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Organosilicon(IV) Complexes of 3-Hydroxy-2-pyridine Carboxylic Acid and 2-Pyridine Carboxylic Acid and Their Antimicrobial Activity

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Organosilicon(IV) complexes of the types $R_2Si(Cl)_n(L_1\text{-}L_2)_{2\text{-}n}$ where (R = methyl, ethyl or phenyl, L_1 = 3-hydroxy-2-pyridinecarboxylate and L_2 = 2-pyridine carboxylate, n = 0 or 1) have been synthesized and characterized by elemental analyses, IR, ^1H, ^{13}C and ^{29}Si NMR spectroscopy. These studies indicated that ligands L_1 and L_2 chelated through nitrogen of pyridine and oxygen of carboxylate group and have penta- and hexa-coordinated state around the silicon atom. The ligands and their organosilicon complexes have been screened for their *in vitro* antimicrobial activities against several fungi and bacteria in order to explore their possibility to use as biocidal agents.

Key Words: Organosilicon(IV) complexes, 3-Hydroxy-2-pyridine carboxylic acid, 2-Pyridine carboxylic acid, Antimicrobial activity.

INTRODUCTION

The pyridine carboxylic acids and their derivatives belong to the category of ligands present in natural products as well as in biological systems. Nicotinic acid and nicotinamide are present in cells as the pyridine nucleotides, belong to coenzymes and vitamins and are necessary for their metabolisms. Complexes of hydroxy substituted pyridine carboxylic acid as ligands are of bioinorganic interest and also pose structural ambiguities because of different number of possible bonding modes[1,2], as these are potential tridentate ligands but can act as bidentate either having N,O-chelation or O,O-chelation. Organosilicon compounds exhibit a broad spectrum of biological activities[3,4] and the activity of some biologically active compounds was appreciably enhanced on coordination with metal ion or with organosilicon halides[5]. Keeping this in mind we have synthesized organosilicon(IV) complexes of 3-hydroxy-2-pyridine carboxylic acid and 2-pyridine carboxylic acid and evaluated for *in vitro* antimicrobial activity against the bacteria *Bacillus subtilis, Escherichia coli*, *Staphylococcus aureus* and fungi *Candida albicans* and *Aspergillus niger*. Some of these complexes were found to be quite active against these microorganisms.

EXPERIMENTAL

All the operations were carried out under nitrogen atmosphere in a vacuum line. All the solvents used were dried by conventional methods. Dichlorodimethyl/ ethyl/ phenylsilane, 3-hydroxy-2-pyridine carboxylic acid and 2-pyridine carboxylic acid were obtained through Aldrich and were used as such without any further purification. IR spectra were obtained as KBr pellets using Perkin-Elmer spectrum RX1 instrument. ^{1}H and ^{13}C NMR spectra were determined on Bruker Avance II 400 MHz NMR Spectrometer in $CDCl_3$ and two drops of DMSO-d_6 using TMS as an internal standard. Elemental analysis were carried out on Perkin-Elmer 2400. Molar conductance measurements were carried out using a Model-306 Systronics conductivity bridge in DMSO solvent. Silicon was determined gravimetrically as SiO_2.

Synthesis of organosilicon(IV) complexes, $R_2Si(Cl)_n(L_1\text{-}L_2)_{2\text{-}n}$: The sodium salt of the ligand (NaL_1, NaL_2) was obtained by mixing the ligand and sodium ethoxide in dry benzene with stirring for about 30 minutes. The diorganodichlorosilanes were added dropwise in 1:1 or 1:2 molar ratios with constant stirring at room temperature. The mixture was then refluxed for 0.5 h under continuous flow of nitrogen. On completion of the reaction, the precipitated sodium chloride was removed by filtration and the excess solvent was removed under reduced pressure to yield crude solid organosilicon complexes, which were then repeatedly washed with dry hexane so as to ensure their purity and dried under reduced pressure. The elemental analysis of these silicon complexes are given in Table-1.

