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Branched-chain Sugars. XX. Kinetic Studies on the Epimerization of 1,2:5,6-Di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose[1]

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A study was made on the kinetics of the epimerization of 1,2: 5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose in nitromethane to its 3-epimer in the presence of a small amount of sodium methoxide. The activation energy was found to be 75±8 kJ/mol, the intermediate in epimerization being 1,2: 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose with use of the labelled compound.

Cyanohydrin and nitromethane syntheses have been widely used in the reaction of carbohydrate field for lengthening the carbon chain of reducing sugars. The stereoselectivity in the formation of two isomers is explicable on the basis of conformational grounds, since in the zigzag conformation the β-hydroxyl groups come into unfavorable eclipsed proximity in the 2,4-*erythro* isomer but not in the 2,4-*threo* isomer.[2] However, alteration of the reaction conditions such as pH can sometimes reverse the selectivity.[3] Recently, these reactions were applied to branched-chain sugar synthesis.[4] Data accumulated indicate that one epimer or a mixture of epimers is obtained depending on the rate of epimerization of the kinetically-controlled product to thermodynamically stabler isomer.

In a previous paper a report was given on the composition of isomers in the reaction of nitromethane with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) in the presence of a slight excess of sodium ethoxide over the equivalent. It was found that the reaction at −78 °C for 30 min or at 20 °C for 3 min in the usual solvent gives exclusively 1,2:5,6-di-*O*-isopropylidene-3-*C*-nitromethyl-α-D-allofuranose (**2**), while the reaction at 25 °C for 30 min only the corresponding D-*gluco* isomer (**3**).[5] The results indicate that the kinetically-controlled product **2** epimerizes rapidly into **3** at room temperature. This paper deals with the measurement of activation energy and deduction of the pathway of epimerization.

Experimental

Solutions were evaporated under reduced pressure at bath temperature not excceding 50 °C. NMR spectra were taken with a JEOL SP-100 spectrometer in deuteriochloroform containing tetramethylsilane as an internal reference. TLC was carried out on glass plates coated with Kieselgel 60F 254 (Merck) equilibrated in the atmosphere before use. The solvent system employed was ether–hexane (1:1 v/v). R_f values of compounds **1**, **2**, and **3** were 0.07, 0.26, and 0.30, respectively.

*1,2:5,6-Di-*O*-isopropylidene-3-*C*-(nitromethyl-*^{14}C*)-α-D-allofuranose.* To a suspension of excess silver nitrite in ether (20 ml) was added with stirring a solution of methyl iodide [0.3 ml (5.0 mmol) having total radioactivity of 500 μCi, the Radiochemical center, Amersham] in ether (10 ml). The reaction mixture was stirred for 20 h in the dark at room temperature, and then filtered. The filtrate was carefully concentrated to give crude nitromethane (44 mg).

To a solution of **1** (250 ml) in ethanol (1.5 ml) was added a solution of nitromethane-^{14}*C* (44 mg) and sodium ethoxide (15 mg sodium metal in 3 ml ethanol) at a temperature below −30 °C. The reaction mixture was kept at 0 °C for 48 h and then half of the reaction mixture was neutralized with 60% acetic acid and extracted with chloroform. The resulting solution was washed with water and evaporated after addition of an authentic sample of non-labelled **2** (600 mg) to give a solid, which was recrystallized twice from ethanol. Specific activity of **2** (370 mg) thus obtained was 8.62 nCi/mg.

From the remaining half of the reaction mixture was obtained in a similar manner **2** (272 mg) having specific activity of 10.18 nCi/mg. The recrystallized needles were checked on TLC to show one spot (R_f 0.26).

Epimerization of ^{14}C*-Labelled* ***2*** *to* ***3***. To a solution of nitromethane (0.9 ml, 16.7 mmol) and sodium ethoxide (4.5 mg, 19.6 mmol sodium in 0.9 ml ethanol) was added a solution of ^{14}C-labelled **2** (8.62 nCi/mg, 355 mg, 1.11 mmol) in ethanol (9 ml) at room temperature. The reaction mixture heated at 65 °C for 30 min showed the presence of **3** and a trace amount of **1** on TLC, was then neutralized with 60% acetic acid and extracted with chloroform. The extract was washed with water and evaporated to give crystals which were recrystallized twice from ethanol–hexane to give pure **3** (48 mg, R_f 0.30) of 0.585 nCi/mg.

If the activity of ^{14}C-labelled **2** was completely reduced with non-radioactive nitromethane added to the isomerization mixture, the activity of **3** should be 0.537 nCi/mg. Thus, the conversion ratio of the activity corresponded to 99% of the theoretical value.

