Conversion of Acyclic Carbohydrates into Tetrahydrofuran Derivatives. Acid-Catalyzed Dehydration of Hexitols[1]

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Received July 16, 1969

The acid-catalyzed dehydration of hexitols leads primarily to the formation of tetrahydrofuran derivatives. In those cases in which the reaction proceeds readily, ring closure involves displacement of water from the primary alcohol groups in the 1 (or 6) position. Where this reaction is retarded by steric effects, the formation of varying amounts of anhydrides involving ring closure with inversion at the 2 (or 5) position occurs. The rate of the ring-closure reaction involving the primary hydroxyl groups is influenced by changes in the configuration of hydroxyl groups not directly involved in the reaction, by inductive effects, and by an interaction between the hydroxyl group adjacent to the leaving group and the leaving group itself in the transition state.[2] The ease of 1,4-anhydride formation decreases through the series allitol, talitol, iditol, glucitol, altritol, galactitol, gulitol, and mannitol. The formation of 1,4:3,6 anhydrides from the 1,4 anhydrides of iditol and gulitol is approximately 40 times faster than from those of glucitol and mannitol, in which the hydroxyl substituent in the newly formed ring is *endo*.

The acid-catalyzed anhydrization of tetritols and pentitols produces tetrahydrofuran derivatives having the configuration of the starting alditol.[2] The rate of the reaction decreases through the series ribitol, xylitol, arabinitol, and lyxitol and appears to depend on interactions present in the transition states for ring closure. A similar effect of configuration on the rate of 1,4-anhydride ring formation should be observable in the hexitol series if the interactions in the transition state determine the reaction rate.

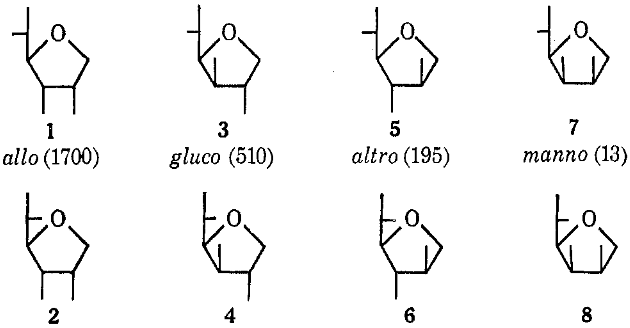
1,4-Anhydrohexitols.[3]—The hexitols have four asymmetric carbons but have primary hydroxyl groups at both ends. Because of this, there are only six different configurations possible rather than the eight possible for the hexoses. Four of the six hexitols can have enantiomers and two are *meso* compounds; *i.e.*, a total of ten hexitols is known. Tetrahydrofuran rings can be formed at either end of the hexitol chain and could be designated as 1,4 anhydrides and 3,6 anhydrides to emphasize this point. However, in this paper the major concern is with the effects of configurational differences within the tetrahydrofuran ring and these can be compared most readily if all compounds are discussed as 1,4 anhydrides. For example, D-glucitol and L-gulitol are names for the same compound; two different tetrahydrofuran rings can be formed by reaction at the primary hydroxyl groups. Both anhydrides could be named as derivatives of D-glucitol, *i.e.*, 1,4-anhydro-D-glucitol and 3,6-anhydro-D-glucitol. However, it is preferable to name them both as 1,4 anhydrides in which case the latter is named 1,4-anhydro-L-gulitol. A similar situation exists with D-talitol and D-altritol. With the other four configurations, allitol and galactitol are *meso* compounds from which racemic mixtures of 1,4 anhydrides are produced by reaction at either end; either enantiomer of mannitol or iditol reacts to give the same 1,4 anhydride. Thus, D-mannitol can form only 1,4-anhydro-D-mannitol.

