

2 Hydroxymethylfurfural, a versatile platform chemical made from renewable resources*

2.1 Introduction

Over the last century, the world has become increasingly dependent on oil as its main source of platform chemicals and energy. Driven largely by the strong economic growth of India and China, demand for oil is expected to increase significantly in the coming years. This growth in demand, combined with diminishing reserves, will require the development of new, sustainable sources for fuels and bulk chemicals. Biomass is the most attractive alternative feedstock, as it is the only widely available carbon source apart from oil and coal. Biomass consists of carbohydrates, lignin, fatty acids, lipids, proteins and others. Carbohydrates in particular show promise, as they form by far the largest natural source of carbon.

The main drawback of carbohydrates as a feedstock is the overabundance of oxygen within their molecular structures. There are three main ways of lowering the oxygen content of carbohydrates. The first option is the removal of small, highly oxidised carbon molecules such as CO₂, formaldehyde and formic acid. An example is the fermentative conversion of carbohydrates into ethanol, butanol and CO₂. The second option is hydrogenolysis, which typically removes oxygen from the molecule by forming water at the expense of one molecule of hydrogen for each oxygen atom. The third option is the removal of water, exemplified by the dehydration of carbohydrates into a wide variety of interesting compounds, especially furans and levulinic acid.

One class of dehydration products, the furan compounds, is considered by many to have especially high potential for the production of chemicals and fuels. Bozell recently published an updated evaluation of the US Department of Energy (DOE) top 10 list of bio-based chemicals,¹ where furan molecules such as 5-hydroxymethyl-furfural (HMF), furfural and 2,5-furandicarboxylic acid are mentioned in the ‘Top 10 +4’ as additions to the original DOE

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list.² In this review, the authors focus on one particular route, namely the dehydration of hexoses to obtain furan-type platform chemicals, HMF in particular.

The first report of sugar dehydration under aqueous acidic conditions dates from 1840, by the Dutchman Mulder.³ He described the formation of formic acid, and what was later found to be levulinic acid⁴, from sucrose. Another important sugar dehydration product is furfural, the formation of which Döbereiner discovered in the early 19th century by the action of manganese oxide and sulfuric acid on sugars, as reported by Newth.⁵ The first publications on HMF (**1**, Scheme 1) synthesis, go back as far as 1895 by Düll⁶ and by Kiermayer.⁷ Since then, there has been continued and growing interest in furan derivatives as important compounds in our diet and as feedstocks with great potential for bulk chemicals and fuels production. Especially the last few years have seen an enormous increase in the number of publications on HMF chemistry, as described in Figure 1.

Table 1 provides an overview of the physical and chemical properties of HMF.

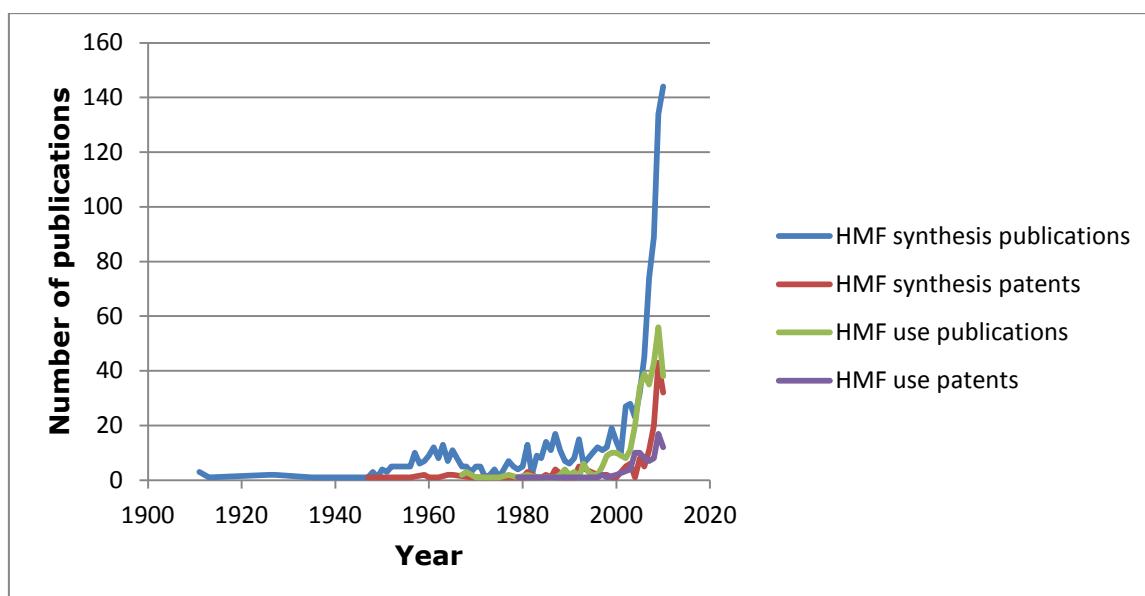
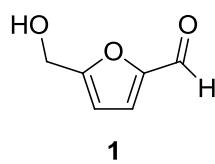


Figure 1. The number of publications on HMF per year, as registered by Web of Science



Scheme 1. 5-Hydroxymethylfurfural (HMF)

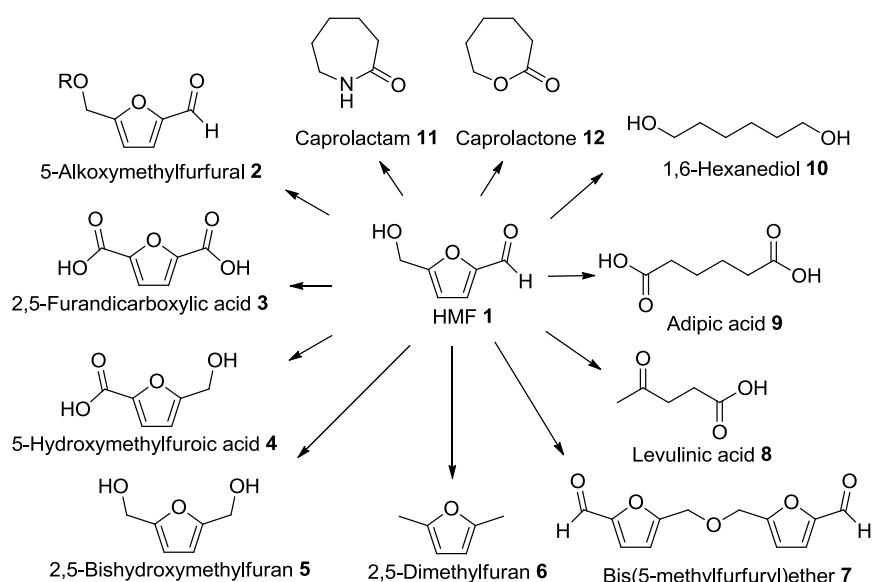
Table 1. Chemical and Physical properties of HMF

CAS Registry Number	67-47-0
EC-No	200-654-9
Chemical Abstracts Name	5-(Hydroxymethyl)-2-furancarboxaldehyde
Synonyms	5-(Hydroxymethyl)-2-furaldehyde; HMF; 5-(Hydroxymethyl)-2-furancarbonal; 5-(Hydroxymethyl)-2-furfural; 5-Hydroxymethyl-2-formylfuran; 5-Oxymethylfurfurole; Hydroxymethyl furfuraldehyde
Molecular Formula	C ₆ H ₆ O ₃
Smiles	C1=C(OC(=C1)C=O)CO
Molecular Weight	126.11
Description	Yellow powder; ⁸ odour of chamomile flowers ⁹
Boiling Point	110 °C at 0.02 mm Hg; ⁹ 114-116 °C at 1 hPa ⁸
Melting Point	31.5 °C; ⁹ 28-34 °C ⁸
Solubility	Freely soluble in water, methanol, ethanol, acetone, ethyl acetate, dimethylformamide; soluble in ether, benzene, chloroform; less soluble in carbon tetrachloride; sparingly soluble in petroleum ether ⁹
Density	1.243 at 25 °C ⁸
Refractive Index	1.5627 at 18 °C ⁹
Flash Point	79 °C - Closed cup ⁸
UV Absorption Maximum	283 nm

The production of furan-type compounds, especially HMF, from carbohydrates has been reviewed regularly. The first was published in 1951 by Newth.⁵ During the rest of the 20th century a number of reviews appeared.¹⁰⁻¹² Lewkowski's furan chemistry review, published in 2001, provides a comprehensive overview of the history of HMF synthesis and its fields of application¹³. In 2004 Moreau *et al.* updated this with a review on furan chemistry¹⁴, followed by updates in 2010 by Tong¹⁵ and 2011 by Rosatella.¹⁶ Recently Stark,¹⁷ Ståhlberg,¹⁸ Lima¹⁹ and Zakrzewska²⁰ reviewed the use of ionic liquids as green and benign solvents for selective sugar dehydration. A broader picture of biomass conversion into useful chemicals by Corma in 2007²¹ also included sugar dehydration and subsequent conversion of the furan products obtained in useful chemicals and polymers.

This review addresses both the general mechanistic aspects of the dehydration reaction from the earlier literature and the recent progress in HMF synthesis. Special emphasis is placed on the use of various solvent systems, and on the different production routes reported in the last decade. The impact of the recent progress on the development of economic production routes (catalysis, purification, etc.) will also be discussed, as well as an overview of chemical conversions possible from HMF, leading to a wealth of interesting products. The literature until 23 June 2012 has been taken into account.

As can be seen in Scheme 2 a number of important C-6 compounds can be formed through one common intermediate molecule, namely HMF. Alkoxymethylfurans (**2**), 2,5-furandicarboxylic acid (**3**), 5-hydroxymethylfuroic acid (**4**), bishydroxymethylfuran (**5**), 2,5-dimethylfuran (**6**) and the diether of HMF (**7**) are furan derivatives with a high potential in fuel and/or polymer applications. Some important non-furanic compounds can also be produced from HMF, namely levulinic acid (**8**), adipic acid (**9**), 1,6-hexanediol (**10**), caprolactam (**11**) and caprolactone (**12**). The difficulty of achieving a highly selective process with a high isolated yield has thus far resulted in a relatively high cost price of HMF, restricting its potential as a key platform chemical.²² However, this may change in the near future. More details on the economics of HMF products will be discussed in section 2.5.6.



Scheme 2. HMF as a platform chemical

Concurrent with these chemical developments the natural occurrence and nutritional and toxicological relevance of HMF and its derivatives in our diet have received increased attention. This will be reviewed in the light of their social and economic relevance in the large scale application of bio-based chemicals.

2.2 Nutritional and toxicological aspects of HMF and its derivatives

2.2.1 HMF occurrence in our diet

Ever since mankind started heating their food, furan compounds have been part of the human diet, as HMF is formed during the thermal decomposition of carbohydrates. Nowadays, HMF is a recognised indicator of non-enzymatic browning, and it is often used as an index of deteriorative changes that take place during excessive heating and/or prolonged storage of foods. However, HMF and its derivative 2,5-methoxymethylfurfural (MMF) can also be isolated from different plants, such as *Schisandra*²³ and *Cornus officinalis*,²⁴ and the marine red algae *Laurencia undulata*²⁵ (HMF) and *Jaborosa magellanica*, a member of the Solanaceae family²⁶ (MMF).

HMF is formed as an intermediate in caramelisation²⁷ and Maillard reactions.^{28,29} Caramelisation occurs during dry heating and roasting of foods with a high concentration of carbohydrates. It starts at relatively high temperatures and depends on the type of sugar. Caramelisation reactions of fructose start already at 110 °C, while other hexoses caramelize

above 160 °C. Maillard reactions can already occur at room temperature. The Maillard reaction is named after the French scientist Louis Camille Maillard (1878-1936), who studied the reactions of amino acids and carbohydrates.^{28,29}

In many cases, such as in coffee, the flavour is a result of both Maillard (described in section 2.3.1.1) reactions and caramelisation. These reactions occur during many different food preparation conditions such as baking, smoking and roasting. Therefore, HMF is present in many different food items (a.o. honey, barley, brandy, citrus juices, tomato products, syrup, grape juice, freeze-dried pears, wine, coffee, caramel products, dried fruit, prune juice and bread) and every person is exposed to HMF and some of its derivatives. Contact with HMF can occur by ingestion, inhalation, or skin absorption. Information concerning the human daily dietary exposure is scarce. In fresh foods, the HMF level is close to zero.³⁰ However, it is found to be at a significant level in processed foods.

The daily intake of HMF from heat-processed food by the Spanish population was recently assessed based on the HMF levels in Spanish foods previously published.³¹ A mean HMF intake of 10 mg/day was analysed, which is only ten-fold lower³¹ than the advised tolerable daily intake of 132 mg person⁻¹day⁻¹. However, there is no consensus yet among the scientific community what the tolerable daily intake should be.³¹⁻³⁶ Coffee and bread are the most important food items that contribute to HMF exposure, at nearly 85% of the total ingested amount. Biscuits, breakfast cereals, beer, pasteurised milk and tomato products are also important sources of HMF exposure.³¹ A median level of 5.26 mg HMF/day was calculated for HMF intake by coffee consumption.³⁷ Ulbricht *et al.* estimated a human ingestion up to 150 mg HMF/day,³⁸ whereas from a recent paper by Delgado-Andrade *et al.*³⁹ a mean HMF intake of 5.1 mg/day for Spanish adolescents was calculated. Whatever the value obtained, it exceeds the intake of other food processing contaminants, such as acrylamide and furan, by many orders of magnitude.³¹

Table 2 gives an overview of the HMF concentrations found in a number of food items. Capuano shows that whatever the formulation and toasting temperature, HMF formation followed a first order kinetic. Moreover HMF formation was highly affected by the residual moisture content of the sample.⁴⁰ A water activity, defined as the vapour pressure of water in a substance divided by that of pure water at the same temperature, of 0.4 has been considered critical, since it reflects a stage in baking where the temperature of bread crisp begins to rise above 100 °C, which greatly accelerates HMF formation.⁴¹ In 40 commercial honey samples from 12 different floral origins 3-deoxyglucosone (3-DG) was detected. The concentrations of 3-DG, a precursor for HMF, ranged from 75.9 to 808.6 mg/kg and were significantly

higher (up to 100-fold) than those of HMF.⁴² Also in 12 commercial high fructose corn syrup (HFCS) samples high concentrations of 3-DG (194-730 mg/l) and glucosone (32-401 mg/l) were found.⁴³

Table 2. The occurrence of HMF in different food items

Food Stuff	HMF (mg/kg dry mass)	Treatment Time (min)	Temperature (°C)
Grain Products			
Rye ⁴⁰	46.7	25	180
Wheat ⁴⁰	47.0	25	180
Whole Wheat ⁴⁰	17.2	25	180
Corn Flakes ⁴⁴	46.8		
Breakfast cereals ^{44,45}	6.6 – 241		
Cookies (sucrose) ⁴⁶	430	10	250
Cookies (fructose) ⁴⁶	215	9	250
Toasted bread ⁴⁷	392	4.2	
Fruit products			
Boiled Pomgranate ⁵ ³⁰	514-3500		
Boiled Grape Juice ³⁰	18-200		
Plum jam ^{44,45}	12-13		
Prunes ⁴⁸	237		
Dried plums ⁴⁹	2200		
Dried pears ⁵⁰	3500		
Apple jam ⁵¹	14.9	63	

Bilberry jam ⁵¹	56.9	60	
Must syrup ⁵²	3500-11000	75	
Processed Grapefruit juice ⁵³	15.1		
Raisins ⁵⁴	444		
Honeys			
Multifloral ^{44,45}	4.6-42.3		
Acacia ⁵⁵	8.4-16.2		
Citrus ⁵⁵	8.1-45.2		
Malaysian ⁵⁶	3 – 1100		
Sugarcane ⁵²	100-300		
Caramels ⁵⁰	9500		
Whole meals			
Paella ⁵⁷	21.2	15 (+20)	180 (@100)
Churros ⁵⁷	19.5	5	180
Kid stew with garlic ⁵⁷	37.9	15 (+45)	180 (@120)
Coffees			
Roasted coffee ^{45,49}	300-1900		
Soluble coffees ^{37,45,48,58}	93-5130		

In addition to HMF, some of its derivatives also occur in foodstuffs. For instance 5-ethoxymethylfurfural (EMF) is regularly observed in alcoholic beverages (Table 3) and 5-acetoxymethylfurfural (AMF) is a regular ingredient in vinegars and related products (Table 3). Masino found a strong correlation of AMF concentration with HMF concentration and with the sugar content. Several vinegars were grouped based on their HMF content.⁵⁹ Balsamic vinegar of Modena (BVM) showed concentrations ranging between 300 and 3300 mg/l and even higher concentrations of up to 5500 mg/kg were found in traditional balsamic

vinegar (TBV) samples.⁶⁰ Other authors reported similar results for BVM.^{61,62} Most likely AMF can be found in all vinegars with high HMF concentrations as reported in Table 4, but has probably not been looked for by other authors.

Table 3. The occurrence of HMF and EMF in different alcoholic beverages

	HMF (mg/l)	EMF (mg/l)	Reducing sugars (g/l)	Treatment
Madeira wine				
Boal ⁶³	74.3	10.9	20.9	3 month at 50 °C, 25 years at ambient and pH 3.5
Malvazia ⁶³	100.3	13.2	29.6	3 month at 50 °C, rest at ambient and pH 3.4
White wine				
Average 13 wines ⁶⁴	Not analysed	0.2		4 years at 5 °C
White Grenache, and 54 Macabeu ⁶⁵		0.43		0.5 years at 37 °C
Red Wine				
Sweet fortified Black Grenache ⁶⁵	149	0.0		0.5 years at 37 °C
Beer				
Beer ⁶⁶		3.3 – 9.2		
Tsingtao Beer ⁶⁷		0.4-2.9		pH 4.1
Brandy				
Brandy ⁶⁸		20-155		

Table 4. The occurrence of HMF in different vinegars

Food Stuff	HMF (mg/l)	AMF (mg/l)	Reducing sugars (g/l)	Treatment
Balsamic vinegar ⁶⁰	300-3200			
TBV ^{a,69}	1590-3200	trace	350-700	
TBV ^a (gem 6) ⁵⁹	2670	68.4	65.7	pH 2.46
Trebbiano Grape must for TBV ^{a,70}	3100	n.d.	354	30 h at 85 °C
Salamino Grape must for TBV ^{a,70}	145	n.d.	445	42 h at 85 °C
Balsamic Wine Vinegar ⁷¹	220-480	n.d.		540 d at pH 2.8
TBV ^{a,72}	2900 – 3900	10-71	67 -70	pH 2.4-2.5

a: Traditional Balsamic Vinegar

The occurrence of HMF and its derivatives is not restricted to pure carbohydrate food sources and products thereof. Capuano observed that the HMF formation in sugar-amino acid model systems is much higher than in sugar systems at temperatures above 100°C and low moisture content.⁴⁰ HMF is the most studied thermal degradation product of sugar, but other furanic congeners (e.g. furoic acid, furfural and acetoxymethylfurfural) could be quantified in traditional balsamic vinegars.^{59,73} Humans can also be potentially exposed to HMF through pharmaceutical preparations and cigarette smoke.⁷⁴

In conclusion, HMF and its derivatives are available in wide variety of human food sources. It is more pronounced in processed foods than in fresh products, but it is nearly impossible to avoid its in-take. Estimated daily consumption of HMF and its derivatives is calculated to be below 5–150 mg/per person.^{28,30-32,67}

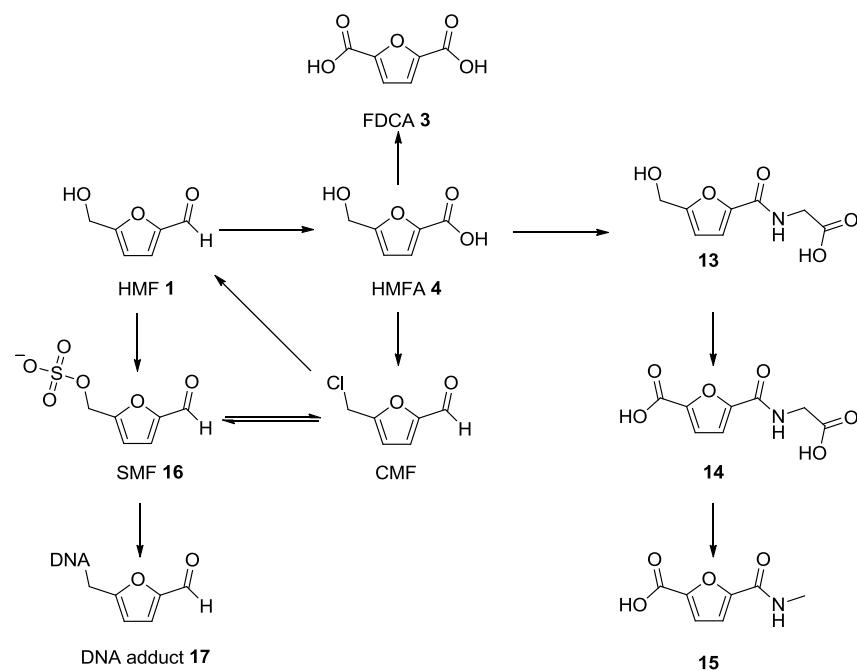
2.2.2 Metabolic breakdown of HMF and derivatives

The estimated daily intake of HMF is 5–150 mg/per person based on reports by several authors (Janzowski *et al.*;⁷⁵ Rufián-Henares;³¹ Arribas-Lorenzo;³⁷ Delgado-Andrade *et al.*;³⁹ Ulbricht *et al.*³⁸). The main degradation product of HMF detected in urine is 5-

hydroxymethyl-2-furoic acid (**4**, HMFA), its concentration was in the range of 0 to 100 mg/L with most of the samples around 10 mg/L.⁷⁶ Jellum, Borresen and Eldjarn determined that fructose solutions used for parenteral nutrition can contain up to 1.2 g/L HMF.⁷⁷ Patients who obtained these fructose solutions metabolised 50% of the HMF to **4** and FDCA (**3**, Scheme 3) in urine samples.⁶⁹ These compounds have also been detected by others.⁷⁸⁻⁸⁰

Additionally, a reaction of a carboxylic acid with an amino acid is possible. Prior, Wu and Gu⁸⁰ detected an HMFA - amino acid conjugate, e.g. *N*-5-(hydroxymethyl)-2-furoylglycine (**13**) at 3.6% of the amount of HMF administered (Scheme 3). Furthermore, Prior *et al.*⁸⁰ detected metabolites in urine derived from **13**, like 5-((carboxymethyl)carbamoyl)furan-2-carboxylic acid (**14**, 4.2% of the administered HMF dose, also detected by Godfrey *et al.*⁷⁸) and 5-(methylcarbamoyl)furan-2-carboxylic acid (**15**, 1.8% from the HMF dose).

In addition to the above mentioned metabolites, HMF can be bioactivated to 5-(sulfoxy)methyl furfural (**16**, Scheme 3), through an enzymatic esterification of its hydroxy group by sulfotransferases.⁸¹



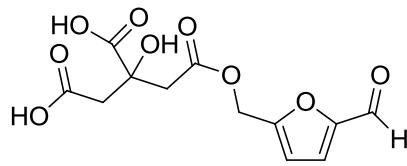
Scheme 3. The biotransformations of HMF (adapted from Glatt and Sommer;⁸² D. Jöbstl *et al.*⁷⁶)

In conclusion, ingested HMF is converted to a number of oxidised metabolites which are excreted from the human body via urine. This has been confirmed by experiments on rats. In rats orally dosed HMF was eliminated for 95-100% after 24 hours, almost exclusively *via* the

urine.⁷⁹ The biochemistry and genetics of the microbial degradation of HMF and furfural has recently been reviewed. The oxidation and/or reduction to the furanic alcohol and acid forms constitute the initial steps of the HMF and furfural degradation pathways.⁸³

2.2.3 Toxicological effects of HMF and its derivatives

Being part of the human diet, the toxicological effects of HMF, its derivatives and metabolites should be considered. HMF was once thought to have only certain negative side-effects,⁸¹ but more and more papers have appeared indicating that HMF can also have a positive pharmacological activity such as propelling blood circulation and anti-oxidant activity⁸⁴⁻⁸⁶ and activity against sickle cell disease.⁸⁷ Ding, Wang and Cai⁸⁸ and Wang *et al.*⁸⁹ recently showed that HMF extracted from wine-processed *Fructus corni* could inhibit hepatocytes oxidative damage caused by H₂O₂. It was suggested that the hepatoprotective effects of HMF might be related to resisting apoptosis. It is claimed that this is the first report on the direct morphological protective effects of HMF against chemical liver cell injury *in vitro*. Sriwilaijaroen *et al.* showed that Mumefural (**18**, Scheme 4), the monoester of HMF and citric acid, and related HMF malic and citric acid esters from Japanese apricot fruit juice concentrate show multiple inhibitory effects on pandemic influenza A (H1N1) virus.⁹⁰



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Scheme 4. Mumefural

Up to now, it is not clear whether normal dietary human exposure to HMF represents a potential health risk, though it is known that HMF is cytotoxic at high concentrations, causing irritation to eyes, upper respiratory tract, skin and mucous membranes.³² Both the national toxicity program of the National Institute of Environmental Health Sciences (NIEHS) as well as the European Food Safety Authority (ESFA) journal extensively addressed the toxicity of HMF.^{32,33} At the time of those reports no positive or negative epidemiological studies or case reports associating HMF with a cancer risk in humans were identified in the available literature. HMF was also found to be inactive in standard genotoxicity tests. The toxicity of HMF has been reviewed by several authors.^{34,35} Janzowski performed an extensive study to elucidate the toxic potential of HMF by assessing cytotoxicity, growth inhibition,

mutagenicity, DNA damage and depletion of cellular glutathione were investigated in mammalian cells, genotoxicity was monitored in *Salmonella typhimurium*.⁷⁵ The author concluded that HMF does not pose a serious health risk, even though the highest concentrations in specific foods approach the biologically effective concentration range in cell systems. Severin and co-workers investigated the genotoxicity of HMF using the Ames test. They concluded that HMF did not induce any genetic mutation in bacteria whatever the concentration in the Ames test. Furthermore, HMF does not induce clastogenic (disruption or breakages of chromosomes) or aneugenic (abnormal number of chromosomes) effects in the HepG2 cells. In contrast, it induced HepG2 DNA damage at concentrations from 7.87 to 25mM in the comet assay suggesting a weak genotoxic effect of HMF in the HepG2 cells which probably is repaired.⁹¹ 5-Hydroxymethylfuroic acid, a metabolite of HMF in humans, was not mutagenic.⁹² However, HMF can be metabolised *in vitro* by sulfotransferases to a chemically reactive intermediate, 5-sulfoxymethylfurfural (SMF, Scheme 3, **16**).⁸¹ The intrinsic mutagenic properties of SMF were enhanced by addition of extra chloride ion to the assay medium. In the resulting ester, the sulfate is a good leaving group, thus producing a highly electrophilic benzylic-like carbocation, which could be stabilised by distribution of charges on the furan ring. The subsequent interaction of this reactive intermediate with critical cellular nucleophiles (i.e. DNA **17**, RNA and proteins) may result in toxic and mutagenic effects. The HMF derivative 5-chloromethylfurfural (CMF) shows a higher mutagenic and cytotoxic activity in bacteria than the sulfuric acid ester⁸¹. It was recently found that direct parental administration of SMF to mice leads to abundant acute necrosis and proteinaceous casts in the proximal tubules as the dominating toxicological effect.⁹³ Additional research provided evidence for the involvement of organic anion transporters in the renal accumulation of SMF. These transport characteristics could be responsible for the selective damage of renal proximal tubules by this reactive metabolite.⁹⁴ In contrast, 5-acetoxymethylfurfural (AMF) was neither mutagenic nor cytotoxic under the same experimental conditions used for SMF and CMF.⁸¹ Both HMF and SMF are weak intestinal carcinogens in Min/+ mice.⁹⁵ As was discussed before, HMF is mainly present in heat treated food. Contrary to most test organisms, humans have been exposed to heat treated food for thousands of years. This likely makes it difficult to directly translate the effects of exposure to HMF/SMF observed in rodents into similar effects in human beings.

The so-called Maillard Reaction Products (MRP, see also section 2.3.1.1) are a group of compounds found in foods that is closely related to the HMF formation. They have been assessed for toxicological effects. It was found that the consumption of a diet rich in MRP,

exemplified by a high content of HMF (3.8 mg/kg), correlates negatively with protein digestibility. Therefore, the possible effects of an excessive intake of MRP's during adolescence needs further research, and also long-term effects should be evaluated.⁹⁶ However, it is unclear what role HMF plays in the observed effect.

Lee *et al.* reported that 3,4-dideoxyglucosone-3-ene (3,4-DGE), a possible intermediate/side product in the HMF formation and present in perennial fluids.⁹⁷, induces apoptosis in leukocytes and renal tubular epithelial cells and it was recently shown that 3,4-DGE also promotes apoptosis on human peritoneal mesothelial cells.⁹⁸ In their recent review Abraham and co-workers concluded that *in vitro* genotoxicity of HMF was positive when the metabolic preconditions for the formation of the reactive metabolite 5-sulfoxymethylfurfural were met. However, so far *in vivo* genotoxicity was negative. Results obtained in short-term model studies for HMF on the induction of neoplastic changes in the intestinal tract were negative or cannot be reliably interpreted as "carcinogenic". In the only long-term carcinogenicity study in rats and mice no tumors or their precursory stages were induced by HMF. Hence, no relevance for humans concerning carcinogenic and genotoxic effects can be derived. The remaining toxic potential is rather low. Various animal experiments reveal that no adverse effect levels are in the range of 80-100 mg/kg body weight and day. Therefore it was concluded that current safety margins are generally sufficient.^{35,36}

2.3 Dehydration chemistry

In this chapter the dehydration of C-6 sugars and their derivatives including di- and polysaccharides will be discussed with an emphasis on the mechanistic aspects. In addition, an overview will be given of side products that can be formed.

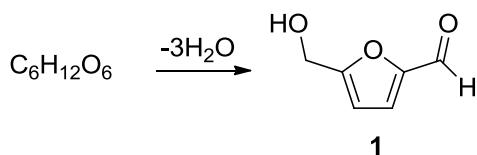
2.3.1 Neutral monomeric sugars

The acid catalysed dehydration of neutral monomeric C₅ and C₆ carbohydrates has long been known to produce a wide variety of products. The most prevalent products reported are HMF, furfural and levulinic acid, with humins as unwanted polymeric side-products. Within this section the focus will be on the chemistry of HMF formation and to a lesser extent on the formation of levulinic acid from hexoses. It will not discuss the formation of furfural from pentoses, which is excellently described elsewhere.⁹⁹⁻¹⁰¹ Furfural from hexoses, however, is discussed briefly as a side product in HMF formation.

In this chapter the various reported mechanisms will be reviewed and discussed in section 2.3.1.1 and the formation of by-products in section 2.3.1.2.

2.3.1.1 Mechanistic aspects

Based on experimental data several different routes for the formation of HMF and derivatives from sugars have been proposed, but no definite proof of the dehydration kinetics has been published. In general three main routes have been described. The first and most widely described route is the direct formation of HMF by acid catalysed dehydration of a hexose, in which three water molecules are consecutively removed from the sugar molecule (Scheme 5). The second route is possible in the presence of amino-acids and amines when the hexoses undergo Maillard reactions and finally HMF can be produced by aldol condensation reactions of smaller C₃ molecules.



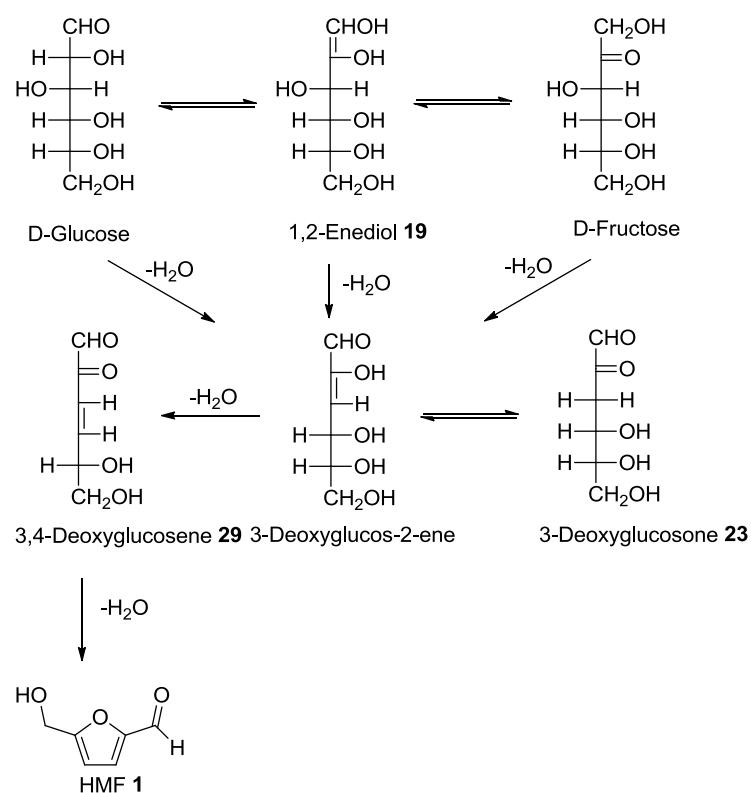
Scheme 5. The general dehydration route of hexoses to HMF

Direct dehydration of hexoses

Several mechanisms for the direct formation of HMF by acid-catalysed dehydration of a hexose by elimination of three water molecules have been suggested in the literature. The mechanistic pathways can be divided in two general groups.

One group assumes the reaction to proceed via acyclic intermediates^{5,11,12,102,103} and the other group assumes cyclic intermediates.^{5,11,12,102-104} The body of experimental evidence to support either of the mechanistic routes is still very small, and a consensus on the actual mechanism has not been reached. It should be noted that almost all the proposed mechanisms so far are based on research in aqueous systems. In recent years a shift towards the use of other solvent systems was observed; here, a different mechanism could be operative.

The acyclic pathways (Scheme 6) assume as the rate-limiting step the formation of a linear 1,2-enediol **19**,^{11,12,104} which is widely accepted as the intermediate in the aldose-ketose isomerisation by the so-called Lobry deBruyn-Alberda van Ekenstein (LBAE) transformation.¹⁰⁵ This is followed by two consecutive β-dehydrations and a ring closure with a final water elimination to yield HMF.



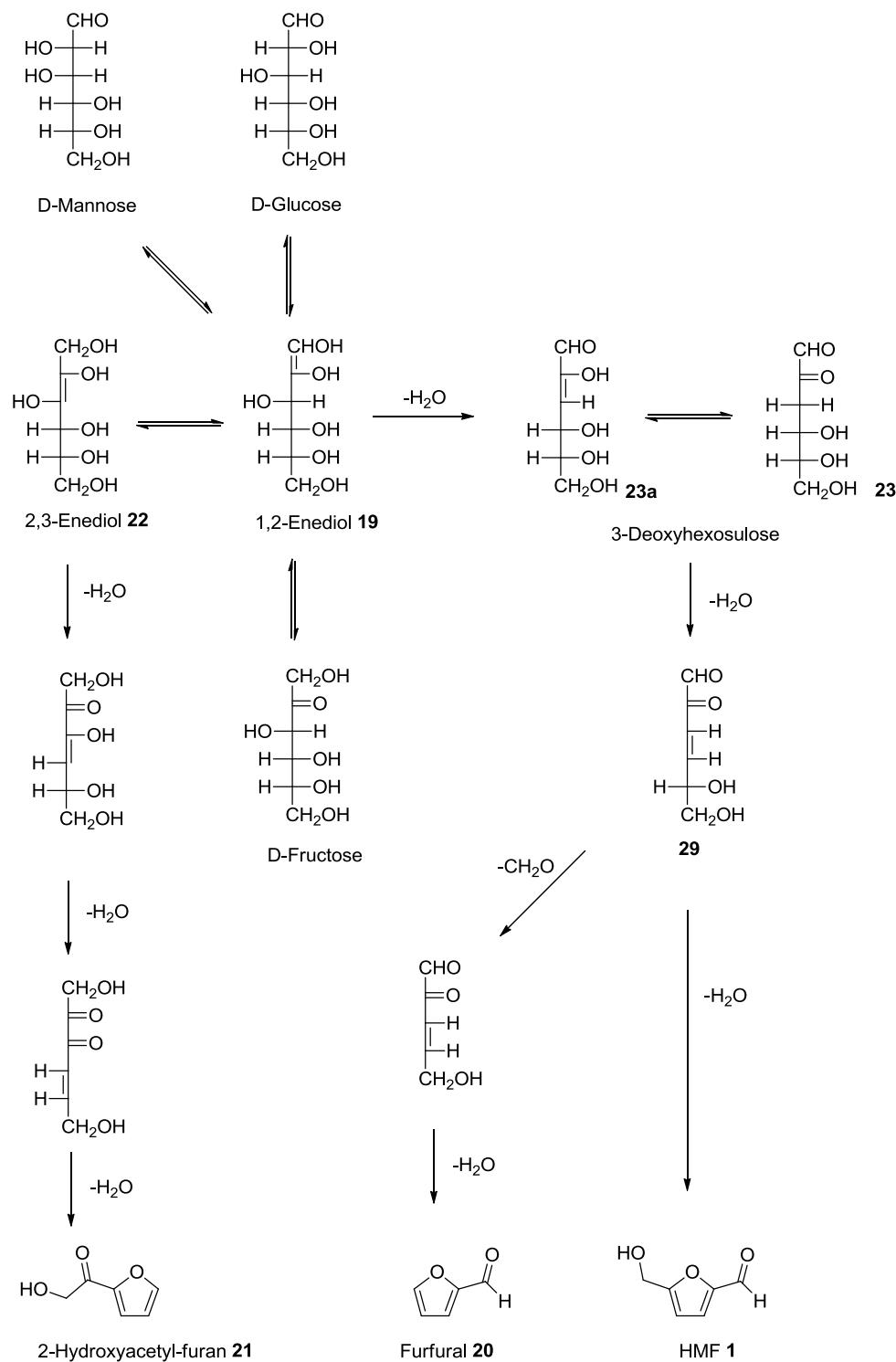
Scheme 6. The acyclic pathway in the dehydration of hexoses to HMF, as proposed by Anet¹⁰³

Moreau *et al.* proposed an acyclic mechanism for the dehydration of fructose, based on the observation of small amounts of glucose and mannose, indicating an isomerisation of fructose through a 1,2-enediol species (**19**), in which the formation of furfural (**20**) and hydroxyacetyl furan (HAF, **21**) are also explained (Scheme 7).¹⁰² The formation of furfural was attributed to a decarbonylation that competes with the final dehydration step to HMF, whereas the formation of HAF was proposed to take place through the consecutive dehydration of a 2,3-enediol species **22**, formed through a rearrangement of the 1,2-enediol, also mentioned by Kuster.¹² The HMF route in this scheme is in essence identical to the one presented by Anet (Scheme 6).^{102,103}

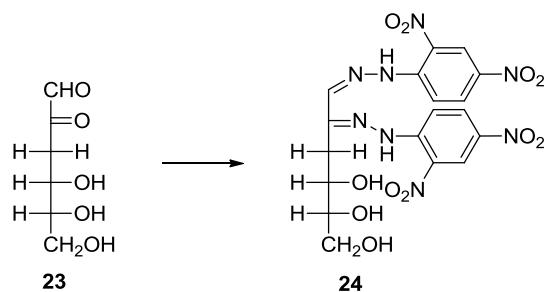
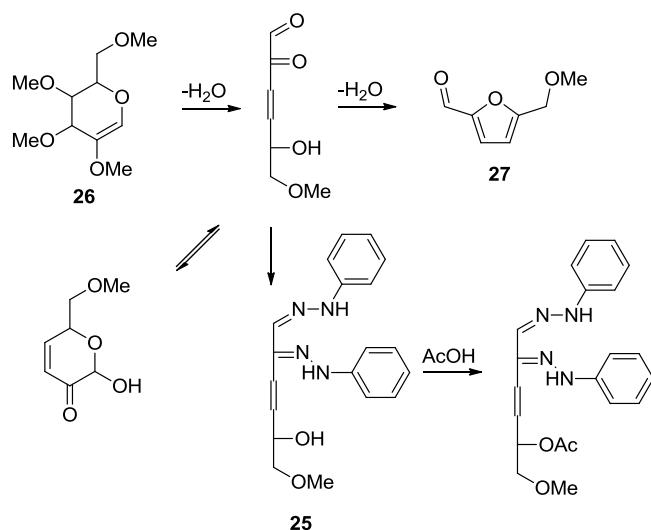
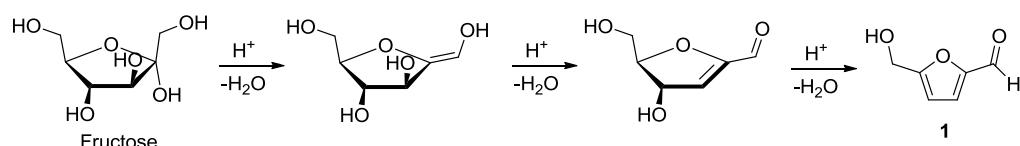
The schemes by Moreau and by Feather and Harris both mention the formation of 3-deoxy-D-glucosone (3-DG, **23**), a keto tautomer of the key intermediate enol **23a** formed after the first dehydration step. Efforts by Anet in the early 1960's led to the identification of many of the intermediates by looking at different hexoses and assumed intermediates.^{103,106,107} The formation of **23**, observed as its (2,4-dinitrophenyl)osazone **24** (Scheme 8), was confirmed in the acid-catalysed formation of HMF from fructose by Anet.^{103,106,107} Similarly Wolfrom *et al.* reported the isolation of a methylated phenyl osazone intermediate **25** (Scheme 9) in the acid catalysed decomposition of 2,3,4,6-tetramethylglucoseen-1,2 (**26**).¹⁰⁸ The 2,3,4,6-

tetramethylglucoseen-1,2 is essentially the tetramethylated pyranose derivative of **23**. Interestingly the major product of the decomposition was methyl methoxyfurfural (MMF, **27**). Recently Jadhav *et al.* compared the formation of HMF from fructose and **23** in which HMF formation from **23** was observed to proceed at a significantly higher rate than from fructose, which showed that **23** cannot be excluded as a potential intermediate in the formation of HMF from fructose.¹⁰⁹

In addition to these acyclic pathways, several cyclic pathways have been proposed as well. The mechanisms of these cyclic pathways (Scheme 10) all start from the cyclic ketofuranose. The first step is expected to be the dehydration of the hemiacetal at C₂, forming a tertiary carbenium cation. This is then followed by two consecutive β -dehydrations in the ring to form the HMF.^{5,11,12,104} Recent ¹³C-NMR studies by Akien *et al.* in DMSO and other polar solvents are in agreement with this cyclic dehydration pathway by assigning peaks in the NMR spectrum to both intermediates mentioned in Scheme 10.¹¹⁰ Furthermore experiments in the presence of D₂O showed that all steps after the first dehydration are irreversible, which was explained by the lack of deuterium incorporation in HMF. This also makes an acyclic pathway highly unlikely, since this would require deuterium incorporation at C-3 of HMF, through intermediate **23** (Scheme 7).



Scheme 7. The formation of HMF, Furfural and hydroxyacetyl furan from Fructose¹⁰²

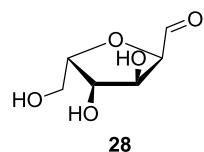
**Scheme 8.** 3-DG and its (2,4-dinitrophenyl)osazone**Scheme 9.** 2,3,4,6-tetramethylglucoseen and its phenyl osazone**Scheme 10.** The cyclic pathway in the dehydration of fructose to HMF.

The first dehydration step from a cyclic D-fructofuranose would yield the enol form of 2,5-anhydro-D-mannose, a 2,5-anhydro sugar also referred to as chitose. Furanic compounds have been observed in the acid dehydration of 2,5-Anhydro sugars.^{103,111} The dehydration of 2,5-anhydro-D-mannose to HMF was observed to proceed slower than when starting from fructose. Based on this observation chitose was excluded as a likely intermediate in the dehydration of fructose to HMF.^{103,111} Anet cited work in which the yield of HMF from chitose (12%) was much lower than from fructose (20-25%).¹⁰³ Dekker and Hashizume

reported the formation of HMF from 2,5-anhydro-L-idose (**28**, Scheme 11), which reacted several hundred times faster than glucose.¹¹²

Feather and Harris explain the necessity of the formation of the C1-aldehyde group upon dehydration at C-2 as a driving force for a consecutive β -elimination by mentioning that hydroxymethyl furancarboxylic acid formation from the C1 carboxylic acid counterparts of 2,5-anhydro-hexoses required much harsher conditions than HMF formation from 2,5-anhydro-hexoses.^{11,113}

Recent *in situ* ^{13}C -NMR studies by Zhang and Weitz using [^{13}C -1]fructose and [^{13}C -6]fructose confirmed that fructose C-1 forms the carbonyl carbon of HMF and fructose C-6 forms the hydroxymethyl carbon of HMF. This is in agreement with both the acyclic and cyclic mechanisms proposed.¹¹⁴

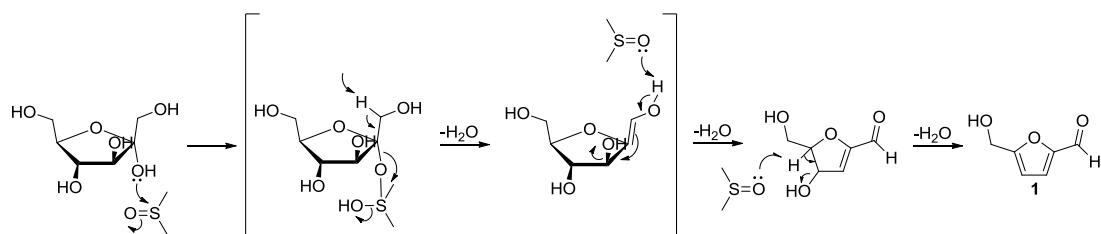


Scheme 11. 2,5-anhydro-L-idose

Another insight in the mechanism of HMF formation can be found in the different reactivity of fructose compared to that of glucose. In general, fructose is much more reactive and selective towards HMF than glucose. Kuster explains that glucose shows much lower selectivity for HMF formation, due to its more stable ring structure, which hinders its ability to form the acyclic enediol intermediate.¹² The cyclic mechanism as postulated above (Scheme 10) requires glucose to isomerise to fructose prior to dehydration to HMF.

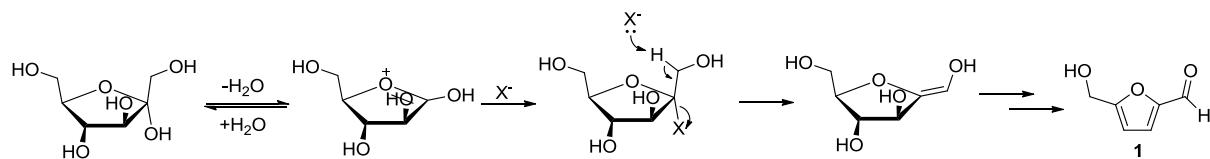
Another point to take into account is the solvent and temperature dependence of the tautomeric distribution of the different sugars. At room temperature glucose exists almost exclusively in pyranose (6-ring) form when dissolved in water. For fructose in water at room temperature the two pyranose forms are prevalent, although the furanose forms are also present in considerable amounts.¹¹⁵ With regard to solvent dependence of the tautomer distribution it is interesting to consider the significant amount of research on HMF formation in other media than water. This includes both organic solvents and ionic liquids as reaction media. It has, however, been reported in recent NMR studies that under reaction conditions the tautomerisation of fructose is very rapid.^{110,116} When tautomerisation proceeds at a significantly higher rate than dehydration this is not expected to be an important factor in improving the selectivity of HMF formation.

In DMSO the furanose forms are prevalent, adding up to around 70% at 20 °C,^{117,118} and this fraction increases with temperature.^{117,118} An NMR study on fructose dehydration in DMSO by Amarasekara showed that DMSO acts both as a solvent and as a catalyst.¹¹⁷ The results of this work show intermediates in the solution that are consistent with a cyclic dehydration mechanism (Scheme 12). This mechanism is very similar to the one described in Scheme 10, where water is present as the solvent. The difference is the coordination of DMSO on the oxygen atoms of C1 and C2 prior to dehydration.



Scheme 12. The proposed cyclic mechanism for fructose dehydration in DMSO by Amarasekara¹¹⁷

A recent publication by Binder and Raines¹¹⁹ describes the use of lithium halide additives in N,N-dimethylacetamide (DMA) as the solvent. A mechanism was described (Scheme 13) in which the halide functions as both a nucleophile and leaving group. It was observed that using bromide and iodide as additives gave significantly higher yields of HMF than in the case of chloride, which was explained by the consensus that bromide and iodide are both better nucleophiles and better leaving groups than chloride. It must be noted though, that the results presented with KCl as additive were obtained at lower temperature (80 °C) and lower salt content (1.5 % w/w) than those obtained with the bromide and iodide additives (100 °C, 10 % w/w). A kinetic study indicated a first-order dependence of the rate of HMF formation on iodide concentration. The authors did not mention why an acyclic mechanism could not explain the observations. Akien *et al.* recently suggested, based on ¹³C-NMR studies, that chloride has a negative influence on the formation of difructose dianhydrides.¹¹⁰



Scheme 13. The cyclic dehydration mechanism for nucleophilic halide catalysed fructose dehydration proposed by Binder *et al.*¹¹⁹

Apart from fructose, other hexoses have also been reported as substrates in the formation of HMF and derivatives. In particular glucose has been studied to a great extent because compared to fructose it is much cheaper and potentially readily available from lignocellulosic feedstock. Typically the HMF yields from fructose are superior to those of glucose under the same reaction conditions. Isomerisation to fructose appears to be necessary in order to obtain HMF from glucose.

Several studies on glucose decomposition in high temperature liquid water in the absence of catalyst report the formation of fructose.¹²⁰⁻¹²² The formation of glucose from fructose was reported to be negligibly low under comparable conditions.¹²² In high temperature liquid water with a mineral acid¹⁰⁴ and organic acid,¹²³ isomerisation of fructose to glucose is also observed, though the amounts of observed glucose are always very small. Recent work on hexose dehydration, catalysed by a three dimensional mesoporous silica Al-TUD-1 at 170 °C showed that starting from glucose the fructose yield was 16% at 61% conversion, whereas starting from fructose less than 3% glucose was obtained.¹²⁴ The reported glucose yield was consistently around 3%, irrespective of conversion (20-100%). The same was reported in work by Antal in which reaction time, initial fructose concentration and acid concentration were varied.¹⁰⁴ Bicker observed similar results in water in the presence of small amounts of ZnSO₄.¹²⁵ These results imply that at high temperature in water, fructose is thermodynamically favoured over glucose. Work by Watanabe *et al.* on glucose reactions in hot compressed water confirms these observations, reporting fructose formation (5-6% after 200 s at 473 K) in the absence of a catalyst.^{126,127} This was later confirmed for even higher pressures and temperatures.¹²⁸ HMF is also formed here, which could be explained by some isomerisation from glucose to fructose, followed by fructose dehydration to HMF. No glucose formation was reported upon treatment of fructose under the same conditions. This is consistent with Kabyemela's work.¹²² Fructose did, however, yield 21% HMF in the absence of catalyst, which was much higher than when starting from glucose. Using anatase TiO₂ (α -TiO₂) as catalyst, fructose and glucose behaved very similar with regard to isomerisation, furfural formation and HMF formation.^{126,127} Watanabe claims that the α -TiO₂ acts both as acid and base, because it enhances the HMF yield from glucose conversion. The HMF yield from fructose is the same in both the absence and the presence of this catalyst (around 20%), but the conversion is much higher in its presence (95% vs. 40%). Combined with the observation that glucose is formed when reacting fructose in the presence of this catalyst suggests that α -TiO₂ behaves exclusively as a basic catalyst that catalyses the glucose-fructose isomerisation. A later publication from the same group using essentially the same

conditions, but using microwave heating, showed significant improvement in HMF yield by adding α -TiO₂ to the fructose reaction mixture.¹²⁹ A number of studies on glucose decomposition also reported isomerisation to fructose.¹²⁰⁻¹²² The formation of glucose from fructose, albeit in smaller amounts, was also reported in high temperature liquid water with both mineral acid¹⁰⁴ and organic acid.¹²³

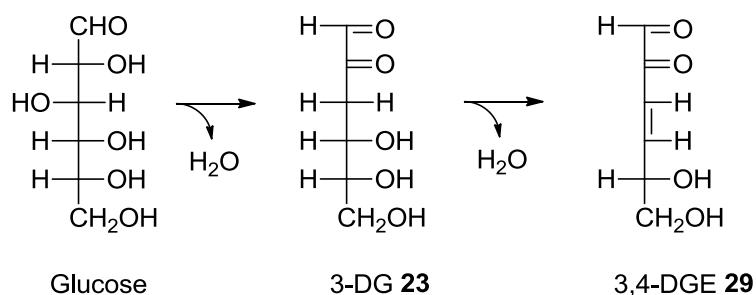
Work by Yan *et al.* on fructose and glucose in DMSO using bifunctional heterogeneous SO₄²⁻/ZrO₂-Al₂O₃ type catalysts provided further clues on the requirement of glucose isomerisation to fructose for the formation of HMF.¹³⁰ In their attempts to find an efficient catalyst for producing HMF directly from glucose, an optimum yield of 48% was obtained using a SO₄²⁻/ZrO₂-Al₂O₃ catalyst with a Zr/Al ratio of 1, compared to only 4% yield in the absence of the catalyst. The rate of fructose formation was found to be dependent on the amount of base sites on the catalyst. The highest HMF yield was 72%, obtained from fructose in the absence of catalyst. Adding catalyst showed a decrease in HMF yield with decreasing Zr/Al ratios. This was explained by increasing basicity of the catalyst with decreasing Zr/Al ratio. Interestingly, starting from fructose, the catalyst with the lowest Zr/Al ratio (1:10) showed the same yield (47%) as the best catalyst for glucose dehydration (48%). These results, combined with the observation that glucose does not dehydrate to HMF in DMSO in the absence of catalyst whereas fructose does, strongly indicate that this heterogeneous catalyst behaves exclusively as an isomerisation catalyst for the glucose-fructose isomerisation.

The notion that glucose dehydration to HMF involves fructose as an intermediate has been challenged by Jadhav *et al.* They proposed a pathway through 3-deoxyglucosone (**23**, Scheme 6) to be dominant, based on the observation that in the dehydration of glucose to HMF in DMA/LiCl both fructose and were observed and that **23** was much more efficiently converted to HMF than fructose, showing a higher rate of HMF formation.¹⁰⁹

Ishida and Seri performed a study on homogeneous lanthanide (III) salt catalysed glucose dehydration to HMF.¹³¹ They observed a clear, though non-linear relationship between the atomic radii of the lanthanide ions and the initial rate of reaction. No change in the NMR spectra of glucose upon addition of the lanthanide ions was observed suggesting that displacement of water as a ligand to the lanthanide by glucose is slow. Thus, the authors concluded the relationship between the atomic number (and thus the radius) of the lanthanide ion and the rate is determined by the ease of coordination with glucose.

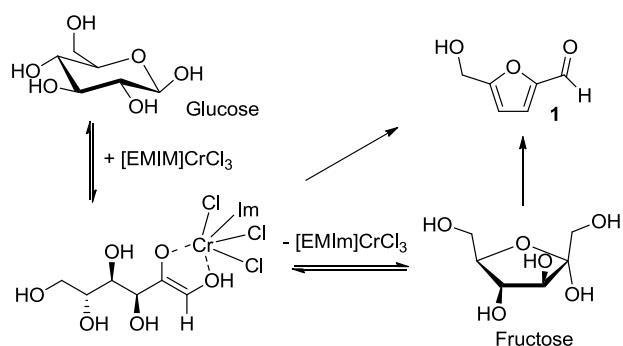
In glucose peritoneal dialysis fluids several glucose degradation products (GDP) have been detected. In addition to HMF (3.3 – 26 μ mol/l), 3-DG (41-564 μ mol/l) and 3,4-

dideoxyglucosone-3-ene (3,4-DGE, **29**) (1.2 - 36 $\mu\text{mol/l}$) were observed in relatively high amounts.⁹⁷ These products can be formed from glucose by the removal of one and two water molecules, respectively (Scheme 14). Erixon mentioned that both molecules can be further dehydrated to HMF.¹³² However, for 3,4-DGE only hydration into 3-DG was shown.¹³³ 3,4-DGE has been identified as the most bioreactive GDP in those fluids. The concentrations of 3-DG and 3,4-DGE produced during heat sterilisation decreased when the pH was reduced to about 2.¹³² An extensive discussion on the role of intermediates between 3-deoxyglucosone and HMF is given by Anet.¹⁰³



Scheme 14. The formation of 3-DG and 3,4-DGE from glucose

In 2007 Zhang and co-workers made an important advance in the synthesis of HMF from glucose.^{134,135} By using a system of 10 mol% of CrCl_2 in ionic liquid (1-ethyl-3-methylimidazolium chloride, [EMIm]Cl) they were able to obtain 70% yield of HMF at 95% conversion. Fructose dehydration in the same system resulted in almost equal HMF yield. Their proposed mechanism (Scheme 15) ascribes the role of CrCl_2 as an isomerisation catalyst for the glucose to fructose isomerisation, followed by fructose dehydration to HMF in the acidic medium.

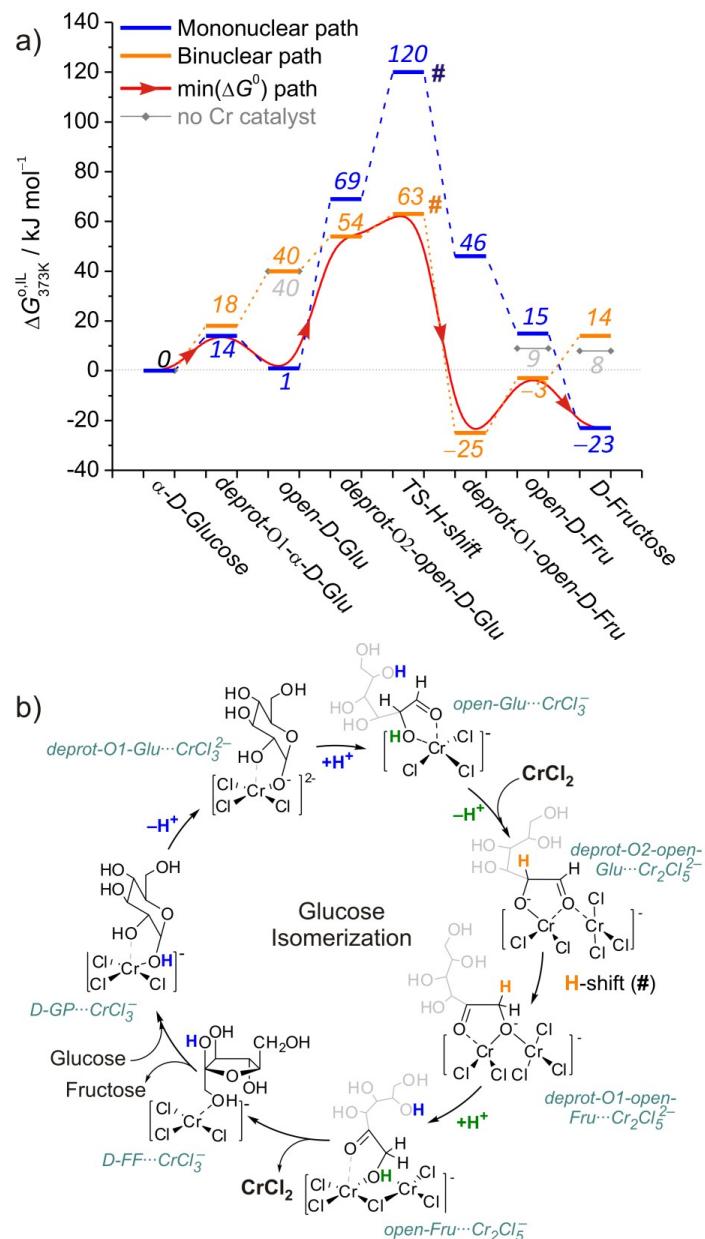


Scheme 15. The role of chromium in the isomerisation of glucose to fructose, followed by dehydration to HMF, as proposed by Zhang *et al.*¹³⁴

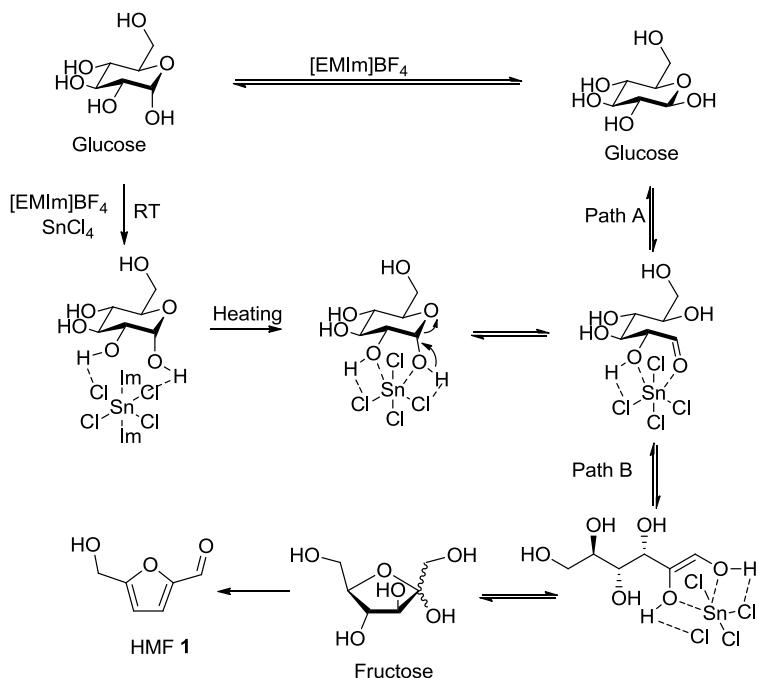
Pidko and co-workers combined X-ray absorption spectroscopy (XAS), density functional theory (DFT) and kinetic experiments to confirm the role of Cr in the isomerisation of glucose to fructose.^{136,137} The EXAFS and DFT results provided strong clues towards a combination of a mono- and binuclear Cr system, in which ring opening of glucose is catalysed by a mononuclear Cr complex and the actual isomerisation to fructose proceeds through a binuclear Cr complex (Scheme 16). In this respect it is interesting to note that a two metal centre is generally accepted to be the active site of typical enzymes that can isomerise glucose to fructose with high selectivity.^{138-140,141} The role of ‘free’ Cl⁻ in this system is important, functioning as a proton acceptor and forming a hydrogen-bonding network with the hydroxyl groups on the carbohydrate. A subsequent publication by the same group showed higher activity and selectivity towards HMF formation for Cr³⁺ than for Cr²⁺ catalysed reactions.¹⁴² This was attributed to the increased Lewis acidity of Cr³⁺ compared to Cr²⁺, resulting in a more efficient stabilisation of the negative intermediates formed during the isomerisation of glucose to fructose.

An important observation in work by Yong *et al.* is the different behaviour of fructose and glucose towards changes in reaction time and substrate concentration.¹⁴³ This suggests a different reaction mechanism for both substrates, which is in accordance with findings by Pidko.¹³⁶ Up to an initial substrate/ionic liquid ratio of 0.5 an increase in the fructose concentration showed a gradual decrease in HMF yield. For glucose there does not appear to be a decrease in HMF yield upon increase of the initial concentration.¹⁴³

Hu *et al.* performed glucose dehydration in [EMIm]BF₄ with SnCl₄ as the catalyst, obtaining HMF yields over 60%.¹⁴⁴ A reaction mechanism was proposed as described in Scheme 17.

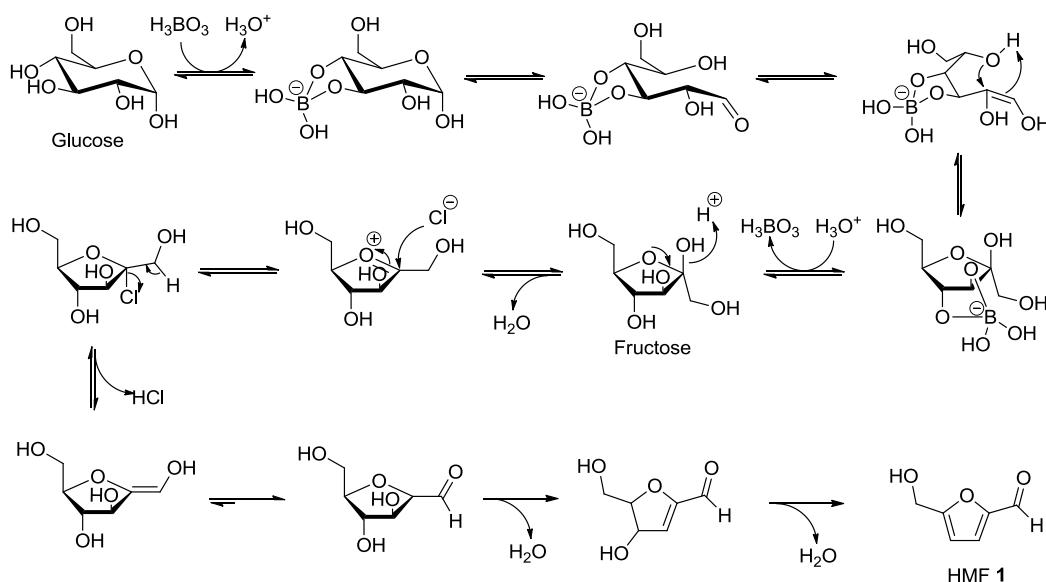


Scheme 16. The proposed mechanism for Cr-catalysed isomerisation of glucose to fructose in ionic liquid, as proposed by Pidko *et al.* Reprinted from Ref.¹³⁶ with kind permission from Wiley-VCH



Scheme 17. Mechanism of the SnCl_4 -catalysed isomerisation and dehydration of glucose to HMF, as proposed by Hu *et al.*¹⁴⁴

Ståhlberg investigated the boric acid-catalysed glucose isomerisation/dehydration to HMF in ionic liquid.¹⁴⁵ This work was based on the premise that boric acid forms an anionic borate complex with carbohydrates to facilitate the isomerisation of aldohexoses to ketohexoses.^{146,147} Based on DFT calculations and deuterium labelling experiments for the boric acid-catalysed isomerisation of glucose to fructose and subsequent dehydration to HMF a mechanism described in Scheme 18 was proposed. In fructose dehydration reactions the presence of >0.2 eq. boric acid, relative to fructose, had a negative effect on the HMF yield, which was explained by the formation of stable fructose-borate complexes. It was also concluded that boric acid acted mainly as an isomerisation catalyst rather than a dehydration catalyst. In the isomerisation a stabilising effect of borate coordination on the open chain form of glucose and the decrease in activation energy on the protonation of the aldehyde on C-1 were calculated. Deuterium labelling on C-2 of glucose yielded HMF with less than 5% deuterium incorporated in the HMF product, corresponding with isomerisation through an enediol mechanism, expelling almost all deuterium into the solution by formation of a ketone at C₂. In the case of a hydride shift, 100% would still be incorporated in fructose and assuming a cyclic dehydration mechanism described in Scheme 10, Scheme 12 and Scheme 13 around 50% should still have been present in HMF.



Scheme 18. Proposed mechanism for the boric acid-catalysed isomerisation of glucose to fructose, followed by fructose dehydration to HMF¹⁴⁵

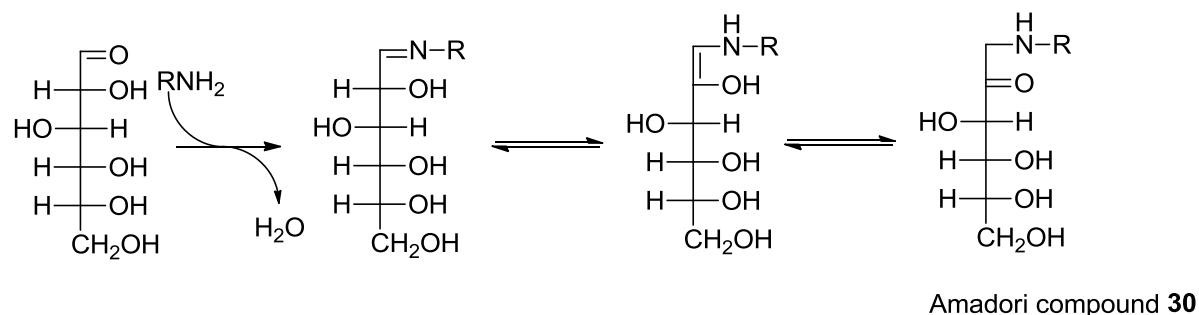
The currently available knowledge of the dehydration of fructose does not allow us to decide which of the proposed mechanistic routes is correct. One exception is Amarasekara's NMR studies on fructose dehydration in DMSO, which clearly showed cyclic intermediates. The authors proposed adducts of the intermediates with DMSO that were not observed in NMR,¹¹⁷ making it inapplicable to dehydration in other solvents, water in particular.

It is clear that fructose is much more readily converted to HMF than glucose. This is corroborated by results that show that an efficient isomerisation catalyst is required for efficient glucose conversion to HMF. This information makes a cyclic dehydration mechanism from fructose much more likely than an acyclic dehydration mechanism from an intermediate enediol, as the latter does not explain the large differences in reactivity and selectivity between fructose and glucose in their reactions to HMF, since the enediol would be a common intermediate.

HMF formation via Maillard reactions

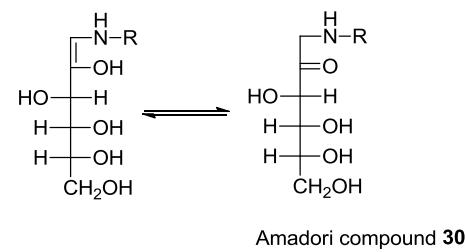
HMF and its derivatives are often reported to be present in food. In many cases it is believed to be formed by the so-called Maillard reaction. The first step of the Maillard reaction is the reaction of a reducing sugar with an amino acid, forming a so-called Amadori compound (**30**, Scheme 19a). Removal of the amino acid results in reactive compounds that are subsequently degraded to the important flavour components furfural and HMF (Scheme 19b). Another reaction pathway is the so-called Amadori-rearrangement, which is the starting

point of several browning reactions (Scheme 19b). The rate of the Maillard reaction and the nature of the products formed are mainly determined by the reaction conditions.¹⁴⁸ The combined influence of time, temperature and pH is most relevant for the formation rate in food systems. Other less important factors are the chemical composition (nature of the reactants and type of buffer), water activity, the presence of oxygen, metals and reaction inhibitors (like sulfur dioxide). These factors thus have a high impact on the quality of processed foods. There is general consensus that a pH below 7 is necessary for substantial HMF formation.¹⁴⁸

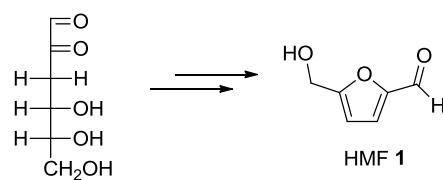
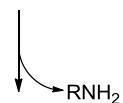


Amadori compound 30

Scheme 19a.



Amadori compound 30



3-DG 23

Scheme 19b

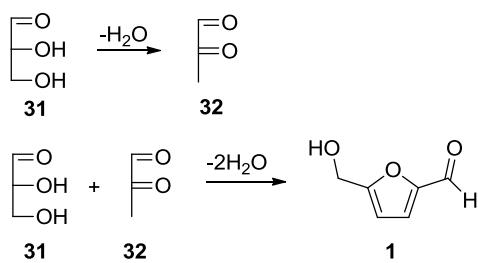
Scheme 19. (a) The initial step of the Maillard reaction between glucose and an amino acid (RNH_2), including the Amadori rearrangement, and (b) the subsequent formation of HMF.

The Amadori compound **30** is depicted in the Fischer projection, which does not necessarily mean it is mainly in its open form.