A similar epimerization of **2** (272 mg, 0.853 mmol. 10.18 nCi/mg) in the presence of non-labelled nitromethane (266.5 mg, 4.37 mmol) gave pure **3** (44.9 mg, 1.56 nCi/mg), its conversion ratio of activity being 101% of the theoretical value.

Measurement of Epimerization Rate of ***2*** *into* ***3*** *at various Temperatures.* A solution **2** (200 mg, 0.627 mmol) in nitromethane (2 ml, 38 mmol) was added into nitromethane (2 ml) containing sodium methoxide (0.109 mmol in 0.25 ml methanol) at various temperatures controlled by means of a thermostat. Each 0.4 ml of the reaction mixture was pipetted out at appropriate intervals, acidified promptly with 60% acetic acid to stop the epimerization, and then extracted with chloroform. The chloroform layer was washed with water, and then evaporated. The extent of the isomerization in the residual solid was estimated from the ratio of the intensities of H-1 (δ 5.91 for **2**, 5.82 for **3**) and OH (δ 3.55 for **2**, δ 3.30 for **3**) protons in the NMR spectrum. Measurements were carried out at 0, 45, 65, and 95 °C (±0.1 °C). The results are summarized in Table 1. No isomerization was observed at 0 °C for 10 h.

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TABLE 1. EPIMERIZATION RATE (%)

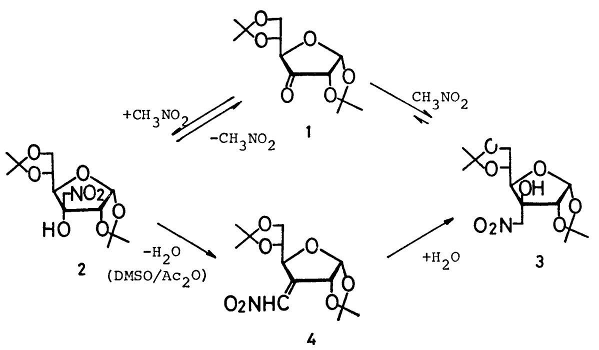
Temp (°C)	Reaction time (min)						
	0	2	4	6	10	30	60
45	0	0	0	0	3.5	9.6	19.3
65	0	0	6.5	10.8	20.0	44.6	67.8
95	0	17.2	36.7	53.5	69.0	92.5	94.0

Discussion

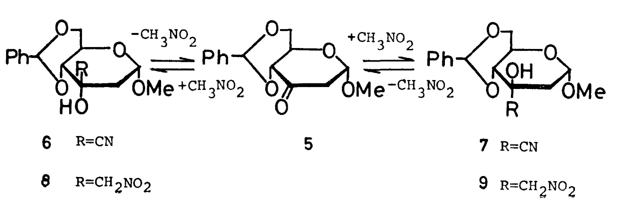
Both cyanohydrin and nitromethane reactions are reversible, epimeric ratios in the asymmetric induction depending on the reaction conditions. However, except for the dependency of reaction rate on pH,6) few kinetic studies have been carried out.

Albrecht and Moffatt7) presumed the dehydration of the initially formed **2** to 1,2: 5,6-di-*O*-isopropylidene-3-*C*-nitromethylene-α-D-*ribo*-hexofuranose (**4**), followed by readdition of water, to be the cause of the formation of a mixture of **2** and **3** from **1** in the presence of excess butoxide. They demonstrated the conversion of **2** into **4** by treatment with dimethyl sulfoxide and acetic anhydride at 20 °C for 24 h, and that of **4** into **3** by the base-catalyzed hydration. Contrary to their presumption, our experimental results with labelled **2** showed complete reduction of the specific activity with non-labelled nitromethane, indicating that the epimerization of **2** into **3** proceeds *via* **1** (Scheme 1). Bourgeois8) reported the epimerization of the cyanohydrin of D-*allo* configuration from **1** isomerizes into D-*gluco* isomer in aqueous potassium cyanide at room temperature. The isomerization should proceed also *via* **1**, since no equivalent intermediate to **4** can be considered in this case.

It seems likely that this type of isomerization is common in the reaction of uloses with hydrogen cyanide or nitromethane under the alkaline conditions, though the factors to control the thermodynamic stability can not be predicted correctly. The reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranoside (**5**) and hydrogen cyanide in pyridine at room temperature gave a 21:1 mixture of methyl 4,6-*O*-benzylidene-3-*C*-cyano-2-deoxy-α-D-*ribo*-hexopyranoside (**6**) and its α-D-*arabino* isomer (**7**),9) the predominancy of **6** being attributed to the hydrogen bonding between axial hydroxyl group at C-3 and methoxyl oxygen at C-1.10) **7** was preponderantly obtained in the same reaction in ether and aqueous sodium hydrogencarbonate.11)



Scheme 1.



