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Synthesis of some Metal Complexes of N-[(sebacoylAmino)thioxmethyl]-AminoAcid

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Abstract

A new series of potential ligands N-[(sebacoylamino)thioxomethyl]-amino acid were prepared by the reaction of sebacoylisothiocyanate with various aminoacids namely L-histidine,L-glutamicacid, L-tryptophane,L-lysine, the ligands were characterized by IR,UV-Vis , ^{1}H NMR,, ^{13}C NMR spectra , Mass specta ,and CHN .The $ML_2.nH_2O$ complexes of ligands [M=Cu(II),Co(II),,Ni(II)]were isolated and have been characterized by UV-Vis and IR spectra.

Keywords: Amino acid,sebacoyl chloride

Introduction

Complexes of thiourea and thiourea derivatives with transition and raremetals ion have earth great attention since these complexes have shown antitumor,antiviral,bacteriostatic and antioxidative activity[1-2].It is well established that many transition metals [3,4] and rare earth metal[5]-amino acid complexes have considerable biological activity,such as antitumor properties.Although complexes of thiourea metals are receiving derivatives of glycine with transition metals[6,7] and rare earth metals[8] have been prepared, however, there has been no report of metal complexes with thiourea derivatives with other aminoacids. The synthesis and characterization of transition metal complexes with a series of ligands: N-[(sebacoylamino)thioxomethyl]-amino acid;were (amino acid): L-histidine,L-glutamicacid,L-tryptophane,L-lysine)are reported here.

Experimental Section

General. Melting Points are uncorrected and were measured on BÜchi melting point apparatus B-55(BÜchi Labortechnik AG, Switzerland).Microanalytical data were obtainted with a Vario,Elemental apparatus (Shimadzu,Japan).NMR spectra were recorded on 400 and 600 MHz (^{1}H) and on 150.91 MHz(^{13}C) spectrometers (Bruker,Germany) with TMS as internal standard and on the δ scale in ppm. Signal assignments for protons were identified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ^{1}H-^{13}C COSY,or HMBC

experiments .Mass spectra were recorded at 70 eV on El.TLC plates F254 were purchased from Merck. The IR-spectra were recordedo on FT.IR ,.The UV-Vis spectra were obtained using Cintra 5 UV-Vis Diuble Beam spectrophotometer(Basrah-Iraq).

Synthesise of the ligands

Prepration of the sebacoyl isothiocyante

A mixture of sebacoyl chloride (0. 01mol) and ammonium thiocyanate(0.01 mol) in 25 ml acetone was refluxed with stirring for 1hr ,then filitered and the filitrate was used for further reaction .

Preparation of N-[(sebacoylamion)thioxomethyl]-histidine

(0.01 mol) of L- histidine from 25ml pure dry acetone were added rapidly onto the solution of sebacoylisothiocyanate and refluxed for 6 hr, after which excess cracked ice was poured into the mixture with vigorous stirring .The resulting soild was collected , washed with water and then with acetone and recrystalliaed from ethanol.

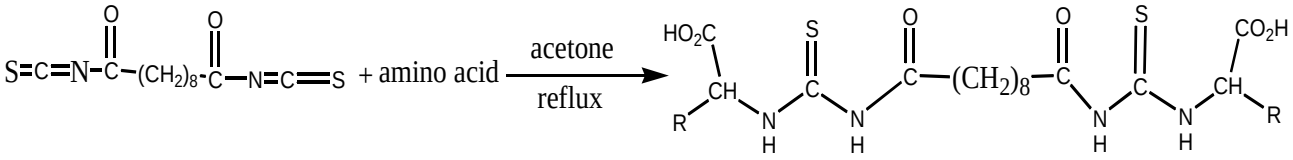
L- Glutamicacid derivative and L-tryptophane derivative and L-lysine derivative were prepared by the same method .

Synthesise of the complexes

2.28 mmol of the ligand was dissolved in 25ml of pure methanol containing 1.24 mmol of NaOH. Asolution of metal nitrate (0.62 mmol) in methanol was added dropwise over the mixture ,and the precipitate appears immediately.After stirring the mixture at room temperature for 2 hours, the precitate was collected by filtration, washed with methanol and dried.

