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KINETIC STUDIES ON THE REARRANGEMENT OF 3,4-DI-*O*-BENZYL-1,2-*O*-(1-METHOXYETHYLIDENE)-β-L-RHAMNOPYRANOSE WITH A CATALYTIC AMOUNT OF 1,1,3,3-TETRAMETHYLUREA–TRIFLUOROMETHANESULFONIC ACID AT DIFFERENT TEMPERATURES

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ABSTRACT

The kinetics of the rearrangement of 3,4-di-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-L-rhamnopyranose to methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside with a catalytic amount of 1,1,3,3,-tetramethylurea–trifluoromethanesulfonic acid in deuterated chloroform was studied by ^{1}H-n.m.r. spectroscopy at different temperatures. This isomerization, irrespective of temperature, seems to occur by an intramolecular mechanism, and it follows first-order kinetics.

INTRODUCTION

Carbohydrate 1,2-orthoesters have long been known[1], and have been used for the synthesis of 1,2-*trans*-glycosides, including some having complex aglycons[2]. The synthesis of 1,2-*trans*-glycosides from 1,2-orthoesters is based on an acid-catalyzed rearrangement reaction[3].

Mechanistic aspects of the formation of 1,2-*trans*-glycosides have been discussed in detail[2–4]. It is now generally accepted that a glycosyl halide derivative containing a participating group at C-2, in the presence of an acid acceptor, will lead to a 1,2-*trans*-glycoside (thermodynamic product) *via* the intermediacy of a 1,2-acyloxonium ion intermediate[2–4]; and it is now recognized that a 1,2-orthoester (kinetic product) enjoys at least transient existence in such reactions[5,6].

In neutral or basic media, the formation of the 1,2-orthoester results from trapping of the 1,2-acyloxonium intermediate with an appropriate glycosyl acceptor[7,8], and this can be rationalized by using the concept of "hard" and "soft" acids and bases[9], if the glycosyl acceptor and the acyloxonium ion are considered to be respectively a "hard" base and a "hard" acid.

As previously reported[10,11] a mixture of silver trifluoromethanesulfonate and 1,1,3,3-tetramethylurea promotes the reaction between glycosyl halides having a

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participating acyloxy group at C-2 and glycosyl acceptors, to yield 1,2-*trans*-glycosides. Evidence suggests that the eventual 1,2-*trans* product is formed *via* the intermediate 1,2-orthoester[12]. The conjugate acid of 1,1,3,3-tetramethylurea appears to serve as a catalyst for the rearrangement of the 1,2-orthoester[12]. Also, it was demonstrated[12] that a catalytic amount of 1:1 trifluoromethanesulfonic (triflic) acid–tetramethylurea effects quantitative and regiospecific isomerization of the 1,2-orthoesters to the corresponding 1,2-*trans*-glycosides. It was of interest to examine the effect of this conjugate acid of tetramethylurea on a 1,2-orthoester other than a member of the D series. An L-rhamnose 1,2-orthoester was therefore selected for this rearrangement reaction, as α-linked L-rhamnopyranosides are contained in plant glycosides, glycolipids[13], and immunologically important polysaccharides[14]. Thus 3,4-di-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-L-rhamnopyranose (**1**) was quantitatively converted by a catalytic amount of the aforementioned conjugate acid into methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**5**).

We now report the results of kinetic studies on the rearrangement of 1,2-orthoester **1** to 1,2-*trans*-glycoside **5** by a catalytic amount of 2:1 tetramethylurea–triflic acid at different temperatures.

RESULTS AND DISCUSSION

The rearrangement of compound **1** with a catalytic amount of 2:1 tetramethylurea–triflic acid, effected in deuterated chloroform at different temperatures, was monitored by ^{1}H-n.m.r. spectroscopy, as the isomerization to methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**5**) would provide a new acetyl signal at O-2, uncomplicated by other signals.

