Methylation and protonation of 1-aza-5-bora-4,6,11-trioxabicyclo-[3.3.3]undecane and 1-aza-5-borabicyclo[3.3.3]undecane

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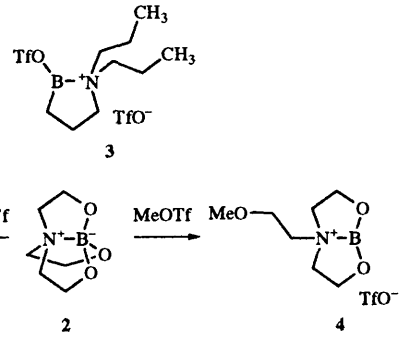
1-Aza-5-bora-4,6,11-trioxabicyclo[3.3.3]undecane (triethanolamine borate) reacts with methyl trifluoromethanesulfonate (triflate) with cleavage of one of the B–O bonds to give 1-(2-methoxyethyl)-1-aza-5-bora-4,6-dioxabicyclo[3.3.0]octan-1-ium triflate, but protonation occurs on nitrogen with cleavage of the intrabridgehead B–N bond. 1-Aza-5-borabicyclo[3.3.3]undecane is unaffected by methyl triflate or triflic acid in dichloromethane or acetonitrile, but undergoes B–C cleavage in neat triflic acid.

1-Aza-5-borabicyclo[3.3.3]undecane **1** and 1-aza-5-bora-4,6,11-trioxabicyclo[3.3.3]undecane (triethanolamine borate) **2** possess B–N bonds.[1–3] Because of our interest in intrabridgehead chemistry,[4] we wondered if these intrabridgehead bonds could be opened by reaction of electrophiles at nitrogen or nucleophiles at boron. Reactions of this type potentially suffer from two penalties (a) the B–N bond is lost, and (b) the strain energy of the system will increase substantially as the boron and nitrogen atoms are pulled apart.[4] In particular, outward pyramidalization of the bridgehead atoms is strongly resisted in the [3.3.3] ring system (the trimethylene bridges are practically strain-free when the bridgehead atoms are planar). Triethanolamine borate **2** has been reported to react extremely slowly with methyl iodide at moderate temperatures, but the product was not characterized.[1] We have examined the reactions of **1** and **2** with methyl triflate and with triflic and other acids.

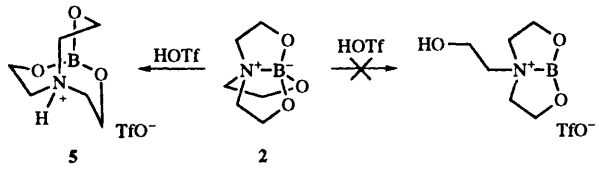
Results and discussion

1-Aza-5-borabicyclo[3.3.3]undecane **1** was made by following a modified literature procedure.[1,2] When **1** was stirred with either methyl triflate or triflic acid at room temperature in dichloromethane or acetonitrile solvent under nitrogen for 24 h, no reaction occurred. In view of the high reactivity of methyl triflate, this lack of reaction speaks for the strength of the B–N bond in this compound. Reaction of **1** with neat triflic acid leads to immediate changes in the ^{11}B spectrum, but no clear evidence for *N*-protonation. On standing, very slow protolysis of the B–C bonds occurs. Proton and ^{13}C spectra of the solution after four months suggest the major component is the result of two B–C cleavages, probably the boron triflate **3**. Triethanolamine borate **2** has been reported to react slowly with methyl iodide at moderate temperatures.[1] However, we observed that 90% of **2** remained unchanged after heating at 60 °C for 2 months with excess methyl iodide in acetonitrile. On the other hand, compound **2** reacted quickly with methyl triflate in acetonitrile to give **4**; the reaction took 24 h to complete when dichloromethane was used as solvent. In both cases, the only product resulted from cleavage of a B–O bond (Scheme 1). We are not aware of any real precedent for this reaction, but kinetically-controlled reaction with the lone pairs on oxygen as opposed to attack (with inversion) on the N–B bond or capture of low concentration of a ring opened form is quite reasonable.

In spite of this preference for *O*-methylation, protonation of **2** appears to give the *N*-protonated species **5** exclusively (Scheme 2). This reaction was measurably slow and the rate was dependent on the strength of the acid. When triflic acid was used, the reaction was complete in 10 min. With trifluoroacetic acid, a milder acid, the reaction required 24 h



Scheme 1



Scheme 2

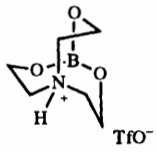
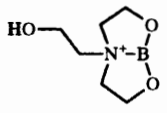
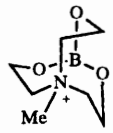
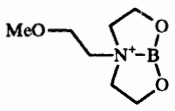
Table 1 Rate of conversion of **2** to **5**

Acid	10 min	2 h	24 h
CF_3SO_3H	100%		
FSO_3H	100%		
CF_3CO_2H	10%	40%	80%
$5CF_3CO_2H$	40%	86%	100%

to reach completion (Table 1). When **2** was reacted with 0.5 equivalent of acid, separate ^1H and ^{13}C NMR spectra for 0.5 equivalent each of **2** and **5** were seen. This shows that interconversion of **2** and **5** is slow on the NMR time scale and rules out the possibility that **2** gives a set of *O*-protonated species, analogous to **4**, which are in rapid equilibrium with one another. When **5** was treated with 1 equivalent of base, such as triethylamine or pyridine, compound **2** was recovered quantitatively, indicating that no irreversible changes to the skeleton of **2** occur on reaction with acids.

