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Microwave Solid Phase Synthesis, Characterization, and Antimicrobial Activities of One Mononuclear Manganese(II) Complex with 4-Chlorobenzoic Acid 4-[3-(4-Chlorophenyl)-3-Hydroxyacryloyl]-3-Hydroxyphenyl Ester[1]

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Abstract—One mononuclear complex has been designed and synthesized by a β-dikertone ligand 4-chlorobenzoic acid 4-[3-(4-chlorophenyl)-3-hydroxyacryloyl]-3-hydroxyphenyl ester (L) with $MnCl_2 \cdot 4H_2O$ in microwave radiation assistance. The complex was characterized by X-ray crystallography, confirming that the central manganese(II) atom was coordinated by four oxygens from two L and two oxygens from two water. 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.

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INTRODUCTION

β-Diketones have been important intermediates in organic synthesis. More current research, a strong reactivity of β-diketones are 1,4-diphenylbutane-1,3-dione, 1,4-dithiohenebutane-1,3-dione, 1,4-bis-(benzo(1,3)diobutane-1,3-dione, 1,4-bis-(3-fluoro-4-methoxyphenyl)-butane-1,3-dione, 3-hydroxy-1,3-diphenylpropenone, 1,3-difuran-2-yl-3-hydroxypropenone [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 [5–13]. 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-chlorobenzoic acid 4-[3-(4-chlorophenyl)-3-hydroxyacryloyl]-3-hydroxyphenyl ester (L), was synthesized by microwave assistance and one mononuclear complex (**I**) was obtained reacting L with $MnCl_2 \cdot 4H_2O$. The complex was 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-2H-tetrazolium bromide (MTT) method.

[1] The article is published in the original.

EXPERIMENTAL

Materials and instruments. 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.

Synthesis 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-chlorobenzoyl chloride (0.04 mol, 7.00 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 mL) and water (200 mL), dried, and recrystallized from ethanol–acetone (1 : 1). The yield was 83%, m.p. > 300°C. UV (λ, nm): 375; 251. Selected IR data (KBr; ν, 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,

Table 1. Crystal data and refinement details for structure **I**

Parameter	Value
Formula weight	947.42
Crystal system	Triclinic
Space group	$P\bar{1}$
a, Å	6.9200(5)
b, Å	13.0699(12)
c, Å	15.0201(14)
α, deg	107.280(2)
β, deg	101.719(1)
γ, deg	104.607(1)
V, Å^3	1197.06(18)
Z	1
T, K	298(2)
ρ_{calcd}, g/cm^3	1.314
μ, mm^{-1}	0.555
F(000)	483
Crystal size, mm	0.42 × 0.13 × 0.11
θ Range, deg	2.67–25.02
Limiting indices	$-8 \le h \le 8$, $-14 \le k \le 15$, $-12 \le l \le 17$
Reflections collected/unique	5905/4032 ($R_{int} = 0.0750$)
Reflections with $I > 2\sigma(I)$	1936
Parameters	277
Goodness-of-fit on F^2	1.074
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0730$[a], $wR_2 = 0.1376$[b]
R indices (all data)	$R_1 = 0.1073$, $wR_2 = 0.1658$
$\Delta\rho_{max}/\Delta\rho_{min}$, e/Å^3	0.661/−0.516

[a] $R = \Sigma[|F_o| - |F_c|]/\Sigma|F_o|$, [b] $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

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 ($C_{22}H_{15}Cl_2O_5^+$, $[M + H]^+$).

For $C_{22}H_{14}O_5Cl_2$

anal. calcd., %:	C, 61.56;	H, 3.29.
Found, %:	C, 61.72;	H, 3.24.

Synthesis of complex I. Compound L (2.568 g, 6 mmol) and $MnCl_2 \cdot 4H_2O$ (0.594 g, 3 mmol) were mixed together and microwave radiated 6 min in 150 W. The nacarat powder was dissolved in water–acetone–DMF (1 : 1 : 1). After standing for 5–7 days, the single crystals of **I** were obtained, separated by filtration, washed with acetone thrice, and dried. The yield was 76%, m.p.: 255–258°C. UV (λ, nm): 383; 257. Selected IR data (KBr; ν, cm^{-1},): 3335.4 m, 1737.1 s, 1665.3 s, 1591.5 s, 1551.6 s, 1481.5 s, 1457.2 s, 1348.2 s, 1294.1 s, 1165.1 m, 1141.5 s, 1112.7 m, 1098.2 s, 1010.9 s, 787.5 s, 755.4 m.

