COMMUNICATION

Synthesis of the first amine–cyanocarboxyboranes, isoelectronic analogues of α-cyanocarboxylic acids

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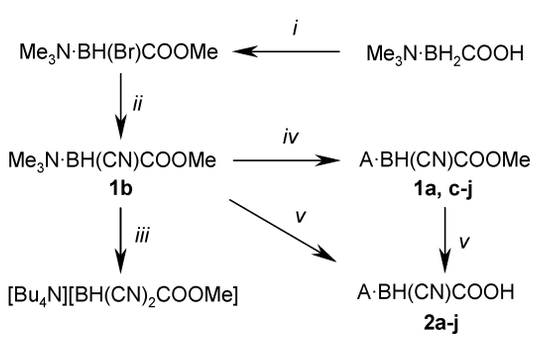
The first amine–cyanocarboxyboranes and their esters are synthesized from trimethylamine–bromo(methoxycarbonyl)boranes with tetrabutylammonium cyanide, followed by amine exchange reactions and acidic hydrolysis; pK_a values of "boracyanocarboxylic acids" are determined and their stability in acidic medium examined.

Amine–cyanoboranes (A·BH_2CN) and amine–carboxyboranes (A·BH_2COOH) have been known for more than two decades. The biological and pharmaceutical activities of these compounds and ester, amide, peptide and transition metal complex derivatives of the acids have been extensively investigated. These efforts revealed anticancer,[1–3] antiosteoporotic,[4] anti-inflammatory[5,6] and hypolipidemic[6,7] properties and their mode of action has also been studied.[2,8] These molecules have also been mentioned as possible boron carriers to tumor cells[9] for boron neutron capture therapy.

Because of these biological properties we have recently prepared several amine–dicarboxyboranes and their ester and amide derivatives.[10] Here we report the synthesis of the first amine–cyanocarboxyboranes, carrying biologically active A·B(H)CN and A·B(H)COOH moieties in the same molecule. A large number of attempts, based on earlier examples for attaching a cyano and/or carboxy group to the boron in amine–boranes failed.[11] Finally, the synthetic sequence outlined in Scheme 1, employing activation and then nucleophilic substitution on the boron, resulted in the preparation of several new amine–cyano(methoxycarbonyl)boranes **1a**–**j** and amine–cyanocarboxyboranes **2a**–**j**. †



Scheme 1 Schematic representation of the synthesis of compounds **1a**–**2j**. *Reagents and conditions*: *i* *N*-bromosuccinimide, methanol, room temp., 30 min; *ii* 1.1 mol equiv. $[Bu_4N]CN$, acetonitrile, room temp., 25 h; *iii* 2 mol equiv. $[Bu_4N]CN$, acetonitrile, reflux, 20 h; *iv* 3 mol equiv. A, acetonitrile, reflux, 2–12 h, yields 48–79%; *v* 0.45 mol equiv. HCl in 0.05–0.2 M HCl in water or water–acetone mixture, 55–95 °C, 0.5–2.5 h, yields 27–86%. (A = morpholine (**a**); Me_3N (**b**); quinuclidine (**c**); Et_2NH (**d**); piperidine (**e**); pyridine (**f**); picoline (**g**); 1-methylimidazole (**h**); 4-aminopyridine (**i**); 4-dimethylaminopyridine (**j**)).

In the first step trimethylamine–carboxyborane was brominated and simultaneously esterified using *N*-bromosuccinimide in methanol, analogously to a known method applied to diamine carboxyboranes.[12] Then the bromide was substituted by cyanide on the boron using $[Bu_4N]CN$ in acetonitrile. The reaction, under optimized conditions, furnished **1b** in good yields, however, even the purified product contained 2–3% starting material, 3–4% Me_3N·BH(NC)COOMe isomer as identified by IR and quantitative ^{13}C NMR spectroscopy, besides 1–2% $[Bu_4N][BH(CN)_2COOMe]$. **1b** can be readily transformed into a number of amine–cyano(methoxycarbonyl)boranes **1a**,**c**–**j** by amine exchange reactions. Fortunately, the amount of the contaminants decreases in these reactions to 1–3% in general and below the limit of NMR detection in the case of **1c**, due to its poor solubility in water.

