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Contribution from the Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300

Preparation and Characterization of an (*N*-Ethylcarbamoyl)borane Cyclic Dimer

M. R. M. D. Charandabi, D. A. Feakes, M. L. Ettel, and K. W. Morse*

Received October 9, 1990

Introduction

In recent years there has been considerable interest in the synthesis and characterization of a series of isoelectronic and isosteric boron analogues of α-amino acids (amine·BH_2X: X = CN, COOH, COOR, C(O)NHR, C(CN)=NC_2H_5, C(S)NHR).[1-7] Interest in these analogues stems from their biological activity as antitumor,[8] antiinflammatory,[9] and hypolipidemic[10] agents. Recently, we reported the synthesis of several borane derivatives of aminomethylphosphonates.[11] The purification of the (*N*-ethylcarbamoyl)borane adduct of diethyl ((dimethylamino)methyl)phosphonate resulted in an unexpected product, an (*N*-ethylcarbamoyl)borane cyclic dimer. Several different preparations of the dimer as well as its characterization are reported here. Reaction of this dimer with N–H-containing amines affords the direct synthesis of the known carbamoylborane adduct[2] of a primary or secondary amine.

Experimental Section

Materials. All glass equipment was dried in an oven at 110 °C and assembled under a stream of dry nitrogen. All reactions were carried out under an inert atmosphere. Silica gels, Kieselgel 60 (230–400 mesh) and 60A (70–230 mesh), were used as received from E. M. Science and Aldrich, respectively. Solvents were dried and distilled[12] prior to use. The (*N*-ethylcarbamoyl)borane adduct of diethyl ((dimethylamino)methyl)phosphonate was prepared as previously described.[11]

Instruments. ^1H and $\{^1H\}^{13}C$ NMR spectra were recorded in $CDCl_3$ with TMS used as the internal standard on a Varian XL-300 spectrometer operating at 300 and 75.44 MHz, respectively, or on a JEOL FX-90Q instrument operating at 90 and 22.63 MHz, respectively. The ^{11}B NMR spectra were recorded on a JEOL FX-90Q spectrometer operating at 28.69 MHz with chemical shifts reported relative to external $BF_3 \cdot O(C_2H_5)_2$. Infrared spectra were obtained on a Perkin-Elmer 1750 FT spectrometer. The elemental analysis was performed by M-H-W Laboratories, Phoenix, AZ.

Preparation of the (*N*-Ethylcarbamoyl)borane Cyclic Dimer [$BH_2C(O)NHC_2H_5$]$_2$. Method I. A flash chromatography column equipped with a flow controller valve was packed with Kieselgel 60.[12] The (*N*-ethylcarbamoyl)borane adduct of diethyl ((dimethylamino)methyl)phosphonate (15.0 g, 0.038 mol) was applied to the column as a 20% solution in the eluant (dichloromethane/ether, 70:30). The fractions, 20 × 10 mL, were collected and the components were identified by using TLC. The pure ring compound was usually found in fractions 7–11. The solvent was removed at reduced pressure from these fractions, and the resulting pure white solid was dried under vacuum. Yield of the product was 44% based on the amount of carbamoylborane adduct placed on the column. MP: 116–118 °C (with decomposition). Mass spectral data (major *m/e*, %): 169 (33), 168 (60), 167 (24), 112 (82), 86 (55), 84 (52), 58 (100), 56 (43), 43 (33).

Anal. Calcd for $C_6H_{16}B_2N_2O_2$: C, 42.44; H, 9.50; N, 16.50. Found: C, 42.57; H, 9.67; N, 16.63.

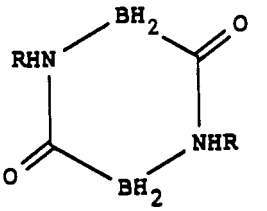

Figure 1. Proposed structure of the (ethylcarbamoyl)borane dimer.

Method II. The (*N*-ethylcarbamoyl)borane adduct of *N*-methylmorpholine (2.0 g, 0.011 m) was synthesized in a procedure analogous to the synthesis of the (*N*-ethylcarbamoyl)borane adduct of pyridine.[13] The adduct was heated at 60–70 °C for 3 h. The adduct was then dissolved in a minimal amount of the eluting solvent (dichloromethane/ether, 70:30) and applied to a short-path silica gel column. The 4 × 5 cm column was prepared with 60A (70–230 mesh) silica gel according to the method of Harwood.[14] Several fractions, 8 × 20 mL, were collected, and the solvent was removed at reduced pressure. The crude product was recrystallized in ether/hexane and dried under vacuum. The pure ring compound was obtained in 20% yield.

