The Catalytic Conversion of D-Glucose to 5-Hydroxymethylfurfural in DMSO Using Metal Salts

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Abstract A wide range of metal halides and triflates were examined for the conversion of D-glucose to HMF in DMSO. Chromium and aluminium salts were identified as the most promising catalysts. The effect of process variables like initial D-glucose concentration (0.1–1.5 M), reaction time (5–360 min) and reaction temperature (100–140 °C) on the yield of HMF were examined at a fixed Al(OTf)₃ concentration (50 mM). Highest yields of HMF (60 mol%) were obtained using 1 M D-glucose (16 wt%), Al(OTf)₃ (5 mol%) at a temperature of 140 °C.

A reaction pathway involving initial isomerisation of D-glucose to D-fructose followed by a number of dehydration steps is proposed. Kinetic analysis reveals that the reaction is second order in D-glucose with an activation energy of 138 kJ mol⁻¹.

Keywords D-Glucose · DMSO · Isomerisation · HMF · Metal salts

1 Introduction

The development of efficient catalytic conversions for renewable resources to platform chemicals is of utmost importance for future bio-based economies. An example is the catalytic conversion of the C6-sugars in lignocellulosic biomass to 5-hydroxymethylfurfural (HMF) [1–3], a versatile building block for the synthesis of polymer precursors such as 1,6-hexanediol [4] and 2,5-furandicarboxylic acid [3] and fuel-additives such as 2,5-dimethylfuran [5]. Highest HMF yields (92.5 mol%) thus far have been reported using D-fructose as the feed, LaCl₃ as the catalyst and dimethylsulfoxide (DMSO) as the solvent at 100 °C [6].

For economic reasons, the use of the much cheaper D-glucose is preferred. Recent studies showed that D-glucose can be converted to HMF in good yields in non-aqueous systems using metal salts as the catalysts. An overview of research activities in this field is given in Table 1. The reaction from D-glucose to HMF is generally assumed to involve isomerisation of D-glucose to D-fructose followed by dehydration to HMF (Scheme 1). Best results so far were obtained in ionic liquids. Zhang and co-workers [7] pioneered the application of metal salts in 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) as the solvent, and CrCl₂ was identified as the most promising catalyst (68 mol% yield of HMF). Following this invention, various research initiatives were carried out to identify less toxic catalysts. For example, Hu et al. [8] used SnCl₄ as the catalyst in a series of ionic liquids and the highest yield of HMF (60 mol%) was obtained in 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF₄). Stahlberg et al. [9] reported only moderate yield of HMF (up to 32 mol%) when a lanthanide salt (YbCl₃) was used. Zhao and co-workers [10] reported the used of germanium (IV) chloride as catalyst in an ionic liquid ([BMIM]Cl) and an HMF yield of 38.4 % was obtained. Though promising, the use of metal salts in ionic liquids has limitations due to the relatively high price of ionic liquids, requiring very efficient recycling strategies.

The use of metal salts for HMF synthesis from D-glucose in organic solvents and water has also been reported. For
instance, we recently showed that both chromium and aluminium salts promote the isomerisation of D-glucose to D-fructose in water, though only marginal yields of HMF (<10 mol%) were obtained [11]. Besides the subsequent rehydration of HMF to give levulinic acid and insoluble humins, the formation of C3-sugars was observed. Ishida and Seri examined lanthanide ions for the conversion of D-glucose in water. [12] The highest HMF yield (8 mol%) was obtained when using ErCl₃ as the catalyst. Better HMF yield from D-glucose were obtained when using aprotic, polar solvents such as N,N-dimethylacetamide (DMA) and DMSO. Binder and Raines reported that DMA containing 10 wt% LiCl and 6 mol% of CrCl₃ is a good catalytic system, and HMF yields of 62 % were obtained in the presence of 20 wt% [EMIM]Cl. [13] When using DMSO as the solvent and CrCl₂ as the catalyst, the HMF yield was only 46 mol%. Yuan et al. [14] reported HMF yields up to 49 mol% for a catalyst system consisting of CrCl₂ and tetraethylammonium chloride (TEAC) as the co-catalyst. Apart from chromium salts, SnCl₄ [8] and GeCl₄ [10] are also active catalysts for the conversion of D-glucose to HMF in DMSO, and HMF yields up to 40 mol% were obtained for both catalysts.