The rearrangement of the 1,2-orthoester **1** with a catalytic amount of the conjugate acid of tetramethylurea did not occur at −70°, and proceeded only very slowly at −40°. At −23°, compound **1** gave an almost quantitative yield of **5** in ~140 min, and, at −10, −8, and −1°, the same isomerization was effected after ~85, ~70, and ~25 min, respectively. At 20°, the rearrangement of **1** to **5** was almost instantaneous.

The rearrangement of the 1,2-orthoester **1** to the 1,2-*trans*-glycoside **5** was found to obey first-order kinetics. The specific rate-constants (k) of the rearrangement reactions at different temperatures were obtained from the slopes of the graphical plots of $\ln(a - x)$ *vs.* time, in the range below 80% completion, as depicted in Fig. 1. The values of $\ln(a - x)$ are given in Table I.

The specific, first-order rate-constant (k) of the rearrangement reactions at different temperatures are listed in Table II. The activation energy, E_A, was determined from the slope, $-E_A/2.303R$, of the appropriate Arrhenius plot of log k *vs.* 1/T, shown in Fig. 2.

The thermodynamic parameters of activation, namely, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$, were obtained from the following expressions[15].

$$\Delta G^* = -RT \ln(kh/\bar{k}T),$$

where k = rate constant, T = absolute temperature (K), $\bar{k}$ = 1.380 54 × 10^{-23} $J.K^{-1}$ (Boltzmann constant), h = 6.6256 × 10^{-34} J.s (Planck constant), R = gas constant = 8.3143 $J.K^{-1}.mol^{-1}$,

$$\Delta H^* = E_A - RT, \quad \text{and}$$

$$\Delta S^* = (\Delta H^* - \Delta G^*)/T.$$

The thermodynamic parameters of activation, ΔG^*, ΔH^*, and ΔS^*, provide a suitable means for studying the properties of the activated complex, and the solvating power of the medium for this rearrangement reaction catalyzed by tetramethylurea–triflic acid. The thermodynamic parameters of activation of the rearrangement reaction of 1,2-orthoester **1** to 1,2-*trans*-glycoside **5** are collected in Tables III and IV, respectively, and, as expected, show very small temperature-dependence. The large, negative value of the free entropy of activation (ΔS^*) seems to suggest, at first sight, the presence of an intimate-pair "acyloxonium triflate" **4**

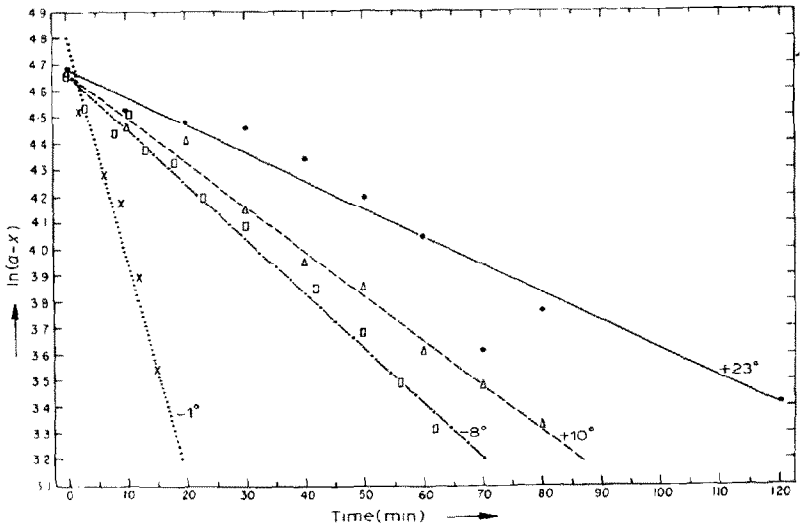


Fig. 1. Plot of $\ln(a - x)$ *vs.* time (min) for the rearrangement reaction at four temperatures (°C). [First-order rate-constant (k) and its confidence interval for each reaction were calculated from slopes of lines.]

