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Nucleophilic Catalysis of Carbohydrate Oxime Formation by Anilines

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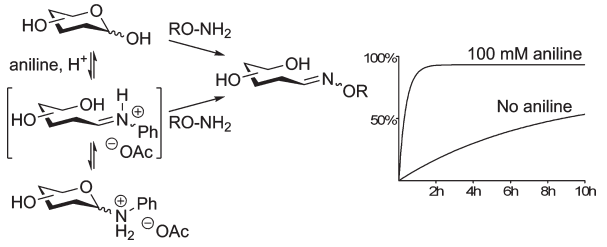
Received November 12, 2009



Chemoselective formation of glycoconjugates from unprotected glycans is needed to further develop chemical biology involving glycans. Carbohydrate oxime formation is often slow, and organocatalysis by anilines would be highly promising. Here, we present that carbohydrate oxime formation can be catalyzed with up to 20-fold increases in overall reaction rate at 100 mM aniline. Application of this methodology provided access to complex glycoconjugates.

An important basis for the functional study of carbohydrate interactions and (automated) analysis of carbohydrate mixtures is the access to well-defined glycoconjugates, in solution or bound to solid phases.[1] Preferably, these glycoconjugates should be constructed in highly chemoselective reactions and in high yields. One methodology entails covalent coupling of reducing glycans with aminooxy nucleophiles to form carbohydrate oxime *O*-ethers, commonly termed oximes. The obtained oximes are in equilibrium with closed-ring *N*-glycosyloxyamines.[2−4] Carbohydrate oxime chemistry has been applied to, e.g., neo-glycopeptides,[5] solution-phase tagging,[6] microarrays,[3,7,8] nanoparticles,[4,9] and solid supports[10,11] and generally displays high chemoselectivity and high yields; however, reaction rates are significantly decreased in certain cases, especially for carbohydrate electrophiles containing a 2-acetamido group (e.g., GlcNAc).[11] Rate enhancements of oxime formation involving exclusively open-chain reactants and products may be obtained by nucleophilic catalysis, as reported initially by Cordes and Jencks[12] and recently revitalized by Dawson and co-workers,[13] for benzaldehyde and *N*-glyoxal electrophiles, respectively. However, reactions of reducing glycans **1** and aniline under aqueous conditions are known to yield *N*-phenylglycosylamines **4** (K_{eq}∼1 at pH 4−5),[14] indicating that catalytic efficiency could be rather different from oxime formation with strictly open-chain aldehydes (Scheme 1). Specifically, the application of reducing glycans as electrophiles in catalytic oxime formation includes additional equilibria due to (i) the dynamic masking of the reactive *aldehydo* tautomer **2** as the cyclic pyranose (and furanose) hemiacetals **1** (>99.9%) and hydrate form (omitted in Scheme 1 for clarity) and (ii) the trapping of iminium ions **3** as (protonated) glycosyl amines **4**, both of which involve potentially rate-limiting intermediates.[12,15] The high reactivity of the imine intermediates is thought to be largely a result of the ease of protonation of these species relative to the carbonyl species, where subsequent elimination of aniline is fast.[12,16]

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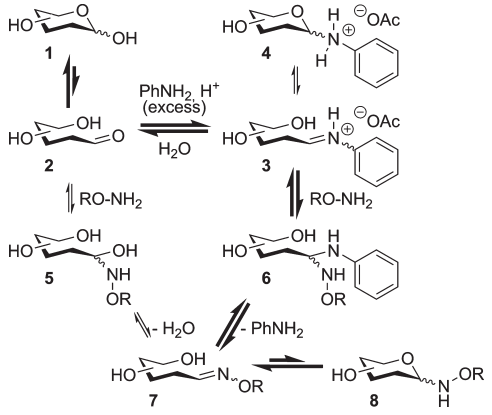
Published on Web 02/04/2010 DOI: 10.1021/jo902425v

SCHEME 1. Proposed Main Reaction Pathways of Nucleophilic Catalysis of Carbohydrate Oxime Formation at pH 4−5

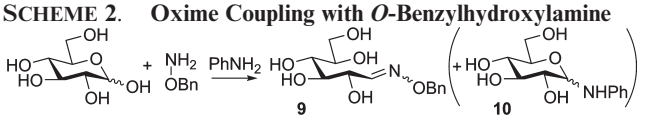


Herein we report for the first time that carbohydrate oxime formation is catalyzed by nucleophiles such as aniline in analogy with oxime formation from open-chain aldehydes. Kinetic studies showed a dramatic increase in reaction rate in the presence of excess aniline, although the kinetic efficiency (i.e., the k_{cat}) was lower for carbohydrate oximes than in reported cases of strictly open-chain reactants. Catalytic effects were demonstrated in all investigated cases, both in solution and on solid phase.

