ISSN 1070-3284, Russian Journal of Coordination Chemistry, 2008, Vol. 34, No. 2, pp. 106–114. © Pleiades Publishing, Ltd., 2008.

Spectral, Analytical, Thermal, and Antimicrobial Studies of Novel Sodium 2-[4(2-Hydroxy-3-Izopropylaminopropoxy)Phenyl]Acetamide (Atenolol) Dithiocarbamate and its Divalent Transition Metal Complexes[1]

A. Gölcü and P. Yavuz

Department of Chemistry, Faculty of Science and Arts, Kahramanmaras Sütcu Imam University, Kahramanmaras 46100, Turkey

E-mail: ag518@ksu.edu.tr

Received November 9, 2006

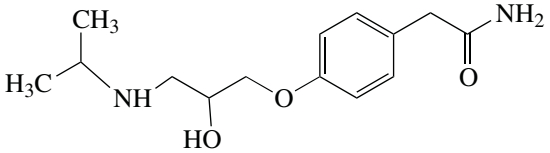
Abstract—Atenolol dithiocarbamate (ADTC) and its complexes with Cu(II), Co(II), Ni(II), Zn(II), and Cd(II) have been synthesized. These newly synthesized products have been characterized by elemental analyses (C, H, N, and S), thermal (thermogravimetry (TG) and differential thermal analyses (DTA)) as well as by spectral (UV, IR, and NMR (^{1}H)) studies. The stability constants (β) of metal complexes of ADTC have been determined by UV-Vis data in solutions in DMSO. The antimicrobial activities of the metal complexes have been screened in vitro against ten bacteria.

DOI: 10.1134/S1070328408020061

INTRODUCTION

Dithiocarbamates are a large family of compounds that have been widely investigated because they are of great interest in different fields. Many studies have been carried out in order to gain information on the complexes formed by dithiocarbamate and metal ions, which are used as fungicides and pesticides [1]. Their range of applications covers several uses in chemical industries, biology, and biochemistry. For example, some of the dialkyl-substituted dithiocarbamate salts have also shown interesting biological effects, which include antialkylation [2, 3] or anti-HIV properties [4, 5]. They are also used as effective antidotes for cadmium intoxication [6, 7]. The ability of dithiocarbamate to bind to metal has been known for many years. It forms a chelate with virtually all transition elements [8]. The bidentate anion is also known to bridge two transition metal centers [9]. Water-soluble dialkyldithiocarbamate complexes have been tested in various medical applications [10]. In our previous study, we reported the spectrophotometric determination of antihypertensive drug propranolol *via* dithiocarbamate metal complexes [11].

Atenolol belongs to the category of β-blockers and, more specifically, it is a hydrophillic β_1-receptor blocking agent. This β_1-andrenoceptor blocking drug is of therapeutic value in the treatment of various cardiovascular disorders, such as angina pectoris, cardiac arrhytmia, and hypertension [12]. Most of the β-andrenoceptor blocking drugs in use are aryloxypropanolamines. Atenolol is an aminoalcohol and induces a chiral center. β-Blockers are exceptionally toxic and most of them have a narrow therapeutic range: the differences between the lowest therapeutic and the highest tolerable doses are small [13]. Many methods have been described for the quantitative determination and analysis of β-blockers including non-aqueous titrimetric [14], colorimetric [15], spectrophotometric [16], fluorimetric [17], and chromatographic [18, 19]. Besides, atenolol have been determined *via* dithiocarbamate metal complexes in pharmaceutical and biological fluids in our laboratory. The chemical structure of atenolol is given below:



In a previous publication, we reported the synthesis and characterization of the Cu(II) and Co(II) complexes of atenolol [20]. The binuclear Cu(II) and mononuclear Co(II) complexes of atenolol have not any biological activity, while metal complexes with atenolol dithiocarbamate (**ADTC**) have high biological activity. In other previous study [21], we synthesized and characterized new propranolol-dithiocarbamate and its metal complexes too. However, we showed that in this study the stability constant values of ADTC metal complexes are

[1] The text was submitted by the authors in English.

Table 1. Some analytical and synthetical data for the dithiocarbamate complexes

Compound	Formula weight	Color	Yield, %	M.p., °C	Contents (found/(calcd)), %				
					C	H	N	S	M
$[C_{30}H_{42}N_4O_6S_4Cu] \cdot H_2O$ (I)	746.5	Brown	55	161	53.4 (53.5)	5.7 (5.9)	7.5 (7.2)	17.2 (17.2)	8.5 (8.2)
$Na[C_{19}H_{27}N_2O_7S_2Co] \cdot 5H_2O$ (II)	631.1	Green	50	291	35.7 (35.6)	5.9 (4.1)	4.6 (5.5)	14.14 (14.15)	9.3 (9.5)
$Na[C_{17}H_{29}N_2O_5S_2Ni] \cdot H_2O$ (III)	505.0	Green	53	175	35.7 (35.6)	6.1 (5.4)	5.5 (6.0)	12.7 (12.1)	11.6 (11.1)
$Na[C_{19}H_{27}N_2O_7S_2Zn] \cdot H_2O$ (IV)	565.4	White	65	291	56.0 (55.9)	5.1 (5.3)	4.9 (4.5)	11.3 (11.5)	11.5 (11.9)
$Na[C_{15}H_{21}N_4O_9S_2Cd] \cdot 2H_2O$ (V)	636.0	Yellow	50	156	28.3 (28.7)	3.3 (3.9)	8.8 (8.5)	10.6 (10.1)	17.6 (18.1)

higher than the propranolol-dithiocarbamate metal complexes.

