Preparation of Novel Fluoro Derivatives of Amine Cyanoboranes and Amine Carboxyborane Esters

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Summary: Sonication of the amine mono- and dibromocarboxyborane esters or the amine mono- and dibromocyanoboranes with excess AgF results in rapid incorporation of fluorine by bromine/fluorine exchange to provide the difluoro derivatives of amine cyanoboranes and amine carboxyborane esters, ***1*****−****10***, *in yields of 59−70%. Bromination of the amine monofluorocyanoboranes and amine monofluorocarboxyborane ester derivatives successfully afforded the expected amine bromofluoro derivatives,* ***11*** *and* ***12***, *in yields of 57−62%. This was confirmed by NMR shifts for all compounds. The* pK_a *value for the fluorinated amine carboxyborane* ***13*** *was determined and found to be 5.15 compared to 8.38 for* $Me_3N{:}BH_2COOH$, *in line with expectations. The molecular structure for compound* ***1*** *was determined by X-ray crystallography.*

Introduction

Amine cyanoboranes, amine carboxyboranes, and amine carboxyborane amides and esters are interesting groups of compounds that have been known to possess various biological activities.[1−13] The mechanism of action of these compounds is not completely known. Halogenated aromatic amino acids (bromine, chlorine, and iodine on the aromatic ring of histidine, tryptophan, and tyrosine) are well known.[14] While a number of studies have been reported in the literature on the preparation of the amine:BH_2I complexes, as well as the monobromo- and dibromoboron-substituted derivatives of amine cyanoboranes, carboxyboranes, and carboxyborane esters, and on their use in substitution reactions,[14,15] the corresponding fluoro derivatives have not been described before. In the present study, a series of novel mono- and difluoro derivatives of amine cyanoboranes and amine carboxyborane esters were synthesized via F/Br exchange.[16] The structure of compound **1** was determined by X-ray diffraction.

Results and Discussion

Fluorination of Amine Monobromocyanoboranes and Amine Monobromocarboxyborane Esters. Amine monofluorocarboxyborane esters and amine monofluorocyanoboranes, A:BHFX (A = Me_3N, ethyldimethylamine, *n*-butyldimethylamine, X = CN, COOR, where R = Me, Et), were prepared from the corresponding amine monobromocarboxyborane esters and amine monobromocyanoboranes, respectively, A:BHBrX. This was accomplished by F/Br exchange using AgF, where the monobromo derivative was dissolved in dry benzene and sonicated for a period of 5 h with 5 equiv of AgF. This produced the desired monofluoro derivatives of both amine cyanoboranes and amine carboxyborane esters in good yields and high purity, **1**−**7** (Scheme 1, Table 1).

Fluorination of Amine Dibromocyanoboranes and Amine Dibromocarboxyborane Esters. Amine difluorocarboxyborane esters, $Me_3N{:}BF_2X$ (X = CN, COOR, where R = Me, Et), **8**−**10** (Scheme 1, Table 1), were successfully obtained from the corresponding amine dibromocarboxyborane esters and the corresponding amine dibromocyanoboranes by F/Br exchange using AgF following the procedure used for preparation of the monofluoro derivatives, but the sonication time was extended to 8 h. The desired products were produced in good yields and high purity, **8**−**10** (Scheme 1, Table 1). Another known fluorinating reagent, $Et_3N{\cdot}$3HF complex, was also tested. Three equivalents of $Et_3N{\cdot}$3HF complex were heated with the bromo derivatives in refluxing toluene for 24 h, to give the desired F/Br exchange in 62% yield. However, fluorination was

