Carbohydrate Research, 114 (1983) 11–19
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

EQUILIBRATION OF ALDITOL ANHYDRIDES IN ACETIC ACID*

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(Received March 5th, 1982; accepted for publication, September 10th, 1982)

ABSTRACT

Dehydration of pentitols in acetic acid containing an acidic catalyst parallels that in aqueous sulfuric acid; 1,4(2,5)-dehydration occurs with inversion of configuration at C-2 or C-4. Acetylated alditols undergo similar processes *via* intermediates having free hydroxyl groups. Configurational inversion of 1,4- or 1,5-anhydroalditols is attributed to intermediate acyloxonium ions that are also proposed as intermediates in the structural isomerisation. Drastic treatment of each alditol gives equilibrium mixtures. The equilibrium concentrations are used to calculate free-energy differences.

INTRODUCTION

Isomerisation–dehydration reactions have been used extensively in the synthesis of sugar derivatives, starting with esters, acetals, and ethers of monosaccharides[1–5], polysaccharides[6,7], glycosides[8], alditols[9], anhydroalditols[10], and cyclitols[11], and generally using either acetic acid or liquid hydrogen fluoride[2,3,12]. Sugar derivatives can be isomerised in acetic acid containing a trace of toluene-*p*-sulfonic acid[13], sulfuric acid[14], acetic acid–acetic anhydride containing sulfuric acid[15], acetic acid, and organic solvents[16,17] containing Lewis acids.

Isomerisation of polysaccharides in acetic acid was accompanied by bond cleavage, giving mono- and oligo-saccharide derivatives[18].

Five-membered, cyclic, acyloxonium ion intermediates derived from vicinal *trans* groups have been proposed for isomerisations in liquid hydrogen fluoride[10,11,19,20] and are probably involved in acetic acid[1], but other mechanisms may also be involved.

We now report on the isomerisation and equilibration of alditols and anhydroalditols.

DISCUSSION

Isomerisation–equilibration reactions of tetritols, pentitols, anhydroalditols,

*Presented at the IX Journées sur la Chimie et la Biochimie des Glucides, Aussois-en-Maurienne, France, January 12–14, 1981.
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TABLE I

YIELDS[a] (%) OF DEHYDRATION PRODUCTS OF TETRITOLS IN ACETIC ACID WITHOUT OR WITH IR-120 (H^+) RESIN AS CATALYST

Acetylated derivative of	*From erythritol in*				*From* DL-*threitol in*			
	acetic acid at 100 during	*acetic acid*		*resin*	*acetic acid at 100 during*	*acetic acid*		*resin*
	72 h	*1 h*	*3 h*	*10 h*	*72 h*	*1 h*	*3 h*	*10 h*
1,4-Anhydro-DL-threitol[b]	--	11	15	38	0.5	25	31	48
1,4-Anhydroerythritol[b]	0.5	25	37	29	-	7	12	16
Erythritol	99.5	37	30	20	--	11	21	20
DL-Threitol	-	27	18	13	99.5	57	36	16

[a]Calculated from the peak areas in g.l.c. [b]Intermolecular dehydration products are not included.

and their acetylated derivatives were performed in acetic acid or in acetic acid containing an acid catalyst. Thus, in acetic acid for 3 days at 100°, tetritols gave 1,4-anhydro derivatives (Table I), whereas pentitols yielded 1,4- and 1,5-anhydro derivatives (Table II), parallelling the behaviour in aqueous solutions of inorganic acids[21-23].

In acetic acid containing Amberlite IR-120 (H^+) resin or perchloric acid, a variety of intramolecular dehydration products (Tables I and II) was formed from tetritols and pentitols. Tetritols also gave ~50% of intramolecular condensation products, but these are not considered here[24].

The products of brief reactions were similar to those obtained when aqueous sulfuric acid[22] was employed, namely, four 1,4-anhydropentitols from D-arabinitol, but only two from xylitol and ribitol.

When acetylated alditols were isomerised in acetic acid, 1,4- and 1,5-anhydro derivatives were detected amongst the products, but were not formed when such derivatives were heated in *N*,*N*-dimethylformamide containing sulfuric acid. Thus, acetic acid was involved in the cyclisation reactions. Acyl–oxygen fission (Scheme 1) could generate free hydroxyl groups in the alditol molecules, and partially acetylated alditol derivatives could be detected by g.l.c. of the product mixture after trimethylsilylation. Since esters of primary alcohols usually react easily by an acyl–oxygen fission mechanism[25], it is probable that free hydroxyl groups in the partially acetylated alditol derivatives are on terminal carbon atoms (Scheme 1). Cyclic, partially acetylated alditol products can be formed by intramolecular reactions involving a protonated ester group or an acyloxonium ion and a hydroxyl group, or two hydroxyl groups one of which is protonated[22]. Each mechanism will result in configurational inversion.

