LIGATIONAL BEHAVIOUR OF FLUOROIMINES TOWARDS ORGANOBORON(III) AND POTENTIATION OF THEIR MICROBIOCIDAL ACTIVITY

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ABSTRACT

Complexes of fluoroimines (prepared by the condensation of 2-fluorobenzaldehyde and 1-(2-fluorophenyl) ethanone with hydrazinecarboxamide or hydrazinecarbothioamide) with organoboron(III) were synthesized and characterized by elemental analyses, conductivity measurements, molecular weight determinations and spectroscopic techniques. It has been concluded that preferential binding of the chelating ligands is anionic bidentate, coordinating with the central boron atom through oxygen of carbonyl group or sulfur of thionyl group and azomethine nitrogen. The complexes, $PhB(OH)(F^nN^X)$, $PhB(F^nN^X)_2$ and their parent fluoroimines have been screened **in vitro** against a number of microbes and it is seen that the coordination of boron atom had pronounced effect on the microbiocidal activity of the ligands.

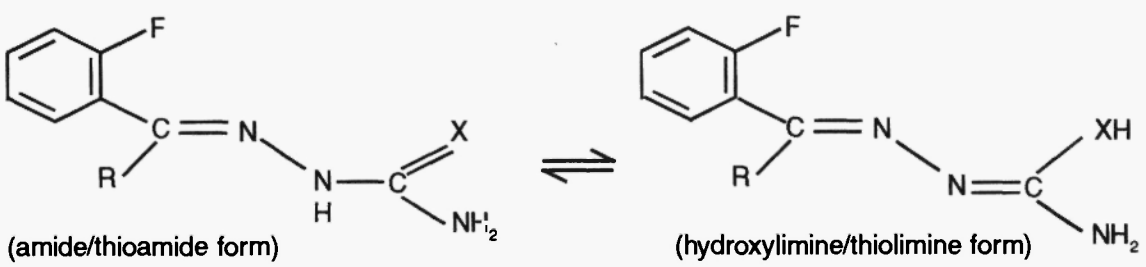
INTRODUCTION

Organoboron compounds occupy a unique place in the development of inorganic chemistry because of the complexity of the structures involved and the subtle types of bonding. Elements in this situation normally adopt metallic bonding, but the small size and high ionization energies of boron dictate covalent rather than metallic bonding. Last decade has seen a wide repertoire of reading material[1-3] dealing with a range of organoboron compounds. The implication of organoboron compounds in cancer treatment was mainly related to their use as neutron capture agents[4,5]. Mixed anhydrides of diarylborinic acids with α- amino acids inhibited HeLa and L-16 cells **in vitro** and Sarcoma 180 and Ehrlich ascites tumour in mice[6,7]. In addition to cancer therapy, some organoboron compounds have also been cross examined for their antifungal, antibacterial and other medicinal uses[8,9]. Organoboranes as insecticides and plant growth regulators have also been mentioned[10].

The biological activity[11,12] and the application of fluoro-organometallic compounds in the pharmaceutical field has also been attested by the available literature[13,14]. It possibly appears that fluorine can alter the activity of molecules or make them specific irreversible enzyme inhibitors[15].

Our interest in the present work is mainly in the synthesis, mode of bonding of functional groups, =Ç-OH, =Ç-SH or >C=N and microbiocidal aspects of organoboron(III) complexes of fluoroimines. The results of these investigations seem to be quite promising.

The fluoroimines used exist in the tautomeric forms[16] in the solution state.



(amide/thioamide form) (hydroxylimine/thiolimine form)

where, ($F^1N\frown OH$), R=H =2-(2-Fluorophenylmethylene)hydrazinecarboxamide
($F^2N\frown SH$), R=H =2-(2-Fluorophenylmethylene)hydrazinecarbothioamide
($F^3N\frown OH$), R=CH_3 =2-[1-(2-Fluorophenyl)ethyledene]hydrazinecarboxamide
($F^4N\frown SH$), R=CH_3 =2-[1-(2-Fluorophenyl)ethyledene]hydrazinecarbothioamide

RESULTS AND DISCUSSION

The phenyldihydroxyborane, $PhB(OH)_2$ reacts with fluoroimines in equimolar and bimolar ratios in dry benzene as shown:

$$PhB(OH)_2+(F^nN\frown XH) \xrightarrow{1:1} PhB(OH)(F^nN\frown X)+H_2O$$
$$PhB(OH)_2+2(F^nN\frown XH) \xrightarrow{1:2} PhB(F^nN\frown X)_2+2H_2O$$

where, $F^nN\frown XH$ represents the fluoroimines, X = O or S and n = 1-4.

