



# The mechanism for cleavage of three typical glucosidic bonds induced by hydroxyl free radical



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## ABSTRACT

A novel mechanism for cleavage of three typical  $\alpha(1 \rightarrow 2)$ ,  $\alpha(1 \rightarrow 4)$  and  $\beta(1 \rightarrow 4)$  glucosidic bonds induced by hydroxyl free radical was examined with DFT theory at B3LYP/6–31 + G(d,p) level using PCM water solvent model. It was found that the hydrogen abstraction from the C–H bonds outside the saccharide rings could induce the hydrogen transfer from the hydroxyl at the radical carbon to the oxygen atom of saccharide ring with the mediation of water, which led to the opening of saccharide ring and the breakage of glucosidic bonds. Alternatively, the hydrogen in  $\cdot\text{C}-\text{OH}$  outside the saccharide ring of maltose and sucrose could also transfer to the adjacent glucosidic oxygen atom with a water molecule mediation to make glucosidic bond break directly. Based on this study, it can be well explained the experimental results that the oxidation of some oligosaccharides with hydroxyl free radicals can produce molecules of glucose, fructose and other monosaccharides.

## 1. Introduction

Starch, cellulose and fructosan are important natural polysaccharides in nature. Starch and fructosan can be depolymerized *in vivo* into oligosaccharides and monosaccharides so as to be utilized by organisms (Dhital, Warren, Butterworth, Ellis, & Gidley, 2017; Koropatkin, Cameron, & Martens, 2012) while cellulose works as important components to form the structure and skeleton of living organisms (especially plants) (Meyers, Chen, Lin, & Seki, 2008). These polysaccharides are commonly depolymerized (Singh et al., 2016) by reactive oxygen species (ROS) which may lead to the aging of paper and wood (Ibn Yaich, Edlund, & Albertsson, 2012). ROS are a series of oxygen-containing compounds, such as hydroxyl radical ( $\cdot\text{OH}$ ), superoxide ( $\cdot\text{O}_2^-$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), organic peroxides ( $\text{ROOR}'$ ), and peroxyxynitrite ( $\text{ONOO}^-$ ) (Apak, Guclu, & Capanoglu, 2016). In nature, ROS come from the activation of oxygen molecules by solar radiation, and cosmic rays (Hao, Sheng, Lu, Tao, & Jia, 2016; Zhang et al., 2016; Zheng et al., 2012) whereas in living organisms, ROS can be produced from the metabolism process and there exists a ROS homeostasis *in vivo*. The ROS concentrations *in vivo* depend on the relative rates of their generation and decay and are mainly controlled by antioxidant enzymes and low molecular weight antioxidants, such as

ascorbic acid, glutathione, tocopherols, carotenoids, flavonoids (Aal, Khutoryanskiy, Nurkeeva, & Mun, 2002; Apel & Hirt, 2004) oligosaccharides and polysaccharides (Van den Ende & Vallura, 2009). ROS also take part in the oxidative depolymerization of polysaccharides (Zhao, Yang, Li, Zhang, & Linhardt, 2013) and fruit ripening (Airianah, Vreeburg, & Fry, 2016; Kawano, 2003). When the ROS production rate surpass their normal levels and shake off the counteraction of the antioxidants within the cell, the imbalance between ROS and antioxidants may lead to some cellular damage to cause senescence (Su et al., 2015; Weyemi et al., 2012), severe clusters of disease such as Alzheimer's disease and cancer in mammals and apoptotic reactions. There are two main techniques for the free radical scavenging *in vivo*. One is the use of enzymes such as catalases, superoxide dismutases (Avelar et al., 2015), hexokinases (Xiang et al., 2011), etc. to eliminate ROS. The other is the direct scavenging of ROS by antioxidants (Fan et al., 2017; Wang et al., 2015). However, there are few investigations on the antioxidation mechanism of polysaccharides.

