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Nucleophilic Catalysis of *MeON*-Neoglycoside Formation by Aniline Derivatives

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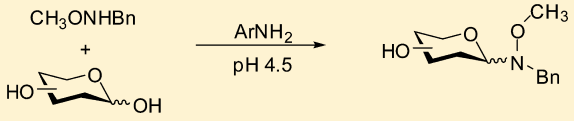
Supporting Information

ABSTRACT: Neoglycosylations are increasingly being employed in the synthesis of natural products, drug candidates, glycopeptide mimics, oligosaccharide analogues, and other applications, but the efficiency of these reactions is usually limited by slow reaction times. Here, we show that aniline derivatives such as 2-amino-5-methoxybenzoic acid enhance the rate of acid-catalyzed neoglycosylation for a range of sugar substrates up to a factor of 32 relative to the uncatalyzed reaction.



Carbohydrate moieties affect the chemical and biological properties of molecules ranging from secondary metabolites and vaccines to glycoproteins and glycolipids.[1] In order to elucidate and modulate the function of such molecules, much effort has been invested toward the development of methodologies that efficiently provide structurally homogeneous glycoconjugates in high yields.[2] In one approach, reducing sugars (**1**, in equilibrium with the open form **2**) are condensed with primary *N*-alkoxyamine derivatives to form open-chain oxime ethers (e.g., **13**, Figure 1).[3] Seminal work by Jencks[4] and further investigations by Dawson and co-workers[5,6] have shown that under acidic conditions anilines can accelerate oxime ether formation with aromatic aldehydes and glyoxal derivatives via nucleophilic catalysis. Jensen and co-workers demonstrated that this method can enhance the rate of formation of *carbohydrate* oxime ethers as well (Figure 1)[7] via complex equilibria involving an imine intermediate (**4**) that is more readily attacked than the corresponding aldehyde (**2**).[4] Unlike primary *N*-alkoxyamines, secondary *N*-alkoxyamines react with carbohydrates to form *closed-ring* neoglycosides (e.g., **14**, Figure 1)[8] that resemble more closely than open-chain oxime ethers the molecular shape and conformational rigidity of natural *O*- or *N*-linked glycosides. Neoglycosylations are increasingly being employed in the synthesis of natural products,[9] drug candidates,[10] glycopeptide mimics,[11] oligosaccharide analogues,[12] and in other applications,[13] but the efficiency of these approaches is usually limited by slow reaction times, namely 1−3 days. To our knowledge, no data have yet been published describing rate enhancements of neoglycoside formation using nucleophilic catalysis. Thus, we investigated conditions for accelerated neoglycoside formation using aniline derivatives as catalysts, as well as the scope of the reaction with respect to reducing sugar.

Our early attempts to generate neoglycoside **16** from *N*-benzyl-*N*-methoxyamine **15** (Scheme 1) using the conditions reported by Jensen and co-workers (1 mM **15** and 10 mM D-glucose in acetate buffer (pH 4.5))[7] failed due to the fact that

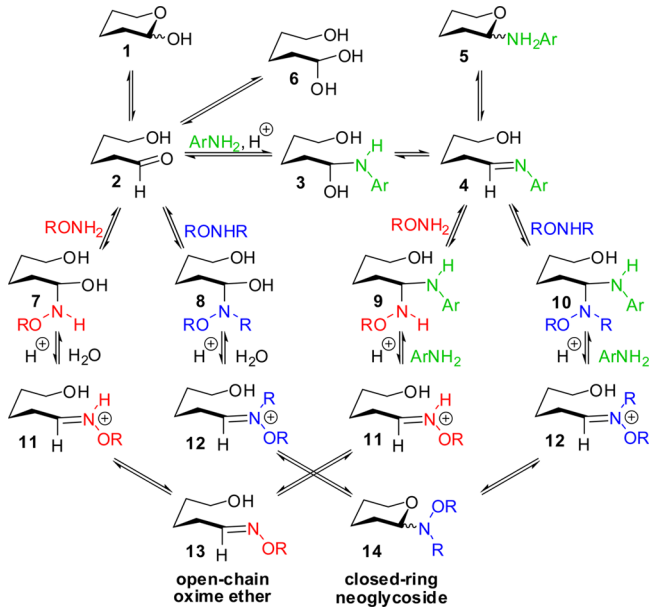


Figure 1. Proposed equilibria of reducing sugars under acidic conditions (pH 4.5) leading to the formation of open-chain oxime ethers (**13**) from primary *N*-alkoxyamines (red) and closed-ring neoglycosides (**14**) from secondary *N*-alkoxyamines (blue). Unreacting hydroxyl groups were omitted for clarity.