Yaylayan and co-workers studied the chemical reactivity of 5-(hydroxymethyl)-2-furaldehyde (HMF) with lysine, glycine, and proline using isotope labeling technique. The formed products were identified using mass spectroscopy. A range of new adducts was discovered.¹⁴⁹

HMF formation from reverse Aldol products of sugars

Cämmerer and co-workers investigated C₃ sugar degradation products during the Maillard and caramelisation reactions.¹⁵⁰ In both reactions traces of HMF (0.3%) were observed. A β -dehydration is claimed to take place on glyceraldehyde (**31**), leading to the formation of pyruvaldehyde (**32**), which then reacts with glyceraldehyde to form HMF (Scheme 20). Follow-up research by Murkovic and Bornik showed that reacting pyruvaldehyde with glyceraldehyde can lead to the formation of HMF (1.5 mol%) while combinations of glyceraldehyde and pyruvate resulted in substantial amounts (4.0 mol%) of 5-hydroxymethylfuroic acid **4**.¹⁵¹ Several research groups have reported the formation of glyceraldehyde and pyruvaldehyde in sugar dehydration.^{104,121,125,152,153} This indicates that a minor part of the detected HMF in those studies could be formed via aldol condensation of C3 retro-aldol degradation products.



Scheme 20. The β -dehydration of glyceraldehyde to pyruvaldehyde, followed by the formation of HMF from pyruvaldehyde and glyceraldehyde.¹⁵⁰

2.3.1.2 By-products

An important factor in the synthesis of HMF through sugar dehydration is the occurrence of side reactions. The reported by-products include organic acids, other furans, aromatics, retro-aldol products, fructose dianhydrides¹⁵⁴ and polymeric materials, including humins. An overview of these by-products is given in Table 5. Quantities of the different by-products

depend on feedstock and process conditions and in many cases quantitative data or even qualitative data on by-product formation are absent.

It is generally accepted that the formation of levulinic acid and formic acid goes through rehydration of HMF and not directly from sugars. This is based on the general observation that the HMF yield has an optimum and that at prolonged reaction time an increase in levulinic acid yield is observed at the cost of the HMF yield.^{102,155-159} Recently an *in situ*¹³C-NMR study with ¹³C labelled fructose on C-1 and C-6 revealed that the carbonyl carbon of HMF is incorporated in formic acid, whereas the hydroxymethyl carbon forms the methyl (C-5) carbon in levulinic acid.¹¹⁴

Table 5. By-products of hexose dehydration

Furans	Organic acids	Aromatics	Retro-aldol products	Others
Furfural	Levulinic acid	1,2,4-Trihydroxybenzene	Pyruvaldehyde	Fructose dianhydrides
2-Hydroxyacetyl furan (21)	Formic acid		Dihydroxyacetone	Polymeric material (incl. humins)
HMF dimers	Acetic acid		Glyceraldehyde	
	Lactic acid		Erythrose	

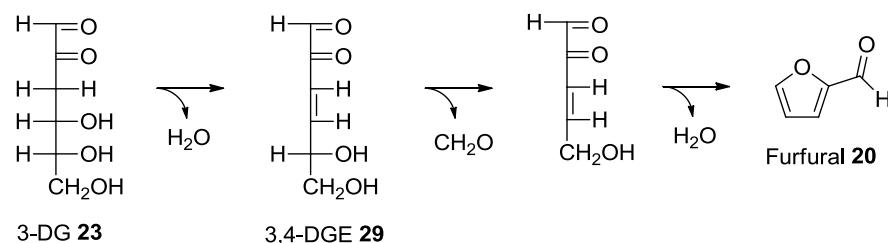
This notion was challenged by Pidko *et al.* for the formation of LA from glucose in recent computational work- in which a pathway from glucose to LA without HMF as an intermediate was calculated to be the most energetically favourable dehydration route.^{160,161} A computational study on the conversion of HMF to levulinic acid was published by Wang *et al.*¹⁶²

High HMF selectivities are generally observed in the initial stage of the dehydration reaction, which was interpreted by Seri *et al.* that the by-product formation, especially humins, does not originate from the substrate only.¹⁶³ Girisuta *et al.* published kinetic data on the rehydration of HMF to levulinic acid.¹⁶⁴ Their research was mainly focussed on levulinic acid production from glucose^{165,166} and untreated biomass.¹⁶⁷ In these studies HMF was observed as an intermediate.

Research on autocatalysis in fructose dehydration, through the formation of organic acids during the reaction, by Kuster showed that HMF formation is pH dependent. Water-based

fructose dehydration in the initial absence of catalyst showed HMF formation and a gradual decrease in pH to a value of 3.2.¹⁵⁷

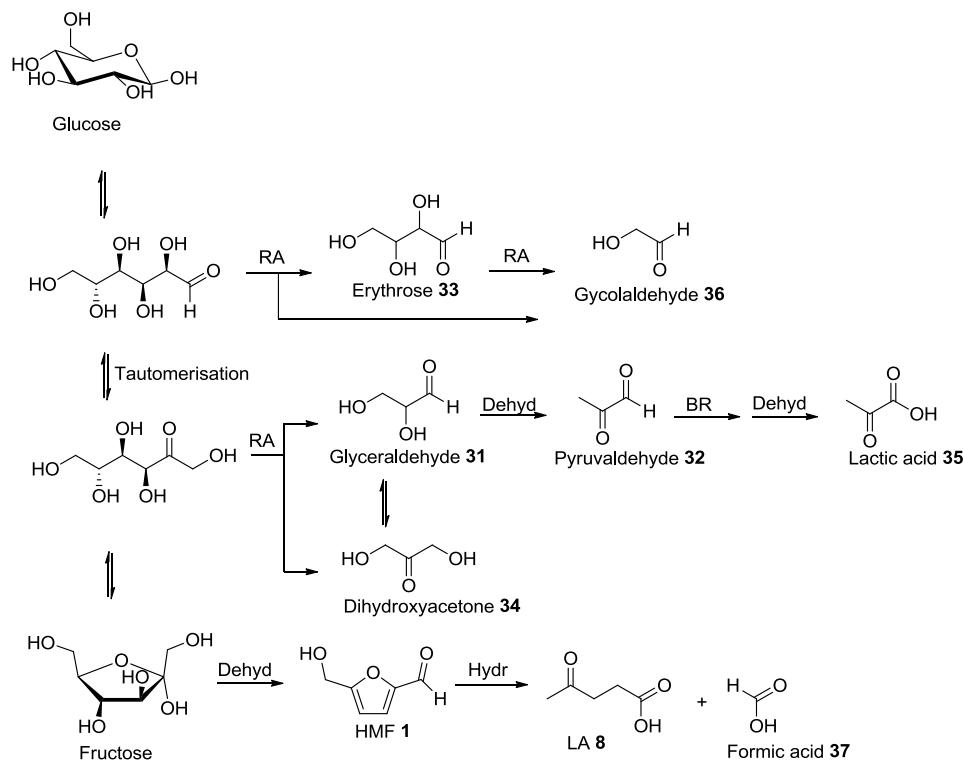
Furfural is another important by-product, that was found in particular in reactions performed in supercritical fluids.^{102,120,122} Until now it is not well understood if this is formed directly from the carbohydrate, from HMF or via another intermediate. The formation of furfural via 3,4-DGE (**29**, Scheme 21) was proposed by Kallury *et al.*¹⁶⁸ and this pathway was incorporated in the dehydration mechanism proposed by Moreau (Scheme 7). *In situ* ¹³C-NMR experiments with ¹³C labelled fructose on C-1 showed for their specific conditions that C-1 on fructose converted into the carbonyl on HMF, as well as the carbonyl on furfural.¹¹⁴ The formation of furfural was not observed in all cases and appeared to depend on which catalyst was used. The result, however, was not in agreement with the mechanism described in Scheme 21, as this scheme proposes the C-2 of the hexose to convert into the carbonyl group of furfural.



Scheme 21. Furfural formation from 3,4-DGE¹⁶⁸

Silberman reported work on the reactions of sugars in the presence of acids,¹⁶⁹ which showed that at higher concentrations, glucose and other aldohexoses undergo condensation to form reversion products (mainly β -isomaltose or β -gentobiose), whereas ketoses are more prone to dehydration and subsequent humin formation.¹⁶⁹ Glucose has been shown to condensate to anhydroglucoses, which apparently cannot be converted to HMF.^{121,128,170}

Other products formed from glucose and fructose under aqueous sub- and supercritical conditions are erythrose (**33**), pyruvaldehyde (**32**), glyceraldehyde (**31**), dihydroxyacetone (**34**), lactic acid (**35**) and glycolaldehyde (**36**).^{121,128,171,172} Scheme 22 describes the formation of these compounds, among others, as explained by Aida *et al.*^{128,172} A complete list of glucose degradation products formed by sterilisation of glucose containing pharmaceutical solutions is provided by Witowski and Jörres (Table 6).¹⁷³



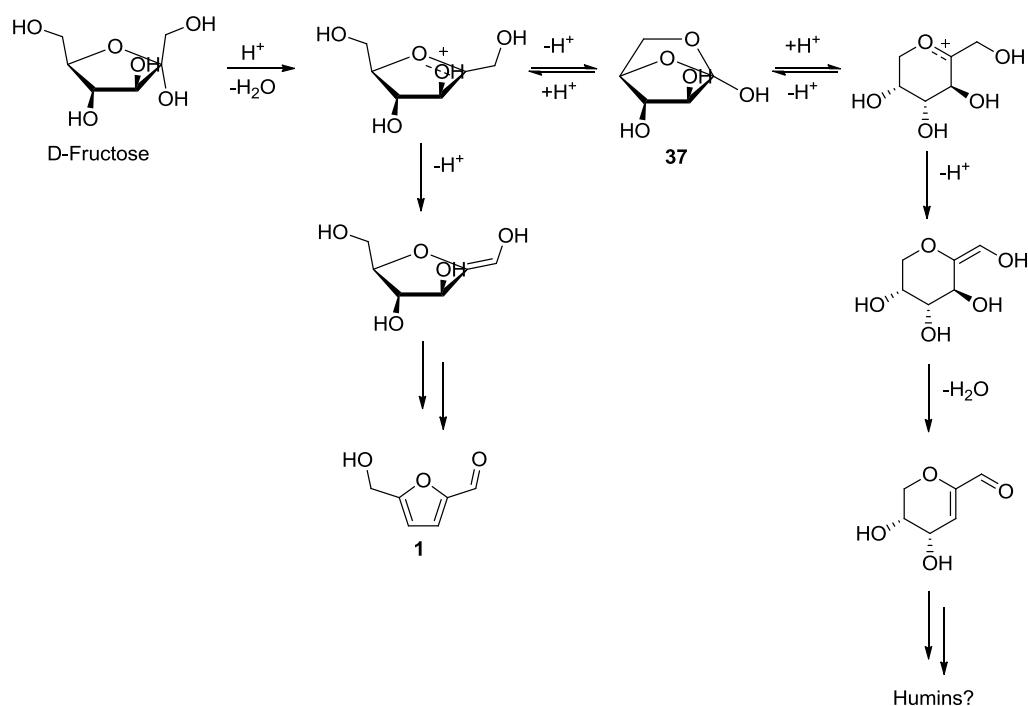
Scheme 22. An overview of the thermal degradation routes of glucose and fructose in sub- and supercritical water.^{128,172} RA = retroaldol, Dehyd = dehydration, BR = benzylic acid rearrangement, Hydr = hydration

Table 6. Glucose degradation products identified in sterilised pharmaceutical solutions

HMF	Formic acid (37)
Acetaldehyde	Levulinic acid (8)
Formaldehyde	5-Hydroxymethylfuroic acid (4)
Furfural (20)	2,5-Furandicarboxylic acid (3)
Glyoxal	2-Hydroxyacetyl furan (HAF, 21)
Pyruvaldehyde (32)	3-deoxy-D-glucosone (3-DG, 23)
Valeraldehyde	

Soluble and insoluble polymeric materials are another group of by-products. The insoluble polymers are generally referred to as humins. Dumesic *et al.* report decreased selectivity of fructose dehydration to HMF when controlled amounts of HMF were initially added to the

reaction mixture, implying a possible reaction between HMF and fructose, or a derivative thereof.¹⁷⁰ Stability tests of HMF in the absence of sugars under reaction conditions showed only marginal loss of HMF.¹⁷⁴ It is generally assumed that the humins are formed from polymeric condensation of HMF with sugars. A similar effect is also observed in furfural production from pentoses where adding furfural to the pentose feed enhances the formation of humin-like materials.¹⁰⁰ A recent ¹³C-NMR study by Akien *et al.* proposed the formation of humins through 2,6-anhydro- β -D-fructofuranose (Scheme 23).⁹⁴ Due to their complex structure and composition, the nature of the oligomeric materials and humins are until now not very well characterised. A recent IR study on humins formed from HMF by Patil and Lund did indicate the presence of the furan and hydroxymethyl groups from HMF and the aromatic ring of benzaldehyde in the humins.¹⁷⁵ At the moment the most likely applications for these humins are either as a fuel, particularly to generate heat for the various unit operations of the HMF production, or as compost.

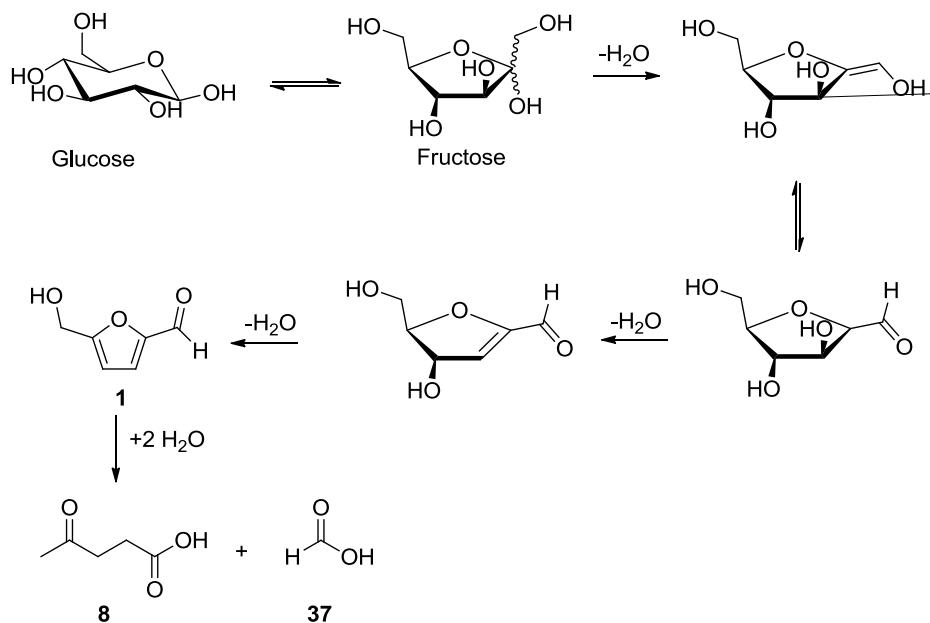


Scheme 23. Proposed pathway for humin formation

Zhang *et al.* studied the formation of carbonaceous microspheres from HMF formed in the dehydration of fructose, also proposing a mechanism for their formation.¹⁷⁶

2.3.1.3 Computational Studies

In a recent computational study on glucose dehydration, through fructose, to HMF via a cyclic mechanism and subsequent hydration to levulinic acid (Scheme 24) the reaction energies were calculated using Gaussian and density functional theoretical (DFT) methods.¹⁷⁷ The Gibbs free energies were calculated at 25 and 175 °C. At 25 °C the solvation effect of water was also taken into account. These calculations all showed an increase in Gibbs free energy for both the isomerisation of glucose to fructose and the first dehydration step of fructose at a combined ΔG_{298K} around 40 kJ/mol. All subsequent steps resulted in a decrease in ΔG , especially the third dehydration ($\Delta G_{298K} \approx -92$ kJ/mol), attributed to the formation of the stable furan ring, and even more for the rehydration to levulinic acid (**8**) and formic acid (**37**) ($\Delta G_{298K} \approx -113$ kJ/mol).



Scheme 24. The cyclic dehydration of glucose and subsequent rehydration to levulinic acid¹⁷⁷

Calculations were also performed on solvent effects of water and DMSO. Water was found to have a significant stabilising effect on glucose compared to fructose whereas with DMSO this was not the case.¹⁷⁷

Apart from solvent effects, these calculations do not explain the significant difference in the ease with which fructose is dehydrated to HMF compared to glucose, because activation energies were not taken into account. The computational calculations are in line with what has already been observed experimentally. The first step is rate determining and all subsequent steps are fast, explaining the difficulty in determining stable intermediates.

Caratzoulas *et al.* performed a computational study on the dehydration of fructose to HMF at 90 °C.¹⁷⁸ The calculations were made for the protonated intermediates. The biggest difference with Assary's work¹⁷⁷ can be found in the intermediate with the highest ΔG (around +210 kJ/mol), which was involved in the second dehydration, where Assary mentioned the first dehydration as the step with the highest increase in ΔG. The difference in calculated ΔG is also quite big at a factor of around 5. The same group recently published work in which the high HMF selectivity of fructose dehydration in DMSO is explained, showing a preferential coordination of DMSO around the HMF molecule, protecting it from side-reactions. Also a specific coordination of DMSO around the fructose molecule was found, preventing reversion and other side reactions.¹⁷⁹

In a recent publication Qian reports calculations that indicate a pathway from glucose to HMF that does not involve formation of fructose as an intermediate, but rather through an aldehyde.¹⁸⁰ This aldehyde is alike to anhydro-D-mannose, which is presented in its enol form in Scheme 10.

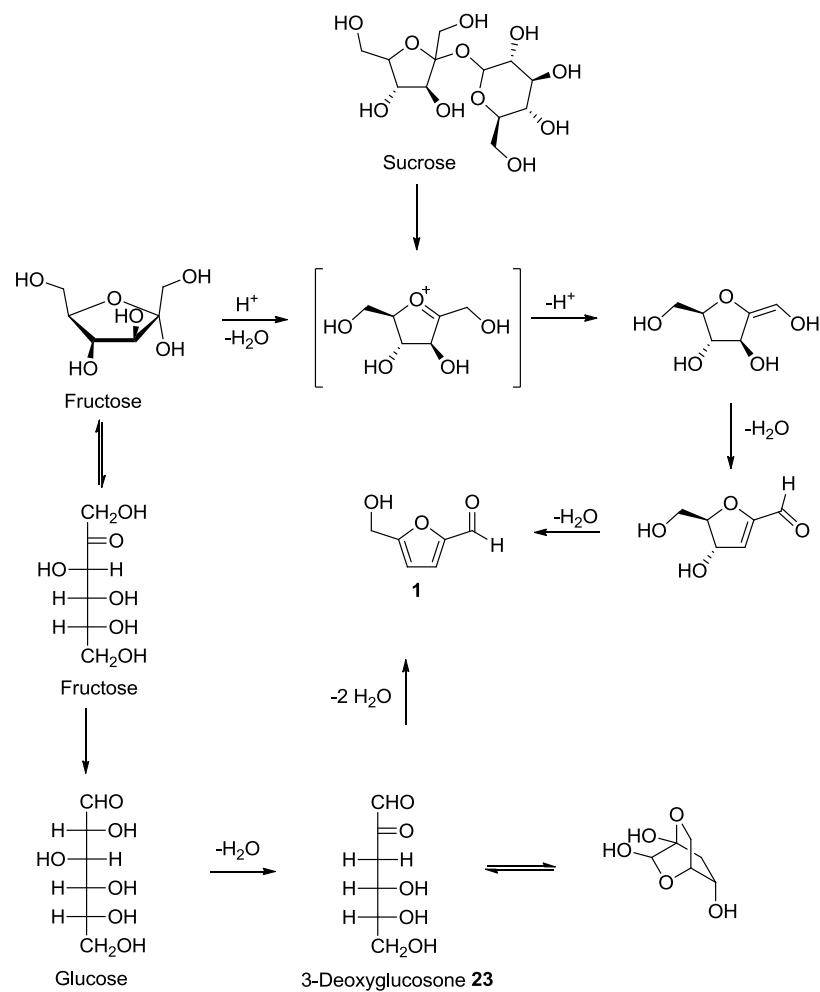
Guan *et al.* performed DFT calculations on MCl_3 catalysed glucose conversion to HMF in 1-butyl-3-methylimidazolium chloride ($[\text{BMIm}]\text{Cl}$) ionic liquid.¹⁸¹ Calculations were performed with FeCl_3 , WCl_3 , CrCl_3 and MoCl_3 . From these calculations it was concluded that WCl_3 would be a very promising catalyst for this chemistry, however, this was not confirmed by experimental data.

2.3.2 Disaccharides and polysaccharides

Most of the work published in the field of HMF synthesis is focussed on the conversion of monosaccharides. From an economical and environmental point of view, it is also interesting to consider polysaccharides. In addition to the challenges connected to the conversion of monosaccharides, these feedstocks have additional physical properties that complicate their application. The two most important factors to take into account are the reduced solubility in almost all solvents and the presence of glycosidic bonds between the sugar moieties that can be difficult to break.

Isotope labeling studies on pyrolysis GC-MS by Perez Locas and Yaylayan focused on HMF formation from sucrose at 250 °C with the purpose of determining the relative contribution of the fructose moiety to the HMF yield.¹⁸² By ^{13}C labelling on the fructose moiety, they determined that 90% of the HMF formed originated from the fructose moiety and 10% from the glucose moiety. At 300 °C HMF formation from sucrose, fructose and 3-DG was observed. The HMF yields from both fructose (4.5 fold) and sucrose (2.4 fold) were

significantly higher than from 3-DG (**23**). Based on these results 3-DG was ruled out as an intermediate in the formation of HMF from fructose or sucrose. Glucose only generated 0.16 fold HMF relative to 3-DG. Based on these results a mechanism was proposed (Scheme 25).

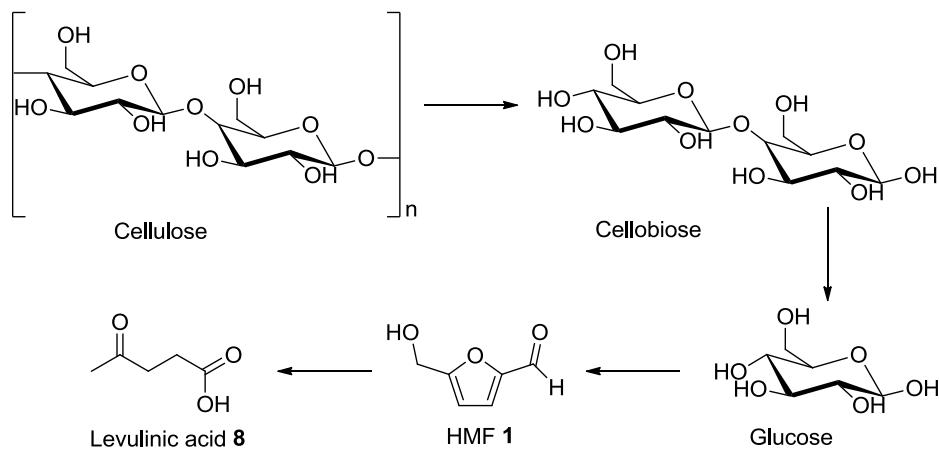


Scheme 25. A mechanism proposed by Perez Locas and Yaylayan¹⁸² for the dehydration of sucrose, fructose and glucose to form HMF (adapted from Perez Locas and Yaylayan¹⁸²)

Research by Carlini *et al.* on sucrose and inulin dehydration showed that in an aqueous medium the hydrolysis of these compounds to monosaccharides was faster than the dehydration of fructose.^{183,184} This is consistent with work by Haworth and Jones, who also showed that the HMF produced from sucrose originates almost entirely from the fructose moiety.¹⁸⁵ In the conversion of inulin and Jerusalem artichoke extracts, which are rich in polyfructans, hydrolysis was also observed to be much faster than dehydration.¹⁸⁶

Mascal showed that cellulose can be readily converted into furan compounds using a mixture of LiCl in concentrated hydrochloric acid¹⁸⁷ and research on La(III)-catalysed cellulose degradation in water by Seri *et al.* showed the formation of cellobiose (a D-glucose

dimer), glucose, HMF and levulinic acid.¹⁸⁸ Based on their research, Seri *et al.* proposed the reaction pathway as described in Scheme 26.

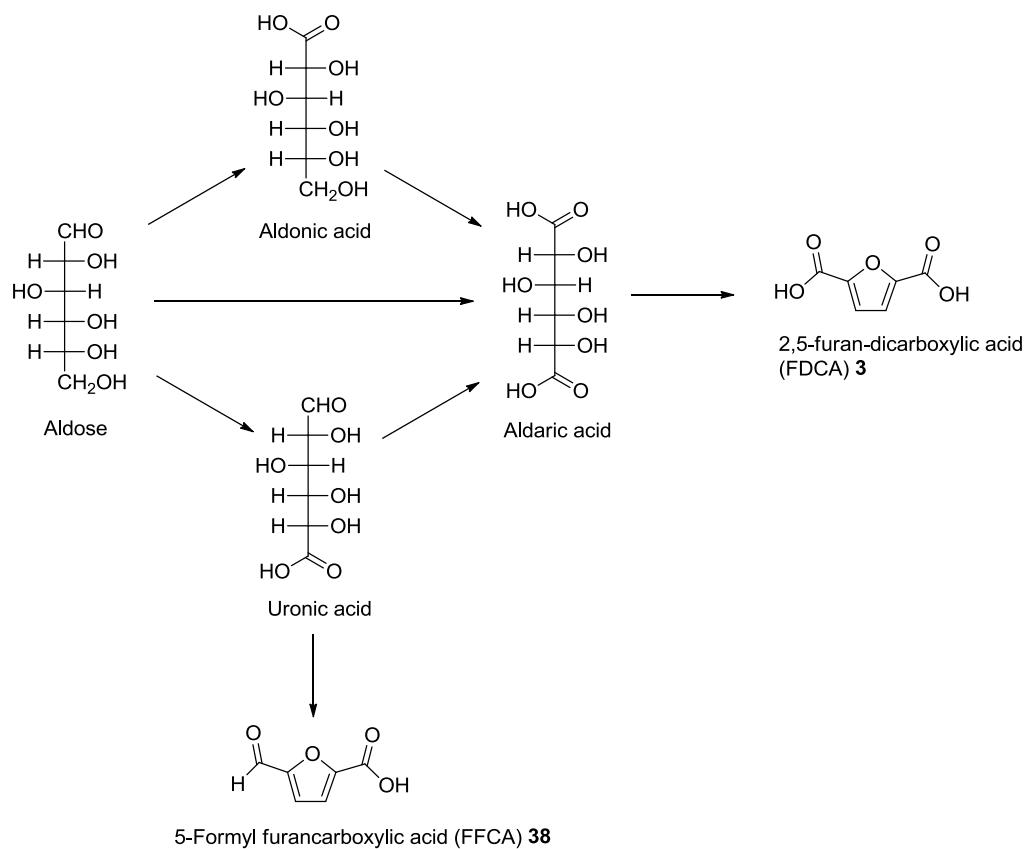


Scheme 26. The reaction pathway for La(III)-catalysed carbohydrate dehydration¹⁸⁸

Research by Girisuta *et al.* on levulinic acid formation from cellulose under aqueous acidic conditions show HMF as intermediate in the conversion of glucose to levulinic acid (**8**).¹⁸⁹ It was observed that higher temperatures lead to higher HMF amounts, which is consistent with observations by Peng *et al.* on levulinic acid production from cellulose.¹⁹⁰

2.3.3 Sugar acids

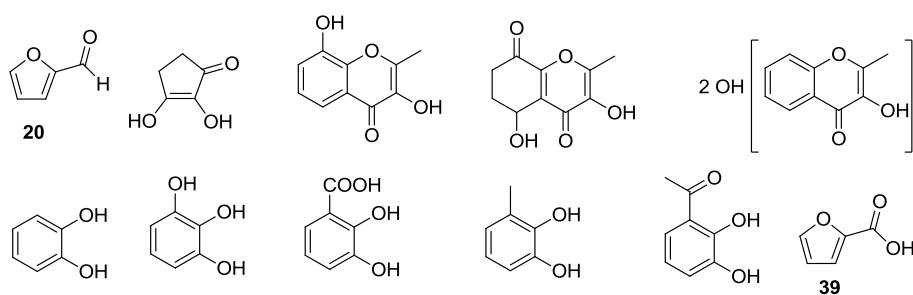
The dehydration to furanic compounds is not exclusive to neutral sugars. Even though HMF is not the primary product formed, the dehydration of sugar acids (Scheme 27) is interesting as these substrates may have similarities in their dehydration. They could thus provide further clues towards the mechanisms of neutral sugar dehydration. In addition, the compounds obtained, can be seen as oxidation products from HMF and thereby an alternative route towards the highly interesting furan dicarboxylic acid (FDCA, **3**) or 5-formyl furancarboxylic acid (**38**).



Scheme 27. An overview of the formation of 2,5-furan-dicarboxylic acid from sugar acids

Several literature references mention the acid-catalysed degradation of galacturonic acid under aqueous conditions. Most of this work deals with the quantification of sugars and studies the decarboxylation reaction via quantification of the released CO₂ and furfural from the remaining pentose. The production of 5-formyl-2-furancarboxylic acid (FFCA) from galacturonic acid has been mentioned but no quantification has been reported.

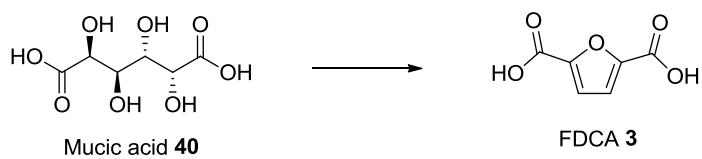
In the work of Popoff *et al.*, the reaction of glucuronic acid and galacturonic acid in aqueous acidic media are reported to yield an array of products (Scheme 28), including furfural and 2-furoic acid (**39**).¹⁹¹ The yields of the majority of these compounds was higher from glucuronic acid than from galacturonic acid.



Scheme 28. Detected products on the acid catalysed reaction of galacturonic acid and glucuronic acid.

Usuki *et al.* observed that the degradation of glucuronic and galacturonic acids proceeds at lower temperatures (140, 150 and 160 °C) than the degradation of pentoses, namely arabinose, xylose and lyxose (200, 220 and 240 °C).¹⁹² The formation of acidic compounds during degradation led to a fast pH decrease. The decomposition of glucuronic acid and galacturonic acid in subcritical water was kinetically analysed. In acidic solution at elevated temperature, hexuronic acids undergo decarboxylation, forming 2-furaldehyde and reductic acid (2,3-dihydroxycyclopenten-1-one). The reaction is nearly quantitative and has been used as an analytical method for hexuronic acids. Only traces of 5-formyl-2-furancarboxylic acid were observed.

In 1876 Fitting and Heinzelman synthesised 2,5-furandicarboxylic acid (FDCA) from mucic acid using concentrated hydrobromic acid, as described in Scheme 29. Several other catalysts and substrates have been tested subsequently. All the reactions required severe conditions (highly concentrated acids, temp > 120 °C, React time > 20h) and all the methods were non-selective with yields below 50%.¹³



Scheme 29. The synthesis of furandicarboxylic acid from mucic acid

2.3.4 Conclusion

We can conclude that there are still many uncertainties with regard to the mechanism(s) of hexose dehydration to furan compounds. A distinction can be made between mechanisms based on cyclic intermediates and mechanisms based on acyclic intermediates. The

differences within either group are only marginal and only limited evidence has been provided.

The effect of the solvent is an additional factor to be taken into account, as for both DMSO and ionic liquids reaction mechanisms have been proposed in which the solvent plays an active role. It is therefore not inconceivable that the mechanism depends on the solvent.

The literature strongly indicates that the first dehydration of fructose is the rate determining step in the formation of HMF, with all subsequent steps proceeding much faster. This makes it almost impossible to determine the reactive intermediates by analysis. A second complicating factor is the inherent reactivity of sugars, facilitating a wide array of side-reactions of the sugar.

With regard to HMF formation from glucose, the information at hand indicates a reaction pathway through isomerisation to fructose. This presents an interesting challenge, because the glucose-fructose isomerisation is base-catalysed and the dehydration of fructose is acid-catalysed. In order to overcome this challenge an increasing amount of work has been published concerning bifunctional catalyst systems (*vide infra*).

2.4 Process chemistry

The development of efficient methods for HMF production from carbohydrates has been on-going for almost a century. Until the 1980's research in this field almost exclusively focussed on the use of homogeneous acids as the catalyst in water-based reaction media, a solvent common for traditional sugar chemistry. The past three decades have seen a shift from water-based chemistry to alternative solvent systems in order to improve the overall yield of HMF. Based on the solvent system used, HMF synthesis from carbohydrates can roughly be divided into three types of processes: traditional single-phase systems; biphasic systems and ionic liquid-based systems.

2.4.1 HMF formation in single-phase systems

Going back as far as the early 20th century most research on the formation of HMF was performed in aqueous systems with mineral acids as catalysts (mainly sulfuric and hydrochloric acid). Water is an obvious choice of solvent because it dissolves the majority of the sugars in high concentrations unlike most organic solvents. Because of the relatively low HMF yields in aqueous systems, the use of organic solvents has grown since the 1980's. Solvents like DMSO, DMF, DMA, acetone, acetic acid and methanol have been reported in the literature. The work discussed in this section will be divided in processes from fructose,

glucose and polysaccharide dehydration, respectively. The substrate concentrations are generally described in weight percentage relative to the total weight of the solution and the catalyst concentrations are described in percentages relative to the amount of substrate where homogeneous catalyst loading is related to the molar amount of hexose monomers and the heterogeneous catalyst loading is given in weight percentages relative to the weight of the substrate. Yields, selectivities and conversions are described in molar ratios unless mentioned otherwise. The yield describes the amount of HMF formed relative to the starting amount of hexose monomers, the conversion describes the amount of sugar monomers converted into non-saccharides and the selectivity describes the amount of HMF formed relative to converted substrate.

2.4.1.1 Fructose dehydration in single-phase systems

Research on fructose dehydration in traditional single-phase liquid systems, including supercritical fluids, will be reviewed here. By far the highest HMF yields reported in the literature have come from fructose dehydration. HMF synthesis in aqueous systems will be discussed first, followed by a summary of the work done in organic solvents and aqueous/organic single-phase mixtures.

Fructose dehydration in water based systems

This paragraph deals with the dehydration of fructose under aqueous conditions, excluding HMF synthesis in the presence of extracting solvent, which is discussed in section 2.4.2. The basic structure is selected as chronological, describing the evolution of the work in the last half-century, combined with clustering comparable work. In this way the initial work at lower temperatures and pressures is first discussed, followed by the more recent work at higher temperatures and pressures. At the end of the paragraph summarising tables and a brief conclusion are given.

Process research on HCl catalysed fructose dehydration in water was published by Kuster and co-workers in 1977.^{155,156,193} The reactions were performed at 95 °C under ambient conditions. The best HMF yields were around 30% and the highest selectivity around 60%. The high HCl concentration (0.25-2 M) in combination with the relatively low temperature favoured formation of levulinic acid over HMF, explaining the low yield/selectivity for HMF.¹⁵⁵ The addition of polyethylene glycol-600 (PEG-600) as a co-solvent led to an improved dehydration rate and subsequently a reduced rehydration rate. A maximum HMF yield of around 70% at 86% conversion was obtained when using 70% PEG-600 in water.¹⁵⁶

In the same series of publications Kuster and Temmink reported work on aqueous fructose dehydration catalysed by formic acid at 175 °C and 50 bar.¹⁵⁷ With a fructose concentration of 0.25 M HMF yields of 50-60% with 80-100% selectivity were reported at pH ≈ 3 at reaction times around 1 h. At a controlled pH of 2.7, 56% HMF yield was reported at 56% conversion after 45 min. An experiment in the absence of catalyst was reported to yield 56% HMF at 70% conversion after 90 min and showed a gradual decrease in pH from 7 to 3.2, which indicated the formation of acids during the reaction.¹⁵⁷ There is no reason to assume that starting the reaction under acidic conditions prevented the formation of organic acids that were formed during the initially uncatalysed dehydration of fructose, which makes the high selectivities obtained at pH 2.7 surprising. In some cases the yield was reported to be higher than the conversion, corresponding with selectivities over 100%. An important observation in the work of Kuster and Temmink is the increase in levulinic acid yield with decreasing pH (at pH > 1).

Following Kuster's work, Van Dam tested the influence of a number of variables, namely substrate concentration, acidity, metal salts and water content, on the formation of HMF from fructose.¹⁵⁸ A maximum HMF yield of around 25% at fructose conversions of 50-60% was obtained with 0.2 M fructose catalysed by 1 M *p*-toluene sulfonic acid, at 88 °C after 4-5 h. The addition of 50 vol% of PEG-4000 increased the yield to around 50%. This is in line with the results of Kuster described above for PEG-600.¹⁵⁶ Vinke and Van Bekkum later used activated carbon as adsorbent for HMF to obtain 43% yield at 72% conversion in the dehydration of 0.25 M fructose at 90 °C for 7 h.¹⁹⁴

A gradual increase in the applied reaction temperature can be observed since the 1980's. In the mid 1980's, the Süddeutsche Zucker-Aktiengesellschaft developed a method for preparing HMF from fructose on 10 kg scale.¹⁹⁵ From the dehydration of 25 wt% fructose in water, catalysed by 1 wt% oxalic acid at 135-142 °C for 130 min a 34% HMF yield at 61% conversion was claimed prior to isolation, of which 80% could be separated by chromatography. The presence of glucose, polysaccharides and humic material before purification is mentioned. With 1% oxalic acid relative to fructose El Hajj *et al.* reported an isolated HMF yield of 23% at 145 °C for 2.5 h.¹⁹⁶

Antal and co-workers continued in the field of homogeneous acid catalysed fructose dehydration under aqueous circumstances at even higher temperatures and pressures. The highest HMF yields obtained were around 50% at 95% conversion with 2 mM H₂SO₄ and 0.05 M fructose concentration at 250 °C and 340 bar.¹⁰⁴

In the 1990's Carlini and co-workers published research on HMF synthesis in aqueous environment using heterogeneous catalysts.^{183,184,197,198} Very high HMF selectivities (85-100%) using niobium phosphate based catalysts in batch experiments at 100 °C were reported.¹⁸³ These selectivities were, however, only obtained at fructose conversions between 25 and 35%. At higher conversions the selectivities dropped significantly. The highest reported selectivity at 50% conversion was around 60%. By applying intermittent extraction with MIBK, a strategy originally developed by Kuster,¹⁹⁹ the selectivities could be kept high (98%) at higher conversions. Comparable results were reported by the same group with heterogeneous titanium and zirconium catalysts.¹⁸⁴ Carlini and co-workers claimed HMF selectivities over 85% at fructose conversions around 50% using a cubic zirconium pyrophosphate catalyst at 100 °C. A heterogeneous γ -titanium phosphate was reported to produce comparable results. Intermittent extraction with MIBK led to 67% HMF yield at 71% conversion. Work by the same group on fructose dehydration under aqueous conditions with vanadyl phosphate catalysts showed comparable results.¹⁹⁸

Carniti *et al.* published work on niobium phosphate and niobic acid.²⁰⁰ Experiments were carried out in a continuous flow reactor under aqueous conditions at temperatures of 90-110 °C. The niobium phosphate was found to be more active, but both catalysts showed the same trends with regard to selectivity vs. conversion. A 25% HMF yield was obtained at 77% fructose conversion. In a recent publication Carniti *et al.* observed HMF to be stable in water in the presence of niobic acid catalyst, showing no levulinic acid formation. In the presence of fructose, however, humin formation was observed.²⁰¹

Seri *et al.* reported fructose dehydration in water catalysed by lanthanide(III) chlorides.¹⁶³ With 0.67 mol% of La, Nd, Eu, Dy and Yb compared to the substrate at 140 °C for 1 h HMF yields between 16 and 19% were reported. The HMF yield for the uncatalysed fructose dehydration was approximately 4%. For DyCl₃ experiments the conversion was tracked over time, along with selectivity and yield. These data showed an HMF yield of 24% at around 60% conversion after 2 h. At low conversions (<10%) the HMF selectivity was over 90%. Lower temperatures were also tested, but this caused the reaction to proceed very slowly.

Very recently Deng *et al.* published work on ZnCl₂ catalysed fructose dehydration, but this showed the best results (53% HMF at 97% conversion) in the presence of HCl, which is a result that can also be expected in the absence of ZnCl₂.²⁰²

The Research Center of Supercritical Fluid Technology from Tohoku University in Japan produced a number of publications on sugar dehydration at high temperatures and pressures in water (HHW).^{126-129,172} Fructose degradation was studied in a flow process at 350 °C and

400 °C at 40, 80 and 100 MPa, showing HMF formation in the absence of catalyst. An HMF yield of 7.8% at 67% conversion was obtained at 350 °C and 100 MPa with a residence time of 0.6 s.¹⁷² The main products under these conditions were retroaldol products, namely pyruvaldehyde and a mixture of dihydroxyacetone and glyceraldehyde, which combined yields up to 60%.¹⁷² Under these conditions it is possible that HMF is formed through aldol condensation reactions (Scheme 20), given the significant amounts of pyruvaldehyde and glyceraldehyde that are present.

HMF yields of around 50% were reported by Li *et al.* from fructose decomposition experiments in high temperature liquid water at 10 MPa and 180-220 °C.¹²³ In the absence of catalyst a consistent maximum yield of around 50% was reported, requiring shorter reaction times with increasing temperature. The conversion was typically between 90 and 95%. At 220 °C a yield of 50% was reached after approximately 10 min, at 200 °C this was after about 30 min and at 180 °C after about 80 min, but here the conversion was lower (around 80%).¹²³ The addition of formic acid and acetic acid led to increased reaction rates and the maximum yields in HMF were around 58%. The increase in reaction rate was much more pronounced for formic acid than for acetic acid.¹²³

Work on fructose dehydration in a high temperature (>200 °C) flow process was performed by Tarabanko *et al.*²⁰³ Phosphoric acid was used as the catalyst with an optimum HMF yield of 40%. This could be obtained either with an acid concentration of 0.01 M at 260 °C or with an acid concentration of 0.05 M at 240 °C. The optimum temperature increased with decreasing acid concentration, together with a trend of increasing yield at higher temperature and lower acid concentration.

Asghari and Yoshida applied heterogeneous zirconium phosphate catalysts in sub-critical water.²⁰⁴ Different H₃PO₄ treatment times and calcination temperatures were tested. Dehydration experiments were performed at 240 °C at 33.5 Bar for 120 s with a fructose concentration of 1 wt% and a catalyst-fructose ratio of 0.5 m/m. With the non-calcined catalysts the HMF yields were consistent around 50% (80% conversion, 59-62% selectivity), with no visible effect of the H₃PO₄ treatment. In the absence of catalyst only 19% yield (59% conversion) was obtained. Calcination decreased the yield by 5-13%. The negative effect of calcination increased with H₃PO₄ treatment.

Hansen and co-workers reported work on microwave assisted synthesis of HMF from concentrated aqueous fructose.¹⁵⁹ Heating a 30% fructose solution in the absence of catalyst yielded only 1% HMF at 5% conversion after 5 min at 160 °C. Increasing the temperature to 190 °C led to around 35% HMF yield at ~70% conversion. The authors point to the presence

of formic acid and levulinic acid as the cause for the enhanced HMF yield under these circumstances. At 1 M HCl concentration a large amount of formic acid (39%) and levulinic acid (30%) were formed together with an HMF yield of 28%. At 0.01 M HCl concentration tests on the influence of temperature and reaction time with 27% fructose solution, showed high temperatures favoured the dehydration reaction to HMF. An HMF yield of 53% at 95% fructose conversion was reported at 200 °C after 60 s. Increasing the initial microwave power from 90 W to 150 W and 300 W had no effect.

Tables 7-9 present an overview of the research on fructose dehydration in water, with a focus on the best yields and selectivities reported in each reference. Some general trends can be seen, such as a decrease in selectivity with increasing conversions and low yields in the absence of a catalyst. The decrease in selectivity with increasing conversion corresponds with the occurrence of rehydration to LA and polymerisation reactions of HMF under those reaction conditions. The general consensus is that an increase in fructose concentration favours polymerisation reactions, which has a negative effect on the HMF selectivity.

There does not appear to be a clear trend in the results obtained with homogeneous and heterogeneous catalysts. Under similar conditions with similar catalysts a great variation in the reported HMF yields can be observed that cannot be easily explained. This also makes it essentially impossible to make a comparison between heterogeneous and homogeneous catalysts.

The fact that HMF reacts further to levulinic acid and formic acid in the presence of acid and water, makes it surprising that some publications claim high selectivities (>90%) at significant conversions (>50%) using Brønsted acid catalysts, where others report selectivities of around 50% at best under similar conditions. An explanation for these divergent results in Tables 7-9 could lie in the challenging analytics, especially for the polymeric by-products. In addition, most of the analytical results have been obtained without the use of internal standards, which may lead to serious errors. Thus the reader is advised to exercise caution, in particular regarding the reports on high selectivities at high conversions.

Many authors have drawn the conclusion that in order to increase the selectivity to HMF at higher conversions, its rehydration should be prevented by either stabilisation, for instance with a specific solvent, by removal of water or through its continuous removal from the reaction mixture.

Table 7. Fructose dehydration to HMF in aqueous systems in the absence of catalyst

Fructose concentration (wt%)	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
5	140	1 h	4	-	-	163
30	160 ^a	5 min	1	5	28	159
4.5	175	1.5 h	56	72	78	157
30	190 ^a	5 min	36	67	54	159
11	200	30 min	51	89	57	123
2	200 ^a	5 min	13	28	46	129
9	200	5 min	21	40	53	126,127
0.9	350	0.59 s ^b	8	67	11	172

a: heating by microwave irradiation; *b*: continuous flow process

Table 8. Fructose dehydration to HMF in aqueous systems, catalysed by homogeneous catalysts

Fructose concentration (wt%)	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
11	Acetic Acid	100 wt%	200	20 min	58	92	64	123
5	AlCl ₃	50 mol%	120 ^a	5 min	50 ^c	-	-	205
4.5	Formic Acid	pH 2.7	175	45 min	56	56	100	157
11	Formic Acid	100 wt%	200	10 min	58	96	61	123
1	H ₂ SO ₄	10 mM	180	600 s ^b	28	80	35	206
2	H ₂ SO ₄	50 wt%	200 ^a	5 min	47	97	48	129
9	H ₂ SO ₄	1 mM	200	5 min	23	93	25	126
0.9	H ₂ SO ₄	4 mol%	250	32 s ^b	50	95	53	104
4.5	H ₃ PO ₄	16 mol%	240	3 min ^b	40	-	-	203
4.5	H ₃ PO ₄	4 mol%	260	3 min ^b	40	-	-	203
4.5	HCl	320 mol%	90	7 h	43 ^{c,f}	72	60	194
9	HCl	400 mol%	95	16 min	26	46	57	155
9	HCl	400 mol%	95	24 min	30	62	48	155

9 ^d	HCl	200 mol%	95	1.5 h	68	86	79	156
2	HCl/ZnCl ₂	100 mol%/ 2381 mol%	120	-	53	97	55	202
27	HCl	1 M	130	5 min	28	99	28	159
30	HCl	0.25 M	180	2.5 - 3 min	25	50	51	170
27	HCl	0.01 M	200 ^a	1 min	53	95	56	159
26	Oxalic acid	1 mol%	145	2,5	23 ^{c,e}	-	-	196
25	Oxalic acid	2 mol%	135-142	130 min	34	61	55	195
9 ^d	PTSA	200 mol%	88	190 min	50	88	57	158
3.6	PTSA	500 mol%	88	4 h	25	53	47	158
5	YbCl ₃	0.67mol%	140	1 h	18	34	54	163
5	YbCl ₃	0.67mol%	140	2 h	24	59	40	163

a: heating by microwave irradiation; *b:* continuous flow process; *c:* isolated yield; *d:* PEG as cosolvent; *e:* analysis by NMR only; *f:* *in situ* HMF adsorbance by activated carbon

Table 9. Fructose dehydration to HMF in aqueous systems, catalysed by heterogeneous catalysts

Fructose concentration (wt%)	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
6	10%-wt AlVOP	35 wt%	80	2 h	58	76	76	198
30	3.75%-wt FeVOP	1.8 wt%	80	1 h	60	71	84	198
6	Cubic ZrP ₂ O ₇	55 wt%	100	2 h	43	53	81	184
2	Dowex 50wx8-100	100 wt%	150	15 min	73 ^d	90	81	207
2	Dowex 50wx8-100	100 wt%	150	30 min	33	54	62	207
6	γ-TiP	55 wt%	100	2 h	39	57	69	184
6	γ-TiP	55 wt%	100	1 h	67 ^c	71	95	184
6	H ₃ PO ₄ -treated niobic acid	63 wt%	100	0.5 h	28	29	98	197
6	H ₃ PO ₄ -treated niobic acid	63 wt%	100	2 h	22	61	35	197
5.4	Niobium Phosphate	Fixed bed (3-4 g)	110	n/a ^b	25	77	33	200
6	NiP ₂ O ₇	71 wt%	100	0.5 h	29	29	100	197

6	NiP ₂ O ₇	59 wt%	100	3 h	30	51	59	183
2	SO ₄ ²⁻ /ZrO ₂	20 wt%	200 ^a	5 min	26	59	44	208
9	TiO ₂	100 wt%	200	5 min	22	98	22	126,127
9	TiO ₂	100 wt%	200	5 min	22	98	22	126,127
2	ZrO ₂	50 wt%	200 ^a	5 min	31	65	48	129
9	ZrO ₂	100 wt%	200	5 min	15	90	17	126,127
9	ZrO ₂	100 wt%	200	5 min	15	90	17	126,127
1	ZrP	50 wt%	240	2 min	49	81	61	204
2	α -TiO ₂	50 wt%	200 ^a	5 min	38	84	45	129

a: heating by microwave irradiation; *b*: continuous flow process, reaction time not applicable; *c*: HMF extraction with MIBK after 0.5 h and 1 h; *d*: 70 wt% acetone as co-solvent

Fructose dehydration in organic solvents

Research by Kuster,¹⁵⁶ Van Dam¹⁵⁸ and Qi²⁰⁷ showed the positive effects of the addition of organic solvents on the rate of HMF formation and on the HMF yield through a decrease in the rate of its decomposition/rehydration/condensation. It is thus not surprising that many groups have started investigating non-aqueous solvent systems in order to prevent rehydration of HMF to levulinic acid. Sugars typically have very low solubility in organic solvents, with the exception of polar coordinating solvents, *i. e.* DMSO and DMF. The work done on these coordinating solvents will be discussed first, followed by work in other organic solvents.

The first HMF synthesis in DMSO was reported by Nakamura and Morikawa in 1980 and yielded 90% HMF using a Diaion PK-216 ion exchange resin.²⁰⁹ Shortly after, Szmant and Chundury, reported the use of boron trifluoride etherate as a catalyst in DMSO and obtained yields of >90% HMF.²¹⁰ The dehydration was tested at different temperatures, catalyst concentrations and fructose concentrations. The reported maximum HMF yields varied between 55% and 99% at reaction times of 0.5-3 h. With 25 mol% boron trifluoride etherate in a 1.4 M fructose solution 99% HMF yield was reported after 45 min at 100 °C. The quantification was performed with UV spectrometry, making it impossible to distinguish between HMF and other furfural or polymeric (humin) derivatives. An interesting trend was found for an experiment in DMSO with 25 mol% boron trifluoride etherate at 100 °C, showing a maximum furanic yield of about 90% after 0.5 h that decreased to 80% after 1 h and subsequently remained stable for at least 2.5 h. DMF, diethylene glycol monoethyl ether, 2-methoxyethanol and 2-ethoxyethanol were also tested as solvents, resulting in significantly lower HMF yields. In DMF the maximum HMF yield was only 55% with 25 mol% boron trifluoride etherate at 100 °C after 1.5 h. Mercadier *et al.* reported 80% HMF yield in DMF after 5 h at 96 °C with a Lewatit SPC 108 ion-exchange resin.²¹¹

Brown *et al.* also looked at DMSO as the solvent, reporting quantitative conversion to HMF after 16 h at 100 °C in the absence of catalyst.²¹² The yields were estimated by ¹H-NMR analysis only. A number of acid and basic catalysts were tested, showing that the basic catalysts inhibited the HMF formation and the acid catalysts enhanced the rate of HMF formation. With 0.1 M NH₄Cl a complete conversion to HMF in 45 min was claimed. Separating HMF from DMSO through distillation was found to be difficult. For this reason other solvents were tested, such as sulfolane, DMF, ethyl acetate, butyl acetate and a collection of alcohols.²¹² DMF and sulfolane

showed similar results and isolation problems as DMSO. In ethyl acetate the reaction was much slower and less selective, resulting in an isolated HMF yield of 58% at full conversion after 30 h at 77 °C. Contrary to the reaction in DMSO, DMF and sulfolane significant by-product formation was observed in ethyl acetate, i.e. 5-chloromethylfurfural (CMF) and levulinic acid. Butyl acetate did not show this by-product formation, but the isolated HMF yield was only 31% at incomplete conversion after 16 h at 100 °C.

Further work in DMSO by Musau and Munavu²¹³ was based on the knowledge that DMSO facilitates the formation of furans from 1,4-diketones²¹⁴ and tetrahydrofurans from 1,4-diols.²¹⁵ A maximum yield of 92% HMF at 150 °C was reported.²¹³

A comparable yield of 95% was obtained by Seri *et al.* with 2.5 mol% LaCl₃ as catalyst in DMSO after 4 h at 100 °C.²¹⁶ Use of DMA and DMF resulted in almost the same yield.²¹⁶ Use of sulfolane (~50%), 1,4-dioxane and 1-butanol (both ~25%) led to significantly lower yields. Dehydration of fructose and sorbose, another ketose, was tested in DMSO, yielding 93% and 61% HMF respectively after 2 h at 120 °C.²¹⁶

Wang *et al.* investigated scandium and lanthanide triflates as catalysts for fructose dehydration in organic solvents.²¹⁷ In DMSO an HMF yield of 83% at full conversion was obtained with 2 wt% fructose in DMSO in the presence of 10 wt% Sc(OTf)₃ after 2 h at 120 °C.

Shimizu *et al.* published an elaborate study on fructose dehydration to HMF in DMSO with a variety of catalysts, including zeolites, ion exchange resins, heteropolyacids and basic heterogeneous catalysts.²¹⁸ The experiments were carried out with 3 wt% fructose and 6 wt% catalyst in DMSO at 120 °C for 2 h under continuous water removal by mild evacuation. Without additional catalyst a 32% HMF yield at 81% conversion was reported. Very high yields (>90%) were reported for a number of catalysts, such as zeolites, heteropolyacids and acidic resins. Without continuous water removal the yields decreased, except when using powdered Amberlyst 15, which was claimed to yield 100% HMF in either case, even after recycling (three times) and at fructose concentrations as high as 50%. In case of FePW₁₂O₄₀ and H-BEA zeolite the HMF yields decreased to below 50% at 50 wt% fructose concentration. Basic catalysts Al₂O₃ and MgO were found to inhibit HMF formation, but did convert fructose to unknown products.

Yan *et al.* performed a study on fructose dehydration in DMSO with a number of ZrO₂ based catalysts.¹³⁰ A reaction with 7.6 wt% fructose at 130 °C for 4 h in the absence of catalyst yielded

72% of HMF. Adding different basic catalysts had a negative impact on the yield, because of their activity in fructose to glucose isomerisation, as was already discussed in section 2.3.1.1.

Recent work using aspartic acid templated TiO_2 in DMA-LiCl (10%) by De *et al.* resulted in 82% HMF yield.²¹⁹ Dutta *et al.* applied TiO_2 in a number of solvents, obtaining the best yield (54%) in DMSO.^{220a} The same group used hierarchically macro/mesoporous titanium phosphate nanoparticles with aggregated particles of 15–20 nm in DMA-LiCl. Although the large pores were supposed to aid transport, the yield did not improve and HMF was obtained in only 42% yield.^{185b}

Continuing work on acetone/water mixtures,²⁰⁷ Qi *et al.* performed fructose dehydration in acetone-DMSO under otherwise identical conditions.²²¹ With 2 wt% fructose in 70:30 (w/w) acetone-DMSO and DOWEX 50WX8-100 resin as catalyst, 88% HMF yield was obtained at 98% conversion after 20 min at 140 °C. Decrease of the acetone ratio led to a decrease in reaction rate, but the selectivity vs. conversion plots were essentially identical. The catalyst showed only 2% decrease in yield after five recycles. Work was also published with zirconia (ZrO_2) and sulfated zirconia ($\text{SO}_4^{2-}/\text{ZrO}_2$) as catalyst.²⁰⁸ Experiments were performed with 2 wt% fructose in acetone-DMSO (70:30 w/w) in the presence of 20 wt% catalyst. When comparing ZrO_2 with $\text{SO}_4^{2-}/\text{ZrO}_2$, the latter showed higher activity, with HMF yields of 60–66% at 84–91% conversion depending on the calcination temperature. With the regular ZrO_2 the HMF yields were below 50% at lower conversion and varied significantly with calcination temperature. The selectivity was consistently around 10% higher for the sulfated catalysts than for the regular catalyst. In the absence of catalyst the reaction also took place, but at a slower rate, with a reported HMF yield of 66% at 85% conversion after 20 min, which is only slightly lower than those obtained after 20 min in the presence of catalyst.

Research on the use of ionic liquids as homogeneous catalyst was published by Tong and Li.²²² Two types of cations, namely $[\text{HMIm}]^+$ and $[\text{HNMP}]^+$, were tested in combination with either HSO_4^- or CH_3SO_3^- as anion. The NMP based ionic liquids were found to have stronger Brønsted acidity, with $[\text{HNMP}]^+[\text{HSO}_4]^-$ being the most acidic. Experiments were done in DMSO, water, ethanol, *N*, *N*-dimethylacetamide, carbon tetrachloride and acetonitrile. The HMF yield was reported to be by far the highest in DMSO, in which a yield of 72% at 83% conversion was obtained by reacting 7 wt% fructose at 90 °C for 2 h with 7.5 mol% of $[\text{HNMP}]^+[\text{CH}_3\text{SO}_3]^-$. With $[\text{HNMP}]^+[\text{HSO}_4]^-$ an HMF yield of 69% at 99% conversion was obtained.

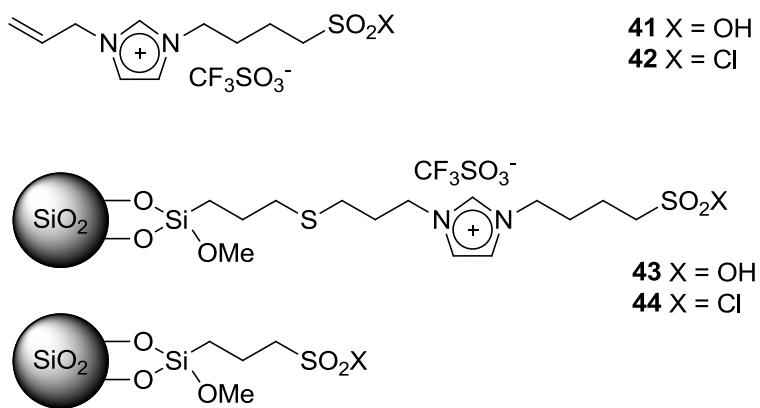
Recently Qu *et al.* published 92% HMF yield in DMSO with [BMIm]OH as the catalyst after 8 h at 160 °C.²²³ As was already mentioned above, Brown reported quantitative HMF yields in DMSO under less severe conditions in the absence of a catalyst. Combined with the other results reported in Table 10 this indicates a negative effect of the ionic liquid additive, since far more severe conditions were applied.

Ohara *et al.* reported 90% HMF yield at 100% fructose conversion in DMF with 100 wt% Amberlyst 15 as the catalyst after 1 h at 100 °C.²²⁴

In 2008 Bao and co-workers published work on fructose dehydration, catalysed by dilute acidic ionic liquids **41** and **42** (Scheme 30) and their immobilised counterparts **43** and **44** in DMSO.²²⁵ Ionic liquid **41** is a Brønsted acid and **42** is its Lewis acid derivative. The dehydration was performed in DMSO at temperatures between 80 and 160 °C under microwave irradiation using 3 wt% fructose in combination with 50 mol% of catalyst. The effects of catalyst loading, temperature, reaction time and recycling of the catalyst were tested. With 200 mol% catalyst loading at 100 °C for 4 min HMF yields of 85% and 88% at full conversion were obtained with **41** and **42** respectively. A decrease of catalyst loading coincided with a decrease in yield and selectivity. Yield and selectivity increased with increasing temperature, an effect that was stronger for the Brønsted acid, which was significantly less active than the Lewis acid in the lower temperature range. This is surprising, since the Lewis acid is expected to convert to the Brønsted acid in the presence of water, which is formed during the dehydration and which is in general present in DMSO. With 50 mol% of either catalyst at 160 °C HMF yields of around 90% were obtained at full conversion after 4 min. Experiments with both these ionic liquids immobilised on silica (ILIS) were reported, resulting in yields of around 70% HMF at full conversion for both types, compared to around 60% at 90-95% conversion for silica gel supported acids SiO₂-SO₂Cl and SiO₂-SO₃H. The selectivities were not significantly different, all between 65% and 70%. Recycle experiments with the ILIS catalysts showed no loss in activity for both immobilised ionic liquids, even after seven cycles. The silica gel supported acids showed a sharp decrease in activity upon recycling, becoming almost inactive after 3 cycles.

Zhang *et al.* investigated the use of polytungstic acid (PTA), encapsulated in MIL-101, as a catalyst for fructose dehydration to HMF.²²⁶ MIL-101 is a metal-organic framework with a chromium carboxylate cubic structure. An encapsulated PTA catalyst (PTA/MIL-101, 40 wt%)

was tested with a 9 wt% fructose solution in DMSO and yielded 63% HMF at 82% conversion after 30 min at 130 °C.



Scheme 30. Ionic liquids used by Bao *et al.*

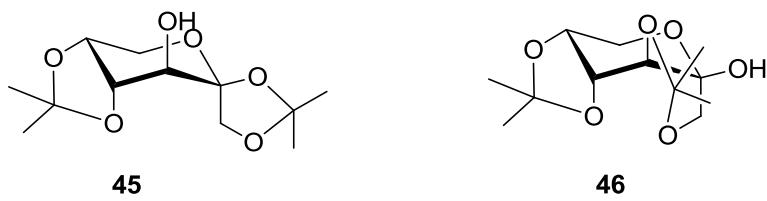
Experiments with immobilised ionic liquid on silica in DMSO were reported by Sidhpuria *et al.* 1-(tri-ethoxy-silyl) propyl-3-methyl imidazolium hydrogen sulfate (IL-HSO₄) was synthesised and immobilised on silica nanoparticles to form Si-3-IL-HSO₄ with a 20 wt% IL loading.²²⁷ Reaction conditions were optimised by experimental design, from which a mathematical model was derived. From an 8 wt% fructose solution in the presence of 80 wt% catalyst an HMF yield of 63% at full conversion was obtained after 30 min at 130 °C. In the absence of any catalyst no activity was observed, which is in contrast with findings by Yan,¹³⁰ Musau²¹³ and Brown.²¹²

Binder and Raines published a collection of results on fructose, glucose and cellulose dehydration to HMF in dimethyl acetamide (DMA) based reaction mixtures.^{119,228} DMA was applied as solvent, combined with alkali metal salts with halogen counterions. The highest HMF yields were obtained using metal bromides and iodides at a concentration of 10 wt% in DMA. Yields of around 90% were obtained by reacting 10 wt% fructose at 100 °C in the presence of 6 mol% sulfuric acid for 2-6 h in DMA/MX, with M = Li, Na, K and X = Br, I. The use of LiF as the salt did not yield any HMF. Systems with ionic liquids as additives were also tested, and the results suggested an improvement of the HMF yield at 80 °C, but no comparative example was reported to verify this. Caes and Raines published work on fructose dehydration in sulfolane, catalysed by various halide salts and acids.²²⁹ At 100 °C with 11 mol% HBr as catalyst 93% HMF yield was reported. In the presence of 207 mol% LiBr the HMF yield was 78%.

Sanborn patented HMF production from Cornsweet® 90 high fructose corn syrup (HFCS), which contains 77 wt% sugars of which 90% is fructose, in N-methyl pyrrolidinone (NMP) and DMA.²³⁰ HFCS is produced as a sweetener by enzymatic isomerisation of glucose to fructose, followed by highly advanced methods of chromatographic separation (Simulated Moving Bed) in which the fructose content is increased and the glucose is recycled for isomerisation. A reaction of 33 wt% HFCS in NMP with 40 wt% Amberlyst 35 at 115 °C was reported to yield 81% HMF at 94% fructose conversion after 5 h. In DMA under similar circumstances, but at 105 °C, the HMF yield was 62% at 75% conversion.

Chen *et al.* adopted a different strategy for avoiding water as main solvent by derivatising fructose in acetone, forming 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose (**45**) and 2,3:4,5-di-*O*-isopropylidene- β -D-fructopyranose (**46**) in order to improve its solubility in organic solvents (Scheme 31).²³¹ A solvent system of 7.5 M water in ethylene glycol dimethyl ether with 0.5 M of substrate and 5 mM H₂SO₄ yielded around 70% HMF at 180 °C. The presence of water in the starting reaction mixture was required in order to generate free fructose, which could subsequently be dehydrated. Partially replacing water with acetone resulted in an increase in reaction rate and HMF yield with increasing acetone content.²⁰⁷ Experiments by Qi *et al.* with acidic ion-exchange resin (Dowex 50wx8-100) under microwave irradiation yielded over 70% HMF upon using at least 70 wt% acetone.²⁰⁷

In alcohols HMF can be converted to the appropriate ether (RMF) in the presence of an acid catalyst. The first publication on 5-methoxymethyl-2-furural (MMF) dates from 1927, by Haworth *et al.*, in which it was observed in an attempt to deduce the structure of sucrose.²³² It was later also synthesised by Wolfrom *et al.* from tetramethyl glucosene.¹⁰⁸



Scheme 31. Di-*O*-isopropylidene- β -D-fructopyranose derivatives; 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose (**45**) and 2,3:4,5-di-*O*-isopropylidene- β -D-fructopyranose (**46**)

Dehydration of fructose in various alcohols by Brown *et al.* led to the formation of the appropriate HMF ether and levulinic acid ester.²¹² The reactions were performed at 14 wt% fructose in the presence of 100 wt% Amberlyst-15 (dry) for 20 h at 100 °C. A number of primary and secondary alcohols was tested, from methanol to 2-butanol. In methanol a yield of 43% MMF was reported in combination with 47% methyl levulinate. In ethanol, 55% of EMF and 25% ethyl levulinate were reported and in n-propanol a 19% PMF yield was reported with 69% propyl levulinate.

Bicker published work on sugar dehydration in flow.^{125,206,233} Experiments were performed in water, acetone/water, acetone, methanol and acetic acid as solvents at sub- and supercritical conditions. In water containing 1 wt% fructose and 10 mM H₂SO₄ 28% HMF yield at 80% conversion was obtained at 180 °C and a residence time of 10 min.²³³ In acetone/water (9:1 V/V) under comparable circumstances with 2 min residence time an HMF yield of 75% at 98% conversion was obtained.^{206,233} When methanol was used as the solvent, the main product was 5-methoxymethyl-2-furfural (MMF), which resulted from the acid catalysed etherification of HMF.²³³ An MMF yield of 78% at 99% conversion was obtained at 240 °C and a residence time of 2 s. At short residence times, especially at lower temperatures significant amounts of HMF were observed and smaller amounts of MMF. The amount of MMF increased with residence time at the cost of the amount of HMF, which indicates that MMF formation goes through HMF. Variation of the pressure between 15 and 35 MPa at 180 °C did not significantly affect the HMF and MMF selectivity. In the absence of sulfuric acid no furan formation was observed. In acetic acid yet another main product was formed, namely 5-acetoxyethyl-2-furfural (AMF), resulting from the esterification of HMF. An AMF yield of 38% was obtained at full fructose conversion at 180 °C with 2 min residence time, with no HMF present.²³³

Tarabanko *et al.* worked on fructose dehydration in several aliphatic alcohols.²³⁴ The alkylated forms of HMF and levulinic acid were the major products. Yields of over 60% EMF were reported for initial fructose concentrations of 0.08 M, 0.11 M and 0.15 M in 1.8 M H₂SO₄ in ethanol at 82.5 °C with reaction times of 30-50 min. The ethyl levulinate yield was always below 10%. Yields of both products decreased with increasing fructose concentration. Comparable experiments were performed in butanol, but at 92 °C. 5-butoxymethyl furfural (BMF) formation was significantly slower than EMF formation, yielding around 60% BMF with 0.15 M initial fructose concentration after 2 h. The butyl levulinate yield was around 30%. No fructose

conversions were mentioned. Recently more work has been published on fructose dehydration in alcohols.²³⁵⁻²³⁸

Several patents have been published by the company Avantium on the production of alkoxymethyl ethers (RMF) and esters (AMF) of HMF.²³⁹⁻²⁴⁵ These patents concern the acid catalysed dehydration of hexose containing starting material in combination with various alcohols²³⁹⁻²⁴⁴ or organic acids and their anhydrides.²⁴⁵ The formation of RMF from hexoses or HMF by using olefins was also patented.^{244,246} Sanborn patented work on fructose dehydration in ethanol to form EMF²³⁰ and in organic acids to form HMF esters.²⁴⁷ The reported yields in the Sanborn patents were low and not clearly quantified.

Tables 10-12 provide an overview of the best results obtained in fructose dehydration in organic solvents. The reported HMF yields and selectivities of fructose dehydration in organic solvents are much higher and more consistent than those in water. In DMSO, DMF and DMA yields of >90% have been reported. Even though water is formed during the reaction, apparently rehydration to LA is limited, which suggests that this group of solvents has a stabilising effect on the HMF molecule, most likely through coordination, making the molecule inaccessible to water for rehydration. Compared to dehydration under aqueous conditions the reaction conditions are typically much milder when using organic solvents. A number of publications even showed significant HMF yields in DMSO in the absence of catalyst at relatively low temperatures, which also places question marks in the proposed effectiveness of some catalyst systems researched in DMSO. Fructose dehydration in DMSO has been published by a significant number of researchers, but has shown varying results, making it very difficult to explain these differences, especially if one finds no HMF yield in DMSO and another finds quantitative conversion in DMSO in the absence of catalyst. Furthermore it is of questionable use to research all kinds of metals as catalysts if in the absence of catalyst this reaction is already selective and when certain heterogeneous acids provide good results (Table 12).

A major disadvantage of the use of DMSO is its known instability at temperatures over 100 °C, something that could also be a factor in its catalytic activity. Furthermore it is difficult to separate the HMF from the DMSO because of its high affinity for the solvent, requiring either large amounts of extraction solvent or the evaporation of DMSO, both of which are energy demanding processes.

In alcohols (Table 13) HMF was mostly obtained as its alkyl ether. The yield and reaction rate generally decrease with increasing chain length of the alcohol. The yields of furanic products are generally higher than in water and lower than in aprotic solvents like DMSO.

