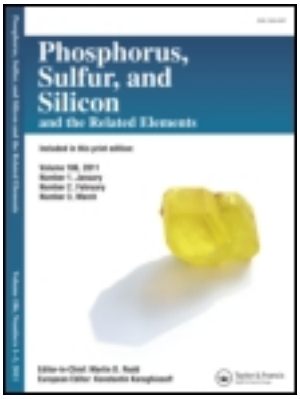


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Important Properties of Sulfur-Bonded Organoboron (III) Complexes with Biologically Potent Ligands

R. V. Singh [a] , Mukesh Kumar Biyala [a] & Nighat Fahmi [a]

[a] Department of Chemistry, University of Rajasthan, Jaipur, India

Published online: 21 Dec 2010.

To cite this article: R. V. Singh , Mukesh Kumar Biyala & Nighat Fahmi (2005) Important Properties of Sulfur-Bonded Organoboron (III) Complexes with Biologically Potent Ligands, Phosphorus, Sulfur, and Silicon and the Related Elements, 180:2, 425-434, DOI: 10.1080/104265090509225

To link to this article: http://dx.doi.org/10.1080/104265090509225

Phosphorus, Sulfur, and Silicon, 180:425–434, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090509225

Taylor & Francis
Taylor & Francis Group

Important Properties of Sulfur–Bonded Organoboron (III) Complexes with Biologically Potent Ligands

R. V. Singh
Mukesh Kumar Biyala
Nighat Fahmi
Department of Chemistry, University of Rajasthan, Jaipur, India

Important properties of sulfur/oxygen and nitrogen bonded organoboron (III) complexes with biologically potent ligands viz., semicarbazone, thiosemicarbazone, and dithiocarbazate having the donor groups ONX and NS have been studied. The unimolar and bimolar reactions of phenylboronic acid with monobasic bidentate and dibasic tridentate ligands result in the formation of colored solids which have been characterized by the elemental analysis, molecular weight determinations, and conductance measurements. The UV, IR, and NMR (^{1}H, ^{13}C, and ^{11}B) spectral studies indicate tetracoordinated geometry for the resulting complexes. Both the ligands and their complexes have been screened for their fungicidal and bactericidal activities, and the results indicate that they exhibit significant antimicrobial properties.

INTRODUCTION

The coordination complexes of the sulfur and nitrogen donor ligands were investigated on their manifestation of novel structural features,[1] unique spectral and catalytic properties[2] relevance to the biological process[3–5] and pest averting properties of sulfur.[6] Tremendous work has been done on non-transition metal complexes for their commercial applications as ceramic precursors, heat stabilizers, disperse dyes , sol-gel process, in polymerization of alkenes, nuclear applications,[7] lubrication technology,[8] carbohydrate research, and in cosmetic preparation due to their film forming properties, substantiality, and hydrophobicity. Boron is an essential element for healthy plants. It is known to be involved in nucleic acid synthesis which is possibly linked to adequate provision of the pyrimidine nucleotides. Boron also plays an

Received May 11, 2004.
Address correspondence to R. V. Singh, Department of Chemistry, University of Rajasthan, Jaipur-302004, India. E-mail: m-elgaby@hotmail.com

important role in the carbohydrate metabolism, hormone action, and membrane formation.[9] The structural study of the mononuclear boron (III) complexes of neobidentate thioimines has also been detected using a wide range of analytical and spectroscopic techniques[10] in our previous work. Boron complexes of semicarbazones, thiosemicarbazones, and S-benzyldithiocarbazate have aroused considerable interest in view of their industrial and biological importance.[11] Many of these compounds possess a wide spectrum of medicinal properties, including activity against tuberculosis,[12] leprosy,[13] and bacterial[14] and viral infections.[15] Their activity is frequently thought to be due to their ability to chelate trace metals.[16] Therefore, an attempt has been made to synthesize and characterize some biologically active organoboron (III) complexes with nitrogen and sulfur/oxygen donor ligands during these investigations. The antibacterial and antifungal activities of the ligands along with their boron derivatives also have been performed using conventional fungicide, Bavistin, and bactericide Streptomycin as the standards for the respective activities.

