NEW N-PROTECTED AMINO ACID BOROACETATES, VERSATILE PRECURSORS FOR THE PREPARATION OF 1,3,2-BENZODIHETEROBOROLE AND -BORIN DERIVATIVES: STRUCTURAL CONSIDERATIONS BASED UPON SPECTRAL (^1H, ^{13}C AND ^{11}B NMR) STUDIES

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Abstract

Some new N-protected aminoacid derivatives of boron of composition $(OAc)_2B[OOC.CH(R).\overline{N.C(O).C_6H_4.C}(O)]$ (where R=-H,$-CH_3$,$-CH(CH_3)_2$, $-CH_2C_6H_5$, $-CH_2CH_2SCH_3$) have been prepared by the direct reaction of boric acid with ligand in 1:1 molar ratio in excess of acetic anhydride. These derivatives on treatment with o-dihydroxybenzene, *o*-hydroxybenzyl alcohol and *o*-aminothiophenol afford 1,3,2-benzodiheteroborole and -borin derivatives possessing B-O, B-N and B-S bonds evincing the reactivity of acetate groups. These derivatives have been characterised by elemental analyses, molecular weight measurements, IR and multinuclei (^1H, ^{13}C & ^{11}B) nmr spectral data. The ^{11}B nmr reveals the presence of four coordinate boron atoms in these derivatives except 1,3,2-benzodiheteroborole derivatives in which tricoordinate boron atoms are present.

Introduction

There has been a resurge of interest in the chemistry of aminoacid derivatives of boron[1] containing intramolecular B←N bond due to their stereochemical considerations, possibility of affording stable heterocycles and as these find applications in boron neutron therapy for the treatment of brain tumors[2].

In marked contrast to the well studied chemistry of N-protected aminoacid complexes of group 4[3-7] and 14[8] metals, little is known on analogous derivatives of group 13[9] elements. Although bis (acetoxy) boron derivatives of ß-diketones[10], heterocyclic ß-diketones[11] and schiff bases[12] have been reported, almost no attempt has been made to prepare similar derivatives of boron with N-protected aminoacids. As an extension of our studies with this class of ligand and to study the reactivity of acetoxy group which is known to be limited[12], we now report the preparation, spectral elucidation and further reactivity of boron acetate derivatives of some N-protected aminoacids leading to the formation of 1,3,2-benzodiheteroborole and -borin derivatives in the present communication.

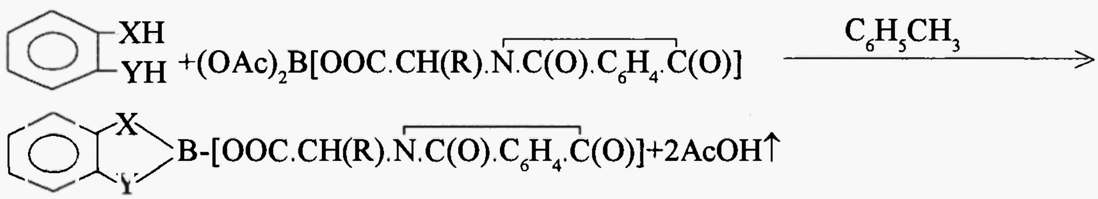
Results and Discussion

Boron N-protected aminoacid derivatives of the type $(OAc)_2B[OOC.CH(R).N.C(O).C_6H_4.C(O)]$ have been synthesised by the interaction of boric acid with N-protected aminoacids in equimolar ratio in acetic anhydride medium.

$$B(OH)_3 + HOOC.CH(R).N.C(O).C_6H_4.C(O) \xrightarrow{Ac_2O} (OAc)_2B[OOC.CH(R).N.C(O).C_6H_4.C(O)] + AcOH$$

where R=-H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2C_6H_5$, $-CH_2CH_2SCH_3$

