Metal-dithiocarbamate complexes: chemistry and biological activity

Graeme Hogarth*

Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, U.K

Abstract: Dithiocarbamates are highly versatile mono-anionic chelating ligands which form stable complexes with all the transition elements and also the majority of main group, lanthanide and actinide elements. They are easily prepared from primary or secondary amines and depending upon the nature of the cation can show good solubility in water or organic solvents. They are related to the thiuram disulfides by a one-electron redox process (followed by dimerisation *via* sulfur-sulfur bond formation) which is easily carried out upon addition of iodide or ferric salts. Dithiocarbamates are lipophilic and generally bind to metals in a symmetrical chelate fashion but examples of other coordination modes are known, the monodentate and anisobidentate modes being most prevalent. They are planar sterically non-demanding ligands which can be electronically tuned by judicious choice of substituents. They stabilize metals in a wide range of oxidation states, this being attributed to the existence of *soft* dithiocarbamate and *hard* thioureide resonance forms, the latter formally resulting from delocalization of the nitrogen lone pair onto the sulfurs, and consequently their complexes tend to have a rich electrochemistry. Tetraethyl thiuramdisulfide (disulfiram or antabuse) has been used as a drug since the 1950s but it is only recently that dithiocarbamate complexes have been explored within the medicinal domain. Over the past two decades anti-cancer activity has been noted for gold and copper complexes, technetium and copper complexes have been used in PET-imaging, dithiocarbamates have been used to treat acute cadmium poisoning and copper complexes also have been investigated as SOD inhibitors.

Keywords: Anti-cancer, chelator, dithiocarbamate, metal complexes, thioureide, lipophilic.

DITHIOCARBAMATES

Dithiocarbamates ($R_2NCS_2^-$ or $RNHCS_2^-$) are just one example of a general class of monoanionic 1,1-dithiolate ligands which also includes other commonly utilized ligands such as xanthates, carbamates, dithiophosphates (Fig. **1**) and many others [1]. While to the untrained eye they look very similar we will see later that dithiocarbamates occupy a unique niche and their chemistry (and likely biological activity) is quite distinct from any of the other members of this series. Dithiocarbamates were probably first prepared over 150 years ago, although at this time they were not formulated correctly. In the intervening century and a half a bewildering array of different dithiocarbamates have been prepared and it is this diversity, which stems simply from the ability to alter the substituents on nitrogen, that has brought this class of ligand to the forefront of transition metal chemistry (Fig. **1**).

SYNTHESIS

The preparation of most dithiocarbamate salts is extremely simple [2]. A range of secondary and primary amines react with carbon disulfide in water and in the presence of a base to afford highly water-soluble dithiocarbamate salts. Many different bases can be used but generally alkali-metal hydroxides suffice (eq. 1). Reactions are generally fast (over in minutes) and can be quite exothermic so they are often best carried out in an ice bath, especially if the amine is volatile. Yields are not always easy to measure but are generally high (> 90%) and in many cases considered to be quantitative. Reactions can result in the development of a slight yellow tinge to the medium and the subsequent chemistry (reaction with a water-soluble transition metal salt) is often carried out *in situ*. If the transition metal salt is not soluble in water but soluble in simple organic solvents (such as dichloromethane) then preparing the dithiocarbamate in methanol or thf and later mixing with the dichloromethane solution of the metal complex generally provides a very simple and efficient reaction manifold. If isolation of the salts is required (for use at a later stage) then this can be effected *via* slow crystallization from the reaction solution or upon removal of the solvent. Dithiocarbamate salts often co-crystallize with one or more molecules of water and their solid-state structures can be quite complex [3]. The most commonly used examples (R = Me, Et) derive from very volatile amines and are best purchased as the tris(aqua) salts, $NaS_2CNR_2.3H_2O$, which can easily be dehydrated in a vacuum oven if required dry. Some amines are unreactive towards carbon disulfide in the presence of alkali-metal hydroxides and in this case a more powerful base is required, with sodium hydride being widely applicable (eq. 2) being particularly useful for aromatic amines [4]. Reactions are carried out in organic solvents and the salt precipitates and can be isolated after filtration. If the dithiocarbamate salt is required to be soluble in organic solvents then it is best to prepare it as an ammonium salt. This can often be done using a tetraalkylammonium hydroxide as base (eq. 3), with longer alkyl groups generally providing greater solubility. In extreme cases, potassium metal can be used to facilitate the

*Address correspondence to this author at the Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, U.K; Tel: 0207-679-4664; E-mail: g.hogarth@ucl.ac.uk

1875-5607/12 $58.00+.00

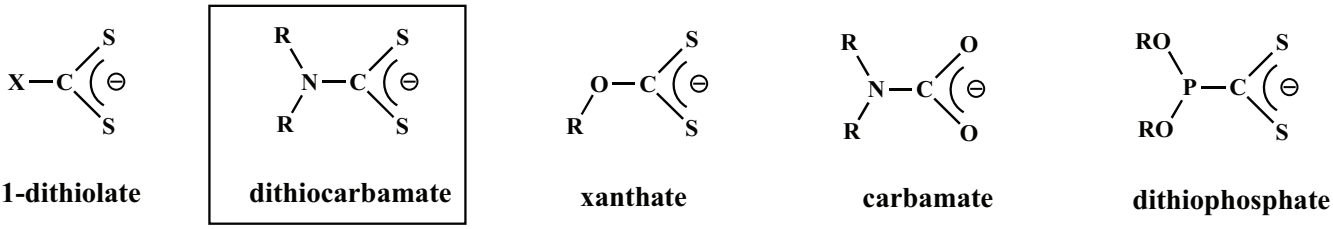


Fig. (1).

reaction with concomitant loss of hydrogen (eq. 4). With the exception of those derived from primary amines, most dithiocarbamates are stable under neutral and basic conditions. For long term storage they should be dried and stored under nitrogen in a fridge or freezer, preferably in the dark. Dithiocarbamates generated from primary amines are less stable than their secondary amine counterparts, and can decompose to give the corresponding isothiocyanate [5]. They are best used *in situ*.

$$R_2NH + CS_2 + MOH \xrightarrow{H_2O \text{ or } ROH} R_2NCS_2M + H_2O \quad \text{(Eq. 1)}$$

$$R_2NH + CS_2 + NaH \xrightarrow{\text{organic}} R_2NCS_2Na + H_2 \quad \text{(Eq. 2)}$$

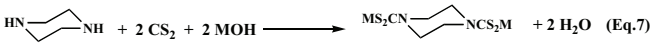
$$R_2NH + CS_2 + [NR_4]OH \xrightarrow{\text{organic}} [R_2NCS_2][NR_4] + H_2O \quad \text{(Eq. 3)}$$

$$R_2NH + CS_2 + K \xrightarrow{\text{organic}} R_2NCS_2K + 1/_2H_2 \quad \text{(Eq. 4)}$$

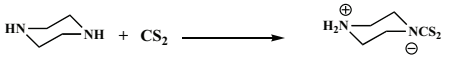
A common misconception in the literature surrounds the stability of the free dithiocarbamic acids. Thus, under acidic conditions dithiocarbamates rapidly decompose to give the free amine and carbon disulfide (eq. 5). Some authors think they have prepared the dithiocarbamic acids simply upon addition of carbon disulfide to the amine. This is indeed often a facile reaction but the stoichiometry of the reaction is 2:1 amine:CS_2; one equivalent of amine acting as a base and the second as a nucleophile and the product is a salt (eq. 6). Such salts generally precipitate rapidly out of aqueous solutions and this can be a very good preparative method. It can also be used to understand how diamines react. For example, addition of two equivalents of base and CS_2 to piperazine readily affords the expected bis(dithiocarbamate) salt (eq. 7), while addition of CS_2 in the absence of base affords primarily a zwitterionic mono(dithiocarbamate) product in which one end of the diamine has acted as a base and the second as a nucleophile (eq. 8) [6]. This very simple strategy then allows for the easy activation-protection of the two amine sites in one step and can be later utilized towards the step-wise synthesis of multimetallic complexes [6,7].

$$R_2NCS_2M + HX \longrightarrow R_2NH + CS_2 + MX \quad \text{(Eq.5)}$$

$$2\,R_2NH + CS_2 \longrightarrow [R_2NCS_2][NH_2R_2] \quad \text{(Eq.6)}$$



(Eq.7)



(Eq.8)

VARIANTS

Dithiocarbamate salts with a wide array of substituents have been prepared, some of which are shown in Fig. (**2**). By far the most commonly used is the diethyl derivative (a) as the sodium salt is commercially available but also since it offers better solubility for metal complexes than the dimethyl compound. Increasing the length of the alkyl chain leads to enhanced solubility of complexes and this can also be tuned using unsymmetrically substituted species, such as the methyl-butyl derivative (b). In biological studies the pyrrolidine derivative (c) has proven very popular [8], while related piperidine derived species such as (d) allow for easier tuning of the steric and electronic properties since a wide range of substituted derivatives are commercially available. Complexes of the 2-hydroxyethyl compound (e) are often used to enhance the water-solubility of transition metal complexes, and the unsymmetrically substituted (f) finds widespread use in technetium radiopharmaceuticals [9]. Derivatives substituted with further amine groups such as (g) [10] are useful as they allow the tuning of organic-aqueous solubility as a function of pH. Sulfonyl groups can be incorporated such as seen in (h) which has been tested for cancer cell apoptosis-inducing activity [11]. Other novel derivatives such as (i-j) find use in radiopharmaceuticals [12,13] (Fig. **2**).

GENERAL CHEMISTRY

Dithiocarbamates are easily oxidized to give the corresponding radicals which combine near the rate of diffusion to give thiuram disulfides (Eq. 9). This process can be monitored by cyclic voltammetry [14] and can also be used to determine the concentration of this dithiocarbamate in water [15]. Synthetically $K_3[Fe(CN)_6]$ is a very useful oxidant as it is self-indicating, changing from yellow to colorless upon reduction to the ferrous state, the thiuram disulfides precipitating out of the aqueous solution. They are generally white solids which are highly soluble in simple organic solvents. They show restricted rotation about the carbon-nitrogen bonds and thus unlike the dithiocarbamate salts, the two substituents are inequivalent on the NMR timescale at room temperature. Few solid state structures are known but those in the literature show that the substituents adopt an *anti* conformation about the central sulfur-sulfur bond [16].

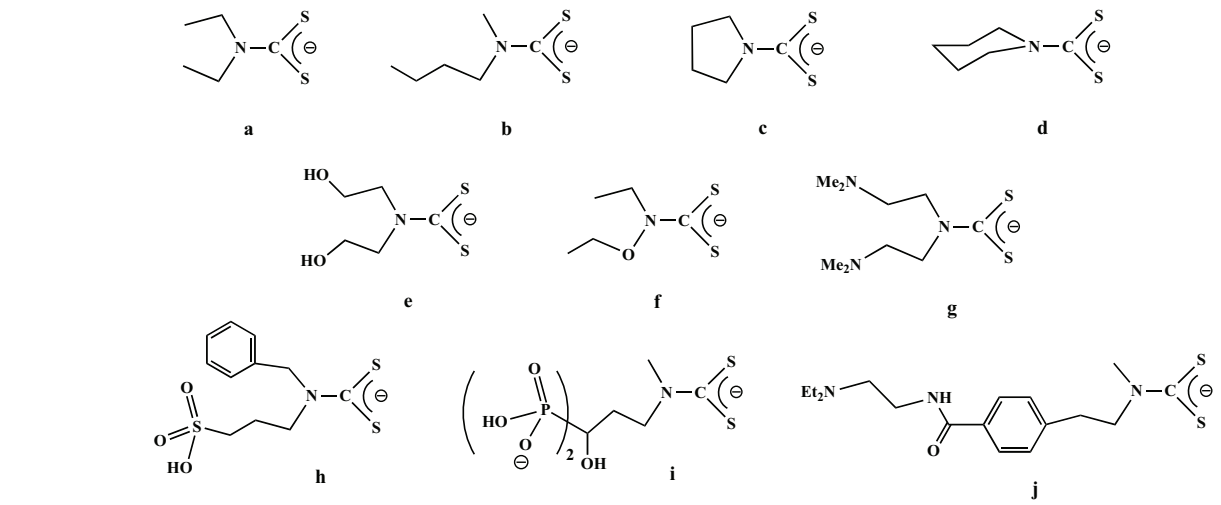
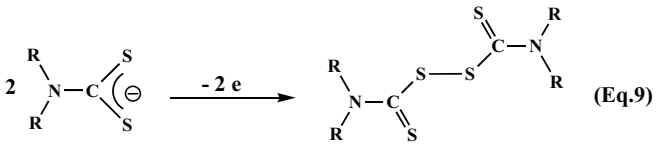
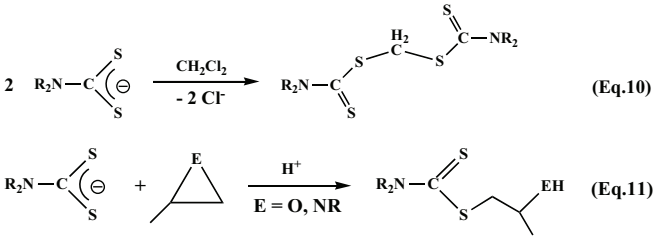


Fig. (2).



