**Minireview**

**Reactivity of D-fructose and D-xylose in acidic media in homogeneous phases**

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**Abstract**

Chemistry development of renewable resources is a real challenge. Carbohydrates from biomass are complex and their use as substitutes for fossil materials remains difficult (European involvement on the incorporation of 20% raw material of plant origin in 2020). Most of the time, the transformation of these polyhydroxylated structures are carried out in acidic conditions. Recent reviews on this subject describe homogeneous catalytic transformations of pentoses, specifically toward furfural, and also the transformation of biomass-derived sugars in heterogeneous conditions. To complete these informations, the objective of this review is to give an overview of the structural variety described during the treatment of two monosaccharides (D-Fructose and D-xylose) in acidic conditions in homogeneous phases. The reaction mechanisms being not always determined with certainty, we will also provide a brief state of the art regarding this.

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**1. Introduction**

To our knowledge, research about the reaction of carbohydrates in acidic media dates back to the mid 19th century especially with the reaction of cane sugar in dilute sulfuric or hydrochloric acid and heat.1 The first publications on this subject report the production of heterocyclic aldehydes such as furfural and 5-hydroxymethylfurfural (5-HMF) by thermal treatment of carbohydrates (starting from starch or pure monosaccharides) under acidic conditions.2,3 These derivatives have various valorization areas covering applications such as solvents, additives for fuels or as precursors for ‘building blocks’ in chemical synthesis.4,5 5-HMF is unfortunately not produced on industrial scale in contrast to furfural. However, furans such as these are already within the top 10 bio-based building blocks.6

The important development of plant biorefinery (valorization of the whole plant) has among its main objectives, the rapid substitution of a part of the fossil molecules by bio-based chemicals (European involvement on the incorporation of 20% raw material of plant origin in 2020). Therefore, the behavior of carbohydrates in acidic media is still an important subject of research and many studies aim to clarify mechanisms. Publications about access to levulinic acid, furfural and 5-HMF but also to other small molecules, under various conditions, have seen their number grow exponentially (Fig. 1).

These studies focus mainly on the aspects of selectivity and conversion of monosaccharides to the desired product formation.8 The variety of products that is provided by these transformations is however much broader and a multitude of molecules have been identified.

The data concerning the formation of other structures by the transformation of carbohydrates in acidic conditions are spread over more than 170 years. Furthermore, these reports have often been the subject of verifications and modifications. Marcotullio et al. and Fatehi et al. have recently published reviews focused on the specific production of furfural or hydroxymethylfurfural.9,10 For their part, Zhang et al. have given an overview of the transformation of biomass-derived sugars using heterogeneous conditions.10 The objective of this review is to supplement these informations with an overview of the structural variety obtained during the treatment of D-fructose (hexose) and D-xylose (pentose)
in acidic conditions in homogeneous phases. The reaction mechanisms being not always determined with certainty, we will also provide a brief state of the art regarding this.

2. Reaction of carbohydrates in acidic media

Whatever the medium used, characterization of the products formed by acidic pathways remains difficult. Only few methods allow monitoring their appearance and their in situ characterization without prior treatment to decrease or neutralize the acidity of the reaction mixture. This is even more true when the literature is old, analytical techniques then being limited. Over the years, studies have confirmed or disproved molecules already described and helped to identify new ones. Dilute acids are most commonly used to study the reactivity of carbohydrates in acidic media. Taking into account researches described in the literature, experimental conditions are rarely similar and it is not easy to compare the results obtained, even for the same substrate. In fact, each study has different conditions of temperature, sugar concentration, solvent, reaction time, pressure or acidity. The first compounds resulting from the structural modification of a monosaccharide in an acidic medium were described in 1840 by Stenhouse,2 Mulder1 and in 1895 by Düll.11 These are the most stable and easily isolable compounds: furfural, levulinic acid and 5-HMF.

Since that time, the development of analytical techniques and interest in the valorization of bio-based compounds have both expanded the range of identified molecules and also proposed mechanisms of transformation that may involve different intermediates and pathways reaction. However, an exhaustive census remains difficult.12 We will focus herein on the description of the structures obtained in the most used acidic conditions, starting from a hexose and a pentose (D-fructose and D-xylose). The mechanisms proposed to explain their formation are from four types of reactions: isomerizations, dehydrations, fragmentations and condensations.

