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Microwave Solid Phase Synthesis, Characterization and Antimicrobial Activities of Mononuclear Cobalt(II) Complex with 4-Chloro-benzoic acid 4-[3-(4-chloro-phenyl)-3-hydroxy-acryloyl]-3-hydroxy-phenyl ester

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One mononuclear complex has been designed and synthesized by a β-diketone ligand 4-chloro-benzoic acid 4-[3-(4-chloro-phenyl)-3-hydroxy-acryloyl]-3-hydroxy-phenyl ester (L) with $CoCl_2·6H_2O$ in microwave radiation assistance. The complex was characterized by X-ray crystallography, confirming that the central cobalt(II) was coordinated by four oxygens from two β-diketone ligand and two oxygens from two ethanols. The complex was assayed for *in vitro* antibacterial (*B. subtilis, S. aureus, S. faecalis, P. aeruginosa, E. coli* and *E. cloacae*) activities and showed better antimicrobial activity against Gram positive strains than Gram negative strains.

Key Words: Microwave solid phase synthesis, β-Diketone ligand, Mononuclear cobalt(II) complex, Antibacterial activity.

INTRODUCTION

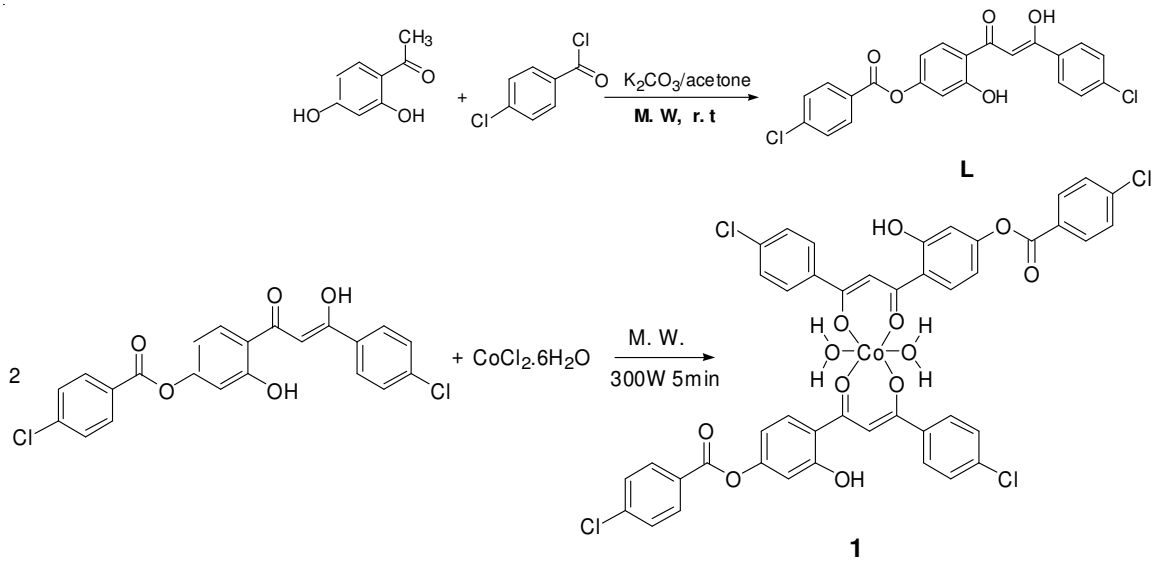
β-Diketones have been important intermediates in organic synthesis. More current research, a strong reactivity of β-diketones are 1,4-diphenyl-butane-1,3-dione, 1,4-dithiohene-butane-1,3-dione, 1,4-*bis*-[benzo(1,3)dio-butane]-1,3-dione, 1,4-*bis*-(3-fluoro-4-methoxy-phenyl)-butane-1,3-dione, 3-hydroxy-1,3-diphenyl-propenone, 1,3-di-furan-2-yl-3-hydroxy-propenone[1-4]. β-Diketones and their derivatives also have a wide range of fields in the application of heat stabilizer, luminescence, catalysis, solvent extraction and pharmaceutical[5-12]. Although these methods synthesize reliable routes for the preparation of β-diketones, most of them follow lengthy procedures and time. Therefore, the development of direct and efficient procedures for these classes of compounds from materials has been the target of synthetic organic chemistry. In this paper, one bidentate β-diketone ligand, 4-chloro-benzoic acid 4-[3-(4-chloro-phenyl)-3-hydroxy-acryloyl]-3-hydroxy-phenyl ester (L), was synthesized by microwave assistance and one mononuclear complex was obtained reacting L with $CoCl_2·6H_2O$. The complex were assayed for antibacterial activities against three Gram positive bacterial strains (*Bacillus subtilis, Staphylococcus aureus* and *Streptococcus faecalis*) and three Gram negative bacterial strains (*Escherichia coli, Pseudomonas aeruginosa* and *Enterobacter cloacae*) by the 3-(4,5-dimethyl-2-triazyl)-2,5-diphenyl-2*H*-*tetra*zolium bromide (MTT) method.

