# Notes

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## Boron Analogues of Amino Acids. 3.[1] 1 Synthesis of (Ethylcarbamoyl)borane Adducts of $Me_3N$, $Me_2NH$, $MeNH_2$, and $NH_3$

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*Received July 5, 1983*

Trimethylamine–(ethylcarbamoyl)borane, $Me_3N{\cdot}BH_2C(O)NHEt$ (**1**), is a precursor in the synthesis of $Me_3N{\cdot}BH_2COOH$, the protonated boron analogue of the dipolar amino acid betaine[3] $^+Me_3NCH_2COO^-$. Both $Me_3N{\cdot}BH_2COOH$ and its ethylcarbamoyl derivative have demonstrated significant antitumor and antihyperlipidemic activity in mice.[3-5] Also, the trimethylamine–(ethylcarbamoyl)borane showed significant antiinflammatory and antiarthritic activities in animal model studies.[6] Because of their potential biological activities, we have therefore prepared the remaining members represented by the general formulation $(CH_3)_xNH_{3-x}{\cdot}BH_2C(O)NHEt$ ($x$ = 0–3) for structure–activity relationship studies. These boron analogues of amino acid amides are also of interest as simple models of a (boron amino acid) peptide linkage. Also, these compounds may be of value for use in boron neutron capture therapy for the treatment of cancer.[7]

### Results and Discussion

A series of (ethylcarbamoyl)borane adducts of different amines and $NH_3$ were prepared according to Scheme I.

**Scheme I**

$$Me_3N{\cdot}HCl + NaBH_3CN \xrightarrow{THF^a} Me_3N{\cdot}BH_2CN \xrightarrow{(C_2H_5)_3OBF_4{}^b} Me_3N{\cdot}BH_2CNC_2H_5{}^+BF_4{}^- \xrightarrow{1\ N\ NaOH^c} Me_3N{\cdot}BH_2C(O)NHC_2H_5 \xrightarrow{RR'NH^d}$$

**1**

$RR'NH{\cdot}BH_2C(O)NHC_2H_5$

**2**, R = $CH_3$, R′ = $CH_3$

**3**, R = $CH_3$, R′ = H

**4**, R = H, R′ = H

[a] Reflux (66 °C) for 48 h. [b] Reflux (45 °C) in $CH_2Cl_2$ for 24 h. [c] Stirring (0 °C) until basic. [d] Room temperature (25 °C) for ca. 1 week.

The parent compound, trimethylamine–(ethylcarbamoyl)borane (**1**) was prepared[3] as previously described by refluxing (under dry $N_2$) a solution of $Me_3N{\cdot}BH_2CN$[8] in $CH_2Cl_2$ with 2 equiv of triethyloxonium tetrafluoroborate[9] for 24 h. The resulting ethanenitrilium salt (not isolated) was hydrolyzed at 0 °C with 1 N NaOH until basic and finally purified by vacuum distillation, giving a 75% yield. Dimethylamine–(ethylcarbamoyl)borane (**2**) was made from **1** by a $(CH_3)_2NH$-exchange reaction in a pressure-glass vessel at room temperature for 8 days, and ca. 80% conversion (by $^1H$ NMR) was obtained. Longer reaction periods (2–3 weeks) gave similar results. Amide **2** is readily purified by washing a $CH_2Cl_2$ solution of the crude mixture with a small quantity of water whereby **1** is removed. The bulk $CH_2Cl_2$ solution containing the product was dried, and rotary evaporation of the solvent gave 78% yield. Finally, the product was distilled under reduced pressure to get an analytical sample. The trimethylamine–(ethylcarbamoyl)borane (**1**) and its dimethylamine analogue (**2**) are thermally unstable at higher temperature (>110 °C) and undergo considerable decomposition when subjected to vacuum distillation at oil-bath temperatures >110 °C. The methylamine–(ethylcarbamoyl)borane (**3**) and ammonia–(ethylcarbamoyl)borane (**4**) were similarly prepared from **1** by exchange reactions with $CH_3NH_2$ and $NH_3$, respectively, in a glass pressure reaction vessel at room temperature for 1 week. The crude amide (**3**) was purified by recrystallization from $CH_2Cl_2$/pentane, giving a 65% yield, whereas the ammonia analogue (**4**) was recrystallized from distilled water, giving a 60% yield.

