

EFFICIENT ULTRASOUND SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(5-CHLORO 2-HYDROXYPHENYL)-3-(5-BROMO 2-CHLOROPHENYL) PROPANE-1,3-DIONE AND IT'S TRANSITION METAL COMPLEXES

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Abstract : 1-(5-chloro 2 hydroxyphenyl)-3-(5-bromo 2-chlorophenyl)propane-1,3-dione and its transition metal complexes were synthesized by ultrasound irradiation and characterized by IR, ¹H-NMR, ¹³C-NMR, magnetic susceptibility, X-ray diffraction, analysis of powdered samples, conductometry, elemental analysis, and screened for disinfectant activity. From the spectroscopic data of IR, it suggested that the ligand shows keto-enol tautomerism by hydrogen bonding hence acts as a chelating agent in the preparation of metal complexes and behaves as a bidentate ligand towards the central metal ion with an O-O,O-O donor atoms sequence. The stoichiometry of the complexes 1:2 (metal : ligand) was found among the microanalytical data and the octahedral geometry for all these complexes were suggested by physic-chemical data. The powder X-ray diffraction data suggested orthorhombic crystal system for Ni(II) complex and monoclinic crystal system for the Co(II), Fe(III), and Cu(II) complexes. The manufactured metal complexes and ligand showed satisfactory disinfectant activity. Usages of ultra sonication method, segregation method, simple reaction conditions and purification makes this swing very interesting from an environmental perspective.

Keywords: Cyclic β-diketone, Baker-Venkatraman transformation, transition metal complexes, ultrasound irradiation, magnetic susceptibility, XRD, antimicrobial screening.

