analysis of a powder sample of $PtIn_7F_{13}$ with ICP[25] resulted in 4.5 mol % Pt and 30.9 mol % In (calculated: 4.8 mol % Pt and 33.3 mol % In).

The magnetic susceptibility of $PtIn_7F_{13}$ was measured using a Superconducting Quantum Interference Device (SQUID)-V.T.S.-Susceptometer (S.H. Corp., San Diego (USA) and Quantum Design (MPMS: Magnetic Property Measurement System)) at a constant external magnetic field as a function of temperature. The diamagnetic contribution for $PtIn_7F_{13}$ of 3.6×10^{-4} emu mol^{-1} is in approximate agreement with the value calculated from atomic increments[26] (F^-: 1.1×10^{-5}; In^{3+}: 1.9×10^{-5}; Pt^{2+} 2.0×10^{-5} emu mol^{-1}).

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A Novel Bovine β-1,4-Galactosyltransferase Reaction To Yield β-D-Galactopyranosyl-(1-3)-Linked Disaccharides from L-Sugars**

Yoshihiro Nishida,* Hideaki Tamakoshi, Yuki Kitagawa, Kazukiyo Kobayashi,* and Joachim Thiem

Among mammalian glycosyltransferases, bovine β-1,4-galactosyltransferase (β-1,4-GalTase) has been the most extensively studied regarding substrate specificity.[1] In nature this enzyme catalyzes galactosyl transfer from UDP-galactose to the 4-OH position of *N*-acetyl D-glucosamine (D-GlcNAc) and also of D-glucose in the presence of α-lactalbumin (α-LA). The enzyme is known to catalyze other reactions, for example, the transfer of *N*-acetyl-D-galactosamine to D-GlcNAc at high concentrations of α-LA.[2] Although the β-1,4-GalTase reaction had long been thought to be regiospecific at the 4-OH position of acceptor sugars, we previously found a new type of reactions that catalyze galactosyl transfer to the β-anomeric position of *N*-acetyl kannosamine (3-acetamido-3-deoxy-D-glucose),[3] *N*-acetyl gentosamines (3-acetamido-3-deoxy-D-xylose),[4] and D-xylose.[5] In this paper, we describe the first β-1,4-GalTase reaction that utilizes L-series sugars as the acceptor substrates. Moreover, the novel

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reaction catalyzes unusual galactosyl transfer to the 3-OH position of the L-sugars, that is, a β-1,3-galactosyl transfer.

Our previous β-1,1-transfer reactions for the 3-acetamido-3-deoxy sugars strongly imply that the 3-NAc group may play a key role in an enzyme–substrate binding event to direct the unusual transfer.[4] Provided this is true, variable glycosyl linkages can be synthesized by this enzyme with acceptor substrates bearing the NAc group at different positions. In this study, we introduced an NAc group to the β-anomeric position of L-glucose, L-xylose, and their D-isomers and examined the effect of this group on the enzyme reactions.

The NAc group was introduced by the treatment of each reducing sugar with ammonium hydrogen carbonate in water followed by acetic anhydride in methanol.[6] The 1-NAc derivatives were subjected to an enzyme assay[7] both in the presence and the absence of α-LA. The reactivity was compared with that of the reducing D- and L-sugars in terms of relative initial reaction rates (r) at substrate concentrations of both 1 and 10 mM (Figure 1).

The enzyme assay has proved that the 1-NAc has a signficant effect on the enzyme reactions for both the D- and L-sugars. The opposite effect is observed between D- and L-enantiomers as follows: The NAc group changes L-glucose and L-xylose into reactive substrates, while the same group renders their D-isomers less reactive to a considerable extent. The reactivity of L-sugar-1-NAc is comparable to that of D-xylose in the presence of α-LA. D-Glucose-1-NAc is reactive only in the presence of α-LA, while D-xylose-1-NAc is not reactive even in its presence. These results apparently indicate a novel phenomenon, whereby the anomeric NAc group switches the enantiomer discrimination of this enzyme from a mode for D-sugars into one for L-sugars.

