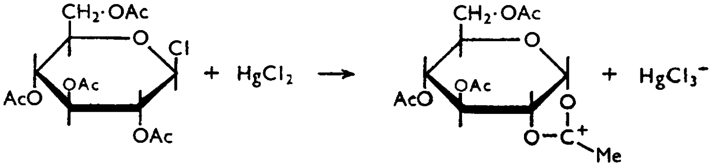
443. *The Reactivity of the* O-*Acylglycosyl Halides. Part VII.* Anomerisation of Tetra-*O-*acetyl-β-D-glucosyl Chloride.*

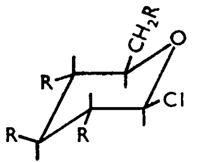
By G. L. MATTOK and G. O. PHILLIPS.

The anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in acetone, measured polarimetrically, is a first-order reaction. The reaction rate is enhanced by addition of lithium chloride or bromide, and by increasing the ionising power of the medium. Experiments using lithium radio-bromide establish that there is negligible halogen-exchange, and that anomerisation is the main process. The results cannot be accounted for solely on the basis of complete ionisation of the halide, and an intramolecular mechanism is therefore postulated for the anomerisation.

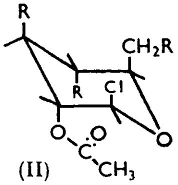
SOLVOLYTIC reactions of tetra-*O*-acetyl-β-D-glucosyl chloride proceed by way of an intermediate cyclic carbonium ion arising from the participation of the neighbouring group at position 2. Addition of mercuric chloride or other electrophilic catalysts increases the reaction rate by assisting the removal of the halogen without affecting the general nature of the ionisation process:



Decreasing the ionising power of the medium markedly decreases the rate of solvolysis.[1] However, in dry acetone, and in other solvents of low ionising power which do not react with the halogen atom, tetra-*O*-acetyl-β-D-glucosyl chloride spontaneously rearranges to the anomeric form.[2] Hassel and Ottar [3] considered this reaction to be related to the general substitution reaction of the S_N2 type where the new and the old substituent were identical. On this basis they considered that interaction between *cis*-erected (axial) 1- and 5-substituents on the same side of the ring is the main factor governing the stability of the anomeric *O*-acylglycosyl halides. Lemieux,[4] however, regards this as an over-simplification and considers that the theory is inconsistent with spontaneous anomerisation. For example, according to Hassel and Ottar's theory, tetra-*O*-acetyl-β-D-glucosyl chloride would exist in the Cl conformation (I) since the 1C conformation (II) would be highly unstable. However, participation of the 2-acetoxy-group in replacement reactions at position 1, now well established, requires the molecule to assume the 1C conformation at the first stage of the reaction. In the present work, the mechanism of anomerisation is investigated, and the rôle of lithium halides clarified.



(I)



(II)

R = OAc

---

* Part VI, *J.*, 1958, 130.

[1] Mattok and Phillips, *J.*, 1957, 268.

[2] Schlubach, Stadler, and Wolf, *Ber.*, 1928, **61**, 287.

[3] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929.

[4] Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 1.

RESULTS

Order of the Reaction.—The rate of anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride is of the first order; good first-order constants, calculated from the first-order rate equation, are given throughout the run (Table 1). Varying the initial concentration of the sugar halides within a two-fold range does not influence the rate constant (Table 2).