K_{eq} is too small to provide observable product (data not shown). After some experimentation, we found that 5 mM of **15** and 500 mM D-glucose resulted in approximately 90% conversion to **16** at equilibrium as estimated by HPLC.[14] Thus, using these reactant concentrations we performed several experiments employing aniline as a catalyst at 25 °C in concentrations ranging from 0 to 100 mM (Figure 2).

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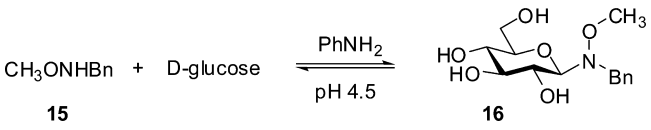
Scheme 1. Reversible Formation of Neoglycoside 16 from *N*-Benzyl-*N*-methoxyamine (15)



Given that the reactions either approached or reached equilibrium,[14] we calculated observed rate constants (Table 1) for both the forward reaction producing **16** (k_1) and backward reaction regenerating **15** (k_{-1}). Values for k_1 and k_{-1} increased in an approximately linear fashion from 0 to 100 mM aniline, and the forward reaction rate at 100 mM aniline was 20 times faster than the noncatalyzed reaction.

Motivated by the recent discovery of organocatalysts for oxime ether formation that provide rate enhancements significantly greater than aniline,[15] we next screened a set of aniline derivatives containing acidic functional groups and/or amines with pK_a values altered by electron-donating or -withdrawing groups (Table 2). We used reactant proportions identical to those employed in our initial experiments, except that the addition of 10% DMF was necessary for catalyst solubility.[16] Unfortunately, the use of an organic cosolvent prevented us from accurately readjusting the pH of each reaction solution to pH 4.5 as we did in the experiments above (Figure 1, Table 1). Thus, to prevent catalyst-dependent pH changes we utilized a relatively concentrated buffer solution (500 mM acetate) in this screen.

Several catalysts in our screen provided modest rate enhancements relative to aniline and others provided diminished activities. For example, the addition of carboxylic acid groups to the aniline scaffold provided small improvements in percent conversion relative to aniline when positioned *ortho* (1.2-fold, entry 3) or *meta* (1.1-fold, entry 4) to the amine, but not when positioned *para* to the amine (2.3-fold decrease, entry 5). Modifying the aromatic ring of anthranilic acid (2-aminobenzoic acid) with a withdrawing 5-nitro group (entry 8) reduced percent conversion dramatically, close to the noncatalyzed value. In contrast, addition of a 5-methoxy group (entry 6) provided the largest percent conversion of the catalysts examined (82%). Adding additional electron-donating groups (entry 7) did not result in further improvement to the activity of the most efficient catalyst, 5-methoxyanthranilic acid (2-amino-5-methoxybenzoic acid).

Table 1. Observed Rate Constants (min^{-1}) and Percent Conversions for the Reversible Formation of Neoglycoside 16 from 15 Using Different Concentrations of Aniline[a]

[aniline] (mM)	k_1	k_{-1}	conversion at 120 min[b] (%)
0	8.3×10^{-4}	9.1×10^{-5}	9
5	1.7×10^{-3}	1.9×10^{-4}	19
10	2.9×10^{-3}	3.1×10^{-4}	29
25	5.7×10^{-3}	6.2×10^{-4}	46
50	1.1×10^{-2}	1.2×10^{-3}	68
100	1.7×10^{-2}	1.9×10^{-3}	83

[a] 5 mM **15**, 500 mM D-glucose, in 100 mM acetate buffer (pH 4.5), 25 °C. [b] Estimated by HPLC.