EXPERIMENTAL

All chemicals were of reagent grade and used as received. UV spectra were recorded on a U-3000 spectrophotometer. IR spectra were recorded on a Nexus 870 FT-IR. ESI-MS spectra were recorded on a Mariner System 5304 mass spectrometer. Elemental analyses were performed on a CHN-O-rapid instrument and were within ±0.4 % of the theoretical values. Melting points were measured on a Boetius micro melting point apparatus.

Preparation of 4-chloro-benzoic acid 4-[3-(4-chloro-phenyl)-3-hydroxy-acryloyl]-3-hydroxy-phenyl ester (L) and its cobalt(II) complex (1): Ligand was designed and synthesized from 2,4-dihydroxyacetophenone and 4-chloro-benzoyl chloride in acetone by microwave assistance[13]. The ligand and $CoCl_2·6H_2O$ were mixed together and microwave radiated 5 min in 300 W. The nacarat powder was dissolved in water/acetone/DMF(1/1/1) and afforded bis(4-chloro-benzoic acid 4-[3-(4-chloro-phenyl)-3-hydroxy-acryloyl]-3-hydroxy-phenyl ester)-*bis*-water-cobalt(II) (**1**) (**Scheme-I**).

Preparation of L: K_2CO_3 (20 g) was slowly added to a round-bottom-flask containing 2,4-dihydroxyacetophenone (0.02 mol, 3.04 g) and 4-chloro-benzoyl chloride (0.04 mol, 7 g) dissolved in acetone (50 mL). The mixture was microwave-irradiated (90 W) for 90 min and then precipitated. After filtration, the yellow solid was washed with acetone (100 L) and water (200 mL), dried and recrystallized from ethanol



Scheme-I: Synthesis of ligand and its Co(II) complex **(1)**

acetone (1/1). Yield: 83 %, m.p.: > 300 ºC. UV (λ nm): 375; 251. Selected IR data (KBr, ν_{max}, cm^{-1}): 3127.7 (m), 1744.1 (s), 1609.1 (s), 1568.8 (m), 1515.5 (s), 1480.9 (s), 1426.9 (m), 1401.6 (s), 1273.4 (s), 1207.0 (m), 1175.9 (m), 1141.3 (s), 1092.2 (s), 1013.8 (s), 970.3 (m), 845.3 (m); ^{1}H NMR ($CDCl_3$) δ ppm: 15.45 (s, 1H), 12.23 (s, 1H), 8. 21 (d, *J* = 7.4 Hz, 2H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 14.6 Hz, 1H), 7.54 (d, *J* = 13.2 Hz, 2H), 7.52 (d, *J* = 12.8 Hz, 2H), 6.90 (d, *J* = 2.6, 1H), 6.80 (s, 1H). ESI-MS: 429.05 ($C_{22}H_{15}Cl_2O_5^+$, $[M+H]^+$). Anal. calcd. for $C_{22}H_{14}O_5Cl_2$ (%): C, 61.56; H, 3.29. Found (%): C, 61.72; H, 3.24.

Complex 1: The β-diketone ligand (L) (2.568 g, 6 mmol) and $CoCl_2{\cdot}6H_2O$ (0.711 g, 3 mmol) were mixed together and microwave radiated 5 min in 300 W. The nacarat powder was dissolved in water/acetone/DMF (1/1/1). After standing for 10-15 days, the single crystals of **1** were obtained, were separated by filtration, washed with acetone thrice and dried. Yield: 72 %, m.p.: 268-271 ºC. UV (λ nm): 377; 256. Selected IR data (KBr, ν_{max}, cm^{-1}): 3325.7 (m), 3130.5 (m), 1736.3 (s), 1662.7 (s), 1592.6 (s), 1550.7 (s), 1479.5 (s), 1456.8 (s), 1347.2 (s), 1293.7 (s), 1207.0 (s), 1163.0 (m), 1140.7 (s), 1111.9 (m), 1097.2 (s), 1064.5 (s), 1012.7 (s), 786.5 (s), 754.1 (m). Anal. calcd. for $C_{47}H_{37}NO_{13}CoCl_4$ (%): C, 55.05; H, 3.61. Found (%): C, 55.13; H, 3.58.

