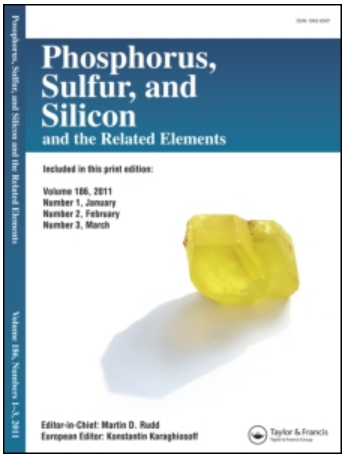

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Hosny, Nasser Mohammed and Sherif, Yousery E.(2009) 'Binary and Ternary Metal Complexes Derived from Cu Acetate with Some Sulfur-Containing Chemotherapeutic Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 11, 2786 — 2798
To link to this Article: DOI: 10.1080/10426500802583579
URL: http://dx.doi.org/10.1080/10426500802583579

Phosphorus, Sulfur, and Silicon, 184:2786–2798, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802583579

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Binary and Ternary Metal Complexes Derived from Cu Acetate with Some Sulfur-Containing Chemotherapeutic Agents

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Two ternary complexes, $[Cu_2(Pir)(Pen)(OH)(Ac)H_2O]$ and $[Cu(Pir)(Cap)(Ac)]\frac{1}{2}H_2O$ (where, Pen = D-penicillamine, Cap = captopril, and Pir = piroxicam) have been synthesized and characterized using elemental analyses, spectroscopic analyses (IR, UV-vis, MS), thermal analyses (TGA), conductance measurements, and magnetic measurements. The binary complexes, $[Cu_2(Pen)(OH)_2(H_2O)_2]\,4H_2O$ and $[Cu(Cap)Ac]\,3/2H_2O$, have also been prepared and characterized by these techniques to facilitate the interpretation of the mixed ligand complexes. The results show that D-penicillamine can coordinate two copper atoms through amino nitrogen, and thiol sulfur after displacement of a hydrogen atom. At the same time, the ligand coordinates to the second copper atom through a carboxyl group after displacement of a hydrogen from the latter group. Captopril coordinates through thiol sulfur and carbonyl oxygen. Piroxicam coordinates as a neutral bidentate ligand in the keto form through carbonyl oxygen and pyridyl nitrogen. The magnetic moment measurements of complexes containing captopril indicate the reduction of Cu(II) to Cu(I) by the thiol group.

Keywords Captopril; copper complexes; D-penicillamine; piroxicam

INTRODUCTION

Experimental evidence collected during decades of research work by many groups proved that the coordination of Cu(II) by nonsteroidal anti-inflammatory drugs (NSAIDs) improves the pharmaceutical activity of the drugs themselves and reduces their undesired toxicity effects in human and veterinary medicine.[1–7] Among NSAIDs, those from the "oxicam" family have been extensively used in a variety of inflammatory

Received 8 July 2008; accepted 27 October 2008.
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and rheumatic diseases in humans.[8–10] Captopril (1-(D-3-mercapto-2-methylpropionyl)-L-proline) was the first orally active angiotensin-converting enzyme (ACE) inhibitor used for treating patients suffering from hypertension. Side effects are often associated with the drug especially when high doses are given.[11–13] This is probably due to Zn or Cu depletion in the plasma. Previous studies showed that captopril can mobilize zinc from the plasma proteins.[14] Torreggiani et al. showed that the ability of the thiolate group in captopril to reduce Cu(II) to Cu(I) depends on the M:L ratio. At a 1:1 ratio, a Cu(II) complex of captopril was obtained.[15] D-penicillamine is a sulfur-containing amino acid, first used as a medication for clearing the human body from excess copper, used in the treatment of Wilson's disease,[16] as a therapeutic agent in treatment of rheumatoid arthritis,[17] as detoxicant (antidote) upon poisoning from heavy metals,[18–20] for inhibiting HIV replication, and for the treatment of hepatitis.[21] Complexation of some transition metal ions with D-penicillamine was studied with Cu(II) in solution.[22] Interest in D-penicillamine as a ligand arises from several possible modes of coordination. D-penicillamine can coordinate through three functional groups (NH_2, S, and COO). It usually forms bidentate complexes by coordination of N and S atoms,[23,24] but formation of monodentate (S),[25,26] tridentate (N, O, S), or tetradentate (N, O, O, S) complexes[27,28] can not be ruled out. The sulfur, nitrogen, or oxygen atoms could also act as a bridging ligand.[29,30] In the present article, the preparation and characterization of binary and ternary Cu complexes with D- penicillamine, captopril, (piroxicam + D-penicillamine), and (piroxicam + captopril) have been reported.

