this was achieved by cooling thoroughly the combined solutions. Upon addition of an excess of cold ether, the product precipitated and could be collected and recrystallized. The other compounds listed in Table I were isolated more readily by evaporation of the washes and reaction mixtures under reduced pressures until either a solid or gummy mass resulted. This solid or gum was then recrystallized from the appropriate solvent. Decolorizing charcoal was used in those cases where the solid or gum was highly colored.

Acknowledgment.—The authors wish to express their appreciation to the Public Health Service, National Institutes of Health, for a research grant, B-889, under which much of this work was carried out.

ATLANTA 13, GA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Relative Rates of Inversion and C1 Acetoxy Exchange During Anomerizations of Acetylated Aldopyranoses[1]

BY WILLIAM A. BONNER

RECEIVED OCTOBER 31, 1958

A series of C1 acetoxy labeled acetylated aldopyranose anomers including hexoses, 6-deoxyhexoses and a pentose has been prepared. Each substance in the series has been subjected at 25° to an anomerizing environment consisting of 1:1 acetic anhydride–acetic acid solvent containing sulfuric acid catalyst, and the rate of the resulting loss of the C1 acetoxy label for each anomer has been compared to its polarimetrically determined inversion rate. It has been found that those acetylated aldopyranose anomers having a *cis* relationship of acetoxy groups at C1–C2 show C1 acetoxy exchange rates identical within experimental error to their inversion rates, regardless of the epimeric configuration at C2 or the nature of the substitution at C6. Acetylated aldopyranose anomers having a *trans* relationship of acetoxy groups at C1–C2, on the other hand, display C1 acetoxy exchange rates 3 (for acetylated pentoses) to 14 (for acetylated hexoses) times as great as their corresponding inversion rates. These observations are amenable to two mechanistic interpretations: (1) the fundamental mechanism for anomerization is an SN2 displacement, accounting for the identical inversion and C1 acetoxy exchange rates for *cis*-C1–C2 acetylated aldopyranoses; the enhanced C1 acetoxy exchange rate for *trans*-C1–C2 anomers is then rationalizable on the basis of competing neighboring group participation by the *trans*-C2 acetoxy group. (2) The mechanism for anomerization is an SN1 ionization producing a hybrid carbonium ion capable of reacting with its anomerizing environment to yield products of both retained and inverted configuration. The present data permit no distinction between these mechanistic alternatives.

Introduction

When an acetylated aldopyranose is dissolved in a mixture of acetic anhydride and acetic acid containing a Lewis acid catalyst, it undergoes more or less rapid conversion to an equilibrium mixture of its anomers (the α-form usually predominating), a process which has had considerable preparative utility in the past.[2] This anomerization reaction has been studied from a fundamental viewpoint by several investigators[3–7] with the discovery of the following generalizations concerning it: (1) the rate of anomerization is first order with respect to acetylated aldopyranose and very nearly first order in acid catalyst,[3,4,7] that is, for the process

$$\alpha\text{-anomer} \underset{k\beta}{\overset{k\alpha}{\rightleftharpoons}} \beta\text{-anomer}$$

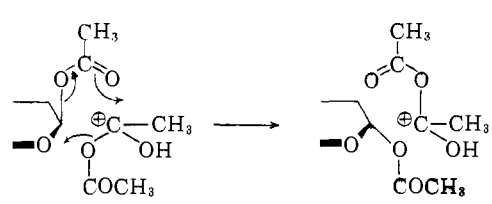
the rate data are expressed quite adequately by the relationship

$$\text{rate} = (k_\alpha + k_\beta)[\text{acid catalyst}][\text{acetylated aldopyranose}] \quad (1)$$

(2) The anomerization reaction is specific for the anomeric center and does not involve inversion[3,5] or acetoxy exchange[6,8,9] at any carbon other than C1 in the acetylated aldopyranose ring. (3) Anomerization does not appear to be subject to any primary salt effect.[3] (4) The rate of anomerization is greatest in pure acetic anhydride solvent, diminishing in a predictable fashion[3] as the acetic anhydride is diluted with acetic acid[3,4] (or butyl ether[3]), and reaching a minimum value in pure acetic acid.[3,4] (5) The products of anomerization and the positions of anomerization equilibria are independent of the acetic anhydride–acetic acid ratio in the anomerization solvents.[3,4] (6) The kinetic features of the anomerization reaction are similar among a broad series of acetylated aldohexoses and aldopentoses.[7] (7) Acetylated aldopentoses undergo anomerization significantly more rapidly than do acetylated aldohexoses.[7] (8) The inversion rate for $\alpha \rightarrow \beta$ is identical with the C1 acetoxy exchange rate for penta-*O*-acetyl-α-D-glucopyranose, whereas the C1 acetoxy exchange rate is about 17 times as rapid as the $\beta \rightarrow \alpha$ inversion rate for penta-*O*-acetyl-β-D-glucopyranose.[6]

Several mechanisms have been proposed to rationalize groups of these facts pertaining to the anomerization reaction. In 1951, we suggested[3] on the basis of polarimetric rate data that the known kinetic features of anomerization could be explained by the intervention of two reactions, 2 and 3, the essential anomerization step involving an SN2 attack by the conjugate acid of acetic anhydride on

$$Ac_2O + H_2SO_4 \rightleftharpoons Ac_2OH^{\oplus} + HSO_4^{\ominus} \quad (2)$$



(3)

(1) We are grateful to the Quaker Oats Co. for their generous support of a portion of this research.

