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Free Energy Surface for Brønsted Acid-Catalyzed Glucose Ring-Opening in Aqueous Solution

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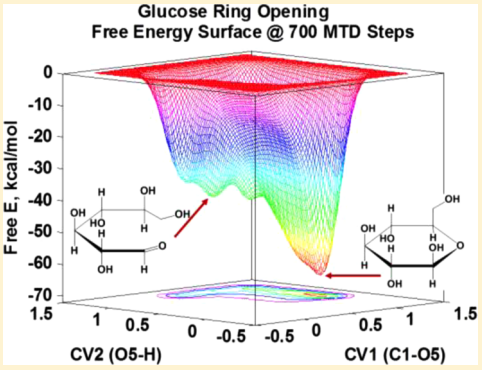
ABSTRACT: Car−Parrinello-based molecular dynamics coupled with metadynamics simulations were used to determine the mechanism and associated free energy surface for opening the ring structure of cyclic glucopyranose in acidic aqueous solutions. The ring-opening process is initiated by the protonation of the ring oxygen atom and the breakage of the C1−O5 bond. The barrier for this process is about 25 kcal/mol, in good agreement with experimental measurements. Moreover, the glucose cyclic conformation is found to be more stable than the open chain form. The barrier for proton-catalyzed ring-opening in aqueous solution appears to be largely solvent induced due to the high affinity of water molecules for protons.

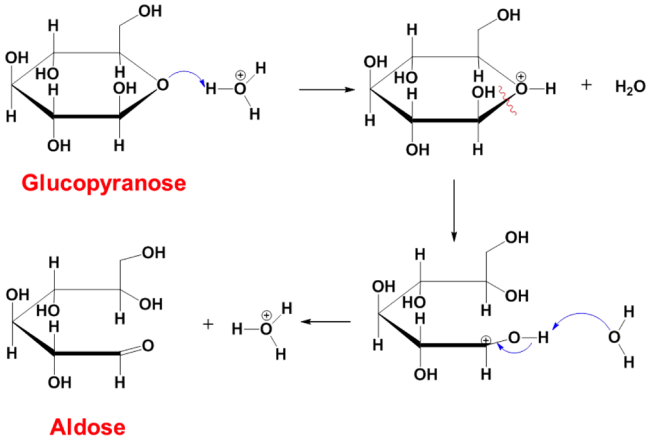


1. INTRODUCTION

D-Glucose is the critical monomeric sugar from cellulose hydrolysis to produce biofuels and other biobased products during lignocellulosic biomass conversion via enzymatic hydrolysis or liquid phase chemical processing.[1] Of the many glucose conformers, the cyclic six-member glucopyranose ring conformers are the most abundant, existing either as α- or β-anomer depending on the position of C1-OH with respect to C2-OH.[2,3] The other conformers such as cyclic five-member ring glucofuranose are not frequently observed.[2] Because the difference in energies between the α- and β-anomer is small typically less than a few kcal/mol,[2,4] both conformers coexist in many commonly used solvents such as water, dimethyl sulfoxide (DMSO), or ionic liquids (ILs). For example, over 99% of glucose in water at room temperature exists either as β- or α-anomer with their ratio almost at 2:1. The aldose or ketose open chain forms are estimated to exist only about 0.0026% in water.[2] However, it appears that α-anomer is more predominant in DMSO and IL solvents.[5] Experimental[6] and theoretical studies involving both classical molecular dynamics (MD)[7−9] and ab initio MD simulations[10,11] were conducted previously to investigate the hydration conformation of glucose in water. Glucose hydration appears to be rather complex in particular with respect to the C6-OH and ring oxygen atom.