RESULTS AND DISCUSSION

The analytical data for the complexes, together with their physical properties, are shown in Table I. All the complexes are stable in air and soluble in DMF and DMSO. The low molar conductivity values in DMSO (1.9–2.0 Ω^{-1} cm^2mol^{-1}) suggest that the complexes are non-electrolytes.[31]

IR Spectra

The most important IR data of the free ligands and their Cu(II) complexes are collected in Table II. The most important bands in the spectra of D-penicillamine assigned to $\nu_{as}(COO^-)$ at 1594 cm^{-1} and $\nu_{as}(NH_3^+)$ at 3174 cm^{-1} correspond to the Zwitterionic form of the amino acid.

TABLE I Analytical Data and Physical Properties of the Complexes

Compound	Color	Mp°C	% Found (Calcd) C	H	Cu
$[Cu_2(Pen)(OH)_2(H_2O)_2]\cdot 4H_2O$	Black	>300	14.5(14.3)	5.4(5.7)	30.5(30.4)
$[Cu(Cap)Ac]\cdot 3/2H_2O$	Olive green	208	36.2(36.0)	5.9(6.0)	17.4(17.3)
$[Cu_2(Pir)(Pen)(OH)(Ac)H_2O]$	Dark green	235	38.0(37.8)	3.5(3.9)	18.6(18.1)
$[Cu(Pir)(Cap)(Ac)]\cdot \frac{1}{2}H_2O$	Light green	225	46.5(46.0)	3.3(3.8)	10.0(9.4)

The band at 1734 cm^{-1} assigned to ν(COOH) is absent, indicating that D-penicillamine is presented in the Zwitterion form.[29]

D-penicillamine binds two copper ions at the same time (Figure 1). It coordinates to the first copper atom through amino nitrogen and thiol sulfur after displacement of a hydrogen atom. At the same time, it coordinates to the second atom through a deprotonated carboxyl group, which acts as bidentate donor. The Cu(II) complex shows a strong band at 1617 cm^{-1} corresponding to δNH_2.[29] The shift of the band assigned to $\nu_{as}(NH_2)$ towards higher frequency (3249 cm^{-1}) is taken as an evidence of the participation of a nitrogen atom in coordination.[29,32] No bands correspond to free the COOH group. The bands observed at 1630 and 1466 cm^{-1} are assigned to $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$, respectively, of the coordinated carboxyl group.[29] The correlation between the positions of the antisymmetric and symmetric stretching vibrations of the carboxyl group and the type of coordination of this group was studied earlier.[33] It was concluded from these studies that while the frequency difference between the two carboxyl stretching in the case of ionic carboxyl groups is usually in the interval ~167 cm^{-1}, longer values were found for monodentate and lower values for bidentate groups.[34] In the present case, the difference between the antisymmetric and symmetric stretching vibrations of carboxyl group is 164 cm^{-1}, indicating the bidentate nature of the carboxyl group. Also, the band position of $\nu_{as}(COO^-)$ matches with a previously reported bidentate carboxyl group of amino acids.[34] The bands at 2609 and 2513 cm^{-1} assigned to ν(S-H) in the spectrum of D-penicillamine disappeared in the spectrum of Cu(II) complex, indicating the participation of S atom in coordination. The spectrum of the complex shows two sharp bands at 3487 and 3573 cm^{-1} assigned to M-OH.[34]

The principle IR bands of captopril and its Cu complex are listed in Table II. Captopril shows bands at 3300, 2562, 1742, 1590, and 1446 cm^{-1} assigned to ν(OH) of carboxyl group hydrogen bonded, ν(SH), ν_{as}(COO), ν(CO)amide, and ν_s(COO), respectively.[35] Captopril chelates