Rationalizing relatively large k_1 differences in this screen, for example, the 13-fold difference in k_1 values between aniline and 5-nitroanthanilic acid, is relatively straightforward. In this instance, the difference is easily understood in terms of the highly attenuated nucleophilicity of 5-nitroanthanilic acid, despite its approximately 2-fold greater free amine population at pH 4.5.[17] However, rationalizing most of these data systematically in theoretical terms is challenging due to small reactivity differences and the multiple factors that could influence the activity of these catalysts, including the distribution of charged/neutral catalyst species at pH 4.5, amine nucleophilicity, and intramolecular hydrogen bonding between amines and adjacent *ortho* carboxylic acid groups.

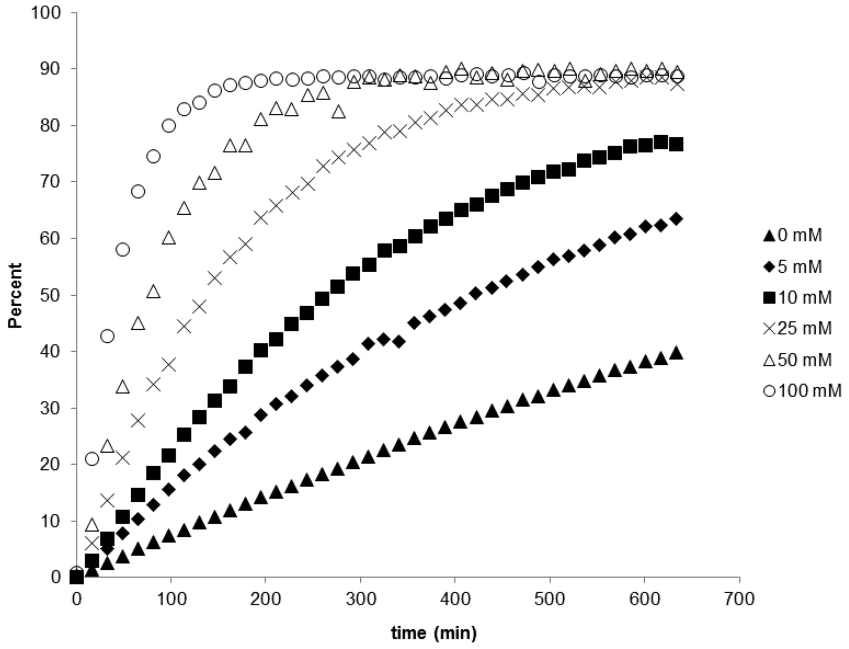


Figure 2. Conversion of **15** to neoglycoside **16** using various concentrations of aniline, as estimated by HPLC (5 mM **15**, 500 mM D-glucose, in 100 mM acetate buffer pH 4.5, 25 °C).

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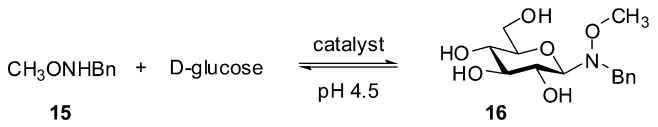
Table 2. Observed Rate Constants (min^{-1}) and Percent Conversions for the Reversible Formation of Neoglycoside 16 Using Different Aniline Derivatives[a]



entry	catalyst	k_1	$k_{1(rel)}$	k_{-1}	conversion at 120 min[b] (%)
1	none	5.6×10^{-4}	1	5.7×10^{-5}	7
2	aniline	9.1×10^{-3}	16	9.4×10^{-4}	62
3	anthranilic acid (2-aminobenzoic acid)	9.5×10^{-2}	17	9.8×10^{-4}	72
4	3-aminobenzoic acid	1.1×10^{-2}	19	1.1×10^{-3}	68
5	4-aminobenzoic acid	2.9×10^{-3}	5	3.0×10^{-4}	27
6	5-methoxyanthranilic acid	1.8×10^{-2}	32	1.9×10^{-3}	82
7	4,5-dimethoxyanthranilic acid	1.4×10^{-2}	25	1.4×10^{-3}	75
8	5-nitroanthranilic acid	6.8×10^{-4}	1	7.0×10^{-5}	8
9	4-methoxy-2-methylaniline	7.2×10^{-3}	11	7.5×10^{-4}	53
10	3,5-diaminobenzoic acid	1.4×10^{-2}	25	1.4×10^{-3}	76
11	3-amino-5-methoxybenzoic acid	9.6×10^{-2}	17	9.9×10^{-4}	64

[a]5 mM **15**, 500 mM D-glucose, 100 mM catalyst, in 500 mM acetate buffer (pH 4.5) containing 10% DMF, 25 °C. [b]Estimated by HPLC.

