Synthesis of the first amine–dicarboxyboranes and their derivatives

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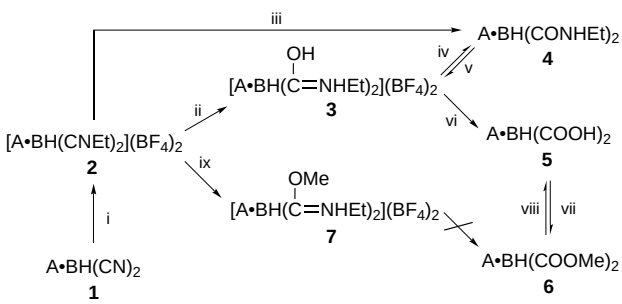
The first amine–dicarboxyboranes and their dimethyl esters are synthesized from amine–dicyanoboranes *via* [amine–bis(ethylnitrilium)hydroboron(2+)] tetrafluoroborates, [amine–bis(*C*-hydroxy-*N*-ethyliminium)hydroboron(2+)] cations and amine–bis(*N*-ethylcarbamoyl)boranes; *C*-methoxy-*N*-ethyliminium groups adjacent to boron undergo unusual hydrolysis.

Amine–carboxyboranes have been known for two decades,[1] and their biological and pharmaceutical activities have been extensively studied.[2] Amine–carboxyboranes and related compounds have shown anticancer,[3] antiosteoporotic,[4] anti-inflammatory[5] and hypolipidemic[6] properties. Since the preparation of the first representative of amine–carboxyboranes they have been generally considered to be the boron analogues of the protonated amino acids,[7] based on the isoelectronic relation between C–N^+ and B–N bonds. On the other hand, amine–carboxyboranes can be regarded as analogues of aliphatic carboxylic acids, since the B–N bond is not only isoelectronic but also isosteric to the C–C bond, according to Langmuir's definition.[8] In contrast to amino acids, amine–carboxyboranes do not form chelates with transition metal ions and their pK_a values are approximately 6 units larger than those of amino acids.[9] These facts, along with many qualitative observations, suggest that the R_3N–B group has a marked electron-donating effect towards its substituents.[10]

Here we report the synthesis of the first amine–dicarboxyboranes, the boron analogues of geminal dicarboxylic acids. Our long-term project, directed towards the synthesis of boron-substituted amine–carboxyboranes,[11] was initiated for two reasons. First, the introduction of new functional groups (here a second carboxylic group) offers potential biological activity. Second, the substitution of a hydrogen for an electron-withdrawing substituent on the boron is expected to increase the stability of the B–H bond, and brings the electron distribution of the carboxylic group closer to that in aliphatic carboxylic acids.

The synthetic sequence is outlined in Scheme 1.† The amine–dicyanoboranes **1a**–**d** were readily synthesized by base exchange (Table 1). The reaction between **1a**–**c** and Et_3OBF_4 in refluxing CH_2Cl_2 afforded the [amine–bis(*N*-ethylnitrilium)hydroboron(2+)] tetrafluoroborates **2a**–**c**. Owing to their low solubility in CH_2Cl_2, pure **2a** and **2c** could be isolated from the reaction mixtures in 80–88% yields. However, **2b** could not be separated from the excess Et_3OBF_4, but it did not cause the formation of byproducts in the subsequent reactions. **2d** could not be obtained at all, though both mono- and di-ethylated products were formed in the initial stage, but later they decomposed when a significant amount of starting material was still present. NMR monitoring of the ethylation reactions showed significant amounts of **1** and/or **2** besides the intermediate [amine–cyanoethylnitriliumhydroboron(1+)] cations during the whole reaction period even when only 1 mol equiv. of Et_3OBF_4 was employed. Consequently, there is only a surprisingly small difference between the rates of the consecutive steps, and preparation of the pure intermediates does not seem feasible.



Scheme 1 (**a** A = quinuclidine; **b** A = Me_3N; **c** A = pyridine; **d** A = DMAP; **e** A = piperidine). *Reagents and conditions:* i, 2.5 mol equiv. Et_3OBF_4, CH_2Cl_2, reflux, 6–10 h; ii, H_2O, room temp. 50–70 min; iii–iv, 1 M NaOH, room temp. immediate; v, HBF_4, H_2O room temp., immediate; vi, 1 M HCl, 120 °C, 1.5 atm, 10 min; vii, 7.5 mM HBr–MeOH, room temp., 5–10 min; viii, 0.05 M HCl, 60 °C, 15 min; ix, MeOH, room temp. 5–10 min.

