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Metal Chelates of Curcuminoids

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METAL CHELATES OF CURCUMINOIDS

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ABSTRACT

Curcuminoids, a group of structurally related 1,3-dicarbonyl compounds, are the most important physiologically active components present in the traditional herbaceous medicinal plant oriental turmeric (*Curcuma longa* Linn., *Zingiberaceae* family). Nickel(II), copper(II), zinc(II) and palladium(II) chelates of synthetic analogues of these 1,7-diaryl-1,6-heptadiene-3,5-diones have been synthesized. UV, IR, ^{1}H and ^{13}C NMR and mass spectral data of the ML_2 complexes clearly indicate that the metal ion replaced the enol proton with the formation of a stable six-membered metal chelate ring involving the dicarbonyl function.

INTRODUCTION

Curcuminoids, a group of naturally occurring 1,3-diketones in which the carbonyl groups are directly linked to olefinic carbons, constitute the major

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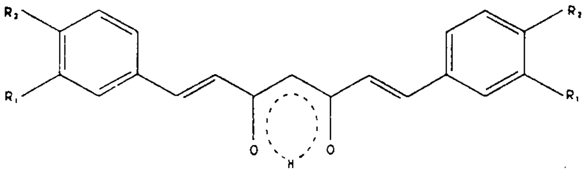


(1)

	R_1	R_2
a	H	H
b	H	OCH_3
c	H	OH
d	OCH_3	OH
e	OCH_3	OCH_3

Fig. 1. 1,7-Diaryl-1,6-heptadiene-3,5-diones (1,7-Diarylheptanoids)

physiologically active principle of the traditional Indian medicinal plant turmeric (*Curcuma longa* L.) and several other related species of wide pharmacological interest[1-3]. Structurally, curcuminoids are 1,7-diaryl-1,6-heptadiene-3,5-diones (**1**)[3-5]. The isolation, characterisation, synthesis and several biological applications of these 1,7-diarylheptanoids are well documented in the literature.[3] Arrieta *et al.*[6] have determined the acid dissociation constants as well as the stability constants of the Cu^{2+} and Ni^{2+} complexes of these compounds by pH-metric titration technique and solid copper(II) complexes of these compounds have also been reported. In continuation of our studies[7] on such biologically important plant products, the present communication reports the synthesis and characterisation of Ni^{2+}, Cu^{2+}, Zn^{2+} and Pd^{2+} chelates of the 1,7-diarylheptanoids (**1a**)-(**1e**).

RESULTS AND DISCUSSION

The ligand compounds (**1a**)-(**1e**) were synthesised by the condensation of benzaldehyde/substituted benzaldehyde with acetylacetone under specified conditions and purified by column chromatography (silica gel). These ligands formed well-defined crystalline metal complexes with sharp melting points. Elemental analytical data (Tables I-IV) of all the complexes suggest their ML_2 stoichiometry. All the complexes behave as non-electrolytes (specific conductance $<15\ \Omega^{-1}\ cm^{-1}$ in DMF) and do not contain the anion of the metal salt used for their preparation. The copper(II) complexes show a normal magnetic moment (1.75-1.83 B.M.) and the others are diamagnetic. The electronic, IR, NMR and mass spectral data of the complexes are compatible with the structure that results when the chelated enol proton of the ligand is replaced by metal ion as in (**2**).

Infrared Spectral Data

The intramolecular hydrogen bonded *cis*-enol form of the ligands, as in structure (**1**), has been established from IR and ^1H NMR spectral data.[3] Thus, the spectra of all the compounds are characterised by the presence of a strong band at ~1615 cm^{-1} due to the stretching of the intramolecular hydrogen bonded carbonyl function and a broad band in the range 2600-3800 cm^{-1}. In the spectra of the metal complexes, the former band almost disappeared but instead, another strong

Table I
Analytical and Physical Data of Copper(II) Chelates of
1,7-Diarylheptanoids

Copper(II) chelate of	Molecular formula (Formula Weight)	Colour	Yield (%)	M.P. (°C)	Elemental Analysis (%) (Calcd./Found)		
					C	H	M
(1a)	$[Cu(C_{19}H_{15}O_2)_2]$	Brown	70	208	74.33	4.89	10.35
	(613.5)				(74.11	4.78	10.18)
(1b)	$[Cu(C_{21}H_{19}O_4)_2]$	Brown	68	221	68.71	5.18	8.66
	(733.5)				(68.13	5.04	8.52)
(1c)	$[Cu(C_{19}H_{15}O_4)_2]$	Orange	72	218	67.31	4.43	9.37
	(677.5)				(67.08	4.25	9.18)
(1d)	$[Cu(C_{21}H_{19}O_6)_2]$	Brown	75	235	63.20	4.76	7.96
	(797.5)				(62.97	4.61	7.71)
(1e)	$[Cu(C_{23}H_{23}O_6)_2]$	Black	70	261	64.67	5.39	7.44
	(853.5)				(64.27	5.18	7.25)