These reactions were quite facile and the water formed during the course of reaction was removed as benzene-water azeotrope. The resulting white to light yellow solid products are monomers and thermally stable. Conductivities in dry DMF at 10^{-3}M concentration indicates low molar conductance values (12-15 ohm^{-1} cm^2 mol^{-1}) showing their non-electrolytic nature. The mode of coordination of the fluoroimines to the boron atom has been discussed on the basis of spectroscopic studies.

SPECTROSCOPIC STUDIES

In the electronic spectra of fluoroimines, bands around 265 and 305nm remain almost unchanged in the organoboron(III) complexes and these are assigned to the π–π^* electronic transitions within the benzenoid ring[17] and azomethine grouping[18]. However, a band around 370 nm due to n-π^* transitions within the azomethine group in fluoroimines undergoes hypsochromic shift of 15-20nm, due to the polarisation within the >C=N chromophore caused by the boron-fluoroimine electron interaction i.e., due to the donation of the lone pair of electrons by the nitrogen of the fluoro ligand to the central boron atom. The assignments of characteristic IR frequencies for fluoroimines and their organoboron(III) complexes authenticate the proposed coordination. The absorption at ca. 1610cm^{-1} characteristic of the azomethine (>C=N) group[19] in the spectra of fluoroimines, got split into two sharp bands at ~1620 cm^{-1} and 1605cm^{-1} in 1:2 complexes. This splitting of the bands suggests that the azomethine groups are in different chemical environment. The shifting of band at 1620cm^{-1} (higher wavenumber side) unequivocally suggests the coordination of the azomethine nitrogen to the boron atom, whereas the band at 1605cm^{-1} is assigned to the uncoordinated azomethine group. This C=N frequency suffers a positive shift in 1:1 complexes implying its coordination (N→B). A broad weak band observed in the region 3280-3100cm^{-1} in the spectra of fluoroimines due to ν(NH)/(OH) vibrations disappears in the organoboron(III) complexes providing the evidence of deprotonation due to complexation. Two sharp bands at ca.3360 and 3420cm^{-1} due to $\nu_s(NH_2)$ and $\nu_{as}(NH_2)$ modes in the fluoroimines remain unperturbed on complexation indicating their non-involvement in coordination[20]. The additional bands between 1555-1525cm^{-1}, 1350-1335cm^{-1}, 870-845cm^{-1} and 1250-1240cm^{-1} are assigned to ν(B←N)[21], ν(B-O)[22], ν(B-S)[23], and ν(Ph-B)[24], vibrations, respectively.

The ^{1}H chemical shifts of fluoroimines, ($F^{1-4}N\frown XH$) and their 1:1 and 1:2 organoboron(III) complexes recorded in DMSO-d_6 are enlisted in Table 1.

The disappearance of the NH proton signals of the fluoroimines in the case of organoboron(III) derivatives indicates the removal of a proton from the NH group and coordination of nitrogen with simultaneous covalent bond formation by sulfur or oxygen with boron. The azomethine proton and azomethine methyl protons undergo deshielding in the organoboron(III) complexes, supporting the

donation of a lone pair of electrons by nitrogen to the boron atom. The presence of new signals due to (Ph-B) in the spectra of complexes are an additional informative data in support to the given tentative structures.

Table 1 : ^{1}H NMR Spectral data (δ, ppm) of ($F^{1\text{-}4}N\frown XH$) and their 1:1 and 1:2 organoboron(III) complexes.

