Running title: Isomerization and epimerization of hexoses

Isomerization and epimerization of glucose and galactose in arginine solution and phosphate buffer under subcritical fluid conditions

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Abstract

Reaction of glucose or galactose was performed in arginine solution or phosphate buffer (pH 7.0) using a batch reactor at 110°C. The yields of products, pH, and absorbances at 280 nm and 420 nm were measured during the reaction. Fructose, mannose, and allulose were formed from glucose; tagatose, talose, and sorbose were done from galactose. The reaction proceeded more rapidly in arginine solution than in phosphate buffer. In arginine solution, yields of fructose and tagatose were 20% and 16%, respectively, after 30-min reaction; in phosphate buffer, they were 14% and 10%, respectively. However, in both reaction media, the pH drop and increase in absorbances continued even after the yield became almost constant. The absorbance increased particularly in the latter half of the reaction due to formation of browning products. Therefore, to avoid browning, the reaction should be stopped as soon as possible after the yield approaches its maximum value.

Keywords: Green catalyst, hexoses, isomerization, LBAE transformation, subcritical fluid

Rare sugars are defined as monosaccharides and their derivatives that are scarce in nature (Granström *et al.* 2004). Recently, their physiological and food scientific functions have attracted much attention (Levin 2002; Namli, Sumnu and Oztop 2021; Sun *et al.* 2008). For example, it was reported that tagatose (the rare sugar) has physiological functions as a low-calorie sweetener, anti-diabetic, prebiotic, and preventive drug for oral diseases (Bertelsen, Jensen and Buemann 1999; Levin 2002; Mayumi *et al.* 2021; Roy *et al.* 2018).

There are chemical and biochemical (enzymatic) methods for converting naturally abundant common sugars into rare sugars. Most common sugars, such as glucose and galactose, are of the aldose series and are reducing sugars. The isomerization and epimerization of reducing sugars in alkaline solutions, such as sodium hydroxide or potassium hydroxide, via an enediol intermediate is known as Lobry de Bruyn–Alberda van Ekenstein (LBAE) transformation (Delidovich 2023; Isbell *et al.* 1969; Sowden and Schaffer 1952). This method has been used to convert common sugars to rare sugars (Choudhary *et al.* 2011; Dendene *et al.* 1994) and is also used to produce isomerized sugar (high-fructose corn syrup) (Kumar *et al.* 2020; Parker, Salas and Nwosu 2010). The production of rare sugars by isomerization using metal catalysts and enzymes has also been investigated (Delidovich 2023; Gounder and Davis 2013; Shen *et al.* 2012; Shukla, Verykios and Mutharasan 1985), but challenges remain in terms of cost and yield. Meanwhile, we have reported isomerization and epimerization of sugars in pure water (Usuki, Kimura and Adachi 2007), in aqueous alcohols (Gao, Kobayashi and Adachi 2015; Gao, Kobayashi and Adachi 2015; Soisangwan *et al.* 2017), and in phosphate buffer (Adachi *et al.* 2021; Onishi *et al.* 2022; Onishi *et al.* 2020), which were kept under subcritical fluid conditions. These transformations are considered a type of isomerization and epimerization via LBAE transformation.

Recently, isomerization and epimerization of sugars catalyzed by basic amino acids, such as arginine, lysine, and histidine, have attracted much attention. These amino acids are called

"green" catalysts because they are abundant in nature, relatively safe, and environmentally friendly (Milasing, Khuwijitjaru and Adachi 2023; Yang, Sherbahn and Runge 2016). Among these amino acids, arginine was reported as the most efficient for the isomerization of glucose to fructose (Yang, Sherbahn and Runge 2016) and galactose to tagatose (Milasing, Khuwijitjaru and Adachi 2023). Arginine is also efficient in the isomerization of ribose to ribulose (Khuwijitjaru and Adachi 2023). However, during the isomerization and epimerization, browning due to the Maillard reaction is inevitable (Kim and Lee 2008; Lamberts, Rombouts and Delcour 2008). Similarly, browning also occurs in phosphate buffer due to caramelization or formation of humin by polymerization of 5-hydroxymethylfurfural (HMF), etc. (Baltes 1985; Onishi 2022; Onishi 2020; Paravisini *et al.* 2015; van Zandvoort *et al.* 2015; van Zandvoort *et al.* 2013; Yaylayan and Kaminsky 1998). Therefore, the reaction must be performed at a relatively low temperature of around 110°C and for a long time to suppress the browning (Adachi 2021).

As described above, in the method using arginine or phosphate buffer, the browning reaction proceeds together with isomerization and epimerization of the sugar. From the viewpoint of industrialization, it is desirable to suppress browning and increase the yield of major products (rare sugars). However, a comparison of these two methods has not been reported. In this study, the isomerization of two aldoses (D-glucose and D-galactose) into ketoses (D-fructose and D-tagatose) was investigated to compare the reaction behaviors in arginine or phosphate buffer (pH 7.0), or pure water (control), using a batch reactor maintained at 110°C. The side reactions occurring in parallel with the isomerization and epimerization were also investigated.

