Anti-bacterial, Anti-fungi Activity Evaluation and Computational Study of Co(II) and Cu(II)-Dithiocarbamate Complexes

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ABSTRACT

$[Co(\kappa^2\text{-}Et_2DT)_2]$ (**1**), $[Cu(\kappa^2\text{-}Et_2DT)_2]$ (**2**), $[Co(\kappa^2\text{-}PyDT)_2]$ (**3**), $[Cu(\kappa^2\text{-}PyDT)_2]$ (**4**), $[Co(\kappa^2\text{-}PipDT)_2]$ (**5**) and $[Cu(\kappa^2\text{-}PipDT)_2]$ (**6**) (Where Et_2DT = diethyl dithiocarbamate; PyDT= pyrrolidine dithiocarbamate; PipDT = piperidine dithiocarbamate) were synthesized and characterized. The dithiocarbamate (DTC) behave as bidentate chelating ligands to afford a tetrahedral complexes with Co(II) ion and square planner with Cu(II) ion. The dithiocarbamate complexes displayed good activity against the pathogen microbial species (bacteria and fungi). The results showed the Cu-dithiocarbamate complexes are more active against all the tested bacteria then the Co-dithiocarbamate complexes and the DTC-compounds displayed the highest inhibition region against *E. coli* bacteria. Also, The $[Cu(\kappa^2\text{-}PipDT)_2]$(**6**) complex show a highest activity against all fungi types compared with other complexes, also we used the Density Functional Theory (DFT) to characterize the stability of the prepared complexes

Keywords: dithiocarbamate, Complexes, DFT, Anti-bacterial, Anti-fungi

1. Introduction

Dithiocarbamates ($R_2NCS_2^-$ or $RNHCS_2^-$; Where R = alkyl or aryl group) are objective one example of a universal class of mono-anionic 1,1-dithiolate ligands which also contains other generally used ligands such as xanthates, carbamates, dithiophosphates, and many others [**1**]. Metal complexes of dithiocarbamate ligands have been the subject of present and increasing concern because it possesses wide range of medical fields (such as antibacterial, anti-fungal, anti-inflammatory), industry, analytical and organic chemistry [**1-11**]. Dithiocarbamate can link to metal ions in different coordination styles (**Chart 1**) as:

i. Monodentate mode via the S atom of the CSS^- group (**A**)[**10-15**].
ii. Bidentate chelating style via the S atoms of CSS^- group (**B**)[**7,9,16-30**].
iii. Bidentate bridging fashion via the two sulfur atoms, or through the one of the sulfur atom only (**C**)[**26,31-33**].
iv. Poly-dentate style between three center or more (**D**)[**28,31,34-37**].
v.

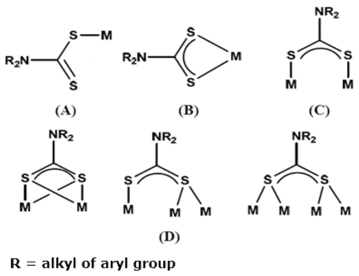


Chart 1: Coordination modes of dithiocarbamate ligands

In this work, we study the effect of the dithiocarbamate complexes with Co(II) and Cu(II) as anti-bacterial against *Staphylococcus aureus* and *Bacillus subtilis* as Gram negative and *E. coli* and *Salmonella typhimurium* as Gram positive bacteria, and anti-fungi against *Candida albicans*, *Trichoderma Virdi*), also, we studies the molecular molding of the compounds to check the stability of prepared complexes.

2. Experimental

2.1. Materials and Methods

All materials (sodium diethyl dithiocarbamate, Ammonium pyrrolidine dithiocarbamate sodium piperidine dithiocarbamate, $CoCl_2.6H_2O$, $CuCl_2.6H_2O$) and solvents are commercially available and are used as received. IR spectra were measured by Shimadzu model FTIR-8400S instrument spectrophotometer in the 400–4000 cm^{-1} range using KBr discs in Department of Chemistry. College of Science, Tikrit University. elemental analysis (CHN), molar electric conductivity and melting point were recorded on Euro-vector model EA 3000, digital conductivity meter model CD-2005 and Stuart model SMP10, respectively. UV-visible spectra were recorded on UV-6100PC Double Beam Spectrophotometer , Shimadzu in 200-1000nm range in DMSO as a solvent in Department of Chemistry, College of Education, University of Samara.