Table II
Analytical and Physical Data of Nickel(II) Chelates of
1,7-Diarylheptanoids

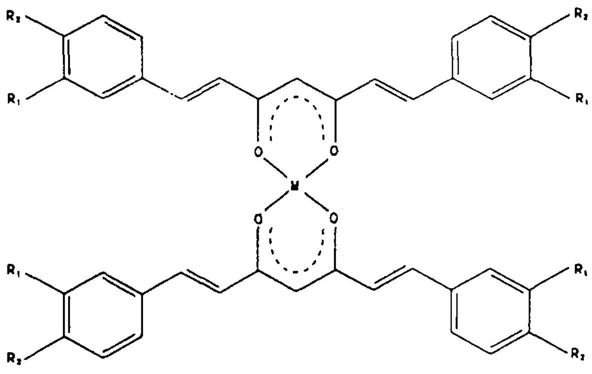
Nickel(II) chelate of	Molecular formula (Formula Weight)	Colour	Yield (%)	M.P. (°C)	Elemental Analysis (%) (Calcd./Found)		
					C	H	M
(**1a**)	$[Ni(C_{19}H_{15}O_2)_2]$	Green	65	211	74.91	4.93	9.64
	(608.7)				(74.56	4.80	9.55)
(**1b**)	$[Ni(C_{21}H_{19}O_4)_2]$	Green	70	241	69.16	5.21	8.05
	(728.7)				(68.97	5.15	8.00)
(**1c**)	$[Ni(C_{19}H_{15}O_4)_2]$	Brown	72	238	67.79	4.46	8.73
	(672.7)				(67.52	4.38	8.58)
(**1d**)	$[Ni(C_{21}H_{19}O_6)_2]$	Greenish brown	72	253	63.58	4.79	7.41
	(792.7)				(63.21	4.56	7.30)
(**1e**)	$[Ni(C_{23}H_{23}O_6)_2]$	Black	75	268	65.04	5.42	6.92
	(848.7)				(64.87	5.28	6.73)

Table III
Analytical and Physical Data of Zinc(II) Chelates of 1,7-Diarylheptanoids

Zinc(II) chelate of	Molecular formula (Formula Weight)	Colour	Yield (%)	M.P. (°C)	Elemental Analysis (%) (Calcd./Found)		
					C	H	M
(1a)	[Zn($C_{19}H_{15}O_2$)$_2$]	Yellow	62	228	74.10	4.87	10.63
	(615.4)				(73.85	4.78	10.34)
(1b)	[Zn($C_{21}H_{19}O_4$)$_2$]	Yellow	60	239	68.53	5.17	8.89
	(735.4)				(68.30	5.02	8.78)
(1c)	[Zn($C_{19}H_{15}O_4$)$_2$]	Orange yellow	55	261	67.12	4.42	9.63
	(679.4)				(66.98	4.25	9.52)
(1d)	[Zn($C_{21}H_{19}O_6$)$_2$]	Brown	60	258	63.05	4.75	8.18
	(799.4)				(62.89	4.53	8.00)
(1e)	[Zn($C_{23}H_{23}O_6$)$_2$]	Brown	65	276	64.53	5.38	7.65
	(855.4)				(64.18	5.20	7.57)

Table IV
Analytical and Physical Data of Palladium(II) Chelates of 1,7-Diarylheptanoids

Palladium(II) chelate of	Molecular formula (Formula Weight)	Colour	Yield (%)	M.P. (°C)	Elemental Analysis (%) (Calcd./Found)		
					C	H	M
(1a)	[Pd($C_{19}H_{15}O_2$)$_2$]	Brown	55	240	69.47	4.57	16.21
	(656.4)				(68.32	4.43	16.10)
(1b)	[Pd($C_{21}H_{19}O_4$)$_2$]	Brown	56	252	64.91	4.89	13.70
	(776.4)				(64.63	4.70	13.45)
(1c)	[Pd($C_{19}H_{15}O_4$)$_2$]	Brown	60	268	63.30	4.16	14.77
	(720.4)				(63.03	4.08	14.43)
(1d)	[Pd($C_{21}H_{19}O_6$)$_2$]	Black	65	275	59.97	4.52	12.66
	(840.4)				(59.37	4.40	12.43)
(1e)	[Pd($C_{23}H_{23}O_6$)$_2$]	Black	60	291	61.60	5.13	11.87
	(896.4)				(61.03	5.03	11.29)