Materials and methods

Materials

D-Glucose, D-galactose, L-arginine (purity >98%), disodium hydrogen phosphate, sodium

dihydrogen phosphate, glycerol, acetonitrile (HPLC grade), and distilled water (HPLC grade) were purchased from FUJIFILM Wako Pure Chemicals (Osaka, Japan). Prefixes D- and L-, showing the three-dimensional structures of sugar and arginine, will be omitted hereafter. Other reagents were purchased from FUJIFILM Wako or Nacalai Tesque (Kyoto, Japan).

Isomerization reaction

Glucose or galactose (substrate) and arginine were dissolved in Milli-Q water at concentrations of 0.20 mol/L and 0.010 mol/L, respectively. The molar ratio of arginine to hexose (glucose or galactose) was fixed at 0.05 mol-arginine/mol-hexose. Each hexose was also dissolved in 0.010 mol/L sodium phosphate buffer (pH 7.0) at 0.20 mol/L. As a control, each hexose was dissolved in Milli-Q water at 0.20 mol/L. The substrate solution (2.5 mL) was placed in a 3-mL screw-cap vial (8 vials were prepared). The vials were placed in a thermostatic bath set at 110°C to start the reaction. At appropriate time intervals, one vial was taken out of the bath and immediately placed in an ice water bath to terminate the reaction. Experiments were performed in triplicate for each hexose in arginine solution, phosphate buffer, or pure water. The same volume (2.5 mL) of water was placed in a separate vial and used to measure the reaction temperature using a thermometer connected to a K-type thermocouple placed in the center of the vial.

Analysis

Concentrations of the remaining hexoses and products formed during the reaction were determined by HPLC. The HPLC system consisted of a separation column (Cosmosil Sugar-D; 4.6 mm I.D. × 250 mm, Nacalai Tesque), guard column (Cosmosil Sugar-D; 4.6 mm I.D. × 10 mm, Nacalai Tesque), pump (LC-10ADVP, Shimadzu, Kyoto), and refractometer (Shodex RI-101, Showa Denko, Tokyo, Japan). The injection volume of the sample was 5 μL, and the

mobile phase was 80 vol% acetonitrile at a flow rate of 1.0 mL/min.

The used hexoses were all reducing sugars, which became brown by Maillard reaction or caramelization, etc. Because the absorbance range of these reaction products is wide (Shen and Wu 2004), absorbances of the reaction mixture were measured at 280 nm and 420 nm using a spectrophotometer (UV-1280, Shimadzu).

The pH of the reaction mixture was measured at room temperature using a pH meter (LAQUAtwin-pH-22, Horiba Advanced Techno, Kyoto).

Results and discussion

Isomerization and epimerization of glucose

Figure 1(a) shows several time courses of the reaction (temperature, remaining glucose, formed sugars, and pH) when glucose was treated in arginine solution. It has been proposed that glucose is isomerized to fructose mainly through a 1,2-enediol intermediate by LBAE transformation, but a small amount of glucose is also epimerized to mannose by the same process (Delidovich 2023; Isbell 1969). A portion of the formed fructose is further converted to allulose via a 2,3-enediol intermediate (Delidovich 2023; Doner 1979). When the temperature of the reaction mixture reached 90°C, the decrease in glucose and the formation of fructose became pronounced. These reactions became slower after approximately 15 min of reaction time, when the temperature reached nearly 110°C. Meanwhile, the pH gradually but steadily decreased throughout the reaction. In addition, when the increase in fructose became slower, the absorbances at 280 nm and 420 nm abruptly increased. The remaining glucose and formed fructose in the reaction mixture at 30 min were 68% and 20%, respectively, and the yields of mannose and allulose were 1.7% and 1.0%, respectively. Thus, approximately 10% of glucose was converted to browning products and other by-products. The yields of fructose and mannose

were close to those reported previously (21% and 0.54%, respectively) in arginine at 0.050 mol/mol-glucose at 110°C; however, the formation of tagatose was not reported in that study (Yang, Sherbahn and Runge 2016).

Figure 1(b) shows the time courses of the glucose reaction in phosphate buffer. Similar to the reaction in arginine solution, glucose decreased and fructose began to form pronouncedly when the temperature exceeded 90°C. Then, after approximately 90 min of the reaction, the remaining fractions of glucose and formed fructose were almost constant at 78% and 14%, respectively, and the yields of mannose and allulose at 150 min were 0.9% and 0.5%, respectively, which were lower than those in arginine solution. The percentage of glucose converted to browning products and other by-products at 150 min was approximately 6.6%, which was somewhat lower than that in arginine solution. This would be because the Maillard reaction does not occur but caramelization does occur in phosphate buffer. This was suggested by the fact that both absorbances were lower in phosphate buffer than in arginine solution.

In both arginine solution and phosphate buffer, the absorbances increased rapidly in the latter stage of the reaction (after 15 min and 60 min, respectively), even though the sum of the concentrations of substrate (glucose) and products (formed sugars) remained almost constant. This suggests that they were not directly converted to browning by-products but that the by-products, such as Schiff bases or HMF, underwent polymerization and conversion into substances with large absorbance coefficients (this would be equivalent to the Maillard reaction or caramelization) (Baltes 1985; Wu *et al.* 2014). Similarly, it was reported that, in arginine solution, browning progresses significantly due to the Maillard reaction (Milasing, Khuwijitjaru and Adachi 2023). However, in phosphate buffer, it was reported that the formation of HMF occurred (Lu *et al.* 2012), and the resulting HMF subsequently polymerizes to browning products (humin (van Zandvoort 2015; van Zandvoort 2013) and caramel (Baltes 1985; Yaylayan and Kaminsky 1998)). In this study, the formation of humin and caramel was also

progressive, and browning was more pronounced probably due to an increase in the degree of polymerization.