2.2 Preparation of [Co(κ^2-Et$_2$DT)$_2$] (1)

A solution of sodium diethyl dithiocarbamate ($NaEt_2DT$) (0.500 g, 2.92 mmol) (15 mL) was added to solution of cobalt chloride ($CoCl_2.6H_2O$) (0.347 g, 1.46 mmol) (10 mL). The ppt. formed was stirred for 1h at room temperature, then filtered off , washed with ethanol and dried under vacuum (Yield: 79%, m.p(°C): 287-289 (decompose)).

The following complexes **[Cu(κ^2-Et$_2$DT)$_2$] (2), [Co(κ^2-PyDT)$_2$] (3), [Cu(κ^2-PyDT)$_2$] (4), [Co(κ^2-PipDT)$_2$] (5)** and **[Cu(κ^2-PipDT)$_2$] (6)** were prepared and isolated using similar methods.

2.3 Antibacterial and anti-fungi studies

The anti-bacterial activity of the complexes (**1-6**) was tested against for pathogenic bacteria, (*Staphylococcus aureus* and *Bacillus subtilis*) as Gram negative and (*E. coli* and *Salmonella typhimurium*) as Gram positive bacteria. in DMSO as a solvent at 10^{-3}M concentration. The activity properties of the complexes were screened by agar disc diffusion method designated by Moulder et al. [**38**] and the results were compared with Cholophenicol as positive control. The anti-fungi study was tested against three fungi types (*Candida albicans* and *Trichoderma Virdi*) in 10^{-3}M concentration of complexes in DMSO, and the results were compared with Fluconazole as positive control.

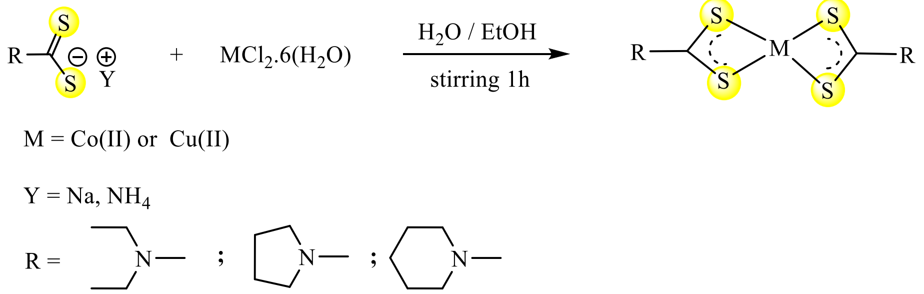
2.4. Molecular modeling of the Prepared complexes

An effort to gain a better understanding the molecular structure of complexes, geometric optimization and conformational analysis were made using semi-empirical PM3 [**39**] by the hyperchem series of program force fields as implemented in hyperchem 8 [**40**].

3. Results and Discussion

3.1 Synthesis of complexes

The reactions of dithiocarbamate salts {($NaEt_2DT$), (NH_4)(PyDT) and (NaPipDT)} with $CoCl_2.6H_2O$ or $CuCl_2.6H_2O$ in (1:2) molar ratio, gave complexes of the type [M(κ^2-dithiocarbamate)$_2$] (**Scheme 1**) in good yield (78-96%) (**Table 1**). The dithiocarbamate ligands were bonded through the S atoms as bidentate mode.



Scheme 1: Preparation of complex (1-6).