Table 10. Fructose dehydration to HMF in organic solvents in the absence of catalyst

Fructose concentration (wt%)	Solvent	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
5	DMSO	100	16 h	100 ^c	100	100	212
3	DMSO	120	2 h	32 ^d	81	40	218
8	DMSO	130	30 min	0	0	0	227
8	DMSO	130	4 h	72	100	72	130
5	DMSO	140	5 min	22	-	-	205
34	DMSO	150 ^c	2 h	72 ^b	-	-	213
21	DMSO	150	-	92	-	-	213
2	Acetone:DMSO (70:30 w/w)	180 ^a	20 min	66	85	78	208

a: heating by microwave irradiation; *b:* isolated yield; *c:* analysis by ¹H-NMR only; *d:* continuous water evacuation

Table 11. Fructose dehydration to HMF in organic solvents, catalysed by homogeneous catalysts

Substrate concentration (wt%)	Solvent	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
3.5	1,4-Dioxane	LaCl ₃	2.5 mol%	100	5 h	27	-	-	216
2	1,4-Dioxane	Sc(OTf) ₃	10 wt%	120	2 h	16	86.2	19	217
32	2-Ethoxyethanol	BF ₃ .OEt ₂	50 mol%	100	2 h	64 ^h	-	-	210
27	2-Methoxyethanol	BF ₃ .OEt ₂	50 mol%	100	1 h	78 ^h	-	-	210
1	Acetone:Water (9:1 V/V)	H ₂ SO ₄	10 mM	180	2 min	75	98	77	206
5	Butyl acetate	NH ₄ Cl	10 mol%	77	16 h	31 ^c	-	-	212
27	Diethylene glycol monoethyl ether	BF ₃ .OEt ₂	50 mol%	100	0.5 h	40 ^h	-	-	210
4	DMA	LaCl ₃	2.5 mol%	100	4 h	92	-	-	216
2	DMA	Sc(OTf) ₃	10 wt%	120	2 h	50	98.4	51	217
10	DMA (1.5 wt% KCl)	H ₂ SO ₄	6 mol%	80	2 h	56	-	-	119
10	DMA (10 wt% NaBr)	H ₂ SO ₄	6 mol%	100	2 h	93	-	-	119

10	DMA (10 wt% KI)	H ₂ SO ₄	6 mol%	100	5 h	92	-	-	119
33	DMF	BF ₃ .OEt ₂	25 mol%	100	1.5 h	55 ^h	-	-	210
4	DMF	LaCl ₃	2.5 mol%	100	4 h	92	-	-	216
5	DMF	NH ₄ Cl	10 mol%	100	1 h	55 ^c	100	-	212
3	DMSO	41	200 mol%	100 ^a	4 min	85	100	85	225
3	DMSO	41	10 mol%	100 ^a	4 min	50	79	63	225
3	DMSO	41	50 mol%	160 ^a	4 min	93	100	93	225
3	DMSO	42	50 mol%	100 ^a	5 min	86	-	-	225
3	DMSO	42	50 mol%	100	3 h	86	-	-	225
3	DMSO	42	200 mol%	100 ^a	4 min	88	100	88	225
3	DMSO	42	10 mol%	100 ^a	4 min	71	98	72	225
3	DMSO	42	50 mol%	160 ^a	4 min	90	100	90	225
5	DMSO	AlCl ₃	50 mol%	140 ^a	5 min	69 ^c	-	-	205
34	DMSO	BF ₃ .OEt ₂	25 mol%	40	3 h	55 ^h	-	-	210
19	DMSO	BF ₃ .OEt ₂	25 mol%	100	45 min	99 ^h	-	-	210
20	DMSO	BF ₃ .OEt ₂	100 mol%	100	45 min	99 ^h	-	-	210

2	DMSO	$\text{Ho}(\text{OTf})_3$	10 wt%	120	2 h	78	100	78	217
3	DMSO	LaCl_3	2.5 mol%	100	4 h	95	-	-	216
3	DMSO	LaCl_3	5 mol%	120	2 h	93	-	-	216
3 ^d	DMSO	LaCl_3	5 mol%	120	2 h	61	-	-	216
2	DMSO	$\text{Nd}(\text{OTf})_3$	10 wt%	120	2 h	64	100	64	217
5	DMSO	NH_4Cl	10 mol%	100	45 min	100 ^e	100	100	212
5	DMSO	NH_4HSO_4	10 mol%	100	2.5 h	100 ^e	100	100	212
7	DMSO	$[\text{HNMP}]^+[\text{CH}_3\text{SO}_3]^-$	7.5 mol%	90	2 h	72	83	87	222
7	DMSO	$[\text{HNMP}]^+[\text{HSO}_4]^-$	7.5 mol%	90	2 h	69	99	70	222
2	DMSO	$\text{Sc}(\text{OTf})_3$	10 wt%	90	2 h	66	95	70	217
2	DMSO	$\text{Sc}(\text{OTf})_3$	10 wt%	120	2 h	83	100	83	217
2	DMSO	$\text{Sm}(\text{OTf})_3$	10 wt%	120	2 h	73	100	73	217
2	DMSO	$\text{Yb}(\text{OTf})_3$	10 wt%	120	2 h	80	100	80	217
5	Ethyl acetate	NH_4Cl	10 mol%	77	30 h	58 ^c	100	-	212
4	n-Butanol	LaCl_3	2.5 mol%	100	5 h	24	-	-	216
9	NMP	$\text{FeCl}_3/\text{Et}_4\text{NCl}$	10 mol%/18	90	2 h	82	100	82	248

			mol%							
2	PEG-400-water, unknown ratio	Sc(OTf) ₃	10 wt%	120	2 h	13	37	35	217	
6.7	Sulfolane	HBr	11 mol%	100	1 h	93	-	-	229	
7	Sulfolane	LaCl ₃	2.5 mol%	100	5 h	52	-	-	216	
6.7	Sulfolane	LiBr	207 mol%	100	2 h	78	-	-	229	
8.3	Sulfolane	LiCl	425 mol%	90	2 h	67	-	-	229	
5	Sulfolane	NH ₄ Cl	10 mol%	100	30 min	100 ^e	100	100	212	
15 ^f	MeOCH ₂ CH ₂ OMe (7.5 M H ₂ O)	H ₂ SO ₄	1 mol%	180	5 min	72	>98	73	231	
15 ^g	MeOCH ₂ CH ₂ Ome (7.5 M H ₂ O)	H ₂ SO ₄	1 mol%	180	5 min	68	>98	69	231	

a: heating by microwave irradiation; *b:* continuous flow process; *c:* isolated yield; *d:* Sorbose as substrate; *e:* analysis by ¹H-NMR only; *f:* 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose as substrate; *g:* 2,3:4,5-di-*O*-isopropylidene- β -D-fructopyranose as substrate; *h:* distinction between different furans could not be made due to the analytical method; *i:* See Scheme 30 for a description of this catalyst

Table 12. Fructose dehydration to HMF in organic solvents, catalysed by heterogeneous catalysts

Fructose concentration (wt%)	Solvent	Catalyst	Catalyst loading (rel. to substrate)	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
2	Acetone:DMSO (70:30 w/w)	Dowex 50WX8-100	100 wt%	150 ^a	20 min	88	98	90	221
2	Acetone:DMSO (70:30 w/w)	SO ₄ ²⁻ /ZrO ₂ ^d	20 wt%	180 ^a	5 min	63	84	74	208
2	Acetone:DMSO (70:30 w/w)	SO ₄ ²⁻ /ZrO ₂ ^c	20 wt%	180 ^a	5 min	62	88	70	208
2	Acetone:DMSO (70:30 w/w)	ZrO ₂ ^d	20 wt%	180 ^a	5 min	24	37	66	208
2	Acetone:DMSO (70:30 w/w)	ZrO ₂ ^c	20 wt%	180 ^a	5 min	41	71	57	208
35	DMA ^e	Amberlyst 35	40 wt%	105	5 h	62	75	83	230
5	DMA (10 wt% TiO ₂ LiCl)		50 wt%	130 ^a	2 min	74	-	-	219
4	DMA (10 wt% TiO ₂ LiCl)/[BMIm]Cl (5:1 w/w)		50 wt%	130 ^a	2 min	82	-	-	219

3	DMF	Amberlyst 15	100 wt%	100	1 h	90	100	90	224
26	DMF	Lewatit SPC 108	0.61 meq/mol	96	5 h	80	-	-	211
3	DMSO	Amberlyst 15	6 wt%	120	2 h	92 ^b	100	92	218
3	DMSO	Amberlyst 15	6 wt%	120	2 h	76	100	76	218
3	DMSO	Amberlyst 15 powder	6 wt%	120	2 h	100 ^b	100	100	218
3	DMSO	Amberlyst 15 powder	6 wt%	120	2 h	100	100	100	218
50	DMSO	Amberlyst 15 powder	6 wt%	120	2 h	100 ^b	100	100	218
3	DMSO	Cs _{2.5} H _{0.5} PW ₁₂ O ₄₀	6 wt%	120	2 h	91 ^b	100	91	218
8	DMSO	Diaion PK-216	10 meq	80	500 min	90	-	-	209
3	DMSO	FePW ₁₂ O ₄₀	6 wt%	120	2 h	97 ^b	100	97	218
3	DMSO	FePW ₁₂ O ₄₀	6 wt%	120	2 h	49	100	49	218
50	DMSO	FePW ₁₂ O ₄₀	6 wt%	120	2 h	48 ^b	-	-	218
3	DMSO	H ₃ PW ₁₂ O ₄₀	6 wt%	120	2 h	95 ^b	100	95	218
3	DMSO	H-BEA Zeolite	6 wt%	120	2 h	97 ^b	100	97	218
3	DMSO	H-BEA Zeolite	6 wt%	120	2 h	51	100	51	218
50	DMSO	H-BEA Zeolite	6 wt%	120	2 h	40 ^b	-	-	218

3	DMSO	ILIS-SO ₂ Cl	50 mol%	100 ^a	4 min	67	100	67	225
3	DMSO	ILIS-SO ₃ H	50 mol%	100 ^a	4 min	70	100	70	225
3	DMSO	Nafion	6 wt%	120	2 h	94 ^b	100	94	218
3	DMSO	Nafion	6 wt%	120	2 h	75	100	94	218
9	DMSO	PTA/MIL-101	40 wt%	130	30 min	63	82	77	226
8	DMSO	Si-3-IL-HSO ₄	80 wt%	130	30 min	63	100	63	227
3	DMSO	SiO ₂ -SO ₂ Cl	50 mol%	100 ^a	4 min	60	92	65	225
3	DMSO	SiO ₂ -SO ₃ H	50 mol%	100 ^a	4 min	63	95	66	225
3	DMSO	SO ₄ ²⁻ /ZrO ₂	6 wt%	120	2 h	92 ^b	100	92	218
7.6	DMSO	SO ₄ ²⁻ /ZrO ₂ -Al ₂ O ₃	20 wt%	130	4 h	57	99	57	130
4	DMSO	TiO ₂	50 wt%	140 ^a	10 min	54	-	-	220
3	DMSO	WO ₃ /ZrO ₂	6 wt%	120	2 h	94 ^b	100	94	218
8	DMSO	Zeolite H-beta (Si/Al = 25)	80 wt%	130	30 min	63	100	63	227
33	NMP ^e	Amberlyst 35	40 wt%	115	5 h	81	94	86	230

a: heating by microwave irradiation; *b:* continuous water evacuation; *c:* calcination at 500 °C; *d:* calcination at 700 °C; *e:* Cornsweet 90 high fructose syrup as the substrate

Table 13. Fructose dehydration to HMF derivatives in alcohols and organic acid

Fructose concentration (wt%)	Solvent	Catalyst	Catalyst loading	T (°C)	Reaction Time	Conversion (%)	HMF yield (%)	HMF selectivity (%)	RMF Yield (%)	RMF selectivity (%)	R group	Reference
14	2-BuOH	Amberlyst	100 wt%	100	20 h	-	-	-	19 ^b	-	sec-Butyl	212
			15 dry									
1	AcOH	H ₂ SO ₄	10 mM	180	15 s	93	7	8	24	26	Acetyl	233
1	AcOH	H ₂ SO ₄	10 mM	180	120 s	98	0	0	37	38	Acetyl	233
14	EtOH	Amberlyst	100 wt%	100	20 h	-	-	-	55 ^b	-	Ethyl	212
			15 dry									
1.8	EtOH	H ₂ SO ₄	1.8 M	82.5	30 min	-	-	-	62 ^b	-	Ethyl	234
2.5	EtOH	H ₂ SO ₄	1.8 M	82.5	35 min	-	-	-	66 ^b	-	Ethyl	234
3.4	EtOH	H ₂ SO ₄	1.8 M	82.5	40 min	-	-	-	60 ^b	-	Ethyl	234
14	<i>i</i> -PrOH	Amberlyst	100 wt%	100	20 h	-	-	-	45 ^b	-	<i>i</i> -Propyl	212
			15 dry									
14	MeOH	Amberlyst	100 wt%	100	20 h	-	-	-	43 ^b	-	Methyl	212
			15 dry									
0.6	MeOH	H ₂ SO ₄	10 mM	180	30 s ^a	-	-	-	-	82	Methyl	233

7	MeOH	H ₂ SO ₄	10 mM	180	30 s ^a	-	-	-	61	Methyl	233	
1	MeOH	H ₂ SO ₄	10 mM	240	2 s ^a	99	-	-	77	78	Methyl	233
3	<i>n</i> -BuOH	H ₂ SO ₄	1.8 M	92	125 min	-	-	-	61 ^b	-	<i>n</i> -Butyl	234
14	<i>n</i> -BuOH	Amberlyst	100 wt%	100	20 h	-	-	-	0 ^b	-	<i>n</i> -Butyl	212
			15 dry									
4	<i>n</i> -BuOH	LaCl ₃	2.5 mol%	100	5 h	-	24	-	-	-	<i>n</i> -Butyl	216
14	PrOH	Amberlyst	100 wt%	100	20 h	-	-	-	19 ^b	-	Propyl	212
			15 dry									

a: continuous flow process; *b*: Significant yield of levulinic acid ester observed

2.4.1.2 Glucose dehydration in single-phase systems

In this section the glucose dehydration in traditional single-phase systems will be reviewed, along with more recent progress in this area using sub- and supercritical conditions. Publications on HMF synthesis in aqueous systems will be discussed first, followed by a review of the research on reactions in organic solvents and aqueous/organic single-phase mixtures.

Glucose dehydration under aqueous conditions

This paragraph describes research performed on glucose dehydration to HMF in water. First the thermal decomposition studies on glucose in the absence of catalyst are described, followed by work using homogeneous and heterogeneous catalyst systems, respectively.

Jing and Lü reported significant HMF yields from glucose decomposition experiments in water at 180-220 °C and 100 bar in the absence of catalyst.²⁴⁹ An HMF yield over 30% at around 70% conversion was reported when a 1% glucose solution was heated for 30 min at 220 °C. An interesting observation was that the HMF degradation rates between 180 and 220 °C were substantially lower than the degradation rates of glucose.

Work by Aida *et al.* on glucose decomposition in water at 350 and 400 °C at pressures of 40, 70 and 80 MPa and at short residence times (<2 s) showed HMF yields under 10%.¹²⁸ The reported furfural yields increased with residence time and pressure, rather than temperature, up to 12%.

Mednick performed aldose dehydration with combinations of weak acids and bases, based on the knowledge that ketoses are much more readily dehydrated to HMF than aldoses and the hypothesis that the keto-enol isomerisation is acid-base-catalysed.^{105,250} A 20 wt% glucose solution was reacted at 160-190 °C for around 20 min with a warm-up time around 35 min. The main focus was on ammonium salts, phosphoric acid and phosphates. The HMF yields varied between 3 and 23%. The highest yield was obtained with a combination of phosphoric acid and ammonia at an initial pH of approximately 4. Pyridine-phosphoric acid systems with pH ~4.5 were studied for a solution of glucose (20 wt%) in H₂O/*p*-dioxane (1:1 v/v). At 200-230 °C for 30 min with around 35 min warm-up time, HMF yields of ~45% were obtained.

In 1964 ammonium sulfate catalysed aldose dehydration was patented by Smith *et al.*²⁵¹ Using a 10% glucose mixture at pH 1.65 at 150-155 °C an HMF yield of 31.5% after 50 min was claimed.

Glucose dehydration with 10 wt% sulfuric acid by Li *et al.* under microwave irradiation at 400W for 1 min yielded 49% HMF.²⁵² In the absence of catalyst the yield was less than 1%.

Tyrlik and co-workers have done work on glucose dehydration in aqueous systems under reflux with a variety of metal salts.²⁵³⁻²⁵⁵ The highest HMF yield of 9% was achieved with 15 wt% glucose in a 5 M MgCl₂ system.²⁵⁴

Work on glucose dehydration by Seri *et al.*, using lanthanide(III) chlorides in water at 140 °C for 1h, yielded between 3 and 8% HMF.¹⁶³ In the absence of catalyst only traces of HMF were observed. The same experiments with galactose and mannose showed comparable yields.¹⁶³

Y-zeolite catalysed glucose decomposition studies in water by Lourvanij showed the formation of HMF at relatively low yields (<10%).²⁵⁶ In this work a 33% fructose yield was found after 2 min at 160 °C.

Watanabe *et al.* reported work on glucose reactions in hot compressed water at 200 °C with a substrate concentration of 9 wt%.^{126,127} An HMF yield of 20% at 81% conversion was obtained after 5 min in the presence of anatase TiO₂.^{126,127} Rutile TiO₂ did not contribute to the dehydration to HMF, showing identical results to those obtained in the absence of catalyst, which was 6.6% HMF yield at 20% conversion after 10 min. ZrO₂ was tested as a catalyst under the same conditions yielding 13% fructose and only 5.2% HMF at 47% conversion. Later work on TiO₂ catalysed dehydration using a 2 wt% glucose solution and microwave heating resulted in an HMF yield of 19% at 64% conversion after 5 min.¹²⁹

Chareonlimkun and co-workers looked at reactions of glucose with differently prepared TiO₂ and ZrO₂ catalysts in hot compressed water at 250 °C for 5 min.²⁵⁷ The work was focussed on the preparation of the catalysts, looking at different calcination temperatures (500-700 °C) and different precursors, namely nitrates and chlorides. The highest reported HMF yield was 27%, using TiO₂ from its chloride precursor, calcined at 500 °C. Increasing the calcination temperature resulted in lower HMF yields, decreasing to 25% at 600 °C calcination and 20% at 700 °C calcination. At 500 °C TiO₂ was found to be mainly in the anatase phase, whereas at higher temperatures some rutile phase formation was detected. This is consistent with what Watanabe observed with regard to anatase and rutile phase TiO₂ catalyst, in which rutile TiO₂ was much less active.^{126,127} Yields obtained with titania from its nitrate precursor were typically around 5% lower at each calcination temperature than those from titania prepared from its chloride precursor. This is explained by temperature programmed desorption (TPD) results, which showed that TiO₂ from TiCl₄ had a higher acid site density than TiO₂ from TiO(NO₃)₂, but the acidity of the sites was lower. The highest

reported HMF yield with ZrO_2 as catalyst, calcined at 500 °C, was around 17%. ZrO_2 showed the same trends with regard to precursor and calcination temperature as TiO_2 . The TPD results showed a lower acid site density for ZrO_2 than for TiO_2 . In the absence of catalyst an HMF yield of 10% was reported. Apart from HMF, other products were also formed: furfural, levoglucosan and fructose. The fructose yield was consistently about 3% when either TiO_2 or no catalyst was used. When ZrO_2 was used the fructose yield was consistently over 5%. Furfural and AHG (anhydroglucose) yields were always around 2%.²⁵⁷ A $\text{TiO}_2\text{-ZrO}_2$ mixed oxide catalyst was used in glucose dehydration at 250 °C and 34.5 MPa for 5 min, showing almost 30% HMF yield, based on carbon balance, at around 80% conversion.²⁵⁸

Asghari and Yoshida looked at glucose dehydration catalysed by a heterogeneous ZrP catalyst.²⁰⁴ With 1 wt% glucose and a 1:1 (w/w) catalyst/substrate ratio at 240 °C and 33.5 bar they obtained 23.5% HMF yield (72% conversion) at a residence time of 240 s.

Recently a combination of immobilised D-glucose/xylose isomerase and oxalic acid was applied as catalyst system for glucose dehydration in seawater.²⁵⁹ Glucose was first isomerised at 60 °C to fructose until equilibrium, followed by removal of the heterogeneous enzyme and addition of oxalic acid for dehydration of the fructose in the reaction mixture at 140 °C. The HMF was extracted with 2-methyl tetrahydrofuran and the oxalic acid crystallised out, leaving an aqueous glucose solution for potential recycle to the enzyme. An HMF yield of 64% was mentioned, based on the amount of fructose from the isomerisation. No explanation is given for the extremely high fructose yield of 64% reported for glucose isomerisation, while the authors mention a 50:50 equilibrium between glucose and fructose.

Tables 14-16 show an overview of results published on glucose dehydration to HMF under aqueous conditions. HMF yields in processes catalysed by heterogeneous metal oxides are generally somewhat higher than those obtained in homogeneous systems. A bifunctional type of catalyst with basic sites for isomerisation and acid sites for dehydration showed the most promise. Results from Chareonlimkun²⁵⁸ and Watanabe^{126,127} indicated that ZrO_2 functioned mainly as an isomerisation catalyst to form fructose, whereas anatase TiO_2 functioned as an acidic catalyst for dehydration to HMF. A $\text{ZrO}_2\text{-TiO}_2$ mixed oxide catalyst appeared to combine these functions to achieve a relatively high HMF yield of 30% under aqueous conditions.

Table 14. Glucose dehydration to HMF in aqueous systems in the absence of catalyst

Glucose concentration (wt%)	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
9	200	10 min	7	31	23	126
2	200 ^a	3 min	3	15	23	129
9	200	5 min	3	21	15	126,127
1	220	30 min	32	71	45	249
9	250	5min	10 ^c	21	51	257
0.9	350 ^d	0.7 s ^b	2 ^{c,f}	72	3	128
0.9	350 ^e	0.8 s ^b	4 ^{c,g}	83	5	128
0.9	350 ^e	1.6 s ^b	7 ^{c,g}	84	8	128

a: heating by microwave irradiation; *b:* continuous flow process; *c:* small amounts of fructose were observed; *d:* at 400 Bar; *e:* at 800 Bar; *f:* 14% furfural yield; *g:* 7-8.5% furfural yield

Table 15. Glucose dehydration to HMF in aqueous systems, catalysed by homogeneous catalysts

Glucose concentration (wt%)	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
20	(NH ₄) ₂ HPO ₄	0.07 M	172-182 ^b	20 min	11 ^c	-	-	250
20	(NH ₄) ₂ HPO ₄ /H ₃ PO ₄	0.07 M/ 0.05 M	174-180 ^b	20 min	23 ^c	-	-	250
5	AlCl ₃	50 mol%	120 ^a	20 min	40	-	-	205
8	DyCl ₃	0.7 mol%	140	1 h	7	17	41	163
8	DyCl ₃	0.7 mol%	140	2 h	12	30	40	163
2	H ₂ SO ₄	50 wt%	200 ^a	3 min	2	11	23	129
9	H ₂ SO ₄	1 mM	200	5 min	2 ^e	32	8	126
10	H ₂ SO ₄ :(NH ₄) ₂ SO ₄	pH 1.65	150-155	50 min	32	-	-	251
20	H ₃ PO ₄	0.13 M	173-187	20 min	5 ^c	-	-	250
14	Immobilised isomerase/oxalic acid ^f	3 wt%/0.1 M	60/140	2 h/1 h	64 ^g	-	-	259

13	MgCl ₂	593 mol%	Reflux	3 h	9 ^d	-	-	254
1	H ₃ PO ₄ /Nb ₂ O ₅	1000 wt%	120	3 h	52	92	57	260
20	Pyridine:H ₃ PO ₄	0.3 M/0.2 M	200-225 ^b	8.5 min	45 ^c	-	-	250

a: heating by microwave irradiation; *b*: warm up time of 0.5 h or more; *c*: isolated yield; *d*: 26% yield of humins reported; *e*: 3% fructose observed; *f*: two-steps; *g*: yield based on fructose yield from isomerisation

Table 16. Glucose dehydration to HMF in aqueous systems, catalysed by heterogeneous catalysts

Glucose concentration (wt%)	Catalyst	Catalyst loading (wt%)	Temperature (°C)	Reaction Time (min)	Yield (%)	Conversion (%)	Selectivity (%)	Reference
12	HY-zeolite	50	160	3	8	83	10	256
9	TiO ₂	100	250	5	27 ^c	39	71	257
9	TiO ₂ -ZrO ₂	100	250	5	29 ^c	44	67	258
2	ZrO ₂	50	200 ^a	3	10	57	18	129
9	ZrO ₂	100	200	5	5 ^b	48	11	126,127
9	ZrO ₂	100	250	5	17 ^c	38	46	257
2	A-TiO ₂	50	200 ^a	5	19	64	29	129
9	A-TiO ₂	100	200	5	20 ^c	81	25	126,127

a: heating by microwave irradiation; *b:* 13% fructose yield; *c:* 2-2.5% fructose yield

Glucose dehydration in organic solvents

The developments in fructose dehydration and the work by Mednick²⁵⁰ on glucose dehydration suggest that lowering the water content is favourable for the HMF yield. For this reason a number of groups has tested organic solvents as reaction media for glucose dehydration.

Yan *et al.* studied HMF formation from fructose (section 2.4.1.1) and glucose in DMSO.¹³⁰ A typical experiment was performed with 7.6 wt% glucose at 130 °C. In the absence of catalyst an HMF yield of 4.3% at 94% conversion was found after 4 h. The highest HMF yield of 48% was obtained when SO₄²⁻/ZrO₂-Al₂O₃ catalysts with an Al-Zr molar ratio of 1:1 was used at 20 wt% relative to glucose. This was not influenced by an increase in reaction time to 6 and 15 h, showing stability of HMF under the reaction conditions.

Seri *et al.* performed LaCl₃ catalysed glucose dehydration in DMSO at 120 °C and found an HMF yield of 9.8%.²¹⁶ Other aldoses, namely galactose and mannose, showed even lower yields of 6.7% and 4.8% respectively.²¹⁶ Beckerle and Okuda recently performed comparable research with rare earth metals in DMA as the solvent, reporting much higher HMF yields of up to 30% from glucose.²⁶¹

Hu *et al.* performed glucose dehydration in DMSO with 10 mol% SnCl₄ and reported a 44% HMF yield at 96% conversion with a 9 wt% glucose solution at 100 °C after 3 h.¹⁴⁴

The group of Ebitani examined the possibility of a combined isomerisation and dehydration catalyst system for glucose conversion in DMF.²²⁴ The isomerisation of 3 wt% glucose catalysed by 1 wt eq. hydrotalcite at 80 °C yielded 40% fructose at 47% conversion after 3 h. When a combination of hydrotalcite and Amberlyst 15 was used HMF formation was observed. The highest HMF yield of 42% at 73% glucose conversion, with no observed fructose, was obtained with 3 wt% glucose in combination with 2 wt eq. hydrotalcite and 1 wt eq. Amberlyst 15 at 80 °C after 9 h. Essentially the same result was obtained at 100 °C after 3 h, but in this case 4% of fructose yield was also observed. When glucose was first reacted for 2.5 h with hydrotalcite at 100 °C before addition of Amberlyst 15 an HMF yield of 45% was obtained at 61% conversion. No HMF formation was reported when either catalyst was tested separately under otherwise comparable conditions. DMA, DMSO, acetonitrile and water were also tested with the same Hydrotalcite/Amberlyst system

at 100 °C. With DMSO at 80 °C an HMF yield of 25% at 41% conversion was obtained. The results of the other solvents are described in Table 17.²²⁴ DMF was found to give the highest HMF yield. In water no HMF was formed, but 23% fructose yield was observed. The authors attributed this to the loss of activity of Amberlyst-15 in water. Addition of a small amount of water (3%) to DMF was claimed to be beneficial to HMF selectivity, anhydroglucose formation, with results comparable to DMSO at 80 °C. Comparable work was recently reported by the same group.²⁶²

The Amberlyst-15 catalysed dehydration of glucose in DMF resulted only in 1,6-anhydroglucose formation, of which yields of up to 70% were obtained. Higher temperatures favoured the formation of 1,6-anhydroglucose relative to the formation of HMF.^{224,263} As was already discussed in section 2.3.1.2, 1,6-anhydroglucose does not dehydrate to HMF.^{121,128,170}

Binder and Raines published significant HMF yields from glucose dehydration in DMA/LiBr/CrX_n systems (X = Br or Cl).^{119,228} With 10% LiBr and 6% CrX_n in DMA at 100 °C an HMF yield of 80% with in 4-6 h. Essentially the same yields were obtained when using CrCl₂, CrCl₃ or CrBr₃. These HMF yields are by far the highest reported from glucose in systems without ionic liquids.

Based on these results, Chen and Lin applied a mixture of LiCl in caprolactam as solvent in combination with a number of catalysts that are known to facilitate the isomerisation/dehydration of glucose to HMF.²⁶⁴ Yields of around 60% at >90% conversion were obtained with CrCl₂, SnCl₄ and SnCl₂ by reacting 10 wt% glucose in caprolactam:LiCl (3:1 n/n) with 6 mol% catalyst at 100 °C for 3 h.

In addition to their work in 100% aqueous systems,²⁵⁴ Tyrlík *et al.* performed research on glucose dehydration in mixed water-alcohol systems.²⁵⁵ The highest combined yield of HMF and HMF alkyl ether of 22% was obtained in a system in which saturated Al₂(SO₄)₃ in water was combined with ethanol (>30 M).

Some work was also done in acetonitrile by Yasuda *et al.* with a composite of silica and MgCl₂ as the catalyst, reporting an HMF yield of 70% from glucose, but much lower yields from mannose (10%) and galactose (32%).²⁶⁵

In a mixture of water and ethanol Yang *et al.* obtained a combined yield of HMF and EMF of 57% with AlCl₃ as the catalyst.²⁶⁶ Lew *et al.* used a heterogeneous Lewis acid, Sn-beta zeolite, in combination with a heterogeneous acid, Amberlyst 131, in ethanol to obtain an EMF yield of 31%.²⁶⁷

Tables 17 and 18 give an overview of the highest reported HMF yields from glucose in organic solvents. When comparing these results with those in water, it is clear that the yields are generally significantly higher in organic solvents. Especially when dehydration catalysts are combined with isomerisation catalysts in aprotic polar solvents good yields of almost 50% are reported. Use of chromium halides as isomerisation catalyst in HCl/DMA even resulted in yields of around 80% HMF.

Table 17. Glucose dehydration to HMF in organic solvents, catalysed by homogeneous catalysts

Glucose concentration (wt%)	Solvent	Catalyst	Catalyst loading (mol%)	Temperature (°C)	Reaction Time (h)	Yield (%)	Conversion (%)	Selectivity (%)	Reference
10	Caprolactam:LiCl 3:1 (n/n)	CrCl ₂	6	100	3	59	94	62	264
10	Caprolactam:LiCl 3:1 (n/n)	SnCl ₂	6	100	3	55	94	59	264
10	Caprolactam:LiCl 3:1 (n/n)	SnCl ₄	6	100	3	65	98	66	264
10	DMA	LnCl ₃	10	145	2	34	100	34	261
10	DMA (10 wt% LiBr)	CrBr ₃	6	100	6	80	-	-	119
10	DMA (10 wt% LiBr)	CrCl ₂	6	100	4	76	-	-	119
10	DMA (10 wt% LiBr)	CrCl ₃	6	100	6	79	-	-	119
5	DMF	GeCl ₄	10	100	1.25	34	85	40	268
9	DMF	H ₃ BO ₃	80	120	3	7	64	11	145
5	DMSO	AlCl ₃	50	140 ^a	0.08	52	-	-	205
9	DMSO	CrCl ₃	7	100	3	28	79	35	269

5	DMSO	GeCl ₄	10	100	1.25	37	85	43	268
9	DMSO	H ₃ BO ₃	80	120	3	13	35	37	145
3.6	DMSO	LaCl ₃	5	120	2	9.8	-	-	216
3.6 ^a	DMSO	LaCl ₃	5	120	2	6.7	-	-	216
3.6 ^b	DMSO	LaCl ₃	5	120	2	4.8	-	-	216
9	DMSO	SnCl ₄	10	100	3	44	96	45	144
6	Water:Ethanol	Al ₂ (SO ₄) ₃	100	Reflux	144	22 ^c	-	-	255

a: Galactose as the substrate; *b*: Mannose as the substrate; *c*: combined yield of HMF and EMF

Table 18. Glucose dehydration to HMF in organic solvents, catalysed by heterogeneous catalysts

Glucose concentration (wt%)	Solvent	Catalyst	Catalyst loading (wt%)	Temperature (°C)	Reaction Time (h)	Yield (%)	Conversion (%)	Selectivity (%)	Reference
3	DMA	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	3	14	97	14	224
3	DMF	Hydrotalcite/Amberlyst 15 2:1 w/w	300	80	9	42	73	58	224
3	DMF	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	3	41 ^a	72	57	224

3	DMF	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	4.5 ^d	45	61	73	224
3	DMF + 3 vol% water	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	3	29	45	64	224
3	DMSO	Hydrotalcite/Amberlyst 15 2:1 w/w	300	80	3	25	41	61	224
3	DMSO	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	3	12 ^b	94	13	224
7.6	DMSO	SO ₄ ²⁻ /ZrO ₂ -Al ₂ O ₃ (Zr:Al = 1:1 n/n)	20	130	4	48	97	49	130
7.6	DMSO	SO ₄ ²⁻ /ZrO ₂ -Al ₂ O ₃ (Zr:Al = 1:1 n/n)	20	130	6	48	100	48	130
7.6	DMSO	SO ₄ ²⁻ /ZrO ₂ -Al ₂ O ₃ (Zr:Al = 1:1 n/n)	20	130	15	48	100	48	130
3.5	DMSO/water (4:1 v/v)	SO ₄ ²⁻ /ZrO ₂ -Al ₂ O ₃ (Zr:Al = 3:7 n/n)	19	150	4	56	-	-	270
3	MeCN	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	3	10 ^c	88	12	224
3	MeCN + 3 vol% water	Hydrotalcite/Amberlyst 15 2:1 w/w	300	100	3	28	91	31	224

a: 4% fructose yield and 10% AHG yield; b: 6% fructose yield; c: 12% AHG yield; d: Amberlyst 15 was added after 2.5 h reaction time; e: galactose; f: mannose

2.4.1.3 The dehydration of di- and trisaccharides, polysaccharides and biomass feedstock in single-phase systems

Disaccharides and trisaccharides

Mednick *et al.* performed experiments with 19 wt% sucrose in a 1:1 (w/w) mixture of water and dioxane containing 5 mol% of pyridine and 3 mol% of H₃PO₄, relative to the substrate, HMF yields of 44% were obtained at unknown conversion after 32-36 min at 200-230 °C.²⁵⁰

Carlini *et al.* reported an HMF selectivity of >90% relative to the fructose moiety from niobium phosphate catalysed sucrose dehydration in water at 100 °C for 4 h.¹⁸³ No conversion of the glucose moiety was observed. When regarding both the glucose and fructose moieties as substrate the HMF yield was 14% at 30% conversion.

Studies on LaCl₃ catalysed dehydration of fructose containing di- and trisaccharides at a substrate concentration of 0.20 M in DMSO at 120 °C for 2 h showed that only the fructose moiety was converted to HMF.²¹⁶ It was also observed that the type of glycosidic bonding between the fructose and other moieties influenced the HMF yields. In sucrose, glucose and fructose are connected through a Glc α 1 \leftrightarrow 2 β FruF bond, whereas in the isomeric turanose they are connected through a Glc α 1 \rightarrow 3FruF bond. Sucrose to HMF yields of 47% and 12% were reported for sucrose and turanose, respectively. The sugar conversions, selectivities and reaction rates were not mentioned.

Ohara *et al.* applied the hydrotalcite-Amberlyst 15 system already described for the glucose dehydration²²⁴ in the sucrose and cellobiose dehydration to HMF.²⁶³ A reaction of 0.1 g substrate in 3 ml DMF with 0.1 g of either catalyst at 120 °C for 3 h yielded 54% HMF at 58% conversion from sucrose and 35% HMF at 52% conversion from cellobiose.

Tarabanko *et al.* performed dehydration on 0.2 M sucrose in water with 0.6 M acetic acid in a continuous process at 250-260 °C, reporting a 40% HMF yield with respect to stoichiometry, though it is not entirely clear if this is based on the both the glucose and fructose or solely on the fructose moiety present.²⁰³

Polyfructans

The Süddeutsche Zucker-Aktiengesellschaft looked at polyfructan, a polymer of fructose that is also called inulin, as starting material for a potential commercial HMF production process.¹⁹⁵ From 20 kg chicory roots, which contains about 18% inulin on dry-matter base, in 21 kg aqueous sulfuric acid of pH 1.8 at 140 °C for 2 h an HMF yield of 13% was reported. Next to HMF, fructose (30%) and glucose (3.5%) were obtained.

Carlini *et al.* performed research on HMF production from inulin with heterogeneous catalysts. From a 6 wt% inulin solution in water at 100 °C an HMF yield of 31% at 47% conversion was obtained with a niobium phosphate catalyst after 3 h.¹⁸³ Under comparable conditions with γ -Titanium phosphate (γ -TiP) an HMF yield of 42% at 44% conversion was obtained after 1 h.¹⁸⁴ Intermittent extraction of HMF by MIBK after 0.5 h improved the yield to 67% HMF at 71% conversion after 1 h. The same experiments were performed with a cubic ZrP₂O₇ catalyst yielding 35% HMF at 39% conversion after 1 h without intermittent extraction and 70% HMF at 73% conversion after 1 h with intermittent extraction. Experiments with various types of vanadyl phosphate catalysts gave somewhat lower selectivities at comparable conversions.¹⁹⁸

Wu *et al.* published work on inulin dehydration in water with pressurised CO₂.²⁷¹ At 180 °C the effect of CO₂ pressure was investigated by reacting 0.1 g inulin in 2 ml water for 3 h. Experiments were performed with 0, 4, 6, 9 and 11 MPa CO₂. The authors observed a beneficial effect of the CO₂ on the HMF yield, ascribed to the formation of carbonic acid in combination with water. Without CO₂, a maximum HMF yield of around 45% was obtained. When 6 MPa CO₂ was applied an increase in reaction rate and yield, up to a maximum of around 50%, was observed. Data obtained at 160 °C and 200 °C did not show a consistent beneficial effect in yields and reaction rates upon addition of CO₂. A significant increase in reaction rate was observed at higher temperatures, with maximum HMF yields of around 50% at 200 °C after 45 min.

Starch, Cellulose and lignocellulosic biomass

Mednick *et al.* performed experiments with 19 wt% corn starch in a 1:1 (w/w) mixture of water and dioxane containing 5 mol% of pyridine and 3 mol% of H₃PO₄, relative to the substrate. HMF yields of 44% were obtained at unknown conversion after 32-36 min at 200-230 °C.²⁵⁰ This result is essentially identical to that obtained with sucrose, which is unexpected, since the majority of HMF formed from sucrose is generally believed to originate from the fructose moiety of sucrose.

HMF was reported as a degradation product in aqueous dilute acid catalysed cellulose hydrolysis by Mok *et al.*²⁷² At temperatures over 200 °C a yield of around 5% was reported.

Ehara and Saka reported work on cellulose hydrolysis in high temperature liquid water in the absence of catalyst.^{273,274} At 280 °C and 40 MPa the highest HMF yield of 12% was obtained after 240 s.²⁷⁴ Yields of around 10% were reported by Sasaki at 25 MPa and 320 to 350 °C.²⁷⁵

Seri *et al.* published work on La(III) catalysed cellulose degradation at 250 °C in water.¹⁸⁸ They reported a maximum HMF yield of 19%. Work by Peng *et al.* on CrCl₃ catalysed dehydration of cellulose to levulinic acid in water at 180 °C showed traces of HMF to a maximum of 3%, but did yield 40% levulinic and formic acid.¹⁹⁰

Based on the work of Girisuta *et al.*¹⁸⁹ on LA production from cellulose Yin *et al.* performed cellulose hydrolysis/dehydration under basic, neutral and acidic conditions.²⁷⁶ At 300 °C the highest HMF yield of 21%, based on carbon, was reported at a cellulose loading of 3 wt% at a pH of 3.0 (HCl). The residence time was defined as the actual time at the defined temperature. It took about 40 min to reach 300 °C. At neutral pH the carbon yield of HMF was 10%. At a pH of 11 only traces of HMF were observed.

In a 10 wt% LiCl solution in DMA containing 10 mol% HCl and 25 mol% CrCl_x, relative to cellulose, Binder and Raines obtained HMF yields of 22% and 33% using CrCl₂ and CrCl₃, respectively.^{119,228} This difference is surprising since with glucose as substrate (section 2.4.1.2) no difference between CrCl₂ and CrCl₃ was observed^{119,228} and CrCl_x is not expected to influence hydrolysis of cellulose in an acidic environment. Comparable work was recently published by Dutta *et al.*²⁷⁷

As early as 1958, Snyder claimed the formation of HMF by heating oak wood chips, sprayed with 0.6% sulfuric acid, at 286 °C at 69 bar steam pressure. A theoretical HMF yield of 50-80 % was claimed.²⁷⁸

Amarasekara and Ebede examined cellulose degradation in the presence of 0.5 ZnCl₂ mol per mol of glucose unit when heating without added solvent.²⁷⁹ A maximum HMF yield of 9% was reported after 150 s at 200 °C.

Some patents by Lightner describe processes for the production of heterocyclic compounds, including HMF and furfural, from biomass feedstock in aqueous environment, but no yields were given.^{280,281}

Asghari and Yoshida published work on the conversion of Japanese red pinewood into valuable chemicals under aqueous acidic conditions.²⁸² The highest HMF yields of around 25% related to the mass of the starting material were obtained at 270 °C and pH 2 at autonomous pressure after 2 min.

Dedsuksophon *et al.* published research on the combined hydrolysis, dehydration, aldol condensation and hydrogenation of lignocellulosic biomass in organic media, namely acetone/DMSO.²⁸³

Chareonlimkun *et al.* reported HMF production from lignocellulosic biomass in hot compressed water using TiO₂, ZrO₂ and mixed oxide TiO₂-ZrO₂ catalysts.²⁵⁸ The best yields

based on carbon balance were obtained at 250 °C and 34.5 MPa with TiO₂-ZrO₂ at a Ti/Zr molar ratio of 1/1 after 5 min. From sugar cane bagasse the HMF and furfural yields were 6-7% and 10% respectively. The yields of HMF and furfural from rice husk were about 3% and 8% and the yields from corn cob were around 9%, respectively. Glucose, fructose, xylose and anhydroglucosone (AHG) were also formed in small amounts from all three substrates. AHG and fructose were present in significantly smaller amounts than glucose and xylose. The experiments were also performed with cellulose and xylan. At 70% cellulose conversion the yield of furan and sugar products added up to approximately 28%, half of which consisted of HMF. About 2% of furfural, 4% of glucose and 6% of fructose were also detected. Xylan yielded approximately 27% furfural and 7% xylose under identical conditions.²⁵⁸

Work by Zhao *et al.* combined chromium salts with heteropolyacid in order to hydrolyse and dehydrate cellulose to HMF. An HMF yield of 36% at 57% conversion was obtained at 150 °C after 2 h with 5 wt% cellulose and 0.015 M catalyst loading in an aqueous system.²⁸⁴ The yield was improved to 53% at 77% conversion by applying a surfactant type catalyst Cr[(OSO₃C₁₂H₂₅)H₂PW₁₂O₄₀]₃. In the absence of chromium though, no HMF formation was observed.

The formation of small amounts of fructose was generally reported from cellulose under high temperature and high pressure conditions.^{258,282,283} This is in agreement with the work of Kabyemela¹²² and Bicker,¹²⁵ who observed fructose formation starting from glucose under comparable conditions.

Chitosan, a copolymer of glucosamine and *n*-acetylglucosamine, was also shown to yield up to 10 wt% HMF in the presence of SnCl₄ in water.²⁸⁵

Tables 19-21 give an overview of the dehydration of di-, oligo- and polysaccharides in water. An overview of the dehydration in organic solvents is provided in Table 22**Table 22**. Work by Carlini *et al.* showed that HMF yields from inulin are comparable to those from fructose, indicating that hydrolysis proceeds much faster than dehydration. The HMF yields from cellulose are generally very low (<10%). Various lignocellulosic biomass sources show yields in the same ballpark. The main difficulty with these substrates is their low solubility in most solvents, except some ionic liquids. This is improved by initial hydrolysis, which yields glucose that is still difficult to dehydrate to HMF, as described in section 2.4.1.2.

Table 19. The dehydration of polysaccharides to HMF in aqueous mixtures in the absence of a catalyst

Substrate	Saccharide loading (wt%)	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
Inulin	5	160	4 h	40.9	-	-	271
Inulin	5	180	2 h	44	-	-	271
Inulin	5	200	45 min	41	-	-	271
Cellulose	9	250	5 min	4	15	28	257
Cellulose	4	280	4 min ^a	11.9	-	-	274
Cellulose	3	300	0 s ^b	10	-	-	276
Sugar cane bagasse	9	250	5 min	3 ^c	-	-	257
Cellulose	2	350	8.8 s ^a	11	99	11	275

a: continuous flow process; *b:* reaction time excluding 40 min pre-heating time; *c:* 3.9% furfural yield

Table 20. The dehydration of polysaccharides to HMF in aqueous mixtures, catalysed by homogeneous catalysts

Substrate	Saccharide loading (wt%)	Solvent	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time	Yield (%)	Reference
Cellulose	-	Water	H ₂ SO ₄	20 mM	215	1 h ^a	5	272
Cellulose	3	Water	HCl	pH 3.0	300	0 s ^b	21	276
Chicory roots	49	Water	H ₂ SO ₄	pH 1.8	140	2 h	13 ^d	195
Corn starch	19	Water:dioxane 1:1 v/v	Pyridine:H ₃ PO ₄	5% : 3% n/n 5:3 n/n	220-226	30 min ^b	44	250
Inulin	5	Water	CO ₂	6 MPa	160	4 h	45	271
Inulin	5	Water	CO ₂	9 MPa	160	4 h	42	271
Inulin	5	Water	CO ₂	4 Mpa	180	2 h	45	271
Inulin	5	Water	CO ₂	6 Mpa	180	2 h	50	271
Inulin	5	Water	CO ₂	11 Mpa	180	2 h	52	271
Inulin	5	Water	CO ₂	6 MPa	200	45 min	53	271
Inulin	5	Water	CO ₂	9 MPa	200	45 min	49	271

Oak wood chips	Solid	none	H ₂ SO ₄ (0.6 wt% aq)	-	286	90 s ^d	50-80	278
Sucrose	19	Water:dioxane 1:1 v/v	Pyridine:H ₃ PO ₄ 5% : 3% n/n 5:3 n/n	n/n	220-229	30 min ^b	44	250

a: semi-batch flow process; *b*: reaction time excluding >30 min preheating time; *c*: 30% fructose yield and 3% glucose yield; *d*: 69 Bar steam

Table 21. The dehydration of polysaccharides to HMF in aqueous mixtures, catalysed by heterogeneous catalysts

Substrate	Saccharide loading	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
Cassava Waste	2	Sulfonated carbon-based catalyst	100 wt%	250	1 min	9.0 ^a	-	-	286
Cassava Waste ^e	2	Sulfonated carbon-based catalyst	100 wt%	250	1 min	11 ^a	-	-	286
Cellulose	5	Cr[(DS)H ₂ PW ₁₂ O ₄₀] ₃ ^g	15 mM	150	2 h	53	77	68	284
Cellulose	5	Cr[H ₂ PW ₁₂ O ₄₀] ₃	15 mM	150	2 h	36	57	62	284
Cellulose	5	H ₃ PW ₁₂ O ₄₀	15 mM	150	2 h	0	33	0	284

Cellulose	9	TiO ₂	100 wt%	250	5 min	13 ^b	34	37	257
Cellulose	9	ZrO ₂	100 wt%	250	5 min	8.3 ^c	25	33	257
Corn Cob	9	TiO ₂	100 wt%	250	5 min	7.9 ^a	-	-	257
Corn Cob	9	TiO ₂ -ZrO ₂	100 wt%	250	5 min	8.5 ^a	-	-	257
Inulin	6	Cubic ZrP ₂ O ₇	55 wt%	100	1 h	35	39	89	184
Inulin	6	Cubic ZrP ₂ O ₇	55 wt%	100	1 h	70 ^d	73	97	184
Inulin	6	FeVOP	5 wt%	80	2 h	35	42	83	198
Inulin	6	γ-	55 wt%	100	1 h	42	44	94	184
		Ti(PO ₄)(H ₂ PO ₄).2H ₂ O							
Inulin	6	γ-	55 wt%	100	1 h	67 ^d	71	95	184
		Ti(PO ₄)(H ₂ PO ₄).2H ₂ O							
Inulin	6	Niobium phosphate	63 wt%	100	3 h	31	47	66	183
Rice Husk	9	TiO ₂ -ZrO ₂	100 wt%	250	5 min	3.3 ^a	-	-	257
Sucrose	13	Niobium phosphate	53% w/w	100	4 h	14 ^f	30	46	183
Sugarcane bagasse	9	TiO ₂	100 wt%	250	5 min	6.3 ^a	-	-	257

Sugarcane bagasse	9	TiO ₂ -ZrO ₂	100 wt%	250	5 min	6.6 ^a	-	-	257
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a: significant furfural yields (2-11%) observed; *b*: 6% fructose observed in the reaction mixture *c*: 8% fructose observed in the reaction mixture; *d*: HMF extraction with MIBK after 0.5 h and 1 h; *e*: H₂O/acetone/DMSO 90:7:3 (w/w) as the solvent; *f*: The formed glucose was not converted; *g*: DS = dodecylsulfate, a surfactant

Table 22. The dehydration of polysaccharides to HMF in organic solvents

Substrate	Substrate loading (wt%)	Solvent	Catalyst	Catalyst loading	Temperature (°C)	Reaction Time (h)	Yield (%)	Conversion (%)	Selectivity (%)	Reference
Cellobiose	3	DMF	Hydrotalcite/Amberlyst 15	200 wt% 1:1 w/w	120	3	35	52	67	263
Cellulose	4	DMA (10 wt% LiCl)	CrCl ₂ /HCl	25 mol%/10 mol%	140	2	22	-	-	119
Cellulose	4	DMA (10 wt% LiCl)	CrCl ₃ /HCl	25 mol%/10 mol%	140	2	33	-	-	119
Melezitose ^a	10	DMSO	LaCl ₃	5 mol%	120	2	8	-	-	216
Raffinose ^b	10	DMSO	LaCl ₃	5 mol%	120	2	22	-	-	216

Starch	3	DMSO/water (4:1 v/v)	$\text{SO}_4^{2-}/\text{ZrO}_2\text{-Al}_2\text{O}_3$ (Zr:Al = 3:7 n/n)	6 wt%	150	4	48	-	-	270
Sucrose	10	DMA	$\text{CrCl}_3/\text{NH}_4\text{Br}$	9.5 mol% / 55 mol%	100	1	87	-	-	287
Sucrose	3	DMF	Hydrotalcite/Amber lyst 15 1:1 w/w	200 wt%	120	3	54	58	93	263
Sucrose	7	DMSO	LaCl_3	5 mol%	120	2	47	-	-	216
Sucrose	9	NMP	$\text{FeCl}_3/\text{Et}_4\text{NBr}$	10 mol%/18 mol%	90	3	40	-	-	248
Tapioca flour	50	H ₂ O/Acetone/ DMSO unknown ratio	WO ₃ -ZrO ₂	100 wt%	230	-	22	-	-	283
Turanose	7	DMSO	LaCl_3	5 mol%	120	2	12	-	-	216

a: a trisaccharide containing one fructose and two glucose moieties *b*: a trisaccharide containing one fructose, one glucose and one galactose moiety

2.4.2 HMF formation in biphasic solvent systems

The low HMF yields sometimes observed simultaneously with high LA yields point to the importance of repressing the HMF rehydration. In addition HMF is assumed to react with sugars and sugar intermediates to form so-called humins. A number of groups have combined the sugar dehydration under aqueous conditions with an *in situ* extraction of the HMF in an organic phase. By continuously removing HMF, these undesired side reactions can be suppressed to a large extent. The first to apply such a continuous extraction system in HMF synthesis from carbohydrates was Peniston, named as inventor on a patent from 1956.²⁸⁸

2.4.2.1 Fructose dehydration in biphasic solvent systems

Peniston performed HMF synthesis in 0.05 M aqueous sulfuric acid containing 2 wt% fructose, claiming 68% yield after 8 min at 170 °C in the presence of one equivalent of n-butanol.²⁸⁸ The analysis was performed using UV only, without chromatography, which makes the quantification less reliable.

Kuster and Van der Steen performed biphasic HMF formation in a continuous stirred tank reactor (CSTR), studying the effects of temperature, fructose concentration, residence time, phosphoric acid concentration and MIBK-water ratio on the yield and selectivity.¹⁹⁹ In general an increase in temperature and acid concentration led to an increase in the reaction rate. Longer residence times led to higher HMF yields without significant losses in selectivity. An increase in the MIBK-water ratio led to an increase in both yield and selectivity. The highest HMF yield of 69% at 94% fructose conversion was obtained with 1M fructose and 0.1 M H₃PO₄ at 190 °C with an MIBK-water ratio value of 7.5 and a residence time of 5 min.

The laboratory for organic and agricultural chemistry in Toulouse continued in this direction in the first half of the 1980's. Mercadier *et al.* published a three-part study on fructose dehydration in biphasic water-organic systems, catalysed by ion-exchange resins.^{211,289,290} An aqueous fructose solution of about 25 wt% was reacted in the presence of Lewatit SPC 108 and SPC 118 at 88 °C for 5 h. In the absence of extraction solvent the HMF yield was 10% at 69% conversion, whereas in the presence of 9 eq. MIBK the HMF yield was 28% at 45% conversion.²¹¹ Increasing the reaction time to 15 h in the presence of MIBK increased the HMF yield to 56% at 84% conversion. Tests with other extraction solvents under the same conditions for 5 h showed that alkanes, such as heptane, were highly unfavourable with HMF yields below 10% at conversions around 30%.²⁹⁰ The application of

benzonitrile and 2,2'-dichloroethylether as extraction solvents showed results comparable to MIBK with regard to selectivity, but at higher reaction rates with HMF yields of around 40% at around 65% conversion after 5 h.²¹¹ Experiments in which the MIBK:water ratios were varied showed increasing HMF yield and selectivity with increasing amounts of MIBK up to a MIBK:water ratio of 9. In a later publication under comparable conditions yields of >40% at around 80% conversion were reported.²⁹¹

Gaset *et al.* also reported work on a DMSO:MIBK biphasic system.²⁹² A 97% HMF yield was reported by reacting a 20 wt% fructose solution in DMSO at 76 °C in flow (213 ml/h) with an MIBK counterflow (1500 ml/h).

Rigal and Gaset reported an HMF yield of 74% from aqueous fructose with SPC-108 resin as catalyst after 7 h at 78 °C under continuous extraction by MIBK.¹⁸⁶ From sorbose 47% HMF yield was obtained after 12 h.

El Hajj used a number of solid acid resins for aqueous fructose dehydration to HMF in the presence of MIBK.¹⁹⁶ HMF yields as high as 90% were obtained by dehydrating 20 wt% fructose in water, catalysed by 1 wt% Duolite C20 at 90 °C for 14 h in presence of 9 equivalents of MIBK. MIBK was refreshed every 2 h, resulting in a total use of 8 l for 100 ml of water containing 25 g of fructose.

In the mid 1990's Moreau and co-workers ventured into zeolite catalysed sugar chemistry.^{102,293-295} In a water/MIBK (1:5 v/v) system several zeolites were tested: H-Y faujasites and H-mordenite catalysts with different Si/Al ratios, H-beta and H-ZSM5. In general the more active catalysts provided relatively low selectivities at high conversion. Through dealumination higher selectivities were obtained by lowering the activity. A 9 wt% aqueous fructose solution was reacted at 165 °C in the presence of 29 wt% catalyst relative to fructose. The best result of 69% HMF yield at 76% conversion was obtained after 60 min using H-mordenite with an Si/Al ratio of 11.^{102,293,294} A recent publication by Ordomsky *et al.* on zeolite catalysed dehydration of fructose in water and water/MIBK systems showed significantly lower selectivity to HMF at comparable conversion with H-mordenite with an Si/Al ration of 11.7, reporting 42% yield at 64% conversion.²⁹⁶ In the same publication the effect of deactivation of the outer surface of the zeolite on the selectivity was researched. In the absence of extracting solvent the selectivity increased significantly at all conversions, improving the maximum selectivity from 48% to 63% at 56% conversion. This effect was explained by a decrease in the rate of oligomerisation due to steric constraints in the pores of the acid catalyst. Adding 1 eq. of MIBK did not increase the maximum selectivity, but did increase the selectivity at high conversions.

The group of Dumesic performed extensive research on biphasic solvent systems, applying a continuous extraction of an aqueous reaction medium by an organic phase from which HMF was continuously recovered by solvent evaporation.^{170,297-301} Experiments in 0.25 M HCl at 180 °C for 2.5 to 3 min with 30 wt% aqueous fructose yielded 26% HMF at 50% conversion in the absence of an extraction.¹⁷⁰ In the presence of 2 weight equivalents MIBK the yield was improved to 55% at 75% conversion. The HMF yield was further improved by modification of both phases. From 10 wt% fructose in 1:1 (w/w) water:DMSO an HMF yield of 85% at 95% conversion was obtained with HCl at pH 1 after 4 min at 170 °C in combination with 2 eq. (w/w) 7:3 (w/w) MIBK:2-butanol.³⁰⁰ In 3:7 (w/w) water:DMSO in the absence of catalyst and with 1 eq. (w/w) dichloromethane as extracting solvent, an 87% HMF yield at 100% conversion was obtained at 140 °C after 2 h.

To avoid the use of corrosive homogeneous acids, Dumesic *et al.* tested propylsulfonic acid-functionalised and thiopropyl-modified silicas in order to combine acidity with the promoting effect of DMSO and DMF in one catalyst.²⁹⁹ SBA-15, a mesoporous silica with two-dimensional hexagonal pore structure, and A380, a non-porous silica, were used as supports. The experiments were performed in batch with 30 wt% aqueous fructose, 11 wt% catalyst and 2 eq. (w/w) MIBK/2-butanol (7:3 w/w) at 180 °C for 2 h. The SBA-15 experiments showed no beneficial effect of thiopropyl modification, but the installation of propylsulfonic acid groups improved the activity and selectivity, yielding 49% HMF at 66% conversion after 30 min. The A380 experiments showed no improvement upon propylsulfonic acid functionalisation of the thiopropyl modified precursor. An experiment with Amberlyst 70 resulted in 58% yield at 86% conversion after 10 min. The difference in activity between Taa-SBA-15 and Taa-A380 was explained by the higher acid loading on SBA-15. Recently this group published additional work with SBA-15 as the catalyst.³⁰²

In another publication by Dumesic *et al.* different water/DMSO and water/NMP mixtures were tested with either MIBK or DCM as extraction solvent.³⁰¹ The experiments were catalysed by the acidic ion exchange resin DIAION® PK216 at 90 °C and 120 °C with a feed concentration of 10 wt%. An 83% HMF yield at 98% conversion was obtained in 4:6 (w/w) water/NMP at 90 °C after 18 h with MIBK as extraction solvent. An increase in selectivity was observed with decreasing fructose concentration, increasing DMSO or NMP content and increasing extraction solvent.^{170,300,301}

A study on different types of organic solvents as extracting agents in combination with an aqueous phase, saturated with salt, was performed by Román-Leshkov and Dumesic, focussing on primary and secondary alcohols (C₃-C₆), ketones (C₃-C₆) and cyclic ethers.²⁹⁷

Typical experiments were performed with 30 wt% fructose in the aqueous phase, catalysed by HCl (pH 0.6) at 150 °C for 35 min with a $V_{\text{org}}/V_{\text{aq}}$ value of 3.2. The highest yields were around 69%, with 2-butanone and 2-pentanol achieving this at conversions of 84% and 83% respectively. 2-Butanol is presented as the solvent providing the highest HMF selectivity of 85%, though this is only at 67% conversion, resulting in 57% yield. The results indicate that the highest yields at non-complete conversions are obtained with the C₄ and C₅ extracting solvents, with the secondary alcohols leading to the highest selectivities and the ketones resulting in the highest conversions. If the reaction system is assumed to be biphasic, then it is surprising that the type of extraction solvent affects the fructose conversion rate, unless this is dependent on the HMF concentration. Several mineral salts were tested for saturation of the aqueous phase in which application of chlorides showed a beneficial effect compared to bromides and sulfates on the HMF yield and selectivity, especially for sodium, potassium and cesium salts. This is in contrast with what Binder and Raines reported with regard to the effect of halides on the selectivity of fructose dehydration to HMF (section 2.3.1.1, Scheme 13).¹¹⁹

Work by Lima *et al.* in a water-toluene system, catalysed by Al-TUD-1 showed yields of less than 20% HMF from fructose.¹²⁴ A publication by McNeff and co-workers describes the dehydration of a number of carbohydrate feedstocks in a two-phase flow process.^{303,304} TiO₂-catalysed fructose dehydration at 200 °C with 1/3 volume equivalent *n*-Butanol as extraction solvent yielded 18% HMF. An increase in the amount of *n*-butanol decreased the yield.

Hansen *et al.* published results with boric acid-catalysed dehydration of fructose in H₂O, in which the effects of the catalyst, extraction solvent and salt concentration were studied.³⁰⁵ With a 30 wt% aqueous fructose solution containing 85 mol% boric acid and 4 eq of MIBK as extraction solvent 22% HMF yield at 43% conversion was obtained after 45 min at 150 °C. When the catalyst loading was doubled the yield increased to 28% at 53% conversion. The addition of halide salts to the system resulted in a remarkable improvement of the HMF yield and selectivity. The presence of 0.87 M NaCl improved the yield to 46% at 70% conversion. When THF was used as extraction solvent the yield was improved to 51% at 75% conversion after 75 min under otherwise identical conditions. When halide salts were applied the selectivity improved from just over 50% to around 65-70%.

In a publication by Yang *et al.* very high HMF yields and selectivities were reported when niobic acid treated with phosphoric acid (NA-p) was applied.³⁰⁶ A 6 wt% aqueous solution of fructose was reacted in the presence of 8 wt% NA-p and 1.5 eq (V/V) 2-butanol at 160 °C for 50 min, leading to 89% HMF yield at 90% conversion. This is a surprising result, because the

NA-p is a heterogeneous Brønsted acidic catalyst, which would be expected to also catalyse the rehydration of HMF in the presence of water, since even in the presence of extraction solvent, a significant amount of HMF remains in the aqueous phase. When comparing these data to the state of the art described in Tables 23 and 24, it becomes clear that this is the only publication claiming essentially quantitative yields. Similar experiments were performed with modified hydrated tantalum oxide (TA-p).³⁰⁷ From fructose 90% HMF at 94% conversion was obtained after 100 min at 160 °C.

Fan *et al.* applied a solid heteropolyacid, Ag₃PW₁₂O₄₀, to the dehydration of fructose to HMF. A 23 wt% aqueous mixture with a 2.25 volume ratio of MIBK as extracting solvent was reacted at 120 °C.³⁰⁸ Various catalyst loadings and reaction times were tested with a reported maximum HMF yield of 78% at 83% conversion after 1 h. In this work also significant HMF yields were reported in the absence of catalyst, namely 33% HMF at 47% conversion after 1 h at 120 °C. The levulinic acid yields were also reported, showing increased amounts at higher conversions.

Zhao *et al.* applied approximately 20 wt% of Cs_{2.5}H_{0.5}PW₁₂O₄₀ as heteropolyacid catalyst in the dehydration of 30 wt% aqueous fructose in the presence of 3 volume equivalents of MIBK, yielding 74% HMF at 78% conversion after 1 h at 115 °C.³⁰⁹ Also experiments were reported with different catalyst loadings, fructose concentrations and at different temperatures and reaction times. Starting with a 10 wt% fructose solution or a 50 wt% fructose solution both gave almost the same result of 71-74% HMF yield at around 85% conversion, which is slightly worse than the result with 30 wt% fructose. Increasing the temperature increased the reaction rate, but at comparable selectivities.

Brasholz *et al.* published work on fructose dehydration in 32% aqueous HCl in flow with an equal flow of dichloromethane as extraction solvent.³¹⁰ With a 10 wt% fructose solution at 100 °C and a residence time of 1.67 min a CMF yield of 81% was reported. No HMF was observed in this reaction.

Tables 23 and 24 provide an overview of the results of fructose dehydration in biphasic solvent systems. Although some other solvents have been tested the majority of the work was done with MIBK and *n*-BuOH as extraction solvents. It is clear that the selectivity towards HMF formation was increased significantly from the regular water-based systems.

Table 23. Fructose dehydration to HMF in biphasic solvent systems, catalysed by homogeneous catalysts

Fructose conc. (wt%)	Reaction solvent	Extraction solvent	Org./Aq. phase ratio (V/V)	Catalyst	Catalyst loading	T (°C)	Reaction Time	Yield (%)	Conv. (%)	Sel. (%)	Ref.
5	Water	MIBK	2	AlCl ₃	50 mol%	130	5 min	61 ^g	-	-	205
30	8:2 Water:DMSO (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	H ₂ SO ₄	0.25 M	180	2.5-3 min	60	85	71	170
2	Water	n-BuOH	1	H ₂ SO ₄	45 mol%	170	8	68	-	-	288
30	Water (0.87 M NaCl)	7:3 MIBK:2-BuOH (w/w)	4	H ₃ BO ₃	85 mol%	150	45 min	50	72	70	305
30	Water	MIBK	4	H ₃ BO ₃	85 mol%	150	45 min	22	43	50	305
30	Water	MIBK	4	H ₃ BO ₃	171 mol%	150	45 min	28	53	54	305
30	Water (0.87 M LiCl)	MIBK	4	H ₃ BO ₃	85 mol%	150	45 min	45	69	66	305
30	Water (0.87 M NaCl)	MIBK	4	H ₃ BO ₃	85 mol%	150	45 min	46	70	65	305
30	Water (0.87 M KCl)	MIBK	4	H ₃ BO ₃	85 mol%	150	45 min	44	67	65	305
30	Water (0.44 M MgCl ₂)	MIBK	4	H ₃ BO ₃	85 mol%	150	45 min	52	81	65	305
30	Water (0.87 M NaCl)	THF	4	H ₃ BO ₃	85 mol%	150	1.25 h	51	75	68	305

3.6	Water	MIBK	1	H ₃ PO ₄	10 mol%	180	3 min ^a	25	35	70	199
18	Water	MIBK	1	H ₃ PO ₄	10 mol%	180	3 min ^a	25	43	57	199
18	Water	MIBK	1	H ₃ PO ₄	5 mol%	180	3 min ^a	19	31	62	199
18	Water	MIBK	1	H ₃ PO ₄	50 mol%	180	3 min ^a	51	75	68	199
18	Water	MIBK	3.5	H ₃ PO ₄	10 mol%	190	5 min ^a	55	77	71	199
18	Water	MIBK	5.7	H ₃ PO ₄	10 mol%	190	5 min ^a	64	89	72	199
18	Water	MIBK	7.5	H ₃ PO ₄	10 mol%	190	5 min ^a	69	94	73	199
18	Water	MIBK	4.6	H ₃ PO ₄	10 mol%	200	2 min ^a	56	79	71	199
18	Water	MIBK	6.2	H ₃ PO ₄	10 mol%	200	2 min ^a	62	85	73	199
18	Water	MIBK	4	H ₃ PO ₄	10 mol%	200	3.8 min ^a	62	85	73	199
18	Water	MIBK	1	H ₃ PO ₄	5 mol%	213	3 min ^a	48	72	66	199
18	Water	MIBK	1	H ₃ PO ₄	10 mol%	220	3 min ^a	52	85	61	199
10	Water	MIBK	3	HCl	0.25 M	140	15 min ^b	74	-	-	310
10	1:1 Water:DMSO (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl	pH 1	170	4 min	85	95	89	300
10	1:1 Water:DMSO (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl	pH 2	170	8 min	82	95	86	300

30	Water	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl	0.25 M	180	2.5-3 min	69	86	80	170
30	8:2 Water:DMSO (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl	0.25 M	180	2.5-3 min	71	87	82	170
30	7:3 (8:2 Water:DMSO):PVP (w/w)	7:3 MIBK:2-BuOH (w/w)	1 w/w	HCl	0.25 M	180	2.5-3 min	68	82	83	170
30	7:3 (8:2 Water:DMSO):PVP (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl	0.25 M	180	2.5-3 min	76	89	85	170
50	7:3 (8:2 Water:DMSO):PVP (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl	0.25 M	180	2.5-3 min	71	92	77	170
30	Water	MIBK	2 w/w	HCl	0.25 M	180	2.5-3 min	55	75	73	170
10	3:7 Water:DMSO (w/w)	DCM	1 w/w	None		140	2 h	87	100	87	300

a: continuous stirred tank reactor (CSTR); *b:* continuous flow; 6% fructose observed in the reaction mixture *c:* 8% fructose observed in the reaction mixture; *d:* HMF extraction with MIBK after 0.5 h and 1 h; *e:* H₂O/acetone/DMSO 90:7:3 (w/w) as the solvent; *f:* The formed glucose was not converted; *g:* isolated yield

Table 24. Fructose dehydration to HMF in biphasic solvent systems, catalysed by heterogeneous catalysts

Fructose conc. (wt%)	Reaction solvent	Extraction solvent	Org./Aq. phase ratio (V/V)	Catalyst	Catalyst loading	T (°C)	Reaction Time	Yield (%)	Conv. (%)	Sel. (%)	Ref.
23	Water	MIBK	2.25	Ag ₃ PW ₁₂ O ₄₀	6.7 wt%	120	1 h	75	84	88	308
23	Water	MIBK	2.25	Ag ₃ PW ₁₂ O ₄₀	3.3 wt%	120	1 h	78	83	94	308
9	Water	Toluene	2.3	Al-TUD-1	67 wt%	170	2 h	20	76	26	124
30	Water	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	Amberlyst 70	11 wt%	180	10 min	58	86	67	299
23	Water	MIBK	3	Cs _{2.5} H _{0.5} PW ₁₂ O ₄₀	20 wt%	115	1 h	74	78	95	309
10	3:7 Water:DMSO (w/w)	MIBK	1 (w/w)	Diaion PK216	500 wt%	90	4 h	73	87	84	301
10	1:1 Water:DMSO (w/w)	MIBK	1 (w/w)	Diaion PK216	500 wt%	90	12 h	73	90	81	301
10	4:6 Water:NMP (w/w)	MIBK	1 (w/w)	Diaion PK216	500 wt%	90	18 h	83	98	85	301
20	Water	MIBK ^b	9	Duolite C20	1 wt%	90	14 h	89	-	-	196
9	Water	MIBK	5	H-form Zeolite, Si/Al = 11	29 wt%	165	30 min	50	54	92	102,293
9	Water	MIBK	5	H-form Zeolite,	29 wt%	165	1 h	69	76	91	102,293

Si/Al = 11												
9	Water	MIBK	5	H-form Si/Al = 6.9	Zeolite, 29 wt%	165	1 h	53	65	81	293	
6	Water	MIBK	5	H-form Si/Al = 11.7	Zeolite, 67 wt%	165	6.5 h	42	64	66	296	
20	DMSO	MIBK	7	IE resin (acidic)	Fixed bed.	76	- ^a	97	-	-	292	
20	NMP	MIBK	7	IE resin (acidic)	fixed bed	76	- ^a	88	-	-	292	
20	DMF	MIBK	7	IE resin (acidic)	Fixed bed	76	- ^a	84	-	-	292	
30	7:3 Water:DMSO):PVP (w/w)	(8:2 7:3 MIBK:2-BuOH (w/w)	1 (w/w)	IE resin (acidic)	100 wt%	90	8-16 h	54	83	65	170	
4.8	Water	MIBK	11.5	Lewatitt SPC 108	168 meq/l	80	14 h	44	79	56	291	
20	Water	2,2'-dichloroethylether	9	Lewatitt SPC 108 H ⁺	61 mol%	88	5 h	42	68	62	211	
20	Water	Benzonitrile	9	Lewatitt SPC 108 H ⁺	61 mol%	88	5 h	40	63	63	211	
20	Water	Heptane	9	Lewatitt SPC 108	61 mol%	88	5 h	6	21	28	211	

H^+												
20	Water	MIBK	9	Lewatitt SPC 108	61 H^+	mol%	88	15 h	56	84	66	211
20	Water	MIBK	9	Lewatitt SPC 108	61 H^+	mol%	88	5 h	28	45	63	211
4.8	Water	MIBK	11.5	Lewatitt SPC 108	168 meq/l	88	3 h	42	81	52	291	
20	Water	None	-	Lewatitt SPC 108	61 H^+	mol%	88	5 h	10	69	14	211
6	Water	2-Butanol	1.5	NA-p	8 wt%	160	50 min	89	90	99	307	
30	Water	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	SBA-15	11 wt%	180	2 h	31	59	52	299	
-	Water	MIBK	-	SPC-108	fixed bed	78	7 h ^a	74	-	-	186	
-	Water	MIBK	-	SPC-108	Fixed bed	78	12 h ^a	47	-	-	186	
30	Water	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	Taa-A380	11 wt%	180	2 h	38	62	61	299	
30	Water	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	Taa-SBA-15	11 wt%	180	30 min	49	66	74	299	
6	Water	2-Butanol	1.5	TA-p	8 wt%	160	100 min	90	94	96	307	
23	Water	<i>n</i> -BuOH	0.33	TiO ₂	Fixed bed	200	3 min ^a	18	-	-	303	

23	Water	<i>n</i> -BuOH	3	TiO ₂	Fixed bed	200	3 min ^a	11	-	-	303
30	Water	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	TP-A380	11 wt%	180	2 h	43	67	64	299
30	Water	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	TP-SBA-15	11 wt%	180	2 h	32	61	52	299

a: continuous flow; *b*: continuous extraction

2.4.2.2 Glucose dehydration in biphasic solvent systems

Cope was the first to apply biphasic mixtures in HMF production from glucose, claiming 21-25% isolated yield of HMF by reacting a 50 wt% aqueous glucose solution at 160 °C for around 9 h in the presence of approximately 20 volumetric equivalents of MIBK.³¹¹ The only acid present was that formed during the reaction.