(2) *Cf.* ref. 3 for a number of preparative examples.

(3) W. A. Bonner, THIS JOURNAL, **73**, 2659 (1951).
(4) E. B. Painter, *ibid.*, **75**, 1137 (1953).
(5) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **30**, 295 (1952).
(6) R. U. Lemieux, C. Brice and G. Huber, *ibid.*, **33**, 134 (1955).
(7) W. A. Bonner, THIS JOURNAL, **81**, 1448 (1959).
(8) W. A. Bonner, *ibid.*, **80**, 3372 (1958).
(9) W. A. Bonner, *ibid.*, **80**, 3697 (1958).

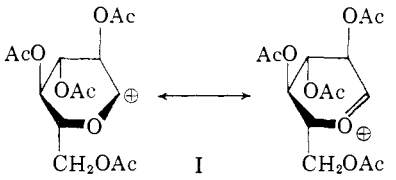
the rear face of the anomeric center. On the basis of similar data Painter has more recently proposed[4] an anomerization mechanism involving a rate-determining SN1 ionization of the conjugate acid of the acetylated aldose to a resonance-stabilized carbonium ion intermediate, which subsequently reacts with solvent to produce original and anomerized product

$$SOAc + AcOH_2^{\oplus} \text{ (or } Ac_2OH^{\oplus}) \longrightarrow SOAcH^{\oplus} + AcOH\ (Ac_2O) \quad (4)$$

$$SOAcH^{\oplus} \rightleftarrows S^{\oplus} + AcOH \quad (5)$$

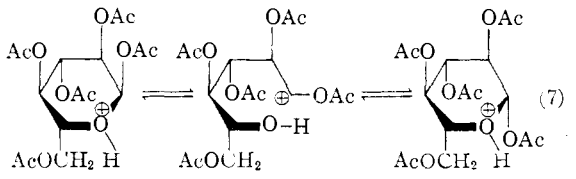
$$S^{\oplus} + AcOH\ (Ac_2O) \rightleftarrows SOAc + H^{\oplus}\ (Ac^{\oplus}) \quad (6)$$

where S is the poly-*O*-acetylaldopyranosyl moiety and S^+ is a hybrid ionic species such as I. More recently Lemieux and co-workers' applications[5,6,10]



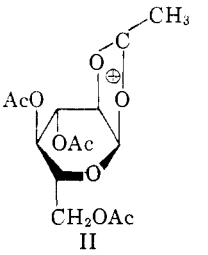
I

of radiochemical techniques to the anomerization reaction have provided additional mechanistic insight. Their discovery[5] that non-labeled penta-*O*-acetyl-D-galactopyranose became radioactive when anomerized in the presence of C1 acetoxy labeled penta-*O*-acetyl-β-D-glucopyranose indicated that anomerization involved complete rupture of the C1 acetoxy bond, excluding a process such as (7) as a mechanistic possibility. The unimportance of such an intramolecular anomerization



(7)

mechanism was later confirmed[6] by the observation that the α-anomer isolated on anomerizing tetra-*O*-acetyl-β-D-glucopyranosyl acetate-C^{14} contained only a trivial fraction of the radioactivity which such a mechanism would predict. While Lemieux's additional establishment of the identity of the $\alpha \rightarrow \beta$ inversion rate with the C1 acetoxy exchange rate for C1 acetoxy labeled penta-*O*-acetyl-α-D-glucopyranose strongly supported our suggestion[3] of an SN2 type mechanism, he argued,[6,10] however, that an ionic mechanism was not rigorously excluded since, depending upon the anomeric source, the oxonium contributing structure of I might exist in several alternative conformations which might react (reversibly) with environment to produce the appropriate inverted anomer. The further discovery[6] that the C1 acetoxy exchange rate for penta-*O*-acetyl-β-D-glucopyranose was some 17-fold greater than the $\beta \rightarrow \alpha$ inversion rate, and that the high exchange rate was diminished by the progressive introduction of electron-withdrawing chlorine atoms into the C2 acetoxy group, led Lemieux and co-workers finally to emphasize the importance of the C2 participating ion II in the anomerization–exchange process.[5,6,10]



II

In view of certain fundamental ambiguities regarding the anomerization process, *e.g.*, whether it is in fact SN1 or SN2, it has seemed desirable to us to pursue additional experiments in the hope of achieving a clearer picture of this reaction. To this end we have recently extended anomerization rate studies[7] to a wider variety of acetylated aldopyranoses than hitherto examined. In the present paper we wish to report the facts and significance of comparative anomerization rate and C1 acetoxy exchange rate experiments in a similar representative array of acetylated aldohexoses and aldopentoses.

