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The Role of Water in Catalyzing Proton-Transfer in Glucose Dehydration to 5-Hydroxymethylfurfural

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Abstract: 5-hydroxymethylfurfural (HMF) is one of the most important and versatile biomass derived platform chemicals for the synthesis of a wide range of industrial chemicals, including biofuels. HMF can be obtained by dehydration of glucose with acid catalyst. It is found that the conversion may proceed via two steps i.e. glucose-fructose isomerization and dehydration of fructose to HMF. Throughout most of the first step, the water plays an important role, functioning as a proton shuttle to promote the reaction, reduce the energy barrier, resulting in the acceleration of the reaction. Besides, water can also block the side reaction. The fact that water joining and catalyzing the reaction is further proved by the experimental findings that by using DMSO/D₂O as solvent deuterium was found at C1 of HMF from NMR analysis.

Introduction

The isomerization of glucose into fructose plays an important role in the synthesis of fuels and chemicals from renewable sources. Through further dehydration of fructose, the valuable compound 5-hydroxymethylfurfural is obtained which is a promising feedstock in the carbohydrate-based economy. U.S. Department of Energy has listed HMF as one of the top ten value-added bio-based chemicals.[1] Glucose isomerization can be catalyzed by both Lewis acids and Brønsted bases. Möller and co-workers reported a Sn-doped Beta zeolite catalyst which produced relatively high yields HMF from glucose within thirty minutes.[2] In a recent work, Fristrup et al. reported boric acid catalyzed metal-free dehydration of glucose to HMF with moderate selectivity and yield.[3] Tessonnier et al. investigated several organic amines catalysts for this isomerization.[4] Compared with strong inorganic bases (yields below 10%), organic amines, in particular triethylamine, show high selectivity (54%) and yield (31%).

Recently, Zhang and co-workers reported metal-free ammonium polymer P-BnNH₂Cl (polystyrene-based benzyl ammonium chloride) as a catalyst for fructose/glucose dehydration to produce HMF in good yields.[5,6] To investigate the reaction mechanism, deuterium oxide/DMSO was used in the glucose dehydration system, and deuterium was found mainly at C1 of HMF from NMR analysis.[8] This result indicated that the reaction mechanism may be via amines and enediol intermediate.

In this mechanism, water may speed up the reaction and increase the yield by involving in the proton transfer process. They found water not only blocked the pathway for forming byproducts (e.g. anhydrosugar) but also facilitated proton transfer.

Water is an essential substance for natural life, but its roles in the organic reactions remain unclear. Water is an ideal medium to perform organic reactions and there are many excellent reviews in this area, such as by Li,[7] Lindstrom[8], and Manabe and Kobayashi.[9-10] It was reported that water could increase the reaction rate when the organic reactants were insoluble in the aqueous phase.[11-14] For both in-water and on-water reactions, water exhibits versatile character in a great number of reactions as highlighted in review articles.[15-16] It was also reported that reaction in aqueous media could achieve better rate acceleration and higher selectivity as compared to those in organic solvents.[17] Yu and co-workers reported that the reaction can be significantly accelerated by adding a minimal amount of water which helps the proton transfer process under Grothuss mechanism.[18, 19] Shi et al. found that the barrier of [1,2]-hydride shift process reduces from 20.2 to 16.4 kcal/mol when an extra water acts a proton shuttle to help proton transfer in Au(I)-Catalyzed Tandem [3,3]-Rearrangement/Nazarov Reaction.[20] The similar role of water is also reported in many other reactions, such as Morita-Baylis-Hillman and related reactions, asymmetric [3+2] cyclization reactions, and others.[21]

