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FORMATION, AND STEREOCHEMISTRY, OF 1,2-*O*-(1-METHYL-1,2-ETHANEDIYL)-D-GLUCOSE ACETALS FORMED IN THE ACID-CATALYZED HYDROLYSIS OF *O*-(2-HYDROXYPROPYL)CELLULOSE

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ABSTRACT

In the hydrolysis of *O*-(2-hydroxypropyl)cellulose, residues of D-glucose substituted with a single *O*-(2-hydroxypropyl) substituent at O-2 (irrespective of the pattern of additional substitution at O-3 or O-6) form 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucose acetals. Based on the characteristics of 2-*O*-(2-hydroxypropyl)-D-glucose and derivatives thereof in aqueous acid, these bicyclic products are shown to comprise a mixture of two furanose and two pyranose species that differ widely in relative stability, depending on the chirality of C-8 of the 1,4-dioxane ring of the compounds. The order of stability is 1,2-*O*-[1-methyl-(*R*)-1,2-ethanediyl]-α-D-glucopyranose > 1,2-*O*-[1-methyl-(*S*)-1,2-ethanediyl]-α-D-glucofuranose > 1,2-*O*-[1-methyl-(*S*)-1,2-ethanediyl]-α-D-glucopyranose > 1,2-*O*-[1-methyl-(*R*)-1,2-ethanediyl]-α-D-glucofuranose. N.m.r. evidence indicates that the two pyranose derivatives possess the "H-inside" conformation. Acetal formation is less prominent in acidic methanol, although the relative stabilities of the products are similar. Possible mechanisms for these various acid-catalyzed transformations are discussed.

INTRODUCTION

A preceding article[1] described neighboring-group participation reactions of 2-*O*-(2-hydroxypropyl) substituents occurring during the solvolysis of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-D-glucofuranosides (*e.g.*, **1**) that give rise to bicyclic acetals (*e.g.*, **5**). These reactions help to account for the formation of structurally related acetals during the acid hydrolysis of *O*-(2-hydroxypropyl)cellulose[2]. The present study furnishes a description of the acetals contained in the hydrolyzate, based principally on the characteristics of 2-*O*-(2-hydroxypropyl)-D-glucose (**9**) and various derivatives thereof in acidic media.

RESULTS AND DISCUSSION

Preparation of starting compounds. — Precursors to all of the starting com-

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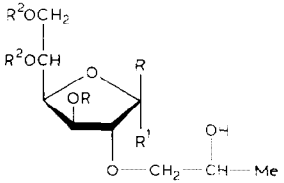
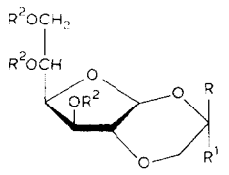




1 R = H, R^1 = OMe, R^2 = Bn
2 R = OMe, R^1 = H R^2 = Bn
3 R = H, R^1 = OMe R^2 = H
4 R = OMe, R^1 = H, R^2 = H

5 R = H, R^1 = Me, R^2 = Bn
6 R = Me, R^1 = H, R^2 = Bn
7 R = H, R^1 = Me, R^2 = H
8 R = Me, R^1 = H, R^2 = H

Bn = $PhCH_2$

TABLE I

^{13}C-N.M.R. CHEMICAL SHIFTS (δ)[a] FOR 1,2-*O*-(1-METHYL-1,2-ETHANEDIYL)- (**7** AND **8**) AND 1,2-*O*-(1,2-ETHANEDIYL)- (**23**) -α-D-GLUCOFURANOSES

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*
7	98.2	81.0	73.0	80.2	71.2	64.5	67.5	69.0	18.5
8	100.5	81.9	75.5	76.6	70.4	64.9	70.1	66.7	16.7
23	99.6	82.6	75.4	77.3	70.5	66.0	65.0	61.1	
$\Delta(\delta 7 - \delta 5)$[b]	1.4	1.6	−4.7	1.7	−5.1	−6.8	0.8	1.9	0.6
$\Delta(\delta 8 - \delta 6)$[b]	1.2	−0.4	−4.3	0.4	−2.2	−6.6	0.7	2.7	0.4
$\Delta(\delta 23 - \delta 22)$[b]	1.0	−0.3	−4.6	1.2	−3.1	−6.7	0.8	1.7	

[a]Assignments of signals facilitated by use of deuterium-induced, differential isotope-shifts[4]; data given are for D_2O solutions [b]Chemical-shift difference between the value listed and the value for the corresponding carbon atom of the 3,5,6-tri-*O*-benzyl derivative (**5**, **4**, or **13**, in Table IV of ref. 1).

pounds were available in the form of 3,5,6-tri-*O*-benzyl-D-gluco-furanose or -furanoside derivatives. The latter were, therefore, *O*-debenzylated, using catalytic-transfer hydrogenolysis[3]. Accordingly, α-glycoside **1** gave methyl 2-*O*-(2-hydroxypropyl)-α-D-glucofuranoside (**3**), whereas acetal **5** yielded 1,2-*O*-[1-methyl-(*R*)-1,2-ethanediyl]-α-D-glucofuranose (**7**). Similarly, β-glycoside **4** was obtained from **2**, and the (*S*) diastereomeric acetal (**8**) from **6**. When due allowance was made for the removal of the *O*-benzyl substituents, the ^{1}H- and ^{13}C-n.m.r. spectra of the products were closely analogous to those of the corresponding starting-compounds. For example, the only substantial changes in ^{13}C-chemical shifts observed (see Table I) for acetals **7** and **8**, as compared with their tri-*O*-benzyl precursors (**5** and **6**), involved the sites of substitution, *i.e.*, C-3, -5, and -6. This indicates that the stereochemistry of the products (in aqueous solution) is essentially the same as reported earlier[1] for the benzyl ethers (in organic media), as well as that the hydrogenolysis step had not introduced any unexpected alteration.