A typical glycosidic bond linkage between  $\alpha(1 \rightarrow 4)$  and  $\beta(1 \rightarrow 4)$  exists in both starch and cellulose and a chain of fructosyl units connected by  $\beta(1 \rightarrow 2)$  or  $\beta(6 \rightarrow 2)$  linkages among sucrose molecules to form fructan (Matsuzaki et al., 2017). In nature or in organism cells, these linkage bonds can be broken during polysaccharides react with

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some ROS. Among the biologically relevant ROS ( $\text{H}_2\text{O}_2$ ,  $\cdot\text{O}^{2-}$ , and  $\cdot\text{OH}$ , etc.), hydroxyl radicals are the most reactive and dangerous species since it can react with various kinds of compounds and there are no enzymatic systems known to neutralize them in any living beings. Therefore, it is important to study in more detail about the radical reactions between  $\cdot\text{OH}$  and different polysaccharides. Up to now, some oligosaccharides and polysaccharides reacting with hydroxyl radical have been successfully tested (Ajisaka et al., 2009; Nishizawa et al., 2008; Wu et al., 2013; Xia, 2015; Yang et al., 2010). It has been suggested that sucrose, as well as some fructans, at high concentrations in the vacuoles may function directly as a protective agent against oxidative stress in plant cells (Van den Ende & Vallura, 2009). Thus, Bolouri-Moghaddam et al. (Bolouri-Moghaddam, Roy, Li, Rolland, & Ende, 2010) hypothesized that vacuolar sugars (e.g. hexoses, sucrose, fructans, raffinose family oligosaccharides) or sugar-like compounds (e.g. mannitol, sorbitol, etc.) and phenolic derivatives form an additional antioxidant redox system in plant, which can directly scavenge the  $\cdot\text{OH}$  and  $\cdot\text{OOH}$  radicals produced in the vicinity of the membranes.

In order to better understand the mechanism of carbohydrates as antioxidants, Hernandez-Marin and Martínez (2012) studied the free radical ( $\cdot\text{OH}$  and  $\cdot\text{OOH}$ ) scavenging properties of some mono- and polysaccharides and found that the carbohydrates can scavenge  $\cdot\text{OH}$  but not able to directly scavenge  $\cdot\text{OOH}$  and confirmed that free radical scavenging reactions are conducted with hydrogen atom transfer mechanism. Peshev, Vergauwen, Moglia, Hideg, and Ende, (2013) used Fenton reactions to compare the  $\cdot\text{OH}$ -scavenging capacities of a range of fructan oligosaccharides in order to uncover relationships between their antioxidant capacity and chemical structure. Their research indicated that a partial breakdown of the polysaccharides to smaller mono- and disaccharide entities occurred during the Fenton reaction and the broken bonds are adjacent to glucose connected with other monosaccharides. However, there are few investigations on the cleavage reaction pathway of glycosidic bonds with the view of energy barriers.

In this study, a novel mechanism for the  $\cdot\text{OH}$  induced cleavage of glycosidic linkages such as  $\alpha(1 \rightarrow 4)$ ,  $\beta(1 \rightarrow 4)$  and  $\alpha(1 \rightarrow 2)$  in starch, cellulose and fructosan respectively, was discovered using density functional theory (DFT).

## 2. Computational details

All the calculations were performed using density functional theory (DFT) as implemented in the Gaussian09 (Frisch et al., 2013) program using the Becke–3-parameter–Lee–Yang–Parr (B3LYP) functional (Becke, 1993; Stephens, Devlin, Chabalowski, & Frisch, 1994) and the 6–31 + G(d,p) basis set for all atoms. Spin unrestricted calculations were used for all the open-shell systems. TS and QST2 methods were used to search the transition states for all reactions. When the transition state geometry optimizations were carried out, a frequency and intrinsic reaction coordinate (IRC) analyses allowed for the verification of the obtained transition state. The solvent effect was included by making use of a polarizable continuum model (PCM) (Miertuš, Scrocco, & Tomasi, 1981). In the case of the disaccharides such as sucrose, maltose and cellulose, the initial structures of them were taken from the Chemistry, Structures & 3D Molecules Website (<http://www.3dchem.com/>).

