Ring Opening of Tetrahydropyran Attached to Undecahydro-*closo*-dodecaborate(1−) by Nucleophiles

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Introduction

Little is known about the reactions of organic moieties attached to *closo*-boranes. In previous investigations we reported the derivatization of $[B_{12}H_{11}SH]^{2-}$, $[B_{12}H_{11}NH_3]^-$, and $[B_{12}H_{11}OH]^{2-}$.[1−3] The alkylation of the latter with dibromopentane gave $[B_{12}H_{11}O(CH_2)_5]^-$, **1**.[3] Compound **1** contains a tricoordinate oxygen atom and therefore was interpreted as an oxonium salt, although it showed surprising stability with respect to hydrolysis. In this note we describe the reactions of **1** with halide and hydroxide ions in THF solution which result in the opening of the tetrahydropyran ring.

Results and Discussion

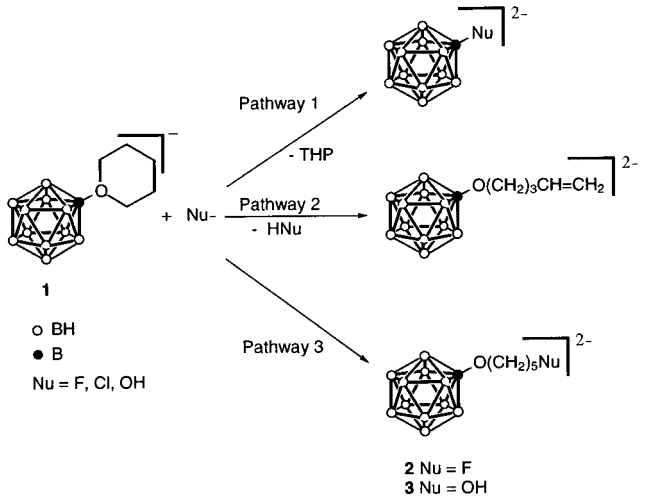
Principally, three different reaction pathways are conceivable in the reaction of $[B_{12}H_{11}O(CH_2)_5]^-$ with nucleophiles due to the positively charged oxygen of **1** (see Scheme 1). The first pathway, the replacement of the cyclic ether by the anion Nu^- (Nu = F, Cl, OH), would afford $[B_{12}H_{11}Nu]^{2-}$ and tetrahydropyran. In the second route, a Hofmann-type dealkylation at the trisubstituted oxygen, the anion Nu^- would act as a base abstracting the β-proton of the tetrahydropyran ring, leading to the formation of HNu and the olefin $[B_{12}H_{11}O(CH_2)_3CH{=}CH_2]^{2-}$. The third possible pathway would be an S_N2 substitution at an α-carbon of tetrahydropyran affording $[B_{12}H_{11}O(CH_2)_5Nu]^{2-}$.

The reactions of compound **1** with tetrabutylammonium fluoride, tetrabutylammonium hydroxide, and tetrabutylammonium chloride, respectively, were carried out in THF solution. In the case of the fluoride and hydroxide ions, the room-temperature conversion of **1** to the new species **2** and **3** was observed by HPLC. However, a solution of **1** and tetrabutylammonium chloride in THF did not react, even when refluxing for 24 h.

It was found that both fluoride and hydroxide ion reacted with **1** according to pathway 3 affording compounds of the type $[B_{12}H_{11}O(CH_2)_5Nu]^{2-}$ (**2**, Nu = F; **3**, Nu = OH). The structures of compounds **2** and **3** were determined by NMR spectroscopy.