In the present work, the synhesis and chemical characterization as well as the biological effects of novel transition metal complexes (Cu(II), Co(II), Ni(II), Zn(II), and Cd(II)) containing dithiocarbamate, are reported. Different complexes, such as $[C_{30}H_{42}N_4O_6S_4Cu] \cdot H_2O$ (**I**), $Na[C_{19}H_{27}N_2O_7S_2Co] \cdot 5H_2O$ (**II**), $Na[C_{17}H_{29}N_2O_5S_2Ni] \cdot H_2O$ (**III**), $(Na[C_{19}H_{27}N_2O_7S_2Zn] \cdot H_2O$ (**IV**) and $Na[C_{15}H_{21}N_4O_9S_2Cd] \cdot 2H_2O$ (**V**), are characterized by elemental analyses, thermal and differential thermal analyses as well as by spectral studies.

EXPERIMENTAL

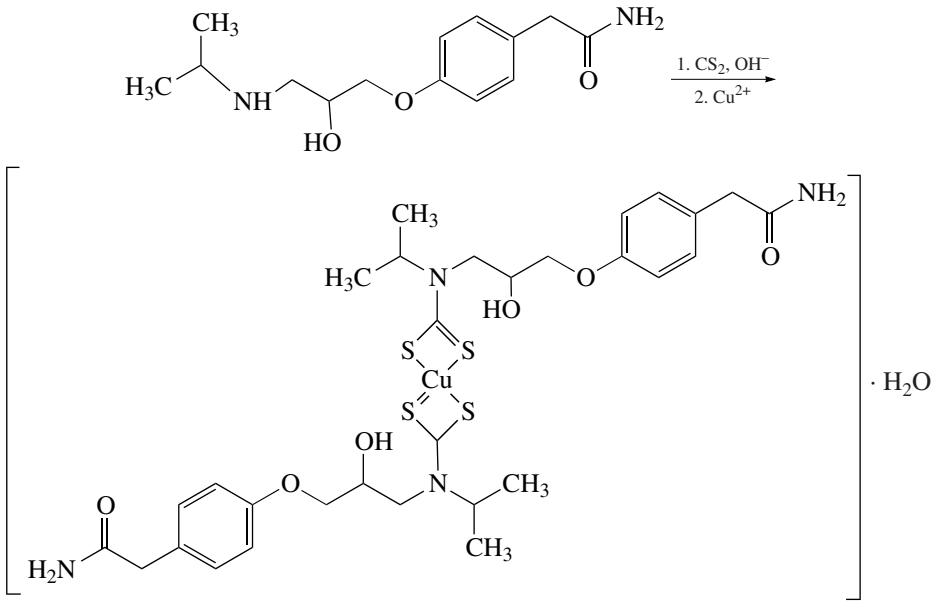
Atenolol was kindly received from Sanofi Dogu Drug Co. (Istanbul, Turkey) and used without further purification. All other chemicals were of analytical reagent grade: $CuCl_2 \cdot 2H_2O$ (Merck), $Co(CH_3COO)_2 \cdot 4H_2O$ (Merck), $NiCl_2 \cdot 6H_2O$ (Merck), $Cd(NO_3)_2 \cdot 4H_2O$ (Merck), and $Zn(CH_3COO)_2 \cdot 2H_2O$ (Merck). Carbon disulfide (CS_2) and NaOH were purchased from Aldrich.

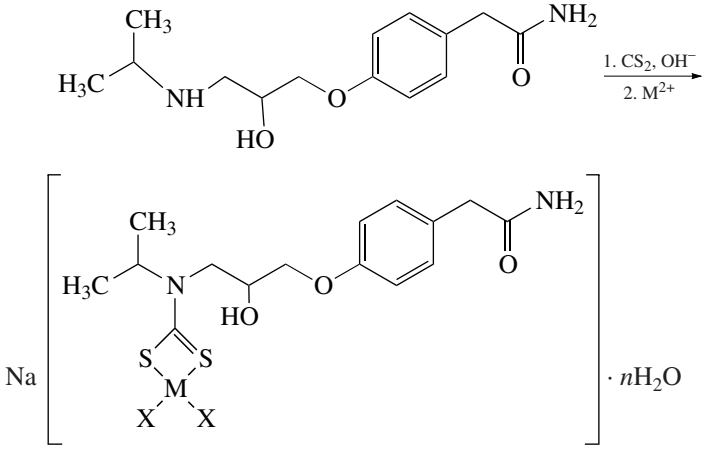
Infrared spectra were recorded on a Shimadzu 8300 FT-IR spectrophotometer using KBr discs in the range 4000–400 cm^{-1}. ^1H NMR spectra were taken on a Bruker Avance DPX–400 NMR instrument. Tetramethylsilan (TMS) was used as a internal standard and deuterated dimethylsulfoxide served as solvent. The thermogravimetric analyses were made by means of a Perkin Elmer Pyris Diamond DTA/TG Thermal System electrobalance converted to a thermobalance by addition of a small furnace and a sample holder. The temperature was measured by using a chromal–alumal thermocouple attached to a suar MF–550 digital multimeter, and the heating rate was adjusted to be 10 K/min. The elemental analysis (C, H, N, and S) was performed at the TUBITAK Instrumental Analysis Laboratory (Besevler/Ankara, Turkey) using a Carlo Erba 1106 elemental analyzer. The ratios of the metal present in all complexes were determined by atomic absorption spectroscopy. The complexes were decomposed in $HNO_3 : H_2O_2$ (1 : 1) and then dissolved in 1.5 N HNO_3. The amounts of Cu, Co, Ni, Zn, and Cd were determined [22, 23]. UV spectra were recorded in DMSO solution at room temperature on a Shimadzu UV–160 A spectrophotometer. The metal contents of the complexes were determined with the aid of an Ati Unicam 929 Model AA spectrometer in solutions prepared by decomposing the compounds in aqua regia and then subsequently digesting them in concentrated HNO_3/H_2O_2 (1 : 1). Molar conductances of all complexes were determined in DMSO (~10^{-3} M) at room temperature using a Jenway Model 4070 conductivity meter. Magnetic measurements were carried out by the Gouy method using $Hg[Co(SCN)_4]$ as a calibrant. Acetate and nitrate ions (in cobalt, zinc, and cadmium dithiocarbamate complexes) were determined gravimetrically as silveracetate and ammonia, respectively [24].

