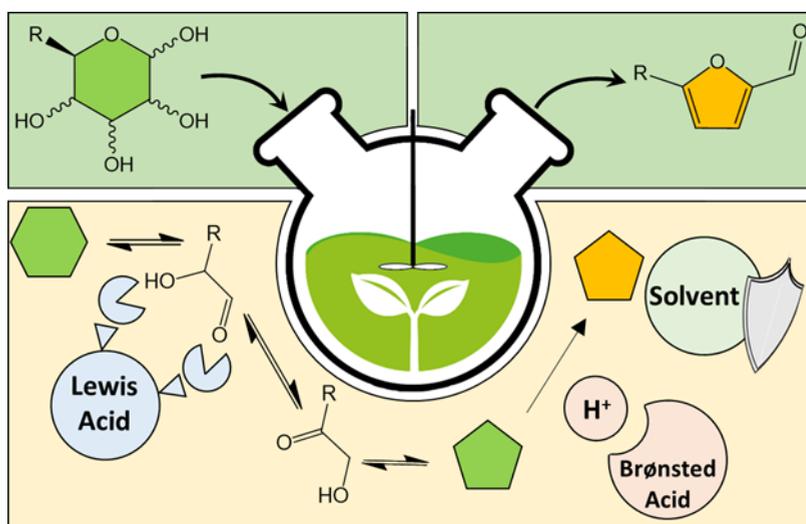


Synthesis of furan derivatives from monosaccharides in reaction media based on choline chloride



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Promotor: Prof. Aurore Richel

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media based on choline chloride**

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Promotor: Prof. Aurore Richel

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Abstract

In the context of fossil resources dependence and climate change due to green-house gas emissions, increasing efforts are devoted to the synthesis of plastic materials from renewable resources using less energy consuming processes. A possible path to produce plastic resins precursors is the transformation of plant saccharides to furan derivatives like 5-hydroxymethylfurfural (5-HMF) and 2-furfural (2-F).

Furan derivatives are obtained through acid-catalyzed dehydration of saccharides and can be converted to new and more performant plastic materials. Their selective synthesis at moderate temperature remains however an important challenge and is the focus of this work.

The first part of the research consists in an extensive review of monosaccharides dehydration mechanisms. Monosaccharides can be separated into two categories: ketoses (e.g. fructose) possessing a ketose moiety under acyclic form and aldoses (e.g. glucose) possessing an aldehyde moiety under acyclic form. The dehydration of ketoses through cyclic intermediates and their different reactivities are clarified. The reaction medium components required for their selective conversion to furan derivatives are methodically examined. Aldoses are more abundant in plants than ketoses and also more difficult to convert to furan derivatives. The study reveals why aldoses structure limits their dehydration and how catalysts and reaction media can be combined to enable a selective transformation.

Given the promising results achieved with imidazolium chloride ionic liquids according to the literature, reaction media based on melted mixtures of choline chloride and organic acids were investigated as a possibly cheaper alternative. The dehydration of a ketose, fructose, was attempted at 90 °C in different mixtures with the aim to understand the role of each reaction medium components. Through reduction of the amount of organic acid and by increasing the acid strength, an 80% 5-HMF yield could be achieved in only 1h at 90 °C. The addition of small amount of an organic solvent like isopropanol enabled the reaction at 60 °C with a similar selectivity.

The potential of choline chloride/organic acids melted mixtures for aldoses dehydration (glucose, mannose, galactose, xylose, arabinose) was then explored. To enable the formation of furan derivatives, boric acid was required for the prior isomerization of aldoses to ketoses. Aldoses transformation remained limited (e.g. 5% 5-HMF yield and 23% glucose conversion after one hour at 90 °C with maleic acid). Combined with α -hydroxyacids however, the reaction was faster and more selective (e.g. 19% 5-HMF yield and 61% glucose conversion after one hour at 90 °C). The synergy between α -hydroxyacids and boric acid was explained by formation of

tetrahydroxyborate esters (THBE). Compared to boric acid, THBE reaction with glucose is energetically favored. THBE formation is associated with H_3O^+ release in the medium increasing its acidity. Dark polymers called humins were the main observed side-product of the reaction and are a major hurdle to the development of selective 5-HMF and 2-F synthesis processes.

To better understand and inhibit their formation, humins were produced from different monosaccharides (hexoses, pentoses, 2-deoxyglucose) and analyzed by infrared spectroscopy and nuclear magnetic resonance. Humins formation during ketoses dehydration can be limited using organic solvents but humins production from aldoses persists even in organic reaction media. Those polymers are suspected to form from acyclic monosaccharides after one or several dehydration steps leading to a conjugated structure. The resulting conjugated product is sensitive to aldol addition/condensation with monosaccharides and furan derivatives. The experiments suggest that isomerization catalysts required for furan derivatives synthesis also exacerbate humins formation in two ways: they stabilize monosaccharides acyclic form and therefore expose their carbonyl moiety; humins possess functional groups which interact evenly or more strongly with the catalyst than reaction medium components or monosaccharides.

Based on humins structure and a better understanding of their formation, advices are provided regarding the design of new catalysts including transition metals or boronic acids. We suggest that the catalyst should be strongly bonded to an organic structure which must prevent simultaneous interactions of several molecules with the catalytic site. The bulkiness of the organic structure must be precisely controlled to prevent humins of large size to inhibit the catalyst but still enable interaction with monosaccharides. The provided strategy should be valid for choline chloride-based medium as well as other solvents.

This research supports the possibility to perform selective dehydration of abundant aldoses (e.g. glucose, xylose) at moderate temperature in commercially available and relatively cheap reaction media based on choline chloride. If polysaccharides depolymerization can be achieved in such media, they will certainly represent a promising path to generate bio-based monomers from renewable resources.

Keywords: 5-hydroxymethylfurfural, fructose, glucose, choline chloride, humins

Résumé

Suite à l'importante dépendance de l'industrie chimique vis-à-vis des ressources fossiles et au changement climatique lié aux émissions de gaz à effet de serre, des efforts croissants sont consacrés à la synthèse de matériaux plastiques à partir de matières premières renouvelables en utilisant des procédés consommant moins d'énergie. Une des voies possibles pour produire des précurseurs pour plastique est la transformation des saccharides de plantes en dérivés furaniques comme le 5-hydroxyméthylfurfural (5-HMF) et le 2-furfural (2-F).

Les dérivés furaniques sont obtenus par déshydratation en milieu acide des saccharides et peuvent être convertis en de nouveaux types de plastiques plus performants. Leur synthèse sélective à température modérée reste toutefois un défi important et représente le cœur de ce travail.

La première partie de la recherche est une synthèse bibliographique approfondie des mécanismes de déshydratation des monosaccharides. Ces derniers peuvent être classés en deux catégories en fonction de la nature de leur groupe carbonyle sous forme acyclique : les cétooses (ex. fructose) possédant une fonction cétone et les aldoses (ex. glucose) possédant une fonction aldéhyde. La revue explique comment les cétooses sont déshydratés via des intermédiaires cycliques et met en évidence leurs différences de réactivité. Les composants du milieu réactionnel nécessaires pour permettre leur conversion sélective en dérivés furaniques sont déterminés. Les aldoses, plus abondants dans les matières végétales que les cétooses, sont aussi plus difficiles à convertir en dérivés furaniques. L'étude révèle pourquoi la structure des aldoses limite leur déshydratation et comment les catalyseurs et solvants peuvent être combinés pour permettre une réaction sélective.

Etant donné les résultats prometteurs obtenus dans les liquides ioniques à base de chlorure d'imidazolium d'après la littérature, des milieux réactionnels à base de chlorure de choline et d'acides organiques en mélange fondu ont été investigués comme alternative potentiellement moins coûteuse. La déshydratation du fructose a été réalisée à 90 °C dans différents mélanges pour déterminer le rôle de chaque composant dans la réaction. En réduisant la quantité d'acide organique dans le mélange et en augmentant sa force, un rendement de 80% en 5-HMF peut être atteint en seulement une heure. L'ajout d'une faible quantité d'un solvant organique comme l'isopropanol permet d'effectuer la réaction à 60 °C en maintenant la sélectivité de la réaction.

Le potentiel de ces mélanges fondus de chlorure de choline et d'acides organiques pour la déshydratation des aldoses (glucose, mannose, galactose, xylose, arabinose) a ensuite été exploré. Pour permettre la formation de dérivés furaniques, les mélanges

devaient cette fois contenir de l'acide borique permettant l'isomérisation préalable des aldoses en cétooses. La transformation des aldoses est restée relativement limitée (ex. 5% 5-HMF obtenu et 23% du glucose converti après 1h à 90 °C dans un mélange chlorure de choline/acide maléique/acide borique). Quand les mélanges contiennent un acide α -hydroxylé en revanche, la réaction est plus rapide et plus sélective (ex. 19% 5-HMF obtenu et 61% du glucose converti après 1h à 90 °C). La synergie entre les acides α -hydroxylés et l'acide borique est expliquée par la formation d'esters de borate. En comparaison de l'acide borique, la réaction d'un ester de borate avec le glucose est favorable énergétiquement. La formation d'esters de borate est associée avec la production de H_3O^+ dans le milieu, augmentant son acidité. Les humines, des polymères brunâtres, sont le principal produit secondaire observé et restent un problème majeur pour le développement de procédé de synthèse de 5-HMF et 2-F sélectifs.

Afin de mieux comprendre et inhiber leur formation, des humines ont été produites à partir de divers monosaccharides et analysées par spectroscopie infrarouge et par résonance magnétique nucléaire. La formation des humines durant la déshydratation des cétooses peut être limitée en employant des solvants organiques mais la production d'humines à partir d'aldoses persiste même dans ces milieux organiques. D'après les analyses, ces polymères seraient générés à partir des formes acycliques des monosaccharides après une ou plusieurs réactions de déshydratation menant à une structure conjuguée. Le produit conjugué résultant est hautement sensible aux réactions d'additions/condensations aldol avec les monosaccharides et les dérivés furaniques.

Il est proposé que les catalyseurs d'isomérisation requis pour la synthèse de dérivés furaniques exacerbent la formation d'humines de deux manières : ils stabilisent les formes acycliques des monosaccharides et exposent ainsi leur groupement carbonyle; les humines possèdent des groupements qui interagissent autant ou plus fortement avec les catalyseurs qu'avec les composants du milieu réactionnel ou les monosaccharides.

D'après les structures des humines et une meilleure compréhension de leur formation, des améliorations des catalyseurs existants sont suggérées. Cette recherche soutient qu'il est possible de réaliser la déshydratation sélective d'aldoses abondants dans les plantes (ex : glucose, xylose) à température modérée dans des milieux réactionnels à base de chlorure de choline. Si la dépolymérisation de polysaccharides est possible dans ces milieux, ils représenteront certainement une voie prometteuse pour la production de précurseurs pour plastiques à partir de ressources renouvelables.

Mots-clés: 5-hydroxyméthylfurfural, fructose, glucose, chlorure de choline, humines

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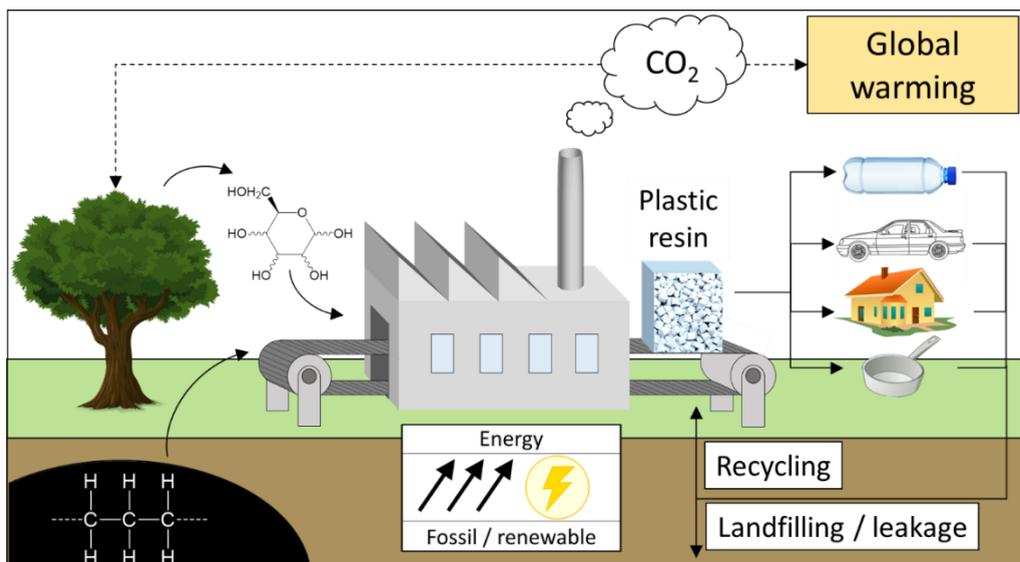
List of Abbreviations

2-F:	2-furfural
5-HMF:	5-hydroxymethylfurfural
BDMIMCl:	1-butyl-2,3-dimethylimidazolium chloride
BMIMBF ₄ :	1-butyl-3-methylimidazolium tetrafluoroborate
BMIMCl:	1-butyl-3-methylimidazolium chloride
BMIMOAc:	1-butyl-3-methylimidazolium acetate
ChBr:	choline bromide
ChCl:	choline chloride
ChI:	choline iodide
DES:	deep eutectic solvent
DFF:	2,5-diformylfuran
DFT:	density functional theory
DMAc:	<i>N,N</i> -dimethylacetamide
DMF:	<i>N,N</i> -dimethylformamide
DMSO:	dimethylsulfoxide
EMIMCl:	1-ethyl-3-methylimidazolium chloride
FDCA:	2,5-furandicarboxylic acid
GHG:	greenhouse gas
HMFA:	5-hydroxymethyl-2-furancarboxylic acid

HSQC:	heteronuclear single quantum coherence
IL:	ionic liquid
LC-MS:	liquid chromatography coupled mass spectrometry
LDVE:	Lobry de Bruyn–van Ekenstein
LTTM:	low-transition-temperature mixture
MIBK:	methylisobutylketone
MIMCl:	3-methylimidazolium chloride
MMF:	methoxymethylfurfural
NHC:	<i>N</i> -heterocyclic carbene
NMP:	<i>N</i> -methyl-2-pyrrolidone
NMR:	nuclear magnetic resonance
OMIMCl:	1-octyl-3-methylimidazolium chloride
PEF:	poly(ethylene furanoate)
PET:	poly(ethylene terephthalate)
TEAB:	tetraethylammonium bromide
THB:	tetrahydroxyborate
THBE:	tetrahydroxyborate ester
THF:	tetrahydrofuran

1

General Context



Graphical abstract 1 : some key elements affecting plastic materials related pollutions: feedstock, energy consumption, objects design and recycling.

1. Challenges of plastic materials manufacture

Innovations in chemistry have drastically changed our daily life. A striking example is the development of plastic materials which find applications in many fields. Main applications of plastics in Europe are packaging (40%), building and construction (20%), the automotive industries (9%), electrical and electronic devices (6%) and agriculture (3%).¹ The functional and economic interests for those plastic materials are still growing. Over the past forty years, global plastics production has quadrupled to reach around 400 Mt in 2015.² This tremendous development results from the unique combined properties of plastics, for example transparency, chemical resistance, low density and shock resistance which are not found together in other materials. Given its importance, the plastic materials industry employs more than one million people (including equipment providers) in the European Union and generates a turnover exceeding 300 billion €.¹

Despite its great successes, the chemical industry must now address important challenges related to its high dependence on fossil resources (oil, gas and coal), the leakage of plastic materials in the environment and greenhouse gas (GHG) emissions.

The petrochemical industry can generate a wide diversity of synthetic polymers from oil and gas. There is a restrained number of dominant plastic polymers produced in Europe, namely polyethylene (29%), polypropylene (19%), polyvinyl chloride (10%), polyurethane (8%), poly(ethylene terephthalate) (7%) and polystyrene (7%), but a wide variety of other plastic materials are synthesized for specific applications (optical fibers, eyeglasses, cable coating, in aerospace, medical implants,...).¹ This wide variety of polymers is generated from a reduced number of key molecules obtained from fossil resources cracking and catalytic reforming as depicted in **Figure 1**. Those key chemicals are called platform molecules because they are intermediates for the manufacture of many substances. The access to fossil resources is therefore of strategic importance because an important part of energy and material production still relies on the use of oil, coal and gas.

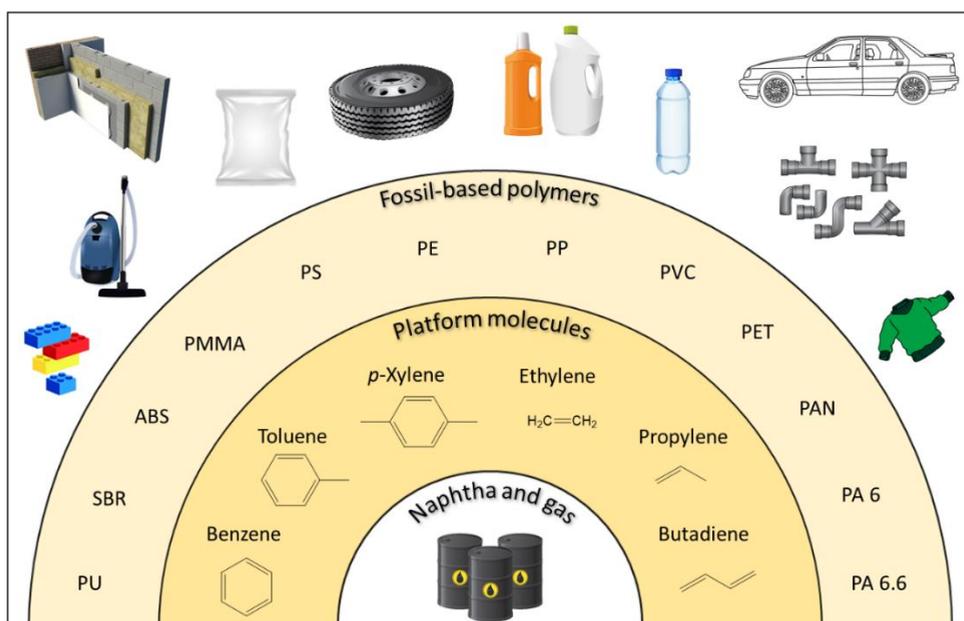


Figure 1: important platform molecules and synthetic polymers derived from the petrochemical industry (this list is not exhaustive). PU: polyurethane, SBR: styrene-butadiene rubber, ABS: acrylonitrile butadiene styrene, PMMA: poly(methyl methacrylate, PS: polystyrene, PE: polyethylene, PP: polypropylene, PVC: polyvinyl chloride, PET: poly(ethylene terephthalate), PAN: polyacrylonitrile, PA 6: polyamide 6, PA 6.6: polyamide 6.6.

In this regard, crude oil production in the European Union (EU) reached 21.4 million tonnes (oil equivalents) in 2018. On the same period, EU imported more than 500 million tonnes of crude oil, mainly from Russia, Saudi Arabia, Norway and Kazakhstan.³ The European petrochemical industry is therefore highly susceptible to the economic and politic contexts in supplier countries. Increasing the use of local and

preferably renewable resources is consequently desirable to ensure the stability of supply and cost of energy and materials.

Among the observed environmental pollutions resulting from the chemical industry, plastic materials leakage in soil and oceans raises growing concerns. In 2010, it was estimated that 275 million tonnes of plastic waste were generated in 192 coastal countries with 4.8 to 12.7 million tonnes entering the ocean. This leakage is expected to increase by one order of magnitude by 2025. Stable for decades to centuries, plastic waste can adsorb hydrophobic toxic contaminants and poses therefore a threat to marine life and human health.^{4,5} Different strategies have been proposed to limit this problem: an improved collection and recycling of plastic waste and the use of biodegradable plastics.

While undeniable progresses have been made, the complete recycling of plastic materials remains challenging. In 2015 in the EU, around 40% of plastic packaging were recycled. By contrast, 76% of metal packaging, 73% of glass packaging and 83% of paper and cardboard packaging were recycled.¹ In 2016 in Belgium, around 340 000 tonnes of plastic packaging waste were produced. 150 000 tonnes (44%) were recycled while 170 000 tonnes (50%) were burned to produce energy.⁶ The challenges of plastic materials recycling lie in their diversity, their design and their loss of mechanical properties after the process.

The design of plastic object is of primary importance for recycling. Most of these objects were initially designed for marketing and use purposes. Many additives and/or different materials (plastic, metal, glass fiber, adhesives, ...) are present in plastic objects and drastically complicate the sorting and recycling steps. Simpler objects designs are progressively considered to improve recycling.

Thermomechanical recycling consists in grinding and re-melting plastic objects, but the different types of plastic resins must firstly be separated. This recycling process leads to a downcycling of the material (discoloration or thermal degradation).⁷ Moreover, thermomechanical recycling is not compatible with temperature-sensitive plastic resins, composites and plastic resins which do not flow at elevated temperature (e.g. thermosets). Practically, the most recycled plastic resins are generally poly(ethylene terephthalate) (PET) and polyethylene (PE).⁸ One way to maintain the mechanical properties of recycled materials would be to break down the plastic resin back into its constitutive monomers. Those monomers could then be repolymerized with the stream of new plastic resin. This depolymerization is achieved through chemical recycling. Plastic materials are again not equal regarding chemical recycling. Because of their chemical structure, some of them are easily depolymerized back to monomers like poly(methyl methacrylate) (PMMA), PET, polycaprolactam and

polylactic acid (PLA) while others like PE and PP are randomly degrading polymers.⁹ Chemical recycling is generally achieved through solvolysis or thermal cracking.⁹

A major discovery is the chemical recycling of plastics through enzymatic processes. Cutinases found in leaf-branch compost are enzymes able to cut polymers constituting plants cuticle. Those polymers are polyesters like PET. Through selections and modifications of cutinases, researchers developed new enzymes able to depolymerize 90% of PET into its monomers in 10h at only 72 °C. This technology is already patented and validated at moderate scale (150 L) for high PET loading (200g/L) using 2mg of enzymes per g of PET. The obtained monomers can be used again for plastic production, guaranteeing identical properties of the recycled product compared to the initial product.^{10,11}

As an alternative to recycling, biodegradable plastic materials have been developed. Some of them like polycaprolactone (PCL) are derived from fossil resources while others like PLA and polyhydroxybutyrate (PHB) are produced from glucose contained in vegetal resources. If, biodegradable plastic materials may appear as a promising initiative to reduce the impact of inadvertent release in aquatic and terrestrial environments, they nevertheless possess several drawbacks: their chemical resistance and mechanical properties are often inferior to their nondegradable counterparts, they do not discourage leakage in the environment and they require specific degradation conditions. PLA is for instance biodegradable under industrial composting conditions (above 50 °C) but is not home compostable. Moreover, many biodegradable plastic materials are not sufficiently degraded in marine and freshwater environments.¹² However, the development of biodegradable plastic polymers is especially useful for biomedical applications when they are also biocompatible.¹³

Besides its dependence to fossil resources and the leakage of materials in the environment, the chemical industry must also address climate change due to anthropogenic activities, which is now recognized as a global threat to our civilization. Means for reduction of greenhouse gas (GHG) emissions are therefore under intensive investigations. The chemical industry alone is responsible for about 15% of global anthropogenic GHG emissions.² In 2013 in EU, the chemical industry released 145 Mt CO₂ eq. Significant progresses have been accomplished since 327 Mt CO₂ eq. were released in 1990 while production of the chemical industries increased by 60% but this emissions reduction was achieved mainly through a limitation of the more powerful GHG like N₂O. More efforts must be made to reduce CO₂ emissions.¹⁴ Two activities of the chemical industry are responsible for a major part of GHG emissions: the production of ammonia, the main source of most synthetic nitrogen fertilizers, and the production of petrochemicals including plastic materials. Steam cracking is the most energy consuming process in the chemical industry and is a key process of the petrochemical sector. It breaks long-chain hydrocarbons into short-chain ones to

generate crucial platform molecules involved in the production of many plastic materials.¹³ Over their life cycle, fossil fuel-based plastics emitted 1.8 Gt CO₂ in 2015 in the world, which is 3.8% of the estimated global emissions that year (47 Gt CO₂).²

Different strategies to reduce emissions and pollution by plastics manufacture and disposal exist:

- Replacement of fossil resources by biological resources. Through photosynthesis, plants convert CO₂ and water to monosaccharides, acting as a carbon sink. Using plants to produce materials such as plastics provides a way to capture CO₂ and store it. Assuming an appropriate management, plants can provide a renewable resource for plastic synthesis. Plastics generated from plants are generally called “bio-based plastics” by opposition to oil-based plastics. The “bio-based” term does not mean that the plastic is biodegradable. “Bio-based” and “biodegradable” are two different possible characteristics of plastics. Polycaprolactone is an example of biodegradable plastic based on fossil resources.
- Improvement of recycling capacity and efficiency. Most of current recycling processes are thermomechanical and lead to a loss of mechanical properties (decrease of molecular weight), reducing the attractiveness of recycled plastics. Intensive recycling would also reduce land area required for the synthesis of bio-based plastic polymers.
- Replacement of fossil-fuel energy by renewable energy for plastics production and reduction of processes energy consumption. Considering plastic materials production and end of life, 61% of CO₂ emissions result from resin synthesis, 30% from plastic transformation and 9% from end-of-life treatment (e.g. incineration).²

Interestingly, the effects of those strategies alone (or combined) on CO₂ emissions in 2050 have been estimated by Zheng and Suh (2019) and are illustrated in **Figure 2**.² Following the current trend, CO₂ emissions related to the synthesis and disposal of plastic materials will reach 6.5 Gt in 2050. To understand the impact of each strategy, the authors compared and combined different idealized situations: 100% of plastic polymers are made from sugar cane (A), 100% of plastic polymers are recycled (B), plastic polymers are produced using 100% renewable energy (C) and the demand growth per year (4% in 2015) is divided by two (D).

While “extreme” and not necessarily feasible, those scenarios highlight important elements. Firstly, energy consumption for plastic materials synthesis seems to be the most impactful factor. Even considering the carbon sink effect, the use of bio-based

plastic polymers has a limited impact on emissions as well as recycling. Those strategies truly shine when combined. Without considering a decrease of demand growth, the exclusive use of bio-based plastics with renewable energy and complete recycling would enable an 84% reduction of CO₂ emissions related to plastic materials manufacture.

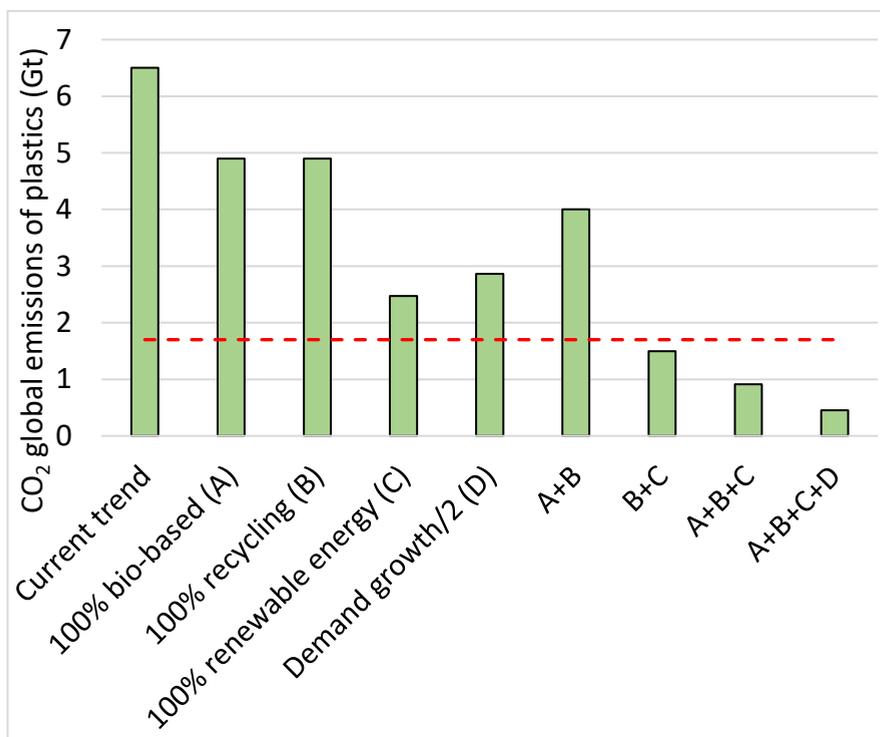


Figure 2 : comparison of strategies to reduce CO₂ global emissions of plastics life cycle based on the work of Zheng and Suh (2019).² Depicted values correspond to idealized projection for 2050. The red dotted line represents CO₂ global emissions of plastics life cycle in 2015. The “100% bio-based plastics” scenario is based on the use of sugar cane as feedstock and the actual trend in end-of-life treatment. The considered petrochemical plastic polymers are PP, L/LLDPE, HDPE, PET, PVS, PS, PUR and PP&A. The considered bio-based plastic polymers are bio-PE, bio-PET, PLA, PHA, TPS.

Reduction of emissions related to plastic resins synthesis remains challenging. The high energy consumption of plastic polymers manufacture can be illustrated with PET (**Figure 3**). This polymer, as many others, can be synthesized from naphtha, a liquid hydrocarbon mixture extracted from oil by distillation. Other sources are also possible such as natural gas or coal tar. Naphtha can undergo different processes to obtain molecules crucial for the chemical industry. A first one is cracking. This process will break naphtha long chain hydrocarbons into simpler molecules. Being a highly

endothermic process, temperatures between 500 and 900 °C are required. Ethylene can be obtained through this process and is considered to be a platform molecule since it is used for the production of many valuable substances: poly(vinyl chloride), polystyrene, poly(ethylene), ethanol. In the context of PET synthesis, ethylene is converted to ethylene glycol after oxidation and hydrolysis. This building block must be polymerized with another one: terephthalic acid. Terephthalic acid is generated from an additional platform molecule: *p*-xylene. *p*-xylene is synthesized by catalytic reforming of naphtha which also requires high temperatures (> 400 °C).¹⁵ If oil-based polymers synthesis may seem impeded by its high energy consumption, it beneficiates from important advantages:

- It is a very mature technology based on decades of research and optimization, achieving therefore high products yields.
- The resource, crude oil, is liquid and all its components can be efficiently extracted and converted to valuable products.

Regarding bio-based plastic polymers, their carbon-sink effect may seem attractive. Moreover, their development could limit the high dependence on virgin fossil feedstock. However, their synthesis also requires high amounts of energy. In fact, energy consumption in the synthesis process is even more critical for bio-based plastic than for fossil-based plastics because the raw material supply chain is more complex and less efficient than oil supply chain (e.g. because of the moisture content in plants, field collection, composition variability). Consequently, if the use of a renewable feedstock remains desirable in the long term to ensure sustainability, the production of bio-based plastic polymers is more constrained in an energetic point of view.

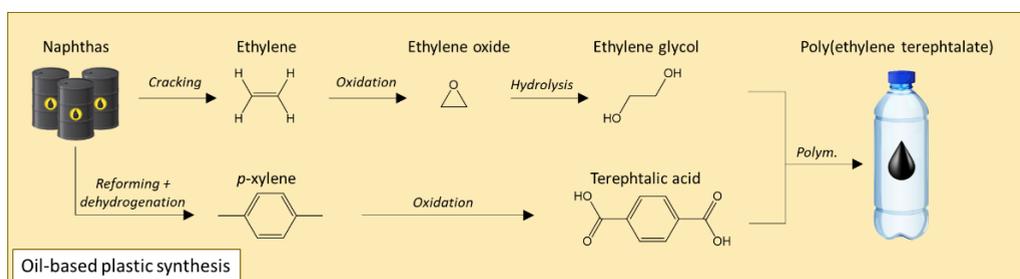


Figure 3: Poly(ethylene terephthalate) synthesis from naphthas.

2. Vegetal biomass as a source of building-blocks for synthetic polymers

Major plants structural components like cellulose, hemicelluloses and lignin (**Figure 4**) are an abundant source of monosaccharides and phenol derivatives. After some chemical modifications, those molecules could represent interesting building blocks for synthetic polymers synthesis. But the extraction of monosaccharides and phenol derivatives is complex and energy-consuming because they are polymerized and entrapped in a solid matrix, the plant, of which composition changes regarding species and environmental conditions.

The use of lignocellulosic biomass as a feedstock for plastic material production therefore requires a first step of fractionation into its main components, namely cellulose, hemicelluloses and lignin (**Figure 4**). Those polymers can then be depolymerized into monomers. D-glucose is obtained from cellulose while hemicelluloses depolymerization can provide a variety of hexoses and pentoses. Monosaccharides possessing many -OH moieties, they are not directly convenient to prepare synthetic polymers in a controlled way. Their prior conversion to building blocks possessing a reduced number of functional groups is consequently preferred. The depolymerization of lignin gives rise to a wide variety of phenol derivatives as for instance vanillin, 4-propyl guaiacol, isoeugenol, dihydroconiferyl alcohol, 4-propyl syringol, 4-propenyl syringol and dihydrosinapyl alcohol depicted in **Figure 4**.¹⁶ Some of those depolymerization products like vanillin directly possess some potential for synthetic polymer production. Vanillin is for instance a potential precursor for epoxy resins or can be converted to divanillin then polyurethane or conjugated polymers. The other depolymerization products require further modifications of their chemical structure. There are two kind of approaches for such modifications: functionalization which consists in changing or adding reactive moieties and defunctionalization which removes most of the chemical functions. The first approach can lead to new kinds of polymers with innovative properties but may require novel synthesis technics and consequently new types of facilities for industrial production. The second approach, called “drop-in” strategy, would consist in converting lignin depolymerization products into phenol and BTX (benzene, toluene, xylene). Being important platform molecules today, this strategy beneficiates of existing facilities for the synthesis of polymers. The resulting synthetic polymers are therefore identical to their petro-based counterpart. Without new or improved properties, the competitiveness of the biobased version of those polymers may be limited which is the main disadvantage of the second approach.

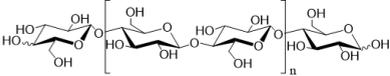
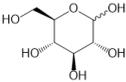
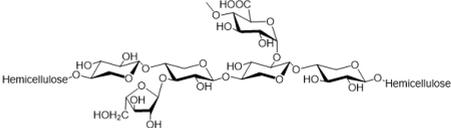
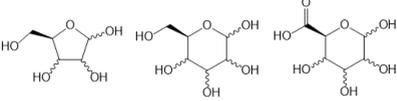
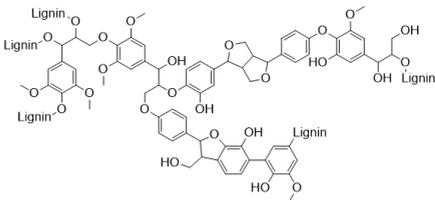
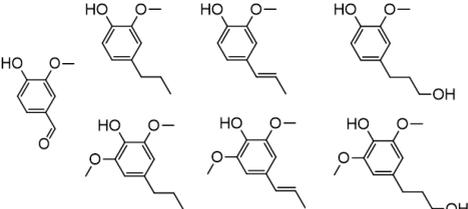
Polymers of lignocellulose	Main depolymerization products
<p data-bbox="226 260 319 283">Cellulose</p> 	<p data-bbox="716 260 816 283">D-glucose</p> 
<p data-bbox="226 420 370 444">Hemicellulose</p> 	<p data-bbox="716 420 1031 444">Monosaccharides, uronic acids</p> 
<p data-bbox="226 620 288 644">Lignin</p> 	<p data-bbox="716 620 911 644">Phenol derivatives</p> 

Figure 4: chemical structure of cellulose, hemicellulose and lignin and examples of depolymerization products. Many other structures are possible for hemicellulose and lignin and the depicted structures only serve illustrative purpose. Other depolymerization products are consequently expected but not represented. Lignin structure is adapted from Sun et al. 2018¹⁶.

Similar strategies also exist for monosaccharides. In this case, the “drop-in” approach proceeds through fermentation into ethanol. Ethanol is then dehydrated to ethylene which is currently widely used for synthetic polymers preparation. For the other approach, monosaccharides can be converted to new building-blocks leading to new synthetic polymers. This transformation of saccharides to new building blocks will be the focus of this work.

Before addressing this topic, it should be noted that saccharides like sucrose and starch have not been mentioned yet. However, those saccharides have been industrially extracted from plants for a long time. The extraction of sucrose (disaccharide composed of glucose and fructose) from sugar beet or sugar cane and the extraction of starch (glucose polymer) from wheat are two striking examples. But those industries mainly serve food purposes. Using the same feedstock for plastic polymer production means therefore a direct competition for arable lands with the food industry. Additionally, saccharides targeted by the food industry are often the energy resource of the plants and are easily accessible (**Figure 5**).

Plants cell walls structural components are a preferable resource for plastic synthesis to limit direct competition with food production. Some of those structural components (e.g. cellulose) can also be used in the food sector but to a limited extent compared to starch and saccharose. Plant cells walls are mainly composed of two types of polysaccharides (cellulose, hemicelluloses), uronic acid polymers (pectins) and an aromatic biopolymer (lignin). Because of the interactions between all these components in cell walls, the selective extraction is difficult and requires what is called a pre-treatment. This is the main activity of the pulp and paper industry which extract cellulose from plants like poplar to produce paper. Kraft pulping is one of the existing process to extract cellulose and consists in using a sodium hydroxide / sodium sulfide solution to break the chemical bonds of lignin and solubilize it. This operation requires temperatures around 170 °C during several hours. Solubilized lignin is often burned to generate energy for the process.

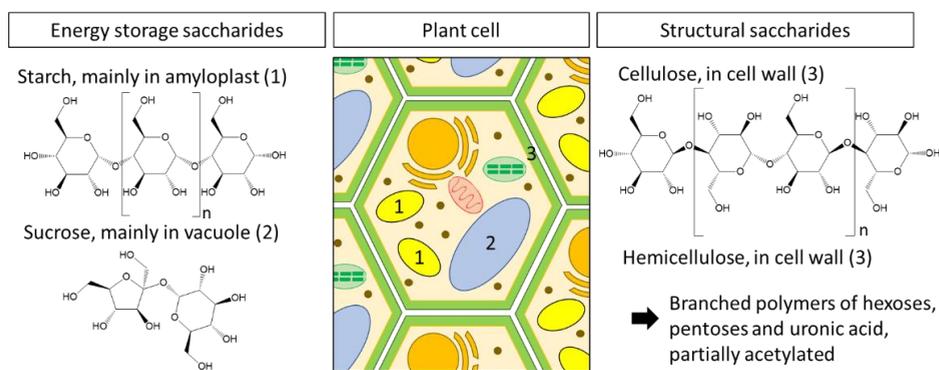


Figure 5 : Roles and location of saccharides in plant cells.

Considering all the difficulties and constraints of plants saccharides refining and transformation, the industrial production of bio-based plastic polymers appears as relatively recent and fragile compared to oil-based plastics. PVC manufacture, based on oil and sodium chloride, began around 1930. In comparison, the industrial production of poly(lactic acid) (PLA) based on glucose as a feedstock began in 2001.

However, the history of bio-based plastic polymers is in reality much older than generally perceived. Around 1930 was built an industrial plant for furfural production. Furfural (2-F) is a platform molecule generated from the degradation of monosaccharides at high temperature as illustrated in **Figure 6**. The original idea was to gain value from Quaker Oats stockpile of cereal waste. The company, well-known in the food industry, generated large amounts of oat hulls. 2-F was then used in the production of phenol-furfural resins. As soon as 1942, the du Pont company started the production of polyamide 6;6 from 2-F. In 1961, however, this process is abandoned

and polyamide 6;6 synthesis from butadiene is preferred. 2-F will then find applications in other sectors like foundry.¹⁷ 2-F market is already well established with a global production of several hundred thousand t/y.^{18,19} 2-F is produced by acid hydrolysis of pentosan in agricultural residues (oat hulls, cornstalks, wheat straw, sugar cane bagasse, ...). 2-F is mainly transformed to furfuryl alcohol for the production of thermosetting resins (metal casting) but can also be used in the manufacture of fuels, pharmaceuticals, plastics, fungicides and nematocides.²⁰ China is the main producer of 2-F (e.g. Hebei Xingtai Chunlei Furfuryl Alcohol Co.).^{18,19} The central Romana Corporation in the Dominican Republic is also an important actor, producing 2-F (40000 t/y) from sugar-cane bagasse.²¹ 2-F is then transformed into furfuryl alcohol by Transfurans Chemicals in Belgium, again mainly to produce thermoset resins for the foundry industry.²² Although the market exists, production processes are still constrained by 2-F yields around 50%, long reaction time and large consumption of vapor (Quaker Oats technology).^{23,24}

The development of low-energy consumption processes to convert saccharides to plastic polymers is still under intensive research. The main investigated chemical processes are fermentation, reduction and dehydration reactions. Fermentation of monosaccharides by micro-organisms can produce useful intermediate chemicals such as lactic or succinic acids. Reduction of glucose and xylose by biological means or by catalytic hydrogenation leads to sorbitol and xylitol. Both products are already used as sweetening agents in the food industry but further transformation could convert them to hydrocarbons suitable for the existing oil refining installation.²⁵

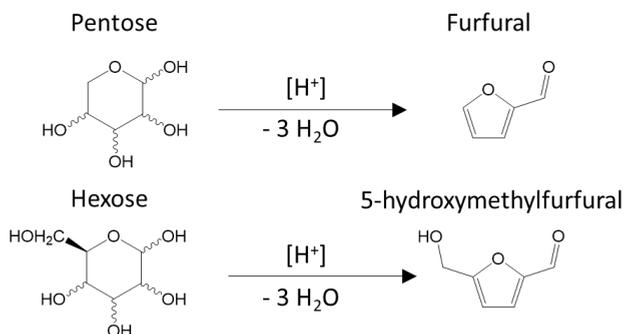


Figure 6 : dehydration products of pentoses and hexoses.

Under heating in acidic conditions, monosaccharides can initiate dehydration reactions involving the loss of three water molecules. Dehydration reactions of monosaccharides lead to furan derivatives (**Figure 6**). The interest of furfural (2-F), obtained by dehydration of monosaccharides with five carbon atoms (pentoses), was addressed but its counterpart generated from monosaccharides with six carbon atoms

(hexoses), 5-hydroxymethylfurfural (5-HMF), is getting more and more attention. The molecule presents indeed an interesting potential as a bio-based platform for the synthesis of various polymers including polyesters, polyamides, polyimines, polyurethanes and polyvinylfuran derivatives (**Figure 7**).^{26,27} Other potential applications in the pharmaceutical sector are also investigated.²⁸

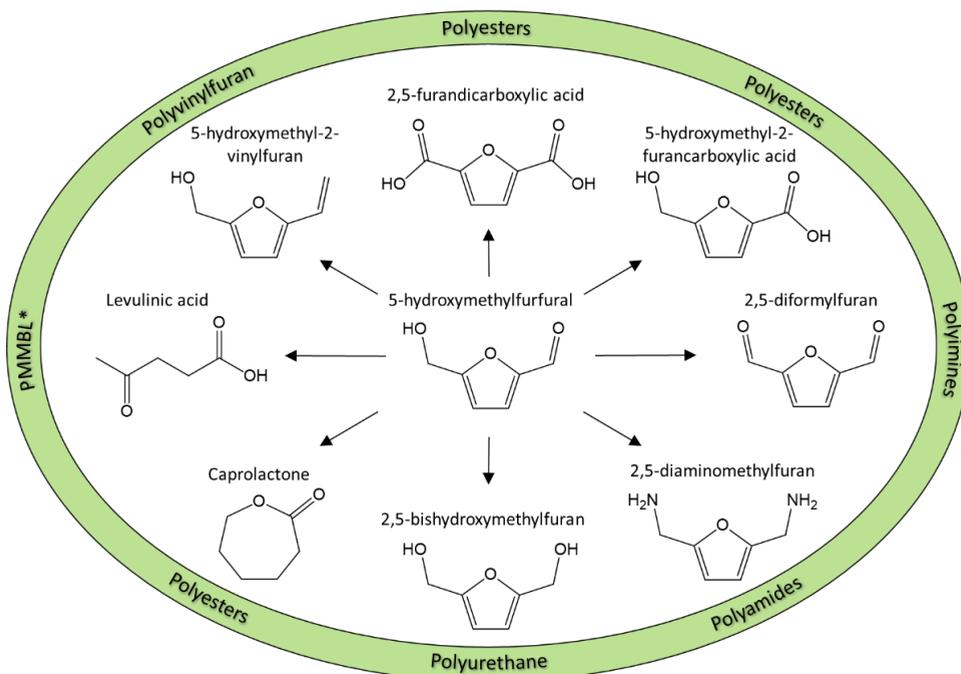


Figure 7: examples of intermediate molecules obtained from 5-HMF for polymers synthesis. *PMMBL or poly- γ -methyl- α -methylene- γ -butyrolactone is a structural analogue of poly(methyl methacrylate) (PMMA).

Several companies are trying to achieve 5-HMF or derivatives production at industrial scale like Avantium (Netherlands), Avabiochem (Switzerland), Corbion (Netherlands), SynbiaS (Ukraine) or Transfurans Chemicals (Belgium). Important efforts have been put to the development of a new bio-based polyester: poly(ethylene furandicarboxylate), also called poly(ethylene furanoate) or PEF. In a structural point of view, the plastic is quite similar to PET and is also based on the polymerization of ethylene glycol with a dicarboxylic acid. Terephthalic acid is however replaced by 2,5-furandicarboxylic acid (FDCA) obtained by oxidation of 5-HMF. The potential synthesis path of PEF is summarized in **Figure 8**.

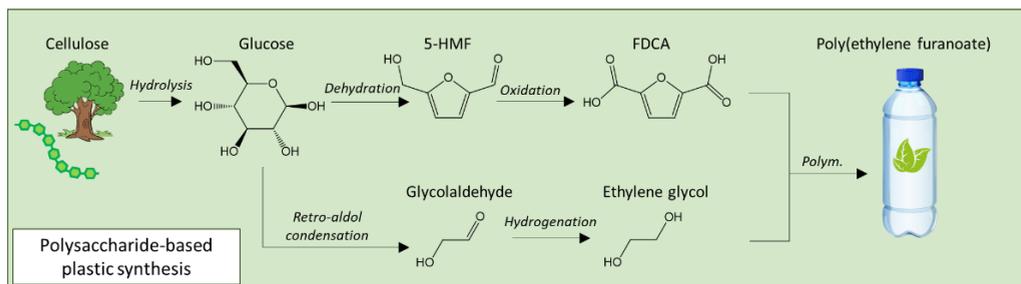


Figure 8 : Poly(ethylene furanoate) synthesis from cellulose.

Compared to PET, PEF possesses enhanced gas-barrier and mechanical properties, increasing its attractiveness (**Table 1**). The polymer also possesses interesting thermal properties like a lower melting temperature (235 °C vs 265 °C) than PET and a higher glass-transition temperature (86 °C vs 74 °C).²⁹ The superior barrier properties of PEF reside in the asymmetric structure of the furan ring in FDCA compared to the phenyl ring of terephthalic acid in PET. In PET, gas diffusion through the material can be assisted by a ring-flipping mechanism. In PEF, ring-flipping is hindered by the nonlinear axis of ring rotation of the furan ring. Oxygen permeability is therefore reduced by a factor 10 while carbon dioxide permeability is reduced by a factor 19.^{30,31} Tg difference between PEF and PET also seems related to the absence of linearity of the furan ring. According to Codou et al. 2016, it “leads to less efficient chain packing in the glassy state which generates a higher free volume and a larger distribution of the free-volume hole. The higher Tg of PEF is then purely related to segmental mobility and specific interactions in PEF”.³² Compared to PET, PEF also exhibits a higher Young’s modulus, a higher yield stress and a higher strain rate dependence resulting possibly from additional motional constraints compared to PET.³³

Table 1 : comparison of PET and PEF properties^{34,35}

Polymer	PET	PEF
Chemical structure		
Melting temperature (°C)	265	235
Glass transition temperature (°C)	74	86
O ₂ permeability (barrer)	0.114	0.0107
CO ₂ permeability (barrer)	0.49	0.026
Young modulus (GPa)	1.3	2.0

3. The synthesis of furan derivatives in the context of green chemistry

Furan derivatives synthesis falls within the context of a new branch of chemistry which has emerged to meet the environmental challenges: green chemistry. Green chemistry is best defined by its twelve principles illustrated in **Figure 9**. Globally, those principles provide indications for the design of more efficient, safer and less polluting chemical processes. Furan derivatives production inherently meets two principles: the use of renewable feedstock and atom economy. The idea behind atom economy is to promote reactions paths where as much as possible of the feedstock mass is converted to the desired product. This concept is independent of the reaction yield and is rather related to the nature of the involved chemical reaction. The atom economy is the ratio of the molecular weight of the desired product over the molecular weights of all reactants used in the reaction.

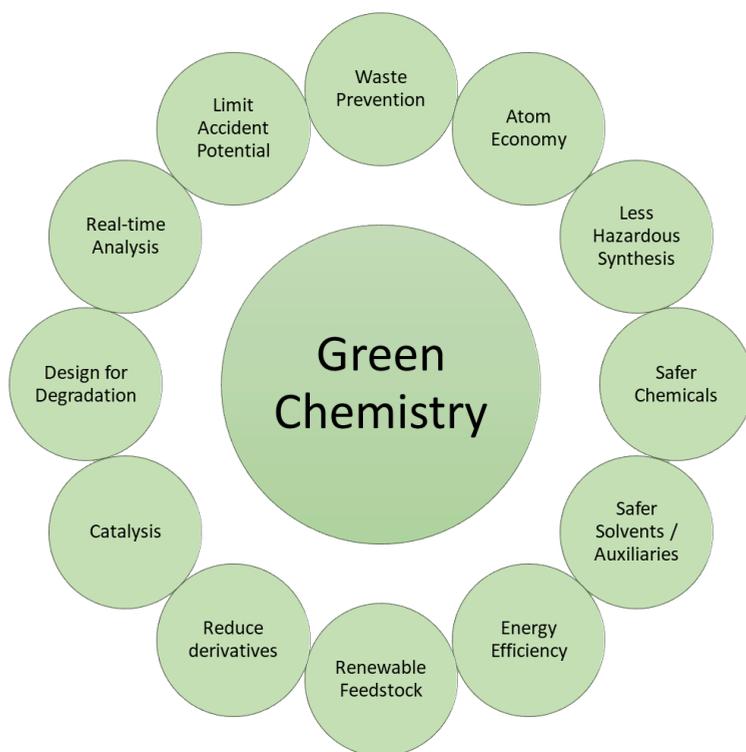


Figure 9 : the 12 principles of green chemistry

The comparison of bio-PET and PEF synthesis from glucose can illustrate this principle. The building blocks for bio-PET are obtained through fermentation of glucose to ethanol, dehydration of ethanol to ethylene and conversion of ethylene to ethylene glycol and p-xylene. In the process, the oxygen atoms of glucose chemical structure are lost. Considering PEF synthesis, one of the building blocks, FDCA, is obtained from 5-HMF oxidation but this intermediate preserve three oxygen atoms of the original glucose chemical structure. The atom economy of the PEF path is therefore superior to the bio-PET path. The other principles are essentially process-dependent and will be further addressed.

Although 5-HMF and 2-F represent promising bio-based platform molecules, the current processes for their synthesis are unfortunately still associated with high energy consumption and limited selectivity and typically involve treatments in water or alcohol at more than 150 °C.³⁶ Another problem specific to 5-HMF is the current feedstock used for its production. Contrarily to **Figure 8** which presents cellulose-derived glucose as the raw material, the main monosaccharide currently transformed to 5-HMF is fructose. This substrate enables a more selective synthesis but is obtained from enzymatic isomerization of glucose. The isomerization of glucose is operating at industrial scale, notably for the manufacture of high-fructose corn syrup, a popular sweetener. While economically viable, enzymatic isomerization is not necessarily ideal in the context of 5-HMF production. The process requires a neutral to slightly alkaline medium while cellulose hydrolysis and fructose dehydration to 5-HMF are acid catalyzed steps. Moreover, enzymatic isomerization is limited by a thermodynamic equilibrium and the enzymatic product is a 50:50 mixture of glucose and fructose rather than pure fructose, which means that a purification stage is needed, increasing fructose cost.

Technologies allowing to achieve high 5-HMF selectivity from glucose exist but are generally complex or too expensive. 5-HMF synthesis consequently remains at pilot scale and is based on fructose dehydration. Avantium (the Netherlands) and Ava-Biochem (Switzerland) were mentioned as companies active in this field. Their annual production is in the order of several dozens of tons, targeting notably FDCA for poly(ethylene furanoate) manufacture.^{29,37} The current pilot plant of Avantium reaches a FDCA production capacity of 20-40 t/y but the company is considering the creation of a flagship facility with a FDCA production capacity of 5000 t/y.^{38,39} Avantium process for the dehydration of fructose is performed in methanol to generate a more stable derivative of 5-HMF, methoxymethylfurfural (MMF).⁴⁰ Ava-Biochem rather developed a water-based process.³⁷

Given the need for sustainable plastic polymers production at reduced energy consumption and the potential of furan derivatives in this field, this work aims to better understand the dehydration processes of monosaccharides and the related side-

reactions to enable the development of selective 5-HMF and 2-F production systems. The research presented in this work focuses on the development of one-pot low temperature ($<100\text{ }^{\circ}\text{C}$) processes to synthesize furan derivatives from monosaccharides, especially via low-melting-temperature mixtures like ionic liquids and deep eutectic solvents.

Those reaction media are composed of several ions (ionic liquid) or molecules (deep eutectic solvent) which, through their interactions, melts at moderate temperature. This principle is illustrated in **Figure 10** for a deep eutectic solvent based on two components. The mixture of both components at a precise ratio shows a melting point far inferior to the melting points of the pure components.

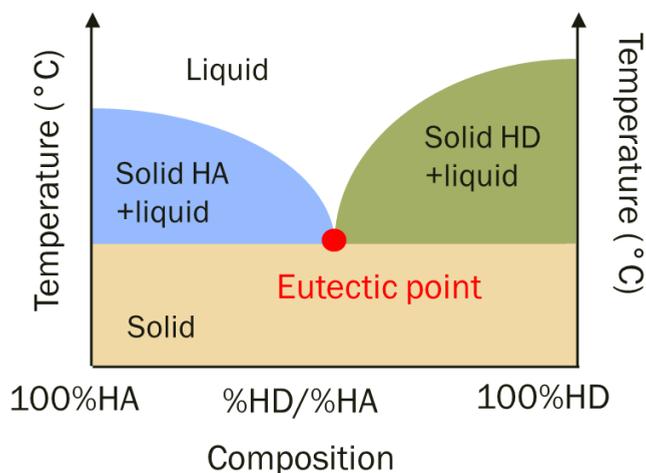


Figure 10: phase diagram of a binary mixture with an eutectic point

Several types of low-transition-temperature mixtures (LTTMs) exist and their ability to form a liquid phase at moderate temperature (e.g. $<100^{\circ}\text{C}$) can have different origins. Mainly two kinds of LTTMs will be mentioned in this work: ionic liquids based on the imidazolium cation and deep eutectic solvents based on choline chloride.

Imidazolium-based ionic liquids are salts composed of imidazolium cations and different possible anions (e.g. Cl^-). To understand why such a salt can melt at moderate temperature, lattice energy has to be described. Lattice energy of a crystalline solid can be defined as the energy released when ions are combined to make a compound. Its measurement enables to estimate the strength of the bond between the anions and cations of the ionic compound. Lattice energy increases with ions charge and decreases with their size. The low melting point of imidazolium salts originates therefore from the imidazolium cation structure. The cation shows indeed a large size and its charge

is delocalized. The bond strength with the anion is consequently relatively weak and the salt melting point is low.

Regarding choline chloride-based LTTMs, the phenomenon is slightly different. The choline cation also possesses a relatively large size but there is no charge delocalization. Pure choline chloride has a melting point far superior to 100°C (> 300°C). The formation of a liquid phase below 100°C is enabled by the addition of another component which can delocalize the charge through anion-dipole interactions. This additional component is generally called the “hydrogen-bond donor” and can be picked among many possible substances: organic acids, monosaccharides, polyols, amino acids, ... Low-melting-temperature mixtures offer a tremendous number of possible components combination and therefore a vast potential for catalysis.

The use of LTTMs based on choline chloride and organic acids or monosaccharides presents several advantages with respect to green chemistry principles. Through mechanisms presented further in this work, they enable monosaccharides conversion to furan derivatives at atmospheric pressure and at moderate temperature compared to treatments in water or alcohol, which reduces hazard potential. Thanks to the wide variety of possible LTTMs components, safer reaction media can be designed. In this respect, choline chloride is a safe chemical currently produced at large scale. According to ECHA, “choline has no potential for bioaccumulation in its non-metabolized form, and the incorporation of its metabolites does not bear a potential for adverse effects”. Moreover, the substance is readily biodegradable which could facilitate waste treatment if the molecule is present in treatments effluents.⁴¹ Similarly, organic acids like maleic, citric or lactic acids are potential LTTMs components which are readily biodegradable and do not present other threat than the danger related to their corrosive nature.⁴¹

As presented further in chapter 2, the conversion of aldoses like glucose to furan derivatives requires a prior isomerization step to an intermediate ketose (e.g. fructose). Isomerization catalysts are therefore needed and raise most of the safety, toxicity and environmental concerns among the components of the reaction media. Mainly two isomerization catalysts will be addressed in this work: chromium trichloride and boric acid. Both catalysts present toxicity for aquatic organisms (LC50 for fish between 50 and 170 mg/L).⁴¹ The industrial use of chromium trichloride remains limited to the plating industry and catalysis. The general population exposure is therefore reduced. Chromium salts toxicity has raised important concerns for safety, especially because of hexavalent chromium known to be carcinogenic and very toxic to aquatic life but trivalent chromium is far less toxic. On the contrary of chromium trichloride, boric acid possesses applications in a large number of sectors (e.g. painting and coating, cements, glass, metallurgy, catalysis, fertilizers, detergents, adhesives, ...). The substance

toxicity is consequently better documented (developmental toxicity, male infertility). It should be noted that boron is naturally present under the form of boric acid and tetrahydroxyborate in seawater with concentrations around 25 mg/L in boric acid equivalent.⁴²

4. Furan derivatives: chemical vs enzymatic synthesis

As many industrial processes, the use of catalysts like chromium trichloride and boric acid implies a careful control of waste effluents composition. It is obviously not intended to release those catalysts in waste effluents since reaction medium recycling is expected but the research for alternative isomerization catalysts remains nevertheless relevant.

