Review Article

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The structural chemistry of zinc(II) and nickel(II) dithiocarbamate complexes

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Abstract: Dithiocarbamate complexes are of immense interest due to their diverse structural properties and extensive application in various areas. They possess two sulfur atoms that often act as the binding sites for metal coordination in a monodentate, bidentate, or anisodentate fashion. These different coordination modes enhance the possibility for complex formation and make them useful in different areas especially in biomedical fields. A synergy exists in the metal ions and dithiocarbamate moieties, which tends to exert better properties than the respective individual components of the complex. These improved properties have also been attributed to the presence of the C–S bonds. Zinc and nickel ions have been majorly found to bind to the dithiocarbamate in bidentate modes, and consequently different geometries have resulted from this interaction. The aim of this review is to present some studies on the synthesis, structural chemistry, and the relevance of zinc and nickel dithiocarbamates complexes especially in biological systems.

Keywords: zinc complexes, nickel complexes, dithiocarbamates, coordination geometry, biological application

1 Introduction

Dithiocarbamates have provided a platform for the synthesis of a wide range of compounds with interesting applications in different areas such as medicine, catalysis, and material science (where they are used as precursors for the synthesis of nanomaterials). The ease of altering the functional groups on the dithiocarbamate group affords the opportunity for structural modifications [1,2]. A variety of factors such as nature of ligand, the type of metal ions, and its oxidation state can affect the complexation reaction and also play significant roles in determining the coordination geometry of the resulting complex. In biology, for instance, the ligands control the activity of metals and also influence the array of molecules in the secondary coordination sphere, which determines the biological targets such as DNA protein and enzymes of interest [1,2].

Dithiocarbamate compounds have received increasing attention in the last few decades due to the ease of preparation, ability to stabilize different metals in the periodic table (even at a varying oxidation states), and adopting a wide range of structural geometry upon coordination to a metal [3]. The ligand possesses sulfur atoms, which are capable of adding a pair of electrons to the metal center during the complexation reaction. This feature has led to the existence of a large catalogue of dithiocarbamate complexes [4]. They have the propensity to form complex structures, which may be due to the low bite angle of the –CSS group; hence, ability to interact with almost all metals in the periodic table [3]. Nickel and zinc dithiocarbamates complexes are some of the common complexes that have been studied extensively over the years due to their relatively nontoxic nature and application in areas such as biology, agriculture, and medicine. Thus, in this study we focus on the structural chemistry of Ni and Zn dithiocarbamate complexes and highlight the effect of their chemistry and structural variation on their biological properties.

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1.1 Zinc, nickel, and their ions

Zinc is a naturally occurring trace element with a white-silvery appearance. It is a strong, hard and ductile metal [5], and the 24th most abundant metal that is mostly produced by electrolysis of aqueous zinc sulfate. Zinc(II) ion has a d^{10} electronic configuration and displays different coordination arrangements including four coordinate tetrahedral or square planer, five coordinate trigonal pyramidal, and six coordinate octahedral geometries [6,7]. The most common four coordinate geometry is tetrahedral [8]. In some of the catalytic binding sites, Zn(II) ions are found in penta-coordinated and hexa-coordinated arrangements. Due to its flexibility, Zn(II) ion is capable of coordinating to six water molecules in aqueous solution [9]. It is borderline between a hard-soft ion, which favors the complexation among a wide range of ligands bearing donor atoms such as soft S^-, and hard N^- and O^- donor groups [10]. It has a zero ligand-field stabilization energy in all coordination environments.

Nickel appears as a hard silver-white ferromagnetic metal up to 358°C. It possesses a common face-centered cubic structure [11]. Its malleablility, ductility, strength, and corrosion resistance properties make it a choice metal. Nickel is also a good conductor of electricity and heat. It is mostly known in its +2 oxidation state, although it also exists in oxidation states between –1 to +4. However, these are not so common. Ni(II) ion forms complexes in which the Ni is in coordination numbers of four, five, and six and displays all the main structural geometries such as square planer, square pyramidal, tetrahedral, trigonal bipyramidal, and octahedral [12]. Among these coordination geometries, Ni(II) complexes form the least number of complexes in the five coordinate entity using other stereochemical arrangements [11]. After the formation of 4 or 5 coordination arrangements, the complexes could also attain the maximum coordination number of 6 by reacting with neutral ligands, especially amines which are quite unstable [11].

2 Dithiocarbamate complexes

Dithiocarbamates are organosulfur compounds, described as the half amides of dithiocarbonic acids. They are the analogs of carbamate anions ($R_2NCO_2^-$), with the general formula of $R_2NCS_2^-$, and also display a resonance structure as shown in Figure 1 [13].

They are soft donor ligands with the ability to stabilize low and high valent metal ions [15]. The presence of

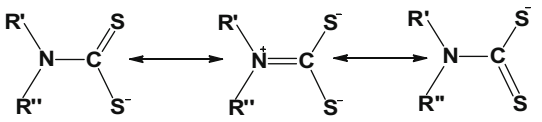

Figure 1: Resonance structure of the dithiocarbamate anion(II) [14].

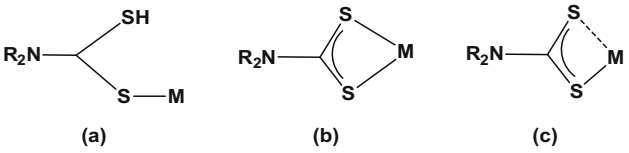

Figure 2: Different coordination modes of dihtiocarbamate complexe (a) monodentate, (b) bidentate and (c) anisobidentate modes [19].

resonance between the two sulfur atoms gives them a strong metal binding property and the ability to form chelates with all transition metal ions [16]. Dithiocarbamates could bond as monodentate (a), bidentate (b), or anisobidentate (c) (chelating or bridging ligands) as presented in Figure 2 and stabilize a wide range of both transition metal and main group elements in different oxidation states [17]. As they possess a small bite angle in the range of 65–80°, the bidentate chelate form is more favored thermodynamically due to the entropic gain [18]. In some cases, although within the expected range for a bond interaction, the two metal-sulfur bonds may possess different bond angles and lengths [19].