Sodium hydroxide (0.200 g, 0.005 mol) dissolved in 100 ml of H_2O was mixed with a diethyl ether solution (100 ml) containing atenolol (1.331 g, 0.005 mol) and CS_2 (0.38 g, 0.005 mol) was added dropwise to this solution in a water–ice bath at about 0°C. The resulting solution was stirred for 60 min at 0°C and then transferred into a separatory funnel. The aqueous phase was separated and evaporated in a water bath at 95°C. Obtained solid sodium atenolol dithiocarbamate (NaADTC) was washed with diethyl ether for several times and dried in air.

Metal chloride/acetate/nitrate (0.0025 mol) dissolved in distilled H_2O: methanol (1 : 10, v : v) (50 ml) was added with stirring a solution of NaADTC (1.82 g, 0.005 mol) in H_2O/methanol (1 : 10, v : v) (50 ml). The metal complexes precipitated immediately as polycrystalline solids and were filtered by suction, washed with H_2O, and diethyl ether and dried in air. The yield was 0.90–1.20 g (50–65%). The melting points of the complexes are between 156–291°C. The relevant synthetic and analytical data for all the complexes are given in Table 1.

Synthesis of the atenolol dithiocarbamate copper(II) and other metal complexes is shown below:





M : Ni, X = MeO, n = 1
M : Cd, X = NO_3^-, n = 2
M : Zn, X = AcO^-, n = 1
M : Co, X = AcO^-, n = 5

The growth inhibitory activity of the chemical matter was tested against ten bacteria (*Bacillus megaterium* DSM 32, *Bacillus brevis* NRS, *Yersinia enterocolitica* CMC 120, *Micrococcus luteus* LA 2971, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATTC 15753, *Kluyveromyces marxianus* CBS 6556, *Candida tropicalis* DSM 4959, *Candida albicans* ATCC 1023 and *Kluvyeromyces fragilis* A 230). These microorganisms were provided from the Microbiology Laboratory Culture Collection (Department of Biology, Kahramanmaras Sütcü Imam University, Turkey). Antimicrobial activities of the chemical matter were determined using the agar-disc diffusion method as will be described below. The bacteria were first incubated at 37 ± 0.1°C for 24 h in nutrient broth (Difco), and the yeasts were incubated in sabouraud dextrose broth (Difco) at 25 ± 0.1°C for 24 h. The cultures of the bacteria and yeast were injected into the Petri dishes (9 cm) an amount of 0.1 ml. Then, mueller hinton agar and sabouraud dextrose agar (sterilized in a flask and cooled to 45–50°C) were homogenously distributed onto the sterilized Petri dishes in an amount of 15 ml. Subsequently, the sterilized blank paper discs 6 mm in diameter were saturated with 1200 μg of chemical matters per disc. The discs

were placed onto the agar plates, which had previously been inoculated with the above organisms. In addition, blank paper discs treated with ampicillin, streptomycin, and nystatin antibiotics were used as positive controls. Afterwards the plates combined with the discs were left at 4°C for 2 h, the plates injected with yeast were incubated at 25 ± 0.1°C for 24 h, and those injected with bacteria were incubated at 37 ± 0.1°C for 24 h. After 24 h, inhibition zones appearing around the discs were measured and recorded in mm. The initial number of microorganisms in the suspension was determined for the total yeasts and bacterial count during 24 h at 37°C for bacteria and 48 h 25°C for yeasts [21].

Job's method [25, 26] was used to determine (in DMSO) the stoichiometric ratios for the reactions between the NaADTC and metal ions. The solutions were prepared by mixing solutions of both components with equal molar concentrations (1.0×10^{-4} M) in ratios varying from 1 : 0 to 9 : 1. The complexes were prepared by mixing in methanol of adequate stoichiometric amounts of NaADTC and the corresponding salts.

Let us consider a complex M_mL_l (where L is ligand and M is the metal ion) formed according to the equation:

$$mM + lL = M_mL_l, \quad (1)$$

with stability constant

$$\beta_{ml} = [M_mL_l]/([M]^m[L]^l). \quad (2)$$

The principle of the method is as follows: the absorbance (***A***) is measured for a series of solutions containing the ligand and cation, so such that the sum of the total concentration of ligand and cation is constant

$$c_L + c_M = c = \text{constant}. \quad (3)$$

The position of the absorbance maximum (A_{max}) is then related to the ratio *m*/*l* as shown below. It is convenient to use the following dimensionless quantity (which is analogous to the molar fraction but not strictly)

$$X = c_M/c_M + c_L. \quad (4)$$

It has been shown [24, 26] that

$$m/l = X_{max}/1 - X_{max}, \quad (5)$$

where X_{max} corresponds to the A_{max} (absorbance maximum) at an appropriate wavelength (chosen so that the changes in absorbance are as large as possible). For the 1 : 1 complex X_{max} = 1/2 according to Eq. (4). In this case

$$M + L = ML,$$

and stability constant K_s = [ML]/([M][L]) can be found [26] from the equation:

$$(A - A_0)/A_{LIM} - A = K_s[M],$$

Table 2. Molar conductance, electronic spectral data and magnetic moments of all complexes in DMSO