Methods and Results

The acetylated aldohexoses, 6-deoxyaldohexoses and aldopentose listed in Table I were prepared having each a carbon-14 label in the acetoxy group at C1. Each substance was in turn anomerized at 25° in a 1:1 mixture of acetic anhydride and acetic acid containing sulfuric acid at the specified molar concentration. At appropriate time intervals an

TABLE I

COMPARATIVE C1 ACETOXY EXCHANGE RATES AND INVERSION RATES FOR ANOMERIZATIONS OF ACETYLATED ALDOPYRANOSES AT 25° IN 1:1 ACETIC ANHYDRIDE–ACETIC ACID CONTAINING SULFURIC ACID

No.	Acetylated D-aldopyranose	$[H_2SO_4]$, *M*	k_{exch}, min.$^{-1}$	k_{inv}, min.$^{-1}$	k_{exch}/k_{inv}
1	α-Glucose	0.50	0.00422[h]	0.0041	1.03
2	β-Glucose	.50	.433[i]	.0296	14.60
3	β-Glucose	.10	.0542	.0047	11.50
4	β-Glucose[f]	.50	.0543	.00414	13.10
5	α-Mannose	.50	.0189	.0020	9.45
6	β-Mannose	.50	.0333	.0314	1.06
7	β-Galactose	.10	.117	.0090	13.00
8	6-Deoxy-α-glucose	.10	.0102	.0100	1.02
9	6-Deoxy-β-glucose	.10	.375	.0469	8.00
10	β-Xylose	.05	.181	.0551	3.29
11	[a,g]	.5	.0498	.0102	4.9
12	[b,g]	.5	.00201	.0046	2.3
13	[c,g]	.5	.0012	.00075	1.6
14	[d,g]	.5	.00188	.00155	1.2
15	[e,g]	.5	.00011	.00012	0.9

[a] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-chloroacetyl-β-D-glucose. [b] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-dichloroacetyl-β-D-glucose. [c] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucose. [d] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-chloroacetyl-α-D-glucose. [e] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-trichloroacetyl-α-D-glucose. [f] Experiment conducted in 100% acetic acid solvent. [g] Averages of data taken from the study of Lemieux, Brice and Huber, ref. 6. [h] Previously reported values: 0.00557 min.$^{-1}$ (ref. 6). [i] Previously reported values: 0.41, 0.460 ± 0.016 min.$^{-1}$ (ref. 6).

(10) R. U. Lemieux, "Advances in Carbohydrate Chemistry," Vol. 9, Academic Press, Inc., New York, N. Y., 1954, pp. 24–34.

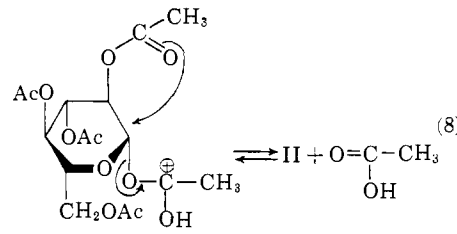
aliquot of each anomerization mixture was removed and processed for product, which then was examined for loss of radioactivity. From the latter data the first-order C1 acetoxy exchange rates (k_{exch}) in Table I were calculated. The first-order inversion rates (k_{inv}) in Table I were obtained by polarimetric anomerization rate studies in the manner fully described previously,[3,7] and have been calculated from our earlier data[7] for comparison purposes.

Discussion

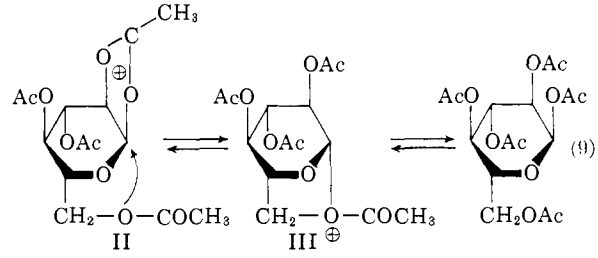
Tables I and III (*cf.* Experimental) confirm the first-order kinetics of the C1 acetoxy exchange process under anomerization conditions, first pointed out by Lemieux and co-workers.[6] Table III indicates further that the gradual decrease[3,7] in first-order anomerization rate constants with time finds a parallel in C1 acetoxy exchange rates. The slight negative departure from a linear relationship between anomerization rate and acid catalyst concentration at lower acid concentrations has already been pointed out.[3,7] The somewhat greater departure from linearity at lower acid concentration for C1 acetoxy exchange in the acetylated β-D-glucose case (Table I, nos. 2 and 3) is noteworthy. The approximately double rate of anomerization[7] of penta-*O*-acetyl-D-galactose over penta-*O*-acetyl-D-glucose, the enhanced rate of anomerization[7] of tetra-*O*-acetyl-6-deoxy-D-glucose over penta-*O*-acetyl-D-glucose and the enhanced rate of anomerization[7] of acetylated aldopentoses over acetylated aldohexoses each have their parallel (Table I, nos. 3, 7, 9 and 10) in C1 acetoxy exchange rates, suggesting that the steric and stereochemical factors[7] which influence anomerization rates are also important in determining acetoxy exchange rates. It should be emphasized, however, that such relationships in anomerization and exchange phenomena do not necessarily require that the two processes be mechanistically related.