Due to their strong metal binding capacity, dithiocarbamates have been used as high-pressure lubricants, accelerators in vulcanization, fungicides, and pesticides [20]. Recently, different types of dithiocarbamate ligands have been synthesized and their metal complexes have generated much research attention [14]. The complexes have interesting structural, magnetic, electrochemical, thermal, and biological properties, which inform their diverse applications [21]. They are mostly insoluble in water, but soluble in nonpolar solvents [22].

Different techniques such as IR, NMR, UV-vis, and mass spectrometry have been employed in the characterization of dithiocarbamate as these techniques offer important information on the structural arrangement in dithiocarbamates [23]. For instance, in the infrared spectra, the characteristic bands for groups such as the thioureide υ(C═N), the υ(C–S), and υ(M–S) are established in the range 1,450–1,550, 950–1,000, and 350–450 cm^{-1}, respectively. A shift in the vibrational frequency usually accompanies either a new coordination or change in geometry. A movement of the thioureide band to a higher frequency by about 15 cm^{-1} is suggestive of electron cloud delocalization

from the thioureide group towards the metal center [24], which then confers a partial double bond character on the C–N [24]. Furthermore, the identity of the bands in the range 1,055 to 961 cm^{-1}, attributed to the C–S group, could determine if the C–S is asymmetric or symmetric. This is significant in the description of the types of coordination that exist between the metal and the ligands [25]. In this region, a strong singlet or a split band (with a splitting distance of 20 cm^{-1}) is indicative of bidentate or monodentate coordination, respectively [25,26]. Another important band in the characterization of metal complexes of dithiocarbamate is the υ(M–S) band, usually found in the far infrared region, which confirms the formation of a metal-sulfur bond in a complex [27].

Similarly, the NMR spectroscopic technique is also valuable in the structural studies [28]. Spectral parameters such as the coupling constant and the chemical shifts (δ) could offer useful information on the geometry of the complexes [29]. The characteristic short $-CS_2$ peak of the thioureide is usually found in the downfield region (185–210 ppm) in the spectra of most dithiocarbamate ligands, and it shifts upfield upon complexation to metal ions [30]. Furthermore, upon the introduction of a Lewis base into a dithiocarbamate complex, thereby increasing the coordination, these peaks could shift upfield or lowfield depending on the nature of the Lewis base. With nitrogenous bases, a lowfield shift is observed due to the additional deshielding in the adduct compared to the parent complexes [31]. The additional coordination to the metal by the nitrogenous bases results in further decrease in the partial double bond character which causes a displacement of the electron density from carbon to nitrogen in the dithiocarbamate group [31,32].

The absorption spectra of dithiocarbamate complexes are characterized by three main bands, derived from the (C═N) bond, the electron pair of sulfur, and the (M–L) bond [33]. In the dithiocarbamate ligand, the absorption band of (C═N) chromophore associated with the intramolecular π–π^* transition has been found around 300 nm. However, changes in this position, either to a lower or shorter wavelength upon complexation, signify the contribution of NCS bond [33]. The peaks found in the region between 240–261 nm are attributed to the existence of n–π^* transition in the nonbonding electron pair of the S atom, while the often broad shoulder peak found above the 300 nm is indicative of the charge transfer transition from metal to ligand [33]. The absorption spectra suggest the existence of a conjugated system emerging from the electronic transition between p-orbitals and d orbitals of transition metals [33,34].

Single crystal X-ray is another important characterization technique and employs scattered (diffracted) X-ray to create a three-dimensional (3D) structure of the molecules [35]. This analytical technique is the most reliable method of characterization of any known molecule, as it gives useful information such as bond angles and bond length and can clearly show the geometry of the understudy molecules [35,36]. Hence, in this review, a lot of attention will be on the structural description based on data obtained from single crystal X-ray analysis of dithiocarbamate compounds.

2.1 Zinc(II) dithiocarbamate complexes

Different approaches have been established for the synthesis of zinc dithiocarbamates. They proceed via the reaction of secondary or primary amines with carbon disulphide in the presence of a strong base such as sodium, potassium, or ammonium hydroxide (equations (1) and (2)) [19]. The prepared dithiocarbamate salt is then reacted with zinc salts to produce zinc dithiocarbamates as shown in the reaction scheme of equation (2) [37]. The synthesis of dithiocarbamate is often achieved under a very reduced temperature [38].

$$RNH_2 + CS_2 + XOH \rightarrow RNHCS_2^-X^+ + H_2O, \quad (1)$$

$$R_2NH + CS_2 + XOH \rightarrow R_2NCS_2^-X^+ + H_2O, \quad (2)$$

$$R_2NCS_2X + ZnCl_2 \rightarrow R_2NCS_2Zn + XCl_2, \quad (3)$$

where X = Na, K or NH_4.

The geometry of Zn(II) dithiocarbamate complexes has been established by X-ray crystallography, FTIR, NMR, and mass spectrometry. Most Zn(II) dithiocarbamates, irrespective of the type of dithiocarbamate ligands used, possess tetrahedral geometry and are sometimes dimeric in the solid state [15]. The complexes could react with nitrogen-donor ligands, resulting in the formulation of adducts with the general formula $[Zn(S_2CNR_2)(N\text{-donor})x]$ (x = 1 or 2) [30]; either octahedral or square pyramidal geometries around the zinc atom are obtained [39]. This has resulted in various reports on the synthesis and geometry of Zn(II)dithiocarbamate complexes and their N-based adducts. Gomathi et al. prepared a zinc complex derived from bis(*N*-benzyl-*N*-(4-methoxybenzyl)-dithiocarbamato-*S*,*S*) [40]. The obtained crystallographic data from the complex showed that it existed as a monomer unit, in which all the four sulfur atoms coordinated to the zinc atom to form a distorted tetrahedral complex as shown in Figure 3 [40].