Acid-catalyzed transformations of derivatives of 2-O-(2-hydroxypropyl)-D-glucose. — A series of experiments was conducted in which glycosides **3** and **4** and the bicyclic acetals (**7** and **8**), using individual diastereomeric forms when available,

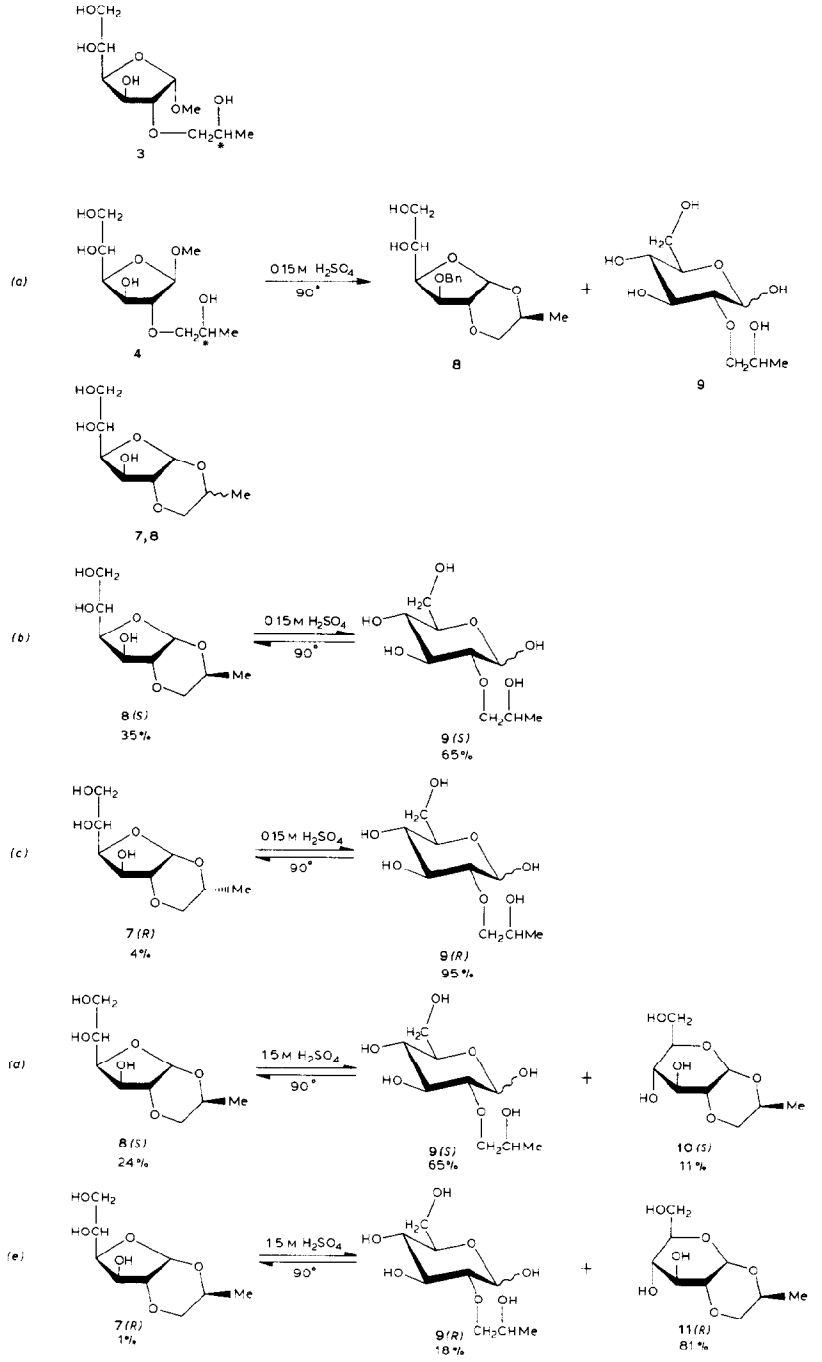


Fig. 1. Acid-catalyzed hydrolysis of various derivatives of 2-*O*-(2-hydroxypropyl)-D-glucose.

were subjected to hydrolysis. The compositions of the hydrolyzates, estimated from their ^{13}C-n.m.r. spectra at (close to) equilibrium, are summarized as follows.

(a) Hydrolysis of the optical mixture of either methyl 2-*O*-(2-hydroxypropyl)-α- and -β-D-glucofuranoside (**3** or **4**), or 1,2-*O*-[1-methyl-(*R*) and (*S*)-1,2-ethanediyl]-α-D-glucofuranose (**7** and **8**) in 0.15M H_2SO_4 at 95° gave mainly a mixture of 2-*O*-(2-hydroxypropyl)-α,β-D-glucopyranose (**9**) and 1,2-*O*-[1-methyl-(*S*)-1,2-ethanediyl]-α-D-glucofuranose (**8**), as illustrated in Fig. 1, reaction *a*; the ratios of **8**:**9**α:**9**β were ~1:1:1.

(b) When the (*S*) diastereomer (**8**) of 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranose was hydrolyzed under the same conditions, 2-*O*-(2-hydroxypropyl)-α,β-D-glucopyranose (**9**; 65%) was equilibrated with the starting material (**8**; 35%) (see Fig. 1, reaction *b*).

(c) By contrast, on hydrolysis of the (*R*) diastereomer (**7**) of 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranose under the same conditions, only 2-*O*-(2-hydroxypropyl)α,β-D-glucopyranose (**9**) was observed (see Fig. 1, reaction *c*).

(d) Under more strongly acidic conditions, when the equilibrated mixture of **8** and **9** from reaction *b* was heated in 1.5M H_2SO_4 for 4 h at 95°, it gave a bicyclic acetal having two 6-membered rings, *i.e.*, 1,2-*O*-[1-methyl-(*S*)-1,2-ethanediyl]-α-D-glucopyranose (**10**; 11%), together with the starting materials [**8**(*S*) and **9**(*S*); 65 and 24%, respectively] (see Fig. 1, reaction *d*).

