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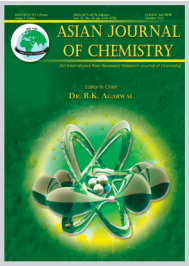

Synthesis, Spectroscopic and Bactericidal Investigation of Some Transition Metal Complexes of Monomethyl phthalate

WAJID REHMAN[1,*], ZONERA HASSAN[2] and YASMEEN SHAKIR[2]

[1]Department of Chemistry, Hazara University, Mansehra, Pakistan
[2]Department of Biochemistry, Hazara University, Mansehra, Pakistan

*Corresponding author: E-mail: sono_waj@yahoo.com

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Seven novel transition metal complexes have been synthesized by using monomethyl phthalate as ligand and characterized through physical techniques such as melting point, elemental analyses, IR and ^{1}H NMR spectroscopy. The complexes of Co(II), Ni(II), Fe(II), Zn(II), Mn(II) and hydrous and anhydrous Cu(II) exhibit trigonal bipyramidal and square planner geometry in solution state. It has been observed that monomethyl phthalate bound to the central metal atom through oxygen atom of the carboxylate group. The complexes formed were then treated with five different types of bacterial strains in order to check whether the synthesized compound is bioactive or not and the results were compared with the standard drug imipenem. Copper(II) complex showed highest inhibition zone against these microbes. The bactericidal activities indicated that metal complexes showed enhanced activity as compared to the free ligand.

Key Words: Monomethyl phthalate, Spectra, Antibacterial, Transition metal.

INTRODUCTION

Modern research on the topic of medicinal substances is a burning issue today. Traditional way of treating any infection and diseases was the use of botanical extracts that was so costly, laborious and time consuming[1]. Coordination compounds are important due to their role in biological and chemical systems in various ways[2]. Some biologically active compounds may become more cytostatic and bacteriostatic upon chelation[3]. The significance of metal ions in various biological fields has become important, as they are more powerful inhibitor of an enzyme as compared to un-complexed biological active compounds. There is large number of metal complexes having anticancer, antitumor and antibacterial activity[4].

In the past, a number of organometallic complexes have been synthesized and characterized together with their biological properties[5-9]. The main objective of the present communication is to synthesize, spectrally characterize and bactericidal study of some novel transition metal complexes with monomethyl phthalate.

EXPERIMENTAL

All the transition metal salts, phthalic anhydride and solvents (acetone, chloroform and methanol) were purchased from RDH/Aldrich/Fluke/Merck, the melting points were measured on a Reichert thermometer (F.G. Bode Co.; Austria). Elemental analyses (C, H, N) were performed on a Carlo Erba 1106 elemental analyzer with antipyrene as standard. IR spectra were obtained in KBr using a Perkin Elmer FT IR-1605 spectrophotometer.

Synthesis of ligand: The ligand was prepared according to the modification in the literature reported method[10] (**Schemne-I**) 7.4 g (50 mmol) of phthalic anhydride was taken in a three neck flask equipped with a condenser, a quick fit thermometer and a calcium guard tube. To this mixture 50 mL (excess) of methanol was added and this mixture was stirred for 20 min. When a clear solution was obtained than the mixture was refluxed for 5 h; water formed during the reaction was removed by using a Dean Stalk funnel, after this the excess of solvent was removed under reduced pressure. The white solid obtained in excellent yield (97 %) was then recrystallized in chloroform/acetone and then placed in a dessicator for further complexation.

Synthesis of Mn(II) and Cu(II) complex with monomethyl phthalate: 0.74 g (10 mmol) of monomethyl phthalate in methanol was taken in a three neck flask equipped with a reflux condenser, a quick fit thermometer and calcium guard tube. To this reaction mixture 5 mmol of manganese(II) and Cu(II) salts in hot methanol were added with constant stirring. The heating and refluxing was continued for next 4 h. The excess of solvent was removed under vacuum. The solid product obtained in promising yield was recrystallized by using ethanol/acetone.

