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Research Article

Biological and electronic transition studies of the previously reported organotin (IV) dithiocarbamates of *p*-Fluoro-*N*methylbenzylaminedithiocarbamate

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Abstract

Four organotin(IV) complexes of *p*-Fluro-*N*-methylbenzylaminedithiocarbamate with general formula R_2SnL_2 where (R= dimethyl, diphenyl and dibutyl)and R_3SnL (R = triphenyl) synthesized earlier in the group were tested for their bioactivity. Antibacterial assay against four Gram-negative and Gram-positive strains including *Salmonella typhi, Escherichia coli, Pneumoniae and Staphylococcus aureus,* while antifungal activity against *Aspergillus Niger* of the compounds were carried out using standard procedures.The tested compounds were found significantly active against *Aspergillus Niger*. Whereas, the antibacterial activity of compounds wasfound moderate as compared to their antifungal activities.

Keywords: Disc diffusion method; ^{1}H NMR; Organotin dithiocarbamates

Introduction

Dithiocarbamates are compounds in which both oxygens of carbamate are replaced by sulphur atoms. Sulphur atoms of dithiocarbamate ligands combine with transition elements form chelates **[1, 2]**. Dithiocarbamates are flexible ligands and have capability of forming complexes with majority of elements and particularly stabilise transition metals in various oxidation states. Dithiocarbamates are widely used in agriculture as fungicides **[3, 4]**. The derivatives of dithiocarbamates are used as antitumor agents **[5, 6]**. Furthermore, dithiocarbamates can increase the intake of zinc and copper and may also produce copper mediated neurological ailments **[7, 8]**. Dithiocarbamate ligands can coordinate with metal centres as bidentate or monodentate ligands **[9, 10]**. In biological systems,dithiocarbamates can act as inhibitor to inhibit the growth of enzymes because of their strong metal binding capacity **[11]**. The significant bioactivity of metal dithiocarbamatesmay be associated with their greater stability **[12]**.

Organotin compounds have at least one carbon tin bond **[13]**.The coordination chemistry of organotin compounds is very rich because of its various coordination numbers stereochemistry **[14, 15]**. The

most common and well-known complexes of organotin (IV) compounds show strong biological activity such as antitumor, antibacterial and antimalarial [16]. The complexes of organotin(IV) shows propitious cytotoxic activities against different types of tumour cells like ovarian, colon, melanoma prostate, renal lungs and breast [17].

In the present study, we have assessed the antibacterial and antifungal activities of the synthesized organotin (IV) dithiocarbamate compounds in view of their marvellous biological activities. Furthermore, these compounds have already shown promising properties [18].

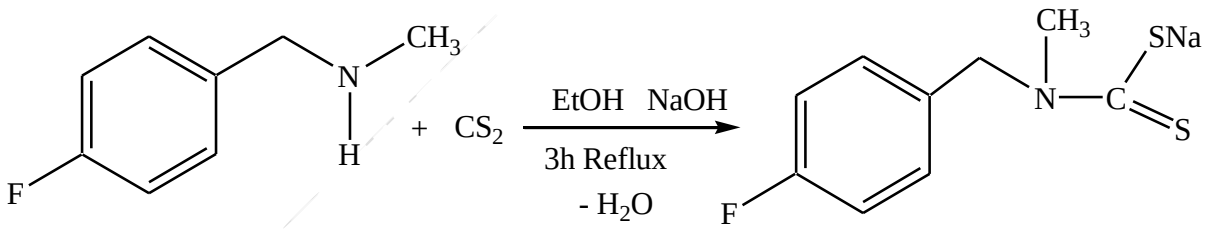
Materials and methods

Experiment

The chemicals were purchased from Merck and Aldrich and used without further purification. For the purity assurance of ligands and complexes TLC techniques was performed. Through electrothermal 9300 digital, melting points were determined in open capillary tubes. Infrared spectra of compounds were recorded by Perkin Elmer spectrophotometer GX. using potassium bromide discs. H^1 NMR spectra of compounds were recorded in $CDCl_3$ / DMSO-$d_6$by BRUKER FT-NMR 600 MHz. UV spectra of compounds were recorded in DMSO-d_6 (Dimethyl sulfoxide).

