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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 BH_3·THF–$AlCl_3$–THF or $LiAlH_4$–$AlCl_3$–Et_2O) follow first order kinetics, while reactions yielding free HO-4 (using BH_3·NMe_3–$AlCl_3$–THF or BH_3·NMe_3–BF_3·OEt_2–THF) follow higher order kinetics. The addition of water to the BH_3·NMe_3–$AlCl_3$–THF results in faster reactions. The BH_3·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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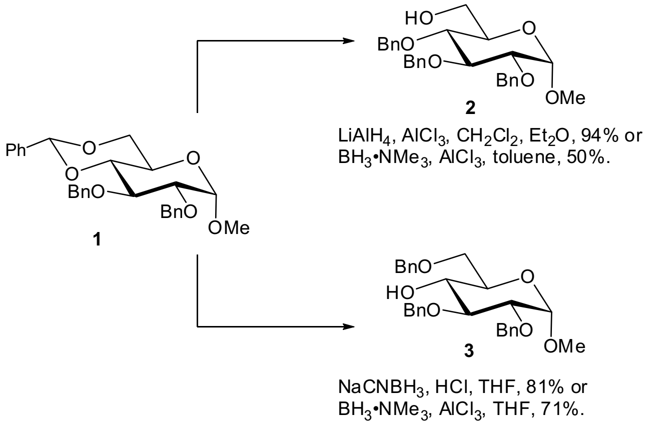
Reductive openings of cyclic acetals (e.g., 4,6-*O*-benzylidene acetals of hexopyranosides) are immensely important in modern synthetic carbohydrate chemistry, and crucial for protective group introduction and manipulation. In the original method, which was intensely explored by Lipták, the reagent combination $LiAlH_4$–$AlCl_3$ 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 BH_3·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 BH_3·NMe_3–$AlCl_3$ in THF, which gives 6-*O*-benzyl ethers, despite the obvious conclusion that the strongly solvated $AlCl_3$·THF would preferably associate with the less sterically hindered *O*-6 to give 4-*O*-benzyl ethers.



Scheme 1. Examples of regioselective openings of benzylidene acetals.

Recently, we presented a mechanistic explanation for these observations.[10] From kinetic experiments, ^{11}B NMR spectroscopy, and Hammett plots, we found that BH_3·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, BH_3·THF is not activated by the Lewis acid and thus, regioselectivity is directed by

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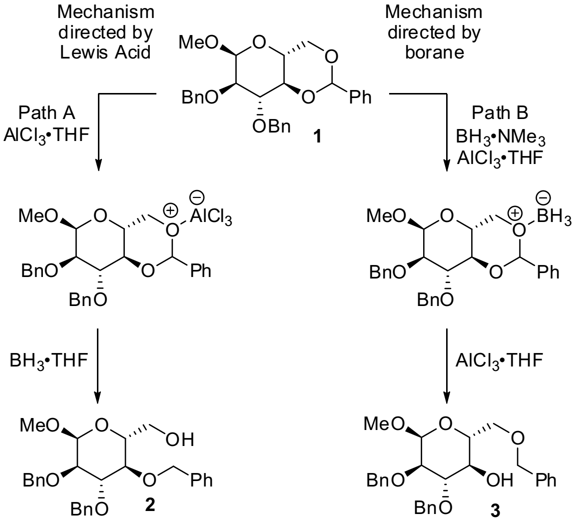

Scheme 2. The regiochemical outcome is directed by the relative nucleophilicity of the acetal oxygens toward the Lewis acid (Path A) or the activated borane (Path B).

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 $BH_3{\cdot}NMe_3$ 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 $BH_3{\cdot}THF$.

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] $Cu(OTf)_2$,[12] other metal triflates,[13] $BF_3{\cdot}OEt_2$,[14,15] or the use of DIBAL[16]), 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 $BH_3{\cdot}NMe_3$ by $AlCl_3$ is the formation of the strong complex $AlCl_3{\cdot}NMe_3$ according to Scheme 3a. While the $AlCl_3{\cdot}NMe_3$ complex is very strong (199 $kJ\,mol^{-1}$), the analogous $BF_3{\cdot}NMe_3$ 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 $BH_3{\cdot}NMe_3$ and $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$ 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 $BH_3{\cdot}NMe_3$, 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–$BH_3{\cdot}NMe_3$–$AlCl_3$ 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 $AlCl_2(H_2O)_4{}^+$ and $AlCl_4{}^-$.[22] Further addition of water led to lowered conductivities due to the formation of uncharged $AlCl_3(H_2O)_6$. 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 $BH_3{\cdot}NMe_3$ 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 $BH_3{\cdot}NMe_3$, 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 ($BH_3{\cdot}SMe_2$, DMSB) lies between those of the other investigated borane complexes ($BH_3{\cdot}THF$: 83 kJ/mol; $BH_3{\cdot}SMe_2$: 101 kJ/mol; $BH_3{\cdot}NMe_3$: 160 kJ/mol),[25] and the possible activation by proton sources and Lewis acids therefore represents a borderline case. $BH_3{\cdot}SMe_2$ has earlier been used for acetal openings in conjunction with TMSOTf[26] or $BF_3{\cdot}OEt_2$,[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 $BH_3{\cdot}SMe_2$–$AlCl_3$ and investigated the initial rate kinetics (Fig. 2).[10]