Figure 1(c) shows the time courses of the glucose reaction in pure water (control). A decrease in pH and slight formation of fructose were observed, with a fructose yield of 6.7% at 150 min. Usuki, Kimura and Adachi (2007) reported that fructose was formed at 3.3% from glucose in pure water at 220°C. The yield obtained in this study (6.7%) was about twice their value. This would be because they performed the reaction at a relatively higher temperature (220°C), at which the fructose yield reaches a maximum value and then drops sharply. This drop would be attributed to the pyrolysis of fructose and the above-described browning. In this study, however, because the reaction was performed at 110°C, which is a relatively low temperature for subcritical water conditions, absorbances at 280 nm and 420 nm increased only slightly, indicating that the proportion of the product (fructose) converted to browning products was quite small.

Isomerization and epimerization of galactose

Figure 2(a) shows the time courses for the reaction of galactose in arginine solution. Similar to the case of glucose, galactose was isomerized to tagatose and simultaneously epimerized to a small amount of talose, mainly via a 1,2-enediol intermediate according to LBAE transformation (Milasing, Khuwijitjaru and Adachi 2023; Onishi 2020). A portion of tagatose was further converted to sorbose via a 2,3-enediol intermediate. When the temperature of the reaction mixture reached 90°C, the decrease in galactose and formation of tagatose became more pronounced, and the reactions of sugars became more gradual after approximately 15 min. The remaining fractions of galactose and formed tagatose at 30 min were 74% and 16%, respectively. Yields of the minor products (talose and sorbose) were 1.3% and 2.0%, respectively. Thus, approximately 6.7% of galactose was converted to browning products in

arginine solution. This percentage was somewhat less than that for glucose (approximately 10%). However, absorbances at 280 nm and 420 nm were higher than those of glucose. This would be because the type of browning products formed by Maillard reaction, etc. depends on the type of sugar (Van Boekel 2006).

Figure 2(b) shows the time courses of the reaction in phosphate buffer. The reaction was slower in phosphate buffer than in arginine solution, with the remaining fractions of galactose and formed tagatose being 80% and 10%, respectively, at 150 min. The yields of talose and sorbose were 0.9% and 1.0%, respectively, which were not significantly different from those in arginine solution. Therefore, the percentage of galactose converted to browning products was approximately 8%, which was slightly higher than that in arginine solution. However, the absorbances were lower in phosphate buffer than in arginine solution throughout the reaction. These results suggest that the side reactions occurring in phosphate buffer were clearly different from those in arginine solution and that caramelization was the major reaction.

In pure water, the pH decreased as shown in Fig. 2(c). However, because no formation of tagatose, talose, or sorbose was observed, the results are not shown in Fig. 2(c-1). The change in absorbance throughout the reaction was also negligible. In addition, the remaining fraction of galactose at 150 min was nearly 97%, meaning that isomerization and epimerization hardly occurred in pure water at 110°C. These results suggest that the presence of arginine or phosphate promotes not only isomerization and epimerization but also side reactions.

Relationship between product yields and pH

Figure 3 shows the relationship between the pH of the reaction mixture and product yields when glucose or galactose was reacted in arginine solution or phosphate buffer. In all cases, the yields increased rapidly at the beginning of the reaction while the pH change was small. When the pH decreased below approximately 9.0 in arginine solution or approximately 6.5 in

phosphate buffer, the yields were almost constant or increased gradually. A similar trend has been reported for the isomerization of galactose to tagatose in arginine solution (Milasing, Khuwijitjaru and Adachi 2023) and the isomerization of various aldoses to their corresponding ketoses in phosphate buffer (Onishi 2022). The final ketose yields were different in arginine solution and phosphate buffer. The difference would be due to the many reactions occurring in parallel with the isomerization, such as conversion to browning products. Due to many of these side reactions, the reaction progress balance would depend on the reaction conditions. From the viewpoint of yields of the major products fructose and tagatose, it is preferable to perform the reaction in the presence of arginine.

Changes in selectivity during the isomerization and epimerization

Figure 4 shows the relationship between the fraction of the substrate (glucose or galactose) consumed during the reaction (i.e., conversion of the substrate) and the yield of the products (selectivity) when (a) glucose or (b) galactose was isomerized in arginine solution or phosphate buffer, respectively. The dashed line in the figure corresponds to the selectivity of 1, such that the selectivity decreases with deviation from the dashed line. The selectivities of the conversion of glucose to its major product (fructose) in arginine solution and phosphate buffer were 0.74 and 0.67, respectively, except in the latter stages of the reaction.

The selectivity for the isomerization of galactose to the corresponding keto isomer (tagatose) in phosphate buffer was almost 1 in the early stage of the reaction. But, in the latter stage of the reaction, the curve deviated from the dashed line significantly, resulting in decreased selectivity. This suggests that tagatose is easily converted to other substances in the latter half of the reaction in phosphate buffer. Meanwhile, in arginine solution, the relationship was almost linear with a selectivity of 0.78, but it slightly decreased in the final stage of the reaction.