(Eq.9)

Dithiocarbamates undergo a range of other reactions but most of this is beyond the scope of this article. Two main reactivity traits should be considered when using them in a medicinal domain. They are relatively nucleophilic and will displace halides, for example in dichloromethane they slowly react as shown to give methylenebis(dithiocarbamate) compounds (eq. 10) and similar reactivity is also noted with benzyl halides. They are also nucleophilic enough to attack epoxides and aziridines resulting in ring-opening (eq. 11) both of which are synthetically useful [17].



(Eq.10)

(Eq.11)

METAL COMPLEXES – BONDING

Dithiocarbamates form complexes with all of the transition elements and in a wide range of oxidation states [2]. For example, molybdenum and tungsten can be stabilized in seven different oxidation states ranging from zero to six, specific examples being $[NEt_4][W(CO)_4(S_2CNC_5H_{10})]$ [18] and $[W(NBu^t)_2(S_2CN^iBu_2)_2]$ [19]. The ability of the dithiocarbamate ligand to stabilize both low- and high-valent metal ions is generally attributed to the adoption of dithiocarbamate and thioureide tautomers (Fig. **3**). The dithiocarbamate form suggests that there is a lone pair of electrons localized on nitrogen (sp^3) and hence this atom should have a pyramidal arrangement of substituents (as seen in amines), while the thioureide is planar (sp^2) with the lone pair being delocalized into the backbone carbon-nitrogen bond (which thus acquires double-bond character) and onto the sulfur atoms. Consequently, we consider the dithiocarbamate form as a *soft* donor ligand, most capable of binding to low-valent metal atoms, while in the thioureide tautomer extra negative charge localized on sulfur and is best considered as a *hard* donor ligand, most suited to high-valent metal binding (Fig. **3**).

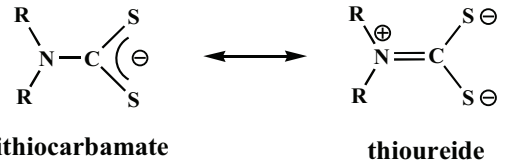


Fig. (3).

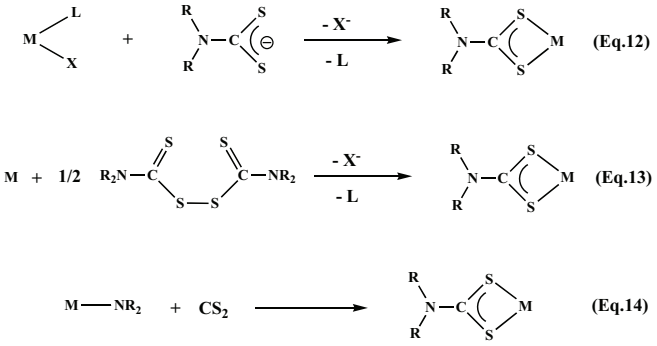
This is necessarily a simplified account of the bonding characteristics of the ligand and it should be noted that in *all* complexes (and indeed in organic compounds) the C_2NCS_2 moiety is planar, being indicative of some degree of adoption of the thioureide resonance form. This is reflected in the shortening of the backbone N-CS_2 bond (1.32 – 1.36 Å) *vs* other N-C bonds (1.45 – 1.48 Å) in all crystal structures of dithiocarbamate complexes [2]. For diamagnetic complexes, the development of double bond character in the backbone is easily probed by NMR spectroscopy. For example in *cis*-$[Ru(CO)_2(S_2CNMe_2)_2]$, two separate methyl resonances are observed at room temperature by ^{1}H NMR spectroscopy and these coalesce into a single resonance upon heating to 100 ^{o}C, the free energy of activation being estimated at 78 ± 1 kJ mol^{-1} [20].

The ability of the ligand to adopt dithiocarbamate and thioureide tautomers gives it unique properties. For example, related 1,1-dithiolate ligands such as xanthate and dithiophosphate (Fig. **1**) have more electronegative oxygen substituents on the backbone and these limit the delocalization of a lone pair onto the sulfur atoms. Consequently, xanthates are good ligands for low-valent metal centers but cannot support high-valent metal ions [21]. Carbamates in contrast are harder ligands and are more able to stabilize high-valent centers, while thiocarbamates, R_2NCSO^-, tend to bind to metal centers in a monodentate manner through the oxygen atom. More closely related are

selenothiocarbamate [22] and diselenocarbamate [23] ligands, however, since these rely on the availability of highly toxic and pungent CSSe and CSe_2 their chemistry has not been explored at anything like the level of the dithiocarbamates.

SYNTHESIS

Transition metal dithiocarbamate complexes are generally prepared *via* simple ligand displacement reactions following the addition of a dithiocarbamate salt to a metal precursor with concomitant loss of anionic (X) (and neutral - L) ligands (eq. 12) [2]. Importantly the oxidation state of the metal does not change throughout this process. A modified procedure is used for the synthesis of five-coordinate technetium(V) nitrides, $[TcN(S_2CNR_2)_2]$, which find extensive utilization as radiopharmaceuticals. Thus they are typically prepared from upon addition of dithiocarbamate salts to the technetium(VII) precursor $[NH_4][TcO_4]$, the Tc(V) ion being generated *in situ* using a hydrazine derivative as the reducing agent [24]. A second route which has some general applicability is the oxidative addition of a thiuram disulfide to a metal centre (eq. 13) [25]. This requires that the starting metal centre be readily oxidized and often (but not always) ends up with the incorporation of two dithiocarbamate ligands. An example is the addition of thiuram disulfides to $CuCl_2$ which affords copper(III) complexes $[Cl_2Cu(S_2CNR_2)]$ [26]. A third route which has more limited applicability is the insertion of carbon disulfide into pre-formed metal-amide functionality (eq. 14). This pre-supposes that such species are stable and synthetically available and is generally constrained to the early transition metal elements, being widely used in the early synthesis of group 4 complexes $[M(S_2CNR_2)_4]$ (M = Ti, Zr, Hf) [27]. It has more recently been utilized for the synthesis of low-valent group 6 complexes starting from secondary amine complexes which are treated with strong bases to (presumably) generate an amide *in situ* [18]. Since there are many primary and secondary amine sites within biological systems this process could potentially lead to the *in situ* formation of dithiocarbamate species *in vivo* if carbon disulfide was present. There are numerous other preparative methods [2] including the insertion of organic isothiocyanates into metal-hydrides [28] or metal-thiolates [29], cleavage of dithioesters [30], oxidative addition of tin and silicon [31] dithiocarbamate compounds, $R_3E\text{-}S_2CNR_2$, to metal centers and addition of secondary amines to related xanthate [32] or alkyltrithiocarbonate [33] complexes, but none of these have any biological applicability and thus will not be considered further.



BINDING MODES

Dithiocarbamates can bind to metal centers in at least nine different coordination modes but only six will be considered here (Fig. **4**) as others are rare and have no obvious biological relevance. Most commonly (> 99%) it acts as a *chelate* ligand (**A**) *via* formation of two approximately equivalent metal-sulfur bonds. In doing so it forms a small bite-angle (S-M-S), ranging from 65 – 80° being dependent upon the size of the ligand metal ion [2]. Metal-sulfur bond lengths are also dependent upon the latter and range from 2.25 – 2.55 Å in simple homoleptic complexes, $[M(S_2CNR_2)_n]$ [2]. Adoption of the chelate binding mode is thermodynamically favoured due to the entropic gain (chelate effect). The *monodentate* coordination mode (**B**) is also relatively common. It tends to be formed when either the steric and electronic demands of the other metal-bound ligands dictate that there is either no room for a second sulfur coordination or that loss of a ligand which would be a pre-requisite for such coordination has a high activation barrier. However, it can also result from the electronic demands of the metal centre, for example when there is not a vacant orbital on the metal centre of the correct symmetry and/or energy which can accept a lone pair on the second sulfur atom. Consequently this coordination mode is relatively common in gold chemistry, for example gold(III) complexes $[Au(S_2CNR_2)_3]$ contain one chelating and two monodentate dithiocarbamate ligands [34]. As might be expected, monodentate ligands exhibit quite different carbon-sulfur bond lengths. In some cases the two metal-sulfur bonds are quite different but nevertheless within the expected range for a bonding interaction. This is commonly termed the *anisobidentate* coordination mode (**C**). A number of gold complexes display this binding mode [35]. Sometimes the anisobidentate coordination is more debatable. For example in $[W(N^tBu)_2(S_2CN^iBu_2)_2]$ the tungsten-sulfur bonds *trans* to the imide ligands [W-S(av) 2.707(1) Å] are significantly longer than those lying *cis* [W-S(av) 2.462(1) Å] but this is attributed to the *trans*-influence of the imide ligands rather than anisobidentate coordination [19] (Fig. **4**).

All other binding modes involve the dithiocarbamate bridging two or more metal atoms, up to a maximum of four as seen in the face-capped copper cube $[Cu_8(\mu_4\text{-}S_2CNPr_2)_6][ClO_4]_2$ [36]. Such a coordination mode is rare and has no known biological relevance, while more common are modes (**D-F**). The latter is found in the tetrahedral copper(I) dithiocarbamate clusters $[Cu_4(\mu_3\text{-}S_2CNR_2)_4]$ [36] which result from the one electron reduction of $[Cu(S_2CNR_2)_2]$ which have been used in ^{64}Cu PET imaging studies [12] and as SOD inhibitors [37]. Cadmium bis(dithiocarbamate) complexes, $[Cd(S_2CNR_2)_2]$, which are proposed to be formed when dithiocarbamate salts are used as antidotes for cadmium intoxication [38] are dimeric in the solid-state containing dithiocarbamates with bonding modes (**A**) and (**D**) [2], although such interactions are unlikely to be maintained in solution. In all of the bridging modes it is one of the lone-pair of electrons on sulfur which is acting as a further Lewis base.

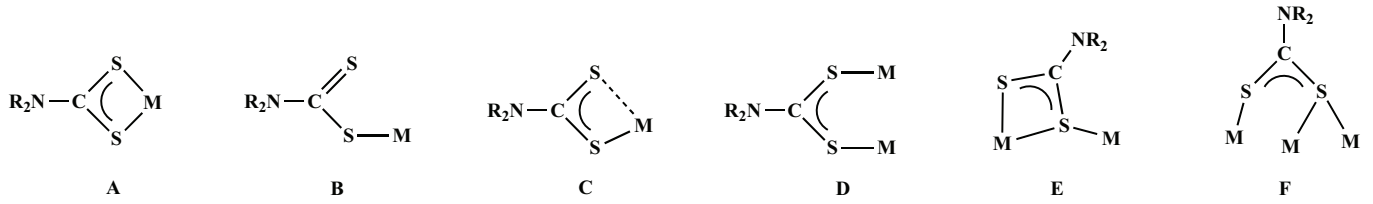


Fig. (4).

STABILITY CONSTANTS

Somewhat surprisingly given the vast numbers of transition metal dithiocarbamate complexes known, there is relatively little information about their binding constants to most metal ions; information which is likely to be of paramount importance when they are utilized in biological applications. Exchange studies between a dithiocarbamate complex and a free metal ion have been reported and two simple pathways can be envisaged, namely, (i) the initial dissociation of the dithiocarbamate ligand (either completely or *via* a monodentate coordination mode (**B**)), or (ii) direct electrophilic attack of the metal ion on the dithiocarbamate complex which would involve the intermediate formation of a bridging species such as (**E**) (Fig. **5**). In an attempt to gather stability constant data, Sachinidis and Grant have studied exchange between metal bis(dithiocarbamate) complexes, $[M(S_2CNR_2)_2]$, some of which have biological relevance (i.e. Ni, Cu, Zn) in the highly coordinating solvent dmso. These reveal that while both pathways are accessible the associative pathway generally dominates and an order of stability for M^{2+} species was determined; Hg > Cu > Ni > Cd >Zn [39]. This order is, however, dependent upon solvent and in ethanol-water mixtures; Zn < Cu > Ni [40]. The nature of the substituents also plays a role in the stability constant and Moriyasu and co-workers have shown that at a Ni^{2+} centre in $CHCl_3$; $Bu_2 > Pr_2 > Et_2 > Me_2 >$ cyclo-C_4H_8 [41]. The later may be important for biological studies as pyrrolidine dithiocarbamates (cyclo-C_4H_8) are widely utilized and their enhanced activity may stem from the relatively low stability constant as compared to other dithiocarbamates. Clearly this is an area where much further study is required if the precise role of transition metal dithiocarbamate complexes in biological systems is to be fully understood (Fig. **5**).