Reductive opening of **1** using $BH_3{\cdot}SMe_3$–$AlCl_3$ 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 $BH_3{\cdot}SMe_3$ 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 $[AlCl_3]$ gave an excellent fit with first order kinetics (Fig. 3b). It is thus reasonable to assume that alanes (probably $AlH_3{\cdot}Et_2O$) react in a similar way as $BH_3{\cdot}THF$.

In addition, we attempted several other reagent combinations, but these reactions proved to be difficult to examine due to too fast (e.g., $BH_3{\cdot}NMe_3$–$BF_3{\cdot}OEt_2$–CH_2Cl_2, $BH_3{\cdot}NMe_3$–$AlCl_3$–toluene, $BH_3{\cdot}SMe_2$–$Cu(OTf)_2$–THF, and $NaCNBH_3$–HCl–THF) or too slow

$$\text{(a)}\quad \mathbf{1} + BH_3{\bullet}NMe_3 + AlCl_3{\bullet}THF \rightleftharpoons \mathbf{1}{\bullet}BH_3 + THF + AlCl_3{\bullet}NMe_3$$

$$\text{(b)}\quad \mathbf{1} + BH_3{\bullet}NMe_3 + BF_3{\bullet}OEt_2 \rightleftharpoons \mathbf{1}{\bullet}BH_3 + Et_2O + BF_3{\bullet}NMe_3$$

$$\text{(c)}\quad \mathbf{1} + BH_3{\bullet}NMe_3 + H^{\oplus} \rightleftharpoons \mathbf{1}{\bullet}BH_3 + HNMe_3{}^{\oplus}$$

Scheme 3. Activation of $BH_3{\cdot}NMe_3$ by Lewis acids and proton sources.