For the reactive substrates, such as L-glucose-1-NAc, L-xylose-1-NAc, and D-glucose-1-NAc, the enzyme reaction was performed on a preparative scale (approximately 30 mg) in a way similar to our previous studies.[3–5] Each of the disaccharide products was isolated in 15–20% yield, and their ^{1}H NMR spectra enabled us to determine that every transfer reaction was regiospecific to produce a single disaccharide product (Table 1). For a disaccharide from D-glucose-1-NAc, the ^{1}H NMR signals of the substrate are deshielded due to a galactosyl linkage at O-4 in the order H-4 > H-5 > H-3 > H-6 > H-2 > H-1. On the other hand, for disaccharides from L-glucose-1-NAc and L-xylose-1-NAc, the deshielding shift is observed in the order H-3 > H-4 > H-2 > H-1 > H-5 > H-6. This reflects a galactosyl linkage at the position O-3. The per-O-acetylation of a disaccharide from L-xylose-1-NAc caused

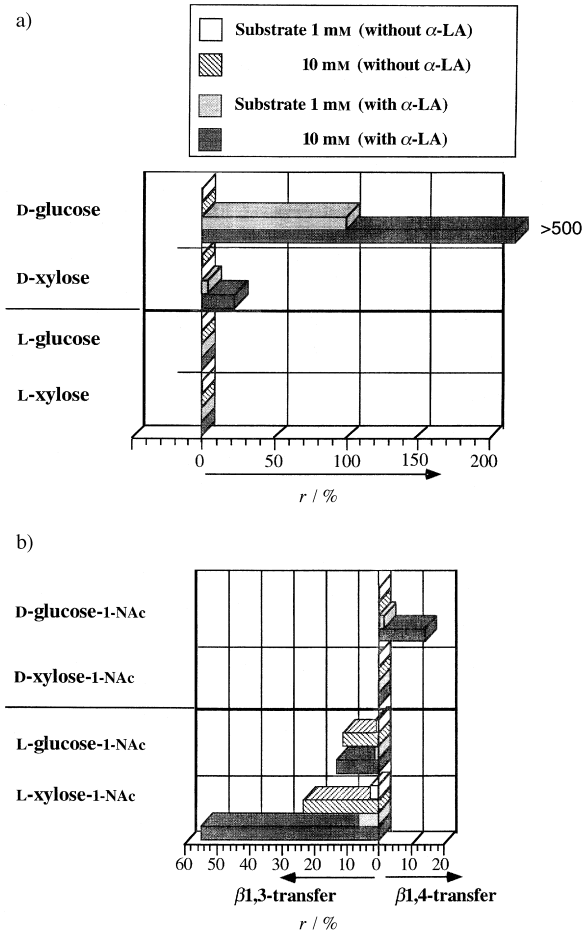

Figure 1. Relative rates (r) for the reaction of bovine β-1,4-galactosyltransferase with enantiomeric glucoses and xyloses (a) and their 1-NAc derivatives (b). The assays were carried for each acceptor substrate at concentrations of 1 and 10 mM and also in the presence and the absence of bovine α-lactalbumin (α-LA; 0.1 mg mL^{-1}). The type of galactosyl transfer in (b) was determined by ^{1}H NMR spectroscopy (see text).

Table 1. Chemical shifts (^{1}H NMR; 500 MHz, D_2O) of the disaccharide products from the β-1,4-galactosyltransferase reactions of *N*-acetyl-β-D- and *N*-acetyl-β-L-glycopyranosyl amines.[a]