Antimicrobial activity: The *in vitro* antibacterial and antifungal activity of ligands HL_1, HL_2 and their organosilicon(IV) complexes were carried out against the bacteria *Bacillus subtilis, Escherichia coli*, *Staphylococcus aureus* and fungi *Candida albicans* and *Aspergillus niger*. Adequate temperature, requisite nutrients and growth media free from other microorganisms were used for the growth of the culture of both bacteria and fungi. The ligands and their organosilicon complexes were dissolved in DMSO and concentration was made up to 100 µg/mL and used as a stock solution. The microbiocidal activity of the synthesized complexes were carried out using two fold serial dilution technique[6] and are presented in Table-2. The incubation period of *A. niger* and *C. albicans* was 7 d at 25 ± 1 °C and 36 h at 37 ± 1 °C, respectively where as for all other bacteria it was 24 h at 37 ± 1 °C. The conventional bactericide tetracycline, chloramphenicol, kanamycin, cefazoline sodium, cefotaxime and fungicide cycloheximide, carbendazim and fluconazole were used as standards for comparing the activity of compounds.

RESULTS AND DISCUSSION

The complexes were obtained by the reaction of dichlorodiorganosilane R_2SiCl_2 (R = Me, Et or Ph) with the sodium salt of 2-pyridine carboxylic acid and 3-hydroxy-2-pyridine carboxylic acid in 1:1 and 1:2 molar ratio at room temperature, in dry benzene/petroleum ether. The reactions proceed as follows:

TABLE-1
ANALYTICAL DATA OF ORGANOSILICON(IV) COMPLEXES

Complexes	Yield (%)	Elemental analysis (%): Found (Calcd.)				
		C	H	N	Si	Cl
$Me_2SiCl(L_1)$	75	41.49 (41.47)	4.32 (4.35)	6.09 (6.04)	12.06 (12.12)	15.35 (15.30)
$Me_2Si(L_1)_2$	67	50.32 (50.29)	4.26 (4.22)	8.34 (8.38)	8.43 (8.40)	-
$Et_2SiCl(L_1)$	65	46.27 (46.24)	5.40 (5.43)	5.42 (5.39)	10.85 (10.81)	13.70 (13.65)
$Et_2Si(L_1)_2$	70	53.08 (53.03)	5.00 (5.01)	7.69 (7.73)	7.70 (7.75)	-
$Ph_2SiCl(L_1)$	66	60.80 (60.75)	4.00 (3.97)	3.92 (3.94)	7.93 (7.89)	9.98 (9.96)
$Ph_2Si(L_1)_2$	73	62.89 (62.87)	3.92 (3.96)	6.16 (6.11)	6.10 (6.13)	-
$Me_2SiCl(L_2)$	68	44.60 (44.54)	4.63 (4.67)	6.52 (6.49)	13.00 (13.02)	16.48 (16.44)
$Me_2Si(L_2)_2$	70	55.59 (55.61)	4.60 (4.67)	9.30 (9.26)	9.33 (9.29)	-
$Et_2SiCl(L_2)$	65	49.0 (49.27)	5.80 (5.79)	5.72 (5.75)	11.56 (11.52)	14.50 (14.54)
$Et_2Si(L_2)_2$	70	58.20 (58.16)	5.44 (5.49)	8.49 (8.48)	8.54 (8.50)	-
$Ph_2SiCl(L_2)$	65	63.65 (63.61)	4.18 (4.15)	4.10 (4.12)	8.29 (8.26)	10.40 (10.43)
$Ph_2Si(L_2)_2$	63	67.53 (67.59)	4.22 (4.25)	6.60 (6.57)	6.55 (6.59)	-

TABLE-2
In vitro ANTIMICROBIAL ACTIVITY* OF LIGANDS AND THEIR ORGANOSILICON(IV) COMPLEXES (MIC in µg/mL)