The mutarotation between α- and β-anomers catalyzed by water or the hydronium ion is thought to occur generally via the protonation of the ring O5 and the opening of the ring structure, followed by the rotation of the C1 atom and the re-formation of the ring structure.[2,4] Experimentally it was estimated that the barrier for mutarotation is at around 22 kcal/mol.[12] The mechanism for proton-catalyzed glucose ring-opening process is shown in Scheme 1. Our previous studies show that BrØnsted acid-catalyzed mutarotation between the α- and β-anomers could also occur directly without opening the glucose ring structure.[4] Protonation of C1-OH and the subsequent breakage of the C1−O1 bond leads to the formation of an oxocarbenium ion. Depending on the position of the nucleophilic attack of the C1 carbocation by water from above or below the ring structure, either an α- or a β-anomer is generated. The barrier for this process is slightly higher at around 28 kcal/mol in an acidic solution.[4]

Scheme 1. Glucose Ring-Opening Mechanism in Aqueous Acidic Solution[a]



[a]Glucose ring-opening is initiated by the protonation of the ring O5 and subsequent breakage of the C1−O5 ether bond, leading to the eventual formation of an open chain aldehyde.

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Currently, there is considerable debate in the literature regarding whether the ring-opening process is the first step for glucose isomerization to other sugar molecules[13,14] or conversion to 5-hydroxymethylfurfural (HMF),[3,15] a critical intermediate during biomass conversion. The ring-opening process was considered by some[14,16] to be a barrierless process and is the first step leading to a variety of products from glucose reactions. Our recent results[13,15,17−20] show that glucose isomerization to fructose and dehydration to HMF do not follow the ring-opening step. Instead a direct transformation from a six-member ring structure to five-member ring conformation was observed. To elucidate the mechanisms of proton-catalyzed glucose reactions, theoretical calculations were performed in this work to investigate the glucose ring-opening process using Car−Parrinello[21] molecular dynamics (CPMD)[22] coupled with metadynamics (MTD)[22−24] simulations to determine its associated free energy surface (FES). Elucidating glucose reaction mechanism(s) will provide insight and understanding to the biomass conversions and is valuable for optimizing these highly complex processes.

CPMD-MTD simulations have been used extensively in our previous investigations to map out the free energy surfaces[3,4,13,15,25] for xylose and glucose condensation reactions, glucose to HMF dehydration, and glucose to fructose isomerization reactions. The rate-limiting steps and associated barriers were determined for these reactions. In addition, it was found that solvent plays a critical role in all of these reactions, and the barriers are largely solvent induced. Here CPMD-MTD simulations are used to investigate the FES for the glucose ring-opening process in the presence of explicit solvent water molecules.

2. COMPUTATIONAL METHODS

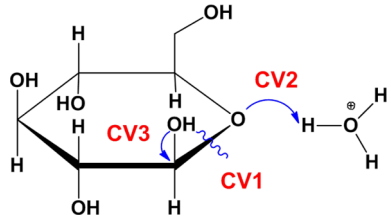
CPMD-MTD simulations have been used successfully to investigate the mechanisms for the condensation, dehydration, and isomerization reaction of xylose and glucose monomeric sugars. CPMD-MTD allows for efficient sampling of chemical reactions involving bond breaking and bond formation processes in the accelerated time scale of typically less than several nanoseconds (ns) by filling the potential wells with repulsive bias potentials.[23,24] The bias potential is added to the reactant and product wells to facilitate barrier crossing. Once the reactant well is filled close enough to the reaction barrier, the system crosses the barrier and moves to the product well. When the product well is also filled, the FES becomes flat and the system can move back and forth without any barrier. The FES is subsequently reconstructed based on the amount of bias potentials added. This method assumes that several collective variables (CV), which distinguish reactants from products, are able to characterize the reaction process. Our previous studies[4,25,26] showed that CVs using coordination numbers (CN) are effective for exploring sugar reaction processes. The equation of CN[27] is given by

$$\mathrm{CN(i,j)} = \frac{1 - \left(\frac{d_{ij}}{d_0}\right)^p}{1 - \left(\frac{d_{ij}}{d_0}\right)^q}$$

where d_{ij} is the distance between atoms i and j, d_0 is the cutoff distance, and p and q are high-power integers used to distinguish between the coordinated and noncoordinated states. The values $p = 6$ and $q = 12$ are typically chosen for calculating the CNs. The choice for the cutoff distance d_0 depends on the specific bond. For C−O and O−H bonds, values of 2.0 Å and 1.5 Å are usually chosen for d_0, respectively, as is done here and previously in our work.[4,13,15,25]

