Carbohydrate Cyclic Acetal Formation and Migration

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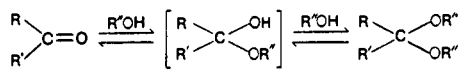
I. Introduction

Acetal and ketal formation is catalyzed by mineral acid and Lewis acids and may be described by the equation



Diols react with aldehydes and ketones to give cyclic acetals and ketals and, as with simple alcohols, the intermediate hemiacetal is not usually isolated. If the alcohol and the aldehyde group are suitably located in the same molecule (as in a sugar), formation of a cyclic hemiacetal occurs spontaneously and extensively. A catalyst is usually necessary to effect reaction with another alcohol molecule to give the full acetal (glycoside). Numerous possibilities exist for cyclic acetal formation when polyhydric alcohols are involved. Early studies by Wurtz[1] and Meunier[2] and a continuing study of the formation of carbohydrate cyclic acetals have revealed reaction patterns that have given value to cyclic acetals as protecting groups[3] in synthesis.

Recently de Belder[4] has published an update of an earlier article[5] on the cyclic acetals of the aldoses and aldosides, and Brady[6] has written a review on the cyclic acetals of ketoses. Also, a number of excellent books on carbohydrates have recently become available and these have included chapters on cyclic acetals.[7-9] Capon[10] included a section on cyclic acetals and ketals in his review on "Mechanism in Carbohydrate Chemistry".

The present article is intended to complement the above literature by studying in greater detail the acetal formation reaction including acetal migration, which has been largely neglected by previous reviewers. Acetal formation may be divided into a kinetic and a thermodynamic phase and the product(s) of each of these may differ considerably from each other. It is proposed to stress the possibility, by varying the conditions of acetalation or by monitoring the reaction, of isolating either a kinetic product or a thermodynamic product. Likewise, selective acid hydrolysis may be used to prepare acetals or ketals that cannot be isolated during the acetalation reaction. A separate chapter is devoted to a more detailed examination of acetal migration including examples from acetal formation and hydrolysis.

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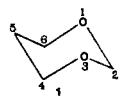
II. Stereochemistry of Monocyclic Acetals

The situation pertaining at equilibrium, in the reaction of sugars with aldehydes and ketones, has been comprehensively reviewed by several workers.[8,9,11,12] The earliest article to deal with the problem in terms of the relative thermodynamic stabilities of the cyclic acetals formed, according to the established tenets of conformational analysis, was by Mills.[13] Thus, only the main features of the configurational and conformational properties of some monocyclic acetals will be dealt with in this section. The application of these principles to the product distribution observed in carbohydrate cyclic acetal formation reactions will be discussed in succeeding sections.

A. 1,3-Dioxane Ring Systems

1,3-Dioxane (**1**) and most of its derivatives have been shown[14-21] to exist as chair conformers. An examination of



molecular models[17,20] indicates that the chair conformer is puckered in the O_1–C_2–O_3 region and flattened in the C_4–C_5–C_6 region. This has been confirmed experimentally by ^1H NMR spectroscopy[20,22] and by an X-ray crystallographic investigation[23] of 2-*p*-chlorophenyl-1,3-dioxane. The orientational preferences of methyl groups on the three different positions of the 1,3-dioxane ring system have been studied by the acid-catalyzed equilibrations of some conformationally biased 2-, 4-, and 5-methyl-1,3-dioxanes. Thus, the conformational free energies of methyl groups on C_2, C_4, and C_5 of the 1,3-dioxane ring have been shown[20,24] to be 3.97, 2.9, and 0.8 kcal mol^{-1}, respectively. These values may be compared with the conformational free energy of a methyl group on the cyclohexane ring (1.70 kcal mol^{-1}).[25] The high value for the conformational free energy of a methyl group on C_2 is a direct consequence of the geometry of the 1,3-dioxane ring which gives rise to increased interactions between the hydrogens of the axial C_2 methyl group and the syn-axial hydrogen atoms on C_4 and C_6. Since an axial methyl group on C_4 is involved in a "normal" interaction with the syn-axial hydrogen atom on C_6 as well as a "severe" interaction with the syn-axial hydrogen atom on C_2, its smaller conformational free energy, compared with that of a methyl group on C_2 is to be expected. The low value of 0.8 kcal mol^{-1} for the conformational free energy of a methyl group on C_5 may be considered to be a result of the smaller syn-axial interactions involving an axial methyl group on C_5 with the axial lone pairs on the oxygen atoms of 1,3-dioxane compared with syn-axial hydrogens atoms of cyclohexane.

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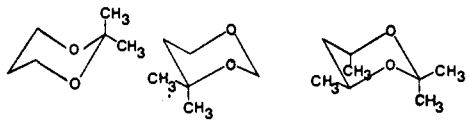
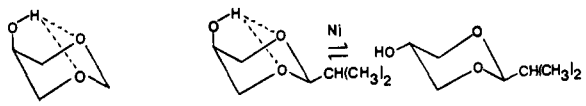
It has been shown that 2,2-dimethyl-1,3-dioxane (**2**)[19] and 4,4-dimethyl-1,3-dioxane (**3**)[18] also exist as interconverting chair



2 **3** **4**

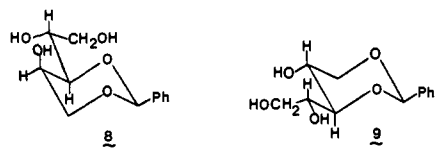
conformers, and thermochemical studies[26-28] have confirmed that the twist-boat conformers of 1,3-dioxane are less stable by at least 3–4 kcal mol^{-1} than the chair conformer. 2,2-*trans*-4,6-Tetramethyl-1,3-dioxane (**4**), however, probably exists predominantly as a twist-boat conformer[20,24,27-29] as a result of the large interaction[27,28] (ΔH°) of 8.9 kcal mol^{-1} between the syn-axial methyl groups of the chair conformers.