EXPERIMENTAL

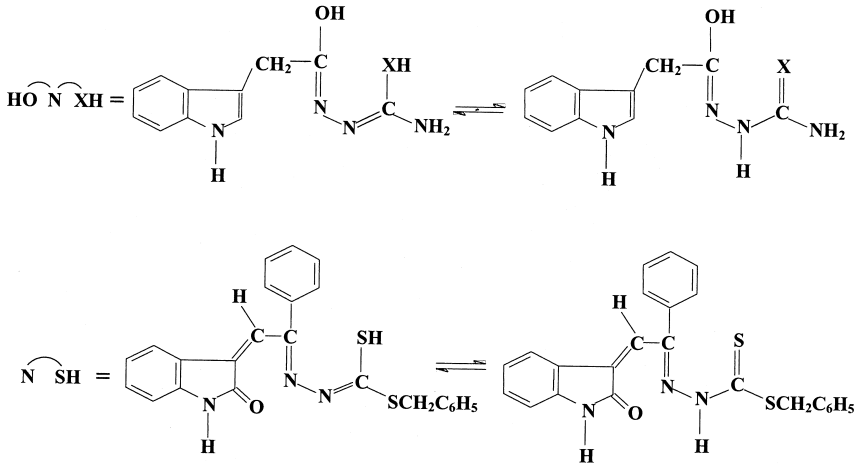
The boron compound, $[(Ph)B(OH)_2]$, isatin, indol-3-acetic acid, and acetophenone were purchased from Sisco, Lancaster, and Lobachemie and as such. All the chemicals and solvents were dried and purified by standard methods. The reactions were carried out under strictly anhydrous conditions.

Preparation of the Ligands

The ligands (L^1H_2) and (L^2H_2) were prepared by the condensation of indol-3-acetic acid with thiosemicarbazide in 1:1 molar ratio and with semicarbazide in presence of sodium acetate in 1:1 molar ratio, respectively. The ligand (L^3H) was prepared by the reaction of isatin with acetophenone in a 1:1 molar ratio, and then the resulted product condensed with S-benzyldithiocarbazate in absolute ethanol in unimolar ratio. This reaction mixture was then refluxed over a water bath for 3–4 h and allowed to stand overnight. The ligands (L^1H_2, L^2H_2, and L^3H) separated out, were purified by recrystallization from the same solvent, and analyzed before use. The parent ligands exist in the tautomeric forms (Figure 1).

Preparation of the Complexes

Phenylboronic acid was dissolved in dry benzene in an 100-mL RB flask and to this the requisite amount (1:2 molar ratio) of the ligands



Here, **X = S or O**

FIGURE 1

were added. The resulting mixture was refluxed for 12–24 hours. The progress of the reaction was monitored by the liberation of water azeotropically. The solid product was dried *in vacuo*. It was then washed several times with dry cyclohexane and again dried *in vacuo* for 3–4 h. The physical properties and analytical data of these complexes are enlisted in Table I.

The purity of the compounds was checked by TLC on silica Gel-G using anhydrous methanol and tetrahydrofuran (1:1) as a solvent. Each of the compound moves as a single spot indicating the presence of only one component, hence their purity. Conductivity measurements were made with a Systronic model 305 conductivity bridge in dry dimethylformamide. Molecular weights were determined by the Rast Camphor method. IR spectra of the solid samples were recorded as KBr discs on a Nicolet Magna FT-IR 550 spectrophotometer. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on a Hitachi Perkin Elmer spectrometer in DMSO-d_6 and THF as a solvent at Delhi University, New Delhi. Nitrogen and sulfur were estimated by the Kjeldahl's and Messanger's methods, respectively. Boron was estimated as boric acid in the presence of mannitol using phenolphthalein as an indicator. Carbon and hydrogen analyses were performed at the CDRI, Lucknow.