REDOX CHEMISTRY

Dithiocarbamates are able to stabilize transition metals in a wide range of oxidation states and consequently the rich and varied electrochemistry shown by them is fully expected. This has been discussed extensively in an excellent review by Bond and Martin [42] and while it is now over 25 years old it still provides an accurate picture of this area. For many metals dithiocarbamate complexes are accessible in all of their known oxidation states, this being especially the case for many of the biologically relevant metals. For the heavier elements, generally dithiocarbamate complexes are not stable in their higher oxidation states probably since the metal centre is too easily reduced which would result in concomitant oxidation of the dithiocarbamate to the thiuram disulfide. This is the case for ruthenium and osmium where the highest oxidation state stabilized by dithiocarbamates is +4. For molybdenum and tungsten the +6 states are easily accessible, but for manganese only +1 to +4 complexes are currently known.

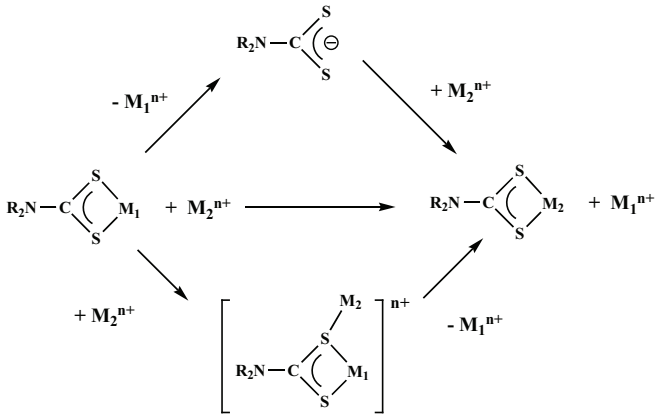


Fig. (5).

Let us look specifically at the redox chemistry of copper complexes [43]. Stable dithiocarbamate complexes of copper are known for oxidation states +1 to +3. The simplest to prepare are the brown copper(II) bis(dithiocarbamate) complexes $[Cu(S_2CNR_2)_2]$. These d^9 complexes all adopt square-planar coordination geometries. They undergo relatively facile one-electron oxidation and reduction processes to afford the copper(III) cations $[Cu(S_2CNR_2)_2]^+$ and copper(I) anions $[Cu(S_2CNR_2)_2]^-$ respectively (Fig. **6**, eqn. 15). The copper(III) complexes are also square-planar (d^8) and this redox couple is fully reversible. Green copper(III) bis(dithiocarbamate) complexes are relatively easily prepared and can be fully characterized in solution and the solid-state. The one-electron reduction of $[Cu(S_2CNR_2)_2]$ also appears to be fully reversible at fast scan rates, however, the reverse oxidation response is strongly dependent upon scan rate as this is a quasi-reversible process. This can be easily understood in terms of crystal field effects as the $[Cu(S_2CNR_2)_2]^-$ anions are d^{10} and thus would be expected to adopt a tetrahedral geometry. Thus the reduction is associated with a structural change and results in quasi-reversibility. Nevertheless on these electrochemical time scales the dithiocarbamate ligands remain attached to the copper(I) centre. Unlike the oxidation products, however, such copper(I) anions cannot be isolated outside of the electrochemical cell. Attempts to do so result in the relatively slow loss of one dithiocarbamate ligand and the formation of tetrahedral clusters $[Cu(\mu_3\text{-}S_2CNR_2)]_4$ in which the remaining dithiocarbamate ligands cap each face (Fig. **4 F**) [36] (Fig. **6**).

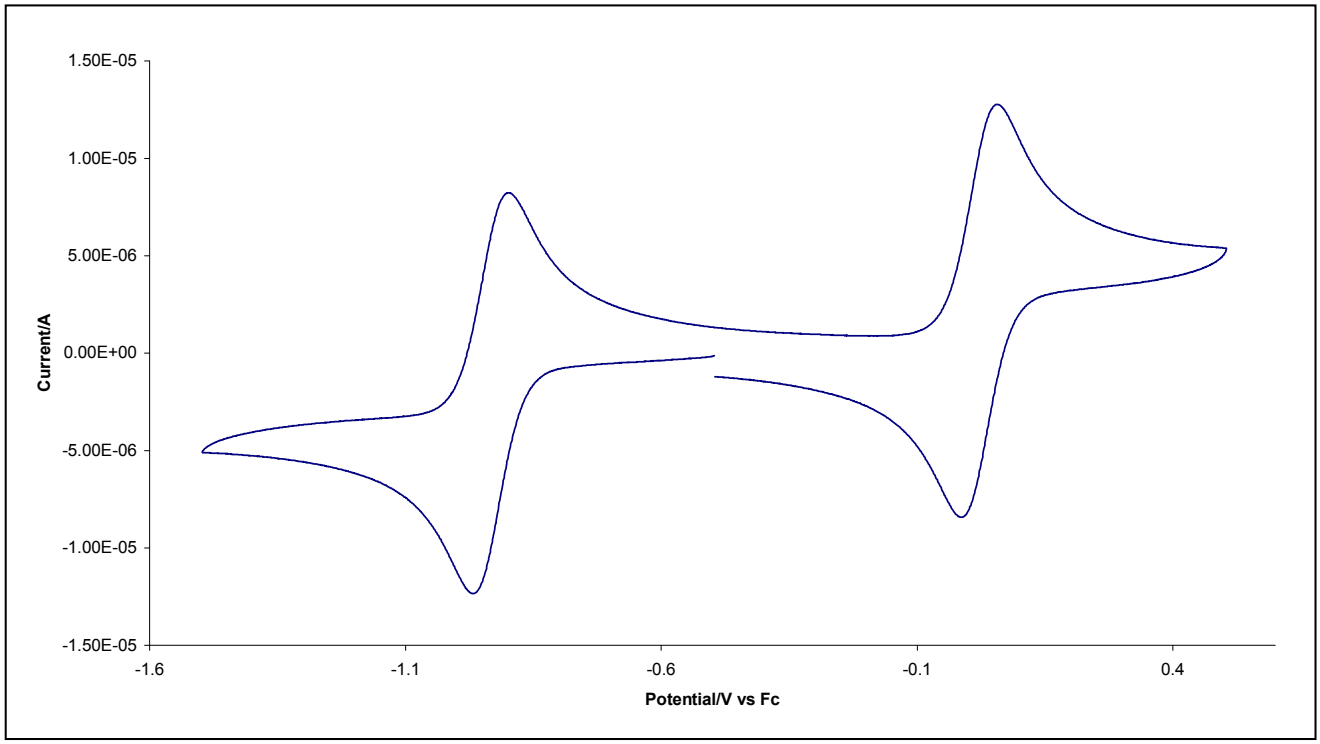


Fig. (6).

$$[Cu(S_2CNR_2)_2]^{\oplus} \underset{-e^-}{\overset{+e^-}{\rightleftharpoons}} [Cu(S_2CNR_2)_2] \underset{-e^-}{\overset{+e^-}{\rightleftharpoons}} [Cu(S_2CNR_2)_2]^{\ominus} \quad \text{(Eq.15)}$$

d^8 square-planar d^9 square-planar d^{10} tetrahedral

Martin and co-workers have shown that both the reduction and oxidation potentials of copper(II) complexes can be tuned over a significant range by simple adjustment of the substituents [43] which suggests that biologically applications could be highly dependent upon the nature of the latter. Administered copper(II) complexes could be oxidized *in vivo* to produce the analogous copper(III) species but the integrity of the complex is maintained and can be later re-reduced. In contrast, reduction leads both to the loss of a ligand and while in a healthy cell rapid re-oxidation could lead to regeneration of the copper(II) complex, in a hypoxic cell dithiocarbamate loss would result in immobilization of copper. Such a strategy potentially results in concentration of copper in hypoxic cells and thus could have applications in radiopharmaceuticals. A second consequence of the loss of a dithiocarbamate ligand is that it can be oxidized to form the thiuram disulfide (eqn. 9). For example, oxidation of $Et_2NCS_2^-$ gives an irreversible response at 0.09 V *vs* Ag/AgCl (*ca.* –0.4 V *vs* Cp_2Fe^+/Cp_2Fe) corresponding to the formation of tetraethylthiuram disulfide (disulfiram) [14]. This is important as disulfiram and its active metabolites reduce the activity of many enzymatic reactions that are relevant to the treatment of alcohol and cocaine dependence [44]. Further, the free dithiocarbamate itself rapidly decomposes to carbon disulfide and diethyl amine under acidic conditions and undergoes oxidative biotransformation to afford diethylthiomethylcarbamate which in turn can be converted to diethylthiocarbamate which inhibits dopamine β-hydroxylase thus limiting noradrenalin synthesis and increasing synaptic dopamine [45]. Thus, the reductive loss of a dithiocarbamate ligand from any metal centre can have important biological consequences.

ZINC AND CADMIUM CHEMISTRY

Zinc(II) bis(dithiocarbamate) complexes are air-stable white solids which are easy to prepare and show good stability [2]. As expected for a d^{10} configuration they adopt a distorted tetrahedral structure in solution but their solid-state structures are more complex. A large number of single crystal X-ray structures have been reported and three different structural types have been identified. The most common of these is a dimeric structure (Fig. **7**) in which the two zinc bis(dithiocarbamate) units are held together by weak secondary zinc-sulfur interactions which highlights the strong Lewis acidic nature of the zinc(II) centre [46]. In solution the dithiocarbamate ligands are extremely labile as demonstrated in a study investigating the exchange between $[Zn(S_2CNEt_2)_2]$ and $^{65}ZnCl_2$ which is proposed to proceed *via* a dissociative rate-determining step [47] (Fig. **7**).

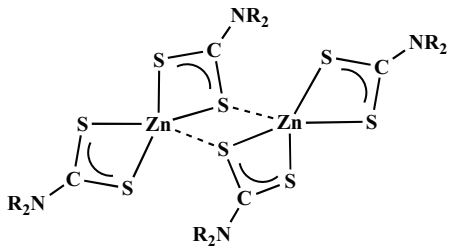
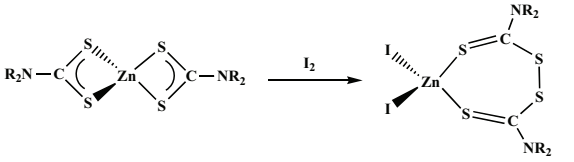


Fig. (7).

A wide range of Lewis base complexes are known. For example, addition of pyridine and related nitrogen bases results in formation of 1:1 adducts with structures part way between square-based pyramidal and trigonal bypyramidal (Fig. **8a**) [48], while with chelating diamines such as 2,2'-bipyridine [49] and 1,10-phenanthroline [50] six-coordinate distorted octahedral complexes result (Fig. **8b**). In all of these complexes the dithiocarbamates retain their bidentate coordination mode, however, when very bulky diamines are used such as 2,9-dimethyl-1,10-phenanthroline the steric congestion around the zinc centre results in both dithiocarbamates binding in a monodentate fashion (Fig. **8c**) [51]. Oxygen-based Lewis bases such as acetates [52] can also bind to $[Zn(S_2CNR_2)_2]$ complexes and also anionic sulfur-based Lewis bases such as xanthates [53], thiolates [54] and even further dithiocarbamate [55] can also form stable complexes. The latter result in the formation of tris(dithiocarbamate) anions $[Zn(S_2CNR_2)_3]^-$, crystallographic characterization of $[Zn(S_2CNMe_2)_3][NEt_4]$ revealing a pseudo-tetrahedral coordination environment four short and two long zinc-sulfur bonds [55]. This can be used to explain why dithiocarbamates are so readily exchanged at zinc(II) centers. These observations might also have relevance in biological systems as they suggest that zinc(II) dithiocarbamate complexes might bind readily to a range of biological Lewis bases, in some instances resulting in displacement of the dithiocarbamate. Indeed, Cvek, Dou and co-workers have suggested that the enhanced activity of $[Zn(S_2CNEt_2)_2]$ against the proteasome in breast cancer cells *versus* analogous copper(II) and nickel(II) complexes may result from binding of the zinc dithiocarbamate centre to the JAMM domain in the 19S proteasome lid *via* a secondary zinc-sulfur interaction [56] (Fig. **8**).