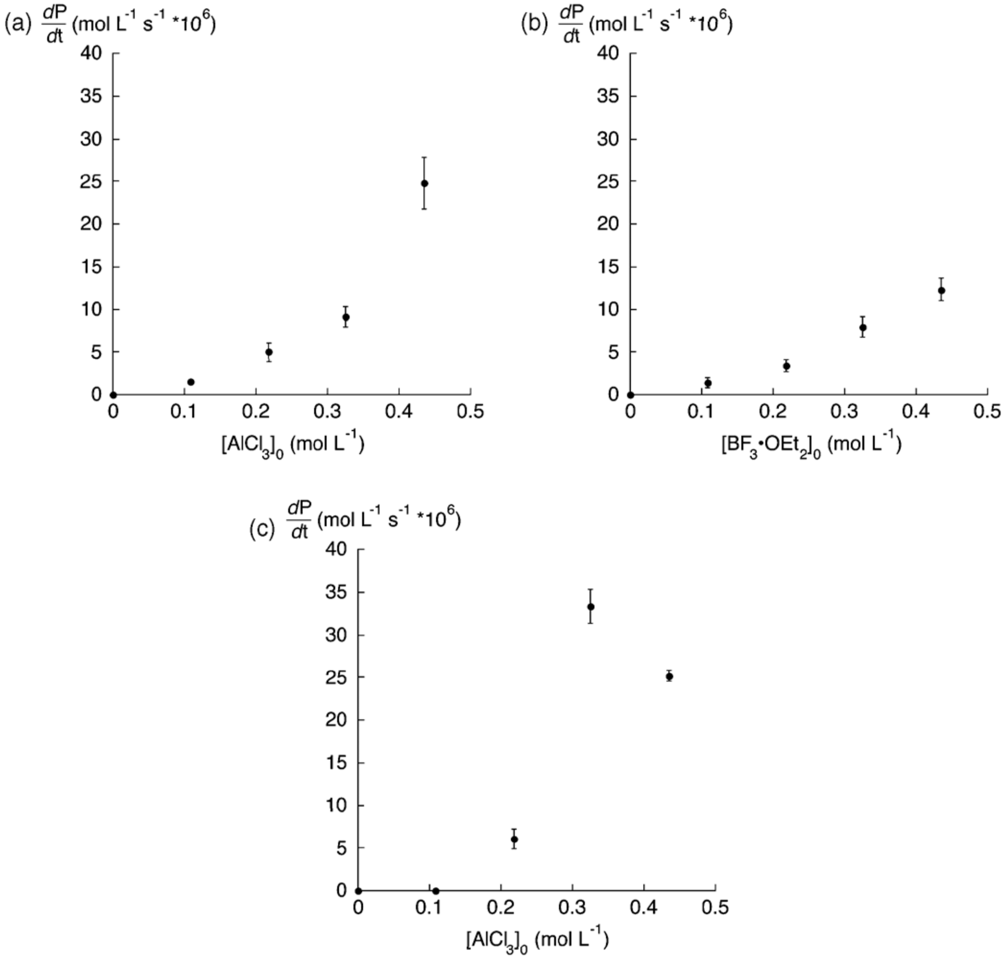

Figure 1. Initial rate analysis for the formation of compound **3** using $BH_3 \cdot NMe_3$. $[\mathbf{1}]_0 = 0.054$ M, $[BH_3 \cdot NMe_3]0 = 0.217$ M. (a) Variation of $[AlCl_3]_0$. Data from Ref. 10. Reactions were run at 0 °C. (b) Variation of $[BF_3 \cdot OEt_2]_0$. Reactions were run at room temperature. (c) Variation of $[AlCl_3]_0$ with water added. $[H_2O]_0 = 0.108$ M. Reactions were run at 0 °C. All reactions were performed at least in duplicate.

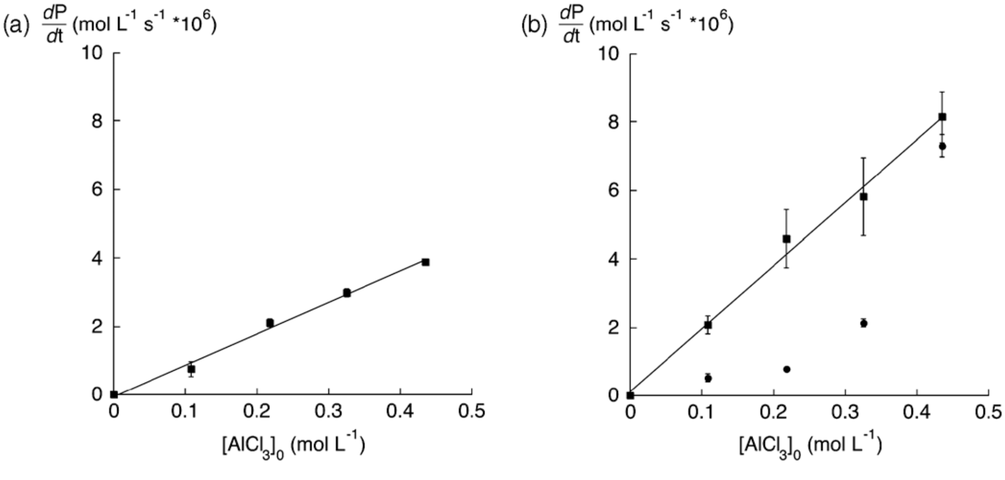

Figure 2. Initial rate analysis for the formation of compound **2** (squares) and **3** (filled circles) using (a) $BH_3 \cdot THF$ or (b) $BH_3 \cdot SMe_2$. $[\mathbf{1}]_0 = 0.054$ M, $[BH_3 \cdot THF]_0 = [BH_3 \cdot SMe_2]_0 = 0.217$ M. (a) Variation of $[AlCl_3]_0$ using $BH_3 \cdot THF$. Data from Ref. 10. (b) Variation of $[AlCl_3]_0$ using $BH_3 \cdot SMe_2$. All reactions were run at room temperature and performed at least in duplicate.

reaction rates (e.g., $BH_3 \cdot THF$–$BF_3 \cdot OEt_2$–THF, $BH_3 \cdot NMe_3$–$Cu(OTf)_2$–THF).

To summarize, we have shown the reaction kinetics for a series of reductive openings of 4,6-*O*-benzylidene acetals. In all cases, the openings to free HO-6 (i.e., 4-*O*-benzyl ethers) follow first order kinetics, while reactions yielding free HO-4 (i.e., 6-*O*-benzyl ethers) follow higher order kinetics. These results correlate well with the concept of regioselectivity by activation of borane complexes.[10]