Complexes/ Ligands	Bacteria			Fungi	
	B. subtilis	*E. coli*	*S. aureus*	*C. albicans*	*A. niger*
HL_1	25	50	50	50	50
HL_2	50	25	25	50	25
$Me_2SiCl(L_1)$	12.5	12.5	25	12.5	12.5
$Me_2Si(L_1)_2$	6.25	12.5	12.5	12.5	12.5
$Et_2SiCl(L_1)$	12.5	6.25	12.5	25	25
$Et_2Si(L_1)_2$	6.25	6.25	12.5	3.12	12.5
$Ph_2SiCl(L_1)$	6.25	12.5	6.25	12.5	12.5
$Ph_2Si(L_1)_2$	3.12	12.5	12.5	6.25	6.25
$Me_2SiCl(L_2)$	25	12.5	12.5	25	25
$Me_2Si(L_2)_2$	12.5	6.25	12.5	12.5	12.5
$Et_2SiCl(L_2)$	25	12.5	25	12.5	12.5
$Et_2Si(L_2)_2$	6.25	12.5	6.25	12.5	12.5
$Ph_2SiCl(L_2)$	6.25	12.5	25	12.5	3.12
$Ph_2Si(L_2)_2$	3.12	6.25	3.12	6.25	6.25

*The MIC of standard drugs for antibacterial activity (tetracycline, chloramphenicol, kanamycin, cefazoline sodium and cefotaxime) and antifungal activity (cycloheximide, carbendazim and fluconazole) were found to be < 3.12 µg/mL.

$$HL + NaOEt \xrightarrow{C_6H_6} NaL + EtOH$$

$$R_2SiCl_2 + NaL \xrightarrow[1:1]{C_6H_6} R_2SiCl(L) + NaCl$$

$$R_2SiCl_2 + 2\,NaL \xrightarrow[1:2]{C_6H_6} R_2Si(L)_2 + 2\,NaCl$$

Where, HL = 2-pyridine carboxylic acid or 3-hydroxy-2-pyridine carboxylic acid; R = Me, Et, Ph.

These organosilicon complexes were white solids, insoluble in most of the common organic solvents except in dry DMSO and DMF. The molar conductivity of these complexes have low values (5-15 ohm^{-1} cm^2 mol^{-1}) indicating non-electrolytic nature.

IR spectra: The infrared spectra of the complexes were compared with that of the free ligands HL_1 and HL_2 to ascertain the coordination sites on the basis of shifting in the frequency of various groups and/or from the lowering in the intensities of the absorptions (Table-3). The ν(C=N) band, occurring in the range of 1600-1591 cm^{-1}, is shifted towards lower frequencies with respect to that of free ligands at 1606 and 1607 cm^{-1}, respectively, which is due to the displacement of electron density from nitrogen to silicon on coordination, thus confirming the involvement of the heterocyclic N coordination. The symmetric mode ν_s(COO) shows shifts (up to 40 cm^{-1}) to higher wavenumber on coordination when compared to the free ligands at 1323 and 1293 cm^{-1}, respectively, suggesting that the ligand is bound to the metal through a carboxylate oxygen[7]. The asymmetric mode ν_{as}(COO) shows small shifts (up to 8 cm^{-1}) on coordination when compared to the free ligand at 1676 and 1716 cm^{-1}, respectively. The formation of the resulting complexes has also been supported by the presence of new strong bands at 810 ± 10, 650 ± 20 and 520 ± 10 cm^{-1} which may be assigned to ν_{as}(Si-O), ν_s(Si-O) and ν(Si-N), respectively[8-10]. IR spectra of dimethylsilicon derivatives show bands at 1460 ± 20 and 1250 ± 15 cm^{-1}, due to the asymmetric and symmetric deformation modes of CH_3-Si respectively[7,11]. Where as the IR spectra of diphenylsilicon derivatives shows bands at 1487 ± 2, 1128 ± 3 and 700 ± 3 cm^{-1}, which is possibly due to ν(Si-C_6H_5) modes[11].