The relevance of this discussion is apparent when the effects of configuration on reactions of the hexitols is compared with that observed for the pentitols. Each 1,4-anhydropentitol can give rise to two 1,4-anhydrohexitols if the carbon chain is extended at C-5 (Chart I). One of the hexitols belongs to the D series and the other to the L series. However, the rate of the dehydration reaction is not influenced by the enantiomeric form of the hexitol, and the configurational relationships between the pentitols and the hexitols are most easily seen in this representation. The relative rates of formation from the corresponding alditol in 2 *N* hydrochloric acid at 100° are given in parentheses beside each structure; those of the pentitols were obtained from ref 2, and those of the hexitols from the data in Table I. The expectation that the hexitol series would have the same dependence of rate on configuration as the pentitol series is fully borne out, although the hexitols anhydrize more rapidly than the corresponding pentitols.

CHART I

ribo (50) *xylo* (29) *arabino* (10) *lyxo* (1)

1,4-anhydropentitols



1 *allo* (1700) 3 *gluco* (510) 5 *altro* (195) 7 *manno* (13)

2 *talo* (930) 4 *ido* (670) 6 *galacto* (173) 8 *gulo* (78)

1,4-anhydrohexitols

The effect of configuration of the hexitols on the rate of 1,4 anhydride formation can be rationalized on the following basis. Only those transition states in which the hydroxyl group at C-2 occupies an axial position are allowed, since, when this group is equatorial, it interacts with the leaving group to prevent its departure[2,4]

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[1] This investigation was supported in part by a Public Health Service Research Grant (GM-11,963) and by a Public Health Service Research Career Program Award (GM-24,808) from the Institute of General Medical Sciences.

[2] B. G. Hudson and R. Barker, *J. Org. Chem.*, **32**, 3650 (1967).

[3] R. Barker, *ibid.*, **29**, 869 (1964).

[4] Axial and equatorial can be used to describe the disposition of groups in a transition state in which the bond being formed is longer than in the product, and the carbon and oxygen atoms of the forming ring are disposed as they would be in a six-membered-ring system.

TABLE I

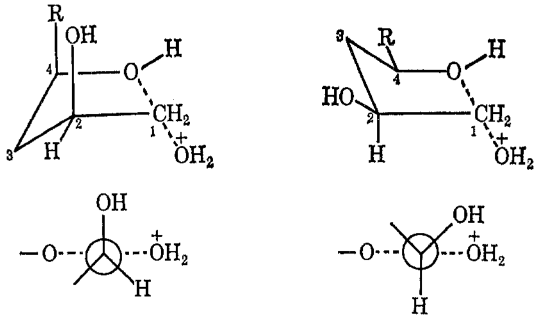
PRODUCTS OF THE ACID-CATALYZED DEHYDRATION OF THE HEXITOLS AND THEIR RATES OF FORMATION[a]

Hexitol	Products[a]	$k_{overall}$ (2 *N*),[b] sec^{-1} ± 0.2	$k_{1,4}$,[c] sec^{-1} ± 0.2	1,4 anhydrides, relative rate of formation[d]	$k_{overall}$ (4 *N*),[e] sec^{-1} ± 0.2
Allitol	1,4-Anhydro-DL-allitol (92)	7.26×10^{-5}	3.3×10^{-5}	133 (1)	2.5×10^{-4}
	One unknown (8)				
D-Talitol	1,4-Anhydro-D-talitol (68)		1.8×10^{-5}	73 (2)	
	1,4-Anhydro-D-altritol (14)	2.66×10^{-5}	3.7×10^{-6}	15 (5)	
	Two unknowns (18)				
L-Iditol	1,4-Anhydro-L-iditol (85)	3.08×10^{-5}	1.3×10^{-5}	53 (4)	1.17×10^{-4}
	2,5-Anhydro-D-glucitol (15)		2.3×10^{-6}		
D-Glucitol	1,4-Anhydro-D-glucitol (85)		9.9×10^{-6}	39 (3)	
	1,4-Anhydro-L-gulitol (13)	1.15×10^{-5}	1.5×10^{-6}	6 (8)	
	2,5-Anhydro-L-iditol (2)		2.3×10^{-7}		
Galactitol	1,4-Anhydro-DL-galactitol (97)	6.67×10^{-6}	3.3×10^{-6}	13 (6)	2.8×10^{-5}
	One unknown (3)				
D-Mannitol	1,4-Anhydro-D-mannitol (41)		2.5×10^{-7}	1 (7)	
	2,5-Anhydro-D-glucitol (45)	1.18×10^{-6}	2.7×10^{-7}		4.2×10^{-6}
	1,5-Anhydro-D-mannitol (14)		8.3×10^{-8}		