1-

2-



N-[(sebacoylamion)thioxomethyl]-aminoacid

R:- L- histidine ,L-glutamicacid ,L-tryptophane ,L-lysine

Scheme 1. Synthesis of N-[(sebacoylamion)thioxomethyl]-amino acid

Results and Discussion

In our present work, sebacoyl chloride (octane-1,8-dicarboxylic acid dichloride) ,has been selected as a spacer building block[9] for the synthesis of new derivatives of sebacoyl-*N*,*N*-bis(substituted-alkyl-2-thioureido)alkyl carboxylic acid or ester aiming for the evaluation of their anti-HIV activity. Koenig *et al.*[10] have used , for the synthesis of 3,3,3',3'-tetraethyl-1,1'-sebacoyl-bis(thiourea) and other analogues *via* the sebacoyl dithiocyanate derivative. Compound sebacoyl isothiocyante was the key intermediate for synthesis of the compounds investigated in our work. Thus,the treatment of sebacoyl chloride with NH_4SCN in acetone, following Kabbani approach,[11] afforded sebacoyl isothiocyante which was directly treated with the desired amino acid derivatives to give, after purification, the sebacoyl-

thioureido-amino acid derivatives in 63-86% yield. The synthetic reactions are summarized in **scheme 1.**

The structures of were N-[(sebacoylamion)thioxomethyl]- amino acid determined by their ^{1}H, ^{13}C NMR and by mass spectra. The sebacoyl protons showed almost a similar pattern. H-7 and H-14 protons appeared as multiplets in the region δ 2.61-1.78 ppm, while H-8 and H-13 proton signals are oriented as multiplets in the region δ 1.81-1.45 ppm. H-9 - H-12 appeared as multiplets in the region δ H-2 of the amino acid moieties are oriented in the region δ with different multiplicities, depending on the functional group adjacent to H-2. The other protons of the amino acids or esters were fully analyzed. . The ^{13}C NMR spectra of N-[(sebacoylamion)thioxomerthyl]-amino acid contained almost similar resonance signals of the sebacoyl C-7 - C-14 and thioureido carbon atoms. The chemical shifts between δ 188.8 and 184.25 ppm were assigned to C=S carbon atom of the thioureido moiety (C-4), while the resonances in the range of δ 177.7-174.1 ppm were assigned to the carbonyl groups of the CSNH*CO* residues. C-2 of the amino acid moieties [*C*H-CO_2H(Me,Et)] appeared in the region δ 66.7-55.9 ppm. The sebacoyl carbon atoms C-7 and C-14 are oriented in the region δ 38.0-35.3, while C-8 and C-13 appeared in the region δ 26.4-25.0 ppm. The signals between δ 31.5 and 24.7 ppm were attributed to C-9 and C-12

N-[(sebacoylamino)thioxomethyl]-histidine .From L-histidine (0.93 g). Yield: 1.43 g (80%); mp 240-242 ^{o}C. ^{1}H NMR (DMSO-d_6): δ 7.38 (s, 1H, $H^{2}_{imidazol}$); 6.37 (s, 1H, $H^{5}_{imidazol}$); 3.64 (dd, 2H, $J_{2',3'a(histidin)}$ = 7.5 Hz, $J_{2',3'ba(histidin)}$ = 13.5 Hz 2x$H^{2}_{histidin}$); 3.10 (m., 4H, 2x$H^{3a}_{hisidin}$ + 2x$H^{3b}_{histidin}$); 2.14 (m, 4H, +CH_2-7 + CH_2-14); 1.63 (m, 4H, CH_2-8 + CH_2-13); 1.28 (m, 4H, CH_2-9 + CH_2-12); 1.23 (m, 4H, CH_2-10 + CH_2-11). ^{13}C NMR (DMSO-d_6): δ 184.2 (C=S); 177.7 (CSNH*CO*); 174.0 (CO_2H); 135.4, ($C^{2}_{imidazol}$); 132.7 ($C^{4}_{imidazol}$); 120.3 ($C^{5}_{imidazol}$); 61.9 (CO_2H-*CH*); 37.4 (C-7 + C-14); 29.9 (C-10 + C-11 + $C^{3}_{imidazol}$): 28.2 (C-9 + C-12); 26.0 (C-8 + C-13). Anal. calc. for $C_{24}H_{34}N_8O_6S_2$ (597.71): C, 48.47; H, 5.76; N, 18.84. Found: C, 48.22; H, 5.66; N, 18.67. MS: m/z (FAB) 598 $[M+H]^{+}$.

