

SHORT PAPER

Antifertility and biocidal activities of organometallics of silicon, germanium, titanium and zirconium derived from 2-acetylthiophene thiosemicarbazone

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A comparative biochemical study of four Group IV element compounds with specific sulphur-containing organic substrates has been carried out and discussed. The structural characterizations of these organometallics, viz. Me_2SiLCl , Me_2SiL_2 , Me_3SiL , Ph_2SiLCl , Ph_2SiL_2 , Ph_3SiL , Ph_3GeL , Cp_2TiLCl , Cp_2TiL_2 , Cp_2ZrLCl and Cp_2ZrL_2 (where $\text{LH} = 2\text{-acetylthiophene thiosemicarbazone}$) had been deduced on the basis of various physico-chemical and instrumental techniques, viz., IR, UV, ^1H NMR, ^{13}C NMR and ^{29}Si NMR spectral studies. All the organometallics and the parent thioimine have been screened against a number of microbes and their sterilizing power in male mice tested. The results of these biocidal studies show that the organosilicon(IV) and organogermanium(IV) compounds are more active than the organotitanium(IV) and organozirconium(IV) derivatives. An attempt has also been made to correlate the structural aspects of the molecule with its biological activity.

Keywords: Antifertility activity, biocidal activity, organosilicon(IV), organogermanium(IV), organotitanium(IV), organozirconium(IV), thio-ligand

INTRODUCTION

The biochemistry of synthetic organometallics has been a subject of active research and its importance may be judged by the large number of articles in the literature^{1–3} relating to their biochemical significance.^{4–6} As organisms consist of sub-

stances composed of both non-metallic and metallic elements, inorganic biochemistry, with special reference to the coordination and organometallic areas, has become one of the most developed fields of inorganic chemistry. Clearly biochemistry is centred mainly on the structures of organic molecules, but it is also important to recognize that without the participation of metallic and metalloid elements in the structure of some organic moieties,^{7,8} metabolic functions would not exist. The importance of metal–nitrogen and metal–sulphur bonding, for example, and their prominence in recent research in the fields of agriculture, medicinal and industrial chemistry, prompted us to screen these thioimine organometallic compounds for their antifungal, antibacterial and antifertility activities.

EXPERIMENTAL

Biological screening against different bacteria and fungi has been evaluated by the inhibition zone technique and the radial growth method, respectively, as previously reported.⁹ Antifertility activity in male mice in terms of motility and sperm count was measured using Neubaur's haemocytometer method. The structural characterisation of these compounds is as reported elsewhere.^{10,11}

The biological methods are briefly summarized as follows.

Antibacterial activity

This was determined by the paper disc method at 1000 ppm compound concentrations in methanol. The 5 mm diameter discs were soaked in the test solutions then placed in a Petri dish on a medium

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Table 1 Antibacterial activity of the ligand (LH) and its organometallic derivatives

Bacteria	Diameter of inhibition zone (mm)											
	1 ^a	2	3	4	5	6	7	8	9	10	11	12
<i>Bacillus subtilis</i>	15	21	23	25	23	26	28	22	20	23	18	21
<i>Escherichia coli</i>	11	15	17	22	19	22	24	21	17	21	13	15
<i>Staphylococcus aureus</i>	13	19	20	20	21	24	22	23	16	17	16	16
Streptococci (+)	16	23	22	28	22	23	28	25	15	18	19	20
<i>Streptococcus viridans</i>	9	14	17	19	17	19	19	18	13	14	11	13
<i>Proteus mirabilis</i>	7	13	16	17	15	18	20	19	12	15	10	12

^a Key to compounds:

1 LH	4 Me ₃ SiL	7 Ph ₃ SiL	10 Cp ₂ TiL ₂
2 Me ₂ SiLCl	5 Ph ₂ SiLCl	8 Ph ₃ GeL	11 Cp ₂ ZrLCl
3 Me ₂ SiL ₂	6 Ph ₂ SiL ₂	9 Cp ₂ TiLCl	12 Cp ₂ ZrL ₂

previously seeded with organism and incubated at 30 °C. The inhibition zones were measured after 24 h.

Antifungal activity

Here the compounds were mixed with a potato dextrose agar/distilled water medium and fungal growth was measured at different compound concentrations. Growth was measured as fungal colony diameter after 96 h. Percentage inhibition was calculated as $(C - T)/T \times 100$ (C and T are diameters of control and test samples respectively).