(e) Likewise, hydrolysis of **9**(*R*), obtained in reaction *c*, in 1.5M H_2SO_4 at 95° yielded mainly 1,2-*O*-[1-methyl-(*R*)-1,2-ethanediyl]-α-D-glucopyranose (**11**; 81%), together with 18% of the starting material **9**(*R*) (see Fig. 1, reaction *e*).

Evidence as to the structure of pyranose derivatives **10** and **11** is presented in the following section. Then, the various observations just listed are treated in terms of reaction mechanisms, and an appraisal is also given of the relative stabilities of the acetal C–O bonds in these systems.

*The structure of 1,2-O-(1-methyl-1,2-ethanediyl)-α-D-glucopyranoses (**10** and **11**).* — According to its ^{13}C-n.m.r. spectrum (see Table II), the major compound (**11**) in the hydrolyzate of reaction *e* (see Fig. 1) is distinctly different in its overall

TABLE II

N.M.R. DATA FOR 1,2-*O*-(1-METHYL-1,2-ETHANEDIYL)-α-D-GLUCOPYRANOSES (**10** AND **11**)

Compound	*Atom (H or C)*									
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
10	^1H	5.34 ($J_{1,2}$ 3.40 Hz)								1.38 ($J_{8,9}$ 6.70 Hz)
	^{13}C	90.2	76.0	71.2	70.3	75.5	62.0	69.4	65.4	16.7
11	^1H	5.15 ($J_{1,2}$ 3.44 Hz)								1.20 ($J_{8,9}$ 6.70 Hz)
	^{13}C	95.5	75.2	73.6	70.5	74.4	61.7	64.6	68.2	16.6

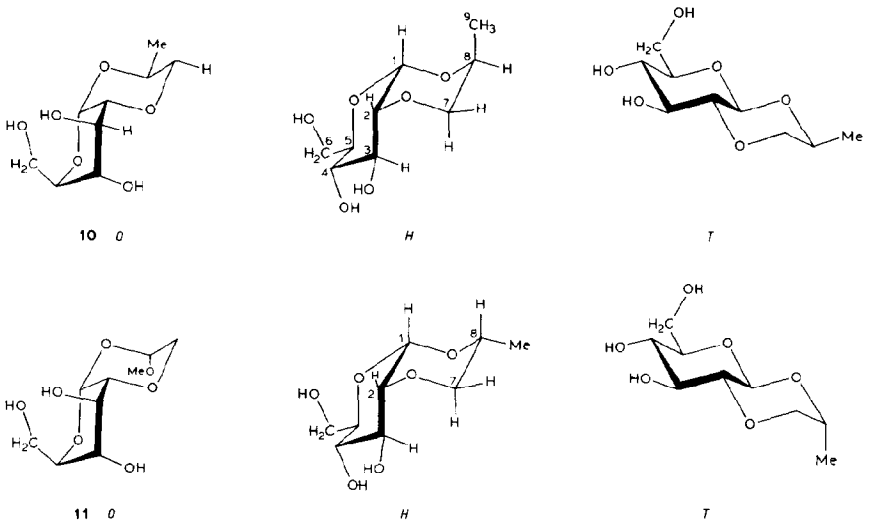


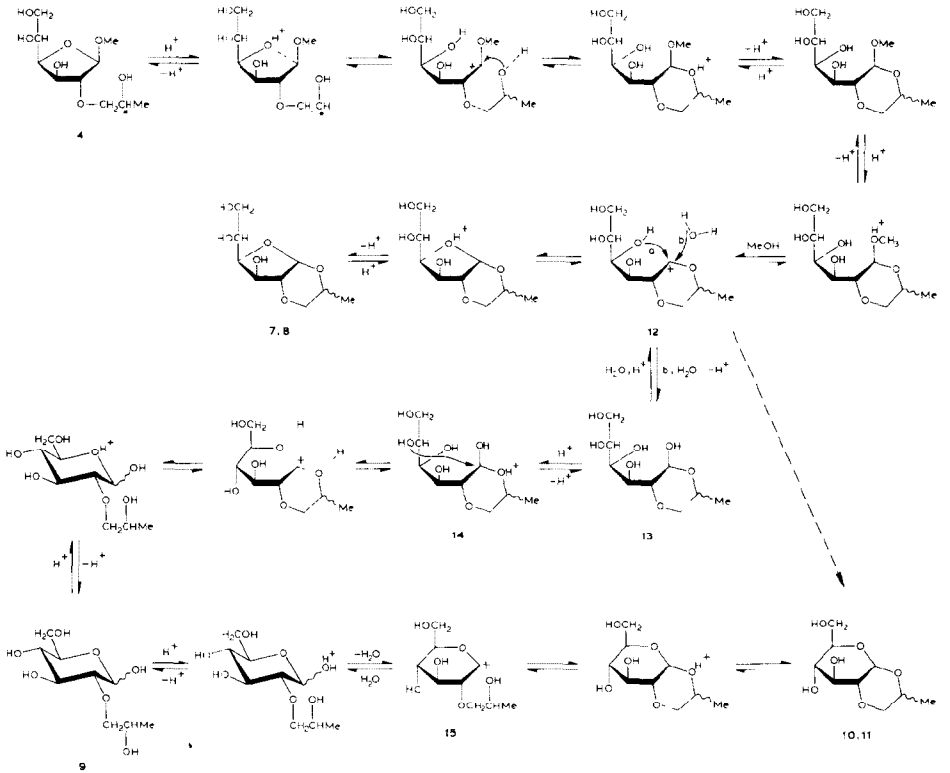
Fig. 2. Representations of possible structures for isomers of 1,2-*O*-(1-methyl-1,2-ethanediyl)-D-glucopyranose (**10** and **11**). [*O*, O-inside; *H*, H-inside; *T*, *trans*-fused.]

characteristics from all of the other compounds encountered. As there are only nine appropriate carbon resonances, the molecule is not a free aldose derivative, because both anomeric forms should then be evident. In terms of the sequence of events leading to **11**, the most reasonable kind of structure to be anticipated for it is a pyranoid derivative containing a 1,4-dioxane ring moiety. The corresponding derivatives of α-D-glucofuranose characteristically[5] give ring-carbon signals much farther downfield (see Table I). However, the chemical shifts for C-7, -8 and -9 of **11** (see Table II) are in the region of those for the 1,4-dioxane ring of **7** and **8**. Hence, **11** is taken to have a bicyclic, pyranoid structure as shown in formula **11**.