We based our kinetic experiments on previous studies of aldose oxime formation with hydroxylamine (Scheme 1, R = H) showing that these reactions typically proceed with a rate optimum at pH 4−5 (coinciding with the pK_a of the anilinium ion of 4.6), and with increasing equilibrium constants with increasing pH in the pH range 2−5.[15] The pH rate optimum partly reflects a change in rate-determining step from the dehydration of the carbinol oxyamine intermediate (**5**) at higher pH to the nucleophilic attack on the *aldehydo* tautomer (**2**) at lower pH. In the pH range 4−5, however, the kinetics are also influenced by the ring−chain tautomerism (mutarotation) of reducing glycans, which is catalyzed by acid or base on either side of pH 4.6.[17] Accordingly, we first investigated oxime coupling between D-glucose and *O*-benzylhydroxylamine in acetate buffer pH 4.6 at 25 °C to allow facile monitoring of formation of oxime **9**[18] by HPLC (Scheme 2).

Initially, reactions were performed under equimolar conditions at 1 mM reactants; however, the observed reaction rates and product conversions (i.e., K_{eq}) were generally too low for straightforward kinetic analyses. In order to increase the reaction rates we performed reactions with 10 equiv of carbohydrate (10 mM) and the catalytic effect was assessed under increasing concentrations of aniline (0, 5, 10, 20, and 100 mM). These conditions allowed the determination of comparative rate constants from simple pseudo-first-order kinetic treatments of the data ($R^2 > 0.99$). The reaction is first-order in electrophile (i.e., **2** or **3**) even though glucose is in excess. Measured k_{obs} values displayed an approximately linear increase with aniline concentration from 0.13 h^{-1} in the absence of aniline to 2.6 h^{-1} in the presence of 100 mM

SCHEME 2. Oxime Coupling with *O*-Benzylhydroxylamine



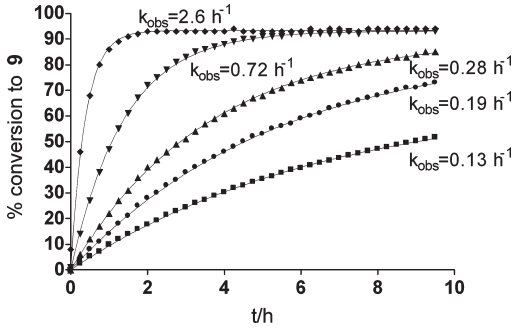


FIGURE 1. Kinetic studies of oxime coupling between D-glucose (10 equiv.) and *O*-benzylhydroxylamine (1 mM) under nucleophilic catalysis by different concentrations of aniline: 100 mM (♦), 20 mM (▼), 10 mM (▲), 5 mM (●), and no aniline (■) in 100 mM acetate buffer pH 4.6. Solid lines represent fitting to pseudo-first-order kinetics.

aniline corresponding to an overall 20-fold rate increase (Figure 1). Thus, catalytic efficieny is substantial albeit approximately 1 order of magnitude lower than for strictly open-chain aldehydes.[13]

In analogy with reported reaction mechanisms, the expected rate-limiting step is the formation of an *N*-phenylglucosyliminium species.[12] However, this species is a common intermediate for formation of oxime product **9** and *N*-phenylglucosylamine **10**. Indeed, we observed concurring formation of **10** during the oxime coupling reaction, reaching levels of 10−15% conversion based on glucose in the presence of 100 mM aniline. Plots of initial rates of formation[19] of **9** versus **10** revealed that glycosylamine formation became increasingly dominant at higher aniline concentrations (Supporting Information). Mutarotation[20] and hydrolysis[14,21] studies of *N*-phenylglucosylamines have shown that the equilibrium between **10** and the imine intermediate is fast at pH 4−5 relative to the mutarotation of glucose, and preformed *N*-phenylglucosylamines have been reported as imine precursors.[22] Our results indicate, however, that glycosylamine (**4**) formation at higher aniline concentrations causes a lowering of the observed catalytic efficiency in carbohydrate oxime formation due to the deprivation of the reactive iminium intermediate (**3**). In agreement herewith, the catalytic efficiency was lowered further to a ∼10-fold increase at 100 mM aniline at high nucleophile conditions (10 equivalents, 10 mM) (Supporting Information).