TABLE I Analytical Data and Physical Properties of the Ligands and Their Complexes

Compound	Colour	M.pt. (°C)	B	Analysis found (Calcd.) (%) C	H	N	S	Mol. Wt. Found (Calcd.)
L^1H_2	Grey	126	—	53.02 (53.20)	4.24 (4.87)	22.22 (22.56)	12.24 (12.91)	246 (248.30)
L^2H_2	Dark Brown	132	—	56.96 (56.88)	5.46 (5.20)	24.43 (24.12)	—	235 (232.24)
L^3H	Coke	158	—	67.02 (67.10)	4.24 (4.45)	9.64 (9.78)	14.67 (14.92)	428 (429.55)
$C_{17}H_{15}N_4OSB$	Brown	152	3.14 (3.23)	60.84 (61.09)	4.32 (4.52)	16.26 (16.76)	9.32 (9.59)	333 (334.20)
$C_{17}H_{15}N_4O_2B$	Dim Brown	161	3.24 (3.39)	64.02 (64.18)	4.64 (4.75)	17.47 (17.61)	—	317 (318.13)
$C_{30}H_{24}N_3O_2S_2B$	Grey	174	2.59 (2.02)	67.74 (67.54)	4.24 (4.53)	12.32 (12.01)	2.17 (2.02)	535 (533.46)
$C_{54}H_{41}N_6O_2S_4$ B	Dark Brown	192	1.24 (1.14)	68.99 (68.63)	4.22 (4.36)	8.99 (8.89)	13.92 (13.57)	946 (944.95)

RESULTS AND DISCUSSION

The reactions of phenylboronic acid with dibasic tridentate, thiosemicarbazone, semicarbazone and monobasic bidentate, and S-benzyldithiocarbazate in different molar ratios yielded products according to the general Eq. (1)–(3).

$$[(Ph)B(OH)_2] + HONXH \xrightarrow{1:1} [(Ph)B(ONX)] + 2H_2O \quad (1)$$

$$[(Ph)B(OH)_2] + NSH \xrightarrow{1:1} [(Ph)B(OH)(NS)] + H_2O \quad (2)$$

$$[(Ph)B(OH)_2] + 2NSH \xrightarrow{1:1} [(Ph)B(NS)_2] + 2H_2O \quad (3)$$

(Where, ONX and NS are the donor systems of the ligands and X = S or O).

These reactions are quite facile and could be completed within 12–24 h of refluxing in benzene. The resulting products are colored solids and insoluble in common organic solvents but soluble in DMSO, THF, and DMF. Boron complexes are quite stable. The molecular weight determinations indicate their monomeric nature. The low molar conductance values (8–12 ohm^{-1} cm^2 mol^{-1}) of these derivatives in DMF at 10^{-3} M concentrations show them to be nonelectrolytes.

Electronic Spectra

The electronic spectra of the ligands L^1H_2, L^2H_2, L^3H, and their boron complexes were recorded in DMF. The bands at *ca* 264 nm and 328 nm in the case of free moieties were assigned to π-π^* electronic transitions within the benzene ring. These bands remain almost unchanged in the spectra of the complexes. Another band observed at *ca* 370 nm in the spectra of the moieties is due to the n-π^* transitions of the azomethine (>C=N) group. However, in the spectra of the compounds this band appears in the region 359–334 nm due to the polarization within the >C=N chromophore resulting after chelation.

Infrared Spectra

The IR spectra of the free ligands and their complexes were scanned in the form of KBr pellets. IR spectra of the free ligands show a medium intensity band at 3395–3100 cm^{-1} due to υNH/υOH vibrations, which are absent in the spectra of the complexes. The bands due to υ(C=O) and υ(C=S) modes in the spectra of the ligands are observed at 1690–1710 cm^{-1} and 1030–1040 cm^{-1}, respectively.[17] These bands disappeared in the spectra of the organoboron compounds, suggesting the enolization and thioenolization of the ligands and their chelation through the amido oxygen and thiolic sulfur, respectively. This fact gets support by the observation of the bands due to υ(C–O) and υ(C–S) modes at lower frequencies in the spectra of the boron compounds. The absorption at *ca* 1615 cm^{-1} characteristic of the azomethine (>C=N)[18] group in the spectra of the ligands, gets split into two sharp bands at *ca* 1610 cm^{-1} and 1630 cm^{-1} in 1:2 complexes. This splitting of bands suggests that the azomethine group is in different chemical environments. The shifting of bands at *ca* 1630 cm^{-1} (higher wave number side) suggest the coordination of the azomethine nitrogen to the boron atom, whereas the band at *ca* 1610 cm^{-1} is assigned to the uncoordinated azomethine group. The υOH band in case of 1:1 boron complexes appears at *ca* 3450 cm^{-1}. There are no changes in the υ_{sym} and υ_{asym} modes of the NH_2 group[19] appearing at *ca* 3360 and 3460 cm^{-1}, respectively, indicating the noninvolvement of this amino group in chelation.