Rigal and Gaset performed aldose dehydration in a water/MIBK system, catalysed by an acidic ion-exchange resin. HMF yields below 10% were obtained at 78 °C.¹⁸⁶

Work on glucose dehydration by the group of Dumesic generally resulted in low HMF yields.³⁰⁰ A 24% HMF yield at 50% conversion was obtained in aqueous HCl (pH 1) from 10 wt% glucose in the presence of 2 weight eq. MIBK/2-butanol (7:3 w/w) at 170 °C after 17 min. Experiments without acid were carried out at 140 °C in water/DMSO 3:7 in combination with an equal weight of dichloromethane resulting in an HMF yield of 30% at 62% conversion after 4.5 h. More recently work has been reported with a bifunctional catalyst system in which AlCl₃ was combined with HCl to yield up to 62% HMF.³¹² A comparable result was obtained by Yang *et al.* in a biphasic water-NaCl/THF system with AlCl₃ as the catalyst.³¹³ Dumesic *et al.* also applied solvents derived from lignin as extracting phase.³¹⁴

In research by Lima *et al.* in a water-toluene system, catalysed by Al-TUD-1 yields of less than 20% of HMF were obtained from glucose.¹²⁴ McNeff *et al.* described the dehydration of a number of carbohydrate feedstocks in a two-phase flow process.^{303,304} In this process an aqueous substrate mixture and organic extraction solvent were pumped into the reactor from separate reservoirs and reacted at 160-200 °C in the presence of a TiO₂ catalyst. n-Butanol and methyl isobutyl ketone (MIBK) were applied as extraction solvents. Different organic/aqueous ratios were tested. The highest HMF yields from glucose were between 25% and 30% at 180 °C with MIBK as extraction solvent (organic:aqueous 10:1) and with aqueous feed containing 23 or 50 wt% glucose. With n-butanol as extraction solvent yields were typically between 6 and 13% from glucose.³⁰³ The authors explain the lower yield compared to MIBK systems by too high solubility of water in n-butanol under reaction conditions. Experiments using Lite Corn Syrup, honey and glucose/fructose/sucrose mixtures were also described.

At 180 °C McNeff also tested the effect of the addition of homogeneous acid to similar reaction mixtures as described above.³⁰³ Both HCl (0.05-0.15 M) and H₃PO₄ (0.10 M) were tested for this purpose. A run with just 0.15 M HCl as catalyst yielded 13% HMF from

glucose. Combining TiO_2 with 0.15 M, 0.10 M and 0.05 M HCl or 0.10 M H_3PO_4 led to yields of 37%, 34%, 26% and 33% respectively.

Hansen *et al.* also used boric acid as catalyst for the glucose dehydration under the same circumstances as applied for fructose, but found that the yields were very low.³⁰⁵ An HMF yield of 14% was obtained at 41% conversion after 5 h at 150 °C in the presence of 50 g/l NaCl and 4 volumetric equivalents of MIBK, compared to 46% HMF at 70% conversion for fructose after 45 min at under identical conditions.

In the same system as applied for fructose, Yang *et al.* reacted glucose, reporting very high HMF yields and selectivities.³⁰⁶ A 6 wt% aqueous solution of glucose, in the presence of 8 wt% NA-p and 1.5 eq (V/V) 2-butanol, yielded 49% HMF at 72% conversion at 160 °C for 110 min. With TA-p as the catalyst 58% HMF yield at 70% conversion was reported after 140 min.³⁰⁷ Similar to the fructose data, the yields and selectivities are much higher than would be expected when comparing to the results of other publications under similar conditions.

Fan *et al.* used $\text{Ag}_3\text{PW}_{12}\text{O}_{40}$ as a catalyst for glucose dehydration to HMF.³⁰⁸ With 13 wt% catalyst at 130 °C a 76% HMF yield at 90% conversion after 4 h was reported. What is surprising about this result when compared to the work with fructose, yielding 75% HMF and 11% levulinic acid at 95% conversion with the same catalyst loading at 120 °C after 1 h, is a significantly lower levulinic acid yield of 6%. This means that under harsher conditions HMF appeared to be more stable.

Nikolla *et al.* published promising results in glucose dehydration with a bifunctional catalyst system of tin and titanium β -zeolites in combination with HCl. From a 10 wt% glucose solution in 26 wt% aqueous NaCl solution at pH 1 an optimum HMF yield of 57% at 79% conversion was obtained in the presence of 0.5 wt% Sn-beta and 3 eq. (v/v) of THF as extraction solvent after 70 min at 180 °C. When Ti-beta was used, the yield was 53% at 76% conversion after 105 min.³¹⁵

Degirmenci *et al.* prepared a heterogeneous catalyst that mimicked the CrCl_2 /ionic liquid system applied by Zhao *et al.*¹³⁴ by covalently binding 1-(3-triethoxysilylpropyl)-3-methylimidazolium chloride on SBA-15, followed by coordination of CrCl_2 .³¹⁶ A number of solvent systems were researched, with a water:DMSO/2-BuOH:MIBK system giving the highest yield (35%) and selectivity (70%). Leaching of chromium caused deactivation of the catalyst in recycling experiments.

Recently some additional work was published on glucose dehydration in aqueous/organic biphasic solvent systems with acidic catalysts.^{317,318,319}

Mascal and Nikitin investigated a water-1,2-dichloroethane system for HCl catalysed carbohydrate conversion to 5-chloromethylfurfural (CMF).¹⁸⁷ In the presence of LiCl a homogeneous mixture of glucose was reacted for 30 h at 65 °C. Three types of furanic compound were isolated with a combined yield of around 85%: CMF at 71% yield, 2-(2-hydroxyacetyl)furan (HAF) at 7% yield and HMF at 8% yield. CMF can be easily converted to HMF, 5-methylfurfural (MF), 5-ethoxymethylfurfural (EMF) and 2,5-dimethylfuran.^{187,320} This system was later improved by application of a closed system at 100 °C for 3 h in which 1,2-dichloroethane was refreshed every hour.³²¹ From a 1 wt% glucose solution 81% CMF yield was reported. Brasholz *et al.* published similar research, in which a 2 wt% glucose solution in 32 wt% HCl_(aq) was reacted in flow at 120 °C.³¹⁰ With a residence time of 5 min and an equal flow of reaction mixture and 1,2-dichloroethane a CMF yield of 58% was obtained.

Table 25 provides an overview of the HMF yields obtained in glucose dehydration reactions in aqueous systems with *in situ* extraction. The data on glucose dehydration in aqueous mixtures, as described in section 2.4.1.2 and Table 15, are difficult to compare with the presented data on glucose dehydration under *in situ* extraction because of the small amount of experiments that were performed under comparable conditions. It is clear, though, that even with extracting solvent present the HMF yields from glucose remain low, with the exception of the results obtained with bifunctional catalyst systems.

Table 25. Glucose dehydration to HMF in biphasic solvent systems

Glucose conc. (wt%)	Reaction solvent	Extraction solvent	Org./Aq. phase ratio (V/V)	Catalyst loading	T (°C)	Reaction Time	Yield (%)	Conv. (%)	Sel. (%)	Ref.
10	3:7 Water:DMSO (w/w)	DCM	1 (w/w)	None	140	4.5 h	30	62	48	300
23	Water	MIBK	2.25	Ag ₃ PW ₁₂ O ₄₀	13 wt%	130	4 h	76	90	85
9	Water	Toluene	2.3	Al-TUD-1	67 wt%	170	6 h	18	76	23
5	Water	MIBK	2	AlCl ₃	50 mol%	130 ^d	5 min	43 ^e	-	-
30	Water (0.87 M NaCl)	MIBK	4	H ₃ BO ₃	85 mol%	150	5 h	14	41	34
10	1:1 Water:DMSO (w/w)	7:3 MIBK:2-BuOH (w/w)	2 (w/w)	HCl (pH 1)		170	17 min	24	50	47
6	Water	2-BuOH	1.5	NA-p	8 wt%	160	110 min	49	72	68
10	2:8 Water:DMSO	7:3 MIBK:2-BuOH	1	SBA-15-[PMIm]Cl/CrCl ₂	-	150	3 h	35	50	70
10	Water	<i>n</i> -BuOH	3	Sn-Beta/HCl (pH 1)	0.5 mol% Sn	160	90 min	20	77	26
10	Water (26 wt% NaCl)	<i>n</i> -BuOH	3	Sn-Beta/HCl (pH 1)	0.5 mol% Sn	160	90 min	41	75	55

1)												
10	Water (26 wt% NaCl)	THF	3	Sn-Beta/HCl (pH 1)	0.5 mol% Sn	180	70 min	57	79	72	315	
-	Water	MIBK	-	SPC-108	Fixed bed	78	22 h ^c	9	-	-	186	
- ^a	Water	MIBK	-	SPC-108	Fixed bed	78	16 h ^c	7	-	-	186	
- ^b	Water	MIBK	-	SPC-108	Fixed bed	78	16 h ^c	5	-	-	186	
6	Water	2-Butanol	1.5	TA-p	8 wt%	160	140 min	58	70	83	306	
10	Water (26 wt% NaCl)	THF	3	Ti-Beta/HCl (pH 1)	0.5 mol% Ti	180	105 min	53	76	70	315	
23	Water	MIBK	10	TiO ₂	Fixed bed	180	2 min ^c	29	-	-	303	
50	Water	MIBK	10	TiO ₂	Fixed bed	180	2 min ^c	26	-	-	303	
50	Water (0.15 M HCl)	MIBK	10	TiO ₂ /HCl	Fixed bed	180	2 min ^c	37	-	-	303	
23	Water	n-BuOH	1	TiO ₂	Fixed bed	200	3 min ^c	13	-	-	303	
23	Water	MIBK	10	ZrO ₂	Fixed bed	180	2 min ^c	21	-	-	303	

a: mannose as the substrate; *b:* galactose as the substrate; *c:*continuous flow; *d:* microwave irradiation; *e:* isolated yield;

2.4.2.3 The dehydration of oligo- and polysaccharides in biphasic solvent systems

Gaset *et al.* reported almost identical HMF yields of ~70% from inulin and crude polyfructans from Jerusalem artichoke as from fructose in an acidic resin-catalysed water-MIBK system at 78 °C.¹⁸⁶ HMF yields from sucrose and raffinose were 41% and 27% respectively. This ratio is consistent with the amount of fructose moieties present in each molecule.

Yang *et al.* applied TA-p catalysts on 6 wt% inulin in water with 1.5 (v/v) 2-butanol as extraction solvent, resulting in 87% HMF yield at 95% conversion at 160 °C after 2.5 h.³⁰⁷

In their studies on fructose and glucose dehydration, the group of Dumesic reported work on di- and polysaccharides.^{300,301} In water/DMSO (5:5 w/w) in the presence of 2 eq (w/w) MIBK/2-butanol (7:3 w/w) and catalysed by HCl, 10 wt% inulin yielded 75% HMF at 98% conversion after 5 min at 170 °C and pH 1.5.³⁰⁰ In water/DMSO 4:6 (w/w), sucrose yielded 50% HMF at 65% conversion after 5 min, starch yielded 26% HMF at 61% conversion after 11 min and cellobiose yielded 27% HMF at 52% conversion after 10 min at pH 1. Experiments without acid were carried out at 140 °C in water/DMSO 3:7, in combination with dichloromethane as organic phase in equal weight to the aqueous phase. At 100% conversion, the HMF yield from inulin was 70% after 2h. From cellobiose an HMF yield of 38% at 85% conversion after 9.5 h and for starch a 36% HMF yield at 91% conversion after 11 h were reported.

In another publication by the same group different water/DMSO and water/NMP mixtures in the presence of acidic ion exchange resin DIAION® PK216 were tested with either MIBK or DCM as extraction solvent.³⁰¹ The feed concentration was 10 wt%, equal amounts (weight) of the aqueous and organic layers were used and the organic/catalyst ratio was 1. Experiments with 10 wt% inulin at 90 °C with H₂O-NMP (4:6 w/w) and H₂O:DMSO (5:5 w/w) yielded 69% and 62% HMF respectively at 100% conversion. At 120 °C in water/DMSO (5:5 w/w) in combination with DCM a 61% HMF yield was obtained at 100% conversion after 5.5 h. The same three experiments were performed with sucrose as substrate, yielding around 40% HMF yield, with regard to fructose content, at around 70% conversion.

McNeff *et al.* described the dehydration of a number of carbohydrate feedstocks in a two-phase flow process.^{303,304} A 23 wt% sucrose solution catalysed by anatase TiO₂ yielded 16% HMF at 180 °C and 3 min residence time under continuous extraction with MIBK, in which the MIBK flow rate was three times as high as that of the substrate solution. A 5% starch

solution yielded 15% HMF at 2 min residence time with ten fold MIBK flow rate. Cellulose dehydration was performed in the same system via a hot extraction of solid cellulose, which meant that hot water was passed through solid cellulose, prior to the entering the reactor. At 270 °C a 30% yields was reported at 87% conversion with a 2 min contact time and five fold MIBK flow.

Work on sucrose dehydration by Tarabanko *et al.* in biphasic systems consisting of an acidic aqueous solution of sucrose in combination with a number of aliphatic alcohols produced the appropriate HMF ethers in yields of 14-25% relative to sucrose.²³⁴ The aqueous phase consisted of 0.44 M sucrose, and 4.2 M Na₂SO₄. The reactions were performed at 102 °C and the organic to aqueous phase ratio was 2. The yields of both the HMF ethers and alkyl levulinates decreased with alkyl chain length.

Mascal and Nikitin developed a biphasic system for cellulose conversion to 5-chloromethylfurfural (CMF).^{187,321,322} A homogeneous mixture of cellulose in concentrated HCl yielded three types of furanic compound with a combined yield of ~85% after 30 h at 65 °C in the presence of 1,2-dichloroethane: CMF at 71% yield, 2-(2-hydroxyacetyl)furan (HAF) at 8% yield and HMF at 5% yield¹⁸⁷. These are essentially equal to the yields reported for glucose, which shows that the rate-limiting step in this process is the glucose dehydration and not cellulose hydrolysis. Sucrose produced comparable, slightly higher combined yields of around 91%. This CMF can be easily converted to HMF, 5-methylfurfural (MF), 5-ethoxymethylfurfural (EMF) and 2,5-dimethylfuran.¹⁸⁷ This system was later improved by application of a closed system at 100 °C for 3 h in which 1,2-dichloroethane was refreshed every hour.³²¹ From a 1 wt% substrate solution cellulose yielded 84% CMF, sucrose yielded 90% CMF and corn stover yielded 80% CMF. Brasholz *et al.* reported 51% CMF yield from 2 wt% sucrose in 32% aqueous HCl at 2.5 min residence time in a flow process at 100 °C, in which dichloromethane was used as extraction solvent in equal flow as the reaction mixture.³¹⁰

Table 26 describes results obtained in the dehydration of sucrose, raffinose and polysaccharide in biphasic solvent systems. From inulin HMF yields >70% were reported at full conversion. Dumesic *et al.* obtained HMF yields of around 50% from sucrose, which is approximately the average between that of the typical yields form fructose and glucose under similar conditions, indicating that sucrose behaves as een equimolar mixture of fructose and glucose. Only very little work has been done on polysaccharides made up of glucose monomers, like starch and cellulose. Cellobiose has been used as a model compound for cellulose, but this is only a disaccharide that presents far less challenges, especially with

regard to solubility. McNeff *et al.* are the only group to publish cellulose dehydration under continuous extraction, presenting around 30% HMF yield. Starch dehydration has also been reported by McNeff *et al.*, as well as by Dumesic's group, both under very different reaction conditions, which makes it difficult to compare their results.

Table 26. Di- and polysaccharide dehydration to HMF in biphasic solvent systems

Substrate	Substrate loading (wt%)	Reaction solvent	Extraction solvent	Org.c/Aq. phase ratio (V/V)	Catalyst	Catalyst loading	T. (°C)	Reaction Time	Yield (%)	Conv. (%)	Sel. (%)	Ref.
Cellobiose	3	Water	Toluene	2.3	Al-TUD-1	200 wt%	170	6 h	12 ^c	98	12	124
Cellobiose	10	3:7 Water:DMSO (w/w)	DCM	1 w/w	None		140	9.5 h	38	85	45	300
Cellulose	- ^b	Water	MIBK	5	TiO ₂	Fixed bed	270	2 min ^a	30	87	34	303
Inulin	10	4:6 Water:NMP (w/w)	MIBK	1 w/w	Diaion PK216	500 wt%	90	18 h	69	100	69	300
Inulin	10	5:5 Water:DMSO (w/w)	7:3 MIBK:2- BuOH (w/w)	2 w/w	HCl (pH 1.5)	-	170	5 min	75	98	77	300
Inulin	9	Water	MIBK	5	H-form Zeolite, Si/Al=11	29 wt%	165	1 h	39	44	88	293
Inulin	6	Water	2-Butanol	1.5	NA-p	8 wt%	160	140 min	54	86	63	306
Inulin	10	3:7 Water:DMSO (w/w)	DCM	1 w/w	None		140	2.5 h	70	100	70	300

Inulin	-	Water	MIBK	-	SPC-108	Fixed bed	78	12 h ^a	67	-	-	186
Inulin	6	Water	2-Butanol	1.5	TA-p	8 wt%	160	140 min	87	95	92	307
Jerusalem Artichoke	9	Water	MIBK	5	H-form Zeolite, Si/Al=11	29 wt%	165	1 h	57	66	87	293
Jerusalem Artichoke	-	Water	MIBK	-	SPC-108	Fixed bed	78	15 h ^a	73	-	-	186
Jerusalem Artichoke Juice	6	Water	2-Butanol	1.5	TA-p	8 wt%	160	2 h	79	91	87	307
Raffinose	-	Water	MIBK	-	SPC-108	Fixed bed	78	10 h ^a	27	-	-	186
Starch	10	3:7 Water:DMSO (w/w)	DCM	1 w/w	none		140	11 h	36	91	40	300
Starch	5	Water	MIBK	10	TiO ₂	Fixed bed	180	2 min ^a	15	-	-	303
Sucrose	3	Water	Toluene	2.3	Al-TUD-1	200 wt%	170	6 h ^d	17	100	17	124
Sucrose	10	4:6 Water:DMSO (w/w)	7:3 MIBK:2-BuOH (w/w)	2 w/w	HCl (pH 1)	-	170	5 min	50	65	77	300
Sucrose	9	Water	MIBK	5	H-form Zeolite, Si/Al=11	29 wt%	165	1 h	28	57	49	293

Si/Al = 11												
Sucrose	10	3:7 Water:DMSO (w/w)	DCM	1 w/w	none		140	4.5 h	51	82	62	300
Sucrose	-	Water	MIBK	-	SPC-108	Fixed bed	78	12 h ^a	41	-	-	186
Sucrose	23	Water	MIBK	3	TiO ₂	Fixed bed	180	3 min ^a	16	-	-	303

a: continuous flow; *b*: chamber with solid cellulose between pre-heater and reactor; *c*: 50% glucose and 10% fructose yield; *d*: 26% glucose and 15% fructose yield

2.4.3 HMF formation in ionic liquids

2.4.3.1 A definition of ionic liquids

Ionic liquids typically consist of a combination of organic and inorganic ions and are unique compared to conventional solvents due to their extremely low vapour pressure. They cannot be classified as simply molten salts as they have some distinctly different properties, like their low melting point, which is typically below 100 °C, and relatively low viscosity.³²³ The first reported ionic liquid stems from 1914.³²⁴

A significant number of reviews on ionic liquids has been published.^{323,325-328} A lot of the early ionic liquids are air and moisture sensitive, greatly limiting their application. An important breakthrough came with the development of a series of air and moisture stable imidazolium type ionic liquids, which were first reported by Wilkes' group in 1992.^{327,329} The most common ionic liquids are *N,N'*-dialkylimidazolium, *N*-alkylpyridinium, alkylammonium and alkylphosphonium based. A good insight on their synthesis is given in reviews by Welton and Marsh.^{326,330}

2.4.3.2 The dehydration of carbohydrates to HMF in ionic liquids

The last 5-8 years have seen a strong growth in interest towards the use of ionic liquids in biomass conversion. This started with a publication on fructose dehydration by Moreau's group in 2003.³³¹ Since then a variety of imidazolium-based ionic liquids has been used in the dehydration of especially fructose. However, already twenty years earlier Fayet and Gelas reported the use of pyridinium chloride, a low melting salt, in sugar conversion, obtaining HMF in 70% yield from fructose.³³²

Zakrzewska *et al.* reported an elaborate research on the solubility of a number of carbohydrates in a wide range of ionic liquids, divided in six categories. Ionic liquids based on imidazolium, pyridinium, benzotriazonium, pyrrolidinium, alkylammonium and alkylphosphonium cations were researched.³³³

Recently the synthesis of HMF has been reviewed by Zakrzewska *et al.*,²⁰ Ståhlberg *et al.*¹⁸ and Lima *et al.*¹⁹

Fructose dehydration in ionic liquids

Lansalot-Matras and Moreau performed fructose dehydration in 1-Butyl-3-methylimidazolium ([BMIm]) type ionic liquids both in the presence and absence of DMSO.

In the absence of DMSO as a solvent a 52% HMF yield was obtained from an 8 wt% fructose solution in 1-butyl-3-methylimidazolium tetrafluoroborate ($[BmIm]BF_4$), catalysed by ~3 weight equivalents of Amberlyst 15 at 80 °C after 3 h.³³¹ At reaction times >3 h the yield started decreasing. When a mixture of ($[BmIm]BF_4$) and DMSO was used the yields improved to 87% after 32 h with 2 eq Amberlyst 15.

In 2006 Moreau *et al.* published work on fructose and sucrose dehydration in the Brønsted acidic 1-H-3-imidazolium chloride $[HmIm]Cl$.³³⁴ With a fructose concentration of 23 wt% a yield of 92% HMF at 98% conversion was reported after 45 min at 90 °C. The sucrose dehydration gave a similar molar yield with respect to the fructose moiety and conversion of the glucose moiety was estimated at around 3%.

Zhao *et al.* used $[EMIm]Cl$ as catalyst in sugar dehydration to HMF. In the absence of catalyst 73% HMF yield was obtained at full conversion by heating 9% fructose in $[EMIm]Cl$ at 120 °C for 3 h.¹³⁴ When 6 mol% $PtCl_2$ was used as a catalyst an HMF yield of 83% was obtained at 99% conversion.

Further research on fructose dehydration in acidic ionic liquids was done by Hu *et al.*³³⁵ PyHCl and $[HMim]Cl$ experiments led to similar results of 70% HMF yield at 90-95% conversion from a 17 mol% fructose solution at 80 °C for 1 h. Experiments in ChoCl/citric acid were reported to yield 75% HMF at 92% fructose conversion. Continuous extraction with ethyl acetate improved overall HMF yield to 92% at 98% conversion in ChoCl/citric acid. HMF was found to be stable under reaction conditions in citric acid for 1 h. Fructose dehydration in $[EMIm]BF_4$ with 17 wt% fructose, catalysed by 10 mol% $SnCl_4$ at 100 °C for 3 h yielded 62% HMF at 100% conversion.¹⁴⁴

Cao *et al.* looked into a number of imidazolium based ionic liquids as solvent and catalyst for fructose dehydration.³³⁶ In the absence of catalyst 63% HMF yield was obtained at 93% conversion from a 9 wt% fructose solution in $[BmIm]Cl$ after 50 min at 120 °C. When using $[HmIm]Cl$ as the ionic liquid at 120 °C the HMF yield was 7% at 66% conversion and at 100 °C no HMF formation was reported for any of the ionic liquids tested, which conflicts with the work of Moreau³³⁴ and Hu,³³⁵ who both found significant HMF yields at lower temperatures under otherwise comparable conditions. Additional experiments were performed with sulfuric acid and chromium(III) chloride hexahydrate as catalysts.³³⁶ With 10 mol% sulfuric acid 83% and 77% HMF yield at full conversion were obtained after 50 min at 100 °C in $[BmIm]Cl$ and $[BeMIm]Cl$ respectively. With 10 mol% chromium(III) chloride hexahydrate HMF yields of 75% and 71% at full conversion were obtained after 2 h at 120 °C in $[BmIm]Cl$ and 1-Benzyl-3-methylimidazolium chloride ($[BeMIm]Cl$) respectively.

A combination of [EMIm][HSO₄] and MIBK as extracting solvent was used by Lima *et al.* to obtain 88% HMF yield from 0.67 M fructose after 30 min at 100 °C.³³⁷ Replacing the MIBK with toluene yielded 79% HMF and subsequently replacing the [EMIm][HSO₄] with [BMIm]Cl led to a drop in yield to 16% at 23% conversion. The authors concluded that the Brønsted acidity plays an important role in fructose conversion to HMF.

Some recent literature on fructose dehydration in imidazolium based ionic liquids in the absence of an additional catalyst provided high yields in the range of 60-97%.³³⁸⁻³⁴² Also work on fructose dehydration in tetraethylammonium chloride³⁴³ and betaine hydrochloride³⁴⁴ was recently published.

GeCl₄ catalysed dehydration of carbohydrates to HMF in ionic liquids by Zhang *et al.* resulted in very high yields of HMF.²⁶⁸ A 5 wt% solution of fructose in [BMIm]Cl, in the presence of 10 mol% GeCl₄ relative to the substrate, yielded 92% HMF at full conversion after 5 min at 100 °C. Recycling of the system showed no significant decrease in yields after at least five cycles. In the absence of GeCl₄ no HMF was detected under otherwise identical conditions, which is consistent with the observations of Cao *et al.*³³⁶ Recently results were also published with GeCl₄ in mixtures of [BMIm]Cl and DMSO or DMF at 25 °C.³⁴⁵ Generally a higher fraction of ionic liquid led to higher yields, up to 70%. It is not clear from the data if this is due to activity or selectivity, since no conversion data are shown.

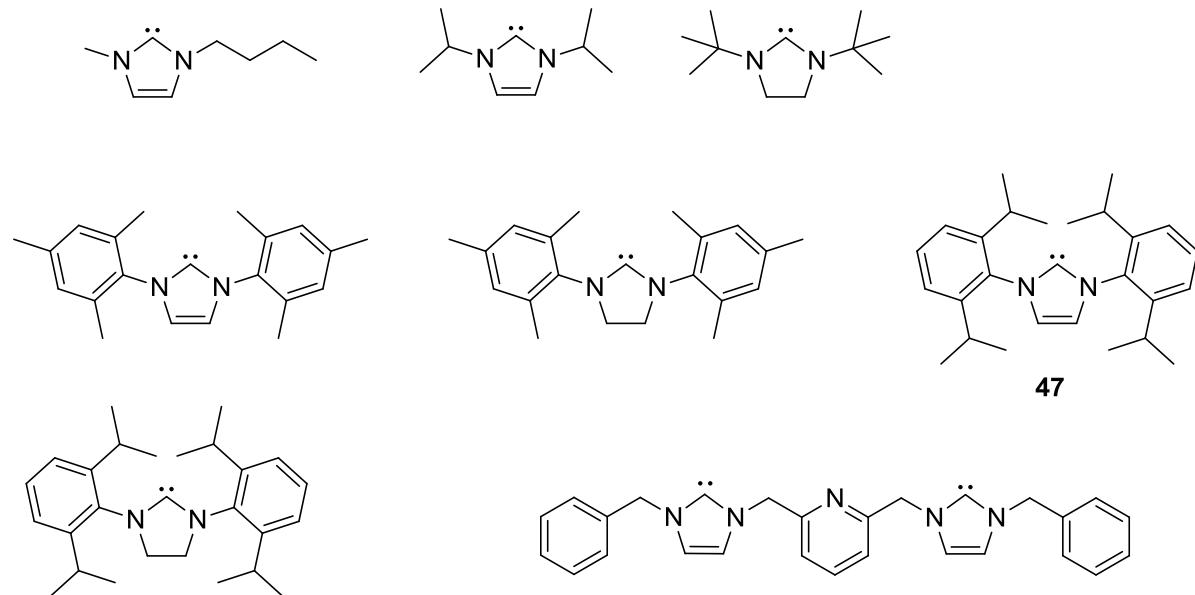
Fructose dehydration in [BMIm]Cl in combination with various homogeneous and heterogeneous catalysts by Qi *et al.* led to HMF yields around 80%.³⁴⁶ With 1 weight equivalent of Amberlyst 15 in a 5 wt% fructose mixture yielded 83% HMF at 100% conversion at 80 °C after 10 min. Increasing the initial fructose concentration resulted in a gradual decrease in HMF yield, leading to a 5% drop in HMF yield at a tenfold increase of initial fructose concentration, past which no additional drop was observed. A similar trend was observed by Yong *et al.*¹⁴³ The ionic liquid was recycled successfully at least seven times. HMF was shown to be stable under reaction conditions in the absence of fructose and water. Water started having a negative effect on the HMF yields when the initial concentration was higher than 5%. A later publication by the same group reported a 78% HMF yield by microwave heating of 5 wt% fructose in [BMIm]Cl with 20 mol% CrCl₃ at 100 °C for 1 min.³⁴⁷ Furthermore Qi published a study on fructose dehydration in various imidazolium based ionic liquids, catalysed by sulfated zirconia (SO₄²⁻/ZrO₂).³⁴⁸ From a 5 wt% fructose solution in [BMIm]Cl with 40 wt% SO₄²⁻/ZrO₂ 88% HMF yield was obtained at 96% conversion after 30 min at 100 °C. With ZrO₂ in [BMIm]Cl under the same conditions a HMF yield of 55% at 60% conversion was obtained, leading to the same

selectivity of around 90%. This showed that the reaction rate was improved by using sulfuric acid treated ZrO_2 .

Recently a number of articles have been published in which heterogeneous acid catalysts were applied for fructose dehydration in ionic liquids,³⁴⁹⁻³⁵¹ reporting very high yields of HMF, up to 94%.³⁵¹

Qi *et al.* also performed dehydration experiments at room temperature.¹⁷⁴ This required the addition of a co-solvent, which decreased the activity of the system, in order to allow proper stirring. Only a small amount of 0.15 molar equivalents of co-solvent was added. Acetone, DMSO, methanol, ethanol, ethyl acetate and supercritical CO_2 (150 Bar at 35 °C) were tested, in experiments with 5 wt% fructose in the presence of 100 wt% Amberlyst 15 and 6 h reaction time. The HMF yields were 78-82% at 89-95% conversion.

Yong *et al.* applied N-heterocyclic carbenes (NHC) as ligands (Scheme 32) for chromium chlorides that were used as catalysts for fructose and glucose dehydration in ionic liquids.¹⁴³ A solution of 9 wt% fructose in 1-butyl-3-methyl-imidazolium chloride ($[\text{BMIm}] \text{Cl}$) was reacted in the presence of 9 mol% of NHC/Cr catalyst at 100 °C for 6 h. HMF yields over 95% were obtained from fructose for one of the NHC ligands (**47**, Scheme 32) in combination with either CrCl_2 or CrCl_3 . The best results were obtained with the most bulky types of NHC tested. The authors explain that this effect could be caused by the protection of the metal centre from steric crowding from the ionic liquid by the ligand.



Scheme 32. *N*-heterocyclic carbene ligands for CrCl_2 and CrCl_3 used as catalysts for fructose and glucose dehydration.¹⁴³

Wei *et al.* published work on fructose dehydration in [BMIm]Cl,²⁶⁹ catalysed by IrCl₃ and AuCl₃·HCl. After 3 h at 80 °C an HMF yield of 63% at 93% conversion and 22% at 50% conversion were obtained in the presence of 7 mol% IrCl₃ and AuCl₃·HCl respectively. With 10 mol% IrCl₃ an HMF yield of 86% was achieved at full conversion after 30 min, however no temperature was mentioned. The IrCl₃ catalysed system led to HMF yields of 70% at 100 °C and 65% at 120 °C, at around full conversion. In the case of AuCl₃·HCl it was suggested that only HCl plays a role and its additional effect disappears at higher temperatures because of the increased catalytic activity of the ionic liquid.

Zhang *et al.* investigated the use of polytungstic acid (PTA), encapsulated in a metal-organic framework built up from chromium carboxylate (MIL-101), as a catalyst for fructose dehydration to HMF.²²⁶ MIL-101 is a metal-organic framework with a chromium carboxylate cubic structure. Various encapsulated PTA (PTA/MIL-101) catalysts were tested and HMF yields as high as 80% at 87% conversion were obtained after 1 h in [EMIm]Cl at 80 °C. The chromium in the MIL-101 structure was found to be essentially inactive in fructose dehydration.

Ilgen *et al.* published work on highly concentrated low melting mixtures of sugars and several hydrogen bond donor and acceptor additives.³⁵² When using a fructose-*N,N,N',N'*-tetra-methylurea melt (9:1 w/w) in combination with FeCl₃ at 100 °C for 1 h an 89% HMF yield was obtained. Fructose-ChoCl (4:6 w/w) with 10 mol% *p*-Toluene sulfonic acid (*p*TsOH) yielded 67% HMF. Recently a comparable HMF yield 72% was reported using a very high fructose concentration in a ChoCl/CO₂ eutactic solvent system.³⁵³

In a 2:1 (w/w) mixture of water and 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate a 92% yield of HMF at 98% conversion was reported in the presence of 9 volumetric equivalents of MIBK after 2 h at 120 °C.³⁵⁴

Avantium patented the formation of HMF ethers and esters from fructose in ionic liquid by adding the appropriate alcohol or carboxylic acid to the ionic liquid.^{355a} In [EMIm]Cl-acetic acid (1:4 w/w) 4 wt% of fructose was reacted in the presence of 4 wt% CrCl₂ at 100 °C for 3 h, yielding 22% HMF and 72% AMF. Similarly, Kraus and co-worker were able to obtain EMF in 54% yield from fructose using imidazolium propanesulfonic acids in and ethanol, hexane mixture.^{289b}

Tables 27-29 give an overview of the results obtained in ionic-liquid based fructose dehydration. High yields, consistently over 65% have been reported. Some groups even reported yields in excess of 90%. The reaction temperatures were generally between 80-100 °C, which is similar to those used in the experiments in aprotic polar solvents and

significantly lower than those used in aqueous systems. The ionic liquids applied in this field of research are often Brønsted acidic, making them catalytically active in sugar dehydration. It is thus difficult to explain the large differences in the reported yields. A strong point in this system is the apparent stabilising effect of the ionic liquid on HMF, blocking rehydration reactions to, among others, levulinic acid.

Table 27. Fructose dehydration to HMF in ionic liquids without additional catalyst

Fructose concentration	Solvent	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
8 wt%	[BMIm]BF ₄ -DMSO (5:3 v/v)	80	32 h	36	-	-	331
23 wt% / 17 mol%	[HMIm]Cl	90	45 min	92	98	94	334
9 wt%	[EMIm]Cl	120	3 h	73	100	73	134
9 wt%	[EMIm]Cl	120	3 h	78	100	78	145
17 mol%	[HMIm]Cl	80	1 h	70	97	73	335
17 mol%	PyHCl	80	1 h	69	92	76	335
17 mol%	[BMIm]HSO ₄	80	1 h	57	100	57	335
17 mol%	ChoCl/citric acid	80	1 h	79	99	80	335
17 mol%	ChoCl/citric acid ^a	80	1 h	92	98	94	335
20 t%	ChoCl/CO ₂	120	1.5 h	72	-	-	353
9 wt%	[EMIm][HSO ₄] ^b	120	30 min	88	100	88	337
9 wt%	[BMIm]Cl	80	3 h	0	4	0	269

9 wt%	[BMIm]Cl	100	3 h	28	60	47	269
9 wt%	[BMIm]Cl, [HMIm]Cl	100	50 min	0	-	0	336
9 wt%	[BMIm]Cl	120	50 min	63	93	68	336
9 wt%	[HMIm]Cl	120	50 min	7	66	11	336
9 wt%	[BMIm]Cl	140	50 min	60	100	60	336
9 wt%	[HMIm]Cl	140	50 min	22	85	26	336
9 wt%	[BenzylMIm]Cl	140	50 min	53	100	53	336
9 wt%	[BMIm]Cl	120	3 h	48	100	48	269
5 wt%	[BMIm]Cl	100	5 min	0	-	0	268
40 wt%	H ₂ O/ [SBMIm][HSO ₄] 2:1 (w/w) ^c	120	2 h	92	98	94	354

a: continuous HMF extraction by ethyl acetate; *b:* 2.3 volume equivalents of MIBK as extraction solvent; *c:* 9 volume equivalents of MIBK as extraction solvent

Table 28. Fructose dehydration to HMF in ionic liquids in the presence of homogeneous catalysts

Fructose concentration (wt%)	Solvent	Catalyst loading (mol%)	Catalyst (mol%)	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
9	[BMIm]Cl	AuCl ₃ ·HCl	7	80	3 h	22	50	44	269
9	[BMIm]Cl	AuCl ₃ ·HCl	7	100	3 h	44	88	50	269
9	[BMIm]Cl	AuCl ₃ ·HCl	7	120	3 h	48	98	49	269
9	[EMIm]Cl	CrCl ₂	6 mol%	80	3 h	60	100	60	142
9	[EMIm]Cl	CrCl ₂	6	80	3 h	65 ^b	92	71	134
9	[EMIm]Cl	CrCl ₃	6	80	3 h	69 ^c	92	75	134
5	[BMIm]Cl	CrCl ₃	20	100 ^a	1 min	78	-	-	347
9	[BenzylMIm]Cl	CrCl ₃ ·6 H ₂ O	10	100	2 h	71	100	71	336
9	[BMIm]Cl	CrCl ₃ ·6 H ₂ O	10	100	2 h	75	100	75	336
9	[EMIm]Cl	CrCl ₃ ·6H ₂ O	6 mol%	80	30 min	80	100	80	142
9	[HMIm]Cl	CrCl ₃ ·6 H ₂ O	10	100	2 h	44	92	47	336

9	[HMIIm]Cl	CrCl ₃ •6 H ₂ O	25	100	2 h	62	100	62	336
5	[BMIIm]Cl	CuCl ₂	18	80	10 min	80	94	85	346
90	<i>N,N,N',N'</i> -tetramethylurea	FeCl ₃	10	100	1 h	89	-	-	352
5	[BMIIm]Cl	GeCl ₄	10	50	20 min	84	96	88	268
5	[BMIIm]Cl	GeCl ₄	10	80	5 min	90	100	90	268
5	[BMIIm]Cl	GeCl ₄	10	100	5 min	92	100	92	268
5	[BMIIm]Cl	H ₂ SO ₄	18	80	10 min	70	82	86	346
9	[BenzylMIIm]Cl	H ₂ SO ₄	10	100	50 min	77	100	77	336
9	[BMIIm]Cl	H ₂ SO ₄	10	100	50 min	83	100	83	336
9	[HMIIm]Cl	H ₂ SO ₄	10	100	50 min	7	55	13	336
9	[HMIIm]Cl	H ₂ SO ₄	25	100	50 min	82	100	82	336
5	[BMIIm]Cl	HfCl ₄	10	100	5 min	58	100	58	268
9	[BMIIm]Cl	IrCl ₃	7	80	3 h	63	93	68	269
9	[BMIIm]Cl	IrCl ₃	7	100	3 h	70	98	72	269

9	[BMIm]Cl	IrCl ₃	7	120	3 h	65	100	65	269
9	[BMIm]Cl	IrCl ₃	10	-	0.5 h	86	100	86	269
9	[BMIm]Cl	NHC/CrCl ₂	9	100	6 h	96	-	-	143
9	[BMIm]Cl	NHC/CrCl ₂	9	100	6 h	89	-	-	143
9	[BMIm]Cl	NHC/CrCl ₃	9	100	6 h	96	-	-	143
9	[BMIm]Cl	NHC/CrCl ₃	9	100	6 h	90	-	-	143
9	[EMIm]Cl	PtCl ₂	6	80	3 h	83	99	84	134
8	[BMIm]BF ₄ ⁻ DMSO (5:3 v/v)	PTSA	10	80	32 h	68	-	-	331
40	ChCl	pTsOH	10	100	0.5 h	67	-	m/a	352
17	[EMIm]BF ₄	SnCl ₄	10	100	3 h	62	100	62	144

a: heating by microwave irradiation; b: 6% glucose yield; c: 3% glucose yield

Table 29. Fructose dehydration to HMF in ionic liquids in the presence of heterogeneous catalysts

Fructose conc. (wt%)	Solvent	Catalyst	Catalyst concentration (wt%)	Temperature (°C)	Reaction Time	Yield (%)	Conv. (%)	Sel. (%)	Ref.
5	[BMIm]Cl:MeOH (6.6:1 n/n)	Amberlyst 15	100	25	6 h	82	93	88	174
8	[BMIm]BF ₄	Amberlyst 15	267	80	3 h	52	-	-	331
8	[BMIm]BF ₄ -DMSO (5:3 v/v)	Amberlyst 15	100	80	32 h	75	-	-	331
8	[BMIm]BF ₄ -DMSO (5:3 v/v)	Amberlyst 15	200	80	32 h	87	-	-	331
5	[BMIm]Cl	Amberlyst 15	100	80	10 min	83	99	85	346
5	[BMIm]Cl	Dowex 50WX8	100	80	10 min	82	92	90	346
9	[EMIm]Cl	PTA/MIL-101 ^b	40	80	1 h	80	87	92	226
5	[BMIm]Cl	SO ₄ ²⁻ /ZrO ₂	40	100 ^a	30 min	88	96	92	348
5	[HexylMIm]Cl	SO ₄ ²⁻ /ZrO ₂	40	100 ^a	30 min	89	100	89	348
5	[BMIm]Cl	ZrO ₂	40	100 ^a	30 min	55	60	91	348

a: heating by microwave irradiation; *b*: MIL-101 encapsulated polytungstic acid

Glucose dehydration in ionic liquids

In 2007 a publication by Zhao *et al.* marked a breakthrough in sugar dehydration to HMF by producing HMF in approximately the same yield from fructose and glucose.¹³⁴ From 9 wt% glucose in [EMIm]Cl with 1 mol% CrCl₂ an HMF yield of 68% at 94% conversion was obtained at 100 °C after 3 h. From fructose under comparable conditions, though at 80 °C, the HMF yield was 65% at 92% conversion in the presence of CrCl₂. Cao *et al.* performed similar experiments in various ionic liquids with CrCl₃•6H₂O at 120 °C for 1 h, obtaining HMF yields around 60%.³³⁶ With the same catalyst in tetraethylammonium chloride 71% HMF yield was achieved after 10 min at 130 °C.³⁵⁶ Also work in tetrabutylammonium chloride in combination with CrCl₂ was performed with a reported HMF yield 56%.³⁵⁷

As discussed in section 2.4.3.2, Yong *et al.* used chromium chlorides in fructose and glucose dehydration in ionic liquids in combination with N-heterocyclic carbene (NHC) ligands, which are described in Scheme 32.¹⁴³ A solution of 9 wt% glucose in 1-Butyl-3-methyl imidazolium chloride ([BMim]Cl) was reacted in the presence of 9 mol% of NHC/Cr catalyst at 100 °C for 6 h. HMF yields of around 80% were obtained from fructose using a number of different NHC ligands in combination with either CrCl₂ or CrCl₃. A separate experiment under the exact same conditions, but under argon instead of air, gave only 65% HMF yield from glucose, leading to the suggestion that oxygen played a role in the catalytic process, though it is unclear how.

Lima *et al.* used 6 mol% of CrCl₃ in 0.67 M glucose in a [BMIm]Cl and toluene mixture to obtain 91% HMF yield at 91% conversion after 4 h at 100 °C.³³⁷

Hu *et al.* applied SnCl₄ as a catalyst for glucose dehydration in a number of ionic liquids and DMSO.¹⁴⁴ Reactions were performed in [EMIm]BF₄ with glucose concentrations between 9 and 26 wt% and 10 mol% SnCl₄ at 100 °C for 3 h. The HMF yield with 9 wt% glucose was 53% at 97% conversion. HMF yields around 60% were reported for glucose concentrations of 13-26 wt%. With fructose, sucrose and cellobiose they reported essentially the same yields.

Zhang *et al.* applied GeCl₄ in [BMIm]Cl to glucose dehydration.²⁶⁸ The effect of temperature, catalyst loading and water content were investigated. When varying the temperature between 80 °C and 120 °C it was shown that both activity and selectivity improved with temperature, whereas increasing the catalyst loading from 5 wt% to 15 wt% only showed a slight effect in initial reaction rate, but not on the selectivity. From a 5 wt% reaction mixture an HMF yield of 48% was obtained at 99% conversion after 30 min at 120

°C. The formation of humins was also observed. The addition of water to the reaction mixture had a negative effect on the HMF selectivity and conversely the addition of mol sieves led to an increase in HMF yield. Experiments in other alkyl imidazolium chloride ionic liquids showed a decrease in HMF selectivity with increasing alkyl chain length. This was later also reported by Shi *et al.* for fructose dehydration in imidazolium based ionic liquids.³⁵⁸ Replacement of the chloride counter ion by non-halides had a detrimental effect on the activity and selectivity of the system. Glucose conversion to HMF in an ionic liquid/CrCl₃ system under microwave irradiation (MI) was investigated by Li *et al.*²⁵² An HMF yield of 91% was reported after reacting 9 wt% glucose in [BMIm]Cl for 1 min under 400 W MI. When applying an oil bath at 100 °C for 60 min only 17% HMF was obtained.

Qi *et al.* published work on glucose dehydration in an ionic liquid system resembling that of Zhao,¹³⁴ using [BMIM]Cl in combination with CrCl₃.³⁴⁷ HMF formation at temperatures between 90 and 140 °C was studied using 5 wt% glucose in ionic liquid containing around 18 wt% CrCl₃. The highest yield of around 70% at 95% conversion was obtained at 120 °C after 10 min and at 140 °C after 30 s. HMF was found to be stable under the reaction conditions in the absence of glucose. Fructose, at a yield of less than 5%, was mentioned as one of the by-products. In recycling experiments a gradual decrease in activity was observed after the third cycle. The authors observed a colour change in the ionic liquid to deep brown that remained upon recycling, which was attributed to soluble humin. Similar ionic liquids with HSO₄⁻ as counterion instead of Cl⁻ performed significantly worse with yields below 10% at conversions over 80%. The authors provide an explanation for the difference between Cl⁻ and HSO₄⁻ based on the difference in acidity. According to other work the metal concentration in the ionic liquid determines if it behaves as a base or as an acid.³⁵⁹ Under the conditions that were used it behaves as a base, explaining its ability to isomerise glucose as described by Zhao.^{134,347} HSO₄⁻, however, was mentioned to be a rather strong Brønsted acid, making the ionic liquid/CrCl₃ mixture too acidic for the selective dehydration to HMF.

A bifunctional catalyst system was applied by Qi *et al.*, using heterogeneous ZrO₂ as a base to catalyse isomerisation to fructose, which subsequently converted to HMF in a mixture of [HexylMIm]Cl and water.³⁶⁰ The highest HMF yield obtained was 53% at 92% glucose conversion in a 1:1 (w/w) mixture of [HexylMIm]Cl and water with 40 wt% ZrO₂ after 10 min at 200 °C.

Recently a very high HMF yield of 68% was reported by Guo *et al.*, applying a lignin-derived solid acid catalyst in DMSO-[BMIm]Cl mixture.³⁶¹ This is a surprising result, since

the state of the art clearly indicates that a basic or Lewis acid catalyst is required in combination with an acid catalyst to obtain such high HMF yields from glucose.

Chidambaram and Bell published work on glucose dehydration to HMF and a subsequent hydrogenation to 2,5-dimethylfuran (DMF) in two steps.³⁶² For the dehydration to HMF a number of mineral acids, organic acids and heteropolyacids was tested in [BMIm]Cl at 1 mol% acid concentration for 3 h at 120 °C. With 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) a yield of 66% at 82% conversion was obtained and with H_2SO_4 a yield of 61% at 93% conversion was claimed. The highest HMF yield of 61% at 93% glucose conversion was obtained in [BMIm]Cl, with 1 mol% H_2SO_4 as catalyst at 120 °C after 3 h.³⁶² Zhang's publication reported only 10% HMF yield at >90% glucose conversion under similar conditions with [EMIm]Cl as ionic liquid at 100 °C.¹³⁴ Chidambaram and Bell tested a number of heteropolyacids, obtaining 66% HMF yield at 82% conversion with $H_3PW_{12}O_{40}$.³⁶² An HMF yield of 63% at 71% conversion was obtained with $H_3PMo_{12}O_{40}$.³⁶² In [EMIm]Cl a 59% HMF yield at 66% conversion was reported. An improvement to 97% HMF yield at 99% conversion was claimed when the experiment was performed in the presence of acetonitrile.³⁶² Differences in activity were found for different types of mineral acid with similar acidity in water. The role of the counterion in the catalysis and a difference in acidic behaviour in ionic liquids were mentioned as possible causes for this phenomenon.

In a publication by Ståhlberg *et al.* ionic liquids were used as solvents in combination with lanthanide catalysts in order to convert glucose to HMF. A 24% HMF yield at 65% conversion was obtained with $Yb(OTf)_3$ in [BMIm]Cl.³⁶³ In contrast to findings by Zhang¹³⁴ longer alkyl chains on the imidazolium ionic liquid were found to increase the activity of the system.

Ståhlberg also applied boric acid as a catalyst at 120 °C, reporting an optimum boric acid/glucose ratio between 0.8 and 1.¹⁴⁵ With 1 eq boric acid an HMF yield of 40% at 87% conversion was obtained after 3 h at 120 °C. With 0.8 eq boric acid 41% HMF yield at 95% conversion was reported. The HMF yield decreased with increasing boric acid concentrations, which is explained by the formation of more stable sugar-boric acid complexes that inhibit dehydration to HMF. It was also shown that the chloride counterion plays an important role in the process, as [EMIm] type ionic liquids with non-halide counterions, apart from 6% HMF yield with sulfonates, did not yield any HMF. Recently Kokhlova *et al.* performed an NMR monitoring of carbohydrate dehydration with boron derivatives in ionic liquids, presenting very high conversions.³⁶⁴

Ilgen *et al.* obtained 45% HMF yield from glucose-choline chloride (4:6 w/w) melt with 10 mol% CrCl₂ at 110 °C after 1 h.³⁵² With CrCl₃ in the yield was only 31%. The conversions were not reported.

Zhang and Zhao published work on glucose dehydration in [BMIm]Cl, catalysed by CrCl₃ immobilised on hydroxyapatite.³⁶⁵ With 5 wt% glucose and 60 wt% catalyst an HMF yield of 40% was obtained at 78% conversion after 2.5 min at 400 W microwave irradiation. In the absence of catalyst 5% HMF was obtained at 81% conversion after 3 min and with chromium-free hydroxyapatite the yield was 8% at 81% conversion.

Avantium patented the formation of HMF ethers and esters from glucose in ionic liquid by adding the appropriate alcohol or carboxylic acid to the ionic liquid.³⁵⁵ In [EMIm]Cl-acetic acid (1:4 w/w) 4 wt% of glucose was reacted in the presence of 4 wt% CrCl₂ at 100 °C for 3 h, yielding 1.3% HMF and 5.1% AMF.

Table 30 provides an overview of the research on glucose dehydration in ionic liquids. It is clear from multiple publications that chromium plays an important role in obtaining high HMF yields from glucose. The HMF yields in the presence of CrCl₂ or CrCl₃ are in the same region as those obtained from fructose in ionic liquids. The differences in activity between CrCl₂ and CrCl₃ are not significant. This phenomenon has been researched by Zhang *et al.*, who compared the activity of CrCl₂, CrCl₃ and CrCl₃•6H₂O.¹⁴² The initial rate of glucose conversion was highest for CrCl₃•6H₂O, followed by CrCl₂ and CrCl₃ respectively, with the latter showing an induction period. The CrCl₃ was observed to dissolve much slower into the reaction mixture than the other CrCl₂ and CrCl₃•6H₂O, explaining the lower initial conversion rate. The system with Cr³⁺ furthermore led to a significantly higher HMF yield of 72% at 97% conversion than 60% HMF yield at 93% conversion obtained from the Cr²⁺ system.

What the publications by Zhang¹³⁴ and Pidko¹³⁶ and Hu¹⁴⁴ have in common is the absence of an added Brønsted acid, so the actual dehydration could take place in a number of ways. As none of the three publications report the presence of fructose in the reaction mixture, starting from glucose, it is also possible that the dehydration takes place from an intermediate species instead of fructose. Given the fact that regular Brønsted acid catalysed dehydration of fructose yields substantial amounts of HMF (depending on the solvent) in the absence of an isomerisation catalyst like CrCl₂ or SnCl₄ and glucose does not, it appears to be more likely that CrCl₂ and SnCl₄ function purely as an isomerisation catalyst. What catalyses the actual dehydration is not yet clear. It could be that free Cl⁻ generates enough hydrochloric acid.

Table 30. Glucose dehydration to HMF in ionic liquids

Glucose conc. (wt%)	Solvent	Catalyst	Catalyst concentration	T (°C)	Reaction Time	Yield (%)	Conv. (%)	Sel. (%)	Ref.
8	[BMIm]Cl	CF ₃ COOH	1 mol%	120	3 h	44	58	75	362
8	[BMIm]Cl	CF ₃ SO ₃ H	1 mol%	120	3 h	40	87	46	362
8	[BMIm]Cl	CH ₃ SO ₃ H	1 mol%	120	3 h	42	73	58	362
9	[BMIm]Cl	Cr(NO ₃) ₃	7 mol%	100	3 h	37	82	45	269
9	[EMIm]Cl	CrCl ₂	6 mol%	100	3 h	62	93	67	142
9	[EMIm]Cl	CrCl ₂	6 mol%	100	3 h	68	94	72	134
40	ChoCl	CrCl ₂	10 mol%	110	1 h	45	-	-	352
2.2 M	NBu ₄ Cl	CrCl ₂	10 mol%	110	4 h	54	-	-	357
5	[BMIm]Cl	CrCl ₃	20 mol%	90 ^a	1 h	40	51	80	347
9	[BMIm]Cl	CrCl ₃	3.6 wt%	100	1 h	17	-	-	252
5	[BMIm]Cl	CrCl ₃	20 mol%	100 ^a	30 min	56	77	73	347

5	[BMIm]Cl	CrCl ₃	20 mol%	100 ^a	1 h	67	85	78	347
9	[BMIm]Cl	CrCl ₃	7 mol%	100	3 h	35	79	45	269
9	[EMIm]Cl	CrCl ₃	6 mol%	100	3 h	44	72	62	134
40	ChoCl	CrCl ₃	10 mol%	110	1 h	31	-	-	352
5	[BMIm]Cl	CrCl ₃	20 mol%	120 ^a	10 min	69	94	73	347
23	[BMIm]Cl	CrCl ₃	20 mol%	120 ^a	10 min	55	97	56	347
5	[BMIm]Cl	CrCl ₃	10 mol%	120 ^a	10 min	66	88	75	347
9	[BMIm]Cl ^b	CrCl ₃	6 mol%	120	4 h	91	91	100	337
5	[BMIm]HSO ₄	CrCl ₃	20 mol%	120 ^a	10 min	5	86	6	347
5	[EMIm]Cl	CrCl ₃	20 mol%	120 ^a	10 min	72	97	74	347
5	[HexylMIm]Cl	CrCl ₃	20 mol%	120 ^a	10 min	63	94	67	347
5	[BMIm]Cl	CrCl ₃	20 mol%	140 ^a	0.5 min	71	96	74	347
9	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	1 min	91	-	-	252
9	[EMIm]Cl	CrCl ₃ •6H ₂ O	6 mol%	100	3 h	72	97	74	142
9	[BenzylMIm]Cl	CrCl ₃ •6H ₂ O	25 mol%	120	1 h	65	-	-	336

9	[BMIm]Cl	CrCl ₃ •6H ₂ O	25 mol%	120	1 h	67	-	-	336
9	NEt ₄ Cl	CrCl ₃ •6H ₂ O	10 mol%	130	10 min	71	-	-	356
5	[BMIm]Cl	GeCl ₄	10 mol%	100	75 min	38	93	42	268
5	[BMIm]Cl ^c	GeCl ₄	10 mol%	100	75 min	48	93	52	268
5	[BMIm]Cl	GeCl ₄	10 mol%	120	30 min	48	99	48	268
8	[BMIm]Cl	H ₂ SO ₄	1 mol%	120	3 h	61	93	66	362
9	[BMIm]Cl	H ₂ SO ₄	10 wt%	Unknown ^a	1 min	49	-	-	252
9	[BMIm]Cl	H ₃ BO ₃	100 mol%	120	3 h	22	68	32	145
9	[BMIm]Cl	H ₃ BO ₃	80 mol%	120	3 h	14	47	30	145
9	[EMIm]Cl	H ₃ BO ₃	100 mol%	120	3 h	40	87	46	145
9	[EMIm]Cl	H ₃ BO ₃	80 mol%	120	3 h	41	95	43	145
9	[HexylMIm]Cl	H ₃ BO ₃	80 mol%	120	3 h	32	68	47	145
9	[HMIm]Cl	H ₃ BO ₃	80 mol%	120	3 h	19	95	20	145
9	[OctylMIm]Cl	H ₃ BO ₃	80 mol%	120	3 h	26	63	41	145
8	[BMIm]Cl	H ₃ PMo ₁₂ O ₄₀	1 mol%	120	3 h	63	71	89	362

8	[BMIm]Cl	H ₃ PW ₁₂ O ₄₀	1 mol%	120	3 h	66	82	81	362
8	[BMIm]Cl	HNO ₃	1 mol%	120	3 h	43	56	77	362
5	[BMIm]Cl	Hydroxyapatite with 4.6 wt% Cr(III)	60 wt%	Unknown ^a	2.5 min	40	78	52	365
9	[BMIm]Cl	NHC/(CrCl ₂) ₂	9 mol%	100	6 h	81	-	-	143
9	[BMIm]Cl	NHC/CrCl ₂	9 mol%	100	6 h	81	-	-	143
9	[BMIm]Cl	NHC/CrCl ₂	9 mol%	100	6 h	80	-	-	143
9	[BMIm]Cl	NHC/CrCl ₃	9 mol%	100	6 h	78	-	-	143
9	[BMIm]Cl	NHC/CrCl ₃	9 mol%	100	6 h	78	-	-	143
9	[EMIm]BF ₄	SnCl ₄	10 mol%	100	3 h	53	97	55	144
9	[BMIm]Cl	Yb(OTf) ₃	10 mol%	140	6 h	24	65	37	363
9	[EMIm]Cl	Yb(OTf) ₃	10 mol%	140	6 h	10	63	16	363
2	[HexylMIm]Cl/H ₂ O 1:1 w/w	ZrO ₂	40 wt%	200	10 min	53	92	56	360
10	DMSO/[BMIm]Cl	Lignin-derived solid acid	50 wt%	160	50	68	99	69	350

a: heating by microwave irradiation; *b*: 2.3 volume equivalents of MIBK as extraction solvent; *c*: molsieves used for water adsorption

The dehydration of disaccharides and polysaccharides in ionic liquids

Ionic liquids have also been used as solvents and catalysts for polymeric carbohydrates, like cellulose and inulin. Because this is a review on HMF, only work focussed on HMF synthesis from these carbohydrates will be discussed. Research on carbohydrate dissolution and hydrolysis are not covered by this review.

Qi *et al.* performed inulin dehydration in [BMIm]Cl in which 5% inulin was dissolved along with ten equivalents of water relative to the amount of fructose units.³⁶⁶ Amberlyst 15 and a number of Brønsted acidic ionic liquids were tested as catalysts at 80 °C. A 67% HMF yield at full conversion was obtained with 100 wt% Amberlyst 15 after 3 h. With 33 mol% [HMIm][HSO₄], [EMIm][HSO₄] and [BMIm][HSO₄] HMF yields of around 55% at full conversion were obtained after 3 h. Fructose formation to a maximum of around 40% was observed in all reactions, but the rate of fructose formation and dehydration were different for all catalysts. An increase alkyl chain length of the ionic liquid corresponds with a decrease in acidity and therefore also a decrease in reaction rate. Experiments in which [BMIm]Cl was replaced entirely by a Brønsted acidic ionic liquid, with [HSO₄⁻] as counterion, showed high fructose yields in the initial stages of the reaction.³⁶⁶ For [HMIm][HSO₄] a 55% fructose and 10% HMF yield were obtained within 3 min. In [EMIm][HSO₄] and [BMIm][HSO₄] the fructose yield exceeded 80% in the first 3-5 min of the reaction. The dehydration rate decreased with increasing alkyl chain length and in [HMIm][HSO₄], [EMIm][HSO₄] and [BMIm][HSO₄] the HMF yields were 60%, 52% and 37% respectively after 3 h. Significant amounts of fructose were still present after 3 h in [EMIm][HSO₄] and [BMIm][HSO₄]. In the presence of Amberlyst 15 as a catalyst, 60-65% HMF yields were obtained within 10 min at 100 °C. A positive influence of the chloride counterion in the dehydration rate of fructose to HMF was suggested as it was observed that the dehydration proceeded at a faster rate in the [BMIm]Cl based experiments. This is consistent with observations by Binder and Raines with regard to the role of halide ions in fructose dehydration to HMF.¹¹⁹ Qi *et al.* reported an HMF yield of 82% by applying a two-step procedure in which 5 wt% inulin was first hydrolysed with 20 molar equivalents of water in [BMim][HSO₄] at 80 °C for 5min, followed by addition of an equal weight of [BMim]Cl and 100 wt% Amberlyst 15 for dehydration at 100 °C for 60 min.³⁶⁶ They also observed brown colouring of the reaction mixture due to humin formation.

Use of inulin/ChoCl (1:1 w/w) melts by Ilgen *et al.* resulted in significant HMF yields around 55% with Amberlyst 15, FeCl₃ and *p*-toluene sulfonic acid as catalysts at 90 °C for 1

h.³⁵² A sucrose/ChoCl (1:1) melt, catalysed by CrCl₂ and CrCl₃ yielded 62% and 43% HMF respectively after 1 h at 100 °C.

Hu *et al.* applied catalyst systems that were found to be efficient in fructose and glucose dehydration on polysaccharides.^{144,367} Choline Chloride was used in combination with oxalic acid (ChoCl/OxAc) and citric acid (ChoCl/CitAc) in inulin dehydration.³⁶⁷ Both organic acids were used as hydrates, providing water for the hydrolysis of the polysaccharides. The ChoCl/OxAc system yielded 56% HMF at complete carbohydrate conversion after 2 h at 80 °C. The ChoCl/CitAc system yielded 51% HMF after 2 h at about 90% carbohydrate conversion. The HMF yield in ChoCl/oxalic acid was improved to 64% at full conversion by applying a two-phase system with ethyl acetate as an extracting solvent. Inulin dehydration in [EMIm]BF₄ in the presence of 10 mol% SnCl₄ yielded 40% HMF at 100% conversion with 17 wt% substrate at 100 °C for 3 h.¹⁴⁴ Reactions with sucrose and cellobiose under the same conditions yielded 65% and 57% HMF respectively at full conversion. A 9 wt% reaction mixture with starch yielded 47% HMF after 24 h at 100 °C.

Jiang *et al.* performed hydrolysis of cellulose in [BMim]Cl, catalysed by various Brønsted acidic ionic liquids.³⁶⁸ HMF yields around 15% were obtained after 1 h at 100 °C with sulfonic acid group containing imidazolium based ionic liquids as the catalysts.

Zhang and co-workers used the system they had developed for the conversion of glucose for the direct conversion of cellulose into HMF.^{369,370} Thus, 6 mol% (based on glucose monomers) of a CuCl₂-CrCl₂ mixture of metal chlorides with a Cu-Cr ratio of 17:83 (n/n) in [EMIm]Cl was used. With a cellulose concentration of 10% at 120 °C for 8 h an HMF yield of 55% was obtained.³⁶⁹ The catalyst in the ionic liquid could be recycled 12-fold without apparent loss of activity.

Li *et al.* investigated CrCl₃-catalysed cellulose dehydration in [BMIm]Cl under 400 W microwave irradiation.²⁵² From different types of cellulose HMF yields between 53% and 62% were obtained with 9 wt% substrate and 3.6 wt% CrCl₃ after 2 min. The authors propose the same mechanism for glucose dehydration as Zhang,¹³⁴ but additionally propose a role for CrCl₃ in cellulose hydrolysis.²⁵² 2,2'-Bipyridine, a strong coordinating ligand, decreased the HMF yield to approximately 2%. The same system was applied in the direct dehydration of lignocellulosic biomass.³⁷¹ A 5 wt% concentration of untreated biomass was reacted for 3 min resulting in HMF yields of around 50% with regard to the estimated amount of hexose present in the sample. In addition, furfural, in yields of around 30% with respect to the estimated amount of pentose were found, originating from the hemi-cellulose present in the biomass. A temperature of approximately 200 °C was reached during 3 min microwave

irradiation. Model feedstock, consisting of cellulose and xylan, led to comparable yields of 53% HMF and 33% furfural after 2.5 min. Heating a reaction mixture of pine wood in ionic liquid with CrCl_3 with an oil bath for 6 min at 200 °C gave clearly lower yields of 35% HMF and 17% furfural.

Qi *et al.* published work on CrCl_3 -catalysed dehydration of di- and polysaccharides in [BMIM]Cl.³⁴⁷ At a 5 wt% substrate concentration with 20 mol% CrCl_3 sucrose yielded 76% HMF after 5 min at 100 °C.³⁴⁷ Reactions with cellobiose and cellulose yielded around 55% HMF at 140 °C after 5 min and 150 °C after 10 min respectively.

Wang *et al.* reported HMF yields of around 60% from cellulose by reacting 2.5 wt% cellulose in [BMIM]Cl containing different ratio's of CrCl_3 and metal chloride (LaCl_3 , LiCl or LiBr), with a combined 100 mol% loading, at 140 °C for 40 min in the presence of 10 wt% of water (relative to cellulose).³⁷² The best results were generally obtained with a 1:1 mixture of CrCl_3 and metal chloride. The total reducing sugar (TRS) yield was typically around 30%. Reducing sugars are sugars that contain an aldehyde group or can form one via isomerisation. With wheat straw similar yields were obtained after 15 min at 160 °C. At 120 °C Hsu *et al.* reported 21% HMF yield from cellulose in [EMIM]Cl in the absence of catalyst.³⁷³

Chun *et al.* reported work on starch dehydration in 1-octyl-3-methylimidazolium chloride ([OMIm]Cl) in combination with aqueous HCl solution an ethyl acetate in a 4:5:0.8 ratio (w/w/w).³⁷⁴ When 0.5 M HCl was applied on 10 wt% starch in the described [OMIm]Cl-HCl_(aq)-EtOAc mixture, 30 wt% HMF was obtained after 1 h at 120 °C. When 20 wt% CrCl_2 was added, the HMF yield increased to 60%. When a specific starch, namely tapioca starch, was used a 73 wt% yield was reported. With 10 wt% sucrose in a 1:1 (w/w) mixture of [OMIm]Cl and 0.5 M HCl a 79 wt% HMF yield was reported after 1 h at 120 °C, but no conversion was reported.³⁷⁵ No conversions and thus no selectivities are reported in this work.

An HMF yield of 89% was reported from cellulose by Zhang *et al.* by reacting 17 wt% cellulose in [EMIM]Cl in the presence of 10 mol% CrCl_2 at 120 °C after 6 h. The yield was determined by acetone extraction, followed by column purification and ¹H-NMR analysis.³⁷⁶

A combined $\text{CrCl}_2/\text{H-Y}$ zeolite system was used by Tan *et al.* in which the zeolite catalysed the hydrolysis of cellulose and the CrCl_2 catalysed the conversion of glucose to HMF.³⁷⁷ With 6 wt% of cellulose in [BMIM]Cl in the presence of 100 wt% of zeolite and 393 mol% CrCl_2 , 34% isolated HMF was obtained after 6 h at 100 °C. When an NHC, namely 1,3-bis(2,6-diisopropylphenyl)imidazolylidene (Ipr), was applied as ligand for CrCl_2 , a 37%

HMF yield was reported. An increase in the reaction time to 12 h, with intermittent ether extraction, increased the yield to 48%.

A significant number of recent publications also mention the combination of ionic liquid and chromium salts for producing HMF from cellulose³⁷⁸⁻³⁷⁹⁻³⁸¹ and starch.³⁸² Tao *et al.* reported a high HMF yield of 48% from cellulose in SO₃H-functionalised ionic liquids in combination with MnCl₂.³⁸³

Tao *et al.* used manganese salts in 1-(4-sulfonic acid butyl)-3-methylimidazolium hydrogen sulfate ([SABMIm][HSO₄]), for the hydrolysis and subsequent dehydration of microcrystalline cellulose in the presence of water and MIBK.³⁸⁴ An IL-water-MIBK mass ratio of 2:1:6.4 was applied, leading to HMF yields of 27-37% at 68-89% conversion depending on the counterion, with consistent selectivity around 40% after 5 h at 150 °C. The yields were defined as weight of product divided by weight of starting material. Significant amounts of furfural and levulinic acid were also observed, with furfural yields of 9-18% and levulinic acid yields of 3-7%. The blank experiment led to 15% HMF yield at 70% conversion. The same experiments performed with CoCl₂ yielded 29% HMF at 81% conversion.³⁸⁵

Work on starch-rich acorn biomass by Lee *et al.* focussed on the application of chromium halide catalysts. Significant HMF formation was observed, but the definition of the yield was not clearly defined.³⁸⁶

Work on glucose-containing di- and polysaccharides by Ståhlberg in [EMIm]Cl, catalysed by 0.5 eq boric acid at 120 °C yielded 66% HMF from sucrose after 8 h, 33% HMF from maltose and 32% HMF from both starch and cellulose after 24 and 8 h respectively.¹⁴⁵ These yields are in line with what was obtained from glucose under similar conditions, but the reaction rates are lower. It is surprising to find a higher reaction rate for cellulose than for starch, because hydrolysis of starch is generally considered to be easier than the hydrolysis of cellulose. With GeCl₄ as catalyst in [BMIm]Cl, HMF yields of 55%, 41% and 35% were obtained from sucrose, cellobiose and cellulose respectively at almost full conversion by Zhang *et al.*²⁶⁸ The same conditions were applied as with glucose (See section 2.4.3.2). When considering a 48% HMF yield from glucose under the same conditions, the yields from cellobiose and cellulose are very good. However, a yield of around 75% should be expected from sucrose, because around 90% HMF was obtained from fructose and almost 50% was obtained from glucose.

Tables 31-33 provide an overview of the research on ionic liquid-based di- and polysaccharide dehydration to HMF. At relatively low temperatures (80-120 °C) HMF yields

over 50% have been reported. For a polyfructan like inulin this is not surprising, though for cellulose and lignocellulosic biomass this is a significant breakthrough. Part of this is caused by the fact that some ionic liquids are able to efficiently dissolve cellulose. This is then combined with the known effectiveness of chromium chloride as a catalyst for HMF production from glucose.

2.4.3.3 Conclusion on HMF production in ionic liquids

In general the selectivities and yields of HMF synthesis in ionic liquids from different types of biomass are high compared to the other systems discussed, with the exception of aprotic polar organic solvents like DMSO. Due to their unique dissolution properties, some ionic liquids could dissolve over 10 wt% cellulose (see Table 32), which is notoriously difficult to solubilise.

In general, hardly any levulinic acid formation has been reported in ionic liquid systems, even though water was present. Thus the ionic liquids apparently stabilise the formed HMF, preventing its rehydration. Brown colouration of the reaction mixtures was however generally observed, indicating formation of potentially polymeric byproducts.

This apparent stabilising effect also has a disadvantage, as it is difficult to separate the HMF from the ionic liquid, requiring large amounts of extracting solvent. Since ionic liquids have essentially no vapour pressure and HMF is heat sensitive, solvent evaporation and HMF distillation are off the table, leaving extraction as the only method for HMF purification.