Compound	Λ, Ohm^{-1} cm^2 mol^{-1}	λ_{max}	μ_{eff}, μ_B*
I		613, 450, 296	1.90
II	11.6	590, 381, 275	4.16
III	16.3	634, 441, 360, 274	Diamagnetic
IV	70.1	440, 361, 267	Diamagnetic
V	90.1	364, 275	Diamagnetic

* Magnetic moment data for per metal.

where *A* is the absorbance of the solution at a chosen wavelength after addition of a given amount of the cation at the concentration [M], A_0 is the absorbance of the free ligand at a given wavelength before the addition of the cation, and A_{LIM} is the absorbance at a given wavelength in the presence of such an excess of cation that the ligand is fully complexed.

RESULTS AND DISCUSSION

The analytical data of the dithiocarbamate metal complexes consist of 1 : 1 or 1 : 2 ligand to metal ratio and support the sructures given in schemes. The values equivalent conductances of complexes I–V were found to be in the 11.6–90.1 Ohm^{-1} cm^2 mol^{-1} range. From these data we can say that these complexes have the cationic nature and conduct electricity in solution [22, 23] (Table 2). The mononuclear $[C_{34}H_{40}N_2O_4S_4Cu] \cdot H_2O$ complex was found to be nonelectrolyte in DMSO [22].

The electronic absorption spectral data of the new dithiocarbamate metal complexes are listed in Table 2, and tentative assignments of the important characteristic bonds have been made with the help of an earlier publication [22, 23, 27].

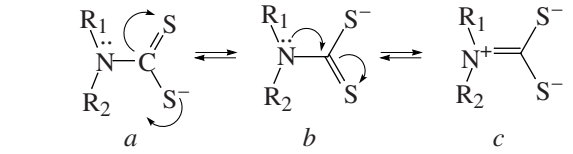
The electronic spectra of these newly synthesized dithiocarbamate metal complexes exhibit some bonds. The most intense bonds (296–274 nm) are assigned to the intramolecular charge transfer of the ligand (π–π* and *n*–π* in the N–C=S group) [28, 29]. The intense bonds at 450, 381, 360, 361, and 363 nm in the spectra of the Cu(II), Co(II), Ni(II), Zn(II), and Cd(II) dithiocarbamate complexes, respectively, are ascribed to charge transfer processes, probably, from ligand to metal, mainly associated with the N–C=S and S–C=S groups. The absorption at higher wave lengths in Cu(II), Co(II), and Ni(II), dithiocarbamate complexes are due to *d*–*d* transitions [30–32].

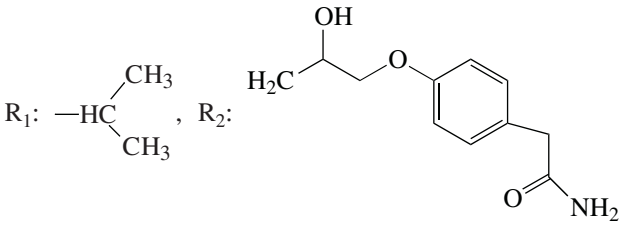
The most significant FT-IR bands assignments are listed in Table 3. These vibrational spectra were analyzed on the basis of general references [33] and by

Table 3. Infrared spectral data of the complexes (cm^{-1})

Compound	ν(OH)	ν(NH_2)	ν(CN)	ν(C–S)	ν(M–S)	ν(M–N)
I	3375.2	1658.7	1510.2	1242.1	575	491
II	3421.5	1659.7	1510.2	1251.7	526.8	453
III	3325.0	1657.7	1510.2	1236.3	518.5	455
IV	3342.4	1624.5	1510.2	1244.0	596	418.5
V	3386.7	1616.5	1510.2	1242.1	520	430

comparison with other related compounds [34]. The free ligand atenolol shows an IR spectrum with two bands (3355 and 3174 cm^{-1}), due to the aliphatic OH and the secondary NH vibrations, respectively, engaged in inter- or intramolecular H-bonds. In the carbamate derivative (ADTC), the nitrogen atom of the secondary NH group interacts with the CS_2 moleculeand hydrogen atom of this group is leaving from the molecule. In the IR spectra of ADTC and its complexes, the bands due to the stretching of the secondary NH-vibrations disappeared. In the spectrum of atenolol, the characteristic band at 1644 cm^{-1} can be due to the amide ν(NH_2) vibrations. In the complexes, this band does not shift to higher or lower regions and this situtation confirms that the nitrogen atom of the amide group did not coordinate to the metal ions or carbamate group. The ν(CN) band in the spectra of the ADTC is observed at around 1250 cm^{-1} [35]. This low value indicates a great contribution of the canonical forms (*a*) and (*b*) for the resonance hybrid form (*c*) in the dithiocarbamate sodium salts. Canonical forms *a*, *b* and hybrid form *c* in ADTC are shown below:





A strong band at 1241.1, 1236.3, 1242.2, 1244.0, and 1261.7 cm^{-1} observed in the spectra of the Cu(II), Ni(II), Cd(II), Zn(II), and Co(II) dithiocarbamate complexes, respectively, is assigned to the *ν*(C=N) vibration of the –R–N=CS_2 group.