The limited studies highlighted above indicate that the use of a combination of metal salts, co-catalysts and a suitable solvent (ionic liquids, aprotic polar organic solvents) have a positive effect on the yield of HMF from D-glucose. However, an exploratory screening study using a wide range of metal salts aimed at the identification of the most promising metal salt is lacking. We herein report a systematic screening study on the use of metal salts for the conversion of D-glucose to HMF with a focus on DMSO as the solvent. Apart from metal halide salts, the use of metal triflates was also explored because of their unique properties such as high solubility and stability in polar solvents [15]. In addition, the performance of selected salts was examined in other aprotic polar solvents such as 1-methyl-2-pyrroldinone (NMP), N,N-dimethylacetamide (DMA) and N,N-dimethylformamide (DMF).

2 Experimental Section

2.1 Chemicals

The various halide and triflate salts were obtained from Sigma Aldrich. The only exceptions are anhydrous CrCl₂ and LaCl₃, which were from Acros Organics. D-glucose (99 %), D-fructose (99 %), HMF, DMA, DMF and NMP

Table 1 Conversion of D-glucose to HMF using metal salts as the catalysts in various solvents

| No | [D-glucose] | Catalyst       | Solvent          | Conditions | Glucose conversion (mol%) | HMF yield (mol%) | References |
|----|-------------|----------------|------------------|------------|---------------------------|-----------------|------------|
| 1  | 100 mg      | CrCl₂ (6 mol%) | [EMIM]Cl         | 100 °C, 3 h | 95                        | 68              | [7]        |
| 2  | 23 wt%      | SnCl₄ (10 mol%)| [EMIM]BF₄        | 100 °C, 3 h | 100                       | 60              | [8]        |
| 3  | 100 mg      | YbCl₃ (10 mol%)| [OMIM]Cl         | 160 °C, 10 min | 70                       | 35              | [9]        |
| 4  | 100 mg      | GeCl₄ (10 mol%)| [BMIM]Cl        | 100 °C, 75 min | 95                       | 38              | [10]       |
| 5  | 0.1 M       | CrCl₂ (5 mol%) | Water            | 140 °C, 6 h  | 97                        | 10              | [11]       |
| 6  | 0.1 M       | AlCl₃ (5 mol%) | Water            | 140 °C, 3 h  | 83                        | 18              | [11]       |
| 7  | 0.3 M       | ErCl₃ (0.67 mol%) | Water       | 140 °C      | 8                         |                  | [12]       |
| 8  | 10 wt%      | CrCl₂ (6 mol%) | DMA-LiCl(10 wt%)-20 wt% [EMIM]Cl | 100 °C, 6 h | –                          | 62              | [13]       |
| 9  | 10 wt%      | CrCl₂         | DMSO             | 120 °C, 3.25 h | –                        | 46              | [13]       |
| 10 | 1.1 M       | CrCl₂ (3 mol%)-TEAC | DMSO          | 130 °C, 3 h  | –                          | 49.3            | [14]       |
| 11 | 100 mg      | AlCl₃ (10 mol%)| DMSO             | 80 °C, 3 h | 27.1                       | 14.5            | [8]        |
| 12 | 100 mg      | SnCl₄ (10 mol%)| DMSO             | 100 °C, 3 h | 96                        | 42              | [8]        |
| 13 | 100 mg      | GeCl₄ (10 mol%)| DMSO             | 100 °C, 75 min | 80                       | 40              | [10]       |

Scheme 1 Proposed reaction pathway for HMF formation from D-glucose

\[ D_{-}\text{glucose} \rightarrow D_{-}\text{fructose} \rightarrow \text{HMF} \]

D-glucose

D-fructose

HMF
were purchased from Sigma Aldrich and used without further purification.

2.2 Experimental Procedures

The reactions were performed in a CEM Discovery SP Microwave system (CEM Corp., Matthews, NC) equipped with a 48-position autosampler. The unit uses a microwave frequency of 230 MHz with a maximum pulsed radiation power of 200 W to heat the samples. The reactions were carried out in 10 ml vials. The vial was loaded with 1.75 ml solution of d-glucose in DMSO containing the predetermined amount of a metal salt. To ensure uniform heating, the reactor content was mixed at a high stirring speed (800 rpm) using a magnetic bar during the reaction. Thirty seconds pre-stirring at room temperature was applied before applying microwave power to heat-up the solutions. The target temperature was obtained within 90 s. The temperature inside the reactor was measured using an IR detector located in the bottom of the microwave device. After reaction, the samples were cooled by blowing compressed air in the microwave cavity containing the reactor vial.

2.3 Analytical Methods

The amounts of d-glucose, d-mannose, d-fructose and HMF in the reaction mixture were quantified using HPLC. The HPLC was equipped with a Hewlett Packard 1050 pump, a Biorad Aminex HPX-87H organic acid column and a Waters 410 refractive index detector. The mobile phase consisted of an aqueous sulphuric acid solution (5 mM) at a flow rate of 0.55 ml/min. The column was operated at 60 °C.