While the zinc(II) centre cannot undergo oxidation, this does not mean that zinc(II) bis(dithiocarbamate) complexes cannot be oxidized. Indeed addition of halogens results in ligand-centered oxidation to give tetrahedral thiuram disulfide complexes $[ZnX_2\{R_2CN(S)S\text{-}SC(S)NR_2\}]$ resulting from sulfur-sulfur bond formation (eqn. 16) [57]. The thiuram disulfide here is only weakly bound and can readily be displaced and thus could potentially be released in a biological system under oxidizing conditions.



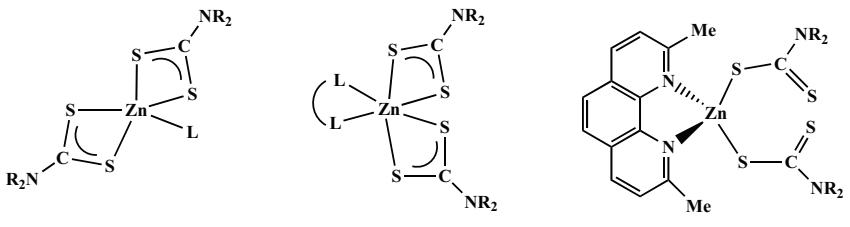
(Eq.16)

Until relatively recently the biological activity of zinc dithiocarbamates was not well studied. The dimethyldithiocarbamate complex, $[Zn(S_2CNMe_2)_2]$, has been used extensively as a agricultural fungicide (Ziram) since 1960 and toxicological studies related to this usage have shown it to be extremely toxic to fish, chicken and rat embryos [58]. In 2004, Ahn and co-workers reported that pyrrolidine dithiocarbamate inhibits the ubiquitin-proteasome pathway by which damaged or misfolded proteins are degraded [59]. Consequently, over the past five years Dou and co-workers have established that zinc dithiocarbamate complexes induce apoptosis in tumor cells by inhibiting the proteasomal activity [56, 60]. They appear not to be as active as copper complexes and probably operate *via* a different mechanism [60]. In 2007, Sakurai and co-workers reported that zinc(II) bis(dithiocarbamate) complexes were orally active anti-diabetics, inhibiting free fatty acid release and enhancing glucose-uptake in adipocytes [61]. The most active of the complexes tested was the pyrrolidine dithiocarbamate, $[Zn(S_2CNC_4H_8)_2]$, which improved hypertension in mice and also the levels of adiponectin in the serum. The activity is generally better than related zinc complexes with S_2O_2 and N_2O_2 ligand sets [62].

Cadmium dithiocarbamate chemistry very closely mirrors that of zinc, although the larger size of cadmium allows greater access to higher coordination numbers. For example, while $[Zn(S_2CNR_2)_3]^-$ adopt a pseudo-tetrahedral coordination environment (see above), $[Cd(S_2CNR_2)_3]^-$ complexes are better described as highly distorted octahedral with six cadmium-sulfur bonds, albeit spanning a wide range of distances [55]. Dithiocarbamates have been shown to be very efficient cadmium chelators and as such have been studied for the treatment of acute cadmium poisoning [38]. Diethyldithiocarbamate itself was found to be unsuitable as it lead to enhanced cadmium deposition in the brain [63] so Jones and co-workers prepared and tested a large number of dithiocarbamates the cadmium complexes of which have enhanced water solubility [64]. Administering ligands derived from 4-carboxamidopiperidene and D-glucamine resulted in a rapid reduction of liver cadmium levels suggesting that they could have a good efficacy as antidotes for acute cadmium poisoning.

COPPER CHEMISTRY

Brown copper(II) bis(dithiocarbamate) complexes are easily prepared and are known for a vast array of dithiocarbamate ligands. These include examples with biologically relevant substituents such as crown-ether appendages [65] and complexes generated from α-amino acids [66]. All contain a square-planar CuS_4 arrangement and in the solid-state complexes often crystallize as dimeric pairs



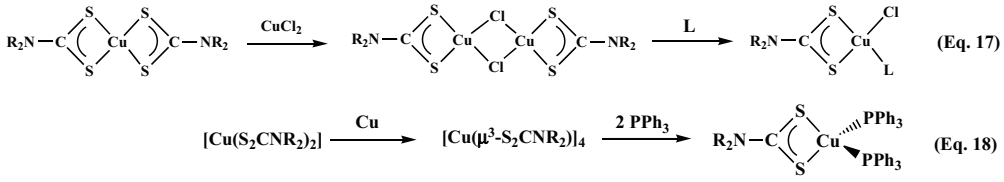
(a) (b) (c)

Fig. (8).

bound by secondary intermolecular copper-sulfur interactions akin to those found in zinc bis(dithiocarbamate) complexes. However, like the zinc complexes, in solution they are simple mononuclear complexes. The d^9-electronic configuration makes them amenable to study by ESR spectroscopy [67] and water-soluble examples have been studied within tissues [68]. The copper(II) centre is not as Lewis acidic as the zinc(II) centre and simple Lewis base adducts are unknown although ESR studies have suggested that they are accessible [69]. Copper(II) bis(dithiocarbamate) complexes react copper(II) halides to afford dimeric $[Cu(\mu\text{-}X)(S_2CNR_2)]_2$ [70] (eqn. 17), which can be cleaved with pyridines and picolines (L) to afford mononuclear adducts $[CuX(S_2CNR_2)L]$ [71].

$[Cu(PPh_3)_2(S_2CNR_2)]$ result [78] (eqn. 18). In the solid-state they adopt the expected tetrahedral coordination geometry but in solution the phosphines are extremely labile and their structures are less understood. Recent work has also shown that octanuclear copper(I) clusters are accessible, $[Cu_8(\mu_4\text{-}S_2CNPr_2)_6][ClO_4]_2$ being one product of the disproportionation reaction between $[Cu(S_2CNPr_2)_2]$ and copper(II) perchlorate [36]. The cluster consists of a cube of copper ions, each face of which is capped by a dithiocarbamate ligand.

A number of biologically related studies of copper dithiocarbamate complexes have been reported. Diethyldithiocarbamate has found extensive use as an



As detailed above, copper(III) bis(dithiocarbamate) cations are electrochemically accessible and are readily prepared upon oxidation of $[Cu(S_2CNR_2)_2]$ with a range of oxidizing agents including $CuClO_4$ [72], $FeCl_3$ [72, 73] and iodine [74]. The structural chemistry of $[Cu(S_2CNR_2)_2][X]$ salts is complex and depends highly upon both the nature of the anion and dithiocarbamate substituents [2]. Polymeric arrays are quite common in which the square-planar copper(III) centers are interlinked by a series of intermolecular copper-sulfur interactions as are pseudo-octahedral structures with anions coordinated above and below the square-plane [72]. However, again in all instances the complexes are monomeric in solution. In theory they should be amenable to study by NMR spectroscopy but in practice this can be complicated by the presence of small amounts of copper(II) complexes. Addition of thiuram disulfides to $CuCl_2$ [26] or reaction of thionyl chloride with $[Cu(S_2CNR_2)_2]$ [75] affords copper(III) dichloride complexes $[CuCl_2(S_2CNR_2)]$ akin to the gold(III) complexes utilized in cancer therapy [76, 77]. Related dibromo complexes are also known [26] but none of these have been studied by X-ray crystallography so the precise molecular structures remain unknown. Given the commensurate nature of the square-planar CuS_4 centers in copper(II) and copper(III) bis(dithiocarbamate) complexes it is perhaps not surprising that mixed-valence copper(II)-copper(III) complexes are accessible [70]. They tend to consist of a copper(III) centre sandwiched between two copper(II) moieties being held together by secondary copper-sulfur interactions.

Tetrahedral copper(I) clusters, $[Cu(\mu_3\text{-}S_2CNR_2)]_4$, are prepared *via* a conproportionation reaction between $[Cu(S_2CNR_2)_2]$ and finely divided copper powder [78]. Their structures in solution are not fully understood and some evidence suggests that they may be in equilibrium with binuclear or even mononuclear fragments. Addition of phosphines to these clusters affords mononuclear phosphines adducts, for example with PPh_3 the bis(phosphine) adducts

inhibitor of copper-zinc superoxide dismutase (SOD) as it has the ability to despoil copper from the protein thus producing the copper-depleted protein [37, 79]. The mechanism of action remains unclear but it is believed that interaction with oxyhemoglobin results in the formation of reactive radicals which spontaneously react with thiols resulting in intracellular glutathione depletion and other intracellular enzyme deactivation. Copper complexes of amino acids show SOD-like activity with those having long-chain oligoether substituents being especially active [80] probably relating to their enhanced hydrophobicity. Copper(II) bis(dithiocarbamate) complexes find applications in radiopharmaceuticals. Thus, ^{62}Cu-labelled $[Cu(S_2CNR_2)_2]$ (R = Me, Et) have been prepared and their biodistribution in mice has been studied *via* the short-lived positron-emission [81]. This study demonstrated high ^{62}Cu-uptake in the brain possibly a result of their lipophilic character. More recently, Blower and co-workers have prepared a ^{64}Cu-labelled complex employing a dithiocarbamatebisphosphonate ligand (Fig. **2i**). They have shown that it has high stability in phosphate-buffered saline and human serum and have bound it to dextran-functionalized Fe_3O_4 nanoparticles for their *in vivo* evaluation as duel-modality PET-MRI agents [12].

GOLD CHEMISTRY

Like copper, gold dithiocarbamate complexes are also known for oxidation states +1 to +3, however, unlike copper where the +2 oxidation state is extremely common, gold(II) is rare and the first gold(II) dithiocarbamate complexes were not discovered until 1981 [82]. Some common gold dithiocarbamate complexes are shown in (Fig. **9**). A wide-range of gold(III) complexes are known. Addition of one equivalent of dithiocarbamate to gold(III) halides affords bis(halide) complexes $[AuX_2(S_2CNR_2)]$ (Fig. **9a**) and related organometallic complexes $[AuAr_2(S_2CNR_2)]$ [83] are also accessible. Fregona and co-workers have shown that the bis(halide) complexes have outstanding cytotoxic properties towards a range of human tumor cell lines

with the ethylsarcosinedithiocarbamate complex $[AuCl_2\{S_2CN(Me)CH_2C(O)OEt\}]$ being particularly active [76]. Their mode of action is not yet fully understood but hydrolysis of the gold-halide bonds akin to the known behavior of *cisplatin* is a likely first step. Their mode of action is however substantially different from that of *cisplatin* and the key gold-modified proteins responsible for triggering apoptosis remain unknown. These complexes have been shown to inhibit proteasomal chymotrypsin-like activity in a concentration-dependent manner, a well-known mechanism for apoptosis induction in cancer cells. Bis(dithiocarbamate) complexes, $[Au(S_2CNR_2)_2]^+$ (Fig. **9b**) are easily prepared upon addition of two equivalents of dithiocarbamate salts to gold(III) halides or oxidative-addition of thiuram disulfides to gold(I) halides [84] and contain a square-planar d^8 metal center akin to that found in analogous copper(III) complexes. Unlike the latter, which do not react with further dithiocarbamate, a third equivalent of dithiocarbamate adds to form $[Au(S_2CNR_2)_2]_3$ (Fig. **9c**) [85]. In the solid-state one dithiocarbamate chelates the gold center while the other two are monodentate, however in solution they interconvert on the NMR timescale (Fig. **9**).