It is interesting to study the reactivity of acetate groups present in these compounds and in order to observe it, the reactions of the derivatives were carried out with *o*-dihydroxybenzene, *o*-hydroxybenzyl alcohol and *o*-aminothiophenol in 1:1 molar ratio in dry toluene to afford 1,3,2-benzodiheteroborole and borin derivatives possessing B-O, B-N and B-S bonds.



where X=O; Y=O, R= $-CH_3$, $-CH_2C_6H_5$

X=O; Y= $-CH_2O-$, R= $-CH_2C_6H_5$

X=NH; Y=S, R=$-CH(CH_3)_2$, $-CH_2C_6H_5$

The acetic acid liberated in these reactions was fractionated off azeotropically with toluene.

These compounds are brown solids and possess sharp melting points. They are soluble in chloroform, benzene, tetrahydrofuran but insoluble in hexane and pet.ether. They were purified by repeated crystallization from chloroform -pet.ether mixture.The osmometric molecular weight measurement in chloroform solution at 45°C indicates the monomeric nature of all the derivatives.

The 1,3,2-benzodioxaborole derivatives could not be synthesised by the direct reaction of 2-isopropoxy-1,3,2-benzodioxaborole and the ligand in 1:1 molar ratio in refluxing benzene. However, they were successfully prepared by the indirect route through boron acetates.

Spectral Data and Structure

The newly prepared boron derivatives were subjected to IR and NMR (^{1}H, ^{13}C and ^{11}B) spectral studies and the information inferred from these studies has been used in structural elucidation and suggesting the nature of bonding.

IR Spectra

The IR spectra of some of the representative boron derivatives were recorded in the region 4000-200 cm^{-1} as KBr pellets. A comparison of the IR spectra of $(OAc)_2BL$ derivatives with the parent ligands furnished the following salient informations:-

1. The disappearance of the broad carboxylic -OH absorption band (observed at 3300-2800 cm^{-1} in the ligands) and appearance of strong absorption bands at 1380±20cm^{-1} and 1040 cm^{-1} in the boron derivatives indicate the formation of B-O[13] bonds.
2. A new medium intensity band present at 700 cm^{-1} is attributed to B←O[14] dative bond.
3. A lower shift of ~90 cm^{-1} (1740-1720 cm^{-1} in ligands to 1670-1630 cm^{-1} in the derivatives) in $\nu(COO)_{asymm}$ further supports the bidentate nature of carboxylic group.
4. A strong band at 1720 cm^{-1} is consistent with unidentate nature of the acetate[13] groups.
5. The medium intensity bands observed at 3300,1430 and 920 cm^{-1} in the spectra of 1,3,2-benzazathiaborole derivative may be assigned to NH ,B-N[15] and B-S[16] bonds, respectively.

NMR

The ^{1}H nmr spectra of boron derivatives were recorded in $CDCl_3$ using TMS as an internal standard and are summarized in table 1. The carboxylic protons observed in the region δ 8.85-10.12 ppm in the ligands[4,9] disappeared in the spectra of $(OAc)_2BL$ derivatives suggesting the bonding to boron through this group. A significant downfield shift of δ 3.46-8.34 ppm (Table 2) in the carboxylic carbon signal of $(OAc)_2BL$ derivatives as compared to ligands reveals the intramolecular coordination through >C=O group of carboxylic group and hence, bidentate nature of the ligand. The available spectral evidences do not support the coordination from the imide nitrogen due to its poor nucleophilic nature. Moreover, the presence of an electron withdrawing group and bulky substituents at the nitrogen will disfavour the formation of strong B-N bond. The spectral evidences and monomeric nature of these compounds suggest the following plausible structure (Fig.1) for these derivatives.