Prolonged treatment of alditols and anhydroalditols in acetic acid with a proton donor causes additional isomerisation. Thus, on treatment with acetic acid containing

TABLE II

YIELDS[a] (%) OF THE DEHYDRATION AND ISOMERISATION PRODUCTS OF PENTITOLS

Acetylated derivative of	*Acetic acid at 100°*			*Acetic acid + 0.01% of 70% $HClO_4$ at 80°*									*Acetic acid + Amberlite IR-120 (H^+) resin at 100°*								
	72 h			*1 h*			*2 h*			*3 h*			*1 h*			*3 h*			*5 h*		
	I[b]	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*[c]	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*
1,5-Anhydroxylitol	—	—	—	—	1	—	—	1	—	—	1.5	—	—	1.5	—	—	1.5	—	—	2	—
1,5-Anhydroribitol	—	—	1	—	—	16	—	—	16.5	—	—	16.5	—	tr	7	—	tr	7	—	tr	7.5
1,5-Anhydroarabinitol	0.5	—	—	9	—	—	11	—	—	11.5	—	—	3.5	1.5	tr	9.5	1.5	1	11	2	1
1,4-Anhydroarabinitol[a]	2.5	1	—	22.5	19.5	—	28	25.5	—	29	49.5	—	11	19	2	31	33.5	2.5	36.5	42.5	3
1,4-Anhydroxylitol[b]	1	1	—	21	19	—	26	25	—	27.5	48	—	6	20.5	2	16.5	35	2.5	19.5	44	3
1,4-Anhydroribitol[c]	tr[d]	—	8	5	tr	59.5	6	tr	63	6	0.5	63	2	3.5	48.5	6.5	3.5	59.5	7.5	4.5	65.5
1,4-Anhydrolyxitol[d]	tr	—	2.5	20	tr	20.5	25	tr	20.5	26	0.5	20.5	8	4	15.5	21.5	4	18.5	25.5	5	20
Ribitol	—	—	88.5	0.5	tr	4	—	tr	—	—	—	—	1	2	24.5	0.5	1	9	—	—	—
Arabinitol	94	—	—	22	2	—	4	3.5	—	—	—	—	67.5	8	0.5	13.5	6	tr	—	—	—
Xylitol	—	98	—	tr	58.5	—	—	44.5	—	—	—	—	1	40	tr	1	14	tr	—	—	—

[a]Calculated from peak areas in g.l.c. [b]I, D-arabinitol; II, xylitol; III, ribitol. [c]For 5 h. [d]Trace.

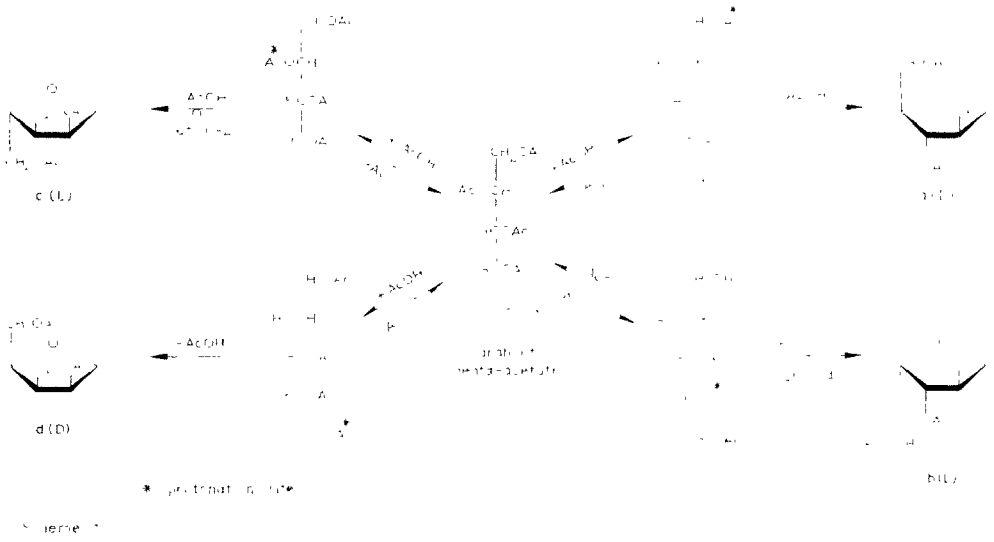


TABLE III

EQUILIBRIUM MIXTURES (GENERATED IN 2% $HClO_4$ IN ACETIC ACID AT 120° AFTER 2 DAYS)