I. INTRODUCTION

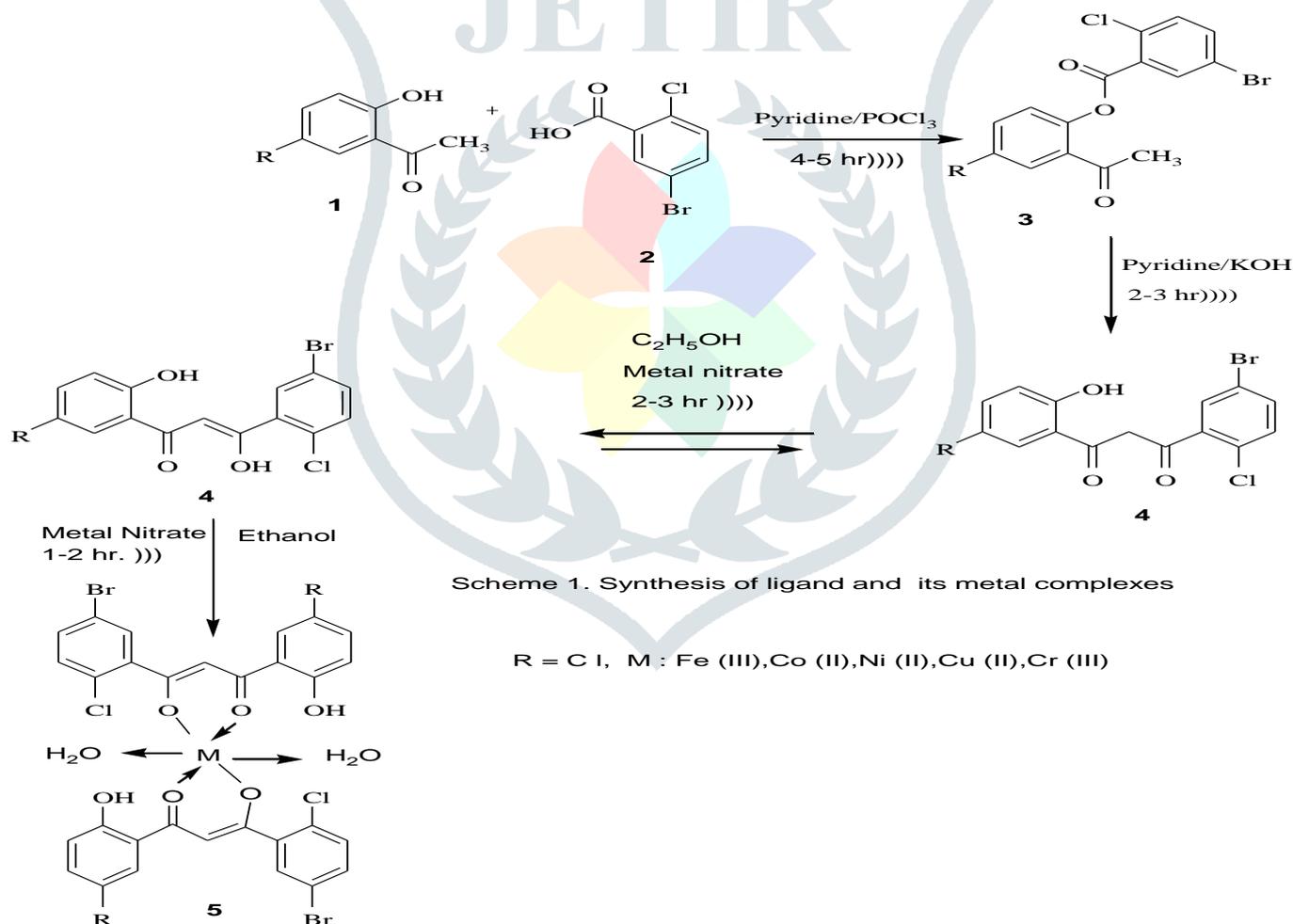
β-diketones exist in the intramolecular hydrogen bonded keto-enol tautomerism hence form metal complexes, as enolic hydrogen atom can be replaced by a metal and a ketonic oxygen, thereby completing the chelate ring. Because of the unique structural features, toughness for light and heat as electroluminescence materials and chemical functionalities, β-diketone and its metal complexes have been widely used in diverse areas.¹ Cyclic β-diketones have gained a lot of interest due to their importance as good ligands² for the midway in the preparation of core heterocycles such as flavones,³ benzodiazepine,⁴ pyrazole,⁵ isoxazole⁶, pyrimidine⁷ and triazole.⁸ β-diketones are well known to have keto-enol tautomerism⁹ and recently it is reported that they have the important pharmacophores for the HIV-integrase(1N) inhibitors.¹⁰ Further, it has been reported recently that a number of β-diketones has warrant examination as breast cancer chemopreventative blocking agent,¹¹ anticarcinogenic agent¹² and antiestrogenic agent.¹³ Cobalt is one of the major constituent of vitamin B₁₂ (Cobalamin) and plays a vital role in many biological potency, shrinkages associated with, protects against brain atrophy or shrinkage associated with Alzheimer's disease and impaired cognitive function¹⁴⁻¹⁵. The coordination functionality of β-diketones has notable influences on the relative stabilities of the mixed ligand complexes as well as their use in biomedicine¹⁶⁻¹⁹. Copper is an essential micronutrient that participates in respiratory reactions, antioxidant, cellular stress response, etc.²⁰⁻²¹ Nickel(II) forms an important component viz. urease, hydrogenase, various enzymes, and carbon monoxide dehydrogenase²². From last twenty to thirty years, most of the researchers used ultra sonication method in organic synthesis as it accelerates the reaction. Within the framework of 'Green Chemistry' we have now developed an environmentally benign and novel approach for the synthesis of different β-diketones and its transition metal complexes²³. A search of the literature revealed that no work has been done on transition metal complexes of the 1-(5-chloro 2-hydroxyphenyl)-3-(5-bromo 2-chloroyphephenyl)propane-1,3-dione. The synthesis of 1-(5-chloro 2-hydroxyphenyl)-3-(5-bromo 2-chloroyphephenyl)propane-1,3-dione formed by rearrangement of 2-acetyl-4-chlorophenyl 5-bromo-2-chlorobenzoate employing Baker-Venkatraman transformation by ultrasound irradiation. The complexes of Co(II), Fe(III), Cu(II), Ni(II), and Cr(III) with this ligand were also prepared in the solid state by ultrasound irradiation and characterized by different physico-chemical methods.

II. EXPERIMENTAL

The analytical grade solvents and reagents were used in the synthetic and purified by distillation or crystallization where necessary and their boiling or melting points were compared with the available literature values. Melting temperature were checked in open glass capillaries and these temperatures were uncorrected. Purity of the products were checked by TLC. Ultrasound assisted synthesis were carried out in Digital Ultrasonic Cleaner (Equitron). All ¹H-NMR and ¹³C-NMR spectra were recorded in CDCl₃ using TMS as the internal standard. By using (KBr) disc on Bruker spectro-photometer, FT-IR spectra were recorded. By using Macro mass spectrometer, mass spectra were recorded. The XRD patterns were recorded on a Philips 3701. By using Gouy balance at room temperature using Hg[Co(SCN)₄] as the calibrant, the magnetic susceptibility of the metal chelates were determined. By using the conductivity meter with inbuilt magnetic stirrer model no. EQ-664 and using 10⁻³M solutions in DMF, the molar conductance of the complexes were measured. The antimicrobial activity were carried from the Microbiology Department, Dayanand Science College, Latur.