Synthesis of Ligands

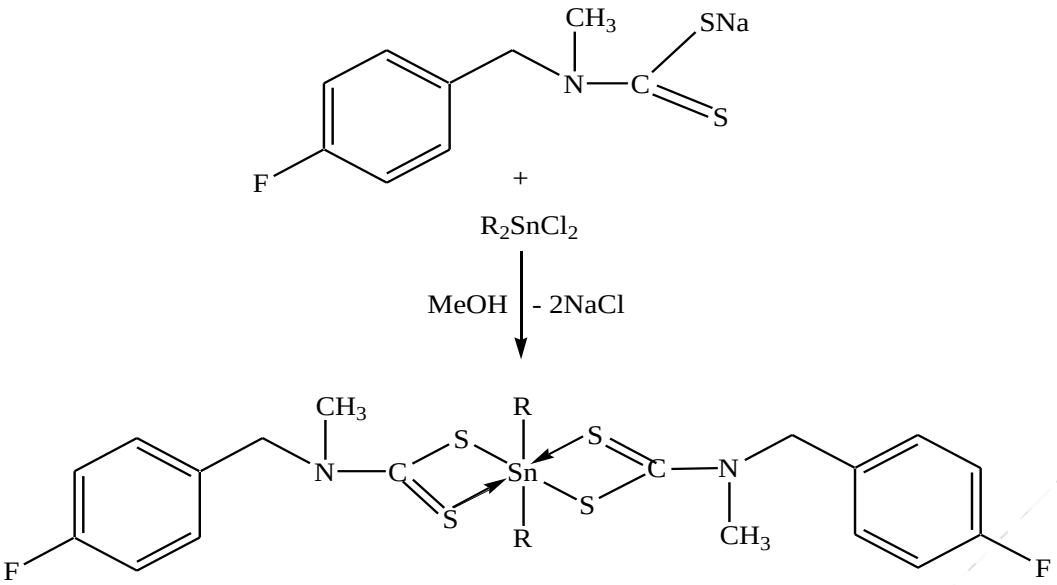
Sodium salt of *p*-Fluro-*N*-methylbenzylaminedithiocarbamate was prepared by dissolving *p*-Fluro-*N*-methylbenzylamine 20.0 mmol (1.24ml) in 30ml of ethanol. Then 20.0 mmol (1.2ml) of pure carbon disulphide was added dropwise with constant stirring in the ethanolic solution. 10ml of 20.0 mmol (0.8g) NaOHdissolved in water was added in mixture. The ethanolic mixture was reflexed for further 3 hours [19]. Colourless crude product obtained, was dried in vacuo over $CaCl_2$ (Calcium Chloride). The synthesized ligand is shown in scheme 1.