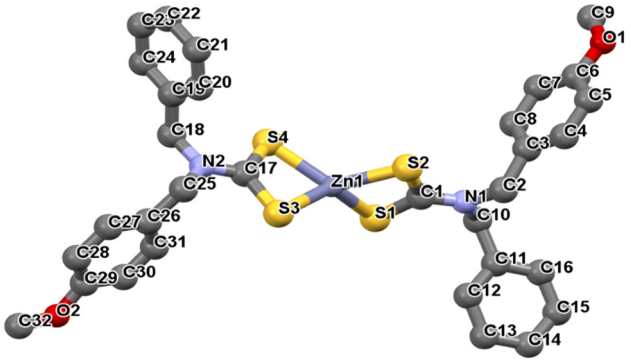

Figure 3: Molecular structure of bis(*N*-benzyl-*N*-(4-methoxybenzyl) dithiocarbamato-*S,S*) zinc(II). Redrawn from ref. [40] with permission from "Taylor and Francis" (Copyright 2020).

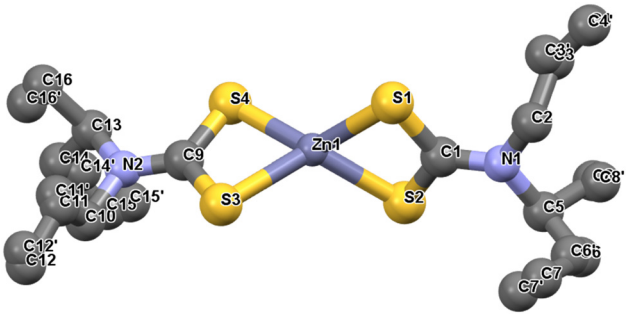

Figure 4: Molecular structure of bis(*N*-isobutyl-*N*-propyl-dithiocarbamato-κ^2 *S,S'*) zinc(II). Redrawn from ref. [41], with permission of the "International Union of Crystallography" (Copyright 2020).

Similar studies [41] also confirmed this geometry, in which the crystallographic structure of bis(*N*-isobutyl-*N*-propyl-dithiocarbamato-κ^2 *S,S'*)zinc(II) complexes showed that two *S,S'*-bidentate ions from the dithiocarbamate ligand formed a chelate with the Zn(II) ion in a tetrahedral geometry. The alkyl chains of the ligands were also disordered (Figure 4) over two sets of sites [41].

The structure of Zn(II) bis(*N*-alkyl-*N*-phenyldithiocarbamate) showed a different geometry, with a bridging bond between Zn and an adjacent S atom to form a bridged dimeric complex as presented in Figure 5 [42]. In this case, a centrosymmetric dimeric structure around the central Zn atom was observed. The dithiocarbamates were found to be chelated in a bidentate fashion to the metal center and nonsymmetrically coordinated to the other dithiocarbamate anion.

Ferreira et al. [43] reported a similar structure with a slight modification. The dithiocarbamate ligands coordinated to the Zn ion in a bidentate fashion, another one formed a monodentate bond with one of its sulfur atoms, while the

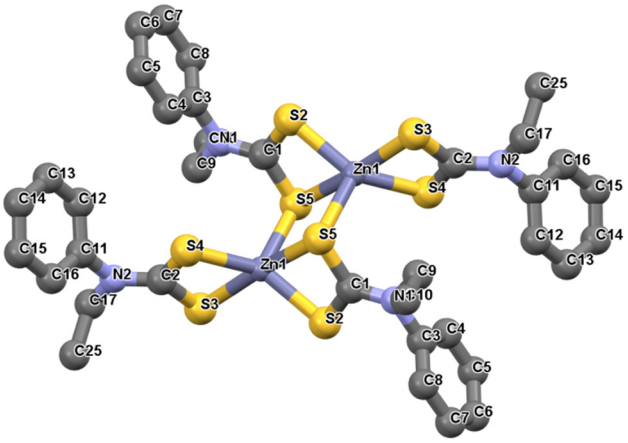

Figure 5: Molecular structure of the [Zn(II) bis(*N*-ethyl-*N*-phenyl dithiocarbamate] complex. Redrawn from ref. [42], with permission from "Taylor and Francis" (Copyright 2020).

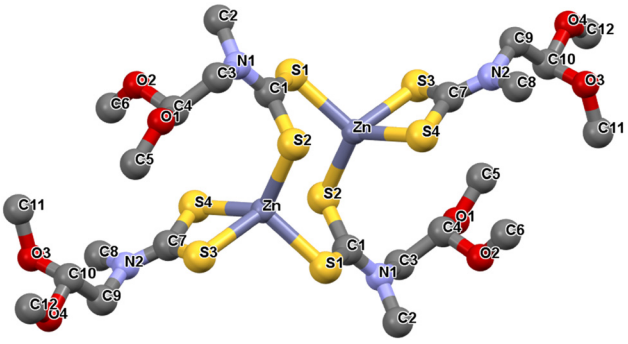

Figure 6: Molecular structure of the centrosymmetric dimer of [Zn $(S_2CNMeCH_2CH(OMe)_2)_2$. Redrawn from ref. [43], with permission from Elsevier (Copyright 2020).

third was involved in a bridging bond to form a bridged dimeric complex. This dimeric bridging coordination also resulted in the formation of an eight-membered ring, with a chair conformation, between [Zn^{i}S1S2C and ZnS1^{i}S2^{i}C] as shown in Figure 6 [43].

When one or two Lewis bases are reacted with zinc dithiocarbamate complex, there is a possibility for the formation of an adduct of higher coordination number. The adduct of zinc(II) bis(*N*-ethyl-*N*-phenyl dithiocarbamate) with pyridine [ZnL_2(py)] has been reported. The crystal structure showed that this compound formed a five coordinate geometry about the central Zn ion, with four sulfur atoms bonded from two units of the dithiocarbamate ligand and one nitrogen from pyridine to create a distorted square pyramidal geometry [44]. This distorted square pyramidal geometry contained one monodentate pyridine ligand and two bidentate dithiocarbamate ligands,

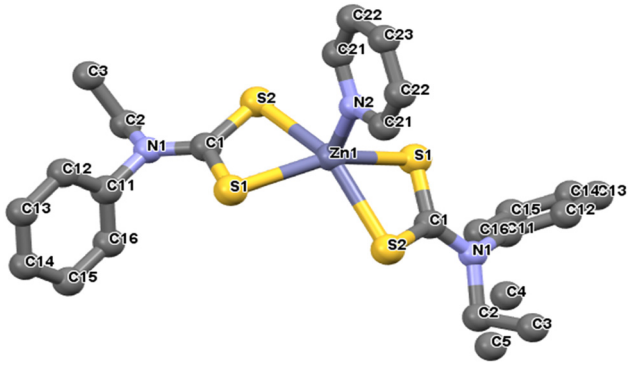

Figure 7: Molecular structure of [ZnL_2(py)]. Redrawn from ref. [44], with permission from Royal society of Chemistry (Copyright 2020).