In this regard, it is worth to describe the potential of enzymes for furan derivatives synthesis, especially since isomerases are currently used at industrial scale to isomerize glucose to fructose. Enzymatic systems offer two main advantages compared to chemical systems: a high selectivity and the possibility of operating in water in mild conditions. Two enzymes are of particular interest regarding the conversion of lignocellulosic biomass to platform molecules: cellulases and glucose isomerases.

Cellulases (EC 3.2.1.4., EC 3.2.1.91., EC 3.2.1.21) produced by the fungus *T. reesei* are currently the most widespread commercial cellulases. This enzymatic mixture comprises three main enzymes classes: exoglucanases (cellobiohydrolases), endoglucanases and β -glucosidases. Exoglucanases hydrolyze the cellulose chain from reducing and non-reducing ends of cellulose, releasing cellobiose. Endoglucanases hydrolyze β -1,4 linkage within the chain creating new reducing and non-reducing ends. β -glucosidases convert cellobiose to D-glucose. The extent and rate of cellulose saccharification can be improved by further addition of β -glucosidase to cellulases mixtures such as Celluclast 1.5L (from *T. reesei*) produced by Novozyme. The addition of β -glucosidase (until 5% of the total enzyme protein) allow to divide nearly 2-fold the enzyme load by limiting product inhibition due to cellobiose.^{43,44}

Glucose isomerase (EC 5.3.1.5.) is a homotetrameric metalloprotein.⁴⁵ The industrial enzyme is immobilized and generally converts 50 % of glucose into fructose. 8 % of glucose is converted to other saccharides during the process.⁴⁶ The enzyme can use several other monosaccharides than glucose like D-xylose, D-ribose, L-arabinose, L-rhamnose and D-allose.⁴⁷ Common glucose isomerase are metalloenzymes (metal activated enzymes) which require cobalt and/or magnesium ions to efficiently convert sugars.^{48,49} Studies have shown that metal centers in the enzyme are responsible for the

stabilization of sugar's open chain form. The subsequent isomerization takes place by way of an intramolecular hydride shift.^{50,51} Ongoing efforts are made to decrease the amount of metal ions and limit the use of cobalt which is an environmental hazard.⁴⁸

Unfortunately, the design of enzymatic systems for the synthesis of furan derivatives suffers from several major drawbacks:

- No enzyme enabling the dehydration of ketoses to furan derivatives have been described and the currently investigated reaction media are not compatible with the use of enzymes in a one-pot process (high temperature, high acidity, organic solvents). Water is indeed not the most adapted medium for monosaccharides dehydration since it will favor side-reactions.
- Most efficient cellulases require slightly acidic conditions (near pH 5), are not stable above 50°C and still needs improvements (production cost, activity, recycling) for industrial use.
- Industrial isomerases require slightly alkaline conditions (pH 7-9) and an optimal temperature comprised between 60-80°C. Moreover, the fructose yield from glucose is limited to 50% by a thermodynamic equilibrium if fructose conversion or extraction is not continuously performed.

The production of 5-HMF by enzymatic means would therefore require at least three separated steps: the hydrolysis of cellulose by cellulases, the isomerization of glucose to fructose by isomerase and the non-enzymatic dehydration of fructose to 5-HMF. The development or discovery of new cellulases and isomerases will likely enable to perform the hydrolysis and isomerization steps in a one-pot fashion. This possibility is further debated with **Supplementary Figures 1**. Dehydration to 5-HMF will however remain as an independent step.

The benefits of a one-pot process are certainly questionable. Reducing the number of steps performed in different conditions (acidity, temperature, solvents) seems advantageous but this choice may complicate the purification of furan derivatives. Nevertheless, this path deserves investigations since it can overcome difficulties brought by product inhibition and thermodynamic equilibrium (e.g. inhibition by cellobiose and D-glucose, equilibrium between D-glucose and D-fructose). This is where reaction media based on ionic liquids or deep eutectic solvents may shine thanks to their tunable catalytic properties offering interesting perspectives for simultaneous cellulose depolymerization, glucose isomerization and fructose dehydration to 5-HMF. These aspects will be discussed all along this work.

2

Research aims

The general purpose of the research is to provide a better understanding of monosaccharides dehydration in the hope of enabling the selective synthesis of furan derivatives at moderate temperature (around 100 °C), thereby supporting the development of bio-based polymers. This document is divided into four main parts according to the following sub-targets:

- ***Understanding the dehydration mechanisms of monosaccharides according to their chemical structure and the elements of the reaction medium.*** The abundance of literature about furan derivatives synthesis hinders progress tracking. Numerous reaction media are developed based on empirical tests rather than reaction mechanisms. Isomerization and dehydration catalysts are sometimes tested without a prior understanding of their properties. Many dehydration mechanisms have been proposed and are generally different for pentoses and hexoses while both monosaccharides types and their corresponding dehydration products share a lot of similarities.
There is a need to harmonize monosaccharides dehydration mechanisms. Additionally, furan derivatives synthesis from ketoses (e.g. fructose, xylulose) is faster and more selective than from aldoses (e.g. glucose, xylose). The latter are nevertheless cheaper and more abundant substrates. It is therefore essential to understand how ketoses and aldoses dehydration proceeds and how the reaction medium can be designed to enable a selective reaction. This first chapter is a literature survey which aims to methodically investigate monosaccharides dehydration mechanisms and catalysis.
- ***Studying fructose dehydration to 5-HMF in reaction media composed of choline chloride and organic acids.*** The literature survey highlights the potential of some imidazolium-based ionic liquids to perform selective monosaccharides dehydration at moderate temperature (100 °C). Those ionic liquids are however still expensive due to complex synthesis pathways. Low-melting-temperature mixtures based on choline chloride and organic acids were consequently investigated in this chapter as a cheaper alternative to imidazolium-based ionic liquids to generate 5-HMF. As a first attempt, the study focuses on the dehydration of a ketose, fructose, described as a more reactive and selective dehydration substrate.

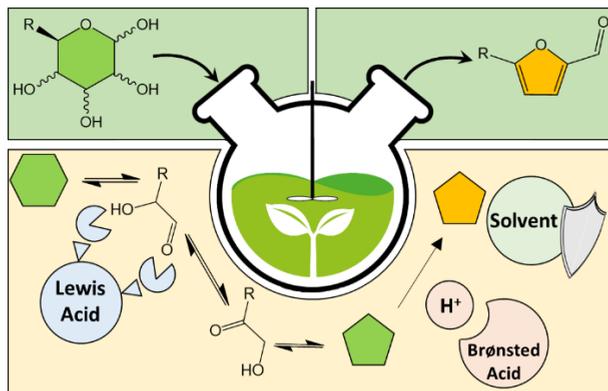
- ***Investigating aldoses dehydration in reaction media composed of choline chloride and organic acids.*** After addressing ketoses dehydration in the choline chloride-based media, the production of 5-HMF from glucose was attempted in similar media. A lewis acid catalyst was added to enable its dehydration into 5-HMF through prior isomerization to ketose. Other aldoses commonly encountered in plants polysaccharides (mannose, galactose, xylose and arabinose) were also investigated for the production of 5-HMF and 2-F.
- ***Understanding the origins of the main side-reaction: humins formation.*** Humins are dark polymers generated from side-reactions of aldoses and/or furan derivatives. Large amounts of those polymers are formed when attempting furan derivatives synthesis from aldoses. While humins have been commonly observed during acidic treatment of aldoses, their origins remain poorly understood. The purpose of this chapter is to investigate humins formation from different substrates (monosaccharides, furan derivatives) to better grasp their formation and propose means to counter it.

2

Mechanistic aspects of saccharides dehydration to furan derivatives

Adapted from:

Istasse T, Richel A. Mechanistic aspects of saccharides dehydration to furan derivatives for reaction media design. *RSC Adv.* 2020;10:23720–42.



Graphical abstract 2: conversion of aldoses to furan derivatives through isomerization to ketoses

Abstract:

The conversion of abundant hexoses (e.g. glucose, mannose, galactose) and pentoses (e.g. xylose, arabinose) to 5-hydroxymethylfurfural (5-HMF) and 2-furfural (2-F) is subject to intensive researches in the hope of achieving competitive production of diverse materials from renewable resources. However, the abundance of literature on this topic as well as the limited number of studies systematically comparing numerous monosaccharides hinder progress tracking. Herein, we compare and rationalize reactivities of different ketoses and aldoses. Dehydration mechanisms of both monosaccharide types are reviewed regarding the existing experimental evidences. Ketoses transformation to furan derivatives likely proceeds through cyclic intermediates and is hindered by side-reactions such as isomerization, retro-aldol reactions and polymerization. Different strategies can improve furan derivatives synthesis from ketoses: limiting the presence of water, improving the dehydration rate, protecting 5-HMF and 2-F reactive moieties with derivatization or solvents interactions and extracting 5-HMF and 2-F from the reaction medium. Contrarily to ketoses, aldoses conversion to furan derivatives is not favored compared to polymerization reactions because it involves their isomerization or a ring contraction. Enhancing aldoses isomerization is possible with metal catalysts (e.g. CrCl_3) promoting a hydride shift mechanism or with boric/boronic acids promoting an enediol mechanism. This catalysis is however far more challenging than ketoses dehydration because catalysts activity depends on numerous factors: Brønsted acidity of the medium, catalysts ligands, catalysts affinity for monosaccharides and their accessibility to several chemical species simultaneously. Those aspects are methodically addressed to support the design of new monosaccharides dehydration systems.

Key words:

5-hydroxymethylfurfural, monosaccharide, dehydration, isomerization, Lewis acid

1. Introduction

Nowadays, most industrial chemicals are obtained from fossil resources. However, depletion and price fluctuations of these resources motivated the research of alternative and renewable sources of building blocks for the chemical industry.

In 2004, the report « Top Value-Added Chemicals From Biomass » of the US department of energy led to a renewed interest in bio-based building blocks.⁵² Among these platform molecules, 5-hydroxymethylfurfural (5-HMF) and 2-furfural (2-F) have been the subject of numerous studies to understand their synthesis and assess their potential for plastics and fuels production. This potential was described in the previous chapter.

5-HMF and 2-F are both dehydration products of monosaccharides obtained through the loss of three water molecules during acid-catalyzed reactions. 5-HMF is specifically generated from hexoses such as fructose, glucose, mannose and galactose while 2-F is produced from pentoses such as xylulose, xylose or arabinose. Several of those monosaccharides are commonly found in plants cells wall as components of cellulose (glucose) and hemicellulose (glucose, mannose, xylose, arabinose, ...) as depicted in **Figure 11**.

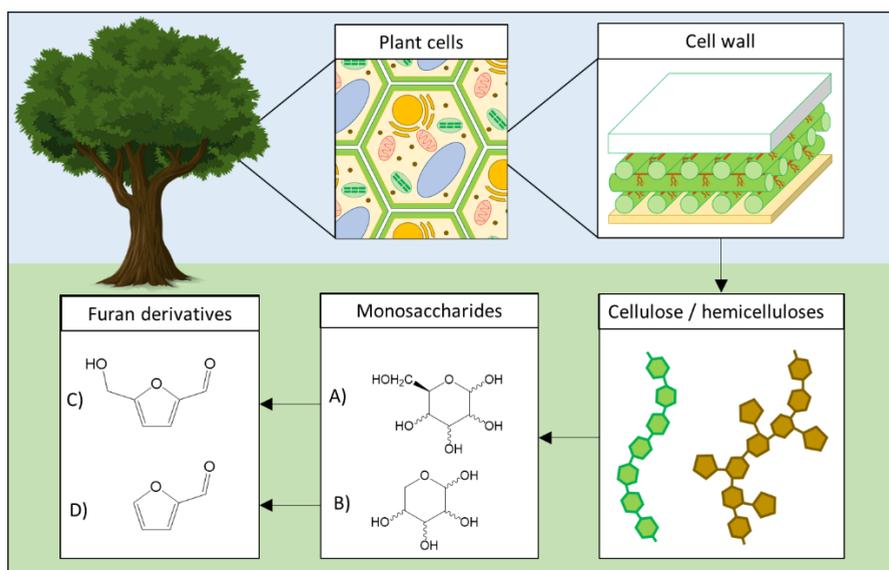


Figure 11 : overview of plant cell wall polysaccharides transformation to monosaccharides and their corresponding furan derivatives. A) hexoses, B) pentoses, C) 5-hydroxymethylfurfural, D) 2-furfural.

While tremendous research efforts have been made to improve furan derivatives synthesis, the abundance of literature about the subject makes progress-tracking as well as mechanistic understanding difficult. The mechanisms explaining hexoses and pentoses dehydration to 5-HMF and 2-F are still not clear. Several chemical pathways have been proposed, sometimes with experimental evidences, but no consensus has been achieved. It is quite surprising that different dehydration mechanisms have been proposed for pentoses and hexoses whereas those substrates and their corresponding furan derivatives share a lot of similarities. Elucidation of dehydration mechanisms is challenging since a tremendous number of solvents and catalysts, often arbitrarily selected, have been tested and compared.

A first purpose of this review is to harmonize monosaccharides dehydration mechanisms regarding the last experimental investigations. Dehydration of ketoses (eg. D-fructose, D-tagatose, D-xylulose, D-psicose, D-sorbose) to furan derivatives is much faster than dehydration of aldoses (eg. D-glucose, D-mannose, D-galactose, D-xylose, D-arabinose). The first part of this work explains why ketoses are readily dehydrated and how selectivity for furan products can be enhanced simply through solvent choice.

However, ketoses are generally not the main components of most plant polysaccharides. Polysaccharides of vegetal biomass rather contains aldohexoses such as glucose, mannose, galactose and aldopentoses like xylose and arabinose. Understanding aldoses dehydration is consequently crucial because they represent a more abundant resource than ketoses. However, lower 5-HMF and 2-F yields are achieved from aldoses (typically less than 5% for D-glucose at 200 °C during 5 min without catalyst) than from ketoses (around 40% for D-fructose treated in similar conditions).⁵³ Aldoses are also notably less reactive than ketose, requiring higher temperature to reach similar dehydration rate. The second part of this chapter details why aldoses are difficult to convert to furan products compared to ketoses and how catalyst/solvent combinations come into play to favor their conversion to 5-HMF or 2-F.

Both those parts highlight the required elements to constitute an efficient reaction medium for monosaccharide dehydration. A close attention is paid to the latest developments about ionic liquids and deep eutectic solvents in this context as well as potential synergy between catalysts.

2. Dehydration of ketoses

Fructose, psicose, sorbose and tagatose are ketohexoses of which dehydration leads to 5-HMF. Xylulose and ribulose are ketopentoses and their dehydration consequently results in 2-F formation (**Figure 12**). While those ketoses are scarce in vegetal biomass,

understanding their fast conversion to furan derivatives brings light on dehydration mechanism of monosaccharides in general.

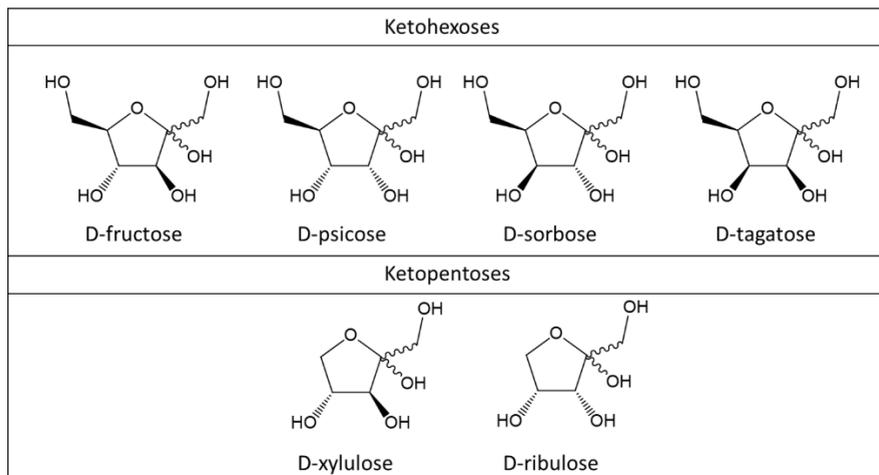


Figure 12 : chemical structures (Haworth's projections) of ketohehexoses and ketopentoses

2.1. Dehydration mechanism

Although numerous mechanisms were proposed to explain dehydration of ketoses to 5-HMF and 2-F, all reaction paths involve three protonation steps and the loss of three water molecules.⁵⁴ Mechanistic studies about ketopentoses dehydration being scarce, the following discussion is mainly based on ketohehexoses dehydration completed by kinetic studies on ketopentoses.

The first attempts to describe D-fructose dehydration mechanisms were initially based on reaction paths involving acyclic intermediates like 1,2-enediol and 3-deoxyhexosulose as depicted in **Figure 13 (A)**.^{55,56,57} Since 1,2-enediol is also an intermediate of the isomerization of D-glucose into D-fructose, D-glucose and D-fructose acyclic dehydration pathways toward 5-HMF were considered similar. Because acyclic D-fructose is relatively more abundant in aqueous solution than acyclic D-glucose, an acyclic dehydration mechanism was thought consistent regarding the higher 5-HMF yields obtained with D-fructose.⁵⁸

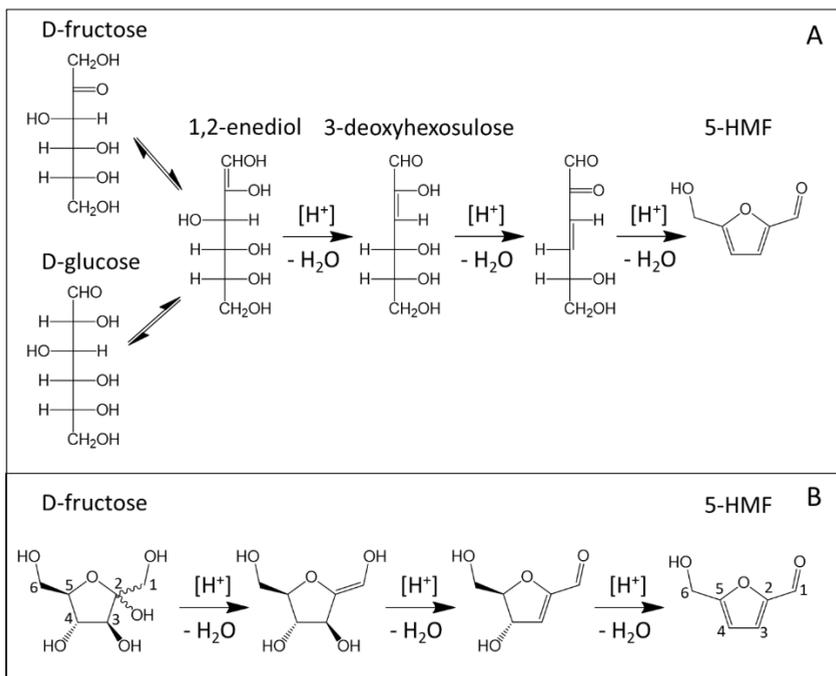


Figure 13 : acyclic (A) vs cyclic (B) D-fructose dehydration pathway toward 5-HMF (carbon atoms labelling displayed in the cyclic path)

More recent works now support reaction paths with cyclic intermediates to explain the dehydration of D-fructose into 5-HMF (**Figure 13, B**).^{55,56,59,60,61} Cyclic paths toward 5-HMF are initiated by protonation of the C2 hydroxyl group on fructose which is the most favored protonation site because of the high stability of the formed fructofuranosyl carbocation (carbon numbers are given in **Figure 13**). The cationic species seems stabilized by its resonant structure (**Figure 14**). The protonations of other oxygens lead to structures not stabilized by resonance and less stable carbocations.⁶⁰

Cyclic mechanisms for 5-HMF formation are supported by several experimental observations. Firstly, dehydration of D-fructose was performed in deuterated water and no deuterium incorporation to 5-HMF was observed while acyclic pathways imply this incorporation because of the equilibrium between 3-deoxyhexosulose and its enolic tautomer. Secondly, 5-HMF yield calculated with the fructofuranosyl unit of sucrose (53 %) is higher than the 5-HMF yield obtained with fructose (42 %) at 250 °C after 32 seconds with sulfuric acid (1 mM). This observation suggests that the fructofuranosyl cation released from sucrose is an important intermediate during 5-HMF synthesis.⁵⁵

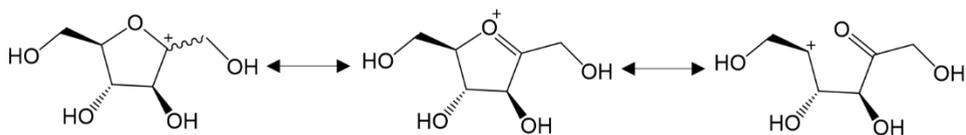


Figure 14: Carbocation resonance hybrids after first protonation and dehydration of D-fructose at O2

After the direct infusion of a D-fructose solution (methanol/water 1:1 V/V, 0.1% $\text{CH}_3\text{COONH}_4$), mass spectrometry analyses highlighted the formation of a diagnostic ion at m/z 85 typical of ring structures (produced by a cross-ring bond cleavage), further supporting a dehydration pathway through cyclic intermediate.⁶² Dehydration product ions were observed at m/z 163, 145 and 127 formed through the loss of one, two and three water molecules respectively.

Cyclic intermediates mechanisms are also supported by the difference in reactivity between ketoses. Fructose, sorbose, psicose and tagatose differ from each other by the position of C3 and C4 hydroxyl groups. In aqueous sulfuric acid (100-160 °C, 33-300 mM H_2SO_4), tagatose and psicose have a higher conversion rate than fructose and sorbose. However, 5-HMF formation is more selective from psicose and fructose.^{63,64} For acyclic pathways involving 1,2-enediol and 3-deoxyhexosulose as intermediates, positions of C3 and C4 hydroxyl groups on ketoses are not relevant to explain the observed differences in reactivity and selectivity, which is why cyclic mechanisms are favored.⁶³

The higher reactivity of tagatose and psicose could be explained by cis orientation of C3-OH and C4-OH. This might cause a higher torsional strain as well as steric hindrance, leaving C2 more vulnerable to reaction on the opposite side of the furanose ring.⁶⁵

Interestingly, several cyclic intermediates of the dehydration pathway in **Figure 13 (B)** have been identified by NMR monitoring of normal and ^{13}C -labelled D-fructose dehydration in DMSO as well as ESI-MS (**Compounds A and B of Figure 15**).^{66,67,68,69} Both compounds are described as intermediates of the reaction since they progressively appear at the beginning of the reaction then disappear at the end of the treatment.^{66,67} Compounds C and D of **Figure 15** are intermediates obtained from fructopyranose and hypothetically lead to polymerized side-products (humins). The only major products observed in DMSO during D-fructose dehydration were 5-HMF, 2,6-anhydro-beta-D-fructofuranose and fructose dianhydrides.

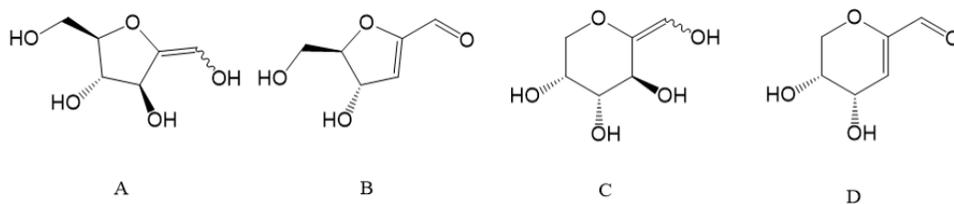


Figure 15: intermediate species observed by NMR during dehydration of D-fructose in DMSO at 150 °C.

NMR dehydration experiments on ^{13}C labelled D-fructose confirmed that the ketose C1 becomes the carbon of the aldehyde moiety in the furan structure.⁶⁹

As well as experimental evidences, reactions simulations support cyclic pathways from D-fructose to 5-HMF since ketoses dehydration acyclic mechanisms involve very high activation barriers.⁷⁰

To our knowledge, no mechanistic insight has been provided yet regarding ketopentoses (xylulose and ribulose) dehydration. However, the higher reactivity of xylulose and ribulose compared to xylose and ribose has been confirmed. After 45 min at 145 °C in an aqueous solution of HCl (pH 1), 66% of xylulose is converted to 2-F. In the same conditions, xylose only leads to a 29% 2-F yield.⁷¹ The same trend was observed by Li et al. (2013) in close conditions (68% 2-F from xylulose after 25 min at 130 °C in 0.1 M HCl).⁷² Energy barrier of xylulose dehydration is lower (23 kcal/mol) than energy barrier for xylose dehydration (30-32 kcal/mol).⁷¹ In deuterated water at pH 1.5 at 96 °C, xylulose and ribulose are converted to 40-60% after 10 min while xylose and ribose are converted to only 0-10% in the same conditions.⁷³

In brief, ketoheptoses and ketopentoses are readily converted to furan derivatives because their cyclisation involves the C2 carbon (bearing the ketone moiety). Consequently, a carbocation stabilized by resonance can be formed after protonation of C2-OH and a first dehydration step, leaving the C1-OH available to constitute the future aldehyde moiety of 5-HMF or 2-F after further dehydrations.

2.2. Side-products of ketoses dehydration

Furan derivatives are major products of ketoses degradation in acidic water but many other side products are also generated limiting the selectivity. Ketoses reactions consist in tautomerization/isomerization, dehydration, retro-aldol reactions and polymerization.^{55,56,60,63,74-80} Those reactions are illustrated with D-fructose in **Figure 16**.

Isomerization of ketose to aldose is a first possible side-reaction. Its rate is however limited compared to other reactions under Brønsted acidic conditions. In that respect, the molar yield of D-glucose from D-fructose is generally lower than 5 % (32 s, 250 °C H₂SO₄ 0-5 mM).⁵⁵ Tautomerization rate between pyranose and furanose forms of ketoses is significantly larger than the isomerization rate to aldose or the dehydration rate to furan compounds according to in situ ¹³C NMR kinetic study.⁷⁵

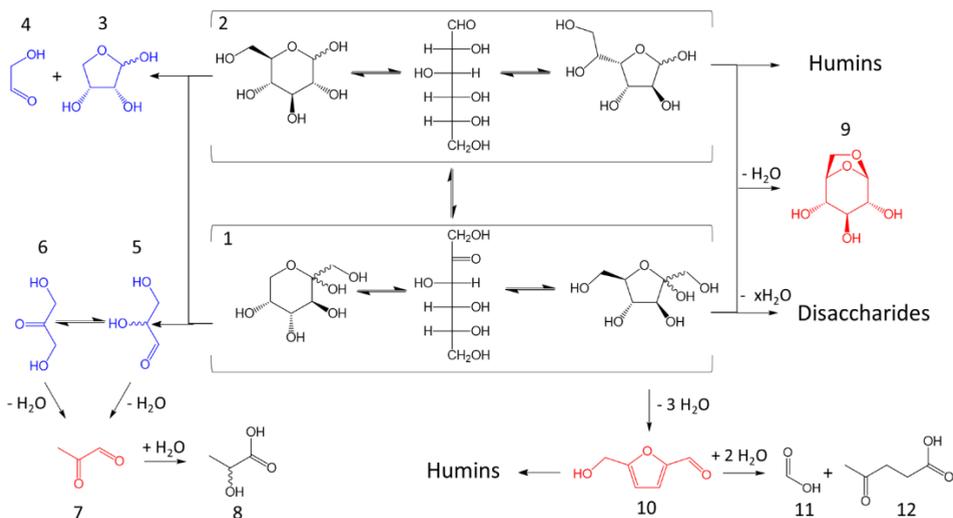


Figure 16: typical compounds observed during subcritical treatment of a D-fructose aqueous solution with Brønsted acid. 1: fructopyranose, acyclic fructose, fructofuranose, 2: glucopyranose, acyclic glucose, glucofuranose, 3: erythrose, 4: glyceraldehyde, 5: glyceraldehyde, 6: dihydroxyacetone, 7: pyruvaldehyde, 8: lactic acid, 9: 1,6-anhydroglucose (1,6-anhydrofructose also observed in subcritical treatment), 10: 5-hydroxymethylfurfural, 11: formic acid, 12: levulinic acid. Blue = retro aldol reaction products, Red = dehydration reaction products.

Dehydration of ketoses mainly leads to 5-HMF or 2-F. 5-HMF molar yield is typically between 20 and 50% for D-fructose dehydration in water at 200-250 °C after 0.5 to 5 minutes with Brønsted acids like sulfuric, hydrochloric, phosphoric or formic acids.^{53,60,81,82} 5-HMF is nevertheless susceptible to rehydration leading to formic and levulinic acids as depicted in **Figure 17 (above)**. Ketoses as well as aldoses can also be dehydrated to anhydro-monosaccharides after the loss of only one water molecule (e.g. 1,6-anhydrofructose, 1,6-anhydroglucose, 1,5-anhydroxylose).

Retro-aldol reactions give rise to many aldehyde or ketone products, fragmenting the initial monosaccharide in molecules with fewer carbon atoms. Glyceraldehyde is a three-carbons product in isomerization equilibrium with dihydroxyacetone. Both

compounds can be dehydrated to pyruvaldehyde which can itself undergoes benzylic acid rearrangement to produce lactic acid.⁷⁴ Through retro-aldol reactions, hexoses can also be converted to erythrose (four carbon atoms) and glycolaldehyde (two carbon atoms). While not confirmed yet, the formation of pentoses (five carbon atoms) and formaldehyde (one carbon atom) has been suggested as well to explain the apparition of furfural during hexoses treatments. In a similar manner, pentoses can be converted to glyceraldehyde and glycolaldehyde.^{55,76,77}

Regarding polymerization, disaccharides formation is frequently observed, especially at high monosaccharide concentrations. In ketoses case, dimerization can be advantageous. Two molecules of D-fructose can reversibly form di-D-fructose dianhydrides. Under this form, the reducing group of D-fructose sensitive to cross-polymerization reactions is blocked, partially limiting humins growth.⁵⁶ This is not the case for aldose as discussed further. A particularly problematic reactions chain is the polymerization to humins. Humins are dark polymers originating from polymerization and/or cross-polymerization of monosaccharides and furan derivatives. Their chemical structure, likely variable, is not fully identified but those polymers are generated through aldol addition/condensation reactions potentially threatening every molecule with a carbonyl moiety.^{56,60} Humins formation pathway involving the transformation of 5-HMF into 2,5-dioxo-6-hydroxy-hexanal has been suggested (**Figure 17**, below) following a parallel road to levulinic and formic acid production. 2,5-dioxo-6-hydroxy-hexanal is suspected to react with 5-HMF by aldol addition then condensation to initiate the polymerization.⁷⁸⁻⁸⁰ This mechanism involves the aldehyde group of 5-HMF, what will be of importance when the effects of organic solvents on 5-HMF generation will be discussed thereafter. Since humins are cross-polymerization products, their abundance will increase with the initial monosaccharide concentration. Kuster et al. (1990) mentioned a humins yield of 20 wt% from a 0.25 M solution of fructose. At higher initial fructose concentration (1M), the humins yield reaches 35 wt%.⁵⁶

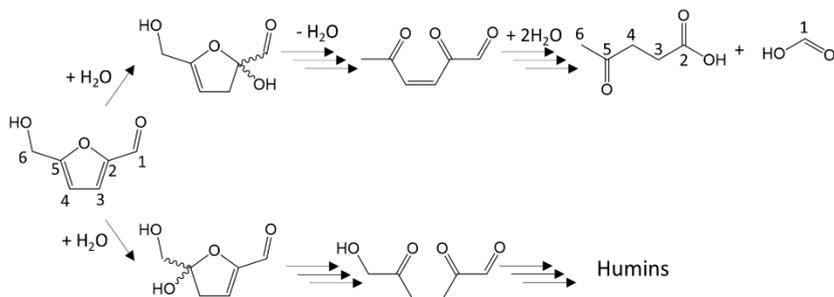


Figure 17: conversion of 5-HMF to levulinic acid and formic acid (above)^{60,69,74} / conversion of 5-HMF to humins through 2,5-dioxo-6-hydroxy-hexanal⁷⁸⁻⁸⁰

2.3. Limitation of side-products formation through solvent selection

Given the different possible degradation paths of ketoses, the selectivity for 5-HMF and 2-F is generally limited in aqueous media. Without catalyst, 5-HMF molar yields range between 0 and 22 % for temperatures comprised between 150 to 250 °C and time of 30 seconds to 2 hours.^{53,55,82,85}

In the same temperature conditions, the addition of Brønsted acid like sulfuric, hydrochloric, phosphoric or formic acid allows to reach higher 5-HMF molar yields comprised between 20-60 % since protonations are critical for the dehydration reaction.^{53,55,81,82} 2-F yields between 60-70% are reached from xylulose dehydration at 110-150 °C with aqueous HCl (pH 1) but undesirable insoluble brown solids are generated during the treatment.⁷²

With the development of dehydration systems with increased complexity, high ketoses conversion and high selectivity towards 5-HMF and 2-F have been achieved. These improved performances mainly result from the use of non-aqueous media. Organic solvents with high or medium polarity are generally preferred since they allow to work at higher D-fructose concentrations. The use of numerous protic solvents (e.g. alcohols and organic acids) as well as aprotic solvents (e.g. acetone, dimethylsulfoxide, *N,N*-dimethylacetamide or 1-methyl-pyrrolidin-2-one) has been reported.^{76,85-91} Organic solvents suppresses side-reactions in several ways:

- Reduced 5-HMF/2-F conversion to humins and organic acids due to the limited presence of water
- Improvement of ketoses dehydration rate to 5-HMF/2-F
- Protection of furan derivatives aldehyde moiety through reversible derivatization or solvent interactions
- Simultaneous extraction of furan product from the reaction medium

The first benefit of organic solvent use is to prevent side-reactions of **Figure 17** enabled by the presence of water. Shi et al. (2019) compared humins formation from 5-HMF and 2-F in water and ethyl acetate after 5h at 220 °C. Respectively 65 and 23% of solid humins (carbon yield) were obtained from 5-HMF and 2-F in water while no solid formation was observed after treatment in ethyl acetate. If organic solvents seem to suppress furan derivatives degradation, they still enable humins formation from monosaccharides. However, they limit the extent of this side reaction compared to

water. Humins production from D-fructose and D-sorbose reaches 50-55% (carbon yield) in water but is reduced to 30-35% in ethyl acetate (5h, 220 °C).⁹²

A second improvement of ketoses dehydration is based on reaction rate enhancement. Dehydration rate of D-fructose to 5-HMF is improved in various organic solvents. In a polar protic solvent like ethanol (78 °C) with sulfuric acid, D-fructose dehydration rate reaches $1.7 \times 10^{-3} \text{ s}^{-1}$. When ethanol is partially replaced with water in the same conditions (76:24 mass ratio), the reaction rate dramatically decreases to $5 \times 10^{-5} \text{ s}^{-1}$.⁹³ Mellmer et al., (2019) highlighted the same trend for polar aprotic solvents. They compared D-fructose dehydration in water, γ -valerolactone/water mixture, tetrahydrofuran/water mixture and dioxane/water mixture in the presence of hydrochloric acid (0.5 M in water, 5 mM in solvents mixtures) at 373 K. The corresponding rate constants are 0.14 ± 0.01 , 62 ± 4 , 28 ± 5 and $95 \pm 6 \text{ M}^{-1}\text{ks}^{-1}$ respectively. The use of organic solvents consequently increases dehydration rate of several order of magnitude. Mellmer et al. (2019) also determined 5-HMF yield at 90% D-fructose conversion and obtained a 40% yield in water compared with more than 70% in polar aprotic solvents/water mixtures, which support a positive effect of the dehydration rate on the reaction yield.⁹⁴ Van Putten et al. (2017) observed a higher reactivity in methanol than in water for fructose, sorbose, tagatose and psicose. For instance, tagatose conversion is 48% after 75 min in 33mM H_2SO_4 . In methanol, such conversion is reached after only 15 min in milder conditions (100 °C, H_2SO_4 17 mM).⁶⁴

The increased dehydration rate of ketohexoses in the presence of organic solvents rather than water could be partially related to the tautomeric distribution. Formation of furan derivatives from ketoses has been recognized as a pseudo-first order reaction, meaning that the reaction rate depends on ketoses concentration. Recent research supports ketofuranose forms as the reaction substrate for 5-HMF formation. Consequently, solvents promoting ketofuranose rather than ketopyranose tautomers are likely to improve the reaction rate. Bicker and coworkers (2005) showed that around 40% of the monosaccharide was in furanoid forms at 25 °C in pure methanol while in water, there is only 25% of D-fructose in these forms.⁹⁵ The promotion of furanoid forms of D-fructose was further confirm by Shi et al. (2018) and extended to ethanol, n-propanol, n-butanol, 2-propanol, isobutanol, 2-butanol and tert-butanol.⁹⁶ This effect could be further improved since the furanoid forms are promoted at higher temperatures.⁹⁷

Compared to water, acetone also shifts the tautomerization equilibrium towards the furanoid forms of D-fructose. Bicker and coworkers observed around 50% of fructofuranose in a mixture of acetone and water (90:10 v/v) at 25 °C. The addition of acetone in water improves 5-HMF molar yield until 60-70 % for temperatures between 150 and 180 °C in less than 15 minutes.^{76,86} In these conditions, no insoluble side-products were detected which implies a limited generation of humins. Although acetone

seems to limit humins formation and 5-HMF rehydration, the solubility of monosaccharides in this solvent is poor. For instance, the solubility of D-fructose in pure acetone is only of 0.5 g/L at 25 °C. The addition of around 10 to 30 wt.% of water increases the solubility of D-fructose to several dozens of grams per liter but allows the apparition of levulinic and formic acids (molar yields until 20% and 2% respectively). Despite this compromise, the low boiling point of acetone (56 °C at 1 atm) is an important advantage for solvent separation.^{76,86} However, reaction of acetone with 2-F has also been reported, leading to the formation trans-furfurylideneacetone followed by apparition of soluble then insoluble polymers. A similar phenomenon was observed with hydroxyacetone and cyclopentanone. This observation suggests that solvents with carbonyl moieties are susceptible to reaction with the furan derivatives in accordance with humins formation by aldol reactions.⁹⁸

Among all the solvents evaluated for D-fructose dehydration, dimethylsulfoxide (DMSO) has been described as an excellent medium for the generation of 5-HMF.^{87,89,99} Without catalyst, 72% of D-fructose (molar yield) are converted into 5-HMF after 4 hours at 130 °C in pure dimethylsulfoxide. Furanose forms of D-fructose are greatly favored (72%) compared to the pyranose forms (28%) in dimethylsulfoxide at 23 °C while the pyranose forms are predominant in water. As mentioned earlier, this shift towards furanose forms increases with temperature. At 150 °C, 79 % of D-fructose is in the furanose forms. As other organic solvent, DMSO improves the rate of D-fructose dehydration to 5-HMF. Replacing water by a mixture of water and DMSO (80:20 v/v) at 160 °C in the presence of aluminium chloride and maleic acid multiplies the reaction rate by three.¹⁰⁰ Psicose, tagatose and sorbose were also successfully converted to 5-HMF in DMSO in the presence of H₂SO₄ and after 120 min, 5-HMF yields of 82%, 61% and 60% were achieved respectively.¹⁰¹ For comparison, dehydration of fructose, tagatose and sorbose in water (H₂SO₄ 33-300 mM, 100-140 °C) did not allow yields higher than 50%.⁶³

If tautomeric distribution possibly affects ketohexose dehydration rate, it should not influence ketopentoses (xylulose, ribulose) dehydration rate because they are only present as furanose forms.

A third way to favor 5-HMF/2-F rather than side-products is to prevent their aldehyde moiety from reacting. Alcohols and organic acids are known to form ethers and esters with 5-HMF and this phenomenon is thought to limit humins formation, which seem consistent regarding humins formation path proceeding through aldol addition/condensation as proposed by Patil and Lund (2011).⁸⁰

Figure 18 reports experimentally observed reaction products of D-fructose in alcohols in the presence of a strong acid catalyst (HCl or H₂SO₄).^{85,91,93,95,102} Those products originate from ethers formation and acetalization reactions.

Interestingly, the nature of the alcohol heavily impacts products selectivity. After a 2h treatment of D-fructose in methanol at 120 °C in the presence of HCl (5 mol%), a mixture of 5-HMF with compounds C, D and E (**Figure 18**) is obtained. In similar conditions in ethanol, 1-propanol and 1-butanol, only 5-HMF and compound C were identified, and no acetal seem to form. In isopropanol and tert-butyl alcohol, 5-HMF is the major product and no ether or acetal was observed in the tested conditions. Small amounts of isoproxymethylfurfural (3%) can appear after 12 h at 120 °C in isopropanol with ammonium chloride but 5-HMF remains by far the dominant furan derivative (68%).⁹¹ These observations suggest that the bulkiness of the alcohol is a key factor in reaction selectivity. The best 5-HMF yield (83 %) was obtained in isopropanol after 2h at 120 °C (HCl 5 mol%). The reaction still proceeds at 80 °C and a 67% 5-HMF yield is achieved after 8 hours.¹⁰² This surprising performance of bulky alcohol in the absence of 5-HMF etherification or acetalization could imply a protection of the molecule through specific solvation structure as discussed further with dimethylsulfoxide.

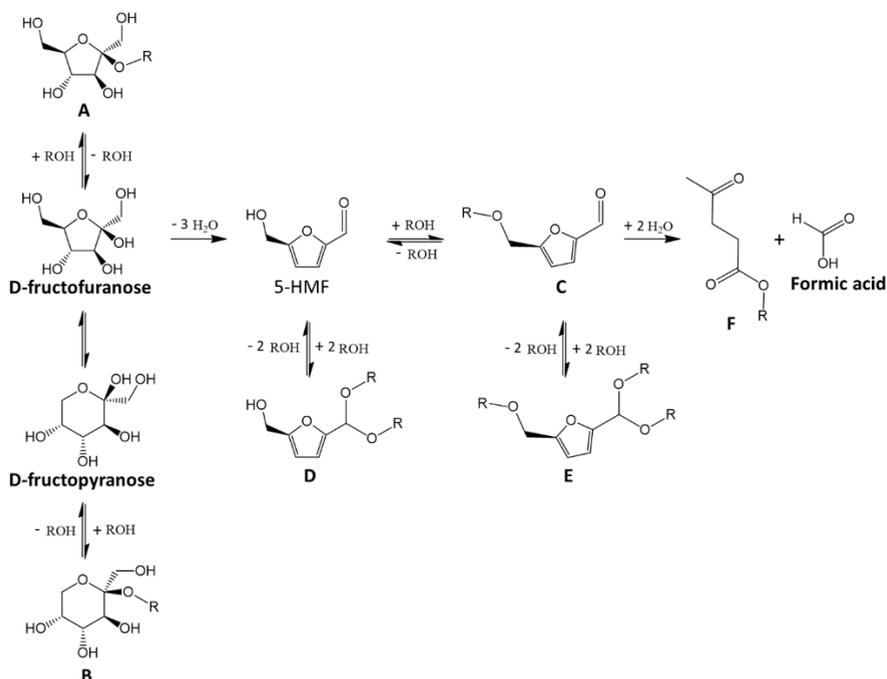


Figure 18: major products generated from D-fructose in alcohols in the presence of strong acid^{84,93}. This figure has been adapted from ref 75 with permission from John Wiley and Sons, copyright 2020.

Like 5-HMF, alkoxyethylfurfural can be used in bio-based plastics or bio-based fuel synthesis. If alcohols limit humins formation (less than 1.9 wt% after 5 h at 78 °C in ethanol with sulfuric acid), the hydration of alkoxyethylfurfural may still take place

since molar yields of ethyl levulinate (**Figure 18 compound F**) as high as 15 % were reported, probably because of in-situ generated water.⁹³

Mixtures of water and concentrated organic acids (at least 20 wt%) are another option to improve D-fructose dehydration and 5-HMF molar yields as high as 43-64% have been achieved at 150 °C in 2 hours.⁸⁵ The use of pure organic acids gives rise to the corresponding hydroxymethylfurfural-ester. In subcritical acetic acid, Bicker and coworkers (2005) produced 5-acetoxymethylfurfural with selectivity and conversion of 38 and 98% respectively after 120 s at 180 °C with 10 mM sulfuric acid. The solubility of D-fructose in this medium is however limited to only 21.5 g/l at 25 °C.⁹⁵

Interactions between 5-HMF aldehyde moiety and solvent molecules are also suspected to suppress side-reactions. During solvation, DMSO binds to 5-HMF more strongly than water, what reduces its susceptibility to nucleophilic attack and limits hydration as well as humins formation.¹⁰³ In the solvation structure of 5-HMF in mixture of water and DMSO, DMSO coordinates best with the carbon of the carbonyl moiety of 5-HMF protecting the group from reactions.¹⁰⁴ A similar phenomenon was suggested for alcohols such as 1-propanol, iso-propanol, 1-butanol and 2-butanol which could prevent 2-F degradation through solvation and steric hindrance compared to reaction in water.⁹⁸

The protective effect of DMSO was also demonstrated on 2-F. In aqueous HCl (pH 1) at 130 °C, 21% of 2-F is lost after 2h and insoluble brown solids are observed. When 2-F is treated in a mixture of aqueous HCl and DMSO (50 : 50) in the same conditions, only 3% of 2-F is lost.⁷² Several authors suggested that DMSO could also act as a catalyst.^{67,68} Acidic species originating from DMSO decomposition in the presence of oxygen interact with the carbocation obtained after the first dehydration step of D-fructose and likely catalyze the formation of intermediate A (**Figure 15**). A possible mechanism is depicted in **Figure 19**.

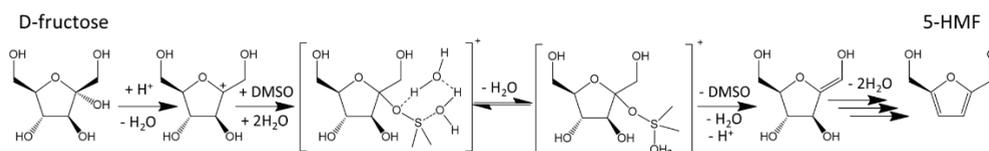


Figure 19: dehydration of D-fructose catalyzed by DMSO as proposed by Zhang et al. (2016)⁴⁹. This figure has been adapted from ref 49 with permission from Elsevier, copyright 2020.

If several organic media are very effective for the dehydration of D-fructose into 5-HMF, their use at industrial scale can be compromised for different reasons. At first, solubility of monosaccharides in polar organic solvents remains lower than their

solubility in water (e.g. 0.5 g of D-fructose per liter of acetone).⁹⁴ Larger amounts of solvent are consequently required for the dehydration step. Regarding other polar aprotic solvents such as DMSO, DMAc and 1-methylpyrrolidin-2-one, their boiling point is high (around 190 °C, 165 °C and 203 °C respectively), which makes the recovery of 5-HMF difficult.⁸⁶

To avoid these drawbacks, biphasic reaction media have been developed. Dehydration of D-fructose occurs in the aqueous phase and the produced 5-HMF is directly extracted in a less polar organic phase to prevent its decomposition into organic acids.^{23,57,81,106} Biphasic mixtures allow the use of higher D-fructose concentrations (0.56 to 1.67 M) compared to monophasic organic mixtures (0.06 to 0.56 M).^{23,57,76,81,85-91,99}

Solvents commonly used as extractive phase are methyl isobutyl ketone, butanol, hexanol, toluene and tetrahydrofuran.^{23,57,81,105}

The critical factor in biphasic “organic solvent/water” mixture is the partition coefficient (defined as the ratio between 5-HMF concentrations in organic and aqueous phases) of 5-HMF since it directs the solvent choice. The higher is the partition coefficient, the more 5-HMF is extracted in the organic phase.¹⁰⁶

Partition coefficients of 5-HMF in previously mentioned apolar solvents are generally lower than two.^{23,105,107} This coefficient can be increased by a factor of 1.5 to 3 thanks to a salting out effect when salts like sodium or potassium chlorides are added to saturation.¹⁰⁵⁻¹⁰⁸ In solution, these salts alter intermolecular forces between both phases and enhance their immiscibility which increases 5-HMF proportion in the organic phase.¹⁰⁸ In that respect, a partition coefficient as high as 7.3 is reached for an aqueous phase saturated with sodium chloride and tetrahydrofuran as the apolar organic phase. This solvents combination results in a 78% 5-HMF molar yields after 50 minutes at 160 °C.¹⁰⁵ In more complex solvents mixtures comprising water, dimethylsulfoxide, methyl isobutyl ketone and 2-butanol (14/13/51/22), an even higher 5-HMF molar yield is achieved (85%) after only 4 minutes at 170 °C.²³ Regarding xylulose dehydration, 2-F yield can be increased from 68 to 90% simply by simultaneously extracting it with MIBK (110 °C, HCl (0.1 M), water/MIBK = 1/3).⁷²

This overview of solvents effects on ketoses dehydration demonstrates that molecular organic solvents can be wisely selected to promote 5-HMF and 2-F formation through dehydration rate enhancement and 5-HMF/2-F functional groups protection. In terms of selectivity, polar aprotic solvents and bulky alcohols (like isopropanol) are solvents of choice for ketoses dehydration. In a practical point of view, bulky alcohols could present advantages compared to polar aprotic solvents, like their lower boiling points which could facilitate extraction/purification processes.

2.4. Anions catalysis of ketoses dehydration

The effects of salts on ketoses dehydration have been investigated in several media including water and polar aprotic solvents. The effect of alkali metals cations (K^+ , Li^+ , Na^+) is generally insignificant.⁹⁴ Transition and post-transition metal cations strongly affect ketose dehydration but their impact is addressed further with aldoses dehydration mechanisms. In water, potassium chloride, bromide, iodide and nitrate accelerate D-fructose conversion and slightly improve selectivity for 5-HMF.¹⁰⁹ Halides are known to promote D-fructose dehydration in numerous dehydration media. In water, effect of halides on ketose dehydration is limited because of their solvation which limits their interactions with the monosaccharides. A great amount of halide salt (> 100 mM) is consequently required. This high amount of halide salts required in protic solvents can be exploited to facilitated 5-HMF extraction by salting-out effect.

In polar aprotic solvents, the interaction of halides with monosaccharides is easier and concentration as small as 5 mM can drastically increase the rate constant of the dehydration (over 10 time).⁹⁴ In γ -valerolactone, chloride alone could not catalyze D-fructose dehydration, but greatly enhanced the reaction combined to an acid catalyst. From computational simulations, it was suggested that the highly localized charge on chloride anions allows them to stabilize carbocations which are dehydration intermediate as well as their deprotonation transition state. Rate constants of D-fructose dehydration in γ -valerolactone (373 K) with triflic acid (5mM) were determined in the presence of different halide salts and the following trend was obtained: KCl (64 ± 5 M⁻¹ ks⁻¹) $>$ KBr (22 ± 3 M⁻¹ ks⁻¹) $>$ KI (4 ± 1 M⁻¹ ks⁻¹) $>$ KF (2 ± 1 M⁻¹ ks⁻¹). A very similar trend was observed when halide anions were provided by acids ($HCl > HBr > HI$).⁹⁴

Halide effects were also observed in *N,N*-dimethylacetamide with lithium chloride (90/10 w/w.%) . This reaction medium can dehydrate more than 60 % of D-fructose into 5-HMF at 120 °C in 2 hours. By addition of sulfuric acid, this result is achieved in one hour.⁸⁸ In the *N,N*-dimethylacetamide – lithium chloride mixture, lithium ions form macrocations with *N,N*-dimethylacetamide. Chloride anions are consequently weakly paired with them. These weakly paired chloride anions are also observed in some ionic liquids known to be very effective to produce 5-HMF.¹¹⁰⁻¹¹³ A direct intervention of chloride anions in the dehydration reaction is suspected, as depicted in **Figure 20**, which results in a limited apparition of side-products.⁸⁸ When alkali metal chlorides ($LiCl$, $NaCl$, KCl) are replaced by their bromide or iodide counterpart, 5-HMF molar yield can exceed 90 % at 100 °C with sulfuric acid after 2 hours. The intermediates depicted in **Figure 15** were also observed during D-fructose dehydration in *N,N*-dimethylacetamide with lithium chloride (90/10 w/w.%) and products distribution was similar to that in DMSO suggesting analogous dehydration paths.⁶⁶

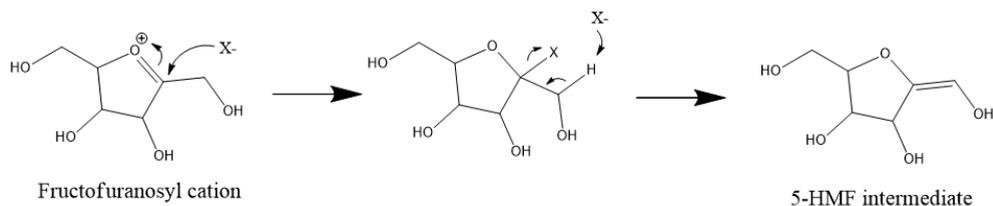


Figure 20: dehydration of *D*-fructose to 5-HMF in the presences of halides (*X*) as proposed by Binder *et al.* 2009.⁸⁸ This figure has been adapted from ref 88 (<https://pubs.acs.org/doi/10.1021/ja808537j>) with permission from ACS Publications, copyright 2020. Further permissions related to the material excerpted should be directed to the ACS.

Halide anions roles were further investigated comparing fructose and tagatose dehydration in the presence of several sodium salts (100 g/L, H₂SO₄ 0.1 M, 105 °C). All salts (NaCl, NaBr, NaI, NaClO₄, NaOMs, NaOTs, NaHSO₄) accelerated the initial 5-HMF formation compared to salt-free samples excepted for nitrates which completely inhibited 5-HMF formation above a salt concentration of 0.8 M. The reaction order with respect to the anion concentration was between 0.12 and 0.68, which suggests a direct participation of the anions. NaHSO₄ had the strongest effect on reaction rate followed by halide salts. Interestingly, tagatose dehydration rate was independent of the halide type on the contrary of fructose whose dehydration was most promoted by chloride, bromide then iodide. This observation suggests once again that C3 and C4 hydroxyl groups position is a key factor influencing the reactivity even in the presence of halide salts.⁶⁵

From the measured order of reaction in the presence of different salts as well as LC-MS experiments studying the insertion of ¹⁸O from labelled water into fructose, nucleophile substitutions likely play an important role in halides dehydration catalysis. Anions could efficiently accelerate dehydration if they have a good leaving group quality, are good nucleophiles and have a small size.⁶⁵

Nucleophilicity is of importance since this property is strongly affected by the solvent type especially in the case of ionic liquids as discussed in further sections. Solvent choice has consequently an impact on anions choice for dehydration catalysis. Nevertheless, chloride and bromide anions generally appear as good dehydration catalysts in numerous molecular solvents probably because of their appropriate balance between nucleophilicity, leaving group quality and size. F⁻ anions should be carefully considered because they are the conjugated base of a weak acid (pK_a = 3.2) on the contrary of the other mentioned halide anions. In an acidic medium (required condition for dehydration reaction), the hydrogen fluoride form will be predominant, which explains the observed inefficiency of F⁻ to catalyze fructose dehydration.⁹⁴ The use of iodide is also delicate since the halide is susceptible to oxidation to iodine which could limit its efficiency.

Halides catalysis possesses however a serious drawback for industrial process: pitting corrosion. In acidic medium, halides are known to rapidly lead to cracks formation in numerous alloys. The aggressiveness of halides considering pitting corrosion is fortunately not similar from one anion to another and follows this order: $\text{Cl}^- > \text{Br}^- > \text{F}^- > \text{I}^-$.¹¹⁴ Iodide, being the less corrosive anion, should therefore be further investigated in the absence of oxygen, especially in polar protic solvents where it has a higher nucleophilicity.

One way to reduce corrosion by halides is the development of treatments at moderate temperature. In this context, several low-transition-temperature mixtures including ionic liquids and deep eutectic solvents enable monosaccharides dehydration below 100 °C, which opens new possibilities to limit corrosion, even the use of non-metallic reactor.

2.5. D-fructose dehydration in low-temperature-transition mixtures (LTTMs)

Ionic liquids (ILs) and deep eutectic solvents (DES) share common advantages as reaction media such as a low vapor pressure and tunable physical (melting point, solubility, viscosity, density) or chemical (hydrophobicity, catalytic activity) properties. Those mixtures are however formed through different kinds of interactions. ILs can be described as liquid compounds displaying ionic-covalent crystalline structures. They are commonly mentioned as liquid electrolytes composed entirely of ions and associated to low melting temperature (often < 100 °C).¹¹⁵ Imidazolium based ILs have been largely investigated for monosaccharides dehydration.^{111-113, 116-120}

Regarding eutectic mixtures, they can be defined as mixtures of two or more compounds which, at a well-defined composition, display a unique and minimum melting point in the phase diagram. When the melting point of the eutectic mixture is substantially lower than those of pure components, the “deep eutectic” term is applied. This melting point drop is associated to non-covalent affinities as hydrogen bonding or van der Waals’ interactions.¹²¹ DES can be obtained by mixing a wide diversity of components, even relatively cheap and abundant substances like choline derivatives, organic acids and monosaccharides.