Scheme1. **Synthesis of *p*-Fluro-*N*-methylbenzylaminedithiocarbamate**

Synthesis of organotin (IV) complexes

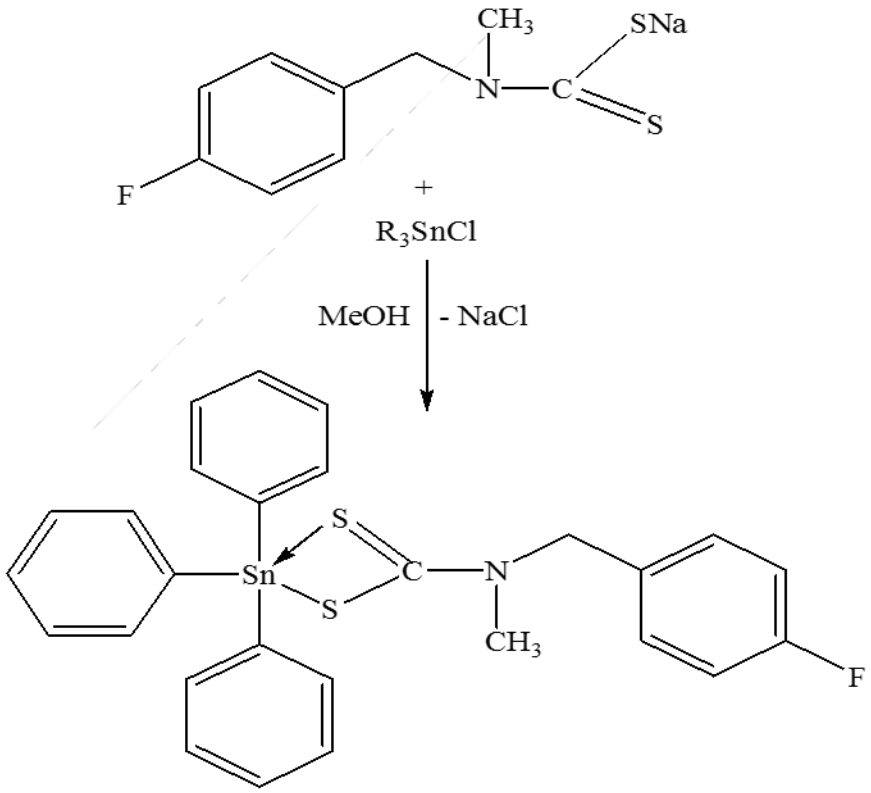
The organotin (IV) complexes of *p*-Fluro-*N*-methylbenzylaminedithiocarbamate were synthesized by adding 5 mmol methanolic solution of ligand in 2.5 mmol of diorganotin (IV) dichloride dissolved in the same solvent in 2:1 molar ratio. Then reaction mixture was reflexed for 3 hours. The obtained crude product was washed with diethyl ether and methanol and recrystallized in ethanol [20, 21].Synthetic method for complexes are given below in scheme 2.



Scheme 2. Synthesis of diorganotin(IV) *p*-Fluro*N*-methylbenzylaminedithiocarbamate

Synthesis of triorganotin (IV) complex

Triorganotin(IV) complex of*p*-Fluro*N*-methylbenzylaminedithiocarbamate was prepared by adding a 5mmolmethanolicsolutionof *p*-Fluro*N*-methylbenzylaminedithiocarbamate in solution of triphenyltin(IV) dissolved in tetrahydrofuran. This solution was refluxed for 4 hours. The solvent was evaporated under reduced pressure and product was purified in chloroform to obtain colourless crystals. The synthesis of triphenyltin(IV) complex is shown in scheme 3. It is worth mentioning that the present ligand and its complexes have already been synthesized and characterized [22].



Scheme3. Synthesis of triphenyltin (IV) *p*-Fluro*N*-methylbenzylaminedithiocarbamate

Antibacterial assay

Disc diffusion method had been utilized for the determination of antibacterial activity of synthesised organotin (IV) dithiocarbamate complexes [23]. The inhibition zones were measured against Gram negative bacteria including *Escherichia coli and Salmonella thyphi* and Gram positive including *Bacillus cereus and Staphylococcus*. Molar Hinton Agar were prepared following its instructions. Agar were spread on petri plates and bacterial strains were cultured on 25ml of medium. Organotin (IV) dithiocarbamatecomplexes were dissolved in dimethylsulfoxide (DMSO) and a 100ml stock solution (4mg/mL in DMSO) of compounds were added in wells. These petri plates were incubated at 37 °Cfor 24 hours. The bactericidal activity of compounds was recorded by measuring the diameter of inhibition zone. Doxycycline (DO 30mg) and DMSO were used as negative and positive control.

Antifungal Assay

The fungi *Aspergillus Niger* was isolated from environment. The solutions of compounds used for antifungal activity were freshly prepared inDMSO (0.02mg/5ml) tested against *AspergillusNiger* fungus. Diffusion method was adopted to measure the antifungal activity [24]. These fungal strains were properly grown in sabouraud dextrose agar slants. The fungal spores sabouraudon to dextrose agar plates. The compounds were dissolved in final concentration from 10-20mg for fungal cultures could stay in the walls. The petri plates were incubated for 4 days and spores were observed after 4, 7 and 14 days. The inhibition zone and activity of all compounds were measured compared with control.