Scheme 2.

Rosenthal and Ong12) reported that the reaction of **5** and excess nitromethane in methanol in the presence of equimolar sodium methoxide at room temperature for 16 h gives methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-nitromethyl-α-D-*ribo*-hexopyranoside (**8**) and the D-*arabino* isomer (**9**) in 63 and 22% yields, respectively. In our experiments, however, the same reaction in chloroform in the presence of three equimolar triethylamine as a basic catalyst at room temperature for 72 h gave only **8** in 82% yield. This indicates that the isomerization rate is smaller in the presence of a weaker base. In fact, treatment of **8** in nitromethane with three equimolar sodium methoxide at room temperature for 1 h gave a 1:1 mixture of **8** and **9**.13)

For measurement of the activation energy of the isomerization of **2** into **3**, the conditions described in Experimental were chosen. The plots of $\ln a/a-x$,

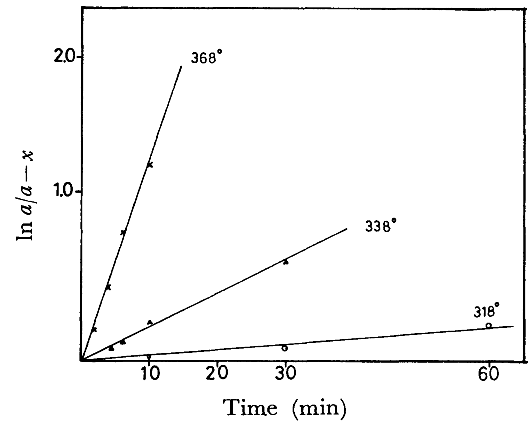


Fig. 1. Plots of a first-order rate equation for the epimerization of **2**.

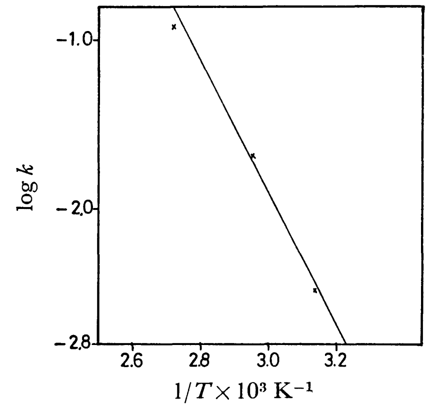


Fig. 2. Arrhenius plot.

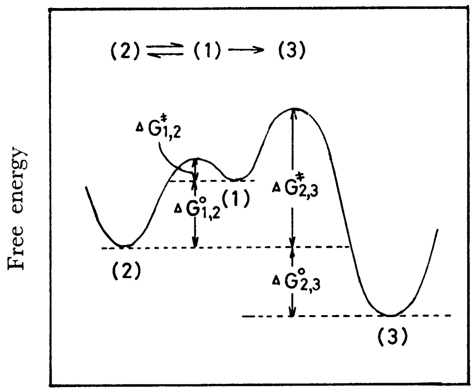


Fig. 3. Energy diagram between **1**, **2**, and **3**.

where x is the epimerization ratio, against time at three different temperatures were found to be linear at the initial stage, indicating that the reaction is of first-order (Fig. 1). The slopes of these lines give the times of half-conversion to be 5.65, 34.7, and 211 min at 95, 65, and 45 °C, respectively, and also the rate constant k. The plot of $\log k$ against the reciprocal of temperature shows a linear relationship (Fig. 2), its slope giving an activation energy of epimerization of 75 ± 8 kJ/mol. The energy diagram of this raction system is given in Fig. 3. Since the reaction of **1** with nitromethane at −78 °C gave kinetically controlled product **2** selectively, $\Delta G^{*}_{1,2}$ value would be small as in the usual equilibration reaction. A comparison of bond energy between **1** and **2** indicates that $\Delta G^{\circ}_{1,2}$ value is *ca.* 50 kJ/mol, and the value of isomerization energy from **2** to **3**, $\Delta G^{*}_{2,3}$ we obtained is reasonable. Although $\Delta G^{\circ}_{2,3}$ value could not be measured, it would be larger than $\Delta G^{\circ}_{8,9}$ in the systems of **5**, **8** and **9**.

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