The most significant comparisons in Table I involve the relative exchange and inversion rates in the anomeric pairs of acetylated glucoses (nos. 1, 2), mannoses (nos. 5, 6) and 6-deoxyglucoses (nos. 8, 9). Here it is quite apparent that those anomers having a *cis* relationship of acetoxy groups at C1 and C2 show inversion rates and C1 acetoxy exchange rates which are identical within experimental error, whereas those anomers having a *trans*-C1–C2 acetoxy relationship have exchange rates from 3–14 times as great as their inversion rates. These features, first shown for the penta-*O*-acetyl-D-glucose anomers by Lemieux,[6,10] are now found to be general ones, independent of the epimeric configuration at C2 or the state of substitution at C6.

Lemieux has adequately rationalized the enhanced rate of C1 acetoxy exchange over inversion in the case of *trans*-C1–C2 anomers in terms of participation by the acetoxy group at C2 producing a cyclic carbonium ion of type II, as in (8). Such C2 participation has been invoked to explain not only sulfuric acid–catalyzed anomerization-exchange observations[5,6,10] but also the enhanced exchange rate of penta-*O*-acetyl-β-D-glucose over the α-anomer and of penta-*O*-acetyl-α-D-mannose over the β-anomer using stannic trichloride acetate-C^{14} in



chloroform,[11] as well as[12,13] certain observations involving the acetolysis of acetylated alkyl glycopyranosides. It should be emphasized, however, that while a participation mechanism such as (8) adequately provides a driving force for rapid C1 acetoxy exchange in *trans*-C1–C2 acetylated aldoses, it does not *of itself* provide a concomitant explanation for inversion, since the ionic intermediate II in (8) must react with its environment by inversion,[10] thus regenerating the original *trans* configuration. To circumvent this difficulty, Lemieux has suggested[10] that more than one ionic intermediate may be required for anomerization. Thus an ion such as II in (8) might yield inverted (*cis*) product if it underwent prior rearrangement either to (a) the appropriate conformation of the oxonium form of ion I[6] or (b) the C-6 participating ion III,[5] as in (9), before reacting with its environment. Winstein and co-workers have more recently suggested[14] an alternative mechanism whereby a *cis* acetoxonium ion such as II in (9) might ultimately provide *cis* product.



We have attempted to assess the importance of C6 participating ions such as III in the anomerization–exchange process by studying the behavior of C1 acetoxy labeled anomers of acetylated 6-deoxy-D-glucopyranose, where C6 participation such as III in (9) would be impossible. Table I indicates, however, that these substances (nos. 8, 9) behave quite normally in that the *cis*-C1–C2 anomer shows identical inversion and exchange rates while the *trans*-C1–C2 anomer shows the usual enhanced C1 acetoxy exchange rate due presumably to C2 acetoxy participation. We thus find no experimental support for the existence of C6 participating ions such as III in (9), even though molecular models suggest that such ions are sterically quite feasible in certain conformations of the pyranose ring, and though C1–C6 interactions are well known in other carbohydrate reactions.[15,16]

(11) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **33**, 109 (1955).
(12) R. U. Lemieux and W. P. Shyluk, *ibid.*, **33**, 120 (1955).
(13) R. U. Lemieux, W. P. Shyluk and G. Huber, *ibid.*, **33**, 148 (1955).
(14) R. M. Roberts, J. Corse, R. Boschan, D. Seymour and S. Winstein, THIS JOURNAL, **80**, 1247 (1958).
(15) Reference 10, pp. 14–17.
(16) C. E. Ballou, ref. 10, pp. 72–79.

TABLE II

PREDICTION OF (k_{exch}/k_{inv}) RATIOS ON THE BASIS OF AN IONIC MECHANISM

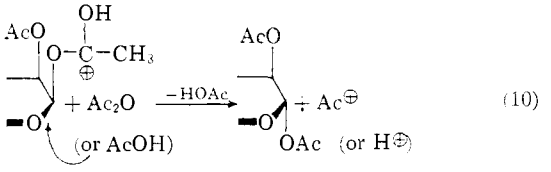
		A		B						
No.	Acetylated aldopyranose	k_2/k_1	$(k_{exch}/k_{inv})_{cis}$	k_1[d]	k_3[d]	K_e	k_2/k_4	$(k_{exch}/k_{inv})_{cis}$ Calcd.	$(k_{exch}/k_{inv})_{cis}$ Found[d]	$(k_{exch}/k_{inv})_{trans}$ Calcd.	$(k_{exch}/k_{inv})_{trans}$ Found[d]
1	Glucose	13.60	1.07	0.00422	0.433	0.137[e]	14.06	1.07	1.03	15.06	14.60
2	Mannose	8.45	1.12	.0333	.0189	15.67[e]	8.89	1.11	1.06	9.89	9.45
3	6-Deoxyglucose	7.00	1.14	.0102	.375	0.130[e]	4.78	1.21	1.02	5.78	8.00
4	[a,c]	3.9	1.3	.00188	.0498	.151[e]	4.00	1.3	1.2	5.0	4.9
5	[b,c]	0.6	2.7	.00011	.0012	.154[e]	1.68	1.6	0.9	2.6	1.6

[a] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-chloroacetyl-D-glucose. [b] 1,3,4,6-Tetra-*O*-acetyl-2-*O*-trichloroacetyl-D-glucose. [c] Calculated from the data of Lemieux, Brice and Huber, ref. 6. [d] From Table I. [e] From Table III of ref. 7.