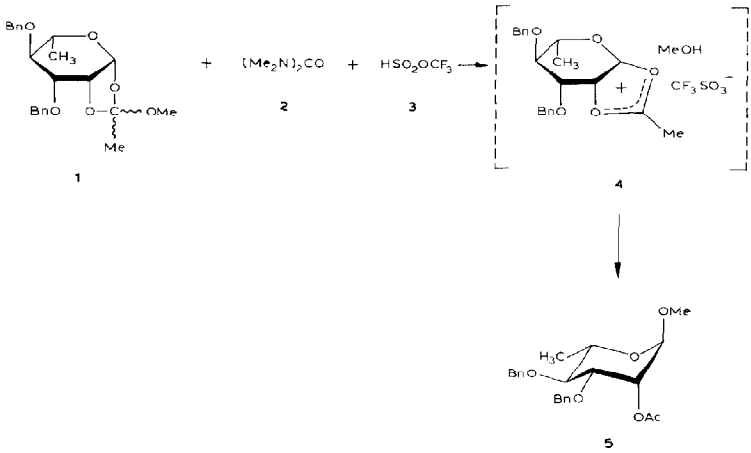
TABLE I

THE VALUES OF $\ln(a - x)$ CALCULATED FOR THE DIFFERENT TIME-INTERVALS AT VARIOUS TEMPERATURES

Time (min)	*1,2-Orthoester (%)*	*1,2-trans-glycoside(%)*	(a − x)	*ln*(a − x)
Rearrangement at −23°				
10	10.62	1	91.4	4.52
20	7.62	1	88.4	4.48
30	6.40	1	86.5	4.46
40	3.29	1	76.7	4.34
50	2.00	1	66.7	4.20
60	1.35	1	57.5	4.05
70	1	1.19	45.5	3.81
80	1	1.29	43.5	3.77
120	1	2	33.3	3.51
Rearrangement at −10°				
10	6.52	1	86.7	4.46
20	4.52	1	81.9	4.41
30	1.74	1	63.5	4.15
40	1.08	1	52.1	3.95
50	1	1.13	46.9	3.85
60	1	1.69	37.1	3.61
70	1	1.07	32.5	3.48
80	1	2.57	28.0	3.33
Rearrangement at −8°				
10	5.57	1	84.8	4.44
13	3.87	1	79.5	4.37
18	3.11	1	75.7	4.32
20	2.00	1	66.9	4.20
22	1.59	1	61.5	4.11
40	1	1.1	47.1	3.85
50	1	1.5	39.6	3.67
62	1	2.6	27.5	3.31
70	1	3.5	22.2	3.10
Rearrangement at −1°				
6	2.49	1	75.1	4.32
10	2.04	1	67.1	4.21
12	1	1.03	49.1	3.89
15	1	1.91	34.4	3.54
18	1	3.14	24.1	3.18
22	1	4.26	19.0	2.94
25	1	6.19	13.8	2.62

(see Scheme 1), which also suggests a very rigid transition-state. It is assumed that, irrespective of the temperature at which the isomerization occurs, the fate of the acyloxonium triflate **4** is to break down to the 1,2-*trans*-glycoside **5** by an intramolecular rearrangement obeying first-order kinetics.

It is known that the stabilization of the activated complex by the solvent molecules involves restriction of motion of some of the solvent molecules. Polar



Scheme 1. Mechanistic proposal for the rearrangement of 1,2-orthoester **1** to 1,2-*trans*-glycoside **5**, catalyzed by the conjugate acid of 1,1,3,3-tetramethylurea.