The coordination through the azomethine nitrogen atom and the enolic oxygen/thiolo sulfur is further substantiated by the appearance of new bands in the region of 1350–1360 cm^{-1}, 830–870 cm^{-1}, 1520–1540 cm^{-1}, and 1230–1250 cm^{-1} in the boron complexes due to υ(B-O), υ(B-S),[20] υ(B← N)[21] and υ(Ph-B)[22] frequencies, respectively.

^{1}H NMR Spectra

The ^{1}H NMR spectra of the ligands and their complexes have been recorded in DMSO–d_6-using TMS as an internal standard. The ^{1}H NMR spectra of the free ligands show signals due to $^-$NH of the indol ring at δ 11.92–11.96 ppm and $^-$NH of the remaining ligand unit disappears indicating deprotonation and a simultaneous covalent bond formation between enolic oxygen and thiolo sulfur and the boron atom. The NH_2 proton signal remains almost unchanged, which shows the noninvolvement of this group in the complexation. The phenyl protons are observed at $\sim\delta$ 6.70–8.24 ppm in the boron complexes, which were absent in the spectra of the ligands. The resonance due to the SCH_2 and aromatic protons in the complexes appears in almost the same positions as in the respective free ligands. The $^-$OH proton signal of the ligands, L^1H_2 and L^2H_2, were observed at δ 4.94 and δ 4.92 ppm, respectively. The $^-$OH proton signal in 1:1 complex is observed at δ 4.20 ppm. Chemical shift values of all the complexes are listed in Table II.

^{13}C NMR Spectra

The ^{13}C NMR spectral data also support the authenticity of the proposed structures. The considerable shifts in the positions of carbon atoms adjacent to the azomethine nitrogen (δ 158.26–162.72 ppm), thiolic sulfur/enolic oxygen (δ 164.34–176.84 ppm) support the proposed coordination in the complexes. Thus the shifts in the position of carbon atoms adjacent to the coordinating atoms clearly indicate the bonding of the azomethine nitrogen and amido oxygen to the boron atom.

^{11}B NMR Spectra

The ^{11}B NMR spectra of the boron complexes have signals in DMSO-d_6 at δ 2.0–5.0 ppm, which unequivocally suggests a tetracoordinated

TABLE II ^{1}H NMR Spectral Data (δ ppm) of the Ligands and Their Complexes

Compound	—NH_2	—NH(1)	—NH(2)	—SCH_2	—OH	Aromatic protons
L^1H_2	3.40	11.26	11.94	—	4.94	6.81–8.24
L^2H_2	3.42	11.28	11.92	—	4.92	6.72–8.18
L^3H	—	11.24	11.96	4.56	—	6.79–8.24
$C_{17}H_{15}N_4$ OSB	3.42	—	11.92	—	—	6.76–8.20
$C_{17}H_{15}N_4O_2B$	3.44	—	11.96	—	—	6.70–8.22
$C_{30}H_{24}N_3O_2S_2B$	—	—	11.94	4.78	4.20	6.74–8.26
$C_{54}H_{41}N_6O_2S_4B$	—	—	11.93	4.82	-	6.70–8.24

environment around the boron atom and the presence of a B←N coordinate bond.[23,24] The driving force for the formation of this coordinate bond is the ability of trivalent $PhB(OH)_2$ to accept a pair of electrons from a suitable donor atom.