Table 1: Color, Yield, m.p, conductivity, and elemental analysis of prepared complexes (1-6)

Seq.	Complexes	Color	Yield (%)	m.p. (°C)	Conductivity $\Lambda_M(\Omega^{-1}\ cm^{-2}\ mol^{-1})$ 1×10^{-3}M/ DMSO	Elemental analysis Calc.(Found)%		
						C	H	N
1	[Co(κ^2-Et$_2$DT)$_2$]	Dark violet	79	287-289D	11.4	33.79 (34.07)	5.67 (5.93)	7.88 (8.12)
2	[Cu(κ^2-Et$_2$DT)$_2$]	Brown- green	96	291-295	7.3	33.36 (33.27)	5.60 (5.43)	7.78 (7.92)
3	[Co(κ^2-PyDT)$_2$]	Violet	81	256-257D	8.9	34.14 (34.26)	4.59 (4.71)	7.97 (8.25)
4	[Cu(κ^2-PyDT)$_2$]	Green- blue	78	312-315D	5.4	33.74 (33.63)	4.53 (4.77)	7.87 (7.98)
5	[Co(κ^2-PipDT)$_2$]	Green- violet	89	278-281	10.1	37.98 (38.11)	5.31 (4.39)	7.38 (7.66)
6	[Cu(κ^2-PipDT)$_2$]	Brown- green	91	>300	8.2	37.53 (37.69)	5.25 (5.42)	7.29 (7.47)

D= Decomposition

3.2 Characterization of complexes

3.2.1 IR spectra

Selected IR bands of the complexes **(1-6)** are recorded in **Table 2**and **Figure 1,2**. In IR spectra (Fig. **1** and **2**) displayed two characteristic band of dithiocarbamate ligand within (1497-1543)cm-1 and (995-1023)cm-1 due to the ν(C-N) and ν(CSS) group, respectively. The band of (CSS) group appeared as one band without splitting, indicated that the dithiocarbamate ligands behave as bidentate chelating ligand[**5,7,41-44**]. The spectra of complexes (**1-6**), displayed the vibration frequency of M-S group within (445-509) cm^{-1} [**5,7,41-44**]. Other bands are listed in **Table 2**.

Table 2 : Selected IR bands (cm^{-1}) of the complexes (1-6)

Seq.	Complex	υ(C-H) Alph.	υ(C-N)	υ(CSS)	υ(M-S)
1	$[Co(\kappa^2\text{-}Et_2DT)_2]$	2974m 2869w	1502s	995m	449w
2	$[Cu(\kappa^2\text{-}Et_2DT)_2]$	2893m 2842w	1523s	1002m	489w
3	$[Co(\kappa^2\text{-}PyDT)_2]$	2934m 2856w	1497s	1006m	493w
4	$[Cu(\kappa^2\text{-}PyDT)_2]$	2891w 2828w	1543s	1034m	504w
5	$[Co(\kappa^2\text{-}PipDT)_2]$	2923m 2854w	1516s	1011m	495w
6	$[Cu(\kappa^2\text{-}PipDT)_2]$	2968m 2866w	1504s	999m	445w