	H-1	H-2	H-3	H-4	H-5*ax*	H-5*eq*	H-6*proR*	H-6*proS*	NHAc
β-D-Glc-1-NAc	5.070	3.516	3.678	3.547	3.643		3.846	4.000	2.200
β-L-Glc-1-NAc	5.070	3.516	3.678	3.547	3.643		4.000	3.846	2.200
β-D-Gal-(1-4)-β-D-Glc-1-NAc									
β-D-Glc-1-NAc	5.085	3.552	3.790	3.730	3.790		3.923	4.041	2.200
β-D-Gal	4.572	3.668	3.784	4.041	3.836		3.913	3.869	
β-D-Gal-(1-3)-β-L-Glc-1-NAc									
β-L-Glc-1-NAc	5.117	3.634	3.951	3.772	3.790		4.010	3.865	2.206
β-D-Gal	4.825	3.745	3.819	4.073	3.867		3.932	3.897	
β-L-Xyl-1-NAc	4.989	3.508	3.617	3.746	3.499	4.055			2.190
β-D-Gal-(1-3)-β-L-Xyl-1-NAc									
β-L-Xyl-1-NAc	5.031	3.626	3.891	3.953	3.533	4.070			2.190
β-D-Gal	4.824	3.735	3.815	4.065	3.855		3.928	3.888	

[a] Assignments of all ring protons are based on ^{1}H-^{1}H COSY spectra, while those of C-6 prochiral protons are based on the spectra of the (6*S*)-(6-$^2H_1$)-D-glucoside and (6*S*)-(6-$^2H_1$)-D-galactoside derivatives reported in ref. [15].

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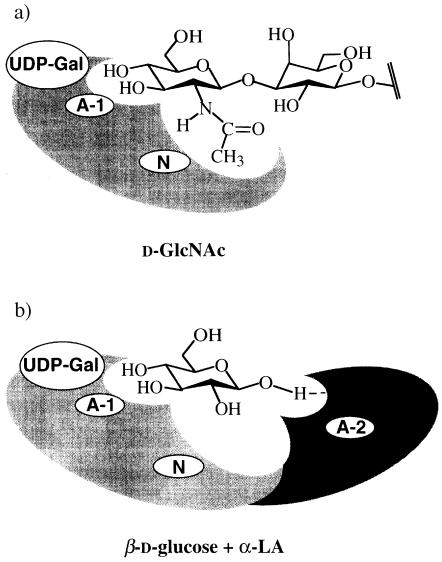

Figure 2. Proposed key enzyme–substrate interactions in reactions of bovine β-1,4-GalTase with natural acceptor substrates. In the absence of α-LA, a catalytic domain (**A-1**) and an NAc binding locus (**N**) provide key binding interactions for the terminal D-GlcNAc residue of oligosaccharides (a). α-LA binds to the enzyme adjacent to an acceptor binding site of D-glucose and induces a supplementary interaction at **A-2** that is key for the D-glucose reaction to yield lactose (b).

strong deshielding and shifting of the H-2 ($\Delta\delta = 1.14$) and H-4 signals ($\Delta\delta = 0.56$), but not of the H-3 signal ($\Delta\delta = 0.05$) supporting the idea of a galactosyl linkage at O-3.

Thus, a 1-NAc group was proved to change L-glucose and L-xylose into unique β-1,4-GalTase substrates and to permit galactosyl transfer at the 3-OH position. It is also of significance that both D- and L-enantiomers of glucose-1-NAc can become substrates, to yield β-1,4- and β-1,3-linked disaccharides, respectively. In order to rationalize these findings, we propose three key interactions at the **A-1**, **A-2** and **N** loci (Figure 2). The **A-1** locus provides a key polar interaction[8] with a reactive hydroxyl group of the acceptor substrate, as suggested by Kajihara et al.[9] This locus is considered to recognize one of the 1,2-*trans* diols with anticlockwise helicity (such as OH-3/OH-4 of D-GlcNAc and OH-2/OH-3 of L-glucose-1-NAc) in a similar way to the recognition by D-glucose/D-mannose-binding lectins (for example, concanavalin A).[10] Although the binding at **A-1** is essential for the enzymatic reaction, the interaction itself is assumed not to be strong enough for reactions below 10 mM substrate concentration under physiological conditions. The enzymatic reaction, thus, requires a supplementary binding either at the **A-2** or the **N** locus. An NAc group binding site (**N** locus), as suggested by Berliner et al.,[11] is considered to provide a key interaction for D-GlcNAc and other substrates carrying an NAc group (Figure 2a). Another important interaction at **A-2** is induced by the action of α-LA, which forms a 1:1 enzyme complex adjacent to the substrate binding site.[11, 12] Judging from the fact that substitution of an anomeric hydroxyl group with NAc and OMe groups[11] suppresses the reactivity of D-glucose and D-xylose significantly, the **A-2** locus is assumed to interact with such a group (Figure 2b).