Synthesis of Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes with monomethyl phthalate: 0.74g (10 mmol) of monomethyl phthalate was taken in a three neck flask equipped with a reflux condenser, a quick fit thermometer and calcium guard tube; then 10 mmol of corresponding metal salts in hot methanol were added with constant stirring. The heating and refluxing was continued for next four hours. The water formed during the reaction was removed by using Dean Stalk apparatus. The excess of solvent was removed under vacuum. The solid product formed, which was recrystallized by using chloroform/acetone.

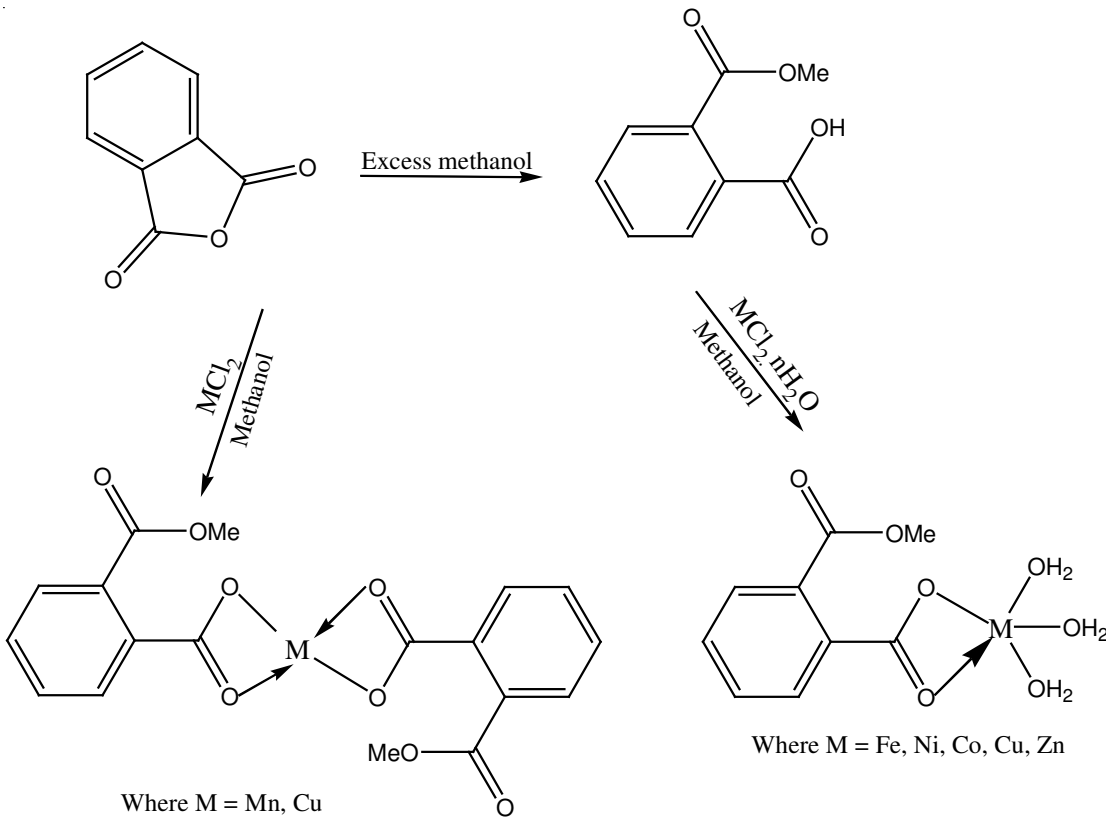
Antibacterial activity: The antibacterial activities were determined at NIH Islamabad, Pakistan by using the agar well-diffusion method[11]. The wells were dug in the media with a sterile borer and 8 h old bacterial inoculums containing *ca.* 10^4-10^6 colony-forming units (CFU)/mL was spread on the surface of the nutrient agar using a sterile cotton swab. The recommended concentration of the test sample (2 mg/mL in DMSO) was introduced into the respective wells. Other wells containing DMSO and the reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated immediately at 37 ºC for 20 h. The activity was determined by measuring the diameter of the inhibition zone (in mm) showing complete inhibition. Growth inhibition was calculated with reference to the positive control.

