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Free energy landscape for glucose condensation and dehydration reactions in dimethyl sulfoxide and the effects of solvent

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ABSTRACT

The mechanisms and free energy surfaces (FES) for the initial critical steps during proton-catalyzed glucose condensation and dehydration reactions were elucidated in dimethyl sulfoxide (DMSO) using Car–Parrinello molecular dynamics (CPMD) coupled with metadynamics (MTD) simulations. Glucose condensation reaction is initiated by protonation of C1—OH whereas dehydration reaction is initiated by protonation of C2—OH. The mechanisms in DMSO are similar to those in aqueous solution. The DMSO molecules closest to the C1—OH or C2—OH on glucose are directly involved in the reactions and act as proton acceptors during the process. However, the energy barriers are strongly solvent dependent. Moreover, polarization from the long-range electrostatic interaction affects the mechanisms and energetics of glucose reactions. Experimental measurements conducted in various DMSO/Water mixtures also show that energy barriers are solvent dependent in agreement with our theoretical results.

1. Introduction

Glucose is the most important and abundant monomeric sugar on earth. Elucidating glucose transformations and reactions is critical to our understanding and manipulation of this vital molecule. Our earlier theoretical studies[1–9] and experimental results[1,10–13] show that proton catalyzed glucose reactions are generally not selective due to multiple protonation sites on the glucose molecule leading to multiple reaction pathways. Protonation of the O5 on the glucose ring leads to the mutarotation between α- and β-glucose. Protonation of the C1—OH on glucose leads to the formation of an oxocarbenium carbocation and the eventual 1, x ($x = 2, 3, 4, 6$) linked oligosaccharides from condensation reactions. Protonation of C2—OH on glucose leads to the formation of 5-hydroxylmethylfurfural (HMF) from dehydration reaction as well as isomerization reaction to fructose. In addition, our earlier results[1–9] indicate that protonation of the ring O or the hydroxyl groups on the glucose molecule and the subsequent breakage of the C—O bond is the rate-limiting step. Moreover, it was found that glucose reactions are strongly solvent dependent due to the competition for proton from the solvent molecules. The reaction barriers are largely solvent induced. Our earlier studies focused on the glucose mutarotation,[14] condensation,[6] isomerization[9] and dehydration[7] reactions in aqueous solutions. Here the critical initial steps during glucose condensation and dehydration reactions in dimethyl sulfoxide (DMSO) are investigated.

Car-Parrinello[15] based ab initio molecular dynamics (CPMD)[16] coupled with metadynamics (MTD)[17] simulations have been successful in elucidating the mechanisms, the rate-limiting steps, and associated barriers as well as free energy surfaces (FES) for glucose reactions in aqueous solutions.[6,7,9,14] For example, excellent agreement was obtained between the calculated and experimental barriers for glucose mutarotation,[14] condensation,[5,6] isomerization[9], and dehydration[7] reactions. Here CPMD–MTD simulations for glucose condensation and dehydration reactions in DMSO solvent medium are conducted to gain insights into the effects of solvent on the mechanisms and barriers for glucose reactions. Moreover, atomic charges of the glucose molecule in the gas phase as well as in H_2O and DMSO solvents were calculated using both Gaussian09[18] and CPMD in order to gain deep insight into the solvent effects on glucose reactivity.

In order to validate our theoretical results, experiments were also conducted for glucose reactions in pure DMSO and several DMSO/Water mixtures at temperatures ranging from 120 °C (393 K) to 140 °C (413 K). The concentrations of glucose, major reaction products, and their time dependence were determined using Nuclear Magnetic Resonance (NMR). Moreover, activation energy barriers in the solvent mixtures for glucose degradation, its dehydration to 1,6-anhydro-β-D-glucopyranose (levoglucosan) and HMF were determined and compared with theoretical results.

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2. Computational details

CPMD–MTD allows for efficient and accelerated sampling of chemical and biological processes for free energy calculations, particularly for chemical reactions involving the bond-breaking and bond-forming processes in the time scale not accessible by the conventional methods. The acceleration of the sampling process is achieved by filling the reactant and product wells with repulsive bias potentials[17,19] to facilitate barrier crossing. Once the reactant well is filled with potentials close enough to the reaction barrier, the system overcomes the barrier and moves to the product well. When the product well is also filled and the FES becomes flat, the system is able to sample the reactant and product states randomly without any barrier. The original FES of the system is subsequently reconstructed based on the amount of bias potentials added to reach the flat FES state. This method assumes that several collective variables (CV), which distinguish the initial state from the final state, are able to characterize the slow, rate-limiting steps.

