



Synthesis, Characterization and Thermal studies of Novel Organomercury Driven from Sulfa Drugs

Part 1

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Abstract:

Two new heterocyclic Organmercury compounds were prepared from the reaction of Sulfamethaxazole and Sulfadiazine with 4-acetaminophenol as a coupler and separated as solids with characteristic colors. these compounds were characterized by F.T.IR-spectroscopy ¹H-NMR , Micro-elemental Analysis and UV-Vis spectroscopic techniques . The work involves a study of acid – base properties compounds at different pH values, the ionization and protonation constants were calculated. The thermal behavior of these two compounds were investigated on the basis of thermogravimetric (TGA) and differential thermogravimetric (DTG) analyses, Thermal decomposition of these compounds is multi-stage processes.

Keywords- Synthesis; Characterization; Organomercury; Thermal properties

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Introduction

The synthesis of metal sulfanilamide compounds has received much attention due to the fact that sulfanilamides were the first effective chemotherapeutic agents to be employed for the prevention and cure of bacterial infections in humans [1]. Organomercurials have been widely employed as both clinical and topical antiseptics and are still in common use today in the cleaning of soft lenses [2]. Furthermore, sulfa drugs and their metal complexes, possess many applications as diuretic, antiglaucoma or antiepileptic drugs [1-3].

Mercury has played a rich role and has made diverse contributions to the field of bioconjugate chemistry, mercury's unique electronic properties have proved useful in designing electrochemical based thiol assay methods [4]. Mercury metal has aided electron microscopy characterization of proteins [5]. It also forms useful amalgams with many metals, which find various applications in diverse fields. Organomercurials such as methyl mercury are more toxic than elemental mercury and other inorganic mercury compounds [6]. Mercury containing ligands e.g., mercuric and mercurous are known to form stable complexes with class b metal ions, such as gold because mercury is considered to be a soft Lewis base [7]. Azo compounds have been receiving much attention and have been widely used in many practical applications such as coloring fibers, cosmetics, plastics and food beverages [8-11]. The azo dyes containing heterocyclic rings result in brighter and often deeper shades than their benzene analogs. Functional dye and nonlinear optical systems, photodynamic therapy, and lasers [12]. Azo dyes of sulfa drugs are well known for their antiseptic activity [13-14] and some are useful as chemotherapeutic agents [15]. Transition metals like Fe, Co, Ag, Au, Cu and Ni have long been used in medicine. A large number of metal sulphonamide complexes are found to be more potent than the parent sulphonamides [16-17]. They are useful as precursors of the synthesis of different organic compounds [18-22]. The area for synthesis of organomercury compounds containing azo group has not been developed so far. Ionization potential and substituent effects on the stability constants were also investigated.

Experimental Section

MATERIALS AND METHODS

All analytical grade chemicals were used directly as purchased. Melting point of the synthesized compounds was determined in scientific melting point apparatus and uncorrected. The progress of reaction was monitored by TLC using silica gel coated plates (0.5 mm thickness, Merck) and spots were visualized under UV radiation. Synthesized compounds were recrystallized using suitable solvent system. IR spectra were scanned on a Shimadzu FT-IR as KBr disk in wave number region 4000-400 cm⁻¹. ¹H NMR spectra were recorded in DMSO with tetramethylsilane (TMS) as the internal standard at 500 MHz on a Bruker spectrophotometer. Elemental Vario EL III Carlo Erba 1108 elemental analyzer, thermal analysis (TG and DTG) were carried out in dynamic nitrogen atmosphere (50 ml/min) with a heating rate of 10°C/min using TGA Q500 V6.7.

Preparation Methods:

Sulfamethaxazole (4-amino-*N*-(5-methylisoxazol-3-yl)-benzenesulfonamide) and Sulfadiazine (4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide) mercury chloride were prepared from reaction of Sulfamethaxazole or Sulfadiazine with mercuric acetate according to literature method [23].