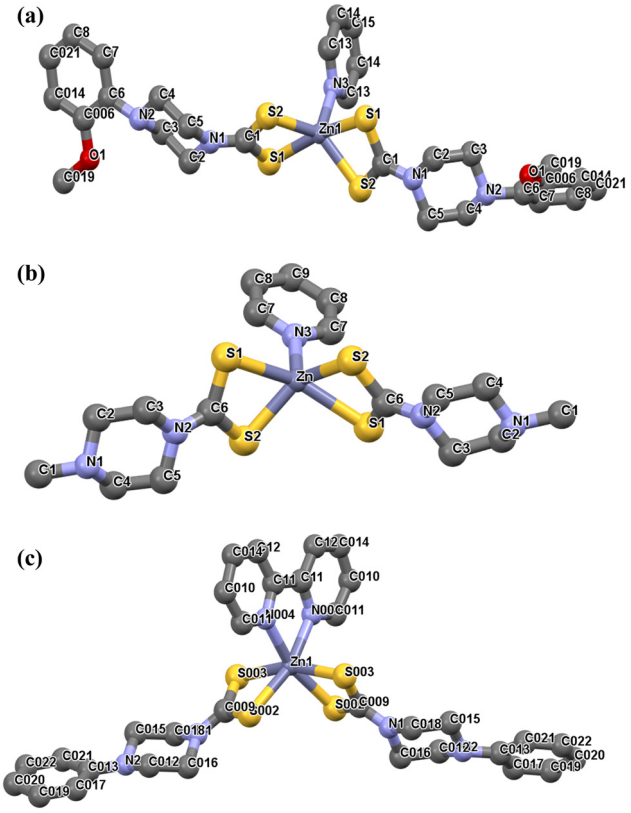

Figure 8: Molecular structure of (a) [Zn(2-mppdtc)$_2$(py), (b) Zn (mpdtc)$_2$(py), and (c) [Zn(ppdtc)$_2$(bipy)]. Redrawn from ref. [39], with permission from Elsevier (Copyright 2020).

which were symmetrically arranged as two-fold rotational axis as shown in Figure 7. The bond length of Zn–S was longer than that of Zn–N bond length, while the bond angles of the two dithiocarbamate ligands and the phenyl group were in acute angles with 47.16(6)°, 72.07(7) Å, and 73.11(16)°, respectively [44].

Three heteroleptic zinc(II) complexes of phenylpiperazine dithiocarbamate [Zn(ppdtc)$_2$(bipy)], 2-methoxyphenylpiperazine dithiocarbamate [Zn(2-mppdtc)$_2$(py)], and methylpiperazine dithiocarbamate [Zn(mpdtc)$_2$(py)] have been reported by Bharti et al. [39]. [Zn(mpdtc)$_2$(py)] and [Zn(2-mppdtc)$_2$(py)] exhibited a distorted square pyramidal geometry as shown in Figure 8a and b via the bonding of the nitrogen atom from the pyridine molecule to the Zn ion and the four sulfur atoms from the dithiocarbamato ligands [39]. On the other hand, [Zn(ppdtc)$_2$(bipy)] was found to be in an octahedral environment as presented in Figure 8c. This geometry was also attained by the coordination of two nitrogen atoms of the bipyridyl moiety and four sulfur atoms present in the dithiocarbamato ligands. The structures of [Zn(2-mppdtc)$_2$(py)] and [Zn(mpdtc)$_2$(py)] (Figure 8a and b respectively) have some differences in the bond length of the pair of Zn–S and C–S bonds. The shorter bonds of the Zn–S were associated with the longer C–S bonds, while the longer Zn–S bonds were associated with shorter C–S bonds. These were attributed to the combined effects of the steric constraints induced by the dithiocarbamato ligands, electron pair repulsion, and the presence of pyridine. Two groups of Zn–S distances were also noted in the [Zn(ppdtc)$_2$(bipy)] complex as shown in Figure 8c. Some Zn–S bonds were relatively shorter than others due to the steric influence of the bipyridyl ligand. Furthermore, the bond length of C–S bond was also shorter compared to a typical bond length of C–S bond. Thus, as established in most dithiocarbamate complexes, all the carbon–sulfur bonds in the current structure possess a partial double bond character [45].

Other alkyl derivatives of five and six coordinate zinc dithiocarbamate complexes involving 2,2-bipyridine and Zn(II) *N*-alkyl-*N*-phenyl dithiocarbamates have been reported by Onwudiwe et al. [15]. The reported alkyl derivatives were methyl, ethyl, and butyl, and the resulting adducts were represented as [Zn(mpdtc)$_2$bpy], [Zn(epdtc)$_2$bpy], and [Zn(bpdtc)$_2$bpy], respectively. The structures of [Zn(mpdtc)$_2$bpy] and [Zn(epdtc)$_2$bpy] showed unusual fashion. The [Zn(mpdtc)$_2$bpy] possessed a five coordinate trigonal bipyramidal geometry as shown in Figure 9a, with one methyl dithiocarbamate bonded to the zinc atom in a monodentate fashion, while another dithiocarbamate ligand and the bipyridine molecule were in a bidentate (*S,S*) coordination via two sulfur and two nitrogens. Both bidentate-coordinated ligands have acute angles, which is the reason for the trigonal bipyramidal structure. All the bond angles between N–Zn–S were different from the expected ones, except N(1)–Zn(1)–S(3) [90.05(4)°]