As mentioned, the mechanism for proton-catalyzed glucose ring-opening process is shown in Scheme 1. A hydronium ion transfers a proton to the ring O5 followed by the breakage of the C1−O5 bond. A neighboring water molecule takes away the proton from $HC1^+$−OH forming a CH═O aldehyde. Thus a cyclic glucopyranose ring structure is transformed into an open chain aldose conformation. Three CVs were used to describe this reaction process as shown in Scheme 2. CV1 is the CN between the O5 and C1 representing the breakage and formation of the C1−O5 bond. CV2 is the CN between O5 and H representing the breakage and formation of the O5−H bond. CV3 is the CN between C1 and O1 representing the formation of an aldehyde C═O double bond from the initial C1−OH single bond during the glucose ring-opening process.

Scheme 2. Three CVs Used To Describe the Ring-Opening Process during CPMD-MTD Simulations[a]



[a]CV1 and CV2 represent the bond breakage/formation processes for C1−O5 and O5−H, respectively. CV3 describes the aldehyde formation process at C1-OH.

The dynamics of the CVs are controlled by the force constant k and fictitious mass m. The values of k = 2.0 au and m = 100 amu were used for all three CVs here. The bias potential used here is a commonly used Gaussian functional. The height and the width of the Gaussian bias potential were chosen to be 0.002 au and 0.100 au, respectively, for all the simulations. The bias potentials were added whenever the displacements in the CVs were larger than 1.5 times the width, but no shorter than 100 MD steps. Studies have shown that this choice of parameters is efficient with uncertainty in the range of 1−2 kcal/mol.[28] More details on the method applied to sugar reactions could be found in our previous work.[3,4,13,15,25,26]

The simulations were conducted using the Becke,[29] Lee, Yang, and Parr (BLYP)[30] functional for the valence and semicore electrons. Goedecker[31] pseudopotential was used for the core electrons. The energy cutoff of 80 Ry was used for the plane wave basis set. The combinations of these parameters have yielded excellent structural properties as well as energetics and reactivity for sugar molecules.[32,33] The simulations were conducted under a canonical (NVT) ensemble at 300 K with a Nosé-Hoover chain thermostat. To effectively separate the fast motions of the electrons from the slow movement of the nuclei, a fictitious mass of 800 amu and a time step of 0.125 fs (fs) were used. The system contains one glucose molecule, 76 water molecules, one proton initially attached to the ring O, and one Cl^- counterion. The simulation unit cell has a dimension of 14.4 × 14.4 × 14.4 $Å^3$ and a corresponding density of 0.92 g/cm^3. Periodic boundary conditions were applied. Ewald

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summation[34] was used to integrate the long-range electrostatic interaction energies.

3. RESULTS AND DISCUSSION

The CPMD-MTD simulations started with one proton attached to the ring O5 of the cyclic β-D-glucopyranose. The simulations were conducted for a total of over 1100 MTD steps. Figure 1 shows the variations of the three CVs during

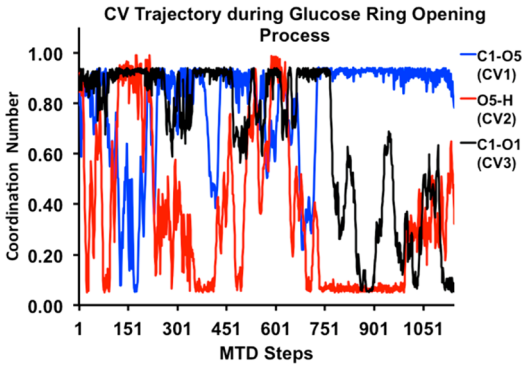

Figure 1. The variations of the three CVs in coordination numbers representing the C1−O5 (CV1), O5−H (CV2), and C1−O1 (CV3) bonds, respectively, during the sampling of glucose ring-opening process for a total of just over 1100 MTD simulation steps.

these simulation steps. The values of all three CVs are set between 0.04 and 0.95. A CV value close to the lower limit indicates bond breakage whereas a CV value close to the higher limit indicates bond formation. However, the difference between singly and doubly bonded states is small in terms of the CV values. The closer the CV3 to 0.95, the stronger the C1−O1 bond.