Synthesis

- i) **Synthesis of 2-acetyl-4-chlorophenyl 5-bromo-2-chlorobenzoate(3)**: The β -diketone ligand was synthesized via stepwise approach. In the first step, 2-acetyl-4-chlorophenyl 5-bromo-2-chlorobenzoate was prepared by stirring mixture of 1-(5-chloro-2-hydroxyphenyl) ethanone (1) (1.70g, 0.01mol), 5-bromo 2-chloro benzoic acid (2) (2.35g, 0.01mol), a dry pyridine (5ml) and POCl_3 (1 ml) at 0°C . At room temperature, the reaction mixture was stirred about 8-9 hr. After completion of the reaction (noticed by TLC), the reaction mixture was poured into 100ml HCl (1M) containing 50g of crushed ice and solid obtained was recrystallized from ethanol, filtered and dried. Yield: 78%, m.p. 142°C .
- ii) **Synthesis of 1-(5-chloro,2-hydroxyphenyl)-3-(5-bromo,2-chlorophenyl)propane-1,3-dione (4)**: Thus formed 2-acetyl-4-chlorophenyl 5-bromo-2-chlorobenzoate (3) was dissolved in dry pyridine (10 ml). In this solution powdered KOH (1.12g, 0.02mol) was added and the reaction mixture was irradiated for about 2-3 hr. under ultrasound. After completion of reaction (checked by TLC), the reaction mixture was poured on ice cold water and acidified with conc.HCl. The yellow solid of the 1-(5-chloro 2-hydroxyphenyl)-3-(5-bromo 2-chlorophenyl)propane-1,3-dione (4) obtained was filtered off and crystallized from absolute ethanol. Yield: 88%, m.p. 162°C .
- iii) **Synthesis of transition metal complexes (5)**: To a hot methanolic solution (15ml) containing 2.0 mmol (0.63g) of 1-(5-chloro 2-hydroxyphenyl)-3-(5-bromo 2-chlorophenyl)propane-1,3-dione (4), a methanolic solution (15ml) of a metal nitrate (1.0 mmol) was added with constant stirring. By adding 10% alcoholic ammonia solution, the pH of the mixture solution were arranged to 7.5- 8.5 by adding 10% alcoholic ammonia solution and irradiated about 1-2hrs under ultrasound. The precipitated solid metal complex (5) was filtered off under hot conditions and washed with hot methanol, petroleum ether ($40\text{-}60^\circ\text{C}$) and dried over anhydrous CaCl_2 in a vacuum desiccators (yield: 82-88%).



Scheme 1

III. RESULT AND DISCUSSION

The analytical, physical, magnetic moment and molar conductance data of the ligand and its metal complexes are given in Table 1. The complexes exhibited 1:2 mole ratio (metal:ligand) by using analytical data & corresponds well with the general formula $[\text{ML}_2(\text{H}_2\text{O})_2]$ ($\text{M} = \text{Co(II)}, \text{Fe(III)}, \text{Cu(II)}, \text{Ni(II)}, \text{and Cr(III)}$). At room temperature the magnetic susceptibilities of all complexes were found to be octahedral geometry having two water molecules coordinated to the metal ion. The solutions of metal chelate in DMF showed low conductance, showed the non-electrolyte nature of the complexes.

Table 1. Analytical, physical, magnetic moment and molar conductance data of the compounds.

compound	F. W.	M. P.	Magnetic moment $\mu_{\text{eff}}(\text{B. M.})$	Molar conductance	Elemental analysis			
					Carbon %	Hydrogen %	Oxygen %	Metal %
L	388	158	46.28	2.19	12.32
[Fe(L ₂)(H ₂ O) ₂]	868	>300	5.56	32.4	41.36	2.46	14.69	6.41
[Co(L ₂)(H ₂ O) ₂]	871	>300	3.10	21.8	41.22	2.48	14.61	6.71
[Ni(L ₂)(H ₂ O) ₂]	871	>300	4.12	28.2	41.23	2.42	14.58	6.68
[Cu(L ₂)(H ₂ O) ₂]	875.5	>300	1.90	17.4	41.09	2.46	14.58	7.19
[Cr(L ₂)(H ₂ O) ₂]	864	>300	3.72	19.6	41.52	2.43	14.76	5.94

¹H-NMR spectrum of the ligand: The ¹H-NMR spectra of the free ligand in the CDCl₃ at room temperature showed the following signals at δ (ppm): 6.71 (s, 1H, vinylic), 6.80-7.81 (m, 6H, Ar-H), 11.98 (s, 1H, Phenolic OH), 16.20 (s, 1H, Enolic-OH).