TABLE 1: ^{1}H and ^{11}B NMR data of boron derivatives of 1,3-dihydro-1,3-dioxo-α-(substituted)-2H-isoindole-2-acetic acids. ($^3J_{HCCH}$ = coupling constants)

S.No	Derivatives	C_6H_4/C_6H_5	CH	$CH_{2(ligand)}$ $-CH_2O-$	$CH_{3(ligand)}$	$CH_{3(acetato)}$	NH	^{11}B
1.	$(OAc)_2B(L_1)$	7.50-7.91m	-	5.45s, 5.53s	-	2.14s	-	+3.22
2.	$(OAc)_2B(L_2)$	7.64-7.92m	5.00q (7.7Hz)	-	1.65d (7.9Hz)	2.03s	-	+4.24
3.	$(OAc)_2B(L_3)$	7.68-8.04m	4.60d (8.0Hz) 2.72st	-	0.84d (8.0Hz) 1.07d (8.0Hz)	2.05s	-	+3.39
4.	$(OAc)_2B(L_4)$	7.48-7.83m 7.12*bs	5.14t (8.0Hz)	3.56d (7.9Hz)	-	2.24s	-	+4.41
5.	$(OAc)_2B(L_5)$	7.61-7.96m	5.19t (8.3Hz)	2.50**bs	2.06s	2.15s	-	+5.94
6.	o-$(OC_6H_4O)B(L_2)$	7.48-7.87m 6.68-6.99bs	4.92q (7.6Hz)	- -	1.62d (7.7Hz)	-	-	+24.11
7.	o-$(OC_6H_4O)B(L_4)$	7.52-7.83m 6.68-7.04bs	5.19t (8.2Hz)	3.52d (8.0Hz)	-	-	-	+24.79
8.	o-$(OC_6H_4CH_2O)B(L_4)$	7.55-7.95m 7.06-7.42bs	5.23t (8.2Hz)	6.12bs 3.53d (8.0Hz)	-	-	-	+10.19
9.	o-$(SC_6H_4NH)B(L_3)$	7.55-8.04m 6.51-7.46m	4.58d (7.8Hz) 2.73***bs	-	0.80d (7.3Hz) 1.12d (7.3Hz)	-	4.10bs	+19.36
10.	o-$(SC_6H_4NH)B(L_4)$	7.50-7.95m 6.43-7.28m	5.09t (8.0Hz)	3.48d (8.0Hz)	-	-	3.97bs	-

LH = $\overline{C(O)C_6H_4C(O)}NCH(R)COOH$ R = -H = L_1H, R = $-CH_3$ = L_2H, R = $-CH(CH_3)_2$ = L_3H, R = $-CH_2C_6H_5$ = L_4H, R = $-CH_2CH_2SCH_3$ = L_5H

* Unresolved complex pattern. ** both CH_2 mixed together to give unresolved broad singlet. *** unresolved broad singlet.

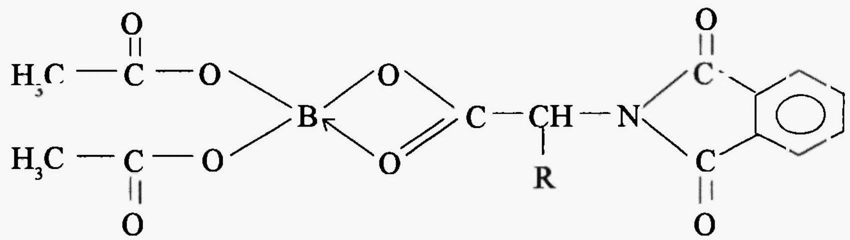
s = singlet, d = doublet, t = triplet, q = quartet, st = septet, bs = broad singlet, m = complex pattern

[^{1}H nmr of ligands[4,9]]

Table 2 : ^{13}C NMR data of boron derivatives of 1,3-dihydro-1,3-dioxo-α- (substituted)-2H-isoindole-2-acetic acids.

