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The Role of Salts and Brønsted Acids in Lewis Acid-Catalyzed Aqueous-Phase Glucose Dehydration to 5-Hydroxymethylfurfural

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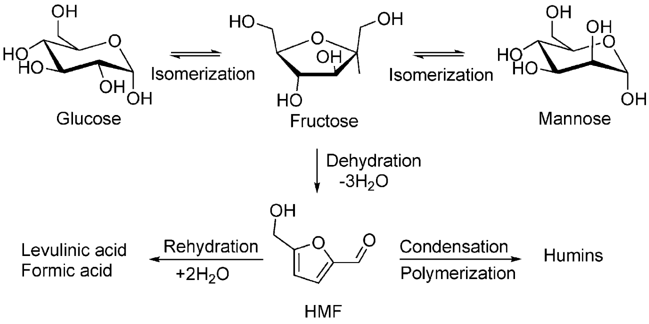
The effect of salts and Brønsted acids on the Lewis acid ($CrCl_3$·6 H_2O)-catalyzed glucose dehydration to 5-hydroxymethylfurfural (HMF) in aqueous media are described. We show that the reaction with bromide salts in place of chlorides leads to higher HMF yields. The influence of salts can be attributed to the anions in solution, specifically to the bromide anions enhancing the fructose dehydration step. Additionally, we demonstrate that the reaction kinetics are governed strongly by acidity. Although the fructose dehydration step is accelerated by the addition of Brønsted acids, even on a catalytic scale, a significant retardation of the glucose conversion rate results in a substantial drop in HMF yields. The suppression in glucose-to-fructose isomerization rate with increasing acidity is ascribed to the restrained formation of the chromium–glucose chelate complex during the reaction.

Introduction

5-Hydroxymethylfurfural (HMF) is identified as a primary bio-derived platform chemical for the sustainable production of a variety of chemicals and alternative fuels to reduce our dependency on fossil resources.[1] HMF is produced from the acid-catalyzed dehydration of hexoses, that is, glucose or fructose by elimination of three water molecules. The formation of HMF is suggested to follow either acyclic[2] or cyclic[3] pathways, yet no consensus of the actual mechanism has been reached. The acyclic pathway is proposed to proceed via the rate-determining formation of a linear enediol intermediate, whereas the cyclic pathway involves direct dehydrations in the ring of a cyclic ketofuranose via a carbenium cation intermediate. Due to the complexity of the reaction and high reactivity of HMF, several side reactions may occur, the most notable of which are the acid-catalyzed HMF rehydration to levulinic and formic acids (Scheme 1),[4] HMF self-condensation reactions, and HMF–glucose cross-polymerization, forming soluble and insoluble polymers named humins.[5]

Brønsted acid-catalyzed dehydration to produce HMF is more efficient starting from fructose than from glucose. Consequently, high yields of HMF from fructose have been reported in aqueous media, organic solvents, and ionic liquids, whereas glucose dehydration typically leads to very low HMF yields.[6] However, the development of an efficient process for a large-scale production of HMF directly from glucose would be more beneficial due to the high cost of fructose and the fact that glucose is the most abundant monosaccharide found in nature.[7]



Scheme 1. Glucose isomerization to fructose and dehydration to HMF.

An alternative approach for glucose transformation to HMF is to develop an efficient catalytic one-pot tandem glucose-to-fructose (aldose-to-ketose) isomerization–dehydration process (Scheme 1). An important advance was made by Zhao et al. discovering that Lewis acids are able to catalyze the glucose dehydration to HMF by facilitating the hydride transfer in the glucose-to-fructose isomerization.[8] The use of $CrCl_2$ in ionic liquid (1-ethyl-3-methylimidazolium chloride) afforded HMF in 70 % yield. Since then, high yields of HMF have been reported in ionic liquids and high-boiling-point organic solvents with various transition metal salts as isomerization catalysts.[9] However, the high cost, toxicity of the solvents, and the difficulty in recycling the reaction media due to the problematic isolation of HMF present major challenges for large-scale biorefinery applications. In this respect, water appears to be the better choice of solvent for the sustainable production of HMF.