TABLE II Experimental IR Spectra of D-Penicillamine, Captopril, Piroxicam, and Their Metal Complexes

Compound	νOH	ν NH	ν_{as}COO	νCO	ν_{s}COO	δNH_3^+	νM-O	νM-N	νM-S
Pirox	3464	3339	—	1630	—	—	—	—	—
Capt	3250	—	1742	1590	1446	—	—	—	—
Penicil	—	3174	1617	—	1594	—	—	—	—
$[Cu_2(Pen)(OH)_2(H_2O)_2]4H_2O$	—	3372	1630	—	1466	1617	567	453	402
$[Cu(Cap)Ac]3/2H_2O$	3417	—	1734	1610	1442	—	551	—	432
$[Cu_2(Pir)(Pen)(OH)(Ac)H_2O]$	3338, 3458	3391	1637	1605	1477	1570	522	475	379
$[Cu(Pir)(Cap)(Ac)]1/2H_2O$	3338, 3420	3100	1743	1618, 1605	1445, 1596	—	528	—	378

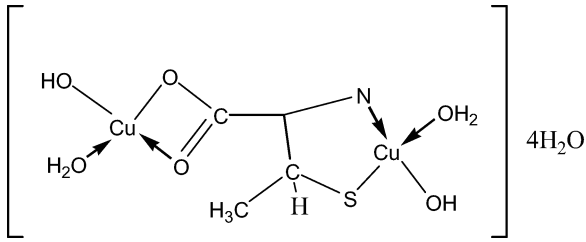


FIGURE 1 Suggested structure of $[Cu_2(Pen)(OH)_2(H_2O)_2]4H_2O$.

to the Cu(II) as a mononegative bidentate ligand through the oxygen of the amidic carbonyl and sulfur of (SH) group after deprotonation of the latter group (Figure 2). This suggestion is supported by the following evidence: (i) The disappearance of the band at 2562 cm^{-1} assigned to ν(SH), indicating that this group takes part in coordination after displacement of hydrogen; (ii) the shift of the band assigned to ν(CO) to higher wave number[35]; (iii) the presence of the bands assigned to the COOH group more or less unaltered, indicating that this group does not take part in coordination; (iv) the presence of two new bands at 1566 and 1411 cm^{-1} assigned to $\nu_{as}(CH_3COO)$ and $\nu_s(CH_3COO)$ (The difference between these two bands, 155 cm^{-1}, is taken as an evidence of bidentate nature of this group.[33]); and (v) the spectrum of the complex showing several new weak bands at 551, 460, and 432 cm^{-1} assigned to ν(M-O), ν(M-N), and ν(M-S) respectively.[34]

The IR spectrum of [Cu(Pir)(Cap)(Ac)] $1/2H_2O$ shows that the captopril can act as mononegative bidentate coordinating to Cu(II) ion through amidic carbonyl oxygen and mercaptal sulfur after deprotonation (Figure 3). This behavior is suggested on the basis of the following IR evidence: (i) The shift of the band assigned to amidic carbonyl group

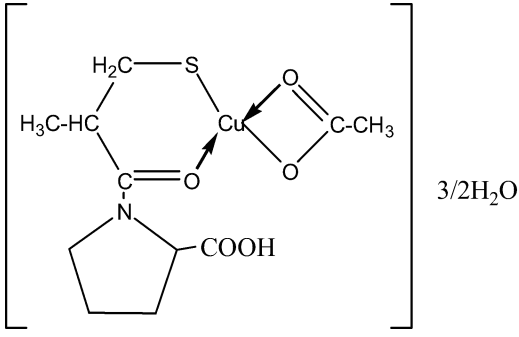


FIGURE 2 Suggested structure of $[Cu(Cap)Ac]3/2H_2O$.

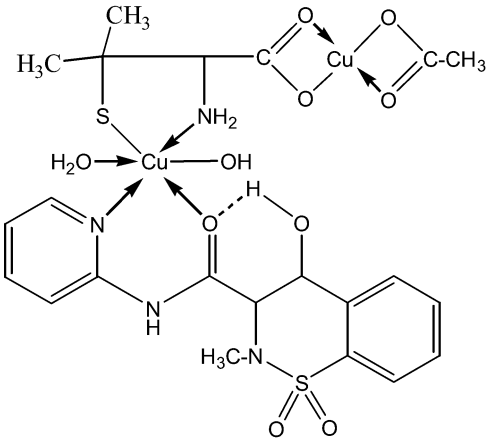


FIGURE 3 Suggested structure of $[Cu_2(Pir)(Pen)(OH)(Ac)H_2O]$.