Next, we applied nucleophilic catalysis to neo-glycopeptide synthesis with galacturonic acid on Leu-Enkephalin derived peptide **11** containing an *N*-terminal aminooxyacetyl functionality (Table 1). After 1 h at 25 °C, a 3-fold increase in conversion to **12** was observed in the presence of 100 mM

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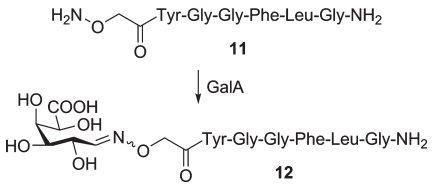
TABLE 1. Neoglycopeptide Synthesis with GalA[a]



entry	catalyst[b]	temp (°C)	time (h)	conversion[c] (%)
1		25	1	30
2		25	70	96
3	aniline	25	1	87
4	aniline	25	6	90
5		60	1	79
6		60	2	91
7	aniline	60	0.17[d]	95

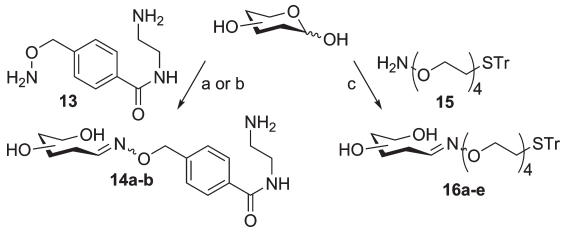
[a]Conditions: **11** (2.5 mM), GalA (6.5 mM), 100 mM NH_4OAc buffer pH 4.5. [b]100 mM. [c]By HPLC. [d]10 min.

aniline. Gentle heating (60 °C) promoted a similar increase in reaction rate, and aniline catalysis at 60 °C provided a shortening of reaction time from 70 h to 10 min.

A series of experiments were conducted to investigate the potential of nucleophilic catalysis of carbohydrate oxime formation with heterobifunctional linkers containing amino (**13**[8]) or thiol (**15**[4]) groups for anchoring to various surfaces. The catalytic effect was assessed by comparison of reactant conversion in the presence or absence of 100 mM aniline. The observed increase in conversion levels of reaction of **13** was 3-fold with glucose (**14a**) and 2-fold with lactose (**14b**[8]) after 3 h. Reactions with **15** were performed in $H_2O-MeCN$ 1:2 due to the apolar nature of the nucleophile and with 300 mM acetic acid (pH ca. 4.3). For glucose (**16a**[4]), the conversion level was almost 3-fold higher after 1 h in the presence of aniline, and the conversion for the less reactive *N*-acetylglucosamine (**16b**) was 2−3-fold higher after 1 and 6 h. In cases of galactose (**16c**), mannose (**16d**), and galacturonic acid (**16e**), the uncatalyzed reactions proceeded too rapidly for an evaluation of the catalytic effect, although in all cases the conversion levels in the presence of aniline were higher. The reaction rates for the various monosaccharides in Table 2 follow the trends Man ≈ Gal > Glc and GlcA > Glc > GlcNAc in accordance with previous data,[15] confirming that ring−chain tautomerism[23] (to produce open-chain *aldehydo* form) influences the overall rate of oxime formation. It is worthy to note that conditions involving a raise of the temperature to 50 or 60 °C in the absence of aniline in some cases provided increases in reaction rate superior to aniline catalysis conditions; however, in some of these cases additional byproducts were apparent after longer reaction times.

We subsequently applied carbohydrate oxime coupling with linker **15** for chemoselective labeling of a complex lipochitin oligosaccharide[24] (nodulation factor) isolated from *Mesorhizobium loti*. Oxime coupling with the isolate, which contained a mixture of three main species (two monoacetylated and a nonacetylated), could be accomplished under very mild conditions in 25 mM acetate buffer

TABLE 2. Capture of Glycans on Heterobifunctional Linkers[a]