An efficient catalytic system transforming glucose to HMF in water is yet to be identified. In contrast to organic solvents and ionic liquids, aqueous-phase glucose dehydration promotes side reactions. This has led to the development of several water–organic biphasic reaction systems, aiming to reduce

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the formation of byproducts as HMF is extracted continuously to an organic phase during the reaction. By exploiting this strategy, modest HMF yields from glucose have been reported for biphasic water–methyl isobutyl ketone, (water+DMSO)–(methyl isobutyl ketone+2-BuOH) and (water+DMSO)–DCM solvent systems.[10]

Recently, the focus has been on methods that combine isomerization catalysts with Brønsted acids utilizing biphasic $NaCl_{(aq)}$–organic solvent systems. The use of saturated aqueous salt solution as a reactive media has two major advantages: firstly, the salts enhance the HMF distribution to the organic phase and, secondly, it allows the use of water-miscible solvents as the organic phase, such as THF and DMF, which are expected to dissolve HMF better than common non-water-miscible solvents. For example, an HMF yield of 20% was reported with a Lewis acidic Sn-Beta zeolites in a $HCl_{(aq)}$–*n*BuOH biphasic system,[11] with the addition of NaCl to the system improving the HMF yield to 41%. Notably, changing the extractive media to THF further improved the HMF yield to 57%. Dumesic and co-workers described the use of lanthanide halides and $AlCl_3$ in a ($HCl+NaCl_{(aq)}$)–alkylphenol biphasic solvent system, obtaining HMF yields of up to 62%.[12] More recently, Choudhary et al. reported an HMF yield of 59% with $CrCl_3{\cdot}6H_2O$ catalyst in a biphasic $(HCl+NaCl)_{(aq)}$–THF system.[13] However, the authors did not report the biphasic reaction without Brønsted acid nor the influence of different salts on the reaction outcome, although their use has been shown to affect the HMF yields in organic solvent (*N*,*N*-dimethylacetamide).[14] Consequently, there is a need to establish a fundamental understanding of the role of the additional salts and Brønsted acids in these reactions.

Herein, we investigate the effect of Brønsted acids and salts on a Lewis acid-catalyzed aqueous-phase glucose transformation to produce HMF by using a biphasic solvent system.

Results and Discussion

Initial catalyst testing

We initiated the studies by screening various metal halide catalysts including $MnCl_2{\cdot}4H_2O$, $ZnCl_2$, $ZnBr_2$, $CoCl_2{\cdot}6H_2O$, $LaCl_3$, $YbCl_3{\cdot}6H_2O$, $FeCl_3{\cdot}6H_2O$, $NiCl_2$, $NiBr_2$, $RuCl_3$, $PdCl_2$, $GeCl_4$, $GaCl_3$, $CrCl_3{\cdot}6H_2O$, $CrCl_2$, and $AlCl_3{\cdot}6H_2O$ in glucose dehydration to HMF. The experiments were performed by using 10 mol% Lewis acid catalyst at 140 °C for 2 h in a biphasic solvent system comprising saturated aqueous NaCl as a reactive media, in which the metal halides and 10 wt% glucose were dissolved. The organic extractive phase consisted of a 3:1 (v/v) mixture of acetone/toluene, to which the addition of toluene ensured the phase separation during the reaction (for HMF yields tested with other organic solvents, see Figure S2 in the Supporting Information). Among all the metal halides tested, only $CrCl_3{\cdot}6H_2O$, $CrCl_2$, and $AlCl_3{\cdot}6H_2O$ showed significant activities affording HMF in 35, 25, and 23% yields, respectively. Notably, lanthanide halides, such as $LaCl_3$ and $YbCl_3$, which have all recently shown promising results in the reaction under biphasic conditions, afforded HMF in less than 10% yields.[12] With the other metal halides tested, no reaction occurred or less than 5% HMF yields were recorded.

Influence of salts

Recently, it was proposed that salts contribute to the increase in HMF yield by enhancing the fructose dehydration step in organic solvent.[14,15] In view of this, we investigated the effect of different salts, namely NaCl, NaBr, KF, KCl, KBr, and KI, in the glucose dehydration, applying the best catalysts from preliminary studies ($CrCl_3{\cdot}6H_2O$, $CrCl_2$, and $AlCl_3{\cdot}6H_2O$).

The results in Table 1 show that $CrCl_3{\cdot}6H_2O$ display considerably better catalytic activity than $CrCl_2$ and $AlCl_3{\cdot}6H_2O$ in terms of HMF yield, regardless of the salt employed in the reaction.