As a result, the plots of the selectivities of tagatose in arginine solution and phosphate buffer intersected. This phenomenon can be explained as follows: The initial pH of arginine solution was high, and the selectivity was low from the beginning in arginine solution because high pH tends to cause side reactions such as browning as well as isomerization. However, even as the reaction progressed, the presence of arginine prevented a drop in pH, and the isomerization continued, resulting in a low decrease in selectivity. However, the initial pH was relatively low in phosphate buffer. At low pH, side reactions were less likely to occur, and the selectivity was close to 1. As the reaction progressed and the pH decreased, isomerization by LBAE transformation was less, and side reactions such as HMF formation became dominant (Antal, Mok and Richards 1990). Thus, these two different trends in selectivity were probably due to the initial pH and the pH change associated with the reaction (isomerization and side reactions).

It is noted that the selectivity for the conversion of glucose to mannose and allulose was extremely low, ranging from 0.02 to 0.06. The selectivity of the conversion of galactose to talose and sorbose was also low, ranging from 0.03 to 0.09.

Relationship between absorbances at 280 nm and 420 nm

Figure 5 shows the relationship between the absorbances at 280 nm and 420 nm when glucose or galactose was reacted in arginine solution or phosphate buffer. In both cases, the absorbance at 280 nm gradually increased at the beginning of the reaction, and then both absorbances at 280 nm and at 420 nm began to increase almost linearly. As a result, the plots are bent near the lower left. This bending may occur for the following reasons: Substances with absorption at 280 nm were formed first, followed by the formation of browning products. In phosphate buffer, HMF was formed first and showed absorption at 280 nm but did not show absorption at 420 nm at this time. The subsequent polymerization (caramelization) of HMF

would result in absorption at 420 nm (Yaylayan and Kaminsky 1998). However, the reaction mixture obtained in the presence of arginine showed absorption at 280 nm due to the gradual formation of Schiff bases, etc. during the initial stage of the reaction. It is thought that the Maillard reaction progressed further steeply by the polymerization of Schiff bases to produce substances with stronger absorption at 420 nm (Wu *et al.* 2013; Wu 2014; Yu *et al.* 2012).

Relationship between the yield of the major product and absorbance at 420 nm

Figure 6 shows the relationship between the absorbance at 420 nm and the yield of the major product (ketose) when glucose or galactose was reacted in arginine solution or phosphate buffer. In both cases, there was little increase in absorbance in the early stage of the reaction, but absorbance increased abruptly in the latter stage when the increase in the yield slowed down. Although the yield was higher in arginine solution than in phosphate buffer, the increase in absorbance in the latter stage was also greater in arginine solution. This tendency was particularly pronounced during the isomerization of galactose to tagatose. Therefore, it is desirable to stop the reaction as soon as possible after the yield reaches a desired value to prevent browning. The increase in the absorbance in the latter stage suggests that browning products were further converted to substances with higher absorption coefficients, as described above.

As shown in Figure 5, the absorbance at 280 nm was 7 to 20 times greater than at 420 nm. This indicates that substances with absorption at 280 nm remained after purification, although they were not necessarily present at high concentrations. Therefore, even if substances with absorption in the visible light region are removed from the major product during the purification process, substances with absorption in the ultraviolet region may remain. Therefore, it is necessary to pay attention not only to browning products but also to substances with ultraviolet absorption during the purification.

Conclusions

When 0.20 mol/L glucose was reacted in 0.010 mol/L arginine solution or 0.010 mol/L phosphate buffer (pH 7.0) at 110°C, the yields of fructose (ketose) were 20% and 14%, respectively. When 0.20 mol/L galactose was also reacted under the same conditions, the yields of the major product tagatose were 16% and 10%, respectively. Thus, the yields were higher in arginine solution than in phosphate buffer at shorter reaction times. In both cases, the decrease in pH and increase in absorbances at 280 nm and 420 nm continued even in the latter stages of the reaction when the product yield became almost constant. This suggests that by-products, such as HMF and Schiff bases, were converted into substances with higher absorption coefficients by polymerization, etc. during the latter stage of the reaction. Therefore, for the efficient production of major products, the reaction should be stopped as soon as possible after the yield reaches the apparent reaction equilibrium. In addition, the formation of ketoses by isomerization of substrates in pure water was only slight, and the decrease in pH and increase in absorbance at 280 nm were also slight, indicating that the presence of arginine or phosphate promoted both the isomerization and by-product formation.

Declaration of competing interests

The authors have no conflicts of interest to declare.