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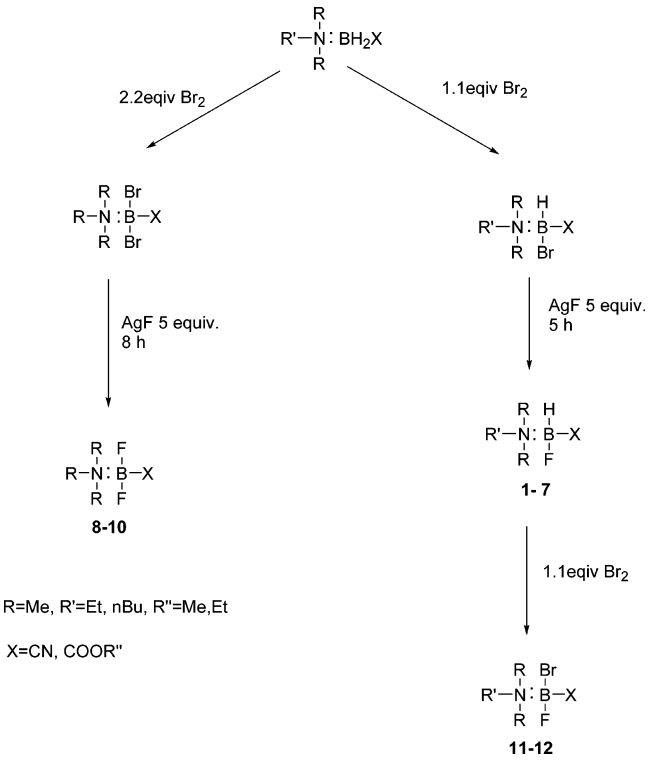
Scheme 1. Preparation of Compounds 1−12 from the Corresponding Amine Cyanoboranes and Amine Carboxyborane Esters



accompanied by an amine exchange. In addition, the reaction was accompanied by cleavage of the ester group, possibly due to the acidic medium and high temperature used and triethylamine difluorocarboxyborane ($Et_3N{:}BF_2COOH$), **13**, was obtained (Scheme 2, eq 2).

Bromination of Trimethylamine Monofluorocyanoborane and Trimethylamine Monofluoromethoxycarbonylborane. Reaction of trimethylamine monofluorocyanoborane, **1**, or trimethylamine monofluoromethoxycarbonylborane, **4**, with 1.1 equiv of Br_2 in methanol at 0 °C for a period of 4 h produced the desired trimethylamine bromofluorocyanoboranes, **11**, or trimethylamine bromofluoromethoxycarbonylborane, **12**, in high purity and good yields (Scheme 1, Table 1).

Spectroscopic Analysis. All compounds were fully characterized by ^1H, ^{11}B, and ^{13}C NMR, FT-IR, LC-MS, and elemental analysis. The ^1H and ^{13}C NMR spectra showed an upfield shift of the Me_2N peak when bromine was replaced by the highly electronegative fluorine (Table 1). This indicates that the replacement of the bromine atom by fluorine reduces the Lewis acidity of the compound. This is unexpected in view of the increase of the electronegativity from bromine to fluorine, which would predict a decrease in the electron density surrounding the boron atom and thus an increase in the Lewis acidity. A consequence of this is the upfield shift of the fluoro derivatives in the ^1H NMR as well as the ^{13}C NMR spectra compared to the bromo derivatives. For $Me_3N{:}BH_2CN$, in the ^1H NMR spectrum the chemical shift for the methyl groups was 2.71 ppm, while in $Me_3NBHBrCN$, the peak absorbed at 2.88 ppm, and for $Me_3N{:}BHFCN$, **1**, it was at 2.66 ppm. The B−N bond in the fluoro derivatives of amine cyano and carboxyboranes is longer and weaker in comparison to that of the bromo derivatives and the parent amine cyano- and carboxyboranes.[16,17] This was confirmed for compound **1** by the X-ray structure determination, where the detected B−N bond length was 1.6074 Å for compound **1** compared to 1.592 Å for the dibromo derivative of the same compound. An expected downfield shift was observed for all compounds due to the deshielding effect caused by the highly electronegative fluorine atom, in the ^{11}B NMR (Table 1). For $Me_3N{:}BH_2CN$ the ^{11}B NMR spectra showed a triplet at −13.72 ppm, while for $Me_3N{:}BHBrCN$, a doublet was obtained at −11.12 ppm, and for $Me_3N{:}BHFCN$ **1**, a doublet of doublets was obtained at −2.3 ppm. In the monofluoro derivatives, the ^{11}B NMR peaks were obtained as a doublet of doublets due to splitting by both hydrogen and fluorine atoms attached to boron (see figure a in Supporting Information), while a triplet was observed in the difluoro derivatives (see experimental data in the Supporting Information). In the ^{19}F NMR, a quartet was observed for the amine difluorocyanoborane derivative, **8**, and the amine diflourocarboxyborane ester, **9** and **10** (see experimental data in the Supporting Information). This was expected due to coupling to the ^{11}B atom, which has spin of 3/2. A quartet of doublets was observed for all the amine monofluorocyanoboranes, **1**−**3**, and the amine monoflourocarboxyborane esters, **4**−**7**, because of the splitting of both boron and hydrogen neighbor atoms (see figure b in the Supporting Information). We found that the differences in the chemical shift ranges in the mono- and difluoro derivatives in all cases are large: ∼145 ppm (−25 to −27 ppm for the monofluoro derivatives and −165 to −167 ppm for the difluoro derivatives). This is reasonable because in the ^{19}F NMR it is known that the fluorine atom is much more sensitive to the local environment than hydrogen. The IR vibrations are in the expected range: (2955−2971 cm^{-1}) C−H, (2219−2260 cm^{-1}) C≡N, (1455−1493 cm^{-1}) C−N, (1680−1705) C═O, (534−607 cm^{-1}) B−Br, (1104−1193) B−F, (2413−2473) B−H stretching vibrations. Molecular weights (LC/MS) were observed for all compounds **1**−**13**.