entry	glycan	catalyst[b]	temp (°C)	time (h)	conditions, product	conversion[c] (%)
1	Glc		25	3	a, **14a**	14
2	Glc	aniline	25	3	a, **14a**	43
3	Glc		25	18	a, **14a**	52
4	Glc	aniline	25	18	a, **14a**	84
5	Lac		50	3	b, **14b**	62
6	Lac	aniline	50	3	b, **14b**	100
7	Glc		25	1	c, **16a**	35
8	Glc	aniline	25	1	c, **16a**	88
9	Glc		60	1	c, **16a**	97
10	Glc		25	6	c, **16a**	90
11	Glc	aniline	25	6	c, **16a**	100
12	Glc		25	16	c, **16a**	74[d]
13	GlcNAc		25	1	c, **16b**	7
14	GlcNAc	aniline	25	1	c, **16b**	20
15	GlcNAc		60	1	c, **16b**	72
16	GlcNAc		25	6	c, **16b**	37
17	GlcNAc	aniline	25	6	c, **16b**	80
18	GlcNAc		25	48	c, **16b**	69[d]
19	Gal		25	1	c, **16c**	90
20	Gal	aniline	25	1	c, **16c**	100
21	Gal		25	16	c, **16c**	73[d]
22	Man		25	1	c, **16d**	88
23	Man	aniline	25	1	c, **16d**	100
24	Man		25	16	c, **16d**	75[d]
25	GalA		25	1	c, **16e**	100
26	GalA		25	16	c, **16e**	84[d]

[a]Conditions: (a) **13** (50 mM), glycan (150 mM), ammonium acetate buffer pH 4.5; (b) **13** (5 mM), glycan (5 mM), ammonium acetate buffer pH 4.5; (c) **15** (20 mM), glycan (40 mM), HOAc (300 mM), $H_2O-MeCN$ 1:2. [b]100 mM. [c]By HPLC. [d]Isolated yield.

pH 4.6 at 25 °C in the presence of 100 mM aniline. Conversion to oxime **17** (Scheme 3) was estimated by HPLC at 73% (55% isolated yield) after 19 h as compared to only 8% in the absence of aniline.

Finally, we examined the effect of added aniline in the protocol for solid-phase oligosaccharide tagging (SPOT) reported by Lohse et al.[11] Specifically, amino-functionalized controlled-pore glass (CPG) was derivatized through an ester linkage to the *p*-carboxyl group of benzylhydroxylamine (**18**, Scheme 4) at a density of 68 μmol/g. A solution of Gal, GlcNAc, and maltoheptose (G7) (100 μM each) was incubated overnight with beads under two different sets of conditions expected to result in the trapping of Gal (**19a**), GlcNAc (**19b**), and G7 (**19c**) as the oximes. The efficiency of capture was evaluated following reduction, tagging with tetramethylrhodamine isothiocyanate (TMR-NCS), and cleavage using aqueous LiOH, and the products **20a**−**c** were quantitated by fluorescence detection in capillary electrophoresis (Table 3) as previously described.[11] Under ideal conditions for oxime formation (pH 4.5), aniline improved the capture efficiency for the more difficult sugars but less than 3-fold. At pH 7.0, conditions reported to be favorable for 4-anisidine catalysis, the improvement was much more dramatic for both aniline and 4-anisidine though not

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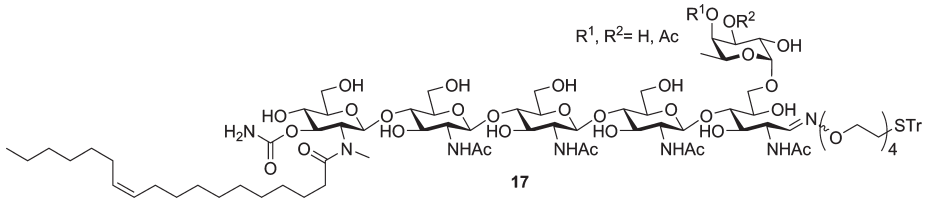
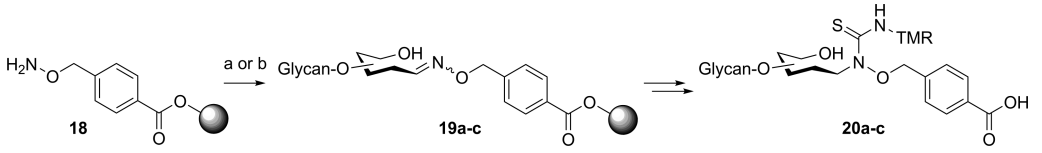
SCHEME 3. Labeling of Isolated Lipochitin Oligosaccharide As Glycan Oxime



SCHEME 4. Solid-Phase Oligosaccharide Tagging[a]



[a]A carbohydrate mixture of Gal (**a**), GlcNAc (**b**) and maltoheptaose (G7) (**c**) at 100 μM each was used. The corresponding oximes (**19a**−**c**) were reduced (8 M borane−pyridine), tagged (TMR-NCS), and cleaved by saponification to give **20a**−**c** as described.[11] Conditions: (a) 100 mM acetate buffer pH 4.5; (b) 100 mM phosphate buffer pH 7.0.