Synthesis of compounds

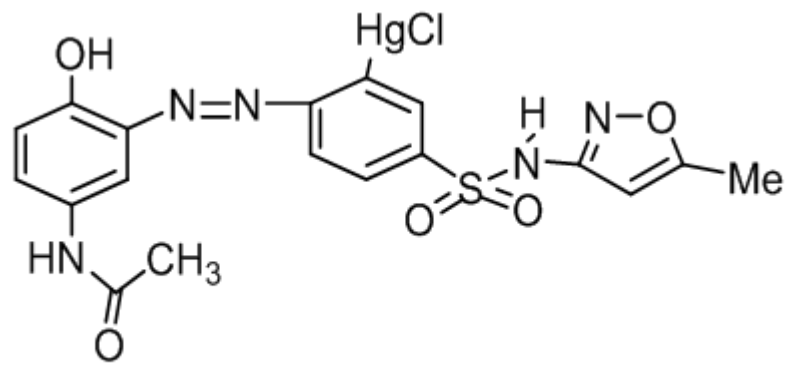
Diazotization- NaNO₂ (0.025 mol) was slowly added with stirring to distilled water while allowing the temperature to -5.0°C. The solution of 4-Acetaminophenol (paracetamol) was then cooled to -5.0°C. NaOH (10%) was added drop by drop with stirring. The reaction mixture was then cooled to -5.0°C, and the diazo component Acetaminophenol (0.025 mol) was added drop by drop and stirring was continued at this temperature for 3 h. The clear diazonium salt solution thus obtained was used immediately in the coupling. Sulfamethaxazole or Sulfadiazine mercury chloride (0.006 mol) was dissolved in 50 ml of distilled water and 6 ml of concentrated hydrochloric acid was added the solution was then cooled to 0 - 5°C in ice-bath and maintained at this temperature. Sodium nitrate (0.006 mol) solution in (5 ml water) was then added drop wise with stirring was continued for 30 min to produce diazonium salt [24].

Preparation-2-((5-acetamidio-2-hydroxyphenyl) diazenyl)5-5-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)mercury(11)chloride (M1)

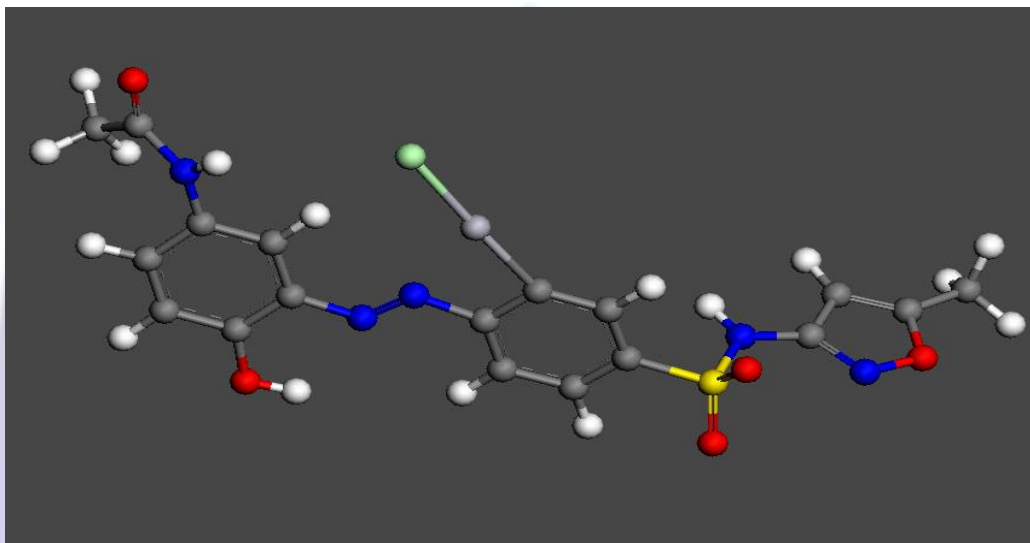
The diazonium solution of Sulfamethaxazole mercury(11)chloride was added portion wise to the coupling component solution prepared by dissolved (0.006 mol) of Paracetamol (4-acetaminophenol) in 100 ml of alkaline solution. The mixture was stirred for further 1 hr at 0°C and then the mixture was neutralized with dilute hydrochloric acid. The solid product (M1) was collected and recrystallized from ethanol. The purity of the dye was determined by TLC. The yield of reaction was 82% and its physical properties were listed in table (1).