The proton is initially attached to the ring oxygen atom on the β-D-glucose molecule. However, the proton is quickly transferred to a neighboring water molecule. During the subsequent 100 MTD simulation steps, the proton transfers back and forth between the ring oxygen atom and the nearest water molecule. At around 110 MTD simulation steps, the proton is firmly attached to the ring oxygen atom and the C1−O5 bond dissociates completely. The value of CV3 reaches 0.95, indicating the formation of a double bond between the C1 and O1 atoms. The cyclic glucopyranose ring structure has been transformed into an open chain form. For the subsequent 120 MTD simulation steps, the glucose molecule remains in the open chain aldehyde form. CV3 remains at the maximum value of 0.95, indicating the formation of the C1H═O1 aldehyde group. At around 230 MTD steps, the proton starts to transfer back to the neighboring water molecule and the broken C1−O5 bond forms again. The glucose molecule is transformed back into the cyclic ring conformation. The C1═O1 double bond again becomes a single bond. From 230 to 425 MTD steps, the proton is seen to associate largely with the water molecules in the vicinity of the ring O5. Starting from 425 MTD step, the proton is again seen to transfer back and forth between the water molecules and the ring oxygen atom. CV1 and CV3 show more substantial variations as well. At around 650 MTD steps, the proton moves away from the ring oxygen and is seen to attach to the neighboring hydroxyl group O1H on the glucose molecule. At around 770 MTD steps, the protonated O1H departs from the ring structure and breaks the C1−O1 bond. The glucose molecule transforms into an oxocarbenium ion, a C1 carbocation, retaining the cyclic ring conformation for the next 300 MTD simulation steps. However, at the end of the over 1100 MTD simulation steps, another water molecule attacks the C1 carbocation transforming the β-D-glucose into an α-D-glucose. This transformation between β-D-glucose and α-D-glucose via the C1-carbocation has been observed and studied previously in acidic aqueous solutions.[4]

During the sampling process, an intramolecular hydrogen bond between C6-OH and the ring O5 was occasionally observed in particular when the proton moves away from the ring oxygen atom. The importance of this intramolecular hydrogen bonding interaction to the conformational stability of the glucose molecule has been investigated previously.[9] The hydrogen bonding interaction between C6-OH and O5 may also contribute to the stability of the cyclic form. This will have some contribution to the barrier for protonation of the ring oxygen atom and the subsequent ring-opening process. The exact contribution from the primary alcohol is not quantifiable here. The contribution from the primary alcohol to the barrier for ring-opening is not likely to be substantial because the strength of hydrogen bonding interaction is only a few kcal/mol. However, it is possible to quantify its contribution in future work by investigating the xylose ring-opening process where the primary alcohol is absent. Further, stereoelectronic effects[9] were also found to play an important role in glucose conformational stability. However, during the sampling of the proton-catalyzed glucose ring-opening process, the glucose molecule adopts a variety of conformations besides the chair conformation. From the FES reconstructed and discussed later, the barrier for glucose ring-opening process is largely solvent induced. It is likely that stereoelectronic effects have only limited influence on the barrier for the glucose ring-opening process.

The free energy surfaces are reconstructed at three different simulation periods based on the cycles of transformation between the cyclic glucopyranose and open chain aldehyde conformations either excluding or including the sampling of protonated water clusters during the ring-opening process. The three simulation periods are chosen to understand the effects of solvent water on the FES of glucose ring-opening process. The initial FES reconstructed is based on the bias potentials added for the first 230 MTD steps describing the first cycle from the cyclic to open chain and back to the cyclic conformational changes without the extensive sampling of protonated water clusters. Two more FESs are reconstructed based on bias potentials added for the first 425 and 700 MTD simulation steps, respectively, with additional samplings of the cyclic as well as the open chain conformations including the sampling of the protonated water clusters. The FES reconstructed for the first 425 MTD steps includes substantial sampling of the states when the proton has been transferred to the neighboring water molecules. Finally, the more accurate FES involves 700 MTD steps with additional sampling of the cyclic and open chain forms just before the proton is transferred to the neighboring C1-OH. Because CV3, describing the state of the C1−O1 bond, does not appear to be involved in the rate-limiting step during the glucose ring-opening process, the FESs are reconstructed based on the bias potentials added between CV1 and CV2, only mapping the FES of the critical protonation of the ring O5 and the breakage of the C1−O5 bond step.