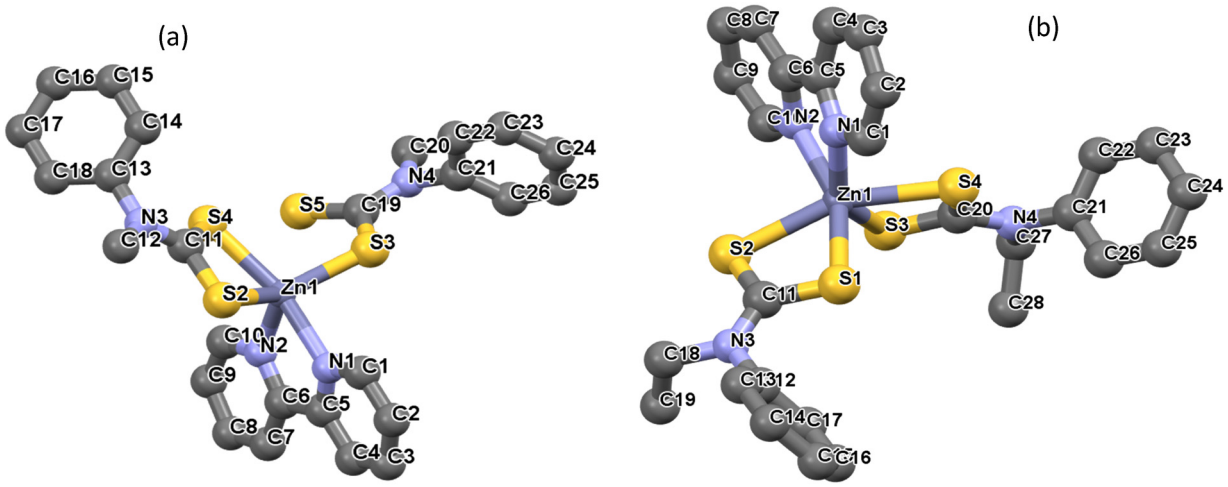

Figure 9: Molecular structure of (a) [Zn(mpdtc)$_2$bpy] and (b) [Zn(epdtc)$_2$bpy]. Redrawn from ref. [15], with permission from Elsevier (Copyright 2020).

and N(1)–Zn–S(2) [87.71(4)°], which were very close to the ideal value of 90°, and the angle of S(3)–Zn–S(2) [129.62(2)°] was greater than 120°. This could be ascribed to the presence of the bipyridine and the steric requirement of the dithiocarbamate moiety. The Zn–S bond lengths in [Zn(mpdtc)$_2$bpy], S(3)–Zn(1) [2.3444(6)°], and S(4)–Zn(1) [2.4228(6)°] were close to those found in other penta-coordinated complexes with similar ligands [39], while the Zn–N showed similar bond lengths in both complexes. The structure of [Zn(epdtc)$_2$bpy] was obtained in a ZnS_4N_2 format and the two nitrogen atoms from the bipyridine molecule along with the four sulfur atoms from the dithiocarbamate ligands generated an octahedral geometry (Figure 9b) [15]. The C–S bond length was shorter in comparison to a typical C–S single bond. This then suggests that the C–S bonds in the complex possess a partial double bond character, which is common in most dithiocarbamate compounds.

2.2 Nickel(II) dithiocarbamate complexes

The synthesis of nickel dithiocarbamate complexes usually involves a similar procedure typical of most metal dithiocarbamate complexes [24], whereby the ligands (in aqueous or ethanol solution) react in stoichiometric ratio with the metal salt to form a precipitate of the metal complex. Onwudiwe et al. reported the addition of the aqueous solution of nickel salt into a cold solution of freshly prepared *N*-butyl-*N*-phenyldithiocarbamate ligand. The green precipitate, obtained after stirring for a few minutes, was then washed thoroughly and recrystallized using a mixture of solvents to give dark green crystals [46]. Some recent studies [47] have reported a slight modification in the synthetic procedure such as *in situ* synthesis, which involved a one–pot preparation of the metal complex without necessarily isolating the ligands.

Studies on Ni(II) dithiocarbamate complexes have shown that they exist as square-planar geometry and exhibit diamagnetic property [48]. Masnovi et al. [47] reported some homoleptic mixed-organic bis-dithiocarbamates of [Ni(S_2CN(ethyl)(*n*-butyl)]$_2$ and [Ni(S_2CN(phenyl)-(benzyl))]$_2$ [47]. The structural studies showed that both complexes appeared to give a slightly distorted square-planar coordination environment, as shown in Figure 10a and b, with the nickel ion at the center, coordinated to two dithiocarbamate ligands on opposite sides of the metal. The Ni–S bond lengths were between 2.2020–2.2084 Å [47]. A heteroleptic mixed ligand complex of [NiP(C_6H_5)$_3$(S_2CN(C_6H_5)($CH_2C_6H_5$))Cl] was also reported (Figure 11), with a somewhat longer Ni–S bond length. Furthermore, in the mixed ligand complex, the Ni–S(1) trans bonding of chloride (electron-withdrawing) was shorter than the Ni–S(2) trans bonding of phosphine by 0.0464(8) Å. This was because phosphine-based ligands are stronger trans-influencing ligands than chloride as reported also in other similar square-planar metal-based complexes [49]. The chelated S–Ni–S bond angle for the homoleptic compounds was between 79.28(2)° and 79.55(2)°, while the heteroleptic compound has a smaller bite angle of 78.31(12)°. The S–C–S bond angle was approximately

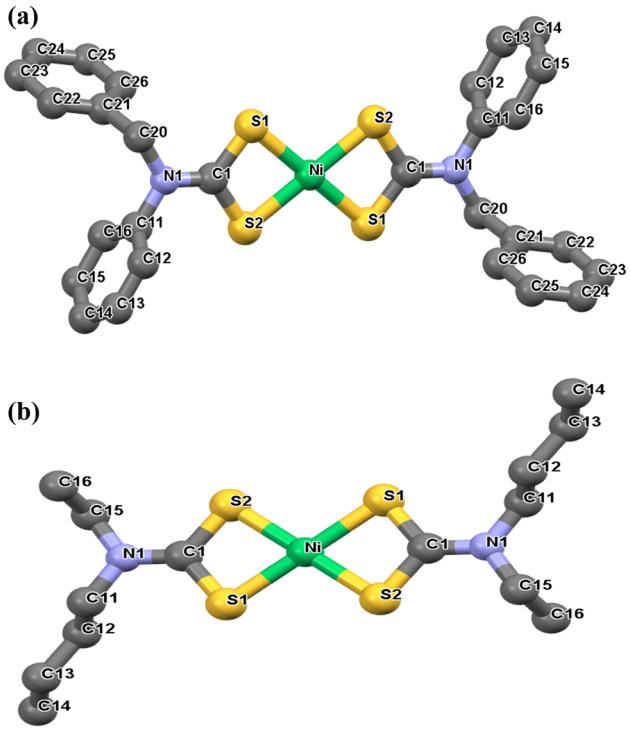

Figure 10: Molecular structure of (a) Ni(S_2CN(phenyl)(benzyl))$_2$ and (b) Ni(S_2CN(ethyl)(*n*-butyl))$_2$. Redrawn from ref. [47], with permission from Elsevier (Copyright 2020).