Preparation 2-((5-acetamidio-2-hydroxyphenyl) diazenyl)5-5-(*N*-(5-pyrimidine-2-yl)sulfamoyl)phenyl)mercury(11)chloride (M2)

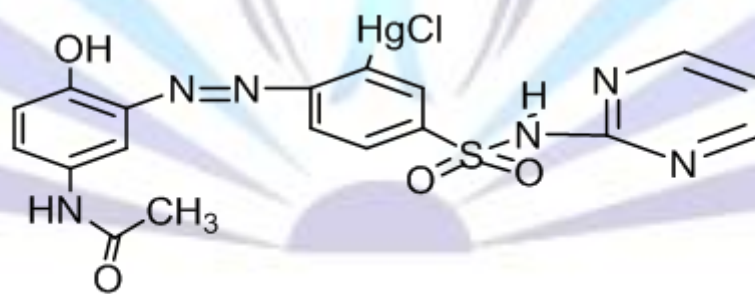
The diazonium solution of Sulfadiazine mercury(11)chloride was added portion wise to the coupling component solution prepared by dissolved (0.02 mol) of Paracetamol (4-acetaminophenol) in 100 ml of alkaline solution. The mixture was stirred for further 1 hr at 0°C and then the mixture was neutralized with dilute hydrochloric acid. The solid product was collected and recrystallized from ethanol give M₂. The yield of reaction was 73% and its physical properties were listed in table (1).



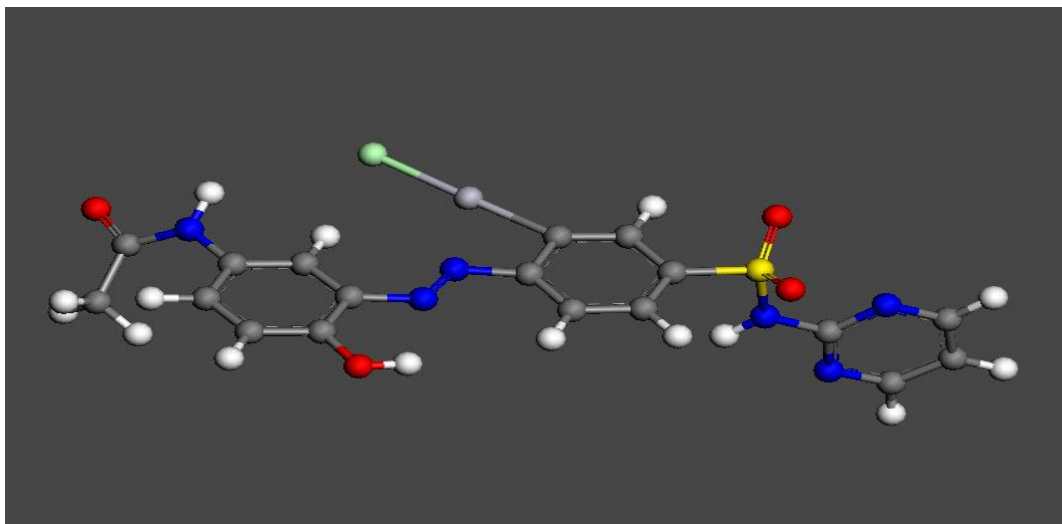
(2-((5-acetamido-2-hydroxyphenyl)diazenyl)-5-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)mercury(II) chloride



Formula1- structure of M1



(2-((5-acetamido-2-hydroxyphenyl)diazenyl)-5-(*N*-pyrimidin-2-ylsulfamoyl)phenyl)mercury(II) chloride



Formula2- structure of M2.

To calculate the ionization for hydroxy group and protonation constant of nitrogen, a series of acetate and universal buffer solutions were prepared with different pH values [0.5-12] for each compounds [25].