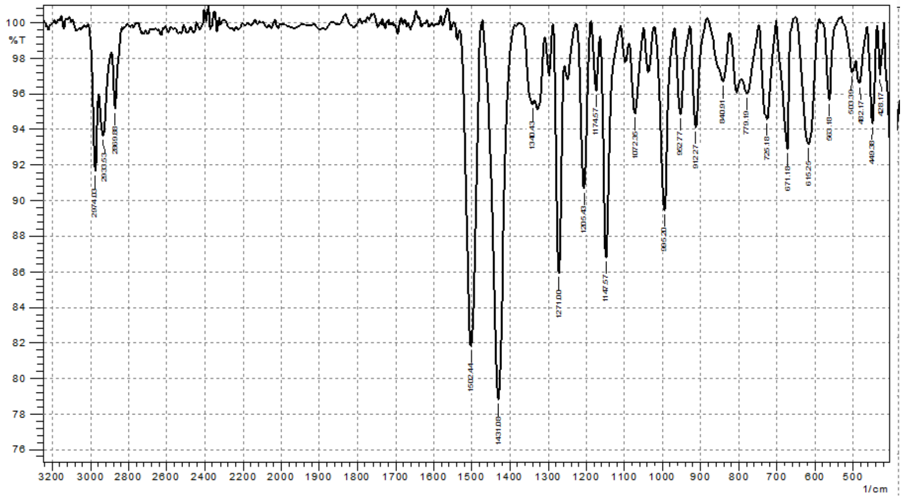


Figure. 1: IR Spectrum of complex 1

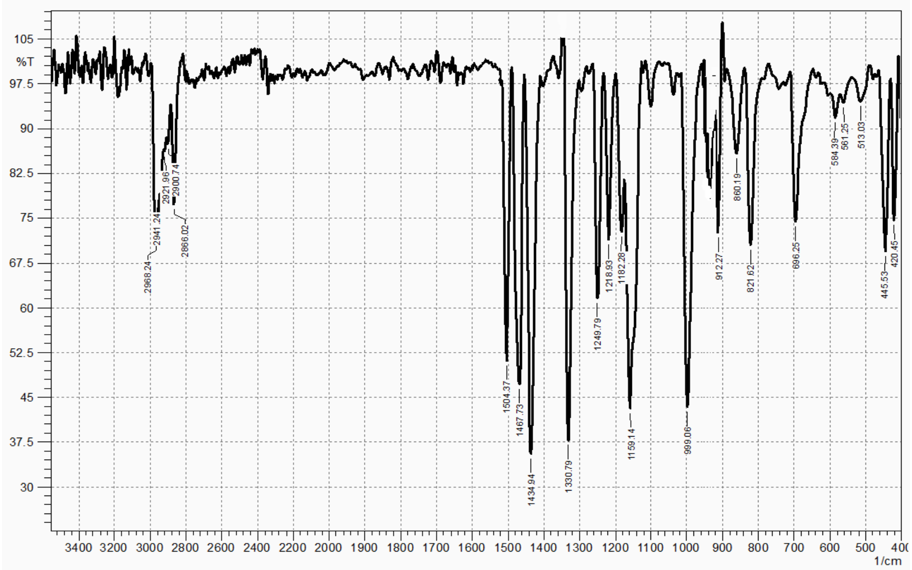


Figure. 2: IR Spectrum of complex 6

3.2.2 Electronic spectra

The electronic spectra of complexes **(1-6)** (**Table 3**) displayed three bands in the region (200-400)nm, these bands due to the dithiocarbamate ligand as following:

1- The first and second bands appeared within (237-252)nm and (269-297) nm due to $\pi\rightarrow\pi^*$ transitions in the N-CSS group.

2- Third band displayed within (298-328)nm assigned to $n\rightarrow\pi^*$ transitions of the nonbonding electron of the pair on S atom.

In addition the dithiocarbamate bands, the spectra of Cu complexes displayed two weak to medium intensity and broad bands as following:

1- First band within (573-591) nm assigned to the charge transfer (CT) transition of the type M→L and L→M between Cu-DTC ligands.

2- Second band appeared within (821-835)nm due to the d-d transitions of Cu (${}^2B_1g\rightarrow 2Eg$) in square planner.

The electronic spectra of Co-dithiocarbamate complexes showed two bands within (438-462)nm and (608-618)nm due to the ${}^4A_2(F)\rightarrow{}^4T_1(F)$ and ${}^4A_2(F)\rightarrow{}^4T_1(P)$ transitions, which are characteristic bands of tetrahedral around Co(II) ion.