Crystallography. Crystals suitable for X-ray structure determination were obtained for compound **1** from water. The structure of compound **1** was confirmed by single-crystal X-ray diffraction analysis (Figure 1). The measurements were carried out at ca. 110 K, to optimize the precision of the crystallographic determination, with Mo Kα radiation.

Crystal data: $C_4H_{10}BFN_2$, M = 115.95, triclinic, space group $P\bar{1}$, a = 5.5341(1) Å, b = 13.6738(5) Å, c = 19.0172(6) Å, α = 110.802(1)°, β = 95.012(2)°, γ = 90.643(2)°, V = 1338.74(7) Å^3, Z = 8, T = 110(2) K, D_c = 1.151 g·cm^{-3}, μ(Mo Kα) = 0.09 mm^{-1}, 5799 unique reflections to $2\theta_{max}$ = 56.3°, 341 refined parameters, R_1 = 0.046 for 4456 observations with $I > 2\sigma(I)$, R_1 = 0.065 (wR_2 = 0.125) for all unique data. The asymmetric unit of this structure is four crystallographically independent molecules of $(CH_3)_3N{:}B(H)(F)CN$. This should be attributed to the conformational disorder around the sp^3 boron atoms, which is characterized by alternating orientations of the B−H and B−F bonds. These bonds occupy about the same volume in space and, thus, can

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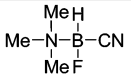
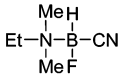
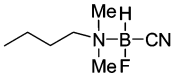
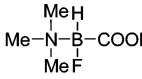
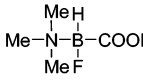
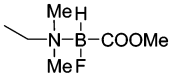
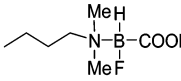
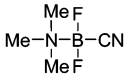
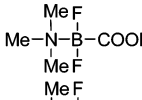
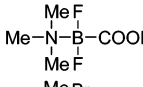
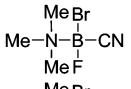
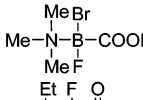
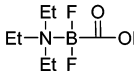
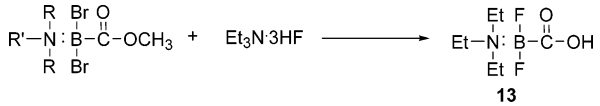
Table 1. ^{11}B and ^{19}F NMR Data for Compounds 1−13 and Their Precursors

No	structure	^{19}F δ (ppm)	^{11}B-δ(ppm)	^{11}B- δ(ppm) of A:BH_2X	^{11}B - δ(ppm) of Br-precursor	Yield %[a]
1*		-27.10	-2.30	-13.72	-11.12	65 %
2		-25.90	-2.42	-16.36	-11.55	63 %
3		-25.50	-2.45	-16.12	-12.11	66 %
4		-27.30	0.26	-10.12	-6.76	69 %
5		-26.98	0.29	-10.12	-6.67	65 %
6		-27.75	-0.23	-13.72	-7.12	69 %
7		-25.50	1.86	-13.26	-6.90	59 %
8		-159.75	0.18	-13.71	-9.89	67 %
9		-167.63	-1.47	-10.12	-3.64	70 %
10		-167.75	-1.64	-10.12	-3.83	66 %
11		-115.32	2.35	-13.72	-11.79	65 %
12		-120.77	2.92	-10.12	-6.67	57 %
13		-130.51	-1.54	-10.12	-3.64	62 %

[a] Isolated yield. *Crystal product.