With the constant development of new LTTMs, the frontier between ILs and DES is sometimes unclear. Therefore, the LTTMs general designation was preferred to ILs and DES to describe advances in D-fructose dehydration in the next part of this document.

The dehydration of D-fructose in imidazolium-based LTTMs was investigated.¹²² Several cations in combination with chloride anions were compared at 120 °C (50 min). The longer was the alkyl chain on the imidazolium cation (1-butyl-3-

methylimidazolium, 1-hexyl-3-methylimidazolium, 1-octyl-3-methylimidazolium), the lower were D-fructose conversion (93.4, 65.7, 42.5%) and 5-HMF yield (63.1, 7.3, 0%). In nearly similar conditions (120 °C, 60 min), the 5-HMF yield gradually decreased for longer alkyl chains from nearly 80% with 3-methylimidazolium chloride (n=0) to less than 5% with 1-decyl-3-methylimidazolium chloride (n=10).¹¹¹ The performance of 3-methylimidazolium chloride (MIMCl) was further confirmed in another test reaching a 92% 5-HMF yield at only 90 °C after 45 min. Moreover, the LTTM was able to solubilize a significant amount of D-fructose (250 g of D-fructose per kg).¹²³ MIMCl enabled D-fructose dehydration without addition of a Brønsted acid evidencing its potential as solvent and catalyst. It should be noted that the effect of imidazolium side-chain length was measured comparing similar masses of LTTMs. This implies that chloride anions concentration significantly changes from one test to another. For a same mass of LTTM, chloride concentration is twice higher in MIMCl than in 1-octyl-3-methylimidazolium chloride (OMIMCl), which could strongly affect the rate and selectivity of the reaction as discussed in point 2.4. Imidazolium cation structural effect should be assessed on mole basis.

Besides the alkyl chain, the C-2 hydrogen seems to play a critical role in D-fructose dehydration since a poor D-fructose conversion (44.3 %) is achieved and no 5-HMF is obtained if the 1-butyl-3-methylimidazolium (BMIM⁺) cation is replaced by 1-butyl-2,3-dimethylimidazolium (BDMIM⁺). C-2 hydrogen of imidazolium is thought to play the role of an acid catalyst. When sulfuric acid is added to BMIMCl and BDMIMCl, their performances become similar (82.9 and 77.6 % 5-HMF yields respectively after 50 min at 100 °C. Moreover, the reaction can still be conducted at 40 °C. At this temperature, dehydration of D-fructose to 5-HMF in BMIMCl (Fructose/IL weight ratio = 1/10) in the presence of sulfuric acid (24 mol%) leads to a 5-HMF yield as high as 83.3%.¹⁰⁴ In both cases, humins were generated as the main side-product. Without the additional acid catalyst, BMIMCl do not enable the formation of 5-HMF at 100 °C showing that the alkyl chain on imidazolium also affects the minimum possible temperature for the reaction to proceed.¹²²

The effects of anions in LTTMs are likely similar to the trends highlighted for the common molecular solvents of the previous section and halide anions have been proven to effectively support the dehydration reaction. Among HSO₄⁻, Cl⁻, BF₄⁻, PF₆⁻, OTf and SCN⁻ combined to BMIM⁺, only HSO₄⁻ and Cl⁻ allowed a significant production of 5-HMF from D-fructose with around 70% and 50% yields respectively.¹²³

Choosing the appropriate halide for a specific ionic liquid is however much more complicated than for molecular solvents. In a previous section, nucleophilicity of halides was presented as one of the key factors explaining their efficiency to catalyze D-fructose dehydration. This property being solvent dependent, nucleophilicity of

halide anions in ILs will depend on their interactions with the associated cations as demonstrated in several works provided by Lancaster et al. (2001, 2002, 2004).¹²⁴⁻¹²⁶

If acidic LTTMs containing halide anions are efficient media/catalyst to perform D-fructose dehydration, the minimum reaction temperature remains limited by their melting or freezing point as well as their viscosity. For example, 1-ethyl-3-methylimidazolium chloride (EMIMCl) melts around 89 °C and will remain liquid until 33 °C (supercooling).¹²⁷ Several works overcame this problem by the addition of cosolvents to LTTMs.^{118,128-131} In pure DMSO with GeCl₄ as a catalyst, a max 5-HMF yield of 40% was reached from D-fructose at 25 °C and did not improve after 12h. Adding 0.5 g of BMIMCl to 2.5 g of DMSO increased reaction rate more than twice without enhancing the yield. However, increasing BMIMCl mass to 1.5 g (with 1.5 g of DMSO) enabled a 70% 5-HMF yield after 12h.¹²⁸ Similarly, the addition of small amounts (0.9 mmol) of acetone, DMSO, methanol, ethanol or ethyl acetate to BMIMCl (5.73 mmol) enabled efficient dehydration of D-fructose (around 80% 5-HMF yield) at 25 °C after 6 hours. The cosolvents decreased the reaction medium viscosity by around 6800 mPa.s.¹²⁹ Room temperature (23 °C) D-fructose dehydration was also achieved thanks to the addition of HCl and few drops of CHCl₃ to BMIMCl. A 5-HMF yield of 72% was reached after 24h.¹³¹ This effect of cosolvents was also observed in mixture of choline chloride and maleic acid. In previous work, we showed that addition of water to the choline chloride-maleic acid mixture strongly inhibited D-fructose conversion to 5-HMF at 60 °C. However, replacing water by an organic solvent (methanol, ethanol, isopropanol) still enabled the formation of a liquid reaction medium at this temperature as well as 5-HMF formation (62, 73 and 79 % 5-HMF yields respectively after 5h).¹³⁰

In appropriate ratio, mixtures of organic solvents with LTTMs present promising catalytic performances associated to a reduced viscosity and a potentially reduced energy consumption.

A careful choice of LTTMs components can provide a selective process at moderate temperature with efficient furan compounds isolation. Simeonov et al. (2012) demonstrated that 5-HMF could be synthesized and isolated in very high yield (97%) and purity (99%) from a LTTM (**Figure 21**). They produced 5-HMF in tetraethylammonium bromide (TEAB) at 100 °C in only 15 min in the presence of water (10-15%) and a heterogeneous Brønsted acid catalyst (Amberlyst-15, 10-15%). The LTTM was then dissolved in hot ethanol and precipitated by the addition of ethyl acetate at room temperature. LTTM could be re-used seven times before catalyst was added to maintain the performances.¹³²

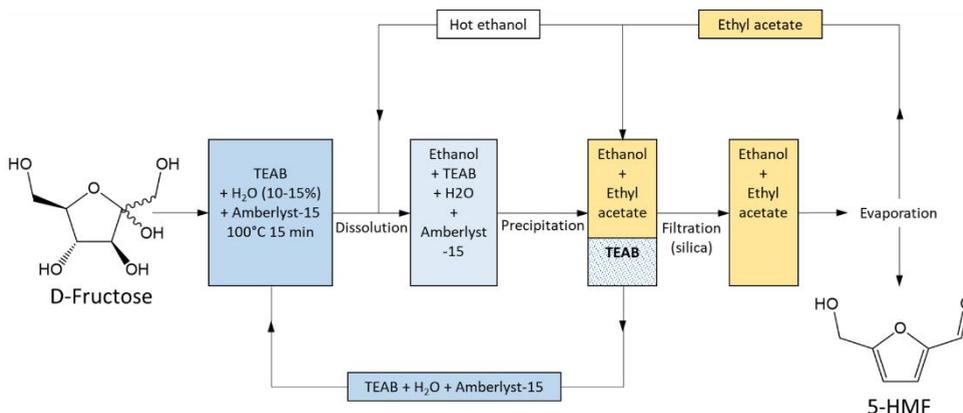


Figure 21: process for D-fructose dehydration and 5-HMF isolation according to Simeonov et al. 2012.¹³² This figure has been adapted from ref 132 with permission from John Wiley and Sons, copyright 2020.

3. Dehydration of aldoses

Glucose, mannose and galactose (**Figure 22**) are examples of aldohexoses of which dehydration leads to 5-HMF. Xylose, lyxose and arabinose (**Figure 22**) are aldopentoses and their dehydration consequently results in 2-F formation. Glucose and xylose are major components of plant cell walls.

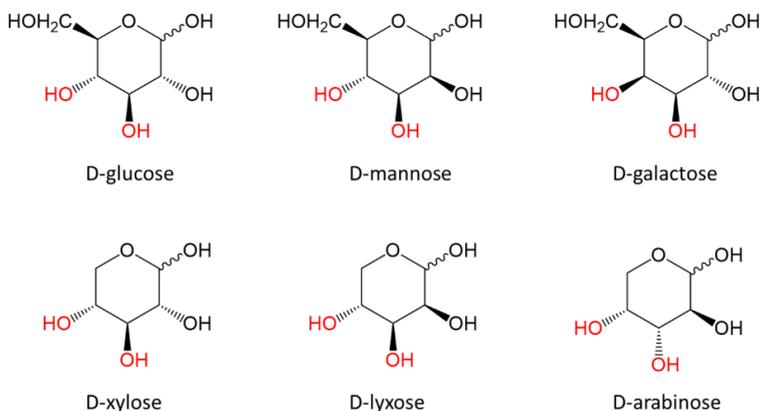


Figure 22 : aldoses chemical structures with highlighted C3 and C4 hydroxyl groups

However, they cannot be selectively converted to 5-HMF and 2-F using reaction media effective for ketose dehydration (e.g. Brønsted acid in organic solvents or

LTTM). Understanding their dehydration is therefore a key to develop biorefining process targeting furan products.

3.1. Mechanism of aldoses dehydration and limitations

Because aldoses possess an aldehyde moiety rather than a ketone moiety, C1 carbon is necessarily a part of the pyranose or furanose ring on the contrary of ketose. Consequently, a resonance stabilized carbocation is formed after protonation of C1-OH rather than C2-OH. This carbocation further reacts and leads preferentially to reversion products and humin precursors rather than 5-HMF.^{60,83,133} This favored pathway is consistent with experimental observations of the major compounds generated from D-glucose in hot water or hot acidic aqueous solution. A 1 M solution of D-glucose containing sulfuric acid (0.01 M) can reach a yield in insoluble humins of 35 wt.% after 6 hours at 180 °C.¹³⁴ Considering reversion products, the condensation of D-glucose into disaccharides was observed in water at 100-170 °C with sulfuric acid (1.2 wt.%).¹³⁵ Up to 12 wt. % of D-glucose was transformed into disaccharides at high sugar loading (300 g/L). In contrast to di-D-fructose dianhydrides, D-glucose disaccharides are engaged in irreversible cross-polymerization reactions responsible for humins growth.⁵⁶

Attempts to find pathways resulting in 5-HMF and 2-F formation led to several possibilities. Aldoses dehydration mechanisms can be sorted in two categories: reaction paths with at least some acyclic intermediates (**Figure 23**) and reaction paths with exclusively cyclic intermediates (**Figure 24**). While valid for all the described mechanisms, isotopic labelling demonstrated that carbon atoms positions in aldoses were maintained in the furan derivatives. For instance, C1 on D-glucose corresponds to the C1 bearing the aldehyde moiety on 5-HMF.^{70,83,136}

Regarding dehydration mechanism involving acyclic intermediates, a fully acyclic path was firstly considered (**Figure 23, A1**). This path proceeds through the formation of an enediol intermediate followed by two dehydration steps leading to acyclic intermediates. A2 mechanism consist in isomerization of the aldose to the corresponding ketose by formation of the enediol intermediate. A3 pathway also involves isomerization to ketose but through a hydride shift from C2 to C1.

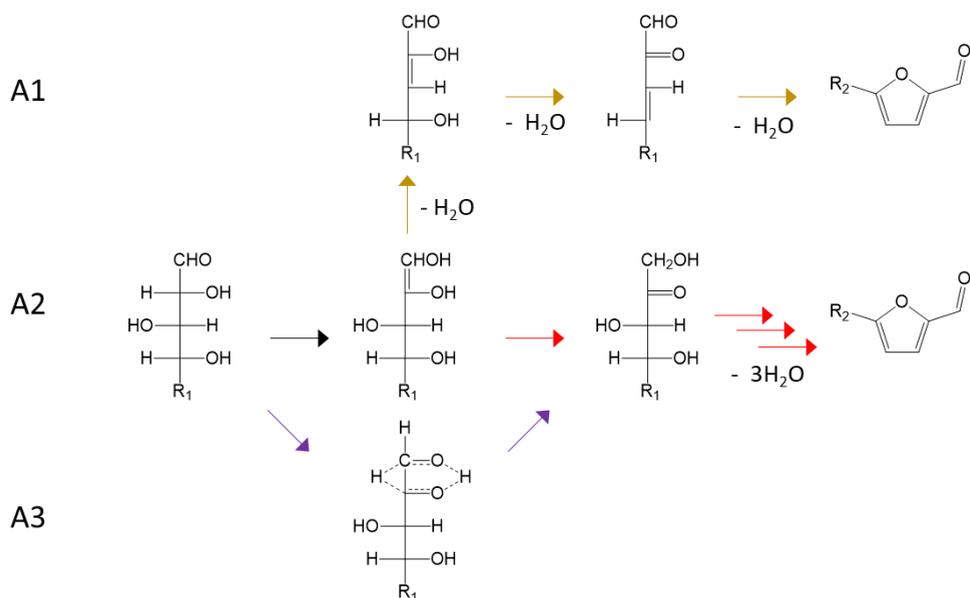


Figure 23: acyclic pathways for aldoses conversion to furan derivatives. For hexoses: $R_1 = -CHOH-CH_2OH$ and $R_2 = -CH_2OH$. For pentoses: $R_1 = -CH_2OH$ and $R_2 = H$. A1 (brown path): reaction path through enediol and other acyclic dehydration intermediate, A2 (red path): isomerization to ketose through an enediol intermediate, A3 (purple path): isomerization to ketose by hydride shift.

Dehydration pathways depicted in **Figure 24** involve only cyclic intermediates. All paths consist in a ring contraction of aldoses pyranose form enabling the formation of an aldehyde group on C1.

While no consensus has been achieved yet, some reactions pathways are supported by experimental evidence. The mechanism A1 is generally ruled out because its intermediates are subject to keto-enol tautomerism. Consequently, dehydration reactions performed in D_2O should result in the incorporation of deuterium in the formed furan compounds. However, this incorporation of deuterium is low ($< 5\%$) or absent.^{73,101} Compared to the other acyclic pathways (A2, A3), the fully acyclic path A1 shows a higher effective free energy barrier (34 kcal/mol compared to 26 and 24 kcal/mol in Brønsted acid catalyzed dehydration under ambient temperature).¹³⁷

Mechanism A2 is associated to the Lobry de Bruyn-van Ekenstein transformation and leads to the ketose formation. Ketoses formation during aldoses treatment in acidic water has been reported, supporting the A2 path.^{75,138-140} However, this reaction path is mainly active under base catalysis and involves proton exchange with the solvent

because of keto-enol tautomerism. The absence of such exchange in strong acidic conditions implies that A2 path is probably limited in the presence of Brønsted acid. A3 mechanism involving an intramolecular hydride shift is supported by tritium labelling of D-glucose and D-xylose at the C2 position. After the treatment of D-glucose-2-³H in sulfuric acid (2N) under reflux during 16h, D-fructose-1-³H is obtained, confirming the hydride shift.¹³⁹ Similarly, the formation of D-xylulose-1-³H was observed from the treatment of D-xylose-2-³H in sulfuric acid (1N) at 100 °C during 3 h.¹⁴⁰ A3 pathway is compatible with the limited deuterium incorporation from the reaction medium as well as with ketose apparition.

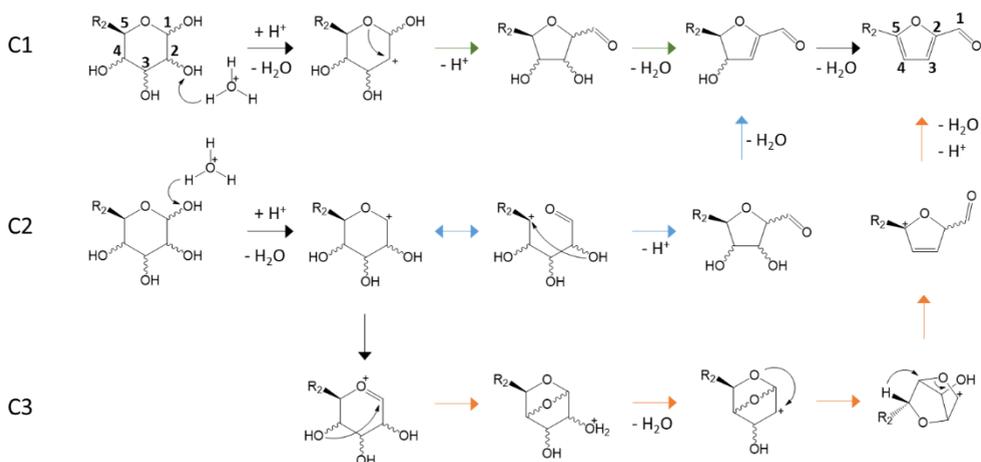


Figure 24: cyclic pathways for aldoses conversion to furan derivatives. For hexoses: R₂ = -CH₂OH. For pentoses: R₂ = H. C1 (green path): protonation of C2 hydroxyle and ring contraction after ring O attack on C2 (Ref:24,61,74,121,124,132), C2 (blue path): protonation of C1 hydroxyle and ring contraction after C2 O attack on C5 (133), C3 (orange path): protonation of C1 hydroxyle and ring contraction assisted by formation of a bicyclic cation (gas phase study) (134)

Cyclic reaction paths (**Figure 22**) are mainly supported by DFT calculations and gas phase studies with mass spectrometry.^{61,70,83,133,142-144} Decomposition of many aldoses (8 aldohexoses, 3 hexoketoses, 4 aldopentoses) has been studied by mass spectrometry.^{136,142-144} Typical observed fragments are m/z 181, 163, 145, 127 for hexoses and m/z 151, 133, 115, 97 for pentoses, which corresponds to the loss of three water molecules from the protonated monosaccharides. A diagnostic ion (m/z 85) obtained by cross ring cleavage is generated from m/z 181, 163, 145, 151, 133, 115 ions suggesting that all the intermediates of the degradation pathways are cyclic.¹⁴²⁻¹⁴⁴ ¹⁸O-C1 labelling experiment supports that the dehydration is initiated by C1-OH protonation. However, the presence of solvent is likely to strongly influence the dehydration activation energy.⁷⁰ Several DFT calculations support the C1 mechanism starting from C2-OH protonation.^{61,70,83,133} This less energetically favorable protonation

site compared to C1-OH is consistent with the low selectivity to produce 5-HMF and 2-F from aldoses. However, cyclic mechanisms do not explain the observed hydride shift from C2 to C1 positions. Interestingly, when ^{18}O -labelled D-xylose (ring oxygen) was dehydrated in aqueous HCl (140 °C, 50 mM), 69% of the obtained 2-F has ^{18}O in the ring while 31% of ^{18}O was observed at the aldehyde moiety. In the presence of NaCl (5M), 48% of ^{18}O was at the C=O group.¹⁴⁵ This oxygen transfer from D-xylose ring to 2-F aldehyde group could be explained by the C2 cyclic mechanism. This mechanism could possibly explain the higher reactivity of D-xylose compared to D-glucose in aqueous Brønsted acid solution.¹⁴⁶ Considering the C2 mechanism, the ring contraction occurs through C2-O attack on C5. For hexose, C5 is more substituted than for pentose which could affect the reactivity according to this cyclic mechanism.

Consequently, the most likely pathway to explain furan derivatives formation from aldose in Brønsted acid solution is currently the prior isomerization to ketose through hydride shift. Other mechanisms cannot be excluded at very high temperature or in neutral pH conditions, but further experimental evidence is still required to support them. Additional ^{18}O isotopic labelling experiments should be performed to assess the occurrence of C2 cyclic mechanism during the dehydration of different aldohexoses and aldopentoses in Brønsted acid solutions.

In conclusion for this second part, aldopentoses and aldohexoses are not readily dehydrated to 2-F and 5-HMF because their ring includes the C1 carbon as illustrated in **Figure 25**. Consequently, the most stable carbocation is formed after protonation of C1-OH. The involvement of C1 in the carbocation ring eliminate the possibility of the furan derivative aldehyde function direct formation.

Isomerization or cycle contraction being required to make the formation of the carbonyl moiety possible, other products more energetically favored such as humins or oligosaccharides are generated. The reactivity of hexoses and pentoses towards the dehydration reaction to furan products is therefore a direct consequence of the position of their carbonyl moiety. Whether the conversion of aldoses to 5-HMF and 2-F is direct or proceeds through isomerization to ketoses, it is not favored in most solvents compared to the generation of polymers. It is however certain that promoting aldoses isomerization to ketoses enhances their conversion to furan derivatives.

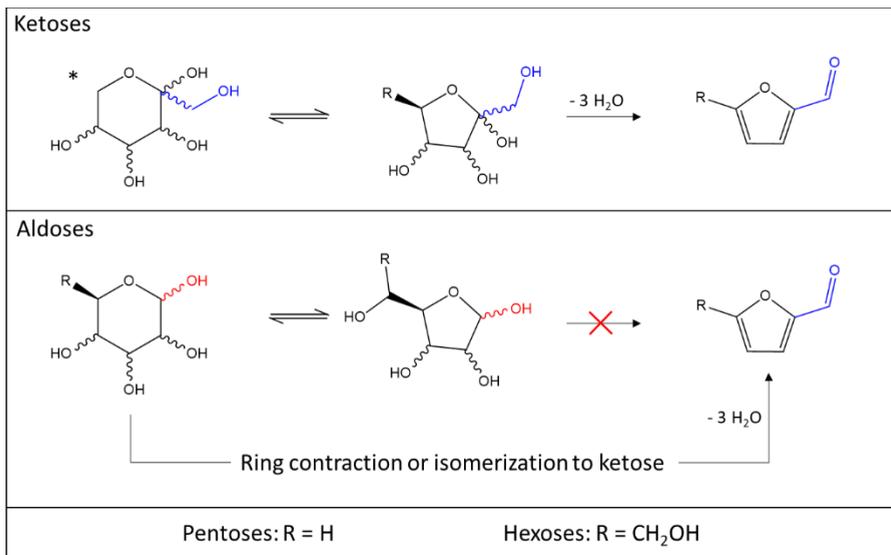


Figure 25: comparison of ketoses and aldoses dehydration to 5-HMF and 2-F. *This form is only valid for hexoses since ketopentoses only exist in furanose form.

Understanding both aldoses and ketoses dehydration is therefore crucial. It is illustrated by a less selective formation of 5-HMF from galactose compared to glucose and mannose which are generally converted to 5-HMF in similar yields in the presence of isomerization catalysts.^{101,147-149} This phenomenon could arise from the intermediate ketose. Glucose and mannose are both isomerized to fructose whereas galactose is isomerized to tagatose. Tagatose, being more reactive and less selective than fructose, could therefore result in a limited 5-HMF formation. A similar trend is observed for arabinose conversion to 2-F compared to xylose and lyxose.^{71,147,150} Xylose and lyxose share a similar selectivity for 2-F likely because they isomerize to the same ketose: xylulose. Arabinose is rather converted to ribulose. This trend should be further investigated because it means that all aldoses do not share similar selectivity for furan derivatives in the presence of isomerization catalysts.

3.2. Improving aldoses isomerization through catalyst/solvent combination

There are two main pathways to promote aldoses isomerization to ketoses: the Lobry Debruin Van Ekenstein (LDVE) path, mainly promoted in the Brønsted base route, and the Lewis acid path. LDVE pathway requiring an alkaline reaction medium, the simultaneous acid-catalyzed dehydration of ketoses to furan derivatives is not possible.

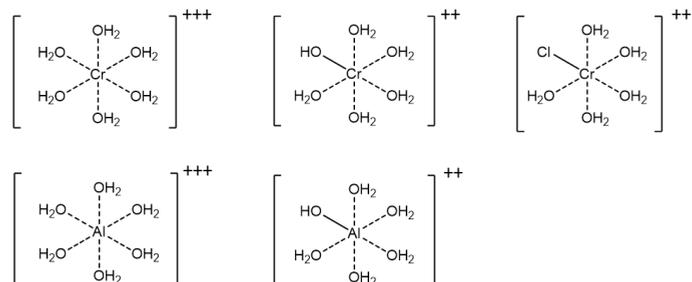
Both reaction steps must be performed in two different media. This problem becomes even greater when more complex feedstock such as polysaccharides are considered to produce 5-HMF and 2-F because their depolymerization generally requires acidic conditions. This alternation of acidity conditions being undesirable in the perspective of an industrial process, Lewis acid catalyzed isomerization has gained a lot of attention for the past few years.

A large number of Lewis acids have been investigated including compounds based on transition metals (Cr, Mo, W, Fe, Ru, Cu, Mn, Pd, Pt, V), post-transition metals (Al, Zn, Ga, In, Sn), lanthanides (La, Dy, Yb) and metalloids (B, Ge) elements.^{110,117,151-153} Given the tremendous number of explored catalysts in different reaction conditions (temperature, solvents), reactivity trends are not easily identified. It is however possible to illustrate important aspects of this catalysis with transition metal, post-transition metal and lanthanides chlorides.

Aldoses isomerization is assisted by coordination of their C1=O and C2–OH moieties to the metallic center of the metal chloride, what facilitates the hydride transfer from C2 to the C1. This hydride transfer mechanism has been confirmed for many Lewis acids (CrCl₃·6H₂O, AlCl₃, InCl₃, GaCl₃, LaCl₃, DyCl₃, YbCl₃) thanks to conversion of D-glucose-2-²H to D-fructose-1-²H and 5-HMF-1-²H as well as the absence of hydrogen/deuterium exchange with the solvent.^{101,154,155} The same mechanism has been demonstrated for Sn-β zeolites catalyzed isomerization.¹⁵⁴ This catalysis is firstly detailed considering an aqueous reaction medium.

Some Lewis acids (e.g. CrCl₃·6H₂O, AlCl₃, GaCl₃, InCl₃) are known to be water sensitive and will rapidly dissociate in water.¹⁵¹ They are then solvated to form complex ions which releases H₃O⁺, decreasing therefore the pH of the solution. In this sense, Lewis acids also produce Brønsted acidity, useful for dehydration catalysis of the formed ketoses. Dissociation of chromium and aluminum trichlorides in water is depicted in **Figure 26** as well as the observed dominant species.¹⁵⁴ The dissociation equilibrium is shifted to the right when temperature increases meaning that the Brønsted acidity can be modulated with temperature. Attention should be paid to anhydrous CrCl₃. This chromium species is known as kinetically inert and will not dissolve in solvents. However, CrCl₃·6H₂O and CrCl₂ can be readily dissolved and are generally used as catalyst. The in-situ generated Brønsted acidity in aqueous media explains why some Lewis acids (e.g. CuCl₂, FeCl₃), while inefficient for aldoses conversion to 5-HMF, have a strong ability to catalyze ketose dehydration.¹⁵³

Dominant cationic species after chromium and aluminium solvation and reaction in water:



Formation and hydrolysis of chromium complex ions:

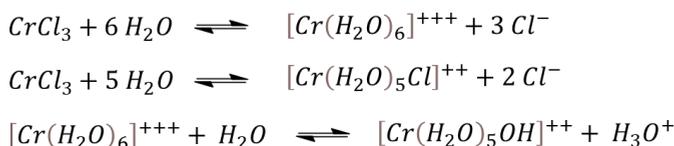


Figure 26: dominant species of some Lewis acid in water

Some Lewis acid ($LaCl_3$, $DyCl_3$, $YbCl_3$) are said “water compatible” and are less susceptible to dissociation.¹⁵¹ The Lewis acid-solvent combination is consequently crucial for isomerization catalysis. Following the hydrolysis equation depicted in **Figure 26**, the pH will likely influence the catalysis in aqueous media, especially if the different metal species possess different isomerization abilities. Assuming that the hydrolyzed metal complex is the active species for isomerization catalysis as proposed further in **Figure 27**, an excessive initial Brønsted acidity could limit the formation of this active species. In this regard, the addition of Brønsted acids to a $CrCl_3$ aqueous solution decreased D-glucose conversion rate and 5-HMF yield which confirms this hypothesis.^{156,157} The phenomenon was explained by an increased fructose dehydration rate thanks to HCl and a decreased glucose isomerization rate related to a shift of **Figure 26** equilibrium to the left.¹⁵⁶ However, the opposite trend was observed with $AlCl_3$, $InCl_3$ and $GaCl_3$. The conversion rate of D-glucose to 5-HMF in the presence of $AlCl_3$ was far superior when a Brønsted acid was added to lower the initial pH. To demonstrate that conversion rate increase was not due to the higher initial Brønsted acid concentration, the reaction was conducted in the presence of $YbCl_3$ in different pH conditions. With this water compatible Lewis acid, no significant change of the conversion rate was observed.¹⁵¹ The effect of Brønsted acid addition on Lewis acid reactivity was also investigated for xylose dehydration. HCl addition to a $CrCl_3 \cdot 6H_2O$ solution decreased xylose conversion rate but enhanced 2-F yield compared to HCl and $CrCl_3 \cdot 6H_2O$ separately. In a biphasic system (water/toluene at 140 °C, 120 min), a 76.3% 2-F yield is achieved with the combination of HCl (0.1M) and $CrCl_3 \cdot 6H_2O$

(6mM) while 2-F yield was limited to respectively 26.7 and 34.7% with HCl (0.1M) or $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (6mM) alone.⁷¹

Given the different effects of Brønsted acid addition for different metal chlorides, it is likely that Brønsted and Lewis acidities have to be specifically optimized for each catalyst in order to balance isomerization and dehydration rates and limit side products formation.

Isomerization catalysis is illustrated in **Figure 27**. The depicted metal (M) species could for instance correspond to $[\text{Cr}(\text{H}_2\text{O})_5\text{OH}]^{++}$, thought to be one of the possible active species generated by reaction of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ with water. The metal center is coordinated to oxygen atom and has a covalently bonded hydroxyl group.¹⁵⁴ The isomerization reaction comprises several steps. Firstly, a proton transfer from C2-OH is enabled by the covalently bonded hydroxyl of Cr (III), acting as a Brønsted base. Then, the hydride shift from C2 to C1 can occur followed by another proton transfer from the metal species to C1-O. The metal species acts therefore as a bifunctional catalyst possessing a Lewis acid site (the metal center) and a Brønsted base site (the ligand).¹⁵⁴ Both aspects should be considered to enable efficient isomerization to ketoses.

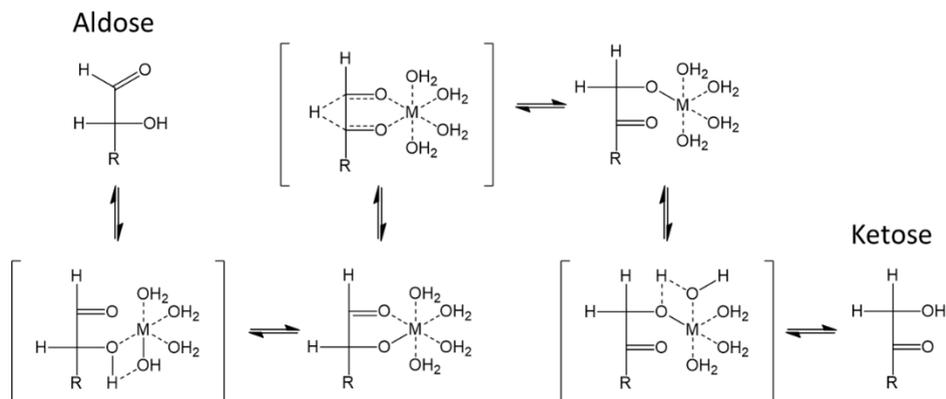


Figure 27: isomerization of aldoses to ketoses assisted by a metallic Lewis acid in water.¹⁵⁴ This figure has been adapted from ref 154 with permission from John Wiley and Sons, copyright 2020.

Considering first ligand properties, coordination strength and basicity are critical for the isomerization. During the reaction, -OH and =O groups of aldoses must replace ligand molecules in the coordination sphere. Strongly coordinating ligands will limit this exchange and lead to poor catalytic performances.¹⁵⁸ This has been illustrated in imidazolium based LTTMs. In EMIMCl, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ will form a CrCl_6^{---} octahedrally coordinated complex. This complex is surrounded by EMIM⁺ cations which

compensate the negative charge. Replacement of Cl⁻ ligands by -OH groups is energetically favored, which explain how isomerization takes place in ionic liquids. Cl⁻ can assist proton transfers like -OH bonded to the metal center for the catalysis in aqueous phase.¹⁵⁸ However, strongly coordinating ligands drastically limit the catalysis. In EMIMCl, several chromium complexes were compared. All catalysts were activated in the LTTM during 20 min at 150 °C prior to use. This step could be specific to chromium (III) which is again known for its substitution inertness meaning that high temperatures are required for continuous introduction of other species into the coordination sphere.¹⁵⁹ Compared to CrCl₃·6H₂O which resulted in a 48% 5-HMF yield (3h, 100 °C), chromium species with acetate (Cr₂(OAc)₄), ethylenediamine (Cr(en)₃Cl₃) and acetylacetonate (Cr(acac)₃) led to 5-HMF yields of 15, 7 and 4% respectively. In contrast, the introduction of weakly coordinating ligand such as THF (CrCl₃(THF)₃) and n-butanol (CrCl₃(n-BuOH)₃) improved 5-HMF yield to 71 and 69% respectively.¹⁵⁹ The insignificant 5-HMF yield obtained from glucose with GeCl₄ in 1-butyl-3-methylimidazolium acetate (BMIMOAc) could further support the inhibition by strongly coordinating ligand.¹⁶⁰

Ligand basicity has also been suggested as an important parameter and weakly coordinating non basic PF₆⁻ and BF₄⁻ anions are expected to be inefficient, which could be supported by the poor conversion to 5-HMF in BMIMBF₄ (around 5% yield after 75 min at 100 °C with GeCl₄).^{158,160}

Beside ligand properties, the nature of the metallic center obviously affects aldoses isomerization catalysis. Metal affinity for carbohydrates generally increases in the order of univalent, divalent and trivalent metals.¹⁵⁵ This is a first element explaining why alkali and alkaline earth metals cannot efficiently promote isomerization of aldose. The bond strength between metal center and -OH, =O groups of aldoses is a key factor.¹⁶¹ Glucose conversion to 5-HMF was studied in BMIMCl at 100 °C during one hour in the presence of different metal chlorides: CrCl₃, VCl₃, FeCl₃ and PtCl₂. 5-HMF approximative yields of 65%, 30%, <5% and 5% were achieved. To understand those results, far infrared spectroscopy was used in experiments with cyclohexanone, n-butanol and glycolaldehyde as model compounds representative of aldose functional groups. Adding cyclohexanone or butanol during the treatment with CrCl₃ did not affect the reaction but the introduction of glycolaldehyde strongly inhibited the formation of 5-HMF (around 15% yield), which confirmed that the metal interacted with aldose through their carbonyl and hydroxyl moieties at C1 and C2 position. In VCl₃ case, n-butanol did not change the reaction result, but cyclohexanone suppressed 5-HMF formation (5% yield). Compared to chromium, vanadium binds carbonyl moieties more strongly. Moreover, vanadium is more likely to coordinate with glycolaldehyde and an additional carbonyl moiety than chromium, favoring polymerization reactions leading to humins formation. For PtCl₂, the replacement of Pt-Cl bond by Pt-O bond is less favored. The metal thus possesses a low catalytic

activity for aldose conversion. Regarding FeCl_3 , the metal strongly binds to the different oxygen sources (alcohol, carbonyl) which do not enable a selective reaction. In addition, it also binds strongly with water oxygen, leading to complete reaction inhibition in the presence of water. These experiments highlight the efficiency of chromium compared to other metals and show that isomerization performances are directly linked to a fine tuning of coordination strength.¹⁶¹ Similarly to PtCl_2 , CuCl_2 do not likely exchange Cu-Cl bonds to Cu-O bonds. Cu(II) is also susceptible to reduction to Cu(I) by glucose.¹⁶²

Besides chromium, aluminum and tin chlorides are also generally reported as particularly effective catalysts for aldoses conversion to furan derivatives in water, polar aprotic solvents and LTTMs.^{117,152,153,163-166} Their coordination to the previous model compounds should be further investigated. In this sense, galactose dehydration to 5-HMF by $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ (130 °C in DMSO/ H_2O 9/1 v/v) was completely inhibited by addition of glyceraldehyde confirming the coordination to C1=O and C2-OH for the aluminum catalyst. Without glyceraldehyde, galactose transformation to 5-HMF was again less selective than glucose transformation achieving a 34.6% 5-HMF yield after 60 min vs 54.3% for glucose. This limited selectivity was rationalized by dehydration of tagatose, in similar conditions. Only a 30-35% 5-HMF yield was obtained from the ketose at a nearly complete conversion explaining the poor dehydration selectivity of galactose.¹⁴⁹

Among Lewis acids, boric and boronic acid derivatives that possesses a non-metallic center stand apart from a mechanistic point of view. They are known to form borate esters with 1,2- and 1,3-diols (**Figure 28**), including monosaccharides as well as with several organic acids (e.g. salicylic, oxalic, glycolic, tartaric acids).^{167,168,169} The formation of borate esters in aqueous solution is associated with a pH decrease.¹⁷⁰

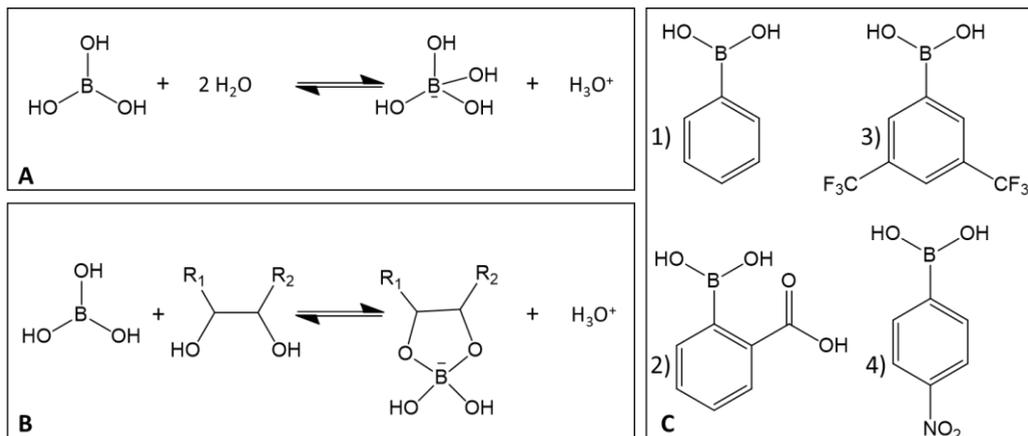


Figure 28: A) reaction of boric acid with water B) reaction of boric acid with a cis-diol C) examples of boronic acids : phenylboronic acid (1), 2-carboxyphenylboronic acid (2), 3,5-bis(trifluoromethyl)phenylboronic acid (3), (4-nitrophenyl)boronic acid (4).

Using boric acid as a catalyst, a 42% 5-HMF yield is achieved from D-glucose after 3h at 120 °C in EMIMCl.⁹⁵ DFT studies suggest that chelation of boric acid with D-glucose (coordination to C3-OH and C4-OH) results in a stabilization of the open chain glucose. The relative energy of acyclic glucose compared to β -glucopyranose was 20 kJ/mol. β -glucopyranose coordinated to boric acid at C3 and C4 positions has a relative energy of -50 kJ/mol and the acyclic coordinated form -90kJ/mol. Protonation of O1 becomes more favorable than in the absence of boric acid (probably because of the negative charge of boric acid). This protonation step is then followed by proton transfer resulting in the formation of an enediol intermediate still coordinated to boron. An additional proton transfer leads to the formation 3,4-borofructose. Fructose can then be dehydrated to 5-HMF.¹¹³

An enediol mechanism (**Figure 23, A2**) was confirmed by the reaction of D-glucose-2-²H. Less than 5% deuterium remained in the produced 5-HMF contrarily to the expected 50% for a 1,2-hydride shift mechanism (considering 100% incorporation of deuterium at D-fructose C1 position, theoretically 50% of deuterium should be lost in the solvent through the formation of the dehydration intermediate A of **Figure 15**).¹¹³ This study implies that boric acid catalyzed isomerization proceeds through a mechanism different from other metallic Lewis acid for which the hydride shift is validated.

The enediol mechanism is also supported for boronic acid derivatives. Dehydration of D-glucose-2-²H to 5-HMF was performed in dimethylacetamide with MgCl₂.6H₂O and 2-carboxyphenylboronic acid (molecule 2, **Figure 28 C**) as the catalyst. No deuterium was retained in the produced 5-HMF. Moreover, substantial amounts of

deuterium are incorporated in 5-HMF at C1 position when D₂O is present during the treatment.¹⁷¹

Boric and boronic acids have been used in different media (imidazolium based LTTMs, water, dimethylacetamide, dimethylsulfoxide) resulting in furan derivatives yields comprised between 5 and 60% from various aldoses (glucose, mannose, galactose, allose, xylose, arabinose).^{113,171-173}

Boric and boronic acids catalyzed aldoses dehydration being based on complex formation, the stability of those complexes strongly affects the reaction rate and selectivity. This stability depends on several factor including: the amount of boron catalyst, its associated organic chemical structure and aldose nature.

An excessive amount of boric or boronic acids (e.g. a 2/1 molar ratio with the aldose) will produce complexes including two boron entities limiting the aldose reactivity.^{113,173}

Additionally, the organic structure of phenylboronic acid (molecule 1, **Figure 28 C**), especially the position and nature of substituents on the aromatic ring, modulates the catalytic activity. Phenylboronic acids with an ortho carboxylic acid or ester enhanced 5-HMF yield from glucose in dimethylacetamide with MgCl₂.6H₂O compared to other substitution patterns. A 54% 5-HMF yield was obtained from D-glucose after 4 h at 120 °C in DMA, MgCl₂.6H₂O thanks to the use of 2-carboxyphenylboronic acid (10 wt% glucose, 2 eq. MgCl₂.6H₂O, 5 eq. of added water, 1 eq. of boronic acid). The presence of MgCl₂.6H₂O greatly enhanced the reaction (54% 5-HMF with MgCl₂.6H₂O and only 2% 5-HMF without the salts) as expected from a chloride anions source. The oxygen of the ortho carboxyl group is suspected to supply electron density to the empty p orbital of boron decreasing the strength of the complex.¹⁷¹ A similar trend was also observed in BMIMCl (105 °C, 2h). 24%, 11% and 7% 5-HMF yield were achieved from glucose with ortho-carboxyphenyl, meta-carboxyphenyl and phenylboronic acids respectively. Ortho-carboxyphenylboronic acid enabled a 58% 5-HMF yield when used in DMF containing BMIMCl (0.19 M) at only 95 °C for one hour.¹⁷⁴

The substituents effects on phenylboronic acid catalyzed dehydration of aldoses were further studied in EMIMCl (120 °C, 3h). Without catalyst, no 5-HMF was obtained from glucose. The introduction of phenylboronic acid to the system enabled a limited formation of the product (17%). Many substituted derivatives were then compared, and a 44% 5-HMF yield was reached using 3,5-bis(trifluoromethyl)phenylboronic acid (molecule 3, **Figure 28 C**). The presence of inductive electron withdrawing groups could strongly activate arylboronic acids.¹⁷³

Boric and boronic acids dehydration catalysis is also impacted by hydroxyl groups positions on aldoses ring. The dehydration of glucose, mannose, galactose and allose

with 3,5-bis(trifluoromethyl)phenylboronic acid leads to the following 5-HMF yields: 50, 37, 19 and 5%. When the same procedure was repeated with CrCl_2 rather than the boronic acid, 5-HMF yields of 66, 61, 13 and 44% were reached respectively. As discussed earlier, galactose resulted in a poor yield probably because of the tagatose intermediate. However, glucose and mannose conversion to 5-HMF are similar with CrCl_2 and different with the boronic acid. Strikingly, the transformation of allose is strongly limited in the presence of the boronic acid.¹⁷³ This phenomenon is hypothetically due to the favored complexation of cis vicinal diol compared to trans vicinal diol.^{169,173} Considering hydroxyl positions on C2, C3 and C4 of aldoses, glucose possesses two trans vicinal diol sites while mannose and galactose only possess one. Allose only possesses cis-vicinal diol sites. The complexation of a boronic acid with a trans vicinal diol would induce a distortion of the pyranose ring and could in this way favor ring opening, explaining the different dehydration yields achieved from the different aldoses.¹⁷³

Boric and boronic acids interacting with diols, those catalyst are inefficient in solvents with a diol moiety (e.g. ethylene glycol, glycerol).¹⁷³

Boron catalysts promoting the enediol pathway, a possible synergy with other Lewis acids acting on hydride shift could be expected. While limited, the synergy has been experimented in several works. Hu et al. (2012) compared the isomerization/dehydration of D-glucose in the presence of boric acid or hydrated chromium trichloride in BMIMCl. They demonstrated that chromium trichloride had a far superior ability to catalyze glucose isomerization compared to boric acid alone (60.3 % of HMF against 1.4%). However, when both Lewis acids were combined, the 5-HMF yield was enhanced to 69.1% suggesting a synergy between both catalysts.¹⁷⁵ 52% of glucose was converted to 5-HMF with a combination of boric acid with tungstophosphoric acid in BMIMCl (140 °C, 40 min). Only 0.8 and 23.5% 5-HMF were obtained with the isolated catalysts.¹⁷⁶ The use of boric acid also enhanced dehydration of D-glucose by $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ in water with NaCl at 170 °C.¹⁷⁷

Despite improvement of aldose isomerization to ketose, Lewis-acid catalysis is still confronted to the major problem of humins formation. This phenomenon is widely reported for various catalysts (even CrCl_3) in many reaction media: water, BMIMCl, DMSO, NMP, DMA, DMF.^{98,151,156,161,163,164} In water, as much as 40% of glucose is transformed to humins (carbon yield) at 75% glucose conversion (130-150 °C) in the presence of CrCl_3 .¹⁵⁶ Humins formation has also been reported during catalysis by H-Beta zeolith (Si/Al = 25) progressively covering the heterogeneous catalyst.⁹⁸ This phenomenon may be surprising considering that solvents like DMSO protect ketoses from degradation during treatment but the polymerization to humins is likely inherent to the coordination to the metal center. Through coordination, metals can bring reactive species with carbonyl or alcohol moieties closer to aldoses. Blocking only a part of the

coordination sites with strong ligands could reduce humins formation by limiting the access to the metal center. This could be suggested in the work of Yong et al. (2008) which highlighted that the conversion of D-glucose to 5-HMF was enhanced using chromium complexed with bulky N-heterocyclic carbene (81% 5-HMF yield after 6h at 100 °C in BMIMCl).¹¹⁰ This strategy would probably affect the reaction rate but should be further investigated in attempt to suppress humins formation.

4. Conclusions

Through a cyclic dehydration mechanism initiated by protonation of C2-O, ketoses can be selectively converted to 5-HMF and 2-F with the help of halide anions in different media, preferably alcohols for their protective effect and low boiling point or LTTMs which enable treatment temperature below 100 °C. Ketopentoses dehydration path should be further investigated with isotopic labelling to complete the current knowledges. A deeper understanding of C3-OH and C4-OH orientation effect on ketoses reactivity is still required.

Globally, ketoses dehydration has been largely improved and is now possible at moderate temperature (<100 °C) with high selectivity (>80%). The current understanding of dehydration catalysis and solvents effects should enable the development of selective low cost 5-HMF and 2-F synthesis processes which is why D-fructose dehydration to 5-HMF or derivatives is on the verge of reaching commercial scale.

Understanding and improving aldoses conversion to 5-HMF and 2-F remains challenging, but progresses importance is undeniable. Currently, the most supported mechanism explaining aldoses dehydration by Brønsted acids proceeds through isomerization to ketoses via a hydride shift. However, ¹⁸O labelling experiments suggests that ring contraction remains a possibility. The extent of this mechanism compared to the isomerization path should be further explored in a systematic study on several hexoaldoses and hexopentoses. The main way to improve 5-HMF and 2-F formation from aldoses consists in enhancing their isomerization to ketoses. In this purpose, two categories of catalysts have been explored in literature: metallic Lewis acids promoting the isomerization through hydride shift and boric/boronic acids promoting the isomerization through an enediol intermediate. This catalysis is however far more complex than ketoses dehydration because catalysts activity depends on numerous factors: the Brønsted acidity of the medium, catalysts affinity for monosaccharides, catalysts accessibility to several chemical species and catalysts ligands. Consequently for further development of aldoses dehydration systems, a particular attention should be paid to the following elements:

- The acidity of the medium can strongly impact the reaction rate and selectivity and should be estimated or compared for different catalysts/solvent systems, especially in LTTMs. Some efficient catalysts may not be identified if not used under optimized acidic conditions.

- Testing isomerization catalysts in the presence of model compounds representative of monosaccharides reactive moieties (alkyl alcohols, aldehydes/ketones, diols, α -hydroxycarbonyl compounds) can rapidly provide useful information regarding catalyst affinity or the risk of side reactions.

- The activity of metallic Lewis acids is affected by ligands type. Special care should consequently be taken regarding catalysts preparation. The different possibilities of ligands exchange in the reaction medium should also be assessed to prevent catalyst inhibition. Similarly, the activity of boronic acid-based catalysts can be modulated via their associated organic structure. Dehydration systems involving boric and boronic acids are also susceptible to interferences of the reaction medium (e.g. competition with diols or diketones).

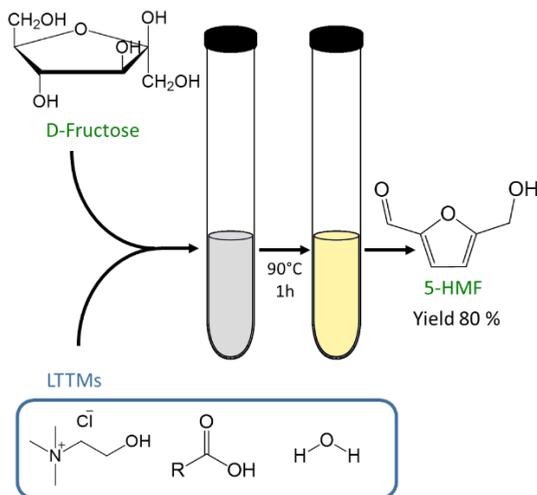
Humins formation during Lewis acid catalysis remains an important issue for furan products synthesis. The polymers are probably formed because of the acidity conditions or the coordination of multiple chemical species to the catalyst. Additional research should focus on humins formation mechanisms. Humins precursors likely derive from furan compounds in aqueous media but other origins are possible as suggested by aldoses degradation in organic solvents.

From the accumulated knowledges concerning monosaccharides dehydration, selective furan derivatives synthesis from aldoses appears feasible provided that all potential interactions of catalysts with monosaccharides and the reaction medium are considered. Further investigations on humins formation will likely provide the tools to inhibit their apparition, enabling the development of efficient aldoses dehydration media.

Ketoses dehydration to furan derivatives in low-transition-temperature mixtures

Adapted from:

Istasse T, Bockstal L, Richel A. Production of 5-Hydroxymethylfurfural from D-Fructose in Low-Transition-Temperature Mixtures Enhanced by Chloride Anions and Low Amounts of Organic Acids. *ChemPluschem*. 2018;83(12):1135–43.



Graphical abstract 3: *D-fructose dehydration to 5-HMF in reaction media composed of choline chloride, organic acids and water.*

Abstract:

The research for safe and sustainable solvents able to solvate reagents and to catalyze their reactions at temperatures below 100 °C is an innovative strategy to develop future lignocellulosic biorefineries. Many low-transition-temperature mixtures (LTTMs) have been investigated for this purpose. Among them, natural deep eutectic solvents (NADESs) have been proposed as cheap and renewable alternatives to ionic liquids for the synthesis of bio-based chemical building blocks. We compare herein the ability of several organic acids/choline chloride/water LTTMs to perform *D*-fructose dehydration to 5-hydroxymethylfurfural (5-HMF). The addition of chloride salts as well as an increased proportion of choline chloride promote 5-HMF formation which seem to indicate a beneficial effect of chloride anions on *D*-fructose dehydration. Besides improving selectivity by at least 10%, increasing the choline chloride / acid ratio could enhance LTTMs biodegradability. Unlike other acidic components, maleic and citric acids are especially selective at early *D*-fructose conversion. Maleic acid was the most selective acidic component among the tested chemicals allowing to achieve an 80% 5-HMF molar yield in 1h at 90 °C.

Key words:

Choline chloride, fructose, 5-hydroxymethylfurfural, low-transition-temperature mixtures, organic acids

1. Introduction

Many reaction media for 5-HMF synthesis were discussed in previous chapter. Cheapest solutions to generate 5-HMF use water or organic solvents in the presence of an acid catalyst to promote the dehydration of hexoses at high temperature (100-250 °C).^{55,76,81,82,85,91} These methods often suffer from side-products generation like levulinic and formic acids which are obtained by rehydration of 5-HMF (**Figure 29**). Humins are another type of major side-products frequently observed during 5-HMF synthesis. These dark polymers are formed by reaction between several molecules of 5-HMF. Sugars and organic acids are also suspected as humins precursors. 5-HMF molar yields higher than 80% can be achieved in more complex solvents like biphasic systems.⁹²

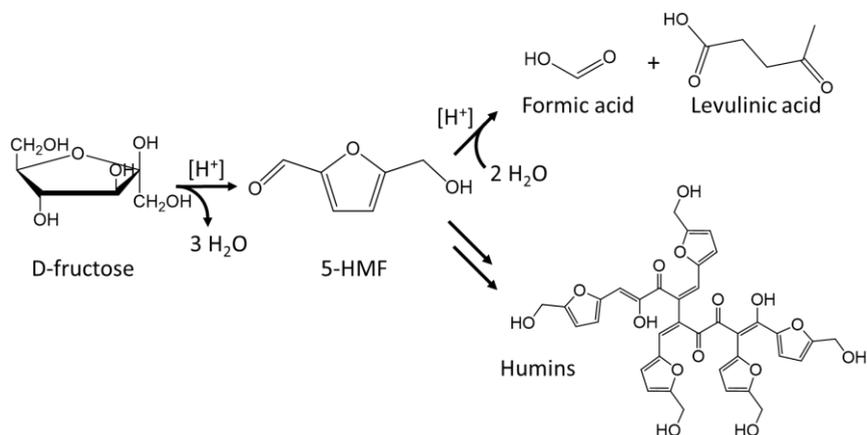


Figure 29: Dehydration of D-fructose to 5-HMF and side-reactions.

Even higher yields have been obtained in ionic liquids at temperatures lower than 120 °C.¹¹⁰⁻¹¹³ For instance, Moreau and coworkers (2006) reached a 92% 5-HMF yield in 45 minutes at 90 °C in 1-H-3-methylimidazolium chloride.¹¹¹ These ionic liquids possess a low vapor pressure, are non-flammable and their properties in extraction or catalysis can be tuned by selecting specific anionic and cationic components. Ionic liquids advantages are however balanced by their generally high cost as well as their poor biodegradability and sustainability. Among the low-transition-temperature mixtures (LTTMs), including the ionic liquids group, other solvents have been recently investigated to perform hexoses dehydration: natural deep eutectic solvents (NADESs). According to Durand et al. (2016), eutectic mixtures can be defined as “mixtures of two or more compounds which, at a precise composition, display a unique and minimum melting point in the phase diagram”.¹²¹ The difference in melting temperatures between pure components and the mixture is sometimes so important that

two solid compounds mixed at a precise ratio form a liquid at ambient temperature, which is why the term “deep eutectic solvent” (DES) has been used.

Interestingly, specific mixtures of primary metabolites like sugars, amino acids, organic acids and choline derivatives can form deep eutectic solvents too. In such a case, these mixtures are generally called “Natural Deep Eutectic Solvents” (NADESs). Dai and coworkers (2013) reported more than a hundred stable combinations of primary metabolites to prepare NADESs. The mechanism responsible for the large drop in melting temperature observed for these solvents is suspected to involve hydrogen bonds between components. NADESs are consequently prepared by mixing a hydrogen bond donor (e.g. organic acids or glycerol) with a hydrogen bond acceptor (e.g. choline chloride).¹⁷⁸

Like ionic liquids, the so-called NADESs have tunable properties and a low vapor pressure. In addition, NADESs are cheaper than imidazolium-based ionic liquids, less toxic and often biodegradable.¹⁷⁹ Their constitutive components are abundant and the mixtures are easily prepared from a melt of one of the component in which the second is dissolved, from the direct mixing of heated solid components or from concentrated solutions.¹⁸⁰ Moreover, enzymatic reactions are possible in these media, even in the presence of normally denaturing component like urea.¹⁷⁹ All these advantages explain the recent interests in NADESs in the context of green chemistry.

Regarding 5-HMF synthesis from D-fructose, Hu and coworkers (2008) attempted the dehydration reaction in mixtures of choline chloride with malonic, oxalic or citric acid at 80 °C. A 78% 5-HMF yield was achieved in one hour in the citric acid/choline chloride mixture. The continuous extraction of 5-HMF with ethyl acetate during the process improved this yield to more than 90%.¹⁸¹

Based on these promising dehydration results and the list of stable NADESs provided by Dai and coworkers (2013),¹⁷⁸ we explored the potential of several primary metabolites or derivatives combinations for 5-HMF production from D-fructose.