MICROBIAL ASSAY

Antimicrobial Screening

The synthesized ligandss and their complexes were tested for the *in vitro* growth inhibitory activity against pathogenic fungi, *Alternaria cymopsidis* and *Macrophomina phaseolina* and bacteria *Escherichia coli* (−) and *Staphylococcus aureus* (+). The proper temperature, necessary nutrients and growth media were employed for the preparation of cultures of the fungi and bacteria using aseptic technique.[25]

Antifungal Screening

The antifungal activity of the boron (III) complexes has been evaluated against *Alternaria cymopsidis* and *Macrophomina phaseolina*. The Radial Growth Method[26] using Czapek's agar medium having the composition glucose 20 g, starch 20 g, agar–agar-20 g and distilled water 1000 mL was employed to measure fungicidal activity. The compounds were mixed directly with the medium in different concentrations. Spores of the fungi were placed on the medium with the help of an inoculum needle. The petri dishes were wrapped in polythene bags containing a few drops of alcohol and were placed in an incubator at $30 \pm 1^{\circ}C$. Controls were also run and three replicates were used in each case. The linear growth of the fungus was obtained by measuring the fungal colony diameter after 4 days. The amount of growth inhibition in each of the replicates was calculated by the equation $(C\text{-}T)\ 100\ C^{-1}$, where C is the diameter of the fungal colony on the control plate and T is the diameter of the fungal colony on the test plate.

Antibacterial Screening

Antibacterial activity was evaluated by the Paper Disc Plate method.[27] For this purpose, pure cultures of the organisms were dissolved in peptone-water (1:1) and then uniformly seeded on the nutrient agar plates having the composition peptone 5 g, beaf extract 5 g, NaCl 5 g, agar-agar 20 g, and distilled water 1000 mL. The compounds were dissolved in 500- and 1000-ppm concentrations. Paper discs of Whatman No. 1 with a diameter of 5 mm were soaked in different solutions of

the compounds. These discs were placed on the medium previously seeded with the organisms in the petri dishes at suitable distances. The petri dishes were stored in an incubator at $30 \pm 2^{\circ}C$ for 24 h. The zone of inhibition thus formed around each disc containing the test compound was measured accurately in mm. The organisms used in the present investigations included *Escherichia coli* (−) and *Staphylococcus aureus* (+).

Mode of Action

The ligands and their corresponding boron complexes were screened against the selected pathogenic fungi and bacteria to examine their growth-inhibiting potential towards the test organism. The results show that these compounds exhibit antimicrobial properties. Boron complexes show more inhibitory effects than the parent ligands (Tables III and IV). The ligand with sulfur and nitrogen donor system might have inhibited enzyme productions since enzymes, which require reactive groups for their activity, appear to be especially susceptible to deactivation by the complexes. The complexes facilitate their diffusion through the lipid layer of the spore membrane to the site of action, ultimately killing them by combining with the reactive groups of certain cell enzymes. The results show that the activity is enhanced by undergoing chelation.[28] It is a well known fact that the concentration plays a vital role in increasing the degree of inhibition. As the concentration increases, the activity increases. The fungicidal activity was better when compared to the bactericidal activity. It is interesting to

TABLE III Fungicidal Screening Data of the Ligands and Their Complexes (Average % Inhibition after 96 h, Concentration in ppm)

	Alternaria cymopsidis		*Macrophomina phaseolina*	
Compound	100 ppm	200 ppm	100 ppm	200 ppm
L^1H_2	38	51	37	52
L^2H_2	32	48	33	47
L^3H	49	59	48	57
$C_{17}H_{15}N_4OSB$	44	54	42	55
$C_{17}H_{15}N_4O_2B$	40	52	41	53
$C_{30}H_{24}N_3O_2S_2B$	52	63	51	62
$C_{54}H_{41}N_6O_2S_4B$	56	67	55	68
Bavistin	86	100	82	100

TABLE IV Antibacterial Activity of the Ligands and Their Complexes (Diameter of Inhibition Zone after 30 h, Concentration in ppm)

	Escherichia coli (−)		*Staphylococcus aureus* (+)	
Compound	500 ppm	1000 ppm	500 ppm	1000 ppm
L^1H_2	7	9	7	10
L^2H_2	9	7	6	9
L^3H	9	12	10	13
$C_{17}H_{15}N_4OSB$	10	13	11	12
$C_{17}H_{15}N_4O_2B$	8	11	9	11
$C_{30}H_{24}N_3O_2S_2B$	12	14	13	15
$C_{54}H_{41}N_6O_2S_4B$	11	15	14	16
Streptomycin	17	18	15	17

note that the synthesized boron complexes with thiosemicarbazone and S-benzyldithiocarbazate have more activity than the semicarbazone. This may be due to the presence of the sulfur atoms in such ligands.