Water readily adds to **2a**–**c** in 50–70 min in water or in 1 M HCl at room temp. affording [amine–bis(*C*-hydroxy-*N*-ethyliminium)hydroboron(2+)] tetrafluoroborates **3a**–**c**. **3a** could be prepared and characterized as a solid,‡ since it precipitated from water. Such stability of protonated aliphatic amides in aqueous medium is quite unusual,[12] and is probably due to the strong electron-releasing effect of the R_3N–B group. Water addition also takes place when **2a**–**c** are exposed to moisture.

In 1 M NaOH **2a**–**c** were transformed to the corresponding amine–bis(*N*-ethylcarbamoyl)boranes **4a**–**c** within 5 min, and the pure products were obtained from the CH_2Cl_2 extracts of the alkaline solutions. **4d** and **e** were synthesized from **4a** or **b** employing base exchange reactions (Table 1). Protonation of **4** leads to **3**: addition of 50% HBF_4 to a concentrated aqueous solution of **4a** resulted in the precipitation of **3a**.

In contrast to amine–*N*-ethylcarbamoylboranes, the acidic hydrolysis of amine–bis(*N*-ethylcarbamoyl)boranes **4**, presumably *via* **3** cations formed *in situ*, required vigorous conditions, probably owing to the much larger steric hindrance of the acyl carbons.[14] **4a** and **e** could be transformed into the amine–dicarboxyboranes **5a**§ and **e**. Best yields (60%) were achieved

Table 1 Syntheses employing base exchange

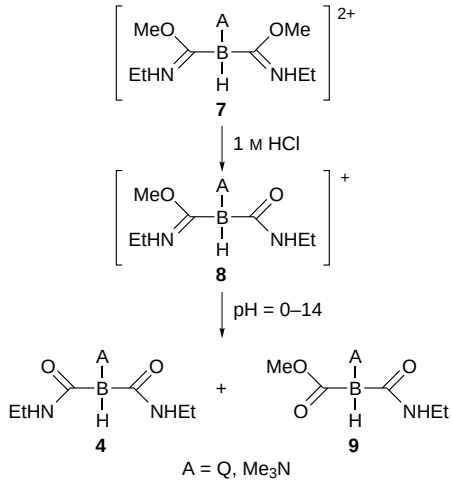
$$A{\cdot}BHX_2 \xrightarrow{MeCN} A'{\cdot}BHX_2$$

Product	A	A′	A : A′	X	*t*/min	*T*/°C	Yield[a] (%)
1a	4-CN-py[b]	Q[c]	1 : 1.03	CN	5	25	96
1b	4-CN-py[b]	$Me_3N_{(g)}$	—	CN	15	25	97
1d	4-CN-py[b]	DMAP	1 : 1.03	CN	5	25	100
4d	Me_3N	DMAP	1 : 1	CONHEt	240	80	88
	Q[c]	DMAP	1 : 10	CONHEt	180	80	67
4e	Me_3N	Piperidine	1 : 100[d]	CONHEt	300	80	93
	Q[c]	Piperidine	1 : 30[d]	CONHEt	600	80	81
5d	Q[c]	DMAP	1 : 10	COOH	360	80	83[e]
5e	Q[c]	Piperidine	1.25[d]	COOH	60	80	30[e]
6e	Q[c]	Piperidine	1.25[d]	COOMe	180	80	50

[a] Yields are not optimized. [b] For preparation see ref. 13. [c] Q = quinuclidine. [d] The reaction was run in piperidine. [e] The crude product was a mixture of **5** and its salt formed with the corresponding base. Pure **5d**, **e** were obtained from the suspension of the crude products in 0.1 M HCl.