[a] Figures in parentheses are percentages of initial products as determined by gas chromatography. The dianhydrides of glucitol, mannitol, and iditol are formed slowly and are only important at later stages of the reaction. [b] Pseudo-first-order rate constants for the disappearance of hexitol in 2 *N* hydrochloric acid at 100°. [c] Pseudo-first-order rate constants for anhydride formation from hexitol in 2 *N* hydrochloric acid at 100° corrected for symmetry of substrates. [d] Numerals in parentheses refer to structures in Chart I. [e] Pseudo-first-order rate constants for the disappearance of hexitol in 4 *N* hydrochloric acid at 100°.

(Chart II). This requirement fixes the conformation of the carbon chain from carbon 1 to carbon 4. Differences in rate then depend upon the nonbonded interactions between substituents in this conformation. The important nonbonded interactions are those between adjacent *cis*-hydroxyl groups and between a bulky substituent at carbon 4 and a *cis*-hydroxyl group at carbon 3 or at carbon 2.

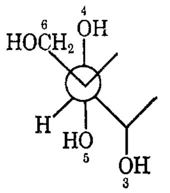
CHART II



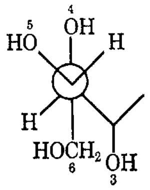
projection along C-2-C-1 bond, 2-OH axial; leaving group can depart

projection along C-2-C-1 bond, 2-OH equatorial; interacts with the leaving group

Differences in rate between isomers differing only in configuration at carbon 5 appear to be due to interactions between the substituents at C-5 and those at C-3. When the hydroxyl groups are *cis* (in the Fischer projection) the rate is always greater than when they are trans. The rate difference is substantial only between the *gulo* and *manno* compounds; the former cyclizes six times faster than the latter. If the transition states are similar to that proposed for the parent *lyxo* configuration, then that for the *manno* compound has hydroxyls at C-3 and C-5 eclipsed, while in the *gulo* configuration the hydroxymethyl of C-6 and the hydroxyl at C-3 would be eclipsed. If the important interactions are polar ones, then the conformer having an interaction between hydroxyl groups is less stable.



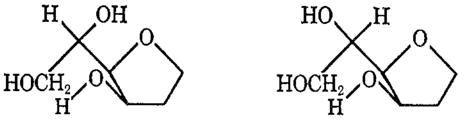
manno



gulo

1,4:3,6-Dianhydrohexitols.—The 1,4 anhydrides of iditol, gulitol, glucitol, and mannitol are converted into the corresponding 1,4:3,6 anhydrides under the conditions of the reaction. The pseudo-first-order rate constants obtained using authentic samples are 5.6×10^{-4}, 5.0×10^{-4}, 1.2×10^{-5}, and 1.3×10^{-5} min^{-1}, respectively. There is a 40-fold difference between rates of formation of 1,4:3,6 anhydrides from 1,4 anhydrides in which the hydroxyl at C-5 is *endo* in the product and those in which this hydroxyl is *exo*. In the former case (the 1,4 anhydrides of mannitol and glucitol) the hydroxyl at C-5 must approach an eclipsed orientation with respect to the oxygen of the 1,4-anhydride ring, whereas in the latter (the 1,4 anhydrides of iditol and gulitol) the C–O dipoles are oriented so as to minimize their interactions (Chart III).

