Reaction media dominated product selectivity in the isomerization of glucose by chromium trichloride: From aqueous to non-aqueous systems

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\textbf{A R T I C L E   I N F O}

Article history:
Received 16 November 2013
Received in revised form 21 January 2014
Accepted 18 February 2014
Available online 19 March 2014

Keywords:
Glucose isomerization
Chromium trichloride
Fructose
General behavior
Aqueous media
Mixed solvents

\textbf{A B S T R A C T}

While chromium trichloride hydrate (CrCl\textsubscript{3}·6H\textsubscript{2}O) effectively catalyzed the isomerization of glucose into fructose in aqueous solution, a general product selectivity behavior was observed independent of reaction variables such as reaction time, temperature, catalyst loading, halide ion, and initial glucose concentration. By studying the mixed solution of dimethylsulfoxide (DMSO) and water at varied DMSO/H\textsubscript{2}O ratios, it was found that deviation from the general water-phase fructose yield curve, with concomitant 5-hydroxymethyl-2-fural (HMF) formation, occurred when the fructose concentration in available water became sufficiently high in DMSO rich solvent mix. Therefore, tuning the solvent system was the most effective approach to change the product distribution from CrCl\textsubscript{3}·6H\textsubscript{2}O catalyzed glucose conversion. The apparent activation energy of glucose conversion in the studied system was estimated to be 58.6 kJ mol\textsuperscript{-1}. Special attention was also given to gain some mechanistic insights by control experiments with simple model compounds and additives, \textsuperscript{13}C NMR and UV–vis spectroscopic analyses.

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\textbf{1. Introduction}

With the growing consumption of fossil fuels and the consequential emission of green house gases, the world faces increasing pressure to develop technologies that enable the efficient utilization of alternative sources of energies and renewable feedstocks. Biomass has recently been proposed as a potential feedstock toward sustainable development in both alternative energy and chemicals [1].

In the past decade, saccharides have attracted tremendous attention toward the development of a new biorefinery industry, since they can be utilized to synthesize a variety of valuable chemicals [1]. Dehydration of fructose into 5-hydroxymethyl-2-fural (HMF) was a mostly studied pathway for this purpose. The fructose dehydration proceeds relatively easily, which can be catalyzed by mineral acid [2–7], organic acid [8,9], metal salt [10–13], solid acid [14–18] in varieties of reaction media, such as dimethylsulfoxide (DMSO) [8,11,13,19,20], dimethylacetamide (DMA)-LiCl [21], water/organic solvent biphasic system [2,9,17,18], ionic liquid [3,4,12,14–16], and even water [5,22]. Establishing a protocol to produce HMF based chemicals from sugars offers the potential to reduce society’s reliance on traditional fossil resources to some extent. Unfortunately, fructose has a low abundance in nature [1], with high cost [23], and is not a suitable feedstock for industrial development. By contrast, glucose is the most abundant monosaccharide and available from many non-edible cellulosic materials. However, the effective conversion of glucose into HMF based products always remained a great challenge until Zhang and co-workers discovered that chromium chloride (CrCl\textsubscript{3} or CrCl\textsubscript{2}) significantly facilitated HMF production from glucose in ionic liquids [24]. The key role of CrCl\textsubscript{3} was to isomerize glucose into fructose in situ [24]. Thereafter, a spate of researches focused on the conversion of glucose based feedstocks into HMF by employing CrCl\textsubscript{x} in ionic liquids as well as DMSO or DMA-LiCl system [21,25–32]. Other metal salts, such as tin chloride (SnCl\textsubscript{2} or SnCl\textsubscript{4}) and germanium chloride (GeCl\textsubscript{4}), were also found to be effective for the dehydration of glucose in ionic liquids via fructose intermediate [33–35]. In general, the bottleneck of converting glucose into HMF lies on effectively isomerizing glucose into fructose in a reaction medium.