Method III. The (*N*-ethylcarbamoyl)borane adduct of *N*-methylmorpholine (2.0 g, 0.011 m) was placed in a Schlenk flask equipped with a cold finger and placed under high vacuum. The flask was slowly heated to a temperature of 65–70 °C and kept at that temperature for a period of 3 h. The residue was dissolved in dichloromethane and filtered and the solvent removed under reduced pressure. The product was recrystallized from dichloromethane/hexane. After the purified product was vacuum-dried, the yield was calculated to be 20%.

Reaction of [$BH_2CONHC_2H_5$]$_2$ with Methylamine. The (*N*-ethylcarbamoyl)borane cyclic dimer (0.0765 g, 0.450 mmol) was placed in a medium-wall NMR tube equipped with a 10/30 standard taper joint, and an excess of anhydrous methylamine was vapor transferred into the apparatus. After several freeze/thaw cycles, the NMR tube was flame-sealed and slowly warmed to ambient temperature. The progress of the reaction was monitored by ^{11}B NMR spectroscopy. After 1 week the reaction was shown to be 81% complete by ^{11}B NMR spectroscopy. The reaction was complete in 2 weeks. Spectral analyses of the product agree with published values[2] for the reaction of methylamine with the (ethylcarbamoyl)borane adduct of trimethylamine. Similar results have been obtained with the (ethylcarbamoyl)borane dimer and dimethylamine and trimethylamine.

Results and Discussion

The use of a silica gel column in the attempted purification of $(C_2H_5O)_2P(O)CH_2N(CH_3)_2BH_2C(O)NHC_2H_5$ resulted in the unexpected reaction of the adduct on the column and the formation of an (*N*-ethylcarbamoyl)borane cyclic dimer. In this instance, the N–B bond cleavage appears to be facilitated by interaction of the phosphonate with the silica gel and is supported by the fact that only P(V) fragments can be isolated from the column materials and not any identifiable intact adduct. With the *N*-methylmorpholine adduct, heating apparently facilitates dimer

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0020-1669/91/1330-2433$02.50/0

Table I. Spectral Data for the Carbamoylborane Cyclic Dimer and the Carbamoylborane Adduct of *N*-Methylmorpholine

type		$[BH_2C(O)NHC_2H_5]_2$	$O(CH_2CH_2)_2N(CH_3)BH_2C(O)NHC_2H_5$
infrared[a]	(N—H)	3410	3440, 3360
	(B—H)	2400	2369
	(amide I, C=O)	1570	1595
	(amide II, N—H)	1520	1477
^{11}B NMR[b]		-8.6 (t, J_{BH} = 95 Hz)	-9.9 (t, J_{BH} = 97 Hz)
^{1}H NMR[b]	N-CH_2CH_3	1.18 (t, J_{HCCH} = 7.5 Hz)	1.09 (t, J_{HCCH} = 7.4 Hz)
	N-CH_2CH_3	3.38 (m, J_{HCCH} = 7.5 Hz, J_{HNCH} = 5.7 Hz)	3.24 (m)
	N-H	6.42 (b s)	5.7 (b s)
	N-CH_3		2.88 (s)
	ring-H		2.85 (m), 3.49 (m), 3.75 (m)
			4.03 (m)
^{13}C NMR[b]	N-CH_2CH_3	13.51 (s)	14.98 (s)
	N-CH_2CH_3	33.75 (s)	31.70 (s)
	N-CH_3		48.85 (s)
	O-CH_2CH_2-N		57.63 (s)
	O-CH_2CH_2-N		61.18 (s)

[a] All spectra were taken as $CHCl_3$ solutions. [b] Key: s = singlet; m = multiplet; t = triplet; b = broad.

formation. The reasons for this are currently being studied. The structure of the cyclic dimer can be considered to be analogous to the cyanoborane oligomer that is formed from $[BH_3CN]^-$ in the presence of an acid.[15]