Table 1. The effect of salts on HMF yields with various catalysts.[a]

Entry	Salt	Catalyst [10 mol%]	HMF yield[c] [%]
1	NaCl	$CrCl_3{\cdot}6H_2O$	36
2	NaBr	$CrCl_3{\cdot}6H_2O$	46
3	KCl	$CrCl_3{\cdot}6H_2O$	36
4	KBr	$CrCl_3{\cdot}6H_2O$	47
5	KI	$CrCl_3{\cdot}6H_2O$	30
6	KF	$CrCl_3{\cdot}6H_2O$	0
7	KBr	$CrCl_3{\cdot}6H_2O$ (5 mol%)	31
8	NaCl	$CrCl_2$	25
9	KBr	$CrCl_2$	29
10	NaCl	$AlCl_3{\cdot}6H_2O$	23
11	KBr	$AlCl_3{\cdot}6H_2O$	28
12[b]	KBr	$CrCl_3{\cdot}6H_2O$	42

[a] Reaction conditions: ≈10 wt% glucose in $salt_{(aq)}$–(acetone+toluene) [1:(3:1), v/v], 140 °C, 2 h; [b] THF was used as an extractive phase.

Furthermore, the use of different salts in the aqueous phase affects the HMF yields. Accordingly, the reaction with $CrCl_3{\cdot}6H_2O$ catalyst and excess NaCl or KCl afforded HMF in equal yields (entries 1 and 3), which under identical conditions were significantly improved as NaBr or KBr were employed (entries 2 and 4). Similar behavior was observed also with $CrCl_2$ and $AlCl_3{\cdot}6H_2O$ catalysts (entries 8, 9 and 10, 11). Notably, the use of KI resulted in lower HMF yields, whereas no HMF was observed with KF as the salt (entries 5 and 6). The positive effect of halide ions on the HMF yields decreased in the order $Br > Cl > I \gg F$.

From the results, we can ascribe the influence of different salts on HMF yields to the presence of different anions rather than cations in solution and specifically that bromide anions have a more beneficial effect than chloride anions. This observation cannot be attributed to the salting-out effect because the partitioning coefficients for HMF (ratio of HMF concentrations in organic and aqueous media) are reported to be higher in the presence of chloride anions than bromide anions.[16]

Next, we studied the reaction at different temperatures with $CrCl_3{\cdot}6H_2O$ catalyst under biphasic conditions. For comparative purposes, NaCl and KBr were used as salt additives. The temperature for the reaction was set to 130, 140, and 150 °C with a time range of 1–6 h.

The main products observed in these experiments were HMF, glucose, fructose, mannose, solid humins, and levulinic acid (according to HPLC analysis). The presence of mannose, due to the aldose–ketose equilibrium (Scheme 1), was detected in all experiments with yields ranging from 1 to 6%. In general, levulinic acid was produced in higher quantity with KBr. The quantity of the acid increased with time and maximum yields of 5, 8, and 9% were obtained at temperatures of 130, 140, and 150 °C in 5, 4 and, 2 h, respectively. The small amount of levulinic acid observed could be attributed to the biphasic reaction system reducing the rehydration of HMF, which was dissolved mainly in the organic phase during the reaction.

The time evolution of glucose conversion and fructose and HMF yields at 140 °C (for results at 130 and 150 °C, see the Supporting Information) is shown in Figure 1. The initial glucose conversion rate, catalyzed by $CrCl_3 \cdot 6H_2O$, is faster with increasing temperature, regardless of the salt employed. Comparison of KBr and NaCl shows that glucose is consumed faster in the presence of KBr. Also, the reactions performed with KBr afforded higher HMF yields at any recorded time and temperature. Initial rates for HMF formation with NaCl and KBr at 140 °C were 0.0028 and 0.0038 mmol min^{-1}, respectively (Figure S3). The highest HMF yields for KBr at temperatures of 130, 140, and 150 °C were 45, 53, and 52% and for NaCl, 43, 48, and 49%, respectively.