Were ions such as III of importance as anomerization intermediates, one might reasonably expect an enhancement of C1 acetoxy exchange rates for *cis*-C1–C2 anomers qualitatively similar to that observed for *trans*-C1–C2 anomers, as suggested in (9).

Table I (nos. 1, 6, 8, 14, 15) shows clearly that, within experimental error, each time a labeled C1 acetoxy group is removed from a *cis*-C1–C2 acetylated aldopyranose undergoing anomerization an unlabeled acetoxy group enters the molecule *with essentially complete inversion of the anomeric configuration*. This conclusion follows, independent of mechanism, from the identities in inversion and exchange rates for all *cis*–C1–C2 anomers in Table I, and appears to apply regardless of the epimeric configuration at C2, the nature of the acyl substituent at C2 or the type of substituent at C6.

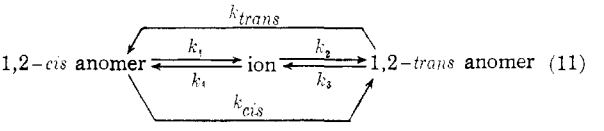
We believe that the simplest mechanistic interpretation of these observations is one involving a simple SN2 displacement at the anomeric center of the *cis*-C1–C2 acetylated aldopyranose. Whether such a mechanism involves inverting attack on the anomeric center by the conjugate acid of acetic anhydride or acetic acid (equation 3) as originally suggested,[3] or whether the SN2 attack is on the conjugate acid of the acetylated aldose, as in (10), is a question which cannot be answered at the present time.



(10)

If the fundamental mechanism for inversion is an SN2 displacement such as (3) or (10), then the enhanced C1 acetoxy exchange rate in *trans*-C1–C2 acetylated aldoses is logically interpreted as a separate process, unrelated as such to anomerization and competing simultaneously therewith *via* its well documented[5,6,10–13] ionic mechanism involving C2 acetoxy participation in an *intramolecular* SN2 attack. The k_{exch}/k_{inv} ratios for the *trans*-C1–C2 anomers in nos. 2, 11, 12, 13 in Table I appear to us to offer some support to this interpretation. The progressively increasing presence of chlorine atoms on the participating acetoxy group at C2 should make the carbonyl function of this group progressively less nucleophilic and hence progressively less disposed toward participation such as II in the sequence of compounds in nos. 2, 11, 12, 13. Such phenomena should permit *intermolecular* SN2 attack leading to inversion to compete progressively more effectively with *intramolecular* SN2 attack leading to C1 exchange without inversion, thus explaining the monotonic decrease in the k_{exch}/k_{inv} ratios in the sequence in question.

While the above interpretation provides an adequate qualitative rationalization of the data in Table I it should be emphasized that such an interpretation is not a unique one. An ionic mechanism such as that generalized in (11) is also capable of accounting for the data in Table I, at least when k_3 (the specific rate of C1 acetoxy exchange for the



(11)

1,2-*trans* anomer) is appreciably larger than the inversion rate, k_{trans} for this anomer due to participation such as II, and when k_1 (the C1 acetoxy exchange rate for the 1,2-*cis* anomer) approximately equals the inversion rate k_{cis}. The adequacy of a mechanism such as (11) for rationalizing such data in Table I may be demonstrated as follows. It is evident that the ratios of exchange to inversion rates for the two anomers are expressible as

$$(k_{exch}/k_{inv})_{trans} = k_3/(k_3k_4/(k_2 + k_4)) = 1 + k_2/k_4 \quad (12)$$

whence

$$k_2/k_4 = (k_{exch}/k_{inv})_{trans} - 1, \text{ and} \quad (13)$$

$$(k_{exch}/k_{inv})_{cis} = k_1/(k_1k_2/(k_2 + k_4)) = 1 + k_4/k_2 \quad (14)$$

Calculation of the ratio k_2/k_4 from the observed $(k_{exch}/k_{inv})_{trans}$ ratio by means of (13) provides a number whose reciprocal may be used to predict the $(k_{exch}/k_{inv})_{cis}$ ratio by means of (14). The values predicted for $(k_{exch}/k_{inv})_{cis}$ are given in section A of Table II. They may be compared to those observed by reference to column 6 of section B in Table II, where it is seen that the ratios so predicted by mechanism 11 are in reasonable accord with those found experimentally, except in the case of no. 5 which is discussed below.