Author contributions

Takashi Kobayashi: Conceptualization, Funding acquisition, Methodology, Investigation, Formal analysis, Data curation, Writing original draft. Pramote Khuwijitjaru: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. Shuji Adachi: Conceptualization, Methodology, Writing – review & editing, Validation, Supervision.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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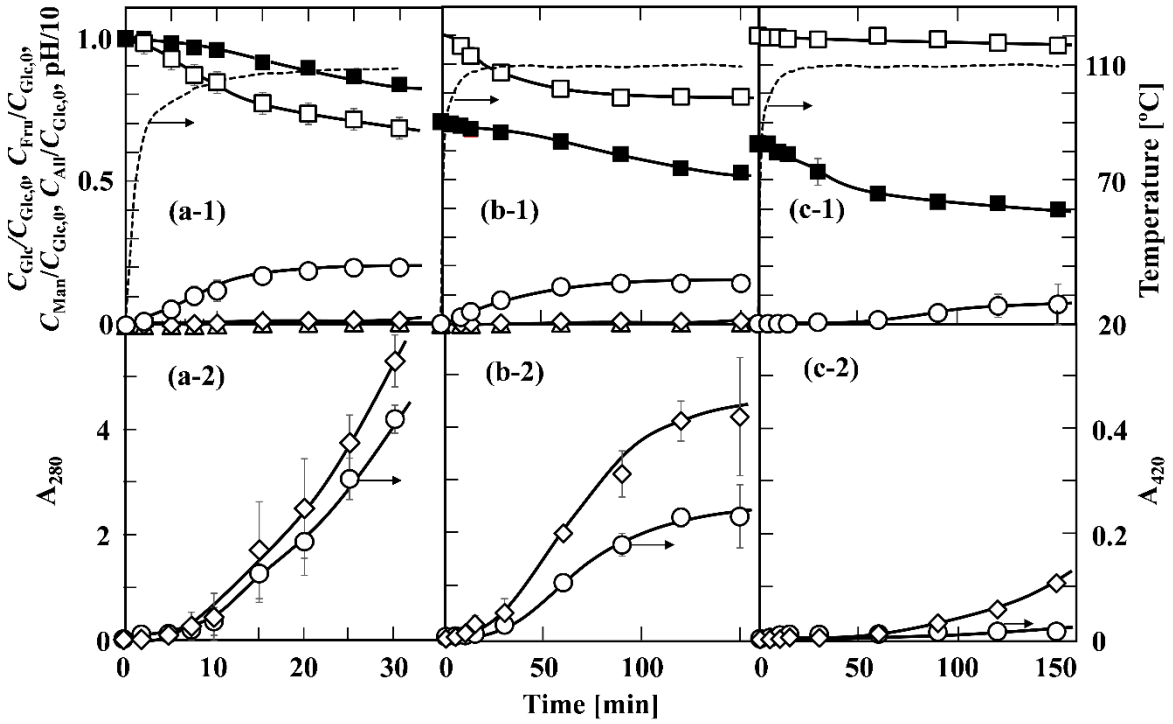


Figure 1. Time courses of the reaction of glucose under subcritical fluid conditions in (a) arginine solution, (b) phosphate buffer, and (c) pure water; (a-1) Temperature (dashed curve) of the reaction mixture, the remaining fraction of glucose ($C_{Glc}/C_{Glc,0}$; □), yields of fructose ($C_{Fru}/C_{Glc,0}$; ○), mannose ($C_{Man}/C_{Glc,0}$; ◇), and allulose ($C_{All}/C_{Glc,0}$; △), and pH (■); (a-2) Absorbances at 280 nm (A_{280}; ◇) and 420 nm (A_{420}; ○); (b-1) and (b-2) are the time courses in phosphate buffer, and (c-1) and (c-2) are those in pure water. Symbols and bars indicate mean and standard deviation, respectively (n = 3). The temperature of the reaction bath was set at 110°C. The solid curves smoothly connect the points.