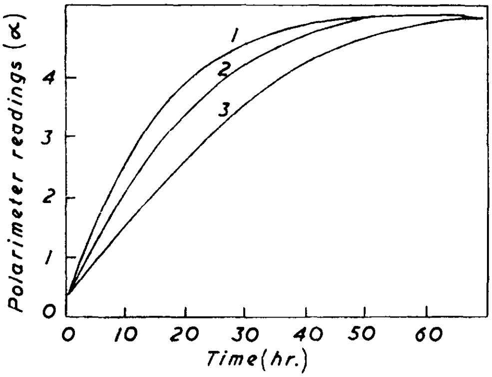
Addition of Lithium Halides.—The rate of anomerisation is enhanced on addition of lithium halides. The first-order constant increases linearly with lithium bromide concentration in the range 1·9—5·0 × 10^{-2}M and for lithium chloride in the range 5·0—7·4 × 10^{-2}M (Table 3). The order with respect to lithium chloride is 0·5, and with respect to lithium bromide is 0·4. Extrapolation of the rate constants indicates that the linear relation is maintained to zero concentration of lithium halide. The extrapolated value of k_1 for zero concentration of lithium chloride is 9·3 × 10^{-6} sec.$^{-1}$ and for that of lithium bromide is 9·2 × 10^{-6} sec.$^{-1}$; and these values are in good agreement with the rate of anomerisation in dry acetone (k_1 9·5 × 10^{-6} sec.$^{-1}$). The final rotation of the solution is not affected by the presence of either of the lithium salts see (Figure). The constant value corresponds to 80% conversion of the β- into the α-anomer.

TABLE 1. *Anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in acetone at 25°. First-order constants.*

Time (min.)	4	29	55	84	130	186
α	−0·02°	+0·04°	+0·11°	+0·19°	+0·30°	+0·45°
$10^6 k_1$ (sec.$^{-1}$)		9·95	9·85	9·99	9·65	9·85

TABLE 2. *First-order anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride. Variation of initial concentrations.*

10^2[RCl] (M)	7·92	6·45	4·98	4·11	3·6
$10^6 k_1$ (sec.$^{-1}$)	9·90	9·72	9·63	9·81	9·69



*Anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in acetone with or without lithium bromide or chloride.*

[RCl] = 0·05M. 1, [LiBr] = 0·05M. 2, [LiCl] = 0·05M. 3, *Dry acetone.*

TABLE 3. *Effect of lithium halides in the anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in acetone at 25°. First-order constants.*

[LiBr] (10^{-2}M)	5·01	4·57	4·16	5·37	2·52	1·87
$10^5 k_1$ (sec.$^{-1}$)	1·81	1·78	1·66	1·52	1·38	1·24

[LiCl] (10^{-2}M)	7·43	6·33	5·00
$10^5 k_1$ (sec.$^{-1}$)	1·83	1·75	1·52

Rate of Exchange with Lithium Radio-bromide.—Lithium radio-bromide was added to tetra-*O*-acetyl-β-D-glucosyl chloride in acetone at 25°, and the sugar halide examined for radioactivity at intervals, after separation from the inorganic halide. The proportion of radioactivity transferred to the sugar halide in 0·5, 2·5, and 6 hr. was 0·0, 0·05, and 0·5% respectively.

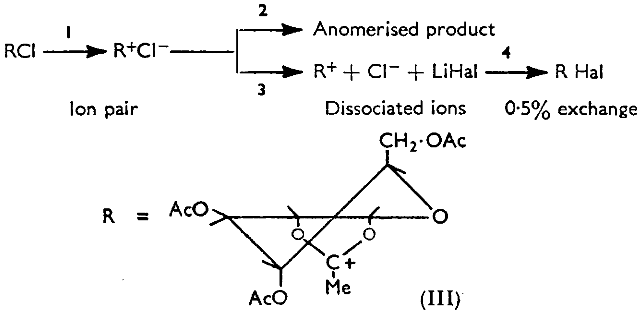
Effect of Varying the Ionising Power of the Solvent.—In benzene (ε 2·28 at 20°) no anomerisation was detected after 48 hr. In nitromethane (ε 39·4 at 20°) first-order anomerisation occurred with k_1 1·45 × 10^{-5} sec.$^{-1}$ at 25°, which is a 50% increase on the anomerisation rate in dry acetone (ε 21·0 at 20°).