Another basis for testing the adequacy of the generalized ionic mechanism 11 involves predictions based on a steady-state treatment. Application of the usual steady-state equations to mechanism 11, followed by introduction of equilibrium restrictions, leads to the conclusion that

$$K_e = \frac{[1,2\text{-}trans]_e}{[1,2\text{-}cis]_e} = k_1k_2/k_3k_4, \text{ whence} \quad (15)$$

$$k_2/k_4 = K_ek_3/k_1 \quad (16)$$

Values of $(k_{exch}/k_{inv})_{trans}$ may then be predicted from (16) by application of (12), and values for

$(k_{exch}/k_{inv})_{cis}$ may be predicted from the reciprocal of (16) by application of (14). Calculated values for the k_{exch}/k_{inv} ratios in question, made on the above bases, are compared with the experimentally observed ratios in section B of Table II. It is seen again that calculations based on the assumed applicability of mechanism 11 give results in reasonable agreement with observed values except in the case of no. 5, whose 2-*O*-trichloroacetyl substituent has been shown less capable of participation such as II in the case of the 1,2-*trans* anomer.

The data in Table I are thus amenable to interpretation on the basis of either an SN2 displacement or an SN1 ionization as the fundamental mechanism for the anomerization process, and there appears to be no criterion permitting a distinction between these two mechanisms in the examples heretofore studied. An unambiguous distinction between the two mechanisms might be made, we believe, by a study of the relative C1 acetoxy exchange and inversion rates in anomerization systems where C2 acetoxy participation is impossible. Such a study is currently in progress.

Experimental

Silver acetate-1-C^{14} was prepared typically as follows. The appropriate number of millicuries of sodium acetate-1-C^{14} was diluted (to 8.2 g.) with sodium acetate and the mixture was dissolved in distilled water (100 ml.). A solution of silver nitrate (18.7 g., 10% excess) in distilled water (50 ml.) was added slowly with stirring to the above sodium acetate-1-C^{14} solution and the precipitate was filtered and rinsed four times with cold distilled water. The product was dried *in vacuo* over phosphoric anhydride, weighed 13.9 g. (83%) and was used directly in the syntheses below.

Tetra-*O*-acetyl-β-D-glucopyranosyl Acetate-1-C^{14}.—Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (6.00 g.), the above labeled silver acetate (3.76 g., 54% excess) and glass beads were mixed in anhydrous ether (100 ml.). The mixture was stirred under reflux for 2 hours and at room temperature for 1.5 hours, then was filtered (Celite). The cake was rinsed with dry ether and the filtrate and washings were evaporated to dryness, yielding 5.85 g. (103%) of sirup which smelled slightly of acetic acid and quickly crystallized, $[\alpha]^{25}D$ +23.9° (*c* 2.13, $CHCl_3$). This was recrystallized twice from mixtures of 2-propanol (15 ml.) and water (32 ml., 15 ml.), producing 2.10 g. of the desired product having m.p. 129.5–130°, $[\alpha]^{25}D$ +2.4° (*c* 0.68, $CHCl_3$) and a specific radioactivity of 1.849 ± 0.010 mc./mole.

Tetra-*O*-acetyl-β-D-galactopyranosyl Acetate-1-C^{14}.—Tetra-*O*-acetyl-α-D-galactopyranosyl bromide was prepared by the action of an acetic acid–hydrogen bromide solution on penta-*O*-acetyl-β-D-galactopyranose after the procedure of Ohle and co-workers.[17] Failing to crystallize, the sirupy product had $[\alpha]^{25}D$ +226° (*c* 8.06, C_6H_6) as compared with +236.4° (C_6H_6) for the crystalline material[18] of m.p. 82–83°. It was used directly in the succeeding synthesis. The above sirup (7.75 g.), silver acetate-1-C^{14} (3.87 g.) and glass beads were added to a solution of anhydrous ether (70 ml.) and benzene (30 ml.). After a 2.5-hour period of stirring under reflux the crude product (7.45 g., 101%) was isolated as above and crystallized from 2-propanol (15 ml.), yielding 2.17 g. of solid, m.p. 130–135°. After four additional recrystallizations from 2-propanol the 1.40 g. of product had a constant m.p. of 139–139.5° and $[\alpha]^{25}D$ +24.8° (*c* 2.06, $CHCl_3$) in reasonable agreement with the literature values[19] of m.p. 142°, $[\alpha]^{20}D$ +25° ($CHCl_3$). Its specific radioactivity was 1.831 ±0.010 mc./mole.

Tri-*O*-acetyl-β-D-xylopyranosyl Acetate-1-C^{14}.—Tri-*O*-acetyl-α-D-xylopyranosyl bromide and silver acetate-1-C^{14} were allowed to react in the manner described above. The crude product, $[\alpha]^{25}D$ −4.7° (*c* 4.47, $CHCl_3$), was recrystallized three times from dilute 2-propanol, producing a sample having m.p. 125–125.5°, $[\alpha]^{26}D$ −26.4° (*c* 2.84, $CHCl_3$) and a specific radioactivity of 1.903 ± 0.015 mc./mole. Literature values[17] are m.p. 128°, $[\alpha]^{20}D$ −24.7° ($CHCl_3$).