To our knowledge, the role of each NADESs component in the dehydration of D-fructose has not been investigated yet. By testing components with close chemical structures, we attempted to find first clues regarding dehydration catalysis in those media.

2. Materials and methods

2.1. Preparation of low transition temperature mixtures (LTTMs):

LTTMs were prepared by mixing components described in **Table 2** with distilled water (15 wt% of total weight) at 60 °C in closed vessels excepted for Ch-SA which was heated at 90 °C to obtain a homogeneous phase. D-(-)-fructose (99%), choline chloride (99%), L(+)-tartaric acid (>99%) and fumaric acid (>99%) were purchased at Acros Organics. Glycerol (>99%), dihydroxyfumaric acid hydrate (98%), DL-malic acid (>99%), trimethylglycine (>99%), maleic acid (>99%) and D-(+)-glucose (>99.5%) were acquired from Sigma-Aldrich. Succinic acid (99%) was obtained from Fischer Scientific. All chemicals were used as received. Each LTTM was stored in a sealed container directly after preparation.

Table 2 : LTTMs composition (all mixtures contain 15 wt% water) for the first (from Tri-CA to CH-Mea) and second (from Ch-FA to Ch-MeA (16:1)) sets of experiments.

Solvent label	Component 1 (C1)	Component 2 (C2)	Molar ratio (C1/C2)
Tri-CA	Trimethylglycine	Citric acid	1
CA-Sor	Citric acid	D-sorbitol	1
Ch-Gly	Choline chloride	Glycerol	1
Ch-Sor	Choline chloride	D-sorbitol	3
Ch-CA	Choline chloride	Citric acid	1
Ch-MeA	Choline chloride	Maleic acid	1
Ch-FA	Choline chloride	Fumaric acid	1
Ch-SA	Choline chloride	Succinic acid	1
Ch-MiA	Choline chloride	Malic acid	1
Ch-TA	Choline chloride	Tartaric acid	1
Ch-DA	Choline chloride	Dihydroxyfumaric acid	1
Ch-LA	Choline chloride	Levulinic acid	1
Ch-MeA (2:1)	Choline chloride	Maleic acid	2
Ch-MeA (4:1)	Choline chloride	Maleic acid	4
Ch-MeA (16:1)	Choline chloride	Maleic acid	16

2.2. Characterization of LTTMs:

Densities of LTTMs were determined at 25 °C with pycnometers. Hygroscopicity were compared by exposing 1 g samples of LTTMs at ambient air and by observing mass gains during 24 hours at 25 °C. Solubilities of D-fructose, acetic acid, formic acid, levulinic acid and 5-HMF in each mixture were determined by high performance liquid chromatography (HPLC). LTTMs were heated until 40 °C beforehand. Each substance with unknown solubility was then added until saturation. Mixtures were leaved to cool down until 25 °C. After centrifugation (2000 rpm, 10 min), 0.1 g of each mixture were sampled and dissolved in water for HPLC analyses. D-fructose and D-glucose were quantified using a Ca Rezex RPM monosaccharides column heated at 80 °C with a water flow of 0.6 ml/min. Detection was performed with an evaporative light scattering detector (40 °C, gas flow of 0.8 L/min). Organic acids and 5-HMF were separated on a HPX-87H Aminex column heated at 45 °C using a 5mM H₂SO₄ aqueous solution at a 0.6 ml/min flow. UV detection was used to measure organic acids concentrations at 210 nm and 5-HMF concentration at 284 nm.

2.3. Dehydration of D-fructose in LTTMs and aqueous solutions:

Typical dehydration tests were performed by adding 2 g of LTTMs to 0.1 g of D-fructose in sealed glass tubes. Mixtures were homogenized prior to the test. Samples were then heated at 90 °C in a water bath with an agitation of 1000 rpm. After the treatment, mixtures were immediately dissolved with water, filtered on 0.45 µm and stored at -20 °C. For 5-HMF simultaneous extraction, 5 ml of ethyl acetate were added to 2 g of LTTM and 0.1 g of D-fructose. Samples were placed in a water bath at 70 °C for two hours. After the treatment, samples were cooled at ambient temperature in another water bath and ethyl acetate was recovered, mixed with water (water was added until a volume of 200 ml to obtain a single phase) and filtered for analysis. The LTTM phase of the samples was treated as for the other experiments.

2.4. Soluble products analyses:

Organic acids and furan compounds were analyzed by HPLC-UV following the protocol used to determine solubilities. Organic acids and furan compounds detection was performed at 210 nm and 284 nm respectively.

2.5. Insoluble products analyses:

To increase the precision on insoluble mass measurements, dehydration tests on larger D-fructose masses were realized, typically 0.5 g. Proportions of D-fructose and

solvents used for previous tests were maintained. Preparation of samples after the treatment followed the same procedure as for the other tests excepted for the filtration step. Filtration was performed on weighed filter crucibles (porosity between 1 and 1.6 μm). Insoluble products were washed three times with 100 ml of distilled water and dried at 105 °C during 24 hours for gravimetric determination of humins. The first filtrate and the washing filtrates were combined, filtrated on 0.45 μm and stored at -20 °C before the HPLC analyses. The presence of small humins in samples filtered on 0.45 μm was also investigated by dynamic light scattering (DLS) using a Zetasizer ZS90 from Malvern.

2.6. Calculation of residual D-fructose, D-fructose conversion, 5-HMF yield and selectivity

Residual D-fructose and D-fructose conversion were calculated as follows:

$$\text{Residual fructose} = \frac{\text{Final moles of fructose}}{\text{Initial moles of fructose}} \times 100\%$$

$$\text{Fructose conversion} = 100\% - \text{Residual fructose}$$

5-HMF yield and selectivity were obtained as follows:

$$\text{HMF yield} = \frac{\text{Moles of HMF}}{\text{Initial moles of fructose}} \times 100\%$$

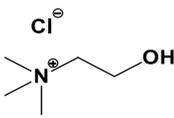
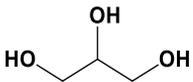
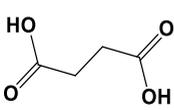
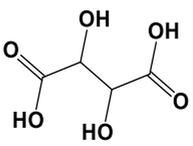
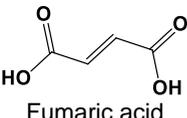
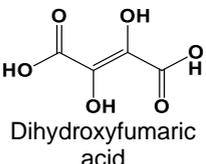
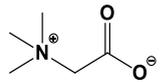
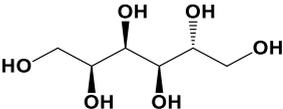
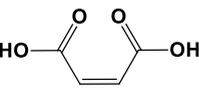
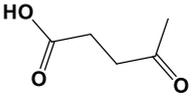
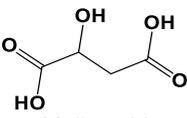
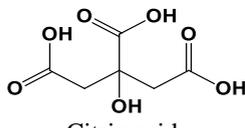
$$\text{Selectivity} = \frac{\text{HMF yield}}{\text{Fructose conversion}} \times 100\%$$

To express selectivity as a function of conversion rather than time, curves of residual D-fructose and 5-HMF yield as functions of time were approximated by second degree polynomial equations. Conversion equations were used to calculate the time corresponding to 20, 30, 40, 50 and 60% fructose conversion. For these conversion values, curves fit well with the experimental points ($R^2 > 0.977$). The calculated times were then used in yield equations to determine HMF yields at 20, 30, 40, 50 and 60% fructose conversion. Knowing yield and conversion, selectivities were calculated according to the previously mentioned formula.

3. Results and Discussion

Chemical structures of NADESs components used in this work are depicted in **Table 3**. During a first set of experiments, NADESs were based on the following substances: choline chloride, citric acid, maleic acid, glycerol, D-sorbitol and betaine (trimethylglycine). The prepared mixtures were characterized. Their density, their behavior during air exposure and the solubility of several molecules (D-fructose, D-glucose, formic acid, levulinic acid, 5-HMF and 2-F) were determined. The water content of each solvent was set at 15 wt% to decrease the viscosity and compare solvents effects on the same basis. These different NADESs as well as several aqueous solutions of their constitutive components were used to determine the role and importance of each component in the D-fructose dehydration reaction. The main formed side-products like organic acids and insoluble humins were analyzed to understand the observed 5-HMF yields.

Table 3 : LTTMs components used in this work.

Quaternary ammonium	Polyols	Organic acids	
 Choline chloride	 Glycerol	 Succinic acid	 Tartaric acid
		 Fumaric acid	 Dihydroxyfumaric acid
 Trimethylglycine	 Sorbitol	 Maleic acid	 Levulinic acid
		 Malic acid	 Citric acid

In a second time, several other organic acids namely succinic, fumaric, malic, tartaric, dihydroxyfumaric and levulinic acids that possess chemical structures close to that of maleic acid were tested with choline chloride to study the effect of acidic components structures on reaction rate and selectivity in D-fructose dehydration to 5-HMF. Components ratio are shown in **Table 2**. Because the prepared mixtures are not necessarily at the eutectic point (the transition temperature was not determined), they are designated as LTTMs rather than NADESs in the following sections of this paper as recommended by Durand and coworkers (2016).¹²¹

Additional experiments were performed to simultaneously extract the produced 5-HMF from LTTMs with ethyl acetate and to study the effect of water in LTTM composition on the temperature required for the dehydration of D-fructose.

3.1. First set of experiments:

The first six LTTMs, prepared for preliminary tests were characterized as shown in **Table 4**. LTTMs densities are all superior to water density. After exposure to ambient atmosphere (relative humidity between 80 and 90%) for 24 hours, a mass loss was observed for all the citric acid based LTTMs. This mass loss was limited to less than 2 wt% of the initial LTTMs mass. All the other LTTMs rapidly gained mass (7 to 9 wt%) without reaching equilibrium after 24 hours. If the preparation of LTTMs is straightforward, these results confirm that those solvents are sensitive to air moisture and have to be stored in closed vessels. The mass of some mixtures can increase by almost 10 wt% in a day without an adapted storage.

The solubility of common expected reaction products observed during hydrothermal treatment of biomass and sugars dehydration, namely D-fructose, D-glucose, formic acid, acetic acid, levulinic acid and 5-HMF, was assessed in each solvent. The highest solubility observed is limited to 104.89 ± 2.91 g/kg for D-glucose in the Ch-Sor mixture. While the solubilities of D-glucose and D-fructose in Ch-CA and Ch-Gly mixtures are very similar, D-glucose is 1.2 to 4 times more soluble than D-fructose in the other solvents.

The difference in solubility is especially important in the mixture of CA-Sor. Formic acid, acetic acid, levulinic acid and 5-HMF were perfectly miscible in all the LTTMs on the tested range of concentrations (until 25 wt%).

Table 4: density of LTTMs and solubility of D-fructose and D-glucose.

Solvent label	Density (g/cm ³)	D-fructose solubility at 25 °C (g/kg)	D-glucose solubility at 25 °C (g/kg)
Ch-CA	1.2800 ± 0.0003	61.02 ± 0.68	58.54 ± 0.99
Ch-Gly	1.1441 ± 0.0011	78.23 ± 2.64	76.53 ± 6.86
Ch-Sor	1.1714 ± 0.0006	67.94 ± 0.87	104.89 ± 2.91
Tri-CA	1.3271 ± 0.0006	13.35 ± 1.11	26.21 ± 5.26
CA-Sor	1.4097 ± 0.0004	11.82 ± 0.64	43.73 ± 1.13
Ch-MeA	1.1941 ± 0.0004	81.53 ± 1.69	102.42 ± 8.58

The dehydration of D-fructose in each LTTMs at 90 °C in closed vessel was monitored for 2 h. The evolution of the 5-HMF molar yield (calculated as the ratio between produced 5-HMF and initial D-fructose) is given in **Figure 30**. The furan compound rapidly appeared in the two mixtures containing choline chloride and an organic acid. A 5-HMF yield of 58.80 ± 0.97 % was reached in Ch-CA after 2 h as expected regarding previous works.^{179,180}

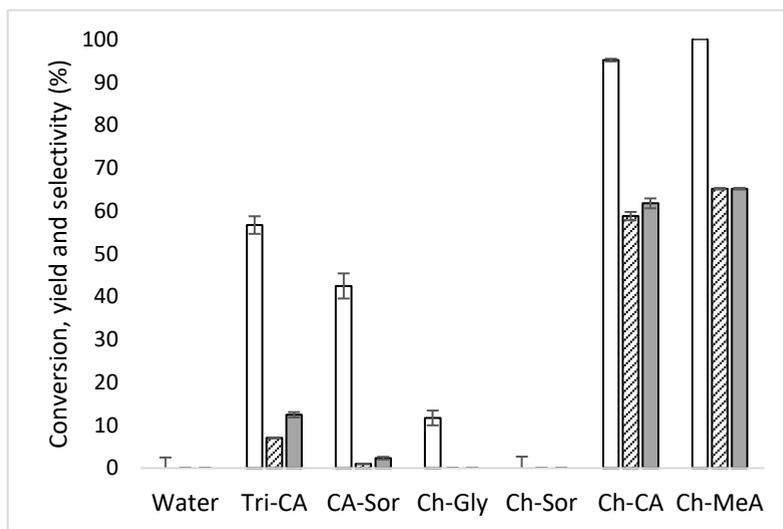


Figure 30: Dehydration of D-fructose to 5-HMF in LTTMs after two hours at 90 °C (blank: D-fructose conversion, hatched: 5-HMF molar yield, shaded: 5-HMF selectivity).

In Ch-MeA, molar yields over 60 % were achieved after only 20 minutes with a 5-HMF yield of 68.00 ± 0.23 % after 1 h. Surprisingly, only low amounts of 5-HMF were obtained in Tri-CA (7.04 ± 0.11 %) and CA-Sor (0.98 ± 0.07 %) which suggests that

both choline chloride and an organic acid are required to rapidly dehydrate D-fructose. As expected, non-acidic LTTMs (Ch-Gly and Ch-Sor) did not allow the apparition of 5-HMF in the tested conditions. The fact that choline chloride and trimethylglycine possess chemical structure similarities without resulting in close 5-HMF yields could indicate the involvement of chloride anions in the dehydration mechanism. Analysis of residual D-fructose allowed to determine the selectivity for 5-HMF (calculated as the ratio between 5-HMF yield and D-fructose conversion). After two hours at 90 °C, conversion of D-fructose reached $95.19 \pm 0.31\%$, $56.70 \pm 2.05\%$ and $42.49 \pm 2.93\%$ in Ch-CA, Tri-CA and CA-Sor respectively, which resulted in the following selectivities: $61.77 \pm 1.16\%$, $12.44 \pm 0.62\%$ and $2.32 \pm 0.32\%$.

Halide anions are suspected to assist the dehydration of fructose.^{88,119,123} Several works described in the previous chapter suggest that halide anions facilitate the formation of an intermediate species through nucleophilic substitutions.^{65,88}

To determine if chloride anions affected the dehydration reaction in our conditions, lithium chloride and hydrochloric acid were added to Tri-CA and Ch-CA mixtures. The results are compared in **Figure 31**.

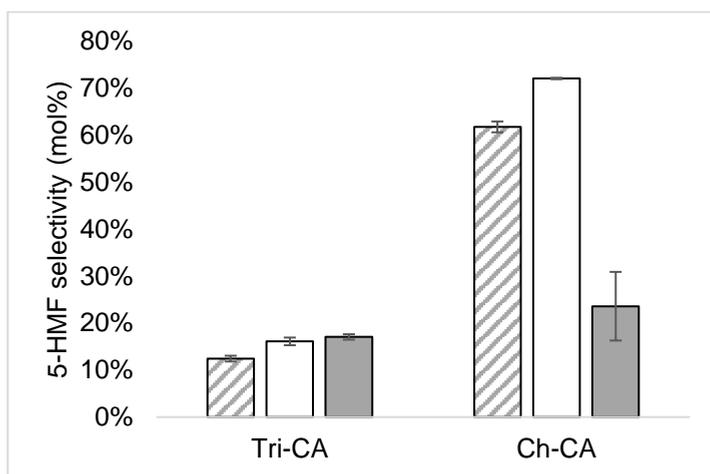


Figure 31: 5-HMF selectivity after two hours at 90 °C in Tri-CA and Ch-CA without additive (hatched), with 0.5 mmol of LiCl (blank) or with 0.5 mmol of HCl (filled).

The addition of HCl to Ch-CA resulted in rapid dehydration of D-fructose and then disappearance of 5-HMF which explains the lower observed selectivity. However, the addition of LiCl and HCl to Tri-CA improves selectivities from $12.44 \pm 0.62\%$ to $16.10 \pm 0.82\%$ and $17.05 \pm 0.58\%$ respectively. In Ch-CA, selectivity is increased by around 10% in the presence of LiCl. These experiments suggest indeed a beneficial effect of chloride anions in the dehydration mechanism. The comparison of different choline

salts further supports the important role of halide anions in the reaction as depicted in **Figure 32**. Choline chloride, choline bromide and choline iodide were compared in 1:1 (mol) mixture with maleic acid for the dehydration of D-fructose.

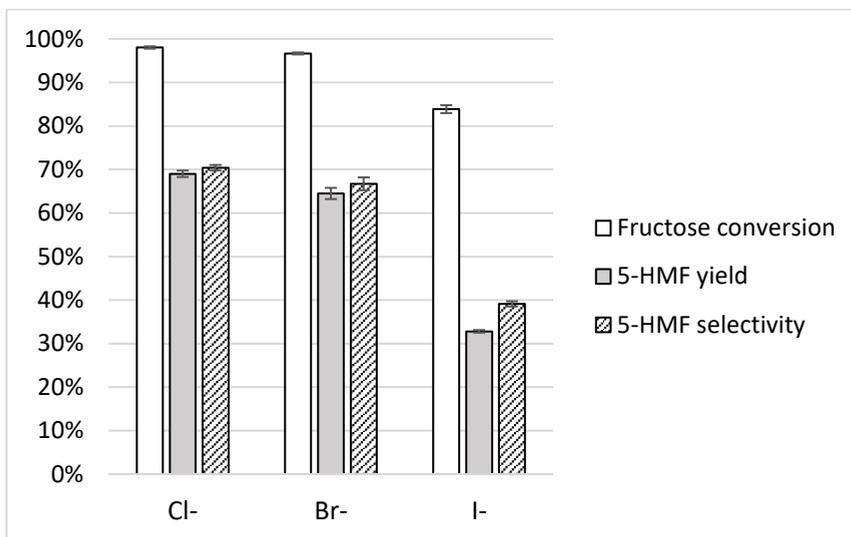


Figure 32 : comparison of choline chloride, choline bromide and choline iodide in the dehydration of D-fructose. Reaction media consist in 1:1 (mol) mixtures of choline salts and maleic acid. Each mixture contains 15 wt% of water. 6.6 mmol of choline salt, 6.6 mmol of maleic acid, 0.56 mmol of D-fructose and 16.7 mmol of water were mixed and put in a water bath at 90°C. The reaction was performed during one hour. Those conditions were based on the previous test using 2 g of a 1:1 mol mixture of choline chloride and maleic acid with 15 wt% water.

The resulting D-fructose conversion, 5-HMF yield and selectivity increased in the following order with respect to the halide anions: I⁻ < Br⁻ < Cl⁻. As described in chapter 2, a similar trend was observed for the corresponding potassium salts in water.⁹⁴ Halide anions are suspected to facilitate the formation of a dehydration intermediate species through nucleophilic substitution.⁶⁵ An interesting hypothesis comes from the different dehydration behavior of D-fructose and D-tagatose in the presence of Cl⁻, Br⁻ or I⁻. Different dehydration rates were observed for each anion during the dehydration of D-fructose but no significant difference was noticed during the dehydration of D-tagatose.⁶⁵ Assuming an interaction of halide anions with C2 of ketoses as depicted in **Figure 20** of chapter 2, the accessibility to C2 could be affected by -OH moieties positions on the cyclic monosaccharide. For D-tagatose, both -OH are on the same side of the cycle while they are on opposite side in D-fructose. Chloride anions being smaller than bromide and iodide anions could therefore have a better access to C2. The limited performance of iodide may also be attributed to its oxidation to iodine. A faster color shift than usual (from transparent to yellow-brown) was indeed noticed during the reaction.

Considering the calculated selectivity, side-products were generated during the reaction. No levulinic acid and very small amounts of formic acid (molar yield lower than 4%) were observed after HPLC-UV analysis of the reaction products which implies that rehydration of 5-HMF in these media is limited in the tested conditions.

Insoluble dark substances were generated during D-fructose treatment in choline chloride/organic acids based LTTMs. Increasing amount of humins was visually noticeable as the color of the LTTMs turned from yellow to dark brown during the treatment.

Insoluble products larger than 1.0-1.6 μm were quantified after dehydration of D-fructose in choline chloride/organic acids mixtures. The generation of insoluble particles (estimated as the mass ratio between insoluble products and initial D-fructose) in citric acid/choline chloride and in maleic acid/choline chloride after two hours at 90 °C was limited to only 1.86 ± 0.62 wt% and 1.80 ± 0.42 wt% respectively. Nevertheless, a second filtration on 0.45 μm after the first filtration on 1.0-1.6 μm filter crucibles still revealed the presence of humins. Tsilomelekis and coworkers (2015) studied humins formation and growth in aqueous solution with or without dimethylsulfoxide (DMSO). In water, they observed the apparition of humins particles with different sizes from 100 nm to 5 μm . In the presence of DMSO, particles sizes was reduced between 50 and 100 nm.¹⁸² Consequently, the average size of humins generated in LTTMs could be smaller than 1 μm . However, DLS analyses on 0.45 μm filtered samples did not reveal any particles smaller than 0.45 μm which suggest a superior size for humins generated in the prepared LTTMs after two hours.

As depicted in **Figure 33**, concentrated aqueous solutions of individual LTTMs components were compared to understand the role of each of them in the dehydration reaction. 5-HMF molar yields reached only 11.78 ± 0.07 % and 3.80 ± 0.10 % in concentrated maleic acid and concentrated citric acid respectively after 2 h at 90 °C. No 5-HMF was detected in concentrated choline chloride at 35.88 and 85.00 wt%. The resulting selectivity in acidic aqueous solutions is drastically lower than in LTTMs: 26.05 ± 2.86 % and 13.81 ± 5.94 % for maleic acid and citric acid solutions compared with 65.18 ± 0.19 % and 61.77 ± 1.16 % in the corresponding LTTMs. When hydrogen bond acceptors coupled with citric acid are ranked by decreasing order of selectivity, the following sequence is obtained:

choline chloride > trimethylglycine \approx water > sorbitol.

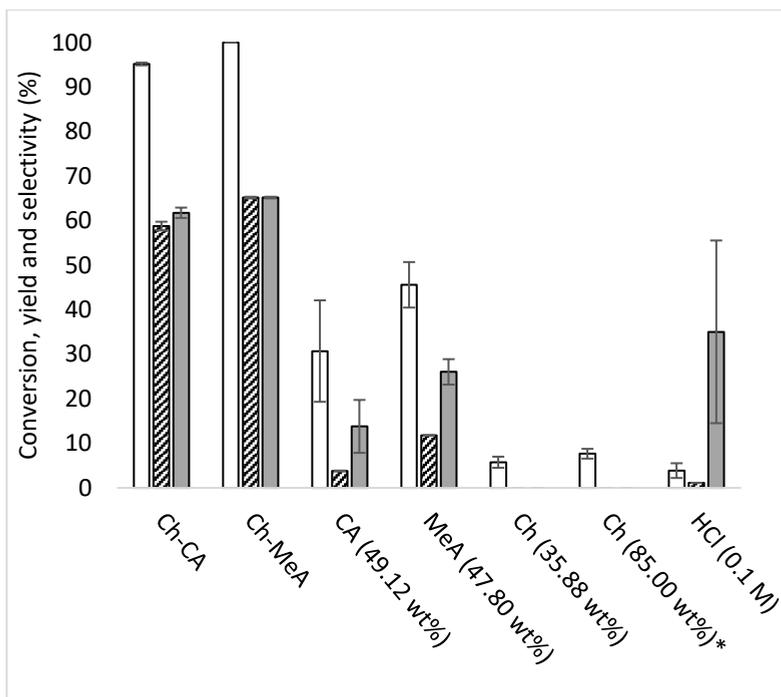


Figure 33: Dehydration of D-fructose to 5-HMF in LTTMs and several aqueous solutions after two hours at 90 °C (blank: D-fructose conversion, hatched: 5-HMF molar yield, shaded: 5-HMF selectivity).

To highlight a possible synergy between organic acids and choline chloride in water, diluted mixtures of citric and maleic acids with choline chloride (0.1 M) were prepared but only limited amounts of 5-HMF were obtained (molar yields below 0.5 %). All these results are in accordance with the work of Caratzoulas and coworkers (2011) who mentioned high activation energy induced by the excessive presence of water during the second dehydration step of D-fructose transformation to 5-HMF.⁵⁹ The adverse effect of excessive water is also supported by Kuster and coworkers (1977) who reported a faster 5-HMF formation from D-fructose by water displacement with polyethylene glycol.¹⁸³

3.2. Second set of experiments:

In order to understand the efficiency of maleic acid with choline chloride for 5-HMF production, several other organic acids with a four-carbon “structure” were tested. These acids were mixed with choline chloride and water (15 wt%) following proportions mentioned in **Table 2**. LTTMs were easily prepared at 60 °C excepted for those containing succinic, fumaric and dihydroxyfumaric acids. For succinic acid, a temperature of 90 °C was required to obtain a homogeneous phase. No homogeneous

phase was achieved with fumaric acid even at 90 °C. Among the tested acidic components, succinic and fumaric acids both have the highest melting points (184 and 287 °C respectively). The lower melting point resulting from their mixtures with choline chloride remains too high to obtain completely melted LTTMs.

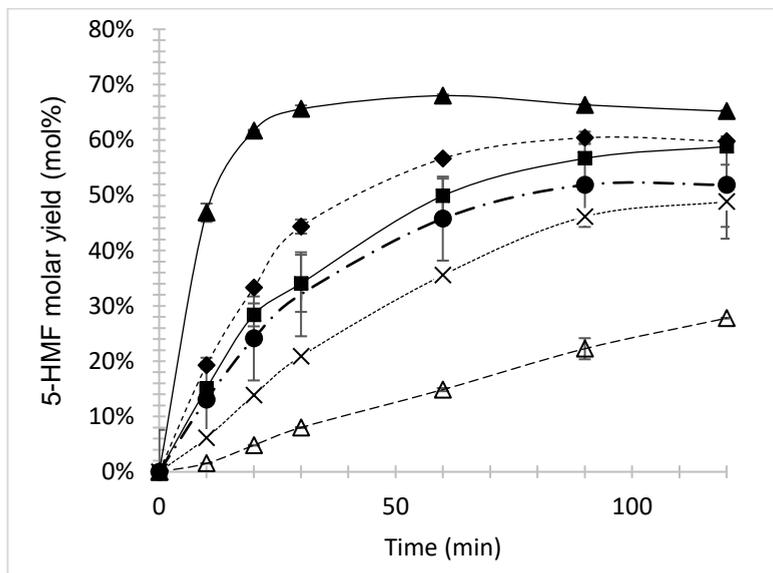


Figure 34 : 5-HMF generation during dehydration of D-fructose at 90 °C in organic acids/choline chloride LTTMs (Ch-MeA: ▲, Ch-TA: ◆, Ch-CA: ■, Ch-MiA: ●, Ch-SA: X, Ch-LA: ▲ dotted line).

Regarding the mixture containing dihydroxyfumaric acid, gas release was rapidly observed during the heating at 60 °C as well as a color shift from white to yellow. Dihydroxyfumaric acid is known to be unstable in aqueous solution. Its decomposition leads to carbon dioxide formation.¹⁸⁴ Changes in mixture composition were confirmed by infrared spectra of the LTTMs and pure components. All the other LTTMs were stable at 25 °C during at least one week. New D-fructose dehydration tests were performed in these acidic LTTMs. 5-HMF yields were monitored again as shown in **Figure 34**.

D-fructose conversion could not be evaluated for levulinic acid because of the coelution of the acid with D-fructose peak in HPLC.

Regarding the dehydration kinetics depicted in **Figure 34**, the differences observed for acidic LTTM's components seem well explained by their pKa. This trend is confirmed in **Figure 35** where the initial rates for 5-HMF production (expressed in mmol 5-HMF/L.s) follow pKa values order. Acids with a low pKa value being more

likely to dissociate, it is expected that protonations required for D-fructose dehydration to 5-HMF will be accelerated, which is in accordance with the observed results.

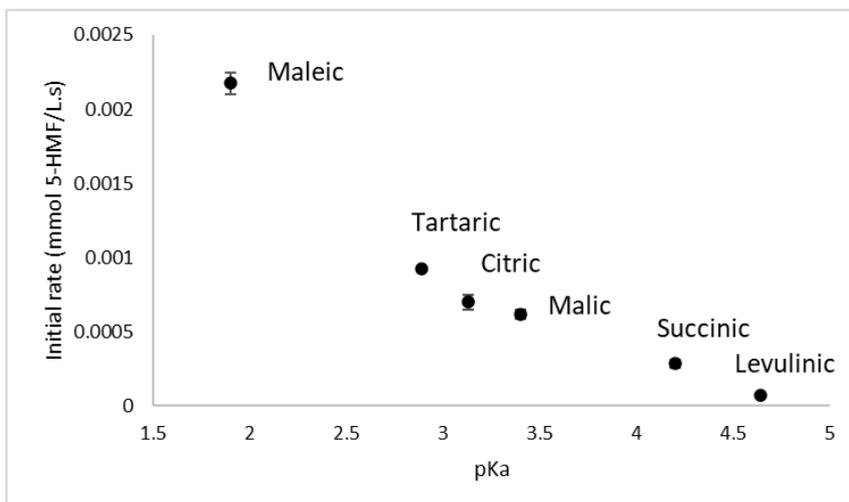


Figure 35: Initial rate of 5-HMF synthesis at 90 °C as a function of the pKa value of acidic components in LTTMs.

Calculated selectivity for each acidic component of LTTMs is depicted as a function of D-fructose conversion in **Figure 36** to take into account the effect of D-fructose concentration. It can be seen that acids structures impact the selectivity for 5-HMF, maleic and citric acids being particularly selective. For all these acids, the selectivity progressively increases with the conversion of D-fructose, which is a known effect since a high fructose concentration favors side reactions like polymerization by increasing the probability of effective collision between D-fructose molecules. However, this improvement of selectivity with the conversion is particularly pronounced for tartaric, malic and succinic acids. Citric and maleic acids remain nearly as selective at low conversion as at high conversion which implies that both acids could limit interactions between D-fructose molecules. Thanks to its low pKa value (1.9), maleic acid allows a fast dehydration of D-fructose with a good selectivity (around 66%).

Since maleic and citric acids are more selective for 5-HMF production compared to the other tested acids, their performances could be explained by conformational similarity. Considering that the conformational isomerism of maleic acid is restrained by a double bond which brings both carboxylic moieties closer and that the best selectivity is achieved with this acid in the tested conditions, the probability of apparition of a mimicking structure should be investigated in other acids. In succinic, malic and tartaric acids, free rotation limits the apparition of conformations with close

carboxylic moieties. However, in a tricarboxylic acid like citric acid, carboxylic moieties are statistically more likely to be closer despite free rotations. This hypothesis could explain the selectivity observed for this acid and should be investigated in further works.

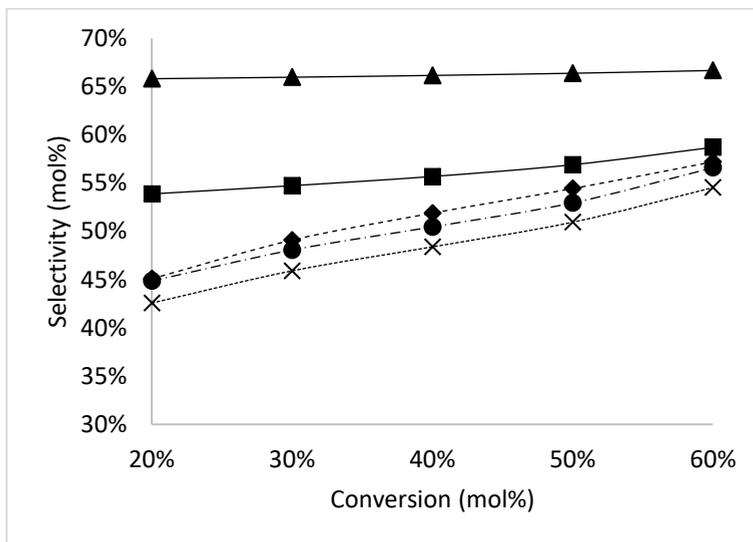


Figure 36: Evolution of selectivity for 5-HMF with D-fructose conversion at 90 °C for each LTTM acidic component (Ch-MeA: ▲, Ch-TA: ◆, Ch-CA: ■, Ch-MiA: ●, Ch-SA: X).

5-HMF yield achieved in the Ch-MeA mixture, though promising, remains moderate. Several parameters must be optimized such as temperature, stirring or water proportion.

Another potential factor able to influence the reaction is the proportion between the hydrogen bond donor and acceptor. LTTMs with organic acids and choline chloride have been generally used at a defined molar ratio without evaluating its effect on reactions. Changing this ratio will of course change the melting point of the LTTM which could result in a solid state in the tested conditions. We chose to investigate this parameter in order to see the impact of a reduced amount of acid on mixture preparation and reaction selectivity.

The mixtures Ch-MeA (2:1), Ch-MeA (4:1) and Ch-MeA (16:1 mol) were prepared at choline chloride / maleic acid molar ratio of 2, 4 and 16 respectively. Both components were mixed in closed vessel with water (15 wt% based on total weight) at 60 °C.

A homogeneous liquid phase was rapidly obtained for each one of them. However, Ch-MeA (16:1) crystallized in less than two hours at 25 °C. Interestingly, the other LTTMs remained stable at 25 °C. These LTTMs were used for D-fructose dehydration tests and the resulting selectivity and yields are shown in **Figure 37**.

This experiment demonstrates that decreasing maleic acid proportion improves selectivity by at least 10%. For a 4-fold decreased in acid proportion, a 5-HMF yield of 79.23 ± 0.26 % was achieved after one hour at 90 °C. The same outcome was observed with tartaric acid and a 10% gain in selectivity was achieved by using a choline chloride / acid molar ratio of two rather than one. Since the lower acid content in the prepared LTTMs comes with an increased choline chloride concentration, the improved selectivity supports once again a beneficial effect of chloride anions on the dehydration reaction.

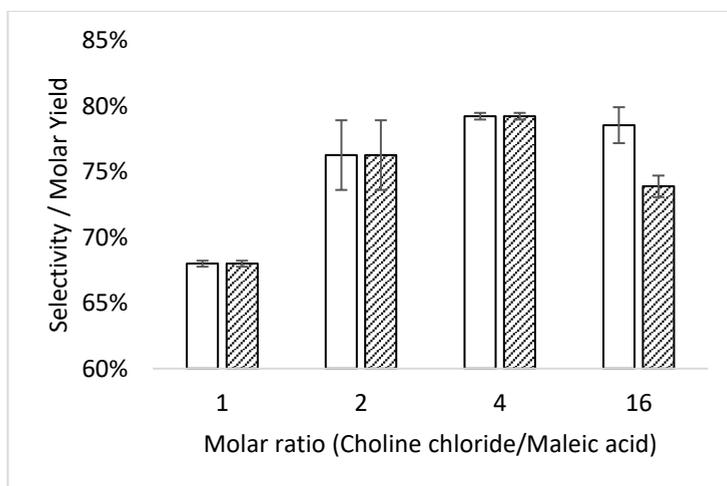


Figure 37: Comparison of selectivity and 5-HMF yields after one hour at 90 °C at several choline chloride/maleic acid molar ratio (5-HMF selectivity: blank, 5-HMF molar yield: shaded).

This encouraging result demonstrates that the acidic component proportion in LTTMs can be diminished without necessarily compromising mixture stability while enhancing dehydration selectivity. The reduced amounts of acid in LTTMs could improve safety by limiting cytotoxicity and facilitate mixture disposal after several dehydration cycle by increasing biodegradability.¹⁸⁵ These findings strengthen the potential of biodegradable LTTMs in future biomass transformation processes.

3.3. 5-HMF simultaneous production and extraction

To check that 5-HMF could be recovered from the LTTMs, dehydration experiments in the presence of ethyl acetate were performed. Ethyl acetate (5 ml) was added to two different LTTM's (2 g): Ch-CA (4:1) and Ch-MeA (4:1). The Ch-CA (4:1) mixture was prepared as the other LTTMs and contains also 15 wt% of water. Two phases were observed for each mixture. Treatment temperature was kept at 70 °C, below ethyl acetate boiling point to avoid the development of a high pressure within a closed vessel. These tests were compared to treatments without ethyl acetate to observe a potential effect of the extraction phase on 5-HMF yield. After two hours, the LTTM and ethyl acetate phases were separated and 5-HMF was quantified in both phases. The obtained 5-HMF molar yields are shown in **Figure 38**.

Residual D-fructose was observed in the LTTM phase but no trace of the monosaccharide was found in ethyl acetate. 5-HMF yield seem slightly improved in the presence of the second phase but this results from a superior D-fructose conversion. Without ethyl acetate, D-fructose conversion achieved in Ch-CA (4:1) and Ch-MeA (4:1) were 23.56 ± 1.64 % and 67.77 ± 3.01 % respectively. In the biphasic system, conversions were increased to 30.22 ± 1.35 % and 76.45 ± 3.00 %. Consequently, the selectivity in the absence and presence of ethyl acetate remained similar (68.23 ± 5.38 % and 68.83 ± 9.00 % for the Ch-CA (4:1) mixture and 67.40 ± 8.57 % and 67.74 ± 6.40 % for the Ch-MeA (4:1) mixture).

Shifting treatment temperature from 90 °C to 70 °C decreased the selectivity observed for Ch-MeA (4:1) from 77.20 ± 0.81 % to 67.40 ± 8.57 %. The selectivity achieved with the Ch-CA (4:1) mixture (68.23 ± 5.38 %) at 70 °C suggests once again that reducing proportion of the acidic LTTM component has a positive impact considering the selectivity observed for the Ch-CA (1:1) mixture (61.77 ± 1.16 %).

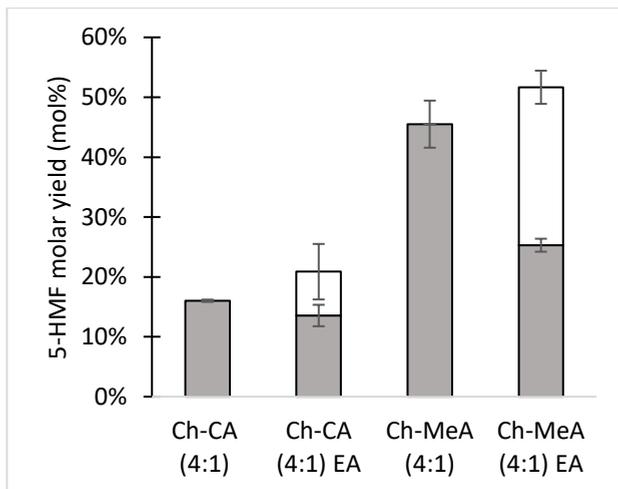


Figure 38: Effect of 5-HMF simultaneous extraction with ethyl acetate after 2 hours at 70 °C on D-fructose dehydration in Ch-CA and Ch-MeA at a 4:1 molar ratio between choline chloride and organic acid. (Extracted 5-HMF: blank, 5-HMF in LTTM phase: shaded).

For the Ch-CA (4:1) and Ch-MeA (4:1) biphasic systems, respectively 33.50 ± 15.92 % and 50.97 ± 2.74 % of the produced 5-HMF was recovered in the ethyl acetate phase. The acidic component choice has therefore an impact on the partition coefficient of 5-HMF and is crucial to optimize the extraction step. While this extraction experiment shows that recovery of 5-HMF from LTTMs is possible, many efforts still have to be made. Assuming that the selective recovery of 5-HMF can be achieved, LTTM phase recycling will be necessary to ensure competitiveness at industrial scale.

The work of Hu and coworkers (2008) demonstrated that LTTM recycling is possible. The authors recycled their citric acid/ choline chloride LTTM 8 times.¹⁸¹ After the 4th recycling, they removed water generated by the dehydration of fructose by drying their LTTM to maintain the 5-HMF yield to its initial value.

3.4. Role of water in dehydration required temperature

LTTM's based on natural components offer a cheaper alternative to ionic liquid while being biodegradable and easy to prepare. Their catalytic performances are close to those of ionic liquids. Nonetheless, the presented LTTMs contain high concentrations of chloride anions and organic acids which make them corrosive.¹¹⁴ The use of corrosive reaction media implies additional costs for the dehydration process. Corrosiveness should therefore be reduced. We showed in this work that the amount of acid in LTTMs could be reduced however chloride anions remain corrosive, especially at high temperature in the presence of water. One way to decrease the corrosion rate is

to decrease the treatment temperature and limit the presence of water. Since it has been mentioned that fructose dehydration energy barrier was mainly solvent induced, we chose to investigate the effect of water on the temperature required to dehydrate fructose to 5-HMF. We studied the influence of water in the Ch-MeA (2:1) mixture. Without the initial presence of water, a 5-HMF yield of 77.49 ± 1.01 % was achieved after 1h30 at 80 °C. To check a potential inhibitory effect of water at low temperature, we replaced it by several organic solvents for fructose dehydration tests at 60 °C. In a first time, 2 ml of water, methanol, ethanol and isopropanol were added to 1.4 g of a (2:1) choline chloride/maleic acid mixture (without water). After 5h30, the following 5-HMF yield were obtained: 0, 3.21 ± 0.15 , 15.95 ± 0.03 and 41.45 ± 0.53 %. The same test was performed a second time but the amount of added solvents was reduced to 0.6 ml. This time, the following 5-HMF yields were achieved: 7.69 ± 0.02 , 62.45 ± 1.69 , 72.80 ± 0.01 and 79.03 ± 0.17 %. It can be concluded that water strongly limits the catalysis of fructose dehydration by LTTMs components at low temperature. The generation of water during the reaction nevertheless remains unavoidable and has to be controlled. These preliminary results show that the required temperature for D-fructose dehydration can be dramatically reduced if water is not initially present. Water however reduces LTTM preparation time and viscosity. Its replacement by a small quantity of organic solvent solves these problems while allowing a low treatment temperature which could be a strong argument in favor of the use of a biphasic system for simultaneous extraction of 5-HMF.

Further experiments were conducted to compare cosolvents effects on a molar basis as described in **Figure 39**. Polar aprotic solvents (DMSO and DMF) were also investigated. D-fructose conversion and 5-HMF yield increase in the following order: water < methanol < ethanol < 2-propanol = DMSO = DMF. This result suggests that smaller protic solvents molecules possess a stronger inhibitory effect on the reaction. Given the suspected role of halide anions in the dehydration of D-fructose, solvation of those anions is expected to affect the reaction and small protic solvent molecules could likely better “shield” chloride anions, decreasing the chances of interaction with monosaccharides. In polar aprotic solvents, anions are more prone to interact with D-fructose which is in accordance with the high yield (80% 5-HMF) observed. This phenomenon will be further discussed in chapter 6. A control test with only maleic acid in DMSO was performed and confirmed once again that the addition of choline chloride is beneficial to the reaction. In the absence of choline chloride, 5-HMF yield reached 48.04 ± 2.04 % while the presence of the chloride salt improved it to 79.56 ± 4.78 %.

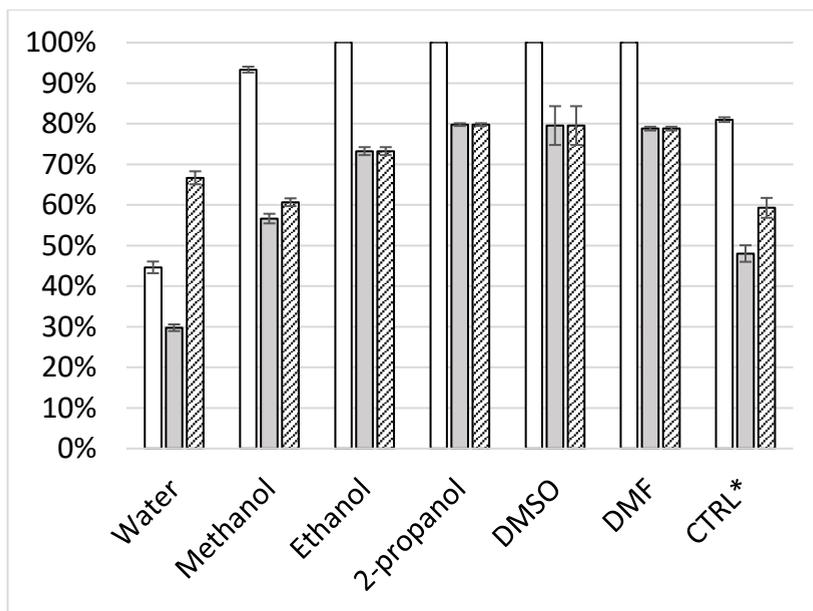


Figure 39: effect of cosolvents on D-fructose dehydration to 5-HMF in a mixture of choline chloride and maleic acid (2:1 mol) at 60 °C (5h30, 210 rpm). Practically, 10 mmol of choline chloride, 5 mmol of maleic acid, 25 mmol of cosolvent and 0.56 mmol of D-fructose were mixed and put into a water bath at 60°C. * This control test contained only 25 mmol of DMSO, 5 mmol of maleic acid and 0.56 mmol of D-fructose. White bars: D-fructose conversion, grey bars: 5-HMF molar yield, hatched bars: 5-HMF selectivity.

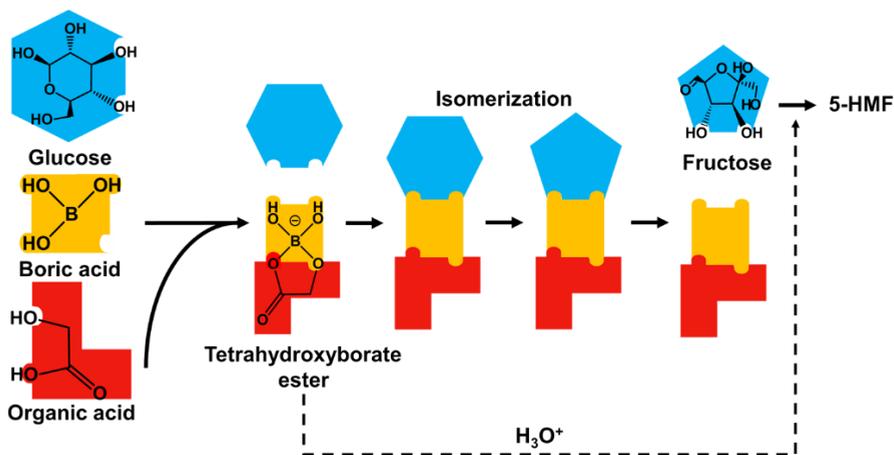
4. Conclusions

In LTTMs, choline chloride and organic acids have a synergic effect on the dehydration of D-fructose to 5-HMF. More specifically, the presence of chloride anions in acidic LTTMs seem to increase reaction selectivity. While the rehydration of 5-HMF to levulinic and formic acids is limited in these media (molar yield lower than 4%), small amounts of humins are generated. Regarding the acidic component of the LTTMs, maleic and citric acids are especially selective to catalyze dehydration among all the tested acids. Their selectivity is weakly influenced by fructose conversion suggesting that those acids limit fructose molecules interactions. Finally, the acid proportion in LTTMs can be decreased to improve dehydration selectivity. Switching the choline chloride / maleic acid ratio from one to four allowed to improve the 5-HMF yield from 68 to 79 %.

Aldoses dehydration assisted by borate esters of α -hydroxyacids in low-transition-temperature mixtures

Adapted from:

Istasse T, Lemaur V, Debroux G, Bockstal L. Monosaccharides Dehydration Assisted by Formation of Borate Esters of α -Hydroxyacids in Choline Chloride-Based Low Melting Mixtures. *Front. Chem.* 2020;8:1–15.



Graphical abstract 4: mechanism for glucose conversion to 5-HMF in the presence of boric acid and α -hydroxyacids.

Abstract:

The synthesis of 5-hydroxymethylfurfural (5-HMF) and 2-furfural (2-F) by hexoses and pentoses dehydration is considered as a promising path to produce materials from renewable resources. Low-transition-temperature mixtures (LTTMs) enable selective (> 80%) dehydration of ketoses to furan derivatives at moderate temperature (< 100 °C). Among LTTMs, deep eutectic solvents (DES) prepared by mixing relatively cheap molecules have been proposed as an alternative to ionic liquids (ILs) for 5-HMF and 2-F synthesis. However, the production of those building blocks from aldoses generally requires higher temperatures and an isomerization catalyst. Chromium trichloride has been reported as one of the most efficient catalyst but its kinetic inertness could limit its performances below 100 °C. Consequently, we investigate herein boric acid catalysis of aldoses dehydration in LTTMs based on choline halides and organic acids at 90 °C. Boric acid enables isomerization of aldoses to ketoses to a limited extent in choline chloride/organic acid based LTTMs (e.g. 5% 5-HMF yield and 23% glucose conversion after one hour at 90 °C with maleic acid). Combined with α -hydroxyacids however, the reaction is faster and more selective (e.g. 19% 5-HMF yield and 61% glucose conversion after one hour at 90 °C). The synergy between α -hydroxyacids and boric acid is explained by formation of tetrahydroxyborate esters (THBE). Compared to boric acid, THBE reaction with glucose is energetically favored. THBE formation is associated with H_3O^+ release in the medium increasing its acidity. Humins are the main observed side-product of the reaction, generated from aldol addition/ condensation involving monosaccharides and furan products. Their formation is favored by the excessive acidity generated in-situ and possibly by residual boric acid. We demonstrate that boric acid catalysis is not straightforward and that the use of THBE under moderate

acidity should be further investigated to limit humins formation and promote furan derivatives synthesis.

Key words:

Low-transition-temperature mixtures, 5-hydroxymethylfurfural, glucose, choline chloride, boric acid

1 Introduction

Synthesis of renewable platform chemicals from biomass carbohydrates is considered as a milestone in the development of an efficient use of renewable resources. Among these chemicals, 5-hydroxymethylfurfural (5-HMF) and 2-furfural (2-F), resulting from the dehydration of hexoses (e.g. D-fructose, D-glucose) and pentoses (D-xylulose, D-xylose) respectively, receive particular attention.^{186,187} Both platform chemicals possess numerous applications in material synthesis including plastics, thermoset resins, pharmaceuticals and fuels.^{20,186} Their production was intensively investigated and high temperature processes ($> 150\text{ }^{\circ}\text{C}$) were generally required to achieve acceptable selectivity of the reaction.^{23,24,53} However, research is currently turned towards eco-friendly and low-temperature processes. In this sense, the use of ionic liquids (ILs) was studied in order to perform dehydration of monosaccharides to 5-HMF and 2-F at moderate temperature ($100\text{ }^{\circ}\text{C}$) with high selectivity ($> 80\%$).^{86,111,132}

ILs have been highlighted as promising solvents due to their tunable properties resulting from the mixing of different cationic and anionic species.^{112,188} ILs exhibit major advantages such as low vapor pressure, lower temperature required for selective reactions, and potential recyclability. Nevertheless, most of them remain expensive and their synthesis can require several reaction and purification steps.¹⁸⁸ Moreover, constitutive cations like pyridinium and imidazolium can be toxic as they may inhibit crucial enzymes like acetylcholinesterase, which plays an important role in nerve response and function.¹⁸⁹ Besides ILs, deep eutectic solvents (DES) are another type of low-transition-temperature mixtures (LTTMs) which has been investigated. Their components are cheap, abundant and less hazardous than ionic liquids and include in particular monosaccharides, organic acids, choline chloride, amino acids and water.^{121,178,180,185,188} LTTMs are obtained by mixing and heating together two or three of the aforementioned components in proper ratio. This very simple synthesis process enables a 100% carbon efficiency.¹⁹⁰

The efficiency of LTTM's composed of choline chloride and organic acids to perform D-fructose dehydration to 5-HMF at $60\text{ }^{\circ}\text{C}$ was demonstrated.¹³⁰ However, it is worth noting that even though the synthesis of furan derivatives from ketoses (e.g. D-fructose, D-xylulose) is straightforward, their production from aldoses (e.g. D-glucose, D-xylose) remains challenging. Selective and low-cost dehydration process of those abundant hexoses has still to be developed.^{186,187}

Contrarily to ketoses, aldoses cannot be directly dehydrated to furan derivatives. They first have to undergo isomerization to ketoses or ring contraction, which are mechanisms that are less energetically favored compared to side-reactions including polymerization reactions.^{60,139,145} In order to improve 5-HMF and 2-F formation, isomerization catalysts are added to the reaction medium (**Figure 40**). CrCl_3 is

generally reported as the most efficient catalyst as it promotes D-glucose isomerization to D-fructose by coordination of the metallic center to the monosaccharide, facilitating the required hydride shift.^{101,161} However, trivalent chromium is kinetically inert, which means that high temperatures are required to introduce new chemical species in the coordination sphere.¹⁵⁹ This could limit its potential for reaction catalysis below 100 °C. As an alternative, boric acid has been studied as isomerization catalyst. This cheap and abundant non-metallic Lewis acid favors isomerization through an enediol mechanism rather than through hydride shift. However, its performances in aldoses dehydration catalysis are mitigated (10-40% yield) compared to the results obtained with metallic catalysts (80% yield with CrCl₃).^{113,175}

In contrast to these trends, Matsumiya and Hara (2014) used boric acid in LTTMs composed of choline dihydrogen citrate and organic acids and achieved a 60% 5-HMF yield after 4 h at 140°C. Only 1-3% 5-HMF were generated with CrCl₂ or CrCl₃ in close conditions. More surprisingly, the use of choline chloride rather than choline dihydrogen citrate did not lead to 5-HMF yields above 5% which seems in contradiction with the elements highlighted in the previous chapter. Those intriguing observations encouraged us to conduct aldoses dehydration experiments using boric acid as a catalyst in choline chloride-based media.¹⁹¹

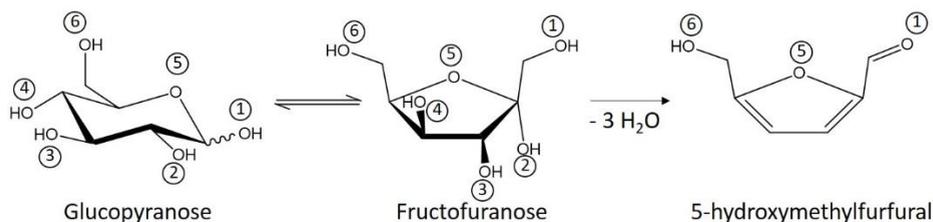


Figure 40: Glucose conversion to 5-hydroxyméthylfurfural (with labelling of oxygen atoms)

The aim of this work is to better understand the mechanism of action of boric acid as catalyst in order to explain his limited performances compared to metallic catalyst as well as the possibilities of improvement. Consequently, we explored 5-HMF and 2-F formation from monosaccharides in LTTMs composed of choline chloride, boric acid and organic acids. Firstly, the dehydration of several hexoses and pentoses is performed in a mixture of choline chloride / maleic acid with and without boric acid. Then dehydration of D-glucose is further investigated in mixtures of choline chloride/boric acid combined with different organic acids in an attempt to identify an effect of the organic acid structure (number of carboxylic acid functions, carbon chain length and presence of additional hydroxyl moieties). The role of halide anions is explored by comparing mixtures with choline chloride, choline bromide and choline iodide. 2D HSQC NMR (¹H-¹³C) analyses are performed to confirm the production of 5-HMF and identify other soluble side-products. A reaction mechanism is proposed for the

conversion of D-glucose to 5-HMF based on experiments and Density Functional Theory (DFT) calculations. The formation of undesirable polymeric substances called humins was also investigated through experiments with different LTTMs, infrared spectroscopy and 2D HSQC NMR (^1H - ^{13}C) analyses.

2 Material and methods

2.1 Chemicals

D-(-)-fructose (99%), choline chloride (99%), maleic acid (99%), m-hydroxybenzoic acid (99%) and L-(+)-tartaric acid (>99%) were purchased at Acros Organics. D,L-malic acid (>99%), o-hydroxybenzoic acid (>99.0%), p-hydroxybenzoic acid (>99%), 3,4-dihydroxybenzoic acid (>97.0%), 1,2-dihydroxybenzene (>99%), D-(+)-xylose (>99%) and 5-HMF (>99%) were acquired from Sigma-Aldrich. Succinic acid (99%) and D,L lactic acid (>88%) were obtained from Fischer Chemical. Boric acid (99.5-100.5%) and 2-F (>98%) were purchased at Merck. Formic acid (99%) was acquired from Biosolve LTD. Acetic acid (99-100%), citric acid (99.8%) and anhydrous D-(+)-Glucose (GPR Rectapur) were obtained from VWR Chemicals. D-(+)-mannose (>99%) and D-(-)-arabinose were purchased at Fluka. Anhydrous oxalic acid (98%) and choline iodide (98%) were obtained from Alfa Aesar. Benzoic acid (>99.5%) was purchased at Roth. Choline bromide (>98.0%) and glycolic acid (>98.0%) were obtained from TCI Chemicals. All chemicals were used as received. Each LTTMs was stored in a sealed vessel directly after preparation.

