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ISOMERIZATION OF D-GLUCOSE WITH SODIUM ALUMINATE: MECHANISM OF THE REACTION

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ABSTRACT

A mechanism for the isomerization of D-glucose to D-fructose by sodium aluminate is proposed, involving transformation of a β-D-glucopyranose–1,3-aluminate complex into an α-D-fructofuranose–1,3,6-aluminate complex through an enol–aluminate complex that inhibits the formation of a D-mannose–aluminate complex. The α-D-fructofuranose–1,3,6-aluminate further reacts to form a D-psicose–aluminate complex in substantial yield. Constant degradation of the 6-carbon sugars occurred during the reaction because of the high pH of the solution. The C_6 sugars were analyzed chromatographically but the degradation products were not identified.

INTRODUCTION

The use of sodium aluminate for the isomerization of D-glucose to D-fructose has been reported in two patents[1,2] claiming yields of 70–80% of D-fructose. Recently, Rendleman and Hodge[3] reported isomerization of D-glucose to D-fructose by use of an anion-exchange resin in the aluminate form. No literature dealing with the mechanism of this reaction or of its kinetics has been reported.

This paper* considers the high yields of D-fructose and proposes a mechanism capable of explaining the observed results. The accompanying article[4] deals with the kinetics of the isomerization process as a function of temperature, based on the proposed mechanism.

The interconversion of D-glucose, D-fructose, and D-mannose in alkaline media has been examined by several researchers[5–7]. The enol-intermediate theory under alkaline conditions is widely accepted. Isbell[5b] suggested a mechanism based on an acyclic-ring structure, as shown in Fig. 1. The formation of D-glucose, D-mannose, or D-fructose would be governed by the mode of proton addition to the pi bond of the enol intermediate. If it added to either side of C-1, D-fructose would be formed. If it added to C-2, D-glucose or D-mannose would be formed according to the side of proton addition.

The equilibrium conversion of D-glucose into D-fructose by action of isomerases

*Taken mainly from the Ph D. thesis of Arthur J. Shaw III, Purdue University, December, 1976.

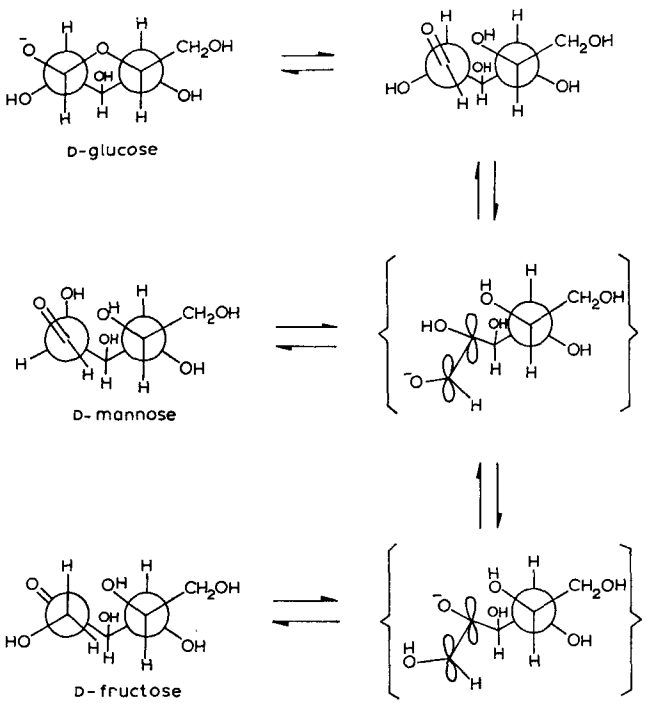


Fig. 1. Postulated mechanism for the alkaline-induced, acyclic transformation of D-glucose, D-mannose, and D-fructose. The enol intermediates indicated by the bracketed formulas could afford either of the sugars shown, by suitable proton-addition to one of the four pi-orbital sites. Ring closing of D-mannose and D-fructose is not shown, but would occur shortly after proton addition to the pi bond.

can be shown to range between 45–58%, depending on the temperature[8]. When sodium aluminate is added to a solution of D-glucose in equimolar ratio, the equilibrium distribution between D-glucose and D-fructose, after removal of the sodium aluminate, may approach values[2] of 1 to 4.

Rendleman and Hodge[3] have shown that D-glucose, D-fructose, and D-mannose do form reversible complexes with aluminate. If the mechanism for the interconversion between the sugars were the same for the sodium aluminate-induced reaction as a general base-induced reaction, then the product distribution of the sugars would be altered by the affinity of each species for the aluminate ion. This hypothesis would suggest that concentrations of D-fructose and D-mannose would be increased by complexing with aluminate to a greater extent with these species than with D-glucose.