DISCUSSION

Our results support an ionic mechanism for the anomerisation of tetra-*O*-acetyl-β-D-glucosyl 1-chloride rather than the bimolecular replacement suggested by Hassel and Ottar.[3] In dry acetone the rate is dependent on the first power of the concentration of sugar halide only, and on the ionising power of the solvent. Addition of lithium halides slightly increases the rate. The results indicate that the halide ions from the lithium salts do not participate by a bimolecular process, but exert a positive salt effect which facilitates the partial ionisation; this is supported first by experiments with lithium radio-bromide wherein no appreciable radioactivity was transferred to the sugar halide; and secondly, for tetra-*O*-acetyl-β-D-glucosyl chloride in acetone, the final optical rotation of the solution is independent of the nature of the lithium halide, indicating that the main product is the same in the presence of either lithium chloride or bromide (see Figure). Under comparable conditions for several *O*-acylglycosyl 1-halides, however, bimolecular exchange of halogen predominates. For example, when sodium iodide is added to tetra-*O*-acetyl-α-D-glucosyl bromide in acetone, the corresponding iodide[5] is formed. Evidence for similar exchange reactions will be presented in a later paper.

On theoretical grounds also it would be expected that ionisation to form the well-established cyclic ion (III) would be energetically more favourable than the S_N2 transition state[3] where there would be appreciable steric hindrance between the departing groups and the erected groups at positions 3 and 5.

The small amount of halogen exchange in the tracer experiments also indicates that the sugar halide does not completely ionise to give a free cyclic carbonium ion. Clearly the free ion would combine with radio-bromide ions present in the solution. Rather the insignificant amount of halogen exchange indicates an intramolecular mechanism involving the departing halogen atom. Mechanisms of this type by way of undissociated ion pairs now appear well founded. Lemieux and his collaborators[6] have shown that a similar mechanism operates during the anomerisation of acetylated alkyl glucopyranosides. Moreover, Winstein and Schreiber[7] pointed out that the ion-pair phenomenon can in principle be present in all processes which involve neighbouring participation. Salt effects involving lithium perchlorate in S_N1 acetolysis have also been explained in this way.[8] The mechanism of anomerisation in the presence of lithium halides may therefore be represented:



(III)

Ionisation occurs initially to give an undissociated ion pair, the carbonium ion R^+ (III) assuming the half-chair form and thus facilitating the conformation change 1C to C1 which occurs during the formation of tetra-*O*-acetyl-α-D-glucosyl chloride from the β-anomer.

---

[5] Fischer and Fischer, *Ber.*, 1910, **43**, 2535.

[6] Lemieux and Brice, *Canad. J. Chem.*, 1956, **34**, 1006; Lemieux and Cipera, *ibid.*, p. 906; Lemieux and Shyluk, *ibid.*, 1955, **33**, 120.

[7] Winstein and Schreiber, *J. Amer. Chem. Soc.*, 1952, **74**, 2165.

[8] Fainberg and Winstein, *ibid.*, 1956, **78**, 2763, 2767, 2780; Fainberg, Robinson, and Winstein, *ibid.*, p. 2777; Winstein and Clippinger, *ibid.*, p. 2784.

The main process (reactions 1 and 2) is intramolecular, leading to tetra-*O*-acetyl-α-D-glucosyl chloride, while a small amount of dissociation of the ion pair (reaction 3) allows halogen exchange (0·5%) with lithium halides (reaction 4).

It should be emphasised also that anomerisation is most unlikely in polar solvents such as methanol, which react with the sugar halide, as reported previously.[4] The agreement between the polarimetric and the titrimetric rate constant [1] for solvolysis of tetra-*O*-acetyl-β-D-glucosyl chloride supports this view and it may be concluded accordingly that the products are formed as a result of initial racemisation to the carbonium ion.

EXPERIMENTAL

Acetone was purified as described in earlier papers. Nitromethane was dried over phosphoric oxide, and the fraction boiling at 101—102° collected.

Tetra-*O*-acetyl-β-D-glucosyl chloride was prepared as described in Part V of this series.

The polarimetric technique used was described in Part IV,[9] and rate constants were evaluated from the initial rates of the anomerisation. Rotations were measured in 2·2 dm. polarimeter tubes with sodium light.