S.No.	Derivatives	COO	CO	C_6H_4*/C_6H_5*	CH	CH_2	$CH_{3(acetato)}$	$CH_{3(ligand)}$
1.	$(OAc)_2B(L_1)$	174.72	167.34	131.97,123.57,134.19	-	38.75	21.18	-
2.	$(OAc)_2B(L_2)$	178.33	167.12	131.04,123.41,134.00	47.51	-	21.72	14.90
3.	$(OAc)_2B(L_3)$	178.83	167.61	131.53,123.46,134.13	57.69 28.38	-	21.56	20.80 19.34
4.	$(OAc)_2B(L_4)$	182.40	167.29	131.42,123.46,133.81 128.66,126.55,128.28,136.79	54.01	34.29	22.15	-
5.	$(OAc)_2B(L_5)$	181.77	167.34	131.37,123.24,134.02	50.92	30.50(-C) 27.46(-S)	21.61	14.90
6.	*o*-$(OC_6H_4O)B(L_2)$	175.03	167.61	131.53,123.57,134.29 121.35,110.47,140.12	47.24	-	-	14.95
7.	*o*-$(OC_6H_4O)B(L_4)$	174.22	167.50	131.21,123.51,134.13 128.66,126.82,128.50,136.25 121.73,111.08,143.75	52.98	34.24	-	-
8.	*o*-$(SC_6H_4NH)B(L_3)$	173.98	167.31	131.84,123.43,134.10 125.42,122.60,121.41,140.45 121.44,116.84	57.08 28.41	-	-	20.18 18.88

* Values are given in the order of ipso (i), ortho (o), meta (m) & para (p) carbons, resectively
[^{13}C nmr of ligands [4,9]]



where R=-H,-CH_3, -$CH(CH_3)_2$, -$CH_2C_6H_5$, -$CH_2CH_2SCH_3$

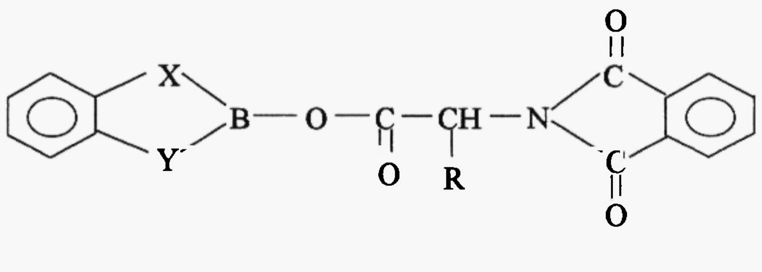
Fig. 1

The tetrahedral[17] environment of boron nucleus in these compounds is further corroborated by their ^{11}B nmr chemical shifts which lie in the region δ 3.22-5.94 ppm.

The aromatic protons of the compounds $(OAc)_2B(L_1)$, $(OAc)_2B(L_2)$, $(OAc)_2B(L_3)$ & $(OAc)_2B(L_5)$ may be described as AA'BB' system. In case of bisacetatoboron (N-phthaloyl glycine) derivative, a splitted signal of -CH_2- proton at δ 5.45 and 5.53 ppm indicates the presence of non-equivalent methylene protons. The most plausible explanation for the non-equivalence of >N-CH_2- protons may be the restricted rotamers[18] of C_α-N and C_α-CO single bonds which enhances dissymmetry in the molecule and hence, non-equivalence. The phenomenon of restricted rotation is relevant in boron derivatives due to the presence of bulky acetate groups.

The splitting of the protons of methyl groups of isopropyl moiety into two doublets in the compound $(OAc)_2B(L_3)$ reveals the diastereotopic nature of the -CH_3 groups. This fact may be explained on the basis of low symmetry of valine[19] or the ramified structure of the isopropyl group. As a result of this, the two methyls are projected in space towards different atoms and hence, experience different environments. The non-equivalence of the methyl carbons is further supported by the appearance of two signals for methyl carbons in the ^{13}C nmr spectra of the compounds $(OAc)_2B(L_3)$ and $(o\text{-}SC_6H_4NH)B(L_3)$. The resonance at δ 2.72 ppm due to >CH- of isopropyl group in the compound, $(OAc)_2B(L_3)$, has been observed as septet at 90MHz. Further resolution is only possible with the help of high resolution nmr. On the other hand, the doublet due to the protons of benzyl group in the compound, $(OAc)_2B(L_4)$, is not further splitting due to its non-ramified nature. The ^{13}C nmr data is consistent with this observation.