N-[(sebacoylamino)thioxomethyl]-L-glutamic acid. From L-glutamic acid (0.88 g). Yield: 1.47 g (85%); mp 195-196 ^{o}C. ^{1}H NMR (DMSO-d_6): δ 11.08 (br s., 2H, CO_2H); 3.86 (br s., 1H, NH); 3.59 (dd, 2H, $J_{H2\text{-}glutamic,H3a\text{-}glutamic}$ = 3.5 Hz, $J_{H2\text{-}glutamic,H3b\text{-}glutamic}$ = 11.5 Hz, CO_2H-$H^{2}_{glutamic}$); 2.29 (m, 4H, $H^{4a,b}_{glutamic}$); 2.14 (m, 4H, CH_2-7 + CH_2-14): 2.11 (m, 4H, $H^{3a,b}_{glutamic}$); 1.81 (CH_2-8 + CH_2-13); 1.31-1.21 (m, 8H, CH_2-9 + CH_2-10 + CH_2-11 + CH_2-12). ^{13}C NMR (DMSO-d_6): δ 185.7 (C=S); 177.5 (CO_2H); 174.7 (CSNH*CO* + CO_2H); 61.9 (CO_2H-*CH*); 35.7 (C-7 + C-14); 30.8 (C10 + C-11 + $C^{4}_{glutamic}$); 29.2 (C-9 + C-12); 26.4 (C-8 + C-13 + $C^{3}_{glutamic}$). Anal. calc. for $C_{22}H_{34}N_4O_{10}S_2$ (578.66): C, 45.66; H, 5.92; N, 9.68. Found: C, 45.35; H, 5.87; N, 9.42. MS: m/z (FAB) 579 $[M+H]^{+}$.

N-[(sebacoylamino)thioxomethyl]-L-tryptophane. From L-tryptophane (1.23 g). Yield: 1.4 g (67%); mp 255-257 ^{o}C. ^{1}H NMR (DMSO-d_6): δ 10.90 (s, 1H, CO_2H); 7.20 (1H, d, $J_{2,NH}$ = 2.2 Hz, $H^{2}_{trypt.}$); 7.56 (d, 1H, J = 7.8 Hz, H^{7}_{trypt}); 7.34 (d, 1H, = 8.0

Hz, H^{4}_{trypt}); 7.07 (t, 1H, *J*= 8.0 Hz, H^{5}_{trypt}); 6.98 (t, 1H, *J*= 7.8 Hz, H^{6}_{trypt}). 3.43 (dd, 2H, $J_{2,\ CH2a\text{-}trypt.}$ = 4.0 Hz, $J_{2,CH2b\text{-}trypt.}$ = 9.0 Hz, CO_2H-2x$H^{2}_{trypt.}$); 3.31 (dd, 1H, CH_2a-trypt); 2.93 (dd, 1H, $J_{Ha,Hb\text{-}trypt.}$ = 15.0 Hz, CH_2b-trypt); 2.33 (m, 4H, CH_2-7 + CH_2-14); 1.69 (m, 4H, CH_2-8 + CH_2-13): 1.29-1.23 (m, 8H, CH_2-9 + CH_2-10 + CH_2-11 + CH_2-12). ^{13}C NMR (DMSO-d_6): δ 184.9 (C=S); 174.3 (CSNH*CO* + CO_2H); 137.1, 127.3, 123.3, 119.8, 111.2, 109.9 ($C_{trypt.}$); 62.7 (CO_2H-*CH*); 35.5 (C-7 + C-14); 31.5 (C-10 + C-11); 29.0 (C-9 + C-12); 26.4 (C-8 + C-13). Anal. calc. for $C_{34}H_{40}N_6O_6S_2$ (692.85): C, 58.94; H, 5.82; N, 12.13. Found: C, 58.72; H, 4.09; N, 11.97. MS: m/z (FAB) 693 $[M+H]^{+}$.