Results and Discussion

Elemental analysis data and physical properties are summarized in Table 1. The compounds were prepared in good yield by reaction the diazonium solution of Sulfamethaxazole or Sulfadiazine mercury(11)chloride with 4-acetaminophenol. The compounds are stable in air and light and are soluble in organic solvents such as CHCl_3 and DMSO. Elemental analysis data and physical properties of compounds are summarized in Table 1.

Table 1.. Elemental analysis and physical properties of the M1 and M2

Comp.	Physical state	Yield %	M.Wt g/mole	M.P $^{\circ}\text{C}$	C%found (calc.)	H%found (calc.)	N%found (calc.)	S%found (calc.)
M1	Orange crystal	82	650	325	33.53 (33.23)	2.51 (2.46)	10.98 (10.76)	5.34 (4.92)
M2	Brown powder	73	647	360	33.76 (33.38)	2.36 (2.31)	13.21 (12.98)	5.21 (4.94)

1-The FTIR spectra

The IR spectral analysis of compounds are in good arrangement with the synthesis compounds. The sharp medium band at 3650 cm^{-1} indicating the presence of free phenolic OH group, The band at 1430 and 1420 cm^{-1} ($-\text{N}=\text{N}-$) of the compounds undergoes negative shift in the compounds indicating nitrogen coordination of the diazo moiety. the low frequency and the broadening of these bonds suggest that these compounds having a Intermolecular $\text{N}\rightarrow\text{Hg}$ Interactions bonding in the solid state [1,25,26]. The presence of a sharp band at 1586 , 1580 cm^{-1} spectrum and owing to the $\nu(\text{C}-\text{C})$ (ring) vibrations, and band at 1619 , 1615 cm^{-1} owing to the $\nu(\text{C}=\text{N})$ for the M1 and M2 respectively. The medium bands at $(2972)\text{ cm}^{-1}$ can be attributed to C-H stretching of aromatic and isoxazole rings respectively for M1[27], The peak appearing in the region $1610\text{-}1615\text{ cm}^{-1}$ are attributed to $\nu(\text{C}=\text{N})$ stretching vibration. The band belonging to $\nu(\text{N}-\text{H})$ stretching vibration is not observed probably due to overlapping with the broad hydroxy peak. The other characteristic peaks of M1 and M2 are given in fig (1) and table (2). These data are in agreement with those previously reported for similar compound [1,28]

Table (2) The I.R spectral data of the azo-dyes (KBr disk)

Comp.	V-OH,N-H	V _{C=O}	V _{C=N}	V _{N=N}	V _{O=S=O}	v _{Hg-N}
M1	3377	1653	1620	1410	1340	455
M2	33448	1662	1614	1423	1327	430

