Inorganica Chimica Acta, 57 (1982) 227–228

Basicity and Metal Ion Binding Capability of Amine-Carboxyboranes, $R_3N \cdot BH_2COOH$, Boron Analogs of Glycine and N-Methylated Glycines

KURT H. SCHELLER, R. BRUCE MARTIN

Chemistry Department, University of Virginia, Charlottesville, Va. 22901, U.S.A.

BERNARD F. SPIELVOGEL and ANDREW T. McPHAIL

Paul M. Gross Chemical Laboratory, Duke University, Durham, N.C. 27706, U.S.A.

Received May 13, 1981

Ionization of the carboxylic acid proton from net zero charged amine-carboxyboranes, where amine = NH_3, CH_3NH_2, $(CH_3)_2NH$, and $(CH_3)_3N$, occurs with pK_a values of 8.33, 8.23, 8.14, and 8.38, respectively, at 0.5 M ionic strength and 21 °C. There is no evidence for amine nitrogen deprotonation in the first three compounds at pH < 11. In contrast to glycine and its mono- and di-N-methylated derivatives, the boron analogs do not chelate Zn^{2+} or Cu^{2+}. Up to pH 11, both metal ions coordinate to the four amine-carboxyboranes only through the carboxylate group. For the binding of Zn^{2+}, the respective stability constant logarithms are: 2.47, 2.43, 2.32, and 2.67.

Introduction

The isoelectronic and isosteric boron analogs of the amino acid glycine and its N-methylated derivatives, $R_3N \cdot BH_2COOH$ (R = H, CH_3) exhibit antitumor and hypolipidemic activities in mice [1–4]. Glycine, along with other amino acids, strongly chelates metal ions in neutral solutions [5]. We here report on the basicity and Zn^{2+} binding capability of the boron analog of glycine and each of its successively N-methylated derivatives, to yield finally the analog of betaine. This research represents the first quantitative evaluation of the basicity and metal ion binding capability of amine-carboxyboranes, boron analogs of the amino acids.

Experimental

The amine-carboxyboranes were synthesized as described elsewhere [1, 2]. The appropriate amount of compound was weighed directly for each titration. Potentiometric titration curves were obtained on a Radiometer RTS 822 recording titration system at ligand concentrations of 6 and 12 m*M* at 0.5 *M* ionic strength controlled with KNO_3 and at 21 °C. Both pK_a and logK values were evaluated by a non-linear least-squares fitting program. Titrations were performed at relatively high speed owing to a tendency for the compounds to undergo hydrolysis as evidenced by formation of gas bubbles [2]. Reacidification and retitration of a solution required somewhat more base than the original titration. The tendency for hydrolysis decreases as the number of methyl groups increases. For stability constant determination, a ten-fold excess of Zn^{2+} was used and points considered up to pH 6.8.

Results and Discussion

Table I lists acidity constants for carboxylic acid deprotonation as pK_a, and stability constants for Zn^{2+} binding as logK for the boron analog of glycine and its N-methylated derivatives. With an average $pK_a = 8.3$, the carboxylic acid group in these amine-carboxyboranes may be the weakest known simple carboxylic acid of net zero charge. That the pK_a is about 6 log units more basic than the carboxylic acid in the corresponding glycines (for glycine, $pK_1 = 2.4$ [6]), is due in large part to replacement of the methylene group by a BH_2^- group of one less positive nuclear charge. Malone and Parry [7] found a similar change of 6 log units in pK_a on comparing $[H_3BCOOH]^-$ with H_3CCOOH. The trend of pK_a values in Table I upon successive N-methylation parallels those of methylated glycines, except that the pK_a of glycine betaine is the lowest of the four [5]. There is no evidence for amine nitrogen deprotonation at pH < 11 in the first three compounds listed in

TABLE I. Amine-carboxyboranes, pK_a and logK (Zn^{2+}) for $R \cdot BH_2COOH$[a].

Amine, R	pK_a[b]	logK[c]
NH_3	8.33	2.47
$(CH_3)NH_2$	8.23	2.43
$(CH_3)_2NH$	8.14	2.32
$(CH_3)_3N$	8.38	2.67

[a] I = 0.5 *M*, 21 °C. [b] ±0.02. [c] ±0.05.

Table I. In glycine, the ammonium group deprotonation occurs with $pK_2 = 9.7$ [5].

Stability constants for Zn^{2+} binding to the amine-carboxyboranes, tabulated in Table I as logK, follow the order of increasing basicity (pK_a). Efforts were made to detect chelation of $CH_3NH_2 \cdot BH_2COOH$ to Zn^{2+} and Cu^{2+} by release of an amine proton, but no additional proton release was detected up to pH 11. Thus, Zn^{2+} and Cu^{2+} are unable to displace an amine proton at pH < 11, and the compounds coordinate as simple carboxylates. These results stand in marked contrast to glycinate ligand, which chelates strongly to both metal ions in neutral solutions [5].

As expected from their appreciably greater basicity ($pK_a \sim 8.3$), the amine-carboxyboranes bind Zn^{2+} more strongly than does acetate, for which $pK_a = 4.7$ and logK = 1.0. For a logK *versus* pK_a plot of acetate and the four compounds in Table I, the slope is 0.42, a typical value. This result supports the conclusion that the ligands bind to Zn^{2+} as simple carboxylates and not as chelates. The logK values reported in Table I are comparable to that of Zn^{2+} with NH_3, which is slightly more basic ($pK_a = 9.3$), but which contains a different donor group.

In summary, replacement of the methylene group in glycine and N-methylated glycines by a negative BH_2^- group increases the basicity of the carboxylate by 6 log units. The amine group basicity is increased beyond the range of determination by potentiometry in aqueous solution ($pK_a > 11$). The boron analogs listed in Table I do not chelate with Zn^{2+} or Cu^{2+}. Stability constants for Zn^{2+} binding are compatible with the amine-carboxyboranes coordinating only as simple carboxylates.

Acknowledgements

This research was supported at the University of Virginia by a grant from the National Science Foundation (to R.B.M.) and at Duke University by a grant from the Army Research Office.

References

1 B. F. Spielvogel, L. Wojnowich, M. K. Das, A. T. McPhail, and K. D. Hargrave, *J. Am. Chem. Soc., 98*, 5702 (1976).
2 B. F. Spielvogel, M. K. Das, A. T. McPhail, K. D. Onan, and I. H. Hall, *J. Am. Chem. Soc., 102*, 6343 (1980).
3 I. H. Hall, C. O. Starnes, B. F. Spielvogel, P. Wisian-Neilson, M. K. Das, and L. Wojnowich, *J. Pharm. Sci., 68*, 685 (1979).
4 I. H. Hall, M. K. Das, F. Harchelroad, Jr., P. Wisian-Neilson, A. T. McPhail, and B. F. Spielvogel, *J. Pharm. Sci., 70*, 339 (1981).
5 R. B. Martin, *Met. Ions Biol. Systems, 9*, 1 (1979).
6 J. T. Edward, P. G. Farrell, J.-C. Halle, J. Kirchnerova, R. Schaal, and F. Terrier, *J. Org. Chem., 44*, 615 (1979).
7 L. J. Malone and R. W. Parry, *Inorg. Chem., 6*, 817 (1967).