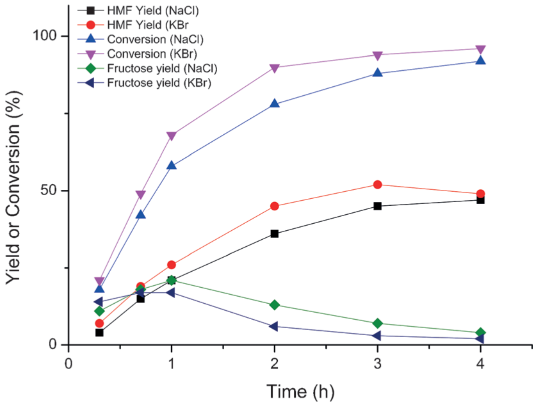


Figure 1. Glucose conversion and HMF yields with $CrCl_3 \cdot 6H_2O$ catalyst in excess NaCl or KBr. Reaction conditions: ≈10 wt% glucose and 10 mol% $CrCl_3 \cdot 6H_2O$ in salt$_{(aq)}$–(acetone+toluene) [1:(3:1), v/v], 140 °C, 1–4 h.

The effect of temperature and salt on HMF selectivity is shown in Figure 2. With time, the selectivity first increases, passes through a maximum and then decreases due to the decomposition of HMF to side products. Comparing the salts, the presence of KBr improves HMF selectivity at every temperature studied, thus explaining the higher HMF yields obtained with bromide salts.

The dominant intermediate product observed in the reaction is fructose, the concentration of which is highest in the early stages of the reaction (Figure 1). With time, fructose is consumed with concurrent formation of HMF. The fructose concentration during the reaction at any recorded time is lower if using KBr instead of NaCl. Consequently, it is reasonable to assume that KBr accelerates the fructose dehydration step and, due to the equilibrium, enhances the glucose conversion rate (Scheme 1). This behavior is apparent from Figure 1 as the HMF yields are higher and the glucose consumption rate faster in the reactions with KBr than those with NaCl, as discussed earlier.

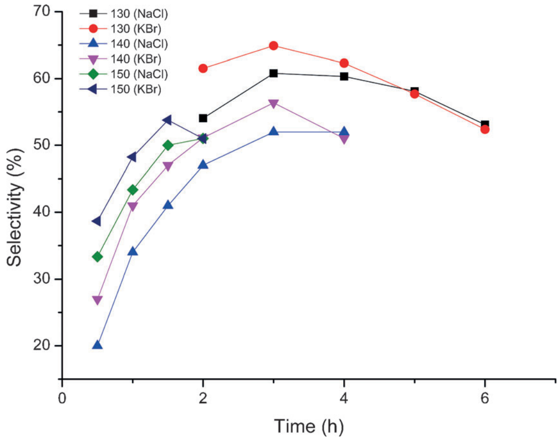


Figure 2. Selectivity to HMF in the transformation of glucose to HMF in excess NaCl or KBr at different temperatures. Reaction conditions: ≈10 wt% glucose and 10 mol% $CrCl_3 \cdot 6H_2O$ in salt$_{(aq)}$–(acetone+toluene) [1:(3:1), v/v], 130–150 °C, 1–6 h

To support this assumption, we performed fructose dehydration experiments in the presence of NaCl or KBr at 140 °C with $CrCl_3 \cdot 6H_2O$ catalyst (Figure 3). Clearly, in respect to NaCl, the presence of KBr accelerated the fructose conversion rate, resulting in higher HMF yields. Importantly, this difference was equal to the HMF yield difference observed between KBr and NaCl, showing that the effect of salt on the reaction was linked to the fructose dehydration step. Initial rates for HMF formation with NaCl and KBr were 0.0076 and 0.0104 mmol min^{-1}, respectively (Figure S4).

The difference between the effects of anions on HMF yields can be attributed to the better nucleophilicity and leaving

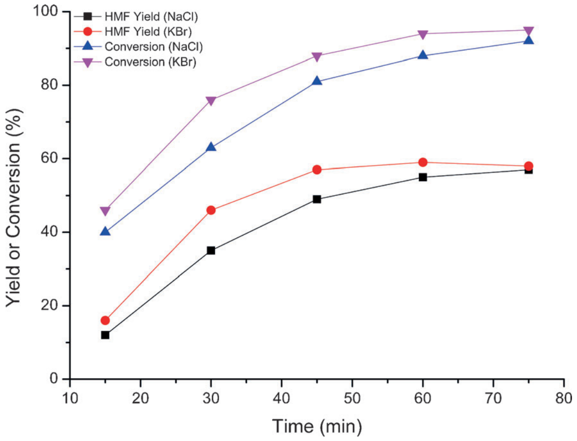


Figure 3. Fructose dehydration to HMF with $CrCl_3 \cdot 6H_2O$ catalyst in excess NaCl or KBr. Reaction conditions: ≈10 wt% fructose and 10 mol% $CrCl_3 \cdot 6H_2O$ in salt$_{(aq)}$–(acetone+toluene) [1:(3:1), v/v], 140 °C, 15 to 75 min.