Result and discussion

^{1}HNMR spectroscopy

In spectra of complexes, slight variation is observed in the absorptions of methyl groups attached with nitrogen and aromatic protons which indicates formation of complexes and the values are in accordance with the previous reports.

In the spectra of ligand, methyl group attached with nitrogen atom shows absorbance at2.89 ppm in ligand's spectrum. The aromatic protons of ligand appear in the range 6.99 and 7.25 ppm. Whereas, the aromatic protons of complexes show multipletsin the range6.97-7.98 ppm. In spectrum of dimethyltin(IV), the methyl group attached with tin is observed at 1.56 ppm. In dibutyltin (IV) complex,the methylene protons appear at 5.09 ppm [25].

Infrared spectroscopy

The solid state vibrational spectra are recorded for the dithiocarbamateligand and its complexes in the range 4000-370 cm^{-1} which matches the exact value already reported by Naqeeb*et al*. [26]. The appearance of C-N peak in spectra of ligand at 1472 cm^{-1}confirms the formation of ligand. The C=S peak is observed at 954 cm^{-1}. The slight variation in main peaks along with appearance of Sn-S wave numbers in their respective ranges confirm the formation of four coordinated organotin(IV) complexes as reported earlier. The dithiocarbamate ligand are coordinated only via singly bonded sulphur donor site exhibiting four coordinated complexes and in accordance with the NMR spectral interpretations [27, 28].

Ultraviolet spectroscopy

The Ultraviolet absorbance of these ligands and complexes is studied for the first time. UV-Vis spectroscopy is carried out to observe the change in the electronic transitions of ligands and their complexes. Dimethylsulfoxide (DMSO) was used to make the solutions of ligands and complexes. The concentration for the complexes are 1.00 x 10^{-4} M and 1.00 x 10^{-3} M and the wavelengths were in the range of 200-400 nm. In UV spectrum of ligand two bands appear at 264 and 379 nm due to π-π* and n-π*. The n-π* in spectrum ligand is because of transition of lone pair of electrons of sulphur atom to π* orbital. Whereas, in UV spectra of complexes, the π-π* and n-π* are

observed in the range238-265 nm and 262-301, respectively. The slight variation in absorption values of π-π* and n-π* in spectra of complexes confirms the formation of complexes. The UV studies of the ligand and its complexes have been performed previously [29, 30].

Antibacterial Activity

The in-vitro antibacterial activity of ligand *p*-Fluro*N*-methylbenzylaminedithiocarbamate and its complexes *Di butyl-N*-methyl *p*-Flurobenzylaminedithiocarbamate, *Di-phenyl-N*-methyl *p*-Flurobenzylaminedithiocarbamate, *Di-methyl-N*-methyl *p*-Flurobenzylaminedithiocarbamateand*Tri-phenyl-N*-methyl *p*-Flurobenzylaminedithiocarbamateandd oxycline (standard drug) have been analysed by disc diffusion and agar well methods against four various pathogenic bacterial strains. Gram negative (*Salmonella typhi, Escherichia coli*,) Gram positive (*Staphyloccouse aureus and Pneumoniae*) [31]. The inhibition zones are recorded in mm and given in the table 1. Below 10mm zone inhibition diameter arenoted as weak. Moderate inhibition zones are of 10-16mm and higher from 16mm are stated as active. Ligand *p*-Fluro*N*-methylbenzylaminedithiocarbamatesho ws significant activity against *Klesbsella* and moderate activity against *S.aureus* and *E.coli* and other strains. Different biological impacts of organotin (IV) complexes is ascribedto the existence of different organic groups attached with tin centre. Antibacterial activity is because of the interaction of organotin moiety with deoxyribose nucleic acid (DNA) of bacteria. The dimethyltin(IV) complex shows good activity against all the tested and it might be due toits low molecular mass and greater penetration through cell wall of bacteria [32].