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http://dx.doi.org/10.1016/j.cattod.2014.02.038
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Up to now, Cr-catalyzed systems are still the most active for HMF production from glucose based feedstocks, and almost all of these systems employ ionic liquids or other non-aqueous solvents [21,24–32]. However, the chemistry of Cr catalysts in isomerizing glucose to fructose is shadowed by that of fructose dehydration to HMF which is rapidly formed as the most abundant product in the non-aqueous solvent systems. Some solvents used above are expensive and some may display toxicity, so alternative cheaper and greener solvents are more desirable. One may be concerned of the potential toxicity of Cr catalyst. In fact, hexavalent chromium is highly toxic while trivalent chromium, found in most foods and nutrient supplements, is an essential nutrient with very low toxicity [36]. Thus, trivalent chromium catalysts should be avoided in an oxidation reaction. Because glucose is a reducing sugar, the oxidation of Cr(II, III) to Cr(VI) is unlikely to occur. Water is the most environmentally benign and naturally abundant solvent. Exploring the ability to utilize water for glucose conversion will be highly attractive for reducing cost of solvent and potential pollution. Recently, a series of studies on the isomerization of glucose into fructose have already been carried out in aqueous solution with solid bases or zeolites as catalysts [37–40]. However, most of the above systems have not been extended for the further use of the in situ formed fructose yet. Nikola and co-workers have showed reasonable potential for one-pot synthesis of HMF from glucose over Sn-Beta zeolite in water/tetrahydrofuran biphasic system at 160–180 °C [41]. However, the Sn-Beta also has drawbacks, for examples, the aging time for the preparation of this catalyst is very long (>1 month) and it can be poisoned by a certain solvent/additive, such as DMSO [42]. Choudhary et al. recently studied the consecutive conversion of glucose into levulinic acid and xylene into furfural, respectively, in aqueous solution with CrCl3·6H2O and hydrochloric acid (HCl) as catalysts, and demonstrated that Cr complexes isomerized glucose and xylene into fructose and xylulose, respectively [43,44]. The results offer an opportunity to realize efficient conversion of sugars in aqueous media.

In this work, we investigated the effect of reaction variables on the CrCl3·6H2O catalyzed isomerization of glucose into fructose in aqueous media in great detail. It is remarkable that these results for the first time revealed a general behavior of glucose isomerization in the studied system independent of the process parameters. It is also noted that other published works involving aqueous systems used for glucose conversion fit into this general behavior. In this work, special attention was also given to gain some mechanistic insights using simple model compounds and additives. Ultraviolet–visible spectroscopic analyses provided information on the interaction between chromium species and glucose during the reaction process.

2. Experimental

2.1. Materials

D-glucose (99%), D-fructose (99%), 1,6-anhydro-β-D-glucose (AGP, 99%), D-cellobiose (98%) and chromium bromide hexahydrate (CrBr3·6H2O, 98%) were purchased from Alfa Aesar. Chromium chloride hexahydrate (CrCl3·6H2O, 96%) and D-glyceraldehyde (≥90%) were purchased from Sigma–Aldrich. 5-Hydroxymethylfurfural (HMF, 98%), levulinic acid (LA, 99%) and 1,3-dihydroxyacetone dimer (97%) were purchased from Aladdin. Glycerol (99%), dimethyl sulfoxide (DMSO, 99%) and 1,2-propanediol glycol (99%) were purchased from Sinopharm (China). Hydrochloric acid (HCl, 36–38 wt%) was provided by a local supplier. All the chemicals were used as received. Deionized water (DI H2O) was produced by a Milli-Q Integral 5 system, having a resistivity of 18.2 MΩ cm.

2.2. Typical reaction procedure

Glucose (50 mg), CrCl3·6H2O (3.7 mg, 5 mol% with respect to glucose) and 1 mL of DI H2O were added into each reaction vial (5 mL) with a magnetic stir bar. Then, the reaction vials were sealed, inserted into a heating and stirring module (TS-18821, Thermo Scientific, USA), and stirred at 500 rpm for a specified time at the reaction temperature. After the reaction was quenched in ice water bath, 1 mL of DI H2O and the internal standard were added into the reaction mixture. Then, a small amount of sample was taken out and further diluted by ~15 times and analyzed by high performance liquid chromatography (HPLC).

2.3. Analysis method

HPLC analysis was performed on an Agilent 1260 series with a refractive index detector and a PL Hi-Plex H column (300 mm × 7.7 mm, 8 μm). Diluted H2SO4 solution (0.005 M) at a flow rate of 0.6 mL/min was used as the mobile phase. The column and detector temperatures were 65 and 50 °C, respectively. Authentic chemical compounds were used to identify the retention times. Glycerol was added as an internal standard for the quantitative calculations. For the control experiments with glycerol, D-α-glyceraldehyde or 1,3-dihydroxyacetone as simple model compounds or additives, 1,2-propylene glycol was used as the internal standard instead of glycerol. Glucose conversion and product yield are defined as in Eqs. (1) and (2). The pH values were measured by a Mettler-Toledo G20 Titrator with a DGG115-SC electrode or Core Module 3 (CM3) System (Fineslate). 13C NMR spectra were recorded on a Bruker DRX-400 spectrometer. Ultraviolet–visible (UV–vis) spectra were collected on a Shimadzu UV-2600 spectrophotometer.