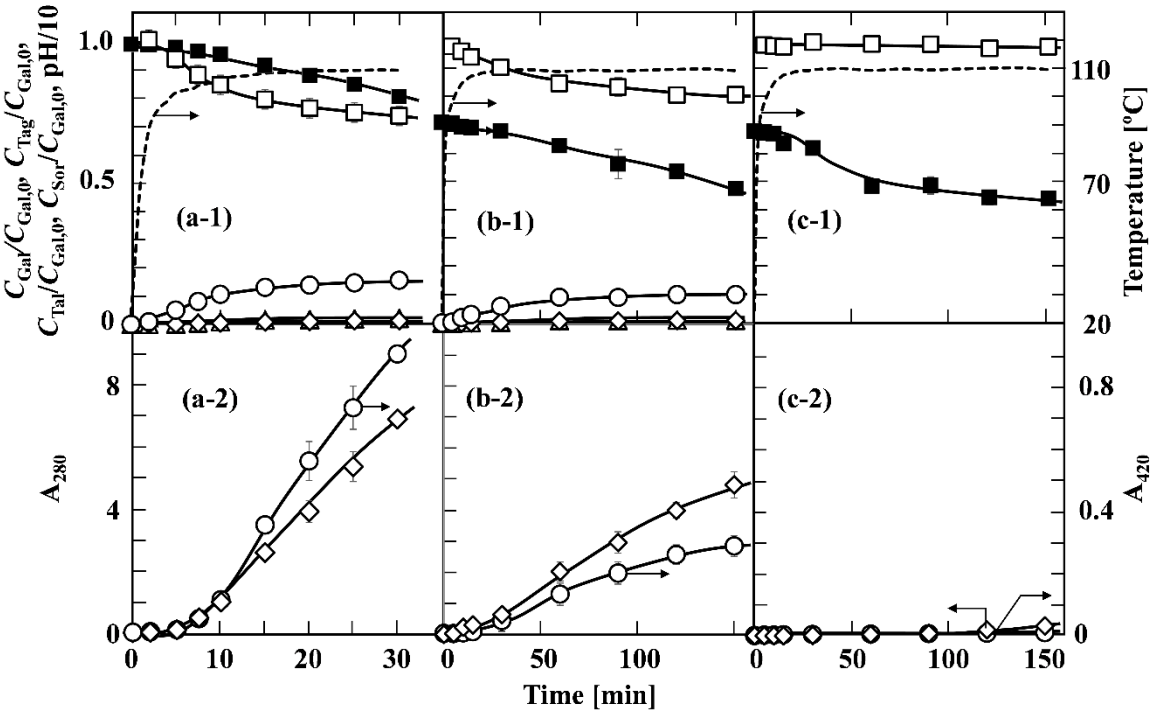


Figure 2. Time courses of the reaction of galactose under subcritical fluid conditions in (a) arginine solution, (b) phosphate buffer, and (c) pure water: (a-1) Temperature (dashed curve) of the reaction mixture, the remaining fraction of galactose ($C_{Gal}/C_{Gal,0}$; □), yields of tagatose ($C_{Tag}/C_{Gal,0}$; ○), talose ($C_{Tal}/C_{Gal,0}$; ◇), and sorbose ($C_{Sor}/C_{Gal,0}$; △), and pH (■); (a-2) Absorbances at 280 nm (A_{280}; ◇) and 420 nm (A_{420}; ○); (b-1) and (b-2) are the time courses in phosphate buffer, and (c-1) and (c-2) are those in pure water. Symbols and bars indicate mean and standard deviation, respectively (n = 3). The temperature of the reaction bath was set at 110°C. The solid curves smoothly connect the points.

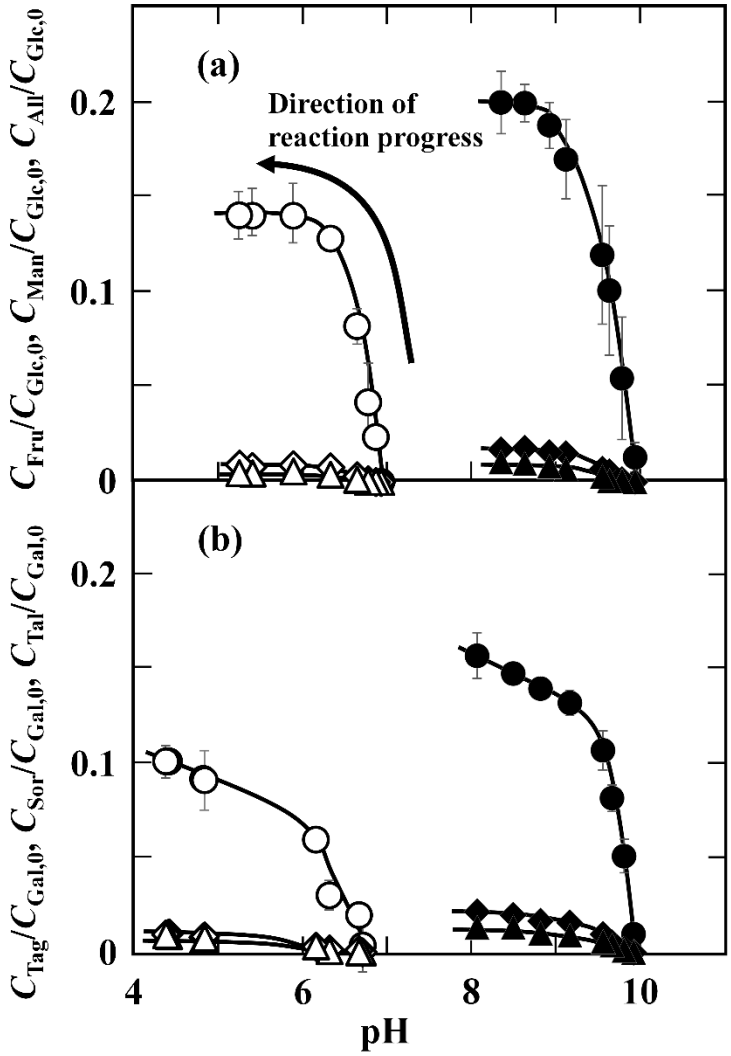


Figure 3. Relationship between the yields of formed sugars and pH of the reaction mixture in arginine solution (closed symbols) or phosphate buffer (open symbols). (a) Relationship in the glucose reaction for fructose ($C_{Fru}/C_{Glc,0}$; ●, ○), mannose ($C_{Man}/C_{Glc,0}$; ◆, ◇), and allulose ($C_{All}/C_{Glc,0}$; ▲, △). (b) Relationship in the galactose reaction between tagatose ($C_{Tag}/C_{Gal,0}$; ●, ○), sorbose ($C_{Sor}/C_{Gal,0}$; ◆, ◇), and talose ($C_{Tal}/C_{Gal,0}$; ▲, △). Symbols and bars indicate mean and standard deviation, respectively (n = 3). The pH was measured at room temperature. The curved arrow in (a) indicates the direction of reaction progress.