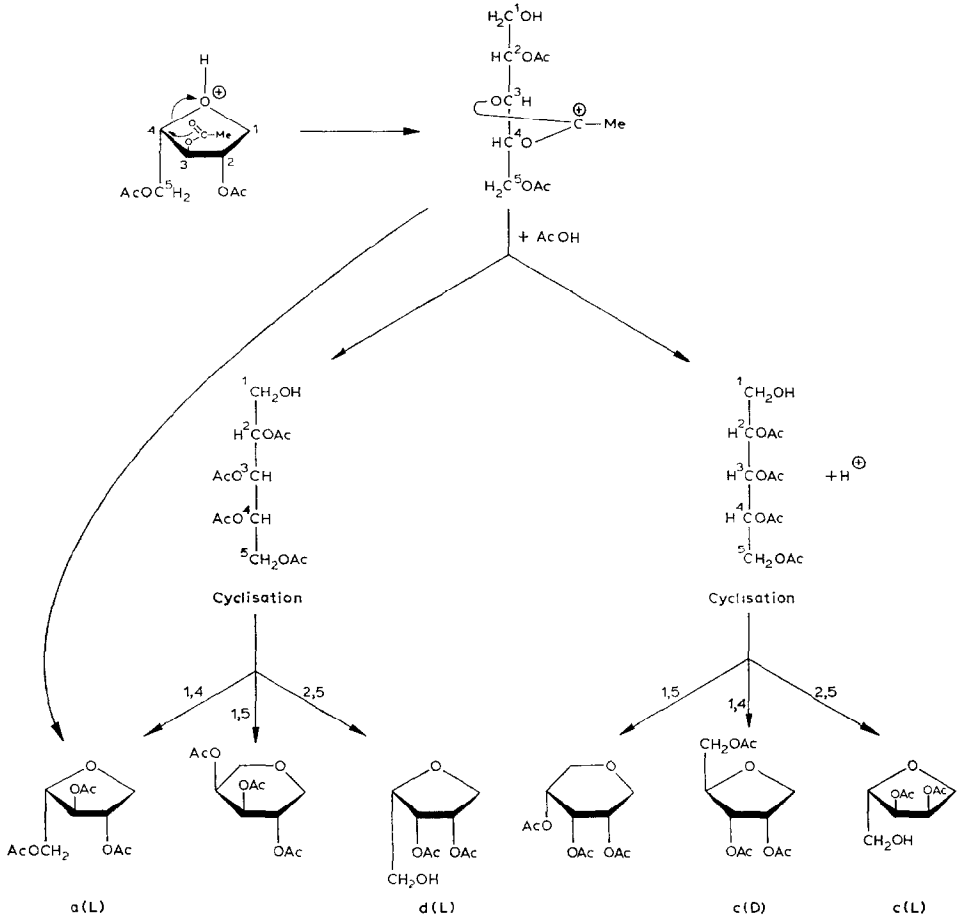
(a) Anhydrotetritols

Diacetate of	*G.l.c. retention-index*[a,b]	*Yields (%)*	*Free-energy differences (kcal/mol)*
1,4-Anhydrothreitol	14.98	84	1.3
1,4-Anhydroerythritol	15.05	16	

(b) Anhydropentitols

Acetylated derivatives of	*G.l.c. retention-index*[a,c]	*Yields (%)*	*Free-energy differences*[d] *(kcal/mol)*
1,5-Anhydroxylitol	18.39	7.6	1.1
1,5-Anhydroribitol	18.71	4.3	1.5
1,5-Anhydroarabinitol	18.86	25.8	0.15
1,4-Anhydroarabinitol	19.13	30.9	—
1,4-Anhydroxylitol	19.23	15.3	0.5
1,4-Anhydroribitol	19.32	12.6	0.7
1,4-Anhydrolyxitol	19.46	3.5	1.7

[a]Measured in methylene units. [b]From 65° at 1°/min. [c]From 110° at 1°/min. [d]Calculated as an excess compared to that of 1,4-anhydroarabinitol: $\Delta G = RT\ln K_e$, T = 393 K.

