1 Aldo (and Keto) Hexoses and Uronic Acids

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1 Introduction

1.1 Historical

As soon as information became available at the beginning of this century concerning the structure of the different monosaccharide moieties of complex plant polysaccharides, hypotheses were advanced to explain the origin of the various hexoses, hexuronic acids, and pentoses which are present in such vast abundance in plants. It was proposed and generally accepted that hexosyl moieties found in a particular polysaccharide were converted by in situ oxidation to the corresponding polyuronides and the latter then yielded pentosans by decarboxylation. Thus in the D-glucose series of hexoses, cellulose, a linear \((1 \rightarrow 4)-\beta-D\text{-glucan}\), would be converted to a polyglucuronide which upon decarboxylation would yield D-xylan. A similar sequence of reactions was thought to be responsible for the conversion of polymers in the D-galactose series to poly-D-galacturonides such as pectic acid, which would be expected to produce L-arabinans upon decarboxylation.

As more knowledge concerning the structure of plant polysaccharides accumulated, it became evident that the original hypothesis was untenable. In many cases it was found that the carbohydrate moieties were present in different ring forms and anomeric linkages in the presumably related aldosans, polyuronides, and pentosans. The original hypothesis was therefore modified with the proposal by Hirst (1942) that the hexose \(\rightarrow\) uronic acid \(\rightarrow\) pentose transformation occurs at the monosaccharide level, followed by subsequent incorporation, by an unspecified mechanism, of these monomers into polysaccharides.

Polysaccharide synthesis in vitro was first accomplished by Cori et al. (1939), with \(\alpha-D\text{-glucopyranosyl} \text{ phosphate (GlcIP)}\) as D-glucosyl donor in the synthesis of glycogen. In reactions catalyzed by bacterial enzymes, sucrose was shown to be the donor of the D-glucosyl moiety in the synthesis of dextran (D-glucan) (Hehre and Sugg 1942) and of the D-fructosyl moiety in the synthesis of levan (D-fructan) (Hestrin et al. 1943). However, the mode of synthesis of the vast majority of oligosaccharides and polysaccharides, as well as most of the glycosyl moieties comprising them, remained a mystery until the discovery of nucleotide sugars.

During the late 1940’s, Luis Leloir and his collaborators in Argentina were studying the conversion of \(\alpha-D\text{-galactopyranosyl} \text{ phosphate (GalIP)}\) to GlcIP by extracts of D-galactose-grown \textit{Saccharomyces fragilis}. It was found that this conversion actually represented the sum of two reactions:
in the first of these reactions the Gal1P is incorporated into a nucleotide structure by reacting with a compound present in the extract and subsequently shown to be uridine 5'-\((\alpha-\beta\text{-glucopyranosyl pyrophosphate})\) (UDPGlc). UDPGlc was enzymatically transformed to uridine 5'-\((\alpha-\beta\text{-galactopyranosyl pyrophosphate})\) (UDPGal). Thus the sum of the two reactions is conversion of Gal1P to Glc1P.

A number of seminal discoveries were made by Leloir and his collaborators during the course of these investigations. Perhaps the most important were the discovery of UDPGlc (Cardini et al. 1950, Caputto et al. 1950) and demonstration of its conversion by 4-epimerization to UDPGal (Leloir 1951) and the isolation of guanosine 5'-\((\alpha-\beta\text{-mannopyranosyl pyrophosphate})\) (GDPMan) from yeast (Cabib and Leloir 1954). Although it was not recognized at the time, this work marked the beginning of a new era of understanding and progress in the synthesis of complex glycosides.

Buchanan et al. (1952–1953), while tracing the path of carbon from \(^{14}\text{CO}_2\) to carbohydrate during photosynthesis, observed that UDPGlc was labeled more rapidly than sucrose phosphate. On the basis of these observations, these workers suggested that “compounds of the UDPG (UDPGlc) type could be concerned in the transformation of sugars and their subsequent incorporation into polysaccharides”. Dutton and Storey (1953) soon after reported the first example of glycosyl transfer from nucleotide sugars with their demonstration that uridine 5'-\((\alpha-\beta\text{-glucopyranosyluronic acid pyrophosphate})\) (UDPGlcA) was the glucuronide donor in liver extracts. Synthesis of trehalose phosphate by transfer of the d-glucosyl moiety from UDPGlc to d-glucose 6-phosphate catalyzed by an extract from yeast was reported in the same year by Leloir and Cabib (1953). Demonstration that enzymes present in wheat germ extracts catalyze the transfer of d-glucose from UDPGlc to d-fructose 6-phosphate to yield sucrose or sucrose-phosphate by Cardini et al. (1955) confirmed the suggestion of Buchanan et al. (1952–1953) and firmly established the position of higher plants in nucleotide sugar research.

In addition to Leloir and his coworkers, the group of researchers led by Herman Kalckar made important early contributions to the new field of nucleotide sugars. The synthesis of UDPGlc from UTP and Glc1P catalyzed by an enzyme (UDP-d-glucose pyrophosphorylase) from d-galactose-grown Saccharomyces fragilis was first clearly shown by Munch-Petersen et al. (1953). This reaction represents a general mechanism for nucleotide sugar synthesis, and occupies a place of major importance in the biosynthesis of monosaccharide moieties. Strominger et al. (1954) demonstrated the NAD-linked conversion of UDPGlc to UDPGlcA, thus elucidating the mechanism of formation of d-glucuronic acid moieties. Perhaps the most important contribution of these workers was the demonstration of the involvement of NAD\(^+\) in the action mechanism of UDP-d-glucose-4-epimerase (Maxwell 1957). As will be detailed...