Glucose conversion (mol%)

\[
\text{Glucose conversion (mol%)} = \left(1 - \frac{\text{Mole of remaining glucose detected by HPLC}}{\text{Mole of initially added glucose}}\right) \times 100\% \tag{1}
\]

Yield (mol%)

\[
\text{Yield (mol%)} = \left(\frac{\text{Mole of product detected by HPLC}}{\text{Mole of ideal amount of product from added feedstock}}\right) \times 100\% \tag{2}
\]

3. Results and discussion

3.1. Isomerization of glucose into fructose in aqueous solution

Chromium dichloride (CrCl2) has been mostly reported to be the effective catalyst for HMF production in non-aqueous solvent system [24,25,27,28,31]. However, to avoid CrCl2 oxidation by air, especially in H2O which may cause the oxidation [45,46], chromium trichloride (CrCl3) is used in this work. CrCl3 is also an effective catalyst [24], of which the hydrated form, CrCl3·6H2O, has better solubility in the solvents [30]. Since water is used as a reaction medium in this work and anhydrous CrCl3 has poor solubility in H2O [30], CrCl3·6H2O was selected as the catalyst for isomerization of glucose into fructose.

Fig. 1 shows the results of glucose isomerization at 90, 110, and 130 °C for 0.5–4 h in 1 mL of H2O each, to which 50 mg of glucose and 3.7 mg of CrCl3·6H2O (5 mol%, with respect to glucose) were added. The reaction proceeded very slowly at 90 °C, at which glucose conversion and fructose yield reached 13.6% and 10.8%, respectively, after 4 h. Elevating the reaction temperature boosted the isomerization of glucose. At 110 °C, the yield of fructose increased to 21.8% after 4 h, while it reached the maximum
of ~26% even after 1 h at 130 °C. The isomerization of glucose is slightly endothermic (ΔH = 3 kJ mol\(^{-1}\)) [47], so it is expected that higher temperature will accelerate the isomerization of glucose. However, it is remarkable to observe that, when the fructose yield is plotted against the glucose conversion as shown in Fig. 1, as the primary product of glucose isomerization, fructose yield essentially followed a general trend of linear increase with respect to glucose conversion of about 3–30% at different temperatures. Fructose production gradually deviated from the linear increase at higher glucose conversion (>~30%), implying more secondary and consecutive reaction products were produced. This is indeed the case when the yields of other products are inspected. For example, HMF is one such secondary reaction product, from the dehydration of fructose. As illustrated in Fig. 1, the formation of HMF remarkably accelerated at higher glucose conversion (>~30%). Choudhary et al. recently studied the consecutive conversion of glucose into levulinic acid (LA) and the mechanism of glucose isomerization in aqueous media at 140 °C [43,48]. Their published data also followed the relationship between fructose yield and glucose conversion as established in this work (Fig. 1) to a large extent. Except for fructose and HMF, other products such as cellobiose, 1,6-anhydro-β-D-glucopyranose/glucouronose (AGP/AGF) and LA, were also detected in the system. Cellobiose, AGP and AGF are the primary products by undesired intermolecular or intramolecular dehydration of glucose, while LA is a downstream product from the rehydration of HMF. The yields of cellobiose, AGP, AGF and LA were very low, so they were not listed. Other products remained unknown, possibly humins, accounting for some loss of fructose. It should be noted that mass balance is an important indicator for a reaction. To circumvent undesired side reactions, further study is essential for reducing mass loss.

We next investigated the effect of CrCl\(_2\)·6H\(_2\)O loadings on the isomerization of glucose into fructose at 110 °C and the other conditions remained the same as above. As shown in Fig. 2, fructose production still followed the general curve as depicted above, with CrCl\(_2\)·6H\(_2\)O loadings from 2.5 mol% to 12.0 mol% (with respect to glucose). At the glucose conversion of about 8–30%, fructose formation showed a linear increase trend, while it gradually deviated from the general curve again at higher glucose conversion. As illustrated in Fig. 2, more HMF was produced at higher glucose conversion, accounting for the deviation of fructose yield from the general curve to some extent as mentioned above. The deviation from the linear increase in fructose yield versus glucose conversion is indicative of consecutive reactions consuming fructose when fructose concentration becomes sufficiently high.