for **5a** in 1 M HCl, at 120 °C. **4b**–**d** completely decomposed at even lower temperatures and/or less acidic solutions to the corresponding amine hydrochlorides. The lower hydrolytic stability of **4b** and **c** may be due to the relatively weak B–N bond in these complexes. On the other hand, the B–N bond in both **4d** and **5d** is presumably stronger than in **4a** and **5a**, since **4d** and **5d** could be prepared *via* a base exchange reaction (Table 1) from **4a** and **5a**. In accordance with our expectations, preliminary observations (salt formation during base exchange, –COOH chemical shifts) suggest that amine–dicarboxyboranes are stronger acids than amine–carboxyboranes. Decomposition during the hydrolysis of **4d** in acidic medium may be the consequence of the strong electron-donating property of DMAP (4-dimethylaminopyridine), which increases the hydridic character of the hydrogen attached to the boron. Such phenomena have been reported in the case of amine–(alkyl)carbamoylboranes.[15]

Similarly to amine–carboxyboranes,[16] all amine–dicarboxyboranes **5a**, **d**, **e** can be conveniently esterified in methanol in the presence of a catalytic amount (3 mol% relative to carboxyl groups) of HBr. Hydrolysis of the resulting amine–bis(methoxycarbonyl)boranes **6a**, **d**, **e** yielded the corresponding amine–dicarboxyboranes in minutes at 50 °C at pH ≈ 1. The latter reaction might offer a different, mild route to amine–dicarboxyboranes, so we attempted to synthesize **5** through the path **2** → **7** → **6** → **5**, since the acidic hydrolysis of alkylimidate salts $[RC(OR')=NR''R''']^+$ typically yields the corresponding esters $RC(O)OR'$.[17] [Amine–bis(*C*-methoxy-*N*-ethyliminium)hydroboron(2+)] tetrafluoroborates **7a**–**c** were readily obtained in minutes after dissolving **2a**–**c** in methanol. Unexpectedly, the hydrolysis of **7a**–**c** does not result in the formation of **6a**–**c** even in 1 M HCl (Scheme 2). Instead, NMR studies of the hydrolysis of **7a**, **b** showed release of methanol, and the resulting [amine–*N*-ethylcarbamoyl-(*C*-methoxy-*N*-ethyliminium)hydroboron-(+1)] tetrafluoroborates **8a**, **b** could be isolated.¶ Further hydrolysis of **8a** leads to a mixture of **4a** and quinuclidine–*N*-ethylcarbamoylmethoxycarbonylborane **9a** in both 1 M HCl and 1 M NaOH, producing more **4a** in alkaline medium. Hydrolysis of **8b** follows a similar pattern, but yields other products as well. **7c** undergoes no reaction in 1 M HCl at 25–80 °C, but it slowly decomposes to give boric acid and pyridinium chloride at 100 °C. Our results for **7c** are in agreement with those observed in the acidic hydrolysis of pyridine–(*C*-methoxy-*N*-ethylimino)borane.[18]



Scheme 2

In conclusion, we have investigated three different synthetic methods for the preparation of amine–dicarboxyboranes, boron analogues of geminal dicarboxylic acids. Based upon our findings three amine–dicarboxyboranes and their derivatives have been prepared and several more compounds of this type may be synthesized in the future.

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Footnotes and References

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† General comments: all manipulations, except those involving aqueous solutions, were performed using general Schlenk techniques under dried and O_2-free nitrogen atmosphere. All solvents were absolutized before use. All new compounds were characterized by analytical and spectroscopic methods.

‡ *Selected data* for **3a**: ν_{max} (KBr)/cm^{-1} 3353 (OH), 2468 (BH), 1618 (C=N); ^{1}H NMR (360 MHz; [$^2H_6$]acetone): δ 1.20 (6 H, t), 1.89 (6 H, dt), 2.04 (1 H, spt), 3.24 (6 H, br t), 3.45 (4 H, m); ^{11}B NMR (64.2 MHz; acetone; $BF_3{\cdot}OEt_2$): δ −5.8 (s), −10.8 (d, *J* 105 Hz).

§ *Selected data* for **5a**: ν_{max} (KBr)/cm^{-1} 2448 (BH), 1655, 1635 (C=O); ^{1}H NMR [360 MHz; $(CD_3)_2SO$]: δ 1.72 (m), 1.93 (spt), 3.28 (dt), 10.7 (br s); ^{11}B NMR (64.2 MHz; Me_2SO; $BF_3{\cdot}OEt_2$): δ −10.4 (br d).