Antifertility activity

This was measured by Neubaur's haemocytometer method. Thirty adult male mice (weight 40–50 g) were divided into six groups of five animals. The animals were kept in 25 cm × 20 cm × 20 cm cages and were fed mouse-feed pellets. Tap-water was provided freely. Of the six groups, one was used as a control, receiving 0.2 cm³ of olive oil per day per animal. The test substances were separately suspended in olive oil and given to the mice at a dose of 20 mg kg⁻¹ orally by gavage for 20 days; 24 h after the last dose the mice were sacrificed and dissected. Motility and sperm count were measured.

RESULTS AND DISCUSSION

The achievement of biocidal activity of all the compounds against different fungi and bacteria, and antifertility activity in male mice, are discussed individually.

Antibacterial activity

The results of antibacterial testing for the 11 compounds, along with the parent ligand, against different bacteria are reported in Table 1. Almost all the compounds were found to be more active than the parent ligand against all the organisms used. It may therefore be concluded that the biochemical properties of the molecule are greater if the halogen atom is replaced by the thioimine ligand moiety. The studies indicated that triorganosilicon(IV) complexes having phenyl groups exhibit similar activity to that of the triorganogermanium(IV) complexes against *Staphylococcus aureus*, *Streptococcus viridans* and *Proteus mirabilis* while the methyl-substituted compounds were found to be less potent than the corresponding phenyl derivatives of silicon(IV). It may also be inferred that the complexes which contain the triorganosilicon(IV) moiety and sulphur are more active than the corresponding diorganosilicon(IV) complexes. The present screening data, as well as some previously reported data of the ligand and its titanium(IV) and zirconium(IV) complexes, show that the former has greater activity than the later from the biochemical point of view. Comparing the results in general, it may be concluded that the organosilicon(IV) and triorganogermanium(IV) complexes have greater inhibiting power than the titanium(IV) and zirconium(IV) derivatives against all the microbes used. Although it is difficult to deduce an exact structure–activity relationship between the structure of these complexes and their microbial activity, it can perhaps be concluded that chelation as well as addition of an organic substrate enhances the activity of the complexes. Furthermore, the greater activity of

Table 2 Antifungal activity of the ligand and its organometallics

Compound	Average percentage inhibition after 96 h															
	<i>Alternaria solani</i>				<i>Aspergillus niger</i>				<i>Alternaria alternata</i>				<i>Macrophomina phaseolina</i>			
	Concn used (ppm)				Concn used (ppm)				Concn used (ppm)				Concn used (ppm)			
	20	40	60	80	20	40	60	80	20	40	60	80	20	40	60	80
1	14	17	21	26	18	27	35	44	21	28	31	38	17	23	29	43
2	36	41	49	66	73	87	100	100	81	100	100	100	80	100	100	100
3	40	45	52	71	73	81	100	100	84	100	100	100	82	100	100	100
4	43	51	58	82	79	84	100	100	86	91	100	100	79	87	100	100
5	46	53	62	83	37	55	58	71	67	74	79	90	52	58	74	80
6	51	59	68	86	68	82	100	100	77	100	100	100	74	100	100	100
7	54	61	70	91	79	85	100	100	84	91	100	100	82	88	100	100
8	49	53	59	78	77	87	100	100	87	92	100	100	75	85	100	100
9	37	41	47	62	25	31	45	56	40	58	71	90	35	55	64	85
10	40	45	51	67	28	45	57	79	45	68	84	90	43	61	79	89
11	39	44	53	71	33	61	66	76	73	80	83	90	70	78	82	89
12	46	49	61	75	36	65	68	80	71	79	81	90	61	67	80	85

Concn is for whole compound in ppm

the complexes may also be explained on the basis of their higher solubility.

Antifungal activity

All these complexes exhibited high activity against all the fungi, even at low concentrations, and inhibition of fungal growth has been found to be dependent on the concentration of the compounds. The fungicidal screening data (Table 2) show that the silicon(IV) complexes are more

active than the corresponding titanium(IV) and zirconium(IV) complexes, while the triorgano-germanium(IV) derivatives have an almost similar activity to those of the triorganosilicon(IV) complexes. It has also been noted that lower concentrations of the compounds can check sporulation in the fungi and that higher concentrations inhibit the growth of organisms completely. In some cases, at 60 and 80 ppm concentrations the complexes completely inhibit the growth of the fungi.