DISCUSSION AND RESULTS

Physical differences between D-glucose–aluminate and D-fructose–aluminate. — During the preparation of the D-glucose–aluminate and D-fructose–aluminate complexes, several physical differences were observed between the alcohol-precipitated

complexes. D-glucose–aluminate forms a tight gel on the bottom of the container and has an adhesive, paste-like appearance. It is slow to dissolve in water and requires more mixing to break up the polymer than does D-fructose–aluminate. It appears that the alcohol causes the aluminate ions to polymerize through condensation to give Al–O–Al bonding. The solubility of the D-fructose–aluminate complex in 90.9% alcohol at $-10°$ is about 10 times greater than the D-glucose–aluminate under the same conditions.

The borate ion has similar geometry and chemistry to the aluminate ion under alkaline conditions. Boron has a covalent bonding-radius of 0.8 Å, whereas the covalent bonding radius of aluminum is 1.2 Å. Kennedy and How[9] showed that D-glucose forms a 1,2-pyranoid complex in the presence of borax. Arnoff, Chen, and Cheveldayoff[10] recently proposed, on the basis of p.m.r. studies, that D-glucose reacts with borate to form a D-glucofuranose–1,2-borate complex, whereas D-fructose forms a tridentate D-fructofuranose–1,3,6-borate complex. Working with molecular models, it was found that a 1,2 complex of D-glucopyranose or D-glucofuranose with aluminate was not likely, because of the bond-strain involved. However, a D-fructofuranose–1,3,6-aluminate complex was possible. The formation of a tridentate complex with D-fructose as compared to a mono or bi-dentate complex of D-glucose, would explain the observed physical differences between the carbohydrate complexes precipitated by alcohol. However, this gives little clue as to how the aluminate is complexed to the sugars.

Table I reports the associate constants for the D-glucose– and D-fructose–aluminate complexes, as defined by $K = [\text{complex}]/[\text{free sugar}][\text{free aluminate ion}]$. The D-glucose–aluminate complex appears to be more temperature-sensitive than the D-fructose–aluminate complex. The increase in the association constant with decreasing temperature is similar to borate–complexation with D-glucose. Conner and Fulgrin[11] showed that the association constant for complexation of D-glucose

TABLE I

ASSOCIATION CONSTANTS AS A FUNCTION OF TEMPERATURE FOR D-GLUCOSE AND D-FRUCTOSE–ALUMINATE

Temperature (°C)	*Association constants*[a] *(liters/mol)*	
	D-*Glucose–aluminate*	D-*Fructose–aluminate*
43.0	0.146, 0.152	3.14
29.0	—	2.74
30.2	0.25	—
22.8	—	1.62
24.8	0.27, 0.32	—
16.0	—	2.60
16.7	0.59, 0.34	—
5.5	0.39, 0.78	—
3.9	—	3.41

[a]Association constant defined as [complex]/[free sugar][free $Al(OH)_4^-$]

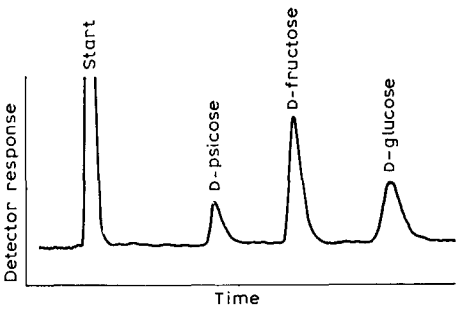
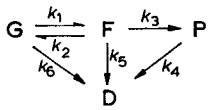


Fig. 2. Liquid chromatograph of typical products from a sodium aluminate-induced transformation of D-glucose. If D-mannose were present in measurable amounts, its peak would emerge between D-fructose and D-glucose.

with borate increased with decreasing temperature ($K^{35} = 125$, $K^{0} = 215$). The association constant of D-fructose–aluminate, as compared to D-glucose–aluminate, is approximately 5–10 times greater. This supports a closer association of aluminate with D-fructose than with D-glucose.