2.2 Dehydration of monosaccharides in choline chloride/maleic acid

A mixture of choline chloride and maleic acid (molar ratio: 2/1) was prepared by mixing both solid components in a closed vessel at 90 °C until a liquid phase was obtained. The choice of both components and their ratio is based on previous work.¹³⁰ Except if specified, all reactions were carried out under air.

Preliminary tests were performed in sealed glass tubes by adding 2 g of this mixture (corresponding to 10 mmol of choline chloride and 5 mmol of maleic acid) to hexoses (0.56 mmol) or pentoses (0.56 mmol). Mixtures were homogenized prior to the test. Samples were then heated at 90 °C in a water bath with an agitation of 210 rpm. After the treatment, mixtures were immediately dissolved with water, filtered on 0.45 μm syringe filter and stored at -20 °C.

For the preliminary tests with boric acid, a mixture of choline chloride, maleic acid and boric acid was prepared (molar ratio: 10/5/1). For dehydration tests, 2 g of the

LTTMs were again added to 0.56 mmol of hexose or pentose, which correspond to 9.8 mmol of choline chloride, 4.9 mmol of maleic acid and 1 mmol of boric acid in each tube.

2.3 Comparison of organic acids in mixtures with choline chloride and boric acid for the dehydration of D-glucose

Compared to the preliminary experiments, the ratio between boric acid and the organic acid in LTTMs was rapidly optimized regarding 5-HMF yield. Considering the large number of organic acids under consideration, LTTMs were directly prepared in glass tubes by homogenizing 0.56 mmol of D-glucose (0.56 mmol) with choline chloride (10 mmol), the organic acid (2.5 mmol) and boric acid (2.5 mmol). Samples were heated at 90 °C during 1 h at 210 rpm. During the first 5 min of the treatment, samples were again thoroughly homogenized to ensure the rapid formation (about 5 min) of the liquid phase. After the treatment, mixtures were immediately dissolved with water, filtered on 0.45 µm syringe filter and stored at -20 °C. The addition of water cools down the reaction medium and inhibit monosaccharides dehydration as demonstrated in previous work.¹³⁰ The same procedure was followed for the tests with benzoic acid derivatives.

2.4 Inhibition of D-glucose dehydration by addition of 1,2-dihydroxybenzene

Additional tests were performed to identify a potential inhibition of the reaction by other molecules with a vicinal diol moiety. D-glucose (0.56 mmol) was dehydrated in LTTMs prepared as described in **Table 5**. Unlike the other LTTMs mentioned in this work, 10 wt% water was added and these assays were performed at 100 °C to ensure the formation of a homogeneous liquid phase.

Table 5 : Organic acids and phenol derivatives added to choline chloride (10 mmol) and boric acid (2.5 mmol) for LTTMs preparation

Assay	Organic acid (2.5 mmol)	Phenol and hydroxyphenol (2.5 mmol)
1	Benzoic acid	1,2-dihydroxybenzene
2	/	Phenol
3	/	1,2-dihydroxybenzene
4	<i>o</i> -hydroxybenzoic acid	Phenol
5	<i>o</i> -hydroxybenzoic acid	1,2-dihydroxybenzene
6	<i>o</i> -hydroxybenzoic acid	/

2.5 Dehydration of monosaccharides in choline chloride/boric acid/glycolic acid

0.56 mmol of hexoses or pentoses were heated at 90 °C in a mixture of choline chloride/boric acid/glycolic acid (molar ratio: 4/1/1) during 1h at 210 rpm. The LTTMs was prepared beforehand. Samples were prepared as previously mentioned.

2.6 Effect of choline halides on 5-HMF formation

Choline chloride, bromide or iodide (10 mmol) was mixed with boric acid (2.5 mmol), glycolic acid (2.5 mmol) and D-glucose (0.56 mmol) and heated at 90 °C during 1h at 210 rpm following the same protocol than for the other experiments.

2.7 Acidity comparison between LTTMs

Using a UV-1800 Shimadzu spectrophotometer, the absorbance of different mixtures of choline chloride (20 mmol), boric acid (5 mmol) and organic acid (5 mmol) containing 13 wt% water and 50 µL of thymol blue in ethanol (0.05 g/10 ml) was measured at 548 nm. The presence of water ensures the formation of a homogeneous liquid mixture during the absorbance measurement at ambient temperature. To perform the tests with choline chloride/H₃BO₃ (molar ratio: 2/1) with or without hydrochloric acid, HCl (35.7%) was added to a 3 g mass of mixture to reach the desired concentration. Different amounts of water were added for each HCl concentration in order to keep the total water content at 13 wt%. 50 µL of thymol blue in ethanol (0.05 g/10 ml) were again added before homogenization and absorbance measurement. The tests with different HCl concentrations were performed to confirm the increase of the absorbance at 548 nm with the acidity (see **Supplementary Table 1**).

2.8 Analyses of 5-HMF and monosaccharides

Monosaccharides were quantified by high performance liquid chromatography (HPLC) using a Ca Rezex RPM Monosaccharides column heated at 80 °C with a water flow of 0.6 mL/min. Detection was performed with an evaporative light scattering detector (40 °C, gas flow of 0.8 L/min). 5-HMF and 2-F were separated on a HPX-87H Aminex column heated at 45 °C using a 5mM H₂SO₄ aqueous solution at a 0.6 mL/min flow. UV detection was used to measure 5-HMF and 2-F concentrations at 284 nm. Monosaccharide conversion, 5-HMF/2-F yield and selectivity were calculated as follows:

$$\text{Residual monosaccharides (\%)} = \frac{\text{Final moles of monosaccharides}}{\text{Initial moles of monosaccharides}} \times 100$$

$$\text{Monosaccharides conversion (\%)} = 100 - \text{Residual monosaccharides}$$

$$5 - \text{HMF or 2 - F yield (\%)} = \frac{\text{Moles of 5 - HMF or 2 - F}}{\text{Initial moles of monosaccharides}} \times 100$$

$$\text{Selectivity (\%)} = \frac{(5 - \text{HMF or 2 - F yield})}{\text{Monosaccharide conversion}} \times 100$$

2.9 NMR analyses

A LTTMs composed of choline chloride, boric acid and oxalic acid (molar ratio 4/1/1) was prepared with 10 wt% of deuterated water. Mixtures of LTTMs and D-glucose (20 to 40 wt%) were then heated at 80 °C during 10 min or 60 min to easily distinguish reaction substrate from products. The high load of D-glucose enabled a better discrimination of monosaccharides and choline chloride signals. Samples without D-glucose were also prepared to rapidly identify LTTMs signals.

The reaction was quenched by addition of deuterated water (12.5 ml of water /g of mixture) containing an internal standard (0.75 wt% of 3-(trimethylsilyl)propionic-2,2,3,3 d4 acid sodium salt) and the resulting NMR samples solutions were filtered (0.45 µm).

2D HSQC (¹H-¹³C) NMR spectra of these solutions were recorded at 298 K on a Bruker Ultrashield 700 Plus equipment operating at 700 MHz for ¹H and 175 MHz for ¹³C. All NMR experiments were performed using a triple resonance inverse-probe. The datasets were acquired with 2048 and 512 data points for the f2 (¹H) and f1 (¹³C) dimensions, with spectral widths of 11 161 and 38463 Hz, respectively. Four scans were performed and the relaxation delay was 2 s.

2.10 Mass spectrometry

Mass spectrometry analyzes in positive mode were performed using direct injection in a Bruker Esquire HCT mass spectrometer equipped with an electrospray and ions trap. The sample was produced from the reaction of D-glucose (0.56 mmol) at 90 °C in a mixture of choline chloride/boric acid/glycolic acid (10 mmol / 2.5 mmol / 2.5 mmol) during 1h at 210 rpm followed by dilution in an appropriate amount of water (with formic acid and ammonium formate). The used parameters are summarized in **Table 6**.

Table 6 : mass spectrometry parameters

Nebulizer (psi)	15.0	Skimmer (V)	69.3
Dry gas (l/min)	8.0	Cap exit (V)	156.6
Dry temp. (°C)	365	Oct. 1DC (V)	11.53
Scan (m/z)	50 - 900	Oct. 2DC (V)	1.80
Capillary (V)	-4500	Trap drive	34.8
End plate offset (V)	-500	Gas	Nitrogen

2.11 Density Functional Theory calculations

The ground-state geometries of all molecules were optimized at the Density Functional Theory (DFT) level using the B3LYP functional and a 6-31G** basis set. The PCM (Polarizable Continuum Model)¹⁹² scheme was coupled to all DFT calculations to account for solvent (dichloromethane) effects. Within this model, the solute is embedded in a shape-adapted cavity surrounded by the solvent implicitly described by a dielectric continuum that is characterized by a dielectric constant. The dielectric constant of dichloromethane ($\epsilon = 8.93$) was used in this work following the approach of Stahlberg et al. (2011) for their study of D-glucose dehydration in ionic liquids containing boric acid.¹¹³ The literature about LTTMs dielectric constant being scarce, this choice enables comparison between both works to obtain mechanistic insights. For each optimized geometry, a normal-mode analysis was performed for the thermochemical analysis (using a temperature of 298.15K) and it was verified that an energy minimum was obtained. The reported Gibbs free energies were then estimated as the energy difference between the sum of the energies of the isolated products and the sum of the energies of the isolated reactants. All the DFT calculations were performed with the Gaussian16 package.¹⁹³

3 Results and discussion

3.1 Dehydration of monosaccharides in LTTMs

In a preliminary experiment, several hexoses (D-fructose, D-glucose and D-mannose) and pentoses (D-xylose and D-arabinose) were heated during two hours in a mixture of choline chloride and maleic acid at 90 °C. Although maleic acid is known to efficiently dehydrate D-fructose to 5-HMF, this attempt did not lead to the apparition of 5-HMF from D-glucose and D-mannose or 2-F from D-arabinose.¹⁹ Only 2.26 ± 0.04 % of 2-F was generated from D-xylose. As expected, large amounts of 5-HMF were produced

from D-fructose (71.43 ± 1.05 %). Conversion of monosaccharides in the LTTM is depicted in **Figure 41** (5-HMF and 2-F yields evolution with time are provided in **Supplementary Figure 3**). The conversion of all monosaccharides is above 70 % in less than an hour at 90 °C. D-fructose, a ketose, is converted faster than the other monosaccharides (aldoses) as suggested by the work of Van Putten and Soetedjo (2013).⁶³ The selectivity of the dehydration of aldoses to 5-HMF and 2-F is however insignificant. Esterification of monosaccharides with maleic acid is a possible side-reaction. Esterification between citric acid and glycerol has been reported to occur even at 90 °C.¹⁹⁴ Consequently, a similar reaction with monosaccharides seems likely to occur in mixtures of organic acids and choline chloride. It could explain the observed plateau trends in aldoses conversion (**Figure 41**) assuming they are in equilibrium with their esters. Fructose, being easily dehydrated to 5-HMF, rapidly achieves 100% conversion.

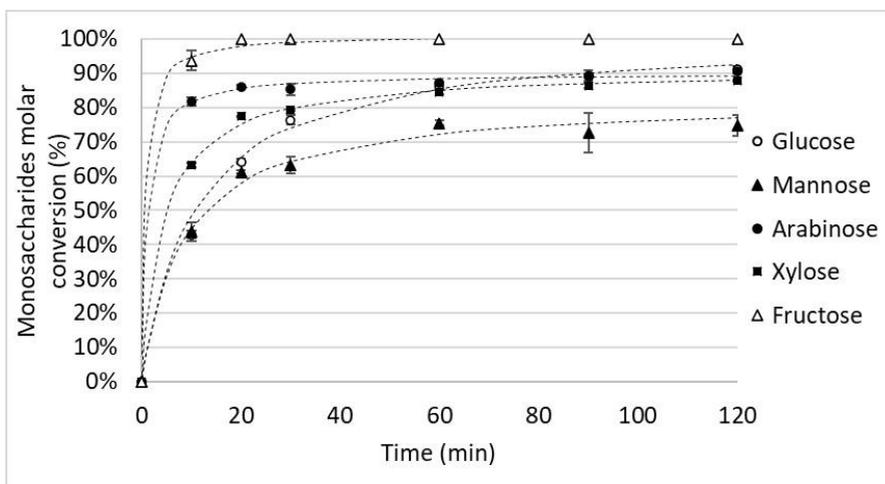


Figure 41 : Evolution of hexoses (0.56 mmol) and pentoses (0.67 mmol) molar conversion (%) in a mixture of choline chloride (10 mmol) and maleic acid (5 mmol) at 90 °C.

After addition of boric acid to the choline chloride/maleic acid mixture, 5-HMF and 2-F were produced from all the tested monosaccharides, as described in **Table 7**. 5-HMF yields of 55.72 ± 0.98 %, 6.54 ± 0.67 % and 4.02 ± 0.15 % were achieved from D-fructose, D-glucose and D-mannose, respectively. 2-F yields of 9.56 ± 1.42 % and 4.80 ± 0.06 % were obtained from D-xylose and D-arabinose. The selectivity of the conversion of those monosaccharides to furan derivatives reached 55.72 ± 0.98 (D-fructose), 11.88 ± 1.87 (D-glucose), 5.35 ± 0.21 (D-mannose), 16.71 ± 2.63 (D-xylose) and 6.92 ± 0.20 % (D-arabinose).

Table 7 : monosaccharides conversion and 5-HMF and 2-F yields/selectivity obtained after treatment of several hexoses (0.56 mmol) and pentoses (0.67 mmol) in a mixture of choline chloride (10 mmol) and maleic acid (5 mmol) with or without boric acid (1.08 mmol) during 1 h at 90 °C. 5-HMF is the dehydration product obtained from glucose, fructose and mannose. 2-furfural is the dehydration product obtained for xylose and arabinose.

Mono-saccharides	No boric acid			Boric acid		
	<u>Conversion</u> (%)	<u>Yield</u> (%)	<u>Selectivity</u> (%)	<u>Conversion</u> (%)	<u>Yield</u> (%)	<u>Selectivity</u> (%)
Glucose	86.41±0.94	<1	<2	55.37±3.43	6.54±0.67	11.88±1.87
Fructose	100.00±1.00	71.43±1.03	71.43±1.03	100.00±1.00	55.72±0.98	55.72±0.98
Mannose	75.52±0.67	<1	<2	75.12±0.41	4.02±0.15	5.35±0.21
Xylose	84.56±0.65	1.91±0.05	2.26±0.04	57.28±0.77	9.56±1.42	16.71±2.63
Arabinose	87.24±0.32	<1	<2	69.33±2.27	4.80±0.06	6.92±0.20

The reaction selectivity increased for all the aldoses in the presence of boric acid but the production of 5-HMF from D-fructose, a ketose, was more selective in the absence of boric acid (71.43 ± 1.05 %). Considering that boric acid enables the reversible isomerization of D-glucose to D-fructose, this observation is not surprising and could be a first clue that D-glucose conversion to 5-HMF proceeds indeed through isomerization to D-fructose in the tested conditions. The presence of boric acid opens a new reaction path for D-fructose which consequently decreases the selectivity for 5-HMF. This point is further discussed after DFT calculations and additional experiments.

Boric acid also seems to slow monosaccharides conversion. (Table 7) This phenomenon can be expected since borate ester formation with monosaccharides likely reduces the reactivity of the involved -OH moieties. In this regard, the amount of boric acid in respect to monosaccharides heavily impacts their reactivity and the excessive presence of boric acid will promote the formation of borate esters with two molecules of boric acid per molecule of monosaccharide, completely stopping their conversion.

For the next set of experiments, the effect of the organic acid structure was investigated. LTTMs were prepared by mixing each acidic component presented in Figure 42 with boric acid and choline chloride (molar ratio: 1/1/4).

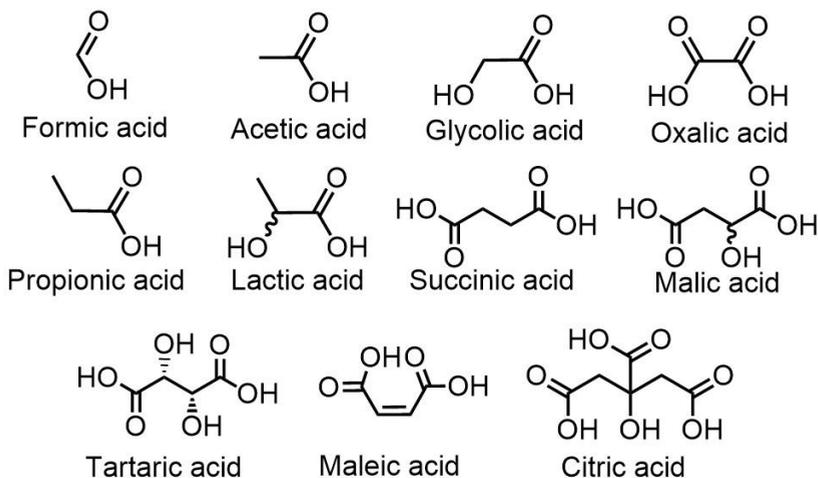


Figure 42: Organic acids used as LTTMs components for the first set of experiments

The 5-HMF yields obtained from D-glucose after 1 h at 90 °C are described in Figure 43 (the corresponding conversion and selectivity are provided in **Supplementary Figures 4 and 5**). Noticeable differences were observed between acids: some organic acids lead to 5-HMF yields above 15 % (hatched bars, **Figure 43**) while 5-HMF yields lower than 6% are achieved with the others (grey bars, **Figure 43**). Strikingly, large amounts of humins were generated with all the acids allowing significant 5-HMF formation. This trend was also observed for the conversion of the monosaccharide: more than 60 % conversion was achieved in the presence of lactic, oxalic, tartaric, malic, citric or glycolic acids while less than 30 % of D-glucose was converted in the presence of formic, acetic, propionic, maleic or succinic acids. Considering selectivity for 5-HMF, the same trend was observed except for the selectivity of maleic acid (22.33 ± 2.10 %), which was comparable to those of lactic, oxalic, tartaric, malic, citric and glycolic acids (18-28 %). The best selectivity was obtained with lactic and glycolic acids (28.42 ± 0.27 and 26.10 ± 0.11 % respectively). A control test was performed in the same conditions with a mixture of choline chloride and boric acid (molar ratio: 2/1). Only 16.19 ± 2.32 % of D-glucose was converted and a 5-HMF yield of 3.24 ± 0.07 % was reached (corresponding to a 20.30 ± 2.70 % selectivity).

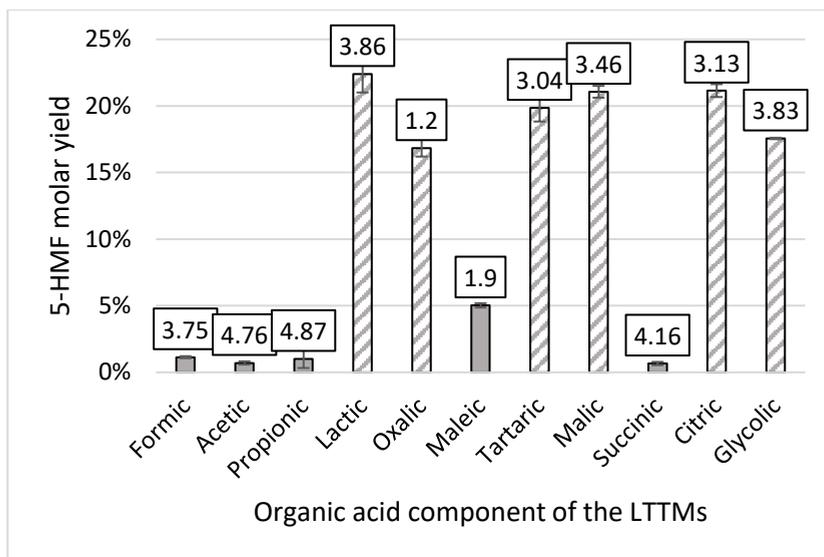


Figure 43: 5-HMF yields obtained from D-glucose (0.56 mmol) in mixtures of choline chloride (10 mmol), organic acid (2.5 mmol) and boric acid (2.5 mmol) after 1 h at 90 °C, 210 rpm. The pKa of each organic acid component is depicted above each bar. Hatched bars correspond to α -hydroxyacids.

In a first attempt to understand those results, the pKa of the tested organic acids in aqueous solution were compared (displayed in **Figure 43**). In LTTMs, the dissociation constant of acids could differ from the aqueous medium. Abbott and coworkers (2017) studied the Brønsted acidity of several organic acids (oxalic, salicylic, succinic, citric, benzoic, lactic, propanoic and acetic acids) in LTTMs composed of choline chloride and ethylene glycol, glycerol or urea.¹⁹⁵ The authors demonstrated that these organic acids were only slightly less dissociated in LTTMs, with pKa values only 0.2 - 0.5 higher than in water.¹⁹⁵ The pKa values in water seem therefore appropriate to compare the acidity of the LTTMs prepared in this work. However, no relationship seems to emerge between the acid pKa and the observed 5-HMF yields. By comparing the chemical structures of the organic acids, it appeared that all α -hydroxyacids allowed a faster and more selective reaction.

3.2 Investigations about dehydration catalysis by boric acid and α -hydroxyacids

Additional tests were consequently performed to confirm and identify the role of the proximity between the –OH –COOH groups in the dehydration of D-glucose to 5-HMF. New dehydration tests were performed in mixtures of benzoic acid or derivatives with boric acid and choline chloride (molar ratio: 1/1/4) during 1 h at 90 °C. Those benzoic acid derivatives are depicted in **Figure 44**. The choice of benzoic acid derivatives as

model compounds to better understand the reaction is based on several elements. Firstly, benzoic acid derivatives are widely available at moderate price and show a large diversity of chemical structures. Secondly, compared to linear molecules possessing similar functions, they generally have higher degradation temperature and present a rigid structure which does not enable conformation changes (chemical functions on the benzene ring are always at the same distance).

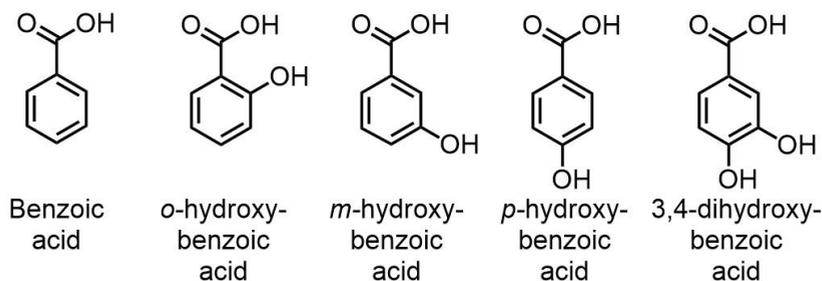


Figure 44: Derivatives of benzoic acid used as LTTMs components for the second set of experiments

While benzoic, m-hydroxybenzoic and p-hydroxybenzoic acids did not enable the production of more than 2 % of 5-HMF (**Figure 45**), o-hydroxybenzoic acid rapidly converted D-glucose to 5-HMF (yield of 20.60 ± 3.59 %), which confirmed the necessity of a -OH group nearby the carboxylic acid function. Again, humins rapidly appeared. Surprisingly, an intermediate 5-HMF yield of 9.11 ± 0.49 % was achieved with 3,4-dihydroxybenzoic acid suggesting that acids with a diol moiety also enhance the reaction.

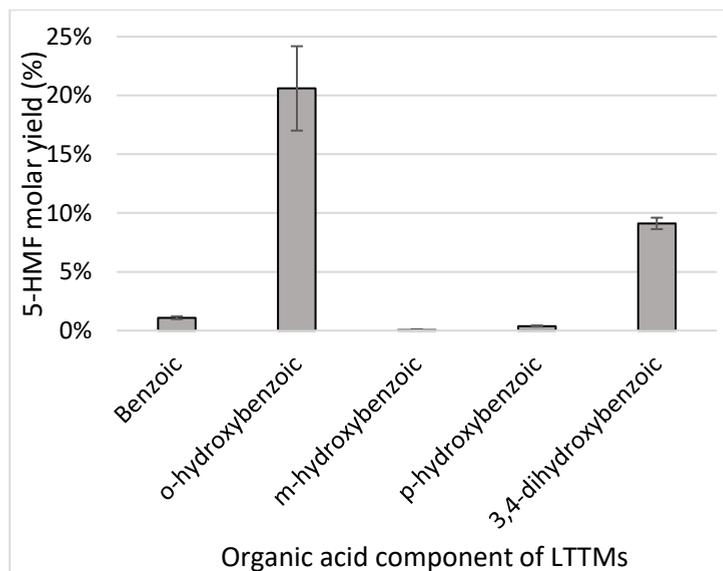


Figure 45: 5-HMF yields obtained from D-glucose (0.56 mmol) in mixtures of choline chloride (10 mmol), benzoic acid derivatives (2.5 mmol) and boric acid (2.5 mmol) after 1 h at 90 °C, 210 rpm.

An additional test with a mixture of benzoic acid and 1,2-dihydroxybenzene led to a low amount of 5-HMF (**Figure 46**, result 1). The involvement of a vicinal diol or a -OH moiety nearby the acid function was further confirmed when 1,2-dihydroxybenzene (2.5 mmol) was added to the mixture containing o-hydroxybenzoic acid (**Figure 46**, result 5). The resulting 5-HMF yield decreased significantly suggesting that 1,2-dihydroxybenzene interfered with D-glucose conversion to 5-HMF, most probably because of its vicinal diol moiety. It is worth noting that the mixture of choline chloride, boric acid and 1,2-dihydroxybenzene enabled the formation of 5-HMF without the addition of an organic acid (**Figure 46**, result 3), even at a lower extent.

The enhanced generation of 5-HMF and humins in the presence of boric acid and specific organic acids (α -hydroxyacids, o-hydroxybenzoic and 3,4-dihydroxybenzoic) led us to consider the formation of tetrahydroxyborate esters (THBE) as a potential explanation of the catalytic mechanism. Boric acid and its corresponding tetrahydroxyborate anion (THB) are known to reversibly form borate esters with monosaccharides. More generally, they can form borate esters with diols.^{169,196} Interestingly, boric acid and THB can also react with some organic acids with -OH group nearby the acid function. Oxalic, glycolic, tartaric and lactic acids THBE have been observed as well as o-hydroxybenzoic acid THBE.^{167,168,197} THBE involving one THB and two molecules of lactic acid or two molecules of monosaccharides have also been described.¹⁹⁷

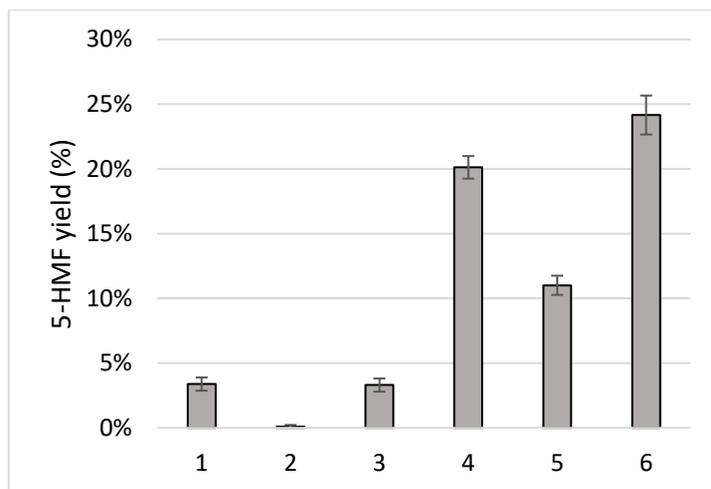


Figure 46: 5-HMF yield (%) from D-glucose heated 1h at 100 °C in mixtures of choline chloride, boric acid, organic acids and/or hydroxyphenol. Each mixture contains water (10 wt%). 1: benzoic acid + 1,2-dihydroxybenzene, 2: phenol, 3: 1,2-dihydroxybenzene, 4: o-hydroxybenzoic acid + phenol, 5: o-hydroxybenzoic acid + 1,2-dihydroxybenzene, 6: o-hydroxybenzoic acid

To get insights into the reaction mechanisms leading to the formation of 5-HMF from D-glucose, DFT calculations were performed and, in particular, the Gibbs free energies of selected reactions involving boric acid, α -hydroxyacid and/or a monosaccharide were estimated (**Figure 47**). The reaction of boric acid with the α -hydroxyacid is a more favorable process (I) than that with glucose (II), suggesting that organic acid-THBEs are first formed and then react with the monosaccharide. When considering D-glucose, the latter reaction is exergonic (III) and produces water molecules, which can lead to the formation of THB from boric acid. As found for boric acid, our calculations suggest that THB will also preferentially associate with the α -hydroxyacid (IV) than with D-glucose (V). Organic acid-THBEs are definitely the chemical species that will react with monosaccharides; the reaction between boric acid and D-glucose followed by the association with an organic acid is very unlikely. This result is consistent with previous works that demonstrated that THBEs formed with carboxylic acids were more stable than THBEs formed with diols of D-glucose or 1,2-dihydroxybenzene.¹⁹⁸ The lower pKa (9.3) of 1,2-dihydroxybenzene compared to D-glucose (>10) could consequently explain the inhibition presented in **Figure 46** (result 5). Interestingly, the calculations show that the nature of the monosaccharide plays an important role on the thermodynamic character of the reactions with THBE: the chemical reaction with D-glucose is slightly exergonic (III) while it is clearly endergonic for D-fructose (VI). This different behavior originates from the ring constraints of the monosaccharide, as confirmed by the values of the distance between the oxygen atoms of the two hydroxyl functions before and after reaction with THBE. For an isolated D-fructose molecule, this distance amounts to 3.24Å while it is much smaller for D-glucose (2.84Å). In

contrast, when bound to the THBE, the distance between the two oxygen atoms is now similar whatever the monosaccharide (2.43Å and 2.39Å for D-fructose and D-glucose, respectively) and significantly smaller than for the isolated monosaccharides. The larger distortion from equilibrium found for D-fructose is in full consistency with the increase of the Gibbs free energies.

The formation of D-fructose/organic acid-THBE being endergonic (VI), the assistance of D-fructose dehydration to 5-HMF by the organic acid-THBE seems unlikely. After the isomerization step, D-fructose would rather be released from the THBE. In fact, the rapid conversion of D-fructose to 5-HMF in mixtures without boric acid (**Table 7**) suggests that the THBE is not required for the dehydration step. However, if D-fructose reacts with THBE, its conversion to glucose-THBE is energetically favored ($\Delta G^\circ = -10.61$ kcal/mol) which could explain the selectivity loss observed in the presence of boric acid (**Table 7**).

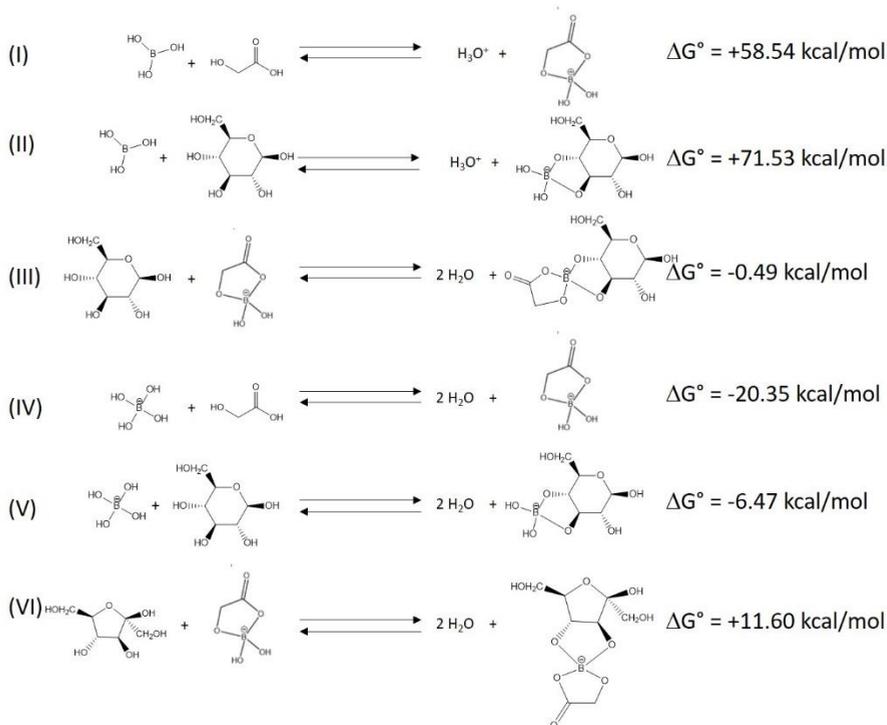


Figure 47: DFT (B3LYP/6-31G**) -calculated Gibbs free energies of reactions between boric acid, α -hydroxyacid and/or a monosaccharide. In all cases, solvent effects have been taken into account through the use of the PCM scheme.

In the light of the discussed experiments and DFT calculations, THBE could catalyze 5-HMF formation in several ways:

- A first possibility is the catalyzed production of 5-HMF by in situ generation of H_3O^+ resulting from the reaction between boric acid and the α -hydroxyacid. In this case, THBE would act similarly to boric acid by stabilizing the acyclic form of D-glucose and favor the isomerization step. Dehydration of D-fructose to 5-HMF would then be accelerated by the increased acidity of the medium.
- For the second possibility, THBE could enhance isomerization further than boric acid. DFT calculations shows that the formation of organic acid-THBE and their reaction with D-glucose (+58.05 kcal/mol) is energetically favored compared to the reaction of boric acid with the monosaccharide (+71.53 kcal/mol).

To demonstrate the in-situ formation of H_3O^+ , LTTMs containing choline chloride, boric acid and an organic acid (4/1/1 mol) were prepared again as well as a mixture of choline chloride and boric acid (2/1). Small amounts of a solution of thymol blue (in ethanol) were added to each mixture to compare their acidity based on indicator dissociation. The absorbance of the indicator protonated form was measured at 548 nm. According to the organic acid, mixtures acidity increases in the following sequence: acetic < formic < no organic acid < maleic < glycolic ~ malic (**Figure 48** and **Supplementary Figure 2, Supplementary Table 1**). While formic and glycolic acids possess a nearly similar pKa (around 3.8), their mixtures with choline chloride and boric acid showed completely different acidity, strongly supporting borate ester formation with H_3O^+ release. The mixture containing only choline chloride and boric acid was somehow more acidic than mixtures with formic or acetic acid. This can be understood observing reaction (I) in **Figure 47**. THB formation could be partially suppressed by the acidity provided with non- α -hydroxyacids.



Figure 48 : Acidity assesement of mixtures of choline chloride and boric acid with maleic (1), malic (2), glycolic (3), formic (4) and acetic (5) acids in the presence of thymol blue. Thymol blue is pink-red in highly acidic conditions and yellow in medium acidity conditions.

The acidity generated by THBE formation in mixture of choline chloride, α -hydroxyacids and boric acid can be better appreciated by comparison with the acidity generated by HCl addition in a mixture of choline chloride and boric acid (**Supplementary Table 1, Supplementary Figure 2**). The acidity of the mixture containing glycolic acid is comprised between the acidities of mixtures containing 0.1 mol/kg and 0.01 mol/kg of HCl. The acidity of the mixture containing formic acid is far below the acidity of the 0.001 mol/kg HCl mixture.

The in-situ formation of H_3O^+ explains why 5-HMF formation is enabled in the presence of 1,2-dihydroxybenzene and 3,4-dihydroxybenzoic acid. The low to intermediate 5-HMF yields result from a moderate THBE formation compared to α -hydroxyacid-THBE which are formed in greater amounts.

The proposed mechanism for 5-HMF formation assistance by THBE is depicted in **Figure 49**. α -hydroxyacids-THBE formation releases H_3O^+ and THBE react with D-glucose, favoring isomerization to D-fructose through a mechanism similar to the pathway proposed in the work of Stahlberg et al. (2011).¹¹³ Contrarily to metal catalysts (e.g. CrCl_3 , AlCl_3 , SnCl_4 , ...), boric and boronic acids catalyze isomerization of aldoses to ketoses through an enediol intermediate rather than through a hydride shift. This was demonstrated in previous studies both experimentally with deuterium labelling experiments and theoretically at the DFT level.^{113,171} We explained that ΔG° calculated for reaction of THB with glucose or fructose are different because of the ring constraints of the monosaccharides. When monosaccharide ring opens, these constraints are reduced which is why borate esters favor the acyclic form of monosaccharides.¹¹³ It was also demonstrated that protonation of glucose O1, leading to the formation of a 1,2-enediol intermediate, is more favorable than in the absence of boric acid, which is probably because it is facilitated by the negatively charged borate.¹¹³ After additional proton transfer, the enediol intermediate can be converted to fructose.

The catalysis with α -hydroxyacids-THBE is likely to proceed in a similar way even though two differences could occur compared to boric acid:

- the formation of organic acid-THBE and their reaction with D-glucose is energetically favored compared to the reaction of boric acid with the monosaccharide.

- THBE, bearing only two available B-OH moieties, could limit the extent of polymerization reactions compared to boric acid or tetrahydroxyborate which possess three and four available B-OH moieties, respectively. While rarely addressed in the context of furan compounds synthesis, polymerization through coordination of several chemical species (glucose, 5-HMF) to a same catalyst has been experimentally suggested, specifically for vanadium trichloride.¹⁶¹

Free cyclic D-fructose being energetically favored compared to D-fructose-THBE, D-fructose could be released from THBE and initiate dehydration to 5-HMF catalyzed by H_3O^+ . The proposed mechanism implies an important role of water for reversible hydrolysis of THBE, which may seem inconsistent with the initially anhydrous composition of the reaction medium. However, it is expected that the THBE formation releases a significant amount of water as proposed in **Figure 49**.

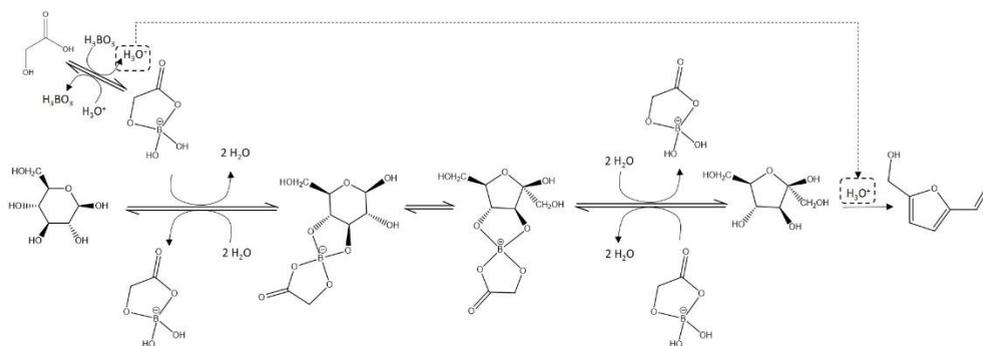


Figure 49: Mechanism for transformation of D-glucose into 5-HMF assisted by boric acid and α -hydroxyacids

After determining the role of organic and boric acids, it is important to understand the function of choline chloride. While the role of the choline cation is mainly to ensure the formation of a melted mixture at moderate temperature, halide anions are known to strongly affect monosaccharides dehydration. Different choline halides were used in combination with boric and glycolic acids (4/1/1 mol) to precise the anion importance. The results (**Figure 50**) suggest that chloride is the most effective anion for the catalysis of D-glucose conversion to 5-HMF followed by bromide. The amounts of humins after the reaction were $6.60 \pm 0.32\%$ and $0.61 \pm 0.20\%$ for choline chloride, and choline bromide respectively. Choline iodide led to negligible amounts of humins.

These results follow the same trend as highlighted in the work of Mellmer et al. (2019).⁹⁴ The author studied D-fructose dehydration in γ -valerolactone with Brønsted acid and different salts. They demonstrated that chloride alone could not catalyze D-fructose, but greatly enhanced the dehydration reaction combined to an acid catalyst. The highly localized charge on chloride anions allows them to stabilize carbocations which are dehydration intermediate as well as their deprotonation transition state. Iodide being a strong reducing agent was likely oxidized to iodine which limited its efficiency. A fast color shift from transparent to yellow-brown was indeed observed in the LTTM during the test, which could be attributed to dipolar interactions between iodine and oxygen. Choline fluoride was not investigated since fluoride, being a weak base, could allow the formation of hydrofluoric acid ($\text{pK}_a = 3.2$). Isolating the effect of fluoride anions would therefore not be possible.

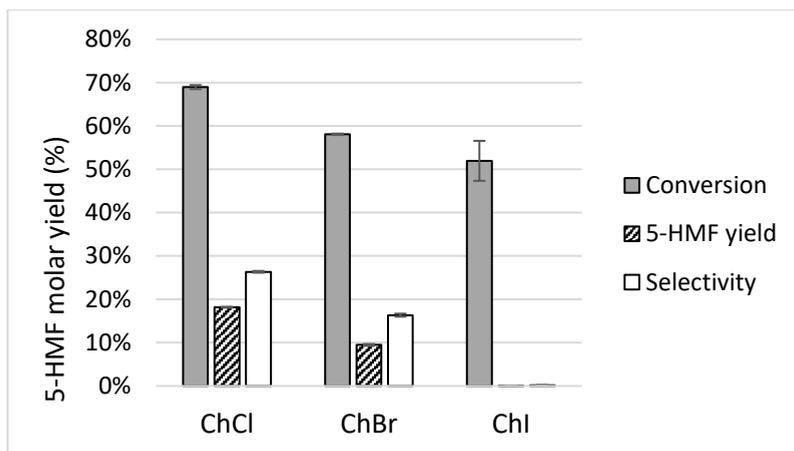


Figure 50: Comparison of choline chloride (ChCl), choline bromide (ChBr) and choline iodide (ChI) in mixture with boric and glycolic acids for the dehydration of D-glucose to 5-HMF (90 °C, 210 rpm, 1h)

1D ^1H and 2D ^1H - ^{13}C HSQC NMR analyses were performed on a mixture of choline chloride, oxalic and boric acids (4/1/1 mol) after 1h of treatment at 90 °C to confirm the formation of 5-HMF as well as to determine if LTTMs were stable in the tested conditions (**Supplementary Figures 6, 7, 8 and 9**). The presence of 5-HMF was confirmed by ^1H - ^{13}C correlation signals at (9.3, 180.6) ppm for the aldehyde function, at (7.4, 126.9) and (6.6, 110.5) ppm for the furan ring C-H and at (4.6, 55.9) for CH_2 near the $-\text{OH}$ moiety. Large signals at (5.1, 92.0) and (4.6, 95.8) ppm are attributed to α -D-glucopyranose and β -D-glucopyranose, respectively. No signal corresponding to levulinic (2-3, 25-40 ppm) or formic (8.5, 174 ppm) acid was observed. The stability of LTTMs composed of choline chloride and organic acids has been questioned since esterification reactions were reported.¹⁹⁹ Rodriguez et al. (2019) observed the apparition of NMR 1D ^1H signals near 3.25, 3.8 and 4.7 ppm corresponding to choline ester formation in a mixture of choline chloride and oxalic acid. Regarding the choline chloride, oxalic acid, boric acid mixture, a small signal is present near 3.12 ppm but no other signal was observed (**Supplementary Figure 6**).

Direct injection of the diluted reaction medium during mass spectrometry experiments provided additional information (**Supplementary Figures 10-13**). Firstly, 5-HMF formation was further confirmed by the presence of a signal at m/z 127.0 corresponding to protonated 5-HMF (**Supplementary Figure 10**). Secondly, a signal at m/z 161.9 could correspond to choline-glycolic acid ester (**Supplementary Figures 10 and 11**). While not confirmed in NMR, esterification between organic acids and choline chloride seems supported by mass spectrometry and is therefore possible in the explored conditions.

It was suggested in part 3.1 that esterification of glucose with organic acid could be a main side reaction in mixture of choline chloride and organic acid to explain conversion trends in Figure 2. A ΔG° of +5.07 kcal/mol was calculated for the esterification of glucose with glycolic acid at glucose O1 position. This value suggests that esterification is indeed possible from an energetic point of view. However, the presence of boric acid reduces aldoses conversion (glucose, xylose, arabinose) and promotes furan derivatives in **Table 7**.

3.3 Comparison of monosaccharide dehydration in LTTMs

The synergy between boric acid and the α -hydroxyacid was evaluated for other monosaccharides: D-fructose, D-mannose, D-galactose, D-xylose and D-arabinose. Monosaccharide conversion, 5-HMF / 2-F yields (for hexoses and pentoses, respectively) and selectivity after a treatment of 1 h in a mixture of choline chloride, glycolic acid and boric acid (molar ratio: 4/1/1) are depicted in **Figure 51**. Compared to the preliminary test with maleic and boric acid, the dehydration selectivity of all aldoses to furan derivatives is improved. For D-fructose however, the selectivity for 5-HMF is slightly reduced since isomerization to D-glucose enables the formation of side-products (e.g. humins). Humins were observed after the treatment of each monosaccharide.

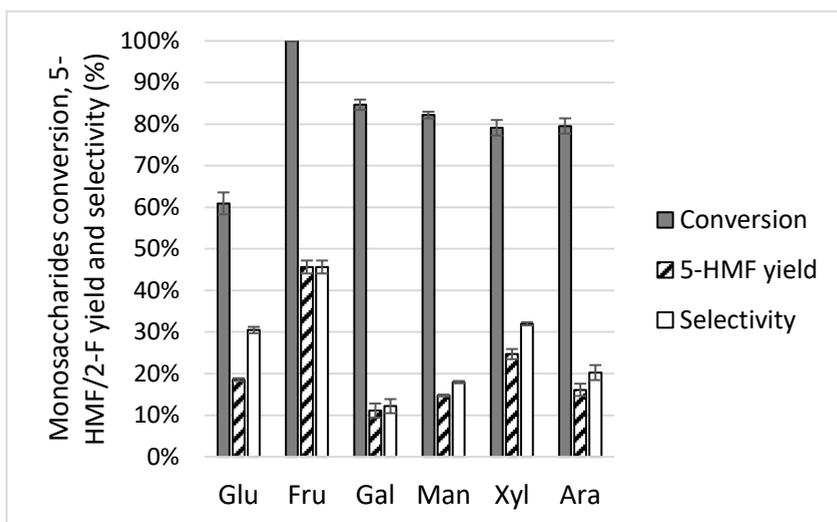


Figure 51: Conversion of monosaccharides (0.56 mmol) and 5-HMF / 2-F yield/selectivity in a mixture of choline chloride (10 mmol), boric acid (2.5 mmol) and glycolic acid (2.5 mmol) after 1 h at 90 °C.

Compared to D-glucose, 5-HMF synthesis from D-mannose and D-galactose were less selective. This was tentatively explained in the work of Lukamto and coworkers (2013).¹⁷³ Complexation of boric/boronic acids with cis vicinal diol is favored compared to complexation with trans vicinal diol. Observing hydroxyl positions on C2, C3 and C4 of aldoses pyranose ring, it can be concluded that D-glucose possesses two trans vicinal diol moieties while mannose and galactose only possess one. Since complexation of trans vicinal diol would induce a distortion of the pyranose ring, the opening of the aldose cyclic form could be favored, which is a key step of the isomerization process.¹⁷³ The lower selectivity achieved with D-galactose can also be rationalized considering its corresponding ketose, D-tagatose, which is more reactive than D-fructose and a less selective substrate for 5-HMF synthesis.⁶⁴

We suspect that the number of available B-OH groups affects the reaction selectivity because they could facilitate the meeting of several molecules on the catalyst, thereby favoring side reactions. The proportion of THBE relative to the initial boric acid content in the tested LTTMs is not known. THBE, possessing only two available B-OH moieties could limit the extent of polymerization reactions compared to boric acid or tetrahydroxyborate which possess three and four available B-OH moieties respectively. Moreover, the dehydration rate is likely faster than the isomerization rate since no fructose could be observed during the reaction. Further investigations should be conducted on THBE catalysis of monosaccharides dehydration. More specifically, mixtures of choline chloride, boric acid and α -hydroxyacids could be partially neutralized in order to promote THBE as well as decreasing the acidity of the medium in order to reduce humins formation.

4. Conclusion

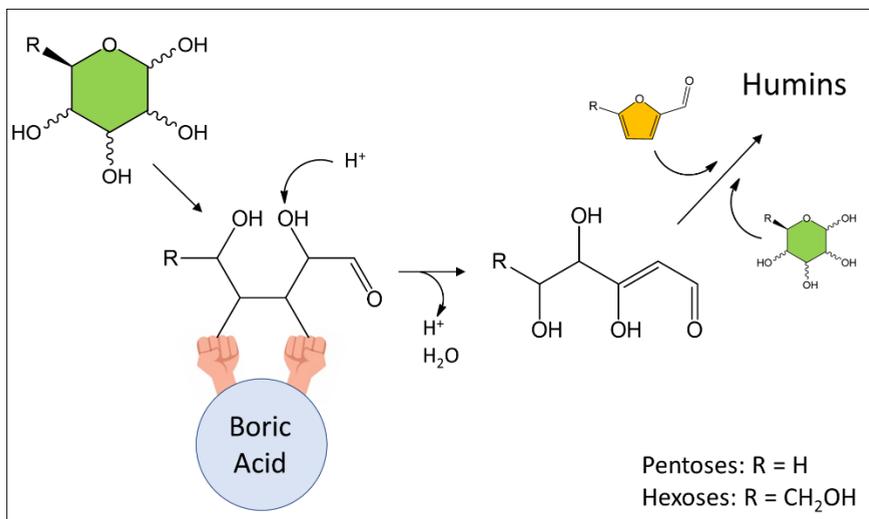
Boric acid enables isomerization of aldoses to ketoses to a limited extent in choline chloride/organic acid based LTTMs (e.g. 5% 5-HMF yield and 23% glucose conversion after one hour at 90 °C with maleic acid). Combined with α -hydroxyacids however, the reaction is faster and more selective (e.g. 19% 5-HMF yield and 61% glucose conversion after one hour at 90 °C). The synergy between α -hydroxyacids and boric acid is explained by formation of tetrahydroxyborate esters. Compared to boric acid, THBE reaction with glucose is energetically favored. THBE formation is associated with H_3O^+ release in the medium increasing its acidity.

During experimentation with α -hydroxyacids, humins are generated as the main side-product. Those humins originate from monosaccharide and furan derivatives polymerization. Humins formation is likely favored by the high acidity produced from THBE formation and possibly by residual boric acid.

We suggest that furan derivatives synthesis could be promoted by a partial neutralization of the medium in order to drive THBE formation and limit the proportion of boric acid as well as reducing acidity to better balance isomerization and dehydration rates. Consequently, boric acid potential as a catalyst for furan derivatives synthesis has not been fully explored yet. THBE catalysis should be further investigated because it could improve performances of cheap and abundant catalyst (boric acid and organic acids).

5

Humins formation control



Graphical abstract 5 : hypothetical mechanism for the formation of humins from aldoses and furan derivatives through dehydration and aldol reaction.

Abstract:

The Lewis acid-catalyzed synthesis of furan derivatives (e.g. 5-hydroxymethylfurfural, 2-furfural) from saccharides is a promising path towards materials production from renewable feedstocks. Process selectivity is however limited by the formation of dark polymers called humins, especially during the treatment of aldoses. Humins emergence in the context of Lewis acid-catalyzed synthesis of 5-HMF and 2-F is not well understood yet. Understanding the phenomenon is however crucial to develop efficient inhibition strategies.

We therefore investigated humins formation from various monosaccharides in low-transition-temperature mixtures based on choline chloride, in water and in dimethylsulfoxide. Reactions were performed in the presence of H₃BO₃ or CrCl₃·6H₂O used to promote furan derivatives synthesis and the generated humins were analyzed by infrared spectroscopy.

From the large humins yield achieved from 2-deoxyglucose, the presence of an infrared band near 1590 cm⁻¹ attributed to β-diketones in most humins and the required presence of boric acid, humins formation is suspected to be initiated by the dehydration of acyclic monosaccharides followed by aldol reactions. The Lewis acid used to promote 5-HMF/2-F synthesis also favors humins development. β-diketone groups

could interact with the catalysts and limit their selectivity. Based on the suspected mechanism for humins formation, potential inhibition strategies are proposed.

Keywords: hexoses, pentoses, 5-hydroxymethylfurfural, 2-furfural, aldol, boric acid, chromium chloride, β -diketone

1. Introduction

The conversion of saccharides to furan derivatives like 5-hydroxymethylfurfural (5-HMF) generated from hexoses and 2-furfural (2-F) generated from pentoses involves three acid-catalyzed dehydration steps.¹⁸⁶ If ketoses (e.g. fructose, xylulose) are readily dehydrated to 5-HMF and 2-F in the presence of a Brønsted acid, aldoses (e.g. glucose, xylose) are more difficult to convert. Firstly, they must be isomerized to their corresponding ketoses in the presence of a Lewis acid (e.g. chromium trichloride, aluminium trichloride, boric acid).¹⁸⁶

However, the treatment of monosaccharides in acidic conditions remains hindered by a major side-reaction, namely humins formation. Humins are dark polymers generated during the treatment of saccharides at high temperature and/or in the presence of acid. In water at 130-150°C, Swift et al. (2015) reported the conversion of as much as 40% of glucose to humins (carbon yield) trying to synthesize 5-HMF in the presence of CrCl₃, recognized as one of the most selective catalyst.¹⁵⁶

Before a more complete introduction, the “humins” term deserves further description. “Humin” is an ambiguous term for which multiple definitions exist. A first possible definition of “humin” is related to humic substances in soil. Sutton and Spósito (2005) described humic substances as “refractory, dark colored, heterogeneous organic compounds produced as byproducts of microbial metabolism”. Attempts to characterize those materials in soil led to three different fractions defined by their behavior under extraction: “humin” which is the insoluble fraction of humic substances in an alkaline solution, “humic acids” which are soluble under alkaline conditions but precipitate below pH 2 and “fulvic acids” which remain soluble under all pH conditions.²⁰⁰

Another definition of humins is rather related to monosaccharides degradation, more precisely to the dark polymers commonly generated during the treatment of monosaccharides investigated to produce their furan derivatives.

Humins of both definitions share common features: they are dark polymers of which chemical structures are still not fully explored and defined. But their origins and compositions are different. Humic substances result from the decomposition of organic matter in soil. They contain lignin, carbohydrates and peptides alteration products as well as aliphatic hydrocarbon functionalities likely originating from waxes, lipids, cuticular material and suberin. On the other side, humins generated during furan derivatives synthesis have fewer possible origins: monosaccharides and/or furan derivatives.

In the context of monosaccharides dehydration, humins formation was firstly thought to originate essentially from furan derivatives degradation reactions. This hypothesis is well supported by the generation of humins from 5-HMF in water. It has been proposed that rehydration of 5-HMF leads to the production of 2,5-dioxo-6-hydroxy-hexanal, a molecule highly susceptible to aldol addition/condensation reactions responsible for polymerization to humins.⁸⁰ Aldol addition/condensation reactions principle is illustrated in **Figure 52**. Assuming furan derivatives are indeed the major precursors of humins, the use of organic solvents as reaction or extraction media is expected to limit the formation of those dark polymers. The beneficial effect of organic solvents has indeed been observed, especially during the dehydration of ketoses like fructose or sorbose. For instance, the treatment of fructose in water during 5h at 220°C resulted in a 54% humins yield (carbon yield). For similar conditions in ethyl acetate, the humins yield was limited to 33%.⁹² Organic solvents have therefore been advantageously used to improve the selectivity of ketoses dehydration to furan derivatives. In this way, the dehydration of xylulose to 2-F (water, 110°C, HCl 0.1 M) was increased from 68 to 90% by adding methylisobutylketone (MIBK) as an extractive phase.⁷² 5-HMF yield obtained from fructose is also improved by simultaneous extraction with various organic solvents.¹⁰⁵

Unfortunately, recent work comparing humins formation from ketoses and aldoses may suggest that furan derivatives are not the only precursors.⁹² While humins formation from ketoses was limited in the presence of organic solvents, their formation from aldoses remained important. Glucose and xylose conversion led to 61 and 43% humins yields (carbon yield) in water and 73%, 57% in ethyl acetate after 5h at 220°C.⁹² Humins formation from aldoses has been reported in other organic solvents like dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), N,N-dimethylacetamide (DMA), N,N-dimethylformamide (DMF) and 1-butyl-3-methylimidazolium chloride (BMIMCl).^{98,151,161,163,164} This is problematic because aldoses are a far more abundant feedstock than ketoses for the production of furan derivatives. Treatments/extractions with organic solvents offering a limited potential to control humins formation from aldoses, new inhibition strategies should be developed, which is not possible without a better understanding of humins formation mechanisms.

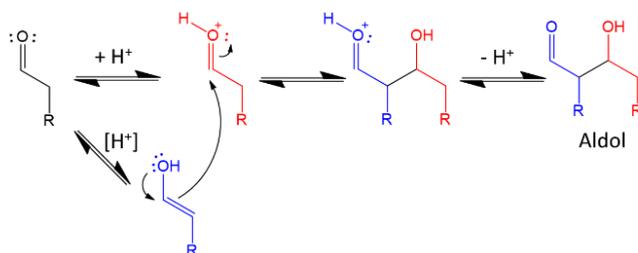
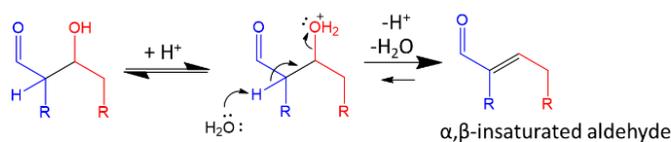
Aldol addition:Aldol condensation:

Figure 52 : acid-catalyzed aldol addition and condensation

In the previous chapter on 5-HMF and 2-F synthesis from saccharides in low-transition-temperature mixtures (LTTMs) based on choline chloride, we observed humins formation from various hexoses (fructose, glucose, mannose, galactose) and pentoses (xylose, arabinose) at only 90°C.²⁰¹ The studied reaction media were composed of choline chloride, an organic acid and boric acid. Boric acid was investigated as a catalyst enabling the isomerization of aldoses to ketoses prior to their dehydration to 5-HMF and 2-F. Humins being rapidly form (1h) at moderate temperature in some of the studied media, we conducted additional experiments in attempt to better understand the origins of those polymers and provide means to limit their development.