The occurrence of **10** is shown by the presence of groups of ^{13}C resonances, most notably the anomeric signal at δ 90.2, that are not attributable to the other components of the mixture. The ^{13}C chemical-shift data in Table II were obtained by difference. These data also correspond more closely to a pyranoid than to a furanoid acetal.

Each isomer of 1,2-*O*-(1-methyl-1,2-ethanediyl)-D-glucopyranose (**10** and **11**) may exist as a *cis*-fused system in two possible chair conformations ["O-inside" (*O*) or "H-inside" (*H*)], or as a *trans*-fused system (*T*), as shown in Fig. 2. Among these, the *trans*-fused form can be readily precluded, because the ^1H–^1H coupling constant ($^3J_{1,2}$) for both **10** and **11** is 3.4 Hz (see Table II), which is consistent with an *a,e* arrangement of H-1 and H-2 [in (*O*) or (*H*)], but definitely not with the antiperiplanar arrangement of H-1 and H-2 in the *trans*-fused system (*T*).

The "O-inside" (*O*) conformer[6] is highly improbable, because the glucopyranose ring would then incorporate the strongly destabilizing, nonbonding interactions arising from axially oriented O-3, O-4, and C-6. By contrast, the "H-inside" conformation corresponds to the stable $^4C_1$ conformer for α-D-gluco-



Scheme 1. Proposed reaction mechanisms of acid-catalyzed transformations involving 2-*O*-(2-hydroxypropyl)-D-glucose and derivatives thereof.

pyranose. Hence, it may be presumed that both **10** and **11** have the "H-inside" conformation.

Stereochemically, then, the difference between **10** and **11** resides in the configuration of C-8. This leads to an axial orientation for the methyl group (C-9) of **10**, and an equatorial one for this group in **11**. In accord with this difference, it may be seen (see Table II) that C-1 and -8 of **10**, in particular, are substantially more shielded than those of **11**, and this is attributable to the (shielding) influence of the axial methyl group. Clearly, therefore, both the n.m.r. data and the conformational analysis are consistent with assignment of the (*R*) configuration to C-8 of **11**, and the (*S*) configuration for **10**, as well as with the corresponding assignments already proposed[1] for the compounds from which these two acetals were derived. Additional comments on these points are contained in the following section.

Reaction mechanisms of transformations involving 2-O-(2-hydroxypropyl)-D-glucose and derivatives thereof. — By analogy with discussions[1,7] on the corresponding tri-*O*-benzyl derivatives, methyl 2-*O*-(2-hydroxypropyl)-α-D- and -β-D-glucofuranoside (**3** and **4**) may be expected to undergo transformation into 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranoses (**7** and **8**) through the lactol-ring-

opening mechanism shown in Scheme 1. In addition, the evidence just presented indicates that the 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranoses (**7** and **8**) and 2-*O*-(2-hydroxypropyl)-α,β-D-glucopyranose (**9**) are formed through a common intermediate; in Scheme 1, this intermediate is represented by **12**. Three possibilities are shown for an attack on **12** by nucleophiles available: by a molecule of water, or by two intramolecular nucleophiles, *i.e.*, O-4 and O-5. In order to form 2-*O*-(2-hydroxypropyl)-D-glucopyranose (**9**), the carbonium-ion intermediate **12** must react with the water molecule at C-1, perhaps in a nonstereospecific attack, to give a 1,4-dioxan-2-ol intermediate (**13**). The conjugate acid of the latter has possibilities for subsequent C–O bond-breaking–bond-forming reactions leading to the formation of a pyranose ring through attack by O-5 (**14**) (or by O-4 to yield a furanose which then undergoes tautomerization). Hence 2-*O*-(2-hydroxypropyl)-D-glucopyranose (**9**) is formed from the reaction of intermediate **12** with a water molecule, whereas 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranoses (**7** and **8**) result from intramolecular attack by O-4. If O-5 were to serve as the nucleophile, the bicyclic pyranoid system (**10** and **11**) would be generated. Clearly, as the equilibrium in these reactions is governed by the relative stability of the products, a good correlation with steric and stereoelectronic effects within these molecules should be evident.

The ratios of the glucofuranose to glucopyranose systems are especially dependent on their structures at C-8. Hence, although **8**, having the (*S*) configuration of C-8, is equilibrated with 65% of its D-glucopyranose derivative **9**(*S*) (see Fig. 1b), **7** is almost completely converted into its D-glucopyranose derivative **9**(*R*) (see Fig. 1c). This may be rationalized in terms of structural instabilities induced by nonbonding interactions. As **7** should incorporate strong steric interactions (so that it appears[1] to favor a twist conformation), its inherent instability probably accounts for its easy transformation into 2-*O*-(2-hydroxypropyl)-D-glucopyranose under weakly acidic conditions.

When the concentration of acid in the mixture of **8** and **9**(*S*) obtained from the hydrolysis of **8** (see Fig. 1d) was increased to 1.5M H_2SO_4 at 95°, another species, namely, 1,2-*O*-[1-methyl-(*S*)-1,2-ethanediyl]-D-glucopyranose (**10**), was formed. The ratios of **8**:**9**(*S*):**10** were 24:65:11. In the analogous reaction of the mixture of **7** and **9**(*R*), the diastereomeric form of **10**, *i.e.*, 1,2-*O*-[1-methyl-(*R*)-1,2-ethanediyl]-α-D-glucopyranose (**11**), was much more strongly favored (81%) (see Fig. 1c). Here, as with **7** and **8**, the configuration of C-8 may be correlated with the stability. That is, the axial methyl (C-9) in the favored conformation of **10**, as compared with the equatorial CH_3 of **11** (see Scheme 1), appears to account adequately for the higher proportion of **11** (relative to **9**) produced in these parallel reactions.