The left panel in Figure 1 shows the CVs for the critical steps during glucose condensation (left panel) and dehydration (right panel) reactions. Our previous results[6] for glucose condensation reaction in aqueous solution show that the rate-limiting step involves the protonation of C1—OH and the breakage of the C1—O1 bond. The C1 carbocation formed and subsequently the more stable oxocarbenium ion are the critical intermediates for various 1, x ($x = 2,3,4,6$) linked disaccharides. For glucose condensation reaction in DMSO, a similar mechanism is assumed. As a result, CVs for the first steps in glucose condensation reaction comprise protonation of C1—OH (CV2) and breakage of C1—O1 bond (CV1). In addition, our earlier studies[5,6] in aqueous solution also show that partial dehydration due to the migration of the hydronium ion to the neighborhood of the sugar molecule also contribute substantially to the barrier for condensation reaction.

Three CVs are needed for the critical steps during glucose dehydration to form a cyclic HMF intermediate in aqueous solution as shown in the right panel of Figure 1. Glucose dehydration reaction is initiated by the protonation of C2—OH, the breakage of the C2—O2 bond, and the formation of C2—O5 bond leading to the formation of a five-member aldehyde ring intermediate.[7] However, our previous results[7] show that proton partial dehydration does not contribute to the barrier for glucose dehydration reaction in aqueous solution since the barrier of 30–35 kcal/mol is dominated by protonation followed by the breakage of the C2—O2 bond only. Once a C2-carbocation is formed, the formation of C2—O5 bond appears to be spontaneous without any barrier. In this study, an analogous mechanism for glucose dehydration to HMF in DMSO was investigated. However, it does not exclude the possible existence of an alternative reaction pathway in DMSO. Similar to aqueous solution, three CVs are adopted for proton-catalyzed glucose dehydration to HMF in DMSO. These three CVs comprise protonation of C2—OH (CV3), the breakage of the C2—O2 bond (CV1), and the formation of C2—O5 bond (CV2).

Our earlier studies[5–9,20] showed that CVs using coordination numbers (CN) are effective for exploring sugar reaction processes. The equation of CN[19] is given by

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

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 non-coordinated 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 and 1.5 Å are usually chosen for d_0 respectively as is done here and previously in our work.[5–7,9]

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 the CVs here. The bias potential chosen is a commonly used Gaussian functional. The height and the width of the Gaussian bias potential were chosen to be 0.001 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.[21] More details on the method applied to sugar reactions could be found in our earlier work.[5–9,20]

The simulations were conducted using the Becke,[22] Lee, Yang, and Parr (BLYP)[23] functional for the valence and semi-core electrons. Goedecker[24] pseudopotential was used for the core electrons. The energy cut-off of 80 Ry was used for the plane wave basis set. The combinations of these parameters have found to yield excellent structural properties as well as energetics and reactivity for sugar molecules.[25,26] The simulations were conducted under constant volume and constant temperature (NVT) with a Nosé–Hoover chain thermostat.[27,28] The temperature was kept at 27 °C (300 K) for the condensation reaction initiated by the protonation of C1—OH and at 227 °C (500 K)for the dehydration reaction initiated by the protonation of C2—OH. To effectively separate the fast motions of the electrons from the slow movement of the nuclei, a

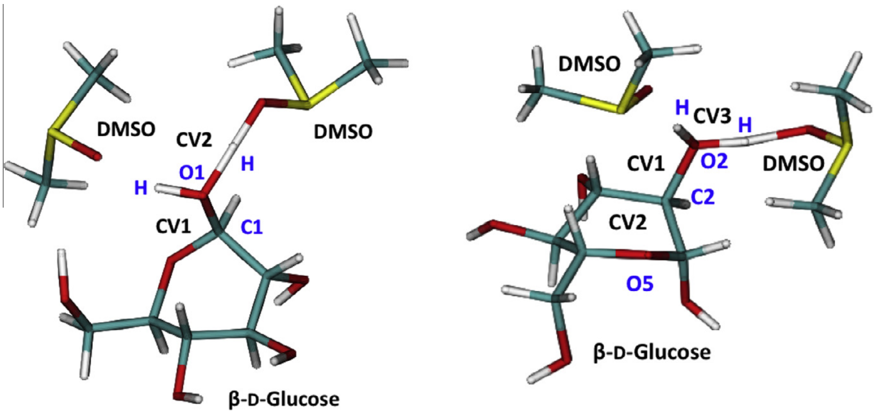

Figure 1. The collective variables (CVs) for critical steps during glucose condensation reaction are shown in the left panel with CV1 representing C1—O1 bond and CV2 representing O1—H bond. CVs for critical steps during glucose dehydration reaction are shown in the right panel with CV1 representing C2—O2 bond, CV2 representing C2—O5 bond and CV3 representing O2—H bond.