# Spectral and Pharmacological Studies on Organosilicon and Organotin Complexes of Thiopicolinamides

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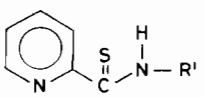
Thioanilides of α-picolinic acid are known to exhibit a wide variety of biological properties such as anti-bacterial, anti-tubercular, and anti-fungal activity [1–3]. Several complexes of these ligands with molybdenum were recently studied by Larin [4]. Due to the widespread applications of organosilicon and organotin in medicine [5–7], it was decided to undertake a systematic study of the synthesis, characterization and biological activities exhibited by thioanilides of α-picolinic acid and their complexes with dimethyldichlorosilane and diphenyltindichloride.

## Experimental

### *Preparation of Ligands*

Reagent grade chemicals were used. No further purification was required for these chemicals. Thioamides of α-picolinic acid were prepared according to the procedure described by Lions and Martin [1]. 0.02 mol of aniline, 0.01 mol of α-picoline and 0.015 mol of monoatomic sulfur were heated in a 250 ml round bottomed flask in an oil bath maintained at 170–175 °C for 12 h. The reaction mixture was vacuum distilled to remove the unreacted α-picoline and analine giving α-thiopicoline analide at 75% yield. The product was purified by recrystallization from a mixture of n-hexane and benzene. The following ligands were prepared.



| Ligand | R′ | Name | Melting point (°C) |
|---|---|---|---|
| **A** | $C_6H_5$ | α-Thiopicoline-anilide | 46–47 |
| **B** | *o*-$CH_3$-$C_6H_4$ | α-Thiopicolin-*o*-toluidide | 69–71 |
| **C** | *m*-$CH_3$-$C_6H_4$ | α-Thiopicolin-*m*-toluidide | 78–80 |
| **D** | *p*-$CH_3$-$C_6H_4$ | α-Thiopicolin-*p*-toluidide | 98–100 |
| **E** | *o*-$OCH_3$-$C_6H_4$ | α-Thiopicolin-*o*-anisylamide | 182–183 |
| **F** | *p*-$OCH_3$-$C_6H_4$ | α-Thiopicolin-*p*-anisylamide | 100–102 |
| **G** | α-pyridyl | α-Thiopicolin-α-pyridylamide | 81–82 |

### *Preparation of Complexes*

Dimethyldichlorosilane (DMDCS) was used without further purification. Diphenyltindichloride (DPTDC) was prepared according to a previously established procedure [8]. 52.7 g dry benzene and 4.1 g of sodium metal were heated in a 150 ml three-necked round bottomed flask. The materials were allowed to reflux until the reaction was complete. Then a mixture of 6.1 g of tin(IV) chloride (BDH) and 13.3 g of chlorobenzene was slowly added; the mixture was refluxed for 3 h. The separated solid was filtered. The filtrate was cooled. The product was colorless crystals of tetraphenyltin (melting point 230 °C, yield 80%). DPTDC, (melting point 46 °C), was obtained by refluxing an equimolar ratio of tetraphenyltin and tin(IV) chloride on an oil bath. The bath was maintained at 220 °C for 10 h. The resulting mixture was vacuum distilled to obtain the desired product. Maximum product yield was 80%.

The complexes were prepared by mixing the respective ligands and either DMDCS or DPTDC in equimolar quantities with dry benzene. The mixture was stirred vigorously for 1 h; the separated complex was allowed to stand overnight. It was then filtered, repeatedly washed with dry benzene, and dried in vacuum over $P_2O_5$.

### *Physio-chemical Measurements*

Elemental analyses were carried out by a procedure previously described [9]. Chlorine was estimated as silver chloride precipitate; the Kjeldahl method was used to determine nitrogen content; carbon was estimated by microanalysis; tin was estimated as tin oxide; sulfur was determined gravimetrically as barium sulfate.

Molar conductivities were measured in dimethylformamide (DMF) using an Elico-CM-82 conductivity bridge (the cell constant was 0.829 $cm^{-1}$). All

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TABLE I. Analytical and Physical Data for DMDCS Complexes.