Tris(dithiocarbamate) complexes $[Au(S_2CNR_2)_2]_3$ undergo an irreversible two-electron reduction generating gold(I) complexes $[Au(\mu\text{-}S_2CNR_2)]_2$ (Fig. **9d**) [86], also prepared upon addition of dithiocarbamate salts to gold(I) halides [87]. All are dimeric consisting of an Au_2 unit bridged by two dithiocarbamate ligands [88]. In the solid-state they crystallize to form linear chains of gold atoms characterized by alternating short and long metal-metal interactions. The dimeric units can be broken down upon addition of phosphines to give pseudo-tetrahedral complexes such as $[Au(PPh_3)_2(S_2CN^iPr_2)]$ [89]. Related complexes with a single phosphine such as $[Au(PCy_3)(S_2CNEt_2)]$ can be prepared by addition of dithiocarbamate salts to gold(I) phosphine-halide precursors [90]. These contain a linear two-coordinate gold center the dithiocarbamate binding in a monodentate manner. Monomeric gold(II) bis(dithiocarbamate) complexes are not stable and all gold(II) dithiocarbamate complexes prepared to date are dimeric. Addition of halides to $[Au(\mu\text{-}S_2CNR_2)]_2$ at low temperatures affords gold(II) dimers $[XAu(\mu\text{-}S_2CNR_2)]_2$ but these disproportionate upon warming to room temperature affording $[Au(S_2CNR_2)_2][AuX_2]$ [82]. Related gold(II) dimers $[Au_2(\mu\text{-}S_2CNR_2)(\mu\text{-}CH_2PPh_2CH_2)]$ also undergo oxidative-addition of halides but now the gold(II) products $[X_2Au_2(\mu\text{-}S_2CNR_2)(\mu\text{-}CH_2PPh_2CH_2)]$ are stable at room temperature and have been crystallographically characterized [91].

An exciting new development in the area of gold-dithiocarbamate chemistry is the stabilization of gold nano-particles by chelating dithiocarbamate ligands [92-97]. These are extremely easy to prepare, show good stability and allow decoration of the nanoparticles with a range of different functional groups. Very recently Cao and co-workers have attached copper bis(dithiocarbamate) groups to gold nanoparticles showing that they dismutate the superoxide radical extremely efficiently (IC_{50} = 0.074 mM) [96] suggesting that this approach may have many biological applications.

IRON AND RUTHENIUM CHEMISTRY

Iron is an extremely important biological element and iron dithiocarbamate complexes are known in oxidation states +2 to +4. Octahedral iron(III) tris(dithiocarbamate) complexes $[Fe(S_2CNR_2)_3]$ are very common and can exist in both high-spin and low-spin forms [2]. The energy difference between the two d^5-configurations is small and they exhibit $^6A_1$-$^2T_2$ spin crossover (Fig. **10**), the population of each state being dependent upon a wide range of factors including temperature, pressure and the nature of the dithiocarbamate substituents (Fig. **10**).

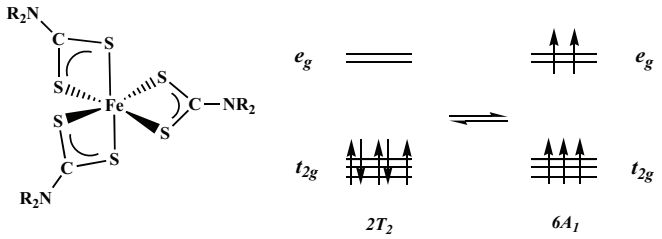


Fig. (10).

Akin to the copper(II) bis(dithiocarbamate) complexes, $[Fe(S_2CNR_2)_3]$ undergo a fully reversible one-electron oxidation to afford d^4 cations $[Fe(S_2CNR_2)_3]^+$ [98]. One-electron reduction of $[Fe(S_2CNR_2)_3]$ is quasi-reversible on the electrochemical timeframe but the generated anions $[Fe(S_2CNR_2)_3]^-$ cannot be isolated. Rather they lose a dithiocarbamate to produce the extremely air-sensitive bis(dithiocarbamate) complexes $[Fe(S_2CNR_2)_2]$ which on the basis of the X-ray crystal structure of $[Fe(S_2CNEt_2)_2]$ [99] adopt a square-planar coordination geometry. Iron dithiocarbamate complexes have been used as endogenous NO trapping agents [100], both iron(II) and iron (III) complexes reacting with NO to afford square-pyramidal complexes, $[Fe(NO)(S_2CNR_2)_2]$ [101]. For the iron(II) complexes this is a simple addition reaction but for

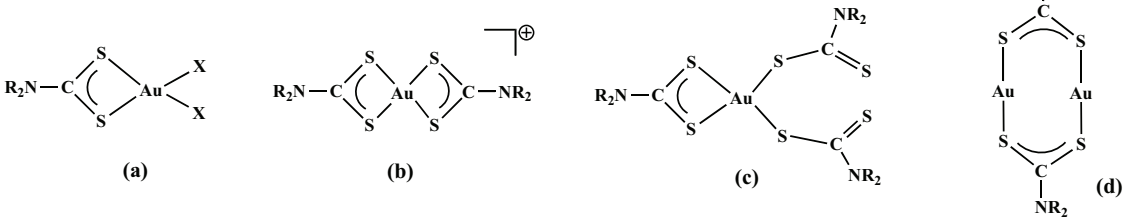


Fig. (9).

$[Fe(S_2CNR_2)_3]$ a series of redox transformations are required with formation of $[Fe(NO)(S_2CNR_2)_2]$ and half an equivalent of thiuram disulfide (eqn. 19).

$$[Fe(S_2CNR_2)_2] \xrightarrow{NO} [Fe(NO)(S_2CNR_2)_2] \xleftarrow{NO} [Fe(S_2CNR_2)_3] \quad \text{(Eq.19)}$$
$$- 0.5\ (R_2CNS_2)_2$$

Fregona and co-workers have reported that well-studied ruthenium(III) monomeric and dimeric dithiocarbamate complexes $[Ru(S_2CNR_2)_3]$ and $[Ru_2(S_2CNR_2)_5]^+$ respectively have promising anti-cancer activity being less toxic than *cisplatin* [102, 103]. The tris(dithiocarbamate) complexes all have a low-spin d^5 electronic configuration and are easily converted into $[Ru_2(S_2CNR_2)_5]^+$ upon addition of Lewis acids [104]. Isomers of the latter are known containing two (α-isomers) or three (β-isomers) bridging dithiocarbamate ligands [104, 105]. Seven coordinate ruthenium(IV) complexes $[RuCl(S_2CNR_2)_3]$ are also known but when dissolved in coordinating solvents such as acetonitrile the halide is displace to give ionic complexes $[Ru(MeCN)(S_2CNR_2)_3]Cl$ [105]. Extensive electrochemical studies have been carried out on tris(dithiocarbamate) complexes $[Ru(S_2CNR_2)_3]$ [102,105]. The oxidation chemistry is highly dependent upon the nature of the solvent and in acetonitrile the one-electron oxidation product is $[Ru(MeCN)(S_2CNR_2)_3]^+$ [105]. In dichloromethane two one-electron oxidations are observed, the first of which is irreversible while the second has some reversibility [102]. Fregona has attributed the former to a ligand-based oxidation, while the second process is metal-based. Tris(dithiocarbamate) complexes also undergo a reversible one-electron reduction to presumably to afford ruthenium(II) complexes $[Ru(S_2CNR_2)_3]^-$, although neither these or simple bis(dithiocarbamate) complexes $[Ru(S_2CNR_2)_2]$ have ever been isolated. A wide range of stable ruthenium(II) dithiocarbamate complexes can, however, be easily synthesized. The best studied are the dicarbonyl complexes *cis*-$[Ru(CO)_2(S_2CNR_2)_2]$ which can be prepared in a number of ways including the oxidative-addition of thiuram disulfides to $Ru_3(CO)_{12}$ [106]. Related dimethylsulfoxide and triphenylphosphine complexes $[Ru(Me_2SO)_2(S_2CNR_2)_2]$ and $[Ru(PPh_3)_2(S_2CNR_2)_2]$ also have a *cis* disposition of ligands, however, exchange of the dmso ligands by $CNBu^t$ affords *trans*-$[Ru(CNBu^t)_2(S_2CNR_2)_2]$ [107]. Ruthenium(II) diphosphine complexes $[Ru(diphosphine)(S_2CNR_2)_2]$ can also be easily prepared [108]. NMR spectra are temperature dependent being associated with the exchange of dithiocarbamates *via* a solvent-stabilized intermediate with one monodentate dithiocarbamate.

TECHNETIUM CHEMISTRY

^{99m}Tc is a radioactive isotope produced from the decay of ^{99}Mo. It has a half-life of six hours and decays by emitting only γ-rays and consequently finds widespread uses as a radioactive tracer [109] being used for over 20 million diagnostic nuclear medical procedures annually. It is produced as $[TcO_4]^-$ which was shown by Baldas to react with diethyldithiocarbamate in the presence of hydrazine to afford the technetium(V) complex $[TcN(S_2CNEt_2)_2]$ [24]. In the intervening thirty years a wide range of such complexes have been prepared including that with the N-ethyl-N-ethoxydithiocarbamate (NOET) ligand (Fig. **2f**) [110] which is FDA-approved (^{99m}TcN-NOET). These complexes contain a square-pyramidal technetium(V) centre, the nitride ligand occupying the axial site (Fig. **11a**), being a strong π-donor which serves to stabilize the technetium(V) state. A range has been used as heart and brain imaging agents. ^{99m}TcN-NOET has the advantage of having a high first pass extraction coefficient as compared to some related reagents, but is only slowly cleared from the liver and this has hampered its development as a commercial product. Attempts are on-going to develop technetium-nitride-dithiocarbamate complexes as radioactive tracers [111-114], for example the fluoroquinoline derivative (Fig. **11b**) shows promise as a bacteria-specific infection imaging agent [111]. Related cationic complexes such as ^{99m}Tc-DBODC5 (Fig. **11c**) [115] are also under investigation and have been shown to have much better liver clearance (Fig. **11**).

Technetium dithiocarbamate complexes are also known in the +3 to +1 oxidation states. For example technetium(III) carbonyl complexes, $[Tc(CO)(S_2CNR_2)_3]$, are prepared from $[TcO_4][NH_4]$ and dithiocarbamate salts in the presence of aminoiminomethane sulfinic acid as a reducing agent [116]. They are extremely stable and ^{99m}Tc variants have been tested in mice, showing efficient hepatobiliary behavior clearing the livers of mice more readily than corresponding nitride complexes [117]. ^{188}Re is readily available from the decay of ^{118}W and while not studied to the same extent as their technetium counterparts, rhenium dithiocarbamate complexes have potential to act as radiopharmaceuticals [118].

CONCLUDING REMARKS

Hopefully this review article has served to introduce the non-specialist to the chemistry of the dithiocarbamate ligand. As highlighted in this topical edition of this journal, the developing use of dithiocarbamate complexes in anti-cancer treatments [119,120] and the well-established toxicology of dithiocarbamate ligands and complexes [121,122] suggests that it is likely to be an increasingly fruitful area for inorganic chemists, biochemists and medical practitioners to collaborate.

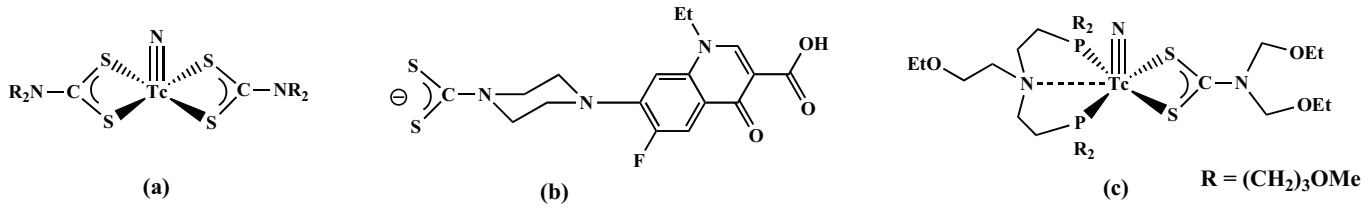


Fig. (11).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT OF FUNDING

Declared none.

REFERENCES

[1] Coucouvanis, D. The chemistry of the dithioacid and 1,1-dithiolate complexes, 1968-1977. *Prog. Inorg. Chem.*, **1979**, *26*, 301-469.

[2] Hogarth, G. Transition metal dithiocarbamates: 1978-2003. *Prog. Inorg. Chem.*, **2005**, *53*, 71-561.

[3] Heard, P.J. Main group dithiocarbamate complexes. *Prog. Inorg. Chem.*, **2005**, *53*, 1-69.

[4] Kupchick, E.J.; Calabretta, P.J. Some phenyltin, -lead, and antimony dithiocarbamates. *Inorg. Chem.*, **1965**, *4*, 973-978.

[5] Li, G.; Tajima, H.; Ohtani, T. An improved procedure for the preparation of isothiocyanates from primary amines by using hydrogen peroxide as the dehydrosulfurization reagent. *J. Org. Chem.*, **1997**, *62*, 4539-4540.