$(CO)_{capt}$ to higher wavenumber suggests that carbonyl oxygen takes part in coordination[35]; (ii) the absence of the band at 2562 cm^{-1} assigned to ν(SH) suggests that this group coordinates to the metal ion through sulfur atom after displacement of hydrogen; (iii) the shift of the band assigned to ν(C-S) to higher wavenumber 1237 cm^{-1} in the spectrum of the complex may be taken as an additional evidence of the participation of the sulfur atom in bonding; and (iv) the presence of the bands assigned to ν(OH), $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ more or less unaltered in the spectra of copper complex indicates that carboxyl group does not take part in coordination.

At the same time, piroxicam binds to the same copper atom as neutral bidentate coordinating *via* pyridyl nitrogen and carbonyl oxygen in the keto form. This behavior is suggested on the basis of the following evidence: (i) The shift of the band assigned to $\nu(C{=}O)_{pirox}$ to lower wavenumber 1605 cm^{-1} is taken as an evidence of the participation of carbonyl oxygen in bonding; and (ii) the negative shift of the band at 1565 cm^{-1} assigned to $\nu(C{=}N)_{py}$ indicates the participation of this group in bonding. The spectrum shows strong band at 3338 cm^{-1} assigned to hydrogen bonded phenolic OH of piroxicam. The remaining of this band unaltered is taken as evidence that this group does not take part in coordination.

The bands at 3420, 3338, 1352, and 1182 cm^{-1} assigned to ν(OH) of captopril, $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$, respectively, remain more or less unaltered indicating that these groups do not take part in coordination.[36] The spectrum of the complex shows several new bands at 528, 454, and 378 cm^{-1} assigned to ν(M-O), ν(M-N), and ν(M-S), respectively.[34]

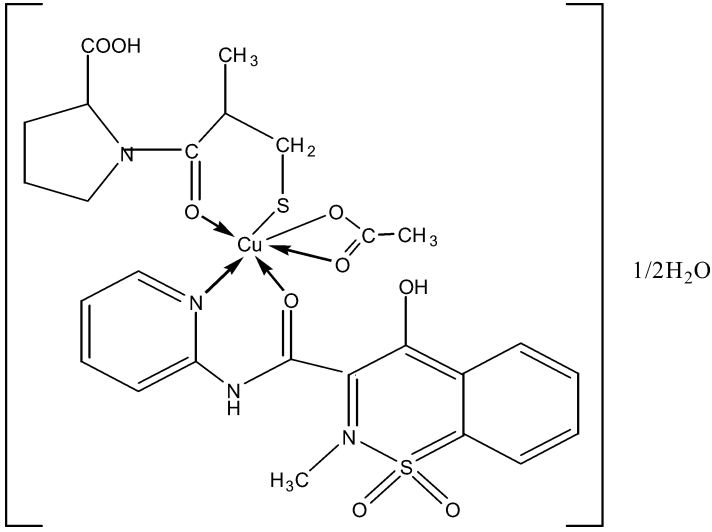


FIGURE 4 Suggested structure of [Cu(Pir)(Cap)(Ac)]$\frac{1}{2}H_2O$.

IR spectrum of [Cu_2(Pir)(Pen)(OH)(Ac)H_2O] shows that D-penicillamine can coordinate two Cu(II) atoms as binegative tetradentate. It coordinates to the first Cu atom through (SH) group after deprotonation and (NH_2) group (Figure 4). This behavior is suggested on the basis of the following evidence: (i) The disappearance of the bands assigned to ν(SH); (ii) the shift of the bands assigned to $\nu(NH_2)$ to higher wavenumbers 3272 and 3245 cm^{-1} is taken as evidence of the participation of amino group in bonding. At the same time, D-penicillamine coordinates to the second Cu atom through the carboxylate group after displacement of hydrogen from the latter group. This suggestion is supported by the shift of the bands assigned to $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ to lower wavenumbers 1637 and 1479 cm^{-1}, respectively, which is taken as evidence of the participation of the carboxyl group in coordination. The difference between these two bands indicates the bidentate nature of this group.[34]