N-[(sebacoylamino)thioxomethyl]-Llysine. From L-lysine ethyl ester dihydrochloride (1.48 g). Yield: 2.14 g (78%), mp 108-110 ^{o}C. ^{1}H NMR (DMSO-d_6): δ 8.73, br s., 2H, 2xNH); 8.23 (br s., 2H, 2xNH); 4.22 (q, 4H, J= 7.0 Hz, 2xO*CH*$_2$CH$_3$); 3.92 (t, 2H, $J_{H2\text{-}lysin,H3\text{-}a,b)}$ = 6.1 Hz, 2xH^{2}_{lysin}); 2.72 (br s., 8H, 2x*CH*$_2$-NH_2+2xNH_2); 1.82-1.77 (m, 8H, 2xCH_2-3$_{lysin}$+CH_2-7 + CH_2-14); 1.59 (m, 6H, 2xCH_2-5$_{lysin}$ + 2xNH); 1.47 (m, 4H, CH_2-8 + CH_2-13); 1.38 (m, 4H, CH_2-9 + CH_2-12); 1.23 (m, 10H, 2xOCH_2*CH*$_3$ + CH_2-10 + CH_2-11). ^{13}C NMR (DMSO-d_6): δ 187.9 (C=S); 174.1 (CSNH*CO*); 170.6 (*CO*Et); 61.7 (O*CH*$_2$$CH_3$ + CO_2Et-*CH*); 51.1 (CH_2NH_2); 37.8 (C-7 + C-14); 29.2 (C^{3}_{lysin} + C-9 + C-10 + C-11 + C-12); 26.0 (C-8 + C-13); 21.1 (C^{4}_{lysin}); 13.9 (OCH_2*CH*$_3$). Anal. calc. for $C_{28}H_{52}N_6O_6S_2$ (632.88): C, 53.14; H, 8.28; N, 13.28. Found: C, 52.94; H, 8.19; N, 13.05. MS: m/z (FAB) 633 $[M+H]^{+}$.

Uv-vis absorption spectra

UV-vis absorption spectra of ligands characteristic peaks in the region 250-350 nm .The spectra of complexes show additional peaks due to **d-d** transition in the range 400-700 nm, **(Table 1**).

compound	λmax (nm)
N-[(sebacoylamino)thioxomethyl]-histidine	264,304,345
N-[(sebacoylamino)thioxomethyl]-histidine –copper nitrate	266,351,314 ,435
N-[(sebacoylamino)thioxomethyl]-histidine –cobalt nitrate	268,321,412 ,477,
N-[(sebacoylamion)thioxomethyl]-histidine –nickek nitrate	260.301,412 ,437
N-[(sebacoylamino)thioxomethyl]-L-glutamic acid	221,310
N-[(sebacoylamino)thioxomethyl]-L-glutamic acid- copper nitrate	222,312,380 ,340,
N-[(sebacoylamino)thioxomethyl]-L-glutamic acid -cobalt nitrate	220,312,520, 380,
N-[(sebacoylamino)thioxomethyl]-L-glutamic acid- nickek nitrate	221310,383, 420,
N-[(sebacoylamino)thioxomethyl]-L-tryptophane	254,302
N-[(sebacoylamino)thioxomethyl]-L-tryptophane- copper nitrate	254,306,320 ,436
N-[(sebacoylamino)thioxomethyl]-L-tryptophane -cobalt nitrate	256,321,425 ,467
N-[(sebacoylamino)thioxomethyl]-L-tryptophane- nickek nitrate	255,307,417, 330
N-[(sebacoylamino)thioxomethyl]-Llysine	230,265
N-[(sebacoylamino)thioxomethyl]-Llysine - copper nitrate	233,267,360, 520,660
N-[(sebacoylamino)thioxomethyl]-Llysine -cobalt nitrate	232,266,323 ,419,466
N-[(sebacoylamino)thioxomethyl]-Llysine- nickek nitrate	233,265,308,419, 308

Infrarad spectra

Most of this work has been confined to the higher frequency region in wicth internal vibrations of the ligands are observed (tables 2-5) although several authores have extended measurements to **250** cm^{-1} . **Below 600** cm^{-1} modes occur due to n(M-L), range deformation and deformations associated with R,or to some admixture of them .Regarding the nature of the M-O bond in these complexes,the bond is regarded as essentially ionic with no M-O stretching frequency above **350 c**m^{-1},on the other hand aeair amount of covalent nature is assumed resulting in the assignment of bands mainly due to n(M-O) in the range **536-556 cm^{-1}**. This variation depends on the type of amion acid and on the metal atom used.The infrared spectra of these complexes are fundamentally similar which reveals that they have the same general structure but differ from free ligand.The shape of the band near ~**1700** cm^{-1} N(C=O) mode of the ligand carboxyl group is clearly asymmetric with noticeable spectral broadening at the lower frequencies.This may be due to hydrogen bonding between more than two carboxylic groups.The peak broadening might be rooted in short range interactions of carbonyl dipoles,and the asymmetry of the peak might be produced owing to hight probability of antiparallel arrangement of dipoles .The charecteritic peak at **1700 cm^{-1}** shifts to lower frequency upon complexation .The complexes displayed both symmetric and assmmetric stretching vibrations of **COO^- (1385-1485 cm^{-1}) (1550-1771cm^{-1})** associated with the stretch vibrations of the charged from of carboxylic group which suggested the coordination of the ligand carboxyl group with the M(II) ions as abidentate chelate fashion .