Why should protonation take a different course to methylation? As pointed out many years ago,[5] the relative strengths of normal O–H, N–H, O–Me and N–Me bonds are such that, at equilibrium, methylation of a species with oxygen and nitrogen sites should favour nitrogen more than in the case

Table 2 AM1 and MNDO Calculations[a]

				
ΔH_f/kJ mol^{-1}	−46.2	−32.0[b]	−10.6	−17.3[b]
C–N–C°	115.1		113.5	
O–B–O°	119.8		119.4	
B–O[c] Å	1.375		1.375	
C–O–B–O°	122.4		121.5	
B···N Å	2.86		2.93	
MNDO ΔH_f/kJ mol^{-1}	108.0	18.5[d]	183.0	41.6[d]

[a] All data refer to AM1 calculation unless otherwise indicated. The more recent PM3 method is not parameterized for boron in our version of MOPAC (MOPAC 94). [b] The preferred structure is gauche at the non-cyclic C–O bond. [c] The AM1 calculated B–O distance in $(MeO)_3B$ is 1.360 Å. [d] The preferred structure is *anti* at the non-cyclic C–O bond.

of protonation. While the formation of **4** seems to have no precedent, it is the *N*-protonation to form **5** which is really the more surprising reaction. *O*-Methylation is presumably kinetically-controlled; but attempts to convert **4** into the corresponding *N*-methylated species led either to no reaction or to decomposition. In an attempt to shed further light on these reactions, semi-empirical molecular orbital calculations on the various species have been carried out (Table 2). Calculations using the AM1 method actually lead to the prediction that *N*-protonation is preferred to *O*-protonation, while *O*-methylation is preferred to *N*-methylation (at equilibrium) in apparently complete agreement with experiment. Unfortunately semi-empirical methods are known to be relatively unreliable for boron and calculations using the alternative MNDO method give quite different results, although, even here, protonation relatively favours nitrogen compared to the case of methylation. A significant factor is that the products from reaction at nitrogen have large C–N–C angles in the rings, and therefore there will be quite severe crowding of the group which has added to the nitrogen atom. Both semi-empirical methods yield reasonable geometries for all the species; large C–N–C angles in the rings of the [3.3.3] species are indeed found (Table 2). The longer B–O bond lengths in the [3.3.3] species compared to trimethyl borate should also be noted; these are reasonable in view of the reduced overlap between the oxygen lone pair orbitals and the empty orbital on boron.

Experimental

All NMR spectra were obtained on a JEOL JNM-GX270 or JEOL JNM-GX400 spectrometer. Chemical shifts are reported in ppm relative to an internal tetramethylsilane reference for ^1H and ^{13}C spectra unless otherwise stated and to BF_3/Et_2O for ^{11}B spectra unless otherwise noted. *J* values are given in Hz. All reactions, except those carried out in aqueous media, were performed under an atmosphere of nitrogen using flame-dried glassware. All transfers and additions were performed with flame-dried syringes and needles. All solvents were freshly distilled over drying agents before use. Reagents were obtained from commercial suppliers (Aldrich and Lancaster) and used without purification unless noted otherwise.

Reaction of 1-aza-5-borabicyclo[3.3.3]undecane 1 with methyl trifluoromethanesulfonate

A solution of **1** (0.007 g, 0.045 mmol) in acetonitrile (or dichloromethane) (0.5 cm^3) and methyl triflate (0.005 cm^3, 0.045 mmol) was left to stand at room temperature under nitrogen for 24 hours. NMR analysis showed that **1** was unchanged.

Reaction of 1-aza-5-borabicyclo[3.3.3]undecane 1 with triflic acid

Solutions of **1** (0.007 g, 0.045 mmol) in acetonitrile (or dichloromethane) (0.5 cm^3) and triflic acid (0.004 cm^3, 0.045 mmol) were left to stand at room temperature under nitrogen for 24 h. NMR analysis showed **1** was unchanged. When **1** (0.012 g, 0.08 mmol) was dissolved in neat triflic acid (0.6 cm^3), some changes were apparent immediately from the ^{11}B NMR spectrum, since the absorption for **1** at 6 ppm was replaced by several broad and overlapping peaks between 0 and 16 ppm. After standing for 2 weeks, the formation of **3** (see below) was apparent, but at least one other species was present, probably a product of single B–C cleavage. After 4 months, the spectra were cleaner and indicated almost complete conversion to **3**; no tripropylammonium ion, the potential final cleavage product, was present. Spectroscopic data for **3**: δ_H(270 MHz, C_6H_6 internal standard) 3.34 (2 H, t, *J* 7.9, $NCH_2CH_2CH_2B$), 3.08 (4 H, m, $NCH_2CH_2CH_3$), 2.15 (2 H, m, $NCH_2CH_2CH_2B$), 1.87 (4 H, m, $NCH_2CH_2CH_3$), 1.58 (2 H, m, $NCH_2CH_2CH_2B$) and 1.17 (6 H, t, *J* 7.2, CH_3); δ_C(68 MHz, C_6H_6 internal standard) 57.9 ($NCH_2CH_2CH_2B$), 53.3 ($NCH_2CH_2CH_3$), 17.4 ($NCH_2CH_2CH_2B$), 15.3 ($NCH_2CH_2CH_3$), 10.8 (br, NCH_2-CH_2CH_2B) and 9.8 (CH_3); δ_B(128 MHz) 10 (br).