¶ *Selected data* for **8a**: ν_{max} (KBr)/cm^{-1} 3398, 3237 (NH), 2460 (BH), 1637, 1576, 1535, 1487, 1465 (amide bands); ^{1}H NMR (360 MHz; $CDCl_3$): δ 1.16 (3 H, t), 1.30 (3 H, t), 1.87 (6 H, dt), 2.07 (1 H, spt), 3.04–3.19 and 3.28–3.42 (6 H, m), 3.28 (2 H, m), 3.53 (2 H, m), 4.37 (3 H, s), 7.05 (1 H, br s), 11.2 (1 H, br s); ^{11}B NMR (64.2 MHz; $CHCl_3$; $BF_3{\cdot}OEt_2$): δ −1.2 (s), −12.4 (br d).

1 B. F. Spielvogel, L. Wojnowich, M. K. Das, A. T. McPhail and K. D. Hargrave, *J. Am. Chem. Soc.*, 1976, **98**, 5702.
2 See for example: I. H. Hall, C. O. Starnes, A. T. McPhail, P. Wisian-Neilson, M. K. Das and L. Wojnowich, *J. Pharm. Sci.*, 1979, **68**, 685; A. Sood, C. K. Sood, B. F. Spielvogel and I. H. Hall, *Eur. J. Med. Chem.*, 1990, **25**, 301; M. E. Murphy, R. P. Shrewsbury, A. Sood, B. F. Spielvogel and I. H. Hall, *Met.-Based Drugs*, 1995, **2**, 257; S. Y. Chen, B. S. Burnham, B. F. Spielvogel, A. Sood, S. D. Wyrick and I. H. Hall, *Appl. Organomet. Chem.*, 1996, **10**, 279.
3 See for example: C. K. Sood, A. Sood, B. F. Spielvogel, J. A. Yousef, B. Burnham and I. H. Hall, *J. Pharm. Sci.*, 1991, **80**, 1133; S. Karthikeyan, A. Sood, J. Tomasz, B. F. Spielvogel and I. H. Hall, *Amino Acids*, 1995, **8**, 323.
4 K. G. Rajendran, S. Y. Chen, A. Sood, B. F. Spielvogel and I. H. Hall, *Biomed. Pharmacother.*, 1995, **49**, 131; K. G. Rajendran, A. Sood, B. F. Spielvogel, I. H. Hall, V. M. Norwood, III and K. W. Morse, *Appl. Organomet. Chem.*, 1995, **9**, 111.
5 See for example: I. H. Hall, K. G. Rajendran, S. Y. Chen, O. T. Wong, A. Sood and B. F. Spielvogel, *Arch. Pharm.* (*Weinheim*), 1995, **328**, 39.
6 See for example: I. H. Hall, B. F. Spielvogel, A. Sood, K. W. Morse, V. M. Norwood, III and O. T. Wong, *Met.-Based Drugs*, 1994, **1**, 329.
7 C. Morin, *Tetrahedron*, 1994, **50**, 12 521, and references therein.
8 I. Langmuir, *J. Am. Chem. Soc.*, 1919, **41**, 1543.
9 K. H. Scheller, R. B. Martin, B. F. Spielvogel and A. T. McPhail, *Inorg. Chim. Acta*, 1982, **57**, 227; V. M. Norwood, III and K. W. Morse, *Inorg. Chem.*, 1986, **25**, 3690.
10 B. Györi, Z. Kovács and Z. Berente, in preparation.
11 B. Györi, Z. Kovács, J. Emri and Z. Berente, *J. Organomet. Chem.*, 1994, **484**, 225.
12 B. C. Challis and J. A. Challis, in *Comprehensive Organic Chemistry*, ed. D. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 2, p. 995.
13 B. Györi, J. Emri and I. Fehér, *J. Organomet. Chem.*, 1983, **255**, 17.
14 B. C. Challis and J. A. Challis, in *Comprehensive Organic Chemistry*, ed. D. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 2, p. 1007.
15 A. Sood and B. F. Spielvogel, *Main Group Met. Chem.*, 1989, **12**, 143; C. H. Sutton, M. W. Baize and L. J. Todd, *Inorg. Chem.*, 1992, **31**, 4911; 1994, **33**, 4221.
16 B. Györi, Z. Berente, J. Emri and I. Lázár, *Synthesis*, 1995, 191.
17 D. G. Neilson, in *The Chemistry of Amidines and Imidates*, ed. S. Patai, Wiley, London, 1975, p. 422.
18 M. Mittakanti and K. W. Morse, *Inorg. Chem.*, 1990, **29**, 554.

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