Amine exchange reactions were performed in refluxing acetonitrile, except for **1d**, where the solvent was the reaction partner Et_2NH. The liberated trimethylamine was purged from the reaction atmosphere by a slow N_2 stream into a bubble counter filled with a known amount of aq. HCl, so as to make it possible to monitor the reaction. After completion of the base exchange, the reaction mixtures were evaporated to dryness and the products were generally extracted into ether from the evaporation residue. **1d** is a colourless oil, the other compounds are white, crystalline solids. The anisotropy of the *N*-ethyl protons in **1d** indicates that the configuration of the stereogenic centre on the boron atom is unchanged on the NMR time scale. ‡

Simultaneously with ester hydrolysis, decomposition takes place accompanied by H_2 formation to various extents depending on the amine. The products **2a**–**j**§,¶ were found to be considerably more stable, showing hardly any decomposition under the applied conditions, so the end or considerable decrease of the effervescence indicated completion of the ester hydrolysis. The products crystallized on evaporation of the reaction mixtures at 0–5 °C (Scheme 1).

Since the preparation of their first representative, amine–carboxyboranes have been generally considered to be the boron analogues of the protonated amino acids, based on the isoelectronic relationship between C–N^+ and B–N bonds. On the other hand, as we recently pointed out,[12] the B–N ↔ C–C rather than B ↔ C^+ isoelectronic analogy makes it more appropriate to regard amine–carboxyboranes as boron analogs of aliphatic carboxylic acids rather than α-amino acids. This view is supported by experimental data. Potentiometric studies revealed that amine–carboxyboranes are very weak acids (pK_a = 8.14–8.62, 12 compounds, A = NH_3, RNH_2, R_2NH).[13] This fact suggests that the R_3N–B group has a marked electron-donating effect towards its substituents. pK_a values of **2a**–**j** were determined by pH potentiometry in order to explore the electron effect of the amines and the cyano group on the carboxylic group. In addition, semiquantitative data were collected by ^1H and ^{11}B NMR spectroscopy for the half-lives of the hydrolysis reactions proceeding in 0.5 M D_2SO_4–D_2O solutions at 100 °C (Fig. 1).

A comparison of the acidity of A·BH_2COOH, the carboxylic acids and their corresponding alpha-cyano derivatives revealed that cyano substitution on both the boron and the carbon atom gives the same 2–2.5 units drop of the pK_a values and the type of amine only has a small impact on the magnitude (Fig. 1). A plot of pK_as *versus* pK_bs of the amines[14] shows a nearly linear correlation for all compounds except **2h**. It clearly indicates

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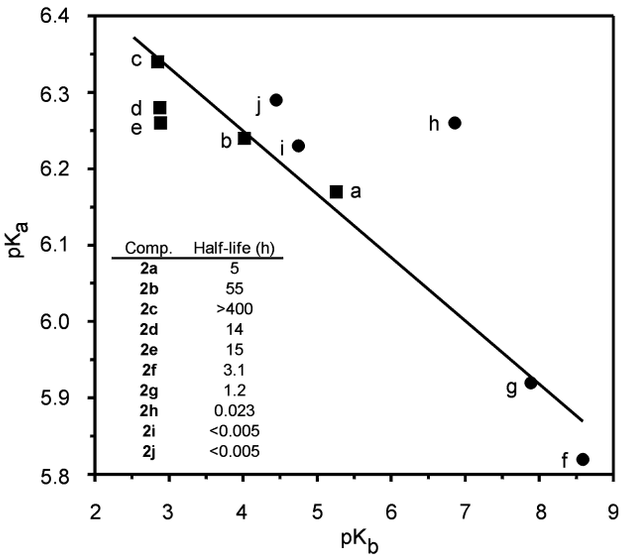