Table I. Physical and Spectroscopic Data for Amine–(Ethylcarbamoyl)boranes

| compd | bp or mp, °C (*P*, torr) | % yield | $^{11}B$ NMR data,[a] δ | $J_{B-H}$, Hz |
|---|---|---|---|---|
| $Me_3N{\cdot}BH_2CONHEt$ (**1**) | 80 (0.15) | 75 | −7.40 | 90 |
| $Me_2NH{\cdot}BH_2CONHEt$ (**2**) | 110–112 (0.2) | 77 | −11.55 | 88 |
| $MeNH_2{\cdot}BH_2CONHEt$ (**3**) | 99–110 | 65 | −15.37 | 84 |
| $NH_3{\cdot}BH_2CONHEt$ (**4**) | 125–126 | 60 | −19.59 | 80 |

[a] $BF_3{\cdot}Et_2O$ was used as an external standard, and the chemical shifts shown were negative upfield from the standard.

All of the compounds were characterized by elemental analyses, and IR, $^1H$, $^{11}B$, and $^{13}C$ NMR spectroscopy. The physical and spectral data of these amides are given in Table I. The IR spectra exhibited characteristic B–H, and C=O absorptions. The $^1H$, $^{11}B$, and $^{13}C$ NMR spectral data were consistent with the structures of these compounds.

Studies of the biological activity of these compounds are in progress.

### Experimental Section

**General Procedures.** IR spectra were recorded on a Perkin-Elmer 297 spectrometer. Solid samples were prepared as Nujol mulls between NaCl disks; oils were recorded neat. Proton NMR spectra were obtained on Varian EM 360A or JEOL-FX 90Q spectrometers. Carbon and boron NMR spectra were obtained on a JEOL-FX 90Q spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and M–H–W Laboratories, Phoenix, AZ. The following compounds were purchased and used without further purification: $(CH_3)_3N{\cdot}HCl$ (Aldrich), $NaBH_3CN$ (Aldrich), $(CH_3)_2NH$ (Eastman Kodak), $CH_3NH_2$ (Union Carbide), $NH_3$ (Matheson). $(C_2H_5)_3OBF_4$ solution was either purchased (Aldrich) or made by a known method.[9] $(CH_3)_3N{\cdot}BH_2CN$ was prepared[8] from

(1) Part 2: Spielvogel, B. F.; Das, M. K.; McPhail, A. T.; Onan, K. O.; Hall, I. H. *J. Am. Chem. Soc.* **1980**, *102*, 6343.
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(3) Spielvogel, B. F.; Wojnowich, L.; Das, M. K.; McPhail, A. T.; Hargrave, K. D. *J. Am. Chem. Soc.* **1976**, *98*, 5702.
(4) Hall, I. H.; Starnes, C. O.; Spielvogel, B. F.; Wisian-Neilson, P.; Das, M. K.; Wojnowich, L. *J. Pharm. Sci.* **1979**, *68*, 685.
(5) Hall, I. H.; Das, M. K.; Harchelroad, F., Jr.; Wisian-Neilson, P.; McPhail, A. T.; Spielvogel, B. F. *J. Pharm. Sci.* **1981**, *70*, 339.
(6) Hall, I. H.; Starnes, C. O.; McPhail, A. T.; Wisian-Neilson, P.; Das, M. K.; Harchelroad F., Jr.; Spielvogel, B. F. *J. Pharm. Sci.* **1980**, *69*, 1025.
(7) Spielvogel, B. F. "Boron Chemistry-4", IUPAC, Inorganic Chemistry Division; Parry, R. W., Kodama, G., Eds.; Pergamon Press: New York, 1980; pp 119–129.
(8) Wisian-Neilson, P.; Das, M. K.; Spielvogel, B. F. *Inorg. Chem.* **1978**, *17*, 2327.

0020-1669/84/1323-1776$01.50/0 

$(CH_3)_3N{\cdot}HCl$ and $NaBH_3CN$. The amine-exchange reactions were carried out in 250-mL glass pressure reaction vessels. The pressure reaction vessels and their safety shields were purchased from Lab-Crest Scientific Co., Warminster, PA. Although the $NH_3$ exchange has been carried out in the glass vessel without incident, the use of stainless-steel vessels is greatly preferred for safety.