Crystal structure determinations and refinements: The crystallographic date for **1** was collected on a Bruker Smart 1000 CCD area detector diffractometer equipped with MoK_α (λ = 0.71073 Å) radiation using ω-scan mode. Empirical absorption correction was applied to the data. Unit cell dimensions were obtained with least-squares refinements and all structures were solved by direct methods with SHELXL-97. All non-hydrogen atoms were located from the trial structure and then refined anisotropically. All hydrogens were generated in idealized positions. All calculations were performed with SHELXL-97 programs[14]. Other relevant parameters of the crystal structure are listed in Table-1.

Antimicrobial activity: The antibacterial activity of L and **1** was tested against *B. subtilis, S. aureus, S. faecalis, P. aeruginosa, E. coli* and *E. cloacae* using MTT medium. The minimum inhibitory concentrations of the test complexes were determined by a colourimetric method using the dye MTT[15]. A stock solution of the synthesized complex (50 μg/mL) in DMSO was prepared and graded quantities of the test complexes were incorporated in specified quantity of sterilized liquid medium. A specified quantity of the medium containing the complex was poured into microtitration plates. Suspension of the microorganism was prepared to contain approximately 10^5 cfu/mL and applied to microtitration plates with serially diluted complexes in DMSO to be tested and incubated at 37 ºC for 24 h for bacterial. After the minimum inhibitory concentrations were visually determined on each of the microtitration plates, 50 μL of PBS (phosphate buffered saline 0.01 mol/L, pH 7.4: $Na_2HPO_4{\cdot}12H_2O$ 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g,

TABLE-1
CRYSTALLOGRAPHIC AND EXPERIMENTAL DATA FOR **1**

Compound	**1**
Empirical formula	$C_{47}H_{37}C_{14}CoNO_{13}$
Formula weight	1024.51
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	6.9450(5)
b (Å)	13.11610(12)
c (Å)	14.84090(13)
α (°)	105.812(2)
β (°)	102.4600(10)
γ (°)	105.326(2)
V ($Å^3$)	1192.62(9)
Z	1
T (K)	298(2)
Density (g/cm^3)	1.426
μ (mm^{-1})	0.648
F(000)	525
Data/restrains/parameters	4154 / 0 / 313
θ Range (°)	2.65 to 25.02
Reflections collected/ unique	6320 / 4154
R_{int}	0.0357
Final R indices [I >2σ(I)]	R_1 =0.0727, wR_2 = 0.1858
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ ($e/Å^3$)	1.157 and -0.256

$^aR = \sum||F_o| - |F_c|| / \sum|F_o|$, $^bwR = [\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]]^{1/2}$

KCl 0.2 g, distilled water 1000 mL) containing 2 mg/mL of MTT was added to each well. Incubation was continued at room temperature for 4-5 h. The content of each well was removed and 100 µL of isopropanol containing 5 % 1 mol/L HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density was measured with a microplate reader at 570 nm. The observed minimum inhibitory concentrations were presented in Table-2.

TABLE-2
MINIMUM INHIBITORY CONCENTRATIONS (MICs) OF THE SYNTHETIC COMPOUNDS

Compound	Microorganisms MICs (µg/mL)					
	Gram positive			Gram negative		
	B. subtilis	*S. aureus*	*S. faecalis*	*P. aeruginosa*	*E. coli*	*E. cloacae*
1	6.25	6.25	3.125	12.5	6.25	12.5
L	12.5	25.0	12.5	25.0	25.0	25.0
Penicillin	1.562	1.562	1.562	6.25	6.25	3.125
Kanamycin	0.39	1.562	3.125	3.125	3.125	1.562

RESULTS AND DISCUSSION

The complex of the formula $C_{47}H_{37}NO_{13}CoCl_4$ were prepared in moderate yield (72 %). IR spectra of β-diketone ligand show four bands at 1600-1480 cm^{-1}, characteristic of the mixed modes of vibrations arising from normal coordinates having contributions from ν(C=O) and ν(C=C) of β-diketone groups[16]. The infrared spectra of complex **1** (KBr pellets) display an intense absorption band at *ca*. 1662.7 cm^{-1} attributable to the ν(C=O) stretching frequency. This band is shifted *ca*. 54 cm^{-1} tower above wavenumbers compared to the *ca*. 1609 cm^{-1} attributable to the ν(C=O) stretching frequency of L. The UV spectra of the complexes display an intense absorption peak at 251-256 nm ($\pi\rightarrow\pi^*$) and 375-377 nm ($n\rightarrow\pi^*$).