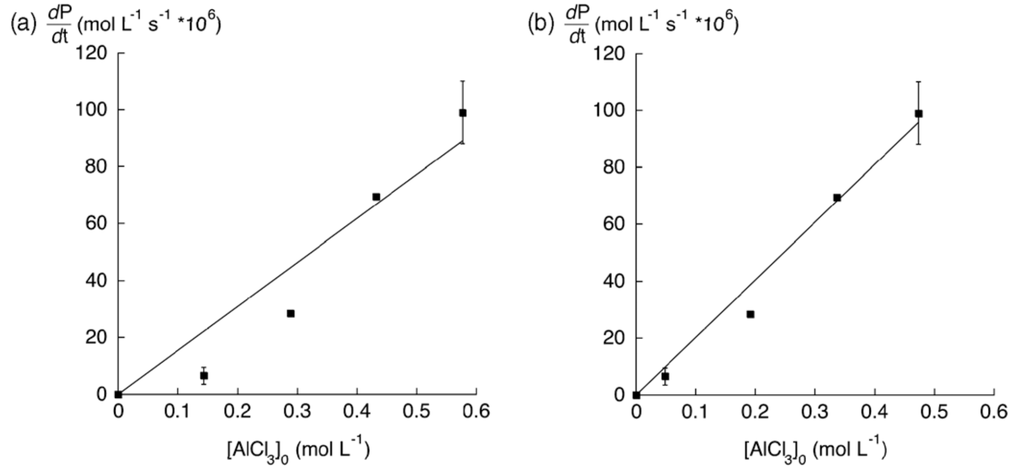

Figure 3. Initial rate analysis for the formation of compound **2** using $LiAlH_4$ and $AlCl_3$ in THF. $[\mathbf{1}]_0 = 0.072$ M, $[LiAlH_4]_0 = 0.288$ M. (a) Initial rates plotted versus added amount of $AlCl_3$. (b) Initial rates plotted versus real $AlCl_3$ concentration. All reactions were run at 0 °C and performed at least in duplicate.

$$3\ LiAlH_4 + AlCl_3 \longrightarrow 4\ AlH_3 + 3\ LiCl$$

Scheme 4. Formation of AlH3 by reaction of $LiAlH_4$ and $AlCl_3$.

1. Experimental

1.1. General experimental details

Reactions were monitored by TLC using alumina plates coated with silica gel and visualized by charring with *p*-anisaldehyde. THF was distilled from sodium, and other reaction solvents were dried on Al_2O_3. Known and commercially available compounds were in agreement with previously published data (e.g., NMR). Samples (0.050 mL) were taken and quenched in micro vials with $NaHCO_3$ (0.500 mL, satd aq) and extracted with ether (0.200 mL). The samples were analyzed by quantitative TLC.[17,18] Stock solutions in THF: **1** 100 mg/mL, 0.216 M; $AlCl_3$ 145 mg/mL, 1.088 M; $BH_3{\cdot}NMe_3$ 64 mg/mL, 0.877 M; H_2O 19 mg/mL, 1.077 M; $BH_3{\cdot}SMe_2$ was diluted from 2 M to 1 M and $BF_3{\cdot}OEt_2$ was not diluted.

1.2. Borane dimethylsulfide-complex—$AlCl_3$

A mixture of stock solutions of **1** (0.250 mL, 0.054 mmol), $BH_3{\cdot}SMe_2$ (0.220 mL, 0.220 mmol), and THF (0.130–0.430 mL) was stirred at rt under N_2 for 15 min. Then, a stock solution of $AlCl_3$ (0.100–0.400 mL, 0.109–0.435 mmol) was added.

1.3. Borane trimethylamine—$BF_3{\cdot}OEt_2$

A mixture of stock solutions of **1** (0.250 mL, 0.054 mmol), $BH_3{\cdot}NMe_3$ (0.250 mL, 0.219 mmol), and THF (0.450–0.490 mL) was stirred at rt under N_2 for 15 min. Then, $BF_3{\cdot}OEt_2$ (0.014–0.055 mL, 0.111–0.434 mmol) was added.

1.4. Borane trimethylamine–H_2O–$AlCl_3$

A mixture of stock solutions of **1** (0.250 mL, 0.054 mmol), $BH_3{\cdot}NMe_3$ (0.250 mL, 0.219 mmol), H_2O (0.100 mL, 0.108 mmol) and THF (0–0.300 mL) was stirred at 0 °C under N_2 for 15 min. Then, $AlCl_3$ (0.100–0.400 mL, 0.109–0.435 mmol) was added.

1.5. Lithium aluminum hydride—$AlCl_3$

Compound **1** was dissolved in CH_2Cl_2 to give a stock solution of 100 mg/mL, $AlCl_3$ was dissolved in Et_2O to give a stock solution of 58–230 mg/mL (2–8 equiv). To $LiAlH_4$ (15–20 mg, 0.40–0.53 mmol) was added a stock solution of **1** (0.480–0.615 mL, 0.103–0.133 mmol) and Et_2O (0.480–0.615 mL), the mixture was stirred at 0 °C under N_2 for 15 min. Then, $AlCl_3$ (0.480–0.615 mL, 0.220–1.00 mmol) was added.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.08.022.

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