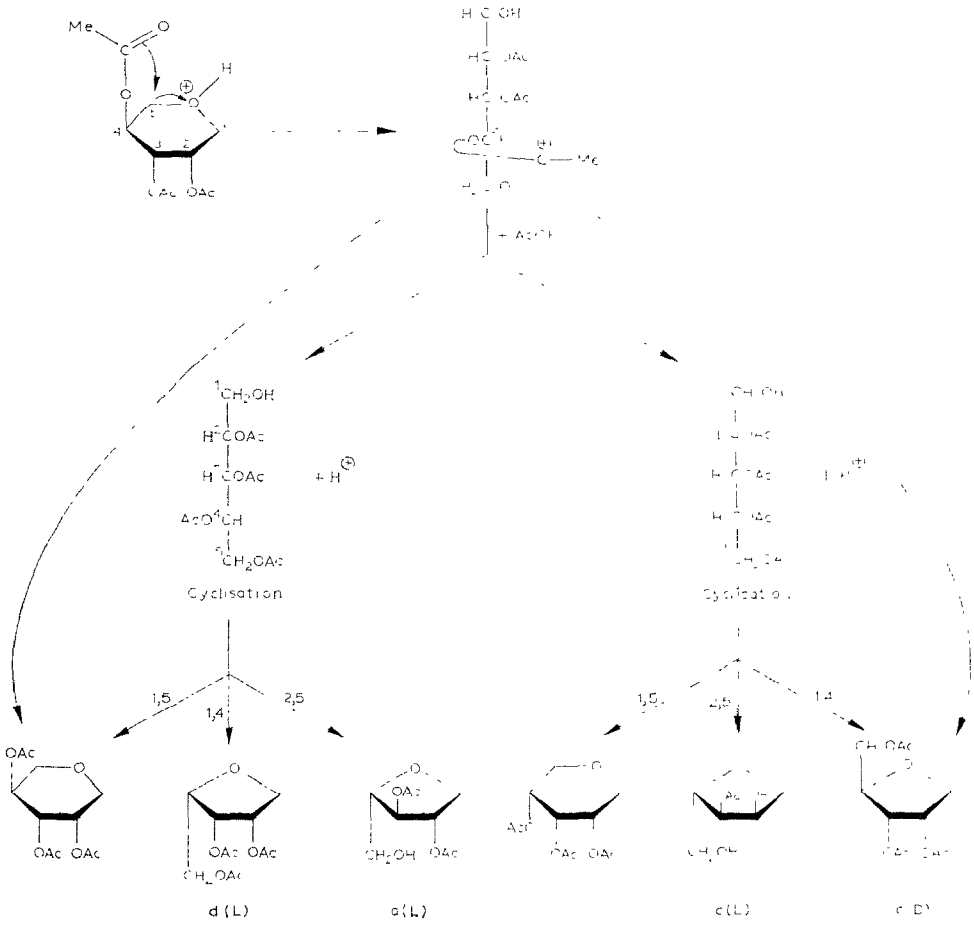


Scheme 2

2% of perchloric acid for 2 days at 120°, alditols and 1,4- or 1,5-anhydroalditols or their acetylated derivatives gave equilibrium mixtures (Table III). Establishment of these equilibria involved epimerisation and reversible ring-cleavage reactions (Schemes 2 and 3).

Acid-catalysed isomerisation of acetylated 1,4- and 1,5-anhydroalditols has been explained[10,11,19,20] in terms of a mechanism involving acyloxonium mono- or di-acetate intermediates (Scheme 4). Cleavage of the intermediate, cyclic acyloxonium ion gives an isomer having the same ring size, and this type of reaction occurs under mild conditions. Unlike the reactions of pentitols in aqueous sulfuric acid, the above-mentioned processes can provide products with inverted configurations at C-3 alone or at both C-2 and C-4.