Although L-glucose and L-xylose do not satisfy dual interactions at **A-1** and **A-2** per se (Figure 3a), introduction

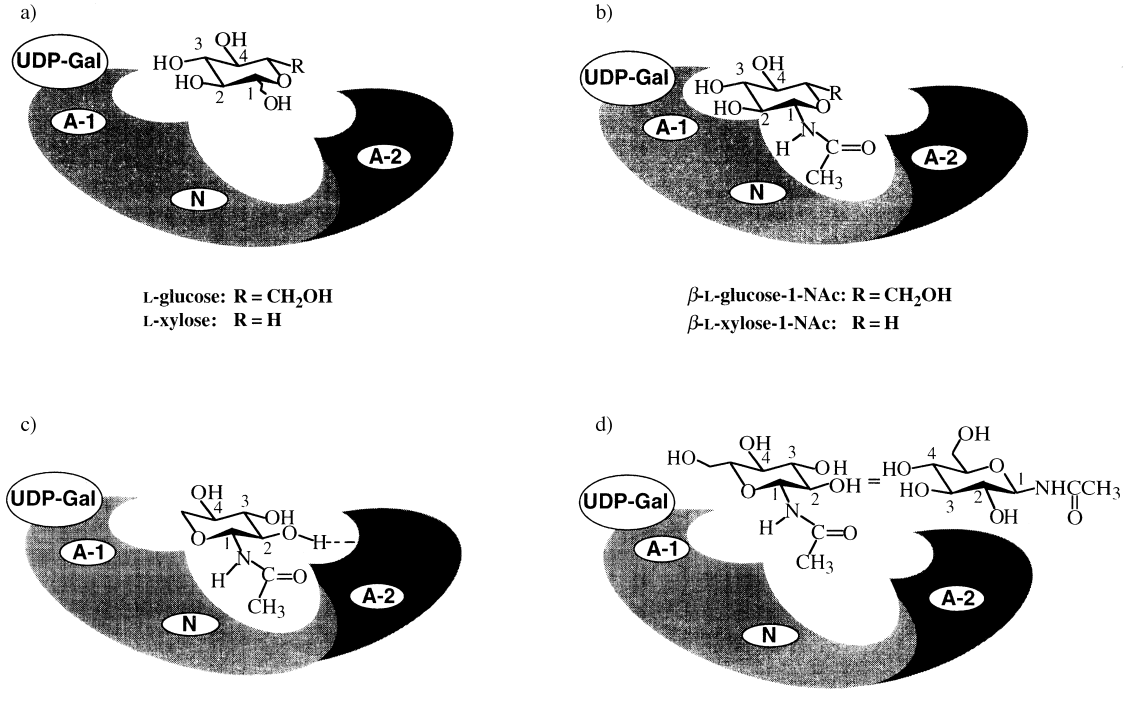

Figure 3. Possible roles for the 1-NAc group of D- and L-sugars in β-1,4-GalTase reactions. L-Glucose and L-xylose are inactive since they cannot locate hydoxyl groups simultaneously at the **A-1** and **A-2** loci (a). The 1-NAc group allows them to have an interaction at the **N** locus leading to galactosyl transfer at the 3-OH position (b). D-Glucose-1-NAc and D-xylose-1-NAc cannot adopt the **A-1** + **N** or the **A-1** + **A-2** interactions. Instead, an alternative binding at the **N** and **A-2** loci may be possible for D-xylose-1-NAc, in which the reaction site **A-1** is not occupied (c). The exocyclic 5-CH_2OH group of D-glucose-1-NAc disrupts any binding at **N** and **A-2** and instead, it provides a peripheral binding interaction that allows the natural β-1,4-transfer reaction (d).