The ^{19}F NMR spectrum of **2** consists of a multiplet at −217.0 ppm with a pattern typical for the CH_2CH_2F moiety. This signal is split into a triplet of triplets due to the geminal $[^2J(^1H-^{19}F) = 47.5$ Hz] and vicinal proton coupling $[^3J(^1H-^{19}F) = 25.0$ Hz]. Five $^{13}C\{^1H\}$ NMR resonances were observed, of which the signals at 84.0, 30.0, and 21.6 ppm appeared as doublets due to the direct $[^1J(^{13}C-^{19}F) = 161.8$ Hz], geminal $[^2J(^{13}C-^{19}F) = 18.6$ Hz], and vicinal $[^3J(^{13}C-^{19}F) = 5.4$ Hz] coupling to fluorine. The ^1H NMR spectrum of **2** contains a doublet of triplets for a CH_2F group recorded at 4.4 ppm. Since the chemical shifts as well as the $^nJ(^{13}C-^{19}F)$ ($n = 1-3$) and $^2J(^1H-^{19}F)$ coupling constants are consistent with a terminal fluoroalkyl group, the structure of **2** is readily assigned to the fluoropentamethylene derivative $[B_{12}H_{11}O(CH_2)_5F]^{2-}$.

Scheme 1. Pathways in the Reaction of **1** with Nucleophiles



The ^1H NMR spectrum of **3** recorded in DMSO-d_6 contained a triplet at 4.3 ppm which was assigned to the hydroxyl proton since it vanished upon addition of D_2O. A multiplet at 3.4 ppm resolved into two triplets upon the addition of D_2O and was attributed to the two CH_2O hydrogens. Five singlets were found in the $^{13}C\{^1H\}$ NMR spectrum of **3**. All NMR data for **3** are consistent with the derivative $[B_{12}H_{11}O(CH_2)_5OH]^{2-}$. No evidence for an olefinic group was found, ruling out the possibility that reaction pathway 2 had taken place.

Of the three possible reaction pathways described in Scheme 1 only one took place, the nucleophilic substitution reaction at the α-carbon atom of the trisubstituted oxygen. The replacement of the boron-bound tetrahydropyran ligand by a nucleophile is not feasible, probably due to the strong boron−oxygen bond. We assume that compound **1** might react according to pathway 2 with the application of a sterically hindered base such as potassium *tert*-butoxide. The anticipated product of this reaction, $[B_{12}H_{11}O(CH_2)CH{=}CH_2]^{2-}$, would provide a double bond with the potential for further derivative chemistry. The oxonium salt **1** reacted only with fluoride and hydroxide ions. No conversion was observed in the case of the chloride ion. This was unexpected taking into account that the chloride ion is usually a better nucleophile than the fluoride or the hydroxide ion. We conclude that the hardness of the applied base is an important factor for the observed reactions. Both the fluoride and the hydroxide ion are hard bases. It is possible for these two ions to replace the softer base, the uncharged disubstituted oxygen. The chloride ion, on the other hand, cannot displace the ether oxygen, since chloride is considered to be a softer base than the fluoride or the hydroxide ion.

A somewhat similar ring opening of a cyclic ether has been reported previously.[4] The boron cluster $[B_{20}H_{18}]^{2-}$ was found to react in the presence of NaOMe in THF to afford the $[B_{20}H_{18}O(CH_2)_4OMe]^{4-}$ anion. However, in this case no evidence for a chemical bond between the THF molecule and the boron cluster could be found prior to the ring-opening reaction.

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Conclusion

In this study it was shown that the formally positively charged oxygen of tetrahydropyran bound to $B_{12}H_{11}^-$ polarizes the α-carbon atoms of the ether ring. This polarization allows for the nucleophilic attack of hard bases like fluoride and hydroxide ions, whereas the softer chloride anion did not react. The substituted pentamethylenealkoxy derivatives of $B_{12}H_{11}^-$ were isolated in good yields. The monohydroxy compound **3** is a useful synthon for further derivative chemistry. It can be described as a $B_{12}H_{11}^-$ moiety to which a hydroxy group is attached to the boron cage with a pentamethylenealkoxy chain as a spacer. It should therefore be possible to utilize the reactivity of the hydroxy group in order to attach the icosahedral boron cluster to tumor-seeking compounds, which is of considerable interest in boron neutron capture therapy.[5]