Although it is well recognized that water plays important role in many reactions, little is known about the detailed mechanisms of how water assists or catalyzes these on water or in water reactions.[12, 22] Understanding the solvent effect on reactivity and selectivity is one of the most attractive challenges to the theoretical community. To further prove the role of water in glucose isomerization reaction pathway, detailed density functional theory (DFT) based calculations for the benzyl ammonium catalyzed glucose isomerization process with explicit water solvent are performed. In Zhang's experiment,[5] water was identified to be a key reactant in this system. The presence of water not only blocked the pathway to anhydrosugar formation from glucose but also facilitated proton transfer, thus speeding up overall reaction. The optimized water content of 12 vol% in the reaction system for highest HMF selectivity was observed.[8]

In the present work, our calculations show that the water molecule plays a substantial role, which acts as a proton shuttle to promote the conversion.
Results and Discussion

Glucose isomerization into fructose can be divided into three steps: 1) ring-opening of glucose, 2) formation of intermediate ene-diol, and 3) ring-closure of fructose. Fructose dehydration into HMF consists of three cycles of dehydration which can be further divided into three steps: 1) protonation, 2) dehydration, and 3) deprotonation.

As shown in figure 1, without water, the whole pathway (glucose into fructose) is 2.17 kcal/mol endothermic, with the highest barrier of 21.12 kcal/mol. With an extra water molecule in the system, the whole reaction becomes -3.87 kcal/mol, with the highest barrier of 18.99 kcal/mol. The hydrogen bonds (O…H or N…H) existed in all intermediates and transition states which can stabilize all these compounds. The initial glucose ring opening proceeds through a proton transfer from Bn-NH₂⁺ to O in glucose, while the adjacent hydroxyl group (OH) is deprotonated. The relative free energy barrier was 21.12 kcal/mol uphill from 1a to 2a. If one water molecule joins in the reaction, the reaction barrier reduces to 18.75 kcal/mol. In TS1b, the water molecule acts as a proton shuttle, accepting a proton from Bn-NH₂⁺ and transferring another one to the hydroxyl group at C1 atom, to promote the break of the C1–O6 bond and formation of the C1=O bond. Liu et al. calculated the barrier of this ring opening step to be 8.3 kcal/mol using SO₃H₃ functioned ionic liquids as catalysts. However, the barrier of the rate-limiting step in their work is 26.3 kcal/mol, much higher than our data (18.99 kcal/mol). After a rearrangement of Bn-NH₂⁺ and Bn-NH₃⁺, the intermediate 3a/3b progresses through two proton-transfer elementary steps and is converted to 4a/4b, realizing the transformation of the substrate from ketone to enol through TS2a/2b. Transition state TS2b has an energy barrier of 18.49 kcal/mol where the water molecule plays again a role of a proton shuttle to carry out the ketone–enol isomerization. Li et al. calculated the barrier of this step to be 26.3 kcal/mol, much higher than our data. After another proton transfer, Transition State TS3a/3b converts the ene-diol (5a/5b) into acyclic form of fructose 6a/6b (a keto carboxylic acid) with an energy barrier of 16.32/18.99 kcal/mol relative to 5a/5b. Li et al. calculated the barrier of this step to be 17.1 kcal/mol, comparable to our data. Stahlberg et al. found using boric acid as catalyst can reduce the barrier of direct hydride shift from 43.74 to 17.93 kcal/mol compared to the case without any catalyst. However, they did not calculate the barrier for other steps like ring-open and ring-closure. So in their work it cannot be concluded that the direct hydride shift step is the rate-limiting step. Furthermore, the yield in their work is low (42%) compared to Zhang’s work (>80%) most likely due to the formation of stronger fructose-borate chelate complexes which cease the further dehydration of fructose. In TS3b the water molecule accepts a proton from Bn-NH₂⁺ and transferring another one to the C1 atom leading to enol–ketone isomerization. This water-assisted proton-transfer process can explain the experimentally observed incorporation of deuterium in the 1-position of the final product. Finally, the ring closure yields the coupled fructose (8a/8b) through TS4a/TS4b, with a relative energy barrier of 12.39/13.47 kcal/mol. In the water involved pathway, TS4 has the lowest barrier and has the optimal bond angle of hydrogen bonds which is about 169° for N–H…O and 111° for H…O–H. Any bond angles deviate from these optimal values will increase the reaction barriers as shown in TS1, TS2 and TS3. It should be noted in our study the whole isomerization reaction is thermodynamically unfavorable without water involved, with an overall energy increase of 2.17 kcal/mol. With the help of water, the whole reaction becomes thermodynamically favorable, and the reaction barrier of the rate-limiting step reduces, which is defined as the step with the highest activation barrier on the calculated PES. In the Bn-NH₂⁺/Bn-NH₂ catalyzed pathway, the rate-determining step is the first transition state where the six-membered ring is opened with a barrier of 21.12 kcal/mol. In the Bn-NH₂⁺/Bn-NH₂ catalyzed pathway, the rate-determining step is the second transition state where the hydrogen of water transfers to C1 of the six-membered ring with a barrier of 18.99 kcal/mol. More importantly, when combining Arrhenius relationship with Boltzmann distribution, the energetic span term in Bn-NH₂⁺/Bn-NH₂ catalyzed pathway is 30.68 kcal/mol which is 1.49 kcal/mol lower than Bn-NH₂⁺/Bn-NH₂ catalyzed pathway. This provides a direct connection with...
The reaction barrier for the whole reaction reduced by 2.13 kcal/mol with the help of water. The similar water assisted proton transfer phenomena were reported in inorganic phosphotungstic acid system and Au(I)-Catalyzed [1,2]-hydride shift process.\(^{[20]}\)