The structure of complex **1** were confirmed by a single-crystal X-ray diffraction and is shown in Figs. 1 and 2. The crystal structure consists of mononuclear complex. The molecular structure of complex **1** crystallize in triclinic with space group P ; bond distances and angles are provided in Table-3. The complex **1** is electronically neutral mononuclear compound. The central metal (Co), on an inversion center, are in pseudo octahedral coordination geometry with two H_2O occupying both axial positions and oxygen donors from two β-diketone fragments binding in equatorial positions; each *bis*-β-diketonate is essentially planar[17]. The general Co-O bond lengths are in the range 2.012(3)-2.191(4) Aº, unexceptional and similar to the corresponding bonds in other cobalt diketonate complexes[17-19]. As shown in Table-4 intermolecular H-bonds (O-H… O) formed between adjacent molecules.

TABLE-3
SELECTED BOND LENGTHS (Å) AND BOND ANGLES (º) OF Co(II) COMPLEX (**1**)

Bond	Dist.
Co(1)-O(2)#1	2.012(3)
Co(1)-O(1)	2.020(3)
Co(1)-O(2)	2.012(3)
Co(1)-O(6)	2.191(4)
Co(1)-O(1)#1	2.020(3)
Co(1)-O(6)#1	2.191(4)
Angle	**(º)**
O(2)#1-Co(1)-O(2)	180.00(11)
O(2)#1-Co(1)-O(1)	90.61(14)
O(2)#1-Co(1)-O(6)	87.84(15)
O(1)-Co(1)-O(6)	90.85(15)
O(1)#1-Co(1)-O(6)#1	90.85(15)
O(2)#1-Co(1)-O(1)#1	89.39(14)
O(2)-Co(1)-O(1)	89.39(14)
O(2)-Co(1)-O(6)	92.16(15)
O(2)#1-Co(1)-O(6)#1	92.16(15)
O(1)-Co(1)-O(6)#1	89.15(15)
O(2)-Co(1)-O(1)#1	90.61(14)
O(1)#1-Co(1)-O(1)	180.000(1)
O(1)#1-Co(1)-O(6)	89.15(15)
O(2)-Co(1)-O(6)#1	87.84(15)
O(6)-Co(1)-O(6)#1	180.0

Symmetry transformations used to generate equivalent atoms: #1 -x+1, -y+1, -z+1

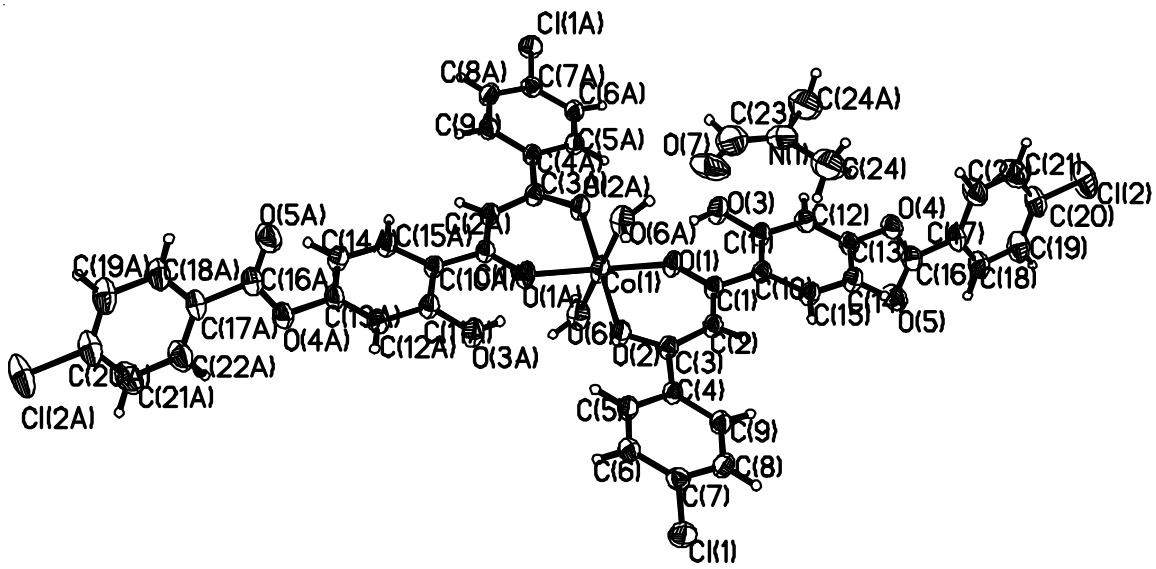


Fig. 1. Crystal structure of complex **1**, showing 30 % probability displacement ellipsoids (arbitrary spheres for the H atoms)