2.1. Example of a hexose: D-fructose

2.1.1. Structures obtained

D-Fructose remains the predominant hexose for which reactivity in acidic media has been studied and it can be obtained industrially in large quantity by enzymic conversion of glucose from corn starch. It proves to be a prime substrate to access 5-HMF. However, many studies have shown that this compound is far from being the only molecule formed in such conditions. Most structures which can be obtained appear in references in the work of Antal et al.,13 Dumesic et al.14 and more recently De Jong.
Heeres, De Vries et al.\textsuperscript{15} According to the authors, they can be classified into categories related by the reactions involved in their formation (Table 1).

Humins comprise a mixture of highly colored insoluble molecules, with an oligomeric or polymeric structure.\textsuperscript{27,29} The analysis of their structures is still the subject of research\textsuperscript{28,30} as well as the intermediates involved in their formation (Fig. 2).

Scheme 1 includes a compilation of all the compounds obtained during the reaction of D-fructose in an acidic medium and for which a mechanism has been proposed. It consists of four distinct parts according to the molecules resulting from 2,3-enediol, 1,2-enediol, oxocarbenium ions and retroaldolisation reactions.

2.1.2. Mechanisms of formation

The formation of 5-HMF has been the subject of many studies. Two mechanisms are described, via intermediates of the linear enediol type or via a cyclic oxocarbenium ion.

The formation of this compound has been reported by Anet,\textsuperscript{34} Tatum et al.,\textsuperscript{17} and Moreau et al.\textsuperscript{16} who described 1,2- and 2,3-enediol as reaction intermediates (Scheme 2). The enediol system is obtained by the Lobry De Bruyn—Alberda Van Ekenstein transformation, usually conducted under basic conditions, which helps to explain the enolization of aldoses to ketoses and conversely.\textsuperscript{41} However, these enediols can also be formed in an acidic medium as reported by the works of Speck.\textsuperscript{42} Regardless of the enediol formed, it is followed by a dehydration involving the carbon atom C-4, and the formation of an additional double bond. A last

\begin{scheme}
\textbf{Scheme 2.} Formation of 5-HMF via acyclic intermediates, according to Moreau et al.\textsuperscript{16}
\end{scheme}

\begin{scheme}
\textbf{Scheme 3.} Products formed from oxocarbenium ions using D-fructose (A: Horváth,\textsuperscript{12} B: Mednick\textsuperscript{31}).
\end{scheme}
cyclization step involves the site either 3,6 (leading to 2-(2-hydroxyacetyl)furan) or 2,5 (leading to 5-HMF). These enediol intermediates can also lead to fragmentations by retroaldolisation and enable access to furfural.

2.1.2.1. Mechanisms involving intermediates of oxocarbenium type. Various studies (Feather, Antal et al., Horváth et al.) report the involvement of oxocarbenium ions in the formation of compounds including furfural derivatives, anhydrides or humins. These authors emphasize the contribution of cyclic intermediates rather than a sequence implying acyclic structures by relying on studies of dehydration of D-fructose in D₂O that highlight less than 1% of deuterium integration in 5-HMF at the C-3 position. This result casts doubt on mechanisms involving linear intermediates. As the

Fig. 3. Structures of the difructose dianhydrides (DFAs). a Old notation system. b α-fructose-α-glucose mixed dianhydrides.
existing equilibrium between 3-deoxyglucos-2-ene and the 3-deoxyglucose (Scheme 2) requires, by tautomerism, the incorporation of a deuterium atom in position C-3. Similarly, the passage through the 1,2-enediol should lead to the incorporation of deuterium at C-1. The low percentage of deuterium incorporated tends to favor the involvement of cyclic intermediates (Scheme 3). These results have been corroborated by in situ NMR analyzes.

In summary, two different pathways may be advanced which involve oxocarbenium intermediates based on a scaffold either pyranose (17) or furanose (18). These can explain the formation of the major products identified (5-HMF; humins; 2,6-anhydro-β-D-fructofuranose 19; difructose dianhydrides).

Even if these new results tend to confirm the pathway implying cyclic intermediates, no mechanism has been definitively refuted. To date, both are accepted by the scientific community.