Piroxicam coordinates to Cu(II) as a neutral bidentate through carbonyl oxygen and pyridyl nitrogen. This behavior is suggested on the basis of the following evidence: (i) The shift of the band assigned to $\nu(CO)_{pirox}$ to lower wavenumber 1605 cm^{-1}; (ii) the disappearance of the band assigned to ν(OH) from the spectrum of the complex; and (iii) the negative shift of the bands assigned to pyridyl nitrogen at 1557, 1042, 657 cm^{-1}, indicating the participation of pyridyl nitrogen in coordination. The spectrum shows two bands at 1530 and 1398 cm^{-1} assigned to

TABLE III Thermoanalytical Results (TG) of Cu(II) Complexes

Complex	T range (°C)	Mass loss Estd (Calcd%)	Assignment
[Cu(Pir)(Cap)(OAc)] 1/2H_2O	30–100	2.0 (1.3)	Loss of 1/2 H_2O molecule of hydration
	165–265	46.7 (45.9)	Loss of $C_{10}H_9N_2O_4$+ acetate
	265–443	28.5 (27.1)	Loss of $C_9H_{14}NO_3$
	446–982	13.0 (11.5)	Loss of Py
	983–1000	15.7 (14.0)	Residue (CuS)
[Cu_2(Pir)(Pen)(OH) (Ac)H_2O]	119–174	3.2 (2.6)	Loss of one coordinated H_2O molecule
	176–236	28.0 (27.1)	Loss of Penicillamine-S, CH_3COO and CH_3
	237–384	28.2 (29.5)	Loss of $C_{10}H_8O_2NS$
	386–879	13.2 (13.3)	Loss of PyNH
	879–1000	27.1 (25.0)	Residue CuS + CuO
[Cu_2(Pen)$(OH)_2(H_2O)_2$] 4H_2O	48–137	18.1(17.3)	Loss of 4H_2O molecules of hydration
	197–336	4.5 (4.3)	Loss of one coordinated H_2O molecule
	600–671	7.5 (8.1)	Loss of 2 (OH)
	672–732	23.1 (23.7)	Loss of $(CH_3)_2CCHNHCO$
	732–800	41.6(42.0)	Residue of CuS and CuO
[Cu(Cap)Ac]3/2H_2O	41–180	8.0 (7.4)	Loss of 3/2H_2O molecules of hydration
	181–219	11.4(12.0)	Loss of CO_2 molecule
	219–318	35.0 (35.3)	Loss of CH_3 and C_4H_7NCOOH
	318–660	14.7 (14.8)	Loss of CH_2CHCH_3C
	660–800	26.2(26.0)	Residue of CuS

$\nu_{as}(CH_3COO^-)$ and $\nu_s(CH_3COO^-)$, respectively. The difference between these two bands indicates bidentate nature of this group.[33] Also, there is a band at 3458 cm^{-1} assigned to the phenolic OH group.

Thermal Analyses

The thermal analysis (TGA and DTG) curves of the complexes were carried out within a temperature range from 25°C up to 800°C. The estimated mass losses were computed based on the TGA results, and the calculated mass losses were computed using the results of micro-analyses (Table III). The determined temperature range and percent losses in mass of the solid complexes are given in Table III.

Thermal analyses curves (TGA and DTG) show that [Cu(Pir)(Cap)(Ac)]1/2H_2O decomposes in four stages. The first

stage, which lies in temperature range 30–100°C corresponds to the loss of 1/2 H_2O molecule of water of hydration. The second stage lies in the temperature range 165–265°C. This stage corresponds to the loss of piroxicame molecule without the pyridyl moiety ($C_{10}H_9N_2O_4$) and acetate group. The third step lies in the temperature range 265–443°C. This step corresponds to the loss of captopril molecule without a sulfur atom ($C_9H_{14}NO_3$). The last step lies in the temperature range 446–982°C and corresponds to the loss of pyridyl moiety. The estimated residue corresponds to CuS.