[6] Wilton-Ely, J.D.E.T.; Solanki, D.; Hogarth, G. Multifunctional dithiocarbamates as ligands towards the rational synthesis of polymetallic arrays: An example based on a piperazine-derived dithiocarbamate ligand. *Eur. J. Inorg. Chem.*, **2005**, 4027-4030.

[7] Macgregor, M.J.; Hogarth, G.; Thompson, A.L.; Wilton-Ely, J.D.E.T. Multimetallic Arrays: Symmetrical and Unsymmetrical Bi-, Tri-, and Tetrametallic Organometallic Complexes of Ruthenium(II) and Osmium(II). *Organometallics*, **2009**, *28*, 197-208.

[8] Zhang, J.-J.; Xu, Z.-M.; Zhang, C.-M.; Dai, H.-Y.; Ji, X.-Q.; Wang, X.-F.; Li, C. Pyrrolidine dithiocarbamate inhibits nuclear factor-κB pathway activation, and regulates adhesion, migration, invasion and apoptosis of endometriotic stromal cells. *Mol. Hum. Reprod.*, **2011**, *17,* 175-181.

[9] Colombo, F.R.; Torrente, Y.; Casati, R.; Benti, R.; Corti, S.; Salani, S.; D'Angelo, M.G.; DeLiso, A.; Scarlato, G.; Bresolin, N.; Gerundini, P. Biodistribution studies of ^{99m}Tc-labeled myoblasts in a murine model of muscular dystrophy. *Nucl. Med. Biol.*, **2001**, *28*, 935-940.

[10] Hogarth, G.; Rainford-Brent, E.-J.C.-R.C.R.; Kabir, S.E.; Richards, I.; Wilton-Ely, J.D.E.T.; Zhang, Q. Functionalized dithiocarbamate complexes: Synthesis and molecular structures of 2-diethylaminoethyl and 3-dimethylaminopropyl dithiocarbamate complexes $[M\{S_2CN(CH_2CH_2NEt_2)_2\}_n]$and $[M\{S_2CN(CH_2CH_2CH_2NMe_2)_2\}_n]$(n = 2, M = Ni, Cu, Zn, Pd; n = 3, M = Co). *Inorg. Chim. Acta*, **2009**, *362*, 2020-2026.

[11] Wang, F.; Zhai, S.; Liu, X.; Li, L.; Wu, S.; Dou, Q.P.; Yan, B. A novel dithiocarbamate analogue with potentially decreased ALDH inhibition has copper-dependent proteasome-inhibitory and apoptosis-inducing activity in human breast cancer cells. *Cancer Letters*, **2011**, *300*, 87-95.

[12] Martin de Rosales, R.T.; Tavare, R.; Paul, R.L.; Jauregui-Osoro, M.; Protti, A.; Glaria, A.; Varma, G.; Szanda, I.; Blower, P.J. Synthesis of $^{64}Cu^{II}$-Bis(dithiocarbamatebisphosphonate) and its conjugation with superparamagnetic iron oxide nanoparticles: In vivo evaluation as dual-modality PET-MRI agent. *Angew. Chem., Int. Ed.*, **2011**, *50*, 5509-5513.

[13] Auzeloux, P.; Papon, J.; Masnada, T.; Borel, M.; Moreau, M.-F.; Veyre, A.; Pasqualini, R.; Madelmont, J.-C. Synthesis and biodistribution of technetium-99m-labeled N-(diethylaminoethyl)benzamide via a bis(dithiocarbamate) nitridotechnetium(V) complex. *J. Label. Compd. Radiopharm.*, **1999**, *42*, 325-335.

[14] Bond, A.M.; Colton, R.; Hollenkamp, A.F.; Hoskins, B.F.; McGregor, K. Voltammetric, coulometric, mercury-199 NMR, and other studies characterizing new and unusual mercury complexes produced by electrochemical oxidation of mercury(II) diethyldithiocarbamate. Crystal and molecular structure of octakis(N,N-diethyldithiocarbamato)pentamercury(II) perchlorate. *J. Am. Chem. Soc.*, **1987**, *109*, 1969-1980.

[15] Radovan, C.; Manea, F. Determination of sodium diethyldithiocarbamate in water by anodic voltammetry using a boron-doped diamond electrode. *Electroanalysis*, **2007**, *19*, 91-95.

[16] Karle, I.L.; Estlin, J.A.; Britts, K. The crystal and molecular structure of tetraethylthiuram disulfide, $C_{10}N_2H_{20}S_4$. *Acta Cryst.*, **1967**, *22*, 273-275.

[17] Alagiri, K.; Prabhu, Kandikere R. Catalyst-free regio- and stereospecific synthesis of β-sulfonamido dithiocarbamates: Efficient ring-opening reactions of N-tosyl aziridines by dialkyldithiocarbamates. *Chem. Eur. J.*, **2011**, *17*, 6922-6925.

[18] Yih, K.-H.; Chen, S.-C.; Lin, Y.-C.; Lee, G.-H.; Wang, Y. New syntheses of $[Et_4N][(C_5H_{10}NCS_2)M(CO)_4]$(M = Cr, Mo and W): Insertion reaction of carbon disulfide into the metal-nitrogen bond. *J. Organomet. Chem.*, **1995**, *494*, 149-155.

[19] Edwards, A.; Hogarth, G.; Hollingsworth, N.; Oller, J.J. Illusive tungsten-imido-dithiocarbamate complexes: Facile carbon-nitrogen bond formation. *Inorg. Chem. Commun.*, **2011**, *14*, 1932-1936.

[20] Deeming, A.J.; Forth, C.; Hogarth, G. Reactions of trans-$[RuCl_2(CO)_2(PEt_3)_2]$with 1,1-dithiolates: Stepwise formation of cis-$[Ru(CO)(PEt_3)(S_2X)]$ (X = $CNMe_2$, $CNEt_2$, COEt, $P(OEt)_2$, PPh_2). *J. Organomet. Chem.*, **2006**, *691*, 79-85.

[21] Tiekink, E.R.T.; Winter, G. Inorganic xanthates: a structural perspective. *Rev. Inorg. Chem.*, **1992**, *12*, 183-302.

[22] Dietzsch, W.; Duffy, N.V.; Boyd, D.; Uhrich, D.L.; Sinn, E. Mössbauer spectra of tris(diorganothioselenocarbamato)- and tris(diorganodiselenocarbamato)iron(III) complexes. *Inorg. Chim. Acta*, **1990**, *169*, 157-160.

[23] Deplano, P; Trogu, E.F.; Bigoli, F.; Leporati, E.; Pellinghelli, M.A.; Perry, D.L.; Saxton, R.J.; Wilson, L.J. Synthesis and magnetochemical, spectroscopic, and structural studies of new tris(N,N-dialkyldiselenocarbamato)iron(IV) tetrafluoroborate complexes. *J. Chem. Soc., Dalton Trans.*, **1983**, 25-30.

[24] Baldas, J.; Bonnyman, J.; Pojer, P.M.; Williams, G.A.; Mackay, M.F. Synthesis and structure of bis(diethyldithiocarbamato)nitridotechnetium(V): a technetium-nitrogen triple bond. *J. Chem. Soc., Dalton Trans.*, **1981**, 1798-1801.

[25] Victoriano, L.I. The reactivity of metal species towards thiuram sulphides: an alternative route to the synthesis of metal dithiocarbamates. *Coord. Chem. Rev.*, **2000**, *196*, 383-398.

[26] Victoriano, L.I. Copper(III) dithiocarbamates. *J. Chem. Ed.*, **2002**, *79*, 1252-1253.

[27] Bradley, D.C.; Gitlitz, M.H. N,N-Dialkyldithiocarbamates of transition metals of Groups IV and V. *J. Chem. Soc., Chem. Commun.*, **1965**, 289-290.

[28] Bianchini, C.; Ghilardi, C.A.; Meli, A.; Midollini, S.; Orlandini, A. Reactivity of copper(I) tetrahydroborates toward carbon disulfide and phenyl isothiocyanate. Structures of $(PPh_3)_2Cu(\mu$-$S_2CSCH_2SCS_2)Cu(PPh_3)_2$, $(PPh_3)_2Cu(S_2COEt)$, and $(PPh_3)_2Cu(S_2CNHPh).CHCl_3$. *Inorg. Chem.*, **1985**, *24*, 932-939.

[29] Kovács, I.; Lebuis, A.-M.; Shaver, A. Ruthenium-Assisted Insertion of Isothiocyanates into the Silicon-Sulfur Bond: A Comparative Study on the Reactivity of the S-Si and S-H Bonds in $CpRu(PPh_3)_2SX$ (X = H, Si^iPr_3) Complexes. *Organometallics*, **2001**, *20*, 35-41.

[30] Montagner, D.; Sanz Miguel, P.J. Unique Pt_5 metallacycle : $[Pt^{II}Cl(pyrrolidinedithiocarbamate)]_5$. *Dalton Trans.*, **2011**, *40*, 10809-10811.

[31] Tan, L.S.; Goeden, G.V.; Haymore, B.L. New nitrene complexes of niobium and tantalum of the type $M(NR)(S_2CNR'_2)_3$. *Inorg. Chem.*, **1983**, *22*, 1744-1750.

[32] Vizi-Orosz, A.; Markó, L. Reaction of nickel(II) xanthates with amines and carbon monoxide: formation of thiourethanes and nickel tetracarbonyl. *Trans. Met. Chem.*, **1986**, *11*, 408-410.

[33] Fackler, Jr, J.P.; Seidel, W.C. Sulfur ligand complexes. IX. Reactions of metal xanthates and their derivatives. The formation of bisphosphine-dithiocarbonate and -trithiocarbonate complexes of palladium(II) and platinum(II). *Inorg. Chem.*, **1969**, *8*, 1631-1639.

[34] Noordik, J.H. Tris(N,N-diethyldithiocarbamato)gold(III), $C_{15}H_{30}AuN_3S_6$. *Cryst. Struct. Commun.*, **1973**, *2*, 81-84.

[35] Fernandez, E.J.; Lopez-de-Luzuriaga, J.M.; Monge, M.; Olmos, E.; Gimeno, M.C.; Laguna, A.; Jones, P.G. Dithiocarbamate ligands as building-blocks in the coordination chemistry of gold. *Inorg. Chem.*, **1998**, *37*, 5532-5536.

[36] Cardell, D.; Hogarth, G.; Faulkner, S. A dithiocarbamate-stabilized copper(I) cube. *Inorg. Chim. Acta*, **2006**, *359*, 1321-1324.

[37] Cocco, D.; Calabrese, L.; Rigog, A.; Argeseg, E.; Rotilio, G. Re-examination of the reaction of diethyldithiocarbamte with the copper of superoxide dismutase. *J. Biol. Chem.*, **1981**, 256, 8983-8986.

[38] Jones, M.M.; Singh, P.K.; Jones, S.G. Optimization of chelating agent structure for the mobilization of aged renal and hepatic cadmium deposits: Sodium N-benzyl-4-O-(β-D-galactopyranosyl)-D-glucamine-N-carbodithiolate. *Chem. Res. Toxicol.*, **1990**, *3*, 248-253.

[39] Sachinidis, J.; Grant, M.W. Metal exchange reactions between divalent metal ions and their dithiocarbamate complexes in dimethylsulfoxide: a kinetic and mechanistic study. *Aust. J. Chem.*, **1981**, *34*, 2195-2215.

[40] Yamuna, K.; Ramana, V.V.; Emmanuel, K.A.; Saraswati, K. Stability constants of metal complexes of dithiocarbamates. *Asian J. Chem.*, **1992**, *4*, 387-389.

[41] Moriyasu, M.; Hashimoto, Y. Kinetic studies of fast equilibrium by means of high-performance liquid chromatography. III. Ternary complex formation between nickel(II) diethyldithiocarbamate and other unlike nickel(II) chelates. *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 3374-3378.

[42] Bond, A.M.; Martin, R.L. Electrochemistry and redox behavior of transition metal dithiocarbamates. *Coord. Chem. Rev.*, **1984**, *54*, 23-98.

[43] Henrickson, A.R.; Martin, R.L; Rohde, N.M. Dithiocarbamates of Cu(I), Cu(II), and Cu(III). An electrochemical study. *Inorg. Chem.*, **1976**, *15*, 2115-2119.

[44] Malcolm, R.; Olive, M.F.; Lechner, W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. *Expert Opin. Drug Saf.*, **2008**, *7*, 459-472.

[45] Johansson, B.; Angello, H.R.; Christensen, J.K.; Moller, I.W; Ronsted, P. Dose-effect relationship of disulfiram in human volunteers. II A study of the relation between the disulfiram-alcohol reaction and plasma concentrations of acetaldehyde, diethyldithiocarbimic acid methyl ester, and erythrocyte aldehyde dehydrogenase activity. *Phamacol. Toxicol.*, **1991**, *68*, 166-170.

