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Note

Synthesis and properties of bis(amine)carboxyhydroboron(1+) cations

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Abstract

Carboxy-*O*-methyl, carboxylic and carboxylate groups containing bis(amine)hydroboron(1+) cations, including the boron analogue of tetramethyl-proline, have been synthesized and characterized. The latter is the first representative of those boron compounds which are truly isosteric to the α-amino acids.

Keywords: Boron complexes; Carboxylate complexes; Amine complexes

Amine-carboxyboranes are considered as boron analogues of the α-amino acids since they can be formally derived by a C^+–B exchange. These compounds themselves as well as their ester, amide, thioamide and other derivatives [1–3] have been thoroughly investigated in the last 15 years. They showed significant antitumor, antineoplastic, antiinflammatory, antiarthritic, analgesic and hypolipidemic activity in rodents and their applicability in BNCT (boron neutron capture therapy) has been studied as well [4].

In this paper we present the syntheses of the $[LL'BH(COOR)]^+$ cations (where L, L' = amine; R = H, Me) and the first members of the carboxylate group containing boron zwitterions, $[LL'B^+H(COO^-)]$. In contrast to the neutral amine-carboxyborane derivatives synthesized previously, these new molecules might show novel biological activities modulating the cell membrane processes based on their positive electrical charges.

According to our studies symmetrical boronium salts of the $[L_2BH(COOMe)]Br$ type can be prepared in the reaction of $Me_3N \cdot BH(Br)COOMe$ [5] with large excesses of tertiary amines or pyridine bases (Eq. (1)).

$$Me_3N \cdot BH(Br)COOCH_3 + 2L \xrightarrow[\text{reflux}]{\text{L or } CH_3CN} [L_2BH(COOCH_3)]\,Br + Me_3N \quad (1)$$

L = 1-methyl-pyrrolidine, 1-Me-Pyr; quinuclidine (1-aza-bicyclo-[2.2.2]-octane), Q; pyridine, Py; 4-methylpyridine, Pic; 4-dimethyl-aminopyridine, DMAP
2L = *N*,*N*',*N*'',*N*'''-tetramethylethylenediamine, TMEDA

Formation of boronium salts has not been observed, however, in the reaction of $Me_3N \cdot BH(Br)COOMe$ with primary or secondary amines, instead, decomposition of the complex took place through evolution of H_2 and CO. Tertiary amines gave reactions only in cases when the steric demand of the amine was not too high, or, as with TMEDA, the formation of a product containing a five-membered chelate ring was energetically preferred. Exchange of Me_3N was not complete with 1-Me-Pyr and Q and the symmetrical boronium salts could not be separated from $[L(Me_3N)BH(COOMe)]Br$. In all other cases hexafluorophosphate salts of the boron(1+) cations were precipitated in pure form by treating aqueous solutions of the corresponding boronium bromides with KPF_6. The physical data of these salts are summarized in Table 1.

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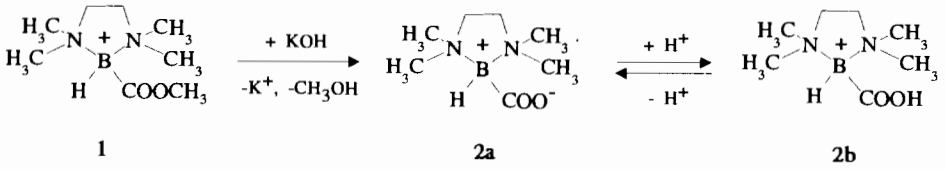
Table 1
Selected data for bis(amine)carboxyhydroboron(1+) compounds