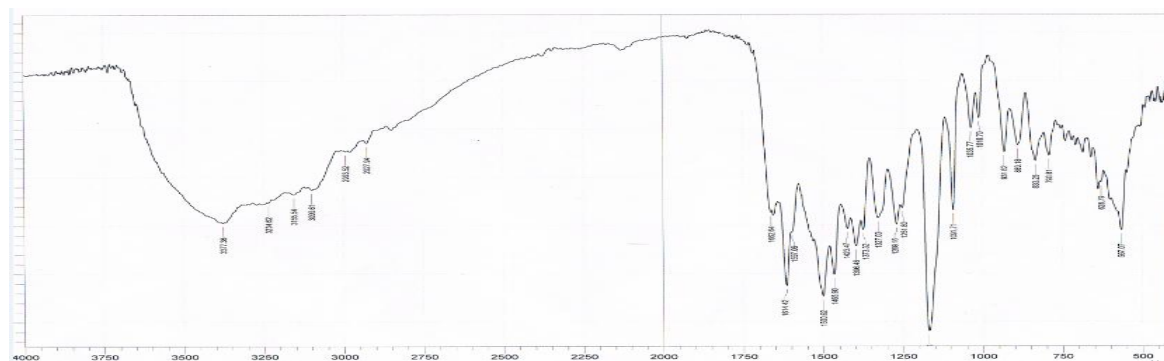


Fig 1: FT-IR spectra of M1

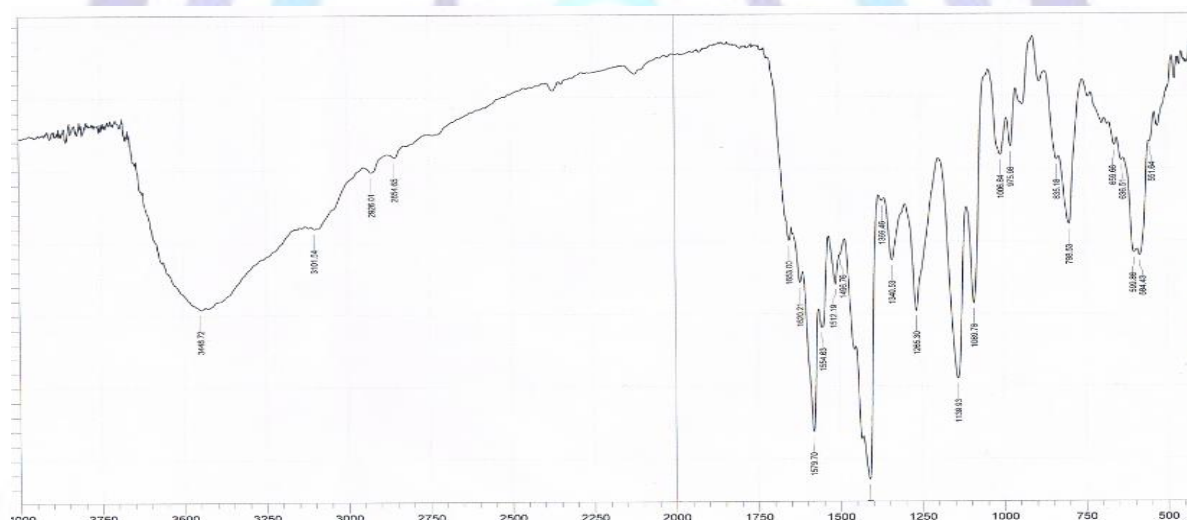


Fig 2 :FT-IR spectra of M2

2-Electronic spectra

The electronic absorption spectral characteristics of M1 and M2 in ethanol were also recorded, they give three strong absorption bands. The shorter wave length appearing in the range 243, 247 and 277, 281 nm may be assigned to a $\pi \rightarrow \pi^*$ transition of the aromatic ring and a $n \rightarrow \pi^*$ transition of the $-N=N$ group, respectively. The third band appearing in the visible region (380&525 nm)for M1 and (385 &535) for M2 can be assigned to $\pi \rightarrow \pi^*$ transition involving the whole electronic system of the mercury compounds [29-30]