Figure 2 is the 2-D free energy contour plot based on the first 230 MTD steps, respectively. As shown, the initial cyclic

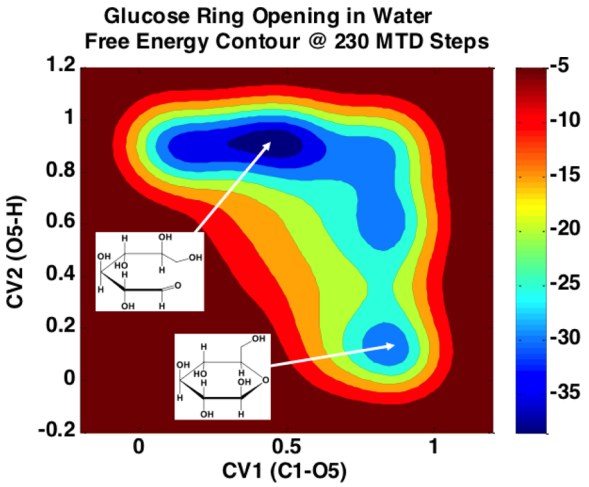

Figure 2. The 2-D free energy contour plot between CV1 and CV2, describing the glucose ring-opening process during the initial 230 MTD sampling steps. CV1 and CV2 represent the C1−O5 and O5−H bonds, respectively.

glucopyranose structure is located at around CV1 = 0.85 and CV2 = 0.10. There is an activation energy of about 5 kcal/mol for the partial protonation of the ring O5. An additional barrier of 2−3 kcal/mol is needed for the complete transfer of the proton to the ring O. Once the proton is firmly attached to the ring O5, the breakage of the C1−O5 bond appears to be spontaneous with very little or no barrier at all. It also appears that the open chain aldehyde conformation is more stable than the cyclic conformation during the first 230 MTD sampling. This result actually agrees with other static quantum mechanical calculations in vacuum that the ring-opening process is a low barrier or barrierless process in the absence of solvent.[16] Perhaps that is the reason why several proposed mechanisms in literature assume that the first step for glucose reactions is the opening of the ring structure. However, our previous CPMD-MTD simulations show that the protonation of the hydroxyl groups is critically involved in the rate-limiting step(s) for the sugar condensation, isomerization, and dehydration reactions due to the competition for protons from the solvent water molecules. The activation energies for these proton-catalyzed sugar reactions are found to arise largely from the presence of solvent water molecules due to their relative high affinity for proton. It is important to point out that the sampling process in the current study starts when a proton is already attached to the ring O5. Moreover, the majority of the sampling steps involving a proton's association with the neighboring water molecules are not included in the reconstructed FES based on the first 230 MTD steps. During the first 230 MTD simulations, the proton is interacting with one H_2O molecule close to the ring O5 only. Therefore, the bias potentials added during the subsequent CPMD-MTD samplings have to be included in reconstructing the FES to include the free energy contribution from the neighboring water clusters. Indeed it is shown that the free energy landscape changes dramatically when the sampling of the neighboring water molecules is included.