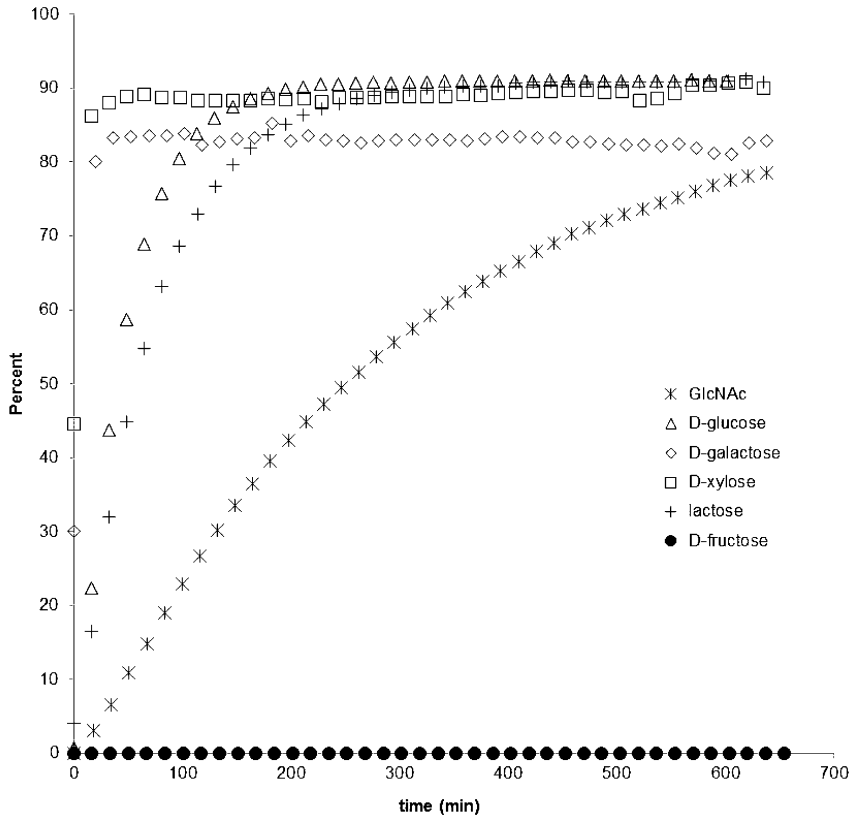


Figure 3. Conversion of **15** to the corresponding neoglycosides using various sugars as estimated by HPLC (5 mM **15**, 100 mM 5MA, 500 mM sugar, in 100 mM acetate buffer (pH 4.5) containing 10% DMF, 25 °C).

Having identified 5-methoxyanthranilic acid (5MA) as an optimal catalyst, we next explored its viability in the context of alternative sugar substrates including aldohexoses (a representative glucose epimer, an *N*-acetylamino sugar, and a disaccharide), an aldopentose, and a ketohexose. The reaction between **15** and D-glucose, D-xylose, and lactose reached approximately 90% conversion at equilibrium, whereas D-galactose and GlcNAc provided lower equilibrium conversions (Figure 3).[14] Even within a short period of 2 h, good percent conversions for D-glucose, D-xylose, lactose, and D-galactose were observed (Table 3). Only D-fructose failed to react, consistent with the previously noted incompatibility of ketohexoses toward neoglycosylation.[10a] We compared observed rate constants (Table 3) for both the forward (k_1) and reverse (k_{-1}) reactions between **15** and the panel of sugars. The k_1 value for D-galactose and D-xylose were 2.0- and 2.8-fold higher, respectively, than the k_1 value for D-glucose; the k_1 values for lactose and GlcNAc were 1.5- and 6.5-fold lower. The relatively sluggish rate observed for GlcNAc is consistent with previous findings.[10d,18]