3-The ¹H-NMR spectra

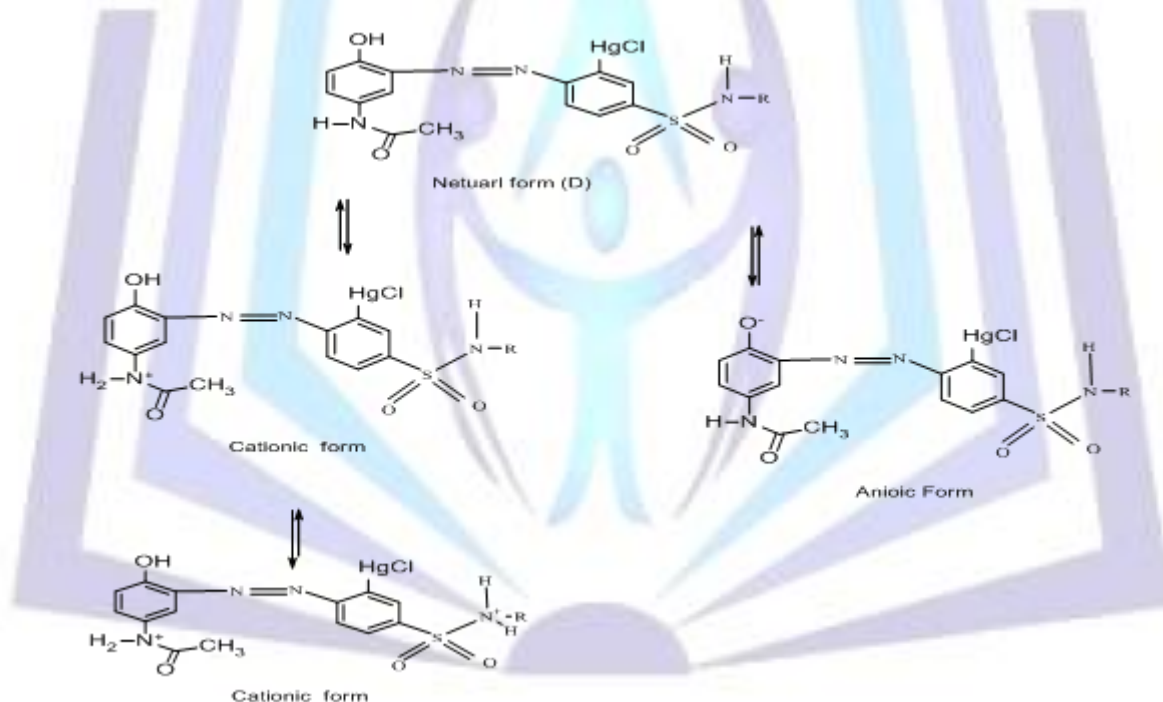
¹H-NMR spectra of the prepared organomercury compounds were performed in deuterated dimethyl sulfoxide solutions with tetramethylsaline as an internal standard. H-NMR spectra showed a peak at 2.5 ppm which was due to DMSO solvent and some spectra showed a sharp peak at 3.33 ppm due to dissolved water in DMSO, Table3 represent the data of M1and M2 [31]

Table (3): ¹H-NMR- Spectra of M1 and M2 compounds.

Comp.	δ (ppm)
M1	O 2.2(S, 3H, NH-C-CH ₃), 6.9-7.9(m, , Ar-H,) 9.8 (S, 1H, NH), 10.9 (S, 1H, OH)
M2	O 2.02(S, 3H, NH-C-CH ₃), 6.5-8.2(m, Ar-H), 2 9.65 (S, 1H, NH), 9.8(S, 1H, OH)

4-Ionization and protonation constants of M₁ and M₂

The protonation and ionization constants (pK_p and pK_a) of were determined from their spectral behaviour in buffer solution of varying pH, shows the electronic spectra 360-650 nm of (0.8×10^{-4} M) of M₁ and M₂ at varying pH values (1-12) , The spectra characterized by two bands at λ_{max} 380 and 525 nm with three isosbestic points at 428 nm. , 490nm. and 580 nm. for M₁. And three bands at λ_{max} 385 nm and 535 nm with three isosbestic points at 428 nm. , 470 nm. and 565 nm. for M₂ . The three isobestic points are due to ionization of dyes in acidic and basic medium (scheme 2)