The present chapter methodically investigates humins formation in LTTMs through experiments with different feedstocks (fructose, glucose, mannose, galactose, xylose, arabinose, 2-deoxyglucose, 5-HMF, 2-F) isolated or combined and infrared spectroscopy. The comparison of the formed humins highlights a key role of monosaccharides as precursors rather than furan derivatives in the tested conditions. The isomerization catalyst (boric acid) is also involved in humins emergence. Based on the experiments, we suggest that humins formation is initiated by dehydration of acyclic monosaccharides followed by aldol addition/condensation reactions with other monosaccharide molecules and their furan derivatives. Aware of the complexity of the studied reaction media, we also performed experiments in water, DMSO and a mixture of choline chloride and CrCl₃.6H₂O to support our findings and generalize them to more common and simpler dehydration systems.

2. Material and methods

2.1. Chemicals

D-(-)-fructose (99%) and choline chloride (99%) were purchased at Acros Organics. D-(+)-xylose (>99%), $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (> 98%) and 5-HMF (>99%) were acquired from Sigma-Aldrich. Boric acid (99.5-100.5%) and 2-F (>98%) were purchased at Merck. Acetic acid (99-100%) and anhydrous D-(+)-Glucose (GPR Rectapur) were obtained from VWR Chemicals. D-(+)-mannose (>99%), D-(+)-galactose (>99%) and D-(-)-arabinose (>99%) were purchased at Fluka. Glycolic acid (>98.0%) was obtained from TCI Chemicals. Dimethylsulfoxide (> 99%) was purchased at Fisher Chemicals. All chemicals were used as received.

2.2. Humins production

Table 8 indicates the preparation of different assays to produce humins. All tests were performed in triplicate in closed vessels at 90°C (210 rpm) in a water bath. All the components of the reaction medium, including monosaccharides or furan derivatives were mixed together in a one-step protocol. A liquid phase was rapidly obtained (less than 5 min) after heating and frequent mixing using a vortex mixer. The agitation was maintained at 210 rpm for the rest of the treatment. The typical treatment time was 60 min.

Table 8 : humins production tests in LTTMs at 90 °C (1h, 210 rpm). Test 1-4 were performed during 10, 20, 30, 60, 90 and 120 minutes.

Assay	Choline chloride (mmol)	Boric acid (mmol)	Glycolic acid (mmol)	Acetic acid (mmol)	Mono-saccharide	Mono-saccharide (mmol)	5-HMF (mmol)	2-F (mmol)
1	10	2.5	2.5	0	Glucose	0.56	0	0
2	10	2.5	2.5	0	/	0	0.56	0
3	10	2.5	2.5	0	/	0	0	0.56
4	10	2.5	0	2.5	Glucose	0.56	0	0
5	10	2.5	0	2.5	/	0	0.56	0
6	10	2.5	2.5	0	Fructose	0.56	0	0
7	10	2.5	2.5	0	Mannose	0.56	0	0
8	10	2.5	2.5	0	Galactose	0.56	0	0
9	10	2.5	2.5	0	Xylose	0.56	0	0
10	10	2.5	2.5	0	Arabinose	0.56	0	0

11	10	2.5	2.5	0	2-deoxyglucose	0.56	0	0
12	10	0	5	0	Glucose	0.56	0	0
13	10	0	5	0	Glucose	0.28	0.28	0
14	10	5	0	0	Glucose	0.28	0.28	0
15	10	2.5	2.5	0	Glucose	0.28	0.28	0
16	10	2.5	2.5	0	Glucose	0.56	0	2.6
17	10	2.5	2.5	0	Xylose	0.56	2.6	0

Table 9 indicates the conditions of humins production from glucose and xylose in different solvents in the presence of chromium trichloride hexahydrate ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$). For the tests based on choline chloride (22, 23), this compound was premixed with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and heated at 90°C to form a liquid phase before the addition of monosaccharides. Experiments with choline chloride-based LTTMs were conducted in glass tubes in a water bath (90°C). Tests with water and DMSO were performed at 140°C in 75 mL reactors (Series 5000 Pressure Reactor System, Parr). Temperature increased from 25 to 140°C in 20 min and was then maintained during 120 min. At the end of the treatment, temperature decreased from 140 to 50°C in 15 min (water cooled). Sulfuric acid was added to the tests with DMSO and choline chloride to ensure that sufficient amounts of humins were obtained for the analyses.

Table 9: humins production from glucose and xylose in different solvents in the presence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$.

Assay	Solvent	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (mmol)	H_2SO_4 72% (μL)	Glucose (mmol)	Xylose (mmol)	Temp. ($^\circ\text{C}$)	Time (min)
18	Water (1.11 mol)	5.55	0	11.11	0	140	120
19	Water (1.11 mol)	5.55	0	0	11.11	140	120
20	DMSO (0.28 mol)	5.55	50	11.11	0	140	120
21	DMSO (0.28 mol)	5.55	50	0	11.11	140	120
22	Choline chloride (10 mmol)	5	20	0.56	0	90	120
23	Choline chloride (10 mmol)	5	20	0	0.56	90	120

2.3. Recovery and analyses of humins

Immediately after the treatment, LTTMs were dissolved with 5 mL of water to stop the reaction.²⁰¹ The generated humins were recovered by centrifugation (2100 g, 10 min), washed three times with 5 mL of water and dried 24h at 105°C . Dissolved LTTMs

and washing water were combined for high performance liquid chromatography (HPLC) analyses.

For treatments in water and DMSO, 80 mL of water were added to the samples after cooling. Humins formed in water and DMSO could not be recovered by centrifugation (2100 g, 10 min). Filtration was therefore used to collect humins. However, the filtrate remained brown/black indicating that large amounts of humins were not recovered by this method either. Filtration was performed on crucibles (porosity grade 4, 10-16 μm). The collected humins were washed five times with 100 mL of water and dried at 105°C during 24h.

Humins mass yields were calculated as the ratio between the mass of collected dried insoluble substances and the initial mass of monosaccharide or furan compound. When humins were generated from mixtures of monosaccharides and furan derivatives, the yield was calculated as the ratio between the mass of collected dried insoluble substances and the initial mass of monosaccharide only. This choice was made to better appreciate the contribution of furan derivatives to humins formation, especially for the tests where large amounts of furan derivatives were mixed with monosaccharides.

Dried humins were analyzed by infrared spectroscopy using a Bruker VERTEX 70 FT-IR device. Dried humins were also solubilized in deuterated DMSO for 2D HSQC and HMBC (^1H - ^{13}C) NMR analyses at 298 K on a Bruker Ultrashield 700 Plus equipment operating at 700 MHz for ^1H and 175 MHz for ^{13}C . All NMR experiments were performed using a triple resonance inverse-probe. The datasets were acquired with 1024 and 256 data points for the f2 (^1H) and f1 (^{13}C) dimensions, with spectral widths of 11 161 and 38463 Hz, respectively. Eight scans were performed and the relaxation delay was 1.5 s.

Aldehyde moieties in humins were also detected with the Fehling's test. Fehling's reagent A was a copper sulfate pentahydrate solution in water (0.28 M) and reagent B was an aqueous solution of sodium hydroxide (3.75 M) and sodium potassium tartrate tetrahydrate (0.71 M). Washed and dried humins (10 mg) resulting from monosaccharides conversion were further washed and centrifuged (10 min, 2000 rpm) with water (1 x 5 mL) and ethanol (3 x 5 mL). 3 mL of reagents A and B were added to the residues suspended in 1 mL of residual ethanol and the resulting mixtures were heated 5 min at 80°C before comparing the amount of red precipitate (copper oxide) obtained for each test. The test was also performed on 10 mg of 5-HMF in 1 mL of ethanol, on 1 mL of ethanol and on 1 mL of each washing liquid phase.

2.4. Monosaccharides and 5-HMF/2-F analyses

Monosaccharides were quantified by high performance liquid chromatography (HPLC) using a Ca Rezex RPM Monosaccharides column heated at 80 °C with a water flow of 0.6 mL/min. Detection was performed with an evaporative light scattering detector (40 °C, gas flow of 0.8 L/min). 5-HMF and 2-F were separated on a HPX-87H Aminex column heated at 45 °C using a 5mM H₂SO₄ aqueous solution at a 0.6 mL/min flow. UV detection was used to measure 5-HMF and 2-F concentrations at 284 nm. Monosaccharide conversion, 5-HMF/2-F yield and selectivity were calculated as follows:

$$\text{Residual monosaccharides (\%)} = \frac{\text{Final moles of monosaccharides}}{\text{Initial moles of monosaccharides}} \times 100$$

$$\text{Monosaccharides conversion (\%)} = 100 - \text{Residual monosaccharides}$$

$$\text{5 - HMF or 2 - F yield (\%)} = \frac{\text{Moles of 5 - HMF or 2 - F}}{\text{Initial moles of monosaccharides}} \times 100$$

$$\text{Selectivity (\%)} = \frac{\text{(5 - HMF or 2 - F yield)}}{\text{Monosaccharide conversion}} \times 100$$

3. Results and discussion

In the previous chapter, humins mass yields of $10.33 \pm 0.90\%$ and $14.12 \pm 0.46\%$ were achieved from D-glucose and D-xylose after a one hours treatment (90°C) in a mixture of choline chloride, boric acid and glycolic acid (4/1/1 mol).²⁰¹ When 5-HMF and 2-F were treated in similar conditions, humins mass yield of respectively $0.98 \pm 0.24\%$ and $0.89 \pm 0.07\%$ were obtained, supporting an important role of monosaccharides in the polymerization process (**Figure 53**).²⁰¹ No humins were formed when glucose or 5-HMF were treated with a mixture of choline chloride, boric acid and acetic acid. This is likely due to the limited acidity in the absence of an α -hydroxyacid since those specific acids react with boric acid to generate H₃O⁺.²⁰¹

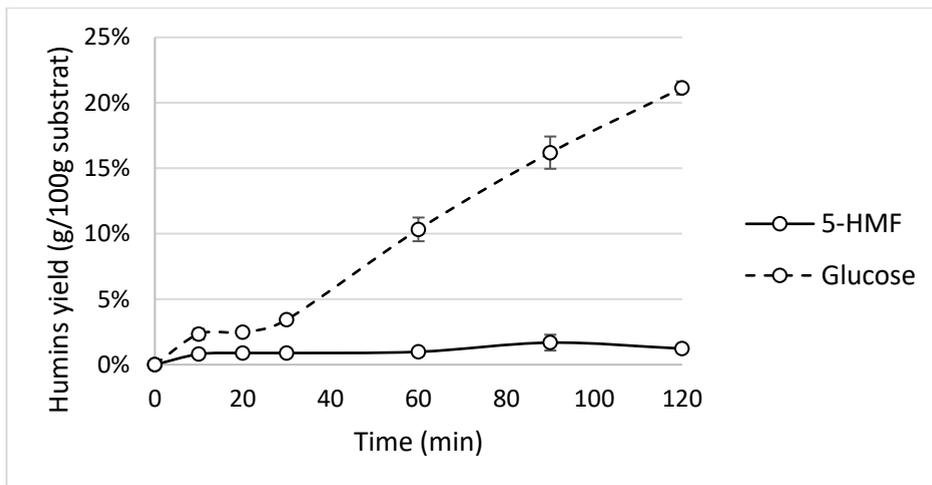


Figure 53: Mass yields of generated humins during treatment of D-glucose (0.00056 mol) or 5-HMF (0.00056 mol) in a mixture of choline chloride (0.0100 mol), glycolic acid (0.0025 mol) and boric acid (0.0025 mol) after one hour at 90°C, 210 rpm. Data from Istasse T, Lemaury V, Debroux G, Bockstal L, Lazzaroni R, Richel A. *Monosaccharides Dehydration Assisted by Formation of Borate Esters of α -Hydroxyacids in Choline Chloride-Based Low Melting Mixtures.* *Front Chem.* 2020;8(July):1–15.²⁰¹

To determine the impact of LTTMs components on humins production, supplementary assays with LTTMs containing only boric acid and choline chloride or only glycolic acid and choline chloride were conducted during one hour. The results, depicted in **Figure 54**, support that D-glucose, boric acid and the α -hydroxyacid are required to produce large amounts of humins. Equimolar quantities of D-glucose and 5-HMF were then used together as the reaction feedstock in the mixture of choline chloride, boric acid and glycolic acid (**test F, Figure 54**). The resulting humins yield ($24.06 \pm 1.98\%$) was largely superior to the yields observed from individual substrate (from 5-HMF: $0.98 \pm 0.24\%$; from glucose: $10.33 \pm 0.90\%$) (**tests A and B, Figure 54**).

These observations indicate that 5-HMF is involved in humins production when glucose is also present, especially with boric acid in the reaction medium.

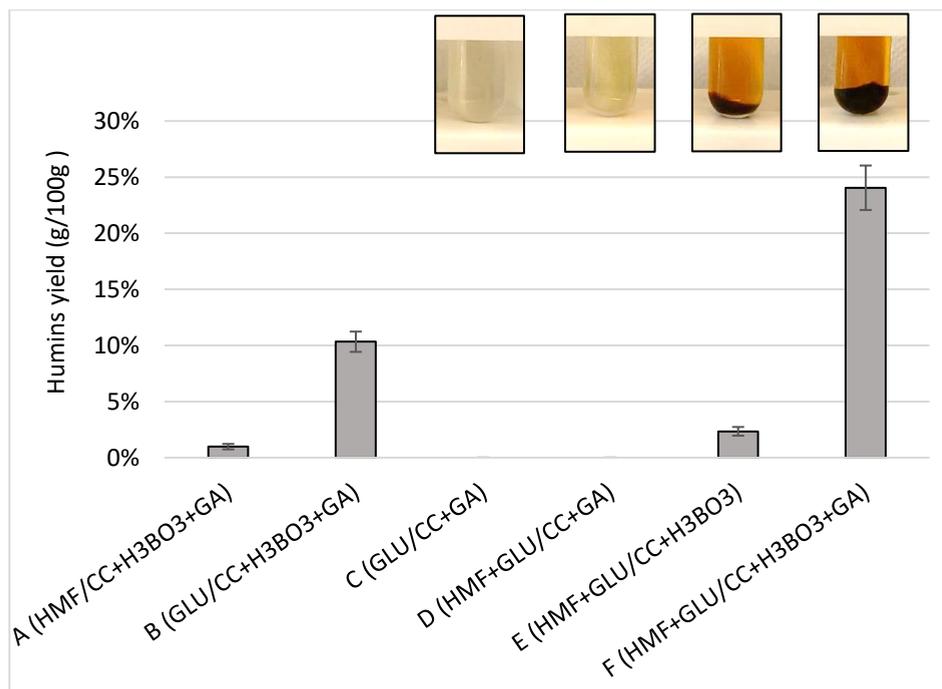


Figure 54: Mass yields of generated humins during treatment of D-glucose (GLU), 5-HMF (HMF) or a mixture of both substrates in mixtures of choline chloride (CC), glycolic acid (GA) and/or boric acid (H₃BO₃) after one hour at 90°C, 210 rpm. The precise conditions of tests A, B, C, D, E and F are depicted in Table 1 and correspond to assays 2, 1, 11, 12, 13 and 14 respectively. Data from Istasse T, Lemaury V, Debroux G, Bockstal L, Lazzaroni R, Richel A. Monosaccharides Dehydration Assisted by Formation of Borate Esters of α -Hydroxyacids in Choline Chloride-Based Low Melting Mixtures. *Front Chem.* 2020;8(July):1–15²⁰¹

Humins were also collected from the reaction (1h, 90°C) of different monosaccharides in a mixture of choline chloride, boric acid and glycolic acid (4/1/1 mol) (**Figure 55**). Assuming 5-HMF may be incorporated in humins by reacting with monosaccharides, the high humins yield achieved from fructose ($19.56 \pm 0.09\%$) likely results from the abundance of generated 5-HMF ($45.63 \pm 1.56\%$ yield) in the medium. A similar conclusion is not valid for the aldoses. Humins formed from D-galactose ($12.08 \pm 0.35\%$) are for instance slightly more abundant than humins produced from glucose ($10.33 \pm 0.90\%$) although the amount of D-galactose dehydrated to 5-HMF ($11.12 \pm 1.69\%$) is lower compared to glucose ($18.56 \pm 0.34\%$). This observation also supports that 5-HMF is not the main precursor of humins in our conditions.

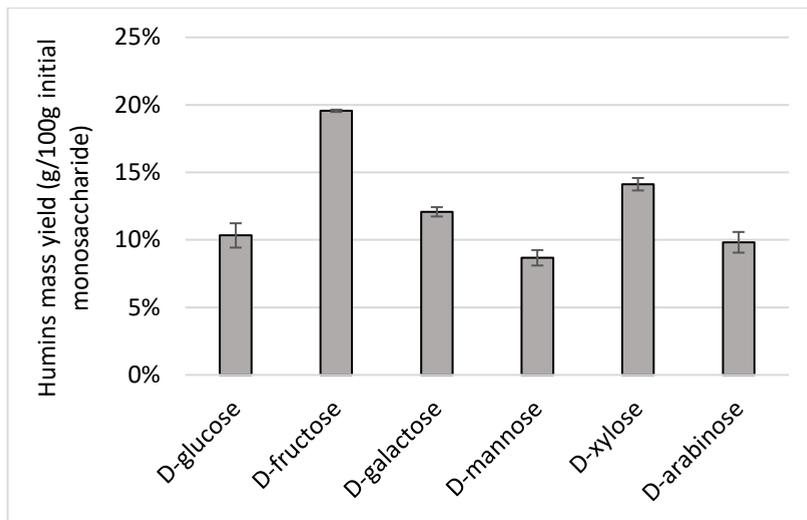


Figure 55: Humins mass yields generated from monosaccharides in a mixture of choline chloride, boric acid and glycolic acid after one hour at 90 °C.

To gain information about humins structure, the dark polymers formed from different monosaccharides were analyzed by infrared spectroscopy. The most striking features, common for humins from all the tested monosaccharides, are the carbonyl stretching bands near 1670-1700 cm^{-1} , the large stretching band around 1590 cm^{-1} and the =C-H bending bands near 740-800 cm^{-1} . For better clarity, those bands and their attribution were highlighted in **Figure 56** using representative infrared spectra. The infrared spectrum of humins generated from each monosaccharide is depicted in **Figure 57**. Carbonyl bands being below 1700 cm^{-1} , they are likely in a conjugated structure. The relatively large and intense band at 1590 cm^{-1} is typical of aliphatic β -diketones like acetylacetone. The unique absorption pattern of β -diketones comes from their keto-enol tautomers. The ketotautomers display a double band near 1700 cm^{-1} while the enolic tautomer possesses a strong absorption band near 1585 cm^{-1} . Bands relative intensity can vary according to the predominance of the keto or the enol forms.²⁰² Two carbonyl bands near 1710-1670 cm^{-1} are observed in humins generated from hexoses while humins formed from pentoses display only one carbonyl band in this region. Assuming that monosaccharides are the main substrate for humins generation, this difference could be attributed to the additional carbon of hexoses compared to pentoses. However, etherification reactions could also explain this absorption pattern. Both hypotheses are further discussed after supplementary analyzes (NMR, Fehling reagent) and experiments. In any case, all humins seem to possess α,β -unsaturated carbonyl moieties in their structure.

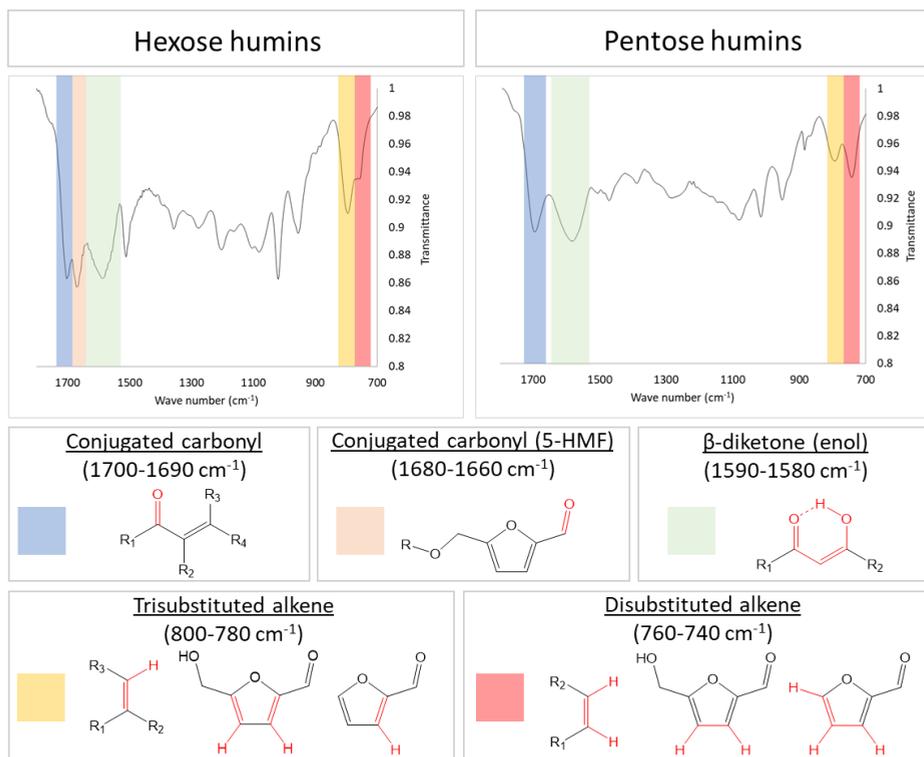


Figure 56 : main infrared signals studied in this work and their attribution on two representative IR spectra of the generated humins.

Besides C=O stretching, =C-H bending bands also show different patterns for hexoses and pentoses humins. To better understand their possible origin, infrared absorption of 5-hydroxymethylfurfural and 2-furfural must be described. (**Supplementary Figure 14 and 15**) According to alkene substitution pattern, bending bands are found at different wave numbers. Trisubstituted alkenes generally present a =C-H band around 780 cm^{-1} while *cis*-disubstituted alkenes show a band near 750-740 cm^{-1} . The furan ring being in resonance, there are several possibilities of =C-H bending bands which should be considered. In this sense, 5-HMF infrared spectrum displays three =C-H bending bands at 806, 768 and 756 cm^{-1} . 2-F rather presents more possibilities of disubstituted alkenes. Its infrared spectrum consequently displays a major absorption band at 748 cm^{-1} .

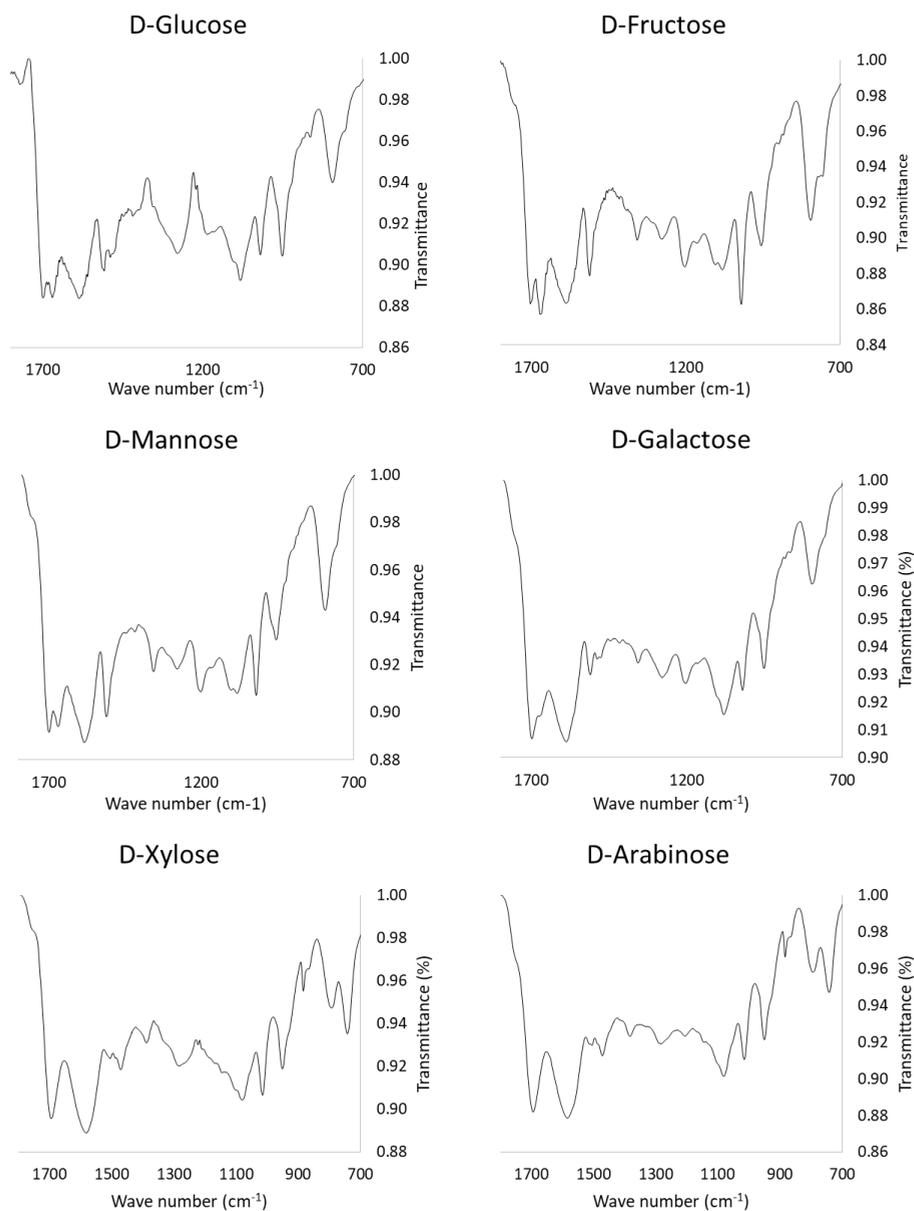


Figure 57 : Infrared spectra of suspected humins. Data from Istasse T, Lemaur V, Debroux G, Bockstal L, Lazzaroni R, Richel A. Monosaccharides Dehydration Assisted by Formation of Borate Esters of α -Hydroxyacids in Choline Chloride-Based Low Melting Mixtures. *Front Chem.* 2020;8(July):1–15²⁰¹

In infrared spectra of hexoses humins, the most intense =C-H bending band is near 795 cm^{-1} with a shoulder around 755 cm^{-1} . In spectra of pentoses humins, the most intense =C-H bending band is rather around 740 cm^{-1} with a second less intense band near 792 cm^{-1} . Considering the main bending bands, the incorporation of furan derivatives in humins is a possibility, hexoses humins incorporating 5-HMF and pentoses humins incorporating 2-F. However, the band at 792 cm^{-1} in pentoses humins spectra is not explained by 2-F furan ring, which suggests that at least a part of trisubstituted alkenes is formed during the reactions leading to humins.

Aldol addition/condensation reactions can explain the formation of trisubstituted alkenes in humins structure, especially the creation of α,β -insaturated carbonyl. Aldol addition in acidic medium involves reaction between an enol obtained through keto-enol tautomerism and a molecule with a protonated carbonyl moiety. A C-C bond is formed between both molecules leading to the formation of an aldol. Then the aldol is generally dehydrated, which results in an α,β -insaturated carbonyl compound. The relevance of this reaction in humins formation is further addressed after additional experiments to gain more information about humins structure.

D-fructose humins were produced in a mixture of choline chloride, boric acid and glycolic acid (4:1:1 mol) at 90°C during 60 min. They were then collected and thoroughly washed with water and dried before dissolution in dimethylsulfoxide- d_6 for 1D and 2D NMR analyses (**Supplementary Figures 16, 17 and 18**). The 1D ^1H and 2D HSQC ^1H ^{13}C NMR experiments confirmed the presence of many hydroxylated carbons (around 3-4; 60-70 ppm) in the structure likely originating from monosaccharide incorporation. Signals ($\delta^1\text{H}$, $\delta^{13}\text{C}$) around (6.47; 112.46) ppm and (7.42; 124.76) ppm as well as a signal at (4.66, 63.57) ppm are compatible with the presence of the furan ring in humins. A signal at (9.49; 177.99) ppm supports that aldehyde moieties are still present in humins, ensuring further polymerization by aldol addition/condensation reactions.

Among NMR data, two groups of signals are particularly informative. A first interesting signal is observed around (8.08; 130.09 ppm) in humins 2D NMR HSQC spectrum. This kind of chemical shifts is expected in aldol reaction products and could result from a reaction between several monosaccharide molecules as represented in **Supplementary Figure 19 (A)**. Another signal was observed around (8.1; 165 ppm) in 2D HSQC NMR spectrum of the diluted and filtrated reaction medium after treatment, although it was notably fainter (**Supplementary Figure 8**). Both signals would be hypothetically explained by the progressive polymerization of monosaccharides as further discussed. In solution, humins precursors could result from aldol addition/condensation between a monosaccharide molecule and a dehydrated monosaccharide molecule (**Supplementary Figure 19 B**). The chemical shift of the carbon linking both monosaccharide molecules would be around 165 ppm but upon

further aldol reaction involving the aldehyde moiety of the structure, this chemical shift could be decreased around 130 ppm.

An additional informative signal is obtained from 2D HMBC NMR analysis of D-fructose humins. The following chemical shifts (3.4; 54.1 ppm), (3.1; 54.1 ppm) and (3.1; 66.9 ppm) indicate the close proximity of several carbons with -OH moieties which further support the role of monosaccharides in humins formation. Other signals with low ^1H chemical shift (> 3 ppm) could not be attributed but are likely related to saturated structures without -OH moieties. In the context of aldol reaction, low chemical shifts could appear in aldol addition products if condensation did not occur but further analyses are required to explain their origins.

Aldehydes moieties in humins were also detected with Fehling's reagent (**Figure 58**). The reaction specifically detects aldehydes through oxidation by Cu^{++} ions. In the initially blue Fehling's reagent, Cu^{++} are complexed by tartrate to avoid precipitation into $\text{Cu}(\text{OH})_2$. After reaction with aldehydes, Cu^{++} ions are reduced and precipitated into red copper oxide (I).



Figure 58: detection of aldehydes with Fehling's reagent. 1: ethanol (negative control), 2: 5-HMF (positive control), 3: third ethanol wash for fructose humins, 4: third ethanol wash for mannose humins, 5: fructose humins, 6: mannose humins

To prove that the aldehyde moiety of humins is a part of their chemical structure and not a residual adsorbed contaminant, humins were thoroughly washed with water and

ethanol. The ethanol used to wash humins was also submitted to the test with Fehling reagent and no aldehyde was detected.

The role of furan derivatives in humins formation was then investigated by adding large amounts of 5-HMF or 2-F to the reaction medium. Humins were firstly produced from D-glucose in a mixture of choline chloride, boric acid and glycolic acid (molar ratio: 4/1/1) during one hour at 90°C. A large amount of 2-furfural (2.6 mmol for 0.56 mmol of D-glucose) was added to the mixture. Being largely dominant in the medium compared to 5-HMF generated by glucose dehydration, it was expected that 2-F could partially replace 5-HMF in the polymer structure. The infrared spectrum of the resulting humins (**Figure 59, C**) revealed the presence of an accentuated infrared band at 754 cm^{-1} compared to the spectrum of glucose humins produced without added 2-F (**Figure 59, A**).

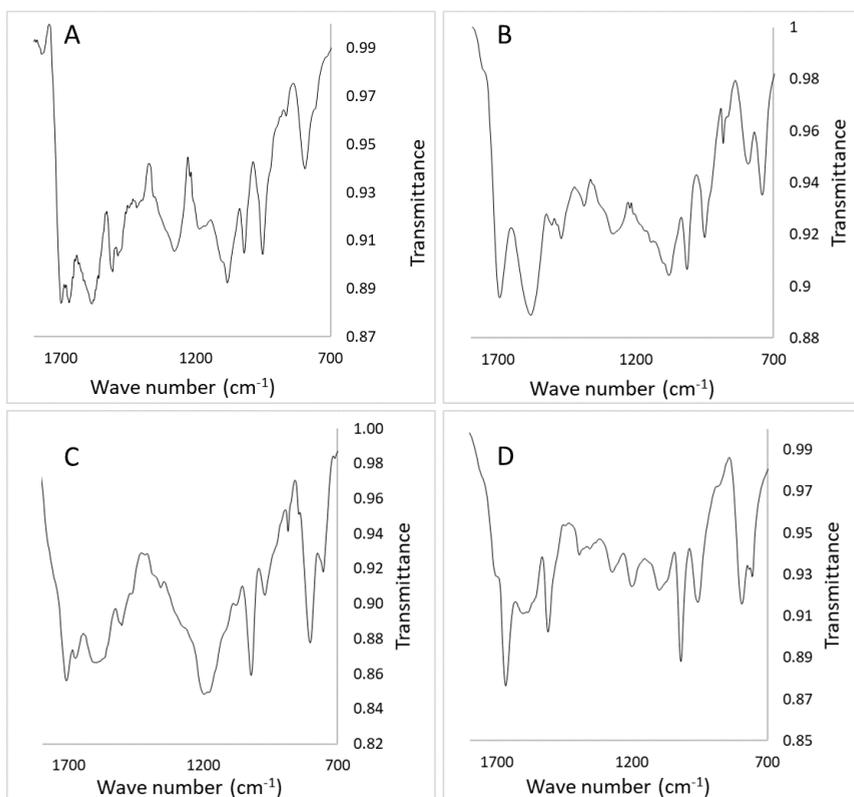


Figure 59 : infrared spectra of humins generated in a mixture of choline chloride, boric acid and glycolic acid after 1h at 90°C, 210 rpm. A. humins formed from glucose, B. humins formed from xylose, C. humins formed from glucose with 2-furfural added in the reaction medium, D. humins formed from xylose with 5-HMF added in the reaction medium.

The selectivity of D-glucose dehydration to 5-HMF was increased from 30.48 ± 0.76 % to 37.86 ± 1.89 %. The amount of humins generated in the presence of 2-F reached 23.63 ± 0.75 % of D-glucose initial mass which is twice as much as humins produced without added 2-furfural.

A similar experiment was conducted with D-xylose in the presence of 5-HMF, leading to a humins yield of 22.54 ± 0.64 % compared to the 14.12 ± 0.46 % yield obtained from xylose alone after 1h at 90°C . In the IR spectrum of humins produced from xylose without added 5-HMF (**Figure 59, B**), a band at 744 cm^{-1} , attributed to 2-F, was present. This band was not observed when 5-HMF was added and the infrared spectrum of the corresponding humins (**Figure 59, D**) rather depicts two close =C-H bending absorption bands at 756 and 777 cm^{-1} .

The results are therefore consistent with the incorporation of the dominant furan derivatives in humins. In the case of glucose humins produced in the presence of 2-F (**Figure 59 C**), two carbonyl stretching bands near 1700 and 1670 cm^{-1} remain present but the band at 1670 cm^{-1} appears relatively smaller than the corresponding band in glucose humins generated without added 2-F. For xylose humins generated in the presence of 5-HMF (**Figure 59 D**), a major carbonyl band is now observed near 1670 cm^{-1} rather than 1700 cm^{-1} . A shoulder remains visible near 1700 cm^{-1} . This implies that the band at 1670 cm^{-1} is likely related to the aldehyde moiety of 5-HMF. IR spectra of humins from different monosaccharides (**Figure 57**) also support this hypothesis since the intensity of this band follows the same trend that the 5-HMF yield (fructose: 46% 5-HMF yield > glucose: 19% >mannose: 15% >galactose: 11%).²⁰¹ Given these results and because the band at 1670 cm^{-1} is not observed for pentoses humins, we suggest that 5-HMF etherification with monosaccharides occurs. However etherification reactions cannot explain the large and intense band around 1590 cm^{-1} . Moreover, large amounts of humins are still generated from pentoses without the involvement of 5-HMF. We therefore performed further tests to determine the extent of etherification compared to other possibilities like aldol reactions.

As a control experiment, glucose (0.56 mmol) and 5-HMF (0.56 mmol) were mixed and treated in a mixture of choline chloride and glycolic acid without boric acid. The acidity of the medium was increased by the addition of HCl (35.7 wt%, $20\text{ }\mu\text{L}$). While both the acidity and total feedstock concentration were higher than previous tests, a humin mass yield of only 1.96 ± 0.96 % was achieved after 1h at 90°C . As a comparison, the reaction of glucose in the mixture of choline chloride, boric acid and glycolic acid produced 10.33 ± 0.90 % humins. The resulting IR spectrum (**Supplementary Figure 20**) shows again a major band at 1670 cm^{-1} with a shoulder near 1700 cm^{-1} , supporting the involvement of etherification reaction in humins formation during the control test. However, the low humins yield achieved in the absence of boric acid suggests that etherification reactions are not the main contributor to humins production.

This was further confirmed by investigating humins formation from 2-deoxyglucose. 2-deoxyglucose is of particular interest to understand humins formation in the studied reaction media because it does not possess C2-OH. Therefore, it cannot isomerize to ketose through an 1,2-enediol intermediate and form 5-HMF. After 1h at 90°C in a mixture of choline chloride, boric acid and glycolic acid (4/1/1 mol), a $54.74 \pm 0.10\%$ humins yield was achieved, which is considerably higher than the humins yield obtained from glucose in similar conditions ($10.33 \pm 0.90\%$). Humins synthesis is particularly favored from 2-deoxyglucose which means that a specific element of 2-deoxyglucose structure facilitates the reaction. As expected, no trace of 5-HMF was observed after the treatment. Infrared analysis of the formed humins (**Figure 60**) reveals a major absorption band near 780 cm^{-1} clearly corresponding to trisubstituted alkenes. The main carbonyl stretching band is at 1710 cm^{-1} which supports the presence of conjugated carbonyl in the structure. Only a very weak band at 1670 cm^{-1} is observed, which is consistent with the absence of 5-HMF. Two other bands at 950 and 1020 cm^{-1} were also observed for all the other humins and could correspond to *trans*-disubstituted alkenes (bending) and C-O (stretching) respectively.

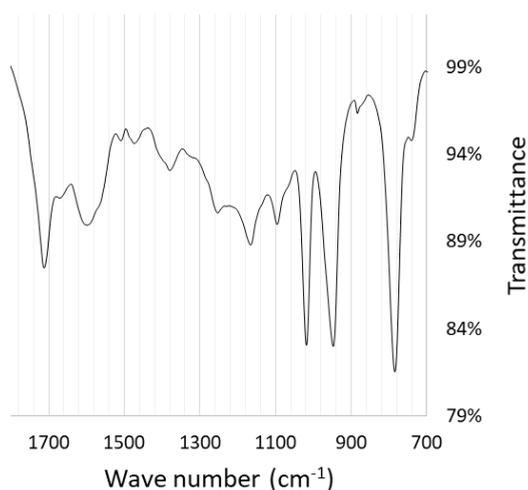


Figure 60: infrared spectrum of humins formed from 2-deoxyglucose.

Low-melting-mixtures of choline chloride, boric acid and organic acids enabled humins formation in large quantity at moderate temperature (90°C) and were consequently convenient to study humins formation. However, those reaction media are complex and the use of boric acid is rather marginal in furan derivatives synthesis.

Humins formation was therefore investigated in other media in the presence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ which has been reported as one of the most efficient catalyst for 5-HMF,

2-F production. Glucose and xylose were treated at 140°C in water and dimethylsulfoxide which are commonly used solvents to investigate the dehydration of monosaccharides. The choice of a higher temperature (140°C) compared to LTTMs experiments (90°C) is based on the lower conversion rate of monosaccharides in water and DMSO compared to LTTMs. Glucose and xylose were also treated in a mixture of choline chloride and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (molar ratio of 2:1) at 90°C. The produced humins were collected and analyzed by infrared spectroscopy as depicted in **Figure 61**.

The infrared band around 1700 cm^{-1} is found in all IR spectra again. The band near 1680 cm^{-1} is once more absent from xylose humins. Regarding glucose humins, this band is absent when the reaction is performed in water, intense when performed in DMSO and medium in the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ /choline chloride LTTM. The band near 1580 cm^{-1} remains clearly visible in all spectra. C-H bending bands between $800\text{-}790$ and $765\text{-}744\text{ cm}^{-1}$ are still observed too. The signal corresponding to trisubstituted alkenes (790 cm^{-1}) is particularly pronounced when humins were generated in the LTTM.

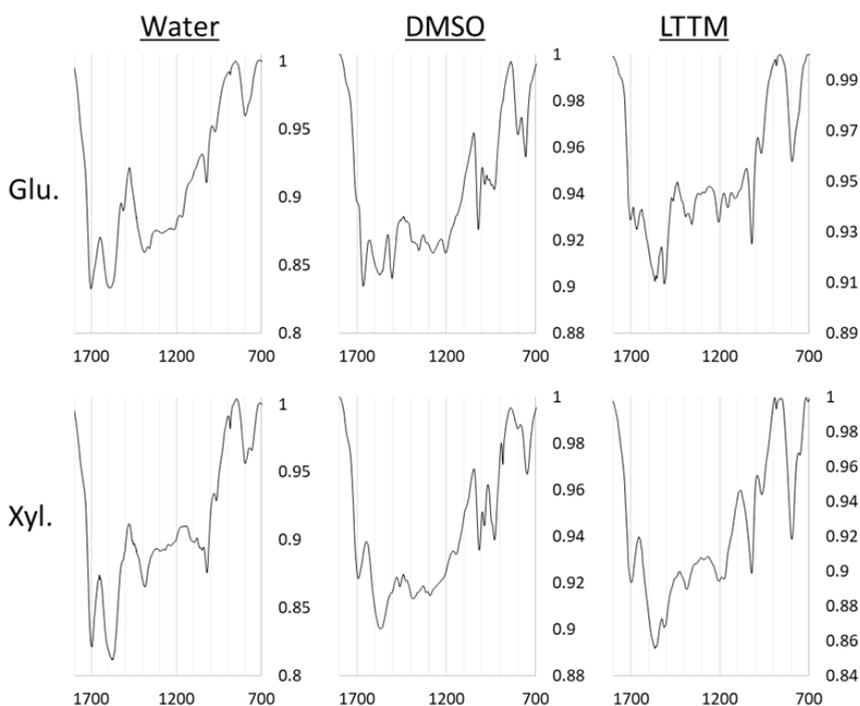


Figure 61 : Infrared spectra of humins generated from glucose and xylose in the presence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in water, dimethylsulfoxide (DMSO) or an LTTM (mixture of choline chloride and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, molar ratio 2:1).

Based on infrared spectroscopy, NMR and the proposed experiments, etherification between hexoses and 5-HMF contribute to humins formation, especially in LTTMs. However, this contribution seems limited and another mechanism, starting from monosaccharides, is largely involved in humins production. Several elements support a major role of aldol reactions:

- the very high humins yield achieved from 2-deoxyglucose compared to other monosaccharides
- the presence of an absorption band near 1580 cm^{-1} attributed to β -diketones in all humins IR spectra
- the presence of conjugated carbonyl deduced from the band near 1700 cm^{-1}
- the limited humins yield when boric acid is absent from the reaction medium

These conclusions are crucial to improve monosaccharides dehydration because, if the furan derivatives can be removed from the reaction medium to reduce its incorporation into the polymers, this action alone will not stop humins formation. A better knowledge of humins formation mechanisms is consequently needed. Potential mechanisms are investigated regarding this work findings and the existing literature in the next point.

4. Humins formation mechanisms

Several mechanisms have been proposed to explain humins formation as depicted in **Figure 62**. Mechanism A considers furan derivatives as the starting point of humins generation and consists in polycondensation reaction through electrophilic substitution. The formation of ether or acetal bonds between furan rings is expected.²⁰³ Mechanism B is more commonly proposed and also starts with the furan derivatives. A water molecule causes a hydrolytic ring opening leading to 2,5-dioxo-6-hydroxyhexanal. This compound possesses several ketone/aldehyde moieties and is highly susceptible to aldol addition/condensation reactions with other aldehydes or ketones.⁸⁰ Mechanism C was proposed by Dee and Bell (2011) and involves acetalization and etherification reactions between monosaccharides and their furan derivatives.²⁰⁴ Mechanism D is a proposal of this work and is particularly relevant in the context of boric acid catalysis. Enolization is indeed suspected to occur during the isomerization of aldose to ketose catalyzed by boric acid.^{113,171} If the carbonyl form of monosaccharides is largely more stable than the enol, the enol obtained from acyclic monosaccharides could still react with any aldehyde in the reaction medium, including furan derivatives or monosaccharides of which acyclic form is promoted by boric acid. Mechanism E is proposed by Shi et al. (2019) and involves two precursors: a dehydration product of

acyclic monosaccharides obtained by β -elimination and 2,5-dioxo-6-hydroxyhexanal. Both compounds are susceptible to aldol addition/condensation and can react together or with other carbonyl-bearing compounds.⁹²

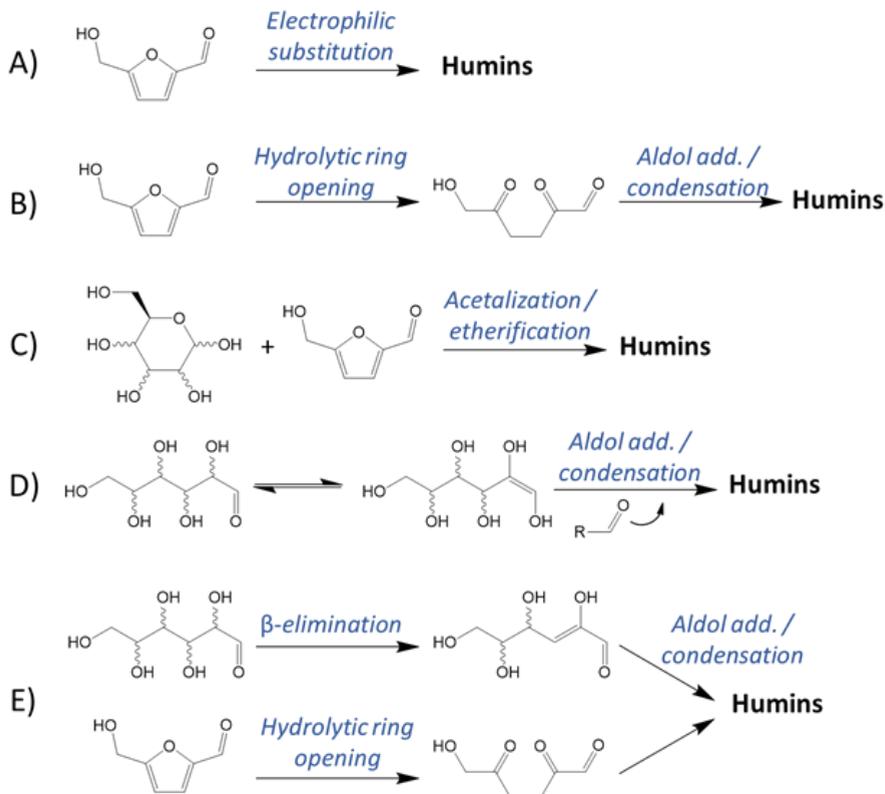


Figure 62: overview of humins formation mechanisms proposed in literature. Add. = addition.

Mechanism A (**Figure 62**) is unlikely in the tested conditions since the treatment of furan derivatives alone did not lead to massive humins production. Mechanism B (**Figure 62**), proceeding through 2,5-dioxo-6-hydroxyhexanal, is supported by several works to explain humins development from 5-HMF but requires the presence of water.^{80,182} As a consequence, the investigated LTTMs do not likely provide the conditions to favor this mechanism. Mechanism C (**Figure 62**) involving monosaccharides etherification with 5-HMF seems relevant and is supported by the infrared absorption band around 1680 cm^{-1} . However, it does not explain why 2-deoxyglucose is a better substrate for humins synthesis.

We proposed mechanism D (**Figure 62**) to illustrate a first explanation of the pronounced humins formation in the presence of boric acid. Boric acid is known to stabilize acyclic monosaccharides.¹¹³ The acyclic form exposes the carbonyl moiety, making it more reactive towards aldol reactions. Keto-enol tautomerism enables the formation of an 1,2-enediol intermediate which can react with aldehydes to generate humins. However, once the 1,2-enediol undergoes aldol addition/condensation, enol and aldehyde moieties disappear from the product structure leaving only a conjugated ketone function. This resulting product seems less reactive than aldehydes or enols and is unlikely to sustain fast polymerization. Mechanism D was therefore discarded.

Shi and coworkers (2019) proposed mechanism E (**Figure 62**) which is of particular interest since it involves acyclic monosaccharides too but does not reduce the reactivity of the products. The authors suggested that α -carbonyl aldehydes and the corresponding α,β -unsaturated aldehydes obtained through keto-enol tautomerism were primary precursors of humins as presented in **Figure 62**. Those molecules are obtained through β -elimination reactions on the acyclic monosaccharide.⁹² We explored further this mechanism and proposed a modified version explaining the observed infrared bands and the different humins yields achieved from various monosaccharides.

Figure 63 described the new proposed paths for humins production from 2-deoxyglucose and glucose. It also includes the steps towards 5-HMF synthesis. While α -carbonyl aldehydes have been observed during glucose degradation (3-deoxyglucosone, pyruvaldehyde),^{205,206} we propose that β -carbonyl aldehydes are a better substrate for humins formation. Contrarily to α -carbonyl aldehyde, the enol form is dominant in β -carbonyl aldehyde because of stabilization through conjugation and possibly hydrogen bonding between the carbonyl and the $-\text{OH}$ moiety. This stabilized enol, generated from the dehydration of acyclic monosaccharides at the C2 position, represents a reactive substrate for aldol addition/condensation involving other aldehydes such as acyclic monosaccharides or furan derivatives. The initial aldehyde moiety can also be engaged in aldol reactions. Further dehydration will extend the conjugated system and create additional sites sensitive to aldol reactions. Following this mechanism, glucose conversion to humins nevertheless requires a first dehydration step.

On the contrary, 2-deoxyglucose can directly undergo conversion to humins without this step. Because no $-\text{OH}$ moiety is present at the C2 position, there is still an α -hydrogen at C2 after enolisation, what enables aldol addition/condensation without losing the initial aldehyde moiety (**Figure 63**).

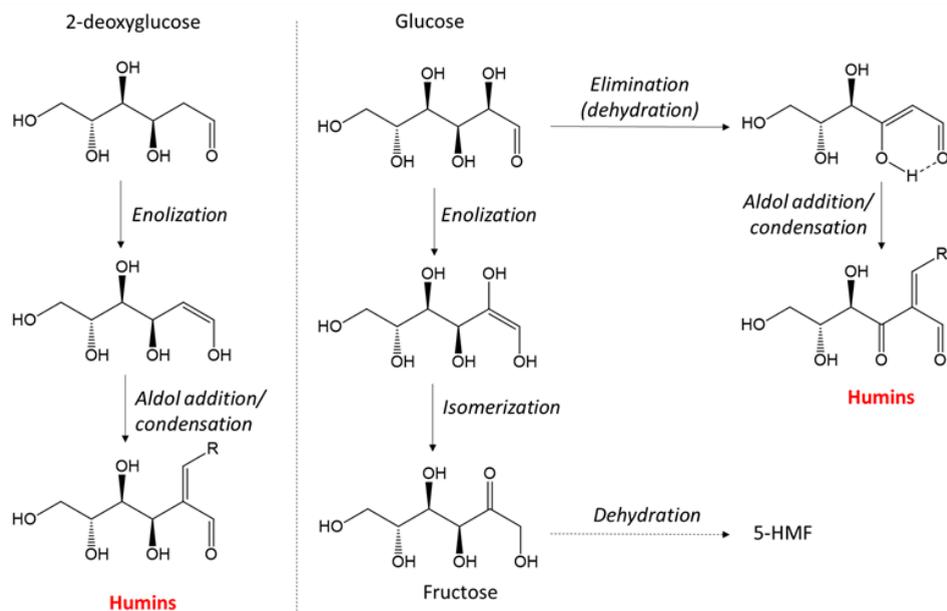


Figure 63 : comparison of 2-deoxyglucose and glucose degradation paths.

Following the proposed mechanism for humins formation, the different infrared absorption patterns of the produced humins are tentatively explained. The band around 1590 cm^{-1} is large and intense for most humins. Such an absorption is quite unique and specifically observed in β -diketones (e.g. acetylacetone, curcumine, 1,3-diphenyl-1,3-propanedione).²⁰⁷⁻²⁰⁹ α -dicarbonyls (e.g. methylglyoxal, 2,3-butanedione) and simple conjugated carbonyls (e.g. crotonaldehyde) structures do not display this pattern.²¹⁰⁻²¹² Infrared spectra of acetylacetone as well as monosaccharides, glycolic acid, boric acid and choline chloride are provided as **Supplementary Figures 21-31**. **Figure 64** describes how β -diketones could be generated through dehydration of acyclic glucose. This scheme only represents one possible path among many possibilities but illustrate the suggested principle for acyclic monosaccharide degradation driven by conjugation extension. Just after a dehydration step, the enol form is stabilized by conjugation. Upon aldol addition/condensation with an aldehyde (e.g. glucose, 5-HMF), the ketone is stabilized. It can therefore be expected that extending the reaction time in the presence of aldehydes will progressively favor keto-forms over enol-forms. In 2-deoxyglucose humins, the band around 1590 cm^{-1} seems less intense, what is consistent with the ability of the monosaccharide to polymerize without prior dehydration step.

Alkenes C-H bending vibrations are also compatible with the proposed mechanism. The absorption around 950 cm^{-1} is attributed to *trans*-disubstituted alkenes, possibly generated from aldol addition reaction involving the C1 of monosaccharides 1,2-

enediol intermediate. Absorption around $800\text{-}790\text{ cm}^{-1}$ corresponds to trisubstituted alkenes expected to form as presented in **Figure 64**. The band near $750\text{-}740\text{ cm}^{-1}$ is associated with cis-disubstituted alkenes. Observed in pentoses humins spectra, it is possibly explained by 2-furfural incorporation. The band around $760\text{-}750\text{ cm}^{-1}$ observed as a shoulder in hexoses humins spectra possibly originates from 5-HMF incorporation.

The infrared spectrum of 2-deoxyglucose humins (**Figure 60**) displays a carbonyl stretching band around 1710 cm^{-1} corresponding to a carbonyl moiety and a strong trisubstituted alkenes band near 785 cm^{-1} . Both these elements are consistent with the 2-deoxyglucose conversion path to humins presented in **Figure 63** since 2-deoxyglucose enolisation makes C2 immediately available for aldol reaction contrarily to the other monosaccharides, enabling humins formation without prior dehydration of the acyclic monosaccharide.

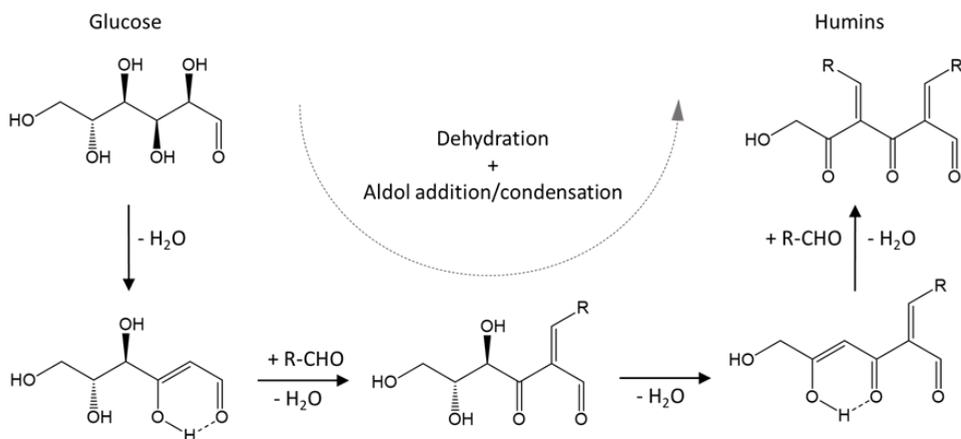


Figure 64: illustration of glucose conversion to humins through multiple dehydration / aldol reaction steps.

In the presence of boric acid, the experiments suggest that humins formation originates from the dehydration of acyclic monosaccharides followed by aldol reactions. Increasing the acid concentration and strength is expected to accelerate acyclic dehydration as observed during glucose treatment in a mixture of choline chloride (10 mmol) and boric acid (2.5 mmol) containing hydrochloric acid (2.5 mmol). No glucose remained after one hour and a 5-HMF yield of $16.76 \pm 0.44\%$ was achieved. Humins yield reached as high as $34.66 \pm 0.10\%$ of D-glucose initial mass. But the step truly responsible for polymers emergence is likely monosaccharides ring opening and the exposure of the carbonyl moiety. Experiments on glucose and xylose conversion in

$\text{ChCl} - \text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ seem to indicate that the proposed mechanism of humins formation is also valid for chromium catalysis.

The main infrared absorption bands of β -diketone moieties are related to the equilibrium between the keto-form and the enol-form. The keto-form is responsible for the absorption around 1700 cm^{-1} while the enol form is responsible for the large absorption band near 1600 cm^{-1} . Those features are perfectly observable in the IR spectrum of acetylacetone provided as **Supplementary Figure 21**. The proposed mechanism for humins formation (**Figure 64**) depicts the appearance of β -diketone structures in equilibrium with their enol-form, however, upon aldol addition/condensation reactions, the keto-form should progressively predominate over the enol-form of which formation requires an α hydrogen. It is therefore expected that the carbonyl absorption band of humins should increase relatively to the enol band at elongated reaction time.