[46] Cox, M.J.; Tiekink, E.R.T. The diverse coordination patterns in the structures of zinc, cadmium and mercury bis(1,1-dithiolates). *Rev. Inorg. Chem.*, **1997**, *17*, 1-23.

[47] Wyttenbach, A. Metal isotopic exchange kinetics between zinc bis(diethyldithiocarbamate) and zinc(2+) in the system chloroform-water. *J. Inorg. Nucl. Chem.*, **1981**, *43*, 1937-1938.

[48] Ivanov, A.V.; Mitrofanova, V.I.; Kritikos, M.; Antzutkin, O.N. Rotation isomers of bis(diethyldithiocarbamato)zinc(II) adduct with pyridine, $Zn(EDtc)_2$·Py: ESR, ^{13}C and ^{15}N CP/MAS NMR and single-crystal X-ray diffraction studies. *Polyhedon*, **1999**, *18*, 2069-2078.

[49] Manohar, A.; Venkatachalam, V.; Ramalingam, K.; Thirumaran, S.; Bocelli, G.; Cantoni, A. Synthesis, spectral, and single crystal x-ray structural studies on (2,2'-bipyridyl)bis(dimethyldithiocarbamato)zinc(II) and (1,10-phenanthroline)bis(dimethyldithiocarbamato)zinc(II). *J. Chem. Cryst.*, **1998**, *28*, 861-866.

[50] Klevtsova, R.F.; Glinskaya, L.A.; Zemskova, S.M.; Larionov, S.V. Synthesis and crystal structure of $ZnPhen(i\text{-}Pr_2NCS_2)$ and molecule packing types in complexes $ZnPhen(R_2NCS_2)$ (R=Me, Et, i-Pr, n-Pr, i-Bu, n-Bu). *Polyhedron*, **1999**, *18*, 3559-3565.

[51] Lai, C.S.; Tiekink, E.R.T. (2,9-Dimethyl-1,10-phenanthroline)bis(N,N-pyrrolidinedithiocarbamato)zinc(II) chloroform hemihydrate. *Appl. Organomet. Chem.*, **2003**, *17*, 255-256.

[52] McCleverty, J.A.; Spencer, N.; Bailey, N.A.; Shackleton, S.L. Aspects of the inorganic chemistry of rubber vulcanization. Part 1. Reactions of zinc bis(dithiocarbamates) and bis(benzothiazole-2-thiolates) with carboxylates, and the structure of $[NBu_4][\{Zn(S_2CNMe_2)_2\}_2(\mu\text{-}OCOMe)]$. *J. Chem. Soc., Dalton Trans.*, **1980**, 1939-1944.

[53] Baggio, R.; Frigerio, A.; Halac, E.B.; Vega, D.; Perec, M. Synthesis and characterization of dithiocarbonate derivatives of zinc and cadmium bis(dithiocarbamates). *J. Chem. Soc., Dalton Trans.*, **1992**, 1887-1892.

[54] McCleverty, J.A.; Morrison, N.J.; Spencer, N.; Ashworth, C.C.; Bailey, N.A.; Johnson, M.R.; Smith, J.M.A.; Tabbiner, B.A.; Taylor, C.R. Aspects of inorganic chemistry of rubber vulcanization. 2. Anionic mixed-ligand zinc complexes derived from 2-mercaptobenzothiazole, -benzoxazole, and -benzimidazole. Structures of $[NEt_4][Zn(S_2CNMe_2)_3]$, $R[Zn(C_7H_4NS_2)_3(OH_2)]$, $R[Zn(S_2CNMe_2)_2(C_7H_4NS_2)]$.EtOH, and $R[Zn(S_2CNMe_2)(C_7H_4NS_2)_2]$(R = NBu_4). *J. Chem. Soc., Dalton Trans.*, **1980**, 1945-1957.

[55] McCleverty, J.A.; Gill, S.; Kowalski, R.S.Z.; Bailey, N.A.; Adams, H.; Lumbard, K.W.; Murphy, M.A. Aspects of the inorganic chemistry of rubber vulcanization. Part 3. Anionic cadmium complexes derived from dialkyldithiocarbamates, 2-mercaptobenzothiazole and its derivatives, and dialkyl dithiophosphates, and the crystal and molecular structures of $[NBu_4][Cd(S_2CNEt_2)_3]$, $[NEt_4][Cd(C_7H_4NS_2)_3]$, and $[NMe_4][Cd\{S_2P(OCHMe_2)_2\}_3]$. *J. Chem. Soc., Dalton Trans.*, **1982**, 493-503.

[56] Cvek, B.; Milacic, V.; Taraba, J.; Dou, Q.P. Ni(II), Cu(II), and Zn(II) diethyldithiocarbamate complexes show various activities against the proteasome in breast cancer cells. *J. Med. Chem.*, **2008**, *51*, 6256-6258.

[57] Brinkhoff, H.C.; Cras, J.A.; Steggerda, J.J.; Willemse, J. Oxidation of dithiocarbamate complexes of nickel, copper, and zinc. *Recl. Trav. Chem.*, **1969**, *88*, 633-640.

[58] Van Leeuwen, C.J.; Helder, T.; Seinen, W. Aquatic toxicological aspects of dithiocarbamates and related compounds. IV. Teratogenicity and histopathology in rainbow trout (Salmo gairdneri). *Aquat. Toxicol.*, **1986**, *9*, 147-159.

[59] Kim, I.; Kim, C.H.; Kim, J.H.; Lee, J.; Choi, J.J.; Chen, Z.A.; Lee, M.G.; Chung, K.C.; Hsu, C.Y.; Ahn, Y.S. Pyrrolidine dithiocarbamate and zinc inhibit proteasome-dependent proteolysis. *Exp. Cell Res.*, **2004**, *298*, 229-238.

[60] Milacic, V.; Chen, D.; Giovagnini, L.; Diez, A.; Fregona, D.; Dou, Q.P. Pyrrolidine dithiocarbamate-zinc(II) and -copper(II) complexes induce apoptosis in tumor cells by inhibiting the proteasomal activity. *Toxic. Appl. Pharm.*, **2008**, *231*, 24-33.

[61] Yoshikawa, Y.; Adachi, Y.; Sakurai, H. A new type of orally active anti-diabetic Zn(II)-dithiocarbamate complex. *Life Sci.*, **2007**, *80*, 759-766.

[62] Nishide, M.; Yoshikawa, Y.; Yoshikawa, E.U.; Matsumoto, K.; Sakurai, H.; Kajiwara, N.M. Insulinomimetic Zn(II) complexes as evaluated by both glucose-uptake activity and inhibition of free fatty acids release in isolated rat. *Chem. Pharm. Bull.*, **2008**, *56*, 1181-1183.

[63] Jones, S.G.; Basinger, M.A.; Jones, M.M.; Gibbs, S.J. A comparison of diethyldithiocarbamate and EDTA as antidotes for acute cadmium intoxication. *Res. Commun. Chem. Pathol. Pharmacol.*, **2982**, *38*, 271-278.

[64] Jones, M.M.; Cherian, M.G. The search for chelate antagonists for chronic cadmium intoxication. *Toxicology*, **1990**, *62*, 1-25.

[65] Beer, P.D.; Cheetham, A.G.; Drew, M.G.B.; Fox, O.D.; Hayes, E.J.; Rolls, T.D. Pyrrole-based metallo-macrocycles and cryptands. *J. Chem. Soc., Dalton Trans.*, **2003**, 603-611.

[66] Macías, B.; Villa, M.V.; Chicote, E.; Martín-Velasco, S.; Castiñeiras, A.; Borrás, J. Copper complexes with dithiocarbamates derived from natural occurring amino acids. Crystal and molecular structure of $[Cu(en)(EtOH)(H_2O)_3][Cu(dtc\text{-}pro)_2]$. *Polyhedron*, **2002**, *21*, 1899-1904.

[67] Bereman, R.D.; Nalewajek, D. Preparation of dithiocarbamate ligands derived from indole, indoline, carbazole, and imidazole and representative transition-element complexes. *Inorg. Chem.*, **1978**, *17*, 1085-1087.

[68] Suzuki, Y.; Fujii, S.; Tominaga, T.; Yoshimoto, T.; Yoshimura, T.; Kamada, H. The origin of an EPR signal observed in dithiocarbamate-loaded tissues copper(II)-dithiocarbamate complexes account for the narrow hyperfine lines. *Biochim. Biophys. Acta, Gen. Subj.*, **1997**, *1335*, 242-245.

[69] Solozhenkin, P.M.; Anufrienko, V.F.; Kopitsia, N.I.; Poluboiarov, V.A.; Shvengler, F.A.; Ivanov, A.V. Formation of copper(II) bis(diethyldithiocarbamate) adducts. *Dokl. Akad. Nauk SSSR*, **1984**, *274*, 1420-1422.

[70] Hendrickson, A.R.; Martin, R.L.; Taylor, D. Synthesis and X-ray structure of bis(diethyldithiocarbamato)(μ-dichloro)-dicopper(II), $Cu_2(Et_2dtc)_2Cl_2$, and the X-ray structure of $Cu_3(Et_2dtc)_2Cl_3$, an unusual mixed valence Cu(II)/Cu(I) reduction product. *J. Chem. Soc., Chem. Commun.*, **1975**, 843-844.

[71] Yusuff, K.K.M.; Basheer, K.M.; Gopalan, M. Synthesis of new mixed ligand complexes of copper(II) dithiocarbamates. *Polyhedron*, **1983**, *2*, 839-842.

[72] Hogarth, G.; Pateman, A.; Redmond, S.P. Crystal structures of copper(III) dithiocarbamate complexes $[Cu(\eta^2\text{-}S_2CNMe_2)_2][ClO_4]$and $[Cu(\eta^2\text{-}S_2CNEt_2)_2][FeCl_4]$with and without anion-cation interactions. *Inorg. Chim. Acta*, **2000**, *306*, 232-236.

[73] Beer, P.D.; Berry, N.; Drew, M.G.B.; Fox, O.D.; Padilla-Tosta, M.E.; Patell, S. Self-assembled dithiocarbamate-copper(II) macrocycles for electrochemical anion recognition. *J.Chem. Soc., Chem. Commun.*, **2001**, 199-200.

[74] Fox, O.D.; Drew, M.G.B.; Beer, P.D. Resorcarene-based nanoarchitectures: metal-directed assembly of a molecular loop and tetrahedron. *Angew. Chem., Int. Ed. Engl.*, **2000**, *39*, 136-140.

[75] Yuseff, K.K.M.; Mathew, E.J. Reaction of thionyl chloride with bis(dithiocarbamato)copper(II) complexes. *Synth. React. Inorg. Met.-Org. Chem.*, **1992**, *22*, 575-583.

[76] Ronconi, L.; Marzano, C.; Zanello, P.; Corsini, M.; Miolo, G.; Macca, C.; Trevisan, A.; Fregona, D. Gold(III) dithiocarbamate derivatives for the treatment of cancer: Solution chemistry, DNA binding, and homolytic properties. *J. Med. Chem.*, **2006**, *49*, 1648-1657.

[77] Milacic, V.; Dou, Q.P. The tumor proteasome as a novel target for gold(III) complexes: Implications for breast cancer therapy. *Coord. Chem. Rev.*, **2009**, *253*, 1649-1660.

[78] Victoriano, L.I.; Cortés, H.B. Cuprous dithiocarbamates. Syntheses and reactivity. *J. Coord. Chem.*, **1996**, *39*, 231-239.

[79] Misra, H.P. Reaction of copper-zinc superoxide dismutase with diethyldithiocarbamate. *J. Biol. Chem.*, **1979**, *254*, 11623-11628.

[80] Warshawsky, A.; Rogachev, I.; Patil, Y.; Baszkin, A.; Weiner, L.; Gressel, J. Copper specific chelators as synergists to herbicides: 1. Amphiphilic dithiocarbamates, synthesis, transport through lipid bilayers, and inhibition of Cu/Zn superoxide dismutase activity. *Langmuir*, **2001**, *17*, 5621-5635.

[81] Matsumoto, K.; Fujibayashi, Y.; Konishi, J.; Yokoyama, A. Radiolabeling and biodistribution of ^{62}Cu-dithiocarbamate--an application for the new ^{62}Zn/^{62}Cu generator. *Radioisotopes*, **1990**, *39*, 482-486.