RESULTS AND DISCUSSION

Monomethyl phthalate (MMP) was prepared by modification from the literature (**Scheme-I**). The complexes [Fe(MMP)·3H_2O], [Co(MMP)·3H_2O], [Ni(MMP)·3H_2O], [Cu(MMP)·3H_2O], [Cu(MMP)$_2$], [Zn(MMP)·3H_2O], [Mn(MMP)$_2$] were prepared according to the **Scheme-I** in methanol.

The reactions were completed in 4-5 h and resulting complexes were obtained in good yields (80-97 %). The complexes were microcrystalline or amorphous and stable under atmospheric conditions. All the complexes were insoluble in H_2O and MeCN and were soluble in benzene, toluene, $CHCl_3$, CH_2Cl_2, acetone, THF, DMF and DMSO. The elemental analyses confirm their stoichiometry, while conductance study shows their non-electrolytic nature. Structural proposals are based on FT-IR, ^{1}H NMR studies. The results obtained through these techniques are in agreement with the proposed 1:1 and 1:2 stoichiometries (Table-1).

The imperative infrared absorption frequencies (cm^{-1}) and their assignments for the ligand and their organo-transition complexes are given in Table-2. As the carboxy H-atom is more acidic the deprotonation occurs in the COOH group. This is confirmed by the coordination of the carboxylato group. Coordination of the complexes was based on the Δν difference between (COO) sym and (COO) asym and on the corresponding band position. It is proposed that the carboxylate group acts as a bidentate ligand in all these complexes[12]. According to Lebl *et al.*[12] the values of Δν[$\Delta\nu = (\nu_{asym} - \nu_{sym})$] can be divided into three groups: (i) Δν(COO) > 350 for the complexes in which the carboxylato group monodentate, (ii) Δν(COO) < 200 for bidentate; (iii) Δν(COO) < 350 and > 200 contain the carboxylate groups in an intermediate state between monodentate and bidentate, which is called anisobidentate. A broad absorption at 3380 cm^{-1} in the spectra of the complexes was attributed to the presence of coordinated H_2O in case of



Scheme-I: Synthesis of MMP and its metal(II) chelates

TABLE- 1
PHYSICAL DATA OF THE LIGAND AND METAL COMPLEXES

Compounds (m.w.)	Solubility	Yield (%) (Color)	m.p. (ºC)	Elemental analysis (%) calcd. values are in parenthesis		
				C	H	Metal
$C_9H_8O_4$ MMP (180)	Chloroform/acetone	97 (White)	78	59.98 (60.00)	4.42 (4.44)	–
$C_9H_{13}O_7Fe$ (289)	Ethanol/chloroform	88 (Light brown)	97	37.33 (37.40)	4.47 (4.53)	19.26 (19.32)
$C_9H_{13}O_7Ni$ (291)	-do-	91 (Green)	95	36.95 (37.03)	4.43 (4.49)	20.01 (20.11)
$C_9H_{13}O_7Co$ (292)	-do-	87 (Reddish pink)	123	36.91 (37.00)	4.41 (4.49)	20.09 (20.17)
$C_9H_{13}O_7Cu$ (296)	-do-	78 (Light blue)	132	36.36 (36.43)	4.37 (4.42)	21.33 (21.41)
$C_9H_{13}O_7Zn$ (297)	-do-	82 (White)	127	36.14 (36.20)	4.31 (4.39)	21.82 (21.90)
$C_{18}H_{14}O_8Mn$ (413)	Chloroform/acetone	73 (White)	104	52.28 (52.32)	3.33 (3.41)	13.21 (13.29)
$C_9H_{13}O_7Cu$ (422)	Chloroform/acetone	81 (Blue)	105	51.18 (51.25)	3.29 (3.35)	14.91 (15.06)

