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Synthesis and Characterization of the Cyano- and Carboxyborane Adducts of Quinuclidine

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A base displacement reaction has been used to prepare the new compound quinuclidine–cyanoborane from trimethylamine–cyanoborane. Such reactions have been used previously to prepare amine–boranes and other derivatives, but their application to preparing cyanoboranes has received little attention. By a literature method quinuclidine–cyanoborane was converted to quinuclidine–carboxyborane, which is of interest because of the unusual biological activity of amine–carboxyboranes.

Introduction

Syntheses have recently been reported for an extensive series of amine·BH_2R (R = CN, COOH, COOR′, C(O)NHR′) adducts.[1-4] Interest in these adducts stems from their extraordinary biological activity. In the case of trimethylamine–carboxyborane it was proposed that the isoelectronic and isostructural relationship of the compound with the dipolar amino acid betaine, $(CH_3)_3N^+CH_2CO_2^-$, might be responsible for the observed activity. Some other amine–carboxyboranes and related compounds also exhibited activity, however, and we undertook to prepare the carboxyborane adduct of quinuclidine (azabicyclo[2.2.2]octane) with the goal of comparing its activity with those mentioned earlier. The large cagelike amine, it is assumed, will assure that the structure bears no likeness to common amino acids.

The present report deals with the synthesis of quinuclidine–cyanoborane via the base displacement reaction shown in eq 1 and the subsequent conversion of the cyanoborane

$$HC(CH_2CH_2)_3N + (CH_3)_3N{\cdot}BH_2CN \xrightarrow[25\ ^\circ C]{C_6H_6} HC(CH_2CH_2)_3N{\cdot}BH_2CN + (CH_3)_3N \quad (1)$$

product to quinuclidine–carboxyborane using the alkylation–hydrolysis route developed by earlier workers.[2]

Experimental Section

All compounds described herein were manipulated either under dry nitrogen or with use of usual vacuum line methods. IR, NMR, and mass spectra were obtained with commercial instrumentation. The frequencies of ^1H and ^{11}B NMR spectrometers were 80 and 32 MHz, respectively. Elemental analyses were carried out by Canadian Microanalytical Service, Ltd.

Materials. Solvents were purified and dried according to standard methods.[5] Trimethylamine–cyanoborane was prepared from $NaBH_3CN$ (Aldrich) and $(CH_3)_3NHCl$ in THF solution by a literature method.[6,7] The crude product was purified by sublimation in vacuo at 50 °C (mp 64 °C, lit.[6] mp 63 °C; ^1H NMR in C_6H_6 δ 2.70, lit.[8] δ 2.74). Quinuclidine was dissolved in hot petroleum ether, filtered, and allowed to stand (under N_2) after the solution had been concentrated by evaporation to a rough vacuum (10–20 torr) for short intervals (quinuclidine is lost quickly to a better vacuum). The crystals thus obtained (mp 156 °C, lit.[9] mp 158 °C) were then sublimed in a cold-finger vacuum sublimer at 40 °C. Triethyloxonium tetrafluoroborate, $(C_2H_5)_3O^+BF_4^-$, was prepared from $(C_2H_5)_2O{\cdot}BF_3$ and epichlorohydrin according to the procedure of Meerwein.[10] The reactants were distilled immediately before use. Where this was not done, the product obtained was a grey semisolid and subsequent reactions with it gave unsatisfactory results. To a magnetically stirred solution of 90 mL of $(C_2H_5)_2O{\cdot}BF_3$ in 200 mL of $(C_2H_5)_2O$ (under N_2) was added 65.5 mL of epichlorohydrin in 30 mL of ether from a pressure-compensated dropping funnel. The rate of addition was chosen to just maintain reflux of the reaction mixture. An oil that formed initially was converted to a white precipitate during rapid stirring over 2 h. After the mixture stood overnight, the solvent was removed from the reaction mixture and the white solid product was washed three times with ether and dried under dynamic vacuum for 48 h. Yields ranging from 70 to 80% were obtained in several preparations. Portions of $(C_2H_5)_3O^+BF_4^-$ not used immediately were stored under nitrogen at or below 0 °C.