Scheme 2. Reactions of Amine Dibromocarboxyborane Esters with $Et_3N{\cdot}3HF$



13

occupy either of the two possible directions around the tetrahedral boron. In the observed structure, the refined structural model of best fit to the diffraction data is represented by four molecular species with differently populated 2-fold conformational disorder (with 64−70% to 30−36% ratio) of this type. Figure 1 shows the four molecules of this compound in their major conformation.

The covalent parameters exhibit standard values characteristic of boron in tetrahedral sp^3 hybridization, with B−N, B−C, and B−F (major conformation) within 1.603(19)−1.609(18) Å, 1.614(2)−1.617(2) Å, and 1.333(3)−1.364(3) Å, respectively. The conformation around the boron atom is nearly ideally tetrahedral with N−B−C bond angles within 107.9(11)−108.6(11)°, F−B−C angles within 110.4(18)−110.9(18)°, and N−B−F angles within 109.8(19)−110.3(12)°.

The molecules are rather loosely packed in the crystal structure (as reflected by the calculated density of only 1.15 g·cm^{-3}), which explains the difficulties encountered in growing diffraction-quality crystals of this compound. Correspondingly, all interatomic distances between neighboring molecules in the crystal are equal to, or longer than, the sums of the corresponding van der Waals radii. Indeed, not even weak intermolecular hydrogen-bonding interactions of C≡N···H−C or C−F···H−H could be detected in this structure, due to the lack of adequately acidic protons and the "hard" nature of the potential N and F acceptors. The loose crystal packing facilitates the occurrence of the conformational disorder described above. The crystal structure is illustrated in Figure 2.

Effect of B−F Bond on the Acidity Constant of Amine Carboxyboranes. The effect of the presence of a highly electronegative fluorine atom on the acidity constant (pK_a) of the carboxyborane group was determined. The pK_a was measured by acid−base titration using 1 N aqueous NaOH solution. An expected decrease of pK_a value was observed for the fluorinated amine

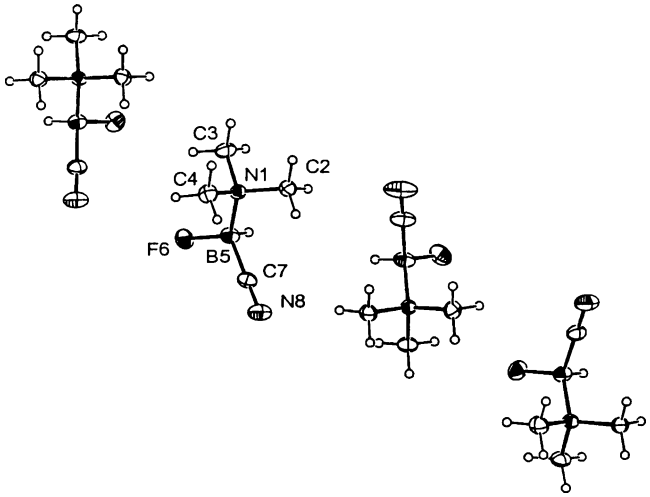


Figure 1. Molecular structure of compound **1**. Ellipsoids represent thermal displacement parameters at the 50% probability level. The selected ranges of bond distances (Å) and angles (deg) are as follows: B−N, 1.603(19)−1.609(18), B−C, 1.614(2)−1.617(2), B−F, 1.333(3)−1.364(3), N−B−C, 107.9(11)−108.6(11), F−B−C, 110.4(18)−110.9(18), N−B−F, 109.8(19)−110.3(12).

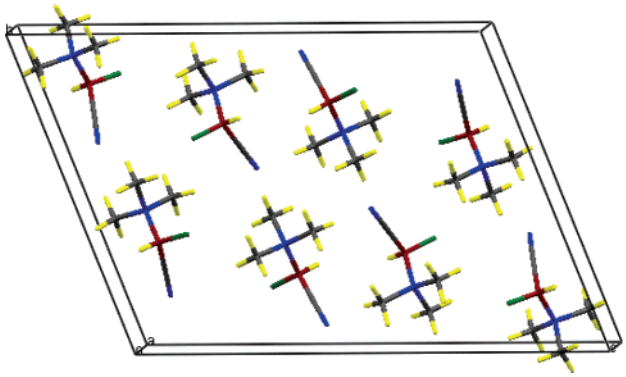


Figure 2. Crystal packing down the *a*-axis (*c* is horizontal) of the crystal, showing eight molecules in the unit cell. Only the major conformers (64−70%) of the molecules are shown. Note their different orientations and the loose intermolecular organization. Color code: B, red; F, green; N, blue; C, gray; H, yellow.

carboxyborane **13** from 8.38 for the unfluorinated amine carboxyborane[18] to a pK_a of 5.15.