Compound	-NH (bs)	-NH_2 (bs)	H-C=N (s)	-CH_3 (s)	Aromatic (m)	-OH (s)	C_6H_5-B (m)
($F^1N\frown OH$)	11.67	2.35	8.42	-	7.68-6.65	-	-
PhB(OH)($F^1N\frown O$)	-	2.36	8.64	-	7.72-6.86	4.12	6.66-6.42
PhB($F^1N\frown O)_2$	-	2.40	8.68	-	7.80-6.92	-	6.58-6.26
($F^2N\frown SH$)	11.24	2.16	8.33	-	7.78-6.70	-	-
PhB(OH)($F^2N\frown S$)	-	2.18	8.56	-	7.96-6.92	4.10	6.62-6.28
PhB($F^2N\frown S)_2$	-	2.14	8.64	-	8.04-6.94	-	6.64-6.40
($F^3N\frown OH$)	9.30	3.08	-	1.88	7.52-6.16	-	-
PhB(OH)($F^3N\frown O$)	-	3.10	-	2.12	7.68-6.28	4.18	6.26-6.14
PhB($F^3N\frown O)_2$	-	3.08	-	2.16	7.66-6.32	-	6.30-6.22
($F^4N\frown SH$)	10.24	3.16	-	2.12	8.28-6.92	-	-
PhB(OH)($F^4N\frown S$)	-	3.12	-	2.40	8.38-7.08	4.16	6.54-6.22
PhB($F^4N\frown S)_2$	-	3.18	-	2.32	8.36-7.10	-	6.44-6.20

bs = broad singlet, s = singlet, m = complex pattern

The ^{11}B nuclear resonance is observed in the region between δ6.52-10.68ppm, which suggests a tetracoordinated[25] environment around the boron atom and the presence of a (B←N) coordinate bond (Table 2). The driving force for the formation of this coordinate bond is the ability of $PhB(OH)_2$ to accept a share of electrons from a suitable donor atom (nitrogen in the present case) and complete its octet. This confirms the conclusions drawn on the basis of the UV, IR, ^{1}H and ^{13}C NMR spectra, regarding the coordination of azomethine nitrogen to the boron atom.

Table 2 : ^{11}B NMR Spectral data [a](δ, ppm) of organoboron(III) complexes of fluoroimines.

1:1	PhB(OH)($F^1N\frown O$)	PhB(OH)($F^2N\frown S$)	PhB(OH)($F^3N\frown O$)	PhB(OH)($F^4N\frown S$)
1:2	PhB($F^1N\frown O)_2$	PhB($F^2N\frown S)_2$	PhB($F^3N\frown O)_2$	PhB($F^4N\frown S)_2$
1:1	6.50	7.42	6.52	8.44
1:2	8.94	7.58	9.36	10.68

a = singlet

The ^{13}C NMR spectra of fluoroimines and their 1:1 and 1:2 organoboron(III) complexes are reported in Table 3. The noticeable shift in the positions of carbon resonances attached with N and O/S in the complexes suggest the bonding of ligands through azomethine nitrogen and amido oxygen/ thiolic sulfur.

Table 3 : ^{13}C NMR Spectral data (δ, ppm) of ($F^{1-4}N^{\frown}$)(H) and their 1:1 and 1:2 organoboron(III) complexes.

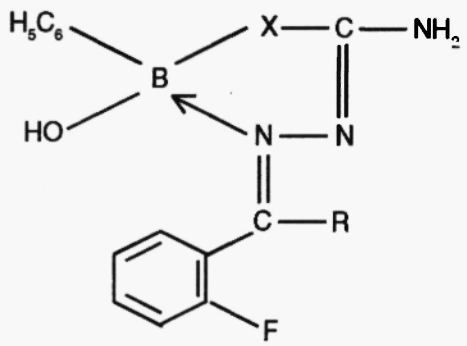
Compound	Chemical shift values				
	C-O/C-S	>C=N	$-CH_3$	Aromatic	Phenyl-B (C_i,C_o,C_m,C_p)
($F^1N^{\frown}OH$)	175.20	160.24	-	144.18,129.30,128.21, 128.85,127.58,125.35	-
PhB(OH)($F^1N^{\frown}O$)	171.48	156.21	-	144.26,129.38,129.02, 128.88,128.52,125.84	134.81,132.12, 128.84,130.62
PhB($F^1N^{\frown}O$)$_2$	172.49	154.66	-	144.12,129.66,128.92, 128.84,127.94,125.43	135.44,132.68, 129.42,131.74
($F^2N^{\frown}SH$)	179.52	157.38	-	143.66,127.85,126.54, 123.34,122.17,120.33	-
PhB(OH)($F^2N^{\frown}S$)	172.86	151.43	-	143.72,127.88,126.54, 123.46,122.29,120.42	134.68,131.94, 128.29,130.44
PhB($F^2N^{\frown}S$)$_2$	174.39	152.91	-	144.68,127.92,126.63, 123.54,122.19,120.41	135.56,132.10, 128.64,130.58
($F^3N^{\frown}OH$)	164.58	156.51	15.88	141.29,129.64,129.10, 126.72,123.52,123.41	-
PhB(OH)($F^3N^{\frown}O$)	159.59	149.28	16.02	141.51,129.68,129.28, 126.71,123.49,123.48	134.54,132.16, 128.68,130.62
PhB($F^3N^{\frown}O$)$_2$	161.27	148.67	16.00	141.32,129.59,129.20, 126.74,123.50,123.44	133.92,131.48, 128.04,130.88
($F^4N^{\frown}SH$)	178.45	147.52	17.34	131.59,129.91,126.50, 124.55,116.69,115.72	-
PhB(OH)($F^4N^{\frown}S$)	170.67	140.24	17.20	131.62,129.88,126.63, 124.71,116.72,115.68	134.72,132.64, 128.65,130.56
PhB($F^4N^{\frown}S$)$_2$	171.55	142.39	17.39	131.61,129.99,126.58, 124.65,116.72,115.77	134.88,132.68, 128.94,130.24