| Complex | Molecular formula | Analysis: calculated (found) (%) | | | | Molar conductivity[a] | Melting point (°C) |
|---|---|---|---|---|---|---|---|
| | | N | Cl | S | C | | |
| I | $(C_{14}H_{16}N_2S)SiCl_2$ | 8.16 (8.21) | 20.69 (20.81) | 9.33 (9.42) | 48.92 (49.05) | 28 | 201 |
| II | $(C_{14}H_{15}N_2S)SiCl_3$ | 7.41 (7.05) | 28.21 (28.40) | 8.47 (8.45) | 44.50 (44.60) | 32 | 185 |
| III | $(C_{14}H_{15}N_2S)SiCl_3$ | 7.41 (7.25) | 28.21 (28.25) | 8.47 (8.50) | 44.50 (44.45) | 30 | 190 |
| IV | $(C_{15}H_{18}N_2S)SiCl_2$ | 7.84 (7.78) | 19.88 (20.05) | 8.96 (8.08) | 50.42 (50.81) | 21 | 220 |
| V | $(C_{15}H_{18}N_2S)SiCl_2$ | 7.84 (7.52) | 19.88 (19.90) | 8.96 (8.12) | 50.42 (50.50) | 20 | 225 |
| VI | $(C_{15}H_{18}N_2OS)SiCl_2$ | 7.50 (7.40) | 19.03 (19.09) | 8.57 (8.41) | 48.25 (48.20) | 18 | 178 |
| VII | $(C_{15}H_{18}N_2OS)SiCl_2$ | 7.50 (7.35) | 19.03 (19.21) | 8.57 (8.72) | 48.25 (48.28) | 15 | 152 |

[a] $ohm^{-1}\ cm^2\ mol^{-1}$.

conductivity measurements were performed at room temperature using $10^{-3}$ M solutions of the complex. The infrared (IR) spectral results from 4000 to 200 $cm^{-1}$ were scanned using a Perkin-Elmer 180 spectrophotometer. Samples were prepared as KBr pellets. Proton magnetic resonance (PMR) spectra were recorded on a S-60-C NMR instrument. All NMR samples were dissolved in deuterated dimethylosulfoxide ($d_6$-DMSO). Tetramethylsilane (TMS) was used as an internal standard.

*Pharmacological Tests*

*Hypoglycemic activity*

Before examining the compounds for hypoglycemic activity, acute toxicity tests were conducted *in vivo* to estimate the safe maximum dose. Male and female albino rats, (150–200 g weight), were used in the experiment. The rats did not eat for 48 h prior to the experiment.

Prior to injection, two drops of Tween 80 were placed in each of the test compounds. The mixtures were administered intra-peritoneously in doses of 50 mg per kg body weight increments, ranging from 50 mg to 200 mg. Rats were observed for behavioral changes for 3 days. Hourly examination was maintained for twelve hours. Observation was then reduced to a twelve hour interval for the remaining study period.

A 200 mg dosage per kg body weight requires test compounds to be suspended in 2 ml of 4% gum-acacia–water solution. These samples were injected into the rats. Blood samples were obtained using a cardiac puncture technique. Samples were drawn at three hour intervals for twelve hours. Blood glucose content was determined by the Nelso–Somogyi [10, 11] method. Tolbutamide was used as a reference compound. This procedure allowed determination of the pharmacological activity of the ligands and complexes. The control group was injected with 2 ml 4% gumacacia solution and given identical treatment to the test animals.

## Results and Discussion

*Analytical Data*

All complexes are crystalline in nature except α-thiopicolin-α-pyridylamide which was too hydroscopic to permit crystallization. The complexes are dark brown in color. They are noted to be soluble in alcohol, chloroform, DMF and DMSO. The analytical and physical data suggest 1:1 (metal: ligand) stoichiometry. Lower values of molar conductivities indicate the non-electrolytic behavior of the complexes in solution (see Tables I and II).

*Infrared Spectra*

Important IR frequency ranges and their assignments of ligands and complexes are given in Table III. Thioamides of α-picolinic acid are known to exhibit thiol-thione tautomerism [12]. It has been shown earlier [13] that, in copper complexes of thioamides of α-picolinic acid, the ligands exist in the thiol form.

In the spectra of ligands (**A–G**), an intense band in the region 3210–3220 $cm^{-1}$ is attributed to the intramolecularly hydrogen bonded γ(N–H) vibration. A band observed in the region 1575–1580 $cm^{-1}$ is assigned to the combination of γ(C=C); γ(C=N) vibrations. The *ortho*-substituted pyridine ring exhibits three characteristic bands around

TABLE II. Analytical and Physical Data for DPTDC Complexes.