For $C_{44}H_{30}O_{12}Cl_4Mn$

anal. calcd., %:	C, 55.85;	H, 3.23.
Found, %:	C, 55.78;	H, 3.19.

X-ray structure determination. The crystallographic data for **I** were 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.

Supplementary material has been deposited with the Cambridge Crystallographic Data Centre (no. 951266; deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

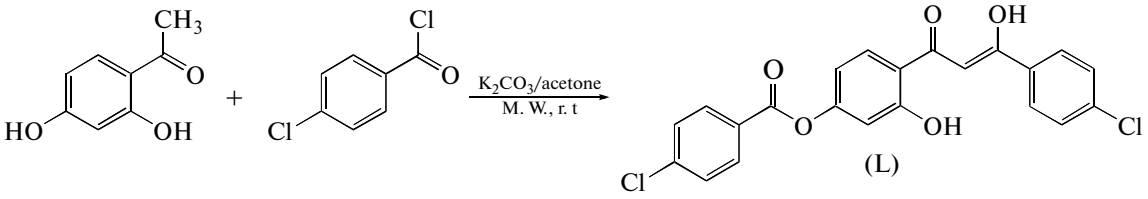
Antimicrobial activity. The antibacterial activity of L and **I** was tested against *B. subtilis*, *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae* using MTT medium. The MICs of the test complexes were determined by a colorimetric method using the dye MTT [15]. A stock solution 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°C for 24 h for bacterial. After the MICs 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, 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 M 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 MICs were presented in Table 2.

Table 2. MICs (minimum inhibitory concentrations) 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*
I	6.25	3.125	6.25	6.25	12.5	12.5
L	25	12.5	12.5	25	25	25
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

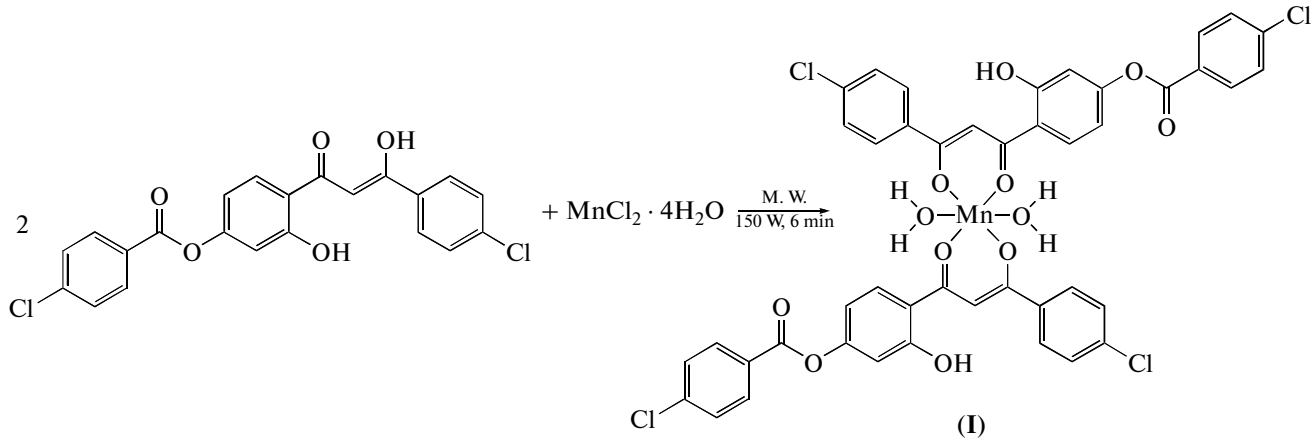
RESULTS AND DISCUSSION

Ligand L was designed and synthesized from 2,4-dihydroxyacetophenone and 4-chlorobenzoyl chloride in acetone by microwave assistance according to scheme:



(L)

Complex **I** was synthesized from the ligand L and $MnCl_2 \cdot 4H_2O$, which were mixed together and microwave radiated 6 min in 150 W. Then the nacarat powder was dissolved in water–acetone–DMF (1 : 1 : 1) and afforded bis(4-chlorobenzoic acid 4-[3-(4-chlorophenyl)-3-hydroxyacryloyl]-3-hydroxyphenyl ester)-bis-water-manganese (II) (**I**). Scheme synthesis of **I** are given below:



(**I**)

The complex of the formula $C_{44}H_{30}O_{12}Cl_4Mn$ was prepared in moderate yield (76%).