**Trimethylamine–(Ethylcarbamoyl)borane (1).**[3,4] A solution of trimethylamine–cyanoborane (11.9 g, 0.12 mol) and 250 mL of 1 M $Et_3OBF_4$ in $CH_2Cl_2$ (0.25 mol) was refluxed under nitrogen for 24 h. The reaction mixture was cooled to 0 °C, and 1 N NaOH was added slowly with vigorous stirring until the solution was basic (pH ~8). After the mixture was stirred for 1 h at room temperature, the organic layer was separated and the aqueous layer was extracted three times with $CH_2Cl_2$. The organic portions were combined and dried over $MgSO_4$, and the solvent was removed in vacuo. The remaining viscous liquid was distilled under vacuum with minimum heating to give **1**: 13.1 g (75%); bp 80 °C (0.15 torr); IR (neat) 3289 ($\nu$(NH)), 2915 ($\nu$ (CH)), 2330 ($\nu$(B–H)), 1590 (amide I), 1480 (amide II) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (t, $CH_3CH_2$), 2.75 (s, $CH_3N$), 3.57 (m, $CH_2CH_3$), 5.43 (br s, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$ 15.3 ($CH_3CH_2$), 31.5 ($CH_2CH_3$), 51.8 ($CH_3N$), 182.8 (CO); $^{11}B$ NMR ($CDCl_3$, $BF_3{\cdot}Et_2O$) $\delta$ −7.4 (1:2:1 t, $J_{BH}$ = 90 Hz). Anal. Calcd for $C_6H_{17}BN_2O$: C, 50.10; H, 11.83; N, 19.49; B, 7.45. Found: C, 49.86; H, 11.69; N, 19.59; B, 7.50.

**Dimethylamine–(Ethylcarbamoyl)borane (2).** Anhydrous $(CH_3)_2NH$ (50 g, 1.1 mol) was cooled to 0 °C and poured into the glass pressure vessel containing **1** (14.38 g, 0.1 mol) kept at 0 °C. The vessel was assembled and kept at room temperature for 8 $^1/_2$ days with occasional shaking each day. The reaction vessel was then cooled to 0 °C and slowly opened. To this solution was added ca. 80 mL of pentane, and the volatile amines were allowed to evaporate off. The remaining amines and solvent were removed by rotary evaporation. A pale yellow liquid was obtained that had ca. 21% unreacted **1** (by proton NMR). The mixture was taken up in $CH_2Cl_2$ and washed once with water. The water washing was repeatedly extracted with $CH_2Cl_2$, and the proton NMR spectrum of the $CH_2Cl_2$ extracts showed that it contained only the starting amide (**1**). The $CH_2Cl_2$ solution containing the product, uncontaminated by **1** (by proton NMR), was dried over $MgSO_4$ and treated with charcoal. The solvent was then removed by rotary evaporation and the pale yellow oil (**2**) (10.1 g (77.7%)) was vacuum distilled: bp 110–112 °C (0.2 torr); IR ($CH_2Cl_2$) 3440 ($\nu$(NH)), 2965 ($\nu$(CH)), 2365 ($\nu$(BH)), 1590 (amide I), 1490 (amide II) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 1.06 (t, $CH_3CH_2$), 2.40 (d, $CH_3N$), 3.18 (m, $CH_2CH_3$), 5.80 (br s, amine H), 6.45 (br s, amide H); $^{11}B$ NMR ($CDCl_3$, $BF_3{\cdot}Et_2O$) $\delta$ −11.55 (t, $J_{B-H}$ = 88 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 15.26 ($CH_3CH_2$), 32.33 ($CH_2CH_3$), 42.91 ($CH_3N$). Anal. Calcd for $C_5H_{15}BN_2O$: C, 46.20; H, 11.63; N, 21.55. Found: C, 45.94; H, 11.58; N, 21.30.

**Methylamine–(Ethylcarbamoyl)borane (3).** Anhydrous methylamine was condensed (ca. 30 mL) at −78 °C from the gas cylinder and transferred to the glass pressure reaction vessel containing 2.86 g (19.85 mmol) of **1** already cooled to −78 °C. The pressure reaction vessel was then assembled and slowly allowed to warm to room temperature and kept for 1 week with occasional shaking. The reaction vessel was then cooled to −78 °C and carefully opened. To this solution was added ca. 100 mL of pentane, and excess amines were allowed to evaporate off at room temperature. Some solid product separated, and the remaining solvent and was removed by rotary evaporation. The crude product was dissolved in $CH_2Cl_2$ (ca. 200 mL) and filtered into *n*-pentane. An off-white solid (0.92 g) separated. To the filtrate was added additional pentane, and 0.57 g of more product was obtained. The combined solid (**3**) (1.49 g (65%)) was recrystallized from $CH_2Cl_2$/pentane: mp 99–100 °C; IR (Nujol) 3330 ($\nu$(NH)), 3120 ($\nu$(CH)), 2380 ($\nu$(BH)), 1620 (amide), 1570 (m, amide) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.09 (t, $CH_3CH_2$), 2.43 (t, MeN), 3.23 (m, $CH_2CH_3$), 4.95 (br s, amine H), 5.69 (br s, amide H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 15.20 ($CH_3CH_2$), 32.30 ($CH_2CH_3$), 32.36 ($Me_3N$); $^{11}B$ NMR ($CDCl_3$, $BF_3{\cdot}Et_2O$) $\delta$ −15.37 (t, $J_{BH}$ = 84 Hz). Anal. Calcd for $C_4H_{13}N_2BO$: C, 41.43; H, 11.30; N, 24.16. Found: C, 41.20; H, 11.07; N, 24.03.