REFERENCES

[1] C. Saxena and R. V. Singh, *Phosphorous, Sulfur and Silicon*, **97,** 17 (1994).

[2] K. R. Adam, M. Antolovich, D. S. Baldwin, L. G. Brigden, P. A. Duckworth, L. F. Lindoy, A. Bashall, M. McPartlin, and P. A. Tasker, *J. Chem. Soc. Dalton Trans*., 1869 (1992).

[3] E. Kimura, S. Wada, M. Shionoya, and Y. Okazai, *Inorg. Chem.*, **33,** 770 (1994).

[4] A. M. Sh. El-Sharief, J. A. A. Micky, N. A. M. M. Shmeiss, and G. El-Ghareib, *Phosphorous, Sulfur and Silicon*, **178,** 439 (2003).

[5] Anna S. A. Zidan, *Phosphorous, Sulfur and Silicon*, **178,** 567 (2003).

[6] C. W. Johnson, J. W. Joyner, and R. P. Perry, *Antibiotics and Chemotherapy*, **2,** 636 (1952).

[7] S. A. Khan, J. H. Morris, M. Harman, and M. B. Hurshouse, *J. Chem. Soc. Dalton Trans.*, 119 (1992).

[8] M. Yanaggida, S. Tonerikawa, and S. Kawai, *Jpn. Kokkoi Tokkyo Koho Jpn.*, **61,** 157, 695 (1987).

[9] A. G. Massey, In *Main Group Chemistry* (Ellis Horwood Limited, West Sussex, England), 1st Ed. p. 487.

[10] R. V. Singh, N. Gupta, S. Saxena, and C. Saxena, *Appl. Organomet. Chem.*, **13,** 175 (1999).

[11] V. P. Singh, S. V. Singh, R. V. Singh, and J. P. Tandon, *Synth. React. Inorg. Met.-Org. Chem.*, **18,** 779 (1988).

[12] D. Domagh, R. Behmisch, F. Mietzch and H. Schmidt, *Naturwissenschaften*, **33,** 315 (1946).

[13] A. Lewis and R. G. Shephard, *Medical Chemistry*, A. Burger (Ed.), (Wiley, New York, 1970).

[14] P. Malatesta, G. P. Accinelli, and G. Quagliana, *Ann. Chem*., **49,** 397 (1959).

[15] R. L. Thomson, S. A. Minton Jr., E. Officer, and G. H. Hitchings, *J. Immunol.*, **70,** 229 (1953).
[16] S. Laly and G. Parameswaran, *Asian J. Chem.*, **5,** 712 (1993).
[17] S. Kato, A. Hori, H. Shiotone, and M. Mizuta, *J. Organomet. Chem.*, **82,** 223 (1973).
[18] G. C. Percy and D. A. Thornton, *J. Inorg. Nucl. Chem.*, **34,** 3369 (1972).
[19] D. Singh and R. V. Singh, *Main Group Met. Chem.*, **13,** 309 (1990).
[20] L. Bhal, R. V. Singh, and J. P. Tandon, *Acta Chim. Hung.*, **115,** 281 (1984).
[21] L. Bhal and J. P. Tandon, *Indian J. Chem.*, **24A,** 562 (1985).
[22] C. Saxena and R. V. Singh, *Indian J. Chem.*, **32A,** 154 (1993).
[23] Yu. N. Babnov, E. E. Demina, and A. V. Ignatenko, *Russ. Chem. Bull*, **46,** 1306 (1997).
[24] K. Dey, M. K. Das, and R. K. Bansal, *J. Organomet. Chem.*, **7,** 535 (1997).
[25] E. R. Rawlins Renelina, *Bentrays Text Book of Pharmaceuticals* 8th ed., (Boilliers Tindall, London, 1997).
[26] A. Kumari, J. P. Tandon, and R. V. Singh, *Appl. Organomet. Chem.*, **7,** 655 (1993).
[27] N. Fahmi and R. V. Singh, *Transition Met. Chem.*, **19,** 12 (1994).
[28] N. Fahmi, J. J. Gupta, and R. V. Singh, *Phosphorous, Sulfur and Silicon*, **132,** 1 (1997).