Fig. 1 Plot of pK_as of A·BH(CN)COOH (**2a**–**j**) *versus* pK_bs of amines (A: **a**–**j**) (■ and ● indicate amines with sp^3 and sp^2 hybridization state, respectively.) Hydrolysis half-lives of **2a**–**j** (0.5 M D_2SO_4–D_2O, 100 °C) are listed on the insert. $K_b = [BH^+][OH^-]/[B]$.

that, in accordance with our expectations, weaker amines donate less electrons to the borane moiety and thus to the carboxylic group, and form stronger acids.

The fact that coordination of soft amines bearing sp^2 hybridization state N-donors to the soft BH(CN)COOH moiety did not result in an extra drop of acidity of **2f**, **2g**, **2i** and **2j** was unexpected. This observation proved to be especially surprising when rates of acidic hydrolyses of the B–H bond (that is reduction of the protons) were taken into consideration. All data indicated a much more rapid reduction with soft amine complexes and the rates were significantly increased by an increase in the basicity of the amines. A similar phenomenon was experienced by Funke and Mayr[15] when carbenium ions were reduced by amine-boranes and this was explained by the increased electron donation capability of pyridine bases, which increased the hydride character of the hydrogen connected to the boron. Since our pyridine base complexes did not show significantly higher electron density on the carboxylate group, an increased electron density on the B–H hydrogens also seems to be unlikely. Thus, the rate determining step of proton reduction is supposed to be the protonation of amine N-atoms which prefer the sterically less crowded sp^2 N-donors. This interpretation is in accordance with the facts that *sec*-amine complexes decompose faster than *tert*-amine complexes as well as that **2c** shows exceptionally high hydrolytic stability due to the rigid structure of bicyclic amine quinuclidine in which proton coordination is unfavoured. A similar explanation was found most recently for the unusual stability of Q·$BH(CONHEt)_2$ and Q·$BH(COOH)_2$ boranes in acidic medium.[10]

Acknowledgements

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Notes and references

† General comments: all manipulations, except those involving aqueous solutions, were performed using general Schlenk techniques under a dry and O_2-free nitrogen atmosphere. All solvents were dried before use. All new compounds were characterized by analytical and spectroscopic methods. pH–potentiometric measurements were performed with PHM 85 pH-meter (RADIOMETER) using pHG211 glass electrode referenced to a K401 calomel electrode filled with saturated aq. LiCl solution.

‡ *Selected data for* **1d**: ν_{max} (KBr)/cm^{-1} 2426 (BH), 2208 (C≡N), 1682, (C=O); ^{1}H NMR (360 MHz; $CDCl_3$): δ 1.302 (3H, t), 1.324 (3H, t), 2.96 (4H, m), 3.64 (3H, s); ^{13}C NMR (90.5 MHz; $CDCl_3$): δ 10.89, 11.38 (C–CH_3), 46.51, 46.94 (C–CH_2), 49.55 (O–CH_2); ^{11}B NMR (115.5 MHz; $CDCl_3$; BF_3·OEt_2): δ −16.7 (d, *J* 96 Hz).

§ *Selected data for* **2b**: ν_{max} (KBr)/cm^{-1} 2419 (BH), 2210 (C≡N), 1662 (C=O); ^{1}H NMR (360 MHz; $CDCl_3$): δ 2.89 (9H, s); ^{11}B NMR (115.5 MHz; $CDCl_3$; BF_3·OEt_2): δ −12.6 (d, *J* 105 Hz).

¶ *Selected data for* **2g**: ν_{max} (KBr)/cm^{-1} 2434 (BH), 2207 (C≡N), 1700, 1684 (C=O); ^{1}H NMR (360 MHz; D_2O): δ 2.58 (3H, s), 7.70 (2H, m), 8.45 (2H, m); ^{11}B NMR (115.5 MHz; D_2O; BF_3·OEt_2): δ −13.9 (d, *J* 86 Hz).

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