Study of New Derivatives of 1,3,4-Thiadiazole and Its Complexes with chromium ion (Cr\(^{+3}\))

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Abstract

The present study included preparing a new ligand from the thiadiazole derivative 2,5-dihydrazinyl-1,3,4-thiadiazol with 4-Dimethyl amino benzyaldehyde with a ratio of (1:2) to preparing the ligand (L\(_1\)). Transition ion complexe (Cr\(^{+3}\)) were prepared with ligand (L\(_1\)) and ligand and its complexe were diagnosed using the elemental analysis (C.H.N.S), Infrared spectrum (FTIR), Proton nuclear magnetic resonance spectrum (\(^1\)H-NMR), Mass spectroscopy, magnetic sensitivity and molar conductivity, the practical results were exactly in line with the molecular formula and structural formulas for the compounds. The results obtained from the study of magnetic sensitivity and molar conductivity of the prepared ligand complexe confirmed that the geometry shape of [L\(_1\)CrCl\(_2\)]Cl is an octahedral complex. The results of molar conductivity also confirmed that the prepared Chromium complexes is electrolytic.

The biological efficacy of the prepared ligand and its complexity were tested against two type of bacteria *Staphylococcus aureus* and *Escherichia Coli* in comparison with the standard inhibitor (Ciprofloxacin), the obtained results confirmed the biological efficacy of the prepared ligand above that of the standard inhibitor (Cipro), against of the bacteria *Escherichia coli*, also the complexe (X\(_1\)) showed higher biological efficacy than standard inhibitor (Cipro) against *Escherichia coli* (Gram negative), the ligand and its prepared complexe don't showed biological activity against *Staphylococcus aureus*.

Keywords: Thiadiazole, Biological Activity, magnetic sensitivity, molar conductivity.

1: Introduction

1-1: Heterocyclic compounds

Heterocyclic compounds are compounds that contain in composition one or more hetero atoms and common types of them often contain carbon atoms in a high rate.

Nitrogen, sulfur, and oxygen atoms are the most common atoms in this type of compound\(^{[4]}\). Heterocyclic compounds have contributed to the development of broad areas in many areas, for example, health, industrial and agricultural, which contributed
to improving the nature of life\(^{(2)}\), heterocyclic compounds are involved in the synthesis of drugs, vitamins and many other natural cyclic compounds, as well as the main structure in the preparation of pharmaceutical compounds and industrial pesticides, specifically cyclic heterocyclic compounds containing nitrogen in their composition, as they are of great importance due to biological efficacy and clinical applications. Significantly effective compounds both in relation to inhibitory activity and selectivity\(^{(3)}\), the chemistry of heterocyclic compounds occupies a wide area of the fields of chemistry, due to its applications in medicine, pharmacy, photography, rocket fuel, veterinary medicinal products, antioxidants such as corrosion inhibitors as well as in many other fields\(^{(4)}\).

The heterocyclic compounds are considered to be one of the most important chemical compounds with applications in various fields, including the health field, in spite of the discovery and development of antibiotics, but increasing the resistance of microbes to the traditional antibiotics used requires research on new compounds while improving their effect against pathogenic microorganisms, the most advanced Its excitement, which was reached in medical chemistry when heterocyclic compounds played an important role in organizing biological events\(^{(5,6,7)}\).

1,3,4-Thiadiazole derivatives are an interesting ligand in coordinate chemistry, because they can achieve diversity in coordinate media by using nitrogen inside the ring, outside the ring, or sulfur as donor atoms\(^{(8)}\), usually they appear in complex interactions with the tautomericism metallic ions, due to the multiple donor sites. Thiadiazole has its derivatives (1) nitrogen atoms\(^{(9)}\), (2) sulfur thiocarbonyl\(^{(10)}\) and (3) a nitrogen atom and a sulfur atom on the same or different sides of the molecule are distinct ligands with transitional metal ions\(^{(11)}\). In addition the electrons (\(\pi\)) in of 1,3,4-thiadiazole aromatic cycle may co-ordinate with the metal ions\(^{(12)}\).