Tri-*O*-acetyl-6-deoxy-β-D-glucopyranosyl acetate-1-C^{14} was prepared by the usual reaction of silver acetate-1-C^{14} with a sample of tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyl bromide having m.p. 145–146°, $[\alpha]^{25}D$ +241° (*c* 2.38, $CHCl_3$). The crude sirupy product (3.5 g.) was crystallized from 1-butanol (12 ml.) yielding 2.02 g. of solid, m.p. 143.5–144°. A second recrystallization from 1-butanol afforded 1.75 g. of product of similar m.p., 144.5°, $[\alpha]^{25}D$ +21.0° (*c* 0.9, $CHCl_3$) and a specific radioactivity of 1.867 ± 0.002 mc./mole. Although the literature values[20] for this substance are m.p. 151°, $[\alpha]D$ +22° (*c* 0.9, $CHCl_3$), we have not observed a m.p. above 144.5° in this or other preparations.

Tetra-*O*-acetyl-β-D-mannopyranosyl acetate-2-C^{14} was prepared by acetylation of 2,3,4,6-tetra-*O*-acetyl-β-D-mannose with methyl-labeled acetic anhydride and pyridine at −5° according to our previously described procedure.[8] The product, thrice recrystallized from dilute 2-propanol, had m.p. 115–115.5° and $[\alpha]^{25}D$ −25.4° (*c* 2.6, $CHCl_3$) in agreement with literature values.[17] Its specific radioactivity was 0.307 mc./mole.

Tetra-*O*-acetyl-α-D-glucopyranosyl Acetate-2-C^{14}.—Penta-*O*-acetyl-β-D-glucopyranose (2.00 g.) was dissolved in methyl-labeled acetic anhydride (5 ml.) and treated with sulfuric acid (0.3 ml.). The mixture was allowed to stand for 1.5 hours, poured into ice-water, stirred for 45 minutes and finally extracted three times with chloroform. The extracts were washed with water and sodium bicarbonate solution, then dried (anhydrous sodium sulfate), filtered and freed of solvent, yielding 2.10 g. (105%) of crude solid product. This was recrystallized four times from 7-ml. portions of 2-propanol, affording 1.15 g. of pure product whose m.p. 112.5–113° and $[\alpha]^{25}D$ +101.5° (*c* 0.58, $CHCl_3$) were in essential agreement with literature values.[17] The specific radioactivity was 0.500 ± 0.005 mc./mole.

Tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyl Acetate-2-C^{14}.—The corresponding β-anomer (1.38 g.), having m.p. 144–145° and $[\alpha]^{25}D$ +120.5° ($CHCl_3$), was dissolved in methyl-labeled acetic anhydride (5 ml.) and treated with sulfuric acid (0.2 ml.). After one hour the reaction mixture was poured into water and the product was isolated as in the preceding experiment. The 1.40 g. (101%) of crude solid was recrystallized (Norit) twice from dilute ethanol and four times from 1-butanol to give 0.48 g. of product having m.p. 118.5° and $[\alpha]^{25}D$ +122° (*c* 0.47, $CHCl_3$), in agreement with the m.p. 117° and $[\alpha]^{25}D$ +122° ($CHCl_3$) reported by Hardegger and Montavon.[20] The specific radioactivity was 0.486 ± 0.001 mc./mole.

Tetra-*O*-acetyl-α-D-mannopyranosyl acetate-2-C^{14} was prepared by acetylation of 2,3,4,6-tetra-*O*-acetyl-α-D-mannose with methyl-labeled acetic anhydride and pyridine at −5° as previously described,[8] affording a product having m.p. 74–75°, $[\alpha]^{25}D$ +56.7° (*c* 1.50, $CHCl_3$) and assaying at 0.0773 mc./mole. The desired product was also prepared by anomerizing crude penta-*O*-acetyl-D-mannopyranose in labeled acetic anhydride with sulfuric acid, in the manner described above. In this experiment the recrystallized product showed m.p. 73.5–74°, $[\alpha]^{25}D$ +54.1° (*c* 2.07, $CHCl_3$).

Polarimetric inversion rate constants were obtained by calculations involving specific anomerization rate data and equilibrium constant data for sulfuric acid-catalyzed anomerizations of the acetylated aldopyranoses in question. These calculations and the errors inherent therein have been fully described previously, and the comparative data in tables have been taken from our earlier papers.[3,5]

C1 acetoxy exchange rate constants were obtained generally as follows. The appropriate weight for a 0.10 *M* solution of the indicated C1 acetyl labeled poly-*O*-acetylaldropyranose was dissolved in a few ml. of a 1:1 mixture of acetic acid and acetic anhydride. At zero time the appropriate volume of 1 *M* solution of sulfuric acid in a similar solvent mixture was added, the stopwatch was started and the solution was diluted to 10.00 ml. with the solvent. All solutions were thermostated prior to mixing, and the reaction mixtures were similarly thermostated at 25.0 ± 0.1° during each experiment. At the indicated time intervals a 2-ml. aliquot of the reaction mixture was removed and quenched

(17) H. Ohle, W. Maracek and W. Bourjau, *Ber.*, **62**, 848 (1929).

