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Minireview

Chemistry of xylopyranosides

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ABSTRACT

Xylose is one of the few monosaccharidic building blocks that are used by mammalian cells. In comparison with other monosaccharides, xylose is rather unusual and, so far, only found in two different mammalian structures, i.e. in the Notch receptor and as the linker between protein and glycosaminoglycan (GAG) chains in proteoglycans. Interestingly, simple soluble xylopyranosides can not only initiate the biosynthesis of soluble GAG chains but also function as inhibitors of important enzymes in the biosynthesis of proteoglycans. Furthermore, xylose is a major constituent of hemicellulosic xylans and thus one of the most abundant carbohydrates on Earth. Altogether, this has spurred a strong interest in xylose chemistry. The scope of this review is to describe synthesis of xylopyranosyl donors, as well as protective group chemistry, modifications, and conformational analysis of xylose.

1. Introduction

Being a major constituent of xylans, a group of hemicelluloses, xylose is one of the most abundant carbohydrates on Earth. The name xylose (Greek ξυλον, *xylon* meaning wood) originates from the isolation of the sugar from wood by Koch in 1886, and xylose is also known as *wood sugar*. Xylose is a pentose and can thus form both pentofuranosides and pentopyranosides, with the latter being the most common configurations (Fig. 1). Hydrogenation, or microbial fermentation,[1] of xylose gives the sugar alcohol xylitol (birch sugar), which is also found in many natural sources, such as birch sap. Xylitol is considerably sweeter than xylose, and is used as a sweetener.

Apart from plant origins, xylose is also found in important mammalian cell surface structures, such as proteoglycans. Due to the biological importance of xylose, it has attracted a great deal of research interest. The development of methods for synthesis of xylopyranosyl donors, acceptors, and analogs of D-xylopyranosides are summarized in this review.

1.1. Xylosides in plants

1.1.1. Xylan and xyloglucan

Plant xylans, in the form of hemicellulose, are among the most abundant renewable bioresources available. Hemicelluloses are plant cell-wall heteroglycans built up by a β-linked glycan backbone of e.g. xylose, mannose, galactose, and/or glucose.[2,3] β-Mannans are the dominant hemicelluloses in softwoods and β-xylans are dominant in hardwoods and grasses. In general, the xylan backbone is substituted to different degrees by sugar residues and/or other components (Fig. 2). Hardwoods contain up to 35% of *O*-acetyl-4-*O*-methyl-glucuronoxylan.[4] Acetylation occurs at C2 and C3 and it is worth mentioning that acetyl migration may occur in vitro.[5] In grasses and softwoods the xylan backbone is substituted with L-arabinofuranoside units in addition to methylglucuronic acid.[6] In grasses, arabinoses may be esterified by phenolic compounds (*p*-coumaric acid and ferulic acid). The xylan content in grasses is similar or higher than that in hardwood, while softwood contains less (up to 15%).[6] The primary cell-walls of many plants contain xyloglucan, which has a β-glucan backbone that is substituted by xylose units,[3] and the xyloglucan structure varies with species and tissue. Xyloses in xyloglucan may be further substituted, e.g. by galactose or arabinofuranoside residues. A further common modification is a fucose unit carried by some galactoses.

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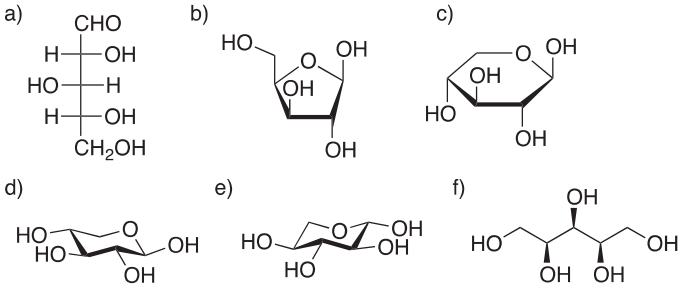

Fig. 1. (a) D-Xylose [58-86-6], open form. (b) β-D-Xylofuranose, Haworth projection. (c) β-D-Xylopyranose, Haworth projection. (d) β-D-Xylopyranose, chair conformation. (e) β-L-Xylopyranose, chair conformation. (f) Xylitol [87-99-0].

Xylans are synthesized in the Golgi-apparatus,[3,7] and some of the glycosyl transferases (e.g. using UDP-xylose as substrate) and other proteins that are involved have been identified. Xylans may furthermore be modified by plant encoded glycoside hydrolases (e.g. endoxylanase or exo-β-xylosidase) which may act outside the Golgi.[7] These processes are, however, not well understood in planta. Recently, an Arabidopsis protein capable of catalyzing xylan acetylation was identified.[8]

1.1.2. Bioconversion of plant xylans and xylosides

Plant xylans and other hemicelluloses are major renewable resources for chemical or microbial conversion to value added products (biofuels, materials, biochemicals) within biorefinery strategies.[9] Following biomass pretreatment and/or extraction, e.g. from hardwoods or agricultural crops such as cereals, xylan can be hydrolyzed by microbial enzymes (glycoside hydrolases) into oligo- or monosaccharides. Xylooligosaccharides produced from e.g. wheat, other cereals, or hardwood xylan, have potential applications as prebiotics since they can stimulate human gut Bifidobacteria.[10–13] Xylose is a valuable feedstock for production of biofuels, biochemicals, and also xylitol for which microbial production is being investigated as an alternative to the established chemical production route.[14,15] Baker's yeast, *Saccharomyces cerevisiae*, is unable to ferment xylose and several strategies for fermentation of xylose to ethanol have been developed, such as the use of other microbes and genetic engineering of yeasts.[16]