Conclusion

Fluoro-containing amino acids are potentially very interesting pharmacological compounds. We have prepared and characterized amine fluorocarboxyboranes on the basis of the exchange of bromide by fluoride using AgF or $Et_3N{\cdot}3HF$ complex. However, the disadvantage of the latter is that the fluorination was accompanied with amine exchange in amine dibromocarboxyborane esters and cleavage of the ester group of the amine dibromocarboxyborane esters. Sonication of the amine mono- and dibromocarboxyborane esters or the amine mono- and dibromocyanoboranes with excess AgF results in the rapid incorporation of fluorine into the compounds, and the mono- and difluoro derivatives of amine cyanoboranes and amine carboxyborane esters were obtained, **1**−**10**. This was determined by various NMR techniques such as ^{19}F, ^{11}B, ^{1}H, and ^{13}C NMR, FT-IR, mass spectra, and elemental analysis. Bromination of the amine monofluorocyanoboranes and amine monofluorocarboxyborane ester derivatives successfully afforded the expected amine bromofluoro derivatives, **11** and **12**.

Experimental Section

Spectroscopic Analysis. ^{1}H, ^{11}B, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ solution on a Varian Unity spectrometer (300, 96, 75, 282 MHz) using Me_4Si as an internal standard. LC-MS analyses were performed on a Finnigan LCQDUO Thermo Quad, with electron spray detector. Infrared spectra were run for samples in KBr disks for solids on a Bruker Vector 22 FT-IR spectrophotometer. Elemental analyses were performed in-house at the Hebrew University Microaanalysis laboratory. Melting points were measured on a Fisher Scientific melting point apparatus.

General Procedures. $Me_3N{:}BH_2CN$ was prepared from $Me_3N{\cdot}HCl$ and $NaBH_3CN$ using the literature method.[12] $Me_3N{:}BH_2COOH$,[13] $Me_3N{:}BHBrCOOR$,[16] and the amine cyanoborane derivatives[17] were prepared using previously reported methods. All other chemicals were obtained from Sigma-Aldrich and used as received without any further purification.

Preparation of Compounds 1−7. A:BHBrX (A = Me_3N, ethyl dimethylamine, *n*-butyl dimethylamine, X = COOR, CN, R = Me, Et) (1 mmol) was dissolved in 2 mL of dry benzene. Silver(I) fluoride 99% (5 equiv) was suspended in 5 mL of dry benzene and added to the reaction mixture, which was then sonicated for 5 h. The solution was then filtered, and the solvent was removed from the filtrate under high vacuum.

Preparation of Compounds 8−10. A:BBr_2X (A = Me_3N, ethyl dimethylamine, *n*-butyl dimethylamine, X = COOR, CN, R = Me, Et) (1 mmol) was dissolved in 2 mL of dry benzene. Then 5 equiv of silver(I) fluoride 99% was suspended in 5 mL of dry benzene and added to the reaction mixture, which was then sonicated for 10 h. The solution was then filtered, and the solvent was removed from the filtrate under high vacuum.

Preparation of Compounds 11 and 12. Trimethylamine monofluorocyanoborane **1** (0.5 mmol) or trimethyamine monofluoromethoxycarbonylborane **4** was dissolved in 2 mL of distilled water and cooled to 0 °C. Then 0.51 mmol of bromine dissolved in 5 mL of distilled water was added dropwise, and the reaction was left to stir at 0 °C for 4 days. The produced precipitate was filtered and recrystallized from hot water.

Preparation of Compound 13. Trimethylamine dibromomethoxycarbonylborane (1 mmol) was dissolved in toluene. $Et_3N{\cdot}3HF$ complex (3 equiv) was added, and the reaction mixture was refluxed for 24 h. Solvent was removed under high vaccum.

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Supporting Information Available: Figures showing ^{11}B NMR spectra and ^{19}F NMR spectra for trimethylamine monofluorocyanoborane **1**, text giving ^{1}H, ^{11}B, ^{19}F, and ^{13}C NMR data, FT-IR data, melting points, and elemental analysis data for compounds **1**−**13**, and CIF files giving atomic positional and thermal displacement parameters, bond distances, bond angles, and torsion angles, together with details of data collection and structure solution and refinement for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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