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Novel Bioactive Thio- and Semi-carbazide Ligands and Their Organotitanium(IV) and Organozirconium(IV) Complexes

SAURABH DAVE, R.V. SINGH*, S.C. JOSHI and D.P. JAROLI†
Department of Chemistry, University of Rajasthan, Jaipur-302 004, India
E-mail: kudiwal@datainfosys.net Fax : +91-141-519221

Organotitanium(IV) and organozirconium(IV) complexes have been synthesized by the reaction of titanocenedichloride or zirconocenedichloride with two different ketimines in the presence of triethylamine. In all the reactions the imines behave as monobasic bidentate ligands. The resulting complexes $Cp_2M(L)(L')$ [where Cp = cyclopentadienyl ring, L = 2-[1-(2-thienyl)ethyledene]hydrazine-carbothioamide and L′ = 2-[1-(2-thienyl)ethyledene]-hydrazinecarboxamide, 2-[1-(2-naphthenyl)ethyledene]hydrazine-carbothioamide, and 2-[1-(2-naphthenyl)ethyledene]hydrazine-carboxamide have been characterized by elemental analysis and IR and ^1H NMR spectral studies. Based on these spectral studies, an octahedral structure has been proposed for all the complexes. The antifungal, antibacterial and antifertility activities of the ligands and their complexes have also been carried out.

Key Words: Organotitanium, Organo-zirconium, Complexes, Semicarbazide, Thiosemicarbazide.

INTRODUCTION

During the last decade, group IV transition metal chemistry has made a major contribution in providing effective complexes for novel metal-assisted organic transformations[1–3]. The sulphur and nitrogen containing complexes of titanium(IV) are becoming more and more important for industrial applications[4]. The use of these derivatives as reagents[5], leaving groups or protective groups is now becoming common in many of the reactions[6, 7]. It became clear that the transmetallation of classical "carbanions" using titanating agents produces new reagents[8] which display a high degree of chemo-, regio- and stereo-selectivity.

Schiff bases and their metal complexes play a key role in our understanding of the coordination chemistry of transition metal ions. They may serve as models for biologically important species, finding applications in biomimetic catalytic activities[9–11]. The compounds containing N, S and O donor atoms are important owing to their significant antifungal, antibacterial and anticancer activity[12]. It is well known that some drugs have increased activity when administered as metal complexes than as free organic compounds[13–15]. In spite of the considerable

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†Department of Zoology, University of Rajasthan, Jaipur-302 004, India.

growth of literature on titanium(IV) and zirconium(IV) complexes[16, 17] containing N, O and S donor ligands, not much work is known about the unsymmetrical complexes of Ti(IV) and Zr(IV). In view of this and because of growing interest in the biological activity of Ti(IV) and Zr(IV) complexes, we report in this paper synthesis, characterization and biocidal studies of some Ti(IV) and Zr(IV) complexes.

EXPERIMENTAL

All reactions were carried out under strictly anhydrous conditions. Tetrahydrofuran was dried on sodium wire overnight and then refluxed until it gave a blue colour with benzophenone. Triethylamine was collected after storing for two days over barium oxide. Titanium(IV) and zirconium(IV) were estimated gravimetrically as their oxides and sulphur was estimated gravimetrically as $BaSO_4$[18]. Nitrogen was determined by Kjeldahl's method[18].

IR spectra were recorded on a Perkin-Elmer model 577 grating spectrometer in the range 4000–200 cm^{-1} in KBr discs. ^1H NMR spectra were recorded on a JEOL Fx 90Q spectrometer in DMSO-d_6. Molecular weights were determined by the Rast camphor method using resublimed camphor. All the melting points are uncorrected.

Preparation of Ligands: The ligands used were prepared by the condensation of 2-acetylthiophene and 2-acetylnaphthalene with thiosemicarbazide and semicarbazide hydrochloride in the presence of sodium acetate in equimolar ratio in refluxing ethanolic medium. On cooling, the crystals formed were filtered, recrystallized in the same solvent and finally dried *in vacuo*. Physical and analytical data of these ligands are presented in Table-1.