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of the 1-NAc group allows them to occupy the **A-1** and **N** loci (Figure 3b). In this case, the 3-OH group at **A-1** is galactosylated, as is actually observed. On the contrary, 1-NAc derivatives of D-sugars can not adopt the supplementary interaction at the **N** or **A-2** loci. Instead, D-xylose-1-NAc may adopt an alternative bonding at the **A-2** and **N** loci where no reactive OH is placed at **A-1** (Figure 3c). For D-glucose-1-NAc, which is reactive in the presence of α-LA, the exocyclic C-5 group may disturb this bonding (Figure 3d). Moreover, judging from the higher reactivity of D-glucose than D-xylose (Figure 1a), a peripheral binding interaction may exist around the C-5 group of D-glucose and contribute to the usual β-1,4-transfer reaction.

In conclusion, we have proved that an anomeric NAc group changes unnatural L-glucose and L-xylose into acceptor substrates for bovine β-1,4-GalTase. The transfer reaction is regiospecific at the 3-OH position and so this is the first β-1,3-transfer reaction for this enzyme. This finding, together with our previous ones, have shown that variable unnatural glycosyl linkages can be produced enzymatically by a single enzyme. This fact may exceed the general concepts of "one glycosyl enzyme for one glycosyl linkage"[13] and "biological homochirality"[14] that express the high substrate and enantiospecificity of enzyme reactions in biosynthetic pathways.

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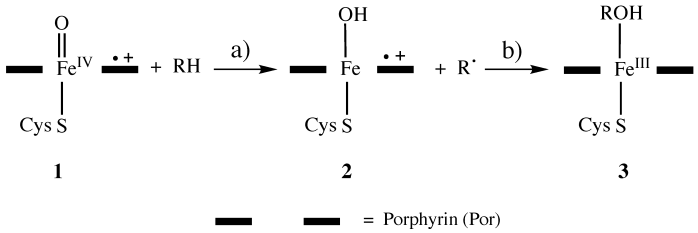
Two-State Reactivity in the Rebound Step of Alkane Hydroxylation by Cytochrome P-450: Origins of Free Radicals with Finite Lifetimes**

Nathan Harris, Shimrit Cohen, Michael Filatov, François Ogliaro, and Sason Shaik*

Alkane hydroxylation[1] by cytochrome P-450 poses tantalizing mechanistic questions. The consensus rebound mechanism, Scheme 1,[2] involves hydrogen abstraction from the



Scheme 1. Schematic representation of the rebound mechanism.

alkane (RH) in step (a), followed by hydroxyl rebound onto the radical to generate the ferric – alcohol complex, in step (b). The rebound mechanism has gained support from findings of rearranged alcohol products, which indicate the presence of a free radical with a finite lifetime.[3] Further support has recently been provided by the kinetic isotope effect (KIE) measurements of Dinnocenzo, Jones et al.[4a] They found that for a few substituted alkanes, the KIE's of cytochrome P-450 hydroxylation are virtually identical to those of a corresponding hydrogen abstraction reaction by *tert*-butoxyl radical, thus implying isostructural transition states for the two processes.[4] In an apparent contrast, mechanistic studies by Newcomb and co-workers,[5] designed to probe the radical using alkane substrates that would yield ultrafast radical clocks, do not concur with a free-radical intermediacy; apparent lifetimes are too fast to correspond to a real free-radical intermediate (for example, $\tau \leq 70$ fs),[5b] and have no correlation with independently clocked rearrangement lifetimes of the free radicals.[5a] Thus, while the evidence for incursion of radicals is strong, their presence is nevertheless controversial and merits elucidation.

The origin of the radicals in the rebound process is the key issue addressed in this communication. Our approach to tackle this question, is to use density functional calculations to ascertain whether the hypothetical rebound process in step (b) of Scheme 1, involves a barrier which would endow the

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