3 Results and Discussion

3.1 Effect of Type of Salts on the d-Glucose Conversion in DMSO

A wide range of metal halide and triflate salts for the conversion of d-glucose to HMF in DMSO at 140 °C was investigated. The reactions were carried out at a high d-glucose concentration (16 wt%, 1 M) using 50 mM metal salt as the catalyst. The effect of the type of metal salt on the d-glucose conversion and HMF yield after 15 min reaction time is shown in Fig. 1. For reference, the reaction in the absence of a catalyst (thermal) is also provided. In this case, a very low conversion of d-glucose (<10 %) was observed, and HMF was not detected in the reaction mixture. It is thus evident that a metal salt is required for the conversion of d-glucose to HMF. Compared to the thermal reaction, higher d-glucose conversions were obtained for all salts. In general, metal triflate salts gave higher conversions than metal halide salts. High d-glucose conversions (>75 %) were obtained for iron, zinc, bismuth, tin, chromium and aluminium salts as the catalyst.

3.2 Effect of Type of Salts on the HMF Yield in DMSO

When considering the HMF yield, it is apparent that only a number of salts are good catalysts for HMF synthesis. Although lanthanide salts [6] such as LaCl$_3$ and rare-earth metal triflates such as Sc(OTf)$_3$ [16] were reported to be highly active catalysts for the conversion of d-fructose to HMF in DMSO, only low HMF yields were obtained (<15 mol%) with d-glucose as the feed. Comparison of these results indicates that the isomerisation of d-glucose to d-fructose is not catalysed effectively by these salts. Significantly higher HMF yields (>30 mol%) at high d-glucose conversion were obtained with Sn$^{IV}$, Cr$^{II}$, Cr$^{III}$ and Al$^{III}$ salts. Chromium and aluminium salts were the most active and HMF yields up to 50 mol% were obtained. Interestingly, the performance of Al(OTf)$_3$ is similar to that of AlCl$_3$, indicating only a minor effect of the counterion in the case of Al. Metal triflate salts are considered environmentally more benign catalysts than chlorides [15, 16] and therefore Al(OTf)$_3$ was selected for further studies.

To gain insights in the role of metal salts, the composition of the reaction mixture as a function of reaction time was determined for d-glucose (1 M) using Al(OTf)$_3$ (50 mM) at 120 °C. The results are depicted in Fig. 2. At the start of the reaction, the formation of d-fructose and
D-mannose was observed. These products are clearly intermediates, and their concentrations are reduced at longer reaction times. It is well possible that aluminium cations act as Lewis acids and promote the isomerisation of D-glucose to D-fructose and D-mannose. This isomerisation was also observed when reacted D-glucose in water using AlCl₃ [11], Cr and Sn salts [7, 8, 13] The ability of these metal salts to isomerise D-glucose to D-fructose likely plays a pivotal role on the rate as well as chemo-selectivity for the reaction of D-glucose to HMF.

HMF is the main reaction product, and is likely formed from D-fructose (Scheme 1). Neither levulinic acid nor formic acid were detected as by-products. Thus, as noticed for the dehydration of D-fructose to HMF in DMSO, further reaction of HMF to levulinic acid is retarded effectively in DMSO [17]. Glyceraldehyde and dihydroxyacetone, possible by-products that are known to be formed in water by retro-aldol condensations, were not detected in DMSO. Reversion products of D-glucose were detected by HPLC, particularly at the beginning of the reaction and when working at higher D-glucose loadings. During reaction, the reaction mixtures turned dark brown, indicative for the formation of soluble humins. Dilution of the reaction mixture with water after reaction indeed produced an insoluble brown deposit. At this stage, we have not quantified and characterised these solid humins.

To verify the role of the Al salt in the reaction, additional experiments were carried out using D-fructose (1 M) as a starting material. The reactions were performed at a temperature of 120 °C and the results are presented in Table 2. Without the addition of catalysts, D-fructose is converted to HMF in a reasonable yield (56 mol% at 95 mol% D-fructose conversion) [18]. When performing the reaction in the presence of Al(OTf)₃, not only the reaction rate is enhanced considerably, but also the HMF yield is improved (69 mol%). These results imply that metal salts indeed catalyse the conversion of D-fructose to HMF.

### 3.3 Catalytic Effect of Al(OTf)₃ on the Conversion of D-Glucose to HMF in Various Polar Aprotic Solvents

The catalytic effect of Al(OTf)₃ on the conversion of D-glucose to HMF in four different polar aprotic solvents was examined (1 M D-glucose, 120 °C, 1 h), and the results are presented in Fig. 3. Among the solvents tested, only NMP gave HMF yields (43 mol%) close to that of DMSO (46 mol%). These results contrast with those from Seri et al. [6] for the conversion of D-fructose to HMF using LaCl₃ as the catalysts in various aprotic solvents (0.2 M D-fructose, 5 mM LaCl₃, 100 °C). Here, the performance of DMA and DMF was about similar. For all solvents, the formation of further rehydration products of HMF (levulinic- and formic-acid) were not observed. Nevertheless,
the reaction mixtures turned dark; indicating the formation of soluble polymers as other by-products of the reaction.