CHART III



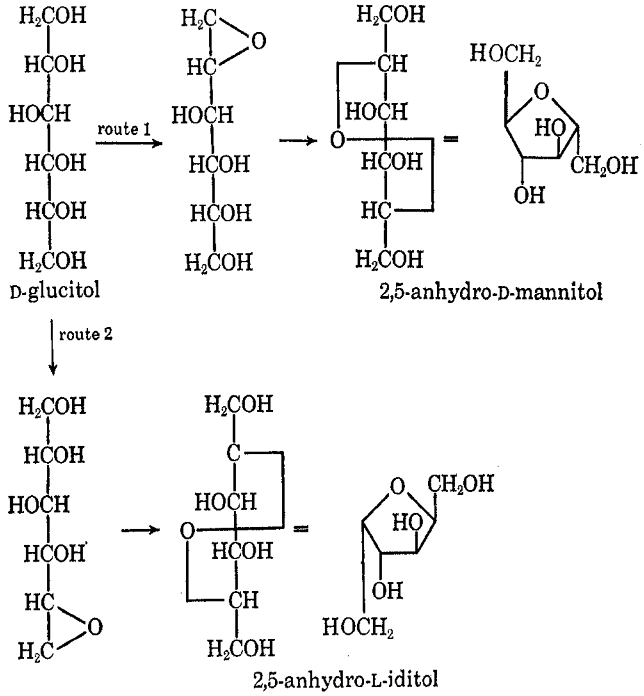
gluco and *manno*

gulo and *ido*

2,5-Anhydrohexitols.—The anhydrization of all of the hexitols except mannitol leads primarily to the formation of 1,4 anhydrides. However, in all cases compounds having the chromatographic characteristics of 2,5 anhydrides are produced. The 2,5 anhydrides of mannitol, glucitol, and iditol were available for comparison with the compounds produced in the anhydrization reaction. In the case of the products from iditol and glucitol, identification is based only on the gas chromatographic behavior of the products. However, 2,5-anhydro-D-glucitol was isolated from the mannitol reaction mixture and characterized as its 1,3-*O*-isopropylidene-6-*O*-trityl derivative.[5]

The occurrence of 2,5 anhydrides is most readily explained on the basis of the intermediate formation of 1,2 epoxides, which can rearrange to form 2,5 anhydrides with inversion of configuration at C-2. Obviously such epoxide formation can involve either end of the hexitol molecule. In the case of glucitol (Chart IV) only 2,5-anhydro-L-iditol was observed (route 2) and it would have been formed from the 5,6 epoxide. Since the formation of a 3,6 anhydride (1,4-anhydro-L-gulitol) occurs with greater difficulty than does the formation of 1,4-anhydro-D-glucitol there would be a correspondingly greater opportunity for epoxide formation.

CHART IV



The anhydrization of iditol leads to a significant proportion of 2,5-anhydro-D-glucitol. Apparently the configuration of this alditol allows the formation of both the 1,4-anhydride and the 1,2 (or 5,6) epoxide, since both are formed with significantly greater ease than are most other anhydrides.

D-Mannitol anhydrizes with greater difficulty than any of the other alditols and a large proportion of 2,5-anhydro-D-glucitol is formed. In addition, a significant proportion of 1,5-anhydro-D-mannitol is formed. This material could arise either by direct displacement of a protonated hydroxyl from C-1 by the hydroxyl at C-5 or by opening of a 1,2 epoxide by the hydroxyl at C-5.

The possibility that 1,2 epoxides are important as intermediates in the formation of 1,4 anhydrides has been considered previously[6,7] and shown to be unimportant in this type of reaction. In addition, compounds lacking a hydroxyl group adjacent to the leaving group form 1,4 anhydrides with ease.[2] To further examine the importance of the 2-hydroxyl group on the rate of 1,4-anhydride formation the anhydrization of 2-deoxy-D-glucitol was examined. The pseudo-first-order rate constant for the disappearance of 2-deoxy-D-glucitol in 2.0 *N* hydrochloric acid at 100° is 1.8×10^{-3} min^{-1}. The major product (approximately 85%) appears to be 1,4-anhydro-2-deoxy-D-glucitol, since the reaction mixture after $10 \times t_{1/2}$ releases 1.04 molar equiv of formaldehyde per mole of periodate consumed. The ratio of the rates of formation of 1,4-anhydro-2-deoxy-D-glucitol and 1,4-anhydro-D-glucitol is 2.6:1, in good agreement with the observation that a hydroxyl group adjacent to the leaving group produces a decrease in rate by a factor of 3.[2] 2-Deoxy-D-glucitol (more properly 2-deoxy-D-*arabino*-hexitol) could as well be referred to as 2-deoxy-D-mannitol, and the fact that it undergoes 1,4-anhydride formation 100 times faster than does D-mannitol clearly demonstrates the importance of configuration, in particular of the relative position of the 2-hydroxyl, to the rate of this reaction.