Zhang *et al.* performed cellulose depolymerisation with [EMIm]Cl of different quality and from different suppliers.^{387,388} They reported clearly different results for different batches (purities) of the same ionic liquid. Because the ionic liquid is typically used as a solvent, it is used in large quantities compared to the amount of substrate; small impurities could therefore significantly influence its catalytic behaviour. This could, for instance, explain why Ståhlberg *et al.*³⁶³ and Zhao *et al.*¹³⁴ published contradictory findings with regard to the effect of the length of the alkyl chains on the imidazolium ionic liquid. Furthermore imidazolium based ionic liquids were recently shown to react with HMF at temperatures over 200 °C.³⁸⁹

In order to apply ionic liquids as reaction media for HMF production from biomass, highly efficient recycling is required because of their high cost price. This will present challenges when using untreated biomass feedstock, because these contain many inorganic (ash) and organic impurities that will have to be removed from the ionic liquid at some point.

Table 31. The dehydration of polysaccharides and disaccharides in ionic liquids, catalysed by ionic liquid

Substrate	Substrate conc.(wt%)	Solvent	Catalyst	Catalyst conc. (mol%)	T (°C)	Reaction Time (h)	Yield (%)	Conv. (%)	Sel. (%)	Ref.
Cellulose	8 ^d	[EMIm]Cl	-	-	120	3	21	-	-	373
Cellulose	4	[BMIm]Cl	[C ₄ H ₈ SO ₃ HMIm]Cl	300	100	1	15	-	-	368
Cellulose	4	[BMIm]Cl	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	300	100	1	13	-	-	368
Inulin	5	[BMIm]Cl ^b	[BMIm]HSO ₄	33	80	3	53	100 ^a	53	366
Inulin	5	[BMIm]Cl ^b	[EMIm]HSO ₄	33	80	3	55	100 ^a	55	366
Inulin	5	[BMIm]Cl ^b	[HMIm]HSO ₄	33	80	3	56	100 ^a	56	366
Inulin	5	[HMIm][HSO ₄] ^b	None	-	80	3	59	97 ^a	61	366
Inulin	5	[EMIm][HSO ₄] ^b	None	-	80	3	52	89 ^a	58	366
Inulin	5	[BMIm][HSO ₄] ^b	None	-	80	3	37	71 ^a	52	366
Starch	10	[OMIm]Cl/0.5 M HCl/EtOAc	None	-	120	1	30	-	-	374
Sucrose	20	[HMIm]Cl	None	-	90	0.5	52	100 ^c	50	334

a: conversion was given as the amount of converted fructose units; *b:* 10 molar equivalents of H₂O added relative to the amount of fructose units; *c:* 3% of obtained glucose was converted; *d:* 10 molar equivalents of H₂O present

Table 32. The dehydration of polysaccharides in ionic liquids, catalysed by homogeneous catalysts

Substrate	Substrate concentration (wt%)	Solvent	Catalyst	Catalyst concentration	Temperature	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Ref.
Cellobiose	5	[BMIm]Cl	CrCl ₃	20 mol%	120 ^a	10 min	49	-	-	347
Cellobiose	9	[BMIm]Cl ^b	CrCl ₃	6 mol%	120	4 h	50	-	-	337
Cellobiose	5	[BMIm]Cl	CrCl ₃	20 mol%	140 ^a	5 min	55	-	-	347
Cellobiose	5	[BMIm]Cl	GeCl ₄	10 mol%	120	30 min	41	99	41	268
Cellobiose	17	[EMIm]BF ₄	SnCl ₄	10 mol%	100	3 h	57	100	57	144
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	Co(NO ₃) ₂	6.5 mol%	150	5 h	19 ^d	51	37 ^d	385
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	CoCl ₂	6.5 mol%	150	5 h	29 ^d	81	36 ^d	385
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	CoSO ₄	6.5 mol%	150	5 h	24 ^d	85	28 ^d	385
Cellulose	17	[EMIM]Cl	CrCl ₂	10 mol%	120	3 h	82 ^e	-	-	376
Cellulose	17	[EMIM]Cl	CrCl ₂	10 mol%	120	6 h	89 ^e	-	-	376
Cellulose	2.5	[BMIm]Cl (10 wt% CrCl ₃ /LiCl)	50 mol%/50	140 ^a		40 min	62	-	-	372

		H ₂ O)		mol%							
Cellulose	5	[BMIm]Cl	CrCl ₃	20 mol%	150 ^a	10 min	54	-	-	-	347
Cellulose ^h	9	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	2 min	55	-	-	-	252
Cellulose	5	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	3 min	62	-	-	-	252
Cellulose ⁱ	9	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	2 min	55	-	-	-	252
Cellulose ^j	9	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	2 min	53	-	-	-	252
Cellulose	9	[EMIm]Cl	CuCl ₂ /PdCl ₂ (1:10)	18 mol%	120	1 h	18	-	-	-	390
Cellulose	5	[BMIm]Cl	GeCl ₄	10 mol%	120	30 min	35	97	36	36	268
Cellulose	9	[EMIm]Cl	H ₃ BO ₃	50 mol%	120	8	32	-	-	-	145
Cellulose	6	[BMIm]Cl	H-Y zeolite/CrCl ₂	100 wt% zeolite/393 mol% Cr	120	6 h	34 ^e	-	-	-	377
Cellulose	6	[BMIm]Cl	H-Y zeolite/Ipr-CrCl ₂ ^k	100 wt% zeolite/393 mol% Cr	120	6 h	37 ^e	-	-	-	377
Cellulose	6	[BMIm]Cl	H-Y	100 wt%	120	12 h	48 ^e	-	-	-	377

			zeolite/Ipr-CrCl ₂ ^k	zeolite/393 mol% Cr							
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	Mn(CH ₃ COO) ₂	6.5 mol%	150	5 h	32 ^{d,e}	84	39 ^d	384	
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	Mn(H ₂ PO ₄) ₂	6.5 mol%	150	5 h	31 ^{d,e}	79	39 ^d	384	
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	Mn(NO ₃) ₂	6.5 mol%	150	5 h	27 ^{d,e}	68	40 ^d	384	
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	MnCl ₂	6.5 mol%	150	5 h	37 ^{d,e}	89	42 ^d	384	
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	MnSO ₄	6.5 mol%	150	5 h	35 ^{d,e}	83	42 ^d	384	
Cellulose	14	[C ₄ H ₈ SO ₃ HMIm]HSO ₄	None	6.5 mol%	150	5 h	15 ^{d,e}	70	21 ^d	384,385	
Cellulose	9	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	2 min	61	-	-	252	
Corn Stalk	5	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	3 min	45	-	-	252	
Inulin	9	ChoCl	Citric Acid	600 mol%	80	2 h	51	100 ^g	56	367	
Inulin	9	ChoCl	Citric Acid	600 mol%	80	2 h	57	100 ^g	65	367	
Inulin	50	ChoCl ^f	FeCl ₃	10 mol%	90	1 h	55	-	-	352	
Inulin	5	ChoCl	Oxalic Acid	600 mol%	80	2 h	56	100	56	367	
Inulin	5	ChoCl ^c	Oxalic Acid	600 mol%	80	2 h	64	100	64	367	

Inulin	50	ChoCl ^f	<i>p</i> TsOH	10 mol%	90	1 h	57	-	-	352
Inulin	17	[EMIm]BF ₄	SnCl ₄	10 mol%	100	3 h	40	100	40	144
Maltose	9	[EMIm]Cl	H ₃ BO ₃	50 mol%	120	8	33	-	-	145
Pine wood	5	[BMIm]Cl	CrCl ₃	3.6 wt%	200	3 min	35	-	-	376
Pine wood	5	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	3 min	52	-	-	376
Rice Straw	5	[BMIm]Cl	CrCl ₃	3.6 wt%	Unknown ^a	3 min	47	-	-	376
Starch	10	[OctylMIm]Cl/0.5 M HCl/EtOAc	CrCl ₂	20 wt%	120	1 h	60	-	-	374
Starch	9	[EMIm]Cl	H ₃ BO ₃	50 mol%	120	24	32	-	-	145
Starch	9	[EMIm]BF ₄	SnCl ₄	10 mol%	100	24 h	47	100	47	144
Sucrose	9	[BMIm]Cl	AuCl ₃ ·HCl	7 mol%	100	3 h	36	-	-	269
Sucrose	50	ChoCl ^f	CrCl ₂	10 mol%	100	1 h	62	-	-	352
Sucrose	10	[OctylMIm]Cl/0.5 M HCl 1:1 w/w	CrCl ₂	20 wt%	120	1 h	79	-	-	375
Sucrose	5	[BMIm]Cl	CrCl ₃	20 mol%	100 ^a	5 min	76	-	-	347

Sucrose	50	ChoCl ^f	CrCl ₃	10 mol%	100	1 h	43	-	-	352
Sucrose	7	[BMIm]Cl ^b	CrCl ₃	6 mol%	120	4 h	100	100	100	337
Sucrose	5	[BMIm]Cl	GeCl ₄	10 mol%	120	30 min	55	98	56	268
Sucrose	9	[EMIm]Cl	H ₃ BO ₃	50 mol%	120	8	66	-	-	145
Sucrose	9	[BMIm]Cl	IrCl ₃	7 mol%	100	3 h	37	-	-	269
Sucrose	17	[EMIm]BF ₄	SnCl ₄	10 mol%	100	3 h	65	100	65	144
Tapioca	10	[OctylMIm]Cl/0.5 M HCl/EtOAc	CrCl ₂	20 wt%	120	1 h	73	-	-	374
Starch										
Wheat straw	2.5	[BMIm]Cl (10 wt% H ₂ O)	CrCl ₃ /LiCl	50 mol%/50 mol%	160 ^a	15 min	61	-	-	372

a: heating by microwave irradiation; *b*: 2.3 volume equivalents of MIBK used as extracting solvent; *c*: ethyl acetate used as extracting solvent ; *d*: in wt%; *e*: significant furfural yield (9-18%); *f*: melt; *g*: around 10% fructose left; *h*: avicel; *i*: sigmacel; *j*: N. spruce; *k*: 1,3-bis(2,6-diisopropylphenyl)imidazolylidene as N-heterocyclic ligand)

Table 33. The dehydration of inulin in ionic liquids, catalysed by Amberlyst 15

Inulin concentration (wt%)	Solvent	Amberlyst 15 loading (wt%)	Temperature (°C)	Reaction Time	Yield (%)	Conversion (%)	Selectivity (%)	Reference
5	[BMIm]Cl ^a	100	80	3 h	67	100 ^b	67	366
50	ChoCl ^c	10	90	1 h	54	-	-	352
5	[EMIm][HSO ₄] ^a	100	100	5 min	65	97 ^b	67	366
5	[BMIm][HSO ₄] ^a	100	100	10 min	61	97 ^b	63	366
2	[BMIm]Cl/[BMIm][HSO ₄] 1:1 w/w ^d	100	100	1 h	82	99 ^b	83	366

a: 10 molar equivalents of H₂O relative to the amount of fructose units; *b:* the conversion was given as the amount of converted fructose units; *c:* melt; *d:* pretreatment in [BMIm]HSO₄ for 5 min at 80 °C

2.5 Process technology

2.5.1 Introduction

This section focuses on HMF manufacturing methods and covers i) kinetic studies on HMF synthesis, ii) reactor configurations and designs, iii) separation and purification strategies, iv) pilot scale studies and v) an overview of HMF manufacturing costs. The most recent reviews covering this topic were published in 1990 by Kuster¹² and a mini review limited to the process technology of HMF synthesis in 2009 by Boisen *et al.*³⁹¹ Literature data until 29 July 2011 are included in this chapter. Details on the catalytic synthesis of HMF from lignocellulosic biomass using a wide range of types of catalysts and process conditions are provided in the Process Chemistry section. Some relevant features regarding solvents and catalyst selection, of prime importance for reactor- and process design, will be highlighted below. Here, a distinction based on reaction solvents is applied, i.e. i) aqueous systems, ii) mixed solvent systems and particularly biphasic systems involving water, and iii) non-aqueous systems including the application of ionic liquids. Solvent effects on HMF yields are pronounced, whereas solvent choice also affects product work-up and solvent/catalyst recycle streams.

To the best of our knowledge, full scale commercial HMF plants are not operational yet. However, pilot scale studies have been reported and will be discussed.

2.5.1.1 Aqueous reaction systems

A well-known and established synthetic strategy for HMF synthesis is the acid catalysed dehydration of C6-sugars at elevated temperatures in aqueous solutions.^{7,392,393} Initially, sucrose was used as the feedstock and oxalic acid was employed as the catalyst. Later, a variety of catalytic systems were explored to obtain highly active and selective catalysts for the formation of HMF, mainly with fructose as a preferred sugar feed. Cottier *et al.*³⁹⁴ divided the catalysts into 5 categories: organic acids, mineral acids, salts, Lewis acids and solid catalysts. Table 34 presents an overview of catalysts used in the dehydration reaction of fructose to HMF in aqueous media based on Cottier's classification³⁹⁴ with a literature update.

Table 34. Catalysts used for the dehydration of fructose to HMF in aqueous solutions

Organic acids	Mineral acids	Salts	Lewis acids	Solid catalysts
oxalic acid	H ₃ PO ₄	Ag ₃ PW ₁₂ O ₄₀	AlCl ₃	ion exchange resins
levulinic acid	H ₂ SO ₄		ZnCl ₂	
maleic acid	HCl		BF ₃	zeolites
formic acid	HI		B(OH) ₃	metal oxides ^a : γ -TiP, C-ZrP ₂ O ₇ ,
acetic acid	HBr		lanthanide salts	ZrP, ZrO ₂ , TiO ₂ , eHTiNbO ₅ -MgO,
p-toluenesulfonic acid				NbOPO ₄ ,
trifluoracetic acid				

^a TiP = titanium phosphate, C-ZrP₂O₇ = cubic zirconium pyrophosphate, ZrP = Zr(HPO₄)₂, eHTiNbO₅ = exfoliated HTiNbO₅, obtained by treating the H-compound with Bu₄NOH.

Despite the advantage of using water as an environmentally benign solvent, the chemistry in aqueous systems suffers from relatively low HMF yields due to subsequent reactions to levulinic acid and insoluble polymeric substances (humins). Typical maximum yield of HMF for synthesis of HMF in water is around 50-60 mol% at fructose conversion level in the region of 50-95 % (Tables 7-9 in section 2.4.1.1). In addition, the formation of insoluble humins during the reaction also complicates work-up of the reaction mixture to obtain a high HMF purity.

2.5.1.2 Non-aqueous reaction systems

HMF synthesis in non-aqueous solvents can be categorised based on the boiling points of the solvents, *viz.* low boiling solvents (bp < 150 °C) and high boiling solvents with ionic liquids as the extreme. The use of low boiling solvents such as acetonitrile,²¹² ethyl acetate,²¹² butyl acetate,²¹² acetone,²⁰⁶ methanol,^{233,244} ethanol,²⁴⁴ 1,2-dimethoxyethane (glyme)²³¹ and acetic acid^{206,395} have been examined in detail. In acetone at sub- and supercritical conditions using sulfuric acid as the catalysts, HMF was obtained in high selectivities (up to 75%) at 95% fructose conversion. In the case of low chain alcohols and acetic acid, subsequent

reactions of the *in situ* formed HMF were observed leading to 5-methoxymethylfurfural (MMF), 5-ethoxymethylfurfural (EMF) and 5-acetomethylfurfural (AMF) as the main reaction product for methanol, ethanol and acetic acid as the solvents, respectively. At fructose conversions exceeding 98%, MMF can be obtained in selectivities up to 78%.²³³ Meanwhile, higher selectivities for HMF and EMF (up to 90%) can be attained at lower (25%) fructose conversions.²⁴⁴ These reactions are typical examples of *in situ* conversions of HMF and will be discussed in more detail in the last part of this section.

Various high boiling solvents such as dimethyl sulfoxide (DMSO),^{117,209,212,213,216,396} 1-methyl-2-pyrrolidinone (NMP),²³⁰ N,N-dimethylacetamide (DMA),^{230,397} N,N-dimethylformamide (DMF)^{212,224,230,263,397} and sulfolane^{212,229} have been investigated for the synthesis of HMF using fructose as the starting material. High HMF yields (up to 92%)²¹³ were observed in DMSO in combination with various catalytic systems ranging from Lewis acids^{213,216} to ion exchange resins²⁰⁹ and even in the absence of catalysts.¹¹⁷ Though advantageous regarding HMF yields, the use of high boiling solvents complicates HMF work-up (*vide infra*).

Recently a number of studies have been carried out on the synthesis of HMF from cheaper feedstocks, such as glucose, cellulose and even lignocellulosic biomass in high boiling solvents, particularly polar aprotic solvents such as DMF, DMA and DMSO has been reported. Takagi *et al.* examined a combination of base and acid solid catalyst for the conversion of glucose to HMF in DMF.²⁶³ A combination of hydrotalcite and amberlyst-15 in DMF gave HMF from glucose with an HMF selectivity of 50% at 73% glucose conversion after 9 h at 80 °C. Binder and Raines reported that DMA containing 10 wt% LiCl is a good solvent to produce HMF in a single step with good yields from lignocellulosic biomass, cellulose, glucose and fructose.¹¹⁹ HMF yields of 48% can be obtained from untreated corn stover using 10 mol% CrCl₃ and 10 mol% HCl as the catalyst in DMA/LiCl in the presence of 60 wt% [EMIM]Cl at 140 °C for 2 h reaction time. Using DMSO as the solvent, the conversion of glucose to HMF in yields up to 60 mol% were reported in the presence of chromium and aluminium salts as the catalysts.^{217,398}

Recently, the use of ionic liquid as solvent/catalyst for the synthesis of HMF has been explored. A description of the various ionic liquids used for the synthesis of HMF is provided in section 2.4.3.2. In general, promising results have been obtained for the conversion of fructose or fructose based polymers (like inulin) to HMF. In addition, a breakthrough for the use of glucose and cellulose as a feedstock was reported recently.^{134,135,252,399} HMF yields of 62% were obtained when converting cellulose and typical examples of lignocellulosic

biomass (e.g. straw) in [BMIm]Cl using CrCl₃/LiCl as the catalysts.³⁷² However, the development of an effective HMF isolation method combined with efficient ionic liquid recycle remains a challenge.

2.5.1.3 Mixed solvent reaction systems

When using mixed solvents for the synthesis of HMF, biphasic or single phase systems should be distinguished. For biphasic liquid-liquid systems, it is the intention to continuously extract the *in situ* formed HMF from the reaction phase to the other liquid phase during the reaction to prevent subsequent reactions of HMF, like hydration to levulinic acid and the formation of humins.

In the 1950's, Peniston introduced the use of 1-butanol in combination with water for sucrose/sulfuric acid systems.²⁸⁸ In this biphasic system, solid humin formation was not observed and the HMF was extracted to the 1-butanol phase. In the given example, a 0.58 M sucrose solution containing 0.1 N H₂SO₄ as the catalyst was contacted two times with fresh 1-butanol at 150 °C for 20 min for each stage. The reactions were carried out at a phase ratio of one for the aqueous and organic phase. After reaction, the yield of HMF was 72.5 % HMF at 86 % sucrose conversion. Most of the HMF was present in the 1-butanol phase (68.6 %) and minor amounts in (3.9 %) in the aqueous phase. This patent also disclosed that the presence of a sugar affects the partition coefficient (P) of HMF between the organic and aqueous phase (1-butanol/water: P= 1.57 and 1-butanol/20% sucrose solution: P= 1.79).

In 1959, Cope was the first to apply methyl isobutyl ketone (MIBK) as an effective solvent for the *in situ* removal of HMF from an aqueous reaction phase.³¹¹ When using a continuous solvent extraction, the yield of HMF improved considerably from 20% to 63%.

Two decades later, the application of biphasic systems consisting of water and MIBK as the organic solvent was revisited for the conversion of fructose to HMF using homogenous mineral acid¹⁹⁹ and ion exchange resins.^{211,289,290,400} In the 1990's, the use of heterogeneous catalysts (like zeolites) as catalysts for biphasic systems was explored.¹⁰² The reactions were performed either in batch^{211,289,290,400} or continuous mode,^{102,199} see the Process Chemistry section for more details. Because the partitioning of HMF is only slightly favourable at best towards the organic layer, with [HMF]_{org}/[HMF]_{aq} between 0.9 and 1.9,¹⁷⁰ it is advantageous to perform the reaction in a solvent mixture with a high MIBK to water ratio (5:1 or even 9:1) in order to obtain high HMF yields.

In 2006, Dumesic and co-workers reported studies to enhance the partitioning of HMF between the reactive aqueous solution and the MIBK phase by applying 2-butanol as a co-

solvent.^{170,300} To suppress undesired side reactions in the aqueous phase, dimethyl sulfoxide (DMSO) and/or poly(1-vinyl-2-pyrrolidinone) were applied as co-solvents. This approach allowed processing at high fructose concentrations (10 to 50%) and yielded HMF with a selectivity of 80% at 90% fructose conversion. Further improvements for the biphasic system were achieved by adding NaCl to the aqueous reaction phase.^{297,401} Recently, Dignan and Sanborn reported on a biphasic aqueous-alcohol (higher alcohol such as fusel oil or pentanol) system in a flow reactor at 240 -270 °C (10–83 bar).⁴⁰² At least 60% fructose conversion was observed to mainly HMF without substantial solids formation.

Apart from biphasic systems, a number of single phase mixed solvents system for the synthesis of HMF from fructose have been reported. Among them are water/dioxane,⁴⁰³ water/triethylene glycol,⁴⁰³ water/PEG-600,¹⁵⁶ water/acetone,^{206,207} acetone/DMSO²²¹ and DMSO/MIBK²⁹² systems. All studies highlight that further degradation of HMF can be suppressed/prevented by using mixed solvent systems, resulting in HMF yield improvements and less humin formation.

2.5.2 Kinetic studies on HMF formation

A number of kinetic studies have been performed on the kinetics of HMF formation from various feedstocks. Kinetic studies are not only of relevance to unravel the mechanism for HMF formation on a molecular level, but also for process development studies to identify optimum reactor configurations and process conditions for the highest HMF yields. In this paragraph an overview of kinetic studies will be provided. It starts with studies using fructose as the feedstock (2.5.2.1, Table 35), with a distinction on studies in aqueous -, non-aqueous- and two solvent systems. Subsequently, kinetic studies using glucose will be provided (2.5.2.2, Table 36), followed by studies using cellulose and more complex lignocellulosic biomass (2.5.2.3, Table 37). Finally, kinetic studies on the decomposition of HMF to levulinic acid and formic acid will be reported and discussed (2.5.2.4, Table 38). The rate of the latter reaction should be suppressed as much as possible to avoid a reduction in the HMF yields.

2.5.2.1 Kinetic studies on the formation of HMF from fructose

As noticed in many studies, fructose is the preferred C6-sugar for HMF formation in water. Compared to glucose, fructose is more reactive and also leads to higher HMF yields. An overview of kinetic studies reported in the literature using fructose as the starting material is given in Table 35.

Single solvent, aqueous systems, homogenous catalysts

Kinetic studies on the conversion of fructose to HMF in aqueous systems using HCl as the catalyst were reported by Kuster *et al.*¹⁵⁵ and Asghari *et al.*⁴⁰⁴ Kuster and van der Baan¹⁵⁵ investigated the reaction of fructose (0.2–1 M) to HMF at 95 °C in a batch reactor. The experimental data were best described using an order of one in fructose. A kinetic model including the formation of humins and the subsequent decomposition of HMF to levulinic acid (LA) and formic acid (FA) was proposed involving unknown intermediates X and Y (Table 35).

Asghari *et al.* reported the conversion of fructose in subcritical water (210–270 °C, 40–150 bar) at fixed initial pH of 1.8.⁴⁰⁴ The reactions were carried out in a continuous flow system with residence times between 0.5–300 s. The initial concentration of fructose was 0.03 M. Main products were HMF, 2-furaldehyde, LA, FA and soluble polymers. A reaction network was proposed (Table 35), involving three parallel reactions for fructose: to 2-furfuraldehyde, to soluble polymers and to HMF. The reaction to HMF was modelled assuming a first order reaction in fructose and the activation energy was reported to be 160.6 kJ/mol.

Li *et al.* reported a kinetic study on the reaction of fructose to HMF using formic or acetic acid as the catalysts in subcritical water (180–220 °C, 100 bar).¹²³ The reactions were performed in a 500 ml batch reactor at a stirring rate of 300 rpm. The authors also examined the thermal decomposition of fructose under these conditions. Experimental data were modelled using a first order approach. At a temperature of 200 °C, the rate constants for fructose are 0.08, 0.12, and 0.32 min⁻¹ for the thermal reaction and the catalytic reaction using acetic acid (10.8 mg/ml) and formic acid (10.8 mg/ml), respectively. Even though the addition of organic acids enhanced the conversion rate of fructose, the maximum yield of HMF (52 %) was similar for all cases. The apparent activation energies of fructose decomposition were 126.8±3.3 kJ/mol, 125.6±3.8 kJ/mol, and 112.0±13 kJ/mol for the thermal decomposition, and reactions catalysed by acetic- and formic acid, respectively.

A kinetic study on the decomposition of fructose in aqueous solutions using sulfuric acid as the catalyst at a wide range of sulfuric acid concentrations (5 mM – 1 M) was reported by Abdilla *et al.*⁴⁰⁵ The reactions were carried out in a batch mode using glass ampoule reactors at temperatures ranging between 140–180 °C with fructose loadings between 0.1–1 M. A kinetic model using a power law approach was established for a reaction network involving formation of side products. The order of reaction for fructose was found to be close to 1 for the main reaction and 1.18 for the side reaction. The activation energy for the side reaction

(147 ± 12 kJ/mol) was higher than the activation energy of the main reaction (123 ± 5 kJ/mol). This indicated that when using sulfuric acid as the catalyst in aqueous media, lower temperatures are preferred to avoid humin formation and thus to increase the production of HMF.

The microwave assisted non-catalysed reaction of fructose to HMF in water at subcritical conditions ($180\text{--}250^\circ\text{C}$) has been reported.⁴⁰⁶ 5-HMF was found to be the major product, with a maximum yield of 47%. The kinetic constant for fructose was $3.6 \times 10^{-3} \text{ s}^{-1}$ at 220°C , assuming a first order reaction in fructose.

Single solvent, aqueous systems, heterogeneous catalysts

Carniti *et al.* reported the application of niobic acid (Nb_2O_5) and niobium phosphate (NbOPO_4) for the dehydration of fructose in water.²⁰⁰ The reactions were performed in a continuous packed bed reactor in a small temperature range ($90\text{--}110^\circ\text{C}$) and a fixed initial fructose concentration of 0.3 M. The results were modelled assuming i) first order reaction in fructose and ii) only kinetic limitations and no mass transfer issues. The activation energy was found to be 65.8 ± 8 kJ/mol when niobium phosphate was used as the catalyst.

Single solvent, non-aqueous systems, homogenous catalysts

Bicker *et al.* reported kinetic studies on the dehydration of fructose in supercritical methanol and supercritical acetic acid.²³³ Reactions were carried out in continuous mode in a high pressure reactor using sulfuric acid (10 mM) as the catalyst and a fixed fructose inlet concentration of 0.06 M. A broad temperature range was applied for methanol ($120\text{--}270^\circ\text{C}$), whereas the reactions in supercritical acetic acid were performed at a fixed temperature of 180°C . A kinetic network was proposed involving fructose conversion to the desired HMF as well as soluble polymeric by-products. The intermediate HMF is not inert under these conditions. In supercritical methanol a furfural ether (5-methoxymethylfurfural) is formed whereas an ester (5-acetoxymethylfurfural) was produced in supercritical acetic acid. All reactions were assumed to be irreversible and first order in substrate. The activation energy for the decomposition of fructose was 80 kJ/mol in supercritical methanol.

Moreau *et al.* studied the conversion of fructose to HMF using an ionic liquid, 1-H-3-methylimidazoliumchloride ([HMIM]Cl).³³⁴ Here, the ionic liquid acts both as a solvent and catalyst. The reactions were carried out on small scale in magnetically stirred batch reactors within a temperature window of $90\text{--}120^\circ\text{C}$. The initial fructose concentration ranged from 0.01–2.5 M. The data were modelled assuming a simple kinetic scheme involving the main

reaction of fructose to HMF and the subsequent decomposition of HMF to products. A first order approach was applied; though the initial rate versus intake of fructose profiles indicate that this approach is valid only at low fructose intakes (< 0.5 mol/l). The activation energy for the reaction of fructose to HMF was 143 kJ/mol.

Recently, Wei *et al.* reported the conversion of fructose to HMF in 1-butyl-3-methyl imidazolium chloride ([BMIM]Cl) using IrCl_3 as the catalyst.²⁶⁹ The reactions were performed in 25 ml stirred flasks in a temperature range of 80–120 °C and a fixed fructose concentration (200 mg fructose in 2 g [BMIM]Cl). A kinetic network was proposed involving fructose conversion to HMF and byproducts. The experimental data were modelled using first order reaction kinetics. The activation energies for fructose decomposition were estimated to be 165 kJ/mol and 124 kJ/mol for the formation of HMF and formation of byproducts, respectively.

Recently, Caratzoulas *et al.* reported the use of hybrid quantum mechanics/molecular mechanics dynamics free energy calculations to investigate the reaction mechanism for the conversion of fructose to HMF in acidic water.⁴⁰⁷ Remarkably good agreement was observed between the calculated and experimentally determined concentration profiles from kinetic studies of Asghari *et al.*⁴⁰⁴

Single solvent, non-aqueous systems, heterogeneous catalysts

Nakamura and Morikawa reported the conversion of fructose to HMF in DMSO using acidic ion-exchange resins.²⁰⁹ The reactions were carried out in glass stirred batch reactors at a constant temperature of 80 °C. Various ion exchange resins were examined as the catalysts, ranging from porous types such as Diaion PK-208, Diaion PK-216, and Diaion PK-228 to gel type catalysts such as Amberlite IR-118, Amberlite IR-120, and Lewatit SC-108. The formation of HMF was described by a first order reaction model. The rate constants for the reactions catalysed by the various resins were determined. Data analyses showed that the use of the porous resins resulted in higher reaction rates than the use of gel type resins.

Mixed solvents, homogeneous catalysts

A kinetic study on the synthesis of HMF from fructose in a biphasic system consisting of water and MIBK using phosphoric acid as the catalyst was reported by Kuster *et al.*^{199,209} The experiments were performed in a continuous stirred tank reactor at temperatures between 170 and 220 °C. The data were modelled using a kinetic scheme involving the reaction of HMF to

an intermediate X, which either reacts to HMF or to humins. In a subsequent step HMF is converted to other products, with the major being LA and FA. The reaction of fructose to HMF was found to be first order in HMF and phosphoric acid concentration, with an activation energy of 93 ± 6 kJ/mol.

Bicker *et al.* studied the use of acetone-water (90:10) mixtures for the conversion of fructose to HMF at subcritical conditions ($180\text{--}300$ °C, 200 bar) in a continuously operated tubular reactor with sulfuric acid as the catalyst (0–5 mM).²⁰⁶ The reaction was modelled using a first order approach without taking any other reactions into account, indicating an activation energy of 98 kJ/mol in the presence of sulfuric acid. The thermal reaction was about twenty times slower than the catalysed reaction (300 °C) and an activation energy of 158 kJ/mol was calculated.

Mixed solvents, heterogeneous catalysts

Moreau *et al.* studied the dehydration of fructose to HMF, catalysed by H-mordenite, in a biphasic water-MIBK batch system at three temperatures (150, 165 and 180 °C).¹⁰² Two reactions were considered in the kinetic analyses: the main reaction of fructose to HMF and the subsequent rehydration of HMF to LA and FA. When assuming first order kinetics for both reactions, the activation energy was 141 kJ/mol for the dehydration and 64 kJ/mol for the rehydration. Experiments with different rotor speeds and estimations of relevant mass transfer criteria revealed that the reactions were carried out in the kinetic regime and therefore were not biased by mass transfer effects.

Qi *et al.* reported the conversion of fructose to HMF in water-acetone mixtures in the presence of a strongly acidic resin (DOWEX 50WX8-100).²⁰⁷ Reactions were performed in a batch reactor using microwave heating in the absence of stirring. The reactions were carried out in a temperature range of 100–180 °C with an initial fructose concentration of 2 wt%. The fructose concentration versus time profiles for 70:30 (w/w) acetone/water mixtures were modelled assuming a first order reaction in fructose. Without considering other reactions this led to an activation energy of 103.4 kJ/mol.

The same group also performed comparable studies on the reaction of fructose to HMF in acetone-DMSO.²²¹ The same catalyst was tested with similar temperature ranges and initial fructose concentrations as applied for the acetone-water mixtures. The activation energy for the reaction of fructose to HMF in a mixture of 70:30 (w/w) acetone/DMSO was considerably lower (60 kJ/mol) than in acetone/water (103.4 kJ/mol).

Discussion

The experimental data of the conversion of fructose to HMF and byproducts (humins, levulinic acid, formic acid, furfural) using various solvents and catalysts at a wide range of experimental conditions have been modelled using numerous kinetic schemes of which some involve up to more than 7 individual reactions. For the reaction of fructose to HMF, a first order approach in fructose is usually applied.

Figure 2 presents an overview of the activation energies for the conversion of fructose to HMF and humins. The activation energy for the hydrothermal decomposition of fructose in water was determined in two separate studies and reported to be about 120 kJ/mol.^{123,408} In aqueous systems, the lowest activation energy (66 kJ/mol) was reported for the dehydration of fructose using a solid catalyst (niobium phosphate) at relatively low temperatures (90–120 °C).²⁰⁰ The highest activation energy (160 kJ/mol) was found for the conversion of fructose at high temperatures (210–270 °C) using HCl as the catalyst at a fixed pH of 1.8.⁴⁰⁴

The reported activation energies for the conversion of fructose to HMF in non-aqueous systems range from 60 to 165 kJ/mol. The lowest activation energy of 60.4 kJ/mol was reported for fructose conversion in acetone/DMSO (70/30) using an ion exchange resin as the catalyst.²²¹ The authors suggest that a higher concentration of the furanoid forms of fructose in acetone/DMSO leads to a lower activation energy.²²¹ As was discussed in 2.3.1.1, Amarasekara proposed a reaction mechanism in which DMSO acts as a catalyst, which could also explain the low activation energy (Scheme 12).¹¹⁷

In some of the kinetic studies both the activation energies for the main reaction of fructose to HMF, and the side reaction to humins were determined and compared in order to gain insights in the temperature effect on HMF selectivity. Different trends were observed. Asghari *et al.* reported a lower activation energy for the side reaction (102 kJ/mol) than for the dehydration reaction (160 kJ/mol) in an aqueous system, catalysed by HCl at a fixed pH of 1 using a flow reactor at 210–270 °C.⁴⁰⁴

In an ionic liquid system at relatively low temperatures of 80–100 °C Wei *et al.* reported an activation energy of 165 kJ/mol for the dehydration of fructose to HMF;²⁶⁹ considerably higher than the activation energy for the side reactions (124 kJ/mol). This implies that for this system higher temperatures favour HMF selectivity. For the conversion of fructose in water with sulfuric acid as the catalyst, Abdilla *et al.* found the opposite, namely an activation energy of 123 kJ/mol for the dehydration and 147 kJ/mol for the side reaction,⁴⁰⁵ which indicates that operation at lower temperatures is favoured for high HMF selectivity.

Apparently, different catalysts and/or solvents behave differently, making it impossible to draw general conclusions.

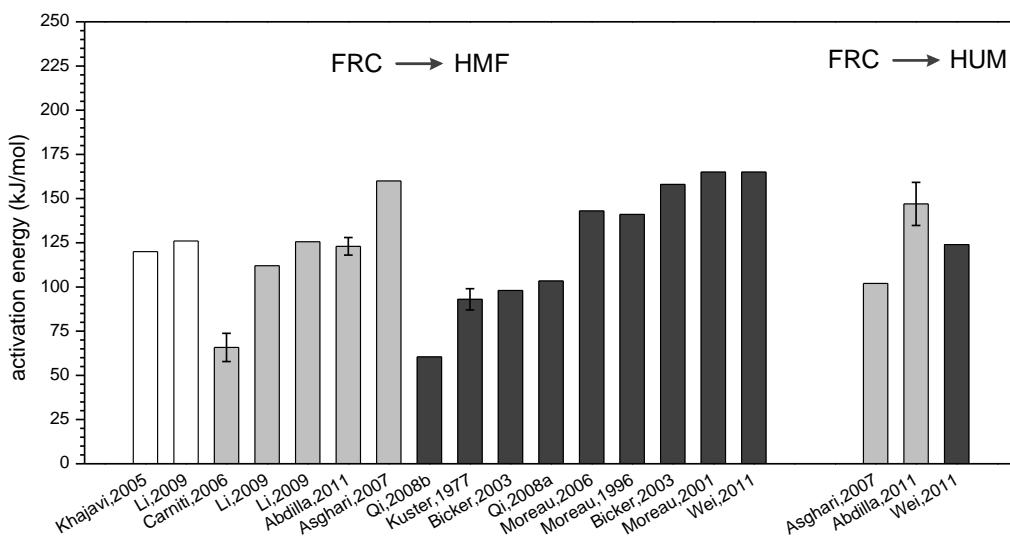


Figure 2. Activation energies for the conversion of fructose (FRC: fructose; HUM: humins; white bars: thermal aqueous systems; light grey bars: catalytic aqueous systems; dark grey bars: non-catalytic aqueous systems including mixed solvents and biphasic systems)

2.5.2.2 Kinetic studies on the formation HMF from glucose

A number of kinetic studies on the dehydration of glucose to HMF have been reported, despite the known lower selectivity to HMF compared to fructose. This attention could be explained by the fact that HMF is an undesired side product when targeting for high glucose concentrations in biomass pre-treatment studies for subsequent fermentation processes. All studies reported so far have been conducted in water, except a recent study by Qi *et al.*, which was performed in an ionic liquid.³⁴⁷ An overview of all kinetic data is provided in Table 36.

Conversion of glucose to HMF in aqueous systems

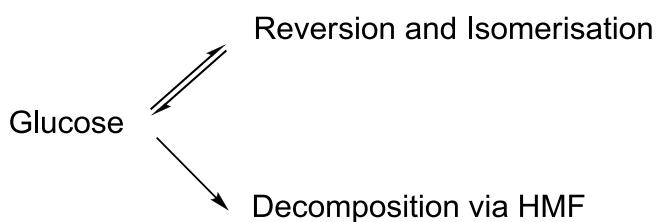
In 1945 Saeman developed a kinetic model for acid-catalysed hydrolysis of glucose in water using sulfuric acid (0.4–1.6 wt%).⁴⁰⁹ This kinetic study was part of a larger study on the acid catalysed decomposition of cellulose and woody biomass (Douglas-fir). The experiments with glucose were carried out in batch setups (sealed glass bombs) at 170–190 °C and an initial glucose concentration of 0.278 M. The overall rate of glucose decomposition was determined, without considering the individual reaction rates to other products. The experimental data were successfully modelled with a first order approach in glucose. The

order in acid was found to be slightly higher than 1 (1.02), with an activation energy of 137.5 kJ/mol.

Heimlich *et al.* investigated the conversion of glucose in aqueous solutions in the presence of 0.35 M HCl at 100–150 °C.⁴¹⁰ The reaction was modelled using a first order approach, leading to an activation energy of 133 kJ/mol.

McKibbins *et al.* studied the kinetics of the reaction of glucose to HMF as well as the subsequent reaction of HMF to LA and FA in water using sulfuric acid as the catalyst (0.025–0.8 N).⁴¹¹ The experiments were carried out in a batch reactor for a wide temperature range of 140–250 °C. The rates for glucose conversion to HMF were modelled using a first order approach in both glucose and sulfuric acid. An activation energy of 136.8 kJ/mol was reported for the dehydration of glucose to HMF.

Smith *et al.* investigated the decomposition of glucose in water using sulfuric acid as the catalyst in a batch reactor (ampoules, 180–224 °C, 0.5–7 min reaction time) and a continuous flow reactor (178–241 °C, 0.06–0.27 min).⁴¹² In the batch reactor, the kinetic data from McKibbins *et al.*⁴¹¹ were reproduced, though the activation energy was slightly lower (128.6 kJ/mol). However, different results were obtained using the flow reactor. Higher initial reaction rates for the decomposition of glucose were obtained in the continuous setup compared to the batch reactor. Moreover, the experimentally determined activation energy was considerably lower (87.8 kJ/mol) for the continuous reactor than for batch (128.6 kJ/mol). It was concluded that the original batch models are not valid for short residence/reaction times (< 20 s). Isomerisation to fructose and reversible oligomerisation (reversion) reactions, particularly for higher loading of intake glucose, were assumed to be responsible for these differences and should be considered in kinetic models for glucose decomposition (Scheme 33).



Scheme 33.

Recently, Pilath *et al.* developed a kinetic model for glucose reversion in aqueous acidic solution.⁴¹³ The experiments were conducted in a robotic microwave-heated batch reactor

system in the presence of 1.2 wt% H₂SO₄ between 120 and 180 °C. Reversion product yields of up to 12 wt% of the glucose feed were observed consisting mainly of di-saccharides. Levoglucosan, an anhydrosugar, was also formed, but larger oligosaccharides were not observed. These reversion products were in equilibrium with glucose, which was reached at t < 10 minutes at temperatures higher than 140 °C. These reversion reactions compete with the dehydration of glucose to form HMF and actually reduce the glucose concentration in solution. The kinetic parameters for the conversion of glucose to ten identified di-saccharides were best modelled using a second-order dependency in glucose.. The rate expression for the reaction of glucose to HMF was determined using a first order model and an activation energy of 133 kJ was obtained.

Bienkowiski *et al.* studied the decomposition of glucose (4-12 wt%) in water, catalysed by 4-20 wt% sulfuric acid.⁴¹⁴ The experiments were performed in sealed glass reactors at 100-144 °C. The experimental data were analysed using five different kinetic models. The best results were obtained using a first order approach in glucose in combination with a more complex term, including the fugacity of H⁺, to describe the effect of acid concentration on the reaction rate. The activation energy was 130.4 kJ/mol, in agreement with the value from Saeman.⁴⁰⁹

Baugh *et al.* investigated the decomposition of glucose in water at initial glucose concentrations of 0.006–0.33 M.⁴¹⁵ The reactions were carried out in batch, catalysed by sulfuric acid at 170–230 °C. The reactions were modelled using a pseudo-first order approach in glucose and a kinetic rate coefficient including three individual terms (no catalysis, acid and base catalysis). An activation energy of 121 kJ/mol was determined, which was slightly lower than determined by Saeman (137.5 kJ/mol).

Xiang *et al.* investigated the kinetics of glucose decomposition in water at pH 1.5-2.2 (sulfuric acid) at 180–230 °C using glass ampoule reactors.⁴¹⁶ The experimental data for glucose decomposition were modelled using a pseudo first order approach. Deviations of this model were observed at short reaction times and high glucose concentrations. Therefore a reaction network involving the rapid and reversible formation of reversion products was applied to improve the modelling results. The temperature dependence of the equilibrium constant for this reaction was also determined. The activation energy for the irreversible decomposition reaction of glucose was 139 kJ/mol, close to the value found by Saeman.

Kabyemela *et al.* investigated the kinetics of glucose isomerisation and decomposition in flow in sub- and supercritical water at 300-400 °C, 25-40 MPa for 0.02-2 s.¹²² The experimental data were modelled using a reaction network involving isomerisation of glucose

to fructose and the decomposition of both glucose and fructose to various products. All reactions were assumed to be irreversible and first order in substrate. The rate constants of both the isomerisation of glucose to fructose and the decomposition of glucose and fructose were independent of the pressure at subcritical conditions, whereas the rate decreased with increasing pressure at supercritical conditions. The activation energy for glucose decomposition was estimated to be 96 kJ/mol.

Kabyemela *et al.* proposed reaction pathways for the decomposition of glucose and fructose in supercritical water in the absence of catalysts.¹²¹ A reaction network was proposed involving (i) isomerisation of glucose and fructose, (ii) dehydration to HMF and (iii) subsequent retro-aldol condensation to C4- and C3-sugars and their fragmented products (glyceraldehyde and pyruvaldehyde). Kinetic constants for reactions to C3-C4 sugars were determined, but the authors did not report the reaction rates for the formation and decomposition of HMF.

Khajavi *et al.* performed kinetic studies on the thermal degradation of various monosaccharides (glucose, galactose, mannose, fructose, and sorbose) in subcritical water.⁴⁰⁸ The reactions were performed in a tubular reactor at 180–260 °C. Activation energies of 155 kJ/mol and 120 kJ/mol were estimated for the thermal decomposition of glucose and fructose, respectively. Fructose gave the highest HMF yields of all the monosaccharides that were tested (up to 50%).

Matsumura reported hydrothermal decomposition studies of glucose in sub- and supercritical water (573–733 K, 25 MPa) in a continuous set-up.⁴¹⁷ The product yields were determined and the highest HMF yield (25%) was obtained at 573 K and residence times of 50–70 s. The reactions were modelled using a very complex reaction scheme involving 12 individual reactions and assuming first order in substrates. The activation energy of the overall decomposition rate (consisting of 4 individual reactions) of glucose was 95.5 kJ/mol.

The microwave assisted non-catalysed reaction of glucose to HMF in water at subcritical conditions (180–250°C) has been reported.⁴⁰⁶ 5-HMF was found to be the major product, with a maximum yield of 30%. The kinetic constant for glucose was $5.2 \times 10^{-4} \text{ s}^{-1}$ at 220 °C, assuming a first order reaction in glucose. The reaction was about 8 times slower than observed for fructose.

As part of a larger study on kinetic modelling of the acid catalysed decomposition of lignocellulosic biomass, Girisuta *et al.* performed a kinetic study on the acid-catalysed decomposition of glucose in water.¹⁶⁵ In glass ampoules the effects of initial glucose concentration (0.1–1 M), sulfuric acid concentration (0.05–1M) and temperature (140–200

°C) were quantified. A reaction network was developed involving two parallel reactions, namely the dehydration of glucose to HMF and the decomposition of glucose to humins. The data were modelled using a power law approach, see Table 36 for details. The activation energy for the decomposition of glucose to HMF was determined at 152 ± 1 kJ/mol for the main reaction and 165 ± 1 kJ/mol for the side reaction.

Chang *et al.* reported a kinetic study on the formation of levulinic acid from glucose using 1-3 wt% sulfuric acid as the catalyst at 170-190 °C.⁴¹⁸ The reactions were carried out in a stainless steel batch reactor (125 ml). A reaction network comprising of two parallel reactions was proposed and the data were modelled using a first order approach. The activation energy was estimated at 86.3 kJ/mol for the dehydration to HMF and 56.9 kJ/mol for the reaction of glucose to solid humins. The activation energy for the lumped decomposition of HMF to levulinic acid and humins was 209 kJ/mol. In a subsequent paper, Chang and co-workers reported a kinetic study on the acid catalysed hydrolysis/dehydration of wheat straw to levulinic acid at 190-230 °C in batch using 1-5 wt% sulfuric acid as the catalyst.⁴¹⁹ The kinetics of the reactions to the main intermediates glucose and HMF were established. An activation energy of 54.5 kJ/mol was reported for glucose dehydration to HMF. Though a side reaction of glucose to humins was proposed in their reaction network, the activation energy of this side reaction was not reported. Meanwhile, an activation energy of 56.5 kJ/mol was reported for the decomposition of HMF to LA , which was considerably lower than the value in their first paper (209 kJ/mol).

Kupiainen *et al.* reported a kinetic study on the decomposition of glucose in 5-20 wt% aqueous formic acid solutions at 180–220°C.⁴²⁰ The experiments were carried out in zirconium batch reactors heated in a fluidised sand bath. The initial concentration of glucose was either 56 mM or 112 mM. The data were modelled using first order reactions. A reaction scheme involving an unknown intermediate in the conversion of glucose to HMF was used to model the kinetic profiles. The activation energy for glucose decomposition to the intermediate was found to be 153 ± 2 kJ/mol. Activation energies for the decomposition of the intermediate to HMF and humins were found to be 117 ± 4 kJ/mol and 110 ± 5 kJ/mol, respectively.

Duru et al. recently reported the conversion of glucose to HMF in water using metal chlorides (CrCl_2 , CoCl_2 , CuCl_2 , SnCl_2 and FeCl_3) at 373 K.⁴²¹ Best yields were obtained using CrCl_2 and CuCl_2 , though yield data were not reported. Remarkably, the yields for

CrCl_2 were highest in alkali media ($\text{pH} > 9$). The reaction was modelled using a first order approach, giving a k value of $6.5 \times 10^{-6} \text{ s}^{-1}$ for CrCl_2 at 373 K.

Wu et al. performed an in depth kinetic study on the decomposition of dilute aqueous glucose solutions ($5.6 \times 10^{-8} - 5.6 \times 10^{-3} \text{ mol/l}$) in the absence of catalysts in hot compressed water ($175\text{--}275^\circ\text{C}$).⁴²² The initial glucose concentration has a major effect on the selectivity of the reaction, ascribed to a change in reaction mechanism. At initial glucose concentrations exceeding $5.6 \times 10^{-5} \text{ mol/l}$ the selectivity to HMF increases significantly. The apparent activation energy for glucose decomposition is a function of the initial glucose concentration and decreases with decreasing glucose concentration (109 \pm 5 kJ/mol at high to 90 \pm 4 at kJ/mol at the lowest initial glucose concentration).

Conversion of glucose to HMF in non-aqueous solvents

Qi et al. reported kinetic research on the conversion of glucose to HMF in the ionic liquid 1-butyl-3-methyl imidazolium chloride ($[\text{BMIm}]^{\text{+}}\text{Cl}^{-}$) using CrCl_3 as catalyst and applying microwave irradiation as a heating source.³⁴⁷ A first order reaction approach was used to model the experimental data. An activation energy of 114.6 kJ/mol was reported for the dehydration of glucose to HMF.

Recently, thermodynamic insights in the reactions of glucose to HMF and anhydroglucose in DMSO/water mixtures were reported using a G4 ab initio method in combination with the COSMO-SAC solvation model.⁴²³ The predicted ΔG values were in quantitative agreement with experimental values. The calculations showed that the conversion of glucose to HMF is irreversible whereas glucose dehydratior to anhydroglucose is reversible, with equilibrium constants depending on reaction conditions and solvent choice.

Discussion

Kinetic studies on the conversion of glucose in aqueous systems are mostly available as part of a reaction scheme on the conversion of cellulosic materials in order to obtain either fermentable sugar or levulinic acid. In the latter reaction, HMF is proposed as the intermediate reaction product, and the formation rate of HMF from glucose is quantified. For the development of kinetic models for producing fermentable sugars, the rate of decomposition of glucose was evaluated as a single, lumped, reaction without considering the individual reactions to various products. Parallel reactions were proposed to incorporate the formation of HMF and humins for the most recent studies on the decomposition of glucose. Both reactions in the presence and absence of catalysts have been studied. The non-catalytic,

hydrothermal decomposition of glucose was studied at elevated temperatures and pressures in sub-and supercritical water (e.g. 180–260 °C, 100 bar).^{122,249,408}

The experimental data for glucose decomposition using mineral acids as the catalysts were successfully modelled using either a first order reaction in glucose or a power law approach. The acid concentration is explicitly added to the rate laws using various approaches, e.g. a power law factor, activity factor, fugacity, pH or concentration.

Figure 3 presents an overview of the reported activation energies for the decomposition of glucose, including the activation energies obtained from studies using cellulose or cellobiose as starting material and modelled with glucose as an intermediate. For the conversion of glucose to decomposition products, most of studies report activation energies ranging from 130 to 140 kJ/mol; close to the activation energy reported in the first study on this topic by Saeman (137 kJ/mol).⁴⁰⁹ Smith *et al.* found a considerably lower activation energy of 82 kJ/mol for acid catalysed glucose decomposition in a flow system compared to experiments at similar conditions in a batch reactor (128 kJ/mol).⁴¹² Isomerisation and reversion reactions have been suggested to be responsible for these differences.

Only a limited number of studies is available for the conversion of glucose in ionic liquid systems. An activation energy of 114 kJ/mol was reported for the conversion of glucose to HMF in [BMIm]Cl, catalysed by CrCl₃.³⁴⁷ As part of the acid-catalysed hydrolysis of cellobiose in [EMIm]Cl the activation energy for the decomposition of glucose was reported to be 90 kJ/mol.⁴²⁴

A number of studies have been reported where the decomposition reaction of glucose is not lumped into a single reaction. Here the rates of the reactions to individual products have been considered. For the dehydration of glucose to HMF the reported values for the activation energy show a large spread and range between 54 and 152.2 kJ/mol. For the reaction of glucose to humins, three datasets are available, which also show a large spread in activation energy of 56–135.7 kJ/mol. The lowest activation energy for the decomposition of glucose of around 50 kJ/mol, far below the value reported in other studies, was reported by Chang and co-workers on the decomposition of glucose or wheat straw to levulinic acid in aqueous sulfuric acid. The authors did not provide an explanation for this anomalous value.^{418,419}

With the kinetic data available for the desired reaction to HMF and the undesired reaction to humins, the effect of temperature on HMF selectivity may be estimated. Girisuta *et al.*¹⁶⁵ (sulfuric acid as the catalyst) and Jing *et al.*²⁴⁹ (no catalyst) found that the activation energy for undesired decomposition reaction of glucose to humins is higher than for the desired

reaction of glucose to HMF; suggesting that high HMF selectivity is preferred at lower temperature for these systems.

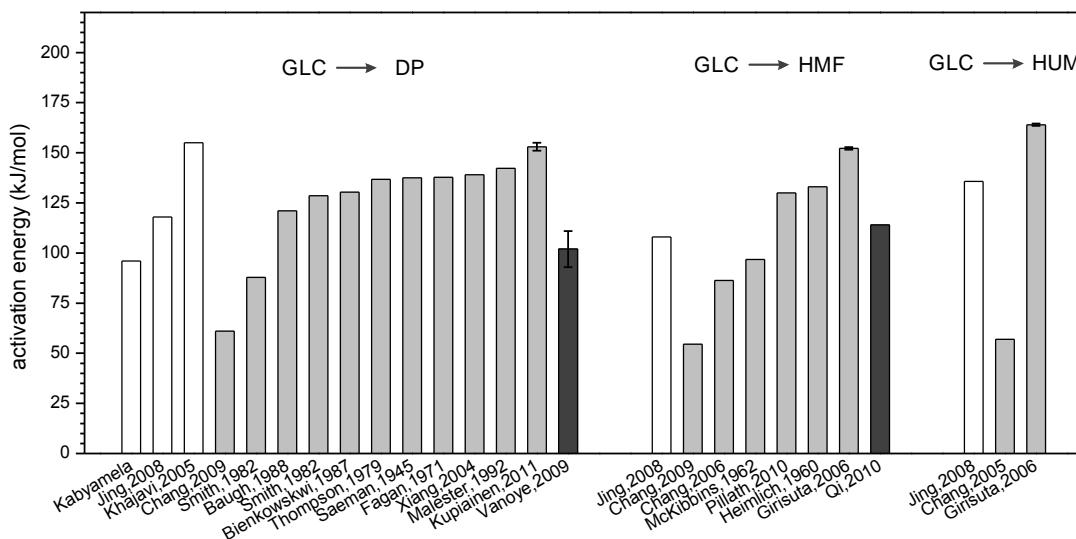


Figure 3. Activation energies for the conversion of glucose (light grey bars: aqueous systems; dark grey bars: non-aqueous systems including mixed solvents and biphasic systems; white bars: thermal aqueous systems), DP = decomposition products; HUM = humins

2.5.2.3 Kinetic studies on the formation of HMF from cellulose, lignocellulosic biomass or fructan based biomass

As the major C6-sugars are available in biopolymers such as cellulose, starch, or inulin, it is relevant to highlight the conversions of these polymers to C6-sugars and derivatives (Table 37). Though the focus of most of these studies is not on HMF formation, HMF is involved as a decomposition or intermediate product in processes for obtaining sugar monomers or subsequent derivates such as levulinic acid. Surprisingly, kinetic studies on the formation HMF directly from polyfructans like inulin are not available.

Cellulose and lignocellulosic biomass, aqueous systems

Saeman was the first to report kinetic studies on the hydrolysis of cellulose in dilute sulfuric acid at elevated temperatures.⁴⁰⁹ Woody biomass (Douglas-fir, 5-20 wt%) was used as feedstock and treated with 0.4-1.6 wt% sulfuric acid at 170–190 °C. The reactions were carried out in an isothermal batch setup (glass bomb). A homogenous pseudo first order reaction was assumed to describe the kinetic decomposition of cellulose to glucose. The

reaction order for sulfuric acid was found to be 1.34. The activation energy was estimated at 179.5 kJ/mol, which was higher than the activation energy of the decomposition of glucose to HMF (137.5 kJ/mol).

Fagan *et al.* performed experiments on the hydrolyses of kraft paper slurry using 0.2–1 wt% sulfuric acid as the catalyst at 180 – 230 °C.⁴²⁵ The experiments were carried out in a non-isothermal batch setup. A kinetic pseudo-first order model developed for the hydrolysis of wood chips by Saeman was used to fit the data.⁴⁰⁹ The activation energies were found to be 188.7 kJ/mol and 137.2 kJ/mol for the decomposition of cellulose and glucose, respectively.

Using an isothermal plug-flow reactor, Thompson and Grethlein performed a kinetic study on the acid-catalysed hydrolysis of purified Solka-Floc® purified cellulose (5–13.5 wt%) using 0.5–2 wt% sulfuric acid at 180–240 °C and short reaction times.⁴²⁶ The experimental data were best described using a the cellulose decomposition model proposed by Saeman,⁴⁰⁹ resulting in estimated activation energies of 177.8 kJ/mol and 136.8 kJ/mol for cellulose and glucose decomposition, respectively .

Malester *et al.* reported the kinetics of dilute acid hydrolysis of cellulose originating from municipal solid waste (MSW) with sulfuric acid as the catalyst.⁴²⁷ The experiments were carried out in a batch reactor at 200–240 °C. Experimental data were modelled using a homogeneous pseudo first order reaction network *viz* the reaction of cellulose to glucose and subsequent conversion of glucose to its decomposition products. The activation energies were estimated at 171.5 kJ/mol for the conversion of cellulose to glucose and 142.3 kJ/mol for the decomposition of glucose.

Antal and co-workers examined the acid catalysed hydrolysis of cellulose in a percolation reactor using 5 mM dilute sulfuric acid as the catalyst at 190–250 °C.²⁷² They reported that the classical model of two sequential reactions for the decomposition of cellulose to glucose does not adequately describe cellulose hydrolysis at temperatures below 220 °C. The authors proposed a side reaction, i.e. the decomposition of cellulose to non-hydrolysable oligomers, to compensate for the imperfect glucose yields. Activation energies of 140 kJ/mol for the decomposition of cellulose to glucose and 100 kJ/mol for the decomposition of cellulose to non-hydrolysable sugars were reported.

Sasaki *et al.*⁴²⁸ investigated the non-catalysed thermal degradation of cellobiose in subcritical and supercritical water. The experiments were carried out in a continuous microreactor at 325–400 °C, 25–40 MPa and residence times of 0.01–0.54 s. The decomposition of cellobiose proceeds through two parallel reactions: hydrolysis to glucose

and retro-aldol condensation to lycosil-erythrose. Both pathways resulted in glucose, which subsequently converted to fragmented products (HMF, furfural, erythrose, glyceraldehyde, dihydroxyacetone). The degradation of cellobiose was modelled using a first-order reaction. An activation energy of 111.2 kJ/mol was obtained. The authors also reported the conversion of microcrystalline cellulose in subcritical and supercritical water.⁴²⁹ The reactions were performed at 290–400 °C, at a fixed pressure of 25 MPa and residence times of 0.02–13.1 s using a continuous microreactor. The rate of cellulose conversion was modelled using a shrinking-core (grain) model, in which two regimes were discriminated. Below 370 °C, the activation energy was 145.9±4.6 kJ/mol. Above 370 °C, the conversion rate of cellulose was much faster due to the contribution of swelling or dissolution of cellulose and possibly pyrolytic depolymerisation of cellulose, with an activation energy of 547.9 ± 27.8 kJ/mol.

Girisuta *et al.* reported the kinetics of the acid-catalysed decomposition of cellulose to levulinic acid using 0.05–1 M sulfuric acid as the catalysts.¹⁸⁹ The reactions were carried out in glass batch reactors with 1.7–14 wt% microcrystalline cellulose as the starting material at 180–230 °C. Experimental data were modelled using a power law model for 6 individual reactions, including that of the formation and degradation of HMF. The activation energy for the degradation of cellulose to humins (174.7 kJ/mol) was higher than the activation energy for the main reaction, i.e. the hydrolysis of cellulose to glucose (151 kJ/mol). This kinetic model was applied on the acid catalysed conversion of a real biomass source, namely water hyacinth.¹⁶⁷ Though these studies were performed to optimise LA yields, HMF was included as an intermediate and the results may also be used to select optimal reaction conditions for high HMF yields.

Recently Shen and Wyman reported a kinetic study on the acid-catalysed decomposition of microcrystalline cellulose using HCl (0.309 – 0.927 M) as the catalyst.⁴³⁰ The reactions were carried out in an isothermal batch reactor at 160–200 °C for up to 50 min. Experimental data were modelled using a homogenous pseudo first order reaction for six individual reactions, involving the formation and degradation of HMF. Compared to the scheme proposed by Girisuta *et al.*,¹⁸⁹ the author did not include the decomposition of cellulose to insoluble products. The activation energy for cellulose decomposition to glucose was estimated at 95.6 kJ/mol, which was considerably lower than the activation energies reported for sulfuric acid catalysed cellulose decomposition (151–184 kJ/mol), indicating that HCl is a more effective catalyst than sulfuric acid for this reaction.

Recently, Vazquez *et al.* reported a kinetic study on the acid catalysed hydrolysis of wheat straw in batch.⁴³¹ The reactions were carried out at a fixed temperature of 130°C using sulfuric acid with the main objective to study optimum conditions for xylose production. Kinetic models were determined, not only for the target xylose but also for HMF and other intermediates, using a pseudo homogeneous irreversible first order approach.

Cellulose and lignocellulosic biomass, non-aqueous systems

Vanoye *et al.* performed a kinetic study on the acid-catalysed hydrolysis of cellobiose in [EMIm]Cl using 3.5 mM methanesulfonic acid as the catalysts and small amounts of water (3.5 mM) as the co-solvent.⁴²⁴ The reactions were carried at 80–110 °C in a magnetically stirred (700 rpm) glass micro-reactor. The hydrolysis of 10 wt% cellobiose was modelled using two successive first order reactions involving the decomposition of cellobiose to glucose and the subsequent decomposition of glucose. Activation energies of 111 ± 12 kJ/mol and 102 ± 9 kJ/mol were reported for cellobiose hydrolysis and glucose degradation.

Bell *et al.* carried out kinetic studies in a batch set up on the hydrolysis of cellulose in typical ionic liquids ([EMIm]Cl and [BMIm]Cl) using mineral acid catalysts with variable amounts of water present.⁴³² Glucose, cellobiose and HMF were observed as primary reaction products. The rate of glucose formation was determined to be first order in the concentration of dissolved glucans and zero order in the concentration of water with an activation energy of 96 kJ/mol.

Polyfructans and Oligofructans

Though several studies revealed that polyfructans such as inulin, are excellent starting materials for HMF production in water^{183,184,186} and ionic liquid systems,^{367,433} attempts to quantify and model HMF yields have not been published to date.

Heyraud *et al.* examined the acid-catalysed hydrolysis of oligofructans obtained from the Jerusalem artichoke. The purified oligofructans with degrees of polymerisation (d.p.) between 2 and 7 were hydrolysed individually at a fixed temperature of 70 °C using aqueous sulfuric acid at pH 2.⁴³⁴ The experimental data were modelled using pseudo first order kinetics. Cleavage of the glucose-fructose linkage was identified as the main limiting step for the acid catalysed hydrolysis of polyfructan from the juice of Jerusalem artichokes.

Christian *et al.* studied the kinetics of the formation of di-D-fructose dianhydrides, a family of isomeric cyclic difructans, during thermolysis of pure inulin in the presence of citric

acid.¹⁵⁴ The reactions were performed at 160–180 °C in a teflon-lined batch reactor immersed in an oil bath.

Blecker *et al.* reported a kinetic study on the acid catalysed hydrolysis of five commercial oligofructans.⁴³⁵ The reactions were carried out at 7 – 130 °C using HCl as the catalyst with pH values between 2.0 and 4.2. The decomposition of the oligofructans was modelled using first order kinetics with fructose considered as the main reaction product. The formation of HMF was not reported. The activation energy for the conversions of oligofructans to fructose was estimated at 109±10 kJ/mol.

L'Homme *et al.* performed experiments on the acid catalysed hydrolysis of oligofructans such as 1-kestose (GF2), nystose (GF3), and fructofuranosylnystose (GF4).⁴³⁶ The reactions were performed in mineral-acid buffered aqueous solutions at pH 4, 7, and 9 at 80–120 °C. Experimental data were modelled using first order kinetics. The decomposition rate of oligofructan is faster in acidic conditions than in neutral or basic conditions. Activation energies of 80.9, 76.2, and 84.6 kJ/mol were reported for 1-kestose, nystose, and fructofuranosylnystose respectively. The formation rates of the decomposition products of these reactions, either fructose or HMF, were not reported.

Discussion

The decomposition of cellulose in aqueous systems is often modelled using homogeneous models based on a pseudo first order approach. Figure 4 shows the reported activation energies for the decomposition of cellulose, cellobiose and oligofructan. The activation energies for the acid catalysed decomposition of cellulose in water are between 79 and 189 kJ/mol. However, when excluding the low values obtained by Chang *et al.*⁴¹⁸ and Shen and Wyman,⁴³⁰ (75 kJ/mol and 96 kJ/mol, respectively), the average value is about 168 kJ/mol. Two studies have been performed on the decomposition of cellobiose, one in water and one in an ionic liquid. The activation energy for cellobiose decomposition in the ionic liquid using methanesulfonic acid as a catalyst was found to be 100 kJ/mol, which is close to the value found for the non-catalytic thermal decomposition of cellobiose in subcritical conditions.

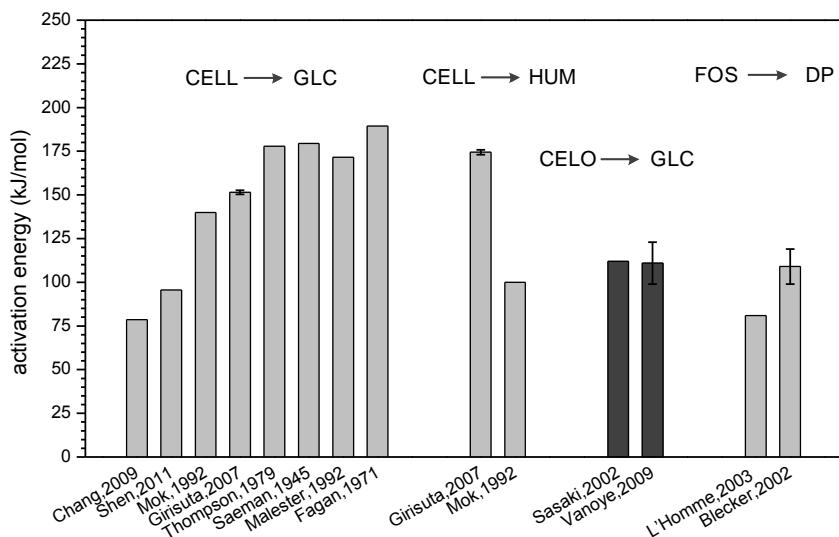


Figure 4. Activation energies for the conversion of cellulose (CELL: cellulose, GLC: glucose, HUM: humin, CELO: cellobiose, FOS: oligofructan, DP: decomposition product; light grey bars: aqueous systems; dark grey bars: non-aqueous systems including mixed solvents and biphasic systems)

2.5.2.4 Kinetic studies on the decomposition of HMF

HMF is an intermediate in the proposed reaction network for the conversion of C6-sugars to levulinic acid. For HMF synthesis, the undesired reactions of HMF to LA, FA and humins should be suppressed as much as possible. To gain insight in the reactivity of HMF, kinetic studies using HMF as the starting material have been reported. An alternative approach involves the investigation of the dehydration of C6-sugars where both the formation and the subsequent conversion of HMF are modelled in an integrated manner (see Table 35). In this paragraph, only the studies with HMF as the starting material are discussed and the results are compiled in Table 38.

Thermal decomposition of HMF

Luijkx *et al.* investigated the non-catalytic decomposition of HMF in subcritical water.⁴³⁷ The experiments were carried out with 0.05 M HMF in a tubular flow reactor at 290–400 °C, a fixed pressure of 27.5 MPa, and residence times ranging from 1 to 15 minutes. 1,2,4-benzenetriol was identified as the main reaction product with selectivities up to 46% at 50% HMF conversion. The rate of HMF decomposition was modelled as a pseudo-first order reaction. A linear Arrhenius plot could only be obtained in the temperature range of 290–350 °C, from which an activation energy of 47.7 kJ/mol was obtained.

Recently Chantanapum *et al.* studied the thermal decomposition of HMF in both subcritical and supercritical water.⁴³⁸ The experiments were performed in a continuous flow reactor at 175–450 °C and a fixed pressure of 25 MPa for 80–400 s. A series of first-order reactions was proposed to model the decomposition of HMF to intermediate liquid products and the subsequent decomposition to gaseous products, mainly CO₂, CO, and H₂. The intermediate liquid products were not identified and thus the kinetic data were analysed using total organic carbon TOC yield of liquid products and carbon content of the gaseous products. A characteristic Arrhenius plot could be obtained for the temperature window of 175 – 450 °C. An activation energy of 75.8 kJ/mol was obtained, which was considerably higher than reported by Luijkx *et al.*⁴³⁷ In addition, contrary to Luijkx's work, the authors found a lower rate of decomposition of HMF and tar, char and other high-molecular-weight compounds were not detected. The authors suggested that these differences were caused by different heating trajectories and the use of more dilute HMF solutions (0.02 M).

As part of a kinetic study on the thermal decomposition of glucose in water, Jing *et al.* investigated the kinetics of the thermal decomposition of HMF in subcritical water in batch (180–260 °C, 100 bar, 300 rpm).²⁴⁹ Experimental data were modelled using a first order approach using a kinetic scheme involving two parallel reactions to incorporate the formation of LA and insoluble humins. Activation energies of 89.28 kJ/mol and 108.5 kJ/mol were reported for the reaction of HMF to LA and the side reaction to humins, respectively.

Acid-catalysed hydrolysis of HMF, aqueous systems

The first kinetic study on the reaction of HMF to LA and FA was performed in water under reflux with a protective atmosphere by Teunissen in 1930.³⁹³ An initial HMF concentration around 0.08 M was applied with a range of acids at 0.1-0.5 N . The reaction was modelled using a first order approach for both HMF and the catalyst. The rate of the reaction was shown to be a function of the acid catalyst, with HI giving the highest reaction rates and oxalic acid the lowest.

McKibbins *et al.* studied the kinetics of the rehydration of HMF (0.06–0.14 M) to levulinic acid in 0.025–0.4 N aqueous sulfuric acid at 160–220 °C in glass ampoules.⁴¹¹ The experimental data were modelled using a first order approach, leading to an activation energy of 96.8 kJ/mol.

Baugh *et al.* performed kinetic studies on the decomposition of HMF in water using a mixture of butyric acid and phosphoric acid as the catalyst at pH values between 1 and 4.⁴¹⁵ The reactions were performed at 170–230 °C in batch. The concentration of HMF versus time

was determined and the data were modelled using a pseudo first order approach in HMF leading to an activation energy of 55.9 kJ/mol.

Girisuta *et al.* investigated the kinetics of HMF decomposition to LA/FA and humins in glass ampoules, with an initial HMF concentration of 0.1–1 M in 0.05–1 M aqueous sulfuric acid at 98–181 °C.¹⁶⁴ An extended kinetic framework was proposed, including the decomposition of HMF to humins besides the reaction to LA and FA, using a power law model. This resulted in an activation energy of about 111 ± 2 kJ/mol for both the main reaction to LA/FA and the side reaction to humins. The order in HMF for the main reaction (0.88) was lower than for the reaction to humins (1.23).

As part of a kinetic study on the decomposition of fructose, Asghari *et al.* examined the decomposition of HMF, catalysed by HCl, in subcritical water.⁴⁰⁴ The reactions were performed at 210–270 °C, 4 MPa and an initial pH of 1.8 in a continuous tubular reactor with residence times of 0.5–300 s. The experimental data were modelled assuming pseudo first order kinetics in HMF for both the reaction to LA/FA and the formation of humins, resulting in activation energies of 94.1 kJ/mol for the main reaction and 121.5 kJ/mol for the side reaction to humins.