Preparation of $HC(CH_2CH_2)_3N{\cdot}BH_2CN$. Trimethylamine–cyanoborane (1.57 g, 16 mmol) and quinuclidine (Q, 2.23 g, 20 mmol) were placed in a flask fitted with a vacuum line adapter and magnetic stir bar. After evacuation, about 25 mL of benzene was condensed into the flask, after which the valve was closed and the reaction mixture stirred at room temperature. After 18 h, the volatiles were separated by fractional condensation through a series of traps and trimethylamine (10.7 mmol) was measured in a calibrated section of the vacuum line. The benzene and quinuclidine were recondensed into the flask, and the reaction continued for another 42 h, after which an additional

Table I. Comparison of IR Bands of Quinuclidine-Borane and -Cyanoborane (cm^{-1})

$Q{\cdot}BH_3$[a]	$Q{\cdot}BH_2CN$[b]	approx descripn[a,c]
(not reported)	2930 (s, br)	(C–H)
2357 (vs)	2380 (s)	ν_s(B–H)
2270 (s)	2320 (sh)	
	2220 (w)	C≡N
	2180 (w)	
	1455 (m)	
	1310 (m)	
1170 (vs)	1115 (s)	$\delta_s(BH_3)$
1055 (m)	1040 (m)	$\rho(CC_3,NC_3)$
935 (w)	950 (w)	ν_{as}(C–C–C–N)
863 (m)	860 (m)	$\delta_{as}(BH_3)$
837 (m)	825 (w)	$\nu_{as}(CC_3,NC_3)$
815 (mw)	795 (sh)	$\nu_s(CC_3,NC_3)$
685 (vw)	680 (w)	ν(B–N)
414 (w)	...	$\delta_{as}(CC_3,NC_3)$
271 (mw)	...	δ(B–N)

[a] From ref 16. [b] This work. [c] Abbreviations: ν = stretch, δ = deformation, ρ = rock, s = symmetrical, as = asymmetrical.

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2.1 mmol of $(CH_3)_3N$ was separated for a total of 12.8 mmol.

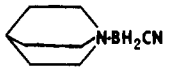
The solid residue was held under dynamic vacuum for about 1 h to ensure removal of quinuclidine and then transferred to a cold-finger sublimer. After sublimation at 70 °C with dry ice in the cold finger, 2.1 g (87%) of white solid sublimate, mp 139–140 °C, was isolated. Anal. Calcd for $C_8H_{15}BN_2$: C, 63.93; H, 10.05; N, 18.63. Found: C, 63.84; H, 10.01; N, 18.22. In several reactions yields from 65 to 88% were obtained. The ^1H NMR spectrum of $Q{\cdot}BH_2CN$ in $CDCl_3$ consisted of two multiplets centered at δ 1.8 and 3.2 (area ratio 7:6), closely resembling the spectrum of free quinuclidine (δ 1.6 and 2.8). The ^{11}B spectrum consisted of a broad but well-resolved triplet (J = 106 Hz) at δ −15.2 (reference $BF_3{\cdot}O(C_2H_5)_2$). The infrared spectrum of the product is shown in Table I. The mass spectrum of $Q{\cdot}BH_2CN$ obtained with use of a heated solid sample inlet (CI, CH_4) exhibited the ions (m/e (relative intensity)) 152 (5.2), 151 (54.9) (M^+ + H for $C_8H_{15}{}^{11}BN_2$), 149 (15.6), 125 (8.0), 124 (100.0), 123 (26.8), 112 (5.3), 111 (8.4), 96 (2.6), 95 (2.6), 94 (3.1), and 82 (2.1).

Preparation of $HC(CH_2CH_2)_3N{\cdot}BH_2COOH$. Best results in this synthesis were obtained with use of freshly prepared $(C_2H_5)_3O^+BF_4^-$ and quinuclidine–cyanoborane that had been sublimed and then held under dynamic vacuum for several days. Under N_2, 2.80 g of $(C_2H_5)_3O^+BF_4^-$ (slight excess) dissolved in 60 mL of CH_2Cl_2 was added to 1.0 g (6.7 mmol) of quinuclidine–cyanoborane in 30 mL of CH_2Cl_2. The reaction mixture was refluxed (42–44 °C) for 72 h, after which all volatiles were removed by vacuum transfer and the solid residue (presumed to be the nitrilium salt[2]) was held under dynamic vacuum 48–72 h. Degassed H_2O was then added to the reaction vessel to effect hydrolysis, and stirring was continued 4–5 days, after which the reaction mixture was extracted with four 30-mL portions of CH_2Cl_2. The combined CH_2Cl_2 solution was dried over activated 4A molecular sieves for 24 h and then transferred to another vessel, where the solvent was removed by vapor transfer.