Mechanism of the transformation. — When batch reactions of D-glucose with sodium aluminate are conducted at temperature ranges from 14.5–60° under nitrogen, the formation of D-mannose is suppressed to less than measurable qualities (<0.5% of the total initial concentration of sugar). Only three, major, sugar species were observed in the transformation reactions, namely D-glucose, D-fructose, and D-psicose. A typical chromagram of the product solution is shown in Fig. 2. If D-mannose were present, it would give a peak between D-glucose and D-fructose. Other degradation-products were formed during the period the sugars were exposed to the highly alkaline conditions necessary for the existence of the aluminate ion, but these products were not identified.

In order to explain this lack of formation of D-mannose, the interaction of aluminate with D-glucose had to be examined. It was obvious from the extremely rapid formation of the complex, and the value of the association constants, that the transformation reaction involved conversion of one complexed species into another complexed species. Two possible reaction-models may be proposed to explain the observed products. The first model examined is shown in Fig. 3, where the k_2 rate constant would be zero. This conclusion would be based on the idea that the lack of formation of D-mannose would be due to an irreversible reaction of D-glucose–aluminate to D-fructose–aluminate, and D-fructose–aluminate to D-psicose–aluminate. A mechanism for this model would be based on a D-glucose–1-aluminate complex, which would be converted irreversibly into a D-fructose–aluminate complex. A reverse reaction ($k_2 > 0$) would necessitate the formation of a D-mannose–aluminate complex, because no mechanism for D-mannose–aluminate inhibition can be postulated from examination of the enol intermediate. To test this idea, kinetic data were collected at 59.5°, as shown in Fig. 4. By using the model shown in Fig. 3 and a mathematical technique based on least-squares minimization (described in detail in ref. 4),



G = D-glucose-aluminate complex; F = D-fructose-aluminate complex;
P = D-psicose-aluminate complex; D = all other products

Fig. 3. General scheme for the transformation of D-glucose induced by sodium aluminate. Based on differential equations describing the system, the specific rate-constants at constant pH and temperature may be determined. This technique is described in ref. 4.

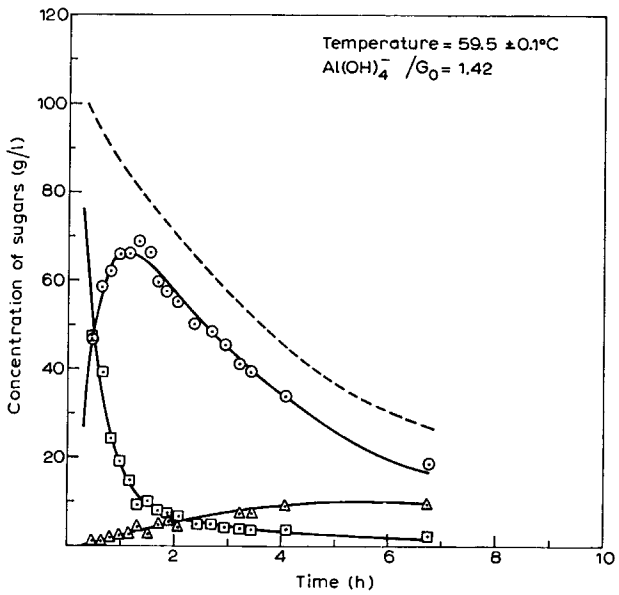


Fig. 4. Time–concentration data for a batch reaction of D-glucose–aluminate. The dashed line denotes the sum of the three reported sugar complexes, D-glucose–aluminate ⊡, D-fructose–aluminate ⊙, and D-psicose–aluminate △. The solid lines through the points represent a computer-generated reaction based on the model shown in Fig. 3, using values of $k_1 = 2.06$, $k_2 = 0.207$, $k_3 = 0.059$, $k_4 = 0.12$, $k_5 = 0.198$, and $k_6 = 0.36$ h^{-1}.

it was found that the reverse reaction of D-fructose–aluminate to D-glucose–aluminate (k_2) was significant and definitely exists. From this information, the first idea was rejected and a second mechanism was postulated, as shown in Fig. 5. This mechanism is based on a β-D-glucopyranose–1,3-aluminate complex proceeding through an enol-aluminate intermediate to α-D-fructofuranose–1,3,6-aluminate.

The enol intermediate remaining in its acyclic structure would shield the pi bond of C-2 from the mode of proton addition that would form D-mannose–aluminate, whereas the site that allows D-glucose–aluminate formation remains completely open. By using molecular models, all other possible complex-sites were examined; however, only the β-D-glucose–1,3-aluminate complex could account for the lack of D-mannose–aluminate complex formation by steric shielding of the pi-bond site.