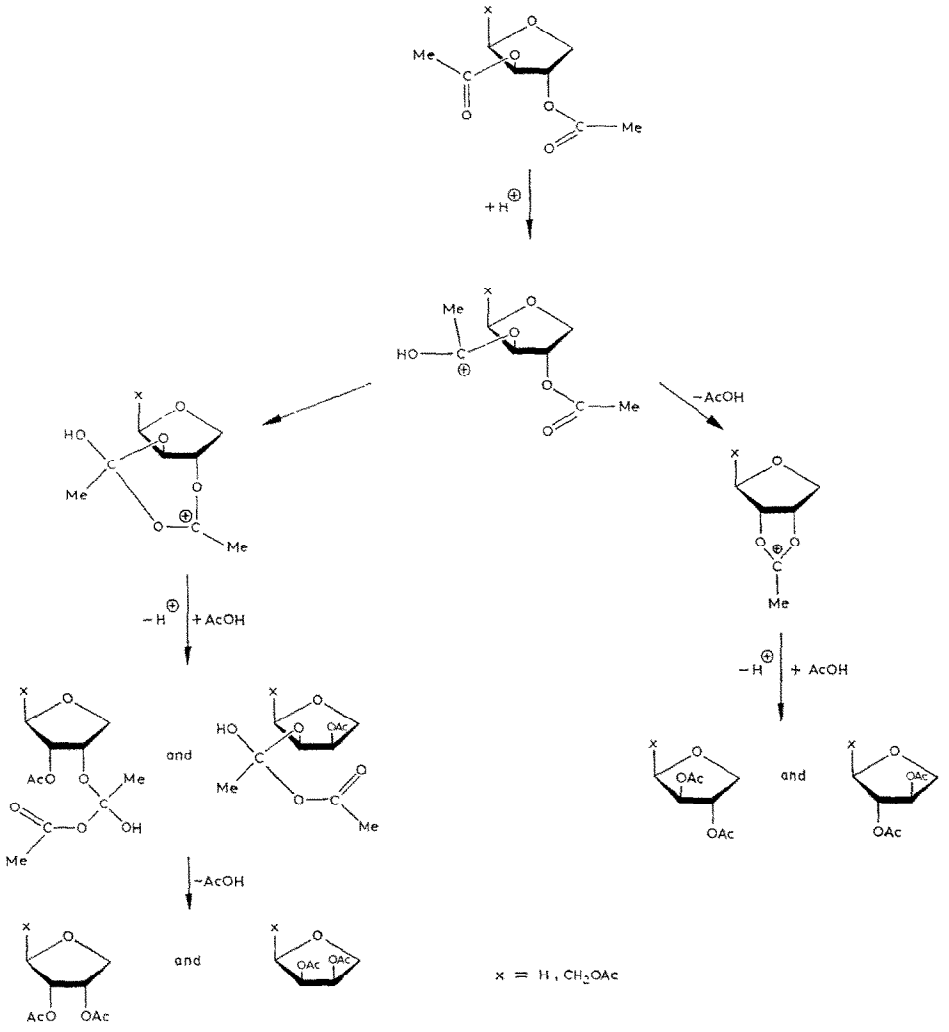
Ring-opening reactions of 1,4-anhydroalditols are well known and a mechanism



Scheme 3

has been proposed[19,20] (Scheme 2). However, no evidence for the ring cleavage of 1,5-anhydroalditol esters[10,11,19,20] has been published hitherto. The cleavage reactions of 5- or 6-membered rings have common features (Schemes 2 and 3), namely, open-chain acyloxy-ion intermediates that collapse to yield partially acetylated alditols which, in turn, produce cyclic derivatives.

The proportions of the acetylated products present at equilibrium (Table III) allowed free-energy differences to be calculated. The most stable 1,4-anhydropentitol, namely, 1,4-anhydroarabinitol, which possesses one weak steric interaction (*cis*-2,4 substituents), was used as a reference compound. Comparison of the free-energy differences for the triacetates of 1,4-anhydroxylitol and 1,4-anhydroarabinitol gave the value ($x - z = 0.5$ kcal/mol) of the differences between the *cis*-3,4 (x) and *cis*-2,4 (z) interactions. The free-energy difference ($y - z = 0.7$ kcal/mol) between the triacetates of 1,4-anhydroribitol and 1,4-anhydroarabinitol reflects the difference



Scheme 4

between the *cis*-2,3 (y) and *cis*-2,4 (z) interactions. The value ($x + y + z = 1.7$ kcal/mol) for the triacetate of 1,4-anhydrolyxitol represents the sum of *cis*-2,3, *cis*-3,4, and *cis*-2,4 interactions. Solution of the three above equations gives the values (kcal/mol) of the *cis*-interactions as 2,4, 0.17; 2,3, 0.87; and 3,4, 0.67.