Reaction of triethanolamine borate, 2, with methyl trifluoromethanesulfonate in dichloromethane

Triethanolamine borate (0.3 g, 1.9 mmol) was dissolved in dichloromethane (25 cm^3) and the solution cooled in an acetone–dry ice bath. Methyl trifluoromethanesulfonate (0.22 cm^3, 1.9 mmol) was added to the solution, and the mixture was then allowed to warm to room temperature and stirred for 3 h under nitrogen during which time a precipitate formed. The supernatant liquid was removed by decantation. The residue was concentrated under reduced pressure to give the *O*-methylated product **4** as a white solid (0.57 g). δ_H(DMSO, 400 MHz) 3.83 (4 H, m, NCH_2CH_2OB), 3.70 (2 H, m, $NCH_2CH_aH_bOCH_3$), 3.45 (2 H, m,), 3.39 (3 H, s, OCH_3) and 3.38 (4 H, m, $NCH_2CH_2OCH_3$ and $NCH_aH_bCH_2OB$); δ_C-(DMSO, 100.6 MHz) 65.77 ($NCH_2CH_2OCH_3$), 59.21 (OCH_3), 56.36 (NCH_2CH_2OB), 55.51 (NCH_2CH_2OB) and 54.25 ($NCH_2CH_2OCH_3$); δ_B(DMSO, 128 MHz) 18.

Reaction of triethanolamine borate, 2, with methyl trifluoromethanesulfonate in acetonitrile

Methyl trifluoromethanesulfonate (0.006 cm^3, 0.05 mmol) was quickly added to a solution of triethanolamine borate (8 mg, 0.05 mmol) in dry CD_3CN (0.5 cm^3) in a NMR tube. After being shaken for 5 min, the reaction was analysed by NMR which showed the exclusive formation of **4**. A solution of **4** in CD_3CN in a sealed NMR tube was heated at 70 °C for 24 h. NMR analysis showed that no change had occurred.

Reaction of triethanolamine borate, 2, with triflic acid in dichloromethane

Triethanolamine borate (0.23 g, 1.5 mmol) was dissolved in dichloromethane (25 cm^3) and the solution cooled in an acetone–dry ice bath. Triflic acid (0.13 cm^3, 1.5 mmol) was added to the solution. The mixture was then allowed to warm to room temperature and stirred for 3 h under nitrogen during which time a precipitate formed. The supernatant liquid was removed by decantation. The residue was concentrated under reduced pressure to give the *N*-protonated product **5** as a white solid (0.39 g). This was too easily hydrolysed for analytical data to be obtained. $\delta_H(CD_3CN, 400\ MHz)$ 3.8 (6 H, br, 2-H) and 3.4 (6 H, br, 1-H); $\delta_C(CD_3CN, 100.6\ MHz)$ 54.05 (C-2) and 53.40 (C-1); $\delta_B(CD_3CN, 128\ MHz)$ 17.9.

Reaction of triethanolamine borate, 2, with triflic acid

Triflic acid (0.0035 cm^3, 0.04 mmol) was quickly added to a solution of triethanolamine borate (6 mg, 0.04 mmol) in dry CD_3CN (0.5 cm^3) in a NMR tube. After being shaken for 5 min, the reaction was analysed by NMR, which indicated the formation of **5**.

Reconversion of 5 to 2

Triethylamine (0.006 cm^3, 0.045 mmol) was added to the solution of **5** in CD_3CN. After 2 h NMR analysis showed the total conversion of **5** to **2**.

Reaction of triethanolamine borate, 2, with 0.5 equiv. triflic acid

Triflic acid (0.0017 cm^3, 0.02 mmol) was quickly added to a solution of **2** (6 mg, 0.04 mmol) in dry CD_3CN (0.5 cm^3) in a NMR tube. After being shaken for 5 min, the reaction mixture was analysed by NMR, and superimposed spectra for a 1 : 1 mixture of **2** and **5** were observed.

Reaction of triethanolamine borate, 2, with trifluoroacetic acid

Trifluoroacetic acid (0.007 cm^3, 0.09 mmol) was quickly added to a solution of triethanolamine borate (0.014 g, 0.09 mmol) in dry CD_3CN (0.6 cm^3) in a NMR tube, and the reaction was monitored by NMR. The reaction was repeated with 5 equiv. of trifluoroacetic acid (0.018 cm^3, 0.22 mmol) (see Table 1).

Acknowledgements

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