2: Procedure

2-1: Synthesis compound (A) 2,5-dimercapto-1,3,4-thiadiazole

The potassium hydroxide (22g, 0.4 mole) was dissolved in ethanol (100ml) in the reaction flask (reflex), then adding hydrazine (16 ml) and heating the reaction mixture for (10-15hr), then cooling at room temperature and then adding (50ml) carbon Disulfide (gradually and in small batches with stirring) heating the reaction mixture for (6-8 hr.) The follow-up of the reaction should be monitored using thin layer chromatography (TLC) or the dissolution of the odor that is similar to The smell of decomposing eggs resulting from the release of hydrogen sulfide gas, or by using lead acetate solution (CH3COO\text{Pb}) when the blackening of the leaf A filtration moistened with a solution resulting from the formation of hydrogen sulfide gas (H\(_2\)S), this indicates the end of the reaction and the formation of the product of the derivative of thiadiazole, cooling by ice for about an hour and then adding a solution of hydrochloric acid (HCl) 10% of the reaction mixture, heating the reaction mixture for one hour and then cooling, we note the deposition of yellow crystals due to the thiadiazole derivative (2,5-dimercapto-1,3,4-thiadiazole)\(^{(13,14)}\). Filter the solution and then wash it with distilled water, and recrystallize it using ethanol, and drying. The weight of the formed product is (22gm, 0.25mole), with yield about (78%), and the melting point (m.p) ranges from (163-165)\(^{\circ}\)C as in Figure (2-1).
2-2: Synthesis compound (B) 2,5-dihydrazinel-1,3,4-thiadiazole

The compound (A) was dissolved in ethanol absolute (100ml) and adding hydrazine (5 ml) and heating the reaction mixture (Reflux) for (9-12hr), Follow the reaction progress until the reaction end point is reached by TLC, after making sure the end of the reaction and the formation of pale white crystals (yellowish), evaporating the solution to the half, and then conducting agent filtration and washing the precipitate with distilled water, and re-crystallization using absolute ethanol and distilled water. The obtained crystals (B) (2,5-dihydrazinel-1,3,4-thiadiazole) obtained with a pale white (yellowish) color (5.2 g, 0.03 mole) weighed their melting point (172-174) ºC, with yield (71%)[15], as shown in Figure (2-3)

2-3: Synthesis ligand (1) 4,4'-(1E,1'E)-((1,3,4-thiadiazole-2,5-diyl)(hydrazin-2-yl-1-ylidene))bis(methaneylylidene))bis(N,N-dimethylaniline)

Mix (3g, 0.02 mole) of the 4-Dimethyl amino benzyaldehyde dissolved in (50ml) of ethanol absolute with (1.46g, 0.01mole) of compound (B) dissolved in (50ml) of ethanol absolute then added glacial acetic acid (3-4 drops) gradually to the reaction flask and in small batches, then heating for (3-4hr), Follow the reaction progress until the reaction end point is reached by TLC, after confirming the end of the reaction and the precipitate being formed, the cooling process is carried out by placing the reaction flask in the ice for about an hour, and then the precipitate is filtered after its concentration (vaporization) to approximately half its volume, washing and re-crystallization, and the
result is in the form of a yellow powder of (3.2 g) The melting point (174-176) °C and with yield about (80%), as shown in Figure (2-4).

Figure (2-4) Synthesis ligand (L₁)

**2-4: Synthesis ligand (L₁) complexe**

Add (mole0.02) of ligand (L₁) in the reaction flask dissolved in (50ml) of absolute and hot ethanol to (0.001 mole) of salt (CrCl₃.6H₂O) to the reaction flask periodically and heat the reaction mixture (Reflux) for (3-4hr), Follow the reaction progress until the reaction end point is reached by TLC, the cooling process is carried out by placing the reaction flask in the ice for about an hour, and then the precipitate is filtered after its concentration (vaporization) to approximately half its volume, washing and re-crystallization using absolute ethanol[^13]. The yield obtained from the crystals of the transitional elements complexes with the ligand (L₁) with some physical properties as shown in Table (2-1).

| Chemical Formula | Yield % | m.p °C | Color          | M.wt  |
|------------------|---------|--------|----------------|-------|
| C₂₀H₂₄N₈S        | 80      | 174-176| Dark yellow    | 408.5 |
| [CrCl₂]Cl        | 61      | 288-290| light brown    | 566.9 |

Table (2-1) Chemical formula and some physical properties.

**3: Results and discussion**

**3-1: Characterize of prepared compounds**

The prepared ligand and its metal complexes were diagnosed based on the results of the Elemental Analyzer Instrument, the infrared spectrum, the proton nuclear magnetic resonance spectrum and the mass spectrum.