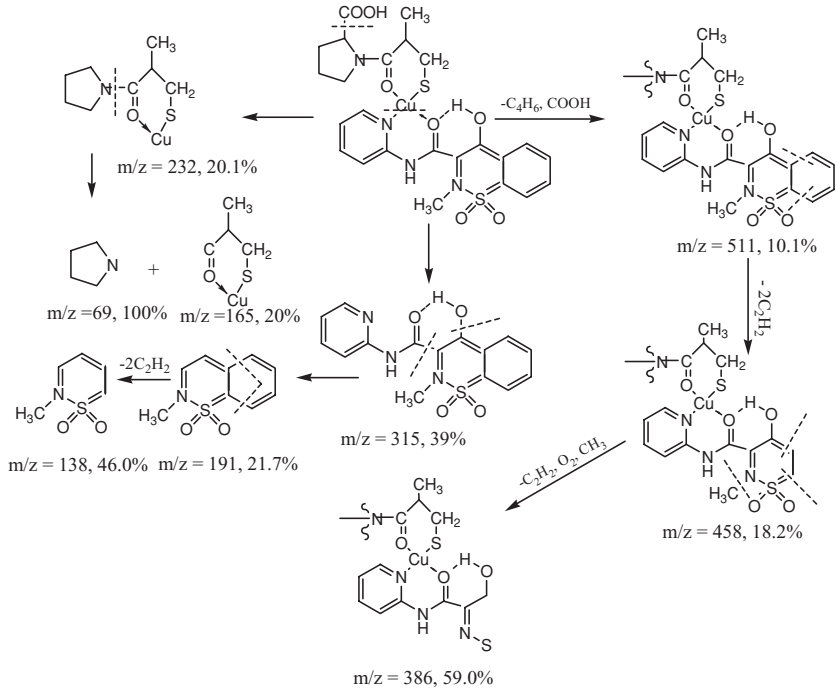
The thermograms of [Cu_2(Pir)(Pen)(OH)(Ac)H_2O] show four stages of decomposition. The first stage lies in the temperature range 119–174°C and corresponds to the loss of one molecule of water of coordination. The second stage lies in the temperature range 176–236°C. This stage corresponds to the loss of penicillamine without sulfur $(CH_3)_2CCHNHCOO$, the acetate group (CH_3COO), and methyl group (CH_3) from piroxicame. The third step lies in the temperature range 236–384°C and corresponds to the loss of piroxicame without PyNH ($C_{10}H_8O_2NS$). The last step corresponds to the loss of PyNH. The estimated residue corresponds to (CuS + CuO).

Thermal analyses curves (TGA and DTG) of [Cu_2(Penicil)$(OH)_2$ $(H_2O)_2$] $4H_2O$ show that it decomposes in four stages. The first stage lies in temperature range 48–137°C and corresponds to the loss of $4H_2O$ molecules of water of hydration. The second stage lies in the temperature range 197–336°C. This stage corresponds to the loss of one coordinated H_2O molecule. The third step lies in the temperature range 600–671°C. This step corresponds to the loss of two hydroxyl groups. The last step lies in the temperature range 672–732°C and corresponds to the loss of $(CH_3)_2CCHNHCO$ moiety. The estimated residue corresponds to CuS and CuO.

The thermograms of [Cu(Cap)Ac] $3/2H_2O$ show four stages of decomposition. The first stage lies in the temperature range 41–180°C and corresponds to the loss of one and one-half molecules of water of hydration. The second stage lies in the temperature range 181–219°C. This stage corresponds to the loss of one molecule of CO_2. The third step lies in the temperature range 219–318°C and corresponds to the loss of CH_3 and C_4H_7NCOO. The last step corresponds to the loss of CH_2CHCH_3C. This step lies in the temperature range 318–660°C. The estimated residue corresponds to CuS.

Mass Spectra

The fragmentation pattern of [Cu(Pir)(Cap)(Ac)]$1/2H_2O$ as shown in Scheme 1. The spectrum (Figure 5) shows the molecular ion peak



SCHEME 1 Fragmentation pattern of [Cu(Pir)(Cap)(Ac)]1/2H_2O.

corresponds to the suggested molecular weight after loss of 1/2 H_2O molecule, CH_3COOH, and two molecules of ethylene $2(C_2H_4)$.