^{1}H NMR spectra: In ^{1}H NMR spectra of the free ligands, single resonance is observed at δ 14.27 and δ 9.22 due to -COOH group in the ligands HL_1 and HL_2, respectively, which is absent in the spectra of the complexes, indicating the coordination of oxygen of carboxylate ion after the deprotonation of the carboxylic acid proton to silicon moiety. Further in ^{1}H NMR spectra of diorganosilicon(IV) complexes of the type $R_2SiCl(L_1)$ and $R_2Si(L_1)_2$ a strong sharp singlet at δ 11.00-12.00 is observed due to the phenolic proton which is not involved in coordination and also it is not intramolecularly hydrogen bonded in the complexes, otherwise it becomes

TABLE-3
IR FREQUENCIES (cm^{-1}) AND ^1H NMR SPECTRA (δ) OF LIGANDS AND THEIR ORGANOSILICON(IV) COMPLEXES

Complexes/ Ligands	IR (cm^{-1})					^1H NMR (δ)
	ν(C=N)	ν_{as}(COO), ν_s(COO)	Δν	ν_{as}(Si-O) ν_s(Si-O)	ν(Si-N)	
HL_1	1606 vs	1676 vs 1323 s	353	-	-	14.27 (s, 1H, COOH), 11.12 (s, 1H, OH), 7.22-8.08 (m, 3H, ligand)
$Me_2SiCl(L_1)$	1588 s	1670 s 1360 s	310	805 s 643 s	522 vs	11.28 (s, 1H, OH), 0.92 (s, 6H, Me), 7.35-8.71 (m, 3H, ligand)
$Me_2Si(L_1)_2$	1589 w	1668 s 1362 m	306	800 s 645 w	515 s	11.29 (s, 1H, OH), 0.93(s, 6H, Me), 7.33-8.72 (m, 6H, ligand)
$Et_2SiCl(L_1)$	1587 m	1666 vs 1358 s	308	820 s 640 m	520 vs	11.32 (s, 1H, OH), 0.92-1.29 (m, 10H, Et), 7.29-8.69 (m, 3H, ligand)
$Et_2Si(L_1)_2$	1589 w	1671 s 1361 m	310	810 m 642 s	522 w	11.35 (s, 1H, OH), 0.91-1.28 (m, 10H, Et), 7.28-8.70 (m, 6H, ligand)
$Ph_2SiCl(L_1)$	1591 s	1668 s 1365 s	303	818 m 650 w	510 m	11.50 (s, 1H, OH), 7.18-7.66 (m, 10H, Ph), 7.30-8.69 (m, 3H, ligand)
$Ph_2Si(L_1)_2$	1593 s	1668 vs 1360 m	308	816 s	512 w	11.52 (s, 1H, OH), 7.19-7.70 (m, 10H, Ph), 7.31-8.68 (m, 6H, ligand)
HL_2	1607 s	1716 s 1293 s	423	-	-	9.22 (s, 1H, COOH), 7.53-8.74 (m, 4H)
$Me_2SiCl(L_2)$	1586 w	1704 s 1328 vs	376	820 m 642 w	522 vs	0.90 (s, 6H, Me), 7.72-8.88 (m, 4H, ligand)
$Me_2Si(L_2)_2$	1587 s	1708 m 1336 s	372	802 m 641 s	527 w	0.92 (s, 6H, Me), 7.71-8.89 (m, 8H, ligand)
$Et_2SiCl(L_2)$	1588 m	1706 s 1327 m	379	815 w 655 s	525 m	0.97-1.30 (m, 10H, Et), 7.70-8.87 (m, 4H, ligand)
$Et_2Si(L_2)_2$	1589 s	1710 s 1330 w	380	812 s 630 w	530 s	0.96-1.32 (m, 10H, Et), 7.73-8.89 (m, 8H, ligand)
$Ph_2SiCl(L_2)$	1590 s	1707 s 1324 m	383	810 w 652 m	515 m	7.20-7.75 (m, 10H, Ph), 7.80-8.95 (m, 4H, ligand)
$Ph_2Si(L_2)_2$	1592 s	1705 m 1328 w	377	807 m 651 s	517 w	7.28-7.74 (m, 10H, Ph), 7.85-9.10 (m, 8H, ligand)