In reported work, CrBr\(_3\) and CrF\(_3\) were found more active than CrCl\(_2\) or CrCl\(_3\) for the conversion of glucose into HMF in some non-aqueous solvents [21,49], implying halide anions may influence the isomerization of glucose. Similarly, CrBr\(_3\) and CrF\(_3\) could be potential catalysts for this work. However, CrF\(_3\) may be hydrolyzed, producing hydrofluoric acid (HF) which is poisonous and can also corrode the used glass reaction vial. Therefore, only CrBr\(_3\)·6H\(_2\)O was employed in the current system for comparison. As shown in Fig. S2, compared with the results over CrCl\(_2\)·6H\(_2\)O, the ones with CrBr\(_3\)·6H\(_2\)O not only followed the general curve for the fructose production, but also give similar absolute values of fructose yield, glucose conversion and HMF yield, indicating that CrBr\(_3\)·6H\(_2\)O is also a good catalyst for isomerizing glucose into fructose. The halide anions had little effect on the isomerization reaction.

As reported, the thermodynamic equilibrium between glucose and fructose has a constant of ~1 at 25 °C [47], implying that the isomerization between glucose and fructose is reversible. We then checked the effect of glucose concentration. The initial concentration of glucose was varied from 50 mg/mL to 120 mg/mL, while maintaining the same concentration of CrCl\(_2\)·6H\(_2\)O. As illustrated in Fig. S3, the production of fructose slightly decreased with increasing the initial glucose concentration, because the amount of catalyst was reduced relatively to the initial concentration of glucose. However, the results indeed behaved in the similar manner as mentioned above. Moreover, the results imply the system may have the potential for a process compatible with high concentration on the other hand.

Based on the results discussed above, it is evident that, independent of the process variables, such as reaction time, temperature, CrCl\(_2\)·6H\(_2\)O loading, halide ion and initial glucose concentration, the production of fructose always followed a general curve in the water medium. Fructose yield increased in a linear manner at the glucose conversion below about 30%, while the formation of secondary and further products was accelerated once the concentration of fructose became high enough in water at higher glucose conversion.

The reported results in literatures on the catalytic conversion of glucose in various solvents, e.g. ionic liquids [24,25,30,32], DMSO [29,32], suggest that the property of solvent plays a dominant role in the product distribution in glucose conversion, and the above results are consistent with this statement. DMSO is a solvent generally used for the preparation of HMF from fructose while suppressing side reactions [2,20,50]. To correlate the deviation point from the general curve with fructose concentration, we select mixed solvents composed of DMSO and H\(_2\)O at various DMSO/H\(_2\)O ratios (v/v). With increasing DMSO/H\(_2\)O ratio, the available water
is decreased. As shown in Fig. 3, the production of fructose showed different behaviors. In the system with DMSO/H2O (v/v) of 2/8, the production of fructose essentially followed the general curve as that in pure H2O. When the volume proportion of DMSO was increased to 50% and 80%, respectively, the production of fructose deviated from the general curve at lower and lower glucose conversion. In pure DMSO system, fructose production did not follow the general curve as those in aqueous solution at all; the maximum fructose yield was only ~5% in DMSO solvent. Table S1 gives the approximate fructose concentration at each deviation point in different DMSO/H2O solutions, which decreased from ~0.056 mmol/mL to ~0.035 mmol/mL with respective DMSO/H2O (v/v) ratios of 0/10–8/2. As shown in Fig. 3, only a little fructose could stably exist in pure DMSO, because the dehydration potential of DMSO is very high that made fructose undergo consecutive conversion. If DMSO and water components in the mixed solvents had displayed their individual intrinsic solvent properties, the volume of the available water would be the real volume of water fraction. On this assumption, the fructose concentrations in available water fraction of the DMSO/H2O solutions at different ratios were estimated to vary from ~0.056 mmol/mL to ~0.175 mmol/mL, with increasing DMSO proportion from 0 to 80% vol.%. The published studies on the DMSO/H2O binary mixture, on one hand, showed that the bonding between water and DMSO molecules is non-linear with varying DMSO/H2O ratio and water–water interaction remains significant, even at water concentration as low as 5% [51], and on the other hand, the mixing of the two solvents is strongly exothermic [52], indicating H-bonding formation that would passivate the dehydration potential of DMSO by the presence of water. The weakened dehydration potential of DMSO, due to the solvation effect of water by H-bonding formation, appears to be responsible for the increased fructose concentration at the deviation point over that solely determined by the volume fraction of available water. In general, it could be expected that a certain fructose concentration will account for the deviation of fructose yield versus glucose conversion. Fructose yield increased in a linear manner at the fructose concentration below ~0.056 mmol/mL (estimated by pure H2O system), while the formation of secondary and further products was accelerated once the concentration of fructose became high enough in available solvent at higher glucose conversion. In addition, the deviation from the general curve reflects fructose conversion into HMF. As illustrated in Fig. 4, the production of HMF in DMSO/H2O (v/v) of 0/10–8/2 showed a similar trend. HMF formation was accelerated when fructose concentration could become high enough for the secondary reaction. Evidently, water is detrimental to the dehydration of fructose, so the more water, the lower HMF yield. However, the formation of HMF behaved differently in pure DMSO. Due to the facile dehydration of fructose in DMSO (non-aqueous solvent), once fructose was produced, it undergoes consecutive conversion into HMF immediately.

