



Note

Reductive openings of benzylidene acetals. Kinetic studies of borane and alane activation by Lewis acids

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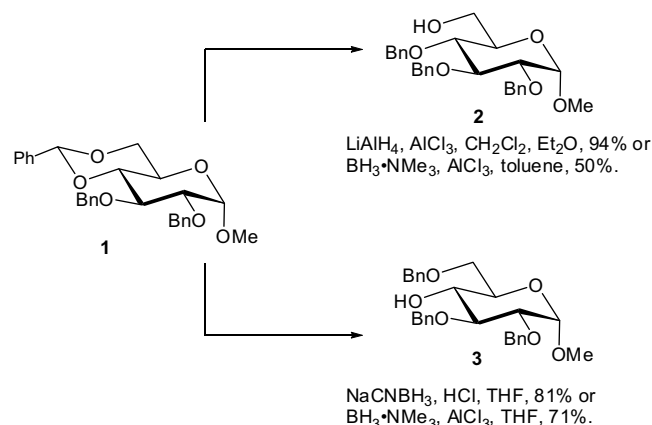
ABSTRACT

The reaction kinetics for a number of reductive openings of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene- α -D-glucopyranoside have been investigated. Openings to give free HO-6 (using $\text{BH}_3\cdot\text{THF}$ - AlCl_3 -THF or LiAlH_4 - AlCl_3 - Et_2O) follow first order kinetics, while reactions yielding free HO-4 (using $\text{BH}_3\cdot\text{NMe}_3$ - AlCl_3 -THF or $\text{BH}_3\cdot\text{NMe}_3$ - $\text{BF}_3\cdot\text{OEt}_2$ -THF) follow higher order kinetics. The addition of water to the $\text{BH}_3\cdot\text{NMe}_3$ - AlCl_3 -THF results in faster reactions. The $\text{BH}_3\cdot\text{SMe}_2$ - AlCl_3 -THF system constitutes a borderline case, yielding both free HO-6 (by a first order reaction) and free HO-4 (by a higher order reaction). These results correlate well with the concept of regioselectivity by activation of borane complexes.

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Reductive openings of cyclic acetals (e.g., 4,6-*O*-benzylidene acetals of hexopyranosides) are immensely important in modern synthetic carbohydrate chemistry, and crucial for protective group introduction and manipulation. In the original method, which was intensely explored by Lipták, the reagent combination LiAlH_4 - AlCl_3 is used to open 4,6-*O*-benzylidene acetals to give 4-*O*-benzyl ethers and a free 6-hydroxyl group.^{1,2} However, these conditions are too harsh for many common protective groups (e.g., acetates) and the reagent combination NaCNBH_3 - HCl -THF was introduced by Garegg. Interestingly, these conditions gave the opposite regioselectivity, compared to the original method.^{3,4} Furthermore, the Garegg group found that the reagent combination $\text{BH}_3\cdot\text{NMe}_3$ - AlCl_3 gave different regioselectivity by variation of the solvent, that is, 6-*O*-benzyl ethers in THF and 4-*O*-benzyl ethers in toluene.^{5–7} However, due to degradation, reactions in toluene usually gave low yields. The methods are summarized in Scheme 1.

The underlying principles for the regioselectivity have not been fully understood.⁸ The generally accepted mechanism, proposed by Garegg,⁹ explains the regioselective outcome by the difference in steric bulk between AlCl_3 and a proton. However, there are several problems associated with this mechanistic explanation, with the major issue to explain being the regiochemical outcome of the reaction with $\text{BH}_3\cdot\text{NMe}_3$ - AlCl_3 in THF, which gives 6-*O*-benzyl ethers, despite the obvious conclusion that the strongly solvated



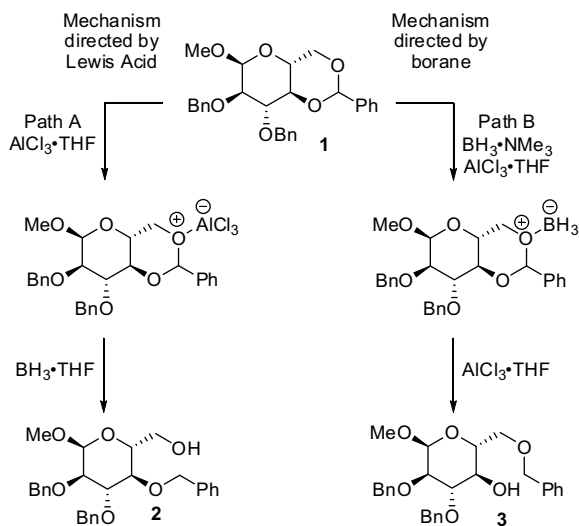
Scheme 1. Examples of regioselective openings of benzylidene acetals.