broadened[12]. The signals for the aromatic protons of the ligands HL_1 and HL_2 are observed in the range δ 7.22-8.08 and δ 7.53-8.74, respectively. The downfield shift of these positions in the spectra of the complexes shows their coordination with these ligands. The spectra show the chemical shift of the methyl, ethyl and phenyl in the range δ 0.90-0.93, δ 0.91-1.32 and δ 7.18-7.75, respectively (Table-3). The integrated proton ratio for each group was in agreement with the proposed structures.

^{13}C NMR spectra: The ^{13}C NMR spectra of the ligands and their organosilicon(IV) complexes were recorded in $CDCl_3$ with a few drops of DMSO-d_6 (Table-4). For ligand HL_1 the C-2, C-3, C-4, C-5 and C-6 carbon of pyridine ring showed signals at δ 137.4, 159.4, 129.4, 129.7 and 140.6, respectively, while for the ligand

TABLE-4
^{13}C NMR CHEMICAL SHIFTS (δ) OF ORGANOSILICON(IV) COMPLEXES

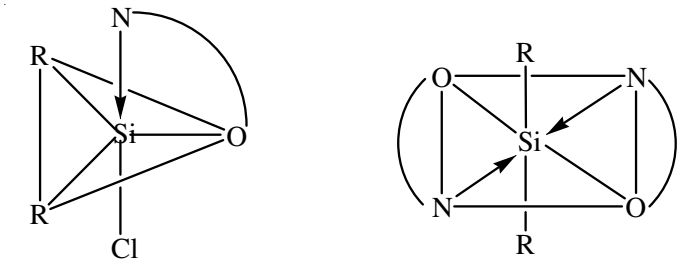
Complexes/ Ligands	(COO)	C-2	C-3	C-4	C-5	C-6	Si–C
HL_1	175.6	137.4	159.4	129.4	129.7	140.6	–
$Me_2SiCl(L_1)$	167.7	132.5	149.6	128.3	128.2	143.5	1.91
$Me_2Si(L_1)_2$	166.5	131.2	148.9	128.2	128.1	143.2	1.94
$Et_2SiCl(L_1)$	167.6	130.5	148.8	127.8	127.9	143.1	2.22, 5.5
$Et_2Si(L_1)_2$	167.5	130.3	148.7	127.9	127.8	143.2	2.29, 5.57
$Ph_2SiCl(L_1)$	167.4	130.4	148.6	127.5	127.7	143.4	129.5, 133.3, 135.6, 137.3
$Ph_2Si(L_1)_2$	167.3	130.5	148.8	127.4	127.8	143.5	130.1, 133.6, 135.7, 137.5
HL_2	167.7	148.4	128.6	137.6	127.2	149.2	–
$Me_2SiCl(L_2)$	157.6	142.2	128.3	139.4	127.1	149.4	1.97
$Me_2Si(L_2)_2$	158.4	142.3	128.2	139.2	127.3	149.5	1.99
$Et_2SiCl(L_2)$	158.5	142.1	128.1	139.3	127.2	149.3	2.32, 5.6
$Et_2Si(L_2)_2$	158.8	142.2	128.3	139.4	127.4	149.1	2.28, 5.8
$Ph_2SiCl(L_2)$	157.6	141.4	128.1	139.1	127.3	149.2	130.2, 133.2, 135.5, 137.4
$Ph_2Si(L_2)_2$	157.8	141.3	128.2	139.2	127.1	149.1	130.4, 133.3, 135.7, 137.5

HL_2 signals due to the same carbons were observed at δ 148.2, 128.6, 137.6, 127.2 and 149.2. These peaks were slightly altered on complexation with organosilicon(IV) halide indicating the involvement of nitrogen of pyridine moiety on complexation. The carbon of carboxylate group of the ligands was observed at δ 175.6 and δ 167.7 for HL_1 and HL_2, respectively and was shifted to δ 167 and δ 156 on complexation indicating the involvement of oxygen atom of COO group. No shift in the position of resonance of C attached to OH group was observed thereby suggesting that OH group is not involved in coordination.