Scheme2 The suggested mechanism for ionization and protonation of M1&M2

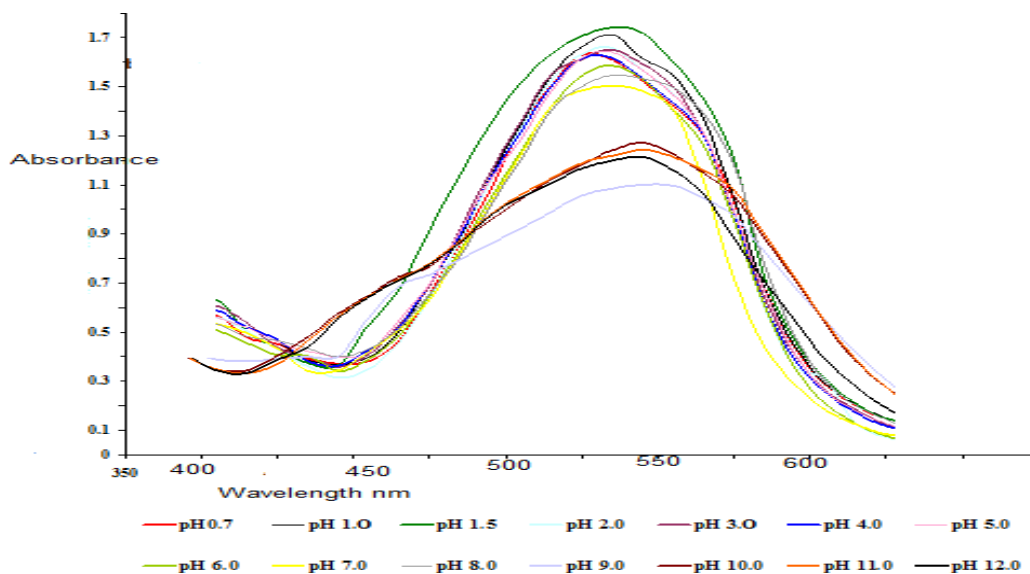


Fig 3-- Electronic spectra for M1 at different pH values

The protonation and ionization constants (pK_p and pK_a) of dyes were determined from their spectral behaviour in buffer solution of varying pH. From the absorbance-pH curves the pK_a and pK_p values were determined by using of half height method [25] as shown in table (4)

Table4: The Dissociation and protonation constants of dyes

Dye	λ_{max} nm.	pK_p	pK_p	pK_a
M ₁	415	3.5	7.72	10.48
M ₂	410	3.4	7.56	11.12

pK_p = protantion constant of -N-; pK_a = ionization constant of -OH group

5- Thermal stability

The compounds M1 and M2 are stable at room temperature and can be stored for several months without any changes. The obtained compounds were studied by thermogravimetric (TG) and differential thermogravimetric (DTG) analysis from ambient temperature to 600 °C under N₂ atmospheres. The TG curves were redrawn as mg mass loss versus temperature (TG) curves and as the rate of loss of mass versus temperature (DTG) curves. Typical TG and DTG curves are presented in Fig. 3, and the thermoanalytical results are summarized in Table 5