group properties of the bromide anion in aqueous media, presumably assisting the dehydration of fructose in the same manner as proposed for organic solvent (*N*,*N*-dimethylacetamide) and ionic liquids.[14,15] According to those reports, bromide anions facilitate the formation of 1,2-enol from fructofuranosyl oxocarbenium ion intermediate, generated by Brønsted acid-catalyzed dehydration of C2 in fructose, more efficiently than chloride anions.[14] The formed enol then undergoes two consecutive β-dehydrations in the ring to form HMF.

The role of $CrCl_3{\cdot}6\,H_2O$ as an isomerization catalyst was confirmed as glucose and mannose were observed to form in equal amounts (Scheme 1 and Table S3). Notably, the reaction starting from fructose led to an HMF yield nearly equal to that from glucose. As a result, and due to the high amount of fructose present in experiments with glucose (Figure 1), the rate-determining step in the glucose dehydration to HMF was evidently fructose dehydration. Moreover, the rapid decrease in the ratio of glucose-to-fructose yield from approximately 5:1 (at 20 min) to a constant of approximately 2:1 (after 60 min) indicated that the glucose-to-fructose equilibrium was reached at a relatively early stage of the reaction (Figure 1 and Table S3). In this respect, increasing the acidity of the reaction should improve the HMF yields due to the accelerated fructose dehydration rate.

Effect of Brønsted acids

Recently, several studies have demonstrated that the combination of Lewis acids with Brønsted acids (typically 0.1 M HCl) in biphasic systems consisting of THF as organic medium led to good HMF yields. For example, 59% HMF yield was reported by using 3 mol% $CrCl_3{\cdot}6\,H_2O$ in 20 wt% NaCl as a reactive aqueous phase,[13] whereas use of 1.5 mol% $AlCl_3$ in a similar system led to 62% HMF yield.[12] As our biphasic procedure was analogous to the aforementioned systems, we anticipated that our best HMF yield would be enhanced by the addition of mineral acids to the reaction system. In view of those reports, we investigated the influence of H_3PO_4, H_2SO_4, HNO_3, and HCl on the reaction.

Surprisingly, as illustrated in Figure 4, we found that all the mineral acids added to the reaction decreased the HMF yields. Likewise, the reaction with a lower catalyst amount (3 and 7% $CrCl_3{\cdot}6\,H_2O$) led to lower HMF yields. Even the reaction with lower concentrations of acids (0.06 M) had reduced HMF yields compared to the reaction with $CrCl_3{\cdot}6\,H_2O$ only. With increased acid concentration (0.3 M HCl) the HMF yield was suppressed further, accompanied by a significant increase in levulinic acid production and simultaneous increase in visible solid side products (humins). The increase in levulinic acid production with additional mineral acids was in accordance with the well-known fact that Brønsted acids catalyze HMF rehydration to levulinic acid, particularly in aqueous solutions.[5] Notably, compared to the reaction without additional Brønsted acids, we observed only traces of fructose in experiments performed with HCl, H_2SO_4, and HNO_3, suggesting that fructose dehydration was indeed very rapid under conditions of increased acidity.

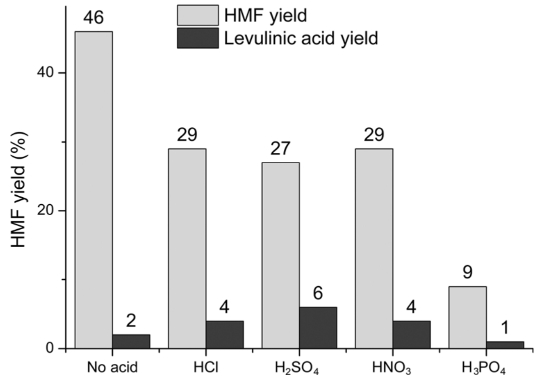


Figure 4. HMF yields with various Brønsted acids. Reaction conditions: ≈10 wt% glucose, 10 mol% $CrCl_3{\cdot}6\,H_2O$, and 0.1 M acid in $KBr_{(aq)}$–(acetone+toluene) [1:(3:1), v/v],140 °C, 2 h.