**3-2: Elemental Analysis**

The results of the Elemental Analyzer Instrument for the prepared ligand shows the extent of congruence between the practical percentages of the elements (S, N, H, C) with the theoretical percentages calculated for this ligand

| Sym. | Chemical Formula | M.wt | Color       | m.p °C | Yield % |
|------|-----------------|------|-------------|--------|---------|
| L₁   | C₂₀H₂₄N₈S       | 408.5| Dark yellow | 176-174| 80      |
| L₁X₁ | [CrCl₂]Cl       | 566.9| light brown | 288-290| 61      |

**Table (3-1) Elemental Analyzer Instrument Data for prepared ligand (L₁)**

| Sym. | Practical Percentages | Theoretical Percentages |
|------|-----------------------|-------------------------|
|      | C %  | H %  | N %  | S %  | C %  | H %  | N %  | S %  |
| L₁   | 58.65| 5.85 | 27.29| 7.85| 58.80| 6.92 | 27.43| 7.85|

**3-3: Infrared Spectra**

The infrared spectra of ligand (L₁) and its complexe showed the presence of groups (CH = N) and (NH), and we note the stretch vibration peak of the group (C = N) in these compounds as a clear package in the area (1603-1630) cm⁻¹, the stretch vibration peak of the (N-H) group, it appeared in the region (3194-3198) cm⁻¹, the stretch vibration peak was shown at (3080-3028) cm⁻¹ returns to the aromatic group (C-H),
and the ligand also contains a stretch in the region (2882) cm\(^{-1}\) due to the stretch vibration of the aliphatic group \((C-H)\), and a peak appears at the region (1603-1489) cm\(^{-1}\) returns to the vibration of the stretch of the group \((C=C)\) present in the aromatic rings of prepared compounds. The five-ring spectrum of thiadiazole was distinguished by the appearance of an absorption package in the region \((1338, 1320, 1319, 1304)\) cm\(^{-1}\) it returns to the structural movement of the ring and the symmetric and asymmetric stretch vibration of the \(C-S-C\) group. The infrared spectra are very important in determining the type of correlation in the case of complexes, where shifting to a higher peak of highest vibration of the group \((C = N)\) appeared in the complexes shifting towards higher wavenumber compared to their location in the prepared ligand, and this confirms bound nitrogen azomethine group for dual electronic component to form coordination bond, the complex spectrum was distinguished by the appearance of the stretch vibration \(M-Cl\) in addition to \(M-N\) which were not present in the ligand this confirm that the complexation process has occurred, as these peaks appeared at the sites \((508-516)\) cm\(^{-1}\), \((276)\) cm\(^{-1}\) are due to stretch vibration \((M-N)\), \((M-C1)\), respectively, as shown in Table (3-2).

**Table (3-2)** Shown the most important peaks in the infrared spectra of the prepared ligand \((L_1)\) and their complexes in units \((cm^{-1})\)

| Sym  | Chemical Formula | N-H | Ar. C-H | Aliph C-H | C=N | M-N | M-Cl |
|------|------------------|-----|---------|-----------|-----|-----|------|
| L    | \(C_{20}H_{24}N_{8}S\) | 3198 | 3080    | 2821      | 1603|      |      |
| \(X_1\) | \([L_1CrCl_2]\) Cl | 3198 | 3028    | 2880      | 1632| 516 | 276  |

**Figure 3-1**: Infrared spectrum of the complex \([L_1CrCl_2]\) in the Potassium bromide disk.
Figure 3-2: Infrared spectrum of the complex [L₁CrCl₂] in the cesium iodide disk.

3-4: Nuclear Magnetic Resonance Spectra (¹H-NMR)

The nuclear magnetic resonance spectra for the ligand (L₁) was distinguished by the appearance of multiple peaks at (7.77-8.19 ppm) and is due to the aromatic ring protons, a peak at (8.98 ppm) is due to the proton of the group (CH=N), a beam at (10.58 ppm) is due to the proton of the group (N-NH-C=), the spectrum also showed another peak at (2.66-3.32 ppm) returning to 12 protons of (-CH₃) groups, in addition to another peak at (2.5 ppm), returning to the solvent Dimethyl sulfoxide (DMSO) (18,19) as shown in the figure (3-3).