¹³C-NMR spectrum of the ligand : At room temperature the ¹³C-NMR spectra of the free ligand in the CDCl₃ showed the following signals at δ 195.2(s, C-1, C=O), 95.22(s, C-2, -CH=), 191.13(s, C-3), 123.24(s, C-1'), 160.17(s, C-2'), 115.69(s, C-3'), 137.02(s, C-4'), 128.20(s, C-5'), 130.09(s, C-6'), 135.33 (s, C-1''), 132.09(s, C-2''), 120.03(s, C-3''), 133.90(s, C-4''), 130.92 (s, C-5''), 131.32 (s, C-6''). The ¹H-NMR spectrum of ligand exhibited a singlet at δ 16.20 ppm due to enolic proton (since enol form in β -diketone is more stable), a singlet at δ 11.98 ppm due to phenolic proton adjacent to the carbonyl group whereas ¹³C-NMR spectra gives singlet at δ 195.20 ppm due to ketonic carbon C-1 and δ 191.13 ppm due to enolic carbon C-3 confirming the formation of β -diketone and the keto-enol tautomerism²⁴.

IR spectra The IR spectrum of free ligand showed characteristic bands at 2862.13 (-OH), 1690.17 (C=O), 1405.22 (Ar C=C). The IR spectra of the metal chelates showed new bands in the 559.62-587.15 cm⁻¹ regions, which can be assigned to $\nu(\text{M-O})$ ²⁵ vibrations. The C=O bond in complex shifted to lower frequency as compared to that of free ligand which indicates the coordination of metal atom with the carbonyl group of diketone. The IR spectra of all complexes showed a strong band in the region 3298.11-3468.22cm⁻¹ which supports that these complexes includes coordinated water molecule and confirmed by appearance of a non-ligand band in the 818-865 cm⁻¹ region, assignable to the rocking mode of water.²⁶

Table 2. IR spectra of β -diketone ligand and metal complexes

Compound	$\nu(\text{C=O})$	$\nu(\text{C=C})$	$\nu(-\text{OH})$	$\nu(-\text{OH})$ coordinated H ₂ O mole.	$\nu(\text{M-O})$
L	1690.17	1405.22	2862.13	-----	-----
[Fe(L ₂)(H ₂ O) ₂]	1662.19	1437.18	2871.12	3468.22	584.62
[Co(L ₂)(H ₂ O) ₂]	1664.20	1432.21	2867.09	3258.07	563.17
[Ni(L ₂)(H ₂ O) ₂]	1657.12	1439.23	2865.10	3317.27	582.13
[Cu(L ₂)(H ₂ O) ₂]	1660.23	1435.17	2870.22	3262.09	587.15
[Cr(L ₂)(H ₂ O) ₂]	1653.18	1433.12	2866.17	3298.11	559.62

Powder X-ray diffraction analysis The X-ray diffractograms of the Fe(III), Co(II) and Cu(II) complexes were scanned in the range 10-90° at wavelength of 1.54Å. The diffractograms and associated data depict the relative intensity, 2 θ value of each peak and interplanar spacing (d-values). Using computer programme, the X-ray diffraction arrangement of the transition metal complexes of β -diketone ligand with respect to major peaks of relative intensity greater than 10% were indexed.²⁷ This indexing method also yields the unit cell parameters, Miller indices (hkl) and the unit cell volume. The unit cell of Ni(II) complex yielded a unit cell volume V = 207.23Å³ and also yielded values of lattice constants: a = 11.38 Å, b = 3.01Å and c = 6.05Å. The unit cell of Fe(III) complex yielded values of lattice constants: a = 4.08Å, b = 8.37Å and c = 8.86Å, and a unit cell volume V = 302.56Å³.

The unit cell of Co(II) complex yielded values of lattice constants: a = 7.92, b = 3.11Å and c = 6.65Å, and a unit cell volume V = 163.79Å³.