Humins were consequently produced again from D-glucose and D-xylose but the reaction time was extended to 3h. The resulting IR spectra are displayed in the following **Figure 65**.

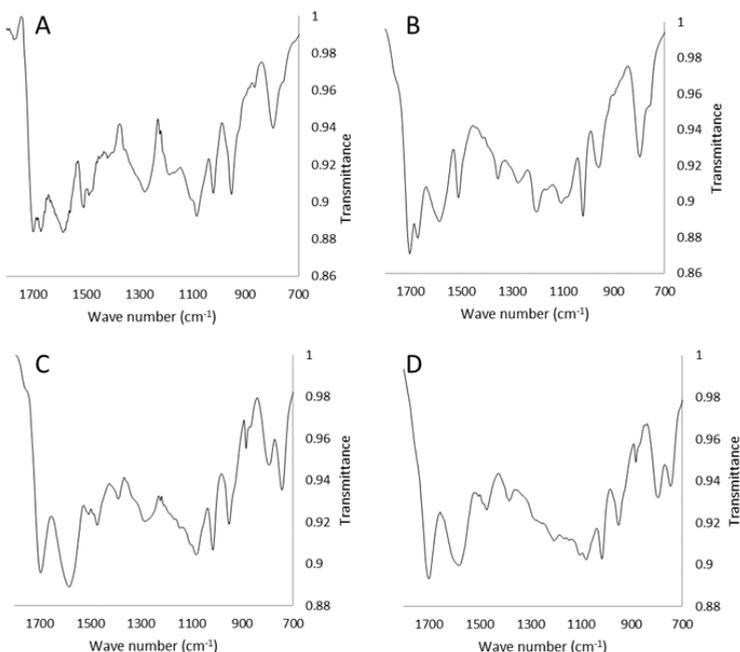


Figure 65 : comparison of D-glucose and D-xylose humins generated after 1h and 3h of treatment in a mixture of choline chloride, boric acid and glycolic acid (4/1/1 mol) at 90°C . A: D-glucose 1h, B: D-glucose 3h, C: D-xylose 1h, D: D-xylose 3h.

After 3h, the absorption bands for carbonyl moieties (1700 cm^{-1} , 1675 cm^{-1}) clearly increased relatively to the enol-form band (1585 cm^{-1}) which is in agreement with the proposed pathway.

To observe the possible involvement of glycolic acid in humins formation during the treatment of D-glucose in a mixture of choline chloride, boric acid and glycolic acid, a control experiment was performed. In the control test, glycolic acid was replaced by HCl. As observed in **Supplementary Figure 32**, the resulting IR spectra are nearly identical. Glycolic acid is therefore not a main component of the humin structure.

Another argument against a large contribution of LTTMs components as humins building blocks is the slowing of humins formation at extended reaction time. For example, after 1h, a humins yield of $54.74 \pm 0.10\%$ is achieved from 2-deoxyglucose. After 3h of treatment, the yield raised to only $58.80 \pm 1.03\%$ which means a plateau is likely reached.

The provided understanding of humins formation and structures highlights three critical elements in the context of Lewis acid-catalyzed monosaccharides transformation to furan derivatives:

- Humins formation, starting from monosaccharides, is possible in the absence of 5-HMF or 2-F. The extraction of those molecules can therefore limit the amount of formed humins but will not prevent their production, especially in the case of aldoses which cannot be readily converted to furan derivatives from their cyclic forms, contrarily to ketoses.
- Assuming acyclic monosaccharides are indeed main humins precursors, the use of isomerization catalysts like boric acid or transition metal catalysts to enable 5-HMF or 2-F synthesis may also promote humins formation. Boric acid is for instance known to stabilize the acyclic form of monosaccharides, exposing therefore their reactive moiety (carbonyl function).
- Isomerization catalysts interact with monosaccharides through vicinal diol bonding (e.g. boric acid) or glycolaldehyde moiety coordination (e.g. CrCl_3).¹⁴³ However, the proposed humins structures also possess such functional groups and can therefore compete with monosaccharide for interaction with the catalysts. Even worse, β -diketones are known as strong ligands and can inhibit catalysis by chromium as demonstrated with acetylacetone.¹⁵⁹

Those elements explain why inhibiting humins formation from aldoses is difficult but also provide clues to better prevent the polymerization phenomenon. Catalyst steric hindrance could affect humins formation. The effect of different bulky organic

structures combined to boronic acids or a metallic center should be investigated. A fine tuning of the bulkiness will likely be required to prevent interactions with humins while enabling interaction with monosaccharides. In this way, we would like to encourage further studies with bulky *N*-heterocyclic carbene-metal complexes. Research on monosaccharides dehydration catalyzed by carbene-metal complexes exists but remains scarce and the existing results seem contradictory.^{110,213} A better knowledge of humins formation and structure is useful to better inhibit their appearance but it could also improve their value as materials.

The valuable uses of humins as materials are still very limited but can be illustrated with the treatment of wood. Humins obtained from D-fructose and D-glucose can be used to improve wood stability regarding water absorption without altering its mechanical properties and fire behavior. The first step is the separation of humins into two fractions: water-soluble and water-insoluble. The wood is impregnated with the water-soluble fraction under vacuum at 60°C (1h) and cured at 150°C (1h). The resulting product has thermochemical properties similar to tropical wood and no toxicity problems exceeding those of natural wood were observed. The modified wood has a lower equilibrium moisture content than the original wood, which can enhance the resistance to degradation by fungi, and absorb less water upon immersion. If the humins-modified wood does not show enhanced fire behavior compared to the original wood, its resistance to ignition is better than wood treated by furfurylation. Furfurylation of wood is achieved through polymerization of furfuryl alcohol within the wood cell wall and increases resistance against biological degradation.²¹⁴ This example shows some potential in humins as a valuable product but there is no doubt that a more complete understanding of their structure and formation will improve their value as materials. In this regard, further evidence of the presence of β -diketones moieties in humins could improve their value in applications related to metal chelation.

5. Conclusion

Humins formation mechanisms are multiple and depends on the reaction conditions (solvent, catalyst, temperature). Degradation of 5-HMF to 2,5-dioxo-6-hydroxyhexanal is probably important in aqueous media while etherification reactions could be pronounced in more anhydrous conditions.

When the catalysis of aldoses isomerization to ketoses is attempted in order to improve furan derivatives synthesis, we support that the used Lewis acid catalysts promotes humins formation through a particular path. Because the catalysts stabilize the acyclic form of aldoses, their carbonyl moiety is exposed. Successive steps of dehydration and aldol reactions will then progressively enable the formation of an extended conjugated system.

If further studies can confirm this mechanism, it would involve the presence of β -diketone and glycolaldehyde moieties on the formed humins which can strongly interact with the catalysts and limit their performance for furan derivatives synthesis.

In such a case, humins formation cannot be inhibited simply by extracting the furan products. New catalysts able to interact with only one aldose molecule at a time should be investigated. A fine tuning of the steric hindrance could limit interactions with humins and protect the monosaccharide during the isomerization step.

6

Discussions, conclusions, perspectives

1. Discussions

As highlighted in the introduction of this work, the path towards bio-based plastic materials production is challenging. It involves many steps including biomass fractionation, polysaccharides depolymerization to monosaccharides, conversion of monosaccharides to platform chemicals and transformation of those chemicals to plastic resin. To limit GHG emissions and pollutions, the production of plastic materials from renewable resources is not enough. This strategy must be associated with an efficient recycling system and the energy consumption of synthesis processes should be reduced as much as possible.

A first step towards these goals is to enable the transformation of monosaccharides to furan derivatives at moderate temperature. In this regard, the presented work provides useful information:

- the transformation of ketoses to furan derivatives is possible below 100°C using relatively cheap reaction media at atmospheric pressure.
- the transformation of aldoses to furan derivatives is also possible below 100°C but solvent/catalyst interactions drastically impact the rate and selectivity of the process and humins formation must be controlled.
- most isomerization catalysts used to convert aldoses to ketoses prior to dehydration to furan derivatives also promote humins formation. Contrarily to the commonly proposed formation mechanisms starting from 5-HMF, several elements support that humins formation starts from monosaccharides.

Each point is further discussed to propose improved monosaccharides dehydration systems based on mechanistic understanding.

1.1. Ketoses dehydration: potential of choline chloride-based media in furan derivatives synthesis

Fructose dehydration to 5-HMF was selectively (80%) performed in a reaction medium based on choline chloride and maleic acid at 90°C (1 h). If a longer reaction time is required (5 h), the reaction still proceeds at 60 °C with a similar selectivity. This result was obtained at atmospheric pressure and at moderate temperature compared to dehydration operated in water or alcohol-based reaction medium. The achieved 5-HMF yield and selectivity is comparable with those obtained in similar conditions in imidazolium-based ionic liquids. However, the reasons behind the selective dehydration to 5-HMF in choline chloride-based medium has not been provided yet.

Several elements of the literature and the performed experiments tends to indicate a crucial role of chloride anions in enabling a selective dehydration at low temperature:

- Most reaction media enabling ketoses dehydration below 100°C contains halide anions, particularly chloride anions.
- The halide type (Cl⁻, Br⁻, I⁻) strongly affects the reaction rate and selectivity.
- The halide amount also affects the reaction rate.
- The introduction of polar protic solvents in the reaction medium decreases the reaction rate and selectivity.

The literature survey explained that chloride anions are suspected to assist the first step of fructose dehydration to 5-HMF. The first intermediate (**molecule A, Figure 15, chapter 2**) is generated after protonation of C2 hydroxyl, loss of a water molecule and deprotonation. Deprotonation is thought to be a rate-limiting step, the following steps proceeding readily towards 5-HMF formation.⁶⁶ A first clue supporting this point is the observed decreased dehydration rate of fructose when the hydrogen on fructose C1 carbon atom, involved in the deprotonation, is replaced by deuterium (kinetic isotopic effect).²¹⁵

Ab initio molecular dynamics simulations and kinetic experiments support that chloride anions facilitate deprotonation of the carbocation formed after the first protonation and dehydration step of fructose.^{65,66,94} To promote this catalysis, chloride anions must interact with the ketose molecule. Therefore, it is not surprising that high amounts of chlorides anions promote the dehydration reaction at moderate temperature in ionic liquids or deep eutectic solvents. However, when a polar protic solvent composed of small molecules (e.g. water, methanol or ethanol) is introduced in such media, this “promotion” effect is drastically reduced. A likely explanation for this phenomenon comes from chloride anions solvation. Small polar protic solvent molecules will constitute a solvation shell strongly interacting with the chloride anions, limiting their interactions with ketoses molecules. Choline chloride-based mixtures are also protic solvents but the abundance of chloride anions (e.g. 1 mole of chloride anions for 1 mole of choline cations and 1 mole of organic acid in a 1/1 choline chloride-organic acid mixture) is sufficient to enable frequent interactions with ketoses. Consequently, even if chloride anions increase ketoses dehydration rate in water or alcohol-based media, higher temperature will be required compared to chloride-based ionic liquids and deep eutectic solvents.

This is further supported by dehydration performed in polar aprotic solvents (dimethylsulfoxide, *N,N*-dimethylacetamide,...) where catalytic amounts of halide

anions drastically improve the reaction rate and selectivity of ketose dehydration. Polar aprotic solvents have the ability to solvate cations but interact very weakly with anions. In those media, anions like halides are thus more reactive than in polar protic solvents. In catalytic amounts, it could however be expected that the effects of chlorides anions should be progressively limited by the water generated from the dehydration reaction. In such a case, the use of catalytic amounts of chloride anions is not compatible with the treatment of ketoses at high load.

Choline chloride appears as an essential component of LTTMs to promote the dehydration reaction. The LTTMs prepared in this work could nevertheless be improved. The organic acid component is the Brønsted acid catalyst of the reaction and form the LTTM mixed with choline chloride. Esterification with choline or monosaccharides is expected and could reduce the selectivity or the recyclability of the medium. The LTTM could rather be based on a mixture of choline chloride, ketose and water with catalytic amounts of a strong acid. The concentration of the ketose will affect the selectivity since polymerization reactions will be favored at high load. Small amounts (e.g. 15 wt%) of water or preferably alcohols (e.g. ethanol) can be added to decrease the viscosity of the medium.

Another important aspect of ketoses dehydration in LTTMs is their extraction and purification from the reaction medium. Different extraction strategies were considered and are discussed with **Supplementary Figure 33**.

1.2. Aldoses dehydration: the impact of isomerization catalyst interactions with the reaction medium

Ketoses conversion to furan derivatives is straightforward in LTTMs composed of choline chloride and organic acid. However, those mixtures do not enable aldoses transformation to 5-HMF and 2-F. As stated in the literature survey, an isomerization catalyst is required to firstly convert aldoses to their corresponding ketoses. Two families of catalysts were described, acting through different mechanisms: metallic Lewis acids like CrCl_3 or AlCl_3 and H_3BO_3 or boronic acids. Both types of catalysts were initially compared in a mixture of maleic acid and choline chloride for the conversion of D-glucose to 5-HMF. (**Figure 66**) The compared catalysts were boric acid and aluminum trichloride. To detect a potential effect of the reaction medium on catalyst performances, various amounts of isopropanol were added. With aluminum trichloride, the selectivity decreased with a reduced amount of isopropanol while the selectivity achieved with boric acid increased. Boric acid was therefore further explored as a catalyst in LTTMS but those distinctive behaviors between aluminum trichloride and boric acid were not immediately understood.

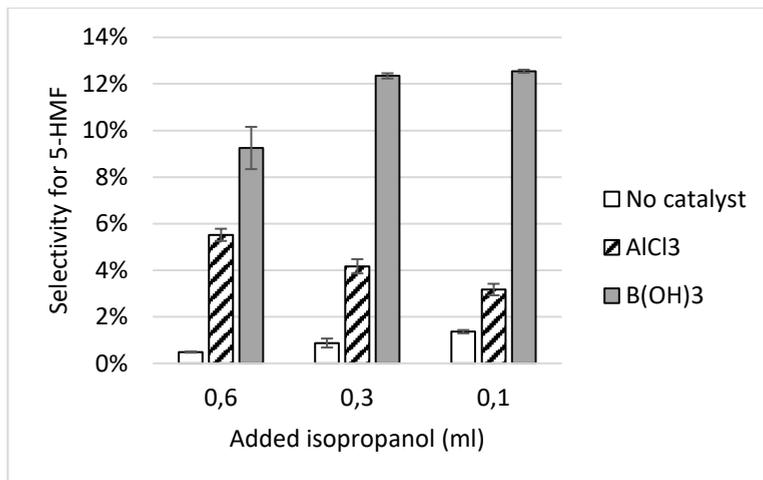


Figure 66: selectivity of the transformation of *D*-glucose (100 mg) to 5-HMF in the presence of aluminum trichloride or boric acid (50 mg) in a mixture of choline chloride (10 mmol) and maleic acid (5 mmol) after 3 h at 80°C.

Those trends are now likely explained by the interactions between aluminum trichloride and maleic acid. Complexes of maleic acid with aluminum species have been experimentally observed in water. They are even suspected to increase the dehydration selectivity when maleic acid and aluminum trichloride are used in equimolar amounts in water (140-180°C).²¹⁶ However, in the prepared LTTM, the amount of maleic acid (5 mmol) is largely superior to the amount of aluminum trichloride (< 1 mmol). Excessive interactions between maleic acid and aluminum trichloride would therefore prevent efficient isomerization of aldoses to ketoses followed by furan derivatives formation. Boric acid preferentially interacts with diols or α -hydroxyacids and is therefore less affected by the presence of maleic acid. In a similar way to aluminum trichloride, it is possible to completely inhibit the catalysis by boric acid by adding for instance an excessive amount of glycerol.

In the absence of organic acid, the catalysis by metallic Lewis acids in LTTMs is expected to be comparable or superior to the catalysis by boric acid. This was indeed observed when chromium trichloride (hexahydrate) was used in mixture with choline chloride at 90°C to convert *D*-glucose to 5-HMF (**Figure 67**). CrCl₃·6H₂O (38.00 ± 0.22% selectivity) is a more selective catalyst than boric acid (20.30 ± 2.70%). The selectivity of CrCl₃·6H₂O is however very similar to the result obtained with glycolic acid-borate esters in the mixture of choline chloride and furfural (37.86 ± 1.89% selectivity) presented in the previous chapter. No insoluble humin was observed in the presence of CrCl₃·6H₂O, probably because of the limited acidity compared to the tests with borate esters. Small amounts of fructose were observed for all tests containing CrCl₃·6H₂O, supporting its ability to specifically catalyze the isomerization step.

Because metallic Lewis acids and boric acid catalyze aldoses isomerization through different mechanisms, the possibility of synergy was explored too. (**Figure 67**). Interestingly, D-glucose conversion, 5-HMF yield and selectivity slightly increases when boric acid is added to $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ before decreasing beyond 75% Cr / 25% B. The amount of fructose (molar yield from initial glucose), generated from D-glucose isomerization, progressively increases from the test with 100% Cr to the test with 25% Cr / 75% B: 2.23 ± 0.24 , 2.38 ± 0.17 , 3.09 ± 0.08 , 4.41 ± 0.39 and 6.14 ± 0.39 %.

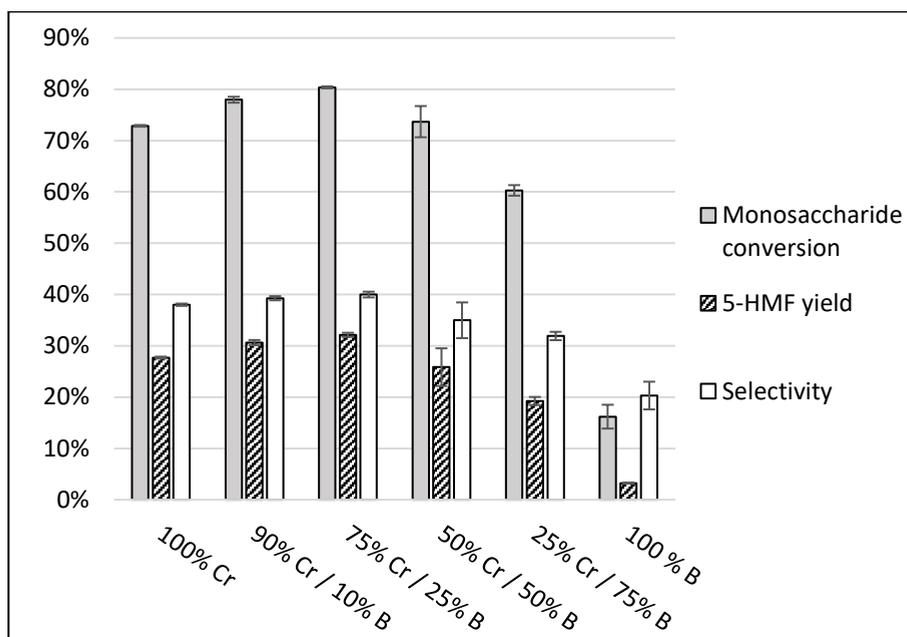


Figure 67: dehydration of glucose (0.56 mmol) to 5-HMF in a mixture of choline chloride (10 mmol) and Lewis acids (5 mmol). Chromium trichloride hexahydrate (Cr) and boric acid (B) were used alone or mixed. For example, the 75% Cr / 25% B mixture was obtained after homogeneization and melting of 10 mmol choline chloride, 3.75 mmol chromium trichloride hexahydrate and 1.25 mmol boric acid. The reaction was performed at 90 °C during 1h (210 rpm).

The selectivity of 5-HMF formation seems limited to around 40% (5-HMF yield: 30%) with chromium trichloride hexahydrate at 90°C. This result can be compared with 5-HMF yields achieved at 100 °C in imidazolium-based ionic liquids presented in **Table 10**. A first observation is that higher yields are obtained in the depicted ionic liquids. However, temperature and time affect 5-HMF synthesis. The results achieved in the choline chloride - $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ mixture (30% yield at 90 °C, 1h) and the result obtained by Bali et al. (2012) (48% yield at 100 °C, 3h; **Table 10** first line) are therefore probably close.¹⁵⁹ Another important observation is the high variability of the 5-HMF yield (from 48% to 80%) resulting from a similar catalyst ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$) in **Table 10**.

Table 10 : 5-HMF yields obtained from glucose treatment at 100 °C in imidazolium-based ionic liquids.

LTTM	Time (h)	Glucose concentration	Catalyst	5-HMF yield (%)	Ref.
[EMIM][Cl]	3	0.5g / 5g LTTM	CrCl ₃ .6H ₂ O (6 mol%)	48	159
[EMIM][Cl]	3	0.5g / 5g LTTM	CrCl ₃ (THF) ₃ (6 mol%)	70	159
[EMIM][Cl]	3	0.05g / 0.5g LTTM	CrCl ₂ (6 mol%)	70	117
[BMIM][Cl]	3	0.1g / 0.7g LTTM	CrCl ₃ .6H ₂ O (7 mol%)	65	217
[BMIM][Cl]	6	0.05g / 0.5g LTTM	Cr-carbene (9 mol%)	80	110

Several factors may be responsible for the different results achieved in various LTTMs with the similar initial catalyst (CrCl₃.6H₂O):

- The presence of water in the reaction medium
- The coordination of different chemical species to chromium
- Carbene-metal complexes formation in 1-alkyl-3-alkylimidazolium chloride

Given the large effect of water on the dehydration of fructose presented in chapter 3, a similar effect is expected in the case of glucose. The use of CrCl₃.6H₂O involves the addition of water to the reaction medium. This choice was made because CrCl₃ cannot be dissolved in the LTTMs under the tested conditions. Converted to a volume, water added with chromium chloride hexahydrate corresponds to 0.54 ml in a choline chloride - CrCl₃.6H₂O mixture mass of 2.7 g. In comparison the addition of 0.6 ml of water to 1.4 g of a choline chloride – maleic acid mixture greatly reduced 5-HMF yield from fructose (79% to 8%). In this last case however, conversion was also drastically reduced (100% to 30%) what is not observed in glucose dehydration assisted by CrCl₃.6H₂O which enabled a conversion higher than 70%. Moreover, the experiments in ionic liquids presented in **Table 10** also involved the use of CrCl₃.6H₂O and high 5-HMF yields could be achieved.

Besides the effect of water on dehydration, coordination is known to strongly affect chromium catalysis.¹⁵⁹ Using chromium coordinated to weak ligands (tetrahydrofuran, n-butanol) increases the transformation of glucose to 5-HMF (70%) compared to CrCl₃.6H₂O (48%) in EMIMCl at 100 °C. In such ionic liquids, those weak ligands are likely exchange with the abundant and more coordinating chloride anions, forming the

CrCl_4^- anion.^{159,218} In this sense, the chromium catalyst efficiency is lower (50% 5-HMF with $\text{CrCl}_3(\text{THF})_3$) if not mixed during a certain amount of time with the ionic liquid prior to the reaction. In the presence of an excess of strongly coordinating ligands like ethylene diamine, bipyridine or acetylacetonate, 5-HMF synthesis is nearly completely inhibited.^{159,117,88} In choline chloride, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ could also form the CrCl_4^- anion because water is less present and less coordinating than Cl^- . Similarly, the $-\text{OH}$ moiety of the choline cation is a weakly coordinating ligand and should not interact too much with chromium. The coordination of CuCl_2 in choline chloride-water mixtures support this hypothesis.²¹⁹ In 95 wt% water, Cu^{++} is coordinated only by water molecule. At 62 wt% water, Cu^{++} is coordinated by two water molecules and two chloride anions. At less than 39 wt% water, Cu^{++} is coordinated by four chloride anions. In a choline chloride - $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ mixture however, the coordination of three chloride anion and one water molecule to Cu^{++} is likely.²¹⁹ Surprisingly, upon cooling from 70 °C to ambient temperature, $\text{Cu}(\text{choline})\text{Cl}$ was precipitated. This solid state was however less abundant than the $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ precipitate and was not observed in liquid phase.²¹⁹ In the prepared mixture of choline chloride and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (2:1 mol), the water content is around 20 wt%. Moreover, the mixture was maintained during several hours at 90 °C under agitation before the addition of glucose. Consequently, the presence of one or several water molecules in the coordination sphere of chromium in the prepared LTTM is not impossible. A lower content of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in the LTTM will likely promote the CrCl_4^- form. Water, being a weaker ligand than chloride, should however not prevent glucose from binding to the metallic center. This is obviously not valid for choline chloride/organic acid mixtures, especially for α -hydroxyacids which constitute bidentate ligands. Additional essays as well as literature demonstrated that chromium chloride activity can be completely inhibited by α -hydroxyacids likely by strong coordination which explains the apparent higher activity of boric acid in media with those organic acids.¹⁹¹

Impurities in LTTMs also raise question regarding catalysis inhibition. Typical impurities found in choline chloride-LTTMs and in imidazolium-LTTMs are trimethylamine and 1-methylimidazole respectively. If a monodentate amine ligand like pyridine is slightly more coordinating than chloride anions, the abundance of chloride anions should limit the occurrence of such amine ligand in the coordination sphere.²¹⁸ The role of amine impurities could however gain importance in LTTMs with less coordinating anions than halides.

Besides the importance of coordination, the possibility of in-situ N-heterocyclic carbene-metal complexes formation in 1-alkyl-3-alkylimidazolium ionic liquids has been debated (**Figure 68**).

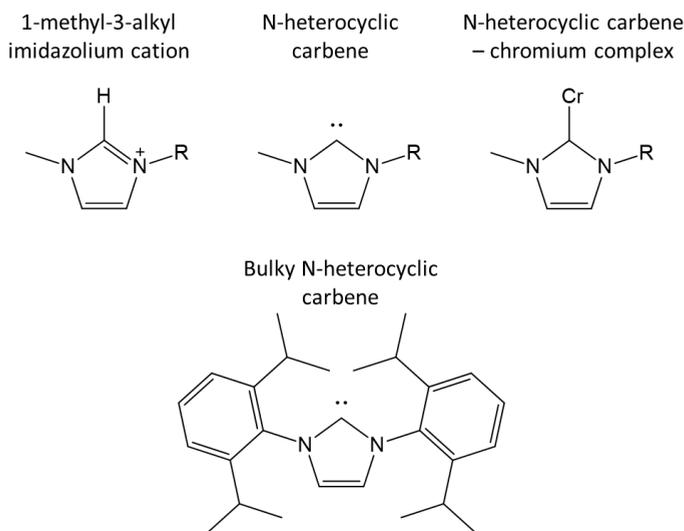


Figure 68: chemical structure of imidazolium cation, N-heterocyclic carbenes and a chromium complex. The depiction of chromium shows its bond with the carbene but does not represent its real configuration since chromium is likely also coordinated/bounded to different chemical species of the reaction medium (e.g. chloride anions, water molecule,...).

N-heterocyclic carbenes are σ -donating ligand able to form very stable complexes with transition-metal. The metal-carbon bond in those complexes is particularly resistant to cleavage compared to complexes involving other carbene types (Fischer or Schrock carbenes).²²⁰

Yong et al. (2008) prepared several N-heterocyclic carbene-chromium complexes and studied their ability to catalyze glucose conversion to 5-HMF in [BMIM][Cl] (fifth entry of **Table 10**). They observed that an 80% HMF yield could be achieved with the bulkier complexes (see bulky N-heterocyclic carbene in **Figure 68**). In a control experiments, they added bipyridine to the reaction medium and the catalysis remained unaffected (76% HMF) while bipyridine completely shut down 5-HMF synthesis when chromium chloride was used rather than the complex.^{110,117} Additionally, 5-HMF yield was relatively insensitive to the glucose/LTTM ratio and remained higher than 70% even for a weight ratio of one.¹¹⁰ This impressive performance of N-heterocyclic carbene-metal (NHC-metal) complexes naturally raised the question of their possible spontaneous apparition in ionic liquids containing transition metal catalysts.

NHC-metal complexes can be synthesized through different routes, for instance by in-situ deprotonation of 1-alkyl-3-alkyl methylimidazolium cations.²²⁰ As explained in chapter 2, those cations possess an acidic hydrogen at C2 position. In the presence of a

strong Brønsted base (e.g. potassium *tert*-butoxide) and metal chlorides, the imidazolium cation is deprotonated to form the carbene which can then react with the metal to form the complex.^{110,220} This reaction is thought to explain the solubilization of metal oxides (AgO, Ag₂O, NiO, CuO, ZnO) in imidazolium ionic liquids. For Ag₂O, the solubilization is complete after 2h at 90 °C.²²¹ This solubilization was observed only for imidazolium ionic liquids with a hydrogen atom at the C2 position. C2-substitution prevented the metal oxide dissolution.²²¹ The carbene-metal complex formation is therefore very likely to occur when metal oxides are used as catalyst in ionic liquids for the synthesis of furan derivatives.²²² Interestingly, metal-carbene complexes were obtained and isolated after dissolution of NiCl₂ in 1-butyl-3-methylimidazolium acetate, showing that a strong base is not necessarily required for their formation.²²¹ Metal-carbene formation without base has been reported for Group 10 metals in 1-alkyl-3-alkylimidazolium bromide.²²³ Consequently, at first glance, the hypothesis of in-situ NHC-metal complexes formation to explain a high efficiency of some ionic liquid in 5-HMF synthesis seems plausible. However, in the specific case of chromium chloride used as a catalyst in 1-alkyl-3-alkylimidazolium chloride, some elements support the opposite trend. For example, Cao et al. (2011) demonstrated that close results were achieved with chromium chloride in 3-butyl-1,2-dimethylimidazolium chloride or in [BMIM][Cl].²²⁷ The 3-butyl-1,2-dimethylimidazolium cation being C-2 substituted should not enable carbene-metal complex formation. Moreover, imidazolium cations being far more abundant than chromium in the reaction medium, the production of entities containing one chromium center attached to two carbenes would completely inhibit the catalysis. Such a poisoning of chromium by an excess of added carbenes has been experimentally demonstrated in ionic liquids.²¹³

The use of N-heterocyclic carbenes for selective glucose dehydration catalysis at moderate temperature is nevertheless a strategy which requires further investigation and brings encouraging perspectives in the context of furan derivatives production.

Based on this discussion and the results presented in chapters 4 and 5, coordination or reactions of isomerization catalysts with molecules of the reaction medium appear more crucial than ever to control aldose dehydration selectivity. A simplified classification of interaction strength between different ligands and a transition metal is presented in **Figure 69**. Monosaccharides being bidentate ligands, they will interact more strongly with the metal than monodentate ligands like most organic solvents, water or halide anions. Each metal will however exchange those ligands at a certain rate which is why prior dissolution in the solvent and mixing for a certain amount of time is important. Other bidentate ligands possessing an α -hydroxycarbonyl group like glyceraldehyde or glycolaldehyde will compete with monosaccharides and reduce dehydration catalysis efficiency. Strongly coordinating bidentate ligands like bipyridine or acetylacetonate completely inhibit the catalysis.

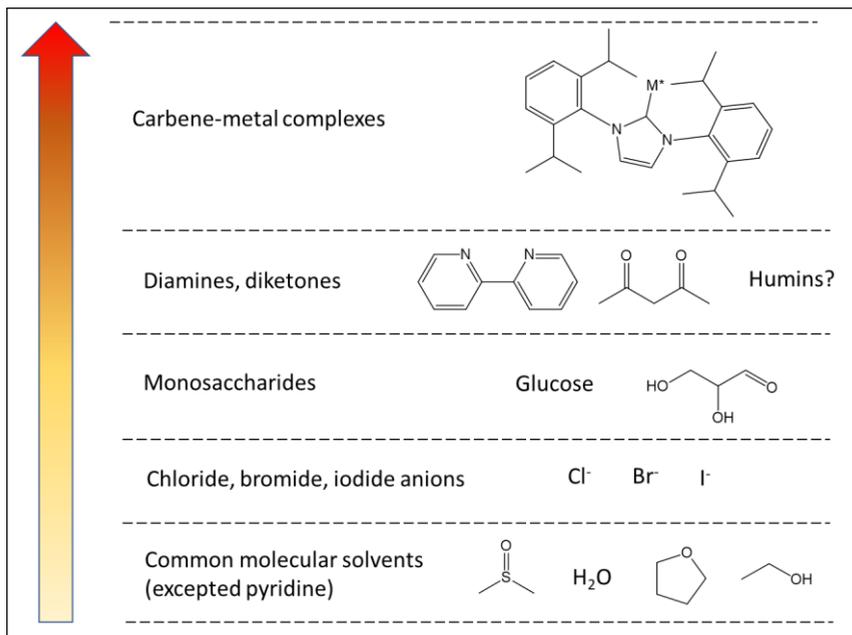


Figure 69: chromium interaction strength with different chemical species. *Other chemical species are normally coordinated to the metal center in the complex but are not represented here for clarity. The classification presented here is for general understanding purpose and does not mean that compounds of a same category possess a similar coordination strength.

1.3. Towards humins formation control and selective aldoses dehydration

This research proposes that the main cause for humins formation in the investigated LTTMs and likely in other organic solvents is the unselective dehydration of acyclic aldoses in the presence of isomerization catalysts. Because fructose can readily undergo cyclic dehydration to 5-HMF, this problem is not observed. However, 5-HMF synthesis from glucose requires ring opening. Acyclic aldoses are then exposed to acid-catalyzed dehydration leading to an increasingly conjugated structure able to grow through aldol addition/condensation. This phenomenon is a significant problem for the development of isomerization/dehydration one-pot processes since ideal conditions for 5-HMF synthesis from ketoses (low water concentration, acidity) will enable humins formation from aldoses.

In fact, humins formation as suggested in chapter 5 and aldoses transformation to 5-HMF share two common elements: both processes proceed through monosaccharides acyclic forms and involve acid-catalyzed dehydration steps. It is consequently difficult to dissociate those reactions paths and components of the reaction medium promoting

5-HMF and 2-F formation (Lewis acids, Brønsted acids, chloride anions) will likely also promote humins formation.

Another critical point is related to the possible structure of humins. In chapter 5, it was suggested that humins possess α -hydroxycarbonyl or even β -diketone groups. This means that isomerization catalysts could interact more strongly with humins than with solvent molecules or monosaccharides. Monosaccharides being also bidentate ligands, the metal center can likely bring them closer of humins precursor and favor polymerization.

Trying to limit the access to the catalyst by strong coordination may seem to be an appropriate strategy. It would require an equimolar amount of strong ligand relatively to the metal because an excess will completely block the access to the metal center. In this case, it can be expected that only one molecule at a time interact with it. However, it now appears unlikely, not only because humins are able to replace most ligand but also because they will interact with the catalyst evenly or preferentially to monosaccharides.

Rather than coordination, boric acid reacts with diols to form bonds but the same reasoning is valid. In chapter 4, it was initially thought that borate esters formation with α -hydroxyacids could limit the extent of humins apparition by blocking some of the B-OH groups. However, large amounts of humins were produced, what now makes sense since humins can compete with α -hydroxyacids for the reaction with boric acid if they indeed possess β -diketone and α -hydroxycarbonyl moieties.

This is where the potential of metal-carbene-like catalysts becomes attracting. Assuming bulky N-heterocyclic carbenes-metal complexes are truly resistant to inhibition by bipyridine, two important points can be deduced:

- The bond between the carbene and the metal is stronger than the interaction with strongly coordinating ligands, preventing several molecules including humins from meeting at the metal center and enabling catalysis at high substrate loading.
- If only one carbene is bonded to the metal center, available coordination sites are still present and coordination to bipyridine and humins should inhibit the catalysis. If this does not occur, it probably means that the bulkiness of the carbene prevent large molecules (bipyridine, humins) from interacting with the metal. Glucose conversion, while slowed down, could remain possible.

Those hypotheses certainly deserve further investigation. Additional studies on N-heterocyclic carbenes-metal complexes should be performed to confirm or invalidate

their potential in furan derivatives synthesis from aldoses. The experiments should compare Cr, Al and Sn chlorides reported as the most efficient isomerization catalysts. Control tests including inhibition by bidentate ligands of different sizes could provide a useful insight (for instance by discovering inhibition by bipyridine but not by acetylacetone). Moreover, **Figure 69** is an oversimplified vision of coordination classification. In each one of the presented categories, the different chemical species do certainly not possess identical coordination strength. The use of strongly coordinating ligands in equimolar quantity to restrain the access to the catalyst should therefore also be further investigated. Even if isomerization is not as efficient as with metal catalysts, other experiments with boronic acid derivatives possessing bulky structures should be realized too.

2. Conclusion

In conclusion of the presented research, important elements of furan derivatives synthesis were discovered and highlighted. Firstly, we demonstrated that LTTMs based on choline chloride can offer a cheap and available alternative to ionic liquids for the selective dehydration of ketoses, enabling 80% molar yields at temperatures as low as 60 °C. The reaction medium can still be improved for example by increasing ketose loading and replacing the organic acid by small amounts of a strong acid. The ability of choline chloride-based media to catalyze ketoses dehydration to furan derivatives at moderate temperature is essentially due to the abundance and reactivity of chloride anions in such mixtures.

Secondly, experiments on aldoses dehydration in the presence of boric acid enabled a better understanding of humins formation mechanisms, providing useful tools to limit their apparition. Rather than furan compounds, our results support a major role of monosaccharides as initiator of humins generation and backbone of their structure, likely by dehydration of the acyclic form followed by aldol-additions/condensations involving all chemical species with aldehyde groups.

The experiments and literature support that choline chloride-based LTTMs are also appropriate for aldoses treatment but, as for other reaction media, isomerization catalyst choice and use require critical attention, especially regarding the following points:

- The knowledge of interaction strength and type between the catalyst and monosaccharide is important. Does the catalyst interact preferentially with diols or α -hydroxycarbonyl groups?

- Based on the favored interaction of the catalyst, what are the possible interference of the reaction medium? Are reactions or coordination by solvent chemical species possible? If reactions/coordination with the solvent are desired to provide the active catalyst, which amount of time is required to obtain this active form before performing the reaction with monosaccharides?
- Is the acidity of the medium optimized regarding furan derivatives synthesis? Are all reactions potentially generating acidity considered?
- For the preparation of selective isomerization catalyst involving ligands or strong bond to organic structures to limit side reactions, are those ligands/organic structures sufficiently interacting with the catalyst to prevent inhibition by humins? Is the ratio ligand/catalyst appropriate to avoid complete inhibition of aldoses isomerization? Is the bulkiness of the catalyst appropriate to avoid inhibition by humins without stopping aldoses isomerization?

To enable the selective dehydration of aldoses to furan derivatives at moderate temperature, the two elements to control are the reactivity of chloride anions and the access to isomerization catalyst by monosaccharides and humins. Although catalysts-reaction media interactions are complexes, the presented research seems to support that the selective synthesis at reduced energy consumption is possible. The next logical step after confirming the efficiency of bulky catalysts will be the treatment of polysaccharides for which LTTMs also bring promising perspectives.

3. Perspectives

Fossil resources are a convenient feedstock which can be readily used to produce materials and energy. Coal, oil and gas were progressively generated over millions of years from the decomposition of biomass by natural processes (e.g. pyrolysis). In some ways, fossil resources are “bio-based” and nature made them easily useable for us but the natural formation rate of those resources is far slower than their current consumption rate, which is why they are not renewable. Assuming an appropriate management, vegetal resources are a renewable feedstock which can act as a carbon sink to partially reduce CO₂ net emissions, but we have to process them from the start, which requires more transformation steps than fossil resources.

The extraction of polysaccharides and their depolymerization to monosaccharides are examples of additional steps and must be mastered to achieve the synthesis of furan derivatives from plants. Among plants structural polysaccharides, hemicelluloses are polymers of pentoses and hexoses with an amorphous and commonly branched

structure. Those polysaccharides are easily depolymerized. Cellulose, a linear polymer of D-glucose with amorphous and crystalline regions, is far more resilient to depolymerization. This chemical resistance can be attributed to strong intra- and intermolecular hydrogen bonding. The disruption of this hydrogen bonds networks is therefore required to enable cellulose depolymerization.

To illustrate the drastic conditions required to depolymerize cellulose in water, only 40-45% of corn stover cellulose is converted after 2 h at 220°C. The main products are oligosaccharides with a molecular weight superior to 400 Da.²²⁴ Softer depolymerization conditions are possible with the use of enzymes. Cellulases from *Trichoderma reesei* can convert around 80% of cellulose (vegetal fibers mikro-technik C200) to glucose at 50°C (**Supplementary Figure 34**) Currently this process nevertheless possesses several drawbacks: enzymes cost, long time of treatment (72 h under the described conditions), the addition of other enzymes to prevent inhibition by the produced intermediate (cellobiose), a low stability of enzymes under the hydrolysis conditions.²²⁵ Moreover, the conditions required for furan derivatives synthesis (temperature, acidity) are currently not compatible with this enzymatic process. Consequently, the produced monosaccharides would be extracted and converted to 5-HMF and 2-F in second step.

LTTMs are explored in the hope to enable one-pot conversion of polysaccharides to furan derivatives. Cellulose solubilization greatly varies given the diversity of the tested LTTMs (from a few % in weight to more than 30 %) and the solubilization mechanisms have not been fully understood yet.²²⁶ There is however an interesting path to explore which nicely fits with monosaccharides dehydration: cellulose solubilization assisted by chloride anions. This phenomenon is not limited to LTTMs and was observed in different solvents, even in water. The previously described depolymerization of corn stover cellulose at 220°C is improved from 40-45% to 95-100% when performed in a 20 wt% solution of NaCl. The main products are still oligosaccharides but their molecular weights is reduced (200-400 Da) compared to the absence of NaCl.²²⁴ In mixture of water (30 wt%) and ZnCl₂ (70 wt%), cellulose solubility can reach as much as 1 g for 2 ml of solvent. The addition of hydrochloric acid can enable depolymerization (80% D-glucose yield, 2h) at only 70°C.²²⁷ An insight to the role of chloride anions was provided in a specific solvent, namely a *N,N*-dimethylacetamide / lithium chloride system. In this system, LiCl remains in the Li⁺-Cl⁻ ion pair form. However, when cellobiose, used as a model compound for cellulose, is added, there is a splitting of the Li⁺-Cl⁻ ion pair and a strong association between the chloride anions and the hydroxyle protons of cellobiose. The Li⁺ cation is solvated by several free *N,N*-dimethylacetamide molecules but remains close to the Cl⁻ to meet the electrical balance, which is thought to disperse cellulose chains to form an homogeneous solution.²²⁸ Chloride anions have

a key role in cellulose dissolution, but cations are likely important too as suggested by **Supplementary Figure 35** where cellulose (vegetal fibers mikro-technik C200) conversion was investigated in choline chloride based-mixtures with additional chloride salts. A better understanding of halide anions and their associated cations on cellulose depolymerization should enable the development of one-pot furan synthesis systems at moderate temperature.

As a comparison, one-pot treatments of less resilient feedstocks like starch and inulin in LTTMs have been accomplished, what supports the possibility to combine depolymerization with furan derivatives synthesis.^{229,230} To illustrate this statement, until 73 wt% of starch could be converted to 5-HMF in the ionic liquid OMIMCl after 60 min at 120°C. CrCl₂ and HCl were both used as catalysts.²²⁹ Starch, like cellulose, is a polymer of D-glucose but the linkages between units are different ($\alpha(1-4)$ and $\alpha(1-6)$ for starch and $\beta(1-4)$ for cellulose) which leads to a different structure of the polymer and an easier depolymerization. Inulin is also an interesting feedstock for 5-HMF synthesis since the polymer contains D-fructose and can be extracted from chicory. Inulin is soluble in a mixture of choline chloride and oxalic acid (150 mg/g at 70°C) and can be converted to 5-HMF (64%) after a 120 min treatment at 80°C in the LTTM. By extracting the produced 5-HMF with ethyl acetate, the LTTMs can be recycled at least six times without additional treatment.²³⁰ One-pot treatments of polysaccharides in LTTMs based on choline chloride seem therefore feasible but more research should be conducted on cellulose to reduce the effect of direct competition with the Feed and Food sectors.

If more fundamental research is still needed, some perspectives regarding the potential of LTTMs for industrial scale synthesis of furan derivatives can be provided. One of the currently most advanced processes for 5-HMF synthesis is based on the treatment of D-fructose with a Brønsted acid in methanol. D-fructose is provided by high-fructose corn syrup or saccharose and the treatment is performed at around 200°C during 1-10 min. An important advantage of this method is the production of 5-methoxymethylfurfural (MMF) rather than 5-HMF. Under this form, the furan derivative is more stable and can be separated by distillation.²³¹ While questionable, the main drawbacks are essentially the high temperature (energy consumption, high pressure) and likely the limited potential for the use of polysaccharides as a feedstock.

Treatments with polar aprotic solvents or LTTMs containing halide salts enable the dehydration of saccharides to moderate temperature at ambient pressure. The advantage of polar aprotic solvents is the limited amount of halide anions required (as low as 5 mM) for the catalysis however, the dehydration of monosaccharides to furan derivatives generates water which could hinder halide catalysis by solvation. Moreover, polar

aprotic solvents like DMSO and DMF are miscible with more organic solvents than water what reduces the options for extraction and purification. Regarding LTTMs based on choline chloride, the high amount of chloride anions could provide some resilience to the effect of generated water. Moreover, monosaccharides can form LTTMs with choline chloride which enables to work at very high substrate loading if desired and choline chloride cost is comparable to common organic solvents.

Further research on cellulose depolymerization and reaction medium recycling is needed to assess the potential of LTTMs in a viable industrial process but the current discoveries and the myriad of possibilities offered by LTTMs are encouraging in this regard.

7

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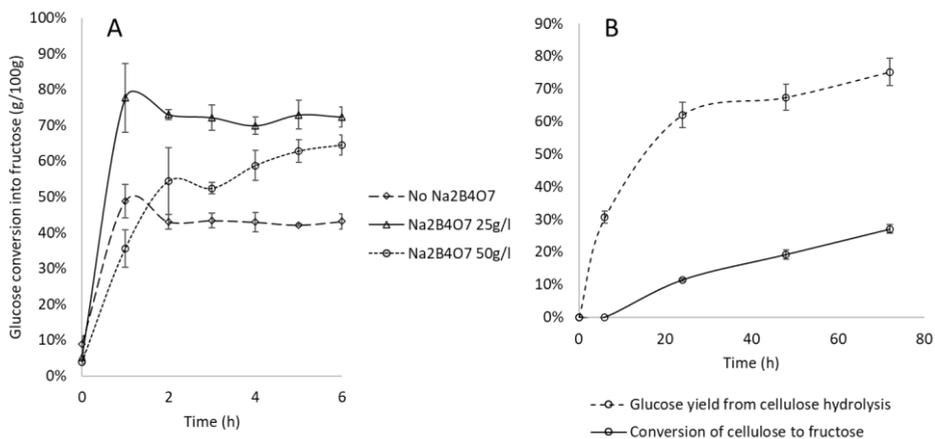
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8

Supplementary material

Assay	Absorbance (548 nm)
ChCl/H ₃ BO ₃ (2/1 mol) + HCl (0.4 mol/kg)	2.96
ChCl/H ₃ BO ₃ (2/1 mol) + HCl (0.1 mol/kg)	2.94
ChCl/H ₃ BO ₃ (2/1 mol) + HCl (0.01 mol/kg)	2.097
ChCl/H ₃ BO ₃ (2/1 mol) + HCl (0.001 mol/kg)	1.564
ChCl/H ₃ BO ₃ (2/1 mol) + HCl (0.0001 mol/kg)	1.508
ChCl/H ₃ BO ₃ (2/1 mol)	1.47
ChCl/H ₃ BO ₃ /maleic acid (4/1/1)	2.059
ChCl/H ₃ BO ₃ /malic acid (4/1/1)	2.562
ChCl/H ₃ BO ₃ /glycolic acid (4/1/1)	2.422
ChCl/H ₃ BO ₃ /acetic acid (4/1/1)	0.337
ChCl/H ₃ BO ₃ /formic acid (4/1/1)	0.784

Supplementary Table 1. Absorbance (at 548 nm) of different mixtures of choline chloride (20 mmol), boric acid (5 mmol) and organic acid (5 mmol) containing 13 wt% water and 50 μ L of thymol blue in ethanol (0.05 g/10 ml). To perform the tests with choline chloride/H₃BO₃ (2/1 mol) with or without hydrochloric acid, HCl (35.7%) was added to a 3 g mass of mixture to reach the desired concentration. Different amounts of water were added for each HCl concentration in order to keep the total water content at 13 wt%. 50 μ L of thymol blue in ethanol (0.05 g/10 ml) were again added before homogenization and absorbance measurement.



Supplementary Figure 1. A. Enzymatic isomerization of D-glucose to D-fructose in the presence of disodium tetraborate. B. Simultaneous enzymatic cellulose hydrolysis and glucose isomerization.

Description of experiments:

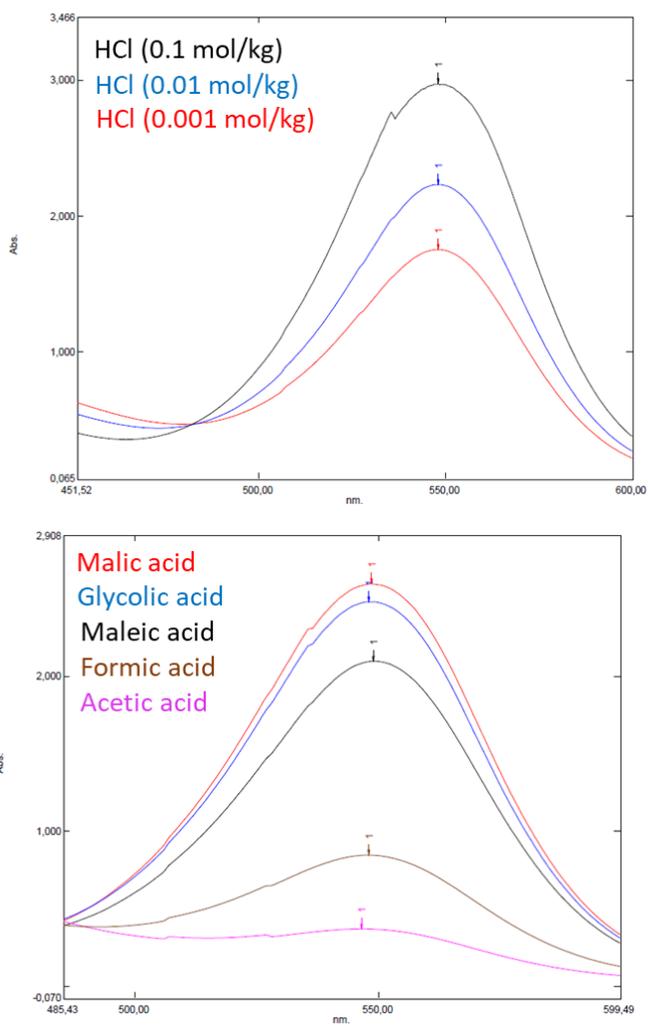
Figure A: 0.5 g of immobilized glucose-isomerase from *Streptomyces murinus* (Sweetzyme IT from Novozyme) were dispersed in 20 ml of phosphate buffer (pH 7.7) heated at 70°C and containing 50 mg of mg MgSO₄. 1 g of D-glucose was added to the dispersion for isomerization to D-fructose. Different amounts of disodium tetraborate (Na₂B₄O₇) were added to observe a shift in the glucose-fructose equilibrium.

Figure B: 150 μL of Celluclast 1.5 L (corresponding to around 15 FPU, cellulases from *Trichoderma reesei*, Novozyme), 50 μL of Novozyme 188 (cellobiases from *Aspergillus niger*, Novozyme) and 0.05 g of immobilized glucose-isomerase from *Streptomyces murinus* (Sweetzyme IT from Novozyme) were dispersed in 40 ml of acetate buffer (pH 5) at 50°C containing 1.25 g/L of MgSO₄, 2.5 g/L of CoCl₂·6H₂O and 150 μL of a 5% sodium azide solution. 0.176 g of cellulose (Alba-Fibre® Cellulose, Mikro-Technik) were added and the evolution of the reaction was followed.

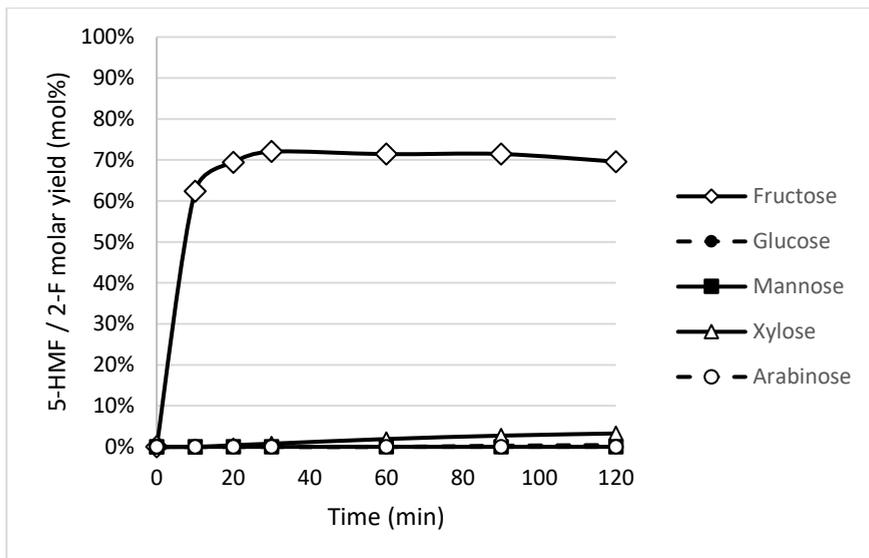
Discussion:

Both figures illustrate the limits of enzymatic processes in the context of furan derivatives synthesis. Those obstacles are however not insurmountable and promising

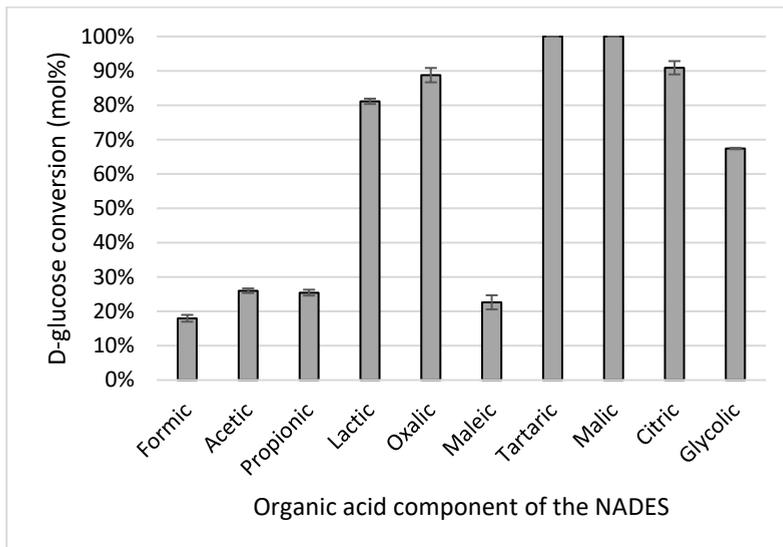
perspectives exist. In Figure A, the isomerization of D-glucose to D-fructose by an isomerase is depicted. The thermodynamic equilibrium (around 40-50%) between both monosaccharides is clearly visible. Interestingly, this equilibrium can be largely shifted towards D-fructose if the monosaccharide is involved in reactions. In this case, the addition of disodium tetraborate leads to monosaccharides-borate esters formation. In their borate esters forms, monosaccharides cannot undergo enzymatic isomerization. D-fructose-borate esters being more stable than D-glucose-borate esters, the equilibrium is shifted. If the equilibrium problem can be overcome, the pH incompatibility between glucose isomerases and cellulases remains a problem. The loss of glucose-isomerase activity in acidic conditions begins at pH 5 and is progressive. The initial tetrameric form of the enzyme decomposes itself successively into trimeric, dimeric and monomeric forms. This acid inactivation is explained by a reversible loss of the metallic cofactors and an irreversible aggregation of proteins. The optimal pH for cellulases from *Trichoderma reesei* (around 5) is therefore at the limit of what can be tolerated by glucose isomerase from *Streptomyces murinus*. Figure B shows however that the isomerase activity remains possible simultaneously to cellulose hydrolysis. Using both types of enzymes together, between 20 and 30 % of cellulose can be converted to D-fructose. This yield may seem limited but is encouraging considering that it was obtained from two enzymes which were normally incompatible. The discovery or development of isomerases stable in acidic conditions should rapidly enable a more efficient conversion of cellulose to D-fructose. Research on this topic is in progress. For instance, Staudigl et al. (2014) produced an isomerase from *Lactobacillus reuteri* (DSMZ 17509) and studied its activity.²⁰⁹ The isomerase was optimally active at 65°C and pH 5.0. The enzyme converted 48% of D-glucose to D-fructose after approximately 7 hours and required divalent cations such as Co^{++} and Mn^{++} for optimal activity. In another study, Kaneko et al. (2000) isolated the glucose isomerase of *Streptomyces olivaceoviridis* E-86.²¹⁰ This enzyme optimally works in alkaline conditions but maintains its activity at pH 5 after incubation at 60°C for 30 hours. Consequently, the authors used this acid-stable glucose-isomerase in combination with α -amylase and glucoamylase to produce high fructose corn sweetener from liquefied starch in a single step.