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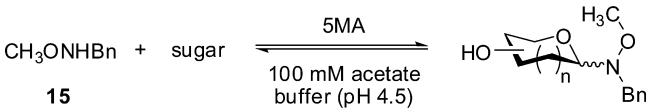
Table 3. Observed Rate Constants (min^{-1}) and Percent Conversions for the Reversible Formation of Neoglycosides Using Different Sugars[a]

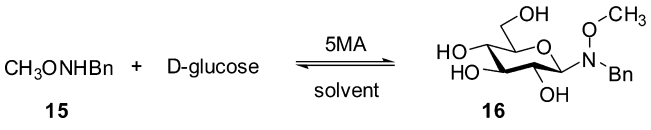


sugar	k_1	k_{-1}	conversion at 120 min[b] (%)
D-glucose	2.0×10^{-2}	2.0×10^{-3}	84
D-galactose	4.0×10^{-2}	8.0×10^{-3}	82
D-xylose	5.6×10^{-2}	5.6×10^{-3}	88
lactose	1.3×10^{-2}	1.2×10^{-3}	75
GlcNAc	3.1×10^{-3}	8.5×10^{-4}	28
D-fructose[c]			

[a]5 mM **15**, 500 mM sugar, 100 mM 5MA in 100 mM acetate buffer (pH 4.5) containing 10% DMF, 25 °C. [b]Estimated by HPLC. [c]No conversion to product was observed.

While forming neoglycosides using a *N*-benzyl-*N*-methoxyamine (**15**) to sugar ratio of 5 mM:500 mM allowed us to simplify our kinetics analyses, utilizing a low concentration of oxyamine and a large excess of sugar is not practical for some synthetic applications. Thus, we next investigated a new series of reactions (Table 4), employing a larger concentration of **15**

Table 4. Percent Conversions for the Reversible Formation of Neoglycoside 16 Using 100 mM 15 and 2−5 molar equiv of D-Glucose at Two Temperatures[a]



entry	[5MA] (mM)	**15**:D-glucose	temp (°C)	conv (%), 1 h[c]	conv (%), 2 h[c]	conv (%), ~1 day[c]
1[a]	0	1:2	25	2	3	24 (23 h)
2[a]	100	1:2	25	32	47	72 (19 h)
3[a]	0	1:2	37	3	8	46 (24 h)
4[a]	100	1:2	37	50	59	63 (24 h)
5[a]	0	1:5	25	4	7	45 (24 h)
6[a]	100	1:5	25	53	73	87 (24 h)
7[a]	0	1:5	37	10	18	74 (24 h)
8[a]	100	1:5	37	79	82	82 (24 h)
9[b]	100	1:5	25	54	74	84 (24 h)
10[b]	100	1:5	37	75	79	79 (24 h)

[a]100 mM **15**, in 100 mM acetate buffer (pH 4.5) containing 10% DMF. [b]100 mM **15**, in 1:9 DMF/H_2O (no buffer). [c]Estimated by HPLC.

(100 mM) and only 2 or 5 equiv of D-glucose; the reactions were conducted with or without 5MA catalyst at 25 or 37 °C in 100 mM acetate buffer (pH 4.5). While the noncatalyzed reactions were too sluggish to be useful, 5MA-catalyzed reactions provided reasonable conversions to neoglycoside **16** in a relatively short time frame (i.e., 2 h). For example, utilizing 5 equiv of D-glucose at 37 °C with 5MA (entry 8) provided the most rapid conversion to neoglycoside **16** (82% conversion in 2 h). In an attempt to simplify reaction conditions, we also explored whether the acidic nature of 5MA obviated the need to use an acidic buffer.[19] Gratifyingly, using water instead of buffer at 25 °C resulted in a percent conversion at 2 h (entry 9, 74%) similar to that of the corresponding buffered reaction (entry 8, 82%). Increasing the temperature of the nonbuffered reaction to 37 °C provided even faster conversion at 2 h (entry 10, 79%) but a slightly lower amount of **16** at 24 h.