TABLE II

SPECIFIC, FIRST-ORDER RATE-CONSTANT k FOR THE REARRANGEMENT OF 1,2-ORTHOESTER **1** TO 1,2-*trans*-GLYCOSIDE **5**, CATALYZED BY THE CONJUGATE ACID OF 1,1,3,3-TETRAMETHYLUREA AT DIFFERENT TEMPERATURES IN DEUTERATED CHLOROFORM

T (°C)	k × 10^3 (min^{-1})	4 + log k
−1	86.58 ±6.41	2.937
−8	21.10 ±4.59	2.324
−10	17.00 ±1.73	2.230
−23	10.79 ±3.44	2.033

TABLE III

FREE ENERGY OF ACTIVATION (ΔG^*) FOR THE REARRANGEMENT OF 1,2-ORTHOESTER **1** TO 1,2-*trans*-GLYCOSIDE **5**, CATALYZED BY THE CONJUGATE ACID OF 1,1,3,3-TETRAMETHYLUREA AT DIFFERENT TEMPERATURES IN DEUTERATED CHLOROFORM, CALCULATED WITH A 95% CONFIDENCE INTERVAL

T (°C)	ΔG^* ($kJ.mol^{-1}$)	
	Mean	*95% Confidence interval*
−1	82.48	82.31–82.65
−8	73.23	72.81–73.77
−10	73.14	72.93–73.35
−23	70.38	69.79–71.18

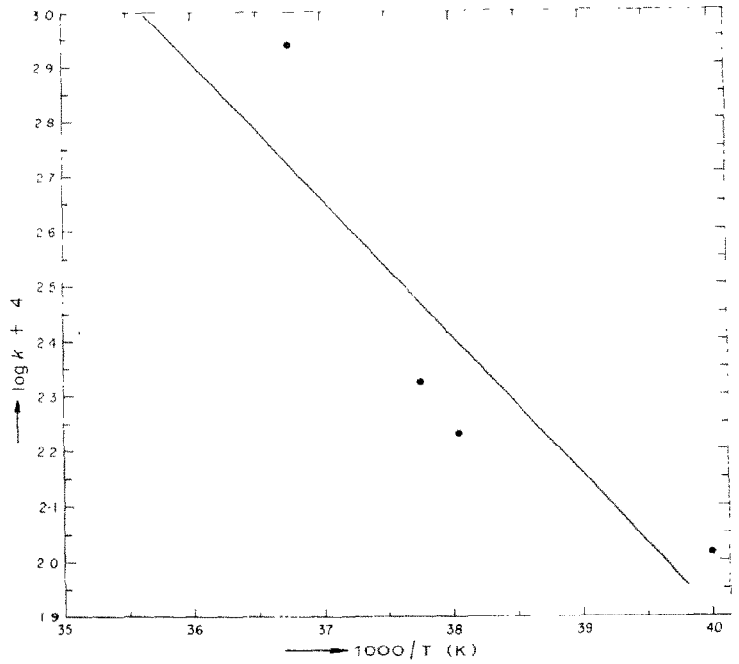


Fig. 2. Arrhenius plot of log (k + 4) *vs.* 1000/T for the rate constants of the reactions plotted in Fig.1

TABLE IV

FREE ENTHALPY OF ACTIVATION ($\Delta H^{\neq}$) AND FREE ENTROPY OF ACTIVATION ($\Delta S^{\neq}$) FOR THE REARRANGEMENT OF 1,2-ORTHOESTER **1** TO 1,2-*trans*-GLYCOSIDE **5**, CATALYZED BY THE CONJUGATE ACID OF 1,1,3,3-TETRAMETHYLUREA AT DIFFERENT TEMPERATURES IN DEUTERATED CHLOROFORM

T(°C)	$\Delta H^{\neq}$ (kJ.mol^{-1})[a]	$\Delta S^{\neq}$ (J.K^{-1} mol^{-1})	
		Mean	*C.I.*
−1	45.08	−136.88	±22.73
−8	45.14	−106.04	±23.45
−10	45.19	−106.48	±23.53
−23	45.27	−108.82	±24.91

[a]The error term used for calculation of $\Delta H^{\neq}$ is ±6.167 kJ.mol^{-1}, calculated for E_A = 47.35 ±6.167 kJ.mol^{-1}.

solvents having permanent dipoles, such as acetonitrile or nitromethane, are frequently used in the synthesis of 1,2-*trans*-glycosides. These solvents will therefore be preferentially oriented around the transition state, hence creating an attractive interaction which will result in a greater loss in entropy and, as a result, solvation. In these solvents, the rearrangement of 1,2-orthoester **1** to glycoside **5** was found to proceed faster than when conducted in the (relatively nonpolar) deuterated chloroform, at the same temperature.