Table 2 . Fundamental infrared bands (cm^{-1}) of N-[(sebacoylamino)thioxomethyl]-histidine and its complexes.

Assignment	Ligand	$Cu(NO_3)_2$	$Co(NO_3)_2$	$Ni(NO_3)_2$
Alphatic C-H	2931	2881	2921	2892
O-H	3419	------	--------	---------
COO(carboxylic asymm)	1771	1624	1633	1635
C=O	1654	1592	1644	1623
C=S	2010	2017	2017	2020
M-O	----------	536	542	522
N-H	3516	3489	3375	3377

Table 3. Fundamental infrared bands (cm^{-1}) of N-[(sebacoylamino)thioxomethyl]-L-glutamic acid and its complexes

Assignment	Ligand	$Cu(NO_3)_2$	$Co(NO_3)_2$	$Ni(NO_3)_2$
Alphatic C-H	2928	2894	2925	2942
O-H	3379	------	--------	---------
COO(carboxylic asymm)	1751	1636	1642	1692
C=O	1676	1574	1673	1662
C=S	2010	2014	2019	2013
M-O	----------	546	547	542
N-H	3506	3476	3375	3366

Table 4. Fundamental infrared bands (cm^{-1}) of N-[(sebacoylamino)thioxomethyl]-L-tryptophane and its complexes

Assignment	Ligand	$Cu(NO_3)_2$	$Co(NO_3)_2$	$Ni(NO_3)_2$
Aromatic C-H	3097	3020	3087	3097
Alphatic C-H	2928	2884	2915	2882
O-H	3419	------	--------	---------
COO(carboxylic asymm)	1761	1643	1651	1676
C=O	1632	1583	1681	1675
C=S	2017	2013	2015	2013
M-O	----------	545	542	549
N-H	3490	3449	3365	3369

Table 5. Fundamental infrared bands (cm^{-1}) of N-[(sebacoylamino)thioxomethyl]-Llysine and its complexes

Assignment	Ligand	$Cu(NO_3)_2$	$Co(NO_3)_2$	$Ni(NO_3)_2$
Alphatic C-H	2938	2899	2926	2932
O-H	3459	------	--------	---------
COO(carboxylic asymm)	1721	1616	1583	1592
C=O	1670	1574	1663	1672
C=S	2017	2014	2010	2013
M-O	----------	556	550	542
N-H	3498	3486	3395	3361