Table 3: Electronic spectra of the complexes (1-6)

Co complexes			Cu complexes		
Comp.	**Electronic bands**	**Possible assignments**	**Comp.**	**Electronic bands**	**Possible assignments**
1	257	$\pi\rightarrow\pi^*$	**2**	248	$\pi\rightarrow\pi^*$
	287	$\pi\rightarrow\pi^*$		275	$\pi\rightarrow\pi^*$
	318	$n\rightarrow\pi^*$		298	$n\rightarrow\pi^*$
	438	CT		573	${}^4A_2(F)\rightarrow{}^4T_1(F)$
	608	d-d (${}^2B_1g\rightarrow 2Eg$)		821	${}^4A_2(F)\rightarrow{}^4T_1(P)$
3	237	$\pi\rightarrow\pi^*$	**4**	252	$\pi\rightarrow\pi^*$
	269	$\pi\rightarrow\pi^*$		285	$\pi\rightarrow\pi^*$
	312	$n\rightarrow\pi^*$		310	$n\rightarrow\pi^*$
	458	CT		589	${}^4A_2(F)\rightarrow{}^4T_1(F)$
	618	d-d (${}^2B_1g\rightarrow 2Eg$)		830	${}^4A_2(F)\rightarrow{}^4T_1(P)$
5	242	$\pi\rightarrow\pi^*$	**6**	256	$\pi\rightarrow\pi^*$
	293	$\pi\rightarrow\pi^*$		297	$\pi\rightarrow\pi^*$
	328	$n\rightarrow\pi^*$		322	$n\rightarrow\pi^*$
	462	CT		591	${}^4A_2(F)\rightarrow{}^4T_1(F)$
	618	d-d (${}^2B_1g\rightarrow 2Eg$)		835	${}^4A_2(F)\rightarrow{}^4T_1(P)$

3.3 Biological activity

3.3.1 Antibacterial activity studies

The anti-bacterial evaluation study of the dithiocarbamate complexes (**1-6**) recorded against four types of bacteria: (*Staphylococcus aureus* and *Bacillus subtilis*) as Gram negative and (*E. coli* and *Salmonella typhimurium*) as Gram positive bacteria. A standard agar diffusion and broth micro-dilution methods were used, and the results are summarized in **(Figure 3)**. The standard error for the test was ± 0.03 %, and the tests were frequent three periods at similar conditions. The diameter of the inhibitory zone (DIZ) was compared to that of azithromycin as control positive. The dithiocarbamate complexes displayed good activity against the bacteria types. the achieved results can be listed as following:

1- The Cu-dithiocarbamate complexes are more active against all the tested bacteria then the Co-dithiocarbamate complexes.

2- Complex **4** is more active for the tested bacteria compared with other dithiocarbamate complexes, whereas the complex **5** exhibits less activity.

3- The dithiocarbamate complexes displayed the maximum inhibition zone against *E. coli* bacteria, whereas the lowest activity of the dithiocarbamate against *Salmonella typhimurium* bacteria.

4- Inhibition order of the complexes are as following:

6> 2> 4> 3 >1>5

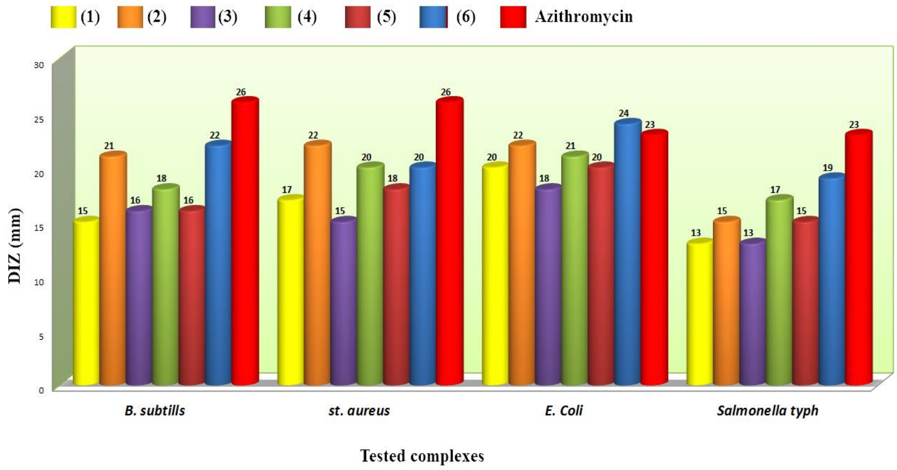


Figure 3: histogram representation of the anti-bacterial activity of the complexes (1-6)