Among reaction mechanism possibilities considered here, as illustrated in Scheme 1, the one most likely to lead to **10** and **11** appears to involve an A-1 mechanism, through carbonium-ion intermediate **15**, which undergoes attack by the *O*-(2-hydroxypropyl) substituent to close the second 6-membered ring, giving the bicyclic system. This proposal is supported by the observation that the hydro-

lysis under mildly acidic conditions yields only D-glucofuranose derivatives, not 6,6-membered bicyclic acetals, and by the fact that a general acid-hydrolysis of glycopyranosides occurs through a carbonium intermediate (A-1) mechanism[8,9].

Overall, these various transformations may be expressed in terms of a series of nucleophilic substitution reactions at the anomeric center, where intra- and inter-molecular nucleophiles compete, and where both SN1 and SN2 types of reaction occur. If it is assumed that equilibrium conditions were approximated in these reactions, then, as would normally be expected, the more thermodynamically stable product tends to be that possessing a 6-membered rather than a 5-membered ring. Although it is not clear how readily monocyclic and bicyclic systems may be directly compared, 2-*O*-(2-hydroxypropyl)-D-glucose (**9**) always preponderates over 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranose (**7** and **8**) (see Fig. 1). Furthermore, 1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucopyranose (**11**) is the most thermodynamically stable product in the entire series. Nevertheless, the 6,6-bicyclic structure of **10** is appreciably less stable than the 5,6-bicyclic structure of **8**, an unusual example of a pyranose–furanose relationship.

Also noteworthy is the fact that the bicyclic systems are *cis*-fused rather than *trans*-fused. In the 6,6-series, as already noted[1], the *trans* system is disfavored stereoelectronically[10–12] by unfavorable interactions of the lone-pair orbital of the oxygen atoms involved.

Bicyclic pyranose **11** is perhaps the most highly resistant of known sugar acetals toward acid hydrolysis*. Obviously, this remarkble stability accounts for its survival in a series of transformations (hydration, dehydration, ring-opening, and ring-closure) involved in the equilibrium between **11** and its hydrolysis product, 2-*O*-(2-hydroxypropyl)-D-glucose (**9**). With conventional glycosides, when the aglycon group is liberated, to give the free alcohol, the latter is unable to compete significantly against the water molecule in a nucleophilic attack on the protonated anomeric center, whereas the 2-*O*-(2-hydroxypropyl) group is always ideally positioned to do so. However, if the bicyclic acetal, such as pyranose derivative **10** and furanose derivative **7**, incorporates sufficiently strong destabilizing interactions, the equilibrium shifts towards the aldose form (**9**).

A substantial number of different molecular types is represented in the transformations described here (see Fig. 1 and Scheme 1), all of which are related to changes occurring at the anomeric center. This provides a series of different C-1–O bonds ranging widely in apparent stability, as implied by the product ratios obtained in the hydrolysis reactions. For example, the C-1–O-4 bond in the furanoside ring of **4** (see Scheme 1) was cleaved, rather than the C-1–OMe bond. Hence, the overall decreasing order of C-1–O bond strengths is as follows: (*1*) C-1–O bond in pyranose ring of 6,6-bicyclic acetal, C-1–O bond in dioxane ring of 6,6-bicyclic acetal (1.5 M H_2SO_4); (*2*) C-1–O bond in glucopyranose ring, C-1–O bond in glucopyranose derivatives; (*3*) C-1–O bond in dioxane ring of 5,6-bicyclic acetal;

*An analogous finding has been reported in the hydrolysis of some cardenolide glycosides[13].