The main xylan backbone hydrolyzing glycoside hydrolases are endo-1,4-β-xylanase that hydrolyzes xylosidic bonds internally in the backbone and exo-β-xylosidase that hydrolyzes terminal non-reducing xylose units.[17] Other glycoside hydrolases and esterases hydrolyze the various substitutions.[18] Glycoside hydrolases are classified in families and clans based on protein sequence similarities (see further the CAZy database[†]).[19] The classification of carbohydrate esterases and auxiliary activities (e.g. polysaccharide oxidases) and carbohydrate-binding protein-modules are also displayed in the CAZy database. The main families containing endoxylanases are GH10 and GH11.[17] Enzymes from both families catalyze hydrolysis by retaining the anomeric configuration.[20] Two main catalytic residues are involved, an acid/base and a nucleophile.

Retaining glycoside hydrolases may catalyze kinetically controlled transglycosylation,[21] which has been shown for several xylanases including the synthesis of tertiary alkyl β-xylosides.[22] In transglycosylation reactions, the enzyme-glycosyl intermediate of the retaining reaction is disrupted by an acceptor molecule, rather than a water molecule, as is the case in hydrolysis. Thus, this results in the formation of a new glycosidic bond. Potential hydrolysis of the reaction product may be overcome by the use of the glycosynthase approach for synthesis of glycosides. Glycosynthases are retaining glycoside hydrolases where the nucleophile has been substituted to a non-functional amino acid, thus rendering them hydrolytically incapable.[23] By use of a glycosyl fluoride as a donor, the glycosyl unit can be transferred to an acceptor molecule resulting in the synthesis of a new glycosidic bond as shown e.g. for a *Cellulomonas fimi* xylanase.[24] Xylanolytic enzymes also have other applications in the food, feed, and pulp industries mainly as catalysts for xylan hydrolysis.[25,26]

1.1.3. Other plant xylosides

Nectar, i.e. the incentive for pollinators, is usually composed of the carbohydrates, glucose, fructose, and sucrose, in various amounts. Interestingly, xylose has been found in high concentrations, up to 39%, in nectar from two genera of Proteaceae, found in southern Africa and Australia.[27] Some of these plants are pollinated by rock mice (*Aethomyces namaquensis*). This is surprising since xylose is considerably less sweet than sucrose,[28] and cannot be metabolized by non-ruminant animals, such as rodents. Instead these animals rely on bacteria for conversion of xylose.[29] Insects and birds show strong adversity toward xylose.[30]

In a screening of plants from the Amazon rain forest, an O3-substituted xyloside (**1**, Fig. 3) was found in *Maieta guianensis*.[31]

1.2. Xylosides in mammalian cells

Xylose is an unusual carbohydrate in mammalian cells and so far only found as the linker between the protein and the glycosaminoglycan chains of some proteoglycans, and in the Notch receptor. UDP-xylose, i.e. the activated building block used in mammalian cells, is synthesized from UDP-glucose. Xylose from dietary sources is not used in the biosynthesis.

1.2.1. Biosynthesis of UDP-xylose

Mammalian cells use a rather small number of monosaccharidic building blocks, activated as nucleoside phosphates (NDP, often UDP) and only a few NDP-sugars are used in eukaryotic cells. Xylose is formed from UDP-glucose in two steps (Scheme 1). UDP-glucose is first oxidized by the enzyme UDP-glucose-6-dehydrogenase (UGDH) to form UDP-glucuronic acid (UDP-GlcA) and then decarboxylated by UDP-xylose synthase 1 (UXS1) to form UDP-xylose.

In 2012, Nidetzky and co-workers expressed, crystallized, and characterized a truncated version of human UXS1 (hUXS1) in *Escherichia coli*.[32] A detailed catalytic mechanism was proposed, using molecular dynamics simulations of the ternary Michaelis complex, mutagenesis experiments, and deuterium incorporation (Scheme 2). These experiments suggests that UDP-GlcA adopts the $B_{0,3}$ boat conformation. The $^1C_4 \rightarrow B_{0,3}$ transition is needed to align the catalytic groups for the NAD^+-dependent oxidation, and is believed to be the rate determining step. The transportation of UDP-xylose across Golgi membranes is mediated by the UDP-xylose transporter SLC35B4.[33]

1.2.2. Glycosaminoglycans and proteoglycans

Proteoglycans (PGs) are large macromolecules that consist of a core protein decorated by large, negatively charged, carbohydrate chains called glycosaminoglycans (GAGs). These GAGs are linear polysaccharides built of repeating disaccharide units consisting of one aminosugar and one uronic acid.[34] There are four different classes of GAGs defined by the kind of disaccharide unit they are composed of: hyaluronate (HA), chondroitin sulfate/dermatan sulfate (CS/DS), heparin/heparan sulfate (HS), and keratan sulfate (KS). The PGs are found on the cell surface as well as in the extracellular matrix where they have important roles in the regulation of growth factor signaling, inflammation, angiogenesis, and cell–cell interaction.[35–37] PG and GAG thus play important roles in cancer,[38] and mutations in genes encoding for enzymes involved in the biosynthesis of

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