Moreover, since HMF is a main secondary product from fructose, a plot of the total yield of fructose and HMF against glucose conversion reveals that the conversion of glucose exhibited a similar trend in DMSO/H2O solution, while the total fructose and HMF yield deviated from the general curve in DMSO at the glucose conversion of ~15%. As seen in Table S2, much cellobiose was produced in pure DMSO system after longer time. In addition, DMSO also favored in the formation of AGP and AGF as reported [53]. The undesired products, such as cellobiose, AGP and AGF, explain why the total production of fructose and HMF deviated from the general curve in Fig. 5.

The suppression of dehydration reaction by water can be beneficially utilized to suppress undesired side reactions. When an adequate amount of water was present in the DMSO mixed solvent, water was found to significantly suppress the intermolecular and intramolecular dehydration of glucose, leading to low yields of cellobiose, AGP and AGF. The results therefore indicate that if
an appropriate aqueous system is employed, more desired product could be produced. For example, as seen in Table S2, more HMF could be obtained in the aqueous solution with 80% of DMSO, which circumvented other by-products, such as cellulose, AGP and AGF. In general, tuning the composition of DMSO and H2O can change the behavior of fructose production and the distribution of products. Aside from DMSO, other solvents, such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl pyrrolidone and so on, are also potential co-solvents to control the distribution of products.

3.2. Kinetic analysis

The kinetic parameters for CrCl3·6H2O catalyzed isomerization of glucose in water were calculated by assuming a rate expression that was first order in the concentration of glucose. The data on glucose conversion at 90, 110 and 130 °C were used for the calculation. As shown in Fig. S4a, the reaction rate was fitted well with the assumption of first order reaction. Fig. S4b gives the Arrhenius plot, and the apparent activation energy (Ea) is estimated to be 58.6 kJ mol⁻¹, close to the reported values. For example, Choudhary et al. reported that the Ea was 15.3 kcal mol⁻¹ (~64.0 kJ mol⁻¹) for glucose conversion with CrCl3·6H2O, while the Ea was 15.5 kcal mol⁻¹ (~64.9 kJ mol⁻¹) for xyllose (aldopentose) conversion [43,44]. The estimated Ea is much lower than those for base catalyzed isomerization of glucose, about 121–129 kJ mol⁻¹ [54–56], indicating that the unique mechanism involved in chromium mediated isomerization of glucose is different from that of base catalyzed one.