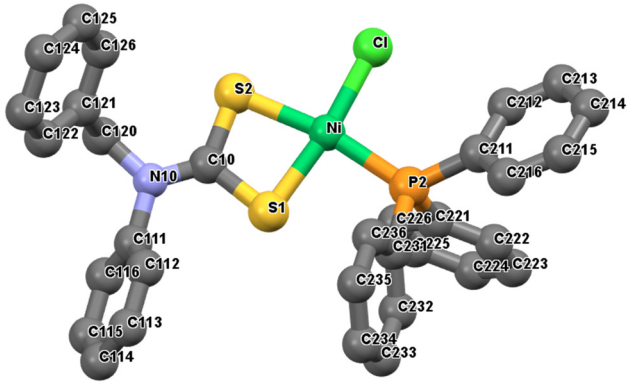

Figure 11: Molecular structure of [Ni(P(phenyl)$_3$(S_2CN(phenyl)(benzyl)Cl]. Redrawn from ref. [47], with permission from Elsevier (Copyright 2020).

110.04° for all homoleptic asymmetric complexes which were comparable to those of similar reported homoleptic compounds [48].

Amine-based Ni(II) dithiocarbamate complex of 3-((pyridine-2-yl)methylamino)propanenitrile has been prepared and characterized by Halimehjani et al. [50]. The obtained single crystal structure showed that the Ni(II) complex contained four coordinate distorted square-planar configurations through four sulfur atoms from two chelating

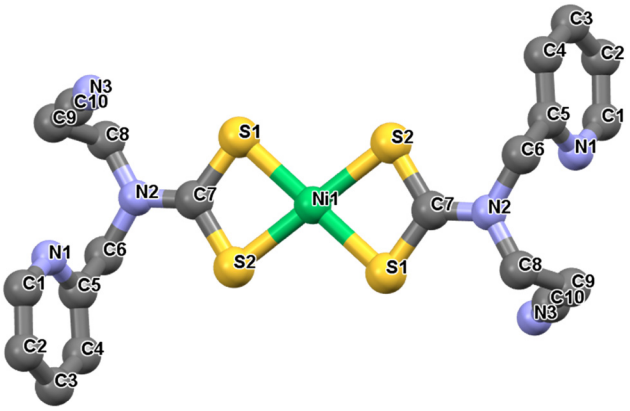

Figure 12: Molecular structure of Ni(S_2CN(3-((pyridin-2-yl)methylamino)propanenitrile). Redrawn from ref. [50], with permission from Elsevier (Copyright 2020).

((2-cyanoethyl)((pyridine-2-yl)methyl)-yl)(methyl)carbamodithionate ligands as shown in Figure 12 [50].

Anastasiadis et al. [51] prepared a series of nickel and zinc bis(dithiocarbamate) complexes with functionalized backbones such as derivatives of isoindoline, tetrahydroisoindoline, 1,2,3,4-tetrahydroisoquinoline, and several functionalized piperazines [51]. Only the nickel dithiocarbamate was reported to exhibit suitable sized single crystals structure, which was identical to other structurally characterized nickel bis(dithiocarbamate)complexes [52]. The geometry of the structure obtained from Ni(II) dithiocarbamate complex of 1,2,3,4-tetrahydroisoquinoline showed that the Ni atom lies on an inversion center, bonded to two dithiocarbamate moieties in a square-planar geometry (Figure 13) [51].

Other geometries, apart from the square-planar environment, have been reported for Ni(II) dithiocarbamate adducts. Sharma et al. [53] prepared some piperidine and morpholine adducts derived from bis(morpholinedithiocarbamato) Ni(II) complex Ni($C_4H_8ONCS_2$)$_2$. The magnetic susceptibility measurement showed that the 1:1 adducts of Ni(C_4H_8-$ONCS_2$)$_2$$L_2$ (L = morpholine and piperidine) displayed diamagnetic properties with the zero magnetic momentum,

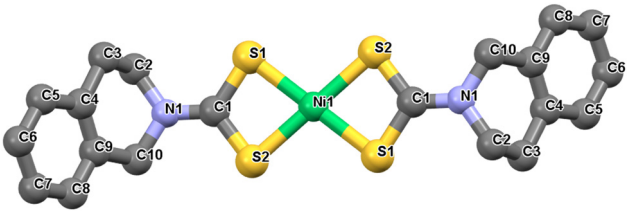

Figure 13: Molecular structure of [Ni(S_2CN($C_3H_6C_6H_4$)$_2$]. Redrawn from ref. [51], with permission from Elsevier (Copyright 2020).

which consequently resulted in a low spin square pyramidal Ni(II) complexes. Furthermore, the 1:2 adducts of $(Ni(C_4H_8ONCS_2)_2)L_2$ were found to be paramagnetic in nature with 3.09 and 3.16 B.M, similar to the values reported for octahedral complexes of Ni(II) [53]. Although there are relatively less reports on the octahedral geometry of nickel dithiocarbamate complex, Pastorek et al. reported three different nickel dithiocarbamate complexes, $[Ni(hmidtc)(bpy)_2]ClO_4$, $[Ni(hmidtc)(phen)_2]ClO_4$, and [Ni (hmidtc)$(phen)_2$]SCN, derived from hexamethyleneimine-dithiocarbamate (hmidtc), 2,2′-bipyridine (bpy), and 1,10-phenanthroline (phen) [54]. Out of the three complexes, $[Ni(hmidtc)(bpy)_2]ClO_4$ gave a distorted octahedral arrangement in the vicinity of the metal center. As shown in Figure 14, the structure showed a three bidentate ligand attachment to the Ni center, with one hexamethyleneimine dithiocarbamato anion (hmidtc) attaching through the S-donor atoms, while two bipyridine moieties formed an unusual attachment with the metal center. A NiN_4S_2 donor set and an octahedral geometry about the Ni center were formed. The bond lengths between the Ni(II) center and donor atoms (S1, S2, N2, N3, N4, and N5) were comparable to others deposited in the Cambridge Structural Database (CSD) [55], while the bond angles were almost equal among (hmidtc and bpyA), (hmidtc-bpyB), and (bpyA-bpyB).