Experimental Section

The NMR data were recorded in DMSO-d_6 at room temperature with ^{1}H NMR (δ(TMS) = 0.0 ppm) at 360.1 MHz, ^{13}C{^{1}H} NMR (δ(TMS) = 0.0 ppm) at 90.1 MHz, and ^{19}F NMR (δ($CFCl_3$) = 0.0 ppm) at 338.9 MHz. Only selected NMR data are given in the Experimental Section. Microanalyses were performed by Analytische Laboratorien, Prof. Dr. H. Malissa und G. Reuter GmbH, Gummersbach, Germany. Melting points obtained on a Gallenkamp melting point apparatus are uncorrected.

Synthesis of $[N(n\text{-}C_4H_9)_4]_2[B_{12}H_{11}O(CH_2)_5F]$, 2. A sample of 200 mg of $[N(n\text{-}C_4H_9)_4][B_{12}H_{11}O(CH_2)_5]$ (0.43 mmol), **1**,[3] and 675 mg of tetrabutylammonium fluoride trihydrate (2.14 mmol) were dissolved in 20 mL of THF. The solution was stirred for 20 h at room temperature, turning slightly orange. The reaction mixture was poured into 100 mL of water, and THF was evaporated *in vacuo*. The precipitate that formed was filtered off and dried. Dissolving the solid in ethanol and allowing diethyl ether to diffuse into the solution afforded 180 mg (0.25 mmol, 58%) of large, colorless crystals (mp 156 °C) of **2**.

^{1}H NMR: 4.4, CH_2F (dt, J = 47.5, 6.3 Hz). ^{13}C{^{1}H} NMR: 84.0, CH_2F (d, J = 161.8 Hz); 67.8, OCH_2; 31.5, OCH_2CH_2; 30.0, CH_2CH_2F (d, J = 18.6 Hz); 21.6, $CH_2CH_2CH_2F$ (d, J = 5.4 Hz). ^{19}F NMR: −217.0, CH_2F (tt, J = 47.5, 25 Hz).

Anal. Calcd for $C_{37}H_{93}B_{12}FN_2O$: C, 60.80; H, 12.83; B, 17.75; N, 3.83. Found: C, 60.83; H, 12.79; B, 17.60; N, 3.82.

Synthesis of $[N(n\text{-}C_4H_9)_4]_2[B_{12}H_{11}O(CH_2)_5OH]$, 3. A sample of 0.32 g of **1** (0.68 mmol) and 2.0 g of tetrabutylammonium hydroxide decahydrate (2.50 mmol) were dissolved in 20 mL of THF. The reaction mixture was stirred for 20 h at room temperature and turned slightly red. After removal of the solvent *in vacuo*, the gummy residue was stirred in 20 mL of water until it solidified. The solid was dissolved in aqueous acetone, and the acetone was allowed to evaporate to precipitate 0.33 g (0.45 mmol, 66%) of (mp 102 °C) **3**.

^{1}H NMR: 4.3, OH (t); 3.4−3.3, 2 OCH_2 (m). ^{13}C{^{1}H} NMR: 68.1, CH_2OB; 61.0, CH_2OH; 32.9, CH_2CH_2OH; 32.0, CH_2CH_2OB; 22.4, $CH_2CH_2CH_2O$.

Anal. Calcd for $C_{37}H_{94}B_{12}N_2O_2$: C, 60.97; H, 13.00; B, 17.80; N, 3.84. Found: C, 60.95; H, 12.88; B, 17.64; N, 3.80.

Reaction of 1 with Tetrabutylammonium Chloride. A sample of 150 mg of **1** (0.21 mmol) and 297 mg of tetrabutylammonium chloride (1.07 mmol) were dissolved in 10 mL of THF. The solution was refluxed for 24 h, and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue showed only signals of the starting material.

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