(18) E. Fischer and E. F. Armstrong, *ibid.*, **35**, 838 (1902).

(19) "Polarimetry, Saccharimetry and the Sugars," F. J. Bates and Associates, Circ. C440, Ntl. Bur. Stand., 1942.

(20) E. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).

in water (20 ml.). The product from each aliquot was isolated by extraction with chloroform as previously described,[8] then dried *in vacuo* over P_2O_5 and NaOH for several days and assayed for radioactivity in the usual fashion.[8] The first-order rate constants for loss of Cl acetoxy were calculated for each aliquot by means of the usual equation[21]

$$k_{exch} = \frac{2.3}{t} \log \frac{a}{a - x}$$

where a is the specific radioactivity of the sample at zero time and $a - x$ that of the product from the aliquot removed at time t. The radio-chemical and rate constant data for each experiment are given in Table III.

TABLE III

ACETOXY EXCHANGE RATE DATA FOR VARIOUS C-1 ACETOXY LABELED ACETYLATED D-ALDOPYRANOSES IN 1:1 ACETIC ANHYDRIDE–ACETIC ACID AT 25°

Acetylated D-aldopyranose	$[H_2SO_4]$, mole/l.	t, min.	Assay, mc./mole	k_{exch}, min.$^{-1}$
α-Glucose	0.50	0	0.500	.....
		60	.389	0.00418
		90	.341	.00429
		120	.303	.00417
		150	.265	.00423
			Av.	0.00422 ± 0.00004
β-Glucose	.50	0	1.849	.....
		1	1.168	0.459
		2	0.784	.428
		3	.489	.443
		4	.342	.422
		5	.235	.413
			Av.	0.433 ± 0.014
β-Glucose	.10	0	1.849	....
		3	1.559	0.0565
		6	1.345	.0531
		9	1.152	.0525
		12	0.970	.0536
		15	0.811	.0550
			Av.	0.0542 ± 0.0013
α-Mannose[8]	.50	..	...	
			Av.	0.0189 ± 0.0004
β-Mannose[8]	.50	..	...	
			Av.	0.0333 ± 0.0018
β-Galactose	.10	0	1.831	...
		3	1.250	0.127
		6	0.905	.120
		9	.656	.114
		12	.473	.113
		15	.344	.112
			Av.	0.117 ± 0.005
6-Deoxy-α-glucose	.10	0	0.486	....
		20	.392	0.0107
		35	.338	.0104
		50	.292	.0102
		70	.243	.0096
			Av.	0.0102 ± 0.0003
6-Deoxy-β-glucose	.10	0	1.867	...
		2	0.804	0.421
		4	.405	.382
		6	.203	.370
		8	.108	.357
		10	.0596	.344
			Av.	0.375 ± 0.021
β-Xylose	.05	0	1.903	...
		4	0.914	0.184
		6	.634	.183
		8	.455	.179
		10	.320	.178
			Av.	0.181 ± 0.003
β-Glucose[a]	.50	0	1.849	....
		30	0.339	0.0565
		60	.0709	.0545
		90	.0175	.0518
			Av.	0.0543 ± 0.0016

[a] In 100% acetic acid solvent testing <0.1% water and <0.5% acetic anhydride by vapor–liquid partition chromatographic analysis. Solvent kindly furnished and analyzed by Prof. R. H. Eastman.

This experimental method was adopted since Lemieux and co-workers have shown[6] that the Cl acetoxy exchange rate constants obtained by radio-activity assay of the crude reaction products accorded with those obtained by assay of the reaction products after separation and purification using column chromatography on Magnesol.

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(21) W. A. Bonner and C. J. Collins, THIS JOURNAL, **77**, 102 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXIII. The Anomeric Ethyl 1-Thio-D-arabinofuranosides

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RECEIVED APRIL 25, 1959

The two crystalline anomeric ethyl 1-thio-D-arabinofuranosides (XV and XXIII) have been prepared. The β-anomer XV was synthesized through the cyclization of 5-O-benzoyl-D-arabinose diethyl mercaptal with mercuric chloride and cadmium carbonate. The synthesis of the α-anomer XXIII involved the stereospecific attack of ethyl mercaptide ion on 3,5-di-O-benzoyl-D-arabinofuranosyl chloride. A possible use of the α-anomer as a precursor in a deoxynucleoside synthesis is discussed.

Although the important aspects of the structure of purine deoxynucleosides have been known for thirty years,[2] efforts toward their synthesis by conventional methods[3] have failed. The recent suc-

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series *cf.* L. Goodman and B. R. Baker, THIS JOURNAL, **81**, 4294 (1959).

(2) (a) P. A. Levene and F. S. London, *J. Biol. Chem.*, **81**, 711 (1929); **83**, 793 (1929); (b) W. Klein, *Z. physiol. Chem.*, **224**, 244 (1934); **255**, 81 (1938).

(3) For a summary of this work, see L. Goodman, A. Benitez and B. R. Baker, paper I of this series, THIS JOURNAL, **80**, 1680 (1958).