Figure 3 shows the 2-D free energy contour plot for the FES reconstructed from the first 425 MTD simulation steps. The

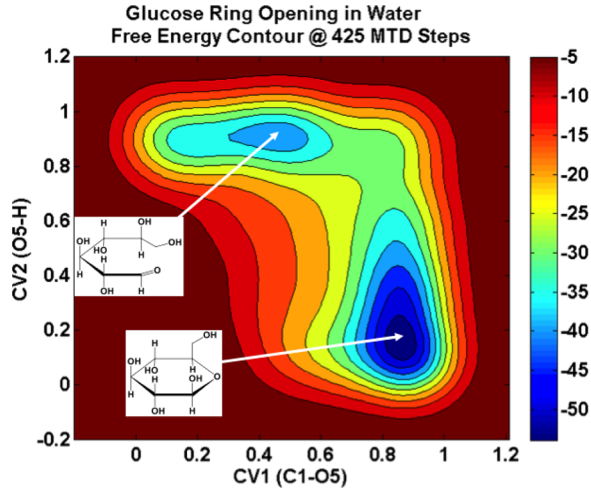

Figure 3. The 2-D free energy contour plot for the glucose ring-opening process during 425 MTD sampling steps. CV1 and CV2 represent the C1−O5 and O5−H bonds, respectively.

free energy landscape has been significantly altered by including 195 more MTD simulation steps. These additional MTD steps involve sampling the protonated water molecules around the ring O5 before the proton starts to transfer back to the ring O5. As discussed in our previous work,[4,25] protons associated with water clusters, forming an extensive hydrogen bonding network, tend to stabilize the protons and lower their free energy. The barrier for protonation of the ring O5 increases to about 25 kcal/mol due to the stability of the protonated water structures surrounding the ring O5. This activation energy agrees very well with the barrier for mutarotation between α-D- and β-D-glucose molecules, during which the ring-opening process is known to be critical. This significant increase in activation energy for protonation of the ring O5 is largely due to the presence of solvent water molecules and their high affinity for proton in agreement with our previous observations. Moreover, the free energy associated with glucose cyclic conformation becomes significantly lower than that for the open chain aldose, as clearly shown in Figure 3. The free energy for the cyclic conformation is about 15 kcal/mol lower than that for the open chain form. This indicates that the water molecules stabilize the glucose ring structure. This is perhaps the reason why the open chain form is hardly detectable in water.

At around 425 MTD steps, the proton starts to transfer back to the ring O on the cyclic glucopyranose. The 2-D free energy contour plot reconstructed based on the first 700 MTD steps is shown in Figure 4. The sampling period during these additional 275 MTD simulation steps includes the proton's transfer back and forth between the ring O5 and the neighboring water molecules as well as the open chain aldose conformation when the proton is firmly attached to the ring O5. The sampling ends when the proton is transferred to the neighboring C1-OH at around 700 MTD steps. All the peaks and valleys on the free energy landscape are deepened compared to the FES constructed from the first 425 MTD steps. However, the free energy difference between cyclic conformation and the open chain form remains more or less the same at around 15 kcal/mol even though the overall appearance looks quite different due to the enhanced sampling of the other regions on the FES. The barrier for protonation of the ring O and breakage of the C1−O5 bond remains at 25 kcal/mol. The sampling with 700

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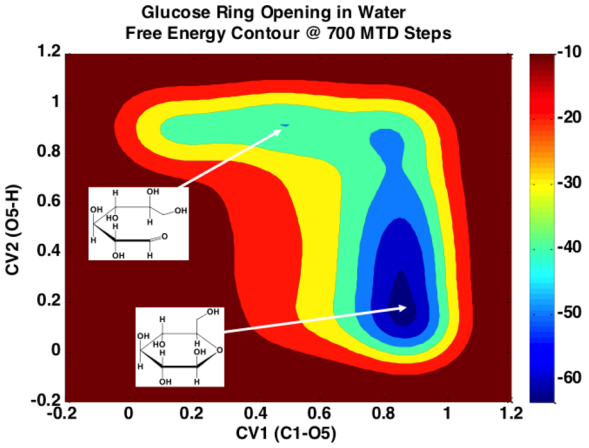

Figure 4. The free energy surface contour plot for the glucose ring-opening process during all 700 MTD sampling steps. CV1 and CV2 represent the C1−O5 and O5−H bonds, respectively.

MTD steps appears to be complete. Additional sampling only involves the protonation of the C1-OH, the breakage of the C1−O1 bond, and the eventual re-formation of an α-D-glucose.