TABLE 3. Aniline Catalysis of Solid-Phase Oligosaccharide Tagging[a]

			conversion (%)[c]		
entry	catalyst[b]	conditions	**20a**	**20b**	**20c**
1		a	100	18	38
2	aniline	a	100	51	53
3	4-anisidine	a	83	38	42
4		b	19	0	0
5	aniline	b	74	9	20
6	4-anisidine	b	80	29	40

[a]Conditions: (a) 100 μM glycan mixture, 100 mM acetate buffer pH 4.5, 50 °C; (b) 100 μM glycan mixture, 100 mM phosphate buffer pH 7.0, 50 °C. [b]100 mM. [c]By capilliary electrophoresis.

reaching the coupling efficiency observed at pH 4.5, in line with previous reports.[13]

In conclusion, we have shown that carbohydrate oxime formation can be catalyzed by anilines. Overall reaction rates were increased up to 20-fold in the presence of 100 mM catalyst. Concurring formation of the *N*-phenylglycosylamines accounted for up to 15% (based on carbohydrate) under the investigated conditions and likely contributes to the lowering of the catalytic efficiency compared to catalysis of oxime formation with strictly open-chain aldehydes. Nevertheless, significant rate enhancements were demonstrated in a range of practical application of glycan capture. Reactions were also well promoted by moderate heating (50−60 °C); however, additional byproducts were apparent after longer reaction times even for monosaccharides, and further degradation may be expected with increasingly complex glycans. The findings described herein are particularly useful for coupling reactions involving complex glycans available in small quantities and glycans containing labile decorations. As expected and in support of the mechanism in Scheme 1, preliminary experiments confirm that these results are readily extendable to carbohydrate hydrazones, *N*-glycosylhydrazides, as well as *N*-glycosyl-*N*-(alkyl)oxyamines (data not shown).

Experimental Section

Kinetic Measurements on Formation of D-Glucose *O*-Benzyloxime (9). Separate solutions of *O*-benzylhydroxylamine hydrochloride (4 mM) and α-D-glucose (40 mM, equilibrated[15] minimum 10 min) were prepared by dissolution of the solids in 100 mM acetate buffer pH 4.6. Aniline solutions (0, 10, 20, 40, or 200 mM) were prepared by dissolution in 100 mM acetate buffer followed by readjustment to pH 4.6 with acetic acid. Reactions were initiated by mixing the above three solutions in the ratio 1:1:2 (v/v/v) to provide final concentrations of 1 mM oxyamine, 10 mM carbohydrate, and 0, 5, 10, 20, or 100 mM aniline. Formation of **9** and **10** was monitored by HPLC.

Neoglycopeptide 12. To peptide **11** (1 μmol) was added D-galacturonic acid (3 μmol) in 100 mM acetate buffer pH 4.5. The conversion to the product was followed by HPLC.

Oxime Coupling with Heterobifunctional Linker 13. All coupling reactions were conducted in 100 mM acetate buffer pH 4.5. Conditions a: solutions of **13** (50 mM) and glucose (150 mM) were shaken at room temperature either in the absence or presence of aniline (100 mM). Product (**14a**) conversion was monitored by HPLC−MS. Conditions b: solutions of linker **13** (5 mM) and lactose (5 mM) were shaken at 50 °C either in the absence or presence of aniline (100 mM). Product (**14b**) conversion was monitored by HPLC−MS.

Oxime Coupling with Heterobifunctional OEG Linker 15. Reactions were conducted in water−acetonitrile 1:2 with **15** (20 mM), glycan (40 mM), and acetic acid (300 mM). Reactions were performed either at (i) room temperature in the absence of aniline, (ii) 60 °C in the absence of aniline, or (iii) room temperature in the presence of aniline (100 mM). Product (**16a**−**e**) formation was monitored by HPLC−MS over periods of 48 h Products were isolated by vacuum liquid chromatography (methanol−dichloromethane 1:20 → 1:8).

Lipochitin Oxime 17. Coupling of lipochitin oligosaccharide (3.3 mM) isolated from *M. loti*[24] with **15** (6.6 mM) through oxime formation was accomplished in water−acetonitrile 1:1, 100 mM aniline, 25 mM acetate buffer pH 4.6. Compound **17** was purified by preparative HPLC.

Acknowledgment. Financial support to K.J.J. from The Danish Council for Strategic Research, the Danish National Research Foundation, and the Danish Council for Independent Research−Technology and Production Sciences is acknowledged.

Supporting Information Available: General experimental methods, compound characterization, and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.