Table 3 Antifertility activity of the ligand and its organometallics

Compound	Sperm motility (%)	Sperm count in cauda epididymis ^a (mi/ml)
Vehicle alone (olive oil)	81.2 ± 4.6	23.4 ± 2.1
1	31.7 ± 6.0 ^b	10.3 ± 3.3 ^d
2	18.4 ± 2.4 ^a	4.6 ± 2.3 ^b
3	19.2 ± 1.28 ^a	7.2 ± 1.2 ^b
4	10.4 ± 2.24 ^a	4.6 ± 1.6 ^a
5	16.3 ± 2.3 ^a	4.0 ± 1.0 ^a
6	14.5 ± 1.5 ^a	3.5 ± 1.5 ^a
7	13.8 ± 1.3 ^a	4.3 ± 0.3 ^a
8	14.0 ± 2.0 ^a	3.0 ± 1.0 ^a
9	22.3 ± 3.3 ^a	9.5 ± 2.5 ^c
10	28.8 ± 4.8 ^b	10.6 ± 1.3 ^b
11	36.9 ± 6.3 ^b	11.2 ± 2.0 ^c
12	30.5 ± 3.5 ^a	8.6 ± 2.6 ^c

Values are expressed as mean ± s.e. ^a $P < 0.001$. ^b $P < 0.01$. ^c $P < 0.02$. ^d $P < 0.05$.

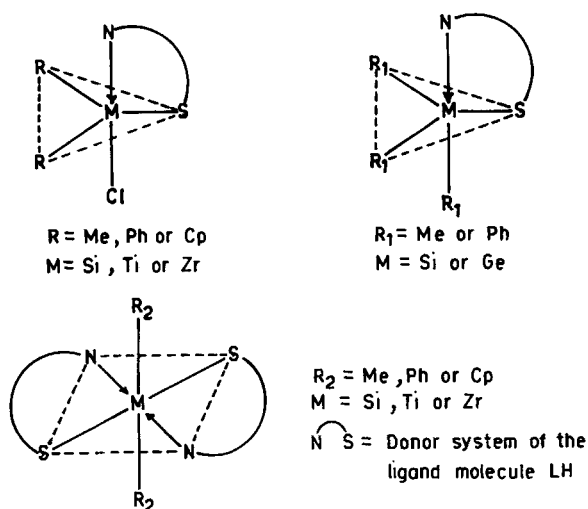


Figure 1

Sulphur atoms are often present in bioactive compounds¹². However, the increased biocidal properties after complexation can also be well explained in the light of the chelation properties. A close morphological relationship between mycobacteria and fungi has been reported by Mayor¹³ and it has been further demonstrated that complexes with antifungal activity also exhibit other types of activity.

Antifertility activity

Antifertility activity of an organic substrate and its corresponding organometallic complexes has been studied (Table 3) in male mice. The reactivity of synthetic products towards biological systems is an important feature of current research and heterocyclic compounds play a significant role in this direction. Present and previously reported results¹¹ indicate that there is a significant decrease ($P < 0.01$) in motility from 81.2 ± 4.6 to 31.7 ± 6.0 in animals treated with the ligand and the sperm count also decreased ($P < 0.001$) from 23.4 ± 2.1 to 10.3 ± 3.3 . A highly significant (a $P < 0.001$) decline in the motility of sperm was observed in the case of the corresponding organometallics. The sperm count was also found to decrease significantly in the treated animals. The data demonstrate that the titanium and zirconium complexes have less activity than silicon and germanium complexes. These results may also be correlated with the fact that certain drugs of the Sulpha type produce infertility in male rats.¹⁴ Thus, it can be postulated that chelation through sulphur atom induces sterilizing activity in the

biological systems. Sulphur-containing compounds with heterocyclic rings are generally more active than oxygen donors.

Characterization of the organometallic compounds

Initially the compounds were characterized on the basis of elemental analysis, molecular-weight determination and conductivity measurement. In addition the IR, UV, ^1H NMR, ^{13}C NMR and ^{29}Si NMR spectral data show that the ligand after coordination through thiolo-sulphur and azomethine-nitrogen atoms, behaves as a monobasic bidentate ligand and accordingly silicon, titanium and zirconium exhibit five- and six-coordination whereas germanium has only five-coordination. Trigonal bipyramidal and octahedral geometries have been proposed for the resulting compounds⁹⁻¹¹ (Fig. 1).

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