Hydrogen bonding may also influence the conformational properties of 1,3-dioxane ring systems since an axial hydroxyl group on C_5 is suitably oriented to become involved in hydrogen bonding with the ring oxygen atoms. Thus, in dilute carbon tetrachloride solution, 5-hydroxy-1,3-dioxane (1,3-*O*-methyleneglycerol) exists[30] to a large extent as the chair conformer **5** with an axial hydroxyl group. Equilibration of 2-isopropyl-5-hydroxy-1,3-dioxane, in three different solvents,[24,31] showed that the syn isomer **6**, with an axial hydroxyl group, was preferred to the anti isomer **7**, presumably as a result of stabilization by



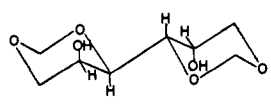
5 **6** **7**

intramolecular hydrogen bonding. This preference, as expected, decreased in hydroxylic solvents. Hydrogen bonding may influence the course of the reaction and thus 1,3-*O*-benzylidene-D-arabinitol (**8**), with an axial hydroxyl group available[30] for intramolecular hydrogen bonding, was obtained[32] in high yield in preference to 3,5-*O*-benzylidene-D-arabinitol (**9**) in the acid-



8 **9**

catalyzed condensation of benzaldehyde with D-arabinitol. Also 1,3:4,6-di-*O*-methylenegalactitol (**10**) was obtained[33] quantitatively from the acid-catalyzed condensation of galactitol with formaldehyde.



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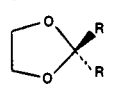
B. 1,3-Dioxolane Ring Systems

Available evidence indicates[34-37] that 1,3-dioxolane (**11**) and 2,2-dimethyl-1,3-dioxolane (**12**) exist in puckered conformations related to the envelope and twist conformations, wherein one atom and two atoms, respectively, are displaced from the plane of the other ring atoms. In fact, a whole range of conformations of about the same energy exists for most 1,3-dioxolane derivatives. The introduction of two methyl groups on C_2 of the 1,3-dioxolane ring was also shown[34,35] to cause an increase in the puckering of the ring.



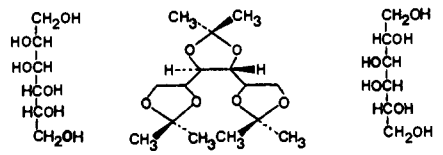
11 R=H

12 R=CH_3

Condensation of alditols with aldehydes or ketones, in the presence of an acid catalyst, to yield 1,3-dioxolane derivatives, results[13] in formation of the isomer having the substituent groups trans (**13**) and involves condensation with hydroxyl groups which have the threo configuration. Reaction involving hydroxyl groups with the erythro configuration form less stable 1,3-dioxolane derivatives where the substituent groups are cis (**14**). This order

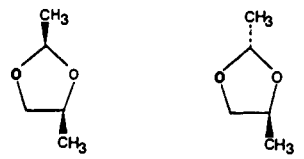
13 **14**

of stability reflects the destablization of the 1,3-dioxolane ring on account of nonbonded interactions between cis 1,2-substituents.[38] Thus D-mannitol (**15**), with hydroxyl groups on C_3 and C_4 in the threo configuration, gives[39] 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**16**) in good yield on acid-catalyzed isopropylidenation, while D-galactitol (**17**), with hydroxyl groups on C_3 and C_4 in the erythro configuration, only forms di-*O*-isopropylidene derivatives.[40]



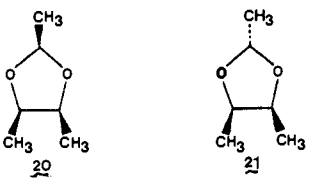
15 **16** **17**

Barker and co-workers[41] have demonstrated the greater stability of *cis*-2,4-dimethyl-1,3-dioxolane (**18**) over its trans isomer **19**. Thus it was found that an equilibrium mixture of the



18 **19**

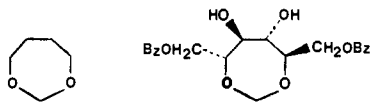
two forms contained 65% of the cis isomer. This result has been confirmed by Salomaa and Kankaanperä.[42,43] Similarly in recent investigations of the configurational stability of 2,4-*cis*-5-trisubstituted 1,3-dioxolanes it has been shown[44-47] that the syn isomers are generally thermodynamically more stable than the anti isomers. Thus, at 25 °C it was shown by Kankaanperä[44,45] that an equilibrium mixture of 2,4-*cis*-5-trimethyl-1,3-dioxolane contains 80% of the syn isomer **20** and 20% of the anti isomer **21**. The result was rationalized[45] by assuming that the 1,3-dioxolane ring adopts a half-chair (or twist) conformation.



20 **21**

C. 1,3-Dioxepane Ring Systems

The conformational properties of 1,3-dioxepane (**22**) and its derivatives would be expected to be rather similar to those of cycloheptane.[48] The flexibility of the 1,3-dioxepane ring may be seen by the ready formation[49] of an *O*-isopropylidene derivative from cycloheptane-*trans*-1,2-diol. Similarly 1,6-di-*O*-benzoyl-2,5-*O*-methylene-D-mannitol (**23**), with *trans*-hydroxyl



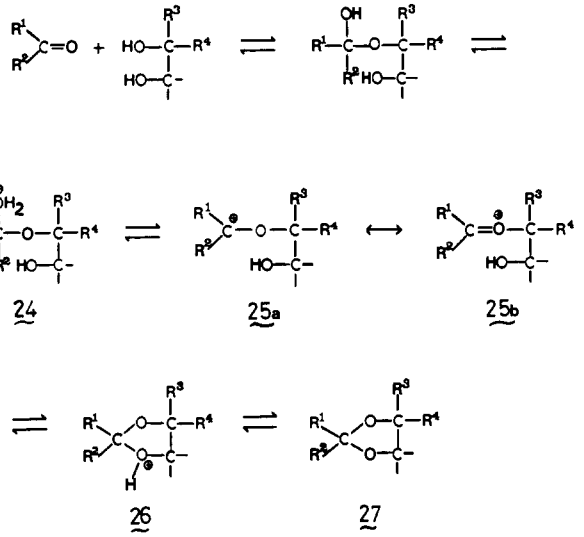
22 23

groups on C_3 and C_4, forms a 3,4-*O*-isopropylidene[50] and a 3,4-*O*-benzylidene derivative.[50-52]