TABLE II
RETENTION TIMES AND MOLAR RESPONSES OF THE ACETATE DERIVATIVES OF HEXITOLS AND THEIR ANHYDRIDES, RELATIVE TO RIBITOL AT 240°

Alditol	Retention time	Molar response
Allitol	2.090	1.168
DL-Talitol	2.412	1.043
L-Iditol	3.043	1.092
D-Glucitol	2.731	0.996
Galactitol	2.725	1.014
D-Mannitol	2.332	1.034
1,4-Anhydro-		
DL-allitol	1.643	0.813
DL-talitol	1.645	0.805
D-altritol	1.151	0.788
D-iditol	1.456	0.894
D-glucitol	1.293	1.024
D-gulitol	1.850	0.856
D-galactitol	1.348	0.902
D-mannitol	1.483	0.935
2,5-Anhydro-		
L-iditol	1.798	0.980
D-glucitol	1.600	0.789
D-mannitol	1.407	0.940
1,5-Anhydro-		
D-glucitol	1.391	0.913
D-galactitol	1.343	1.020
D-mannitol	1.361	0.979
1,4:3,6-Dianhydro-		
L-iditol	0.437	0.586
D-mannitol	0.537	0.554

Experimental Section

Hexitols.—D-Glucitol, D-mannitol, and galactitol were obtained from Pfanstiehl Laboratories, Inc. Samples were at least 99% pure as determined by gas–liquid chromatography of their acetate and trimethylsilyl derivatives and were used without further purification. L-Iditol was a gift from Dr. J. W. LeMaistre, Atlas Chemical Industries, Wilmington, Del. Allitol and D-talitol were prepared by reduction of the corresponding lactones with sodium borohydride according to the method of Abdel-Akher, *et al.*[8] These alditols were recrystallized from

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[5] G. R. Gray and R. Barker, unpublished results.

[6] F. C. Hartman and R. Barker, *J. Org. Chem.*, **28**, 1004 (1963).

[7] B. A. Applegarth, J. T. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 1213 (1965).

[8] M. Abdel-Akher, J. K. Hamilton, and F. Smith, *J. Amer. Chem. Soc.*, **73**, 4691 (1951).

methanol until their physical properties agreed with literature values.

Kinetic Studies.—One milliliter portions of a 4% solution of the hexitol in the appropriate concentration of hydrochloric acid were placed in a series of tubes which were sealed and submerged in a boiling water bath. The variation in temperature observed over a period of several weeks was less than 1°. Samples were withdrawn at intervals and neutralized with sodium hydroxide. They were then concentrated to dryness under a stream of hot, dry air and the acetate derivatives were formed in the presence of the residual salts. It was shown by subjecting known mixtures of hexitols and their anhydrides to this procedure that the salt does not interfere with the derivatization. A suitable aliquot (usually 1 to 5 μl) of the reaction mixture was injected into the gas chromatograph.

All separations were performed on a 5 ft × 1/8 in. column of polyethylene glycol sebacate on Chromosorb Q using helium at 30 ml/min as the carrier gas. The column was maintained at 110–140° for the separation of silyl derivatives and at 200–225° for the separation of acetates. In most cases either derivative could be used to follow the progress of the anhydrization reaction. The detector response to each compound was established when possible using authentic materials and was used with measurements of peak areas to calculate the proportions of the various components present.

In Table II are presented the relative retention times and the molar responses for the hexitols and anhydrohexitols used as standards in this study.

Registry No.—Allitol, 488-44-8; D-talitol, 22576-99-4; L-iditol, 488-45-9; D-glucitol, 50-70-4; galactitol, 608-66-2; D-mannitol, 69-65-8.