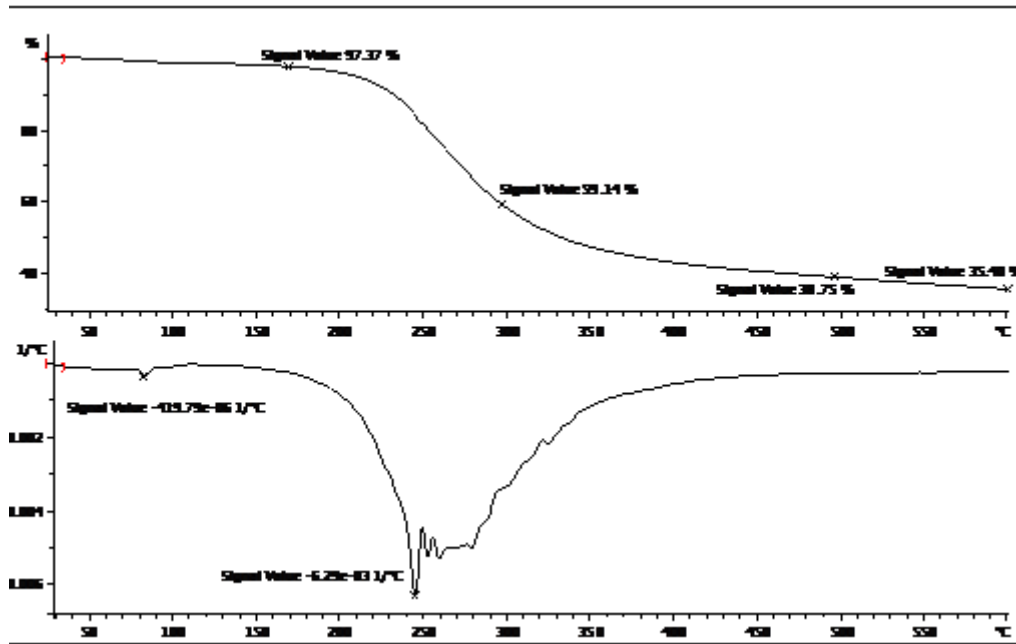


Fig. 4: Tg/DTG curve of M1

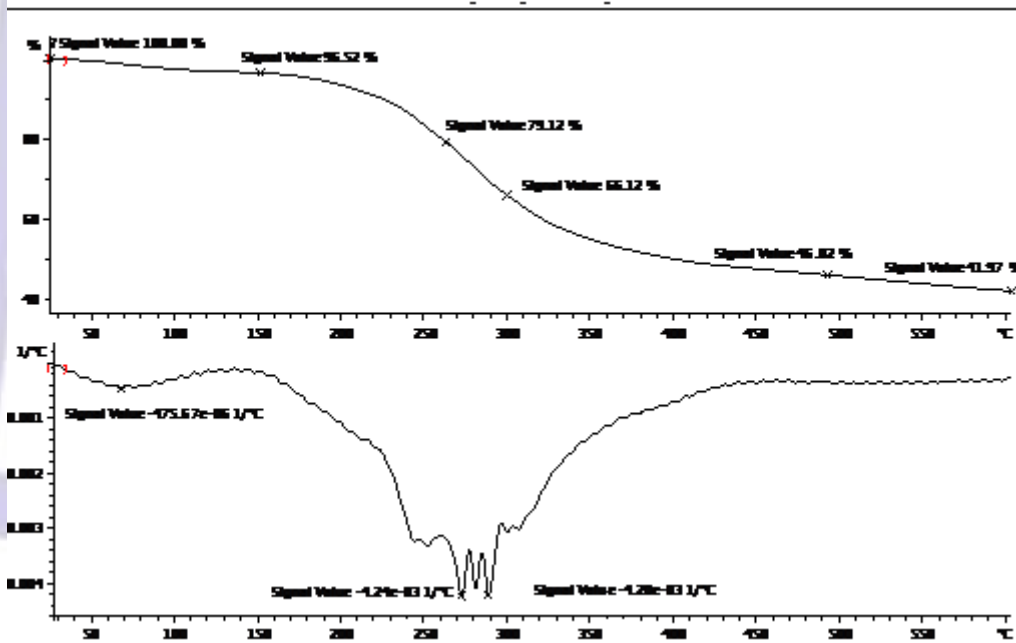


Fig. 5: Tg/DTG curve of M2



Table 5- Thermal decomposition data of the compounds

Comp.	stage	TG rang °C	DTG Max °C	Mass loss%		Assignment
				Found	calculat	
M1	1	60-180		2.64	2.7	H ₂ O
	2	210-290	245	40.86	39.97	SO ₃ N ₂ C ₄ H ₄ +H ₂ O
	3	292-500	340	20.39	20.02	-NHCOCH ₃
	4	500-600		3.4	5.39	-OH
M2	1	60-140		2.7	2.8	H ₂ O
	2	160-260	230	20.88	20.55	C ₆ H ₃ NHCOCH ₃
	3	260-300	270	13.88	15.36	C ₄ N ₂ H ₃
	4	300-490		20.1	19.18	-SO ₂ NH
	5	490-600		4.05	5.04	-HCl

M1 undergoes a stepwise decomposition in four steps well discernible in the TG and DTG curves in the temperature ranges 60-180, 210-290, 292-500 and 500-600°. A small step of weight loss 2.64% at about 100° is attributed to adsorbed water. The second stage of decomposition starts at 210 and ends 290 (DTG max 245) involves a mass loss of about (calc. 39.97, found 40.86%). The mass loss at this step points to the elimination of SO₃N₂C₄H₄+H₂O. The third stage starts at 292 and ends 500 °C (DTG max 340) involves a mass loss of about (calc. 20.02, found 20.39%) which involves the decomposition of the ligand moiety and loss -NCOCH₃[32]. Fig 4

M2- undergoes a stepwise decomposition in five steps well discernible in the TG and DTG curves in the temperature ranges 60-600 °C. A small step of weight loss 2.64% at about 100° is attributed to adsorbed water, and the four stages listed in table (5) fig 5

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