To investigate the effect of additional HCl in more detail, we performed further experiments with $CrCl_3{\cdot}6\,H_2O$ catalyst. To exclude the effect of organic solvent (acetone+toluene), we used THF as an extractive phase and performed parallel experiments applying $(HCl+NaCl)_{(aq)}$–THF, $NaCl_{(aq)}$–THF and $KBr_{(aq)}$–THF biphasic systems (Figure 5).

From Figure 5 it is clear that the addition of HCl results in significantly lower HMF yields and glucose conversion, the latter agreeing with previous reports involving $CrCl_3{\cdot}6\,H_2O$ and

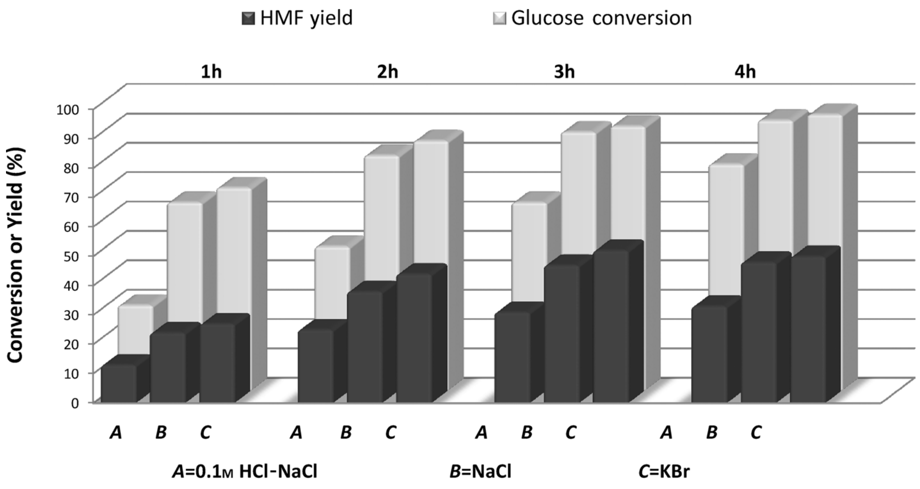
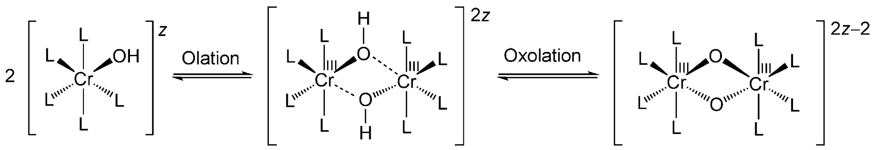


Figure 5. Glucose conversion and HMF yields with $(HCl+NaCl)_{(aq)}$–THF, $NaCl_{(aq)}$–THF, and $KBr_{(aq)}$–THF biphasic systems with $CrCl_3{\cdot}6\,H_2O$ catalyst. Reaction conditions: ≈10 wt% glucose, 10 mol% $CrCl_3{\cdot}6\,H_2O$, 0.1 M HCl, if used, in $salt_{(aq)}$–THF (1:2, v/v), 140 °C, 1–4 h.

$AlCl_3\cdot 6H_2O$ catalysts.[13,17] To understand this, we have to contemplate the characteristics of chromium chemistry taking place in electrolyte solutions. Chromium salts, such as $CrCl_3\cdot 6H_2O$, dissolve in water forming aqua complexes characterized by fairly acidic ions such as $[Cr(H_2O)_4Cl_2]^+$, $[Cr(H_2O)_5Cl]^{2+}$, and $[Cr(H_2O)_6]^{3+}$.[18] In the presence of salts (e.g., KBr) these complexes can undergo aqua ligand exchange in the inner coordination sphere with nucleophilic halogen anions and vice versa to form various hexacoordinated chromium species. As they are more acidic than water, the chromium complexes can ionize protons from aqua ligands (hydrolysis) expressed in Equation (1), thus decreasing the pH of the solution.

$$[Cr(H_2O)_6]^{3+} \rightleftharpoons [Cr(H_2O)_5OH]^{2+} + H^+ \qquad pK_a = 4 \qquad (1)$$