III. Mechanism

Acetal formation is believed to proceed through hemiacetal intermediates[53] and may be represented by Scheme I. In order

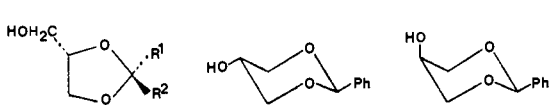
SCHEME I



24 25a 25b 26 27

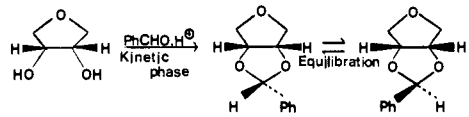
to consider the rate-controlling transition state, it is necessary to decide on the rate-limiting step. This is either **24** ⇄ **25** or **25** ⇄ **26** since it is reasonable to assume that hemiacetal formation and proton exchange will be fast. The generally accepted mechanism for the hydrolysis of most simple acyclic[54] and cyclic[43,55-58] acetals and ketals is the A-1 mechanism involving the rate-determining heterolysis of a protonated intermediate. Thus, if ring opening is rate determining for hydrolysis, the principle of microscopic reversibility requires that ring closure **25** ⇄ **26** be the rate-determining step in the formation of acetals.

In general, the reaction conditions are such that the thermodynamically most stable product is formed. However, the oxocarbonium ion **25** will react with the nearest hydroxyl group to give the first (or kinetic) product **27** which may subsequently rearrange to give a more stable product. This sequence may be illustrated (see succeeding sections for other examples) by the reaction of glycerol with benzaldehyde in *N,N*-dimethylformamide catalyzed by *p*-toluenesulfonic acid.[59] Monitoring the reaction by ^{1}H NMR spectroscopy revealed that the *cis*- and *trans*-1,3-dioxolanes. **28** and **29,** respectively, were formed first. These were then slowly converted into the 1,3-dioxanes. **30** and **31,** which predominated at equilibrium. The formation of a single



28 R^1 = Ph, R^2 = H
29 R^1 = H, R^2 = Ph 30 31

stereoisomer during the kinetic phase of the reaction has also been demonstrated (see sections IV.B, VI, and VIII) and this has important mechanistic consequences. Thus 1,4-anhydroerythritol (**32**) reacts with benzaldehyde to give[60,61] the benzylidene acetal **33** having an *endo*-phenyl group.[62] Subsequently, equilibration occurs and a near-equimolar mixture of the *endo*-**33** and *exo*-phenyl isomers **34** is formed. The formation of a stereospecific



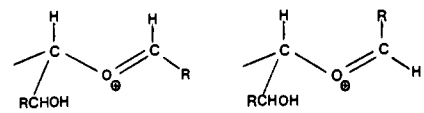
32 33 34

product in the above reaction may be rationalized[63] by making the assumption that the intermediate oxocarbonium ion **25** is highly reactive, and thus closely resembles the transition state. The observed relative rates of formation of particular acetals may then be explained by a consideration of the stability, or ease of formation, of the oxocarbonium ion intermediate. This approach is only valid if the decomposition of the acetal product, by hydrolysis or rearrangement, is negligible. This requirement is probably fulfilled in the early stages of reactions carried out in anhydrous media.

Stabilization of the cation **25** in Scheme I may be subdivided into two effects: (a) direct stabilization of the carbonium ion **25a** by the groups R^1 and R^2, or (b) stabilization of the oxonium ion **25b** which will be critically dependent on the nature of the groups R^3 and R^4 and to a smaller extent on the nature of the substituent at the carbon atom α to the original hydroxyl group. Effect (a), however, will not be important when determining the relative rates of formation of isomeric acetals derived from one aldehyde and a polyhydric alcohol. Effect (b) is involved in the consideration of the stabilities of oxocarbonium ions derived from primary and secondary hydroxyl groups in a polyhydric alcohol. The stabilities of these ions are considered as possible factors in the observed preferential formation of terminal five-membered ring acetals in the kinetic phase of acetal formation.

The preferential formation of a single stereoisomer during the kinetic phase of the reaction of an aldehyde with a diol cannot be explained by the assumption that the transition state resembles the oxocarbonium ion **25** since two products should then be formed from the same intermediate. It is therefore necessary to assume that the transition state resembles the oxocarbonium ion **25** in one of its rotamer forms.

Provided that the intermediate ion **25** has considerable oxonium ion character, two distinct rotamer forms **35** and **36** may



35 36

be recognized and designated transoid and cisoid, respectively. By analogy with olefins[64] the transoid arrangement may be assumed to be more stable. Using Newman projection formulas, **35** and **36** may be depicted by the three staggered conformations shown in Figure 1. Both **37** and **40** may be dismissed as models for the transition state because the potential acetal carbon atom and the hydroxyl group are not sufficiently close for reaction. In the case of the oxocarbonium ion formed from a primary hydroxyl group, the rotamer forms **38** and **39** will have comparable stabilities. For the secondary oxocarbonium ion, the rotamer form **42** with an anti arrangement should be more favorable than the syn arrangement **41.** Thus from these considerations we can predict that, for a reaction at a secondary center, the most likely transition state will resemble an anti-transoid conformation of the oxocarbonium ion.