TABLE-1
PHYSICAL PROPERTIES AND ANALYTICAL DATA OF LIGANDS

Ligand (Colour)	(m.p.) (°C)	% Analysis: Found (Calcd.)				m.w. Found (Calcd.)
		C	H	N	S	
$C_7H_9N_3S_2[L_1]$ (Light yellow)	155	42.55 (42.19)	4.65 (4.55)	20.86 (21.08)	32.24 (32.18)	212 (199)
$C_7H_9N_3SO[L_2]$ (White)	188	45.52 (45.89)	4.79 (4.95)	22.81 (22.93)	17.23 (17.20)	205 (183)
$C_{13}H_{13}N_3S[L_3]$ (White)	144	64.39 (64.17)	5.48 (5.39)	17.13 (17.27)	13.05 (13.18)	268 (243)
$C_{13}H_{13}N_3O[L_4]$ (White)	214	69.04 (68.70)	6.04 (5.77)	18.57 (18.49)	—	248 (227)

Preparation of the Complexes: To a solution of bis(cyclopentadienyl) titanium (IV)/zirconium(IV) dichloride in dry tetrahydrofuran was added two different appropriate Schiff bases. The mixture was refluxed for 14–18 h. The precipitate was removed by filtration and the excess of the solvent was removed under reduced pressure and the resulting complexes were washed repeatedly and dried *in vacuo*. The physical and analytical data of these complexes are enlisted in Table-2.

TABLE-2

PHYSICAL PROPERTIES AND ANALYTICAL DATA OF UNSYMMETRICAL COMPLEXES OF TITANIUM AND ZIRCONIUM

Starting material (g)	Ligand (g)	Ligand (g)	Et_3N (g)	Compound	Colour	m.p. (°C)	% Analysis, Found (Calcd.)					m.w. Found (Calcd.)
							C	H	N	S	M	
Cp_2TiCl_2 0.53	$C_7H_9N_3S_2(L_1)$ 0.43	$C_7H_9N_3SO(L_2)$ 0.39	0.43	$Cp_2Ti(L_1)(L_2)$	Reddish brown	98	51.29 (51.60)	4.57 (4.69)	15.01 (15.04)	17.16 (17.21)	8.49 (8.57)	503.57 (558.57)
Cp_2TiCl_2 0.19	$C_7H_9N_3S_2(L_1)$ 0.15	$C_{13}H_{13}N_3S(L_3)$ 0.19	0.15	$Cp_2Ti(L_1)(L_3)$	Dark brown	70	57.95 (58.24)	4.84 (4.88)	13.47 (13.58)	15.46 (15.54)	7.70 (7.73)	553.67 (618.67)
Cp_2TiCl_2 0.26	$C_7H_9N_3S_2(L_1)$ 0.21	$C_{13}H_{13}N_3O(L_4)$ 0.24	0.21	$Cp_2Ti(L_1)(L_4)$	Yellowish brown	118	59.62 (59.79)	4.83 (5.01)	13.96 (13.94)	10.68 (10.64)	7.91 (7.94)	652.61 (602.61)
Cp_2ZrCl_2 0.51	$C_7H_9N_3S_2(L_1)$ 0.35	$C_7H_9N_3SO(L_2)$ 0.32	0.35	$Cp_2Zr(L_1)(L_2)$	Dark brown	120	47.66 (47.89)	4.24 (4.35)	13.85 (13.96)	15.78 (15.97)	15.22 (15.15)	561.91 (601.91)
Cp_2ZrCl_2 0.73	$C_7H_9N_3S_2(L_1)$ 0.50	$C_{13}H_{13}N_3S(L_3)$ 0.61	0.51	$Cp_2Zr(L_1)(L_3)$	Greenish black	110	54.16 (54.42)	4.42 (4.56)	12.67 (12.69)	14.44 (14.52)	13.69 (13.77)	617.00 (662.00)
Cp_2ZrCl_2 0.51	$C_7H_9N_3S_2(L_1)$ 0.34	$C_{13}H_{13}N_3O(L_4)$ 0.39	0.35	$Cp_2Zr(L_1)(L_4)$	Brown	105	46.38 (46.48)	3.82 (3.90)	12.95 (13.01)	9.78 (9.92)	14.19 (14.12)	615.95 (645.95)

RESULTS AND DISCUSSION

The reactions of titanocenedichloride/zirconocenedichloride with two different monobasic bidentate hydrazinecarboxamide and hydrazinecarbothioamide in 1 : 1 : 1 molar ratio in presence of triethylamine in dry THF proceed fairly with the precipitation of $Et_3N{\cdot}HCl$ being removed by filtration process. The resulting complexes are coloured solids. These are soluble in DMSO, DMF, THF, $CHCl_3$ and methanol. The monomeric nature as indicated by the molecular weight determinations has been established for these derivatives. They are non-electrolytes with molar conductance value [10–14 ohm^{-1} cm^2 mol^{-1}] of 10^{-3} M solution in dry DMF at the room temperature.

