1986), a rare example of a stable transition metal/saturated alkane compound (Greenwood, 1997), different products are obtained in other solvents (Byrne, 1989).

In this race of synthesizing new drugs, cobalt complexes have attracted a great deal of attention amongst the scientific community due to their therapeutic causes as tumor imaging agent (Smith, 2005), antitumor (Liang *et al.,* 2004), transport. Protein transfer in (Tf) (Smith, 2005; Liang *et al.,* 2004), antimycobacterial (Maccari *et al.,* 2004), antiischaemic (Unitt *et al.,* 1999), antiviral (Takeuchi *et al.,* 1999; Capparelli *et al.,* 1984), antiparasitic (Rawlings *et al.,* 1994), antithrombolytic (Rawlings *et al.,* 1994), enzymatic therapeutics (Rawlings *et al.,* 1994). The synthesis and characterization of the novel cobalt (III) complexes as the potential candidates for antimicrobial activity against standard as well as clinically isolated resistant bacterial strains with diminished cytotoxicity on the HEK cell line (Mishra *et al.,* 2008). Moreover, we extended the behavior of α-oxoketene *gem*-dithiols towards some other transition metal halides. Reaction of *gem*-dithiol (1) with cobalt (II) chloride behaves in a different manner and behaved as Co (II) and formed the dipolar adduct (4). On the bases of the forgiving information and on the obtained results, the formed cobalt-sulfur bond uninuclear adduct is in the oxidation state (II).



Structure assignment of Co-S adduct (4) is postulated upon spectral measurements. Infrared spectrum showed peaks for carbonyl at 1735 cm^{-1} and at 1595 cm-1 for CH=CH. Mass spectra gave m/e for $C_8H_7CoCl_2NOS_2$ (330) (M+ 3). ^{1}-H-NMR spectra revealed signals at δ 3.9 for N-CH_3, at δ 6.1 for CH=C and at δ 7.1-7.2 for pyrrole-H. Mercury has been known as a toxic substance for centuries. Whilst the clinical features of acute mercury poisoning has been well described. Chelation agents such as the dithiols sodium 2,3-dimercaptopropanesulfate (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA) are the treatments of choice for mercury toxicity (Rooney, 2007). Mercury organic compounds are in uses as antibacterial and antifungal drugs under trade name (thiomersal; mercurochrome (amongst many) (Claussen, 1999; Weinstein *et al.,* 1997). So, herein we reported on the choice for using *gem*-dithiols as a substrate for trapping mercury on poisoning cases. Mercuric chloride reacted with oxoketene *gem*-dithiol (1) in a different way and gave a dipolar O-Hg-S adduct (5).



The structure of (5) was proved from obtained spectral data. The bipolarity of (5) is attributed to the disappearance of peaks characteristic for of keto group in IR spectra. Mass spectra m/e for $C_8H_8NOS_2HgCl_2$ (473) (M+3). ^{1}-H-NMR spectra proved the presence of SH, N-CH_3, CH=C and pyrrole protons at δ 1.2, 3.9, 6.0 and 7.0-7.3 respectively.

Microbiological survey

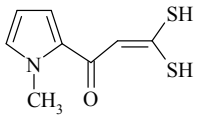
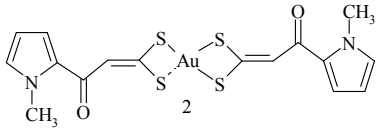
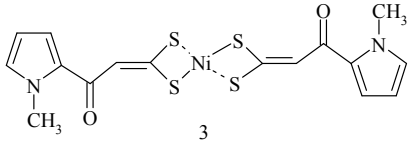
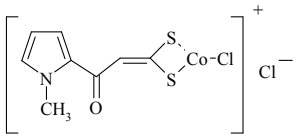
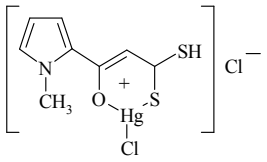
Microbiological studies of the complexes 2-5 beside to the start material, the dithiol (1) have been carried out *in vitro* for antifungal activity on human pathogenic micro-organisms; *Bacillus subtilus*, *Staphylococcus*, and *Lactococcus in vivo*. The following table illustrates screening activity of Au, Co, Ni, and Hg sulfur coordination complexes against some bacteria and the highest activity is attributed for gold–sulfur complex. It was found that these complexes have a satisfied to excellent effect on these organisms. The following table shows the obtained results.

Experimental

Synthesis of 3,3-dimercapto-1-(1-methyl)-1*H*-pyrrol-2-yl) propenone or dithiol (1)

Carbondisulfide (0.01 mol) was added to (0.01 mol) *N*-methyl-2-acetylpyrrole, in 50 ml dry benzene the mixture was cooled

to 0-5 in an ice bath. Potassium tertiary butoxide (0.025 mol) was added gradually to the cooled mixture with continuous shaking. After complete addition of potassium tertiary butoxide, the mixture was left over night in fridge. Cold water was then added with continuous shaking of the previously prepared mixture, the mixture was agitate vigorously and poured in a separating funnel where it divided into two layers benzene layer and aqueous layer which contains the product as soluble salt. After separation of the two layers the aqueous layer was washed several times with petroleum ether 40/60 and then it was acidified with cold concentrated sulphoric acid. The product precipitated and the solution was left in fridge to collect and settle.