The newly synthesised N-protected aminoacid boroacetates were found to be versatile precursors for the preparation of 1,3,2-benzodiheteroborole and -borin derivatives. The formation of these derivatives is supported by the fact that acetoxy protons centered at δ 2.03 to 2.24 ppm in bisacetatoboron derivatives disappear in these derivatives. The carboxylic group behaves as unidentate in 1,3,2-benzodiheteroborole derivatives which is supported by IR spectra exhibiting absorption band around 1740 cm^{-1}. The unidentate nature of ligand is further corroborated by ^{13}C nmr which exhibits no significant downfield shift of the carboxylic carbon signal (Table 2). On the basis of above discussion, the following structure (Fig.II) in which boron is tricoordinate, may be proposed for borole derivatives.



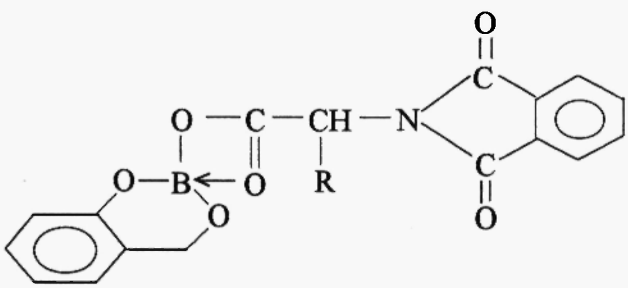
X=O;Y=O,R=$-CH_3$,$-CH_2C_6H_5$

X=NH;Y=S,R=$-CH(CH_3)_2$,$-CH_2C_6H_5$

Fig. II

The structure having tricoordinate[17] boron centre is supported by ^{11}B nmr chemical shifts which is observed in the region δ 19.3-24.7 ppm.

In marked contrast to borole derivatives, the 4H-1,3,2-bernzodioxaborin derivative was found to possess tetracoordinated boron centre which is corroborated by ^{11}B nmr chemical shift (δ 10.19 ppm recorded for a representative compound (o-$OC_6H_4CH_2O$)$B(L_4)$. On the basis of monomeric nature and spectral evidences, the following structure may be suggested.



R=$-CH_2C_6H_5$

Fig. III

It is pertinent to note that ligand is behaving as unidentate in borole and as bidentate in borin derivative. As a consequence of this, boron is tricoordinate in borole and tetracoordinate in borin derivative. A glance at the ^{11}B nmr chemical shift of borole and borin derivatives reveals that boron atom is more shielded in borin derivative (δ 10.19 ppm) than borole derivatives (δ 19.3 to 24.79 ppm). The point of difference between borole and borin derivatives regarding structural feature appears to be the methylene group which is present in borin derivative.

Experimental

The experimental work was carried out under strictly anhydrous conditions. The solvents were dried prior to use. The ligands[20] were synthesised as reported earlier. Boric acid was used as supplied. Acetic anhydride (138°C) and o-aminothiophenol (72°C/0.2mm) were distilled before use. *o*-dihydroxybenzene was sublimed under reduced pressure. Boron[21],nitrogen[22] and acetate[22] groups were estimated by literature methods.

^{1}H,^{13}C and ^{11}B nmr spectra were recorded on a Jeol FX 90Q (90MHz) spectrometer in $CDCl_3/CHCl_3$ solution. ^{11}B nmr spectra were recorded with reference to $BF_3.(C_2H_5)_2O$ and ^{1}H and ^{13}C nmr spectra with respect to TMS as an internal standard. IR spectra were recorded on a Carlzeiss Jena M-80 specord as KBr pellets. Molecular weights were determined on Knauer vapour pressure osmometer in $CHCl_3$ solution at 45°C.