3.3. Mechanistic insights

To understand the mechanism involved in the chromium mediated isomerization in water medium, a series of control experiments were carried out with different feedstocks, catalysts or additives, and the results are listed in Table 1. It is known that CrCl3·6H2O can be hydrolyzed into chromium species and hydrochloric acid (HCl), so we first checked the role of HCl. In a sample containing 3.7 mg of CrCl3·6H2O in 1 mL H2O, the pH value was at ~2.7, which indicates that the aqueous solution (e.g. reactions in Fig. 1) was acidic before reaction took place. After heating at 110 °C for 1 h, the pH of the above solution dropped to ~2.1. Elevating temperature could accelerate the hydrolysis of CrCl3·6H2O, therefore producing more HCl and leading to a lower pH. For comparison, aqueous solution with pH of 2.7 or 2.1 was prepared by diluting concentrated HCl solution and used both as the solvent and catalyst for glucose isomerization. As seen in Table 1 (Entries 2 and 3), little glucose conversion could be detected, clearly indicating that the active component for the isomerization of glucose is chromium species but not HCl. The Fischer projection of glucose can be considered as one glyceral molecule attached to one glyceroldehyde molecule. Therefore, glycerol and glyceraldehyde were employed as additives for understanding the interaction between glucose and chromium species. As seen in Entries 4 and 5, when glycerol was added, the glucose conversion and fructose yield showed a negligible decrease (~1%) compared with Entry 1 (Table 1), indicating that glycerol did not influence the reaction much. After glyceraldehyde was added, the isomerization of glucose was significantly suppressed with the conversion of 3.8%. However, glyceraldehyde underwent effective isomerization into 1,3-dihydroxyacetone, demonstrating that chromium species could interact with the end aldehyde group of glyceraldehyde as other metal ions [57,58]. As reported, only about 0.002% of glucose existed in the chain form in water at ~30 °C [59], with very limited end aldehyde groups, and most aldehyde groups of glucose existed in the hemiacetal form (the ring form). Glucose must undergo a ring open process before interacting with chromium species. In contrast, glyceraldehyde can provide more end aldehyde groups in aqueous solution, so it is more competitive than glucose to react with chromium species. When glyceraldehyde was treated in a HCl solution with a pH of 2.1 (Entry 6), low conversion was observed, and 1,3-dihydroxyacetone yield was negligible. The results thus further demonstrate that chromium species is the active component for the isomerization of glucose and glyceraldehyde. Comparing the data in Entries 5 and 7, it is evident that chromium species did predominantly interact with glyceraldehyde in the competition reaction with respect to their interaction with glucose.

13C NMR spectra of glucose in D2O were collected under different conditions to probe the structural details of glucose in various stages of catalytic transformation in the solvent systems of this study. As shown in Fig. S5a, when glucose was dissolved in D2O at room temperature for 20 min, it existed in α and β-glucopyranose forms simultaneously. The α-glucopyranose was a little more dominant with β/α ratio of 0.7/1. After the solution was heated at 110 °C for 2 min, it was found that the higher temperature significantly promoted the mutarotation of glucose, leading to β/α ratio of 1.48/1 (Fig. S5b). In previous literatures, it was reported that almost all the glucose showed the α-glucopyranose form in ion liquid or dimethylacetamide before reaction [24,60], and catalysts therein facilitated the mutarotation to produce β-glucopyranose. In contrast, there is a mutarotation equilibrium between α and β-glucopyranose in H2O or DMSO, and elevating temperature can accelerate the equilibrium process [61], which explains why both α and β-glucopyranose were detected in Fig. S5. Glucose favors the β-glucopyranose form at equilibrium [59,61]. After glucose and CrCl3·6H2O dissolved in D2O at room temperature for 20 min, the proportion of α-glucopyranose slightly increased, implying chromium species may have an interaction with glucose under those conditions. However, as shown in Fig. S5d, heating promoted the mutarotation again. By extending reaction time at 110 °C, β-glucopyranose appeared more and more dominant, indicating thermodynamic equilibrium was the major factor that affected the distribution of α and β-glucopyranose. In consideration that acid may be produced by CrCl3·6H2O hydrolysis in D2O, we then measured the 13C NMR of glucose in D2O with a pH of ~2.7. As shown in Fig. S6a, when glucose was dissolved in D2O with a pH of ~2.7 at room temperature for 20 min, it showed a higher proportion of α-glucopyranose like that in Fig. S5c, indicating that acidic medium accounts for the reduced mutarotation of glucose to β-glucopyranose. As illustrated in Fig. S6b and c, heating promoted the mutarotation, and extending reaction time led to increased mutarotation to β-glucopyranose. In general, 13C NMR spectra mainly confirmed that the mutarotation of glucose did occur in the studied system. Glucose must undergo a ring opening process to realize mutarotation, accompanied with the formation of open chain glucose [59]. The open chain glucose is likely the key component to react with chromium species, offering the opportunity for the isomerization as discussed in the last paragraph.