Compound No.	*Bacillus subtilus*	*Staphylococcus*	*Lactococcus*
Concentration 0.001%	Inhibition Zoon mm	Inhibition Zoon mm	Inhibition Zoon mm
 1	10	12	9
 2	18	17	10
 3	16	12	11
 4	15	13	7
 5	8	-ve	7

After complete precipitation the solution was filtered off and the precipitate was collected and left a side to dry. It was recrystallized from benzene as red crystals, m. p. 125 ^{o}C, yield 66%, m/e 199. Elemental analysis for $C_8H_9NOS_2$, M. wt 199.29. Cal. %: C 48.21; H, 4.55; N, 7.03; S, 32.18; found %: C, 48.13; H, 4.42; N, 7.11; S, 32.22. $^{1-}$H-NMR (DMSO) δ (ppm.): showed signals at δ (1.3, 1.5 for 2 SH; 3.9 for N-CH_3; 6.07 for CH=C and 6.7-7.2 for pyrrole-H). IR (cm^{-1}): showed peak at 1632 cm^{-1} for C=O.

Synthesis of C-S-gold complex (2)

A mixture of compound (1) (0.001 mol, 0.199 gm) and $NaAuCl_4.2H_2O$ (0.001mol, 0.398 gm) in (30 ml) dry benzene was heated under reflux for 8 hrs, the solution was concentrated and left to cool. The product precipitated and then it was collected and recrystallized from ethanol as yellow powder, m. p. > 300 yield 78 %, m/e 592. Elemental analysis for $C_{16}H_{14}AuN_2O_2S_4$, M. wt. 592.53. Cal. %: C, 32.43; H, 2.55; N, 4.73; S, 21.64; Found %: C, 32.47; H, 2.48; N, 4.67; S, 21.66. $^{1-}$H-NMR (DMSO) δ (ppm.): showed signal at δ (3.9 for 2 N-CH_3; 6.1 for 2 CH=C and 7.1-7.8 for 2 pyrrole ring-H). IR (cm^{-1}): showed peaks at 1737 $cm^{-1}$and 1715 cm^{-1} for C=O.

Synthesis of C-S-nickel complex (3)

A mixture of compound (1) (0.001 mol, 0.199 gm) and (0.001 mol, 0.236 gm) of nickel chloride in (30 ml) ethanol was heated under reflux for 8 hrs, the solution was concentrated and left to cool. The product precipitated and then it was collected and recrystallized from ethanol as red powder, m. p. > 300, yield 66%, m/e 453. Elemental analysis for $C_{16}H_{14}N_2NiO_2S_4$, M. wt. 453.24. Cal. %: C, 42.40; H, 3.11; N, 6.18; S, 28.29; Found %: C, 42.51; H, 3.11; N, 6.13; S 28.17. $^{1-}$H-NMR (DMSO) δ (ppm.): showed signals at δ (3.9 for 2 N-CH_3; 6.0, 6.1 for 2 CH=C and 7.0-7.6 for 2 pyrrole ring-H). IR (cm^{-1}): showed peaks at 1717 cm^{-1} and 1636 cm^{-1} for C=O.

Synthesis of C-S-cobalt complex (4)

A mixture of compound (1) (0.001 mol, 0.199 gm) and (0.001 mol, 0.129 gm) of cobalt chloride in (30 ml) ethanol was heated under reflux for 8 hrs. The solution was concentrated and left to cool, the product precipitated and then it was collected and recrystallized from ethanol as black powder, m. p. > 300, yield 79%, m/e 330 (M+3). Elemental analysis for $C_8H_7Cl_2CoNOS_2$, M. wt. 327.11. Cal.%: C, 29.37; H, 2.16; Cl, 21.68; N, 4.28; S 19.60; found %: C, 29.22; H, 2.09; Cl, 21.56; N, 4.36; S, 19.71. $^{1-}$H-NMR (DMSO) δ (ppm.): showed signals

at δ (3.9 for N-CH_3; 6.1 for CH=C and 7.1-7.2 for pyrrole-H). IR (cm^{-1}): showed peak at 1735 cm^{-1} for C=O.

Synthesis of C-S-mercury complex (5)

A mixture of compound (1) (0.001 mol, 0.199 gm) and (0.001 mol, 0.272 gm) of mercuric chloride in (30 ml) dry benzene was heated under reflux for 8 hrs, the solution was concentrated and left to cool, the product precipitated and then it was collected and recrystallized from ethanol as black crystals, m. p. 158-160 ^oC, yield 81%, m/e 473 (M+3). Elemental analysis for $C_8H_8Cl_2HgNOS_2$, M. wt. 470.78. Cal%: C, 20.41; H, 1.93; Cl, 15.06, N, 2.98; S, 13.62; found%: C, 20. 36; H, 1.99; Cl, 14.77; N, 3.07; S, 13.59; ^{1}-H-NMR (DMSO) δ (ppm.): showed signals at δ (1.2 for –SH; 3.8 for + N-CH_3; 6.0 for CH=C and for 7.0-7.3 pyrrole-H). IR (cm^{-1}): showed peak at 2490 cm^{-1} for -SH.

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