Difructose dianhydrides (DFAs) are spiroketals resulting from the cyclodimerization of two molecules of D-fructose. They were initially observed (at the beginning of the 1920s) by reaction of D-fructose or inulin (polysaccharide mixture mainly consisting of fructose units) in concentrated hydrochloric acid. However, the yields obtained in these conditions remain modest due to concomitant degradation reactions. In addition, the purification even partial of the mixture took several years and involved several research groups. Even if a slight improvement, in term of yields, was achieved using trifluoroacetic acid, purification of these compounds remained extremely complex. This difficulty makes problematic their identification, quantification and evaluation of their biological properties.

Some of these compounds (16 known in the literature, Fig. 3) were identified few years later as natural molecules produced by plants (like for DFAs 1, 10 et 15) or by microorganisms (DFAs 1, 10, 15 et 16). They are found in artichokes and Jerusalem artichokes, chicory and roasted coffee beans, tequila, and especially in commercial caramels where they represent up to 18% by weight.

One of the most effective synthetic methods is the use of Lewatit® S2328 (H⁺), a strongly acidic ion exchange resin having sulfonic acid functional groups. García Fernández’s coworkers have been able to get a more accurate analysis of the resultant mixture using GC/FID (Chart 1).

Moreover, it is the first description (which still constitutes a reference) of a precise relative distribution of DFAs obtained starting from D-fructose. However, a different relative distribution has been observed during thermal treatment of inulin. Defaye, García Fernández et al. have proposed a general scheme for the DFAs formation (Scheme 4).

This mechanism goes through the activation of D-fructose resulting in the formation of an oxocarbenium ion (step A), which will lead to fructodisaccharides after dimerization (step B). DFAs are then obtained by intramolecular glycosylation (step C). While the mechanism may seem simple, many factors can influence the mixture composition.

2.1.2.2. Retroaldolization products. Whatever the favored mechanism for the reactivity of oses in acidic conditions, they can also
lead to low molecular weight products resulting from retroaldolization reactions. The retroaldolization products obtained starting from D-fructose are described in Scheme 5. These compounds can be detected at the end of the reaction as final products, or, as reported by Cammerer et al., be involved in the formation of 5-HMF by aldolization.33

2.2. Example of a pentose: D-xylose

2.2.1. Structures obtained

While D-fructose remains the hexose for which the reactivity in acidic media has been the most studied, it is the reactivity of D-xylose which has been widely explored in the pentose series. In fact, this allows an easy access to furfural. However, this is not the only product to be formed under these acidic conditions and almost all of the compounds obtained were identified by Antal et al.53 As with D-fructose, these products can be divided into several categories depending on reactions allowing their formation (Table 2).

Scheme 6 summarizes all the molecules obtained by the reaction of D-xylose in diluted acidic media and for which a mechanism has been suggested. It consists of three distinct parts, from acyclic intermediates, cyclic intermediates and retroaldolization reactions.

2.2.2. Mechanisms of formation

The formation of furfural has been the subject of many discussions. Two mechanisms are proposed: from open chain (enediol type) or cyclic intermediates.

2.2.2.1. Mechanisms involving open chain intermediates (enediol type).

The production of furfural involving an 1,2-enediol intermediate has been proposed in several works, including those of Isbell56 and Anet34 (Scheme 7). Once again, formation of this intermediate is initiated by the transformation of Lobry De Bruyn–Alberda Van Ekenstein. This is followed by a double dehydration involving sites 3 and 4, adding two additional conjugated unsaturations, and leading to intermediate 20. Finally, a cycloaddition step will allow the formation of furfural (involvement of sites 2,5) or of 2,3-dihydroxycyclopent-2-ene-1-one (involvement of sites 1,5).