(M = Ni^{2+}, Cu^{2+}, Zn^{2+}, Pd^{2+})

(2)

Fig. 2. Suggested Structure of the Metal Complexes of 1,7-Diarylheptanoids (**1a**)-(**1e**).

band assignable to the stretching of the coordinated carbonyl of the β-diketone moiety appeared at ~1570 cm^{-1}. The broad free ligand band in the region 2600-3800 cm^{-1} is replaced in the spectra of metal complexes by weak bands at ~3030 cm^{-1}, attributable to ν(C-H). In the case of the complexes of (**1c**) and (**1d**) that contain phenolic functions, broad medium intensity bands in the region 3400-3800 cm^{-1} are present. This indicates the replacement of the chelated proton of the ligand by metal ion as in structure (**2**). In agreement with this structure, spectra of all chelates show additional bands at ~460 and ~425 cm^{-1} assignable to ν(M-O) vibrations.

A prominent band which appears at ~970 cm^{-1} in the spectra of the free ligands has been attributed as typical of a *trans* orientation of the -HC=CH-

Table V

Characteristic IR Stretching Bands (cm^{-1}) of Copper(II) Chelates of 1,7-Diarylheptanoids

Copper(II) chelates of					Probable assignments
(1a)	**(1b)**	**(1c)**	**(1d)**	**(1e)**	
1568	1570	1572	1575	1578	ν(C=O) (metal chelated carbonyl)
1582	1583	1588	1581	1582	ν(C=C) (phenyl)
1556	1552	1563	1567	1568	
1543	1542	1540	1542	1540	ν(C=C) (alkenyl)
1520	1521	1520	1523	1524	ν_{as} (C-C-C) (chelate ring)
1460	1459	1462	1457	1453	ν_{as} (C-C-C) (chelate ring)
1108	1098	1106	1103	1099	β(C-H) (chelate ring)
1072	1070	1079	1073	1068	
976	963	981	973	972	ν(CH=CH) (*trans*)
731	734	733	732	736	ν(C-H) (chelate ring)
462	463	465	460	462	ν(M-O) (chelate ring)
428	423	425	428	429	

groups.[8] This band remained almost unaffected in the spectra of the chelates. Since all the metal complexes studied have very similar IR spectra, only the characteristic IR absorption data of the copper(II) complexes are tabulated in Table V.

NMR Spectral Data

Further evidence for the bonding mode of ligands is provided by the ^1H NMR spectra of the diamagnetic complexes. The ^1H NMR spectra of all the ligands displayed a singlet (1H) downfield at δ ~17 ppm and another singlet at δ ~6.8 ppm due to the enol and methine protons, respectively, of structure (**1**).[9,10]

The lowfield signal is absent in the spectra of the complexes indicating the replacement of the enol proton by the metal ion. The phenolic OH protons of (**1c**) and (**1d**) (δ 10.043 and δ 10.040 ppm) remained almost unaltered in the spectra of their chelates which strongly suggests that chelate formation has occurred exclusively through the dicarbonyl moiety. The integrated intensities of the aryl and alkenyl protons agree well with the formulation in structure (**2**). That *trans* orientation of the alkenyl groups of the ligands is retained in the complexes is evident from their observed J values (16-16.5 Hz).

That both the carbonyl groups of the free ligands are in identical electronic environments is clearly indicated from the appearance of a single carbonyl carbon resonance signal in the ^{13}C NMR spectra of (**1a**) (δ 183.14 ppm) and (**1d**) (δ 184.25 ppm). This signal shifted appreciably downfield in the spectra of the palladium(II) chelates (δ ~190 ppm), while the methine carbon signal of the complexes showed an upfield shift (~7 ppm) compared to the value observed for the free ligands at δ 101.03 ppm for (**1a**) and δ 101.89 ppm for (**1d**). This clearly suggests a strong interaction between the metal ion and carbonyl oxygens and also that more effective electron delocalisation exists in the metal chelate ring.

Mass Spectral Data

Mass spectra of all the curcuminoids show intense molecular ion peaks, $P^+/(P+1)^+$. The symmetric acyl cleavage at the dicarbonyl function of the compounds is evident from the appearance of two prominent peaks corresponding to m/z $(P\text{-}Ar.CH{:}CH.CO)^+$ and $(P\text{-}Ar.CH{:}CH.CO.CH_2)^+$ in the spectra of all the compounds. Peaks corresponding to m/z = $(P\text{-}O)^+$, $(P\text{-}OH)^+$, $(P\text{-}OH_2)^+$ etc. appeared in all the spectra and are characteristic of diaroylmethanes.[11,12]

The FAB mass spectra of the copper(II) chelates of the ligands show prominent peaks due to $[CuL_2]^+$ which justifies the formulation of the chelates as in structure (**2**). The base peak in all the case is due to the ligand and peaks due to $[CuL]^+$, L^+ and fragments of L^+ are sometimes more intense than the molecular ion peak. The spectra of all the chelates studied showed peaks due to $(P\text{-}nAr)^+$, n = 1 to 4, of appreciable intensity. The presence of these fragments indicates ring closure between adjacent olefinic moieties with the formation of stable cyclic species involving the metal ion under mass spectral conditions.