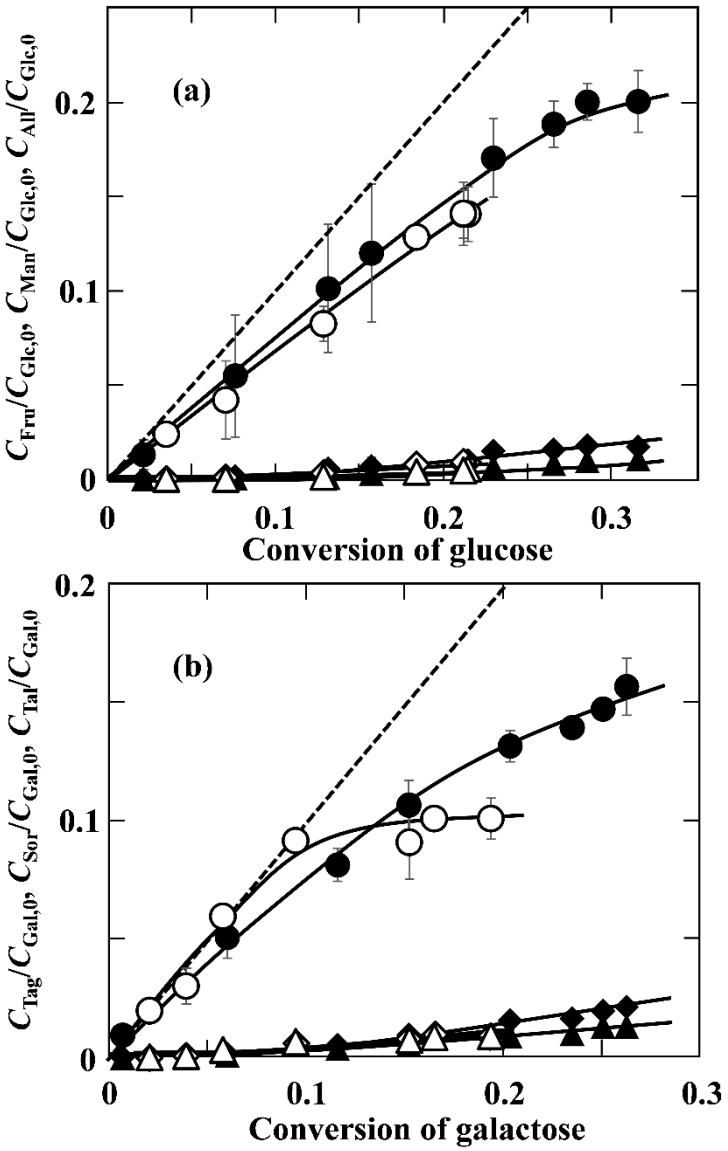


Figure 4. Relationship between the yields of formed sugars and conversion of the substrate in arginine solution (closed symbols) or phosphate buffer (open symbols). (a) Relationship in the reaction of glucose for fructose ($C_{Fru}/C_{Glc,0}$; ●, ○), mannose ($C_{Man}/C_{Glc,0}$; ◆, ◇), and allulose ($C_{All}/C_{Glc,0}$; ▲, △). (b) Relationship in the reaction of galactose for tagatose ($C_{Tag}/C_{Gal,0}$; ●, ○), sorbose ($C_{Sor}/C_{Glc,0}$; ◆, ◇), and talose ($C_{Tal}/C_{Glc,0}$; ▲, △). Symbols and bars indicate mean and standard deviation (n = 3).

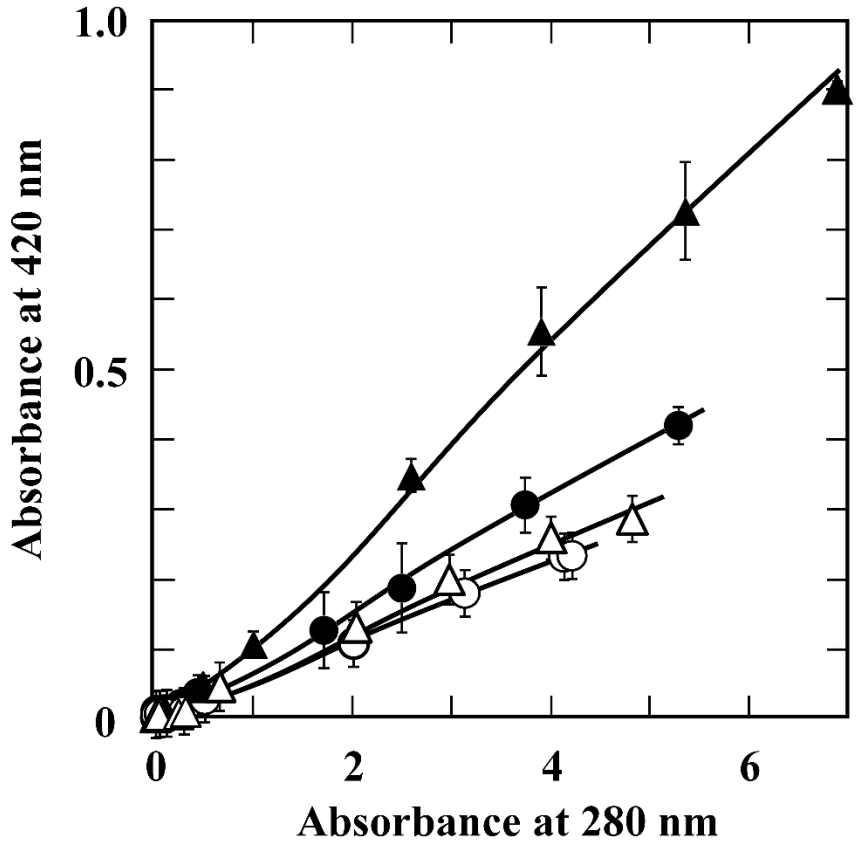


Figure 5. Relationship between the absorbances at 280 nm and 420 nm during the isomerization of glucose (●, ○) and galactose (▲, △) in arginine solution (closed symbols) or phosphate buffer (open symbols) at approximately 110°C. Symbols and bars indicate mean and standard deviation, respectively (n = 3).