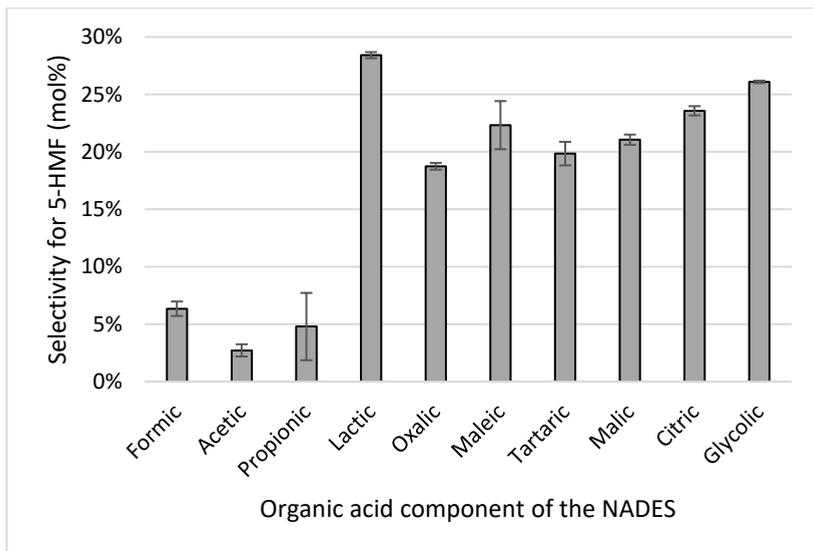
Supplementary Figure 2. Absorbance (from 485 to 600 nm) of different mixtures of choline chloride (20 mmol), boric acid (5 mmol) and organic acid (5 mmol) containing 13 wt% water and 50 μ L of thymol blue in ethanol (0.05 g/10 ml).



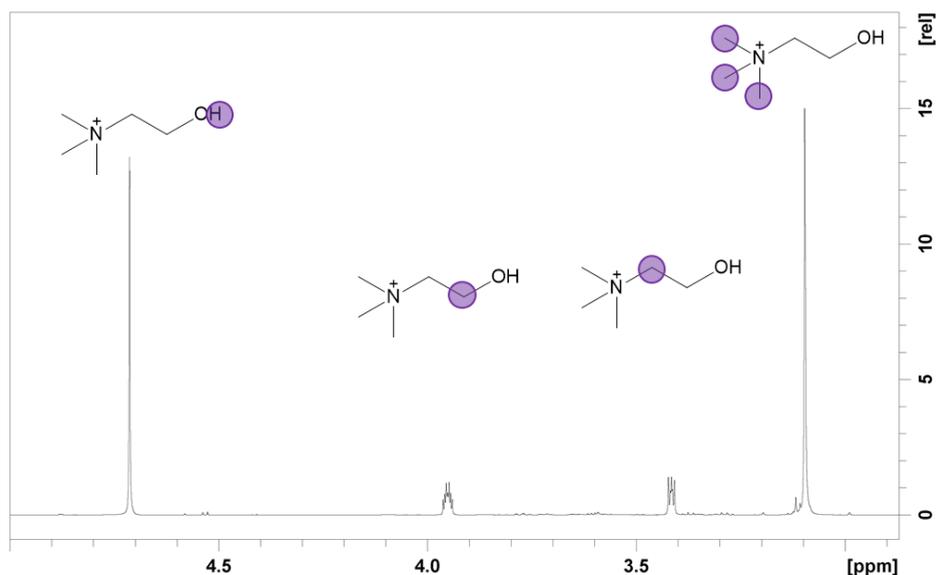
Supplementary Figure 3. Evolution of 5-HMF and 2-F molar yields (mol%), for hexoses (0.56 mmol) and pentoses (0.67 mmol) respectively, in a mixture of choline chloride (10 mmol) and maleic acid (5 mmol) at 90 °C.



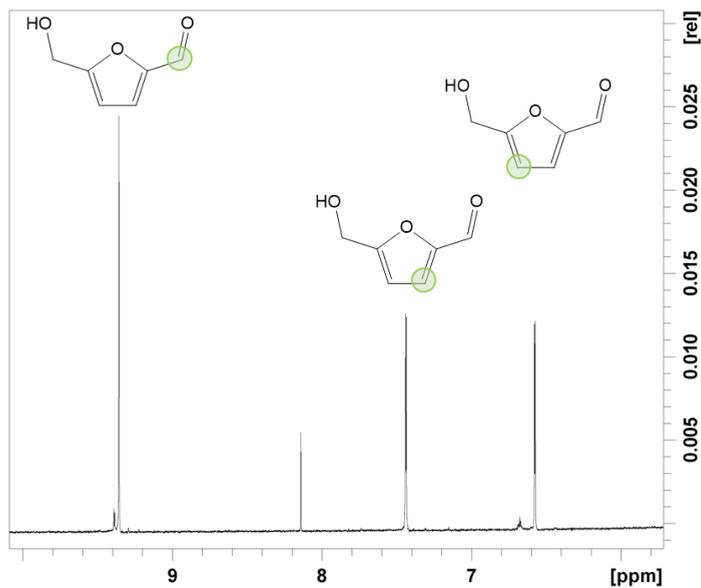
Supplementary Figure 4. D-glucose conversion (0.56 mmol) in mixtures of choline chloride (10 mmol), organic acid (2.5 mmol) and boric acid (2.5 mmol) after 1 h at 90 °C, 210 rpm.



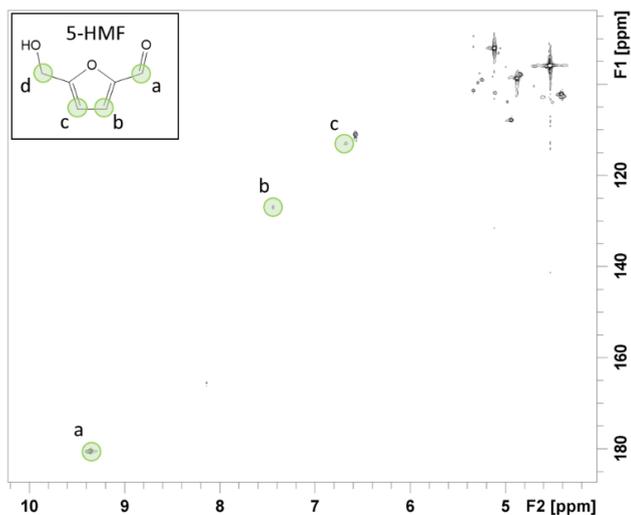
Supplementary Figure 5. Selectivity of D-glucose (0.56 mmol) transformation to 5-HMF in mixtures of choline chloride (10 mmol), organic acid (2.5 mmol) and boric acid (2.5 mmol) after 1 h at 90 °C, 210 rpm.



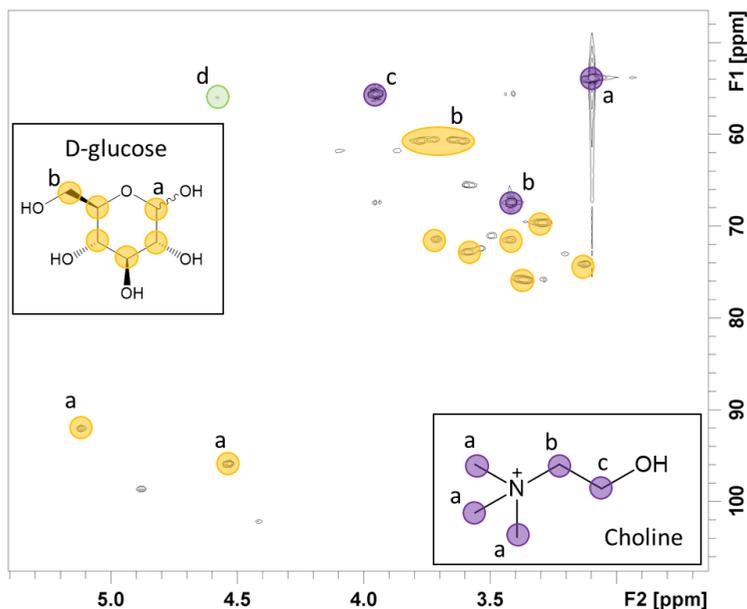
Supplementary Figure 6. 1D ^1H spectrum of a mixture of choline chloride, boric acid and oxalic acid (4/1/1 mol) after a 1h treatment of D-glucose at 90 °C. The sample was dissolved in D_2O before analysis.



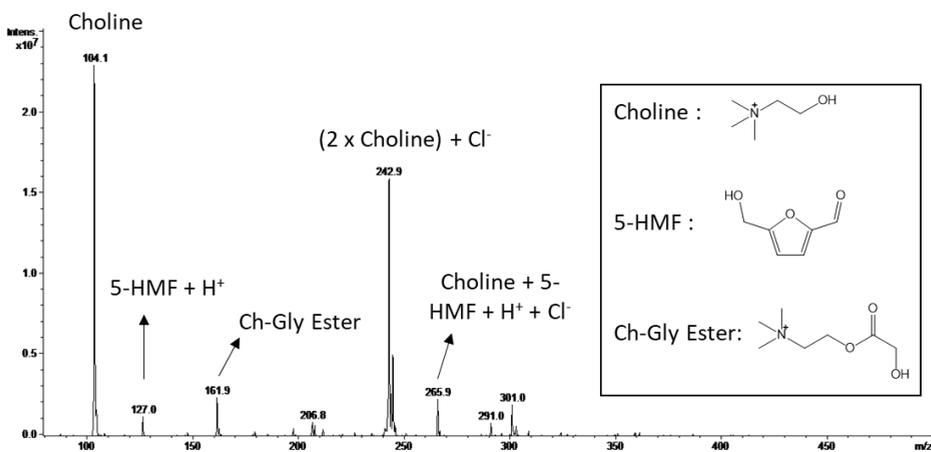
Supplementary Figure 7. 1D ^1H spectrum of a mixture of choline chloride, boric acid and oxalic acid (4/1/1 mol) after a 1h treatment of D-glucose at 90°C . The sample was dissolved in D_2O before analysis.



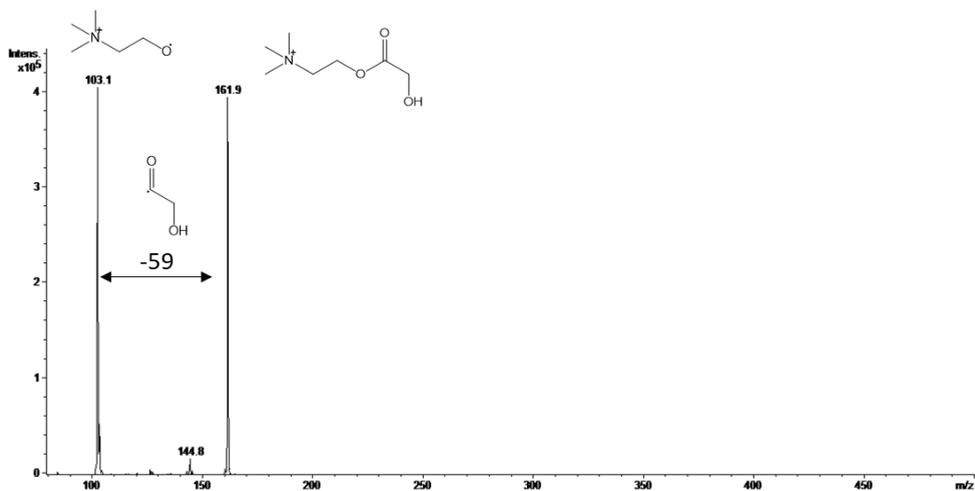
Supplementary Figure 8. HSQC NMR spectrum after treatment of D-glucose 1 hour in a mixture of choline chloride, oxalic acid and boric acid (signals attributed to 5-HMF are highlighted in green)



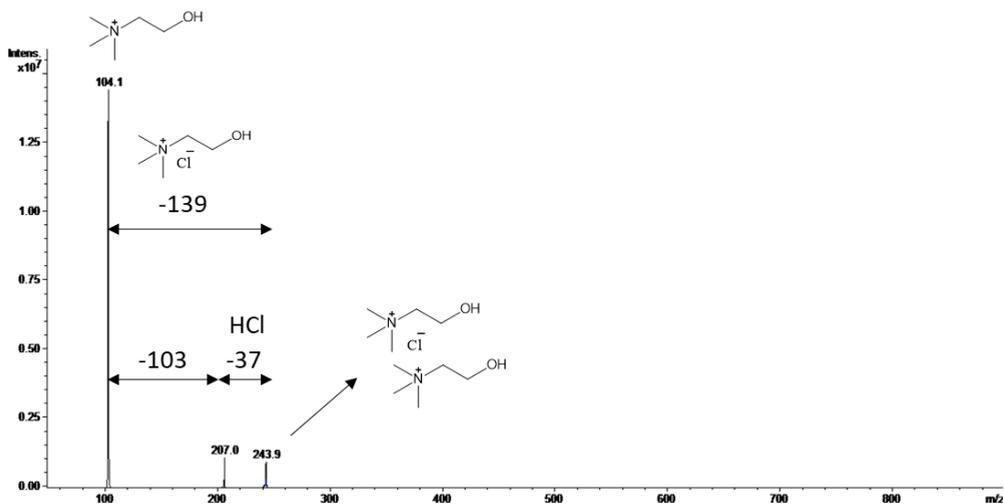
Supplementary Figure 9. HSQC NMR spectrum after treatment of D-glucose 1 hour in a mixture of choline chloride, oxalic acid and boric acid (Signals were attributed to molecules as follows: Green: 5-HMF, Purple: choline chloride, Yellow: D-glucose)



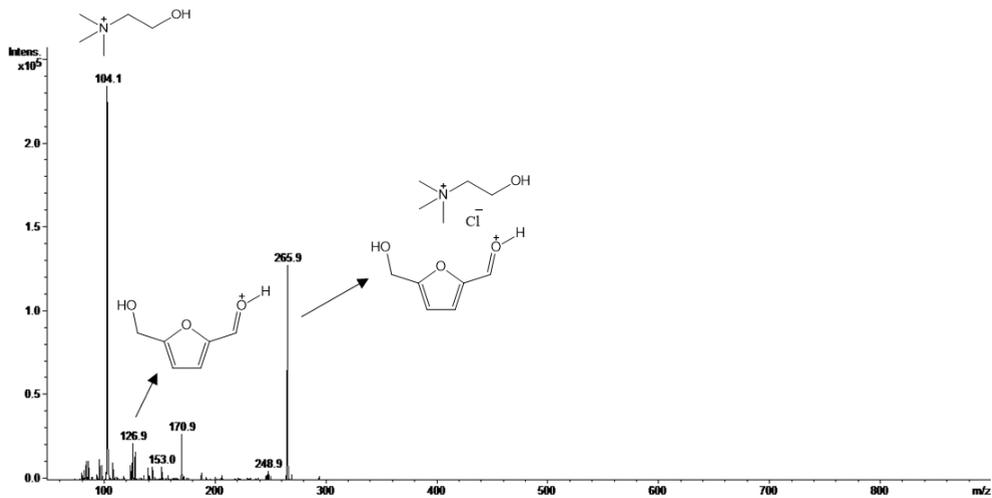
Supplementary Figure 10. Mass spectrum obtained after direct injection of the diluted mixture resulting from D-glucose treatment during one hour in choline chloride, glycolic acid and boric acid (4/1/1 mol).



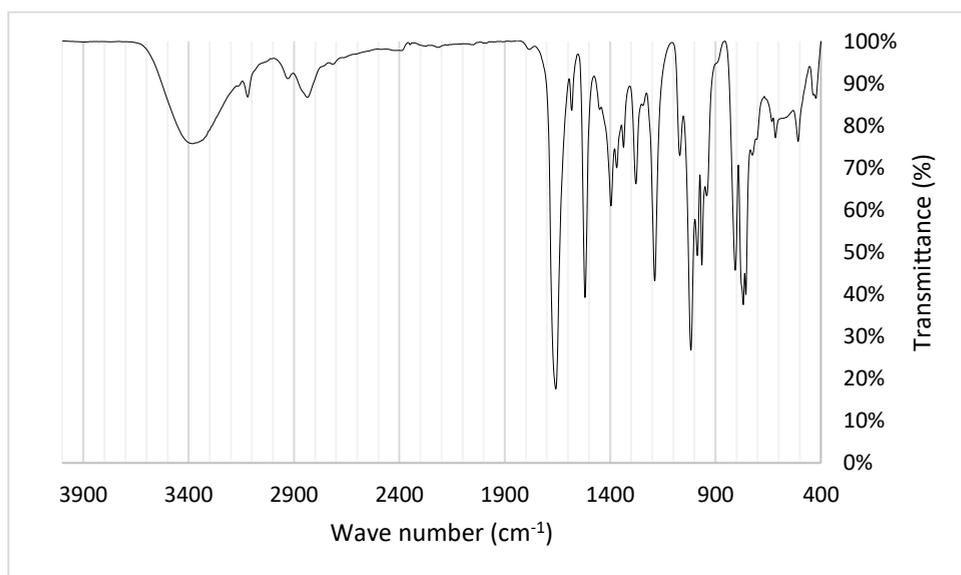
Supplementary Figure 11. Mass spectrum obtained after fragmentation of the ion at m/z 161.9 in Supplementary Figure 10.



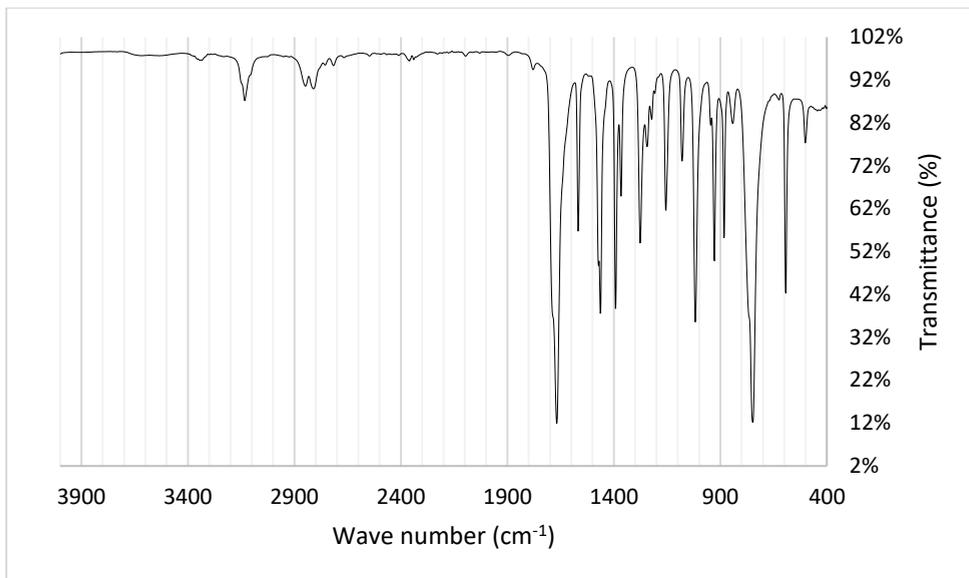
Supplementary Figure 12. Mass spectrum obtained after fragmentation of the ion at m/z 243.9 in Supplementary Figure 10.



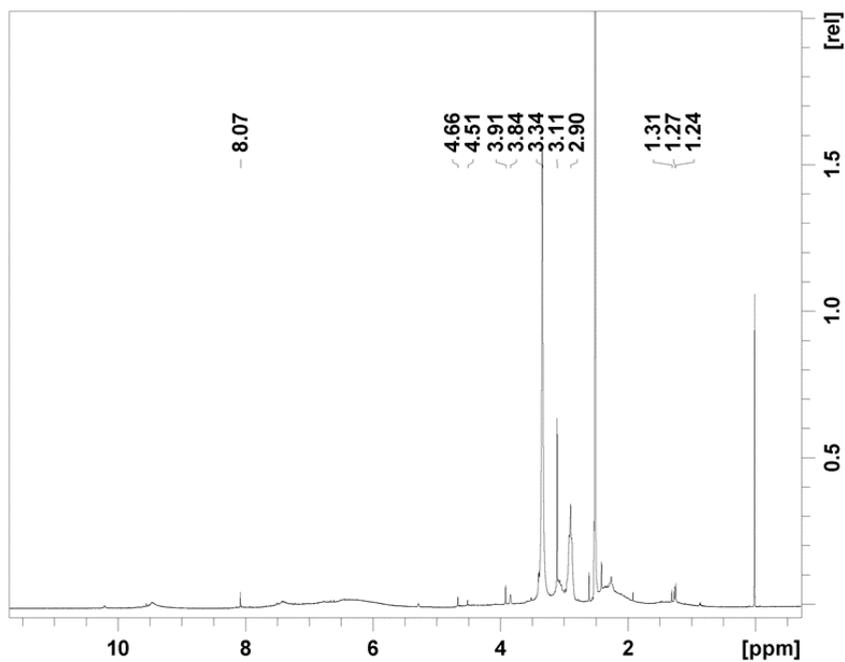
Supplementary Figure 13. Mass spectrum obtained after fragmentation of the ion at m/z 265.9 in Supplementary Figure 10.



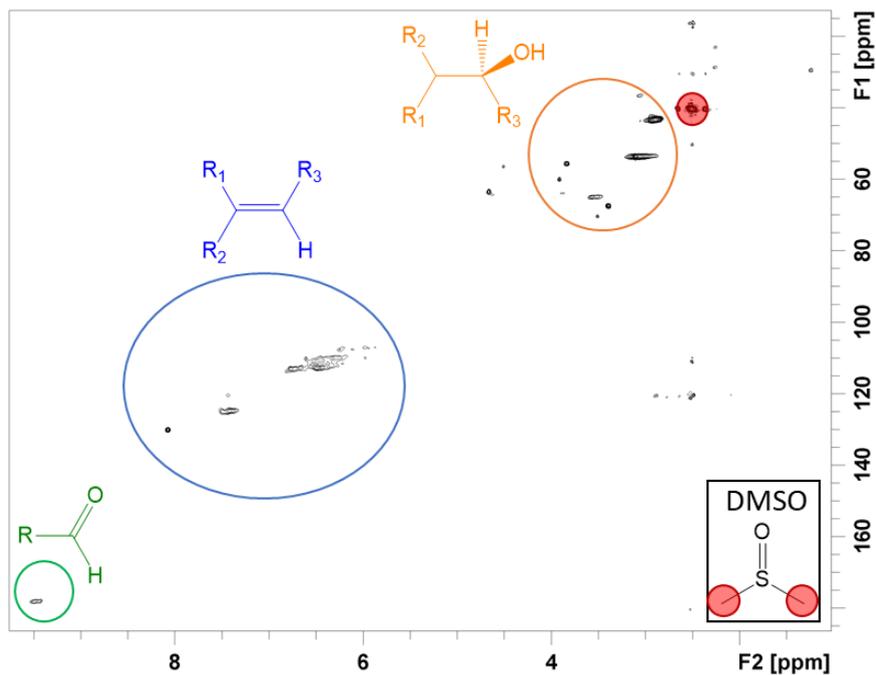
Supplementary Figure 14. IR spectrum of 5-HMF



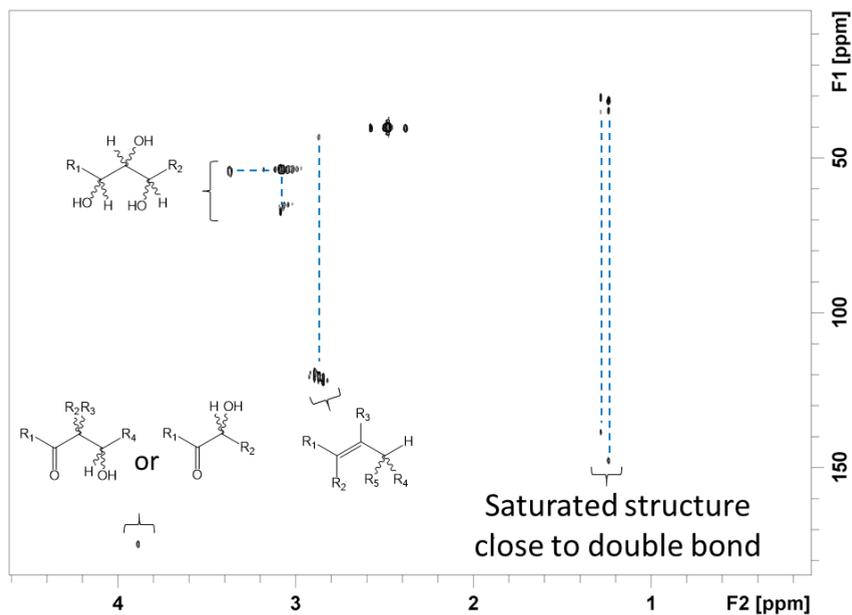
Supplementary Figure 15. IR spectrum of 2-F



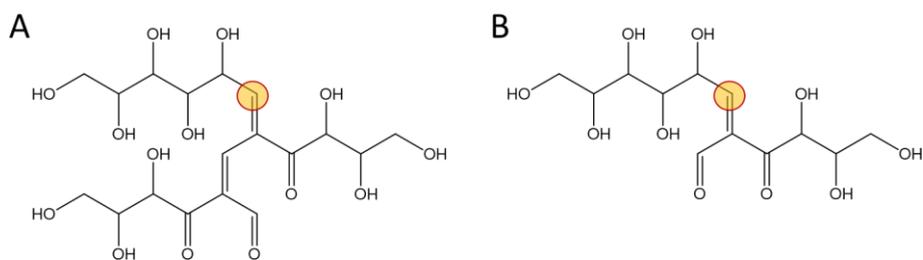
Supplementary Figure 16. 1D ¹H NMR spectrum of D-fructose humins



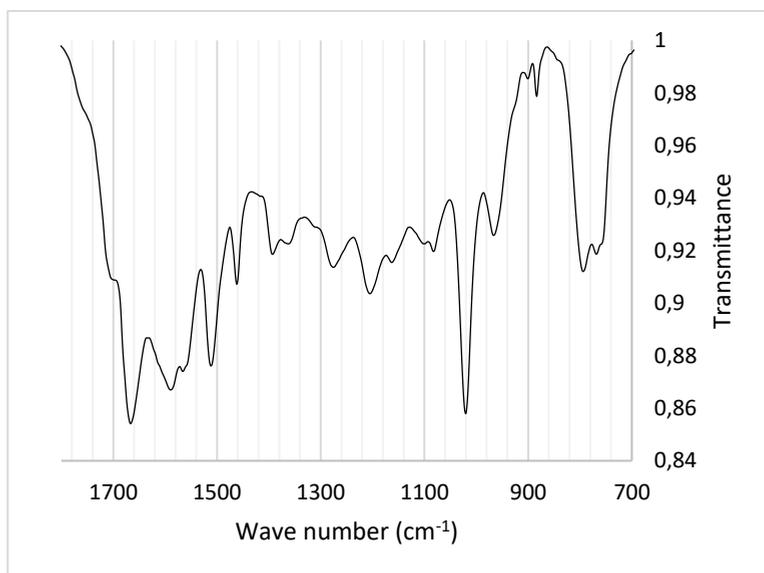
Supplementary Figure 17. 2D HSQC NMR spectrum of D-fructose humins



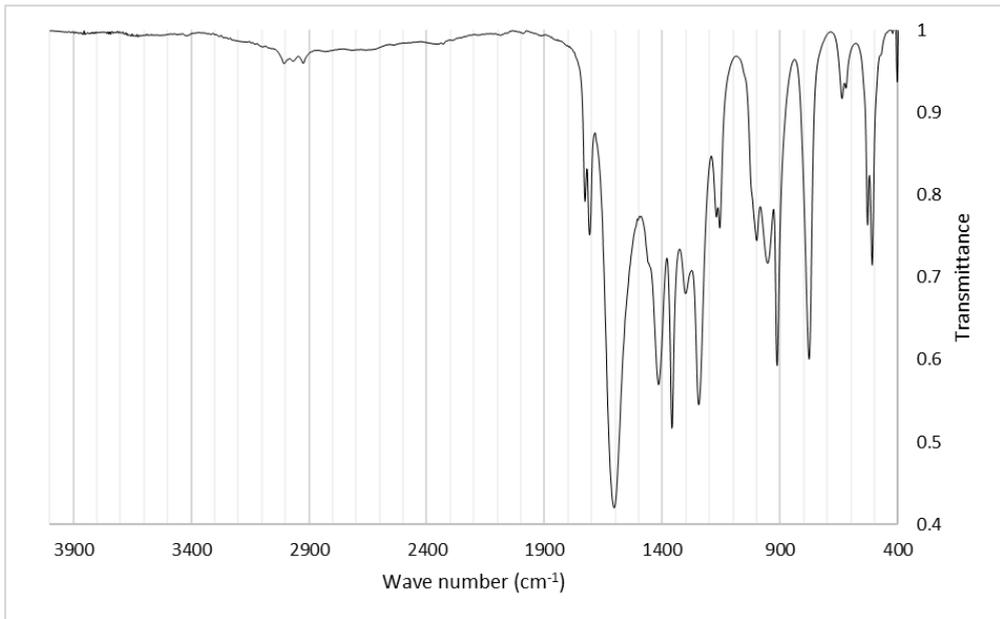
Supplementary Figure 18. 2D HMBC NMR spectrum of D-fructose humins



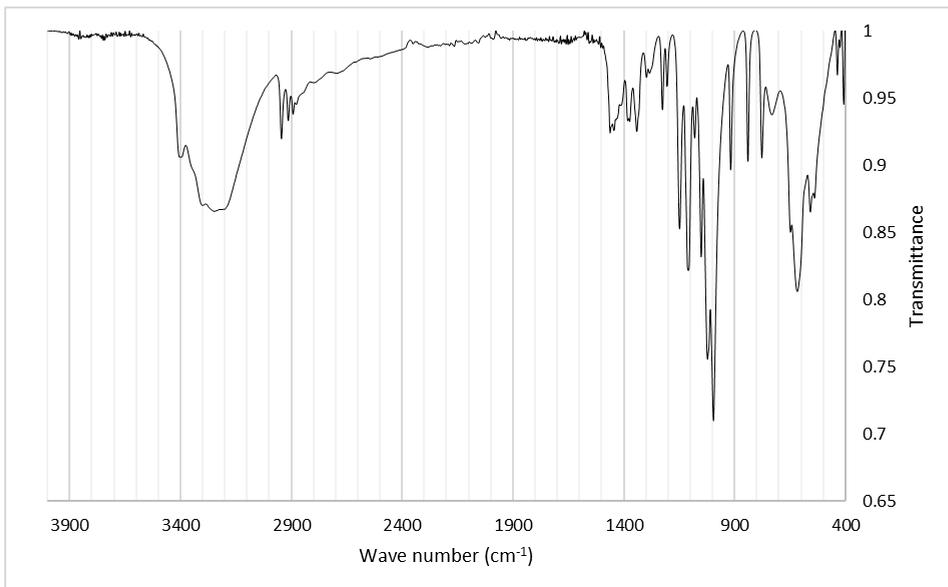
Supplementary Figure 19. Suspected types of structures in humins structure according HSQC NMR signals observed for D-fructose humins around (8.1, 130.0 ppm) (A) and for the diluted reaction medium after filtration around (8.1, 165 ppm) (B).



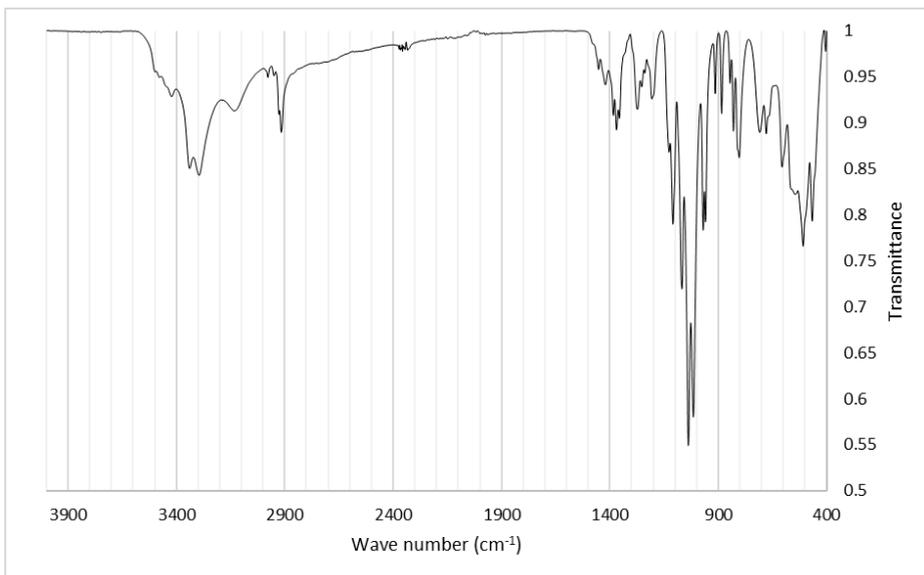
Supplementary Figure 20. IR spectrum of humins generated by the treatment of glucose (0.56 mmol) and 5-HMF (0.56 mmol) in a mixture of choline chloride and glycolic acid without boric acid (90 °C, 60 min, 210 rpm). The acidity of the medium was increased by the addition of HCl (35.7 wt%, 20 μ L).



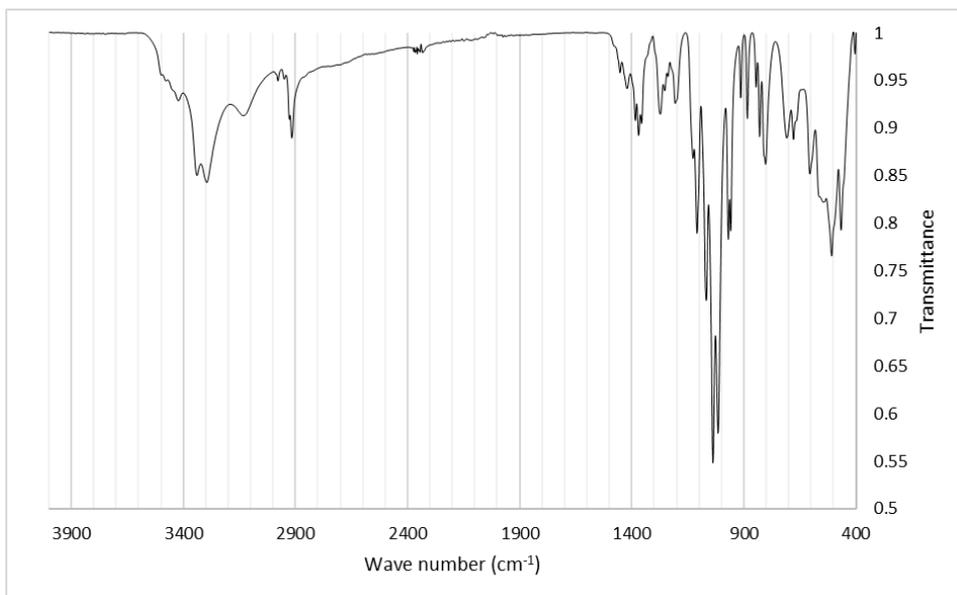
Supplementary Figure 21. IR spectrum of acetylacetone



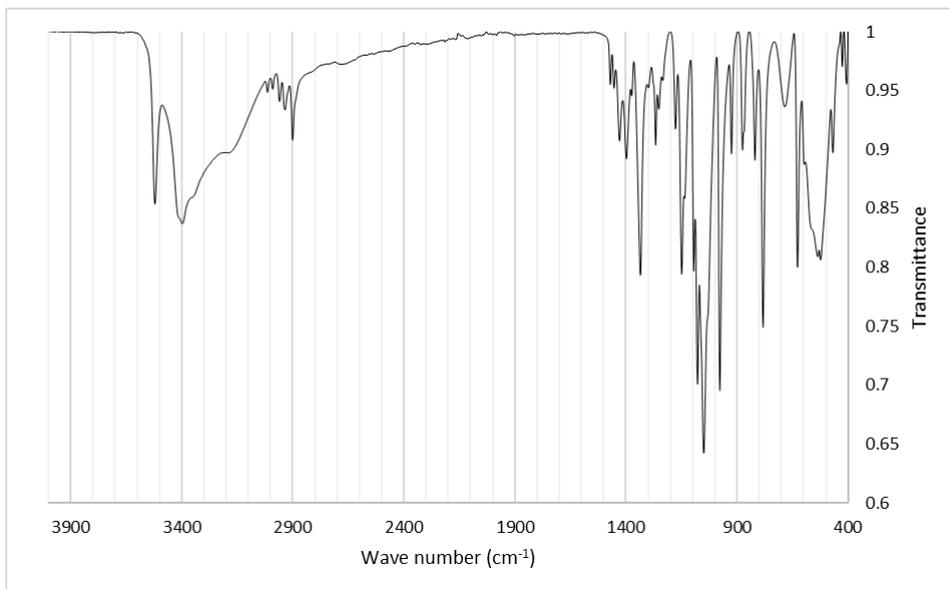
Supplementary Figure 22. IR spectrum of D-glucose



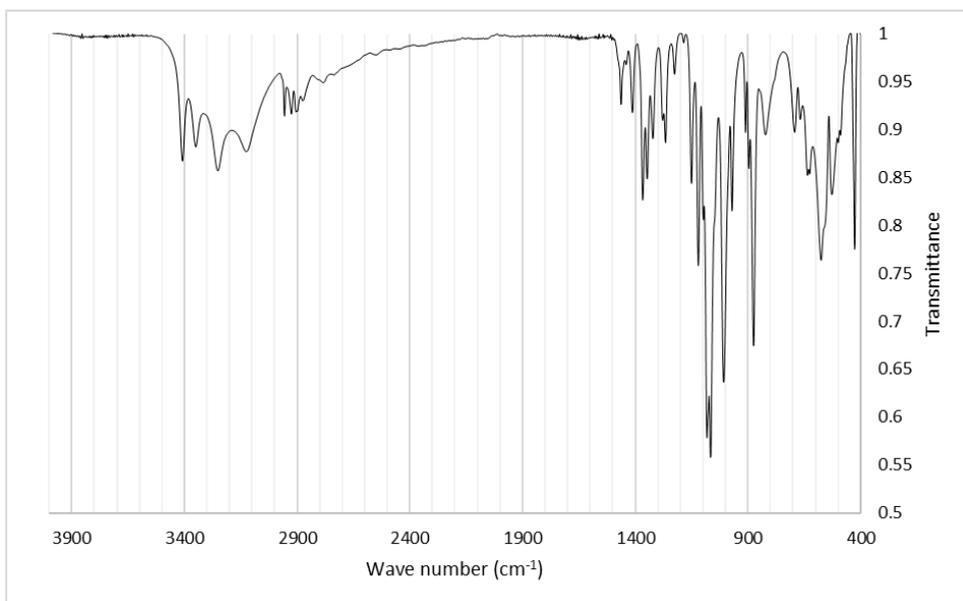
Supplementary Figure 23. IR spectrum of D-mannose



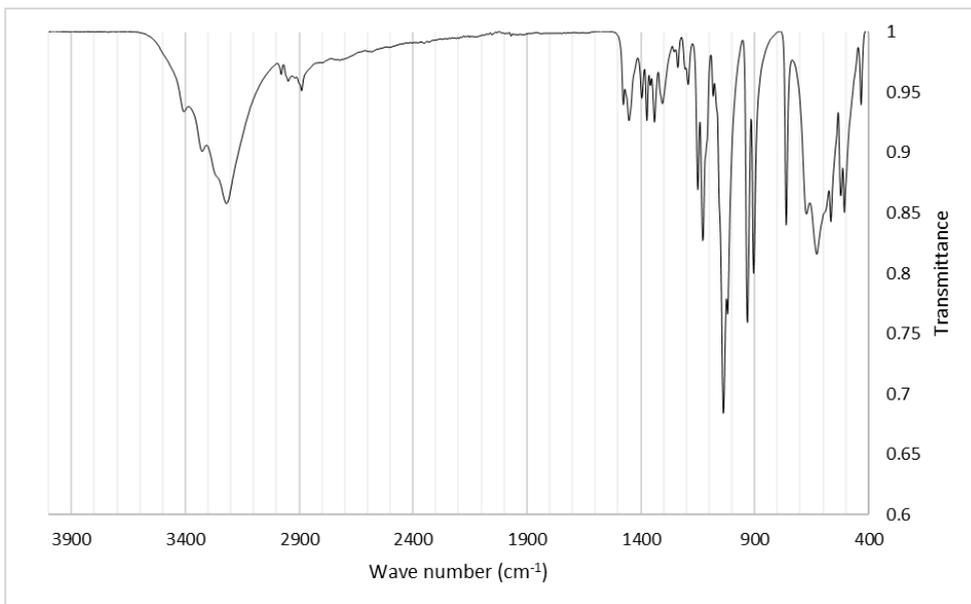
Supplementary Figure 24. IR spectrum of D-galactose



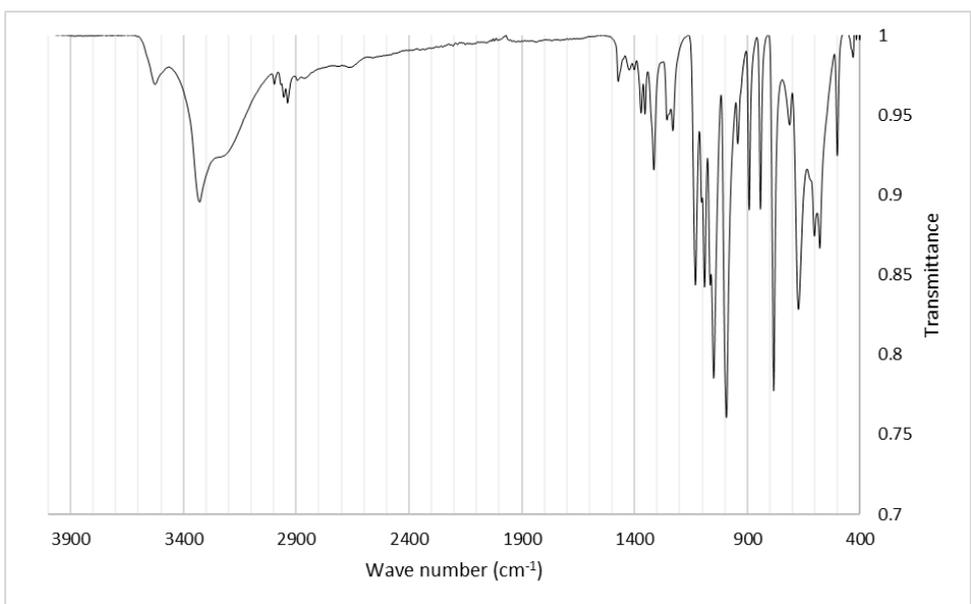
Supplementary Figure 25. IR spectrum of D-fructose



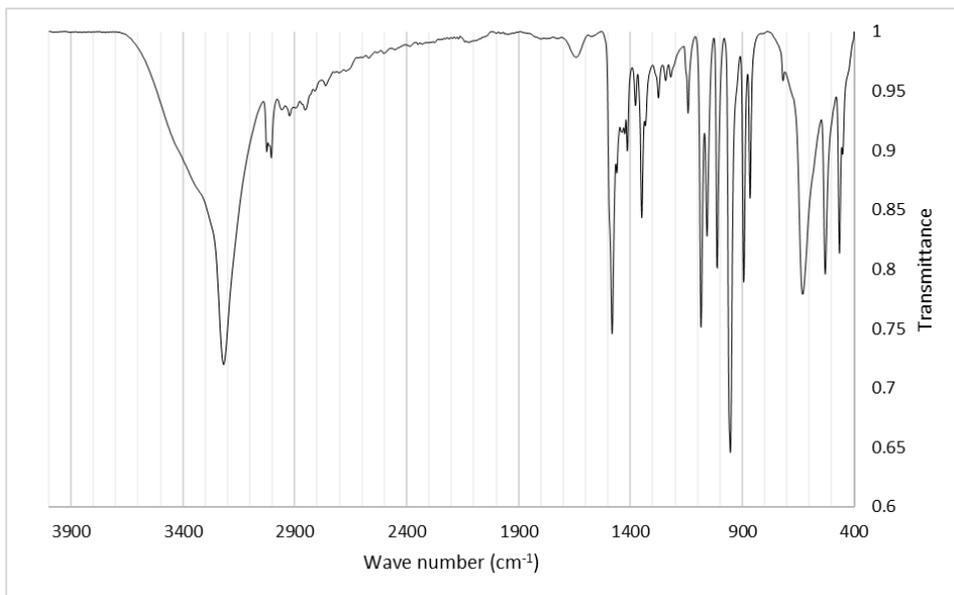
Supplementary Figure 26. IR spectrum of 2-deoxyglucose



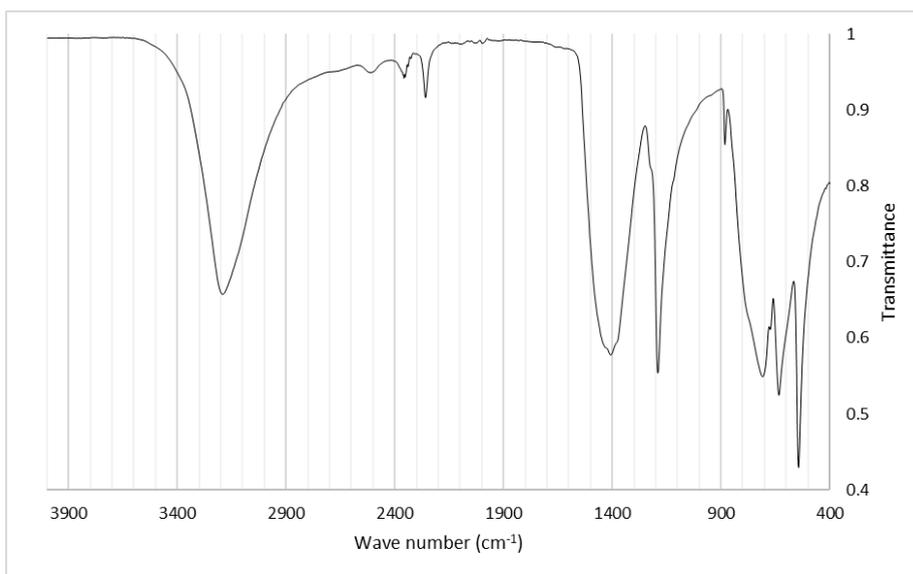
Supplementary Figure 27. IR spectrum of D-xylose



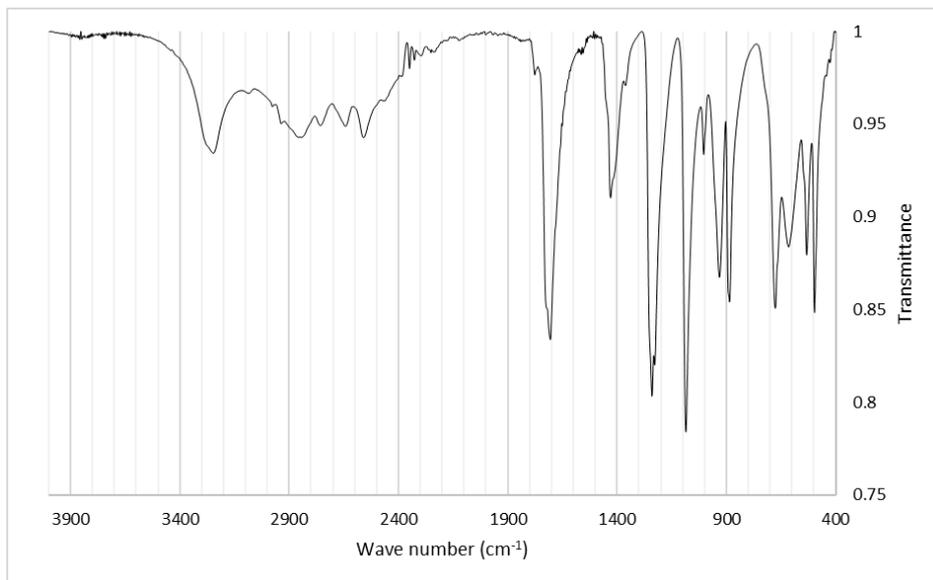
Supplementary Figure 28. IR spectrum of D-arabinose



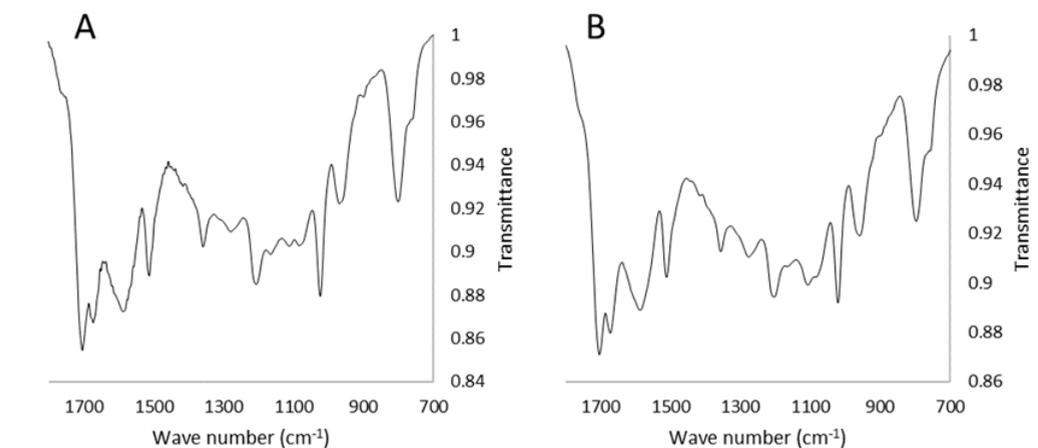
Supplementary Figure 29. IR spectrum of choline chloride



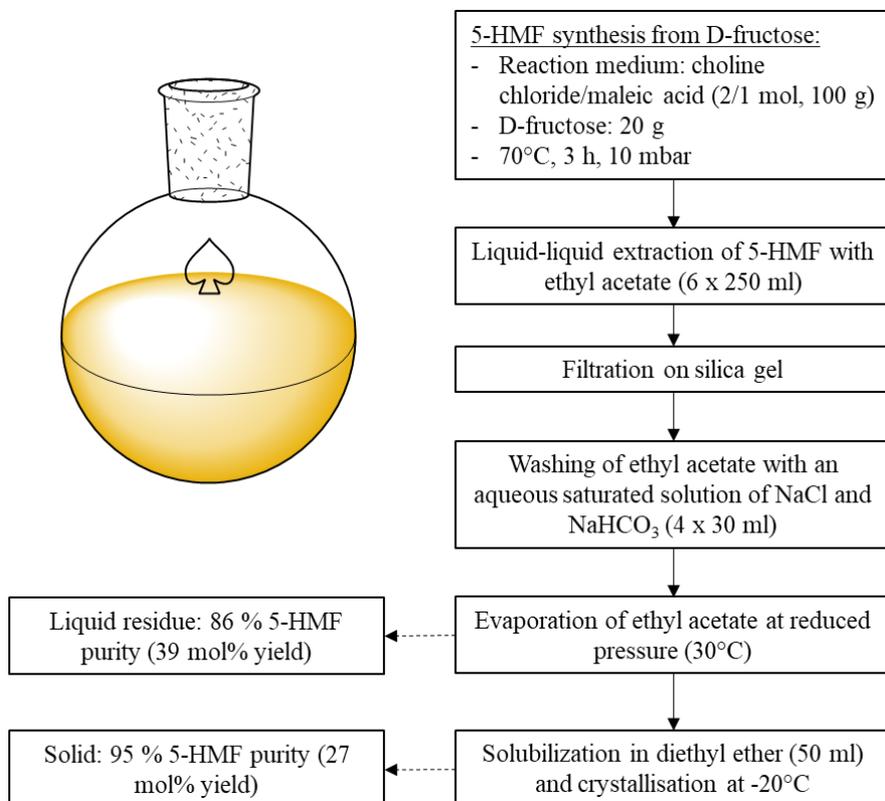
Supplementary Figure 30. IR spectrum of boric acid



Supplementary Figure 31. IR spectrum of glycolic acid



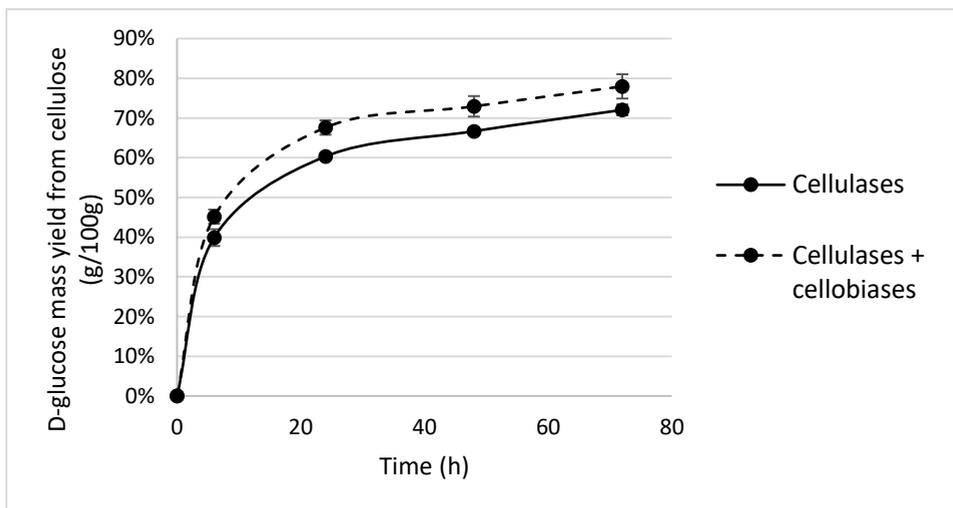
Supplementary Figure 32. Infrared spectra of D-glucose humins produced in a mixture of choline chloride, boric acid, glycolic acid (A) and a mixture of choline chloride, boric acid, HCl (B). The treatment with HCl was performed during 1h while the test with glycolic acid was performed during 3h.



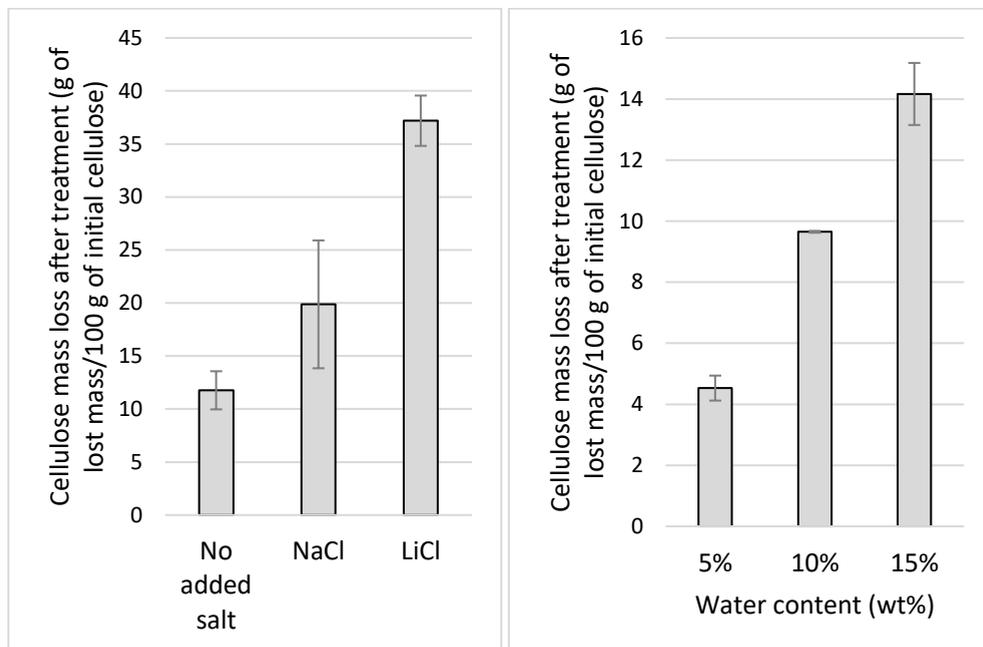
Supplementary Figure 33. Extraction and purification procedure of 5-HMF from LTTMs. While a relatively high purity of 5-HMF can be achieved with this procedure, the method requires large amounts of ethyl acetate and an important part of the produced 5-HMF remains in the reaction medium. The partition coefficient (1 at best) between the LTTM phase and the ethyl acetate phase is low. Alternative extraction methods exist and should be investigated:

- LTTM solubilization in water followed by liquid-liquid extraction: the advantage of this strategy is to use choline chloride as a salting-out agent to increase 5-HMF partition coefficient. The inconvenient is the required evaporation of water to recycle the LTTM.
- LTTM precipitation: at the end of the treatment, small amounts of hot ethanol or isopropanol are added to the LTTM to solubilize it. LTTM components are then precipitated by the addition of ethyl acetate. This method avoids the partition

coefficient limit and facilitate LTTM recycling. However, a fine tuning of the precipitation conditions (temperature, alcohol amount) to avoid LTTM re-formation when ethyl acetate is added.



Supplementary Figure 34. Hydrolysis of cellulose (0.180 g) to D-glucose by cellulases (15 FPU, Celluclast 1.5 L, *Trichoderma reesei*) in a citrate buffer (40 ml, 0.05 M, with 150 μ L of 5% sodium azide) at 50°C (150 rpm). Cellobiases were added for the test with the broken line (50 μ L of Novozyme 188, *Aspergillus Niger*).



Supplementary Figure 35. Cellulose depolymerization (estimated as the % of mass loss, 5 wt% of initial cellulose in the reaction medium) in a mixture of choline chloride and oxalic acid (1/1 mol, 2 g) in the presence of different added salts (2 mmol of salt, no water) or water content after 3 h at 110°C.