3.3.2 Anti-fungi activity

The anti-fungi activity of the dithiocarbamate complexes were tested against ***Candida albicans*** and ***Trichoderma Virdi)*** by using agar disc diffusion method described by Moulder et al. [**38**]. Six dithiocarbamate were used to determine the working mechanism of these compounds as anti-fungi agents against the aforementioned types of fungi compared with Fluconazole as a positive control. The gained data showed in (**Figure 4**). All the dithiocarbamate complexes show moderate activity compared to Fluconazole. The complex **4** shows a highest activity against all fungi types compared with other complexes. Similarly the complex **2** shows a high activity against *Trichoderma viride*.

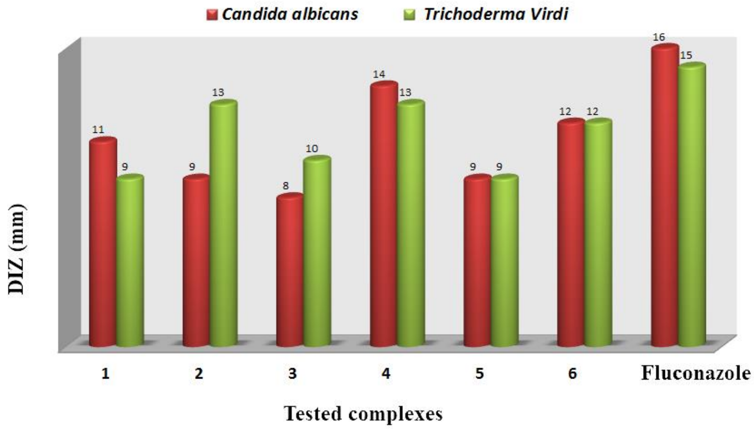


Figure 2: histogram representation of the anti-fungi activity of the complexes (1-6) compared with Fluconazole.

3.4. Molecular modeling of the Prepared complexes

The atomic numeration scheme and the theoretical geometry structures are calculated for the ligand and some of its metal complexes. In **Table 4**, the molecular parameters were calculated and represented: total energy, binding energy, isolated atomic energy, electronic energy, formation heat, dipole moment, HOMO and LUMO. Complexes **1**, **3** are calculated dipole moments greater than those of other complexes . because of its higher dipole moment (1.349 D) complex **1** is more polarizable than the other chelates.

In **Table 5**, quantum chemical parameters describe the complexes reactivity. To order to quantify molecular stability and reactivity, the global electrophilicity index (A) and softness (A) are important properties. A hard molecule has a large energy gap, whereas a soft molecule has a small energy gap. Soft molecules are more reactive than rigid ones, since they are easier to supply electrons. The complexes 2, 4 and 6 which have greater softness (σ) value (0.19 for all) than other complexes. Giving metal electrons is more reactive and simpler, and has a high potential for complexation. Global hardness and softness are important properties to quantify the molecular stability and reactivity.

Table 4: The theoretical parameters of the prepared complexes (1-6).

Complexes	Theoretical parameters							
	Total Energy (kcal/mol)	Total Energy (a.u.)	Binding Energy (kcal/mol)	Isolated Atomic Energy (kcal/mol)	Electronic Energy (kcal/mol)	Core-Core Interaction (kcal/mol)	Heat of Formation (kcal/mol)	Dipole moment (Debys)
1	-87228.64	-139.01	-3545.44	-83683.20	-513204.05	425975.41	-117.99	1.349
2	-78148.28	-124.54	-3740.90	-74407.38	-498572.66	420424.38	-291.76	0.66
3	-92700.64	-147.73	-3887.29	-88813.35	-574373.32	481672.67	-118.07	0.60
4	-83616.11	-133.25	-4078.59	-79537.53	-560300.10	476683.99	-287.66	0.78
5	-85796.64	-136.73	-3319.35	-82477.29	-486108.40	400311.76	-100.31	0.23
6	-76723.31	-122.27	-3521.84	-73201.47	-471630.23	394906.91	-281.11	0.64