The white solid product (0.86 g, 76%) melted with decomposition at 142–142.5 °C. Anal. Calcd for $C_8H_{16}BNO_2$: C, 56.87; H, 9.48; N, 8.30. Found: C, 56.35, 56.25; H, 9.66, 9.62; N, 7.93, 7.99. The ^{11}B NMR spectrum of $Q{\cdot}BH_2COOH$ in $CDCl_3$ consisted of a symmetrical triplet (J = 92 Hz) at δ −11.0. In acetone-d_6 the parameters of the triplet were δ −9.8 (J = 101 Hz). The IR spectrum of the product in a KBr pellet contained the following bands (cm^{-1}): 3600 (w, br), 3050 (sh, br), 2940 (s), 2880 (sh), 2725 (w), 2640 (w), 2580 (vw), 2380 (s), 2275 (w), 2180 (vw, br), 1680 (vs), 1520 (m), 1380 (vw), 1350 (m), 1310 (m), 1260 (s), 1210 (m), 1145 (sh), 1140 (vs), 1050 (s), 975 (m), 930 (m), 875 (m), 815 (m), 715 (vw), 650 (w). Besides chloroform and acetone, $Q{\cdot}BH_2COOh$ was moderately soluble in methylene chloride, slightly soluble in ethyl ether and benzene, and substantially insoluble in hexane and cyclohexane.

Results and Discussion

The goal of the work described here was to prepare the carboxyborane adduct of quinuclidine, **1**, in order to extend investigations carried out by Spielvogel, Hall, and co-workers on the antitumor,[3] antihyperlipidemic,[11] and antiinflammatory activity[4] of amine–carboxyboranes. Quinuclidine was chosen



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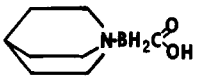
because its large, cagelike structure differs considerably from amines previously studied, permitting, it is hoped, an assessment of the importance of the steric qualities of the amine portion of the adduct to its biochemical activity.

The synthetic route chosen involves two steps. First, the quinuclidine–carboxyborane adduct was prepared by a displacement reaction of the free base on trimethylamine–cyanoborane (eq 1). Although other synthetic approaches are possible, displacement reactions had been used previously in this laboratory for the synthesis of quinuclidine–[12] and triethylenediamine– and piperazine–fluoroboranes.[13] The pronounced donor ability and favorable steric disposition of quinuclidine[14] render it an excellent displacing agent while the choice of trimethylamine, which can be periodically pumped away from the reaction mixture, affords a means toward improved yield by displacing the equilibrium towards products. The use of this type of reaction to prepare amine–cyanoboranes has apparently been very limited. In one previous instance[4] $H_3N{\cdot}BH_2CN$ was made by treating aniline–cyanoborane with liquid ammonia. In another, $(CH_3)_2HN{\cdot}BH_2CN$ was prepared from $(CH_3)_3N{\cdot}BH_2CN$ with use of a procedure described only as an "amine exchange reaction".[8]

The identity of **1** was established by its elemental analyses, mass spectrum, and NMR and IR spectra. The appearance of weak IR bands at 2220 and 2180 cm^{-1} and the absence of bands near 2135 cm^{-1} suggest[6,7,15] that only the cyanoborane isomer is present, no isomerization to isocyanoborane having occurred. This is confirmed by the ^{11}B NMR chemical shift, δ −15.2 (reference $BF_3{\cdot}O(C_2H_5)_2$), which resembles that of $(CH_3)_3N{\cdot}BH_2CN$, δ −15.1,[6] much more closely than that of $(CH_3)_3N{\cdot}BH_2NC$, δ −7.7.[15]

Table I compares IR bands of quinuclidine–borane[16] with those of **1**. A close correspondence between bands of the two adducts is evident except for the aforementioned bands due to C≡N, $Q{\cdot}BH_3$ bands below 650 cm^{-1} not observable with our instrument and unassigned bands at 1455 and 1310 cm^{-1} in the spectrum of **1**. Since B–C stretching frequencies appear in the 1300–1450-cm^{-1} range,[17] the unidentified bands may be associated with B–CN vibrational modes.

The synthetic procedure used to convert **1** into quinuclidine–carboxyborane (**2**) was essentially that described by Spielvogel and co-workers.[1-4] In order to obtain a pure



2

product, however, special care was needed in two areas.[18] First, our attempts to use commercial $(C_2H_5)_3O^+BF_4^-$ (solution in CH_2Cl_2) were uniformly unsuccessful, giving mixtures as detected by thin-layer chromatography that were not cleanly separable in our hands. The use of fresh $(C_2H_5)_3O^+BF_4^-$ prepared from newly distilled trifluoroborane ethyl etherate and epichlorohydrin afforded a clean product that melted sharply (although with decomposition) and did not require further purification. The second area that required special attention was the removal of volatiles immediately after alkylation. Prolonged exposure (2–3 days) to a dynamic vacuum was required to remove all the $(C_2H_5)_2O{\cdot}BF_3$ byproduct which was difficult to remove later in the process.

With these precautions, the method afforded a yield of about 75% for this step, which compares favorably with yields reported earlier.[2] The combined steps produced overall yields of 50–60%, again comparatively favorable; however, this is tempered by the fact that quinuclidine is uniquely suited for the displacement reaction used in the first step and other bases will probably give smaller yields.