Synthesis of Compounds

The N-protected aminoacid derivatives of boron were prepared by general procedures and for sake of brevity, the experimental details of one representative compound of each type are given below and the results of the rest are summarized in Table 3.

Synthesis of $(OAc)_2B[OOC.CH\{CH(CH_3)_2\}.\overline{N.C(O).C_6H_4.C}(O)]$

Boric acid (0.45 g,7.28 mmol) was dissolved in 20 ml of acetic anhydride by gentle heating. The resulting solution was cooled and then a weighed amount of N-protected amino acid (1.80g,7.28 mmol) was added to it. The reaction contents were subsequently refluxed for ~3 hours. During this period, the colour of the solution gradually turned red from yellow. Excess of acetic anhydride was removed under reduced pressure to leave a brown foamy solid which was recrystallized from chloroform/pet.ether mixture.
(Found:B:2.79;Calcd:B:2.88;Found OAc:31.10;Calcd:OAc:31.47)

Synthesis of 2-(1,3-didydro-1,3-dioxo-α-(benzyl)-2H-isoindole-2-acetato)benzo-1,3,2-dioxaborole

To a solution of *o*-dihydroxybenzene (0.29 g,2.63 mmol) in dry toluene, a weighed amount of bisacetatoboron(L_4) (1.11 g,2.62 mmol) in dry toluene was added and the reaction contents were refluxed for a period of 8-10 hours. The liberated acetic acid was fractionated

Table 3: **Synthetic and analytical data of boron derivatives of 1,3-dihydro-1,3-dioxo-α- (substituted) -2H-isoindole-2-acetic acids.**

S.No.	Reactants(gms) H_3BO_3	Reactants(gms) LH= $\overline{C(O)C_6H_4C(O)N}CH(R)COOH$	Product % Yield	m.p. °C	Molecular Wt. Found (Calc.)
1.	0.51	R=H 1.70	$(OAc)_2BL_1$ 75	184	328 (333.0)
2.	0.28	$R=CH_3$ 1.00	$(OAc)_2BL_2$ 78	125	338 (347.0)
3.	0.45	$R=CH(CH_3)_2$ 1.80	$(OAc)_2BL_3$ 71	138	376 (375.1)
4.	0.35	$R=CH_2C_6H_5$ 1.67	$(OAc)_2BL_4$ 79	120	425 (423.1)
5.	0.30	$R=CH_2CH_2SCH_3$ 1.38	$(OAc)_2BL_5$ 74	158	404 (407.1)

S.No	Reactants (gms) $(OAc)_2BL$	Reactants (gms) HYC_6H_4XH	Product % Yield	m.p. °C	Molecular Wt. Found (Calc.)
6.	$R=CH_3$ 0.57	X=O,Y=O 0.18	o-$(OC_6H_4O)BL_2$ 72	146	324 (337.0)
7.	$R=CH_2C_6H_5$ 1.11	X=O,Y=O 0.29	o-$(OC_6H_4O)BL_4$ 74	138	410 (413.1)
8.	$R=CH_2C_6H_5$ 0.50	$X=O,Y=CH_2O$ 0.14	o-$(OC_6H_4CH_2O)BL_4$ 82	176	420 (427.1)
9.	$R=CH(CH_3)_2$ 0.80	X=NH,Y=S 0.26	o-$(SC_6H_4NH)BL_3$ 84	154	374 (380.1)
10.	$R=CH_2C_6H_5$ 0.68	X=NH,Y=S 0.20	o-$(SC_6H_4NH)BL_4$ 84	144	421 (428.1)

Statisfactory elemental analyses were obtained for all compounds.
Compounds 1-5 were recrystallized from chloroform-pet.ether.
Compounds 6-10 were recrystallized from benzene-pet.ether.

off azeotropically with toluene and estimated at different time intervals by titrating it against 0.1N NaOH to ensure the completion of the reaction. The excess of solvent was distilled off and the product was finally dried in vacuo and recrystallized from benzene/pet.ether mixture.

(Found :B:2.55;Calcd:B:2.61).

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