3.4 Kinetic Studies

To gain insights in the effect of process parameters on the conversion of D-glucose to HMF using Al(OTf)₃ as the catalyst in DMSO ([Al(OTf)₃] = 50 mM, T = 140 °C, t = 120 min) was observed when using 1 M D-glucose. Wang et al. [16] reported a similar trend for the conversion of D-fructose to HMF using Sc(OTf)₃ as the catalyst. These results indicate that the reaction may be performed at high initial D-glucose concentrations without considerable reductions in HMF yield, which is a particularly attractive feature regarding process economics.

The effect of reaction temperatures (100–140 °C for 1 M D-glucose and 50 mM Al(OTf)₃) was explored in detail and the results are depicted in Fig. 5. The D-glucose conversion is highly depending on the reaction temperature (Fig. 5a). Essential quantitative D-glucose conversion was achieved within 15 min at 140 °C, whereas 6 h at 100 °C was required for 90% D-glucose conversion. The HMF yield also shows a clear temperature dependence (Fig. 5b). Highest HMF yields (60 mol%) were obtained at the highest temperature in the range (140 °C).

The D-glucose concentrations versus time profiles for different temperatures were fitted assuming either a first- or second-order reaction in D-glucose. The second-order approach gave a very good fit (R² > 0.95 for all series) for the experimental data (Fig. 6a) compared to a first order approach (R² < 0.9 for T > 100 °C). Kinetic data for the catalytic reaction are scarce, the only example reported so far is for an ionic liquid system with CrCl₃ as the catalysts [19]. Here, a reaction order of one in D-glucose was found. The second order reaction in D-glucose in our system may be explained by assuming the reversible coordination of two molecules of D-glucose to an Al-center, followed by a rate determining rearrangement of one of the coordinated glucose units to D-fructose. In addition, reversion reactions may also play a role and complicates the kinetic analyses. Further kinetic modelling including the reaction rates of the conversions of the intermediates (D-fructose and

![Fig. 4](image-url)  
**Fig. 4** Effect of initial D-glucose concentration on HMF yield for the conversion of D-glucose to HMF using Al(OTf)₃ as the catalysts in DMSO ([Al(OTf)₃] = 50 mM, T = 140 °C, t = 120 min)

![Fig. 5](image-url)  
**Fig. 5** Effect of temperature on the D-glucose conversion and HMF yield (D-glucose)₀ = 1 M, [Al(OTf)₃] = 50 mM)
D-mannose) to HMF and the effect of reversion products will be required before definitive conclusions can be drawn. These studies are in progress and will be reported in due course.

The rate constants at different temperatures were used to prepare an Arrhenius plot (Fig. 6b), resulting in an activation energy and pre-exponential factor of 138 kJ mol$^{-1}$ and $4.7 \times 10^{17}$ min$^{-1}$, respectively. This activation energy is considerably higher than provided by Qi et al. [19] (115 kJ mol$^{-1}$) for the conversion of D-glucose to HMF in an ionic liquid ([BMIM][Cl]) using CrCl$_3$ as the catalysts, though considerably lower than the value reported by Girisuta et al. [20] for the conversion of D-glucose in water using sulphuric acid as the catalyst (152 kJ mol$^{-1}$).

4 Conclusions

The potential of a wide range of metal halide and triflate salts for the conversion of D-glucose to HMF in DMSO was explored. Chromium and aluminium salts were identified as the most promising metal catalysts and HMF yields up to 60 mol% were obtained with Al(OTf)$_3$ as the catalysts. D-fructose and D-mannose were identified in the reaction mixtures in the course of the reaction suggesting that the isomerisation of D-glucose to D-fructose plays an important role in the reaction network. Kinetic analyses reveals that the Al(OTf)$_3$ catalysed D-glucose conversion in DMSO is second-order in D-glucose. The mechanistic implications of this finding are the subject of further studies.

The results of this study are also of relevance for the development of heterogeneous catalysts for the conversion of D-glucose to HMF in aprotic, polar solvents likely DMSO. Our findings indicate that solid catalysts such as cross-linked polystyrene-supported aluminium triflates (PS-Al(OTf)$_3$) [21] or silica-supported metal triflate [22] may be envisioned as very promising catalysts for this conversion and studies with these systems are in progress.

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