Consideration of the reaction between 1,4-anhydroerythritol and benzaldehyde shows that four conformations **43-46** may be drawn for the intermediate oxocarbonium ion, such that the

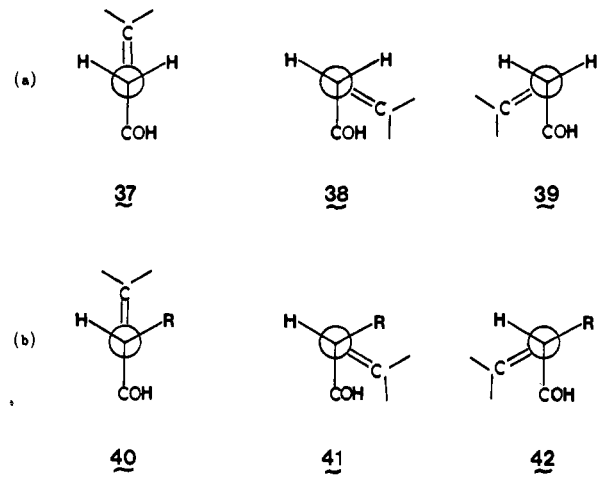
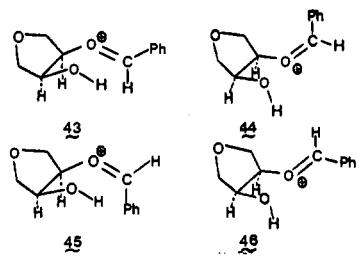


Figure 1. (a) Rotamer forms of (a) the primary oxocarbonium ion and (b) the secondary oxocarbonium ion.

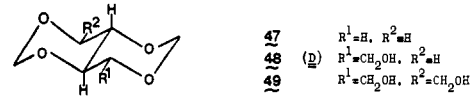


hydroxyl group is well placed for the cyclization reaction, and these may be assumed to resemble rate-limiting transition states. The anti-transoid structure **43** should be the most stable on steric grounds and thus lead to the rapid formation of the acetal with an *endo*-phenyl group. This is in agreement with the experimental observations.[60,61] The result is quite general and it is expected that the isomer with an *endo*-alkyl group will be the kinetic product in the acetal formation reaction. This prediction is in good agreement with the experimental results (see sections IV.B and VI).

IV. Cyclic Acetals Derived from Acyclic Sugar Derivatives

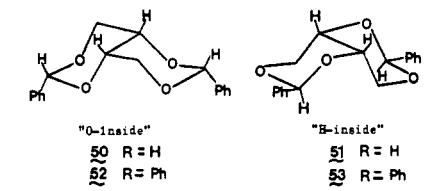
A. Six-Membered Rings

In acid-catalyzed condensations of alditols with aldehydes, trans-fused 1,3,6,8-tetraoxabicyclo[4.4.0]decane ring systems result when carbon atoms previously associated with hydroxyl groups in the erythro configuration form the ring junction. Thus, acid-catalyzed methylation of erythritol, ribitol, and allitol has yielded 1,3:2,4-di-*O*-methyleneerythritol (**47**),[65] -(DL)-ribitol (**48**),[66] and 2,4:3,5,-di-*O*-methyleneallitol (**49**).[67] In the case of allitol

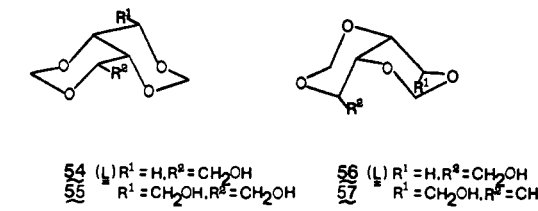


a 1,3:2,4 distribution is also possible with an equatorial 5,6 side chain. However, no 1,3:2,4:5,6-triacetals of allitol have been described, and this indicates that the symmetrical substitution in **49** is more stable.

When carbon atoms previously associated with hydroxyl groups in the threo configuration form the ring junction, then a cis-fused 1,3,6,8-tetraoxabicyclo[4.4.0]decane ring system results. Moreover, two conformers are possible and so 1,3:2,4-di-*O*-methylene-L-threitol,[68] resulting from the acid-catalyzed methylenation of L-threitol, may either have the "O-inside"

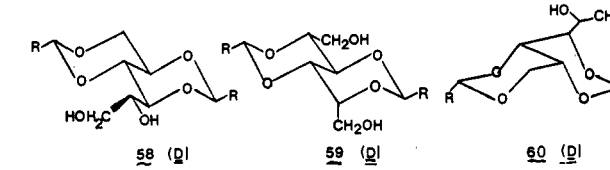


conformation **50** or the "H-inside" conformation **51**.[69] Stoddart[8] has shown by a consideration of free energies that the "O-inside" conformer is 4.2 kcal mol^{-1} more stable than the "H-inside" conformer, and in agreement dipole measurements[68] has confirmed that 1,3:2,4-di-*O*-methylene-L-threitol exists as the "O-inside" conformer to an extent of at least 90% in benzene. If an aldehyde other than formaldehyde is used, then there is the possibility of the formation of diastereomers corresponding to the "O-inside" and the "H-inside" conformers. Thus it has been shown that the acid-catalyzed benzylidenation of L-threitol gives the diastereomer of 1,3:2,4-di-*O*-benzylidene-L-threitol with equatorial phenyl groups on the "O-inside" conformer **52** rather than the alternative isomer **53**, with equatorial phenyl groups on the "H-inside" conformer. 1,3:2,4-Di-*O*-methylene-(DL)-xylitol (**54**),[71] and 2,4:3,5-di-*O*-methylene-L-iditol (**55**)[72] will also exist as "O-inside" conformers, since the "H-inside" conformers, **56** and **57**, respectively, would have axial hy-



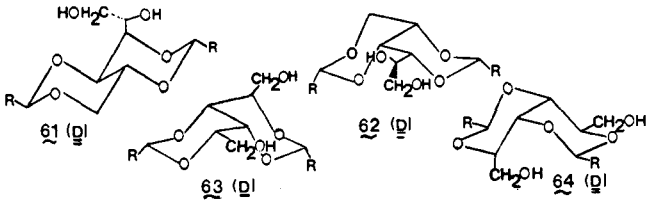
droxymethyl groups "inside" experiencing very large nonbonded interactions. L-Iditol could also form a 1,3:2,4-diacetal with the 5,6-side chain equatorial in an "O-inside" conformation but, since attempts to prepare a tri-*O*-methylene-L-iditol were unsuccessful,[72] it may be concluded, in agreement with the allitol results, that the symmetrical 2,3:4,5 arrangement is preferred. However, a tri-*O*-benzylidene-L-iditol has been prepared,[73] and it undoubtedly has a 1,3:2,4:5,6 distribution of acetal groups.