Kool and co-workers have recently demonstrated that aniline derivatives containing acidic functional groups can catalyze oxime formation at neutral pH.[15] Thus, with an eye toward developing conditions that are bioorthogonal[20] to allow the formation of neoglycosides on more complex biomolecules or within living systems, we next reinvestigated our panel of catalysts, this time at neutral pH. It was necessary to use a lower catalyst concentration (50 mM) than in our earlier screen to prevent catalyst solubility issues, and a relatively concentrated buffer solution (500 mM phosphate) was required to prevent pH changes upon addition of acidic catalysts. Unfortunately, the results of the initial trials were not promising. While some conversion to neoglycoside **16** was observed, the most efficient catalyst (5MA) provided only 7% conversion after nearly 11 h (see the Supporting Information for details).

In summary, aniline derivatives enhance the rate of acid-catalyzed neoglycosylation for a range of sugar substrates by up to a factor of 32, improving the efficiency with which future glycosylated secondary metabolite derivatives,[9,10] glycopeptide mimics,[11] and other glycoconjugates[12,13] can be constructed. Unfortunately, at pH 7.4 the catalytic efficiency of anilines employed under our conditions is too low to be of practical utility.

EXPERIMENTAL SECTION

Reversible Formation of Neoglycoside 16 Using Various Concentrations of Aniline. Five aniline solutions (0, 10, 20, 50, 100, 200 mM) were generated in 100 mM acetate buffer (pH 4.5); if necessary, pH was readjusted to 4.5 using acetic acid. To initiate an experiment, an aniline solution (500 μL), *N*-benzyl-*N*-methoxyamine **15** (250 μL of a 20 mM solution in 100 mM acetate buffer, pH 4.5), and D-glucose (250 μL of a 2 M solution in 100 mM acetate buffer, pH 4.5) were combined, vortexed for 10 s, and immediately monitored by HPLC at 25 °C.

Reversible Formation of Neoglycoside 16 Using Different Aniline Derivatives at pH 4.5. Each aniline derivative (0.10 mmol) was dissolved in DMF (100 μL) in a microcentrifuge tube. To initiate an experiment, D-glucose (250 μL of a 2 M solution in 500 mM acetate buffer, pH 4.5), 400 μL of 500 mM acetate buffer (pH 4.5), and *N*-benzyl-*N*-methoxyamine **15** (250 μL of a 20 mM solution in 500 mM acetate buffer, pH 4.5) were added, and the resulting mixture was filtered through a 0.2 μm syringe filter, and immediately monitored by HPLC at 25 °C.

Reversible Formation of Neoglycosides Using Different Sugars. 5-Methoxyanthranilic acid (16.7 mg, 100 μmol) was dissolved in DMF (0.1 mL) and 0.4 mL 100 mM acetate buffer (pH 4.5). Sugar (250 μL of a 2 M solution in 100 mM acetate buffer, pH 4.5) and *N*-benzyl-*N*-methoxyamine **15** (250 μL of a 20 mM solution in 100 mM acetate buffer, pH 4.5) were added, and then the resulting mixture was filtered through a 0.2 μm syringe filter and immediately monitored by HPLC at 25 °C.

Neoglycoside Formation at Higher Substrate Concentrations. *N*-Benzyl-*N*-methoxyamine **15** (13.7 mg, 100 μmol) was dissolved in 0.9 mL of 100 mM acetate buffer (pH 4.5) and 0.1 mL of DMF. Without pH adjustment, the resulting solution was transferred to a vial containing 5-methoxyanthranilic acid (16.7 mg, 100 μmol) and D-glucose (200 μmol or 500 μmol). The resulting mixture was vortexed for 5 min, filtered through a 0.2 μm syringe filter, and incubated at 25 or 37 °C. Reaction progress was monitored by HPLC.

Reversible Formation of Neoglycoside 16 Using Different Aniline Derivatives at pH 7.4. Conditions identical to those described for pH 4.5 experiments were used, except that instead of acetate buffer, 500 mM phosphate buffer (pH 7.4) was used.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental protocols, additional kinetics data processing information, and supporting figures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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