The spectral region of 1000–900 cm^{-1} is characteristic for disulfuric chelation. The $\nu_{assym}(CS_2)$ vibration was observed at a higher frequency in the spectra of the sodium salts of dithiocarbamates (ca. 978 cm^{-1}) [36] than that in the spectra of the complexes studied here: 904, 914.1, 900.7, 943.1, and 947 cm^{-1} for Cu(II), Ni(II), Cd(II), Zn(II), and Co(II) dithiocarbamate complexes, respectively [37]. The shifts observed in the $\nu_{as}(CS_2)$ and ν_{as}(CN) in the spectra of the compounds studied here, when compared with the spectra of the ADTC ligand, are consistent with the increased importance of the canonical form (*c*) in all metal complexes. The spectra of the complexes also show the expected medium band in the 500–400 cm^{-1} range assigned to the M–S stretching vibration indicating the gem-disulfur ligand.

The magnetic moment of the complexes (Table 2) were measured at room temperature. On the basis of the magnetic and spectral evidence the copper (II) complex has mononuclear structure in which the Cu^{2+} cation has

Table 4. ^{1}H NMR data (δ, ppm) for the dithiocarbamate complexes

Compound	δ, ppm					
	–CH_3	–NCH	–CH_2	–OCH_3	–NH_2	–OH
$Na[C_{17}H_{29}N_2O_5S_2Ni] \cdot H_2O$ (III)	1–1.6	3.85	2.65	3.6	4–5	5.6
$Na[C_{19}H_{27}N_2O_7S_2Zn] \cdot H_2O$ (IV)	1–1.6	3.78	2.75	3–4	4	5.2
$Na[C_{15}H_{21}N_4O_9S_2Cd] \cdot 2H_2O$ (V)	1–5	3.60	3–4	3–4	3.5–4.5	55.5

an approximately tetrahedral environment [27]. The $Na[C_{19}H_{28}NO_5S_2Co] \cdot H_2O$ complex has an effective magnetic moment per cobalt atom of 4.16 μ_B at room temperature, and this complex is tetrahedral around the Co^{2+} ion [35]. The Ni(II) complex has a diamagnetic character and square-planar geometry around the Ni(II) centre [38]. In addition, the zinc (II) and cadmium(II) complexes are diamagnetic with tetrahedral geometry and are mononuclear.

The ^1H chemical shifts of the Ni(II), Cd(II), and Zn(II) dithiocarbamate complexes are listed in Table 4. The ^1H NMR spectra of the atenolol ligand contained absorptions due to the protons of ADTC. The Ni(II), Cd(II), and Zn(II) dithiocarbamate complexes show a sharp singlet at 1.0–1.60 ppm due to methyl protons thus suggesting the magnetical equivalence of these protons. The –CH protons, in the complexes appear as a triplet at 3.60–3.85 ppm and a sharp singlet at 2.65–4.0 ppm due to $–CH_2$ protons, respectively. While the free ligand atenolol has a sharp singlet at 4.00–4.28 ppm due to the –NH protons, this peak disappear in the three dithiocarbamate complex spectra [38–40].

The synthesized complexes were placed into dried Schlenk tube against a dry N_2 flow at atmospheric pressure [41]. The complexes were then heated to the desired temperature under static N_2. The thermal data on the complexes are given in Table 5.

The TG data of the complex $C_{30}H_{42}N_4O_6S_4Cu \cdot H_2O$, show the formation of the anhydrous complex by 175°C, which indicates the loss of water of hydration, and this high-temperature dehydration confirms the loss of coordinated water. The second step at 235°C is endothermal and relates to the decomposition of the DTC ligand. The subsequent decomposition step completed at 359°C produces CuO as the final solid products. The thermal dehydration of $Na[C_{19}H_{27}N_2O_7S_2Co] \cdot 5H_2O$ complex occurs in three steps, giving endothermal effects at 70, 158, and 198°C, respectively. One molecule of crystallization water is removed in the first step of dehydration. The second step, in the temperature range 158–228°C, corresponds to the loss of 4 molecules of water. The third step, between 220–334°C, involves the endothermal loss of two $H_3C–COO$ groups. The following steps involve the endothermal decomposition of the intermediate formed to give metallic Co as the final solid product. The $Na[C_{17}H_{29}N_2O_5S_2Ni] \cdot H_2O$ complex decomposes in two steps. The first step involves endothermal decomposition at 137°C, corresponding to loss of the crystallization water, as indicated by the TG mass loss. The second step at 290°C is endothermal and reveals the loss of two $–O–CH_3$ groups ligand. The subsequent decomposition step completed at 600°C produces NiO as the final product. The $Na[C_{15}H_{21}N_4O_9S_2Cd] \cdot 2H_2O$ complex exhibits three distinct decomposition steps. The first step in the temperature range 168–180°C corresponds to the loss of water molecules. The second step at 290°C corresponds to the loss of the nitrate groups in the complex. In the third step, the DTA curves reveal several simultaneous processes with a large endothermic effect due to the combustion of the intermediate formed. The final product formed at 806.81°C consists of CdO. The $Na[C_{19}H_{27}N_2O_7S_2Zn] \cdot H_2O$ complex decomposes in two steps. The first step between 164–176°C corresponds to dehydration. After dehydration, it melts at 291°C. Degradation of the organic part of the ligand takes place in the second decomposition step in the range 244–450°C. The final decomposition product was identified as ZnO from the IR spectra and mass loss calculations.