In order to clarify the mechanism of glycosidic bond cleavage induced by hydroxyl radical, three disaccharides such as maltose, cellobiose and sucrose containing  $\alpha(1 \rightarrow 4)$ ,  $\beta(1 \rightarrow 4)$  and  $\alpha(1 \rightarrow 2)$  glycosidic linkages respectively were selected as the computational models. Their chemical structures can be seen in Fig. 1 in Dai et al., submitted for publication. In order to facilitate the description, the two rings in three disaccharides were divided into A and B moieties respectively. The hydrogen abstraction reaction of hydroxyl radical from different positions of disaccharides and the process of the glycosidic bond

cleavage were studied. Further, the reaction pathways of the ring opening and glycosidic bond cleavage in sucrose, maltose and cellulose starting from the hydrogen abstraction of C–H by hydroxyl radical were explored. The sketch for the molecular structures and reactions were made by PerkinElmer ChemBioDraw 12.0 and 3D structure visualization were performed using BIOVIA Discovery Studio Visualizer 2016 (Dessault, 2016). The plots of relative energy changes and the reaction pathways were made by Origin 7.5.

## 3. Results and discussion

### 3.1. Hydrogen abstraction from C–H bond of three disaccharides by hydroxyl radical

As the start of free radical reactions, the hydroxyl radical got a hydrogen atom from the C–H bond of the disaccharides, which generated a saccharide radical and a water molecule. The hydrogen abstraction from different C atoms by hydroxyl radical has a similar process, which includes the hydrogen atom gradually leaving from the C atom of the disaccharides and approaching to O atom of the hydroxyl radical over a hydrogen transfer transition state. As a result, a water molecule and a disaccharide radical are formed (Fig. 2 in Dai et al., submitted for publication).

During the investigation, the hydrogen abstraction processes from C1, C5 and C6 of moiety A and C4', C5' and C6' of moiety B in the three disaccharides were calculated (the hydrogen abstraction process from C5 of moiety A for maltose was ignored because of the steric hindrance coming from the hydroxyl group of C6' in moiety B). The hydrogen abstraction process of C1'–H in moiety B of sucrose was also calculated. The system total energies with the zero point energy correction (ZPEC) of reactants (disaccharide +  $\cdot\text{OH}$ ), transition states and intermediates were calculated at B3LYP/6–31 + G(d,p) level with PCM water solvent model and are listed in Table 1. (Su, Ma and Ce represent the sucrose, maltose and cellobiose respectively. A and B represent moieties A and B respectively. P represents products. The Arabic numerals represent the serial number of carbon atoms in each monosaccharide unit and the Roman numerals represent the occurrence order of transition states and intermediates in object chemical reactions). For example, IM(I)<sub>SuA6</sub> represents that the first immediate in the reaction starting from hydroxyl radical attacking H–C6 in moiety A of sucrose. Thus, the relative energy of each state based on that of the reactants and energy barriers of hydrogen abstraction at different positions of three disaccharides can be calculated.

Based on the computing results in Table 1, the energy barriers for the hydrogen abstraction from the carbon atoms outside of the pyran and furan rings of sucrose (C6 in A moiety, C1' and C6' in B moiety) are much lower than that from the carbon atoms on two rings (such as C1, C5 in moiety A and C5' in moiety B). The former energy barriers are less than 3 kcal/mol, however, the latter energy barriers are about 10 kcal/mol. The difference in energy barriers is big enough to make  $\cdot\text{OH}$  prefer getting hydrogen from the former carbon atoms, which greatly weakened the possibility of hydroxyl radical capturing hydrogen from the C–H bonds on pyran and furan rings. However, there are no significant differences in the energy barriers for maltose and cellobiose and they are all less than 4 kcal/mol, which indicate these reactions can take place easily with approximately equal opportunity considered from the energy barriers. It can be seen from Table 1 that the energies of IM(I)s are lower than that of reactants, indicating the hydrogen abstraction is an exothermic process.

### 3.2. Glycosidic bond cleavage induced by hydrogen abstraction from C–H outside pyran or furan ring of sucrose

In order to find a possible reaction pathway for the glycosidic bond cleavage of sucrose induced by hydroxyl radical, the radical formation on C6 (moiety A), C1' and C6' (moiety B) atoms outside the saccharide

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