| Complex | Molecular formula | Analysis: calculated (found) (%) | | | | Molar conductivity[a] | Melting point (°C) |
|---|---|---|---|---|---|---|---|
| | | N | Cl | S | Sn | | |
| **VIII** | $(C_{24}H_{20}N_2S)SnCl_2$ | 5.02 (4.88) | 12.73 (12.75) | 5.73 (5.81) | 21.28 (21.42) | 21 | 182 |
| **IX** | $(C_{24}H_{19}N_2S)SnCl_3$ | 4.72 (4.95) | 17.98 (18.05) | 5.40 (5.45) | 20.04 (20.12) | 18 | 199 |
| **X** | $(C_{24}H_{19}N_2S)SnCl_3$ | 4.72 (4.90) | 17.98 (18.11) | 5.40 (5.41) | 20.04 (19.98) | 11 | 300 |
| **XI** | $(C_{25}H_{22}N_2S)SnCl_2$ | 4.89 (4.57) | 12.41 (12.45) | 5.59 (5.70) | 20.76 (20.85) | 13 | 210 |
| **XII** | $(C_{25}H_{22}N_2S)SnCl_2$ | 4.89 (4.72) | 12.41 (12.60) | 5.59 (5.65) | 20.76 (20.72) | 21 | 185 |
| **XIII** | $(C_{25}H_{22}N_2OS)SnCl_2$ | 4.76 (4.58) | 12.08 (11.95) | 5.44 (5.00) | 20.19 (20.20) | 25 | 225 |
| **XIV** | $(C_{25}H_{22}N_2OS)SnCl_2$ | 4.76 (4.65) | 12.08 (12.10) | 5.44 (5.40) | 20.19 (20.15) | 20 | 250 |

[a] $ohm^{-1}\ cm^2\ mol^{-1}$.

TABLE III. Infrared Results for Ligands and Complexes.

| Ligands (**A–G**) | DMDCS complexes (**I–VII**) | DPTDC complexes (**VIII–XIV**) | Assignments |
|---|---|---|---|
| 3210–3220[a] | 3390–3410 | 3400–3420 | $\gamma$(N–H) |
| 1575–1580 | 1600–1610 | 1595–1605 | $\gamma$(C=C) + $\gamma$(C=N) |
| 1205–1225 | 1205–1225 | 1215–1240 | $\gamma$(C=S) |
| 1415–1425 | 1415–1420 | 1410–1420 | $\gamma$(C=S) |
| 980–990 | 1000–1015 | 1000–1010 | Pyridine ring breathing modes |
| 1035–1295 | – | – | *Ortho*-substituted pyridine ring |
| – | 610–620 | – | $\gamma$(Si–C) |
| – | 700–710 | – | $\gamma$(Si–N) |
| – | 580–590 | – | $\gamma$(Si–Cl) |
| – | – | 560–590 | $\gamma$(Sn–C) |
| – | – | 390–400 | $\gamma$(Sn–N) |
| – | – | 350–355 | $\gamma$(Sn–Cl) |

[a] Frequency ranges given as ($cm^{-1}$).

1295, 1140 and 1035 $cm^{-1}$. The regions 1205–1225 and 1415–1425 $cm^{-1}$ are assigned to $\gamma$(C=S) vibrations of the thioamide group. The pyridine ring breathing vibrations [14] are observed around 980–990 $cm^{-1}$. An out of plane vibration due to $\gamma$(C–H) of *ortho*-substituted pyridine ring is observed in the region 740–760 $cm^{-1}$.

In the spectra of the DMDCS complexes (**I–VII**), the band due to $\gamma$(N–H) is shifted to the region 3390–3410 $cm^{-1}$. This indicates disruption of intramolecular hydrogen bond. Disruption occurs after chelation of the metal ion through the nitrogen of the amide moiety. The vibrations due to $\gamma$(C=C) and $\gamma$(C=N) are shifted to the region 1600–1610 $cm^{-1}$. This indicates participation of pyridine nitrogen during chelation which is also confirmed by an upward shift of pyridine ring breathing modes to about 1015 $cm^{-1}$. An absorption band due to $\gamma$(C=S) does not show any change in its position. That suggests nonreactivity of C=S group in coordination. Taking into consideration earlier reports [15, 16], the bands around 615, 705 and 585 $cm^{-1}$ are assigned to the $\gamma$(Si–C), $\gamma$(Si–N) and $\gamma$(Si–Cl) vibrations, respectively.

In the spectra of the DPTDC complexes (**VIII–XIV**), the band due to $\gamma$(N–H) is observed around 3400–3420 $cm^{-1}$. The bands produced by $\gamma$(C=C) and $\gamma$(C=N) are seen around 1595–1605 $cm^{-1}$. Pyridine ring breathing vibrations are seen around 1000–1010 $cm^{-1}$. The band due to $\gamma$(C=S) did