Finally, we employed UV–vis spectrophotometer to monitor the isomerization of glucose in water. The UV–vis analyses were not carried out in DMSO solution, because more HMF would be produced therein, and the intense absorbance of HMF overshadows the absorbance of CrCl3·6H2O, as will be discussed below. As illustrated in Fig. 6, after CrCl3·6H2O was dissolved in H2O at room temperature, two weak absorption peaks appeared at ~417 and ~582.5 nm, respectively. They could be attributed to the d–d transitions of Cr complexes. For example, Cr3+ could coordinate with H2O molecules to form complexes [43,44]. The molar absorptivity of the bands caused by d–d transitions is relatively low [62], which explains why CrCl3·6H2O solution showed the weak absorption peaks. Glucose does not show signal in the UV–vis analysis. When glucose was added, a blue shift of about 2 nm was observed for the peak of 582.5 nm, possibly a result of Cr complex formation between.
glucose and chromium species. After the solution of CrCl$_3$·6H$_2$O and glucose was heated at 110 °C for different time, the peak at ~284 nm was enhanced remarkably, indicating the formation of more HMF. For the chromium species, both two peaks showed further blue shift. The original peak at ~417 nm slightly shifted to about ~414 nm. Sample (g) (Fig. 6) apparently showed a more remarkable blue shift to ~402 nm, but it may be because the HMF peak was so intensive that the peak at ~414 nm was overshadowed to a certain degree. The original peak of ~582.5 nm showed a blue shift of 10.5 nm after the solution was heated at 110 °C for 60 min, implicating more complexes or coordination between glucose/fructose and chromium species. It was reported that more HCl may influence the UV absorbance of Cr complexes in water [44]. This possibility was also checked. As mentioned above, after the used CrCl$_3$·6H$_2$O solution was heated at 110 °C for 60 min, its pH value decreased from ~2.7 to ~2.1, which means more HCl was produced. Based on this point, sample (a) (Fig. S7) was heated at 110 °C for 30 min and 60 min, respectively, it was then measured by UV–vis spectrophotometer. As shown in Fig. S7, sample (b) heated for 30 min showed peaks at ~415 and ~581 nm, while sample (c) heated for 60 min showed peaks at ~415.5 and ~581.5 nm, indicating that more HCl barely affected the absorbance of chromium species in this work. It can be seen that the absorbance intensities of peaks 1 and 2 increased when the CrCl$_3$·6H$_2$O solution with glucose was heated at 110 °C for longer time (Fig. 6). In fact, when the CrCl$_3$·6H$_2$O solution without glucose was heated at 110 °C for 30 min and 60 min (samples b and c, Fig. S7), respectively, the intensities also increased, implying the heating process may influence the Cr complexes in water. However, when glucose was added and heated at 110 °C for 30 min and 60 min, not only that the absorbance intensity further increased, but also the samples showed the blue shifts, which demonstrates that chromium species interacted with glucose/fructose.

Because most blue shifts for the UV absorbance of CrCl$_3$·6H$_2$O solution were only observed at conditions at which a reaction occurred, we then checked if a particular product could cause the blue shift through its interaction with the chromium species. After reacting glucose with CrCl$_3$·6H$_2$O (5 mol%), with respect to glucose) at 110 °C for 30 min, the detectable products were fructose (10.5%) and little cellobiose (0.4%). Then cellobiose and fructose were used as feedstock and heated with CrCl$_3$·6H$_2$O (5 mol%, with respect to feedstock) at 110 °C for 30 min. As illustrated in Fig. S8, the sample with cellobiose gave two absorbance peaks at ~415.5 and ~579.5 nm. No obvious blue shift for the absorbance of CrCl$_3$·6H$_2$O was observed at such high concentration of cellobiose, indicating that the little cellobiose (a yield of 0.4%) formed in the above reaction was not the major factor that caused the blue shift. Interestingly, the sample with fructose as feedstock showed remarkable blue shift to ~564 nm, while the original peak at ~417 nm disappeared. When fructose was used, more HMF could be produced than glucose, and the intense HMF peak could overshadow the original peak at ~417 nm, which explains why the peak disappeared. In fact, after HMF solution with CrCl$_3$·6H$_2$O (5 mol%, with respect to HMF) was heated at 110 °C for 30 min, the peaks 1 and 2 of CrCl$_3$·6H$_2$O both were overlapped as shown in Fig. S8. To get evident absorbance of CrCl$_3$·6H$_2$O with HMF, the amount of HMF was reduced. For example, when HMF (1.75 mg, 5 mol%) to the amount of HMF as above) with CrCl$_3$·6H$_2$O (1:1 molar ratio to HMF) was heated at 110 °C for 30 min, the absorption bands of CrCl$_3$·6H$_2$O were at ~412 and ~579 nm (Fig. S8), indicating that HMF was not the major factor for the blue shift either. As reported, the isomerization of glucose into fructose is reversible [47]. Moreover, Choudhary and co-workers recently reported that the isomerization of xylose into xylulose followed a reversible intra-hydride transfer mechanism in the presence of CrCl$_3$·6H$_2$O, where chromium species could both interact with xylose and xylulose [44]. According to that, as illustrated in Fig. 7, it is proposed that the chromium species could also coordinate with both glucose and fructose, showing that the isomerization is reversible, so the remarkable blue shift with fructose herein can be ascribed to the interaction between chromium.
species and fructose at C1 and C2 positions. The reason why fructose gave more remarkable blue shift may be due to the fact that more fructose (0.8%) exists in the open chain form in water at $\sim 30 \, ^\circ C$, a more favor structural anomer to form coordination bonding with the chromium species. In comparison, the concentration of the open chain form of glucose (0.002%) is only 1/400 of that of fructose [59].