The unit cell of Cu(II) complex yielded unit cell volume V = 187.57Å³ & values of lattice constants: a = 10.00 Å, b = 3.07Å and c = 6.11Å. By considering the conditions such as a \neq b \neq c and $\alpha = \gamma = 90^\circ \neq \beta$ required for a monoclinic nature, the samples were tested & it is found to be adequate. Hence we came to conclusion that Co(II), Fe(III) and Cu(II) were monoclinic crystal system & Ni(II) complex was orthorhombic. Using the specific gravity method²⁸ the density values of the complexes were determined and found to be 4.1130, 4.0798, 3.1989 and 4.5888 g cm⁻³ for Co(II), Fe(III), Cu(II) and Ni(II) complexes respectively. Using the experimental density values, ρ , Avogadro's number, N, the molecular weight of the complexes, M, and the volume of unit cell, V, the number of molecules per unit cell were computed using the equation $\rho = \text{Mn}/\text{NV}$. With these computed values, the theoretical densities were calculated and found to be 4.1268, 4.0517, 3.2291 and 4.4918 g cm⁻³ respectively. Analogy of theoretical and experimental density value shows good agreement within the limits of experimental error.²⁹

Table 3. XRD data and refinement parameters of Fe(III), Co(II), Ni(II) and Cu(II)

Parameters		Fe	Co	Ni	Cu
Temperature (K)		298	298	298	298
Wavelength (Å)		1.54	1.54	1.54	1.54
Radiation		CuK α	CuK α	CuK α	CuK α
Crystal system		Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Unit cell dimension	a(Å)	4.08	7.92	11.38	10
	b(Å)	8.37	3.11	3.01	3.07
	c(Å)	8.86	6.65	6.05	6.11
α°	90	90	90	90	90
β°	101	90	90	90	90
γ°	90	90	90	90	90
Unit cell volume		302.56	163.79	207.23	187.57

Antimicrobial activity

The antibacterial screening of synthesized compounds was carried out by paper disc diffusion³⁰ method at 100ppm against Gram +ve bacteria *B. subtilis*, *S. aureus* and Gram – ve bacteria *E. coli*. The compounds were tested at the concentration 100ppm in DMSO and compared with known antibiotics viz streptomycin. The antifungal activity of the compounds were assayed using fungal species *F. Oxysporum* and *Aspergillus niger*. Also standard antibacterial streptomycin were screened under similar condition for comparison.

Escherichia coli, *B. subtilis*, & *staphylococcus aureus* determined by paper disc diffusion method³¹ are presented in Table 4. The activity of a known antibiotic viz. streptomycin is compared with the activity of ligand & its metal complexes. The consequence of the in vitro fungicidal activity of the compounds against *F.oxysporum* and *A. niger* are given in same table no. 4, in which the outcomes of the control are also introduced. From Table 4, it is evident that complexes having more antibacterial as well as antifungal activity as compared to free ligand. Also regarding to standard, all the synthesized complexes & ligand were found to be fairly active.

Table 4. Antimicrobial screening of ligand and its metal complexes

Compounds	Conc. (ppm)	Antibacterial activity (Inhibition in mm)			Antifungal activity (Inhibition in mm)	
		<i>Bacillus subtilis</i>	<i>E. coli</i>	<i>Staphyloc. aureus</i>	<i>Aspergill. niger</i>	<i>Fusarium oxysporum</i>
L	100	7	7	7	7	7
[Fe(L ₂)(H ₂ O) ₂]	100	8	8	8	7	7
[Co(L ₂)(H ₂ O) ₂]	100	17	17	17	16	17
[Ni(L ₂)(H ₂ O) ₂]	100	9	8	8	9	7
[Cu(L ₂)(H ₂ O) ₂]	100	18	18	19	18	21
[Cr(L ₂)(H ₂ O) ₂]	100	8	8	6	8	8
Streptomycine	100	6	6	7	7	6

IV. CONCLUSION

In the present work we have been synthesized the ligand and its metal complexes by ultrasound irradiation method. The prepared compounds were characterized by various analytical techniques. The prepared β -diketone ligand joins with the metal ions in a bidentate manner with oxygen as the donor sites. Based upon the spectral and physicochemical data deliberated above complexes as Co(II), Fe(III), Cu(II), Ni(II), and Cr(III) showed octahedral geometry. The IR spectra of ligand and its complexes showed the mode of coordination, Conductivity measurement indicates the nature of complexes as nonelectrolytic. Also the magnetic studies notified the paramagnetic nature of complexes. The XRD pattern pointed out the crystalline nature of the complexes. This study suggested the monoclinic crystal system for the Co(II), Fe(III) and Cu(II) complexes and Ni(II) complex showed orthorhombic crystal system. From antimicrobial screening it is revealed that the synthesized ligand and its metal complexes are biologically active and showed enhanced antimicrobial activities compared to standard.

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