Lithium Radio-bromide.—^{82}Br was obtained from A.E.R.E., Harwell, as ammonium bromide with an initial activity of 35 mc. Treatment with an equivalent quantity of aqueous lithium hydroxide gave lithium radio-bromide. Impurities were removed by several recrystallisations from acetone. The γ-radiation (1·3 Mev) given off by the ^{82}Br necessitates using the conventional shielding and remote-handling procedures. The pure lithium radio-bromide was diluted before use with inactive lithium bromide, and the total bromide content estimated by Volhard's method.

Radioactivity Measurements.—The reaction mixture was prepared by mixing the sugar halide and an aliquot part of the standardised lithium radio-bromide in acetone, and kept at 25°. At intervals 5 ml. samples were withdrawn, the reaction was stopped by cooling to 0°, and the mixture was extracted with chloroform and water. The organic halide was present in the former and the lithium halides in the latter. The radioactivity of the two extracts was measured in a standard liquid-type Geiger–Müller counter-tube. The efficiency of the extraction

TABLE 4. *Anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in acetone.* [RCl] = 0·0411M.

Time (min.)...	3	27	51	74	98	166	188	221	20 hr.	45 hr.	∞
α	−0·03°	0·07°	0·13°	0·18°	0·23°	0·38°	0·43°	0·49°	2·30°	3·62°	3·84°

$(d\alpha/dt)_{t=0} = 2·2 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 9·5 \times 10^{-6}$ sec.$^{-1}$.

TABLE 5. *Anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in the presence of lithium bromide in acetone.* [RCl] = 0·05M. [LiBr] = 0·05M.

Time (min.)...	4	17	33	50	75	89	131	147	166	206	∞
α	−0·04°	0·06°	0·15°	0·24°	0·38°	0·44°	0·65°	0·72°	0·81°	1·00°	4·66°

$(d\alpha/dt)_{t=0} = 5·1 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 1·81 \times 10^{-5}$ sec.$^{-1}$.

TABLE 6. *Anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in the presence of lithium chloride in acetone.* [RCl] = 0·05M. [LiCl] = 0·0743M.

Time (min.)...	10	19	49	63	78	91	116	193	336	365	∞
α	0·03°	0·10°	0·25°	0·35°	0·40°	0·45°	0·57°	0·92°	1·52°	1·65°	4·60°

$(d\alpha/dt)_{t=0} = 5·05 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 1·83 \times 10^{-5}$ sec.$^{-1}$.

TABLE 7. *Anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in nitromethane.* [RCl] = 0·05M.

Time (min.)	5	14	30	56	77	106	147	185	∞
α	0·06°	0·09°	0·13°	0·22°	0·29°	0·40°	0·61°	0·82°	4·66°

$(d\alpha/dt)_{t=0} = 3·9 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 1·45 \times 10^{-5}$ sec.$^{-1}$.

---

[9] Mattok and Phillips, *J.*, 1956, 1836.

was examined and by standardising the procedure a correction was applied to allow for incomplete extraction. A typical extraction-efficiency test is given here: At zero time a 5 ml. aliquot part of the reaction mixture was extracted with chloroform (8 ml.) and water (8 ml.). The chloroform layer in 5 min. gave 65 counts, while in the same counting time the water layer recorded 11,041 counts. The extraction efficiency is thus 99·4%. This small correction may therefore be applied to an identical extraction procedure, irrespective of the fall in radioactivity of the reaction mixture owing to the low half-life (36 hr.) of ^{82}Br. Accordingly the percentage exchange at successive time intervals may be obtained from the ratio of the radioactivity of the chloroform and the water extracts.

Tables 4—7 show typical runs, at 25°, only a part of the experimental observations being given.

The authors thank Professor A. G. Evans for his interest. A maintenance grant by the Department of Scientific and Industrial Research (to G. L. M.) is gratefully acknowledged.

UNIVERSITY COLLEGE, CARDIFF. [*Received, November 28th,* 1958.]