The spectral information of the concerned ligands and their corresponding compounds has the same consistancy as required for the formation of proposed structure and some salient features are reported herein.

IR spectra of the complexes do not show any band in the region 3300–3100 cm^{-1} which could be assigned to ν(NH). This clearly indicates the deprotonation of the ligands as a result of complexation with the metal atom. A strong band at 1620 ± 10 cm^{-1} due to ν(C=N) in the ligand shifts to the lower frequency (*ca.* 10 cm^{-1}) in the complexes, indicating the coordination of the azomethine nitrogen to the metal atom. The chelation of ligands through azomethine nitrogen and thiolic sulphur/amido oxygen further gets support by the appearance of new bands at 550–510, 620–580 and 350–320 cm^{-1}, in the spectra of complexes due to ν(M—N)[19,20], ν(M—O)[21,22] and ν(M—S)[23] vibrations, respectively. However, two strong bands at 3490 and 3300 cm^{-1} due to the symmetric and asymmetric vibrations of ν(NH_2) group remain unchanged in the spectra of complexes showing thereby the non-involvement of this group in coordination. In addition, all these complexes show bands at *ca.* 3100 ν(C—H), *ca.* 1450 ν(C—C), and 1025 and 810 cm^{-1} δ(C—H), in-plane, and out-of-plane, respectively, characteristic of the cyclopentadienyl ring. The persistence of bands due to the cyclopentadienyl ring[24] in the spectra of the complexes indicates that this group remains delocalized and π-bonded (η^5) to the metal and retains its aromatic character.

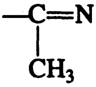
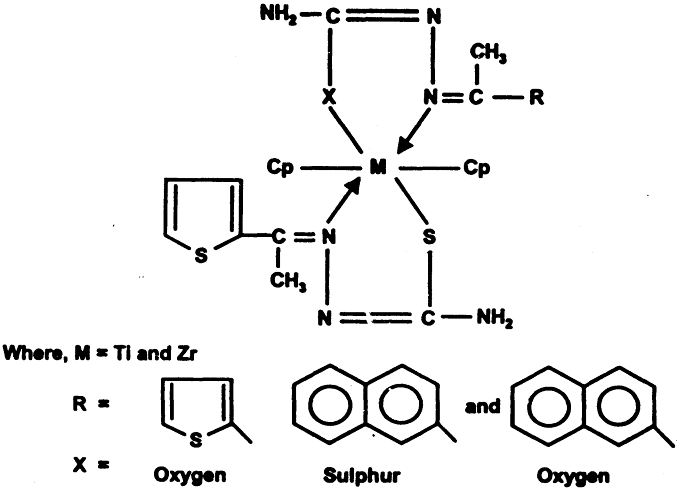
In the resulting complexes, the coordination of oxygen/sulphur and azomethine nitrogen to the metal atom has further been substantiated by the ^1H NMR spectra of ligands and their complexes. The proton signal appearing at δ 9.68–10.68 ppm in the spectra of ligands is due to the NH proton and it disappears in the spectra of the complexes thereby suggesting the deprotonation of NH group. The methyl proton signal of the azomethine moiety  $\underset{\displaystyle CH_3}{\underset{|}{—C}}{=}N$ is observed at δ 1.68–2.32 ppm in the spectra of ligands and gets shifted downfield in the spectra of complexes. The NH_2 proton signals remain at the same position in the ligands and their complexes. A sharp singlet in the δ 6.10–6.25 ppm range provides additional evidence for the presence of η-C_5H_5 group (Table-3).

TABLE-3
^1H NMR SPECTRAL DATA (δ ppm) OF LIGANDS AND THEIR TITANIUM AND ZIRCONIUM COMPLEXES

Compound	—NH (bs)	$—CH_3$ (s)	Aromatic (m)	M—Cp
L_1	10.68	1.68	7.16–8.68	—
L_2	10.68	2.32	7.20–7.84	—
L_3	10.65	1.91	7.55–8.92	—
L_4	10.60	1.88	7.56–8.64	—
$Cp_2Ti(L_1)(L_2)$	—	2.38	7.84–8.69	6.15
$Cp_2Ti(L_1)(L_3)$	—	1.91	7.80–8.80	6.10
$Cp_2Ti(L_1)(L_4)$	—	1.88	7.64–8.87	6.25
$Cp_2Zr(L_1)(L_2)$	—	2.36	7.82–8.68	6.00
$Cp_2Zr(L_1)(L_3)$	—	2.22	7.82–8.80	6.10
$Cp_2Zr(L_1)(L_4)$	—	2.20	7.62–8.88	6.15

On the basis of the above evidences the following tentative structure can be proposed for the resulting hexa-coordinated complexes with these ligands.