The formation of acetals from the remaining alditols is further complicated by the possibility of the formation of fused rings with either a trans- or a cis-ring junction. A decision as to the most stable arrangement, however, can be made by a consideration of normal conformational principles; i.e., equatorial substituents are preferred, and also that "O-inside" is preferred to "H-inside". Thus talitol (altritol) might be expected to form a 1,3:2,4-diacetal (**58**) (3,5:4,6-diacetal of altritol) with a trans-ring junction and the 5,6 side chain equatorial. The alternative 2,4:3,5-diacetal structure **59** with a trans-ring junction would have one axial hydroxymethyl group and the 3,5:4,6-diacetal **60** with a cis-ring



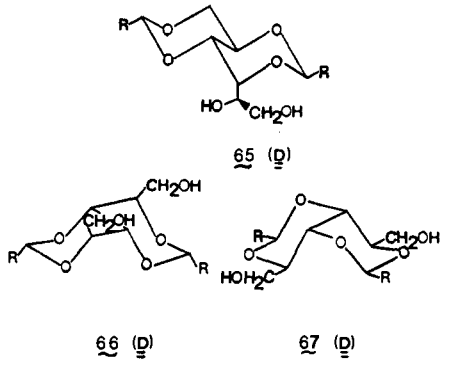
junction would have the 1,2 side chain axial in the preferred "O-inside" conformation. In agreement with this prediction methylenation of D-talitol gives 1,3:2,4:5,6-tri-*O*-methylene-D-talitol,[74] but in poor yield. A tri-*O*-benzylidene-D-talitol has, however, been prepared by several workers,[75] and it undoubtedly has the 1,3:2,4:5,6 structure. In contrast to talitol the 3,5:4,6-diacetal of glucitol **61** (1,3:2,4-diacetal of gulitol) with a trans-ring junction has the 1,2 side chain axial and would not be favored.

The 1,3:2,4-diacetal **62** with a cis-ring junction has the 5,6 side chain equatorial in the preferred "O-inside" conformation, and thus the diacetals of glucitol might be expected to have this arrangement. The alternative 2,4:3,5-diacetal, with a cis-ring junction, would contain an axial hydroxymethyl group in either the "O-inside" **63** or "H-inside" **64** conformers. In agreement with this is the ready formation of 1,3:2,4:5,6-triacetals of glucitol.[76-83]



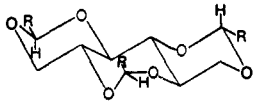
61 (D) 62 (D) 63 (D) 64 (D)

The situation with mannitol is more complicated since the 1,3:2,4-diacetal **65** with a trans-ring junction has an axial side chain, and the 2,4:3,5-diacetal **66** with a cis-ring junction would have two axial hydroxymethyl groups in the preferred "O-inside"



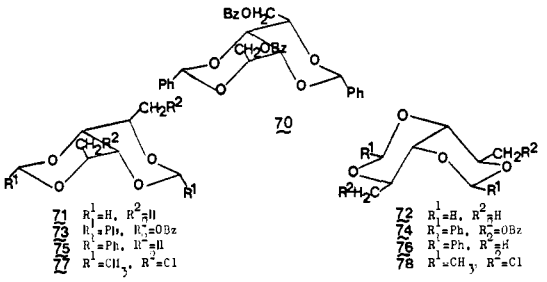
65 (D) 66 (D) 67 (D)

conformation. The alternative "H-inside" conformation **67,** with the two equatorial hydroxymethyl groups, might thus be expected to be the most stable arrangement. There is a third possibility, however, and that is formation of a 1,3:4,6-diacetal with equatorial hydroxyl groups at C_2 and C_5 which allows the formation of the 1,3:2,5:4,6-triacetal with a 1,3-dioxepane ring. That mannitol does, in fact, readily form 1,3:2,5:4,6-triacetals (e.g., **68, 69**)[51,84] is an illustration of the stability of the trans-anti-trans



68 R = H (D)
69 R = Me (D)

configuration and the lack of stability of the "H-inside" conformations. Stoddart and co-workers[85,86] have shown that both the tri-*O*-methylene and tri-*O*-ethylidene acetals exist predominantly in the twist-chair conformers **68** and **69,** respectively. The symmetry of the molecule is such that the acetal carbon of the 1,3-dioxepane ring, for the tri-*O*-ethylidene compound, is not a chiral center, as claimed by Lemieux,[87] and thus only one isomer is expected, in agreement with the assignment of Mills.[13] Methylenation followed by saponification of 1,6-di-*O*-benzoyl-D-mannitol gave[88-90] 2,4:3,5-di-*O*-methylene-D-mannitol which can exist as the "O-inside" conformer **66** (R = H) with two axial hydroxymethyl groups or as the "H-inside" conformer **67** (R = H) with two equatorial hydroxymethyl groups. A comparison[91] of the relative free energies calculated for each conformer indicated that the "H-inside" conformer was preferred by 1.6 kcal mol^{-1}. In agreement with this the ^1H NMR coupling constant data, for 1,6-dideoxy-2,4:3,5-di-*O*-methylene-D-mannitol, showed that