**Ammonia–(Ethylcarbamoyl)borane (4).** Anhydrous $NH_3$ was condensed at −78 °C from the gas cylinder and ca. 40 mL of liquid $NH_3$ transferred to the glass pressure reaction vessel containing 1.48 g (10.20 mmol) of **1** that was previously cooled to −78 °C. The reaction vessel was then assembled, allowed to warm to room temperature, and kept for 1 week with occasional shaking each day. The reaction vessel was then cooled to −78 °C and slowly opened. The excess $NH_3$ and amines were allowed to evaporate off at room temperature, ca. 200 mL of $CH_2Cl_2$ was added to the vessel, and the resultant mixture was filtered. The solution was kept in the refrigerator, and fluffy crystals formed. The crude product was recrystallized from doubly distilled water. The white needles (**4**) (0.62 g (60%) mp 125–126 °C) had the following spectral properties: IR (Nujol) 3350 ($\nu$(NH)), 3270 ($\nu$(CH)), 2340 ($\nu$(BH)), 1620 (amide I), 1550 (amide II) $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$ 1.06 (t, $CH_3CH_2$), 3.15 (q, $CH_2CH_3$); $^{13}C$ NMR ($D_2O$) $\delta$ 16.60 ($CH_3CH_2$), 35.22 ($CH_2CH_3$); $^{11}B$ NMR ($D_2O$, $BF_3{\cdot}Et_2O$) $\delta$−19.59 (t, $J_{BH}$ = 80 Hz). Anal. Calcd for $C_3H_{11}N_2BO$: C, 35.35; H, 10.88; N, 27.48. Found: C, 35.32; H, 10.86; N, 27.72.

**Acknowledgment.** We thank the Army Research Office for support of this work.

**Registry No.** **1**, 60788-35-4; **2**, 88915-69-9; **3**, 88915-70-2; **4**, 88915-71-3.

(9) Meerwein, H. *Org. Synth.* **1966**, *46*, 113.

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## EPR Studies of the Formation of Low-Spin Dimethoxo(tetraphenylporphinato)ferrate(III) in Solution

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*Received September 19, 1983*

The interaction of heme iron with its ligands has been the subject of continuing spectroscopic investigations. In particular, axial ligations in low-spin Fe(III) heme complexes have been studied most extensively by EPR spectroscopy, and various types of axial ligation modes are identified and characterized.[1,2] However, there seems to be no report on the low-spin complex in which O-donor ligands are coordinated to both the fifth and sixth axial positions. It is often tacitly supposed that the axial ligation mode O–Fe–O results in high-spin complexes because of the rather weak field nature of O-donor ligands.

In the present work, we have found, contrary to the above supposition, that the low-spin state can be effected in dimethoxo(tetraphenylporphinato)ferrate(III), $Fe(TPP)(OMe)_2^-$, which forms upon mixing of Fe(TPP)Cl with excess methoxide anion, $MeO^-$, in toluene–methanol. This note will report the first demonstration of the axial ligation mode O–Fe–O in low-spin Fe(III) heme complexes together with EPR characteristics obtained for $Fe(TPP)(OMe)_2^-$.

### Experimental Section

Sodium methoxide (NaOMe, ~28% in methanol) was purchased from Wako Chemicals and used as obtained or by dilution with methanol. The concentration of $MeO^-$ in methanol was determined by titration with hydrochloric acid after dilution with excess water. Toluene was purified by distillation from calcium hydride and stored over 4A molecular sieves. Methanol (Spectroquality, Dojin Chemicals) was used without further purification. Fe(TPP)Cl was synthesized and purified following published methods.[3-5]

(1) Tang, S. C.; Koch, S.; Papaefthymiou, G. C.; Foner, S.; Frankel, R. B.; Ibers, J. A.; Holm, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 2414.
(2) Palmer, G. In "The Porphyrins"; Dolphin, D., Ed.; Academic Press: New York, 1979; Vol. IV, p 313 and cited references.
(3) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.

0020-1669/84/1323-1777$01.50/0 