The hydroxyl complexes of chromium undergo dimerization forming, for example, doubly hydroxyl-bridged $[(H_2O)_4Cr(\gamma\text{-}OH)_2Cr(H_2O)_4]^{4+}$ (Scheme 2).[19] This complex, or any other binuclear chromium complex that contains aqua ligands or ligands that can be exchanged with water (i.e., Cl^- and Br^-), can still act as an acid and henceforth release more protons into the solution. Consequently, higher polynuclear chromium complexes are formed, such as trimers and tetramers.[20] These hydroxyl-bridged complexes can react further to form more stable oxo-bridged complexes (Scheme 2), which are less susceptible to acidic cleavage.[21] The formation of polynuclear chromium hydroxo and oxo-bridged complexes is slow at moderately acidic conditions but drastically accelerated by heating or addition of base. Notably, both processes are reversible, but if the solution is heated and then cooled, a long time is required for the increased acidity to return to its original value (i.e., the reverse reaction is extremely slow).



Scheme 2. Formation of chromium dimers. The charge of the complex depends on the ligands (H_2O, OH^-, or halogen).

In fact, we observed this occurring whilst measuring the pH of the aqueous phases before and after the reactions. Regardless of the added salt, during the reaction the pH value dropped one unit from approximately 2.5 to 1.5, remaining constant thereafter, even after 10 days (the decrease in pH occurred instantly after heating to 100 °C after which the value returned slowly). This confirmed the formation of polynuclear chromium species during the reaction, accelerated by heating as discussed above. The same behavior was observed if glucose was omitted from the reaction, showing that the decrease in pH value was not due to the formation of side products (e.g., levulinic acid and formic acid). Based on these observations, the amount of protons generated by $CrCl_3\cdot 6H_2O$ in electrolyte solutions, originating from the hydrolysis of $Cr(OH_2)_6$ and the formation of polynuclear chromium complexes, drove the fructose dehydration to HMF in the absence of additional Brønsted acid.

$CrCl_3\cdot 6H_2O$ is known to exist predominantly as its aqua complex at pH values below 2,[18] resulting from the equilibrium shown in Equation (1). Recently, the aqua complex has been reported to be more effective in the glucose-to-fructose isomerization than complexes possessing strong σ and π donor ligands, such as $[Cr(H_2O)_5OH]^{2+}$ and $[Cr(H_2O)_5Cl]^{2+}$, and dimeric chromium complexes.[22] Also, it is well-established that at low pH (<2), coordination of alcohols to chromium is strongly restrained.[23] Consequently, based on the evidence above, we can attribute the reduced catalytic activity of $CrCl_3\cdot 6H_2O$ with increasing acidity to the hampered formation of glucose–chromium chelate complex, which facilitates the necessary hydride transfer to form fructose.[8a,24] From our experimental data, although the fructose dehydration rate is accelerated by the addition of mineral acid, the simultaneous strong retardation of the glucose-to-fructose isomerization results in a substantial drop in HMF yields (Figures 4 and 5). In consequence, we can conclude that at low pH, lower than that provided by the intrinsic Brønsted acidity of $CrCl_3\cdot 6H_2O$ in water, glucose-to-fructose isomerization is extremely slow (and the rate-determining step).

Conclusions

$CrCl_3\cdot 6H_2O$ is an efficient catalyst for glucose isomerization to fructose, affording better HMF yields than the other catalyst studied, such as $AlCl_3\cdot 6H_2O$ and $CrCl_2$, at moderate temperatures under biphasic conditions. The use of bromide salts enhances the reaction compared to chloride salts by accelerating the fructose dehydration step. Therefore, as an example, the widely used $NaCl_{(aq)}$–THF biphasic system can be improved in terms of HMF yield by simply substituting NaCl for KBr. Most importantly, we demonstrate that the acidity plays a key role in the reaction kinetics and outcome. Without additional acid, the rate-determining step at 140 °C with $CrCl_3\cdot 6H_2O$ catalyst is the fructose dehydration. As a result, the reaction furnishes almost equal amounts of HMF if starting from fructose (59 %) compared to glucose (53 %). The addition of mineral acids, even in catalytic amount, influences the reaction by decelerating the glucose-to-fructose isomerization rate, although the fructose dehydration rate is accelerated substantially. Thus, the rate-determining step of the reaction shifts to the glucose-to-fructose isomerization, which results in decreased HMF yields (in comparison to the reaction without added acids). The effect of acidity can be explained through the hampered formation of glucose–chromium chelate complex, retarding the hydride shift vital for the isomerization.