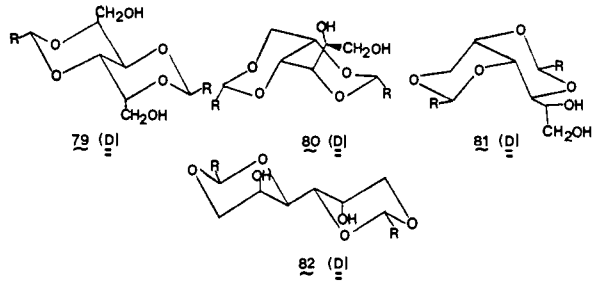
70

71 R^1=H, R^2=H
73 R^1=Ph, R^2=OBz
75 R^1=Ph, R^2=H
77 R^1=CH_3, R^2=Cl

72 R^1=H, R^2=H
74 R^1=Ph, R^2=OBz
76 R^1=Ph, R^2=H
78 R^1=CH_3, R^2=Cl

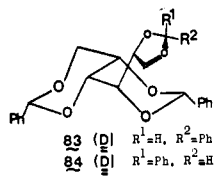
the "H-inside" conformer **72** was the predominant contributor to the conformational equilibrium at room temperature in chloroform solution. However, when the temperature was lowered to −59 °C, the "O-inside" conformer **71** was preferred. Benzylidenation of 1,6-di-*O*-benzoyl-D-mannitol gave[92] a 3,4-*O*-benzylidene derivative in addition to a dibenzylidene derivative. Baggett et al.,[93] from a consideration of the ^1H NMR spectrum, which showed a single benzylic proton signal, assigned the 2,4:3,5 structure to the dibenzylidene derivative. Hudson and co-workers[92] also showed that benzylidenation of 1,6-di-*O*-benzoyl-3,4-*O*-benzylidene-D-mannitol gave the dibenzylidene derivative in good yield, and thus acetal migration must have occurred during the reaction. By a comparison of the chemical shift of the benzylic proton signal of 1,6-di-*O*-benzoyl-2,4:3,5-di-*O*-benzylidene-D-mannitol with the benzylic proton signals of 1,6-di-*O*-benzoyl-2,4:3,5-di-*O*-benzylidene-D-glucitol, which was shown to have the "O-inside" structure **70,** Baggett et al.[93] were able to assign the "O-inside" structure **73** to this compound. In contrast to the above results it has been reported[91] that the acid-catalyzed benzylidenation of 1,6-di-*O*-benzoyl-D-mannitol gave the two diastereomers of the 2,4:3,5-di-*O*-benzylidene derivative corresponding to the "H-inside" structure **74** and the "O-inside" structure **73,** but no information regarding the ratio of the isomers was given. Similarly Zissis and Richtmyer[94] obtained two di-*O*-benzylidene derivatives on benzylidenation of 1,6-dideoxy-L-mannitol, and the major isomer was assigned a 2,4:3,5 distribution with the "O-inside" structure **75** (D-enantiomer) by Baggett et al.[93] These authors considered that the minor isomer was probably one of the two possible 2,5:3,4-di-*O*-benzylidene derivatives. However, in line with the work on the 1,6-dibenzoate, it is possible that it corresponds to the "H-inside" structure **76** (D enantiomer). In agreement the diastereomeric forms of 2,4:3,5-di-*O*-benzylidene-1,6-dibromo-1,6-dideoxy-D-mannitol (**73** and **74;** R^2 = Br) have recently been described,[95] and this would appear to be the first published report of such diastereomers. It is also of interest to note that, in apparent contrast to the above results, the major isomer was assigned the "H-inside" structure **74** (R^2 = Br). Two isomers of 1,6-dichloro-1,6-dideoxy-2,3,4,5-di-*O*-ethylidene-D-mannitol are also known,[96] and Mills[97] considered the possibility that these might correspond to the "O-inside" and "H-inside" structures **77** and **78,** respectively. A 3,4-monoacetal was again isolated during the reaction which suggests that one isomer may have the 2,5:3,4 structure. Acetal migration is a possibility, however, and thus the 3,4-monoacetal is probably a kinetic product which rearranges to give the thermodynamic product, a 2,4:3,5-diacetal.

A similar situation exists for galactitol; the 2,4:3,5-diacetal **79** with a trans-ring junction has two axial hydroxymethyl groups and the 1,3:2,4-diacetal with a cis-ring junction has the 5,6 side chain axial in the "O-inside" conformation **80.** The "H-inside" conformation **81** has an equatorial side chain and, since the alternative 1,3:4,6-diacetal **82** has axial hydroxyl groups at C_2 and C_5, the 1,3:2,4-diacetal with this conformation might be expected. This is not the case, however, and only the 1,3:4,6-diacetals of galactitol have been obtained.[33,98,99] This diacetal, however, may be stabilized by hydrogen bonding (see section II) between the axial hydroxyl groups and the oxygen atoms of



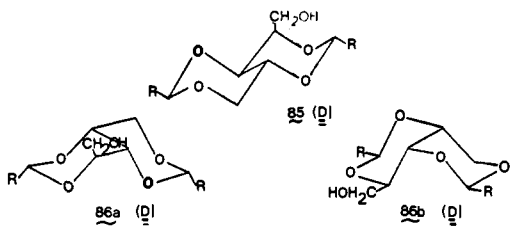
79 (DI 80 (DI 81 (DI 82 (DI

the 1,3-dioxane rings. Recently[93] two isomeric tri-*O*-benzylidene derivatives of galactitol have been prepared under forcing conditions. These were considered to have a 1,3:2,4:5,6 distribution of the acetal groups and the "O-inside" structures **83** and **84,** by analogy with previous results. This is thus further evidence



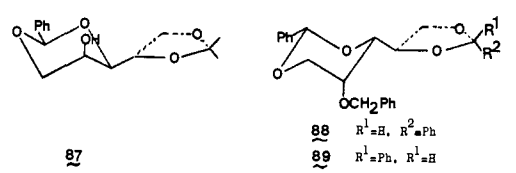
83 (DI R^1=H, R^2=Ph
84 (DI R^1=Ph, R^2=H

of the instability of the "H-inside" conformer since the "O-inside" structure with an axial substituent is preferred to the "H-inside" structure having an equatorial substituent, and is in agreement with observations made by Mills.[100] Arabinitol (lyxitol) may yield the 2,4:3,5-diacetal **85** (1,3:2,4-diacetal of lyxitol) with a trans-ring junction and an axial hydroxymethyl group or the 1,3:2,4-diacetal with a cis-ring junction in which the "O-inside" conformer **86a** has an axial hydroxymethyl group and the "H-inside" conformer **86b** has an equatorial hydroxymethyl group. For the