Electronic Spectral Data

The characteristic UV absorption bands of the ligands at λ max ~266 nm and ~420 nm due to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively, show only slight bathochromic shifts in the spectra of the metal complexes. It is, therefore, evident that no structural alteration has occured to the ligand λ max during complexation.

All the copper(II) complexes show a broad band at λ_{max} ~14,800 cm^{-1} in methanol. This, together with the measured μ_{eff} values suggests square-planar geometry. In agreement with this, in spectra recorded in pyridine, a broad band centered at 11,000 cm^{-1} was observed indicating the formation of octahedral pyridine adducts.

The diamagnetic nickel(II) chelates show a broad band at λ_{max} ~17,700 cm^{-1} in methanol which suggest a planar structure. In pyridine, all the nickel(II) complexes show three well-separated absorption bands at λ_{max} ~8,100, ~13,400 and 24,200 cm^{-1}, corresponding to three spin-allowed transitions of Ni^{2+} ion in an octahedral environment indicating the incorporation of two pyridine molecules. The calculated ligand field parameters, such as LFSE (~22.50 kcal mol^{-1}), *Dq* (~805 cm^{-1}) B (~905 cm^{-1}), β (~0.85) and β% (~14.5) also confirm the octahedral geometry of pyridine adducts.

Biological Studies

The wide range of biological activities exterted by turmeric extracts has been the subject of numerous physiological and clinical studies.[2,3] In the present investigation, the bactericidal and fungicidal activities of the synthetic curcuminoids and their typical metal complexes were studied. Compound (**1d**), the major component of turmeric, shows maximum activity against all tested organisms. The metal complexes studied did not show any significant activity against any of the tested microbes and this may probably due to the unavailability of the free 1,3-dicarbonyl function for significant interaction with the metal ions present in the cell fluids of the microorganisms.

EXPERIMENTAL

Preparation of Ligands

The ligands were prepared by the condensation of aromatic aldehydes (benzaldehyde, *para*-methoxybenzaldehyde, *para*-hydroxybenzaldehyde, vanillin and veratraldehyde) with acetylacetone as reported.[10] The reaction product was a mixture of the monocondensation products, 6-aryl-5-hexene-2,4-diones (10-15%), along with the biscondensation products, 1,7-diarylheptanoids (60-80%). Pure 1,7-diarylheptanoids were obtained by column chromatography over silica gel using 2:1 *v/v* $CHCl_3$-acetone mixture as the eluant. All the compounds isolated were recrystallised twice from hot benzene.

Preparation of Metal Complexes

Copper(II), nickel(II) and zinc(II) chelates of the ligands were prepared by the following general method. A methanolic solution (25 mL) of the metal(II) acetate (0.01 mol) was added slowly with stirring to a solution (30 mL) of the ligand (0.002 mol) in 50% *v/v* ethanol-methanol. The reaction mixture was gently refluxed for ~1 h and subsequently the volume was reduced to half. The complex precipitated on cooling to room temperature, was filtered and recrystallised from hot methanol. Palladium(II) chelates were prepared by the same procedure using palladium(II) chloride (0.01 mol) in 50% *v/v* methanol-acetone mixture.

Biological Screening

The *in vivo* biocidal activities of the investigated compounds (4000 ppm) were screened against *Aspergillus niger*, *Staphylococcus aureus* and *Escherichia coli* stains, following the disk diffusion technique.[13] The petri plates were run in triplicate and the relative activity of the compounds was qualitatively judged from the measured inhibition zones.

Measurements

Carbon and hydrogen percentages reported are by microanalysis, and metal contents by standard gravimetric procedures. Magnetic susceptibilities were determined at room temperature on a Gouy type magnetic balance. Electronic spectra were recorded in methanol solution (10^{-4} M) on a UV-1601 Shimadzu recording spectrophotometer. Infrared spectra (KBr pellets) were recorded on a Shimadzu 8101 A FTIR spectrophotometer, NMR spectra on a Jeol 400 NMR spectrometer and mass spectra on a Jeol / SX-102 mass spectrometer (FAB using argon and *meta*-nitrobenzyl alcohol as the matrix).

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