In conclusion, it may be postulated that the large, negative values for the free entropy of activation (ΔS^*) obtained from the isomerization reaction of the 1,2-orthoester **1** to the 1,2-*trans*-glycoside **5** at different temperatures are consistent with a highly constrained transition-state (acyloxonium triflate **4**), and that the reaction proceeds by an intramolecular mechanism.

EXPERIMENTAL

General. — General methods used were as described earlier[12]. Thin-layer chromatography was performed with Merck precoated plates of silica gel 60 F-254, and the detection of compounds was achieved by quenching of u.v. fluorescence, and by charring after spraying with 5% sulfuric acid in ethanol.

^{1}H-N.m.r. spectra were recorded at 79.9 MHz in the pulsed, Fourier-transform mode with a Varian CFT-20 spectrometer at different temperatures. Proton chemical shifts are expressed relative to 1% tetramethylsilane in deuteriochloroform.

Calculations of regression, standard error, and confidence intervals were made for the specific rate-constants (k), activation energy (E_A), and the thermodynamic parameters of activation (ΔG^*, ΔH^*, and ΔS^*), according to standard methods[16], and the last three are given in Tables III and IV.

*Rearrangement of 3,4-di-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-*L*-rhamnose* (**1**) *to methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-*L*-rhamnopyranoside* (**5**) *with 1,1,3,3-tetramethylurea–trifluoromethanesulfonic acid.* — A solution (0.5 mL) of the 1,2-orthoester[17] **1** (1 mmol) in deuteriochloroform (5 mL) in a n.m.r. tube was cooled for 1 h in the probe of the CFT-20 Varian spectrometer to the desired temperature, and was then treated with a catalytic amount (5 μL) of a solution of 1,1,3,3-tetramethylurea–trifluoromethanesulfonic acid (2:1) in deuteriochloroform that was M with respect to triflic acid and had been precooled to the temperature used for the rearrangement. The ^{1}H-n.m.r. spectra were recorded at different time-intervals at −23, −10, −8, and −1°. The concentration ($a - x$) of the unreacted 1,2-orthoester was calculated from the integration of the C–CH_3 signal at δ 1.73 and the alkoxyl signal at δ 3.29; the concentration of the 1,2-*trans*-glycoside (**5**) was calculated from the integration of the newly formed acetyl signal at δ 2.17, and aglycon signal at δ 3.37.

The ^{1}H-n.m.r. data for **1** in $CDCl_3$ are: δ 1.31 (d, 3 H, $J_{5,6}$ 5.8 Hz, 3 H-6), 1.73 (s, 3 H, C-CH_3), 3.29 (s, 3 H, OCH_3), 3.27–3.79 (m, 3 H, H-3,4,5), 4.40 (dd,

1 H, $J_{2,3}$ 3.7, $J_{1,2}$ 2.4 Hz, H-2), 4.58–5.02 (m, 4 H, 2 PhCH_2), 5.28 (d, 1 H, $J_{1,2}$ 2.4 Hz, H-1), and 7.34 (bs, 10 H, 2 $PhCH_2$).

The ^{1}H-n.m.r. data for **5** in $CDCl_3$ are: δ 1.38 (d, 3 H, $J_{5,6}$ 6.0 Hz, 3 H-6), 2.17 (s, 3 H, CH_3CO), 3.37 (s, 3 H, OCH_3), 3.88 (dd, 1 H, $J_{2,3}$ 4, $J_{3,4}$ 10 Hz, H-3), 5.32 (dd, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 4 Hz, H-2), 7.34 (bs, 10 H, 2 $PhCH_2$), and 3.35–5.0 (remaining protons).

T.l.c. in 3:1 Skellysolve B–ethyl acetate was used to check the complete conversion of the 1,2-orthoester **1** into the corresponding glycoside **5**

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