AlCl_3 -THF would preferably associate with the less sterically hindered O-6 to give 4-*O*-benzyl ethers.

Recently, we presented a mechanistic explanation for these observations.¹⁰ From kinetic experiments, ^{11}B NMR spectroscopy, and Hammett plots, we found that $\text{BH}_3\cdot\text{NMe}_3$ is activated by AlCl_3 , which renders the borane the most electrophilic species. Consequently, the regioselectivity is directed by addition of the borane to the most basic acetal oxygen. In contrast, $\text{BH}_3\cdot\text{THF}$ is not activated by the Lewis acid and thus, regioselectivity is directed by

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Scheme 2. The regiochemical outcome is directed by the relative nucleophilicity of the acetal oxygens toward the Lewis acid (Path A) or the activated borane (Path B).

association of AlCl_3 to the same acetal oxygen, giving the opposite product. To summarize, the regioselectivity is directed by association of the most electrophilic species (i.e., BH_3 or AlCl_3 depending on activation) to the most electron-rich oxygen. The concept is depicted in Scheme 2.

As a consequence, the activation of $\text{BH}_3 \cdot \text{NMe}_3$ by the Lewis acid results in higher order reaction kinetics, with respect to AlCl_3 , compared to first order kinetics, found for the reaction using $\text{BH}_3 \cdot \text{THF}$.

The original method for regioselective reductive openings of cyclic acetals has been developed into an abundance of methods (e.g., boranes activated by Bu_2BOTf ,¹¹ $\text{Cu}(\text{OTf})_2$,¹² other metal triflates,¹³ $\text{BF}_3 \cdot \text{OEt}_2$,^{14,15} or the use of DIBAL¹⁶), and we decided to investigate the initial rate kinetics using quantitative thin layer chromatography,^{10,17,18} to shed further light on the reaction mechanism.

The rationale for the activation of $\text{BH}_3 \cdot \text{NMe}_3$ by AlCl_3 is the formation of the strong complex $\text{AlCl}_3 \cdot \text{NMe}_3$ according to Scheme 3a. While the $\text{AlCl}_3 \cdot \text{NMe}_3$ complex is very strong (199 kJ mol^{-1}), the analogous $\text{BF}_3 \cdot \text{NMe}_3$ is weaker (Scheme 3b, 130 kJ mol^{-1}) and would thus, according to theory, activate the borane to a less extent.¹⁹

We thus subjected compound **1** to $\text{BH}_3 \cdot \text{NMe}_3$ and $\text{BF}_3 \cdot \text{OEt}_2$ in THF and followed the initial rate kinetics. The reaction yielded the expected compound **3** (free 4-OH) and followed higher order kinetics, that is, the borane was activated by the Lewis acid. However, the rates were considerably slower (approximately two times slower using $\text{BF}_3 \cdot \text{OEt}_2$ at room temperature, compared to reaction with AlCl_3 at 0°C).¹⁰ The data are presented in Figure 1a and b.

In a series of low-temperature experiments, Wei and co-workers showed that the addition of acid scavengers (i.e., di-*tert*-butyl-4-methylpyridine) to ensure aprotic conditions severely decelerated the reduction rate.²⁰ The importance of water in the reaction was further showed by Nifantiev and co-workers, where

the addition of water sped up otherwise slow reactions.²¹ The optimized conditions turned out to be 2 equiv of water, 4 equiv of $\text{BH}_3 \cdot \text{NMe}_3$, and 6 equiv of AlCl_3 . To further investigate the importance of water in the reduction, the kinetics of the reduction of compound **1** using the water- $\text{BH}_3 \cdot \text{NMe}_3$ - AlCl_3 system was investigated (Fig. 1c).