After uncovering the origin of rate acceleration of the glucose isomerization reaction in wet Bn-NH\(_3^+\), we then turned our attention to explain the experimentally observed deuterium incorporation.\(^{[19]}\) In the water involved proton-transport catalysis process, the incorporated atoms in the C1-position of HMF can be either from Bn-NH\(_3^+\) or from the water molecules.\(^{[20]}\) This can be understood by comparing the structure of 5a and 5b (Figure 2). For 5b, we try to put water at different site i.e. above C1=C2 plane or below C1=C2 plane and found the structure as shown in figure 2 has lowest reaction barrier. In 5a Ha is transferred from O1 to C1 and H1 is transferred from N1 to O1. In 5b Ha is transferred from N1 to C1. This means that, when the reaction was run in Bn-NH\(_3^+\) saturated with D\(_2\)O, the 1-position of the final enoles could be either hydrogen (from H of Bn-NH\(_3^+\)) or deuterium (from the D\(_2\)O catalyst). Our finding is consistent with experiment result. In DMSO/D\(_2\)O system, a massive quantity of deuterium was detected to be at C1 position in HMF through NMR (Figure 3).\(^{[19]}\) As shown in the above calculation, the water involved pathway shows the lowest energy barrier, which further confirmed that water could facilitate the proton transfer step. The water-assisted proton-transfer process is also in agreement with the experimentally observed incorporation of deuterium in the C1-position of HMF.\(^{[20]}\)