Electronic Spectra and Magnetic Moments

The UV spectrum of $[Cu_2(Pen)(OH)_2(H_2O)_2]4H_2O$ shows a broad band centered at 12345 cm^{-1} of a square-planar arrangement around Cu(II).[37] The magnetic moment value (1.4 B.M.) measured per one copper atom is found to be lower than that reported for the d^9 system. The anomalous moment may be due to the presence of copper–copper

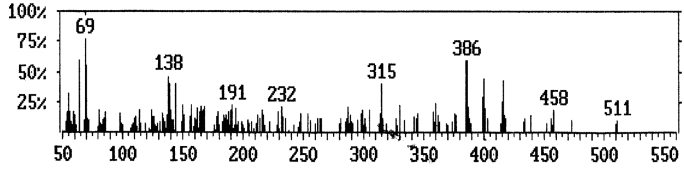


FIGURE 5 Mass spectrum of [Cu(Pir)(Cap)(Ac)]1/2H_2O.

interactions or due to the presence of the Cu^{2+}/Cu^{+} mixture.[38] The electronic spectrum of $[Cu_2(Pir)(Pen)(OH)(Ac)H_2O]$ shows a broad band centered at 13157 cm^{-1} in a square-planar geometry.[37] The spectrum shows also a high energy band at 25641 cm^{-1} assigned to LMCT. The magnetic moment value (1.16 B.M.) suggests the presence of strong copper–copper interaction.[38]

The electronic spectrum of $[Cu(Cap)Ac]3/2H_2O$ shows a broad band centered at 14080 cm^{-1} in a square-planar geometry.[37] The spectrum also shows a high energy band at 27624 cm^{-1}assigned to LMCT.

The electronic spectrum of $[Cu(Pir)(Cap)(Ac)]1/2H_2O$ in DMF shows a broad band centered 15873 cm^{-1}, which is assigned to and $^2E_{2g} \rightarrow {}^2T_{2g}$ transition in a distorted octahedral geometry.[38] The spectrum shows also a band at 26738 cm^{-1} assigned to LMCT transition. The magnetic moment values (0.97 B.M.) in case of $[Cu(Cap)Ac]3/2H_2O$ and (1.29 B.M.) in the case of $[Cu(Pir)(Cap)(Ac)]$ $1/2H_2O$ indicate the reduction of Cu(II) to Cu(I) and the presence of reoxidized Cu(II).[14]

EXPERIMENTAL

Reagents

All the chemicals used were of analytical grade and were used without further purification.

Measurements

Carbon and hydrogen contents were determined at the Microanalytical Unit of Cairo University. Molar conductance measurements of the complexes (10^{-3} M) in DMSO were carried out with a conductivity bridge YSI model 32. The analysis for metal was carried out by standard methods.[39] Infrared spectra were measured using KBr discs on a Mattson 5000 FTIR spectrometer. Calibration with the frequency reading was made with polystyrene film at Mansoura University. Electronic spectra were recorded on UV2 Unicam UV/vis spectrometer using 1 cm stoppered silica cells. Thermal analysis measurements (TGA, DTG) were recorded on a Shimadzu model 50 instrument using 20 mg samples. The nitrogen flow rate and heating were 20 cm^3/min. and 10°C/min, respectively. Magnetic measurements were carried out on a Sherwood Scientific Magnetic Balance England at Mansoura University. Mass spectra were recorded on Jeol TMS-DX 303 (EI-GC 245) mass spectrometer at Cairo University.

Prepration of Metal Complexes

An aqueous solution of copper acetate (0.2 g, 0.001 mol) in 10 mL water was added to an aqueous solution (0.001 mol) of each of captopril or D-penicillamine in 10 mL water in the ratio 1:1 in the case of binary complexes. In the case of mixed ligand complexes of Cu(II) with piroxicam and D-penicillamine mixed ligand or piroxicam and captopril mixed ligand, the ratio was 1:1:1. The reaction mixture was heated under reflux for 10 h on a hot plate. A fine green precipitate was isolated. The isolated metal complexes were filtered, washed with water, dried, and kept in a vacuum desiccator over fused calcium chloride.

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