Antifungal Activity: The ligands and their metal-complexes were screened for antifungal activity against some fungi, namely, *Macrophomina phaseolina, Fusarium oxysporum* and *Aspergillus niger* by Agar plate technique.

Antibacterial Activity: Antibacterial activity was evaluated by the paper-disc plate method against the organisms *Echerichia coli, Klebsiella aerogenosa Pseudomonas cepacicola, Staphylococcus aureus* and *Xanthomonas compestris.*

The results of antimicrobial screening (Tables 4 and 5) reveal that the ligands and their metal chelates inhibit the growth of these micro-organisms. It is interesting to note that the metal complexes are more potent than the parent ligands. The enhanced activity of these metal complexes has been explained on the basis of chelation theory.

TABLE-4
ANTIFUNGAL SCREENING DATA OF LIGANDS AND THEIR TITANIUM AND ZIRCONIUM COMPLEXES

Compound	*M. phaseolina*			*F. oxysporum*			*A. niger*		
	50	100	200	50	100	200	50	100	200
L_1	35	45	50	34	56	60	34	46	52
L_2	6	17	38	7	16	29	—	—	—
L_3	34	45	52	32	54	58	29	46	51
L_4	27	42	48	20	41	56	—	—	—
$Cp_2Ti(L_1)(L_2)$	37	52	70	35	46	68	—	—	—
$Cp_2Ti(L_1)(L_3)$	52	68	78	47	65	78	50	69	76
$Cp_2Ti(L_1)(L_4)$	50	64	68	40	57	68	—	—	—
$Cp_2Zr(L_1)(L_2)$	41	57	75	39	51	74	—	—	—
$Cp_2Zr(L_1)(L_3)$	57	74	85	52	71	85	54	74	82
$Cp_2Zr(L_1)(L_4)$	54	69	75	44	62	74	—	—	—

TABLE-5
ANTIBACTERIAL ACTIVITY OF THE LIGANDS AND THEIR TITANIUM AND ZIRCONIUM COMPLEXES

Compound	*E. coli.*		*K. aerogenosa*		*P. cepaciçola*		*S. aureus*		*X. compestris*	
	500	1000	500	1000	500	1000	500	1000	500	1000
L_1	4	6	4	8	5	10	6	11	5	6
L_2	3	5	4	7	2	3	—	—	4	5
L_3	3	5	4	8	4	6	5	7	4	6
L_4	2	5	3	6	—	—	4	6	3	7
$Cp_2Ti(L_1)(L_2)$	9	15	8	13	4	7	—	—	8	10
$Cp_2Ti(L_1)(L_3)$	9	15	8	14	8	15	10	15	—	—
$Cp_2Ti(L_1)(L_4)$	7	11	6	10	—	—	8	11	—	—
$Cp_2Zr(L_1)(L_2)$	7	14	6	12	3	6	—	—	6	8
$Cp_2Zr(L_1)(L_3)$	7	14	6	13	6	14	8	14	—	—
$Cp_2Zr(L_1)(L_4)$	6	10	5	8	—	—	6	9	—	—

Antifertillity Activity: Antifertility activity was done in the Department of Zoology, University of Rajasthan, Jaipur. This study indicates that oral administration of ligands, their titanium and zirconium complexes leads to a significant reduction in weight of reproductive organs and a sharp decline in sperm motility and sperm counts. The results indicate an inhibitory effect of test substances on testicular sperm production, which consequently results in the gradual decline in the fertility rate. Alterations in the sperm motility, viability and morphology suggest a disturbed testicular and epididymal microenvironment due to treatment as evidenced by significant reduction in tissue weight. Since the optimum levels of protein and sialic acid are necessary for sperm maturation, capicitation and fertilization, and all these are regulated by androgens, therefore, the decreased activity of biochemical constitutents of testes and sex accessories suggests antiandrogenic effects of these compounds. Finally it can be concluded that addition of titanium or zirconium moiety to the ligands enhances their activities.

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