Table 1.Antibacterial activity of organotin (IV) dithiocarbamates

Compound	Inhibition zone (mm)			
	E. Coli	***K.pneumoniea***	***S.typhi***	***S.aureus***
p-Fluro *N*-methylbenzylaminedithiocarbamate	13	10	13	15
Di- phenyl- *N*-methyl p-Flurobenzylaminedithiocarbamate	12	11	10	10
Di butyl- *N*-methyl p-Flurobenzylaminedithiocarbamate	10	13	10	11
Di-methyl- *N*-methyl p-Flurobenzylaminedithiocarbamate	7	05	08	13
Tri-phenyl- *N*-methyl p-Flurobenzylaminedithiocarbamate	11	06	11	14

Antifungal Activity

The antifungal assay of the synthesized compound has been performed by diffusion method. The obtained results of these compounds show strong antifungal activity against *Aspergillus Niger*.All the compounds inhibit the fungus growth completely as shown in figure 1. The amazing antifungal activity of these compounds might be due to their easy penetration through fungal cell wall [33]. It may also be associated with different composition of cell wall structures of fungal and bacterial cells. The bacterial cell wall is composed of cellulose while the fungal cell wall is composed of chitin. The assayed compounds exhibit strong fungicidal activity in comparison to bacterial activity. All the tested compounds inhibit the fungal growth completely as compared to standard drug. The antifungal activity is given below in figure 1.

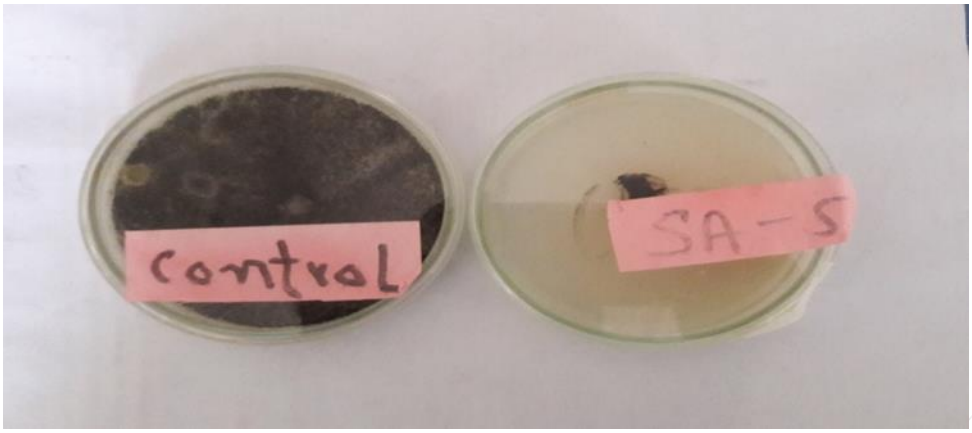


Figure1. Antifungal Activity of organotin (IV) dithiocarbamates complexes

Conclusion

The ligand*p*-Fluro *N*-methylbenzylaminedithiocarbamate and its complexes were resynthesized in the Department of Chemistry,University of Balochistan. Antibacterial assay against four Gram-negative and Gram-positive strains including*S. typhi*, *E. coli*, *Pneumoniae* and *S. aureus* were noted using disc diffusion method. The ligands and its complexes show moderate action against these four strains while the antifungal activity of these compounds is very high which completely inhibit the fungal growth as compared with control. Moreover, the electronic transitions of these compounds were in the range of 200-400nm.

Authors' contributions

Conceived and designed the experiments: A Ghaffar, N Khan & Samiullah, Performed the experiments: A Ghaffar, I Ali, N Khan, A Baqi & Saifullah, Analyzed the data: Samiullah, N Khan & A Rehman, Contributed materials/ analysis/ tools: I Ali, A Akbar & WA Shah, Wrote the paper: A Ghaffar, A Baqi & Samiullah.

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