Furthermore, other octahedral nickel(II) dithiocarbamate complexes involving bidentate and tetradentate nitrogen-donor ligands (phen = 1,10-phenanthroline, bpy = 2,2′-bipyridine, and cyclam = 1,4,8,11-tetraazacycloteradecane) have been synthesized by Trávníček et al. [55]. Different homoleptic parent nickel(II) dithiocarbamate complexes of $[Ni(BzMetdtc)(phen)_2]ClO_4$, $[Ni(Pe_2dtc)(phen)_2]ClO_4$, $[Ni(Bzppzdtc)(phen)_2]ClO_4{\cdot}CHCl_3$, and

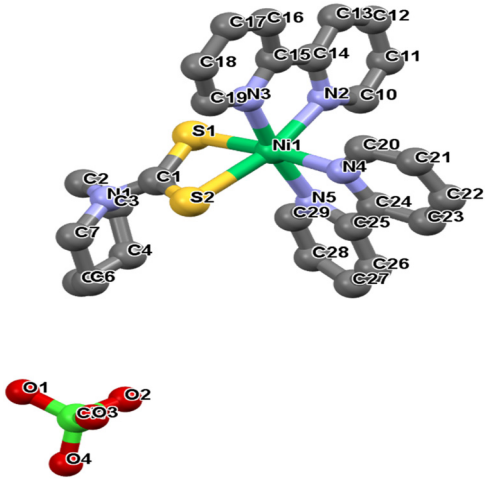

Figure 14: Molecular structure of $[Ni(hmidtc)(bpy)_2]ClO_4$. Redrawn from ref. [54], with permission from Elsevier (Copyright 2020).

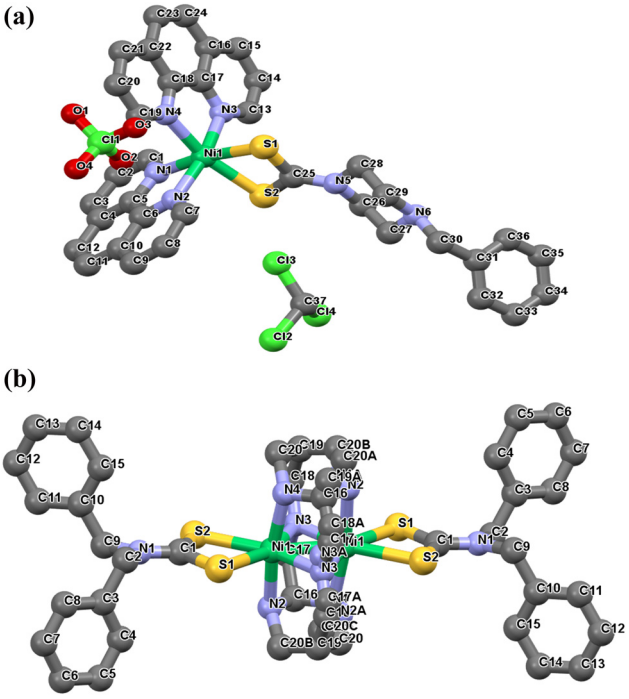

Figure 15: Molecular structure of (a) $[Ni(Bzppzdtc)(phen)_2]ClO_4.CHCl_3$ and (b) $[Ni(Bz_2dtc)_2(cyclam)]$. Redrawn from ref. [55], with permission from Elsevier (Copyright 2020).

$[Ni(Bz_2dtc)_2(cyclam)]$ (where BzMetdtc = *N*,*N*-benzyl-methyldithiocarbamate(1–), Pe_2dtc = *N*,*N*-dipentyldithiocarbamate (1–), Bzppzdtc = 4-benzylpiperazinedithiocarbamate(1–), and Bz_2dtc = *N*,*N*-dibenzyldithiocarbamate(1–) anions) have been reported. The obtained crystallographic data revealed that $[Ni(Bzppzdtc)(phen)_2]ClO_4{\cdot}CHCl_3$ and [Ni $(Bz_2dtc)_2$(cyclam)] gave a distorted octahedral geometry as shown in Figure 15a and b upon the addition of 1,10-phenanthroline [55]. The structure of $[Ni(Bzppzdtc)(phen)_2]ClO_4{\cdot}CHCl_3$ revealed a mixture of $[Ni(Bzppzdtc)(phen)_2]^+$ cation, solvent molecule of $CHCl_3$, and anion of perchlorate $(ClO_4)^-$. The central nickel(II) ion was coordinated by four nitrogen atoms from the 1,10-phenanthroline moiety and two sulfur atoms from 4-benzylpiperazinedithiocarbamate anion, along with the 1,10-phenanthroline, thereby creating an octahedral environment [55].

On the other hand, the structure of $Ni(Bz_2dtc)$(cyclam) consists of a centrosymmetric Ni1/2(Bz_2dtc)(cyclam)1/2 moiety which is connected to its second part by means of inversion center. Thus, the Ni1 atom and some atoms of cyclam adopt non-unit occupancy factors. The crystallographically independent part of the complex molecule connects with the second centrosymmetric part through partially disordered cyclam ligand. Hence, as seen in Figure 15, the structure showed six coordinations about each of the two nickel atoms, which stemmed from

the coordination of four N atoms from the cyclam group and two S atoms from a bidentate coordinated dithiocarbamate ligand [55].