Infrared, ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and mass spectral data support the proposed formulation for the cyclic dimer (Figure 1). The infrared spectrum exhibits absorptions characteristic of C=O, N—H, and B—H moieties. The assignments have been made based on the corresponding spectra of the cyanoborane cyclic oligomer ($[BH_2CN]_x$),[15] the (*N*-ethylcarbamoyl)borane adducts of several trialkylamines,[2,13,16] and the generally accepted assignments for organic amides.[17] The B-H stretching mode of the (*N*-ethylcarbamoyl)borane adduct of *N*-methylmorpholine is reported at 2369 cm^{-1}, which is consistent with solution spectra of other trialkylamine adducts. The shift to higher energy, 2400 cm^{-1}, of the B-H stretching mode in the cyclic dimer is consistent with the change observed when the amine of the (*N*-ethylcarbamoyl)borane is changed from a trialkylamine (2330 cm^{-1}) to a dialkylamine (2365 cm^{-1});[2] this may be attributed to analogous inductive effects occurring in the two systems. The N-H stretching mode in the *N*-methylmorpholine–carbamoylborane adduct exhibits two bands, which suggests some degree of intermolecular hydrogen bonding.[17] However, the shift to higher frequency of the N-H stretching mode, 3410 cm^{-1}, in the dimer ring suggests an absence of intermolecular hydrogen bonding.

In the *N*-methylmorpholine adduct the amide I and amide II bands are observed at 1595 and 1477 cm^{-1} respectively, consistent with solution spectra obtained on other trialkylamine adducts. In contrast, the amide I and amide II bands of the dimer are observed at 1570 and 1520 cm^{-1}. The shift to higher wavenumber of the amide II band corresponds to the dimer structure in that the N-H bond length would be expected to decrease since the lone pair on the amide is bonded to the boron. The shift to lower energy of the C=O mode implies a decrease in partial positive charge on the carbon and a lengthening of the carbon–oxygen bond resulting from the relative increase in electron density on the boron (and concurrent increase in the B-H frequency).

The ^{11}B NMR data for both the *N*-methylmorpholine adduct and the cyclic dimer correlate well with previously reported spectra.[12] Each triplet indicates the presence of a BH_2 moiety (with comparable coupling constants) while the proton-decoupled spectra exhibit only a single resonance, indicating the presence of a single type of boron in each compound.

The ^{1}H and $\{^{1}H\}^{13}$C NMR spectra of the *N*-methylmorpholine adduct show absorptions similar to those reported for other (*N*-ethylcarbamoyl)boranes (e.g. pyridine[13] and trimethylamine[2]) with peaks attributable to the *N*-ethyl group and the N-H on the carbamoyl function. The *N*-ethyl resonances in the ^{13}C NMR of the ring compound correspond to those observed for carbamoylborane adducts.

The mass spectral data for the ring compound, exhibiting no mass higher than 169, supports the assignment of a cyclic dimer structure rather than a linear oligomeric structure. The peak clusters and their relative intensities are what would be expected from the natural abundance of the boron isotopes.

A ring resulting from boron coordination to the carbonyl oxygen atom would be expected to have an IR absorption corresponding to the C=N$^+$R and also a ^{11}B NMR shift downfield of that observed. On this basis, the latter structure can be eliminated.

The reaction of the dimer with methylamine supports the ring formulation since no other product other than the known methylamine–carbamoylborane is generated. Additionally, this result indicates that use of the rings offers potential for formation of primary and secondary amine carbamoylboranes at rates faster than reported exchange reactions.[2] For example, exchange between methylamine and the carbamoylborane adduct of trimethylamine showed the reaction to be slower, being 65% complete in 1 week.[2] Similar reactivity studies are currently underway to establish the synthesis and reactivity of dimers containing different alkyl groups with amino acids and (aminomethyl)phosphonates.

Acknowledgment. Support of this work by the Utah Agricultural Experiment Station, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and a Sigma Xi Grant-In-Aid (D.A.F.) is gratefully acknowledged.

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Contribution from the Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300

Preparation of Monosubstituted Borane Adducts of an NH-Containing (Aminomethyl)phosphonate

Mallaiah Mittakanti and Karen W. Morse*

Received October 9, 1990

Introduction

Initially, the purpose of making a number of boron compounds that were analogues of amino acids was for use in boron neutron capture therapy.[1] However, since the compounds themselves

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0020-1669/91/1330-2434$02.50/0