The free energy landscape for the proton-catalyzed glucose ring-opening process in aqueous solution has been mapped out using combined CPMD-MTD simulations. Protonation of the ring oxygen atom is the rate-limiting step due to the water molecule's high affinity for protons. The protonated water cluster is highly stable due to the extensive hydrogen-bonding network formed and the high mobility of the proton in the protonated water cluster. The proton's high mobility in water is due to the barrierless transfer process assisted by the extensive hydrogen bonding interactions. The high mobility translates into high entropy and therefore low free energy.

As mentioned previously, it is still controversial concerning whether ring-opening is the first step for glucose isomerization and dehydration reactions. Previously, Harris and Feather[35−37] proposed an open chain mechanism for xylose conversion to furfural. A similar mechanism for glucose isomerization to fructose and dehydration to HMF was proposed.[14,38] The reaction is initiated by the opening of the glucopyranose ring to form an open chain aldose structure. The aldose is transformed into a ketose structure via a hydride 1,2 shift from the C2 to the C1 atom. Subsequently, a five-member fructofuranose ring structure is re-formed. Dehydration by losing three water molecules will lead to the formation of HMF. On the basis of this proposed mechanism, many experimentalists[5,14,38] working on biomass conversion to biofuels consider fructose a necessary intermediate for glucose conversion to HMF. In addition, theoretical calculations[16] based on static Gaussian code[39] performed often in the absence of explicit solvent water molecules show that opening the ring structure by protonation of the ring O5 is a barrierless process, even energetically favorable. It seems that opening of the glucose ring is not the critical or the rate-limiting step in glucose reactions or transformations. So far, experimental evidence supporting fructose as an intermediate comes from NMR spectroscopy showing a hydride 1,2 shift.[38]

Our results clearly indicate that the ring-opening step is not a barrierless process, rather a barrier of about 25 kcal/mol in aqueous solution needs to be overcome before forming the open chain conformation. Moreover, an amount of existing experimental evidence[5,16,18,40,41] does not support fructose as the necessary intermediate for glucose to HMF conversion. For example, many existing experimental measurements[5,14,16,18,42] show that fructose is not detectable or exists only in very low concentration during glucose conversion to HMF. Our previous theoretical results[3,4,13,15,17,18,20,25] show that protonation of C2-OH and the subsequent breakage of the C2−O2 bond and the formation of the C2−O5 bond is the critical step during glucose to HMF transformation for proton-catalyzed conversion. A five-member furan aldehyde formed is an intermediate for HMF formation by losing additional two water molecules. The barrier[3,13,15] for the protonation, the breakage of C2−O2 and the formation of C2−O5 is about 35 kcal/mol in excellent agreement with experimental measurement. Our direct cyclic mechanism without opening the ring structure is supported by previous experimental results for xylose by Antal and co-workers.[43]

In addition, our theoretical results[13] show that the C1 carbocation on the cyclic five-member ring intermediate during glucose to HMF conversion is also the intermediate for glucose to fructose isomerization. The hydride transfer from C2 to C1 transforms the primary C1 carbocation to the tertiary C2 carbocation, stabilizing the positively charged intermediate. A neighboring water molecule attacks the tertiary C2 carbocation to form the fructofuranose sugar molecule. Our mechanism could reconcile the existing experimental evidence for Brønsted-acid-catalyzed glucose to HMF and to fructose conversion.

4. CONCLUSIONS

Our current CPMD-MTD simulations clearly demonstrate that solvent water plays a critical role in the glucose ring-opening process during the interconversion between a cyclic conformation and an open chain aldose structure. It is found that the cyclic conformation is much more stable than the open chain form in agreement with experimental measurement. Moreover, protonation is found to be the rate-limiting step for the ring-opening process. The barrier for protonation of the ring oxygen atom is found to be at around 25 kcal/mol in excellent agreement with glucose mutarotation experiments. The barrier arises from the high affinity for proton by the solvent water molecules.

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Notes

The authors declare no competing financial interest.

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