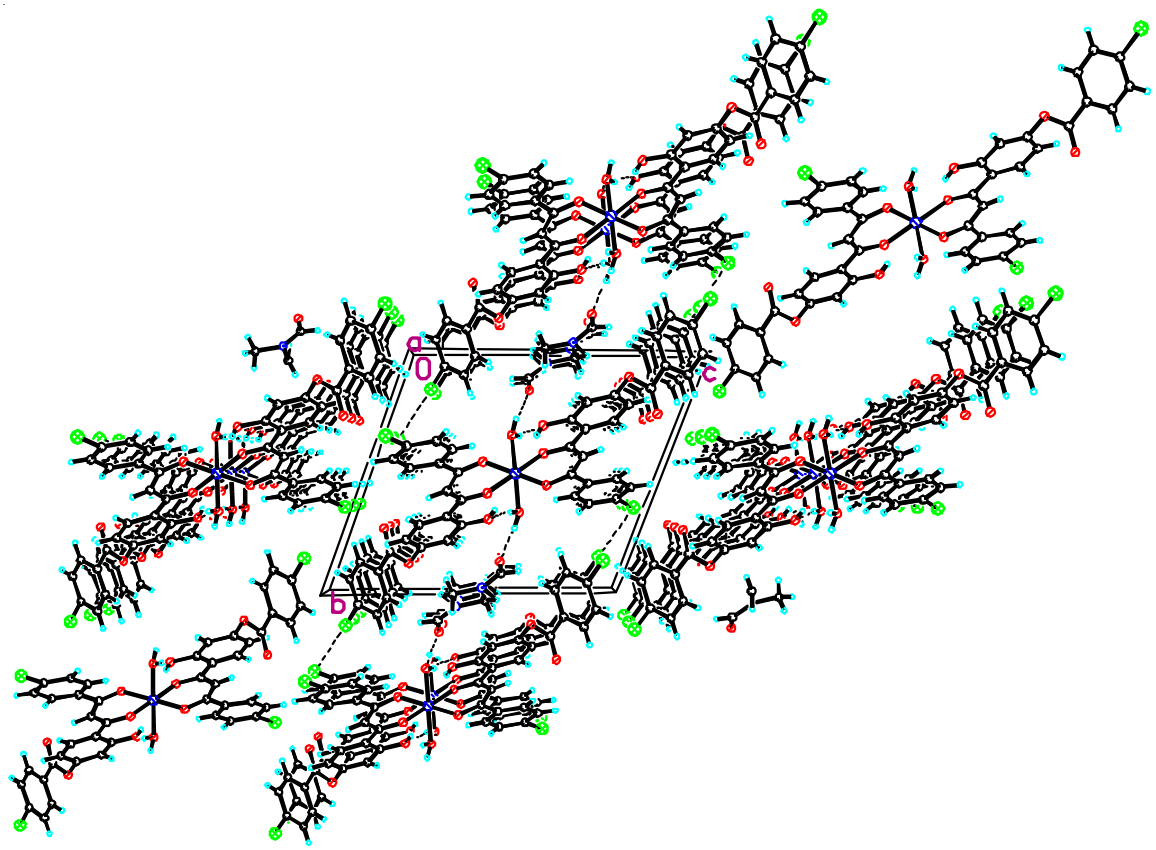


Fig. 2. Packing structure of complex **1** the a-axis

TABLE-4
HYDROGEN BONDS FOR **1** [(Å) and (°)]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O3-H3...O1	0.82	1.74	2.4627	147
O6-H6(C)...O3	0.85	2.05	2.8809	165
O6-H6(D)...O7	0.85	1.76	2.5877	164

From minimum inhibitory concentration (MIC) values (Table-2), the complex was more toxic towards Gram positive strains than Gram negative strains when compared to the positive controls penicillin and kanamycin, respectively. The reason may be the difference in the structures of the cell walls[20]. The walls of the Gram negative cells are more complex than those of Gram positive cells. Lipopolysaccharides form an outer lipid membrane and contribute to the complex antigenic specificity of Gram negative cells. Antimicrobial activity of complexes is due to either killing the microbes or inhibiting their multiplication by blocking their active sites[21]. Since the molecular structure is quite similar, the antibacterial activity of Co(II) complex (**1**) is quite similar.

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