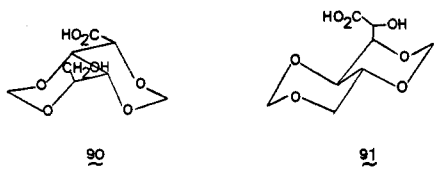
85 (DI **86a** (DI **86b** (DI

methylene diacetals Stoddart,[101] from a calculation of the relative free energies of the constitutional isomers, has predicted that the 2,4:3,5-diacetal **85** (R = H) should be 0.7 kcal mol^{-1} more stable than the 1,3:2,4-diacetal **86** (R = H). It was found,[95] however, that the product of the acid-catalyzed methylenation of D-arabinitol was the 1,3:2,4-diacetal **86** (R = H) formed in low yield. Also formed in low yield was 1,3:2,4-di-*O*-benzylidene-L-arabinitol (5%), which was shown[102] to have the "O-inside" structure **86a** (R = Ph, D enantiomer), in agreement with Stoddart[101] that this would be more stable than the alternative "H-inside" structure **86b** (R = Ph, D enantiomer). Since all the structures discussed have some destabilizing factor, the formation of diacetals with the 1,3:4,5 arrangement might have been expected. Thus. 1,3-*O*-benzylidene-L-arabinitol[102] condenses smoothly with acetone to give a high yield of 1,3-*O*-benzylidene-4,5-*O*-isopropylidene-L-arabinitol (**87**), and 2-*O*-benzyl-D-arabinitol on zinc chloride catalyzed benzylidenation gives,[103] in moderate yield, the diastereomers of 2-*O*-benzyl-1,3:4,5-di-*O*-benzylidene-D-arabinitol (**88** and **89**).



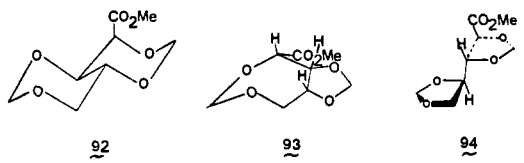
87
88 R^1=H, R^2=Ph
89 R^1=Ph, R^1=H

Also of interest is the formation of 2,4:3,5-di-*O*-methylene-D-gluconic acid (**90**)[104,105] with a cis-ring junction and axial hydroxymethyl group at C-6 rather than the alternative 3,5:4,6-diacetal **91** with a trans-ring junction since this implies that



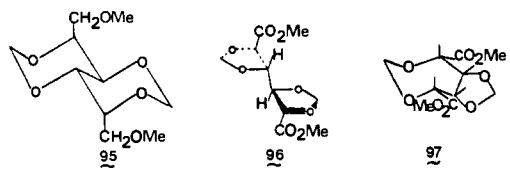
90 **91**

"O-inside" acetals with a cis-ring junction and one axial group are more stable than diacetals with a trans-ring junction and one axial group. Indeed recent work by Stoddart,[65] on the acid-catalyzed methylenation of methyl D-arabinonate and dimethyl galactarate, under conditions of equilibrium control, has shown that methyl 2,4:3,5-di-*O*-methylene-D-arabinonate (**92**), with a trans-ring junction and one axial CO_2Me group, constituted only 24% at isomeric equilibrium. The 2,5:3,4-diacetal **93,** with a five-membered ring fused to a seven-membered ring, formed in 54% yield, was the major contributor and the 2,3:4,5-diacetal **94** was formed in 22% yield. In the case of dimethyl galacturate



92 **93** **94**

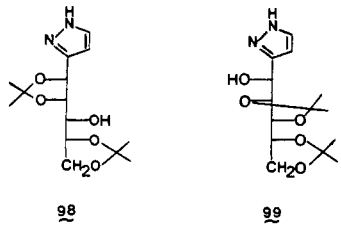
the 2,4:3,5-diacetal **95** with a trans-ring junction would have two axial CO_2Me groups and is not formed at all. Dimethyl 2,3:4,5-di-*O*-methylenegalacturate **96,** formed in 68% yield, was the major product, and the 2,5:3,4-diacetal **97** ('7/5' isomer), which must assume a gauche–gauche conformation,[65] was formed only in 32% yield.



95 **96** **97**

B. Five-Membered Rings

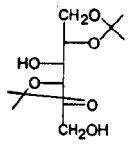
1,3-Dioxolane derivatives formed by condensation with hydroxyl groups having the threo configuration (α-threo ring) are thermodynamically more stable than 1,3-dioxolane derivatives formed by condensation with hydroxyl groups having the erythro configuration (α-erythro ring) (see section II). In agreement is the recently reported[106] rearrangement of the 1,2:4,5-di-*O*-isopropylidene derivative **98,** having an α-erythro ring, to give the 2,3:4,5-diacetal **99** with a α-threo ring.



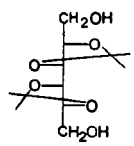
98 **99**

From theoretical considerations,[107] as well as from general experience that a more symmetrical substitution of a ring tends to increase stability, the α-threo ring should be more stable than the terminal α ring. Experimental evidence comes from examples of ketal migration such as the rearrangement[40] of 1,2:

4,5-di-*O*-isopropylidene-(DL)-galactitol (**100**) to 2,3:4,5-di-*O*-isopropylidenegalactitol (**101**), catalyzed by pyridinium chloride

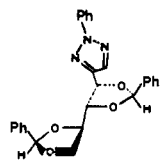


100 (DL)



101

or quinolinium chloride. Further evidence comes from partial acid hydrolysis. Thus the tri-*O*-isopropylidene derivatives of L-iditol,[108] D-glucitol,[109] and D-mannitol,[110] on partial acid hydrolysis, give the respective, 3,4-*O*-isopropylidene derivatives, indicating the stability of the 3,4 distribution over the terminal 1,2 and 5,6 positions. Cyclic acetals also undergo preferential hydrolysis of the terminal 1,3-dioxolane ring, an example[111] being the hydrolysis of 3,4:5,6-di-*O*-(*R*)-benzylidene-D-glucose phenylosotriazole (**102**) to give the 3,4-*O*-benzylidene derivative **103** with the *R* configuration at the acetal carbon. It has also



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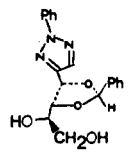
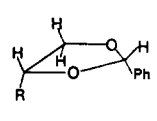


103

been reported[112] that partial acid hydrolysis of syrupy tri-*O*-butylidene-D-mannitol gives a crystalline 3,4 isomer indicating a 1,2:3,4:5,6 distribution of acetal groups in the parent compound.