Acid-catalysed hydrolysis of HMF, multi-solvent systems

In 1931 Teunissen investigated the kinetics of the acid catalysed decomposition of HMF in mixtures of water with up to 40 wt% methanol and 75 wt% ethanol.⁴³⁹ The experiments were either carried out at the boiling point of the mixture in a reflux system or at a fixed temperature of 100 °C in a closed bottle, with 0.5 N HCl as the catalyst for all experiments. In the presence of either methanol or ethanol, the decomposition rate of HMF to levulinic acid and formic acid was considerably lower, with the reaction constants decreasing considerably with increasing alcohol concentration. The hydrolysis of HMF was not observed when heated in 40 wt% methanol or 75 wt% ethanol. The amount of humins produced after 8 h reaction time decreased at higher alcohol intakes. Even though there were indications of alcoholysis reactions, the products of these reactions were not determined at that time. More recently, the formation of HMF-ethers and levulinate esters were reported when reacting fructose and glucose in acidic alcohol mixtures.^{233,440}

Discussion

Figure 5 provides the activation energies for the decomposition of HMF, both from studies using HMF as the starting materials and studies in which data were derived from sugar

dehydration data. The activation energies range between 47 and 210 kJ/mol for the decomposition of HMF to levulinic acid. For the decomposition reaction of HMF to humins, the activation energies vary between 100 and 125 kJ/mol. Asghari *et al.*,⁴⁰⁴ Jing *et al.*,²⁴⁹ and Abdilla *et al.*⁴⁰⁵ reported that the formation of humins from HMF has a higher activation energy than the rehydration of HMF to levulinic acid. Contrary to these observations, Girisuta *et al.* found similar activation energies for both reactions.¹⁶⁴

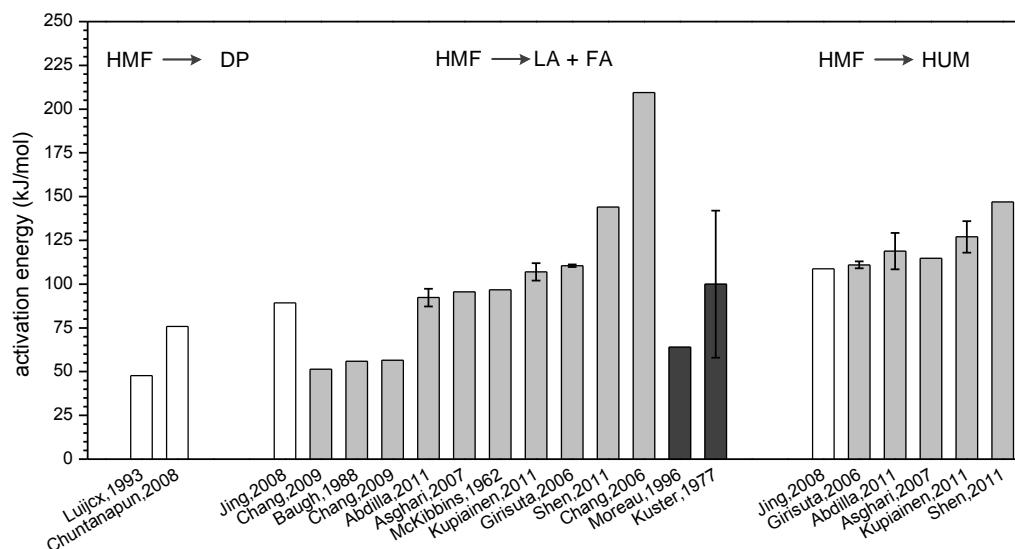
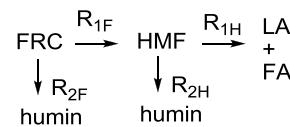


Figure 5. Activation energies for the conversion of HMF (light grey bars: aqueous systems; dark grey bars: non-aqueous systems including mixed solvents and biphasic systems; white bars: thermal aqueous systems)

Table 35. Kinetic expressions for the conversion of fructose

Scheme	Solvent	[FRC] ₀	Catalyst	T	kinetic expression (M/min)	activation energy (kJ/mol)	Ref.
Aqueous Systems							
No catalyst							
FRC $\xrightarrow{R_F}$ Decomposition Product	H ₂ O	0.25 wt%	-	300 – 350 °C (25- 40 MPa)	at T = 300 °C P = 25 MPa $R_F = 28.8 \cdot [FRC]$	-	121
				400 °C (40 MPa)			
Homogenous Catalysts							
FRC $\xrightarrow{R_{1F}}$ X $\xrightarrow{R_{1X}}$ HMF $\xrightarrow{R_{1H}}$ Y $\xrightarrow{R_{1Y}}$ LA + FA ↓ R _{2X} ↓ R _{2Y} humin humin	H ₂ O	0.25–1 M	[HCl] = 0.2–1.0 M	95 °C	$R_{1F} = 0.40 \cdot 10^{-2} [FRC]$ $R_{1H} = 0.42 \cdot 10^{-2} [HMF]$ at [HCl] = 0.5 M	-	155

	H ₂ O	0.03 M	[HCl], pH = 1.8	210–270 °C, 40 – 150 bar	at T = 210 °C, 40 bar	$E_{R1F} = 160.6$	404
					$R_{1F} = 0.272 \cdot [FRC]$	$E_{R2F} = 132.2$	
					$R_{2F} = 0.031 \cdot [FRC]$	$E_{R3F} = 101.9$	
					$R_{3F} = 6.12 \cdot [FRC]$	$E_{R1H} = 95.6$	
					$R_{1H} = 0.181 \cdot [HMF]$	$E_{R2H} = 141.5$	
					$R_{2H} = 0.003 \cdot [HMF]$		
$FRC \xrightarrow{R_F} HMF$	H ₂ O	-		180–220 °C, 100 bar	at T = 200 °C	$E_{RF} =$	123
					$R_F = 0.08 \cdot [FRC]$	126.8 ± 3.3	
		10.8 mg/ml	formic acid = 2.8–13.9 g/ml	180–220 °C, 100 bar	at 10.8 mg/ml formic acid and T = 200 °C	$E_{RF} =$	123
					$R_F = 0.36 \cdot [FRC]$	112.0 ± 13	
		10.8 mg/ml	acetic acid = 10.8 mg/ml	180–220 °C, 100 bar	at 10.8 mg/ml acetic acid and T = 200 °C	$E_{RF} =$	123
					$R_F = 0.12 \cdot [FRC]$	125.60 ± 13	



H_2O	0.1–1M	$[\text{H}_2\text{SO}_4] = 5 \text{ mM–1M}$	140–180 °C	$R_{1F} = k_{1G} [\text{H}^+]^{0.96} [\text{FRC}]^{1.006}$ $k_{1F} = 1.093 \exp\left[-\frac{E_{R1H}}{R}\left(\frac{1}{T} - \frac{1}{413}\right)\right]$	$E_{R1F} = 123 \pm 5$	405
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$$\begin{aligned} R_{2H} &= k_{2H} \cdot [\text{H}^+]^{1.06} [\text{FRC}]^{1.18} \\ k_{2H} &= 0.547 \exp\left[-\frac{E_{R2H}}{R}\left(\frac{1}{T} - \frac{1}{413}\right)\right] \end{aligned}$$

Heterogeneous Catalysts

$\text{FRC} \xrightarrow{\text{R}_F} \text{HMF}$	H_2O	0.3 M	NbOPO_4	90 – 110 °C	$T=100 \text{ }^\circ\text{C} R_F = 0.0229 \cdot [\text{FRC}]$	$E_{RF} = 65.8 \pm 8$	200
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Non Aqueous Systems

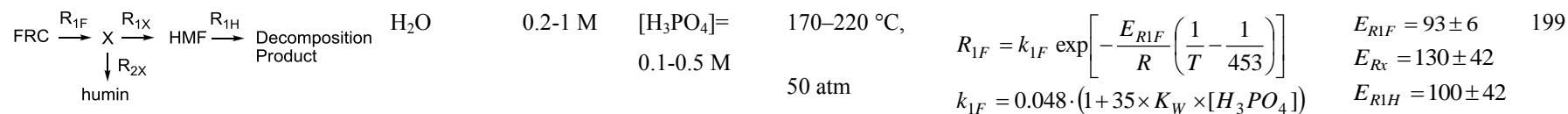
Homogenous Catalysts

$\begin{array}{ccc} \text{FRC} & \xrightarrow{\text{R}_{1F}} & \text{HMF} \\ \downarrow \text{R}_{2F} & & \downarrow \text{R}_{2H} \\ \text{SP1} & & \text{SP2} \end{array}$	MeOH	0.06 M	$[\text{H}_2\text{SO}_4] = 10 \text{ mM}$	120–270 °C, 150–350 bar	at $T=180 \text{ }^\circ\text{C}, 200 \text{ bar}$ $R_{1F} = 8.7 \cdot [\text{FRC}]$ $R_{2F} = 2.88 \cdot [\text{FRC}]$	$E_{RF} = 80$ ($R_F = R_{1F} + R_{2F}$)	233
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			$R_{1H} = 14.6 \cdot [HMF]$		
			$R_{2H} = 0.18 \cdot [HMF]$		
$\begin{array}{ccc} FRC & \xrightarrow{R_{1F}} & HMF \xrightarrow{R_{1H}} AMF \\ & \downarrow R_{2F} & \\ & SP1 & \end{array}$	CH ₃ CO ₂ H	0.06 M	[H ₂ SO ₄]= 10 mM	180 °C, 200 bar	$R_{1F} = 3.18 \cdot [FRC]$ $R_{2F} = 7.38 \cdot [FRC]$ $R_{1H} = 9.12 \cdot [HMF]$
FRC	$\xrightarrow{R_F}$	HMF	$\xrightarrow{R_H}$	Product	[HMIm]Cl 0.01-2.5
					90–120 °C
					$R_F = 0.1681 \cdot [FRC]$
					$E_{RF} = 143$
					$E_{RH} = 69$
$\begin{array}{ccc} FRC & \xrightarrow{R_{1F}} & HMF \\ & \downarrow R_{2F} & \\ & by-products & \end{array}$	[BMIM]Cl	200 mg in 2 g ionic liquid	7 mol% IrCl ₃	80–100 °C at T = 80 °C	$R_{1F} = 0.0019 \cdot [FRC]$ $R_{2F} = 0.0011 \cdot [FRC]$
					$E_{R1F} = 165$
					$E_{R2F} = 124$

Two solvents/Biphasic Systems

Homogeneous Catalysts

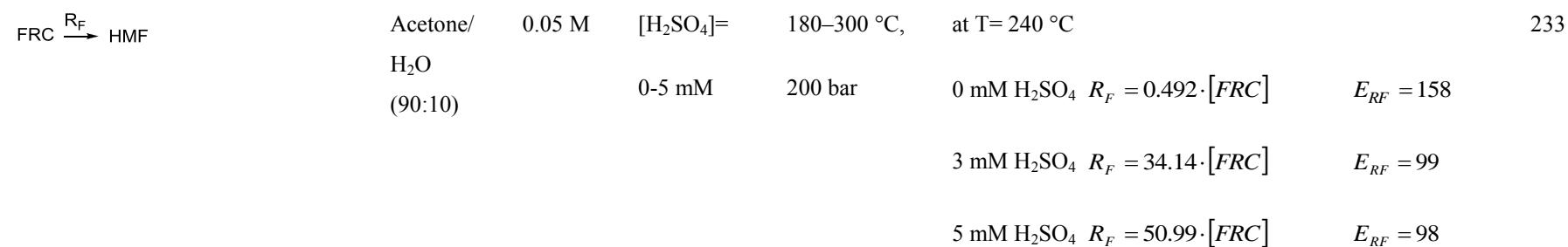


$$R_{1X} + R_{2X} = k_X \exp\left[-\frac{E_{R1F}}{R}\left(\frac{1}{T} - \frac{1}{453}\right)\right]$$

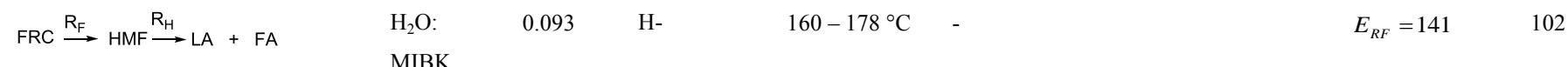
$$k_X = 13 \cdot (K_W \times [H_3PO_4])$$

$$R_{1H} = k_{1H} \exp\left[-\frac{E_{R1F}}{R}\left(\frac{1}{T} - \frac{1}{453}\right)\right]$$

$$k_{1H} = 0.33 \cdot (K_W \times [H_3PO_4])$$



Heterogeneous Catalysts

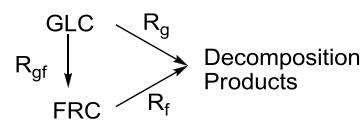


	(1:5)	mordenites	$E_{RH} = 64$
FRC $\xrightarrow{R_F}$ HMF	Acetone/ H ₂ O	2 wt% 50wx8-100 (70/30 w/w)	Dowex 100-180 °C, $R_F = 0.15 \cdot [FRC]$ at 150 °C MW
			$E_{RF} = 103.4$ 207
FRC $\xrightarrow{R_F}$ HMF	Acetone/ DMSO	2 wt% 50wx8-100 (70:30 w/w)	Dowex 100-180 °C, $R_F = 0.1681 \cdot [FRC]$ at 150 °C MW
			$E_{RF} = 60.4$ 221

Table 36. Kinetic expressions for the conversion of glucose

Scheme	Solv ent	[GLC], 0	Catalyst	T	kinetic expression (M/min)	activation energy (kJ/mol)	Ref.
$\text{GLC} \xrightarrow{R_G} \text{Decomposition Product}$	H_2O	0.278 M	$[\text{H}_2\text{SO}_4] =$ 0.4, 0.8, 1.6 wt%	170–190 °C	$R_G = 2.38 \times 10^{14} [\text{H}_2\text{SO}_4]^{1.02} \exp\left(-\frac{E_{RG}}{RT}\right) [\text{GLC}]$	$E_{RG} = 137.5$	409
$\text{GLC} \xrightarrow{R_G} \text{HMF} \xrightarrow{R_H} \text{LA} + \text{FA}$	H_2O	0.056 M	$\text{HCl} =$ 0.35 N	100–150 °C	at 150 °C $R_G = 2.8 \times 10^{-3} [\text{GLC}]$	$E_{RG} = 133$	410
$\text{GLC} \xrightarrow{R_G} \text{HMF} \xrightarrow{R_H} \text{LA} + \text{FA}$	H_2O	0.56– 1.11 M	$[\text{H}_2\text{SO}_4] =$ 0.025 – 0.8 N	140–250 °C	$R_H = 2.4 \times 10^{11} \alpha_H [\text{H}_2\text{SO}_4] \exp\left(-\frac{E_{RH}}{RT}\right) [\text{HMF}]$ $R_G = 9.27 \times 10^{14} \alpha_G [\text{H}_2\text{SO}_4] \exp\left(-\frac{E_{RG}}{RT}\right) [\text{GLC}]$	$E_{RH} = 96.8$ $E_{RG} = 136.8$	411
$\text{GLC} \xrightarrow{R_G} \text{Decomposition Product}$	H_2O	0.4–6 wt%	$[\text{H}_2\text{SO}_4]:$ 0.5–4.0 wt%	180–224 °C	ampoule (0.5 – 7 min): $R_G = 2.55 \times 10^{12} [\text{H}_2\text{SO}_4]^{0.8955} \exp\left(-\frac{E_{RG}}{RT}\right) [\text{GLC}]$	$E_{RG} = 128.6$	412

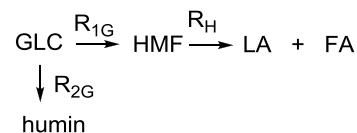
$\text{GLC} \xrightarrow{R_G} \text{Decomposition Product}$	H_2O	0.4–6 wt%	$[\text{H}_2\text{SO}_4] = 0.5\text{--}3.8 \text{ wt\%}$	flow reactor (0.06 – 0.27 min): $R_G = 3.84 \times 10^9 [\text{H}_2\text{SO}_4]^{0.5687} \exp\left(-\frac{E_{RG}}{RT}\right) [\text{GLC}]$	$E_{RG} = 87.8$	412
$\text{GLC} \xrightarrow{R_G} \text{Decomposition Product}$	H_2O	0.006–0.33 M	a mixture of butyric acid and H_3PO_4 adjusted to pH = 1–4	$R_G = k_G \exp\left[\frac{E_{RG}}{RT}\right]$ $k_G = [4.9 \times 10^{11} + 1.5 \times 10^{13} (10^{-pH}) + 4.7 \times 10^{22} (10^{pH-14})]$	$E_{RG} = 121$	415
$\text{Glucose} \rightleftharpoons \text{Reversible Components}$ $k^{\text{Glu}} \searrow \text{Decomposition Products} \quad k^{\text{Rc}} \swarrow$	H_2O	0.125 M	H_2SO_4 , pH 1.5–2.2	$k^{\text{Glu}} = [2.132 \times 10^{13} + 2.148 \times 10^{15} \times H^+]$ $\exp\left[-\frac{E_{RG}}{RT}\right]$ $k_e = [1.2531 - 35.37 \times H^+] \exp\left[-\frac{10640}{RT}\right]$	$E_{RG} = 139$	416
$\text{GLC} \xrightarrow{R_G} \text{Decomposition Product}$	H_2O	4 – 12 wt%	$[\text{H}_2\text{SO}_4] = 4\text{--}20 \text{ wt\%}$	$R_{1G} = 1.91 \cdot 10^{16} [H^+] \cdot fH \exp(-\frac{E_{RG}}{RT}) [\text{GLC}]$	$E_{RG} = 130.4$	414



H ₂ O	0.007M	-	300–350 °C	$R_{gf} = 14.4 \cdot [GLC]$	$E_{Rg+Rgf} = 96$
				$R_g = 12.6 \cdot [GLC]$	122
				$R_f = 49.2 \cdot [GLC]$	



H ₂ O	0.5 %	-	180–260 °C	$\frac{C}{C_0} = \exp(-k\tau^n)$	$E_{RG} = 155$	408
	w/v					



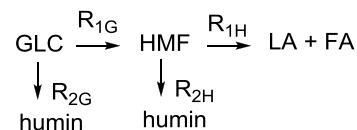
H ₂ O	[H ₂ SO ₄]: 1%, 3%, 5%	170–190 °C	$R_{1G} = k_{1G} [H^+]^{0.427} [GLC]$	$E_{R1G} = 86.33$	418
			$k_{1G} = 4.597 \times 10^9 \exp\left[-\frac{E_{R1G}}{RT}\right]$	$E_{R2G} = 56.95$	

$$R_{2G} = k_{2G} [H^+]^{0.973} [GLC]$$

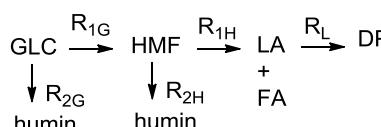
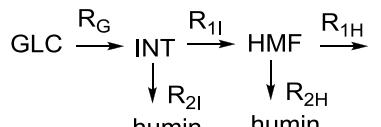
$$k_{1G} = 4.318 \times 10^7 \exp\left[-\frac{E_{R2G}}{RT}\right]$$

$$R_H = k_H [H^+]^{0.119} [GLC]$$

$$k_H = 1.20 \times 10^{23} \exp\left[-\frac{E_{RH}}{RT}\right]$$



H ₂ O	0.1–1 M	[H ₂ SO ₄]: 0.05–1 M	140–200 °C	$R_{1G} = k_{1G} [H^+]^{1.13} [GLC]^{1.08}$	$E_{R1G} =$	165
				$k_{1G} = 0.013 \exp\left[-\frac{E_{R1G}}{R} \left(\frac{1}{T} - \frac{1}{413}\right)\right]$	152.2 ± 0.7	

			$R_{2G} = k_{2G} \cdot [H^+]^{1.12} [GLC]^{1.13}$	$E_{R2G} = 164.7 \pm 0.6$
			$k_{2G} = 0.013 \exp\left[-\frac{E_{R2G}}{R}\left(\frac{1}{T} - \frac{1}{413}\right)\right]$	
	H_2O 0.06 M -	$180\text{--}260\ ^\circ\text{C}$	$R_{1G} = 5.06 \cdot 10^9 \exp(-\frac{E_{R1G}}{RT}) [GLC]$	$E_{R1G} = 108.0$ 249
			$R_{2G} = 4.29 \cdot 10^{12} \exp(-\frac{E_{R2G}}{RT}) [GLC]$	$E_{R2G} = 135.71$ $E_{R1H} = 89.28$ $E_{R2H} = 108.91$
	H_2O 10 200 mg/ml	$120\text{--}180\ ^\circ\text{C}$	$R_{1H} = 2.62 \cdot 10^6 \exp(-\frac{E_{R1H}}{RT}) [HMF]$	
			$R_{2H} = 3.57 \cdot 10^9 \exp(-\frac{E_{R2H}}{RT}) [HMF]$	
	H_2O 56 mM or 112 mM Formic acid: 5-20 wt%	$100\ ^\circ\text{C}$	$R_{1G} = 1.88 \cdot 10^{14} \exp(-\frac{E_{R1G}}{RT}) [GLC]$	$E_{R1G} = 133$ 413
			$R_G = 6.5 \cdot 10^{-6} \cdot [GLC]$	421
			$R_G = k_G \cdot [GLC]$	$E_{RG} = 153 \pm 2$
			$k_G = (0.018 + 2.6[H^+]) \exp\left[-\frac{E_{RG}}{R}\left(\frac{1}{T} - \frac{1}{473}\right)\right]$	

$$R_{1I} = k_I \cdot [INT] \quad E_{R1I} =$$

$$k_{1I} = (0.109 + 8.6[H^+]) \exp\left[-\frac{E_{R1I}}{R}\left(\frac{1}{T} - \frac{1}{473}\right)\right] \quad 110 \pm 5$$

$$R_{2I} = k_{2I} \cdot [INT] \quad E_{R2I} =$$

$$k_{2I} = (0.058 + 2.9[H^+]) \exp\left[-\frac{E_{R2I}}{R}\left(\frac{1}{T} - \frac{1}{473}\right)\right] \quad 117 \pm 4$$

$$R_{1H} = k_{1H} \cdot [HMF] \quad E_{R1H} =$$

$$k_{1H} = (0 + 5.5[H^+]) \exp\left[-\frac{E_{R1H}}{R}\left(\frac{1}{T} - \frac{1}{473}\right)\right] \quad 127 \pm 9$$

$$R_{2H} = k_{2H} \cdot [HMF]$$

$$k_{2H} = (0.031 + 2.5[H^+]) \exp\left[-\frac{E_{R2H}}{R}\left(\frac{1}{T} - \frac{1}{473}\right)\right]$$

Table 37. Kinetic expression for the acid-catalysed conversion of Cellulose and Lignocellulosic biomass

Scheme	Solvent	[Cell] ₀	Catalys	T t	kinetic expression (M/min)	activation energy (kJ/mol)	Ref
Cellulose/Lignocellulosic Biomass							
CEL $\xrightarrow{R_C}$ GLC $\xrightarrow{R_G}$ Decomposition Product	H ₂ O	Douglass-fir, Liquid to solid ratio: 5 – 20	[H ₂ SO ₄]: 0.4, 0.8, 1.6 wt%	170–190 °C	$R_C = 1.73 \times 10^{19} [H_2SO_4]^{1.34} \exp\left(-\frac{E_{RC}}{RT}\right) [CEL]$ $R_G = 2.38 \times 10^{14} [H_2SO_4]^{1.02} \exp\left(-\frac{E_{RG}}{RT}\right) [GLC]$	$E_{RC} = 179.5$ $E_{RG} = 137.5$	409
	H ₂ O	kraft paper, 0.5 g in 20 ml	[H ₂ SO ₄]: 0.2 – 1 wt%	180–230 °C	$R_C = 28 \times 10^{19} [H_2SO_4]^{1.78} \exp\left(-\frac{E_{RC}}{RT}\right) [CEL]$ $R_G = 4.19 \times 10^{14} [H_2SO_4]^{0.55} \exp\left(-\frac{E_{RG}}{RT}\right) [GLC]$	$E_{RC} = 189.4$ $E_{RG} = 137.8$	425

	H ₂ O	Solka-floc, purified	[H ₂ SO ₄]: 0.5 – 2.0	180–240 °C	$R_C = 1.22 \times 10^{19} [H_2SO_4]^{1.16} \exp\left(-\frac{E_{RC}}{RT}\right) [CEL]$	$E_{RC} = 177.8$	426
		cellulose: 5.0	wt% –			$E_{RG} = 136.8$	
			13.5%		$R_G = 3.79 \times 10^{14} [H_2SO_4]^{0.69} \exp\left(-\frac{E_{RG}}{RT}\right) [GLC]$		
	H ₂ O	cellulose from Municipal Solid Waste	H ₂ SO ₄ at pH 0.34 – 0.85	200–240 °C	$R_C = 1.16 \times 10^{19} 10^{(pH)} \exp\left(-\frac{E_{RB}}{RT}\right) [CEL]$	$E_{RC} = 171.5$	427
						$E_{RG} = 142.3$	
Celllobiose $\xrightarrow{R_C}$ Decomposition Product	H ₂ O	Celllobiose	-	325–400 °C (25–40 MPa)	$R_C = k [Celllobiose]$	$E_{RB} = 112$	428
CEL $\xrightarrow{R_C}$ Decomposition Product	H ₂ O	micro crystalline cellulose, 10 wt%	-	290–400 °C (250 bar)		at T < 370 °C	429
						$E_{RC} =$ 145.9 ± 4.6	

					at T > 370 °C
					$E_{RC} =$ 547.9 ± 27.8
	H_2O micro crystalline cellulose 1.7 – 14 wt%	$[H_2SO_4]:$ 0.05 – 1 M	$150\text{--}200\text{ }^\circ C$ $R_{1C} = k_{1c}[CEL]^{0.98}$ $k_{1c} = 0.410 \exp\left[-\frac{E_{R1C}}{R}\left(\frac{1}{T} - \frac{1}{448}\right)\right][H^+]^{0.96}$		$E_{R1C} = 151.5 \text{--} 189$
			$R_{2C} = k_{2c}[CEL]^{1.01}$ $k_{2c} = 0.065 \exp\left[-\frac{E_{R2C}}{R}\left(\frac{1}{T} - \frac{1}{448}\right)\right][H^+]^{0.94}$		$E_{R2C} = 174.7$
	$[EMI\text{M}]Cl$ 0.5 g in [EMIM]Cl	Cellulose methane sulfonic acid	$R_C = k[Cellobiose]$ $R_G = k_G[GLC]$		$E_{RC} = 111 \pm 12 \text{--} 424$
	H_2O $[H_2SO_4]:$ 1,2, 3 wt%	$190, 210, 230\text{ }^\circ C$	$R_C = k_C[H^+]^{1.434}[CELL]$ $k_C = 1.488 \times 10^{10} \exp\left[-\frac{E_{RC}}{RT}\right]$		$E_{RC} = 78.66 \text{--} 419$
					$E_{RG} = 61.06$

$$R_G = R_{1G} + R_{2G}$$

$$R_G = k_G [H^+]^{0.679} [GLC]$$

$$k_{1G} = 1.430 \times 10^7 \exp\left[-\frac{E_{RG}}{RT}\right]$$

$$R_{1G} = k_{1G} [H^+]^{0.268} [GLC] \quad E_{R1G} = 54.51$$

$$k_{1G} = 1.502 \times 10^5 \exp\left[-\frac{E_{R1G}}{RT}\right]$$

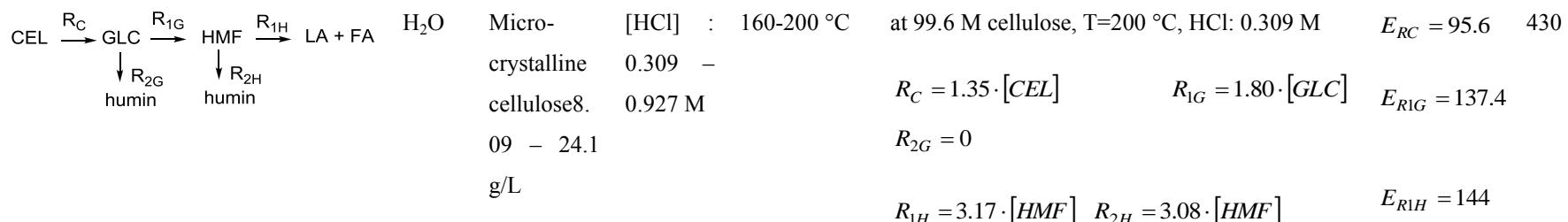
$$R_H = R_{1H} + R_{2H} \quad E_{RH} = 51.37$$

$$R_H = k_H [H^+]^{0.620} [HMF]$$

$$k_{1G} = 2.425 \times 10^6 \exp\left[-\frac{E_{RH}}{RT}\right]$$

$$R_{1H} = k_{1H} [H^+]^{0.804} [HMF] \quad E_{R1H} = 56.47$$

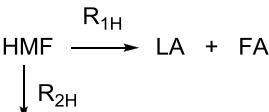
$$k_{1H} = 1.425 \times 10^7 \exp\left[-\frac{E_{R1H}}{RT}\right]$$



Oligofructan

$\text{FOS} \xrightarrow{R_F}$	Decomposition Product	H_2O	Commercial 1 FOS	7- 130 °C	$E = 109 \pm 10$	435
$\text{FOS} \xrightarrow{R_F}$	Decomposition Product	H_2O	1-kestose (GF2) nystose (GF3) fructofuran osylnystose (GF4)	aqueous solutions buffered at pH values of 4.0, 7.0, and 9.0	80 -120 °C at pH: 4, T:120 °C $R_F = 580 \cdot 10^4 \cdot [\text{GF2}]$ $R_F = 472 \cdot 10^4 \cdot [\text{GF3}]$ $R_F = 315 \cdot 10^4 \cdot [\text{GF4}]$	at pH = 4 $E_{GF2} = 80.9$ $E_{GF3} = 76.2$ $E_{GF4} = 84.6$

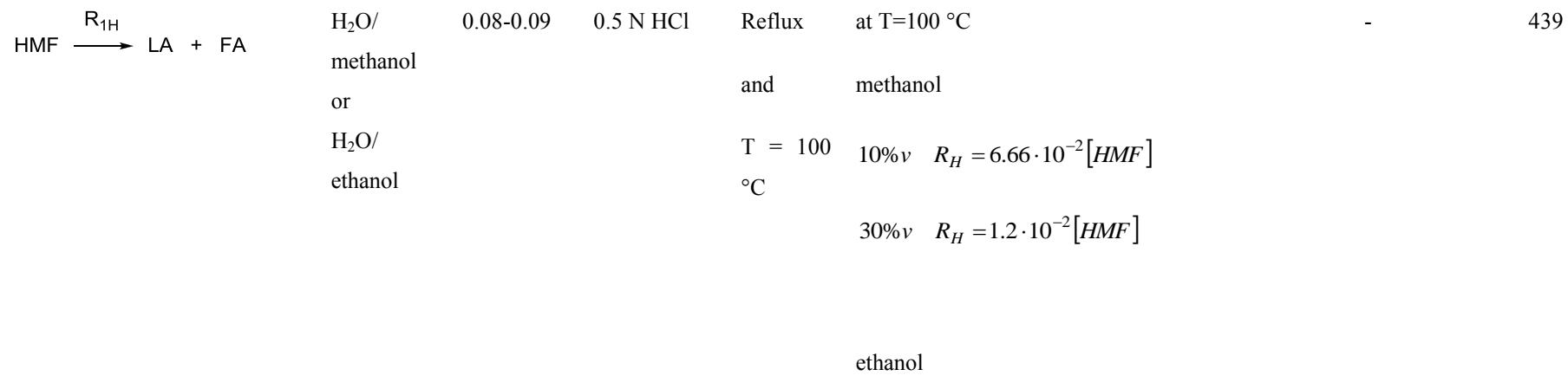
Table 38. Kinetic expression for the decomposition of HMF

$\text{HMF} \xrightarrow{R_{1H}} \text{LA} + \text{FA}$ 	H ₂ O	0.08-0.09	$[\text{H}_2\text{SO}_4]$, $[\text{HCl}], [\text{HBr}]$ or $[\text{HI}] =$ 0.1-0.5 N oxalic acid = 0.2 - 0.5 N	100	0.2 N oxalic acid 0.2 N H ₂ SO ₄ 0.2 N HCl 0.2 N HBr 0.2 N HI	$R_{1H} = 1.24 \times 10^{-2} [H^+] [HMF]$ $R_{1H} = 1.57 \times 10^{-2} [H^+] [HMF]$ $R_{1H} = 3.82 \times 10^{-2} [H^+] [HMF]$ $R_{1H} = 5.67 \times 10^{-2} [H^+] [HMF]$ $R_{1H} = 5.89 \times 10^{-2} [H^+] [HMF]$	-	393
H ₂ O	0.061- 0.139	[H ₂ SO ₄] = 0.025-0.4 N	160-220	$R_{1H} = 2.4 \times 10^{11} \alpha_H [\text{H}_2\text{SO}_4] \exp\left(-\frac{E_{R1H}}{RT}\right) [HMF]$	$E_{R1H} = 96.8$	411		
H ₂ O	0.25-1	[HCl] = 0.5-2.0 N	95	$R_{1H} = 0.001 [H^+]^{1.2} [HMF]$	-	155		
H ₂ O	0.024	a mixture of butyric acid and H_3PO_4 adjusted to	170-230	$R_{1H} = [1300 + 4.1 \times 10^6 (10^{-pH})] \exp\left(-\frac{E_{R1H}}{RT}\right) [HMF]$	$E_{R1H} = 55.9$	415		
		pH = 1-4						
$\text{HMF} \xrightarrow{R_{1H}} \text{LA} + \text{FA}$ 	H ₂ O	0.1-1	$[\text{H}_2\text{SO}_4] =$ 0.05-1 M	98 -181	$R_{1H} = 0.340 \exp\left[-\frac{E_{R1H}}{R} \left(\frac{1}{T} - \frac{1}{413}\right)\right] [H^+]^{1.38} [HMF]$	$E_{R1H} = 110.5 \pm 0.7$	164	

$$R_{2H} = 0.117 \exp \left[-\frac{E_{R2H}}{R} \left(\frac{1}{T} - \frac{1}{413} \right) \right] [H^+]^{1.07} [HMF]$$

$$E_{R2H} = \\ 111.0 \pm 2.0$$

H ₂ O	0.04	[HCl], pH = 1.8	210 270, MPa	- at T = 210 °C 4 R _{1H} = 0.199 · [HMF] R _{2H} = 0.003 · [HMF]	E _{R1H} = 95.6	404
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$$10\%v \quad R_H = 8.34 \cdot 10^{-2} [HMF]$$

$$35\%v \quad R_H = 3.3 \cdot 10^{-2} [HMF]$$

$$50\%v \quad R_H = 1.3 \cdot 10^{-2} [HMF]$$

2.5.3 Reactor Concepts

Most of the reported studies on HMF preparation from monomeric sugars like fructose as well as from more complex feeds are exploratory in nature and have been performed in lab scale equipment. As such, most studies are typically performed in batch setups (autoclaves, glass ampoules). This also appears to be the case for the few reported studies on kg scale HMF production. For instance, Rapp conducted the conversion of 11 kg fructose in water (33 wt%) using oxalic acid as the catalyst at 140 °C for 3 h in a stirred batch autoclave.¹⁹⁵ Using DMSO as the solvents, M'bazoа performed close to a kg-scale operation for the conversion of fructose to HMF in a stirred autoclave.³⁹⁶ In this chapter, reactor concepts other than typical laboratory batch set-ups will be discussed. Further details on pilot scale production are given in section 2.5.5.

2.5.3.1 Reactions in water

Some studies, particularly those at elevated temperature and pressure like in sub- and supercritical water, have been performed in continuous setups to allow for short contact times.^{203,204,404,441} Asghari and Yoshida utilised a home built continuous tubular reactor of SS 316 steel with an inside diameter of 25 mm to develop a kinetic model for the acid catalysed production of HMF from fructose at temperatures of 210 – 270 °C, pressures of 1-15 MPa, and residence times of 0.5 – 300 s. To allow accurate and fast heating, water was preheated separately to the target temperature, then mixed to the feed solution and subsequently passed through the reactor.

Tarabanko *et al.* reported the formation of HMF from fructose and sucrose at temperatures >200 °C in a flow reactor using phosphoric acid as the catalyst.²⁰³ HMF yields up to 40 % were attained when processing 0.25 M fructose at 240–250 °C using 0.01 M phosphoric acid. The corrosion rate of the reactor material (stainless steel 12Kh18N10T) was found to be 1-2 mm/year at the prevailing reaction conditions.

Continuous microreactors have also been explored for the synthesis of HMF in the absence of any catalyst. At extreme severity of 400 °C, 10 MPa and 10 s residence time, Japanese researchers at Advance Industrial Science and Technology (AIST) reported the synthesis of 80% pure HMF at 70% yield from aqueous fructose.⁴⁴¹ The estimated continuous production capacity was 500 kg/year for the setup.

Tuercke *et al.* examined the conversion of fructose to HMF in aqueous solutions using a continuous microreactor setup (Figure 6) at elevated temperatures.⁴⁴² Aqueous fructose and

HCl were introduced to the microreactor via two fluid inlets. A wide range of operating conditions (10–50 wt% fructose, 80–200 °C, 1–20 bar, 0.1–0.5 M HCl, 1–3 min residence times, 0.5–0.6 ml/min) was systematically explored to determine optimum process conditions. At optimum conditions of 10 wt% fructose and 0.1 M HCl in equal flow at 185 °C and 17 bar with 1 min residence time), an HMF selectivity of 75% at 71% fructose conversion was achieved when using a feed consisting of 10 wt% fructose. Compared to batch data at comparable conditions, the selectivity and conversion were increased considerably by 24% and 21%, respectively. Further improvement of the system by using DMSO as a co-solvent and MIBK/2-butanol as an extraction agent resulted in 85 % HMF selectivity at 97% fructose conversion.

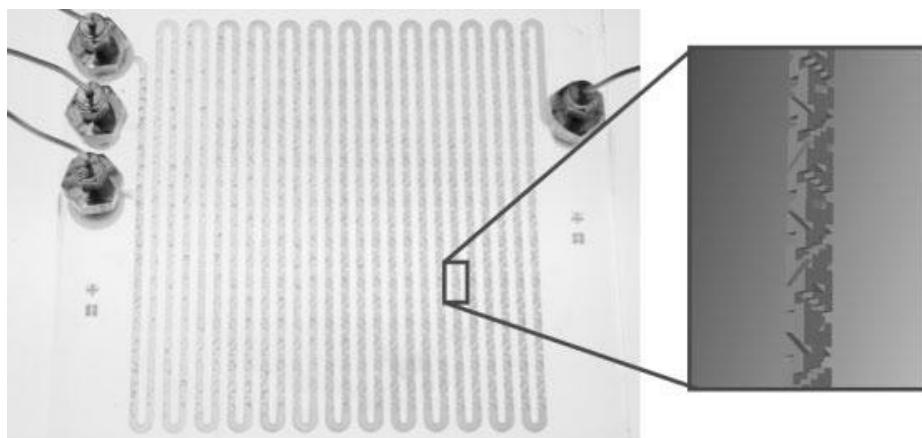


Figure 6. A continuous microreactor setup as used by Tuercke *et. Al.* Reproduced from Ref ⁴⁴² with permission from John Wiley and Sons

2.5.3.2 Reactions in non-aqueous and mixed solvent systems

A continuous setup has also been applied for the synthesis of HMF and derivatives, such as MMF, in low boiling solvents like acetone and methanol at supercritical conditions.^{206,233} The reactions were carried in a continuous high pressure reactor (pipe-in-pipe system) which can be heated up to 350 °C. Bicker *et al.* also proposed a continuous setup, as described in Figure 7, for the technical production of HMF in acetone and MMF in methanol.²³³ The flow system was operated at 180 °C for HMF production and at 240 °C for MMF production at a pressure of 10 MPa. Under milder reaction conditions than mentioned above (180 °C), Gruter and Dautzenberg demonstrated the production of HMF and EMF from sucrose, fructose or glucose in a continuous setup using either sulfuric acid or zeolites as the catalysts.²⁴⁴ The combined selectivity of HMF and EMF was over 90% at 25% sucrose conversion when dilute

sucrose solutions in ethanol/water (10 mM) was used at 195 °C in a continuous reactor with residence times of 6–60 s at a flow rate of 10 ml/min. When zeolite beta was used as the catalyst, the reactor was operated in a fixed bed mode. In this configuration, various sugar solutions, containing 55 mM sugar in 90% ethanol, were reacted at 180 °C. At high sugar conversion (98%), the yields of EMF were 37%, 22% and 28% for fructose, glucose, and sucrose respectively. The HMF yields were 1–2% for all the sugars.

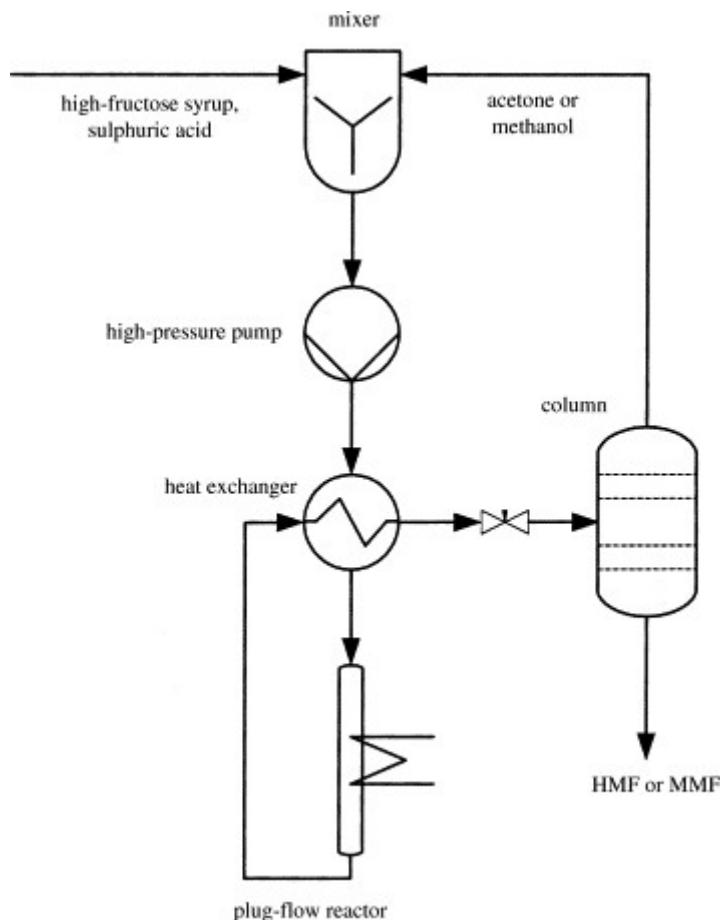


Figure 7. Simplified process flow sheet for HMF and MMF production in supercritical acetone or methanol. Reprinted from Ref²³³ with permission from Elsevier

For mixed solvent systems, both batch stirred reactors²⁹⁸ and continuous reactors (continuous stirred tank reactor (CSTR)¹⁹⁹ and tubular flow reactors^{102,294}) have been explored for the preparation of HMF in mixed solvent systems. For biphasic systems, several reactor configurations were employed to promote intense contact between the reaction and extraction phases. Cope *et al.* used a tubular flow reactor, operated in a semi-batch mode, to study the reaction of fructose in a biphasic system consisting of MIBK and water (7:1 v/v) for 9 h at 175 °C.³¹¹ The 60% HMF yield under prevailing conditions was considerably higher

compared to HMF yield in the absence of the organic extraction solvents, which was only 20–25 %.

Kuster reported the application of a CSTR for the production of HMF from fructose using MIBK as an *in situ* extracting agent at 180–200 °C, catalysed by H₃PO₄. The highest HMF selectivity was 75% at 65–85% conversion, obtained at 200 °C with 0.1 M H₃PO₄ and an MIBK/H₂O feed ratio of 4.

Rivalier *et al.* developed a continuous heterogeneous pulsed column reactor to promote the yield of HMF from fructose in a biphasic water/MIBK system using a solid zeolite as the catalyst.²⁹⁴ Initially, the reactor was operated as a counter current fixed bed column reactor. Pulsing was applied at the base of the column to improve liquid-liquid mass transfer rates. Major disadvantages of this configuration were caused by limitations of hydrodynamic origin, namely flooding and emulsion formation, and also of kinetic origin, due to catalyst inactivation by the formation of brown soluble polymeric material. A considerable improvement was obtained when the reaction was performed in a slurry configuration. With this concept, Moreau *et al.* demonstrated an improvement in HMF selectivity of about 10% in subsequent research on the dehydration of fructose to HMF using H-mordenite as the catalyst.¹⁰²

Recently McNeff *et al.* reported the continuous production of HMF from various feeds such as glucose, fructose, starch and cellulose in a biphasic system consisting of water and MIBK using a fixed bed reactor with a porous metal oxide-catalyst.³⁰³ The two liquids were mixed before entering a pre-heater. In the case of cellulose an additional solubilisation chamber was added after the pre-heater, as described in Figure 8. An HMF yield of 29% was obtained in a biphasic system consisting of a 23 wt% aqueous glucose solution and MIBK (1:3 v/v), catalysed by TiO₂ with a residence time of 3 min at 180 °C. Higher yields up to 34% were obtained when cellulose was reacted at a temperature of 270 °C using a MIBK to H₂O volume ratio of 5, a residence time of 2 min and TiO₂ as the catalyst.

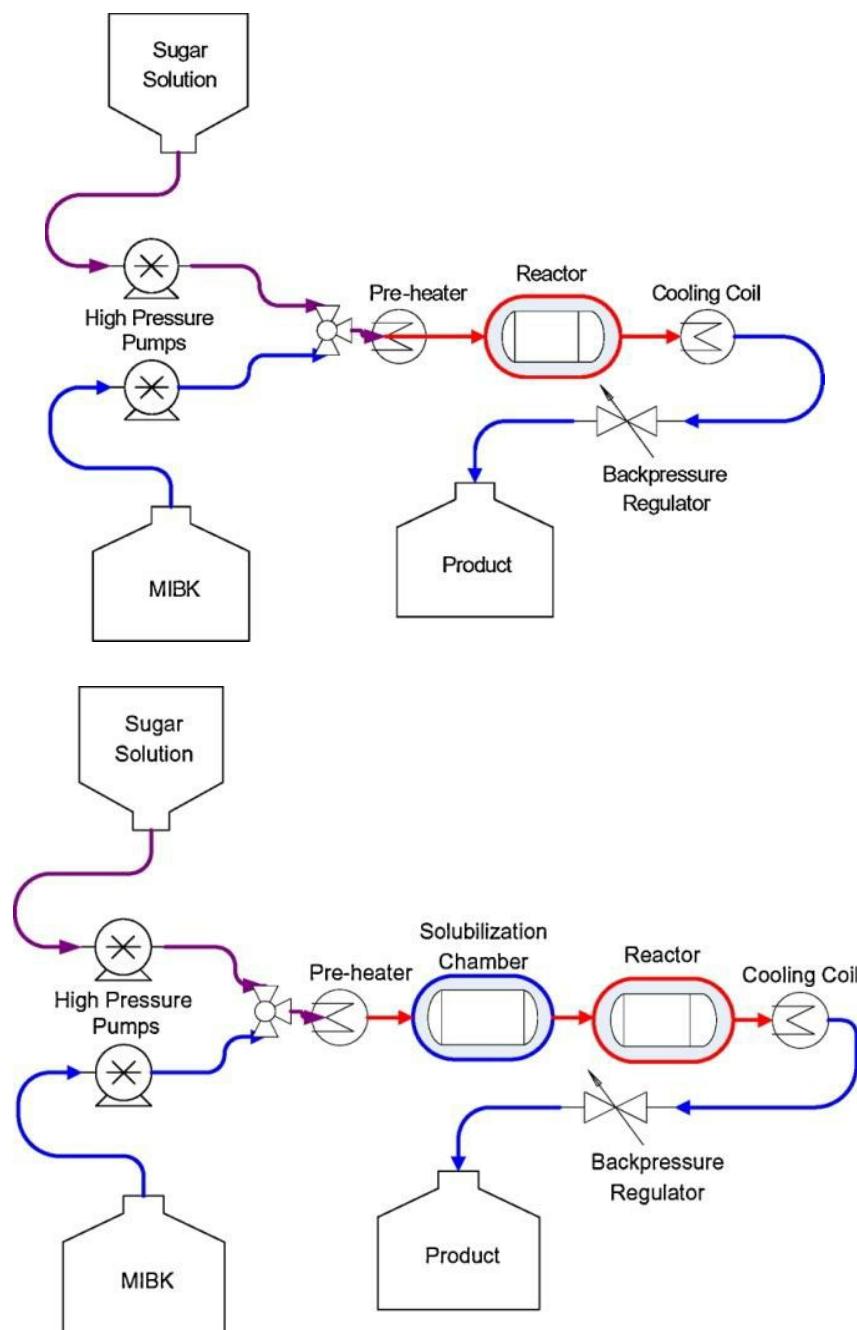


Figure 8. Schematic representation of the continuous flow system for the production of HMF in biphasic systems. Reprinted from Ref.³⁰³ with permission from Elsevier

Mihovilovic *et al.* reported studies on the conversion of glucose and fructose in two continuous microreactor devices (cartridge based and stop flow microwave reactor) in DMSO using HCl as the catalyst.⁴⁴³ Highest yields were obtained for fructose, viz 90.3% using the cartridge based reactor (180°C) and 85.6% undermicrowave heating (150°C). For glucose, the yields were considerably lower and 33% at maximum for the cartridge reactor system (200°C) and 29% for the microwave reactor (200°C).

The main challenge regarding reactor design and operation is the improvement of the HMF yield, which is difficult considering the instability of HMF under reaction conditions. This means that follow-up reactions should be suppressed in order to prevent the formation of rehydration and polymerisation products. The solid polymeric by-products (humins) create an additional problem, complicating reactor design and operation because of plugging and deactivation of heterogeneous catalysts. Some studies mention that the solids are easily filtered from the reaction mixtures.¹⁹⁵ However, other reports indicate that the humins deposit on the reactor wall, affecting heat transfer during the reaction and complicating operation and maintenance. To avoid accumulation of the deposition of humins on the reactor wall, the use of a PTFE layer in the reactor was suggested.⁴⁴⁴

Reactor design is further complicated when starting with cheaper biopolymer feeds like cellulose and lignocellulosic biomass. In these cases, introduction of a solid feed stream to a pressurised reactor poses an additional challenge.

2.5.4 Separation and purification strategies

Separation strategies to obtain pure HMF by removal of by-products, catalysts and solvents depend among others on the solvent system used for the reaction. This section is divided in two main parts, viz. separation and purification strategies for: i) aqueous systems and ii) non-aqueous systems.

2.5.4.1 Separation and purification strategies for aqueous systems

Typically HMF is isolated from aqueous reaction products by the following sequence: i) filtration of solids (humins), ii) neutralisation, iii) HMF isolation (solvent extraction or others) and finally iv) HMF purification (vacuum distillation or others).^{392,393,445} Each step will be discussed individually in the following sections.

Filtration

Rapp reported the use of a pressure filter and stated that separation of the insoluble products is an unexpectedly simple process.¹⁹⁵ Haworth suggested the possibility of centrifugation, though further details are lacking in their paper.⁴⁴⁵

Neutralisation

When using homogeneous acid catalysts, the acid is neutralised before further processing to a pH of about 5-6,¹⁹⁵ for which CaCO₃ is typically used.^{195,392,393,445} The use of other bases

such as K_2CO_3 ³¹¹ and $Ca(OH)_2$ ¹⁹⁵ was also reported. Middendorp³⁹² and Haworth *et al.*⁴⁴⁵ proposed the use of lead acetate after a neutralisation step with $CaCO_3$, though the exact purpose and benefits are unclear.

Isolation: Extractions

Solvent extraction is a traditional approach to isolate HMF from the aqueous phase,^{392,393,445} often with ethyl acetate as the solvent of choice. Generally, the ethyl acetate layer is dried after extraction using typical drying agents, for instance $MgSO_4$ or Na_2SO_4 . Subsequently, the extraction phase is concentrated by a solvent evaporation step to obtain crude HMF, but both systematic solvent screening studies and detailed engineering studies on thermodynamic properties, like partitioning as a function of process conditions, are lacking to date.

In reactive aqueous-organic systems, 1-butanol²⁸⁸ and MIBK³¹¹ were shown to be very useful for the *in situ* extraction of HMF from the aqueous phase. Recently, Román-Leshkov and Dumesic²⁹⁷ examined a number of organic solvents for *in situ* solvent extraction from aqueous systems saturated by NaCl at 180 °C. A broad range of solvents was examined, ranging from primary and secondary alcohols to ketones and cyclic ethers. The partitioning coefficient R of HMF, which was defined as the concentration of HMF in the organic phase divided by the concentration of HMF in the aqueous phase, was determined for all combinations and attempts were made to correlate the R value to the HMF selectivity. The results are described in Figure 9, which evidently shows that a strong relation between HMF selectivity and the partitioning is absent. The effect of the temperature on the partitioning and the mixing of the solvents was not studied.

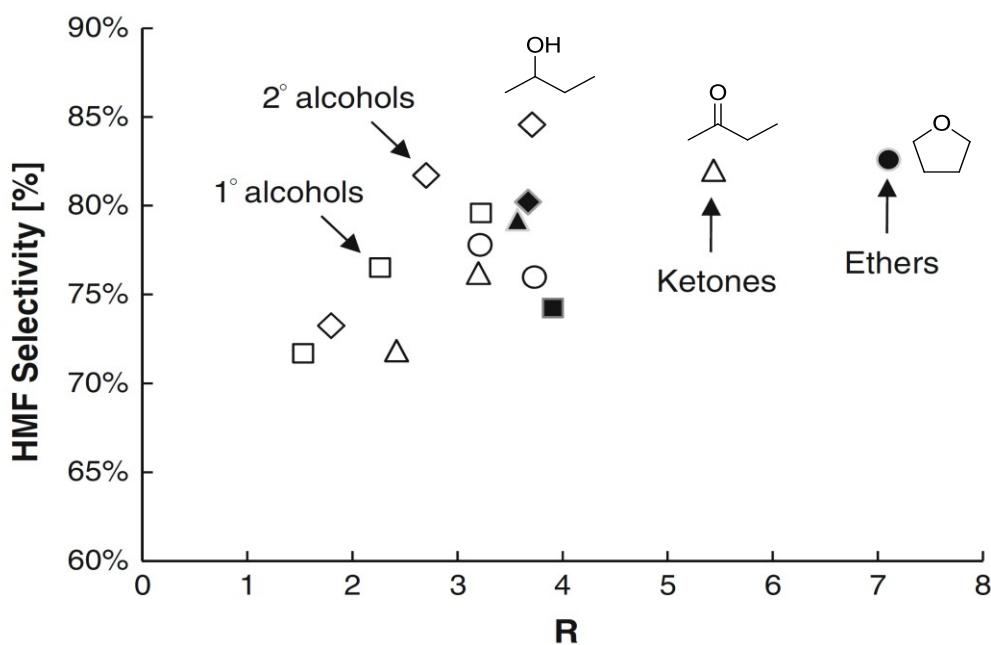


Figure 9. Correlation of HMF selectivity and partition coefficient (*R*), and solvent type for the dehydration of fructose in saturated NaCl (pH=1 HCl, 180 °C). Legend for solvent types: ketones (Δ), ethers (\circ), secondary alcohols (\diamond), and primary alcohols (\square). Open symbols correspond to solvents that are partially miscible with water and closed symbols correspond to completely miscible in water without presence of salts at room temperature. Reprinted from Ref.²⁹⁷ with kind permission from Springer Science+Business Media.

Recently, Menkhaus *et al.* reported the recovery of HMF from aqueous solutions using a polyethyleneimine (PEI), a soluble cationic polyelectrolyte.⁴⁴⁶ After separation of the PEI with adsorbed HMF from the aqueous phase using a membrane filtration (MWCO, 10000 cutof), followed by a centrifugation step and acidification with dilute sulfuric acid, up to 59% of HMF was recovered.

Isolation: Chromatography and adsorption

A second approach to separate and isolate HMF from aqueous reaction mixtures involves chromatographic separations as disclosed in a patent assigned to Sueddeutsche Zucker AG.¹⁹⁵ The HMF was separated from unreacted sugars and other decomposition products by the use of calcium loaded ion exchange columns such as Lewatit TSW 40. The chromatographic process was performed after the removal of solids and subsequent neutralisation. A large scale chromatographic separation trial was performed with water as the eluent, using three columns equipped with 13 m³ of Ca²⁺-resin at preferred temperatures of 55-85 °C. HMF-enriched fractions were separated and crystallised at temperatures below 20 °C to obtain HMF crystals with a purity exceeding 90%. Fructose and disaccharides were identified as

major impurities. In case the reaction mixture is not neutralised, a columns loaded with an ion exchange resins in acidic form can be used.

Recently, a method for the isolation of HMF from aqueous reaction mixtures was described in a patent assigned to Archer Daniels Midland Company.⁴⁴⁷ It involves the use of non-functional polymeric resins to adsorb HMF. The authors demonstrated the concept with a 15.3 wt% HMF mixture containing fructose and furfurals using Lewatit S7768 resin. The adsorbed HMF was subsequently desorbed by elution with a volatile organic solvent such as acetone. After removal of acetone, the HMF-enriched fraction (82.9%) was recovered. Further purification was performed with Finex CS13GC293, a cation exchanger in acidic form, yielding HMF with a purity of 94.1%. In another example furfural was first adsorbed from a 1 kg mixture containing 3.1 wt% of HMF, 18.5 wt% of fructose and 0.37 wt% of furfural, using Lewatit VP OC 1064. After furfural adsorption, fructose and HMF were subjected to a second separation step with the HMF selective Lewatit S7768 resin. After washing of the resin with acetone, 99.1% pure HMF was obtained.

An attempt to adsorb *in situ* formed HMF in aqueous solutions using activated carbon was reported by Vinke *et al.*¹⁹⁴ Isoalting HMF from a mixture obtained by acid-catalysed dehydration of fructose, an HMF yield improvement of up to 40% was obtained. About 90% of the adsorbed HMF was recovered by washing the loaded activated carbon with an organic solvent such as methanol or ethanol.

Subsequent studies on the use of activated biochars as adsorbents for HMF from aqueous solutions were reported by Boihem *et al.*⁴⁴⁸ HMF is readily adsorbed on phosphoric acid and steam activated biochars from agricultural residues. Best results were obtained with steam activated biochars and these were shown to be able remove 99% of the HMF (1 g/L) at a biochar intake of 2.5wt%.

Purification: Distillation

After solvent removal, distillation under reduced pressure is typically used to obtain pure HMF. Table 39 provides an overview of the distillation properties of HMF. Teunissen performed the distillation at 114 – 117 °C at less than 1 mm Hg to obtain pure HMF by following a method described earlier by Middendorp.^{392,393} Cope applied distillation at 118 °C and 0.4 mm Hg to purify the product.³¹¹

The distillation of crude HMF is recognised as troublesome due to thermal degradation of HMF associated with the formation of tarry carbonaceous materials.^{449,450} Jones reported that the isolated yield of HMF from the crude HMF was only 45 – 60 % by distillation.⁴⁵⁰ Two

patents have been published disclosing procedures to prevent further degradation of HMF during the distillation.^{449,450} Jones proposed to protect the crude HMF from moisture by degassing at a high vacuum and continuously distilling the HMF at higher temperature under pressure, claiming a pure HMF yield over 90%.⁴⁵⁰ To reduce contact time at elevated temperatures during distillation of crude HMF, Hunter proposed the use of a falling film evaporator.⁴⁴⁹ Moreover, the addition of a non-volatile flowing agent like PEG-600 was proposed to avoid the formation of tarry materials and deposits in the still during the distillation.

Table 39. Overview of HMF purification by distillation

Temperatures (°C)	Pressures (mmHg)	HMF yield	Reference
114 – 117	< 1	-	392, 393
118	0.4	-	311
175	0.19–3.34	93% ^a	450
130 – 190	0.05–0.5	- ^b	449

a: moisture removal by degassing; *b:* falling film evaporator, additional flowing agent (PEG-600)

Purification: Crystallisation

Crystallisation of HMF from concentrated HMF fractions in aqueous solution and DCM was reported in a Patent assigned to Südzucker AG.^{195,396} After obtaining a crude HMF fraction by a chromatographic process, this was concentrated by heating to 80 °C under vacuum until the remaining water-content was about 7%.¹⁹⁵ The HMF was then crystallised by cooling the concentrated HMF fraction in a multistage stirred crystalliser. The mixture was cooled from room temperature to 10 °C with a cooling rate of 5 °C/h. When the mixture reached 10 °C, it was seeded with HMF-crystals, followed by further cooling to 4 °C. HMF crystals with a purity of 97% were obtained, and further recrystallisation yielded 99.4% of pure crystalline HMF.

2.5.4.2 Separation and purification strategies for non-aqueous systems

When high boiling solvents such as DMSO or even non-volatile solvent such as ionic liquids are applied in the preparation of HMF, the non-isolated HMF yields are generally high. However, only limited attention has been paid to the separation of the HMF from the reaction mixture. M'bazoa *et al.* isolated HMF from a DMSO solution by means of solvent extraction with dichloromethane (DCM).³⁹⁶ In order to allow phase separation, a certain amount of water was added to the mixture. In this way 96% of the HMF was extracted to the DCM phase, along with a small fraction of DMSO. After solvent removal, HMF was purified by crystallisation.

As part of a process to obtain high purity HMF (>99%) from the *in situ* formed intermediate AMF, Reichert and co-workers isolated and purified HMF from a reaction mixture obtained by hydrolysis of AMF to HMF in methanol.³⁹⁵ After removal of impurities and volatiles, HMF was crystallised from a methyl tert-butyl ether (MTBE) solution by cooling it slowly to 5 °C.

Reports on isolation and purification of HMF from ionic liquid systems are hardly available. A wash step with an organic solvent such as ethyl acetate has been successfully tested by Qi *et al.*³⁴⁷ Hu *et al.* reported HMF synthesis from fructose in a biphasic system of ethyl acetate and choline chloride (ChoCl) with citric acid.³³⁵ Chan *et al.* studied the continuous extraction of HMF by THF from tungsten salt catalysed reaction systems in [BMIm]Cl.⁴⁵¹ The extract phase was concentrated under vacuum at room temperature, yielding 80% HMF the purity of which was not reported.

A novel entrainer-intensified vacuum reactive distillation process for the separation of HMF from ionic liquids and particularly [OMIm]Cl was proposed by Ren *et al.*⁴⁵² It involves heating (batch) reaction mixtures under vacuum (ca 300 Pa) to 150 -180 °C under a flow of an entrainer (nitrogen). After 10 min at 180°C, 95% of the HMF was recovered from the reaction mixture. The system was also tested for the integration of the dehydration reaction and subsequent HMF separation.

Recently, Liu and co-workers disclosed a patent application on a process for the recovery of HMF from an ionic liquid system by column adsorption.⁴⁵³ A schematic overview of the adsorption step is presented in Figure 10. Various adsorbents have been examined, ranging from activated carbon and carbon molecular sieves to zeolites, silica based materials and ion exchange resins. The column is fed with the reaction mixture (including an ionic liquid) and de-ionised water in order to adsorb the HMF. The loaded column is subsequently eluted with

water and/or an alcohol in order to wash off the HMF. The ionic liquid and the unconverted feed are recycled after water removal.

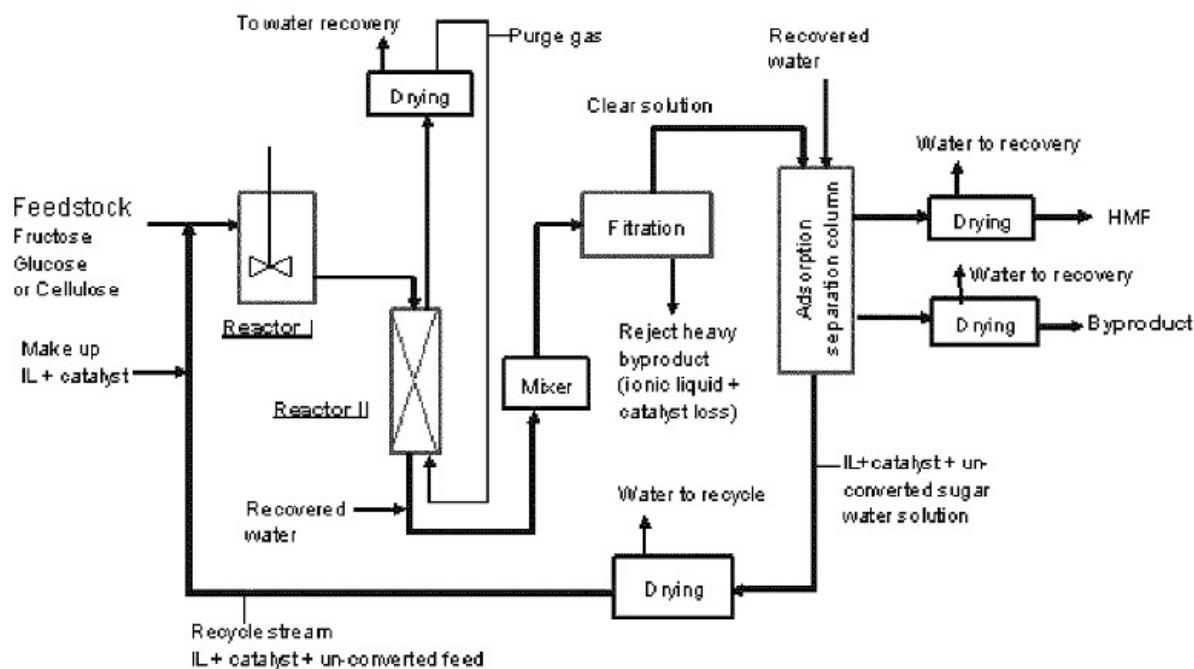


Figure 10. A schematic overview of the adsorption step used by Liu *et al.* Taken from Liu *et al.*⁴⁵³

2.5.5 Pilot Scale Production of HMF

Several studies on pilot scale production of HMF have been reported and will be discussed in this paragraph. It details the challenges for further HMF development activities at larger (commercial) scale. Aqueous phase, non-aqueous phase and mixed solvent reaction systems are discussed separately.

2.5.5.1 Pilot scale studies of aqueous HMF processes

Teunissen prepared HMF by the acid catalysed dehydration of sugar cane on 1 kg scale.³⁹³ Yields of 40 – 50 g of pure HMF were reported. The reaction and subsequent purification of HMF were performed following earlier methods described by Düll,⁶ Kiermayer,⁷ Blanksma⁴⁵⁴ and Middendorp.³⁹² Teunissen heated 30 wt% aqueous sugar cane in the presence of 0.3 wt% oxalic acid in an autoclave at 134 °C for 3 h. The reaction mixture was then neutralised with CaCO₃, followed by HMF extraction with ethyl acetate. The solvent was evaporated and HMF was subsequently distilled under reduced pressure (<1 mm Hg) at 114 – 117 °C.

Pilot scale production of HMF in an aqueous reaction system was disclosed in a patent issued by Süddeutsche Zucker-aktiengesellschaft in 1988.¹⁹⁵ The patent reports the multi-kg scale manufacture of HMF involving chromatographic separation and crystallisation to obtain 99% pure HMF in crystalline form (Figure 11). In one of the examples in the patent, a mixture of 11 kg fructose and 33 L of water was heated in a stirred batch autoclave at 135 – 142 °C for 3 h in the presence of oxalic acid. After the reaction mixture was cooled, the solid material was filtered in an air pressure filter. About 1.3 kg of solid residue was obtained from this filtration step. The filtrate was neutralised to a pH of 5 using CaCO₃. Analysis of the filtrate revealed 55 % fructose conversion and 33 % (2.58 kg) of HMF yield. The isolation of HMF from the filtrate was performed by column chromatography using a calcium loaded ion-exchange resin. Four fractions were obtained: salts, a mixed fraction, unreacted fructose and HMF. The mixed fraction was again separated, the unreacted fructose was re-used, and the HMF fraction was concentrated. Two large HMF batches (143 kg and 176 kg) were concentrated at temperatures below 80 °C under vacuum until the remaining water content was less than 7%. Subsequently, the concentrated HMF solution was crystallised in a crystalliser. The mixture was cooled down from 20 °C with a cooling rate of 5 °C/h. When the mixture temperature reached 10 °C, the mass was seeded with HMF-crystals and further cooled to 4 °C. 124 kg of crystalline HMF (97%) was obtained from processing the two batches. Further re-crystallisation yielded 82.7 kg of crystalline HMF with a purity of 99.4%.

The patent also discloses an example for the use of a polymeric fructose rich feedstock in the form of chicory roots. About 20 kg of chicory roots were mixed with 20 kg of water and then acidified with sulfuric acid to a pH of 1.8. The mixture was heated in an autoclave at 140 °C for 2 h. The reaction mixture was cooled to 70 °C and filtered in a pressure filter. This process yielded 13% HMF and 30% fructose, based on the available amount of inulin in the chicory roots. Two different chicory roots pretreatment were conducted before hydrolysis. Inulin was first extracted from chicory roots in a counter current extraction apparatus (DDS-extractor) at 70 °C, yielding an extract with 16% inulin. The second pretreatment involved liquefaction/pre-hydrolysis of the chicory-roots with 20% sulfuric acid at 80 °C for 2.5 h and subsequent heating by introducing 6 bar of steam for 1 h. After that, the pressure was released and the mixture was filtered before further hydrolysis. Unfortunately, the yield of HMF using these pretreatment methods was not disclosed.

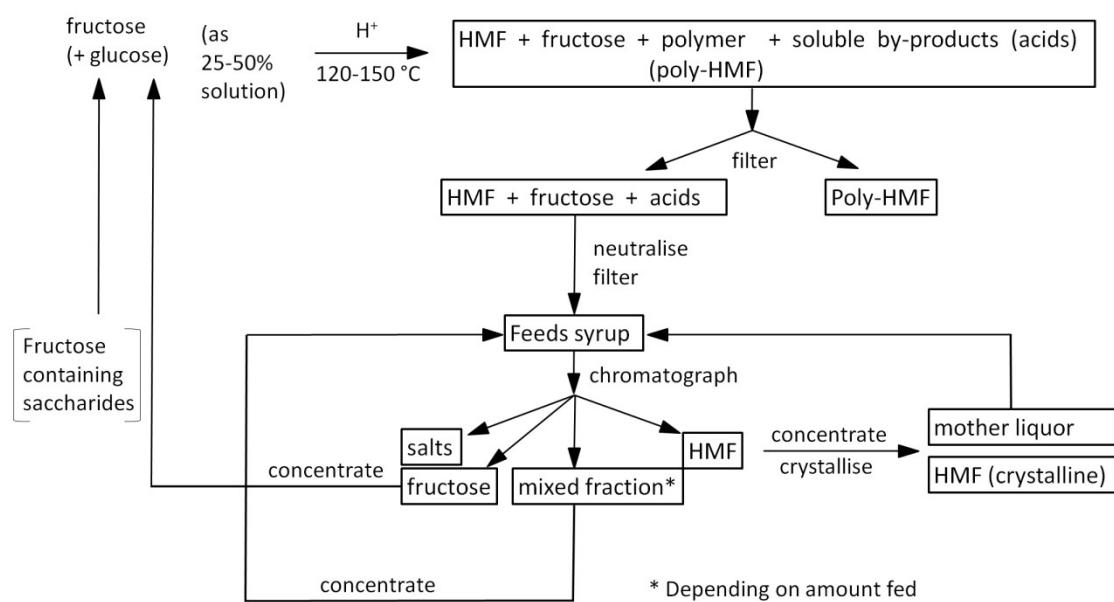


Figure 11. HMF production by Suedzucker¹⁹⁵

2.5.5.2 Pilot scale production using non-aqueous solvents

A pilot scale batch production process for HMF in DMSO was patented by Furchim, France.³⁹⁶ In the absence of catalyst, 0.9 kg of fructose was reacted in 2 kg DMSO at 160 °C for 4 h, yielding 85% HMF at full conversion. Subsequently 2.7 kg water was added to the reaction mixture before extraction with 6.5 kg of DCM in a counter-current column at 20 °C. Around 96% of the HMF was extracted together with 0.05 kg of DMSO. The extraction phase was concentrated by evaporation of the DCM, followed by crystallisation (rapid cooling from ambient temperature to 5 °C, and then to -5 °C at rate of 4-5 °C/h). In total, 0.5 kg of 98% pure crystalline HMF was obtained from processing 0.9 kg of fructose, adding up to a molar yield of over 75%.