In general, due to the rate-determining fructose dehydration without mineral acid additives, the intrinsic Brønsted acidity of $CrCl_3·6H_2O$ provided by hydrolysis of Cr^{III} aqua complexes and the formation of polynuclear chromium complexes in aqueous solutions is not sufficient to drive the reaction to completion at an appropriate rate (increased formation of side products). Accordingly, to improve the HMF yields, higher temperature (>150 °C) should be applied to accelerate the fructose dehydration step. Also, because of the significant influence of acidity on the HMF yields, the pH of the reaction media should be adjusted systematically with respect to temperature and any Lewis acid catalyst employed.

Experimental Section

General

All solvents, sugars, and metal halides were purchased from Acros Organics or Sigma–Aldrich and were used as received, except THF which was dried by using the VAC solvent purification system (Vacuum Atmosphere Systems).

HMF, glucose, fructose, mannose, and levulinic acid yields were determined by using HPLC. HPLC runs were performed on an Agilent 1200 HPLC system equipped with a Phenomenex Rezex ROA (300×7.8 mm) column. Sulfuric acid (0.25 mM) in water was used as an eluent at 40 °C with a flow rate of 0.35 mL min^{-1}. HMF was detected by using a UV detector at $\lambda = 212$ nm. All other compounds (glucose, mannose, fructose, and levulinic acid) were analyzed by using a refractive index detector. The exact yields were calculated from calibration curves prepared for all the compounds from commercially available reagents at six different concentrations.

All reactions were conducted in oven-dried 10 mL vials fitted with an aluminum–silicone crimp cap and heated in a temperature-controlled oil bath.

Glucose dehydration to HMF in $salt_{(aq)}$–organic solvent system

The following method was used in initial catalyst testing, experiments with salts (Table 1), glucose dehydration to HMF (Figure 1), fructose dehydration to HMF (Figure 3), glucose dehydration to HMF with mineral acids (Figure 4), and solvent testing experiments (Figure S2).

In a typical experiment, sugar (0.15 g, 0.83 mmol) and catalyst (10 mol %, 0.083 mmol) were dissolved in aqueous saturated salt solution (1.5 mL; NaCl, NaBr, KCl, or KBr) containing the required amount of mineral acid, if used. Then, organic solvent (6 mL) was added and the reaction heated at 130, 140, or 150 °C for 1–6 h, depending on the experiment. After the required time, the reaction vial was cooled immediately to RT, followed by the addition of brine (7 mL) and ethyl acetate (10 mL). From the aqueous phase of this solution, a HPLC sample was prepared to quantify the presence of glucose, mannose, and fructose. Next, the organic phase was separated and the water layer extracted further with ethyl acetate (4×10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and the solvents evaporated in vacuo to give the crude product as a dark yellow oil. HMF and levulinic acid yields were determined from the crude mixture by HPLC analysis (samples were dissolved in water with vigorous stirring for 30 min).

Glucose dehydration in $NaCl_{(aq)}$–THF, $KBr_{(aq)}$–THF, and $(NaCl+HCl)_{(aq)}$–THF biphasic systems

Glucose (0.15 g, 0.83 mmol) and $CrCl_3·6H_2O$ (22.2 mg, 0.083 mmol) were dissolved in aqueous saturated salt solution (1.5 mL; KBr, NaCl, or NaCl) containing 0.1 M HCl if acid was used. Then, THF (3 mL) was added and the vial heated at 140 °C for 1–4 h, depending on the experiment. After the required time, the vial was cooled immediately to RT and water added to make a total volume of 250 mL. HMF, glucose, mannose, and fructose yields were determined from this solution by HPLC analysis.

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Keywords: 5-hydroxymethylfurfural · glucose isomerization · Lewis acids · metal complexes · rate-determining step

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The Role of Salts and Brønsted Acids in Lewis Acid-Catalyzed Aqueous-Phase Glucose Dehydration to 5-Hydroxymethylfurfural

Glucose to HMF with $CrCl_3 \cdot 6\,H_2O$: Bromide salts in place of chlorides improve the dehydration of glucose to 5-hydroxymethylfurfural (HMF) in aqueous solution by enhancing the fructose dehydration step. The addition of Brønsted acid to the reaction, even in catalytic scale, is not beneficial for HMF yields. This is attributed to the deceleration in the glucose-to-fructose isomerization rate although fructose dehydration is significantly accelerated.