Table (3-3) The peaks shown in the Nuclear Magnetic Resonance Spectra of the prepared ligand (L₁).

| Compound | Group       | Kind of signal | Shift (ppm) | Integration |
|----------|-------------|----------------|-------------|-------------|
| L₁       | N-NH-C=     | Singlet        | 10.5        | 2H          |
|          | CH₃-N       | Singlet        | 3.3         | 12H         |
|          | CH=N-       | Singlet        | 8.9         | 2H          |
|          | Benzene ring| Multiple       | 7.7-8.4     | 8H          |
3-5: Mass Spectra

Most of the research that is concerned with studying and preparing complexes of transition elements depends on the mass spectrum to confirm the structural formulas of the complexes as this spectrum confirms the structural formulas for the prepared Schiff’s bases and their complexes by noticing the molecular ion peak (M⁺) and the appearance of main peak of the ions separated from the mother molecule therefore the mass spectrum was used to diagnose thiadiazole derivatives.

3-5-1: Mass spectra of the ligand (L₁)

The ligand mass spectrum was characterized by the appearance of the molecular ion (M⁺) [C₂₀H₂₄N₈S]⁺ at (408 m/z). The spectrum also showed the following peaks 77, 178, 218, 269, 334, 378 m/z which due to, [C₆H₅]⁺, [C₈H₈N₃S]⁺, [C₉H₈N₅S]⁺, [C₁₂H₉N₆S]⁺, [C₁₆H₁₂N₇S]⁺, [C₁₈H₁₈N₈S]⁺, respectively, as shown in Table (3-4) and Figure (3-4).

| M/Z     | ion Formula               |
|---------|---------------------------|
| 408     | [C₂₀H₂₄N₈S]⁺              |
| 378     | [C₁₆H₁₂N₇S]⁺              |
| 334     | [C₁₂H₉N₆S]⁺               |
| 269     | [C₁₆H₁₂N₇S]⁺              |
| 218     | [C₆H₅]⁺                   |
| 178     | [C₈H₈N₃S]⁺                |
| 77      | [C₆H₅]⁺                   |

Table (3-4) Mass spectra of the ligand (L₁)
Figure (3-4) Mass spectra of the ligand (L₁)

3-5-3: Mass spectra of the complex [L₁CrCl₂]Cl

The mass spectrum of the molecular ion complex, [L₁CrCl]Cl (M⁺), showed a peak at (566 m/z) as noted in the spectrum of the following ion peaks (462, 497, 532 m/z) due to the loss of chlorine atoms [L₁Cr]⁺, [(L₁CrCl)]⁺, [(L₁CrCl₂)]⁺ respectively, as shown in Table (3-5) and figure (3-5).

Table (3-5) Mass spectra of the ligand (X₁)

| M/Z     | [L₁CrCl₂]Cl | [L₁CrCl₂]⁺ | [L₁CrCl]⁺ |
|---------|-------------|------------|-----------|
| 566     |             |            |           |
| 532     |             |            |           |
| 497     |             |            |           |
| 462     |             |            |           |
3-6: Molar Conductivity

The conductivity values indicate that the complex [L1CrCl2]Cl exhibits the behavior of the ionic compounds and the conductivity is different between them (1:1) depending on the number of chloride ions outside the consistency ball as Counter Ions for the central ion, the presence of chlorine outside the coordination ball was also confirmed by adding the aqueous solution AgNO₃ to the complex solution (dissolved in DMSO), where a white precipitate was observed in the presence of chlorine outside the coordination ball, and the turbidity increases with the increase in the number of chlorine atoms outside the coordination ball, and the absence of a precipitate or a non-turbidity of the solution indicates that there is no chloride ion outside the coordination ball as a conjugated ion. The results obtained were consistent with the molecular formula and stereo formula of the proposed prepared complexe (29).

Table (3-6) Molar conductivity values Λm for complexe (L₁X₁) in the solvent DMSO (10⁻³ M) at a temperature of 298K.

| Electrolyte Type | Λm (S. cm².mole⁻¹) | Complexes |
|------------------|--------------------|-----------|
| In (DMSO) 1:1    | 39                 | [L₁CrCl₂]Cl |