Compound	Yield (%)	Boron (%)		^{1}H NMR (200 MHz)[c] δ (ppm)	^{11}B NMR (64 MHz)[c]		ν(CO) (KBr) (cm^{-1})	ν(BH) (KBr) (cm^{-1})
		found	calc.		δ (ppm)	J(BH) (Hz)		
$[Py_2BH(COOMe)]PF_6$	66	2.82	2.89	3.66 sg ($O\text{-}CH_3$); 8.12 t, 8.61 t, 9.07 d (C-H)	5.33 d	104.1	1686	2536
$[Pic_2BH(COOMe)]PF_6$	40[a] 83[b]	2.65	2.69	2.65 sg ($C\text{-}CH_3$); 3.70 sg (OCH_3); 7.87 d, 8.76 d (C-H)	4.95 d	112.7	1700	2462
$[(DMAP)_2BH(COOMe)]PF_6$	72	2.29	2.35	3.24 sg ($N\text{-}CH_3$); 3.54 sg (OCH_3); 6.94 d, 8.19 d (C-H)	3.47 d	100.0	1636	2424
$[Pic(Py)BH(COOMe)]PF_6$	77	2.81	2.79	2.65 sg ($C\text{-}CH_3$); 3.71 sg (OCH_3); 7.87 d, 8.06 t, 8.56 t, 8.77 d, 8.94 d (C-H)	5.20 d	114.8	1690	2472
$[(TMEDA)BH(COOMe)]PF_6$	77	3.24	3.26	3.18 d ($N\text{-}CH_3$); 3.68 sg (OCH_3); 3.86 m ($N\text{-}CH_2$)	6.43 d	114.8	1698	2516
$[(TMEDA)BH(COOH)]PF_6 \cdot KPF_6$ (4/1)	59	2.96	2.97	3.18 d ($N\text{-}CH_3$); 3.85 m ($N\text{-}CH_2$)	1.23 d	121.7[d]	1664	2466
[(TMEDA)BH(COO)]	67	6.34	6.28	2.98 d ($N\text{-}CH_3$); 3.55 m ($N\text{-}CH_2$)[e]	4.01 d	104.6[e]	1684(as) 1652(s)	2430

[a]On the basis of Eq. (1).
[b]On the basis of Eq. (2).
[c]In acetone-d_6.
[d]In CD_3CN.
[e]In D_2O.



1 2a 2b

Scheme 1.

Asymmetrical boronium salts with a chiral boron atom were prepared from Pic·BH_2COOMe (Pic = 4-methylpyridine) with amine perbromides (Eq. (2)).

$$\text{Pic}\cdot BH_2COOCH_3 + L\cdot Br_2 + L \xrightarrow[25\ ^\circ C]{CH_2Cl_2} [\text{Pic(L)BH(COOCH}_3)]Br + L\cdot HBr \quad (2)$$

L = Pic, Py, DMAP

With the strongly basic DMAP a base exchange side reaction takes place and the product is contaminated with [(DMAP)$_2$BH(COOMe)]Br. In other cases the products were isolated, as previously, in pure form as hexafluorophosphate salts, their characteristic data being shown in Table 1.

In all cationic boron compounds formed in reaction (1) or (2) the ester group hydrolyzed readily in diluted KOH solution. The zwitterionic crude products were isolated with ethanolic extractions and purified by re-precipitation from methylene chloride solutions with ether. Acidifying of the zwitterionic products resulted in a carboxylic group containing cations that could be separated as hexafluorophosphate salts. A selected example of these transformations with the TMEDA compounds is presented in Scheme 1.

In correspondence with the cationic structure, the ^{11}B NMR resonances (Table 1) are shifted downfield and the ν(CO) peaks moved to higher wavenumber regions with respect to the corresponding neutral amine-carboxyboranes. The doublet structure of the ^{11}B NMR resonance proves that only one hydrogen atom is attached to the boron. The ^{1}H NMR spectrum of the TMEDA derivatives containing five-membered rings show doublet and multiplet patterns for the N–CH_3 and N–CH_2 hydrogens, respectively.

The hydrolytic stabilities of most of the new compounds are similar to those of amine-carboxyboranes [6]; they are stable in basic and neutral solutions, but decompose in acids under evolution of H_2 and CO. In contrast, the hexafluorophosphate salt of the TMEDA derivative is so stable that it can be recrystallized from hot water without considerable decomposition.

These compounds cannot be brought into isoelectric relation with the α-amino acids by C^+–B replacement as mentioned above. On the other hand, since **2a** can be derived from tetramethyl-proline by an isosteric C–C → B–N exchange, **2b** is isosteric to the tetramethyl-prolinium ion according to Langmuir's terminology [7]. According to our knowledge this molecule is the first representative of boron compounds isosteric to the α-amino acids. The isosteric analogues will probably show much closer similarity than the analogues resulting from a C^+–B exchange. This is confirmed by the fact that both cationic and bipolar forms exist for the isosteric boron compounds (Scheme 1). The expectation is further supported by those potentiometric titration data giving log $K = 5.59$ ($I = 0.2$ M, KCl, 25 °C) for the carboxylic group of the TMEDA derivative. This value is only 3.5 units higher than the log K value of the carboxylic group in proline [8] in contrast to the neutral amine-carboxyboranes, which show approximately 6.5 units elevated log K values [9]. This indicates clearly that R_2N–BH groups are stronger electron donors than the R_2C–CH moiety.

All data suggest that the isosteric boron analogues may show closer similarities to the α-amino acids in biological activity than the known amine-carboxyboranes.

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