The ^{19}F NMR spectra of the complexes along with their imines are listed in Table 4. The complexes display signals in a close range when compared with their imines suggesting that fluorine does not participate in coordination.

Table 4 : ^{19}F NMR Spectral data *(δ, ppm) of fluoroimines and their organoboron(III) complexes.

Fluoroimine	($F^1N^{\frown}OH$)	($F^2N^{\frown}SH$)	($F^3N^{\frown}OH$)	($F^4N^{\frown}SH$)
1:1	PhB(OH)($F^1N^{\frown}O$)	PhB(OH)($F^2N^{\frown}S$)	PhB(OH)($F^3N^{\frown}O$)	PhB(OH)($F^4N^{\frown}S$)
1:2	PhB($F^1N^{\frown}O$)$_2$	PhB($F^2N^{\frown}S$)$_2$	PhB($F^3N^{\frown}O$)$_2$	PhB($F^4N^{\frown}S$)$_2$
Fluoroimine	- 120.98	- 122.34	- 108.36	- 109.00
1:1	- 120.64	- 122.68	- 109.14	- 110.10
1:2	- 122.44	- 122.94	- 108.11	- 109.22

Thus, on the basis of the above spectral features, as well as analytical data, suitable tetracoordinated environment around boron has been suggested for 1:1 and 1:2 organoboron(III) complexes of fluoroimines, respectively.



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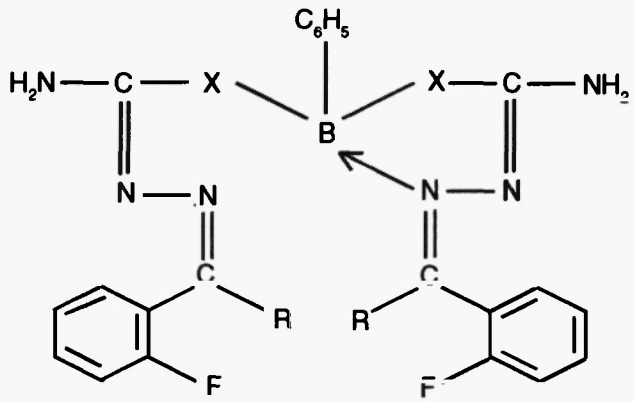

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MICROBIAL ASSAY

Bactericidal and fungicidal activities of fluoroimines and their respective organoboron(III) complexes against pathogenic bacteria and fungi are recorded in Table 5. The toxicity increased as the concentration increased. A perusal of activity data of fluoroimines and their complexes indicated that sulfur containing fluoroimines as well as their complexes were more potent than their oxygen containing counterparts. The results of biocidal activity have been compared with the conventional fungicide, Bavistin and the conventional bactericide, Streptomycin, taken as standards in either case. It is evident that the fluoroimines alone were quite toxic but their activity increased on undergoing complexation. From the table it is clear that some of the newly synthesized complexes killed the fungal pathogens at 100ppm concentration while at 200ppm concentration all the 1:2 complexes killed the pathogens completely. It is apparent from the bactericidal activity that the complexes were more active towards Staphylococcus aureus as compared to Escherichia coli. The reason is the difference in the structures of the cell walls of organisms with (+) and (-) stains, respectively. The walls of Gram (-) cells are more complex than those of Gram (+) cells. The lipopolysaccharide forms an outer lipid membrane and contributes to the complex antigenic specificity of Gram (-) cells.