Conversion of Acyclic Carbohydrates into Tetrahydrofuran Derivatives. Deamination of 1-Amino-1-deoxypentitols[1a]

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Received July 16, 1969

The 1-amino-1-deoxypentitols were prepared from the corresponding oximes by hydrogenation over platinum. The products of deamination with nitrous acid at 0° were examined by gas chromatography. In each case, the 1,4-anhydropentitol having the configuration of the starting material was the major product. The amounts of pentitol with the parent configuration and anhydropentitol formed by ring closure with inversion at position 2 increased through the series *xylo* < *ribo* = *arabino* ≪ *lyxo*. Bis(1-deoxypentitol)amines are also formed during the reduction of the oximes. The D-*arabino* isomer has been characterized.

Other reports in this series describe the acid-catalyzed formation of the tetrahydrofuran rings of methyl pentofuranosides,[2] 1,4-anhydropentitols,[3] and 1,4-anhydrohexitols.[4] Similar effects of configuration on the rates of these reactions were observed and explained on the basis of interactions between substituents in the transition states. In particular, interactions between groups which were forced to occupy 1,3-diaxial orientations and between a 2-hydroxyl or methoxyl group and the group leaving C-1 appeared to be important.

The 1-amino-1-deoxyalditols have been shown to deaminate readily and to give rise to 1,4-anhydroalditols as major products.[5] The deamination reaction differs from the displacement reactions cited above in that it takes place at lower temperatures, and may therefore be influenced by conformations of the ground states. Further, the reaction is not reversible, and, unlike the dehydration of the alditols, reaction with the solvent produces a stable product. Finally, the transition state for the formation of a tetrahydrofuran derivative in the deamination does not contain a leaving group, or contains one which cannot have the kinds of interaction that a protonated leaving group can have with adjacent hydroxyls. Because of these differences we wished to determine whether the effect of configuration in the acid-catalyzed reactions was observed in this ring-closure reaction.

The deamination of the 1-amino-1-deoxypentitols with nitrous acid is rapid and leads to the formation of various amounts of 1,4-anhydropentitol, pentitol, and anhydrides formed by ring closure between C-5 and C-2, which have inversion at C-2. The proportions of these products are given in Table I.

TABLE I
MOLAR PROPORTIONS OF PRODUCTS FROM DEAMINATION OF 1-AMINO-1-DEOXYPENTITOLS[a]

1-Amino-1-deoxypentitol	1,4 anhydride	2,5 anhydride, inverted	Alditol
ribo	78	15	7
arabino	78	9	14
xylo	89	9	2
lyxo	55	24	20

[a] Values are averages of three separate deamination experiments and duplicate analyses.

The deamination reaction leading to 1,4 anhydrides and alditols having the configuration of the starting amine probably proceeds by one of the routes shown in Scheme I. For convenience, the *ribo* configuration is represented; however, the following discussion is concerned with the general case. It is not possible to distinguish between the two routes, but, to rationalize the differences in proportion of products observed with differences in configuration, it is not necessary to do so.

That the rate of formation of the diazo compound **2** was not influenced by changes in the configuration of the amine **1** was shown by measuring the rates of disappearance of the latter (see Experimental Section). However, the reactant for the formation of 1,4 anhydrides is either the diazo compound **2** or the carbonium ion **3**, and differences in rate of formation of **2** or **3** would not influence the proportion of **7** formed in the

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[1] (a) This investigation was supported in part by a Public Health Service Research Grant (GM 11,963) and by a Public Health Service Research Career Program Award (GM 24,808) to R. B. from the Institute of General Medical Sciences; (b) to whom inquiries should be addressed.

[2] D. Dennis Heard and R. Barker, *J. Org. Chem.*, **33**, 740 (1968).

[3] B. G. Hudson and R. Barker, *ibid.*, **32**, 3650 (1967).

[4] R. Barker, *ibid.*, **35**, 461 (1970).

[5] L. F. Wiggins, *Advan. Carbohyd. Chem.*, **5**, 191 (1950); V. G. Bashford and L. F. Wiggins, *Nature*, **165**, 566 (1950).