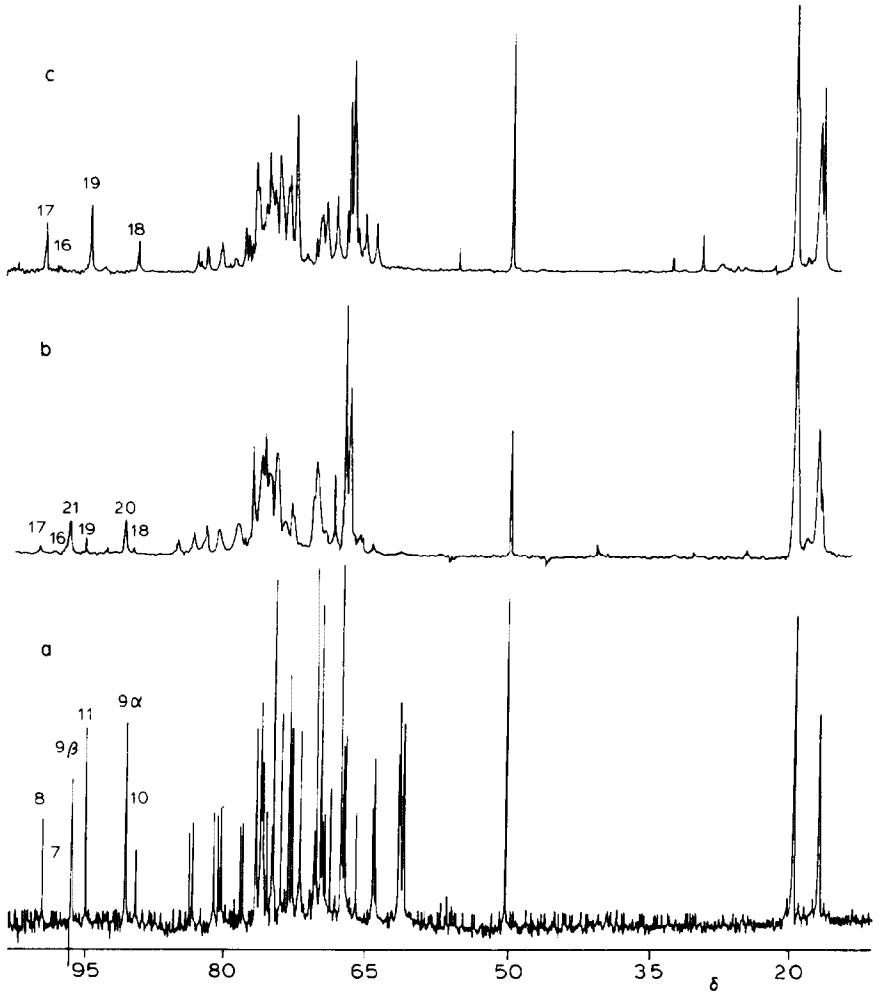


Fig. 3. ^{13}C-N.m.r. spectra of (a) 2-*O*-(2-hydroxypropyl)-α,β-D-glucose (**9**) and bicyclic acetals **7, 8, 10,** and **11**, formed from **9** in 1.5M sulfuric acid (b) the acid hydrolyzate (3M sulfuric acid) of *O*-(2-hydroxypropyl)cellulose; and (c) bicyclic acetals **16–19** isolated from the hydrolyzate.

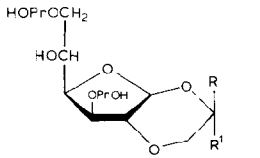
(*4*) C-1–O bond in dioxane ring of monocyclic intermediate; (*5*) C-1–O bond in furanose ring of 5,6-bicyclic acetal; (*6*) C-1–OMe bond in glucofuranoside derivatives; and (*7*) C-1–O bond in glucofuranoside ring.

In summary, the nucleophilic hydroxyl group of a neighboring 2-*O*-(2-hydroxypropyl) group of glucose derivatives may competitively participate in acid-catalyzed reactions as a strong nucleophile. In comparison with other nucleophiles available in the reaction, this intramolecular nucleophile forms stereochemically and stereoelectronically stable systems possessing a (6-membered) 1,4-dioxane ring by neighboring-group participation. A monocyclic or bicyclic product is obtained, depending on the strength of the particular C-1–O bonds involved or, in other words, on whether one leaving-group in the system is better than another.

The overall question of the stability of these types of acetal is again considered later, in relation to transformations in acidic methanol.

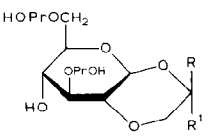
A correlation between the acid-catalyzed hydrolyzate of O-(2-hydroxypropyl)cellulose and acid-catalyzed transformation products from 2-O-(2-hydroxypropyl)-D-glucose. — As already seen, 2-*O*-(2-hydroxypropyl)-D-glucose (**9**) is equilibrated in aqueous acidic media with 5,6- and 6,6-membered, bicyclic acetals (**7, 8, 10,** and **11**), which is clearly demonstrated by ^{13}C-n.m.r. spectroscopy (see Fig. 3a). Based on the ^{13}C-n.m.r. spectrum shown in Fig. 3b, it is evident that the same kinds of transformation occur during the hydrolysis of *O*-(2-hydroxypropyl)cellulose (although under somewhat more-drastic conditions)[2]. That is, ^{13}C signals at δ 100.6, 99.0, 95.7, and 90.4, for example, correspond exactly to the anomeric carbon signals of **8, 7, 11,** and **10**, respectively, and have approximately the same relative intensities. Accordingly, each type of 1,2-*O*-bicyclic product in the hydrolyzate can undoubtedly be identified in the spectrum. This clearly indicates that the hydrolysis of the polymer yields 1,2-*O*-bicyclic acetal derivatives **16, 17** (trace), **18**, and **19** (major), as well as *O*-(2-hydroxypropyl) derivatives (**20** and **21**) of α- and β-D-glucose, all of which occur in almost the same ratio as found in the hydrolyzate of **9**; no other kinds of product are detected.

It was reported earlier[2] that the group of bicyclic acetals in the polymer hydrolyzate was isolated chromatographically. The ^{13}C-n.m.r. spectrum of this mixture is shown in Fig. 3c. Using appropriate data for the related acetals (**7, 8, 10,** and **11**) and substituent effects (β-, γ-effects: +9, −1 p.p.m., respectively), the ^{13}C-

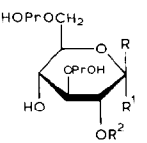


16 R = Me, R^1 = H
17 R = H, R^1 = Me

HOPr = CH_2—CH—Me
OH



18 R = H, R^1 = Me
19 R = Me, R^1 = H



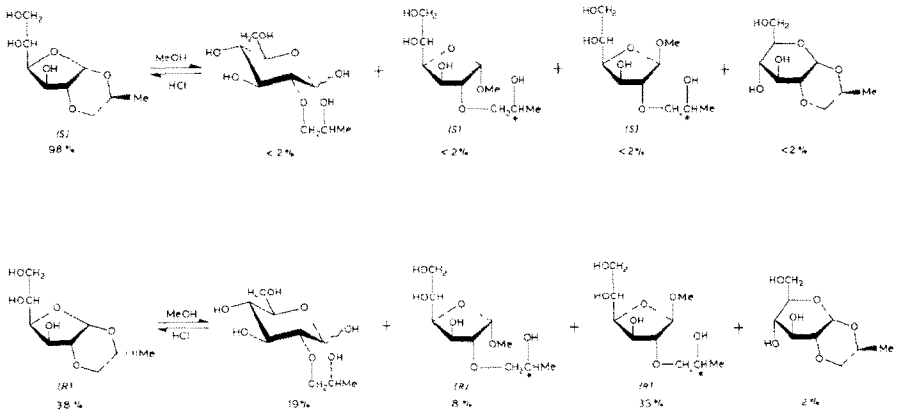
20 R = H, R^1 = OH, R^2 = >1 HOPr
21 R = OH, R^1 = H, R^2 = >1 HOPr