TABLE IV. Effect of Ligands and Complexes on Blood Glucose Levels in Rats.[a]

| Ligand/ complex | mg glucose/100 ml blood | | | Percent change | | |
|---|---|---|---|---|---|---|
| | 3rd h | 6th h | 12th h | 3rd h | 6th h | 12th h |
| **A** | 161.5 | 169.2 | 150.0 | 11.6 | 16.9 | 3.7 |
| **B** | 152.3 | 161.5 | 148.5 | 5.3 | 11.6 | 2.6 |
| **C** | 147.3 | 138.5 | 149.0 | 1.8 | −4.3 | 3.0 |
| **D** | 176.9 | 169.2 | 145.0 | 22.3 | 16.9 | 0.2 |
| **E** | 130.8 | 138.5 | 150.5 | −9.6 | −4.3 | 4.0 |
| **F** | 192.3 | 200.0 | 155.0 | 32.9 | 38.2 | 5.1 |
| **G** | 182.5 | 162.7 | 152.0 | 26.2 | 12.4 | 5.1 |
| **I** | 92.3 | 80.0 | 75.5 | −6.2 | −44.7 | −47.8 |
| **II** | 115.4 | 105.2 | 93.4 | −20.3 | −27.3 | −35.5 |
| **III** | 107.6 | 100.5 | 98.7 | −25.6 | −30.5 | −31.8 |
| **IV** | 110.5 | 92.6 | 74.9 | −23.7 | −36.0 | −48.3 |
| **V** | 123.1 | 107.8 | 100.0 | −14.9 | −25.5 | −30.9 |
| **VI** | 128.5 | 98.7 | 70.9 | −11.2 | −31.8 | −51.0 |
| **VII** | 130.8 | 100.0 | 76.9 | −9.6 | −30.9 | −46.8 |
| **VIII** | 139.0 | 130.5 | 132.0 | −3.9 | −9.8 | −8.8 |
| **IX** | 141.8 | 138.5 | 131.5 | −2.0 | −4.3 | −9.1 |
| **X** | 128.5 | 121.0 | 120.5 | −11.2 | −16.4 | −16.7 |
| **XI** | 140.6 | 141.5 | 138.5 | −2.8 | −2.2 | −4.3 |
| **XII** | 132.5 | 130.8 | 123.1 | −8.4 | −9.6 | −14.9 |
| **XIII** | 125.4 | 115.0 | 110.5 | −13.3 | −20.5 | −23.6 |
| **XIV** | 150.8 | 145.5 | 143.9 | 4.2 | 0.6 | −0.6 |
| Standard[b] | 76.9 | 100.0 | 138.5 | −46.8 | −30.9 | −4.3 |

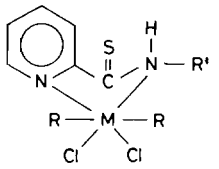
[a]Control: 144.7 mg of glucose per 100 ml of blood. [b]Tolbutamide used as standard.

not change from its original position. In view of the assignments made earlier [17, 18], the regions 560–575, 385–400 and 350–355 $cm^{-1}$ are assigned to the $\gamma$(Sn–C), $\gamma$(Sn–N) and $\gamma$(Sn–Cl) vibrations, respectively.

*Proton Magnetic Resonance Spectra*

The PMR spectra of the ligands contain four characteristic proton signals at 7.08, 7.27, 7.55 and 8.50 ppm. These signals are attributed to protons of the pyridine ring. A signal at 3.28 ppm is assigned to the proton of the amide group. In the spectra of complexes (**I–XIV**), the pyridine ring proton signals are observed at 6.8, 6.86, 7.08 and 8.3 ppm. Similarly, the amide group proton signal exhibits a considerable shift and is located at 4.5 ppm. In the case of the DMDCS complexes, three methyl group protons are seen as multiplets around 1.0 to 1.5 ppm. The region 7.0 to 7.56 ppm is attributed to phenyl ring protons of DPTDC.

Based on the IR and PMR results, the following structure may be tentatively proposed for the complexes (**I–XIV**) under study.




M = Si, Sn
R = $Ch_3$, $C_6H_5$

*Pharmacological Tests*

Data for hypoglycemic activity tests are given in Table IV. The results are expressed as percent difference between mean averages of the test and control groups at the time intervals indicated. In general, the ligands show a larger increase in the blood glucose level at the 3rd hour compared to the 6th and 12th hour. (An exception is to be noted in the *o*-methoxy analogues **E–F**.) A large difference between test and control animals was noted for all the ligands (**A–I**). In the case of substituted anailides, *para*-substitution has shown better activity than its *ortho* isomer. α-thiopicolin-α-pyridylamide (**I**) ligand exhibited notable activity. Silicon complexes (**I–VII**) exhibit pronounced hypoglycemic activity in comparison to the reference hypoglycemic agent, tolbutamide. However, the tin complexes (**VIII–XIV**) exhibit moderate activity. This is seen by observing the limited percentage change as compared to other ligands and the silicon complex.

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