The diacetates of the 1,4-anhydrotetritols exhibit a free-energy difference of 1.3 kcal/mol, that is 0.43 kcal/mol more than predicted ($y = 0.87$ kcal/mol). However, only 1,4-anhydrothreitol is chiral, and the entropy of D,L mixing must be taken into consideration. This results in an increase in energy difference of 0.54 kcal/mol at the temperature employed, giving a predicted overall value of 1.4 kcal/mol (*cf.* the observed value of 1.3 kcal/mol).

The ΔG values for the triacetates of the 1,5-anhydropentitols, as for 1,4-anhydrothreitol diacetate, cannot be interpreted exclusively in terms of non-bonded interactions, since the entropy of mixing is again involved.

The sequence of free-energy values for the triacetates of the three 1,5-anhydropentitols is qualitatively the same as that for the 1,5-anhydropentitols in aqueous solution. The most energy-rich 1,5-anhydropentitol is 1,5-anhydroribitol which, in the $^4C_1$ conformation, according to Angyal[26], has two vicinal *cis* O,O and two syn-diaxial O/H interactions that correspond to 1.6 kcal/mol, in comparison with a hypothetical pyranoid ring devoid of all non-bonded interactions. The free energy of the $^4C_1$ conformation of 1,5-anhydroxylitol is 0.7 kcal/mol, due to two vicinal *trans*-diequatorial O/O interactions.

A more-complicated situation arises with 1,5-anhydroarabinitol, which can adopt $^4C_1$ and $^1C_4$ conformations with an energy difference of 0.55 kcal/mol ($^4C_1$ 1.7 and $^1C_4$ 1.15 kcal/mol). Because there is a mixture of these conformers, the free-energy value is reduced to 0.69 kcal/mol, which reflects the entropy of mixing. Further, the molecule is chiral, and its existence as a racemic mixture results in a further decrease of free energy of ~0.54 kcal/mol, resulting in a final value of 0.15 kcal/mol. Thus, the experimental results (Table III) 1.5, 1.1, and 0.15 kcal/mol, respectively, for the triacetates of 1,5-anhydroribitol, 1,5-anhydroxylitol, and 1,5-anhydroarabinitol correspond well with the calculated values, namely, 1.6, 0.7, and 0.15 kcal/mol, respectively.

EXPERIMENTAL

Dehydration reactions of tetritols and pentitols. — 0.11mM Alditol in acetic acid (100 µL), with or without catalyst, was heated in a sealed ampoule at 80° or 100°. The catalyst, if present, was then removed either by neutralisation or mechanically. The solution was concentrated to dryness in a stream of nitrogen, the residue was acetylated, and the products were subjected to g.l.c. Silar 5CP and OV-17 capillary columns were used and prepared as reported earlier[22,27].

The following conditions were used for the dehydration of tetritols (*A*) and pentitols (*B*).

Reaction medium[a]	*At 100°*		*At 80°*
	A	B	B
I	3 days	3 days	—
II	—	1, 3, or 5 h	—
III	1, 3, or 10 h	—	—
IV	—	—	1, 3, or 5 h

[a] I, acetic acid; II, acetic acid (100 µL) + Amberlite IR-120 (H^+) resin (10 mg); III, acetic acid (100 µL) + resin (30 mg); IV, acetic acid (100 µL) + aqueous 70% perchloric acid (0.01 µL).

Equilibration of tetritols, pentitols, anhydrotetritols, and anhydropentitols. — 11 μM Alditol, anhydride, or acetylated derivative were severally dissolved in a mixture of acetic acid (100 μL) and aqueous 70% perchloric acid (2 μL). Each mixture was heated for 2 days at 120° and the products were subjected to g.l.c.

Mass spectrometry. — Mass spectra (70 eV) of acetylated derivatives were recorded on a LKB 2091 mass spectrometer linked to a PDP e/11 minicomputer. The mass spectrometer was interfaced by a Ryhage molecular separator to a gas chromatograph equipped with a capillary column coated with Carbowax 20M. The temperature of the ion source and the molecular separator was 280°. The mass range m/z 10–680 was scanned in 2 s.

ACKNOWLEDGMENTS

We thank Professor S. J. Angyal for suggesting the free-energy difference correlations. This investigation was supported by the Polish Academy of Science.

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