TABLE III

CALCULATED ^{13}C-CHEMICAL SHIFTS (δ) FOR 3,6-DI-*O*-(2-HYDROXYPROPYL)-1,2-*O*-(1-METHYL-1,2-ETHANEDIYL)-α-D-GLUCOSES

Compound[a]	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*CH$_3$(E)*[b]	*CH$_3$(I)*[c]
16	98.2	79.7	82.0	79.2	70.2	73.5	67.5	69.0	18.5	19.5	17.2
17	100.5	81.1	84.5	75.6	70.6	74.1	70.2	66.7	16.7	19.5	17.2
18	90.0	75.0	84.2	69.3	70.2	71.0	69.4	64.5	16.5	19.5	17.2
19	95.5	74.2	82.6	69.5	73.4	70.7	64.6	68.2	16.6	19.5	17.2

[a]Corresponding to acetals **7, 8, 10,** and **11**, respectively. [b]Methyl carbon atom of terminal substituent. [c]Methyl carbon atom of internal substituent.



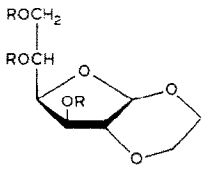
Scheme 2. Acid-catalyzed methanolysis of bicyclic acetals **7** and **8**.

chemical shifts for the isolated acetals (**16–19**) have been calculated (see Table III). These calculated chemical shifts afford an interpretation of much of the ^{13}C-n.m.r. spectrum (see Fig. 3c). For example, ^{13}C signals at δ 84.2, 82.0, and 82.6 correspond to C-3 of **18, 16,** and **19**, respectively. Also, it may be seen that all methyl carbon atoms (C-9) of the dioxane rings resonate at $\delta \sim 17.0$.

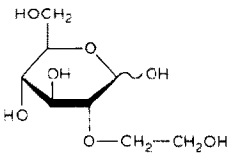
Acid-catalyzed transformations involving 2-O-(2-hydroxypropyl)-D-glucose and derivatives thereof, in methanol. — As shown recently[14], the methanolysis of *O*-(2-hydroxypropyl)cellulose provides a highly effective alternative to acid hydrolysis for converting the polymer into its monomeric constituents. It was of interest, therefore, to compare the characteristics of the methanolysis of model compounds with those observed under conditions of hydrolysis.

When the mixture of **7, 8,** and **9**, shown in Fig. 1a, was transferred into methanol containing 1% of hydrochloric acid and kept for 3 d at room temperature, the product equilibrium was markedly changed. From the ratios of the various constituents present (see Scheme 2), as estimated from the ^{13}C-n.m.r. spectrum, it is seen that the equilibrium tended to favor 1,2-*O*-[1-methyl-(*S*) and (*R*)-1,2-ethanediyl)]-α-D-glucofuranose (**7** and **8**). Indeed, among the components having the (*S*) configuration of C-8, **8** was virtually the only product. In the series of components having the (*R*) configuration, the bicyclic furanose **7** was only slightly more prominent than the β-furanoside **4**(*R*) (note that an appreciable proportion of free aldose **9** still remained after 3 days).

These results parallel the earlier finding that the stability of **8** under hydrolytic conditions is greater than that of **7**, as a result of differences in nonbonding interaction arising from the configurational change at C-8. They also fit the proposal that the reaction step involving intermediate **12** and its precursors (see Scheme 1) is a reversible process. The fact that the proportion of the (1,2-*cis*) α anomer **3**(*R*) is notably lower than that of the (1,2-*trans*) β anomer **6**(*R*) is consistent with the fact that 1,2-*trans* furanosides tend to be the major products in the methanolysis of aldoses under comparable conditions[15]. Only traces of the bicyclic pyranoses (**10** and **11**) were detected.



22 R = Bn
23 R = H



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Under forcing conditions, as shown in the methanolysis of *O*-(2-hydroxypropyl)cellulose, the product equilibrium greatly favors α-pyranosides and the bicyclic acetals. It is now possible to conclude, from the signals at δ 100.6 and 95.7 in the spectrum of the methanolyzate[14], that pyranose derivative **19** is the major, and furanose **16**, the minor, acetal. Not surprisingly, therefore, the general sequence of reactions shows characteristics similar to those found for hydrolysis. It is assumed, therefore, that many features of the reaction mechanisms presented in Scheme 1 apply here as well.

Acid-catalyzed transformations in the O-*(2-hydroxyethyl) series.* — *O*-Debenzylation of 3,5,6-tri-*O*-benzyl-1,2-*O*-(1,2-ethanediyl)-α-D-glucofuranose (**22**) afforded acetal **23**, which corresponds to compounds **7** and **8**, devoid of a methyl group at C-8. In contrast to **7** and **8**, acetal **23** was not appreciably hydrolyzed in 0.15M sulfuric acid at 95°. With 0.5M acid, however, **23** was fully converted into 2-*O*-(2-hydroxyethyl)-α,β-D-glucose (**24**). Although these results suggest that **23** is more stable than **8**, and much more so than **7**, the differences need not be directly associated with the presence or absence of an 8-*C*-methyl group on the 1,4-dioxane ring, but may involve the possibility[16] that the secondary alcohol (*i.e.*, the 2-hydroxypropyl substituent) has a stronger tendency to form a 6-membered-ring acetal with the anomeric carbon atom than has the primary alcohol (the 2-hydroxyethyl substituent).

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter. N.m.r. spectra (^1H and ^{13}C) were recorded with a Bruker WH-90 or a Varian XL-200 spectrometer. Chemical shifts (δ) are reported with reference to tetramethylsilane. Mass spectra were recorded with an LKB 9000 spectrometer at an ionization potential of 70 eV, or by chemical ionization (isobutane) with an HP 5980A spectrometer.