3-7: Magnetic sensitivity

Effective magnetic moment values (μₑ ff) were calculated for the prepared complexe for the purpose of obtaining additional evidence that strengthens the conclusion of the proposed structural formulas for them. The results shown in Table (3-8) show a decrease in the values of magnetic moments of the prepared complexe, which confirms that these complexe are of a low spin this means that the prepared ligand is classified as a strong ligand. The calculated effective magnetic moment values calculated for the triple chromium ion (Cr³⁺) showed the presence of three single electrons and no presence of the orbital contribution (17).
Table (3-7): Effective magnetic moments (μ_{eff}) of prepared ligand complexes

| Symbol  | Complexes | Symbole |
|---------|-----------|---------|
| X1      | [Cr L1Cl3]|         |
| 3.9     |           |         |

3-8: A study of the electronic density of ligands using the Hyperchem program

The Hyperchem program was used to draw the prepared ligands using the PM3 method and demonstrate the Electrostatic Potential. The study of the electrical potential of the molecule is very important for finding effective sites in the molecular system (21). The voltage of the prepared ligand is drawn, as shown in Figure (3-6).

Through the spectroscopic and analytical studies of the prepared thiadiazole derivative and its complex it was concluded that ligand (L1) has its octahedral complex with salts of three-oxidant transition elements (Cr^{3+}), as shown in Figure (3-7).

3-9: Evaluation Biological Activity of ligand and its complex

The activity of ligand (L1) and its complex prepared against two types of pathogenic bacteria, Gram negative and Gram positive, it is a dye that treats bacteria those that respond to this dye take the dye and do not put it outside the cell wall they are positive, which do not respond to this dye so that they take the dye and put it outside the
cell wall, which is negative towards this dye. This difference between the bacteria is due to the nature of its external walls\(^{22}\). For this reason, two types of bacteria were used, the first sensitive and positive Gram (\textit{Staphylococcus aureus}) and the second sensitive and negative for Gram (\textit{Escherichia coli}).

Dissolve (0.05g) of ligand or complex in (1ml) of DMSO and inject the bacteria dishes after making holes in them using a Cork Borer with (0.1ml) of these solutions in each hole and incubated at a temperature (37˚C) for 24 hours, then measured diameters of inhibition zones compared to the inhibition of these materials with standard inhibitor is (Cipro) and the same concentration, as shown in the table (3-8) and (Figure 3-8).

1-The prepared ligand showed higher biological efficacy than standard inhibitor (Cipro) against \textit{Escherichia coli} (Gram negative).

2-The complexes (X\(_1\)) showed higher biological efficacy against \textit{Escherichia coli} (Gram negative) than standard inhibitor (Cipro).

3-The prepared ligand and its complexes don't show any biological efficacy than against \textit{Staphylococcus aureus} (positive Gram).

Table (3-8) The Biology Effect of Compounds Prepared against \textit{Escherichia coli} and \textit{Staphylococcus aureus} Compared to the standard inhibitor (Cipro).

| Symbol  | \textit{Escherichia coli} Inhibition zone(mm) | \textit{Staphylococcus aureus} Inhibition zone(mm) |
|---------|---------------------------------------------|-----------------------------------------------|
| 8 (L\(_0\)) | 17+++                                      | 0-                                          |
| 10(X\(_1\)) | 15+++                                      | 0-                                          |
| Cipro | 9+                                          | 7+                                          |

Note: +++ Very good Inhibition, ++ Good Inhibition, + middle Inhibition, - Not Inhibition.

Figure (3-9): Biological effectiveness of ligand and its complex against \textit{E. coli} on the right and at left and \textit{Staph} Inhibition.
4: Conclusion
1- The new ligand prepared from (1,3,4-Thiadiazole) formed stable metal complexes with a short time with two-and-three-positively charged metallic ions, this consider to be an indication that the prepared ligand has a great ability to coordinate with the metal ions.
2- The triple metal ion (Cr$^{3+}$) gave an octahedral complex.
3- By the results of the measured magnetic sensitivity of the prepared complex, it was found that the prepared ligand possesses a strong ligand field.
4- Spectroscopic and analytical studies have included the results of the infrared spectrum, elemental analysis, NMR spectroscopy and mass spectrometry, as well as measurements of molar conductivity and magnetic sensitivity confirmed the proposed molecular and structural formulas for the prepared compounds.
5- The ligand prepared from 1,3,4-Thiadiazole and its complex showed a strong to moderate inhibition activity against an *Escherichia coli*, which encourages future studies on the biological efficacy of metal complexes and similar types of prepared ligands.
6- The current study showed that the prepared derivatives of 1,3,4-Thiadiazole and its complex do not have an inhibitory biological activity towards a *Staphylococcus aureus*.

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