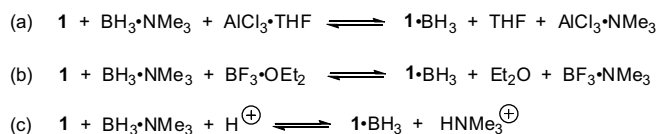
To our surprise, we found that equimolar amounts of AlCl_3 and water completely quenched the reaction, while a 3:1 ratio gave a rate enhancement of approximately four times. However, the addition of even more AlCl_3 lowered the reaction rate, and at 8 equiv of AlCl_3 the rates were similar to reaction without water. These observations can be rationalized by the reactions of water with AlCl_3 . In a series of experiments, Gálová showed that the conductivity of a solution of AlCl_3 in THF reached a maximum at a molar ratio of AlCl_3 and water, of 1:2, which corresponds to the formation of the charged species $\text{AlCl}_2(\text{H}_2\text{O})_4^+$ and AlCl_4^- .²² Further addition of water led to lowered conductivities due to the formation of uncharged $\text{AlCl}_3(\text{H}_2\text{O})_6$. It is reasonable to assume that the formed aluminum complexes can act as proton sources that activate either the borane or the acetal. Because equimolar amounts of water and Lewis acid gave no reaction, the formed complex is not strong enough for activation of both the borane and the acetal. Brown and Murrey showed that the rate of hydrolysis of $\text{BH}_3 \cdot \text{NMe}_3$ in aqueous diglyme is almost negligible, but that the complex can be activated by proton sources such as acetic acid or mineral acids.^{23,24} We therefore propose that protons are strong activators of $\text{BH}_3 \cdot \text{NMe}_3$, which explains the enhanced reaction rates (Scheme 3c). At high molar ratios of AlCl_3 , other complexes are formed, and the effects of the added water are insignificant. It is reasonable that minute amounts of water present in reagents and solvents generally enhance the reaction rates in reductive openings using borane complexes.

The dissociation energy of dimethylsulfide borane ($\text{BH}_3 \cdot \text{SMe}_2$, DMSB) lies between those of the other investigated borane complexes ($\text{BH}_3 \cdot \text{THF}$: 83 kJ/mol ; $\text{BH}_3 \cdot \text{SMe}_2$: 101 kJ/mol ; $\text{BH}_3 \cdot \text{NMe}_3$: 160 kJ/mol),²⁵ and the possible activation by proton sources and Lewis acids therefore represents a borderline case. $\text{BH}_3 \cdot \text{SMe}_2$ has earlier been used for acetal openings in conjunction with TMSOTf ²⁶ or $\text{BF}_3 \cdot \text{OEt}_2$,²⁷ and Saito and co-workers used the latter reagent combination for reductive opening of **1** to give a mixture of **2** and **3** in a 3:1 ratio.¹⁴ To compare the reactivity with other borane complexes, we subjected compound **1** to $\text{BH}_3 \cdot \text{SMe}_2$ - AlCl_3 and investigated the initial rate kinetics (Fig. 2).¹⁰

Reductive opening of **1** using $\text{BH}_3 \cdot \text{SMe}_2$ - AlCl_3 in THF resulted in the simultaneous formation of both compounds **2** and **3**. However, the formation of **2** and **3** showed different kinetics. Compound **2** was formed in a first order reaction, while compound **3** showed higher order kinetics. At 8 equiv of AlCl_3 , the first and the higher order reactions showed essentially the same rates. We conclude that $\text{BH}_3 \cdot \text{SMe}_2$ is a borderline case that, to a certain extent, can be activated by AlCl_3 , but at low amounts of Lewis acid the first order reaction predominates (no activation).

Finally, we decided to investigate the original LiAlH_4 procedure.¹ Thus, we subjected compound **1** to LiAlH_4 and AlCl_3 in Et_2O and CH_2Cl_2 , which yielded **2** in good yields. The initial rate analysis using the weighed amounts of AlCl_3 gave deviation from first order kinetics (Fig. 3a). However, LiAlH_4 reacts with AlCl_3 to form AlH_3 . Because 1 equiv of AlCl_3 is used in this reaction, the real concentration of Lewis acid is lowered (Scheme 4). Recalculation of $[\text{AlCl}_3]$ gave an excellent fit with first order kinetics (Fig. 3b). It is thus reasonable to assume that alanes (probably $\text{AlH}_3 \cdot \text{Et}_2\text{O}$) react in a similar way as $\text{BH}_3 \cdot \text{THF}$.

In addition, we attempted several other reagent combinations, but these reactions proved to be difficult to examine due to too fast (e.g., $\text{BH}_3 \cdot \text{NMe}_3$ - $\text{BF}_3 \cdot \text{OEt}_2$ - CH_2Cl_2 , $\text{BH}_3 \cdot \text{NMe}_3$ - AlCl_3 -toluene, $\text{BH}_3 \cdot \text{SMe}_2$ - $\text{Cu}(\text{OTf})_2$ -THF, and NaCNBH_3 - HCl -THF) or too slow



Scheme 3. Activation of $\text{BH}_3 \cdot \text{NMe}_3$ by Lewis acids and proton sources.

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