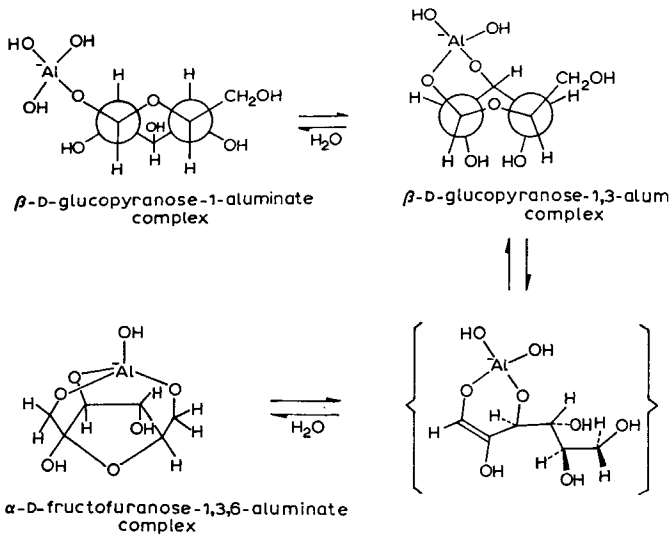


Fig. 5. Theorized mechanism for the transformation reaction. The acyclic structure of the 1,3-bridged, enol intermediate shields the pi-bond site from proton addition, which would otherwise lead to a D-mannose–aluminate complex.

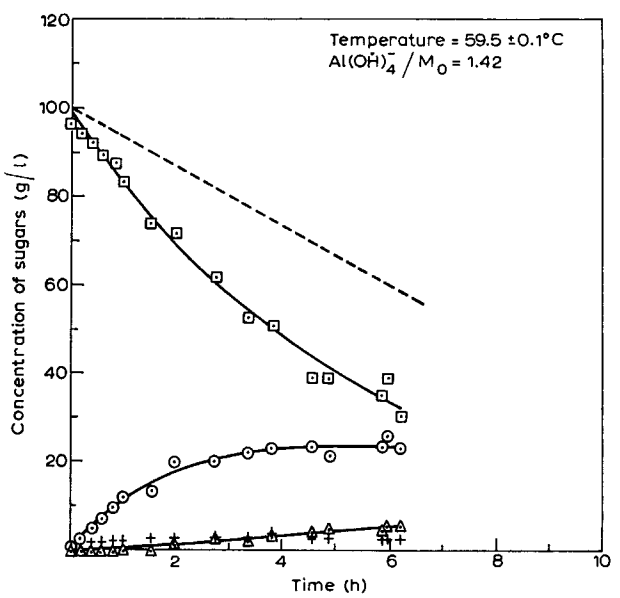
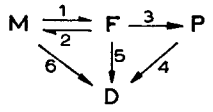


Fig. 6. Time–concentration data for a batch reaction of D-mannose–aluminate. The dashed line represents the sum of the four reported sugars, D-mannose–aluminate ⊡, D-fructose–aluminate ⊙, D-psicose–aluminate △, and D-glucose–aluminate +. The solid line represents a computer-generated reaction based on the model shown in Fig. 7. Note that the D-glucose–aluminate concentration remains relatively low and constant. This allows use of the model in Fig. 7 with less than 2% overall error.



k_1 = 0.130 (h^{-1})
k_2 = 0.000 (h^{-1})
k_3 = 0.068 (h^{-1})
k_4 = 0.153 (h^{-1})
k_5 = 0.155 (h^{-1})
k_6 = 0.050 (h^{-1})

Temperature = 59.5 ±0.1°
Molar ratio of $Al(OH)_4^-/M_0$ = 1.42

Fig. 7. Model scheme for the transformation of D-mannose–aluminate. The reported rate-constants were determined from the data shown in Fig. 6. Note that the reverse reaction (k_2) was found to be zero, thus supporting the mechanism theorized in Fig. 5.

In order to provide additional evidence for the enol intermediate that sterically shields the pi-bonding site responsible for the formation of D-mannose–1,3-aluminate, a batch reaction was conducted with D-mannose–aluminate as the initial reactant. The results of this reaction are shown in Fig. 6. The solid line was generated by using the model and rate constants shown in Fig. 7. The important result of this experiment was that the k_2 rate constant was found negligible, indicating that the enol intermediate is similar in this case to that involved in reactions initially starting with D-glucose–aluminate.

EXPERIMENTAL

Preparation of M *sodium aluminate solution.* — A solution of sodium aluminate was prepared from 32.3 g of $Na_2O \cdot Al_2O_3 \cdot 3H_2O$ (Fisher S-213) and 200 ml of water. The solution was filtered, degassed, analyzed for aluminum, and diluted to 1.0M ±0.03 with distilled water. It was used immediately and was not stored for more than 4 h before using.