All complex formation was studied at the same concentration of NaADTC (1×10^{-4} mol/l) and in a wide range of metal ions (Cu^{+2}, Co^{+2}, Ni^{+2}, Zn^{+2}, and Cd^{+2}) concentrations ($7 \times 10^{-7} – 6 \times 10^{-3}$ mol/l). A low and unchanged concentration of the lectroneutral organic ligand allowed us to exclude from consideration the theoretically possible formation of the biligand or monoligand complexes (according to the equilibrium $2L + M^{+2} = ML_2^{2+}$ or $L + M = ML$), whose detection, under our experimental conditions, requires the complex formation constant to be higher than $10^7–10^9$ mol/l. Information on the stoichiometry of the metal–ligand complexes of compound NaADTC was obtained from the continuous variation method [24–26]. Job's plot for the M^{+2} complex is presented on figure a and b. It was found from Job's plots for $Na[C_{19}H_{28}NO_5S_2Co] \cdot H_2O$, $[C_{17}H_{26}NO_5S_2Ni]Cl \cdot H_2O$, $Na[C_{21}H_{26}NO_6S_2Zn]$, and $Na[C_{17}H_{22}N_3O_9S_2Cd] \cdot H_2O$ complexes that $X_{max} = 1/2$ for these complexes, hence, the stoichiometry of the metal–ligand complexes of NaADTC was found to be 1 : 1 at used concentration of the ligand (1×10^{-4} mol/l) (figure b). The plot reached a maximum at a fraction of 0.3 indicating the formation of 3 : 7 for ADTC–Cu(II) complex. In this situtation, the $[C_{34}H_{40}N_2O_4S_4Cu] \cdot H_2O$ complex is more likely 1 : 2 (figure a) [22, 23, 27–29]. The elemental analyses were satisfactory and show that the complexes have a ligand to metal ratio for 2 : 1 or 1 : 1 too. The calculated values of stability constants for all the complexes are listed bellow:

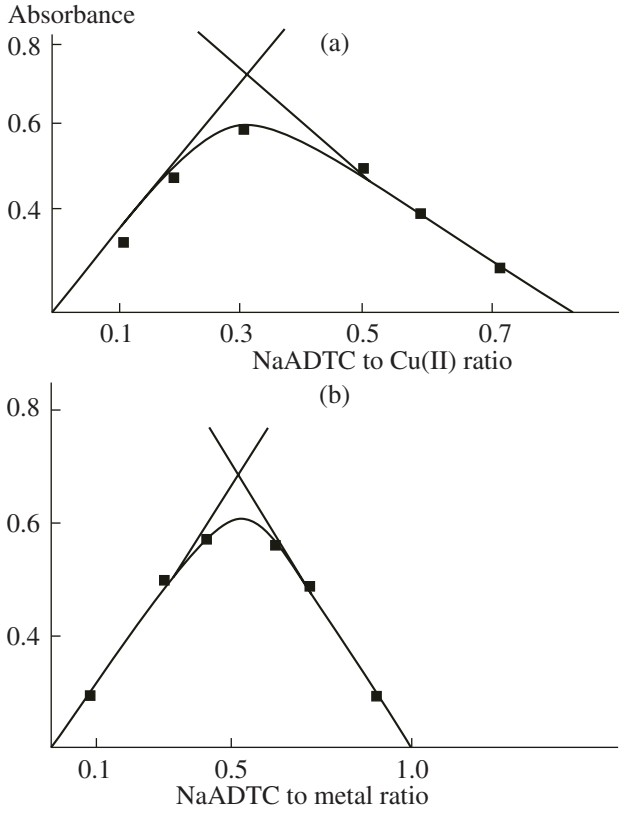
Compound	$\log K_s$
$[C_{34}H_{40}N_2O_4S_4Cu] \cdot H_2O$	5.16 ± 0.01
$Na[C_{19}H_{28}NO_5S_2Co] \cdot H_2O$	2.99 ± 0.04
$Na[C_{17}H_{26}NO_5S_2Ni] \cdot H_2O$	4.01 ± 0.02
$Na[C_{21}H_{26}NO_6S_2Zn]$	3.02 ± 0.01
$Na[C_{17}H_{22}N_3O_9S_2Cd] \cdot H_2O$	4.13 ± 0.02

The bacteria *Bacillus megaterium* DSM 32, *Bacillus brevis* NRS, *Yersinia enterecolitica* CMC 120, *Micrococcus luteus* La 2971, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus feacalis* ATTC 15753 and *Kluyveromyces marxianus* ADH1 and the yeast cultures *Candida tropicalis* FMC 23, *Candida albicans* ATCC 10231 and *Kluyveromyces fragilis* NRRL 2415 were

Table 5. Thermal degradation of the dithiocarbamate complexes

Compound	Loss of coordinated water (found/calcd), %	*T*, °C	Loss of ligands mass (found/calcd), %	*T*, °C	Final product
I	2.50 (2.41)	175	88.98 (89.35)	359–967	CuO
II	14.59 (14.26)	70.74–228.72	89.54 (90.65)	334.68–962	Co
III	3.37 (3.56)	137.53	85.00 (85.15)	290.83–600	NiO
IV	3.46 (3.18)	164.93–176.83	86.04 (85.67)	244.85–450.00	ZnO
V	5.94 (5.66)	168.79–180.71	79.02 (79.87)	290.36–806.81	CdO

used in this study as test microorganisims [27]. The compounds were dissolved in DMSO to a final concentration of 30 μg/ml. Empty sterilized antibiotic discs having a diameter of 6 mm (Schleicher and Schull no: 2668, Germany) were each impregnated with 10 ± 1 of solution. All the bacteria mentioned above were incubated at 30 ± 0.1°C for 24 h by inoculation into Nutrient Broth (Difco), and the yeasts studied were incubated in Malt extract Broth (Difco) for 72 h. An inoculum contannimg 105 bacterial cells or 104 yeast cells/ml was spread on Mueller-Minton Agar plates (1 ml inoculum/plate). The discs injected with solutions were placed on the inoculated agar by pressing slightly, and incubated at 30°C (18–24 h) for bacteria, and at 25°C (72 h) for yeasts. On each plate a appropriate reference antibiotic disc was applied depending on the test microorganisms. The data reported in Table 6 are the average data of five experiments.