[82] Calabro, D.C.; Harrison, B.A.; Palmer, G.T.; Moguel, M.K.; Rebbert, R.L.; Burmeister, J.L. Thiocyanation, selenocyanation, and halogenation reactions of dithiocarbamate complexes of gold(I) and silver(I). Generation of gold(II) and silver(II) complexes. *Inorg. Chem.*, **1981**, *20*, 4311-4316.

[83] Contel, M.; Edwards, A.J.; Garrido, J.; Hursthouse, M.B.; Laguna, M.; Terroba, R. Mesityl gold(III) complexes. X-ray structure of mononuclear $[Au(mes)_2Cl(PPh_3)]$ and the dimer $[Au(mes)_2Cl]_2$. *J. Organomet. Chem.*, **2000**, *607*, 129-136.

[84] Abram, U. $[Au(Et_2dtc)_2][TcNCl_4]$. Synthesis and structure. *Z. Anorg. Allg. Chem.*, **2000**, *626*, 619-620.

[85] Forghieri, F.; Preti, C.; Tassi, L.; Tosi, G. Preparation, properties and reactivity of gold complexes with some heterocyclic dithiocarbamates as ligands. *Polyhedron*, **1988**, *7*, 1231-1237.

[86] Ahmed, M.; Magee, R.J. The reduction of gold(III) dithiocarbamates at the mercury electrode. *Aust. J. Chem.*, **1981**, *34*, 1861-1868.

[87] Akerström, S. N,N-Dialkyldithiocarbamates of the univalent coinage metals. *Ark. Kemi*, **1959**, *14*, 387-401.

[88] Bishop, P.; Marsh, P.; Brisdon, A.K.; Brisdon, B.J.; Mahon, M.F. X-ray crystallographic and extended X-ray absorption fine structure studies of gold(I) complexes containing weak intermolecular interactions. *J. Chem. Soc., Dalton Trans.*, **1998**, 675-682.

[89] Jian, F.; Lu, L.; Wang, X.; Sundara Raj, S.S.; Razak, I.A.; Fun, H.-K. (N,N-Diisopropyldithiocarbamato-S,S')bis(triphenylphosphine-P)gold(I) butane solvate. *Acta Crystallogr., Sect. C*, **2000**, *56*, 939-940.

[90] Ho, S.Y.; Tiekink, E.R.T. (N,N-Diethyldithiocarbamato)[tris(p-methoxyphenyl)phosphine]gold(I). *Acta Crystallogr., Sect. E*, **2002**, *58*, m86-m87.

[91] Bardají, M.; Gimeno, M.C.; Jiménez, J.; Jones, P.G.; Laguna, A.; Laguna, M. Dinuclear Gold(II) Complexes Containing Two Different Bridging Ligands. Crystal Structure of $[Au_2\{\mu\text{-}(CH_2)_2PPh_2\}\{\mu\text{-}S_2CN(CH_2Ph)_2\}Br_2]$. *Organometallics*, **1994**, *13*, 3415-3419.

[92] Knight, E. R.; Leung, N.H.; Lin, Y.H.; Cowley, A.R.; Watkin, D.J.; Thompson, A.L.; Hogarth, G.; Wilton-Ely, J.D.E.T. Multimetallic arrays: symmetrical bi-, tri- and tetrametallic complexes based on the group 10 metals and the functionalization of gold nanoparticles with nickel-phosphine surface units. *Dalton Trans.*, **2009**, 3688-3697.

[93] Knight, E.R.; Leung, N.H.; Thompson, A.L.; Hogarth, G.; Wilton-Ely, James D.E.T. Multimetallic Arrays: Bi-, tri-, tetra-, and hexametallic complexes based on gold(I) and gold(III) and the surface functionalization of gold nanoparticles with transition metals. *Inorg. Chem*., **2009**, *48*, 3866-3874

[94] Knight, E.R.; Cowley, A.R.; Hogarth, G.; Wilton-Ely, J.D.E.T. Bifunctional dithiocarbamates: a bridge between coordination chemistry and nanoscale materials. *Dalton Trans.*, **2009**, 607-609.

[95] Vickers, M.S.; Cookson, J.; Beer, P.D.; Bishop, P.T.; Thiebaut, B. Dithiocarbamate ligand stabilized gold nanoparticles. *J. Mater. Chem*., **2006**, *16*, 209-215.

[96] Cao, R.; Villalonga, R.; Diaz-Garcia, A.M.; Cao, R.; Rojo, T.; Rodriguez-Arguelles, M. C. Gold nanoparticles enhancing dismutation of superoxide radical by its bis(dithiocarbamato)copper(II) shell. *Inorg. Chem*., **2011**, *50*, 4705-4712

[97] Zhao, Y.; Perez-Segarra, W.; Shi, Q.; Wei, A. dithiocarbamate assembly on gold. *J. Am. Chem. Soc.*, **2005**, *127*, 7328-7329.

[98] Chant, R.; Hendrickson, A. R.; Martin, R. L.; Rohde, N. M. Tris(dithiocarbamato) complexes of iron(II), iron(III), and iron(IV). Electrochemical study. *Inorg. Chem.*, **1975**, *14*, 1894-902.

[99] Ileperuma, O.A.; Feltham, R.D. Crystal and molecular structure of iron(II) bis(diethyldithiocarbamate). *Inorg. Chem*., **1975**, *14*, 3042-3045

[100] Mordvintcev, P.; Muelsch, A.; Busse, R.; Vanin, A. On-line detection of nitric oxide formation in liquid aqueous phase by electron paramagnetic resonance spectroscopy. *Anal. Biochem*., **1991**, *199*, 142-146.

[101] Butcher, R.J.; Sinn, E. Proof of a linear Fe-N-O linkage, perpendicular to the S_4 plane in $Fe(NO)(S_2CN\{CH(CH_3)_2\}_2)_2$. A new (aerobic) synthesis of the complex and its crystal structure. *Inorg. Chem*., **1980**, *19*, 3622-3626.

[102] Giovagnini, L.; Sitran, S.; Castagliuolo, I.; Brun, P.; Corsini, M.; Zanello, P.; Zoleo, A.; Maniero, A.; Biondi, B.; Fregoni, D. Ru(III)-based compounds with sulphur donor ligands: synthesis, characterization, electrochemical behaviour and anticancer activity. *Dalton Trans.*, **2008**, 6699-6708.

[103] Nagy, E.M.; Nardon, C.; Giovagnini, L.; Marchio, L.; Trevisan, A.; Fregona, D. Promising anticancer mono- and dinuclear ruthenium(III) dithiocarbamate complexes: systematic solution studies. *Dalton Trans.*, **2011**, *40*, 11885-11895.

[104] Hendrickson, A. R.; Hope, J.M.; Martin, R. L. Tris- and pentakis-dialkyldithiocarbamates of ruthenium, $[Ru(S_2CNR_2)_3]^n$ and $[Ru_2(S_2CNR_2)_5]^n$ *(n* = +1, 0, and -1): Chemical and electrochemical interrelations. *J. Chem. Soc., Dalton Trans*., **1976**, 2032-2039.

[105] Wheeler, S.H.; Mattson, B.M.; Miessler, G.L. Electrochemical and chemical properties of dithiocarbamato complexes of ruthenium(II), ruthenium(III), and ruthenium(IV). *Inorg. Chem.*, **1978**, *17*, 340-350.

[106] Deeming, A.J.; Vaish, R. Complete desulfurization of diethyldithiocarbamato ligands to give a pentaruthenium cluster containing diethylaminomethylidyne ligands. *J. Organomet. Chem.*, **1993**, *460*, C8-C10.

[107] Leung, W.H.; Chim, J.L.C.; Hou, H.W.; Hun, T.S.M.; Williams, I.D.; Wong, W.T. Oxidation reactions of dithiocarbamate complexes of ruthenium(II). *Inorg. Chem.*, **1997**, *36*, 4432-4437.

[108] Lu, X.L.; Ng, S.Y.; Vittal, J.J.; Tan, G.K.; Goh, L.Y.; Hor, T.S.A. Structural dynamics and ligand mobility in carboxylate and dithiocarbamate complexes of Ru(II) containing 1,1'-bis(diphenylphosphino)ferrocene (dppf). *J. Organomet. Chem.*, **2003**, *688*, 100-111.

[109] Liu, S.; Chakraborty, S. ^{99m}Tc-centered one-pot synthesis for preparation of ^{99m}Tc radiotracers. *Dalton Trans.*, **2011**, *40*, 6077-6086.

[110] Pasqualini, R.; Duatti, A.; Bellande, E.; Comazzi, V.; Brucato, V.; Hoffschir, D.; Fagret, D.; Comet, M. Bis(dithiocarbamato) nitrido technetium-99m radiopharmaceuticals: a class of neutral myocardial imaging agents. *J. Nuc. Med.*, **1994**, *35*, 334-341.

[111] Zhang, S.; Zhang, W.; Wang, Y.; Jin, Z.; Wang, X.; Zhang, J.; Zhang, Y. Synthesis and biodistribution of a novel ^{99m}TcN complex

of norfloxacin dithiocarbamate as a potential agent for bacterial infection imaging. *Bioconjugate Chem*., **2011**, *22*, 369-375.

[112] Zhang, J.B.; Lin, X.; Ren, J.; Liu, J.; Wang, X.B. Synthesis and biodistribution of a novel ^{99m}Tc nitrido dithiocarbamate complex containing aromatic group for cerebral imaging. *Appl. Rad. Isotopes*, **2009**, *68*, 101-104

[113] Zhang, J.B.; Luo, G.; Wang, X.B. Synthesis and biodistribution of a novel ^{99m}Tc nitrido dithiocarbamate complex containing ether group as a potential myocardial and brain imaging agent. *J. Radio. Nuc. Chem*., **2009**, *279*, 783-785.

[114] Giglio, J.; Fernández, S.; Rey, A.; Cerecetto, H. Synthesis and biological characterisation of novel dithiocarbamate containing 5-nitroimidazole ^{99m}Tc-complexes as potential agents for targeting hypoxia. *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 394-397.

[115] Bolzati, C.; Boschi, A.; Uccelli, L.; Tisato, F.; Refosco, F.; Cagnolini, A.; Duatti, A.; Prakash, S.; Bandoli, G.; Vittadini, A. Chemistry of the strong electrophilic metal fragment $[^{99}Tc(N)(PXP)]^{2+}$ (PXP = diphosphine Ligand). A novel tool for the selective labeling of small molecules. *J. Am. Chem. Soc.*, **2002**, *124*, 11468-11479.

[116] Baldas, J.; Bonnyman, J.; Pojer, P.M.; Williams, G.A.; Mackay, M.F. Preparation and crystal structure of carbonyltris(diethyldithiocarbamato)technetium(III): an unexpected source of coordinated carbon monoxide. *J. Chem. Soc., Dalton Trans*., **1982**, 451-455.

[117] Baldas, J.; Bonnyman, J. Preparation and biological behavior of some neutral ^{99m}Tc-carbonyl dithiocarbamates showing rapid hepatobiliary excretion. *Nuc. Med. Biol.*, **1992**, *19*, 741-746.

[118] Cowley, A.R.; Dilworth, J.R.; Donnelly, P.S.; Ross, S.J. Rhenium diazenide ternary complexes with dithiocarbamate ligands: towards new rhenium radiopharmaceuticals. *Dalton Trans*., **2007**, 73-82.

[119] Ronconi, L.; Fregona, D. The Midas touch in cancer chemotherapy: from platinum- to gold-dithiocarbamato complexes. *Dalton Trans*., **2009**, 10670-10680.

[120] Giovagnini, L.; Ronconi, L.; Aldinucci, D.; Lorenzon, D.; Sitran, S.; Fregona, D. Synthesis, characterisation, and comparative in vitro cytotoxicity studies of platinum(II), palladium(II), and gold(III) methylsarcosinedithiocarbamate complexes. *J. Med. Chem.*, **2005**, *48*, 1588-1595.

[121] Segovia, N.; Crovetto, G.; Lardelli, P.; Espigares, M. *In vitro* toxicity of several dithiocarbamates and structure-activity relationships. *J. Appl. Toxicol.*, **2002**, *22*, 353-357.

[122] Rath, N.C.; Rasaputra, K.S.; Liyanage, R.; Huff , G.R.; Huff, W.E. Dithiocarbamate Toxicity – An Appraisal, in Pesticides in the modern world – Effects of pesticides exposure, Ed. Stoytcheva, M. Intech, ISBN 978-953-307-454-2, **2011**, *17*, 323-340.

Received: December 13, 2011 Revised: January 18, 2012 Accepted: January 25, 2012