After glucose isomerization, the obtained fructose will proceed through triple dehydration in order to produce the final product HMF. The acid-catalyzed fructose dehydration has been studied by QM/MM\(^{[26]}\) and high level G4 methods.\(^{[27]}\) Here we will explore this dehydration process catalyzed by hydronium in water solvent environment. As shown in figure 3, the dehydration of fructose consists of three cycles of dehydration which can be further divided into three steps: 1) protonation 2) dehydration and 3) deprotonation. As shown in Figure 3, the reaction starts from initial protonation on O1H group, exothermic by 0.7 kcal/mol. After protonation, the hydroxyl group becomes an easy leaving group and leads to the oxonium ion. The first cycle ends with the deprotonation of 10 and formation of intermediate 11, uphill by 11.7 kcal/mol. The second cycle begins with protonation on either O2H or O3H group. The computational results shows protonation on O2H group is 2.6 kcal/mol energetically more favorable its counterpart. The subsequent removal of water is exothermic by 13.1 kcal/mol (from 12 to 13). Deprotonation of 13 results in the key intermediate 14, which is 2.6 kcal/mol uphill from fructose. This 4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde (14) is identified by combination of \(^1\)H NMR and \(^13\)C NMR data in the presence of dimethyl sulfoxide as a catalyst.\(^{[28]}\) The third protonation is enhanced by the special conjugated double bond system in 14, with an energy increasing of 0.5 kcal/mol (from 14 to 15). Following an exothermic dehydration and deprotonation, HMF (17) is formed with an overall energy of -15.2 kcal/mol. The reaction becomes less reversible after the dehydration finished. As shown in the above discussion, in TS3b water offer one hydrogen to C1 and at the same time get another hydrogen from BnNH\(_3^+\). In DMSO/D\(_2\)O system, deuterium will be transferred to C1, this consistent with experiment in which a massive quantity of deuterium was detected to be at C1 position in HMF through NMR (as shown in the lower right of Figure 3).\(^{[19]}\)

Lastly, it is important to make a note on the byproduct, levoglucosenone. Zhang et al observed that the levoglucosenone concentration on this reaction decreased as the water concentration increased, and finally vanished when water concentration exceeded 10 vol\%.\(^{[19]}\) In Hayashi’s work, the conversion of glucose to the levoglucosenone was demonstrated to be the rate-controlling step and determined the yield of levoglucosenone.\(^{[28]}\) The dehydration process of glucose into...
levoglucosenone is investigated from calculations as presented in the Figure 1S. With water’s involvement in the dehydration, the reaction exhibits more endothermic, from 6.98 (without water) to 8.41 kcal/mol (with water), the latter is about 4 times of that of dehydration into fructose (2.17 kcal/mol). Water’s effect also increases the energy barrier from 33.28 (without water) to 36.46 kcal/mol (with water), as compared to the barrier with almost half value, 18.99 kcal/mol of the rate limiting step in the water assisted main reaction. Furthermore, the excess of water also accelerate the reverse reaction rate in the dehydration process, leading the decrease of levoglucosenone. Thus, when adding more water, the side reaction will be significantly suppressed in this system.

Conclusions

In summary, we unravel the peculiar role of water played in the mechanism of ammonium polymer (BnNH3Cl) catalyzed isomerization and dehydration by first principle calculations. First of all, Bn-NH2/Bn-NH3+ is studied as the catalytic related species where Bn-NH2 is proton acceptor while Bn-NH3+ is proton donor. Second, the role of water in glucose isomerization into fructose is discussed. We found that the water molecule, which acts as a proton shuttle in the proton-transfer process, is critical to the rate acceleration of the glucose isomerization reaction in wet BnNH3Cl. Water is found to both facilitate the proton transfer process in the main reaction, and block the side reaction. The involvement of water in the reaction is also proved by 1H NMR experiment. These studies are expected to bring new insight into many other in water reactions involving proton transfer processes.180

Experimental Section

Computational Methods

All computations have been conducted using MO62X(d,p) density functional implemented in Gaussian09 programs. Geometric optimization and energy calculations have been performed at 6-311G(d,p) basis set for all atoms in water solvent using the Polarizable Continuum Model (PCM) 197. PCM using the integral equation formalism variant (so-called IEPCM) was initially devised by Tomasi and coworkers179 and Pasquale-Ahui and coworkers.198 This method creates the solute cavity via a set of overlapping spheres. Free energies have been computed at 298.15 K and 1 atm. All reactants and intermediates have had no imaginary vibrational frequency while only one imaginary frequency has been detected for each transition state. Additionally, intrinsic reaction coordinate calculations have been executed to guarantee the accuracy of transition states.

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Water plays a substantial role, functioning as a proton shuttle to promote the conversion of glucose-fructose isomerization, reduce the energy of the transition state, resulting in the acceleration in the reaction.

Layout 2:

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