3 Effect of structural variation on the biological potentials of Zn and Ni complexes

Different factors such as coordination geometry, oxidation number of metal, and the type of ligand used in the complexation reaction play significant roles in the properties of metal complexes, which also influence their biological relevance and applications [56]. Generally, the action mode of most metal complexes in biological systems is due to the synergy between the metal ion and ligand moiety. Thus, the chemistry and the biological activity of metal dithiocarbamate complexes are the consequence of both the individual properties of the central metal and dithiocarbamate ligand [36]. The ligand plays a modulating role for the associated metal toxicity, while enhancing its own properties. Furthermore, the possibility for the derivation of a dithiocarbamate compound via the C–N backbone and the presence of the C–S bonds have provided a platform for fascinating chemistry, which in turn brings about an improved biological efficiency [56]. Consequently, this has led to a wide range of useful biological properties due to the construction of diverse biologically useful organic intermediates from the wide array of new compounds.

Metal complexes, including those of dithiocarbamate, have been reported to enhance the retention time for the organic ligands and also reduce the bioavailability of metals for undesired side reactions that could harm the host organism [57]. These organic ligands play a major role in determining the nature of the secondary coordination sphere (involved in determining useful biological sites [36]) due to the weak metal ligand interaction. These weak interactions give rise to a possibility for ligand substitution and redox reactions, which enhance the possibility of organic ligands getting to targeted sites [1,58].

Other reasons proposed for the useful biological properties of metal complexes involve the formation of chelating rings. Studies have shown that the delocalization of electron density over the chelating ring favors the permeability of the complexes through the cell membrane or cellular membranes of most organisms [12,48]. In the formation of chelating complexes, metal ions bind to two or more donor group atoms from the same ligand. The chelate prefers metal ions to form a ring complex as opposed to non-chelates, in which two ligands form bonds with similar strength [59]. Hence, chelates formed from donor groups bearing sulfur, oxygen, and nitrogen atoms have generated research interest due to their usefulness in physiochemical processes and their impact on biological systems, especially as models for metalloenzymes dynamic sites [59].

According to Tweedy's chelation theory, chelation about the metal center tends to reduce the polarity associated with the central metal atom due to the partial sharing of their positive charge with donor group atoms, which in turn causes the delocalization around the ring chelate [60]; thus, allowing for easier permeation due to the now increased lipophilic character of the chelate via the cellular membrane. Although most of the dithiocarbamate complexes have generally shown great antimicrobial properties, they vary in their biological potential due to their permeability through the cell membrane [59]. For instance, Mamba et al. [61] reported that the parent dithiocarbamate complexes of Zn and Ni showed better antimicrobial properties than their phosphine adduct derivatives when screened against *E. coli, S. aureus, S. typhi, E. faecalis, P. aeruginosa* and *B. cereus, A. flavus, A. carbonarius, A. niger*, and *A. fumigatus* [61]. These parent complexes showed a wide variety of antimicrobial properties compared to their adduct derivatives. Similarly, our recent studies involving *N*-substituted dithiocarbamate nickel(II) complex revealed that the parent complex exhibited better antimicrobial properties than its derivatives bearing the PPh_3, CN, and SCN donor groups [46]. This trend in which the parent complexes show broader and better activity than their adduct derivatives have been corroborated by other related reports in literature [61–63]. Based on these studies, therefore, the four coordinate structures (tetrahedral/square-planar) of these complexes generally represent the least optimally strained structure among the various derivatives of Ni and Zn dithiocarbamate complexes, which may be due to the structural role played by the four coordinate geometries [64]. The stronger biological activities observed for the four coordinate complexes have been attributed to their ability to form a stable square-planar dithiocarbamate complex with S-donor compounds such as methionine and cysteine. This stems from the stability of the trans-arrangement between the S-donor compounds and the dithiocarbamate backbone of –NCSS [65,66]. With the use of the same type of ligand derivatives, in most cases Zn has shown better biological potential than its Ni counterpart [62].

Furthermore, different homoleptic Zn and Ni dithiocarbamate complexes have also shown similar patterns in

their cytotoxicity properties against different cell lines similar to their antimicrobial activities. The improved activity of the homoleptic complexes compared to the adducts (with heteroleptic system) has been attributed to the four coordinate geometries of the complexes. Rani and Thirumaran [60] reported that four coordinated Zn dithiocarbamate complexes possessed better biological activity against the HeLa cell line than the adducts composed of nitrogen-donor Lewis bases [60]. This agrees with different studies that reported the higher efficiency of four coordinate geometries compared to the six coordinated compounds [60,67].

The exact targeted protein or enzymes by dithiocarbamate compounds have remained evasive till date and continued to remain a subject of much research interest. However, different studies have suggested that dithiocarbamate-based compounds proceed via a mechanism involving the inhibition of proteasome, inhibition of RNA and DNA synthesis, and eventual apoptosis of cancerous cells [56]. Thus, in most biological studies, the DNA seems to be the main targeted action site, except for Au(III) dithiocarbamate complexes, where it has been hypothesized that the mechanism of action does not essentially involve the DNA interactions when examined for anticancer activity[68]. This hypothesis was brought about because the cross-resistance phenomenon that usually accompanies cisplatin and other known anticancer drugs was not observed, even though these Au complexes gave better anticancer properties [68–70]. Other mechanisms of action may emerge due to the presence of S^- group with the molecule. This is because compounds bearing sulfur donor group like dithiocarbamate have been found to act as chemo-protectant in chemotherapy due to their potential to modulate nephrotoxicity, even in harsh acidic conditions [71]. This tendency makes them crucial in cancer treatment, especially in those that involve the secretion of acids such as solid tumors [71]. Furthermore, dithiocarbamates have also been found capable of modulating key proteins involved in many biological processes such as oxidative stress, transcription, degradation, and apoptosis, which in turn make them useful against cancerous cells [72].

4 Conclusion

The interesting structural properties and biological efficiency of multifaceted, mono-anionic chelating dithiocarbamate ligands have necessitated the investigation of their numerous pharmacological properties in recent decades. This review concisely described the structural chemistry of Zn(II) and Ni(II) dithiocarmate complexes. The complexes displayed different bonding modes and varieties of structural configurations, suggestive of their flexibility and ability to adopt a range of coordination structures. Both complexes exert some pharmacological activities including antibacterial, antifungal, antioxidant, and anticancer due to the synergistic effect of both the metals and the dithiocarbamate ligands. They may become useful pharmaceuticals in combating many diseases with different bioactive platforms and improved efficiency in future.

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Conflict of interest: Authors declare no conflict of interest.

Ethical approval: The conducted research is not related to either human or animal use.

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