^{29}Si NMR spectra: ^{29}Si NMR of 1:1 complexes give sharp signals at δ -80 to -110 and the spectra of 1:2 complexes give sharp signals at δ -160 to -180, which clearly indicates the penta- and hexa-coordinated environment, respectively, around the silicon atom and is well in agreement with the reported values[13]. This value of chemical shift varies with the nature of R group attached to silicon atom. When R is phenyl, shielding of the ^{29}Si nucleus is observed because the localized system of phenyl group allows for pπ-dπ interactions. Thus the chemical shift is lowered by δ 12-15 in these complexes as compared to those which have greater '*s*' donation capacity *i.e.* R when R = alkyl group. Thus on the basis of the spectral features, as well as the analytical data, the following structures of 1:1 and 1:2 complexes having around silicon atom have been proposed in Fig. 1.

Antimicrobial activity: The ligands (3-hydroxy-2-pyridine carboxylic acid and 2-pyridine carboxylic acid) and their silicon complexes were evaluated for *in vitro* antibacterial activity against Gram-positive *Bacillus subtilis, Staphylococcus aureus*, Gram-negative *Escherichia coli* and *in vitro* antifungal activity against *Candida albicans* and *Aspergillus niger*. Minimum inhibitory concentrations (MIC) were determined by means of two fold serial dilution technique and are presented in

Table-2. Most of the complexes show lower minimum inhibitory concentration (MIC) values in comparison to the parent compounds against all the bacteria and fungi used, signifying the greater activity of the complexes.



1:1 complex
(R = Me, Et or Ph)

1:2 complex

Fig. 1

REFERENCES

1. P.I. Girginova, F.A.A. Paz, H.I.S. Nogueira, N.J.O. Sliva, V.S. Amaral, J. Klinowski and T. Trindade, *Polyhedron*, **24**, 563 (2005).
2. V.B. Di Marco, A. Tapparo, A. Dolmella and G.G. Bombi, *Inorg. Chim. Acta*, **357**, 135 (2004).
3. L. Moens, H. Maraite, B. Mahieu, E.A. Khloufia, R. Willem and M. Gielen, *Main Group Met. Chem.*, **15**, 275 (1992).
4. M. Gielen, P.V.D. Lelieveld and R. Willem, in ed.: M. Gielen, Metal Based Antitumor Drugs, (Freud Publishing House, Belgium), Vol. 2, p. 95 (1992).
5. R. Malhotra, J. Mehta and J.K. Puri, *Central Eur. J. Chem.*, **3**, 858 (2007).
6. D.F. Spooner and G. Sykes, Methods in Microbiology, Academic Press, London (1972).
7. M. Nath and S. Goyal, *Phosphorus, Sulfur Silicon Rel. Elem.*, **177**, 447 (2002).
8. S.P. Narula, N. Kapur, A. Choda, R. Shanker and R. Malhotra, *Indian J. Chem.*, **26A**, 135 (1987).
9. S.P. Narula, N. Kapur, R. Shanker, A. Choda and R. Malhotra, *Indian J. Chem.*, **27A**, 519 (1988).
10. S.P. Narula, N. Kapur and R. Malhotra, *Inorg. Chim. Acta*, **159**, 87 (1989).
11. M. Nath and S. Goyal, *Synth. React. Inorg. Met-Org. Chem.*, **34**, 187 (2005).
12. F.T. Lee, E.G. Gabe, L.E. Khoo and F.E. Smith, *Polyhedron*, **9**, 653 (1990).
13. J. Wagler and G. Roewer, *Inorg. Chim. Acta*, **360**, 1717 (2007).

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