Continuous variation plots for the stoichiometry of the reaction of ADTC–copper(II) (a) and ADTC and metals (b).

Table 6 shows antimicrobial activities of the complexes. Besides, the inhibition zones formed by standard antibiotic discs are indicated in Table 7. As can clearly be seen from Table 6, all complexes, except the Cu(II) complex, show strong antimicrobial activities against all tested microorganisms. In classifying the antimicrobial activity as Gram(+) or Gram(–), it is generally expected that a much greater number would be active against Gram(+) than Gram(–) bacteria [42]. However, in this study, the complexes were active against both Gram(+) and Gram(–) bacteria. The ADTC cobalt complex has formed the highest antimicrobial effect against all tested microorganisms, while the ADTC cadmium complex has formed the smallest antimicrobial effect against all tested microorganisms. When the results obtained were compared to those of standard antibiotics, the bacterium *Micrococcus luteus* from all the tested bacteria is the most influenced bacterium against the ADTC cobalt complex, having a diameter zone of 26 mm. This complex has a stronger antimicrobial effect than those of the standard antibiotics P10, AMP20, and VA30 aginst *Pseudomonas aeruginosa*. Against the bacterium *Enterococcus feacalis, the* ADTC cobalt, nickel and zinc complexes have higher activities than those of P10, AMP20, CTX30, and VA30. In addition, the ADTC cadmium complex is equivalent to the standard antibiotic P10 against *Bacil-*

Table 6. Antimicrobial activity data for the dithiocarbamate complexes

Microorganisms	Diameter of inhibition zones, mm*				
	II	III	IV	V	VI**
B. megaterium	12	9	14	8	4
B. brevis	19	16	11	12	8
Y. enterecolitica	19	10	12	6	5
M. luteus	26	12	10	8	5
P. aeruginosa	25	8	9	10	4
E. feacalis	25	21	24	6	3
K. marxianus	21	16	12	9	3
C. tropicalis	20	6	12	7	3
C. albicans	28	28	13	6	2
K. fragilis	24	6	11	9	2

Notes: * Antimicrobial activity of complex I is absent for all microorganisms.
** VI – NaADTC.

lus brevis and it has higher antibacterial activity than P10 against *Pseudomonas* too. All complexes, except the ADTC copper(II), have high antimicrobial activity against the yeast cultures used in this study as compared to the standard antifungal antibiotics Ketacanozole and Clotrimaole. Notably, the ADTC cobalt complex shows a higher antiyeast activity than the other complexes. The ADTC cobalt complex has stronger antiyeast activity than those of KET20 and CLT10 against *Candida tropicalis* and *Kluyveromyces fragilis*, while they are equivalent to the standard antibiotics KET20 and CLT10. *C. albicans* is succeptible to the ADTC nickel complex, as compared two standard antiyeast antibiotics [43].

The complexes differ significantly in their activity against tested microorganisms. These diffrences can be attributed to the fact that the cell wall in Gram(+) bacteria consists of a single layer, whereas the Gram(–) cell wall is a multilayered structure and the yeast cell wall is a quite complex.

ACKNOWLEDGMENTS

This work was supported by a grant from the Kahramanmaras Sütcu Imam University Scientific Research Project Foundation (Grant no: 2004/2–7) (Turkey). The authors are grateful to Prof. Dr. Selahattin Serin (University of Cukurova, Faculty of Science and Arts, Department of Chemistry, Adana, Turkey), Assoc. Prof. Dr. Mehmet Tumer and Chem. Mustafa Dolaz (University of Kahramanmaras Sütcu Imam, Faculty of Science and Arts, Department of Chemistry, Kahramanmaras, Turkey) for their useful suggestions and Chem. Gokturk Avsar (University of Cukurova, Faculty of Sci-

Table 7. Antimicrobial activities of some standard antibiotics

Microorganism	Diameter of inhibition zones, mm					
	P10	AMP20	CEF30	VN30	KET20	CLT10
B. megaterium	38	24	40	18		
B. brevis	12	16	43	32		
Y. enterecolitica	28	44	30	22		
M. luteus	22	28	34	32		
P. aeruginosa	8	10	54	10		
E. feacalis	12	10	13	14		
K. marxianus	25	30	18	16		
C. tropicalis	32	32	34	19	21	15
C. albicans					26	20
K. fragilis					16	18

P10 – Penicillin G (10 Units); AMP20 – Ampicillin 10 μg; CEF30 – Cefotaxime 30 μg; VN30 – Vancomycin 30 μg; KET20 – Ketaconazole 20 μg; CLT10 – Clotrimazole 10 μg.

ence and Arts, Department of Chemistry, Adana, Turkey) for TG–DTA analysis.