The carboxyborane, **2**, was characterized by its elemental analyses and IR and ^{11}B NMR spectra. The boron spectrum consisted of a symmetrical triplet, δ −9.8, J = 101 Hz, which collapsed cleanly to a singlet upon broad-band irradiation of the ^1H resonance frequency. No other ^{11}B signals were de-

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tected in the sample of **2**. The absence of **1** was confirmed by the IR spectrum, which lacked the band at 2220 cm^{-1} assigned as a CN absorption. Strong bands at 2380 and 1680 cm^{-1} confirmed the B—C and C=O functionalities, the latter being absent in the spectrum of **1**.

Exposure of samples of **2** to the atmosphere for short periods produced no obvious changes in the solid. Upon being heated to its melting point, **2** decomposed rapidly, releasing copious quantities of gas.

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Kinetic and Equilibrium Studies on Reactions of the Diaquachromium(III) Complex Containing a Saturated Tetradentate Tetraaza 15-Membered Macrocycle Ligand

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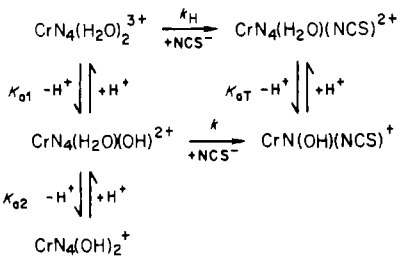
Air oxidation of $CrCl_2 \cdot 4H_2O$ in an aqueous solution of the macrocycle ligand [15]aneN$_4$ gives the diaquachromium(III) complex $[Cr([15]aneN_4)(H_2O)_2]^{3+}$, which is eluted as a single band from a Sephadex SP C-25 column. Reactions studied can be represented by



A sample of the aqua thiocyanato complex was prepared from the diaqua complex (1.0 M NCS^-, pH 6, 1 week) followed by Sephadex SP C-25 separation. From UV–visible spectrophotometric changes $pK_{a1} = 2.9$, $pK_{a2} = 7.8$, and $pK_{aT} = 4.6$ at 25 °C, $I = 1.0$ M ($LiClO_4$). Ion-pair formation constants for $CrN_4(H_2O)_2^{3+}$ and $CrN_4(H_2O)(OH)^{2+}$ with NCS^- are 1.2 and 0.7 M^{-1}, respectively. First-order rate constants, k_{obsd}, for the 1:1 substitution of NCS^- (0.10 M) are dependent on pH, with $CrN_4(H_2O)(OH)^{2+}$ the much more reactive form. At pH >7 rate constants k_{obsd} give a pK_{a2} (8.0) in agreement with that obtained from spectra. However, kinetic plots do not give good linearity (30–75% depending on pH), and over the range pH 1–7 there is a mismatch of dependences of k_{obsd} and absorbance (of $CrN_4(H_2O)_2^{3+}$) on pH. These effects are attributed to the existence of configurational (NH) or cis isomers of the trans [15]aneN$_4$ macrocycle complex.

Introduction

Cobalt(III) complexes of saturated tetraaza macrocycle ligands from [12]aneN$_4$ through [16]aneN$_4$ have been studied, and a correlation of macrocycle ring size with geometry of the isolated product reported. Thus, [12]aneN$_4$ gives cis products only, [13,14]aneN$_4$ give cis and trans isomers, and [15,16]-aneN$_4$ give trans forms.[1-4] For a series of Co[15]aneN$_4$)X_2^+ complexes, Busch and colleagues[4] have obtained evidence in support of configurational isomers resulting from the different orientations of the NH group. With chromium(III) as the central metal, Swisher et al.[5] have demonstrated a similar dependence on macrocycle ring size, with only the cis isomer for [12]aneN$_4$, cis and trans for [14]aneN$_4$, and trans for [15]aneN$_4$. Existing evidence therefore favors the trans isomer of the [15]aneN$_4$ complex as the dominant form. We thought it of interest to examine in some detail the solution chemistry of $[Cr([15]aneN_4)(H_2O)_2]^{3+}$ with emphasis on kinetic and equilibration processes. Thiocyanate was selected as an appropriate complexing anion because it can be used over a wide pH range and has strong nucleophilic properties. Samuels and Espenson[6] have previously reported studies on the reactivity of the $[Cr([15]aneN_4)(H_2O)_2]^{2+}$ complex, which is a strong reducing agent (−0.58 V). Since the latter has potential use as an inner-sphere reductant for the identification of binding sites in electron-transfer reactions of metalloproteins,[7] it was also of interest to explore substitution properties of the Cr(III) complex over a wide range of pH.

Experimental Section

Preparation of $CrN_4(H_2O)_2^{3+}$. The diaqua(1,4,8,12-tetraazacyclopentadecane)chromium(III) complex, $[Cr([15]aneN_4)(H_2O)_2]^{3+}$,

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