The reaction of glyceraldehyde was investigated by UV-vis analysis as well (as shown in Fig. S9). Similarly, after reacting for some time, the absorption peak of chromium species showed more remarkable blue shift. For example, the blue shift reached $\sim 19$ nm from 582.5 to 563.5 nm after 30 min reaction, which indicates that chromium species could have a stronger interaction with glyceraldehyde than with glucose. The results demonstrate that glyceraldehyde was more active, which was consistent with the data in Table 1 (Entry 5). In addition, when glycerol and 1,3-dihydroxyacetone were used as feedstock with CrCl$_3$·6H$_2$O (5 mol% with respect to glycerol or 1,3-dihydroxyacetone) and heated at 110 °C for 30 min, respectively, the sample with glycerol gave two peaks at $\sim 415$ and $\sim 581$ nm, further indicating that the $\sim 400$ and $\sim 563$ nm. The peak shifted to $\sim 400$ nm is because it was overshadowed by the intense absorption peak of 1,3-dihydroxyacetone, and the blue shift to $\sim 563.5$ nm is ascribed to the interaction between chromium species and 1,3-dihydroxyacetone at C1 and C2 positions as those for fructose.

4. Conclusions

In this work, the results obtained in aqueous reaction medium demonstrate that the CrCl$_3$·6H$_2$O catalyst is effective for the isomerization of glucose to fructose as the main primary product and the plot of fructose yield versus glucose conversion follows a general curve independent of reaction variables, such as reaction time, temperature, CrCl$_3$·6H$_2$O loading, halide ion and initial glucose concentration. With glucose loading of 5 wt% in the aqueous solvent, fructose production showed a general linear increase at lower glucose conversion (e.g. below $\sim 30\%$), while it gradually deviated from the general curve at higher glucose conversion (e.g. over $\sim 30\%$), accompanied with more secondary and further products, such as HMF. To change the product distribution from glucose isomerization, changing the solvent system is the most effective approach. For example, when DMSO was employed as a second solvent in this work, it was found that tuning the composition of DMSO and H$_2$O effectively changed the behavior of fructose production and the distribution of products from glucose. In DMSO/H$_2$O (v/v) of 8/2, higher yield of HMF and moderate yield of fructose could be obtained while circumventing the formation of undesired product, such as cellobiose. The Ea of glucose conversion in the studied system was estimated to be 58.6 kJ mol$^{-1}$. Control experiments, $^{13}$C NMR and UV-vis spectroscopic analyses provided some mechanistic insights into the CrCl$_3$·6H$_2$O catalyzed isomerization of glucose. Chromium species played a role as the catalyst in the isomerization by coordinating with end aldehyde group of the chain form of glucose, while the HCl produced by the hydrolysis of CrCl$_3$·6H$_2$O did not work. $^{13}$C NMR spectra confirm that the mutarotation of glucose occurred during the reaction process, implying the formation of the chain form of glucose with end aldehyde group, which is important for the catalyzed isomerization reaction. The findings reported herein offer not only chemistry toward the Cr-catalyzed isomerization of glucose, but also new opportunities for designing appropriate aqueous system for sugar conversion.

Acknowledgements

This work was supported by the China Postdoctoral Science Foundation (2013M530952), National Natural Science Foundation of China (21306186), and the Chinese Government “Thousand Talent” program funding.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.catod.2014.02.038.

References