IR spectra of L show four bands at 1480–1609 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 **I** display an intense absorption band at ~1665.3 cm^{-1} attributable to the ν(C=O) stretching frequency. This band is shifted ~56.2 cm^{-1} tower above wavenumbers compared to the ~1609.1 cm^{-1} attributable to the ν(C=O) stretching frequency of L. The UV spectra of complex **I** display an intense absorption peak at 251–257 ($\pi \longrightarrow \pi^*$) and 375–383 nm ($n \longrightarrow \pi^*$).

The structure of complex **I** was confirmed by a single-crystal X-ray diffraction and is shown in Figs. 1 and 2. The complex **I** is electronically neutral mononuclear compound. The central metal (Mn), on an inversion center, is in pseudo octahedral coordination geometry with two H_2O occupying both axial positions and oxygen donors from two β-diketone fragments

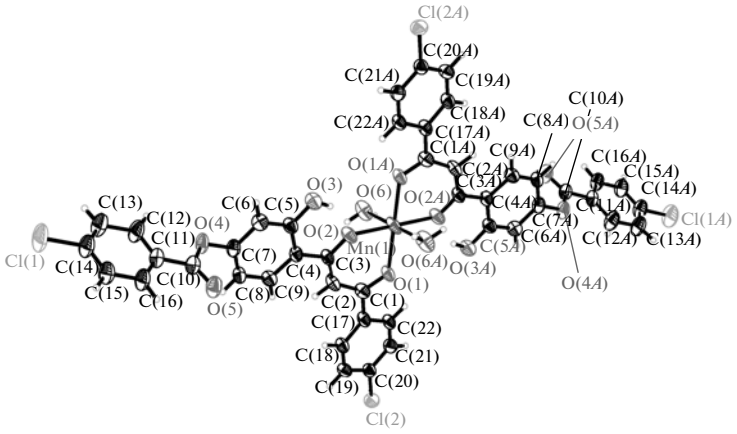


Fig. 1. Crystal structure of complex **I**, showing 30% probability displacement ellipsoids (arbitrary spheres for the H atoms).

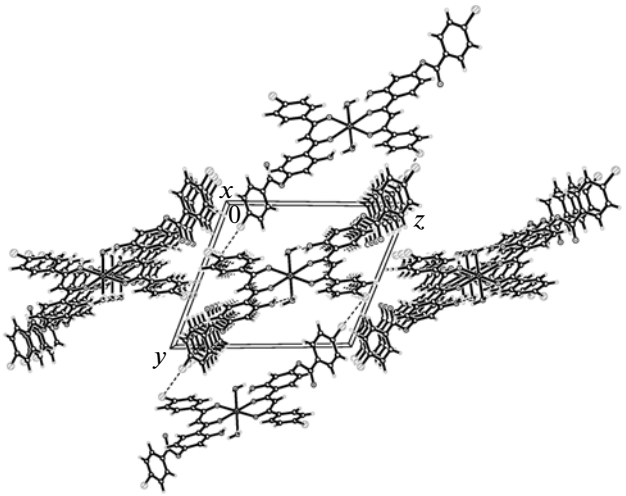


Fig. 2. The packing structure of complex **I** the *x* axis.

binding in equatorial positions; each bis-β-diketonate is essentially planar [17]. The general Mn–O bond lengths are in the range 2.082(6)–2.262(8) Å (Mn(1)–O(1) 2.082(6); Mn(1)–O(6) 2.262(8); Mn(1)–O(2) 2.128(7) Å) unexceptional and similar to the corresponding bonds in other manganese diketonate complexes [17–19]. In structure **I**, some bond angles are: O(1)Mn(1)O(6) 88.5(3)°; O(1)Mn(1)O(2) 83.4(2)°; O(2)Mn(1)O(6) 89.4(3)°. As shown in Table 3, intermolecular H–bonds (O–H···O, C–H···O) formed between adjacent molecules.

From 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. Anti-microbial 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 **I** is quite similar.

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Table 3. Geometric parameters of hydrogen bonds for **I**

Contact D–H···A	Distance, Å			Angle DHA, deg
	D–H	H···A	D···A	
O(3)–H(3)···O(2)	0.82	1.72	2.452(9)	148
O(6)–H(6*B*)···O(3)	0.85	2.47	2.878(4)	110
O(6)–H(6*C*)···O(3)	0.85	2.47	2.878(4)	110
C(12)–H(12)···O(4)	0.93	2.37	2.718(4)	102

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