2.5.5.3 Pilot scale production using mixed solvent systems

Cope reported the production of HMF from a 50 wt% aqueous sucrose solution (3 kg) without catalyst using MIBK as an *in situ* extraction solvent.³¹¹ The reaction was performed at 160 °C for 9 h with about 60 L of MIBK to yield around 63% HMF. After neutralisation of the MIBK phase with K_2CO_3 , MIBK was evaporated using a Turba-film rotavapor at a pressure of 180 mmHg, with a steam pressure of 3 psig. The HMF was isolated after a vacuum distillation at 118 °C and 0.4 mmHg in a batch laboratory setup. The isolated yield and HMF purity were not reported. Using a similar approach with glucose, the yield of HMF in the MIBK phase was 21 to 25% after 9 h reaction time.

A patent assigned to Roquette Frères, France discloses the kg-scale production of HMF from fructose in a water-MIBK biphasic system in the presence of cationic resins at relatively low temperatures of 70-95 °C.⁴⁵⁵ The reaction was performed with 1 kg of fructose in 4 L of water using 36 L of MIBK in a 50 L stainless steel reactor with an overhead stirrer. After dissolution the reaction was performed at 89 °C for 5 h in the presence of 0.6 kg of cationic pre-dried Lewatit SPC 108. Subsequently, the reaction mixture was filtered and the aqueous and organic phases were separated. The aqueous phase was analysed and contained residual fructose and small amounts of HMF and levulinic acid. The organic phase was rich in HMF and also contained some levulinic acid, adding up to an HMF yield of 38% at 51% fructose conversion. Further isolation of HMF from the organic phase and subsequent HMF purification were not described.

2.5.5.4 Pilot scale production of HMF involving an HMF derivative

In this section, studies will be reported involving the (*in situ*) formation and subsequent purification of HMF derivatives followed by a final conversion to HMF. The main idea is that the derivative is obtained in higher isolated yields than HMF itself due to both higher reaction yields as well as improved isolation/purification yields. As such, it resembles the classical protective group approach in synthetic organic chemistry.

Evonik Degussa GmbH. performed a kg-scale production of high purity HMF (>99%) using 5-acetoxymethylfurfural (AMF) as the HMF derivative.³⁹⁵ First about 39.4 kg of fructose in 90 L NMP was reacted in the presence of 5.9 kg Dowex 50WX8-200, an acidic ion exchange resin, at 110 °C for 6 h to form HMF. After cooling, the reaction mixture was filtered and washed with 8 L NMP. Subsequently, the filtrate was mixed with 4-(N,N-dimethylamino)pyridine and acetic acid anhydride at 25 °C . After 1 h reaction, the solvents were removed from the reaction mixture at 90-110 °C at 50-100 mbar. The residue was subsequently mixed with 160 L MTBE, 60 L water and 4 kg activated carbon. The suspension was filtered and phase separated. The solvent was removed from the filtrate by distillation at 50 °C under reduced pressure (20 mbar). The residue was further purified by fractional distillation at 106-110 °C and 5 mbar. About 15.5 kg of AMF (42%) was obtained after solvent removal (distilled at 50 °C under pressure) and subsequent fractional distillation at 106-110 °C at 5 mbar.

About 7 kg high purity HMF (<99 %) was obtained by the hydrolysis of 10.9 kg AMF in 60 L methanol in the presence of 1.1 kg Amberlyst A26 OH, a strongly basic ion exchange resin, at 25 °C for 1 h. After the reaction, the mixture was contacted with activated carbon for

1 h, and subsequently filtered and washed with 10 L methanol. The filtrate was concentrated at 40 °C under reduced pressure. The residue was mixed with 8 L MTBE and subsequently cooled slowly to 5 °C to precipitate the HMF. The crude HMF was washed with 1.5 L ice cold MTBE and dried at 20 °C (under pressure). About 85% of HMF was obtained from AMF using this method.

2.5.6 Techno-economic evaluations of different modes of HMF production

Evaluation of the pilot scale production processes for HMF indicates 2 examples using homogeneous catalysts (oxalic acid), one with a heterogeneous catalyst (a cationic resin) and 2 without the use of a catalyst. The use of a catalyst is considered advantageous regarding activity and selectivity, though the exact effect is a function of the solvent composition. The typical homogeneous catalysts (oxalic acid, mineral acids) have the advantage that they are relatively cheap, though recycling is often cumbersome. In most pilot studies, a neutralization step is incorporated using a base and the resulting salts are discarded, which is evidently not a good example of green chemistry and technology principles. In this respect, the use of heterogeneous catalysts has certain advantages. However, catalyst lifetime needs to be established and a major concern is the deposit of humic substances on the heterogeneous catalysts leading to irreversible catalyst deactivation. Detailed, long duration experiments will be required to address this issue and assess the true potential of heterogeneous catalysts. To the best of our knowledge, these are not available in the open literature yet.

Scattered data are available in the open literature on the manufacturing costs of HMF. An overview of reported data is shown in Table 40. For HMF production from fructose in an aqueous reaction system patented by Südzucker AG, an HMF manufacturing price of 6 DM/kg was reported when fructose is available at a price of 0.5 DM/kg (1988).

Bicker *et al.* investigated the production of HMF from fructose in supercritical acetone.²³³ The process consisted of a flow-reaction system, solvent recovery, and further HMF purification by chromatographic methods. Based on this process, an HMF cost price of 2 €/kg was estimated, using the assumption that fructose is available at 0.5 €/kg.

Table 40. Estimated HMF manufacturing costs

Process	Design Capacity	Fructose Price	HMF Price	Reference
aqueous process	-	0.5 DM/kg	6 DM/kg	195, referenced by Kuster ¹²
Low boiling solvent: acetone	-	0.5 \$/kg	2 €/kg	206
Two solvents: MIBK and 2-butanol	Production of HMF: 7000 Ton/year	0.55 \$/kg	2.16 \$/kg	456
two solvents: water and THF		0.55 \$/kg	1.97 \$/kg	456
two solvents: water and MIBK/2-butanol		0.55 \$/kg	2.43 \$/kg	456
two solvents: water and 1-butanol	Feed rate of fructose: 300 Ton/day (49.2 mega l/year)	0.3 \$/kg	1.33 \$/l (1.08 \$/kg)	457

Recently, two techno-economic evaluations on the production of HMF using a biphasic reaction system were published.^{456,457} Torres *et al.* performed a design case on the continuous production of HMF employing MIBK and 2-butanol as the extraction solvents.⁴⁵⁶ The process design involves a liquid-liquid reactor coupled with an extractor and evaporator (Figure 12). The authors developed a mathematical model of the process consisting of mass balances, equilibrium relations and design constraints based on published work by Roman-Leskhov *et al.*¹⁷⁰ A first order kinetic model proposed by Kuster and Temmink was used as input in the reactor model.¹⁵⁷ The manufacturing costs of HMF production were estimated at 2.16 \$/kg based on a fructose price of 0.55 \$/kg. The fructose price was shown to be the

major factor determining in the HMF cost price at an 80% contribution. The authors suggested also possible process improvements such as the use of extraction solvents with a higher partitioning coefficient for HMF (e.g. THF). In a follow up paper,⁴⁵⁸ an alternative flow sheet was proposed involving combination of the fructose dehydration reaction and HMF separation in a single unit. The minimum HMF costs were estimated and found to be between 0.21 and 0.24 \$/mol.

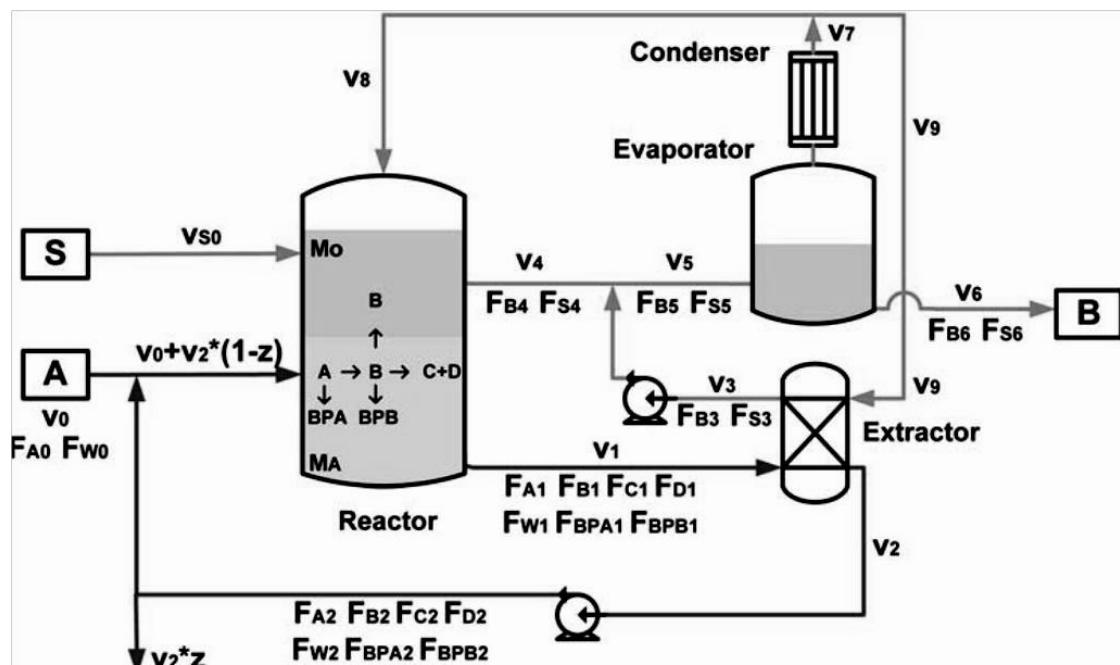


Figure 12. Process diagram for the production of HMF in biphasic systems (Legend: v_i denotes molar flow rate in the stream i ; F_{Ji} stand for the molar flow of component J in stream i , A: fructose, BPA: byproducts from fructose, B: HMF, C: levulinic acid, D: formic acid, BPB: other decomposition products from HMF, W: water, S: solvent) Reproduced from Ref.⁴⁵⁶ with permission of the Royal Society of Chemistry.

As part of a techno-economic evaluation of the production of dimethylfuran, a HMF derivative with potential to be used as a biofuel (component), Kazi *et al.* reported a techno-economic analysis of the production of HMF.⁴⁵⁷ A conceptual plant design, combined with the production of 2,5-dimethylfuran, was proposed based on a biphasic reaction system of water saturated with NaCl and 1-butanol (Figure 13).

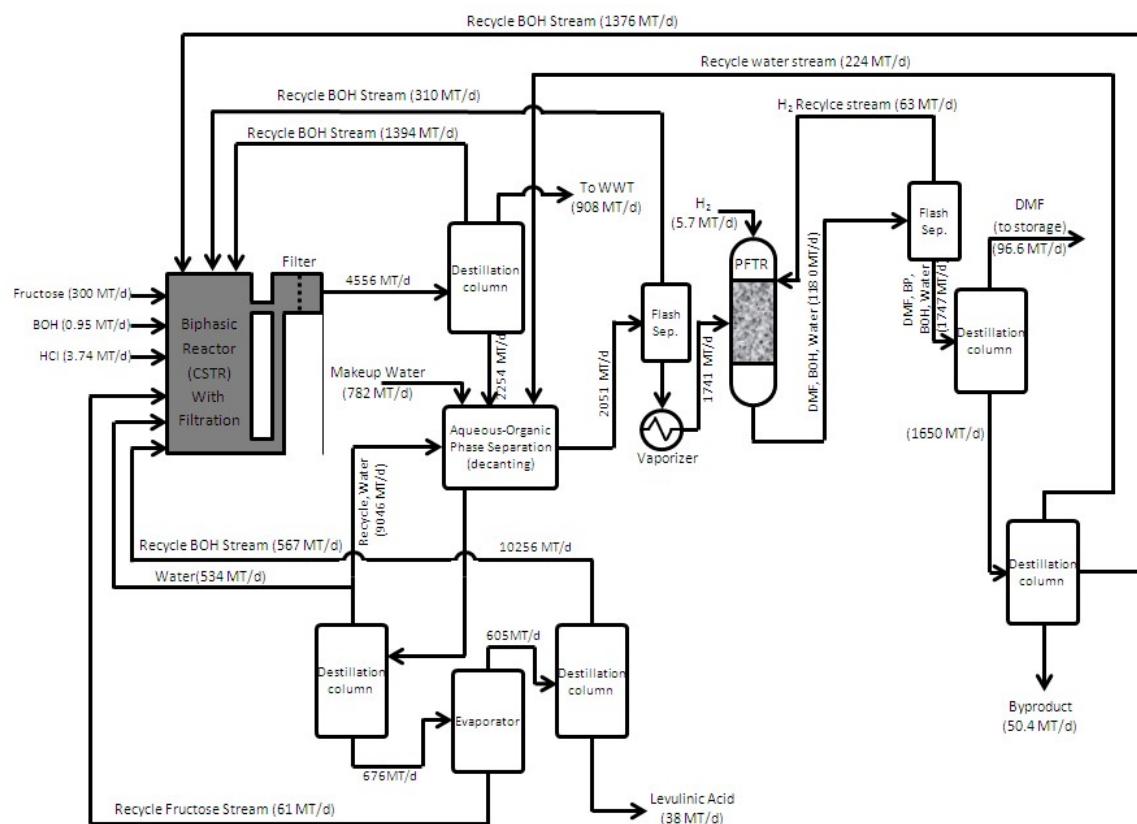


Figure 13. Conceptual design for the production HMF and DMF. Adapted from Ref.⁴⁵⁷ with permission from Elsevier.

The design incorporates a reaction section, HMF purification, reactant and solvent recycle and isolation of valuable by-products such as levulinic acid. For a 300 metric ton/day of fructose input, the minimum cost price of HMF in this highly selective and efficient process was estimated at 1.08 \$/kg. The HMF cost price is very sensitive to the feedstock cost, but also dependent on the HMF yield, by-product price, catalyst cost and total purchased equipment cost (in that order).

A price of around \$ 1.00/Kg of HMF would seem to be a good basis for its use in bulk-scale applications as this is the same order of magnitude as current fossil fuel based raw materials. In order to reach such a price level the plant size should be at least 100 kTon/y. Unfortunately, most bulk products that can be made from HMF, such as FDCA are not drop-ins, i.e. they cannot replace identical existing bulk chemicals, but rather need to find their own place in the market, which may require substantial time and normally goes through a phase where the new products are produced on sub-optimal scale at too high costs. Nevertheless, this process could be accelerated by the finding of favourable properties of the final (polymeric) material. In addition, a strong market pull, caused by a desire for the use of

products based on renewable raw materials and a desire to bring down the carbon footprint of the current product can help to overcome this small volume high price dilemma. And indeed, Avantium has shown that the polyester PEF, based on biobased FDCA and biobased ethylene glycol has both superior barrier properties and a higher Tg than the petrochemical analogue PET. The company recently announced the opening of pilot-scale production of FDCA. Avantium has also announced partnerships with The Coca-Cola Company and Danone. Here, the prime objective is to replace PET for bottle applications, which would allow for immediate large-scale production. Production of HMF for fuel applications is not an easily obtainable target. Here the price should be substantially lower. This would require the direct production of HMF in good yields from cellulose or even lignocellulose. Although proof-of-principle has been obtained for such conversions, the reported methods are still far removed from an industrial process.

2.6 The relevance of 5-hydroxymethylfurfural as a platform chemical

HMF is a very important building block for a wide range of applications. In section 2.5.2.4 the *in situ* formed derivatives were discussed of which levulinic acid is the most important one. In this Chapter other applications in the areas of polymers (section 2.6.1), fine chemicals (section 2.6.2) and fuels (section 2.6.3) are discussed.

2.6.1 Conversion of HMF to monomers for polymers

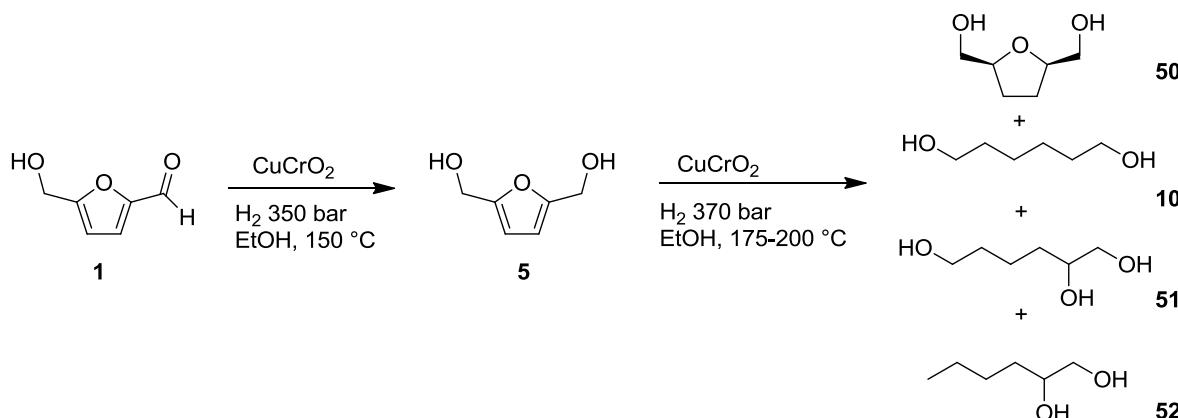
When HMF is produced at high efficiency follow-up products will become an attractive option to replace petrochemical analogs.^{459,460} In addition to FDCA, as mentioned in section 2.1, other platform chemicals can be produced as well. 5-Hydroxymethylfuroic acid, 2,5-diformyl furan, the 2,5-di-aminomethylfuran and 2,5-bishydroxymethylfuran are most versatile intermediate chemicals of high industrial potential because they are six-carbon monomers that could replace e.g. adipic acid, or alkyldiols, or hexamethylenediamine in the production of polymers.^{13,459-462}

2.6.1.1 HMF-based diols

Utne described the hydrogenation of HMF at 350 bar hydrogen pressure and 150 °C to 2,5-bishydroxymethyl-furan (**5**) using copper chromite as a catalyst.⁴⁶³ The product was obtained

in 100% yield. Surprisingly, if the pressure and the temperature were increased somewhat, a mixture of products was obtained containing 2,5-bishydroxymethyltetrahydrofuran (**50**), 1,2,6-hexanetriol (**51**), 1,2-hexanediol (**52**) and 1,6-hexanediol (**10**, Scheme 34). The relative amounts of these could be varied by subtle changes in the solvent and the temperature.

The formation of polymers based on HMF-derived monomers was recently reviewed.⁴⁶⁴



Scheme 34. Reduction of HMF

For synthetic purposes a NaBH_4 reduction of HMF to **5** can be quite convenient. This reduction was reported by Cram and co-workers to proceed in 92% yield.⁴⁶⁵ Descotes performed a systematic study of the use of several different metal catalysts for the hydrogenation of HMF.⁴⁶⁶ He was able to convert HMF to **5** in 100% selectivity using either 10 mol% of $2\text{CuO} \cdot \text{Cr}_2\text{O}_3$ at 60 °C, 1 mol% Pt/C at 30 °C, or 1 mol% PtO_2 at 60 °C. Battelle researchers reported the use of Raney-Co (97% selectivity), Co/SiO_2 (96% selectivity) and $\text{Pt/Al}_2\text{O}_3$ (98% selectivity) as catalysts for the hydrogenation of HMF to **5** at 35 bar H_2 , 60 °C; water was the best performing solvent.⁴⁶⁷ Use of Ra-Ni led to unselective reactions due to over-reduction to **50**, whereas use of Ra-Cu gave poor selectivities. Heeres, de Vries and co-workers reported the use of bimetallic Ni-Cu catalysts on zirconia and Ru on alumina as catalysts for the hydrogenation of HMF to **5** with good selectivity.⁴⁶⁸ Enzymatic methods have also been reported for the conversion of HMF to **5**. Whole bacteria where used by Boopathy and co-workers and reported to give full conversion to **5**.⁴⁶⁹ Ras has done an extensive screening study on the reduction of EMF, the ethyl ether of HMF, into the corresponding alcohol. It was found that Pt and Rh supported on silica are efficient catalysts for the selective hydrogenation of EMF to the unsaturated alcohol, obtaining 100% selectivity for conversions up to 66%.⁴⁷⁰

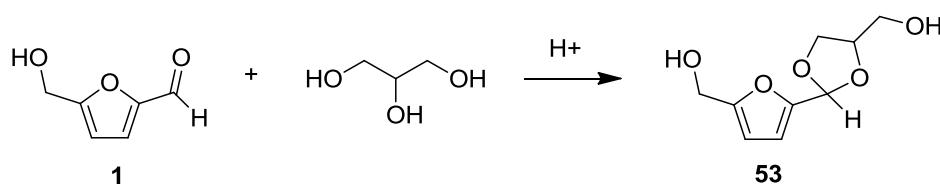
HMF can be quite toxic for microorganisms. This is particularly problematic in industrial yeast fermentations towards ethanol where the presence of HMF can slow down the process. Liu reported the development of a strain of *Saccharomyces cerevisiae* capable of reducing HMF to **5**, which is not an inhibitor.⁴⁷¹

The diol **5** has been converted into polyethers that are used as components in polyurethane foams.⁴⁷²

Hales reported the use of a supported nickel catalyst that also contained small amounts of copper and iron. Using this catalyst in water as solvent at 105–140 bar of H₂ at 70–100 °C, he obtained **50** in 97% yield. Researchers from ADM reported the hydrogenation of HMF to **50** in its *cis*-form using a heterogeneous nickel catalyst doped with zirconium at 103 bar and 200 °C in ethanol. However, as much as 10 mol% of catalyst was necessary.⁴⁷³ Probably the best catalyst for the hydrogenation of HMF to **50** is Raney-nickel. Virtually quantitative yields have been reported using this catalyst by Descotes,⁴⁶⁶ Connolly⁴⁷⁴ and de Vries, Heeres and co-workers⁴⁶⁸

Dumesic and co-workers have tested supported Ru, Pd, and Pt catalysts in monophasic and biphasic reactor systems to determine the effects of the metal, support, solution phase acidity, and the solvent to elucidate the factors that determine the selectivity for hydrogenation of HMF to **50**. Highest yields (88–91%) were achieved using Ru supported on materials with high isoelectric points, such as ceria, magnesia–zirconia, and γ-alumina.⁴⁷⁵

Both **5** and **50** have been used as monomers for polyesters.^{14,476} Reaction with glycerol (Scheme 35) is another method for converting HMF into a diol (**53**) that can be used as a monomer. Use of **53** for the production of polyesters and polyurethanes may lead to materials with a high *t_g* by virtue of the presence of the two rigid rings.⁴⁷⁷ Similarly, it is possible to convert HMF into an aldehyde acid by its reaction with a cyclic anhydride such as phthalic anhydride or maleic anhydride.⁴⁷⁸

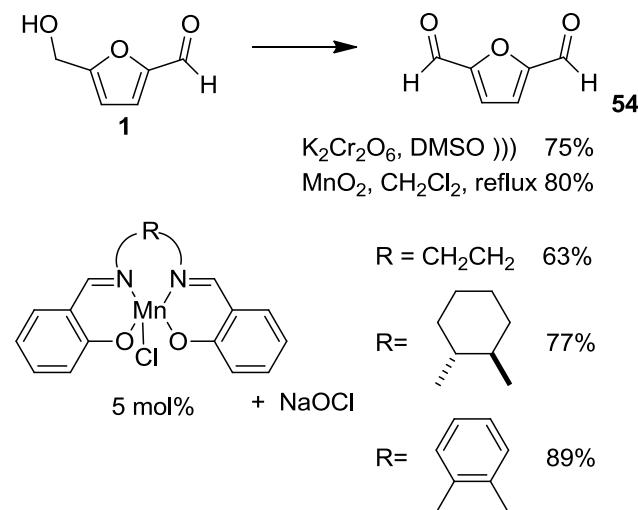


Scheme 35. Acetalisation of HMF with glycerol

2.6.1.2 2,5-Diformylfuran

2,5-Diformylfuran (DFF, **54**) is an attractive building block that can be converted into a host of new products. DFF has been polymerised to polypinacols and polyvinyls; it has been used as a starting material for the synthesis of anti-fungal agents, pharmaceuticals and ligands.^{392,410} It is also possible to decarbonylate DFF to furfural or to furan.⁴⁷⁹

Many methods have been reported for its synthesis from HMF via oxidation (Scheme 36). The stoichiometric oxidation of HMF using potassium dichromate in DMSO under ultrasonic irradiation at room temperature gave DFF in 75% yield.⁴⁸⁰ Use of MnO₂ in refluxing CH₂Cl₂ led to a very clean conversion of HMF to DFF although only 80% conversion was reached after 8 h.⁴⁸¹ HMF was efficiently oxidised to **54** in 63–89% yield using a Mn(III)–salen catalysts and sodium hypochlorite as oxidant in a pH 11.3 phosphate buffer–CH₂Cl₂ biphasic system at room temperature.⁴⁸² Lee and co-workers claimed a yield of 100% of DFF upon stoichiometric oxidation of HMF with immobilised IBX (2-iodoxy-benzoic acid).⁴⁸³



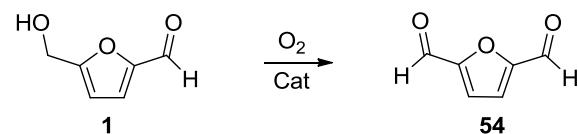
Scheme 36. Manganese-catalysed oxidation of HMF to DFF

A number of catalytic oxidations have been reported using various metal catalysts and oxygen or air as oxidants (Scheme 37). Use of catalytic amounts of TEMPO and CuCl₂ in DMF with O₂ led to the formation of **54** in 55% yield.⁴⁸⁴ Use of the acetamino variant of TEMPO was also reported in conjunction with HNO₃/O₂ as oxidant; the authors claim a 100% yield to DFF.⁴⁸⁵ The use of vanadium catalysts has been reported a number of times. Use of V₂O₅ on TiO₂ in toluene at 170 °C led to the formation of **54** in 64% yield.⁴⁸⁶ With the same catalyst at higher air pressure (16 bar) and lower temperature (90 °C) a much higher selectivity of 97% was obtained, however, relatively large amounts of catalyst were used.⁴⁸⁷

The effect of the carrier material on the structure of the VO_x domains has been investigated.⁴⁸⁸ The results can serve as a guidance for the development of better catalysts. Grushin and co-workers tested a range of different vanadium salts and complexes in DMSO at 150 °C. They were able to combine two steps by first converting fructose into HMF using a Dowex type acidic ion exchange resin at 110 °C for 5h (85% selectivity to HMF) followed by removal of the acidic catalyst and oxidising in the presence of the vanadium salt. Use of 5 mol% of $\text{VOHPO}_4 \cdot 0.5\text{H}_2\text{O}$ led to the formation of **54** in a combined 41% yield.⁴⁸⁹ They also showed that the combination of $\text{PdCl}_2/\text{CuCl}_2$ is an excellent catalyst for the conversion of HMF to DFF in near 100% selectivity. However, the catalysis stalls after about 70% conversion, which the authors ascribe to the presence of water.

Interestingly, Xu and co-workers showed that upon use of $\text{VO}(\text{acac})_2$ as catalyst at 90 °C oxidation of HMF at 10 bar gave up to 52% of maleic anhydride in addition to smaller amounts of DFF.³³ Very high yields of DFF were obtained upon use of a mixed catalyst consisting of $\text{Cu}(\text{NO}_3)_2$ and VOSO_4 .^{33,490}

Chinese researchers were capable of producing DFF from glucose in a 2-step sequence. First they reacted glucose in DMA at 100 °C in the presence of catalytic $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and NaBr for 6 h to give a crude mixture containing 74% of HMF. This mixture was oxidised with air in the presence of catalytic $\text{NaVO}_3 \cdot 2\text{H}_2\text{O}$ at 110 °C for 10 h to give DFF in 51% yield.⁴⁹¹



TEMPO / CuCl_2 , DMF	55%
$\text{V}_2\text{O}_5/\text{TiO}_2$, toluene, 170 °C	64%
$\text{V}_2\text{O}_5/\text{TiO}_2$, toluene, 90 °C	80%
$\text{VOPO}_4 \cdot 2\text{H}_2\text{O}$, DMSO, 150 °C	83%
$\text{Co}(\text{OAc})_2, \text{Mn}(\text{OAc})_2, \text{NaBr}, \text{Zr}(\text{OAc})_4$, 75 °C	57%
$\text{Co}(\text{OAc})_2, \text{Mn}(\text{OAc})_2$, MIBK, HOAc	86%

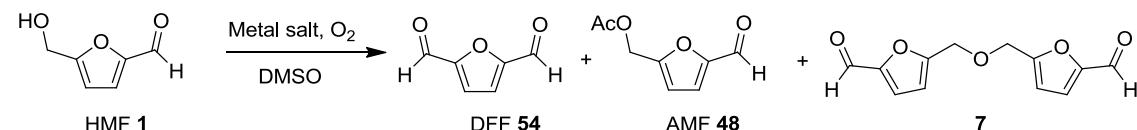
Scheme 37. Metal catalysed oxidation of HMF to DFF in air

Carlini and co-workers also attempted the direct conversion of fructose to DFF by using the same vanadium catalyst both for the dehydration step of fructose to HMF and as oxidation catalyst.⁴⁹² The catalyst $\text{VOPO}_4 \cdot 2\text{H}_2\text{O}$ was quite effective in the dehydration of fructose in water. After 2h at 80 °C 50% conversion was reached with a selectivity to HMF of 82%. The use of biphasic MIBK/H₂O mixtures reduced the selectivity to HMF somewhat to 70-74%.

Oxidation of HMF in water using the same catalyst at room temperature and 1 bar O₂ was very slow with only 3% conversion, albeit with 100% selectivity to DFF. Use of biphasic MIBK/H₂O mixtures led to somewhat higher conversions of HMF, but the selectivity to DFF deteriorated strongly with 5-acetoxymethyl-2-furfural (AMF) and a dimeric ether (OBMF) as main side products. Oxidation of HMF in DMSO at 150 °C led to 84% conversion after 6 h and formation of DFF with 97% selectivity. However, as the product is not easily separated from DMSO the authors also investigated the use of other solvents. Whereas use of MIBK, toluene or benzene led to poor selectivity to DFF, use of DMF at 100 °C gave a 56% conversion of HMF with 93% selectivity to DFF after 6 h. At higher temperatures the selectivity started to deteriorate at higher conversion. Partial substitution of the vanadium in VOPO₄·2H₂O by other metals led to lower selectivities. Use of the vanadium complex (8-hydroxyquinoline)2V(O)O*i*Pr in the oxidation of HMF with air gave DFF in 94% yield.⁴⁹³

Corma and co-workers tested a series of metal catalysts supported on either polyvinylpyridine, cross-linked with polystyrene or on aminopropylated zeolite (SBA-15) that had been treated with 4-pyridinecarboxaldehyde. In the initial tests using the soluble metal salts they obtained some very interesting results (Table 41).

Table 41. Oxidation of HMF to dialdehydes



Catalyst	T (°C)	t(h)	Conv of HMF (%)	Selectivity (%)		
				54	7	48
CuCl/PdCl ₂	160	10	85	97	2.5	0.5
	115	24	20	>99	0	0
CuCl	160	24	26	97	2.5	0.5
CuCl ₂	160	8	65	98.5	1.5	0

^a Reaction conditions: air flow rate 0.5 ml/s, DMSO (7ml), 0.3g of HMF, HMF/Metal = 10, P = 0.1 MPa

After 10 h up to 85% conversion of HMF was achieved using CuCl/PdCl₂ as catalyst and DFF was obtained with 97% selectivity. However, the authors note that DMSO is oxidised to dimethylsulfone in substantial amounts. Use of the immobilised salts led to comparable activities and selectivities. However, addition of extra pyridine was necessary to retain the activity of the catalyst upon reuse. The immobilised catalysts also functioned reasonably well in toluene and very well in trifluorotoluene.

Partenheimer and Grushin have applied the catalyst system that the former had developed for the commercial scale oxidation of xylene to phthalic acid. Thus, use of mixtures of cobalt, manganese and zirconium acetates with bromide allowed the oxidation of HMF to DFF in 57% isolated yield at 1 bar oxygen pressure.⁴⁹⁴ Increase of the pressure to 70 bar gave DFF in 61% yield. More recently Sanborn from Archer Daniels Midland found that oxidation of HMF in acetic acid using cobalt and manganese acetate as catalyst gives up to 86% selectivity to DFF when the reaction is performed without bromide, but in the presence of an equivalent of MIBK.⁴⁹⁵ Indian researchers claimed 100% selectivity to DFF using a catalyst made from calcined manganese mesoporous material substituted with silver in isopropanol at 145 °C.⁴⁹⁶

Direct formation of DFF from fructose and glucose was also reported using a mixed catalyst system of Amberlyst-15 and ruthenium supported on hydrotalcite. Yields of DFF were low to moderate.⁴⁹⁷

Electrochemical oxidation of HMF allowed the isolation of DFF in <68% yield.⁴⁹⁸

HMF has also been oxidised using the enzyme chloroperoxidase and H₂O₂ as oxidant. A selectivity of 60-74% to DFF was reached with FDCA and 5-formyl-2-furancarboxylic acid as main side products. The reaction is relatively fast with 87% conversion obtained after 21 min.⁴⁹⁹

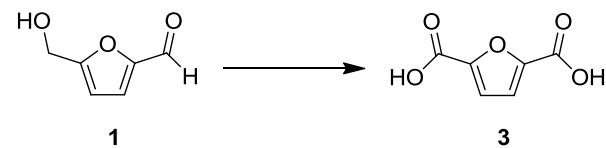
The use of DFF was reviewed by Lewkowski.¹³

2.6.1.3 2,5-Furandicarboxylic acid (FDCA), adipic acid and 5-hydroxymethyl-2-furan carboxylic acid

Another interesting molecule that can be derived from HMF is 2,5-furandicarboxylic acid (FDCA, **3**). It can be obtained via the oxidation of HMF. FDCA was identified by the Department of Energy, USA, to be a key bio-derived platform chemical which can serve as starting point for several interesting molecules including, succinic acid, 2,5-furandicarboxylic acid dichloride and 2,5-furandicarboxylic acid dimethyl ester.^{1,2} 2,5-furandicarboxaldehyde and 2,5-hydroxymethylfuroic acid can be considered intermediates to FDCA in the oxidation

of HMF and were discussed before. Recently, several new applications of FDCA and its diester have emerged, which will be discussed below. Several oxidation methods have been described in the literature (Table 42).

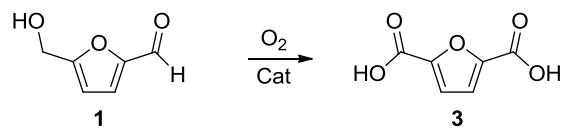
Table 42. Oxidation of HMF to FDCA



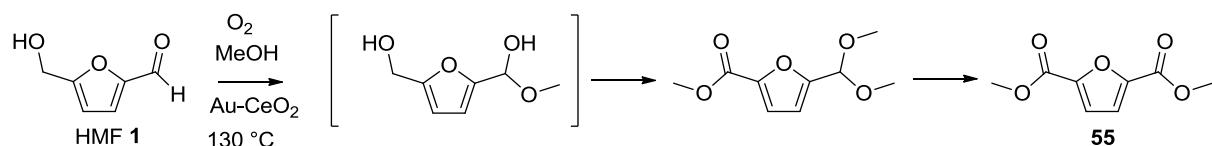
Reaction conditions	HMF conversion (%)	FDCA Yield (%)	Ref.
N ₂ O ₄ in DMSO	100	24	196
Ag ₂ O and HNO ₃	100	47	196
KMnO ₄	100	70	196
Pt/Al ₂ O ₃ (basic conditions)		100	500
Co/Mn/Br (Zn), air	91	61	494
Co/Mn/Br with Mol Sieves in HOAc		70	501
Co(acetylacetone)-SiO ₂ (from Fructose), air	72	99	502
Pb-Pt/C (NaOH), air	100	81	503,504
Pt/C, air	100	95	505
Pt/C, air	100	91	506
Pt-ZrO ₂ ; Pt/Al ₂ O ₃ , air	100	98	507,508
PtBi/C (from fructose, solid acid, H ₂ O/MIBK), air	50	25	509
Au/TiO ₂ (basic conditions/O ₂)	100	71	510
Au (hydrotalcite), air	100	100	511
Pt/C, Pd/C, Au/C, Au/TiO ₂ , air	100	79	512
NiO ₂ /OH anode (electrochemical oxidation)		71	513
Ru on several supports	-	20-100	514,515
Bimetallic Cu-Au nanoparticles on TiO ₂	99		516

HMF oxidation into FDCA (**3**, Scheme 38) was achieved with several different stoichiometric oxidants like N_2O_4 , HNO_3 and KMnO_4 .⁵¹⁷ The oxidation of HMF using air or oxygen has been described using several different catalysts. The catalysts which is currently used for terephthalic acid production (Co/Mn/Br) was used for oxidation under high pressure (70 bar air).^{494,501} Similar processes have also been patented.^{495,518,519} Heterogeneous catalysts also resulted in FDCA *via* HMF oxidation with molecular oxygen. Supported platinum catalysts were first used in the presence of base, resulting in near quantitative FDCA yields. The base is used in stoichiometric amounts to keep the FDCA formed in aqueous solution as the di-alkaline salt.^{500,520} Direct synthesis routes of FDCA from fructose by combining dehydration and oxidation have also been reported using Pt-Bi/C in combination with a solid acid in water/MIBK. An FDCA yield of only 25% was obtained, constituting a 50% selectivity.⁵⁰⁹ Ribeiro reported the direct conversion of fructose to FDCA with high conversion and excellent selectivity (99%) using $\text{Co}(\text{acac})-\text{SiO}_2$ as bifunctional catalyst at 160 °C and 20 bar air pressure.⁵⁰² Recently, two examples were reported using supported gold catalysts for aqueous HMF oxidation.⁵¹⁰ Gorbanev *et al.* demonstrated that Au/TiO_2 could oxidise HMF into FDCA in 71% yield at near room temperature.⁵¹⁰ Casanova *et al.* showed that Au/CeO_2 was more active and selective.⁵²¹ Similar to the Pt systems reported by Vinke⁵⁰⁰ the addition of homogeneous base (1–20 equiv. NaOH) and high oxygen pressure (10–20 bar) are required. This was corroborated in recent research from Davis and co-workers.⁵²² Surprisingly, Saha and co-workers recently reported that addition of trifluoroacetic acid to the oxidation of HMF had a positive effect on yield and selectivity, both with $\text{Co(OAc)}_2/\text{Zn(OAc)}_2/\text{NaBr}$ and with gold nanoparticles immobilised on CeO_2 or TiO_2 as catalyst.⁵²³ Davis and co-workers compared a number of different catalysts and found that Pt/C and Pd/C oxidised HMF to FDCA an order of magnitude faster than Au/C or Au/TiO_2 .⁵²⁴ Recently, Gupta *et al.* reported the base free oxidation over gold catalysts supported on hydrotalcites.⁵¹¹ Since the FDCA formed is an acid, it can be expected that a reaction between the basic hydroxyl groups of the hydrotalcite and the product formed will take place.

Riisager and co-workers used Ruthenium on several different supports as catalysts in the oxidation of HMF (O_2 , H_2O). Best results were obtained using a basic support, such as MgO ; however, the authors found that the metals were leached from the basic support.^{514,515}

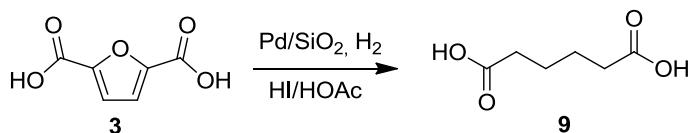
**Scheme 38.** Oxidation of HMF into FDCA

Avantium reported the oxidation of ethers of HMF using a Co/Mn/Br catalyst. The FDCA monoester thus obtained was esterified further to obtain the diesters such as **55**.⁵²⁵ Furthermore Avantium Chemicals have reported the use of FDCA-ethylene glycol polyesters starting from the FDCA dimethyl ester **55**. Though the polymer was already described by Drewitt and Lincoln in 1946⁵²⁶ real progress was only achieved recently. Gruter and co-workers⁵²⁷ and Gandini⁴⁷⁶ have recently published work on FDCA-based polyesters. Gandini has prepared extensive reviews on the synthesis and initial characterisation of a wide range of FDCA based polymers.^{461,462} Avantium has been able to produce multi-kilogram quantities. No details have been reported for the production of this diester, but it highlights the growing interest in these kinds of compounds. An interesting application of this polyester would be the replacement of PET in soft drink bottles. In view of the large size of the market, this could have an enormous impact on energy use and CO₂ emissions.⁵²⁸ The interest in green polymers is also exemplified by a patent of Evonik⁵²⁹ that claims the use of *iso*-decanol ethers of FDCA as good polymer plasticisers. Esterification of FDCA to obtain esters has been described by Gaset.⁵³⁰ Taarning et al. reported production of the diester **55** (dimethyl 2,5-furandicarboxylate) from HMF through oxidative esterification using Au/TiO₂ as catalyst in a sodium methoxide-containing methanol solution under oxygen pressure.^{531,532} Casanova *et al.* demonstrated base-free oxidative esterification of HMF into the diester using Au/CeO₂ as catalyst in methanol under 10 bar oxygen in an autoclave reactor (Scheme 39).⁵²¹

**Scheme 39.** Formation of FDCA di-esters from HMF

From FDCA several other compounds can be made that find application in polymer applications. A useful monomer that can be obtained from FDCA is adipic acid (**9**, Scheme 40), one of the two monomers used in the nylon 6,6. Boussie described the hydrogenation of FDCA to adipic acid in two steps.⁵³³ In the first step **50** was produced in 88% yield by

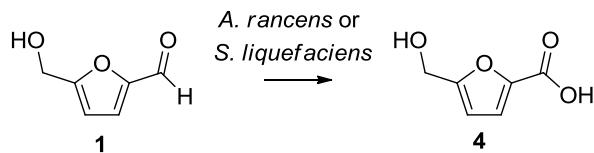
hydrogenating FDCA at 140 °C for 3 h in acetic acid, catalysed by Pd on silica. Yields up to 99% of adipic acid were claimed by reacting **50** under hydrogen at 160 °C for 3 h in acetic acid in the presence 0.2 M of and 5% Pd on silica catalyst.



Scheme 40. Conversion of FDCA into adipic acid

Sato described the preparation of diisocyanates.⁵³⁴ Benecke described the reaction with aromatic amines and their uses as cross-linking agents for polyureas, hybrid epoxy-urethanes, hybrid urea-urethanes, chain extenders for polyurethane and polyurea elastomers.⁵³⁵ Improved hydrogenation of the furan ring to tetrahydrofuran cis-2,5-dicarboxylic acid has been described by Moore.⁵³⁶ Amides and their subsequent hydrogenation to amines have been described by Mndzhoyan⁵³⁷

A highly selective oxidation of HMF to 5-hydroxymethyl-2-furan carboxylic acid **4** using whole cells of *Acetobacter rancens* or *Serratia liquefaciens* was reported by Nagasawa *et al.* (Scheme 41).⁵³⁸ Thus 2.6 mmol of HMF was oxidised in 26 h using 182 mg of whole cells of *S. liquefaciens* with 97% conversion.



Scheme 41. Enzymatic oxidation of HMF

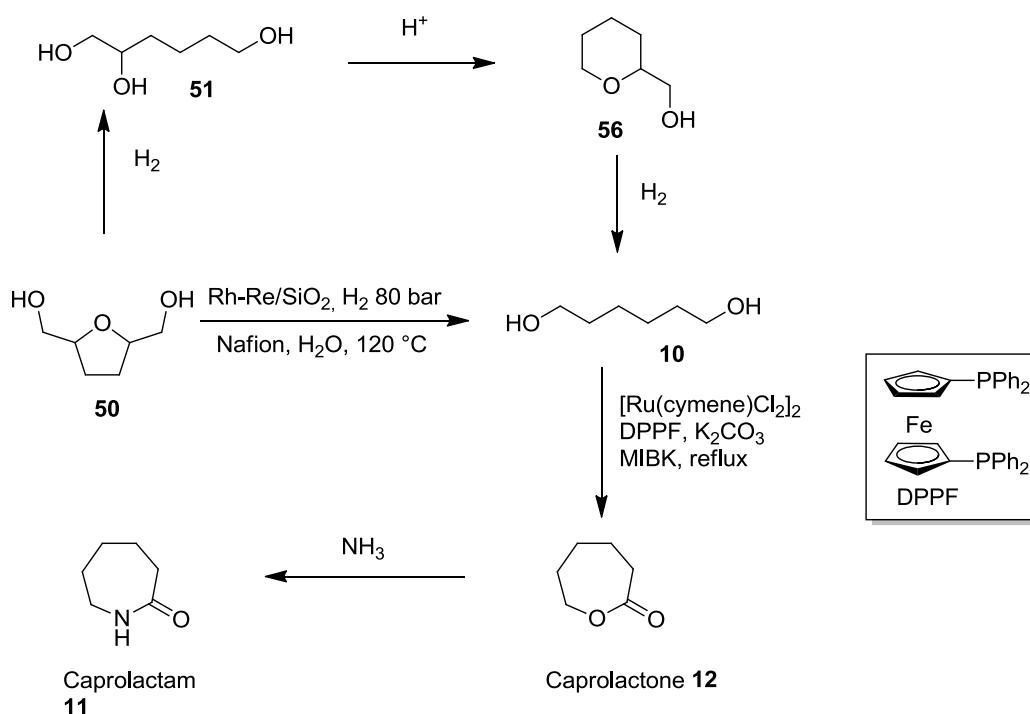
Koopman has described a novel HMF/furfural oxidoreductase from *Cupriavidus basilensis* that converts HMF into FDCA. The oxidoreductase gene was introduced into *Pseudomonas putida* S12. In fed-batch experiments using glycerol as the carbon source, 30 g/l of FDCA was produced from HMF at a yield of 97%.⁵³⁹ This approach has also been patented.^{540,541} The same authors recently published a review regarding microbial metabolism of HMF and other furans.⁸³

Riisager and co-workers have reported the oxidation of HMF in methanol using supported gold nanoparticles as catalyst. The resulting methyl 5-hydroxymethyl-2-furancarboxylate was reacted *in situ* with hexylamine to form the n-hexylamide.⁵⁴²

The oxidation of HMF to FDCA was recently reviewed.⁵⁴³

2.6.1.4 Conversion of HMF into other monomers

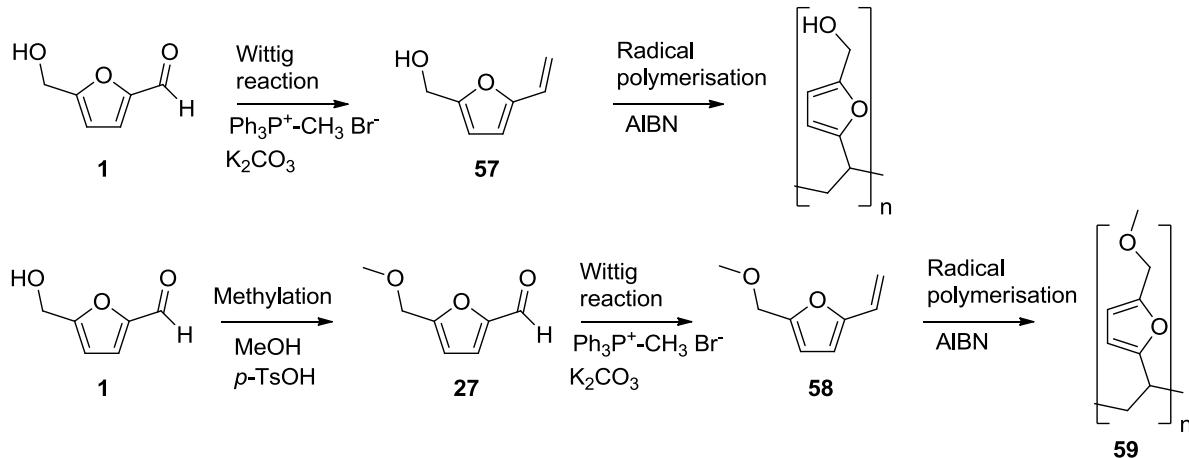
HMF has been converted into caprolactam, the monomer for nylon-6, by de Vries, Heeres and co-workers (Scheme 42).⁴⁶⁸ HMF was hydrogenated in >99% yield to **50**. They were able to hydrogenate **50** to 1,6-hexanediol in 86% yield, by using a Rh-Re/SiO₂catalyst in the presence of nafion. This is in fact a tandem three step process proceeding through formation of 1,2,6-hexanetriol, which is cyclised under the influence of the acid to tetrahydropyran-2-methanol (**56**), which in turn is hydrogenated to 1,6-hexanediol using the same catalyst. The diol was converted into caprolactone using a ruthenium-catalysed Oppenauer oxidation in virtually quantitative yield. Overall selectivity from HMF to caprolactone was 86%. Conversion of caprolactone into caprolactam using ammonia has been practiced on production scale in the past, so this constitutes an interesting route from HMF to Caprolactam in only 4 steps, whereas the current industrial process, which is based on benzene, contains seven steps. Scheme 42 provides an overview of the conversion of **50** into caprolactam.



Scheme 42. Conversion of **50** into caprolactam

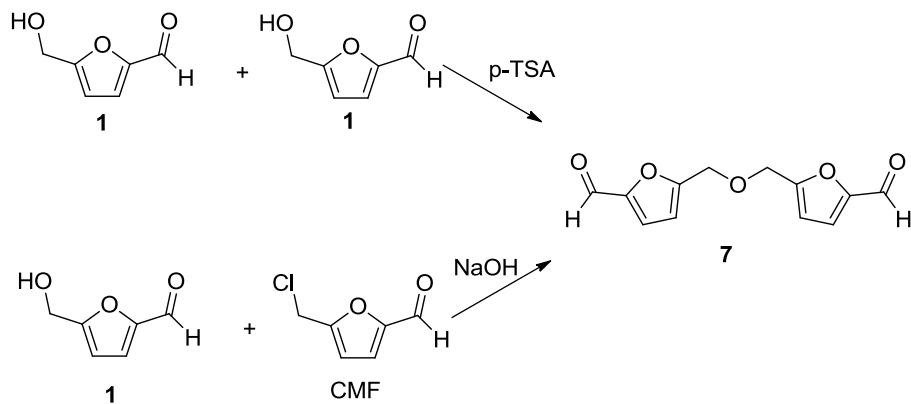
Another outlet for HMF is the synthesis of novel biomass-based vinyl polymers. HMF or its methylated derivative MMF was efficiently converted to its vinyl derivative (**57** and **58**)

by the Wittig reaction in a solid-liquid phase transfer process (Scheme 43), followed by free radical polymerisation in a bulk.⁵⁴⁴ Especially the MMF derived polymers **59** showed good thermal stability.



Scheme 43. Vinyl furans from HMF and their polymers

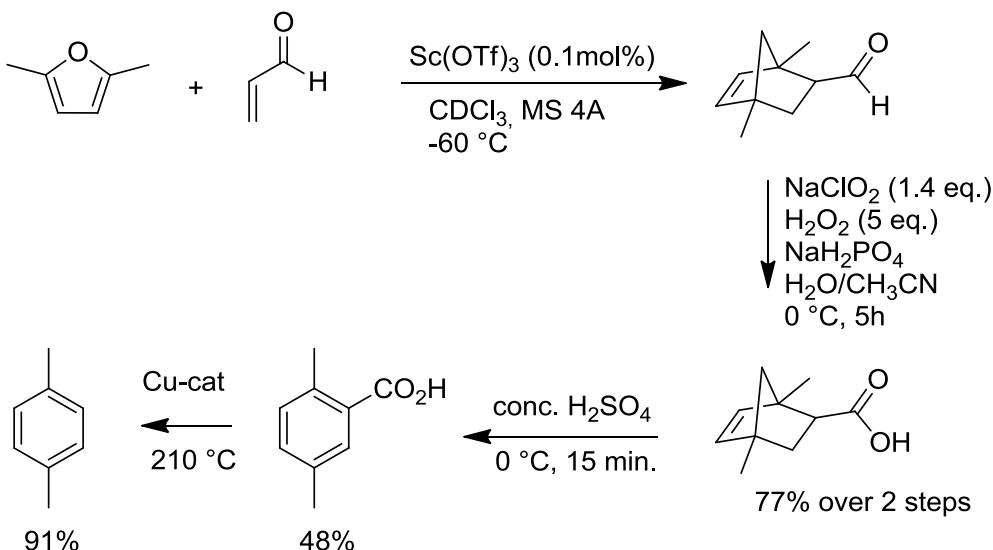
Polymeric building blocks based on dimers from HMF have also been described. Casanova has investigated the conversion of HMF into 5,5'-(oxybis(methylene))-2-furaldehyde (**7**, OBMF), which is an interesting prepolymer and a precursor for an anti-viral compound (Scheme 44).⁵⁴⁵



Scheme 44. Conversion of HMF into 5,5'-(oxybis(methylene))bis(furan-2-carbaldehyde)

Toste has published a synthesis of xylene, which starts from HMF derived 2,5-dimethylfuran which is reacted with glycerol-derived acroleine in a Diels-Alder reaction (Scheme 45). The Diels-Alder adduct is oxidised to the carboxylic acid using a stoichiometric oxidant, followed by acid catalysed rearrangement to 2,5-dimethyl-benzoic acid. This is

decarboxylated in a copper-catalysed reaction to *p*-xylene, which is the raw material for terephthalic acid, an important monomer for polyesters such as PET.⁵⁴⁶

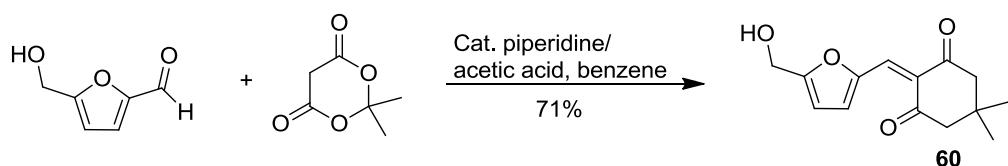


Scheme 45. Xylene synthesis, starting from 2,5-dimethylfuran

2.6.2 Fine chemicals

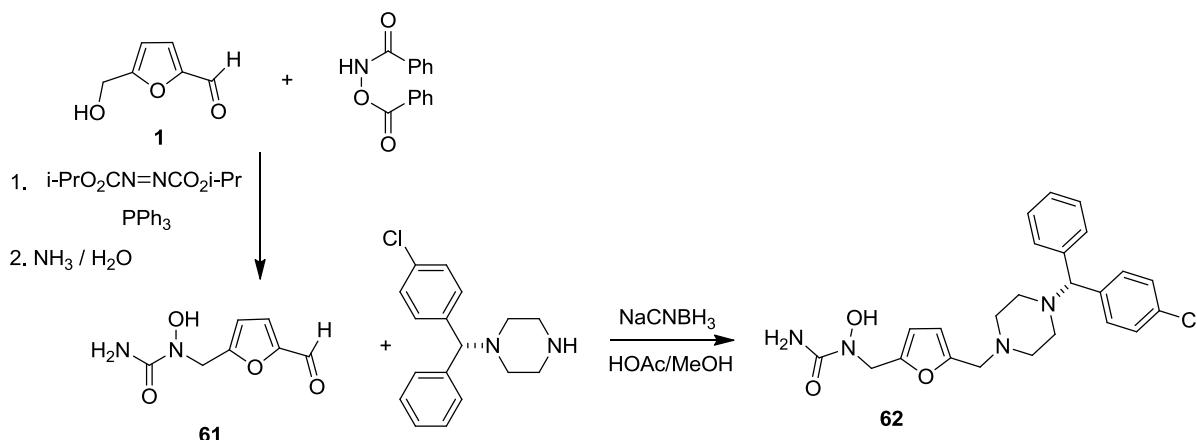
2.6.2.1 Pharmaceuticals

In view of the rigid furan structure and the two substituents that can be easily modified, HMF has been used in quite a number of drug studies. Lukevics and co-workers investigated a series of adducts between Meldrum's acid and substituted furans (Scheme 46).⁵⁴⁷ The derivative **60** made from HMF had some neurotropic activity.



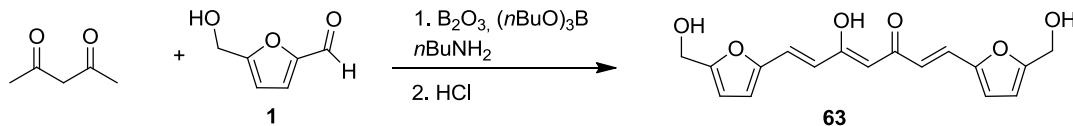
Scheme 46. Meldrum's acid derivative of HMF

Lewis and co-workers synthesised a range of furan containing compounds they designed to be active both as lipoxygenase inhibitors (N-hydroxy-urea moiety) and as Histamine H₁ receptor antagonists (benzhydrylpiperazine moiety).⁵⁴⁸ Compound **62** showed poor lipoxygenase inhibition properties (IC₅₀ = 1700 nm) however, it was an excellent antagonist of the Histamine H₁ receptor (K_i = 4 nM) (Scheme 47).



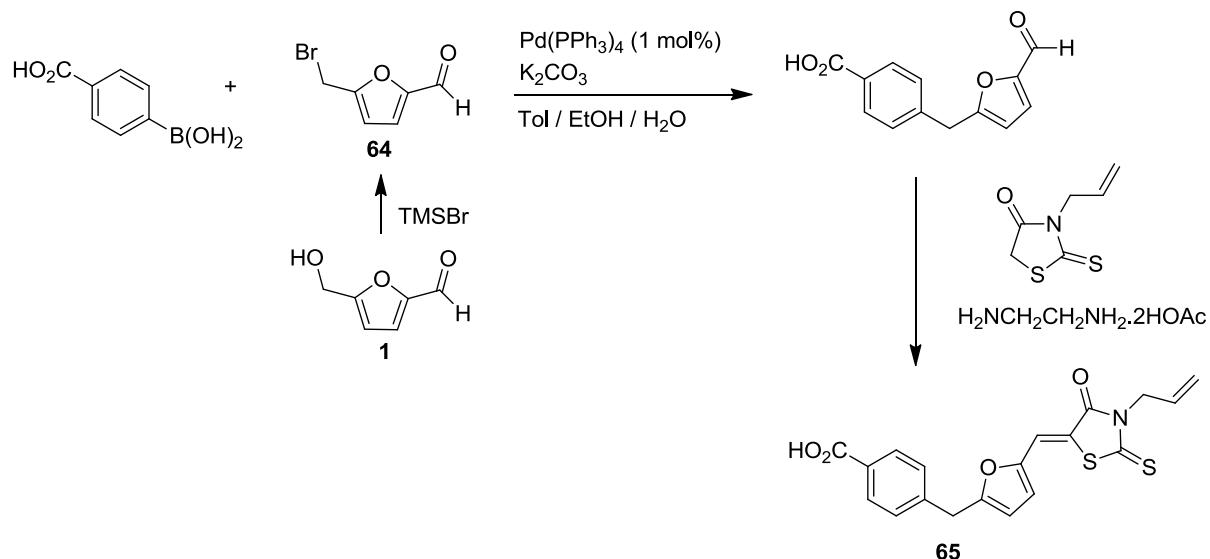
Scheme 47. Dual action lipoxygenase inhibitor and Histamine receptor antagonist based on HMF

Condensation of HMF with 2,4-pentanedione in the presence of B_2O_3 , tri-butylborate and butylamine led to the double Knoevenagel product **63** (Scheme 48) which was tested for cytotoxicity against two tumour cell lines. It did not show activity in these tests.⁵⁴⁹



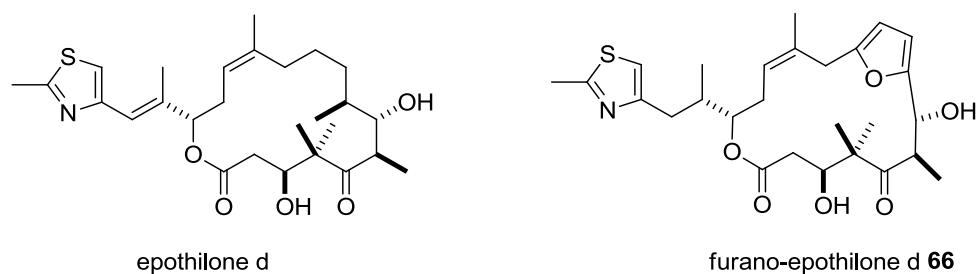
Scheme 48. Furan-based Curcumin analogue as anti-cancer agent

A series of phenyl-furanyl-rhodanines was synthesised and tested as antibacterial inhibitors of RNA polymerase.⁵⁵⁰ These molecules have been evaluated for their ability to inhibit transcription and to affect the growth of bacteria living in suspension or in a biofilm. An HMF-based compound was prepared via the bromomethyl derivative **64** (Scheme 49), which was arylated *via* a Suzuki reaction and aldol condensation of this product with N-allyl-rhodanine. The product **65** showed only low to moderate activity in the antibacterial tests.



Scheme 49. HMF-based reverse transcriptase inhibitor

Schinzer and co-workers reported the total synthesis of an epothilone d analogue **66** (Scheme 50) that was built from HMF. This compound had moderate cytotoxic activity, which was less than paclitaxel, which was used as reference.⁵⁵¹

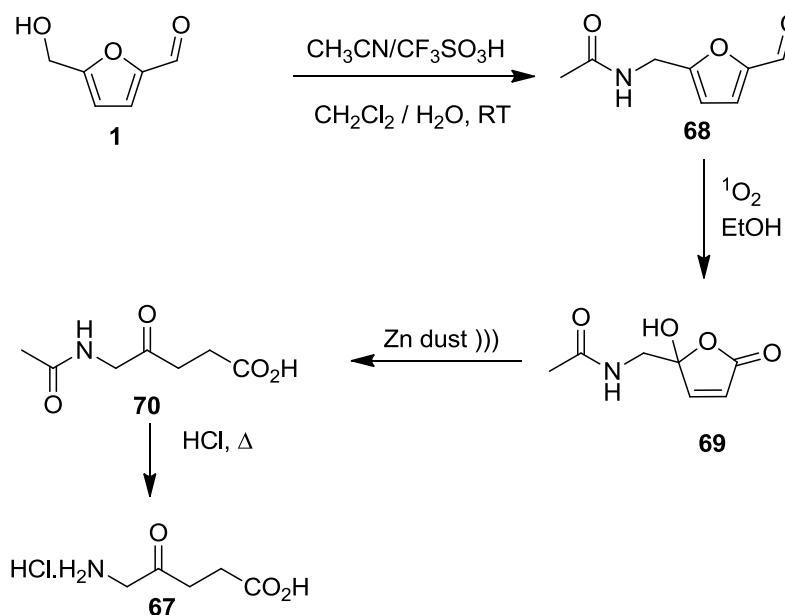


Scheme 50. Epothilone analogue based on HMF

2.6.2.2 Agrochemicals

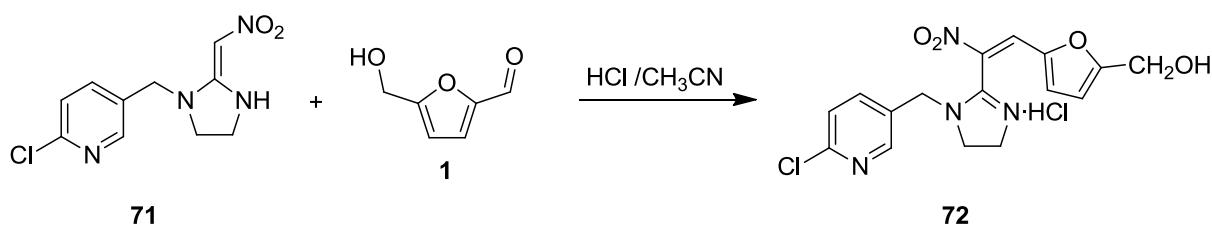
5-Amino-levulinic acid (**67**) and its derivatives are herbicides. A synthesis from HMF, described in Scheme 51, was published by Descotes in collaboration with Südzucker.^{552,553} HMF was subjected to a Ritter reaction with acetonitrile, which delivered the desired amide **68** in 47% yield and 97% selectivity due to incomplete conversion. This amide was subjected to a reaction with singlet oxygen ($^1\text{O}_2$) which was prepared by irradiation of oxygen in the presence of immobilised Rose Bengal. The crude product contained 64% of the furanone **69**,

which was reduced with zinc dust using ultrasonic irradiation to give N-acetyl 5-amino-levulinic acid (**70**) in 55% yield. Hydrolysis to **67** was effected by reflux in hydrochloric acid.



Scheme 51. Conversion of HMF into 5-amino-levulinic acid

Li, Xu and co-workers prepared a series of analogues of Imidacloprid, a much-used insecticide, by reaction of 5-ring aromatic aldehydes with the nitromethylene neonicotinoid 6-Cl-PMNI (**71**), which also has insecticidal activity (Scheme 52). Reaction with HMF in acetonitrile was catalysed by HCl and proceeded in 72% yield.⁵⁵⁴ The product **72** was active against a certain strain of aphids and against armyworm.

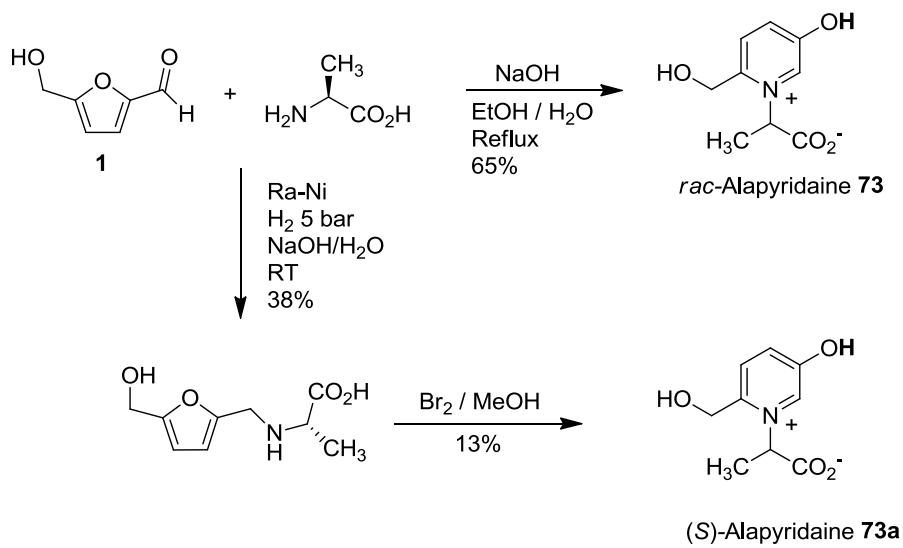


Scheme 52. Insecticide based on HMF

The propionic acid ester of HMF is a fungicide that can be obtained via acylation of HMF with propionic anhydride.¹³

2.6.2.3 Flavours & Fragrances

The Maillard reaction between reducing carbohydrates and amino acids is undoubtedly one of the most important reactions in the F&F world, leading to the development of the unique aroma and taste as well as the typical browning, which contribute to the sensory quality of thermally processed foods, such as cooked or roasted meat, roasted coffee or cocoa. Although numerous studies have addressed the structures and sensory attributes of the volatile odour-active compounds, the information available on non-volatile, sensory-active components generated during thermal food processing is scarce. Researchers in Germany examined the reaction between alanine and glucose in boiling water at pH 5.⁵⁵⁵ From the Maillard reaction product they were able to isolate a compound, which they named alapyridaine. This compound, although tasteless by itself, has the property that it enhances sweet taste. Thus the threshold detection level for tasting glucose was decreased by a factor of 16 in a 1:1 mixture of glucose and alapyridaine. They were able to synthesise alapyridaine **73** in 51-65% yield by refluxing HMF with alanine in EtOH. Although L-alanine was used as starting material the product was isolated as a racemic mixture. A two-step synthetic method was developed that allowed the isolation of the enantiopure compounds in poor yield (Scheme 53).⁵⁵⁶ It was shown that only the (*S*)-alapyridaine **73a** was active as sweetness enhancer, whereas the (*R*)-enantiomer had no effect.



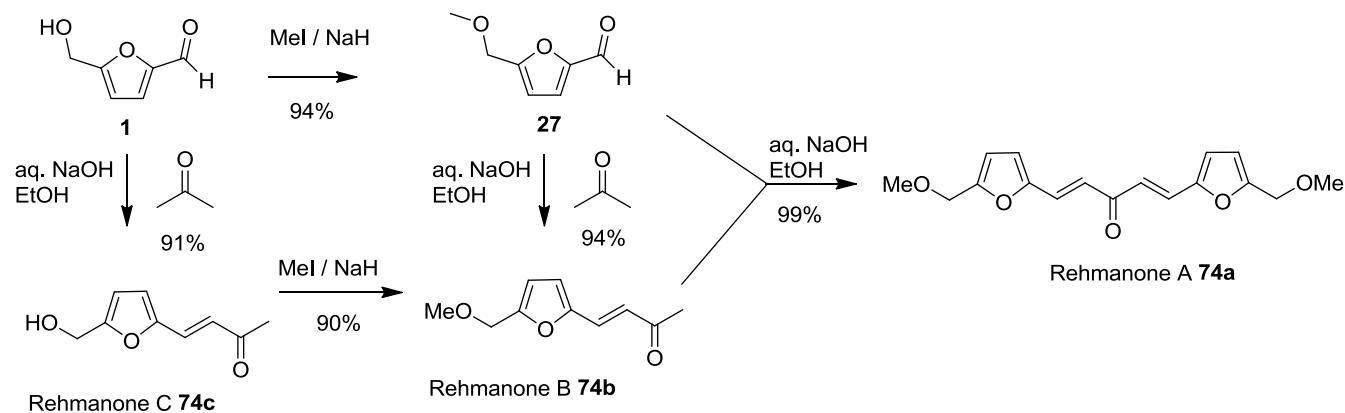
Scheme 53. Sweet taste enhancer from HMF and alanine

Similar pyridinium compounds have been made by the reaction between HMF and methylamine,⁵⁵⁷ 1-propylamine,^{557,558} glycine,⁵⁵⁹ β-alanine,⁵⁵⁹ γ-aminobutyric acid⁵⁵⁹ and *N*-acetyl-lysine.⁵⁵⁷

Terada and co-workers reported the preparation of a trimeric acetal of HMF in only 2.3% yield by treating HMF with an acidic ion exchange resin for a prolonged period of time.⁵⁶⁰ The compound was used for the preparation of flavour enhancing compounds.