REFERENCES

1. *Pesticides. Preparation and Mode of Action*, Cremlyn, R.I., Ed., New York: Wiley, 1978.
2. Zeng, X.Q., Li, J., Wu, X.D., et al., *Tribology International*, 2007, vol. 40, p. 560.
3. Vanin, A.F., Poltorakov, A.P., Mikoyan, V.D., et al., Nitric Oxide-Biology and Chemistry, 2006, vol. 15, p. 295.
4. Rabbi, M.F., Finnegan, A., Al-Hartli, L., et al., *J. Acquired Immune Deficiency Syndromes Human Retrovirol.*, 1998, vol. 19, p. 321.
5. Renoux, G., *Trends Pharm. Sci*., 1981, vol. 2, p. 248.
6. Mustafa, I.A., Taqa, A.A., *Synth. React. Inorg. Met.-Org. Chem*., 2001, vol. 31, p. 517.
7. Zaidi, S.A.A., Siddiqi, K.S., Islam, N., *Indian J. Chem*., 1974, vol. 12, p. 1197.
8. Milacic, V., Chen, D., Ronconi, L., et al., *Cancer Research*, 2006, vol. 66, p. 10478.
9. Sharma, J., Singh, Y.P., Bohra, R., Rai, A.K., *Polyhedron*, 1996, vol. 15, p. 1097.
10. Lockhart, T.P., Manders, W.F., Schlemper, E.O., Zuckerman, J.J., *J. Am. Chem. Soc*., 196, vol. 108, p. 4074.
11. Gölcü, A., Dolaz, M., Serin, S., *Turk. J. Chem*., 2001, vol. 25, p. 485.
12. Niebyl, J.R., In: *Danforth's obstetrics and gynecology*, Scott T., Ed., Philadelphia: Lipincott, 1990.
13. Briggs, G.G., Freeman, R.K., and Yaffe, S.J., In: *Drugs in pregnancy and lactation*, Baltimore: Williams and Wilkins, 1994.
14. Florey, K., In: *Analytical Profiles of Drug Substances 13*, New York: Academic Press, 1983.
15. Shama, S.A., Amin, A.S., *Egypt J. Chem*., 2000, vol. 43, p. 527.
16. Gölcü, A., Yücesoy, C., Serin, S., *Il Farmaco*, 2004, vol. 59, p. 487.
17. Yang, X., Fukushima, T., Santa, T., et al., *Analyst*, 1997, vol. 122, p. 1365.
18. Evrik, M., Kylberg-Hanssen, K., *J. Chrom. Biomed. App*., 1980, vol. 182, p. 341.
19. Leloux, M.S., Dost, F., *Chromatographia*, 1991, vol. 32, p. 429.
20. Gölcü, A., Yücesoy, C., Serin, S., *Synth. React. Inorg. Met.-Org. Chem*., 2004, vol. 34, p. 1259.
21. Gölcü, A., *Trans. Met. Chem*., 2006, vol. 31, p. 405.
22. Reid, E.E., *Organic Chemistry of Bivalent Sulfur 4*, New York: Chemical Publishing, 1962.
23. Dolaz, M., Tümer, M., Gölcü, A., Serin, S., *Turk. J. Chem*., 2001, vol. 25, p. 491.
24. Connors, K.A., *Binding Constants: The Measurement of Molecular Complex Stability*, New York: Wiley, 1987.
25. Job, P., *Ann. Chim*., 1928, vol. 9, p. 113.
26. Posokhov, Y., Ku, M., Biner, H., et al., *J. Photochem. Photobiol., A: Chem*., 2004, vol. 161, p. 247.
27. Gölcü, A., Tümer, M., Demirelli, H., Wheatley, R.A., *Inorg. Chim. Acta*, 2005, vol. 358, p. 1785.
28. Gölcü, A., Serin, S., *Sci. Pharm*., 1998, vol. 66, p. 341.
29. Gölcü, A., Yücesoy, C., Serin, S., *Sci. Pharm*., 2000, vol. 68, p. 235.
30. Gölcü, A., Serin, S., *Sci. Pharm*., 1998, vol. 66, p. 351.
31. Cesur, H., Yazicilar, T.K., Bati, B., Yilmaz, V.T., *Synth. React. Inorg. Met.-Org. Chem*., 2001, vol. 31, p. 1271.
32. Rogachev, I., Kampel, V., Gusis, V., et al., *Pestic Biochem. Physiol*., 1998, vol. 60, p. 133.
33. Coucouvanis, D., In: *Progress in Inorganic Chemistry 11*, Lippard, S.I. Ed., New York: Interscience, 1970.
34. Brown, D.A., Glass, W.K., Burke, M.A., *Spectrochim. Acta*, *A*, 1976, vol. 32, p. 137.
35. Dakternieks, D., Zhu, H., Masi, D., Mealli, C., *Inorg. Chem*., 1992, vol. 31, p. 3601.
36. Potenza, J., Johnson, R.T., Mastropaolo, D., *Acta Cryst*., *B*, 1976, vol. 32, p. 941.
37. Chauhan, H.P.S., Shaik, N.M., Kori, K., *Synth. React. Inorg. Met.-Org. Chem*., 2004, vol. 34, p. 323.
38. Jung, O.S., and Sohn, Y.S., *Bull. Korean Chem. Soc*., 1988, vol. 9, p. 365.
39. Genivaldo, J.P., Marcelo, R.L., Oliveira, J.J., et al., *Polyhedron*, 2003, vol. 22, p. 3355.
40. Oliveira, M.R.L., De Bellis, V.M., *Trans. Met. Chem.*, 1999, vol. 24, p. 127.
41. Yilmaz, V.T., Karadag, A., Icbudak, H., *Thermochim. Acta*, 1995, vol. 261, p. 107.
42. Gölcü, A., Dolaz, M., Demirelli, H., et al., *Trans. Met. Chem*., 2006, vol. 31, p. 658.
43. Yildiz, M., Unver, H., Dulger, B., et al., *J. Mol. Struct*., 2005, vol. 738, p. 253.