Table 5. Calculated EHOMO, ELUMO, energy band gap (EL – EH), chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and softness (σ) for metal complexes.

complexes	**EH / eV**	**EL / eV**	**(EL-EH) /Ev**	**χ / eV**	**μ / eV**	**η / eV**	**S / eV^{-1}**	**ω / eV**	**σ / eV^{-1}**
1	-6.85	-0.84	6.01	3.85	-3.85	3.01	1.503	2.46	0.17
2	-5.96	-0.62	5.34	3.29	-3.29	2.67	1.34	2.03	0.19
3	-6.84	-0.82	6.02	3.83	-3.83	3.01	1.51	2.44	0.17
4	-6.02	-0.66	5.36	3.34	-3.34	2.68	1.34	2.08	0.19
5	-7.08	-1.01	6.07	4.05	-4.05	3.04	1.52	2.69	0.16
6	-5.99	-0.64	5.35	3.32	-3.32	2.68	1.34	2.05	0.19

Conclusion

Co(II) and Cu(II) dithiocarbamate have been synthesized and characterized by CHN analysis and spectroscopic techniques. The DTC ligands are coordinated as bidentate chelating ligand through the sulfur atom of the CSS group to afford a tetrahedral shape around the Co(II) and square planer around Cu(II). The Cu-DTC complexes showed highest activity against all bacteria species compared with Co-DTC complexes and the inhibition order of the DTC complexes as following:

6> 2> 4> 3 >1>5

Whereas the DTC- complexes show moderate activity as anti-fungi compared to Fluconazole. And The [Cu(κ^2-$Et_2DT)_2$] complex shows a highest activity against *Trichoderma viride*. Complexes **1**, **3**are calculated dipole moments greater than those of other complexes. because of its higher dipole moment (1.349 D) complex **1** is more polarizable than the other chelates.

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دراسة الفعالية كمضادات بكتيرية وفطرية ودراسة الحسابية للمعقدات ثنائي ثايوكاربامايت للكوبلت(II) والنحاس (II)

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الملخص

المعقدات $[Co(\kappa^2\text{-}Et_2DT)_2]$ (1), و $[Cu(\kappa^2\text{-}Et_2DT)_2]$ (2), و $[Co(\kappa^2\text{-}PyDT)_2]$ (3) و $[Cu(\kappa^2\text{-}PyDT)_2]$ (4) و $[Co(\kappa^2\text{-}PipDT)_2]$ (5) و $[Co(\kappa^2\text{-}PipDT)_2]$ (6) (حيث ان Et_2DT = ثنائي اثيل ثنائي ثايوكاربامايت، PyDT = بيروليدين ثنائي ثايوكاربامايت ، PipDT = ببيريدين ثنائي ثايوكاربامايت) حُضرت وشخصت. وجد ان ليكاندات ثايوكاربامايت تسلك سلوك ليكاندات ثنائية السن المخلبية لتنتج معقدات رباعية السطوح مع الكوبلت الثنائي ومربع مستوي مع النحاس الثنائي. اظهرت معقدات ثنائي ثايوكاربامايت فعالية جيدة ضد الاصناف المرضية (بكتيريا او فطريات). حيث وجد ان معقدات نحاس – ثنائي ثايوكاربامايت تمتلك فعالية اعلى من معقدات الكوبلت – ثنائي ثايوكاربامايت، وكانت اعلى فعالية تثبيط لمعقدات ثنائي ثايوكاربامايت ضد بكتيريا *E. coli*، فيما اظهر المعقد $[Cu(\kappa^2\text{-}PipDT)_2]$(6) على فعالية تثبيط مقارنة مع بقية المعقدات. بالإضافة الى استخدام نظرية الكثافة الوظيفية (DFT) في دراسة الكيمياء الحسابية واستقراريه المعقدات المحضرة.