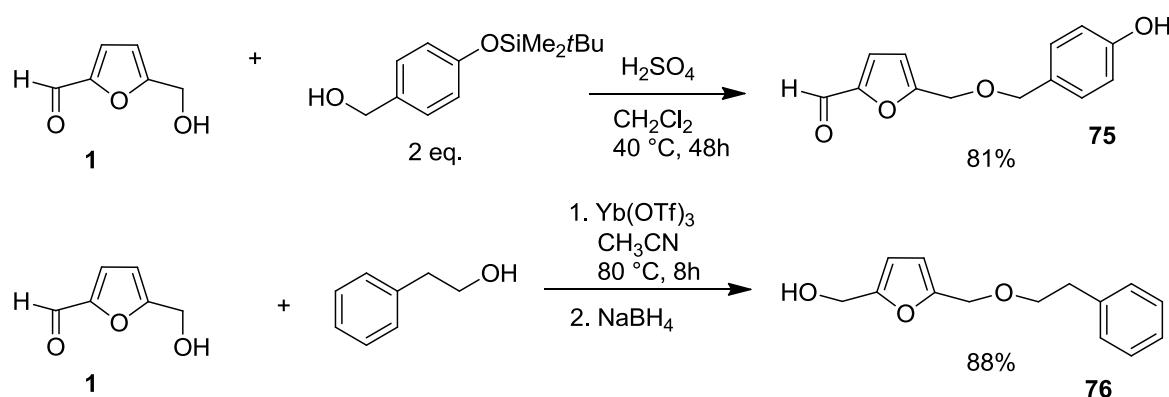
2.6.2.4 Natural Products

The naturally occurring furan derivatives rehmanone A, rehmanone B, and rehmanone C have been recently isolated from the dried roots of *Rehmannia glutinosa*,¹ and 3 from *Salvia miltiorrhiza* Bunge (Labiatae). Rehmanone A (**74a**), B (**74b**) and C (**74c**) display significant biological activity, since Rehmanone A inhibited blood platelet aggregation and Rehmanone A and C promoted immune activity. Moreover, the latter activity is inhibited when Rehmanone B and C are tested at higher concentrations. Their synthesis is straightforward as outlined in Scheme 54 below.⁵⁶¹



Scheme 54. Synthesis of Rhemanones from HMF

Treatment of HMF with 2 eq. of TBDMS-protected *p*-hydroxybenzylalcohol catalysed by sulfuric acid gave a good yield of 5-{[(4-hydroxybenzyl)oxy]methyl}-2-furfural (**75**) (Scheme 55), a compound that was recently isolated from the rhizome of *Gastrodia elata* Blume (Orchidaceae), and exhibited weak cytotoxicity against the HT-29 cell line. Similarly, treatment of HMF with 2-phenylethanol catalysed by Yb(OTf)₃ gave the ether, which was immediately reduced to Pichiafuran C (**76**), a compound that was recently isolated from the yeast *Pichia membranifaciens*, derived from the marine sponge *Petrosia* sp.⁵⁶²

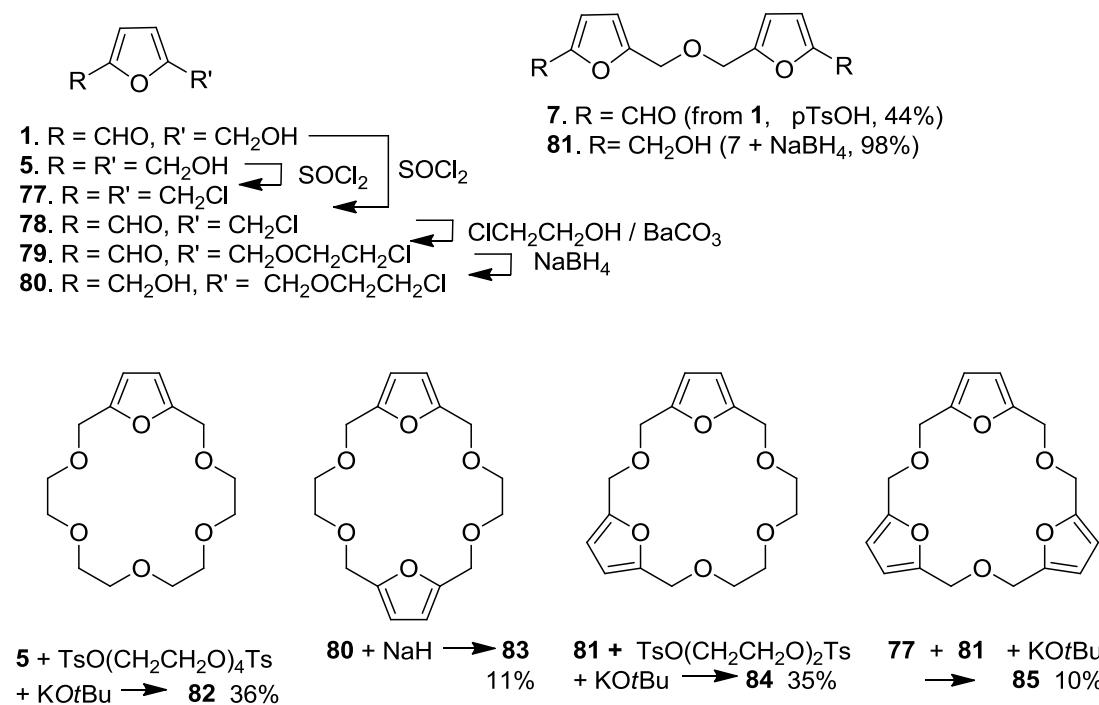


Scheme 55. Etherification of HMF with aromatic derivatives to form natural products **75** and **76**

2.6.2.5 Macrocycles

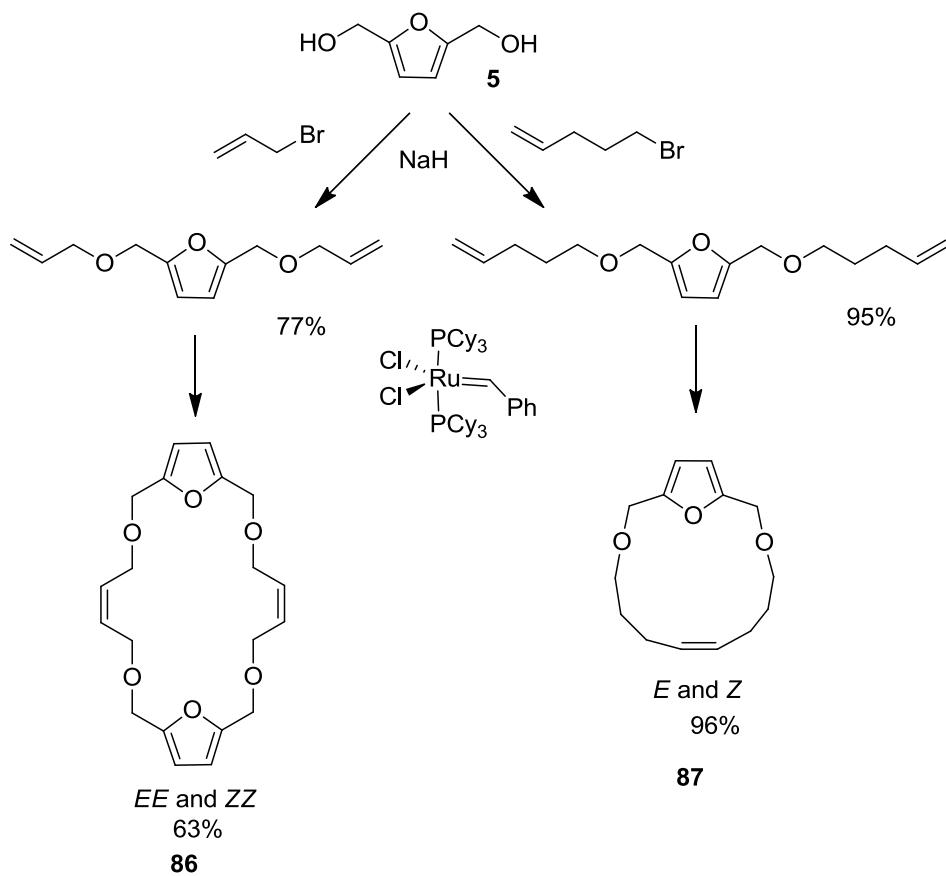
In addition to the epothilone d analogue reported by Schinzer many more macrocyclic compounds have been made using HMF as a building block.

Cram reported a series of crown ethers (**82-85**) that were prepared from HMF and 2-chloroethanol as building blocks (Scheme 56).⁴⁶⁵



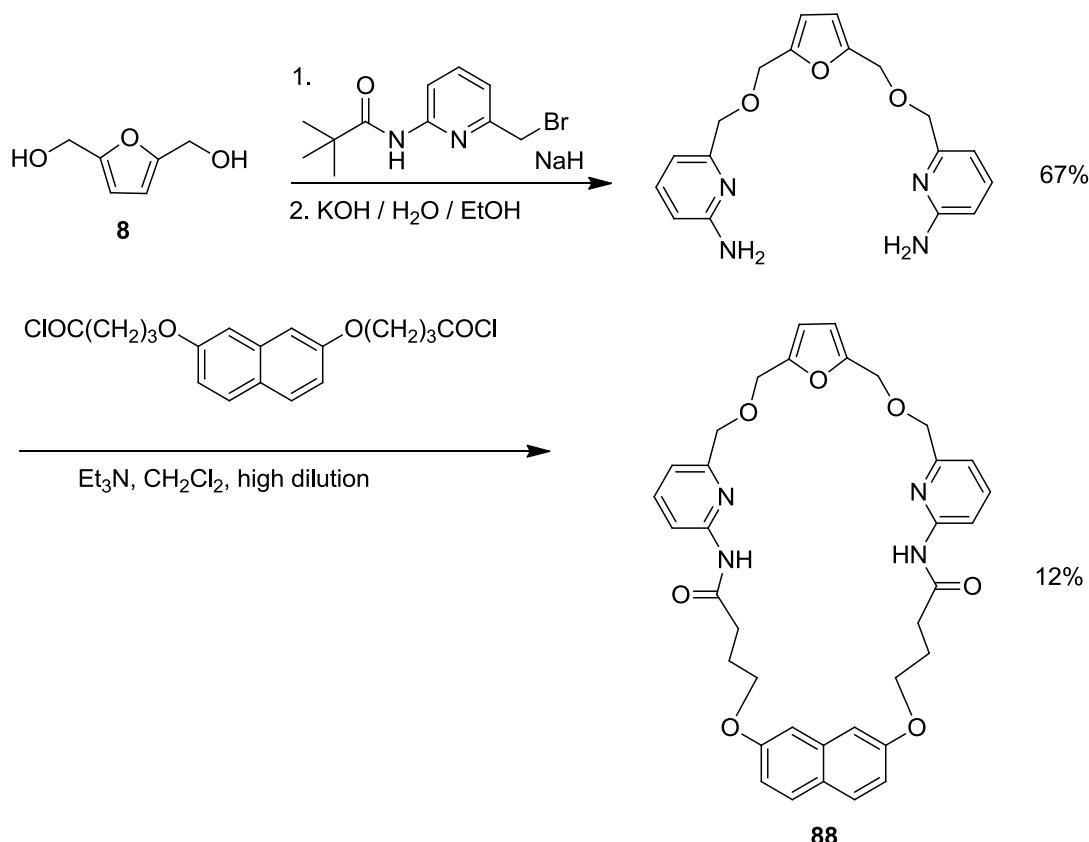
Scheme 56. Crown ethers based on HMF

Cottier and co-workers prepared furan-containing macrocycles from **5** by etherification with bromoalkenes. The resulting bis-olefins were cyclised at high dilution using the Grubbs 1st generation catalyst. High yields of monomeric (**86**) or dimeric (**87**) macrocycles were obtained (Scheme 57).



Scheme 57. Macrocycles from HMF

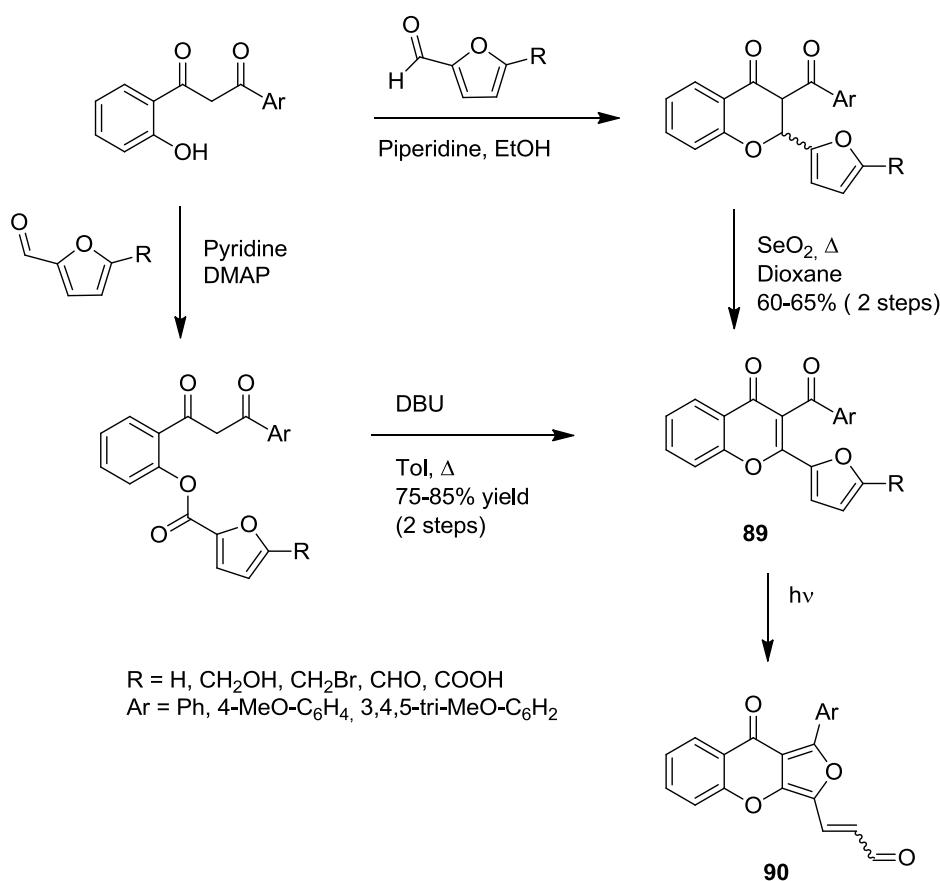
Goswami and co-workers synthesised a ditopic receptor (**88**) for the selective binding of α,ω -dicarboxylic acids in which 2,5-bishydroxymethylfuran was used as a spacer (Scheme 58).⁵⁶³ Binding could be measured via NMR or using fluorescence quenching.



Scheme 58. Ditopic macrocyclic receptors from HMF

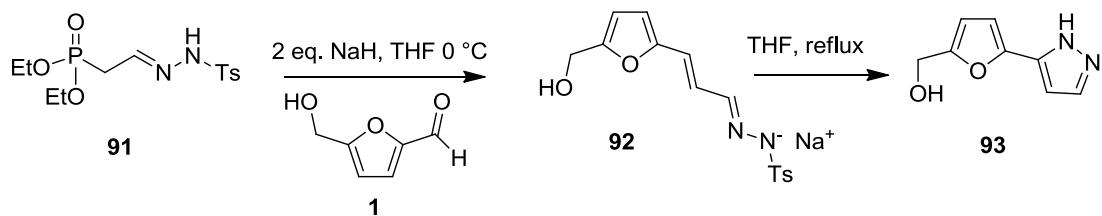
2.6.2.6 Heterocycles

Furan-substituted chromones **89** were prepared by Krafft and co-workers in a two-step sequence (Scheme 59).⁵⁶⁴ These compounds were designed to be photoactivatable fluorophores. Irradiation at 350 nm for 4 min. converts them into an E/Z mixture of the highly fluorescent 1-arylfuro[3,4b]chromones **90** in low yield. Prolonged irradiation (2.5h) resulted in 50% conversion and an E/Z ratio of 97:3.



Scheme 59. Synthesis of furan-substituted chromones

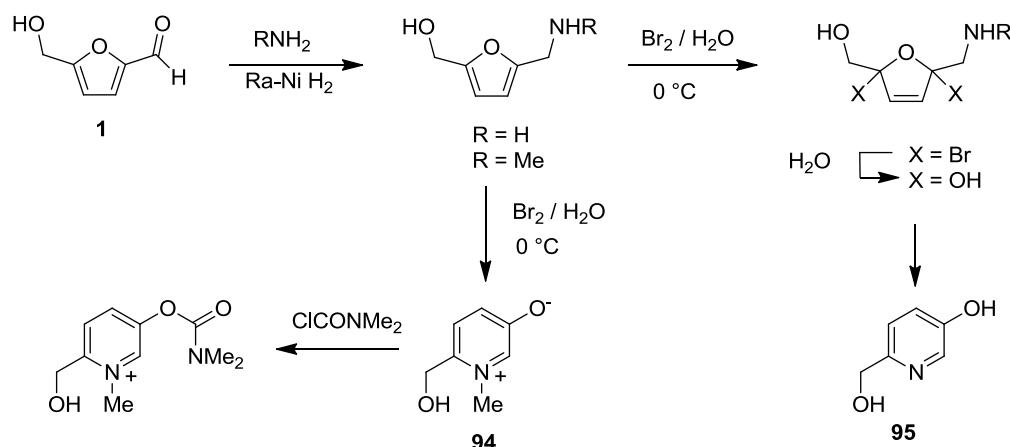
A range of substituted pyrazoles was prepared via a Wittig-Horner reaction between a series of substituted aldehydes with a novel tosylhydrazone phosphonate synthon **91**. The resulting sodium salt **92** of the α,β -unsaturated tosylhydrazone was refluxed in THF to give the pyrazole **93** with concomitant elimination of sodium tosylate (Scheme 60). Thus HMF was converted to the 3-furyl-pyrazole in 60% overall yield.⁵⁶⁵



Scheme 60. Furanylpyrazole from HMF

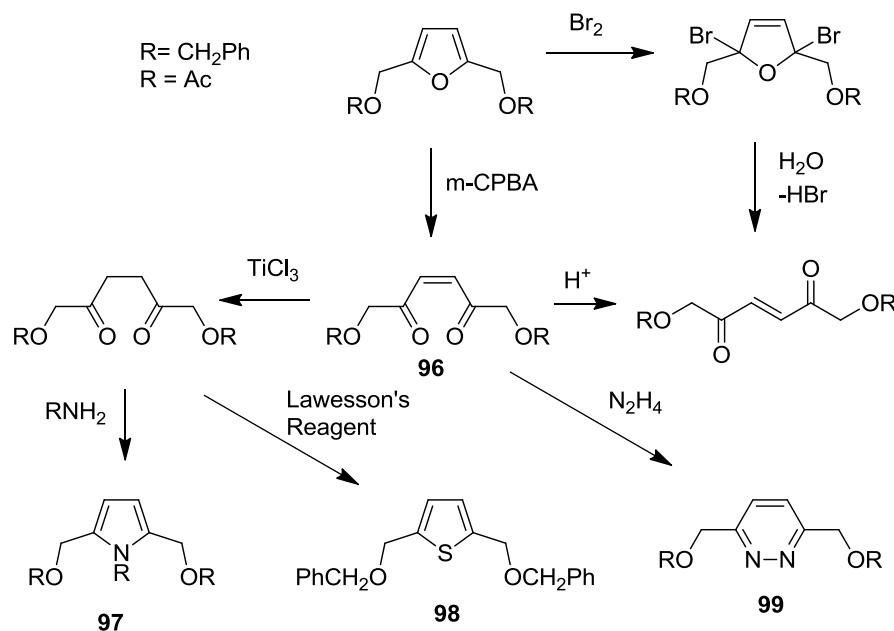
The synthesis of 3-hydroxy-pyridinium compounds from HMF and amino acids or alkylamines was already described above. It is also possible to prepare the parent compound **94** in a two-step sequence from HMF (Scheme 61).⁵⁶⁶ The same authors also prepared

compound **95**, which is a 6-hydroxymethyl analogue of the parasympathomimetic pyridostigmine.



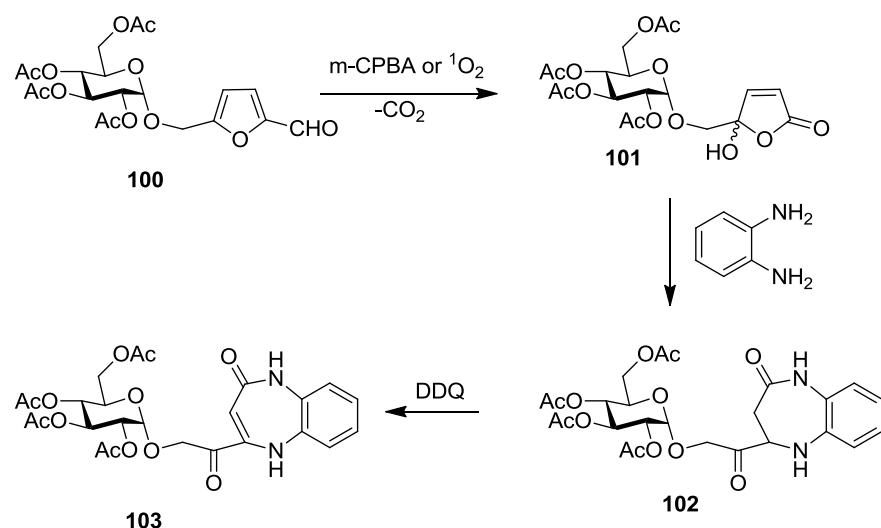
Scheme 61. Pyridinols from HMF

Lichtenthaler and co-workers converted HMF into a number of different heterocycles by first effecting a ring-opening of the furan-ring using oxidative methods. The resulting *E*- and *Z*-1,6-dioxy-3-hexene-2,5-diones **96** were first selectively double-bond reduced and then converted into heterocycles by treatment with either alkyl- or arylamines to afford pyrroles (**97**), or by Lawesson's reagent to afford the thiophenes (**98**) or by hydrazine to afford the pyridazines (**99**) in good yields (Scheme 62).⁵⁶⁷



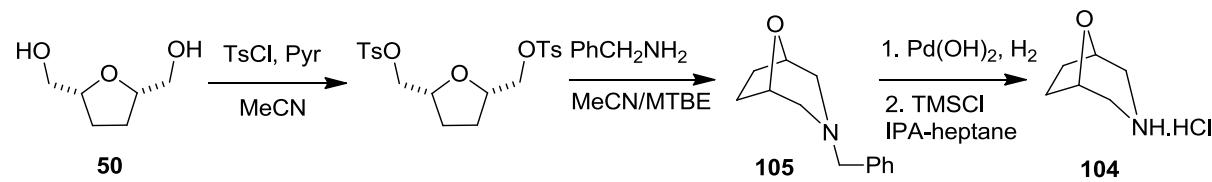
Scheme 62. Conversion of HMF into heterocycles

A similar series of reactions was performed on α -glucosylated HMF (**100**, Scheme 63). Oxidation of the HMF moiety in this adduct, using *m*-chloro-perbenzoic acid or singlet oxygen, provided the glucosylated hydroxybutenolide **101** in yields of 70% and 95% respectively. The reaction of this product with *o*-phenylenediamine led to formation of the glucosylated benzodiazepinone **102** (65%). This could be dehydrogenated using 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) to give the dehydrogenated glucosylated benzodiazepinone **103** in 89% yield.



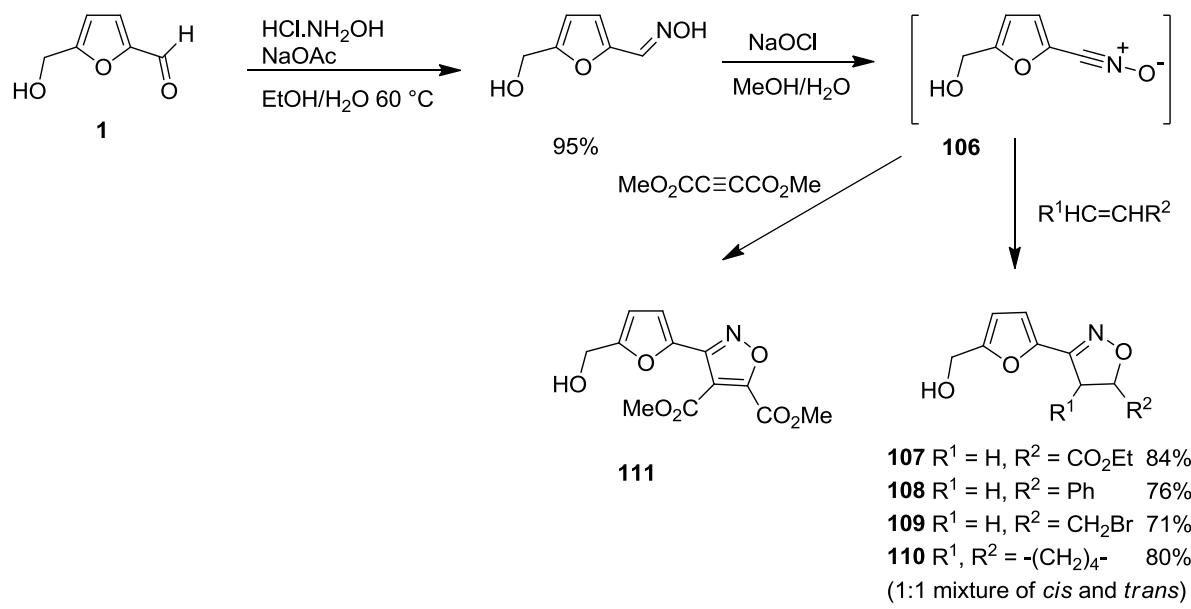
Scheme 63. glucosylated benzodiazepinone from HMF

Connolly and co-workers described the preparation of 8-oxa-3-aza-bicyclo[3.2.1]octane as its HCl-salt **104** in a straightforward 3-step sequence from **50** (Scheme 64).⁴⁷⁴ Thus bistroylation of **50** (83% yield) followed by reaction with benzylamine (93.5% yield) gave the bicyclic N-benzylated compound **105**, which was debenzylation by hydrogenolysis using Pearlman's catalyst ($\text{Pd}(\text{OH})_2$). The product was isolated as the HCl-salt in 68% yield.



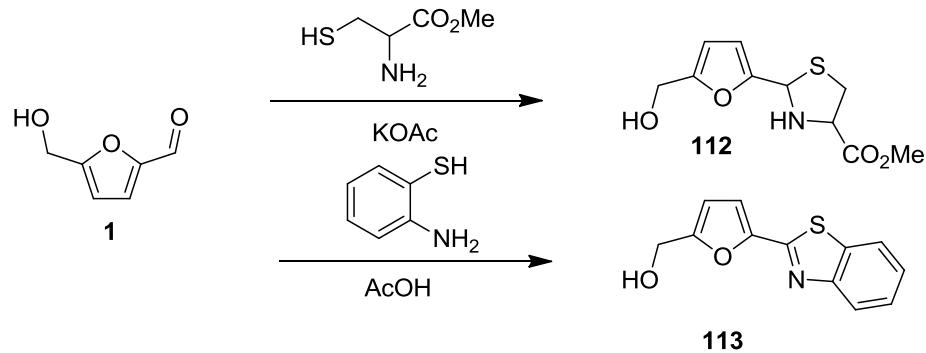
Scheme 64. Synthesis of 8-oxa-3-azabicyclo[3.2.1]octane from **50**

Amarasekara and co-workers converted the aldehyde moiety of HMF into the nitrileoxide, using established technology, forming **106** (Scheme 65). Cycloaddition of the nitrileoxide with a number of alkenes gave the 4- or 4,5-disubstituted 4,5-dihydroisoxazoles substituted in the 3-position (**107-110**) with the furfuryl unit in yields from 71 to 84%. Reaction with dimethyl acetylenedicarboxylate gave the 4,5-disubstituted isoxazole **111** in 96% yield.⁵⁶⁸



Scheme 65. Conversion of HMF into 3-furyl-isoxazole or -4,5-dihydroisoxazoles

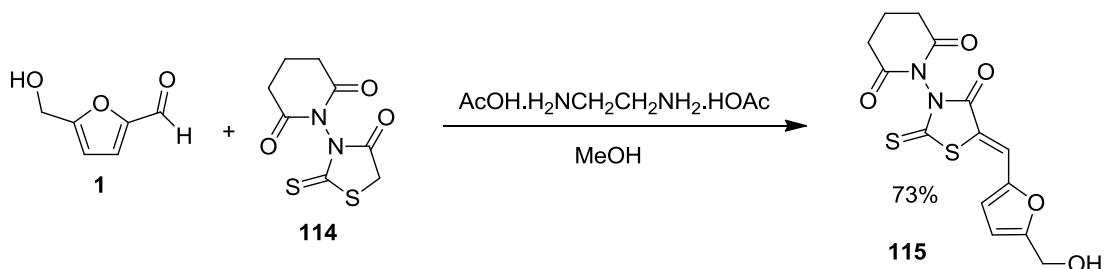
Reaction of HMF with 1,2 aminothiols leads to the formation of thiazolidine- (**112**) or thiazoline-substituted hydroxymethylfuran **113** in good yields (Scheme 66).^{569,570}



Scheme 66. Thiazolidine and thiazoline from HMF

Hanefeld and co-workers synthesised a series of rhodanine derivatives via aldol condensation of a range of aldehydes with the parent compound **114** (Scheme 67).⁵⁷¹ In this

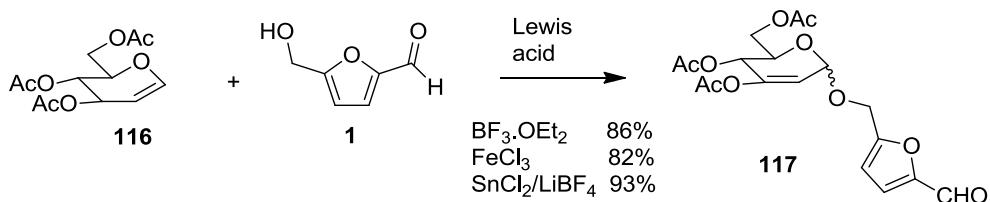
fashion the HMF derivative **115** was prepared in 73% yield. These products are have potential as aldose reductase inhibitors.



Scheme 67. The synthesis of rhodanine derivates via aldol condensation

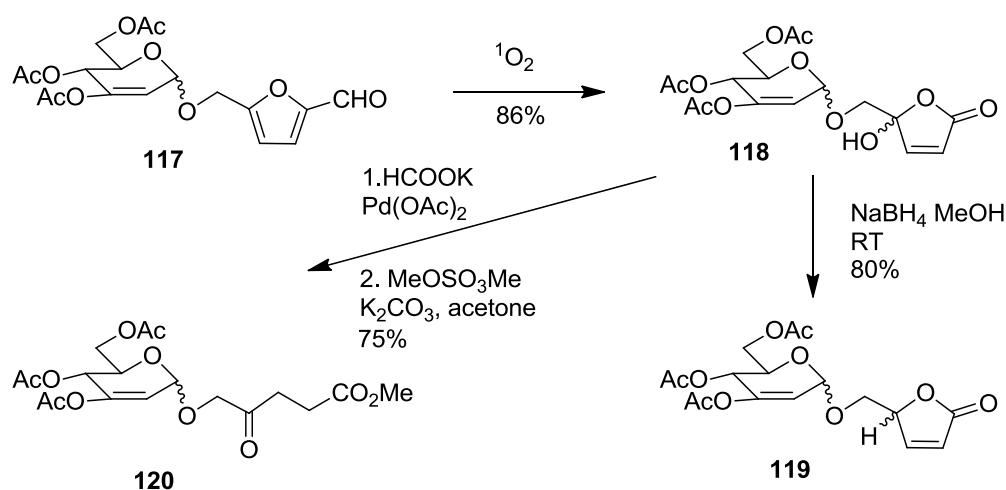
2.6.2.7 Sugar derivatives

HMF has been used as oxygen nucleophile in the Ferrier rearrangement of glycals (**116**) to form **117**. Depending on the Lewis acid that was used as the catalyst, yields of 45-93% were achieved (See Scheme 68; only the best results are shown).⁵⁷²

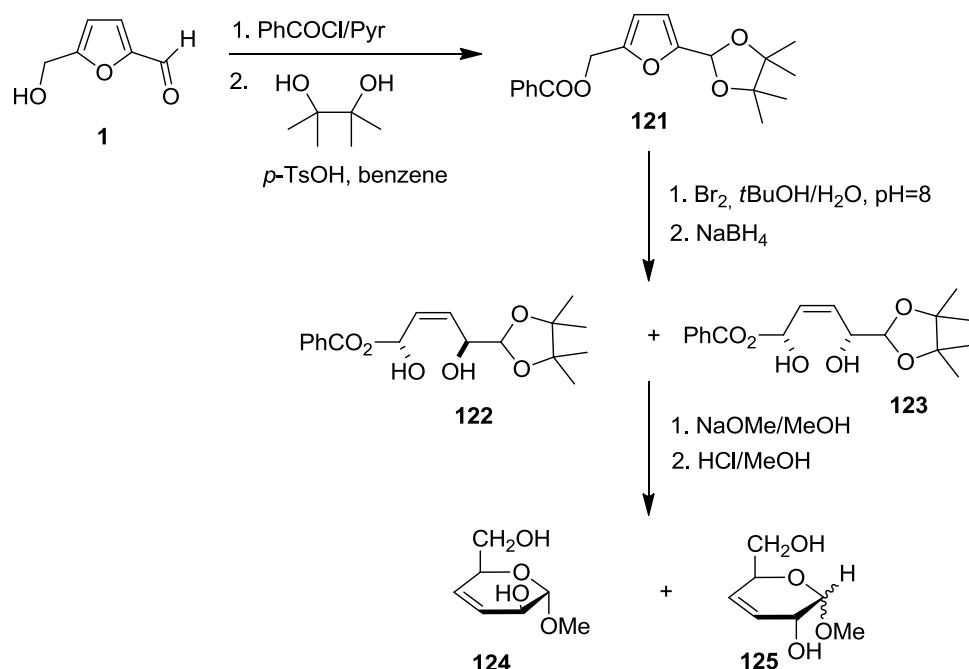


Scheme 68. HMF as a nucleophile in the Ferrier rearrangement

Glucosylated HMF was already mentioned above in the section on heterocycles. Cottier and co-workers explored different methods of preparation of the alpha and beta-anomers. Direct coupling of HMF with protected activated glucose equivalents generally gave the glucosylated HMF in low yields. Better yields were obtained by coupling 2-furfurylalcohol and formylating the adduct afterwards. They also performed some further conversions selectively on the HMF moiety. Thus, treatment with singlet oxygen gave the corresponding glucosylated 5 hydroxy-2,5-dihydro-2-furanone **118**, which could be further reduced to **119**. Palladium-catalysed formate reduction thereof led to the formation of the corresponding glucosylated 5-hydroxylevulinic acid, which was esterified to **120** using dimethyl sulfate and bicarbonate (Scheme 69).⁵⁷³

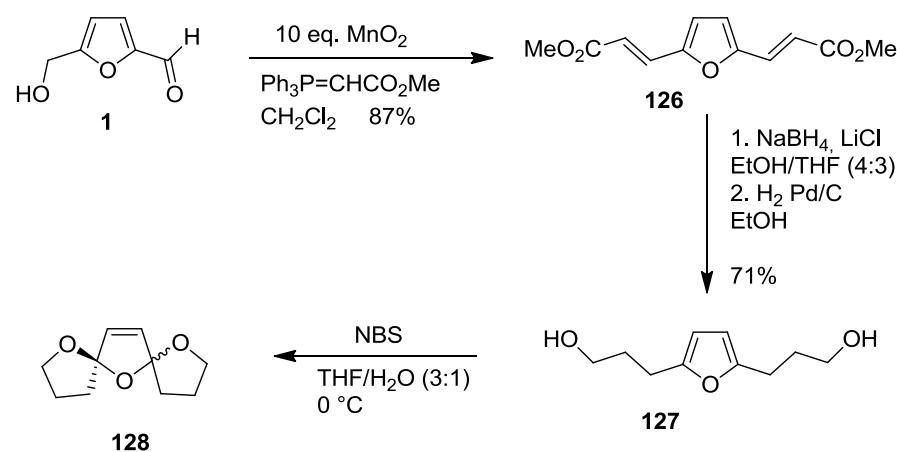
**Scheme 69.** Transformations of glucosylated HMF

Hungarian researchers were able to convert HMF into dideoxysugars (Scheme 70).⁵⁷⁴ HMF was first benzoylated and next the aldehyde functionality was protected as the acetal with pinacol. This compound (**121**) was oxidised with bromine to the diketone (not shown), which was immediately reduced with NaBH_4 to give a mixture of diastereomeric diols (**122** and **123**) which could be separated by chromatography. Removal of the benzoyl group with methanolic sodium methoxide was followed by ring-closure with methanolic HCl, resulting in the formation of the α - and α,β -dideoxysugars (**124** and **125**).

**Scheme 70.** Dideoxysugars from HMF

2.6.2.8 Spiroketals

The trioxadispiroketal functionality is present in a number of biologically active marine natural products as well as in antibiotic polyether ionophores. Stockman and coworker reported a short synthesis of such a unit based on furandialdehyde, prepared in situ from HMF with excess MnO₂, which was immediately converted to the bis-acrylate ester **126** using a stabilised Wittig reagent.⁵⁷⁵ Consecutive reduction of the ester units and the double bonds gave the diol **127**, which was cyclised to the trioxadispiroketal **128** using NBS (Scheme 71). They also prepared the 6,5,6-ring analogue using a Wittig C-3 synthon containing a silylated hydroxygroup. Other steps were similar.



Scheme 71. The synthesis of a trioxadispiroketal, starting from HMF

2.6.2.9 Other synthetic conversions

Acetalisation

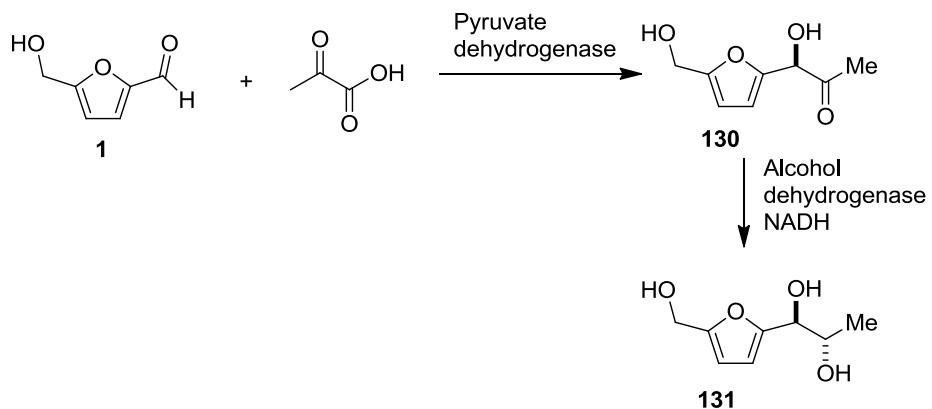
The dimethylacetal of HMF **129** has been prepared by two different methods. The classical acetalisation with MeOH, catalysed by a zeolite, led to formation of the acetal in 96% yield,⁵²¹ whereas use of trimethyl orthoformate in the presence of catalytic ytterbium sulfate immobilised on amberlite led to the product in 80% yield (Scheme 72).⁵⁷³



Scheme 72. The synthesis of the dimethyl acetal of HMF

Acycloine condensation

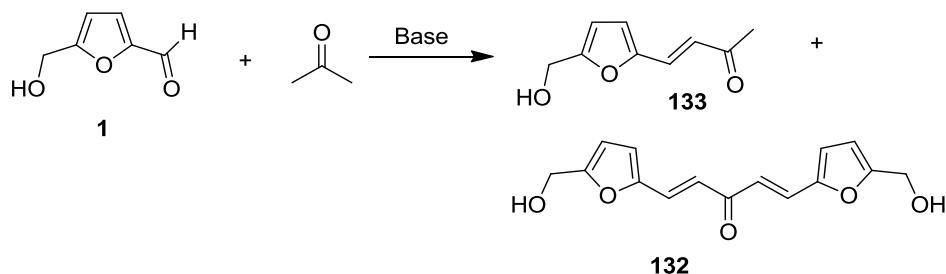
Chinese researchers reacted HMF with pyruvic acid, catalysed by pyruvate dehydrogenase,⁵⁷⁶ resulting in enantiopure hydroxyketone **130** which was reacted with an alcohol dehydrogenase to give the (*1S,2R*)-diol **131** (Scheme 73).



Scheme 73. Enzymatic conversion of HMF

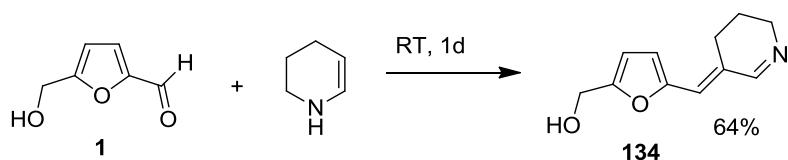
The Aldol condensation

The aldol reaction on the aldehyde moiety of HMF (Scheme 74) has been reported many times and usually proceeds in high yields. Dumesic investigated the condensation between acetone and HMF in biphasic THF/aqueous salt solutions using NaOH as basic catalyst. Using exactly 2 equivalents of HMF to one equivalent of acetone good yields of the double aldol condensation product **132** were obtained.⁵⁷⁷ This product can be seen as a precursor to biodiesel as full hydrogenolysis will give rise to a C-13 hydrocarbon.⁵⁷⁸ Using an excess of acetone, good yields of the single aldol adduct **133** could be obtained. Shantz and co-workers also looked at the aldol between HMF and acetone in acetone solution, using a solid secondary amine type basic catalyst.⁵⁷⁹ The reaction was very slow at 40 °C. No data were given regarding selectivity of the process.



Scheme 74. Aldol condensation products between HMF and acetone

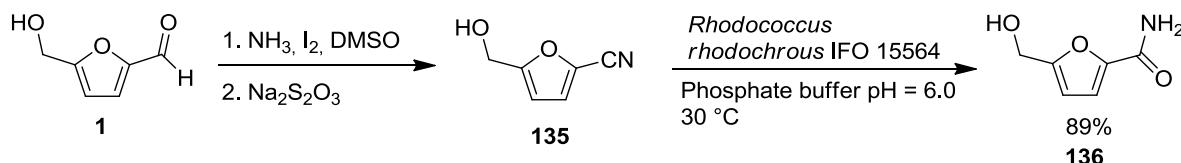
The reaction of HMF with 1,2,3,4-tetrahydropyridine gave the aldol condensation product described in Scheme 75.⁵⁸⁰



Scheme 75. Reaction of 1,2,3,4-tetrahydropyridine with HMF

Aldehyde to amide

Sugai and co-workers described a one-pot procedure to convert aldehydes into amides (Scheme 76).⁵⁸¹ Thus HMF was first converted into its nitrile 135 by reaction with NH₃ and I₂ in DMSO. After reduction of excess I₂ with Na₂S₂O₃, harvested cells of *Rhodococcus rhodochrous* IFO 15564 containing nitrile hydratase enzyme in phosphate buffer (pH 6.0, 0.1 M) were added and the reaction was stirred at 30 °C for 1–24 h to yield 136.

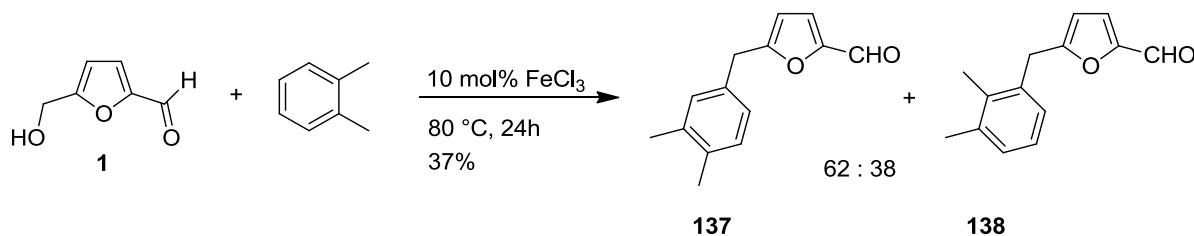


Scheme 76. Conversion of HMF into 5-hydroxymethyl-2-furylamide

Arylation

Beller and co-workers reported a remarkable FeCl₃-catalysed alkylation reaction of activated arenes using benzyl alcohols and benzyl esters (Scheme 77).⁵⁸² They were able to

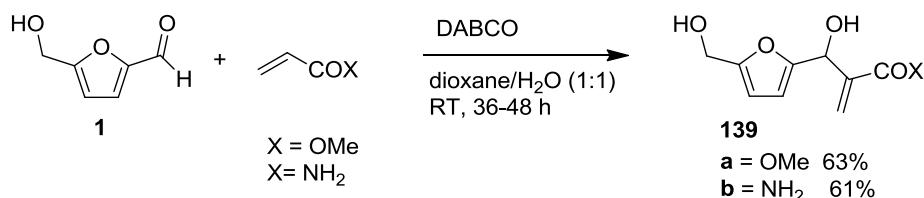
react HMF with *o*-xylene, catalysed by 10 mol% of FeCl₃, which resulted in 37% yield of a mixture of 4- and 3-substituted xylenes **137** and **138** (62:38).



Scheme 77. FeCl₃-catalysed alkylation of xylene with HMF

Baylis-Hillman reaction

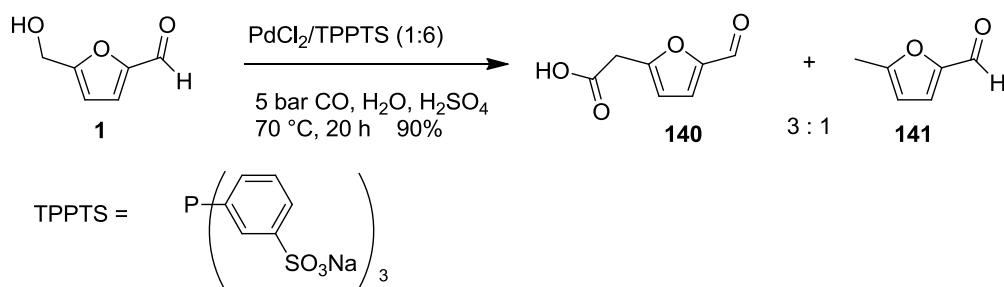
Hu and co-workers reported the Baylis-Hillman reaction between HMF and methyl acrylate in a mixture of dioxane and water, in the presence of DABCO (100 mol%).⁵⁸³ The product **139** was isolated in 63% yield (Scheme 78). It was also possible to effect the Baylis-Hillman reaction between HMF and acrylamide in 61% yield.⁵⁸⁴



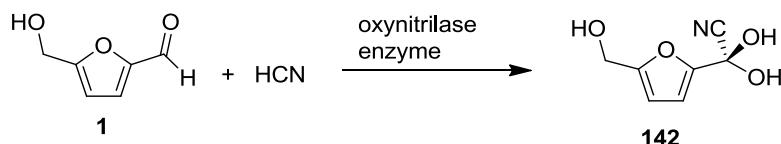
Scheme 78. Baylis-Hillman reaction of HMF and acrylate ester and amide.

Carbonylation

Sheldon and co-workers subjected HMF to palladium-catalysed carbonylation in water using TPPTS as water-soluble ligand, described in Scheme 79.⁵⁸⁵ They used 4 mol% of palladium and 24 mol% of ligand; in addition, H₂SO₄ was used as a promoter. After 20 h a conversion of 90% was achieved. Unfortunately the product was not the pure carboxylic acid **140**, but rather a 3:1 mixture of this compound with the hydrogenolysis product **141**.

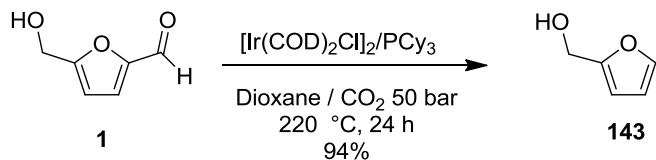
**Scheme 79.** Palladium-catalysed aqueous carbonylation of HMF

Chinese researchers reported the enzymatic conversion of HMF into its cyanohydrin **142**. Using an oxynitrilase enzyme they achieved only 8% conversion and 31% ee (Scheme 80).⁵⁸⁶

**Scheme 80.** Enzymatic cyanohydrin formation from HMF

Decarbonylation

Klankermayer, Leitner and co-workers studied the decarbonylation of HMF to 2-furfurylalcohol (**143**).⁵⁸⁷ Using an iridium precursor in combination with triaryl- or trialkylphosphine ligands they were able to decarbonylate HMF with high selectivity but never exceeding 50% conversion after 48h in refluxing dioxane (110 °C). Increasing the reaction temperature to 220 °C led to full conversions, but the selectivity decreased dramatically and only decomposition products were observed. Surprisingly, use of CO₂-expanded dioxane (50 bar of CO₂) led to 99% conversion at 220 °C with near perfect selectivity to furfurylalcohol (Scheme 81).

**Scheme 81.** Decarbonylation of HMF

Dimerisation and ether formation

A number of papers describe the acid-catalysed formation of dimeric ether **7** from HMF.^{213,465,588} The highest reported isolated yield is 44% (pTsOH, toluene, azeotropic reflux).⁴⁶⁵ Better results were obtained by carrying out the reaction in DMSO as solvent without any acid. In that case the yield reaches a maximum of 55% at 84% selectivity (Scheme 82).⁵⁸⁹



Scheme 82. Dimeric ether from HMF

The HMF dimer **7** was converted into the diisocyanate by Klein and co-workers via the diacid, which was reacted with ethyl chloroformate and sodium azide to from the bis-acylazide. Treatment of this compound at 100 °C in toluene gave the bis-isocyanate which was used to make polyurethanes.⁵⁹⁰

Ethers from HMF have also been formed by acid-catalysed reaction of HMF with alcohols, such as methanol (50% yield) and ethyleneglycol (24% yield).⁵⁹¹ The reaction between HMF and dihydropyran was catalysed by pyridinium *p*-toluenesulfonate. The resulting tetrahydrofurfuryl ether was isolated in 72% yield.⁵⁹² Bell reported the formation of a mixture of HMF ethyl ether (81%) and ethyl levulinate (16%) upon treatment of HMF in EtOH with sulfuric acid as catalyst. He also reported the reductive etherification to the bis ether of furan dimethanol.⁵⁹³ The use of solid acid catalysts, such as mesoporous aluminasilicates, zirconia and sulphated zirconia has also be reported.⁵⁹⁴

It is also possible to make ethers using the Williamson ether synthesis by reacting HMF with an alkyl halide in the presence of a base or a halogen scavenging agent, usually in the form of a silver salt.^{553,561,573}

Esterification

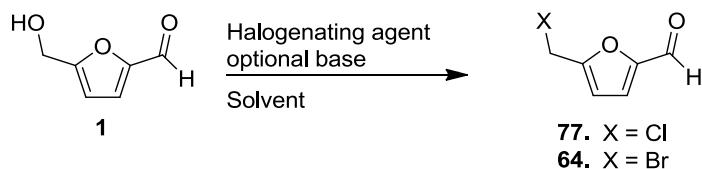
Esters of HMF can be formed quite easily either via acylation with aryl chlorides^{574,595} or treatment with alkanoyl anhydride.⁵⁵³ Esters of HMF were also prepared on solid-phase using a Sieber amide resin that was functionalized by reaction with succinic anhydride. In this case the reaction was accomplished using di-isopropylcarbodiimide with hydroxyl-benzotriazole en 4-dimethylaminopyridine as co-catalysts.⁵⁹⁶ It was found that in mice the enzyme

sulfotransferase converts HMF into the highly carcinogenic sulfate ester.⁹³ These reactions sequences were discussed in more detail in section 2.2.3.

Formation of 5-halomethylfurfuraldehyde

In section 2.4.2 the *in situ* formation of halomethylfurfurals from carbohydrates has been described. Also substantial work has performed on the halogenation of HMF. Gaset and co-workers carefully screened all the possible reagents that can be used to convert the hydroxymethyl moiety of HMF into a chloromethyl (**77**) or bromomethyl (**64**) group (Scheme 83).⁵⁹⁷ They reported the use of HCl and HBr in various solvents: SOCl_2 , with and without pyridine, SOBr_2 , with and without pyridine, SO_2Cl_2 with pyridine, $\text{PCl}_5 + \text{CaCO}_3$, $\text{PBr}_5 + \text{CaCO}_3$, $\text{PCl}_3 + \text{Et}_3\text{N}$, $\text{PBr}_3 + \text{Et}_3\text{N}$, PCl_5 or PBr_3 immobilised on an anionic ion exchange resin and $\text{POCl}_3 + \text{pyridine}$, Me_3SiCl and Me_3SiBr . The authors observed that the acid that was formed as a side product of the halogenation reaction induced tar formation, particularly in the presence of water, hence the need for the addition of base. Nevertheless, best results were obtained with HCl gas in Et_2O (87% yield, 92% selectivity), POCl_3 with pyridine (82% yield, 91% selectivity), Me_3SiCl in CHCl_3 (92% yield, 92% selectivity) and Me_3SiBr in 1,1,2-trichloroethane (99% yield, 99% selectivity).

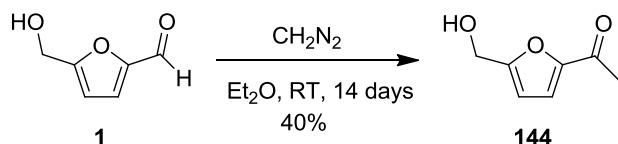
The same authors also converted fructose in a DMF/MIBK mixture using solid acid catalysts in a yield of around 88%. After filtering off the acidic catalyst the solvent was dried by partial azeotropic distillation. Addition of POCl_3 led to *in situ* formation of the Vielsmaier reagent, which they had previously shown to be a highly effective reagent for the chlorination of HMF.⁵⁹⁸ Thus the chloromethyl compound was obtained in 95% yield based on HMF and 85% based on fructose.⁵⁹⁹



Scheme 83. Formation of halomethyl derivatives of HMF

Ketone formation

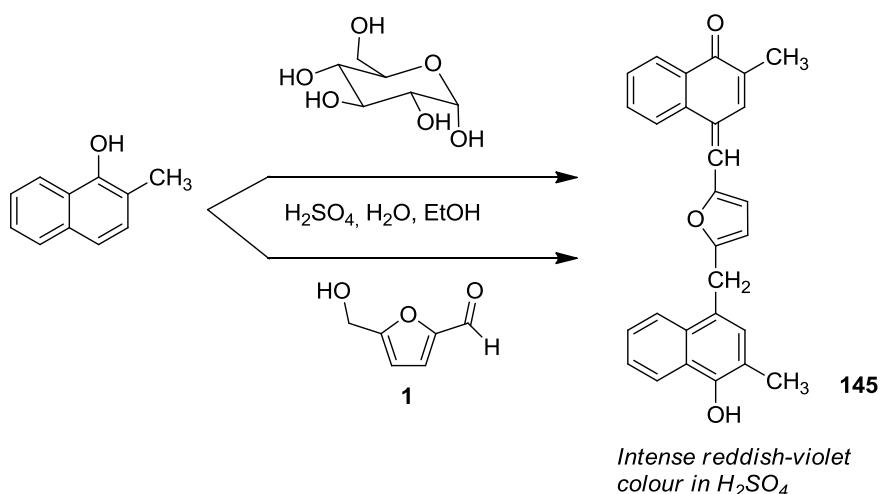
Treatment of HMF with diazomethane for 14 days gave a 40% yield of ketone **144** (Scheme 84).⁶⁰⁰



Scheme 84. Ketonisation of HMF

The Molisch reaction

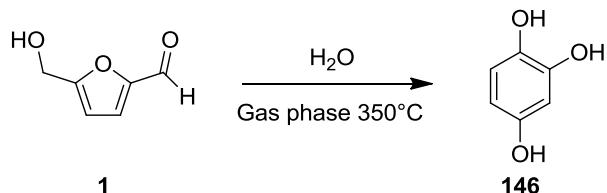
The reaction between hexoses or pentoses with 1-naphthol in sulfuric acid leads to the formation of an intensely reddish-violet colour. This colour test for sugars is known as the Molisch reaction. Unfortunately, so far it has been impossible to isolate a single compound from the Molisch reaction that would allow the identification of the highly coloured product. This is possibly due to random sulfonation of the naphthyl nucleus. Thus, Ueda and co-workers screened a number of 2-substituted 1-naphthols in the Molisch reaction hoping to reduce the number of sulfonated products in this way.⁶⁰¹ Surprisingly, when using 2-methyl-1-naphthol in the Molisch reaction with glucose (Scheme 85) they obtained, after column chromatography, low yields of crystals of a reddish brown compound that gave a reddish-violet colour in concentrated sulfuric acid. The UV-spectrum of this protonated compound was identical to that of an authentic Molisch reaction of 1-naphthol. The compound was identified as the substituted furan **145**. Reaction between HMF and 2-methyl-1-naphthol resulted in formation of the same product.



Scheme 85. Identification of the product of the Molish reaction between glucose/HMF and 2-methyl-1-naphthol

Phenols

Van Bekkum and co-workers subjected HMF to hydrothermal treatment.⁴³⁷ The major product observed was 1,2,4-trihydroxybenzene (**146**, Scheme 86). At 350 °C a maximum selectivity to 1,2,4-trihydroxybenzene of 46% was obtained at 50% conversion of HMF.



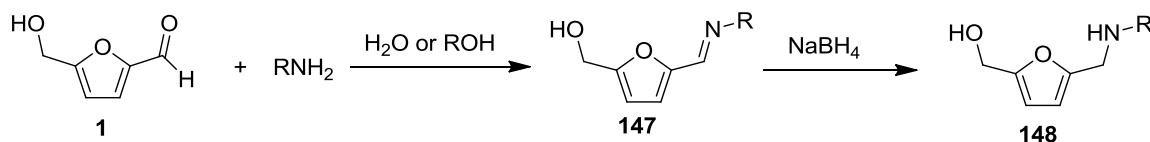
Scheme 86. Hydrothermal conversion of HMF into 1,2,4-trihydroxybenzene

Attempts by Hashmi and co-workers to convert HMF propargyl ether to isobenzofuran-4-ol, catalysed by $AuCl_3$, failed.⁶⁰²

Reactions with N-nucleophiles

The aldehyde functionality of HMF reacts in good yield with nitrogen nucleophiles, such as hydroxylamine, to form the oxime (95% yield)⁵⁶⁸ and substituted hydrazines, mainly for identification purposes.⁶⁰³⁻⁶⁰⁶ It is possible to convert HMF into the imines (**147**) by reaction with aliphatic primary amines in excellent yields by simply stirring in water at room temperature. Anilines reacted more sluggishly and needed methanol or ethanol as solvent. Addition of molecular sieves and heating, either conventional or by microwave, also allowed

the isolation of these imines in good yields. Addition of 1.5 eq. of NaBH₄ to the crude solution of imine gave the amines (**148**) in excellent yields. Scheme 87 describes the reductive amination of HMF through an imine.

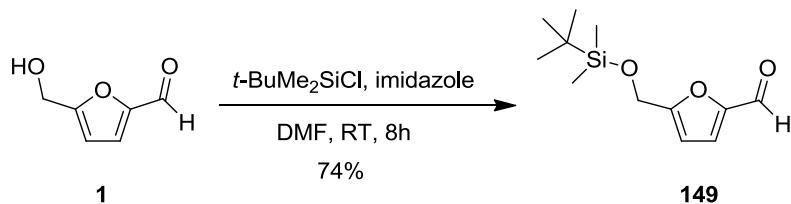


Scheme 87. Reductive amination of HMF

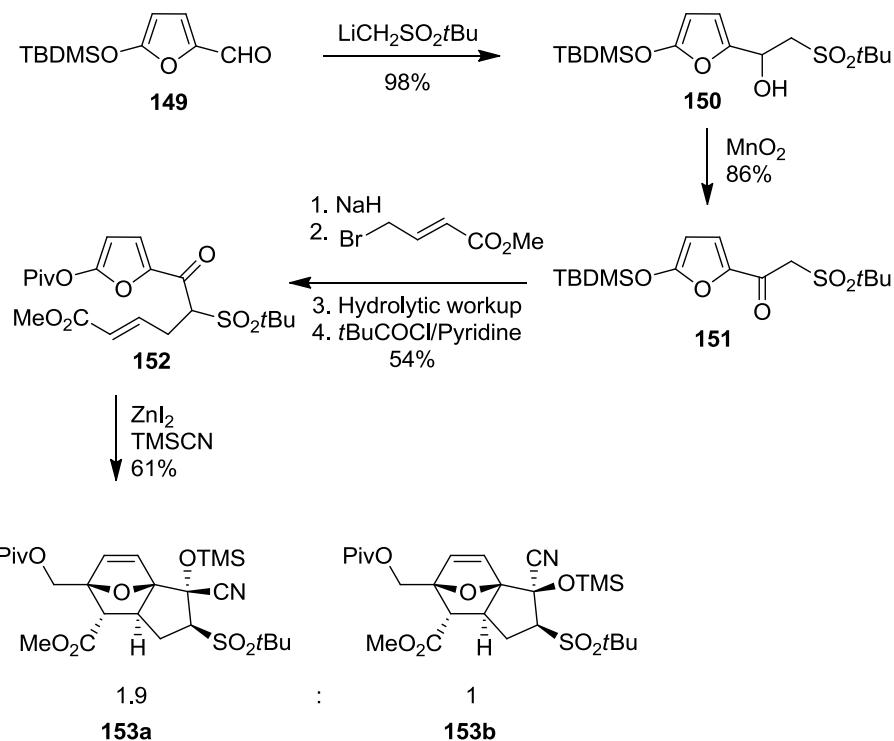
The addition of dialkylphosphite to imines of HMF led to formation of the aminophosphonic acids. A diastereoselective version was also reported.⁶⁰⁷

Silylation

In a study of Diels-Alder activity of substituted furans Sternbach and co-workers silylated the hydroxyl group of HMF with *tert*-butyl-dimethylsilylchloride and imidazole in DMF to form **149** (Scheme 88).⁶⁰⁸ Descotes and co-workers reported both the trimethylsilyl derivative and the *tert*-butyl-dimethylsilyl derivative.^{573,609}



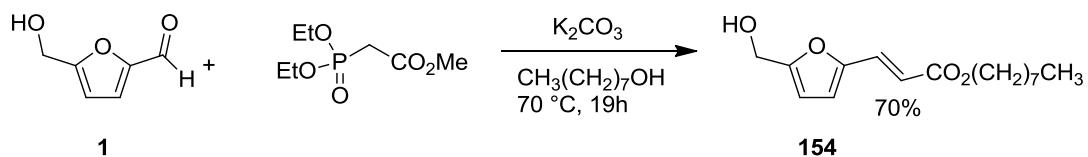
Scheme 88. Silylation of the hydroxyl group of HMF

Diels-Alder reaction**Scheme 89.** Internal Diels-Alder reaction of HMF derivative

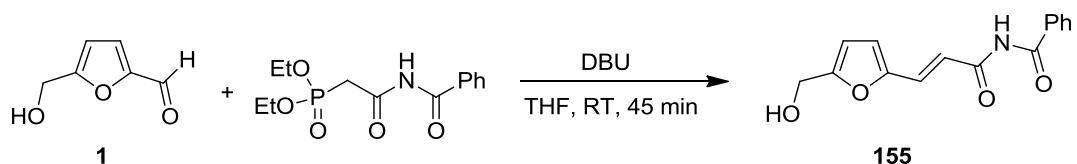
The silylated HMF **149** was further functionalised as shown in Scheme 89 to give compound **152**. During the acidic work up of the alkylation reaction the silyl protection group was hydrolysed off. It was replaced with a pivaloyl group. Compound **152** was treated with ZnI_2 and TMSCN to give 61% of a mixture of isomeric Diels Alder products **153 a,b**.⁵²⁵ Another Diels-Alder reaction of an HMF derived furan was reported by Toste (Scheme 50).⁴⁶⁸

Wittig reaction

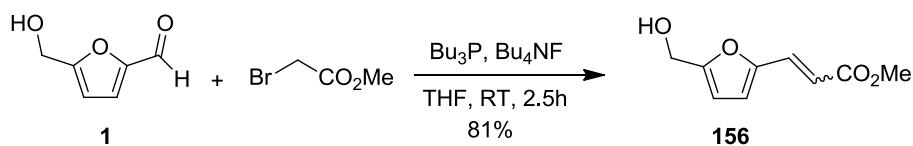
Wittig and Horner-Wittig type reactions have been performed many times on HMF, a number of which were already discussed earlier. Gaset and co-workers performed a Wittig-Horner reaction on HMF with methyl 2-(diethoxyphosphoryl)acetate using K_2CO_3 as base in an alcoholic solvent.⁶¹⁰ Under these conditions a simultaneous transesterification took place with the alcoholic solvent to form **154** (Scheme 90).

**Scheme 90.** Simultaneous Wittig-Horner and transesterification reactions on HMF

Jacobsen and co-worker prepared α,β -unsaturated imides (**155**) *via* a Wittig-Horner reaction. The reaction with HMF proceeded in 81% yield (Scheme 91). The products are interesting substrates for asymmetric azide addition.⁶¹¹

**Scheme 91.** Synthesis of α,β -unsaturated imide from HMF

Orsini and co-workers performed a Wittig reaction using an *in situ* prepared Wittig reagent from ethyl α -bromoacetate and PBu_3 in the presence of tetrabutylammonium fluoride as base (Scheme 92).⁶¹² The reaction with HMF proceeded in 81% yield (**156**, *E:Z* = 85:15).

**Scheme 92.** Reaction of HMF with *in situ* formed Wittig reagent

2.6.3 HMF as precursor of fuel components

HMF is a solid at room temperature with very poor fuel blend properties, therefore HMF cannot be used and has not been considered as a fuel or a fuel additive. The SME company Avantium is developing chemical, catalytic routes to produce furan derivatives “Furanics” for a range of biofuel applications.^{613,614} Avantium targets biofuels with advantageous qualities, both over existing biofuels such as bioethanol and biodiesel as well as over traditional transportation fuels. Another major goal is minimising the H_2 demand for their production. These compounds have a relatively high energy density, and good chemical and physical

characteristics (a.o. boiling point, cloud point, flash point, viscosity).⁶¹³ Using a regular Paccar PR 9.2 litre 183 kW diesel engine Avantium has been testing a range of blends of its novel biofuels (both C5 derived monoethers and C6 derived diethers) with regular diesel, with different concentrations (up to 30%) of Avantium's novel biofuel.⁶¹⁴ At all conditions tested (different blends and different steps in the ESC cycle) no difference in the engine operation was observed. Smoke and particulates as well as sulfur content decreased significantly with increasing furanics blending concentrations. Fuel consumption increases with increasing furanics amount, but is completely in line with the calculated lower energy content of furanics. The CO, CO₂, NO₂ exhaust percentages and THC content appeared to be independent of furanics concentrations. NO_x only shows a slight increase at higher blending percentages (> 10%).

The use of furans, such as HMF and furfural, as precursors of liquid hydrocarbon fuels is also an option for the production of linear alkanes in the molecular weight range appropriate for Diesel or jet fuel. The group of Dumesic has researched and evaluated the different strategies possible for upgrading HMF to liquid fuels.⁶¹⁵ HMF can be transformed by hydrogenolysis to 2,5-dimethyl furan (2,5-DMF) with 76–79% yields over a Cu–Ru/C catalyst or over CuCrO₄ with 61% yield.⁴⁰¹ 2,5-DMF is not soluble in water and can be used as blender in transportation fuels. A techno-economic evaluation of this process was recently published.⁶¹⁶ Binder and Raines also reported the preparation of 2,5-DMF from fructose with a two-step method.¹¹⁹ Luijckx *et al.* reported the production of 2,5-DMF by hydrogenolysis of HMF over a palladium catalyst in 1-propanol.⁶¹⁷ To form larger hydrocarbons, HMF and other furfural products can be upgraded by aldol condensation with ketones, such as acetone, over a basic catalyst (NaOH) already at room temperatures.⁵⁷⁷ Single condensation of MF and acetone produces a C9 intermediate, which can react further with a second molecule of HMF to produce a C15 intermediate. Condensation products can then undergo hydrogenation/dehydration over bifunctional catalysts with metal and acid sites (Pd/gAl₂O₃ at 373–413 K and 25–52 bar; Pt/NbPO₅ at 528–568 K and 60 bar) to produce linear C9 or C15 alkanes that are hydrophobic and separate spontaneously from water, reducing the cost of purification.⁶¹⁸ Silks and co-workers claimed the use of zinc and Ytterbium salts of proline as catalyst for the condensation between HMF and acetone.⁶¹⁹ Huber and co-workers tested a range of solid acid catalysts (MgO–ZrO₂, NaY and nitrogen substituted NaY) in the aldol condensation of HMF with acetone or propanal at 120 °C. With acetone, mixtures of mono- and bis-adduct were obtained. The authors propose that with propanal a double aldol condensation occurs in 100% yield. However, the product was not isolated and

characterised.⁶²⁰ Aldol condensation can be coupled with hydrogenation steps using a bifunctional catalyst like Pd/MgO–ZrO₂, leading to high yields of condensation products (>80%) at 326–353 K.⁵⁷⁸ Although aldol condensation is not itself a hydrogen consuming reaction, it is typically equilibrium limited and products are generally hydrogenated to achieve high yields. Thus, aldol condensations utilise high pressures of hydrogen and bi-functional (metal/base) catalysts. Additionally, biomass derived condensation products, particularly those derived from furfural or HMF, are extensively oxygenated and require a large input of hydrogen to produce alkane fuels. It is estimated that the production of C9 alkanes through condensation of HMF and acetone, for example requires 8 moles of hydrogen per mole of alkane.⁶¹⁸ A major benefit accompanying this large consumption of hydrogen, however, is that strategies based on aldol condensation allow for selective production of jet fuel and Diesel range linear alkanes with minimal carbon branching, which is not possible with hydrogen-neutral strategies such as oligomerisation.

Also several LA derivatives have been proposed for fuel applications, for instance ethyl levulinate (EL), γ -valerolactone (gVL), and methyl-tetrahydrofuran (MTHF).⁶²¹⁻⁶²³ However, these components do not always exhibit satisfactory properties when blended in current fuels. Recently, scientists from Shell presented a new platform of LA derivatives, the “valeric biofuels”, which can deliver both gasoline and diesel components that are fully compatible with current transportation fuels.⁶²⁴ The manufacture of these valeric biofuels consists of the acid hydrolysis of lignocellulosic materials to LA, the hydrogenation of the acid to gVL and valeric acid (VA), and finally esterification to alkyl (mono/di)valerate esters. The potential of LA as an intermediate for biofuel manufacture is further confirmed by the conversion of *gamma*-valerolactone to kerosene- and diesel-range hydrocarbons through decarboxylation to butenes and subsequent butene oligomerisation.⁶²⁵ Many of the different furan and furan derived components are also covered by patent applications.^{245,298,626-628 629-637}

The conversion of HMF to fuels has recently been reviewed.⁶³⁸

2.7 Conclusions

The world’s desire to be less dependent on fossil resources and to lower the carbon foot print of production processes has led to a significant increase in research and development in the field of biomass conversion to building blocks for fuels and chemicals. HMF has been known as a product from hexose dehydration for over 100 years and is an omnipresent

component of especially heat-treated foods. Extensive toxicological assessments have not revealed major concerns. HMF is considered to be one of the most promising platform molecules that can be converted to a wealth of interesting chemicals. This has led to a large number of publications, especially in recent years, illustrated by the size of this review. A general observation here is that the vast majority of the work is exclusively focussed on optimising the yield of HMF by testing a whole range of acidic catalysts without efforts to intrinsically understand the chemistry. This is illustrated by work reporting unrealistically high yields in acidic aqueous reaction systems in which HMF is known to decompose. Nevertheless, very high yields have been obtained in non-protic solvents, in particular in DMSO. However, it seems unlikely that such a reaction can be scaled up to an industrial process.

It has always been a challenge to obtain HMF in an efficient way. Although a lot of improvements have been made in understanding the mechanism and kinetics of the dehydration process, significant challenges still remain in transferring it to an industrial scale. The vast majority of the research summarised in this review has been performed on lab-scale in batch reactions without a real focus on finding an efficient and economically viable process. Improvements have been made in recent years by applying different solvent types and extraction methods, and by applying bifunctional catalyst systems. The use of biphasic systems appears to be straight-forward; good yields of HMF have been obtained, and such processes would appear to be scalable although they require relatively large amounts of extracting solvents. There has been little focus on the purification of HMF and the efficient recycling of reaction- and extraction solvents or catalysts. Application of ionic liquid solvent systems and microwave heating are showing great promise, especially in the conversion of glucose to HMF, but are still mostly uncharted territory. The focus appears to be mainly on testing new ionic liquids in stead of finding efficient ways to tackle the main draw-backs of using ionic liquids, namely efficient separation of HMF from the ionic liquid and recycling it by removing impurities.

The biggest challenge still to overcome is the use of glucose and glucose based polymers, like starch and cellulose, as the carbohydrate feedstock due to the unstable nature of the product HMF and the severe reaction conditions required.

Key to the success of HMF will be an economical production process. So far two pilot plant efforts have not been successful in the direct production of HMF. Recently, Avantium Chemicals started operating a pilot plant for production of furan-based chemicals and plastics in which HMF is *in situ* converted to its ether to help improve yield and purification. A

similar strategy is followed by Mascal in a process that produces 5-chloromethyl-furfural, another more stable derivative of HMF in order to obtain high yields in combination with efficient separation. It is expected that once production has been scaled up to 100-200 kTon/year a cost price of HMF of around \$ 1.00/Kg should be possible. In order to reach the lower cost price that would be necessary for fuel applications, it will be necessary to produce HMF or a derivative directly from cellulose or preferably lignocellulose.

This review underlines the progress that has been made towards an economic production of furan derivatives from biomass; a development which will open the way to a wealth of interesting materials all the way from fuels and bulk chemicals to fine chemicals and pharmaceuticals applications.

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