<table>
<thead>
<tr>
<th>Table 2 Products obtained from the reaction of D-xylose in diluted acidic media, according to Antal’s review</th>
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<tbody>
<tr>
<td>Isomerization</td>
</tr>
<tr>
<td>D-Lyxose13</td>
</tr>
<tr>
<td>2,3-Dihydroxy-2-cyclopent-2-ene-1-one14</td>
</tr>
<tr>
<td>Glycolaldehyde</td>
</tr>
<tr>
<td>Formaldehyde55</td>
</tr>
<tr>
<td>Dihydroxyacetone53</td>
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<tr>
<td>Lactic acid53</td>
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</table>

2.2.2.2. Mechanisms implying cyclic intermediates. Several studies reported in the literature (Antal et al., Zeitsch) have examined the involvement of cyclic intermediates in the formation of furfural (Scheme 8). According to these works, two different pathways involving cyclic intermediates can explain the formation of furfural. The first pathway (B) is also divided into two parts, one of which goes through a cyclic oxocarbenium ion, both leading to the formation of 2,5-anhydroxylose (compound 21) via an intramolecular rearrangement. Furfural is then obtained after a double dehydration. The second pathway (C), suggested in 2000 by Zeitsch, goes through a successive formation of a pyranosidic oxocarbenium ion, a ring opening, a series of protonations/dehydrations and a final cyclization leading to furfural. However, according to a study carried out on D-xylose-1-14C, the labeled carbon is found almost exclusively at the carbonyl of furfural, which is in contradiction with pathway C (for which the carbonyl is in position C-5).

2.2.2.3. Retroaldolization products. As for D-fructose, D-xylose in diluted acidic media can lead to low molecular weight products resulting from retroaldolization reactions (Scheme 9).

As we have seen, both with D-fructose and D-xylose, the structure and the mechanisms of formation of certain compounds are still not understood. For some other products, their reaction mechanisms have been suggested before the products have been observed experimentally. Thus, if Antal et al. assume the formation of a tetrose, coproduct of the D-fructose retroaldolization leading to glycolaldehyde, the confirmation of this hypothesis and the identification of D-erythrose, were done thanks to the works of Yoshida et al., sixteen years later. Similarly, while epimerization of D-xylose to D-lyxose is suggested in the Anet mechanism, it has been detected only twenty-five years later by Antal. Its ketopentose form (D-xylulose) has not yet been identified.

2.2.2.4. A special case: nitric acid. Finally, it is noted that nitric acid, one of the common mineral acids, is not studied in the case of sugar decomposition in an acidic medium. Indeed, the acid property of this one is in competition with its oxidizing power. Thus, in 1888, Sohst and Tollens showed that it is possible to form D-mannaric acid from D-mannose using nitric acid as an oxidizer (Scheme 10). Fischer did the same with D-glucaric acid from D-glucose.

Their work has been taken up by Kiely et al. to improve the protocols used, and make them more attractive from a commercial point of view.

2.2.2.5. Another special case: sulfuric acid. In addition to self-condensation products, different authors have reported sulfation
reactions during the treatment of D-glucose by cold sulfuric acid. Turvey in 1965 and Takiura et al. in 1970 report the production of variously substituted compounds. The first one mentioned the possibility of obtaining a complex mixture of monosulfated (at C-6) and polysulfated D-glucose by dissolving the monosaccharide in concentrated sulfuric acid at 0°C. Takiura et al. describe the production of mono-, di- and trisulfated D-glucose by diluting D-glucose in concentrated sulfuric acid at -5°C. The ratio between the various final products depends on the reaction time. The exclusive formation of the D-glucose 1,3,6-trisulfate (compound 22) is reached after 2.5 h. The D-mannose 1,3,6-trisulfate (compound 23), D-galactose 1,3,6-trisulfate (compound 24) and the D-fructose 1,2,4-trisulfate (compound 25) have been obtained in the same conditions.

Other authors, in the example of Nagasawa et al., also reported the formation of sulfated oligosaccharides during polymerization of monosaccharides in concentrated sulfuric acid. Nevertheless, they have not been able to determine an exact structure for any of these polymers.

### 3. Conclusion

Carbohydrate chemistry is a research field that is still of interest. Environmental challenges are such important that it is necessary to find alternatives to the scarcity of fossil substances. Only a few of molecules resulting from the conversion of sugars in acidic media can be produced on an industrial scale. However, these reactions enable access to a very important structural variety. This allows envisaging the production of a whole range of reagents that could substitute or complete those obtained from non-renewable resources. However further studies are needed before exploiting the structures obtained from biomass. These scientific advances must result in a better understanding of the
mechanisms involved in the conversion of carbohydrates into acidic environments.

**Author contributions**

All authors have given approval to the final version of the manuscript.
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