Preparation of carbohydrate–aluminate complexes. — A measured volume of the M sodium aluminate solution was mixed with an equimolar amount of dry sugar. The solution was mixed until all of the sugar had dissolved, and the water-soluble complex was then immediately precipitated by addition of ethanol at a 1–10 ratio of alcohol. Before decanting off the supernatant, the solution was centrifuged at 1000 r.p.m. for 20 min at −10°. The complex was redissolved in distilled water and the process was repeated two more times. On the last occasion, the complex was dried under vacuum at room temperature. The solubility of the D-glucose–aluminate complex was determined to be 0.06 ± 0.04 μmol/ml at −10° in 90.9% (v/v) ethanol. The solubility of the D-fructose–aluminate complex was determined to be 0.41 μmol/ml at −10° in 90.9% (v/v) ethanol.

Carbohydrate analysis. — The concentration of D-glucose was determined by use of a Beckman model FRA-2001 glucose analyzer. Care was taken to adjust the sampled solution to pH 6–8 before measurement. The other sugars were analyzed by high-pressure liquid chromatography, by use of a Waters Associates, model

M 6000A chromatography pump, model UGK injector, model ALC/GRC 201 differential refractometer, model 660 solvent programmer, and μBondapak/carbohydrate column. A two-pen recorder model A5211-1 by Omniscribe and a computing integrator, model system 1 by Spectra Physics, was coupled with equipment. Peak identification was determined by addition of standards, and concentrations of unknowns were determined by using calibration constants based on peak area with both internal and external standards. Aluminate was removed from samples by formation of aluminum phosphate and precipitation.

Analysis for aluminum ion. — A quantitative analysis of aluminum by using Aluminon (aurintricarboxylic acid) was developed. The essential chemistry involves complexation of aluminum with aluminon accompanied with a color change[12-14], with absorption at 545 nm. The concentration of the unknown was adjusted to between 0.025–0.20 μmol/ml of Al^{3+} per ml of sample. The absorption in this range is independent of sugar concentration and reproducible, but nonlinear. Equipment used in the analysis consisted of a Perkin–Elmer double-beam spectrophotomer, model Coleman 124. The most important variables in the test procedure were the time allowed for color development and the exclusion of traces of iron from the system. Samples of carbohydrate–aluminate complex were prepared for analysis by addition of hydrochloric acid and formation of aluminum chloride.

Determination of association constants. — A stock solution of carbohydrate–aluminate complex was prepared. Duplicate 0.5-ml samples were withdrawn and placed in separate 20-ml test tubes and sealed with parafilm. In separate 10-ml test tubes, 5 ml of abs. ethanol was added and sealed. Water baths were adjusted to a desired temperature and then two samples and two ethanol-filled test tubes were placed in the water bath. After 10 min, the ethanol was added to the 20-ml test tubes and mixed by means of a vortex mixer to precipitate the complex. The solution was then centrifuged for 20 min at $-10°$. The supernatant was then analyzed for aluminum and carbohydrate content. Taking into account the solubility of the carbohydrate–aluminate complex, association constants were calculated.

Procedure for batch reaction. — A water bath equipped with a controller-circulator was set at 59.5 $\pm 0.1°$. A 250-ml vacuum flask was positioned with a magnetic stirrer and apparatus to maintain an oxygen-free atmosphere. To this system was added 217 ml of fresh M sodium aluminate solution and the solution allowed to reach bath temperature. D-Glucose, D-fructose, or D-mannose (27.5 g) was then added with constant mixing, followed by distilled water at the bath temperature to give a total solution-volume of 250 ml. Samples (1 ml) were removed at recorded time-intervals and immediately neutralized to pH 6.8 by addition of aqueous phosphoric acid. The samples were centrifuged to remove aluminum phosphate and were analyzed for carbohydrate content.

CONCLUSIONS

The isomerization of the β-D-glucopyranose–1,3-aluminate complex to the

α-D-fructofuranose–1,3,6-aluminate complex satisfies all the observed experimental data and therefore provides a reasonable mechanism for the use of correlating kinetic data. The lack of D-mannose–aluminate formation and the substantial amount of D-psicose–aluminate formed indicates that the reaction may be greatly controlled by how aluminate interacts with the sugars.

The following paper[4] provides further support for this mechanism by the good correlation observed during kinetic experiments.

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