*Methyl 2-O-(2-hydroxypropyl)-α- and -β-D-glucofuranoside (**3** and **4**).* — When subjected to catalytic-transfer hydrogenolysis[3] with 10% palladium–charcoal in 9:1 methanol–formic acid (under nitrogen), methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α- and -β-D-glucofuranoside (**1** and **2**, respectively) respectively afforded syrupy **3** and **4** in 95% yield. The ^1H-n.m.r. data (D_2O) were: for **3**, δ 5.16

(d, 1 H, H-1), 3.35 (s, 3 H, OCH_3), and 1.15 (d, 3 H, H-9); $J_{1,2}$ 4.4 and $J_{8,9}$ 6.4 Hz; for **4**, δ 4.99 (s, 1 H, H-1), 4.39 (d, 1 H, H-3), 3.99 (dd, 1 H, H-4), 3.93 (s, 1 H, H-2), 3.38 (s, 3 H, OMe), and 1.15 (d, 3 H, H-9); $J_{3,4}$ 4.4, $J_{4,5}$ 7.0, and $J_{8,9}$ 6.5 Hz.

*1,2-*O*-[1-Methyl* (R) *and* (S)*-1,2-ethanediyl]-α-*D*-glucofuranose (**7** and **8**) and acetal **23**.* — Tri-*O*-benzyl acetals **5** (0.2 g), **6** (0.1 g), and **22** (0.4 g) were each *O*-debenzylated by catalytic-transfer hydrogenolysis, using 10% palladium–charcoal in 9:1 methanol–formic acid under nitrogen; yields: of **7**, 43 mg (95%), m.p. 89–90°, $[\alpha]_D$ +19.9° (*c* 7.2, D_2O); of **8**, 45 mg (96%), m.p. 157–158°, $[\alpha]_D$ −27.2° (*c* 5.5, D_2O); of **23**, 166 mg (96%), m.p. 217° (dec.), $[\alpha]_D$ −44.8° (*c* 2.3, D_2O); ^{1}H-n.m.r. data (D_2O): for **8**, δ 5.49 (H-1), 4.33 (H-4), 4.27 (H-3), 4.11 (H-8), 3.94 (H-2), 3.85 (H-5), 3.82 (H-6), 3.76 (H-7), 3.65 (H-6′), 3.35 (H-7′), and 1.08 (H-9); $J_{1,2}$ 2.21, $J_{2,3}$ 1.25, $J_{3,4}$ 3.00, $J_{4,5}$ 8.84, $J_{5,6}$ 2.74, $J_{5,6'}$ 6.18, $J_{6,6'}$ 12.15, $J_{7,7'}$ 11.80, $J_{7,8}$ 2.23, $J_{7',8}$ 10.26, and $J_{8,9}$ 6.51 Hz. For **7**, δ 5.35 (H-1), 4.58 (H-3), 4.30 (H-4), 4.10 (H-2), 3.92 (H-5), 3.90 (H-8), 3.80 (H-6), 3.73 (H-7), 3.56 (H-7′), 3.55 (H-6′), and 1.24 (H-9); $J_{1,2}$ 3.36, $J_{2,3}$ 3.53, $J_{3,4}$ 4.91, $J_{4,5}$ 7.57, $J_{5,6}$ 2.97, $J_{5,6'}$ 6.27, $J_{6,6'}$ 11.97, $J_{7,7'}$ 11.93, $J_{7,8}$ 2.98, $J_{7,8'}$ 6.35, and $J_{8,9}$ 6.54 Hz. For **23**, δ 5.46 (H-1), 4.37 (H-4), 4.28 (H-3), and 4.01 (H-2); $J_{1,2}$ 2.44, $J_{2,3}$ 1.36, $J_{3,4}$ 3.15, and $J_{4,5}$ 9.05 Hz.

Anal. Calc. for $C_9H_{16}O_6$: mol. wt. 220. Found for **7**: *m/z* 220 (M, 0.5%); Found for **8**: *m/z* 220 (M, 0.1%). Calc. for $C_{18}H_{14}O_6$: mol. wt. 206. Found for **23**: *m/z* 188 (M − H_2O, 0.6%).

Acid-catalyzed hydrolysis experiments. — *(a)* A solution of each anomer of methyl 2-*O*-(2-hydroxypropyl)-D-glucofuranoside (**3** and **4**; 0.1 g) in 0.15M D_2SO_4 (30 mL) was heated for 24 h at 95°. According to the ^{13}C-n.m.r. spectrum of the solution, the hydrolyzate consisted of a mixture of acetal **8** (~1 part), and 2-*O*-(2-hydroxypropyl)-α- and -β-D-glucose (~1 part of each). [A closely similar result was obtained when **1** or **2** was boiled for 24 h under reflux in water containing Amberlite IR-120 (H^+) ion-exchange resin.]

(b) In 1.5M D_2SO_4, glycosides **3** and **4** afforded mixtures of the α,β-aldose (**9**), together with acetals **8, 10,** and **11**.

(c) A solution of (*R*)-acetal **7** (0.2 g) in 0.15M D_2SO_4 (2 mL), contained in a ^{13}C-n.m.r. tube, when heated for 40 min, was found to have given the α,β-aldose **9**(*R*) exclusively. The ^{1}H-n.m.r. data (0.15M D_2SO_4): δ 5.42 and 4.67 (2 d, H-1α and H-1β), and 1.05 and 1.13 (2 d, H-9α and H-9β); $J_{1\alpha,2}$ 3.42 and $J_{1\beta,2}$ 7.92 Hz; molar ratio of α:β anomer = ~1:1.

(d) a solution of (*R*)-acetal **7** (0.2 g) in 1.5M D_2SO_4 (2 mL), as in (*c*), afforded acetal **11** (~81%) in 4 h at 95°.

(e) When a solution of mixed (*R*)- and (*S*)-acetals **7** and **8** in 1.5M D_2SO_4 was heated for 4 h at 95°, the ^{13}C-n.m.r. spectrum of the hydrolyzate indicated the presence of **9**(*S*), **9**(*R*), **7, 8, 10,** and **11**, in the ratios of ~65:18:1:24:11:81.

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