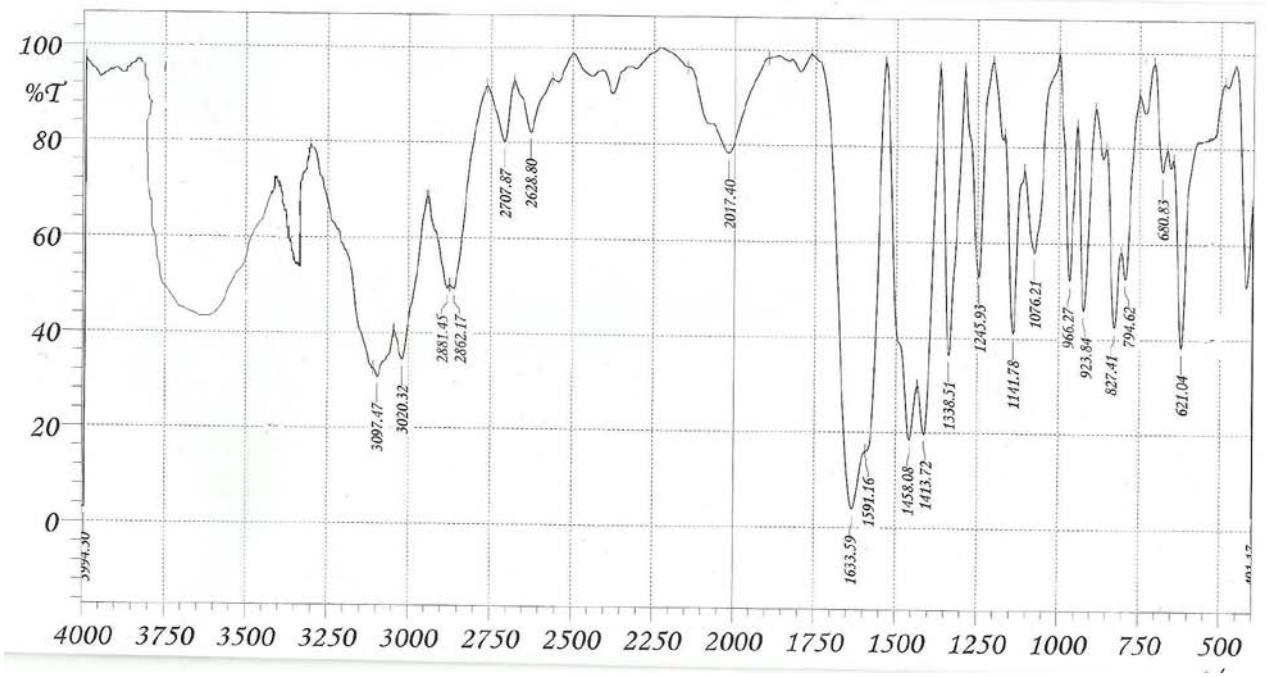


Fig 1. FT.I.R spectrum of N-[(sebacoylamino)thioxomethyl]-histidine

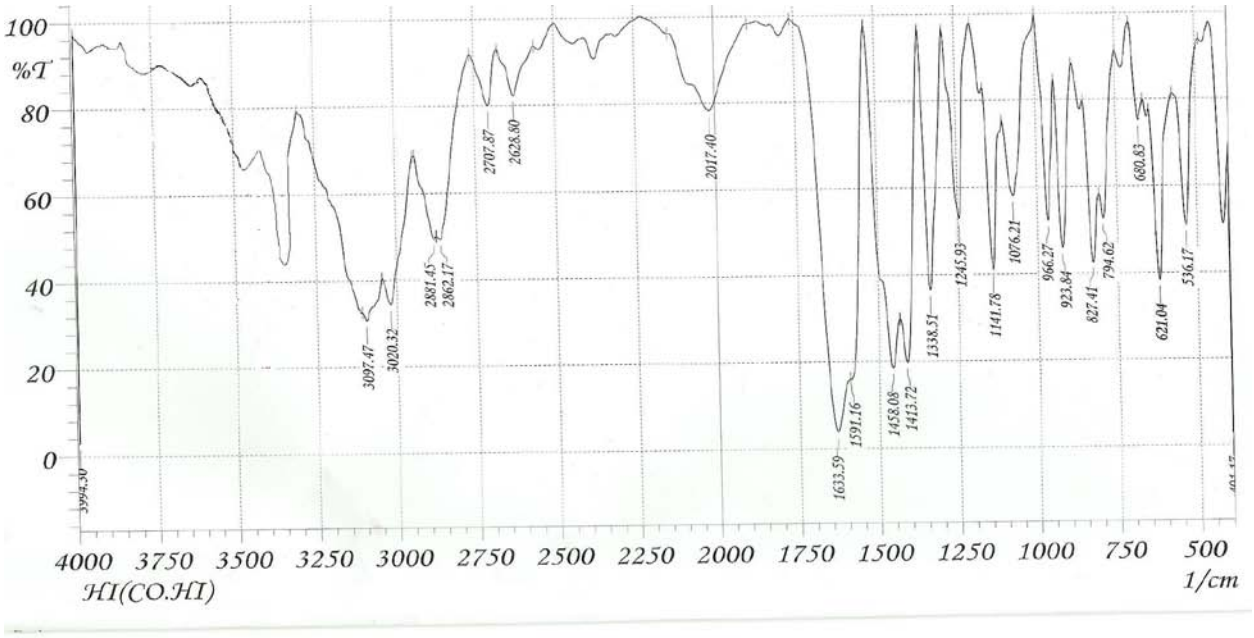


Fig 2. FT.I.R spectrum of complexes of N-[(sebacoylamino)thioxomethyl]-histidine –copper(II)

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