Table 5 : Microbiocidal screening data of fluoroimines and their organoboron(III) complexes.

Compound	Bactericidal activity Diameter of inhibition zone (mm) conc. in ppm				Fungicidal activity % inhibition after 96 h conc. in ppm					
	(a)		(b)		(c)			(d)		
	500	1000	500	1000	50	100	200	50	100	200
Standard	15	17	17	18	82	100	100	86	100	100
($F^1N\frown OH$)	7	10	4	6	66	74	78	72	80	84
$PhB(OH)(F^1N\frown O)$	11	14	6	9	74	88	96	80	92	100
$PhB(F^1N\frown O)_2$	13	17	8	11	87	95	100	96	100	100
($F^2N\frown SH$)	9	12	5	8	69	78	80	74	80	84
$PhB(OH)(F^2N\frown S)$	12	15	8	11	77	89	100	86	92	100
$PhB(F^2N\frown S)_2$	14	17	11	13	84	98	100	94	100	100
($F^3N\frown OH$)	10	14	5	9	72	81	84	74	79	86
$PhB(OH)(F^3N\frown O)$	11	15	6	10	78	86	96	78	88	92
$PhB(F^3N\frown O)_2$	15	18	7	12	84	100	100	88	100	100
($F^4N\frown SH$)	12	16	7	10	85	88	92	83	88	92
$PhB(OH)(F^4N\frown S)$	15	18	9	12	90	94	100	88	98	100
$PhB(F^4N\frown S)_2$	16	20	10	14	96	100	100	92	100	100

(a) = **Staphylococcus aureus(+)**, (b) = **Escherichia coli(-)** - Bacterial pathogens
(c) = **Macrophomina phaseolina**, (d) = **Fusarium oxysporum** - Fungal pathogens

EXPERIMENTAL

Colours and melting points of fluoroimines are recorded in Table 6. These were prepared by the method reported earlier[26].

Table 6 : Physical properties of fluoroimines

Compound	($F^1N^\frown OH$)	($F^2N^\frown OH$)	($F^3N^\frown OH$)	($F^4N^\frown OH$)
Colour	Off white	White	White	White
M.P.(°C)	217-218	188-190	194-195	121-122

The organoboron(III) complexes were prepared by the reactions of phenyldihydroxyborane with fluoroimines in 1:1 and 1:2 molar ratios in presence of refluxing benzene. The liberated water was removed azeotropically with benzene. The product was purified by crystallizing in a mixture (1:1) of dry methanol and cyclohexane and finally dried under vacuo. Satisfactory elemental analyses have been obtained for the organoboron(III) complexes of fluoroimines (Table 7).

Table 7 : Physical properties of organoboron(III) complexes of fluoroimines.

Compound	1:1 1:2	$PhB(OH)(F^1N^\frown O)$ $PhB(F^1N^\frown O)_2$	$PhB(OH)(F^2N^\frown S)$ $PhB(F^2N^\frown O)_2$	$PhB(OH)(F^3N^\frown S)$ $PhB(F^3N^\frown O)_2$	$PhB(OH)(F^4N^\frown S)$ $PhB(F^4N^\frown O)_2$
Colour	1:1	Off white	Cream	Off white	Cream
	1:2	Light yellow	Light yellow	Off white	Cream
M.P.(°C)	1:1	226-228	185-188 d	184-186	156-157
	1:2	210-211	202-204 d	215-218 d	171-173
Yield	1:1	75	70	82	70
	1:2	86	65	73	72

The analytical procedures and details of physical measurements adopted for the fluoroimines and their respective organoboron(III) complexes are conventional and are reported in our previous publication[26].

The synthesized fluoroimines and their organoboron(III) complexes were tested **in vitro** for growth inhibitory activity against pathogenic fungi, viz., **Macrophomina phaseolina** and **Fusarium oxysporum** at 25±1°C and pathogenic bacteria, viz., Gram positive **Staphylococcus aureus** and Gram negative **Escherichia coli** at 30±1°C. A culture of the test organism was grown on PDA media (starch, glucose, agar-agar and water for fungi) and agar media (peptone, beef extract, agar-agar, NaCl and water for bacteria) for seven days at the optimum temperature for growth. All the glassware used were sterilized in an autoclave before use. The radial growth method and the paper disc-plate method were employed to evaluate the fungicidal and bactericidal activities, respectively[27].

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