TABLE-2
IR SPECTRA DATA OF LIGAND AND COMPLEXES

Compounds	ν(C-H)	(OCO)asym	(OCO)sym	Δν	ν(C=O)	ν(O-H)	ν(M-O)
$C_9H_8O_4$ MMP	3027 w	–	–	–	1715 s	3050 br	–
$C_9H_{13}O_7Fe$	3010 w	1625 s	1258 s	367	1711 s	Abs.	220 m
$C_9H_{13}O_7Ni$	3022 w	1618 s	1249 s	369	1695 s	Abs.	288 m
$C_9H_{13}O_7Co$	3013 w	1636 s	1259 s	377	1710 s	Abs.	266 m
$C_9H_{13}O_7Cu$	3031 w	1620 s	1272 s	348	1689 s	Abs.	255 m
$C_9H_{13}O_7Zn$	3008 w	1612 s	1255 s	357	1701 s	Abs.	290 m
$C_{18}H_{14}O_8Mn$	3018 w	1630 s	1269 s	361	1712 s	Abs.	226 m
$C_9H_{13}O_7Cu$	3020 w	1622 s	1272 s	350	1720 s	Abs.	245 m

1:1 stoichiometry while this peak is absent in case of 2:1. The peaks at 290-220 cm^{-1} to the ν(M-O) stretching mode, while a strong band at 1690 cm^{-1} was assigned to C=O stretching frequency.

The ^1H NMR spectrum of the free ligand (MMP) was run in chloroform ($CDCl_3$) solution using tetramethylsilane (TMS) as internal standard, while the spectrum of complexes was recorded in deutarated acetone. All the protons of the ligand were found to be in their estimated region. The conclusions drawn from these studies lend further support to the mode of bonding discussed in IR spectra. The ^1H NMR spectra of the free ligand showed a singlet at 12.2 ppm which is found absent after complexation showing the involvement of carboxylato group to the metal atom[13].

Antibacterial activity: The biological activity of the ligand and its transition metal complexes and imipinem (as a standard compound) were tested against bacteria. The microorganisms used in the present investigations included *Staphylococcus aureus* and *Bacillus subtillis* (as gram positive bacteria) and *Pseudomonas aereuguinosa*, *Escherichia coli* and *Salmonella typhi* (as gram negative bacteria). The diffusion agar technique was used to evaluate the antibacterial activity of the synthesized mixed ligand complexes[14]. The results of the bactericidal study of the synthesized compounds are displayed in Table-3. It was clear from the bactericidal activity, it is apparent that the complexes were more toxic towards gram positive strains than gram negative strains. The reason is the difference in the structures of the cell walls. The walls of gram negative cells are more complex than those of gram positive cells. The zone of inhibition values obtained indicates that the ligand has moderate activity against *Staphylococcus aureus*, *Escherichia coli* and less active in comparison with *Pseudomonas aeruginosa*. Monomethyl phthalate also shows a moderate activity towards *Bacillus subtillis*. It is suggested that the antibacterial activity of the complexes is due to either by killing the bacteria or inhibiting their multiplication by blocking their active sites[15]. It may be expected that the increased liposolubility of the ligand upon metal complexation may contribute to its facile transport into the bacterial cell which blocks the metal binding sites in enzymes of microorganisms. These

TABLE-3
ANTIBACTERIAL ACTIVITY OF MMP AND ITS TRANSITION METAL COMPLEXES

Compound	Microorganism				
	S. aureus	*E. coli*	*S. flexenari*	*B. subtilIs*	*S. typhi*
$C_9H_8O_4$ (MMP)	+	+	+	+	+
$C_9H_{13}O_7Fe$	++	++	++	+++	+++
$C_9H_{13}O_7Ni$	+++	+++	+++	+++	+++
$C_9H_{13}O_7Co$	++	+++	++	++	+++
$C_9H_{13}O_7Cu$	+	++	++	++	++
$C_9H_{13}O_7Zn$	+++	++	+++	++	+++
$C_{18}H_{14}O_8Mn$	++	+++	n.c	+++	+++
$C_{18}H_{14}O_8Cu$	+++	+++	+++	+++	n.c
Imipinem (**standard drug)	++++	++++	++++	++++	++++

++++ = Excellent activity (100 % inhibition), +++ = good activity (60-70 % inhibition), ++ = significant activity (30-50 % inhibition), + = negligible activity (10-20 % inhibition), n.a. = no activity, n.c = not checked, size of well: 6 mm (diameter).

complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism[16]. Among the synthesize complexes the copper complexes exhibit promising activity against all the bacteria used.

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