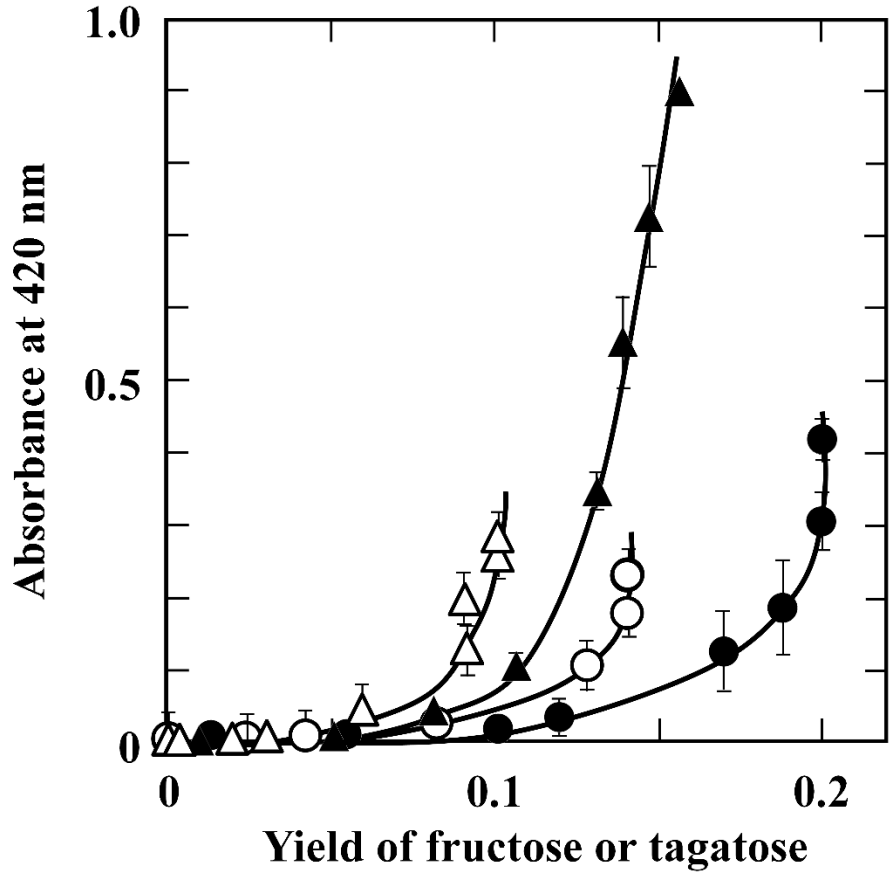
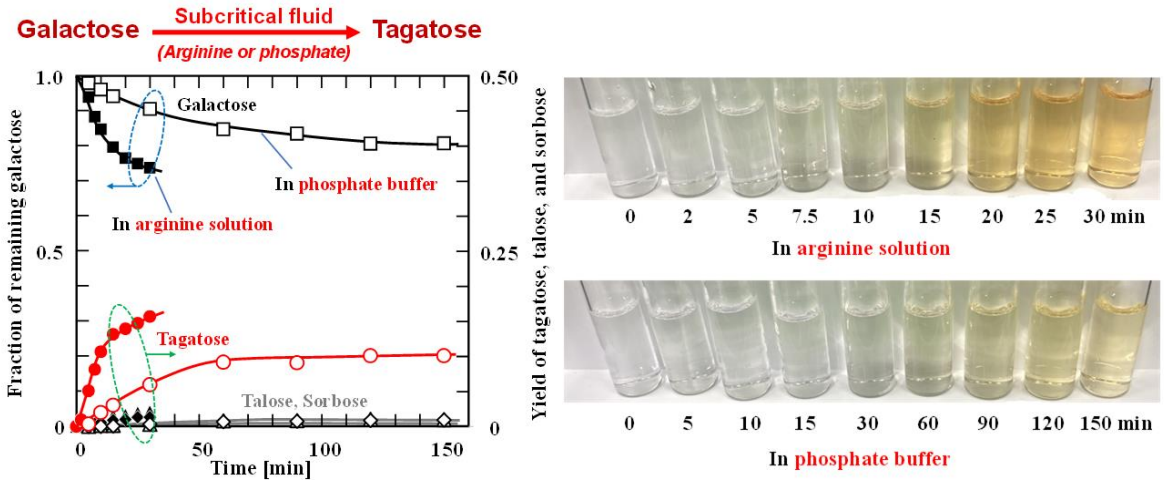


Figure 6. Relationship between the yields of fructose (●, ○) and tagatose (▲, △) and absorbance of the reaction mixture at 420 nm in arginine solution (closed symbols) or phosphate buffer (open symbols). Symbols and bars indicate mean and standard deviation, respectively (n = 3).



Graphical abstract caption

Isomerization of hexoses in arginine solution and phosphate buffer under subcritical condition