When the carbonyl component is an aldehyde (other than formaldehyde), and the substituents on C_4 and C_5 of the 1,3-dioxolane ring are different, then there is the possibility of stereoisomerism about the acetal carbon. If either of the substituents is hydrogen, then we have a terminal acetal and it is found that the two stereoisomers are of comparable thermodynamic stability, and hence, at equilibrium, near-equimolar mixtures are usually formed with the cis isomer slightly preponderating. Thus Barker and co-workers[41] (see section II) have demonstrated the greater stability of *cis*-2,4-dimethyl-1,3-dioxolane over its trans isomer. In contrast Baggett et al.[103] have prepared a series of 4-substituted 2-phenyl-1,3-dioxolane derivatives, including a *tert*-butyl derivative, under conditions of vigorous acid catalysis, and at equilibrium comparable amounts of both stereoisomers **104** and **105** are formed. For α-erythro



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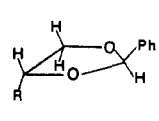
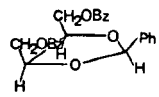


105

rings stereoisomerism will occur at the acetal carbon atom even if the substituents on C_4 and C_5 of the 1,3-dioxolane ring are the same. In section II the preference for the formation of the isomer having the substituent on the acetal carbon atom cis to the substituents on C_4 and C_5 of the 1,3-dioxolane ring was discussed. In agreement benzylidenation of 1,4-di-*O*-benzoylerythritol,[113] which involves condensation across hydroxyl groups with the erythro configuration and formation of a product with the substituent groups cis, gave a mixture of the syn and anti isomers, **106** and **107**, in the ratio 1.8:1. It was suggested, however. that true equilibrium had not been reached since nearly equimolar mixtures of diastereomers are normally formed at equilibrium on the reaction of benzaldehyde with cyclic sugar



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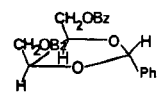
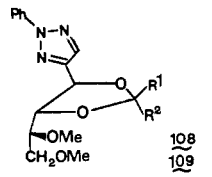


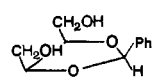
107

derivatives to give cis-fused five-membered cyclic acetals (see section VI). Also the syn isomer **106** is that expected to be formed in the initial kinetic phase of the reaction (see section III). As might be expected nearly equimolar mixtures of diastereomers are formed when the substituents on C_4 and C_5 of the 1,3-dioxolane ring are trans (α-threo ring) and are not the same. Thus benzylidenation of 5,6-di-*O*-methyl-D-glucose phenylosotriazole gave[111] the diastereomeric 3,4-*O*-benzylidene derivatives **108** and **109** in the ratio 6:4 with the *R* isomer **108** predominating.



108 R^1=Ph, R^2=H
109 R^1=H, R^2=Ph

However, in general, the 1,3-dioxolane ring is formed during the kinetic phase of the reaction, the 1,3-dioxane ring is preferred at equilibrium, and thus information regarding the stability of diastereomers is not reliable. That the 1,3-dioxane ring system is the thermodynamically favored ring form is illustrated[113] by the ready rearrangement of "*cis*"-2,3-*O*-benzylideneerythritol (**110**) in dioxane containing *p*-toluenesulfonic acid to give 1,3-*O*-benzylidene-(DL)-erythritol (**111**). An exception is the con-



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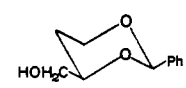
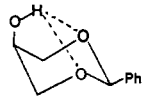


111 (DL)

densation of glycerol with aldehydes to give[114-119] mixtures of 1,3-dioxane and 1,3-dioxolane derivatives. The presence of 1,3-dioxolane derivatives was explained[59] by the fact that the stronger acidity and greater steric accessibility of the primary hydroxyl group facilitates more effective intermolecular hydrogen bonding, compared with the secondary hydroxyl group of the 1,3-dioxane derivatives, thereby increasing the thermodynamic stability of the 1,3-dioxolane derivatives relative to the 1,3-dioxane derivatives. In agreement,[59] equilibration of *O*-benzylideneglycerol mixtures in carbon tetrachloride at 3 °C, with total solute concentrations in the range 0.001–0.5 M, favored the formation of *cis*-5-hydroxy-2-phenyl-1,3-dioxane (**112**). It was

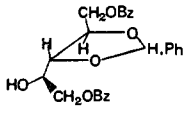


112

considered that in this solvent and at low concentrations intermolecular hydrogen-bonding will diminish and intramolecular hydrogen-bonding will become dominant. Thus, only in the isomer **112** can complete intramolecular hydrogen bonding occur. In a recent publication Angyal and Beveridge[120] have shown that acetal formation by a secondary hydroxyl group is favored over that by a primary hydroxyl group and suggest that this may explain the formation of the 1,3-dioxolane derivatives of glycerol since the six-membered acetal involves two primary hydroxyl groups.

A number of other examples where the formation of a 1,3-dioxolane ring is preferred are known, and usually there is some strong destabilizing factor associated with the 1,3-dioxane ring

form. Thus benzylidenation of 1,5-di-*O*-benzoyl-D-arabinitol results[32] in formation of the 2,3-acetal **113** rather than the 2,4-acetal **114,** which has an axial $-CH_2OBz$ group. Hudson and co-workers[32] isolated **113** as a crystalline compound with a



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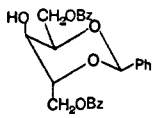
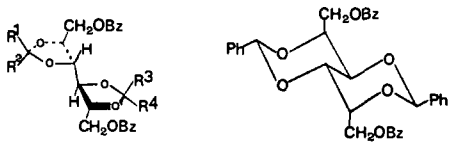


114

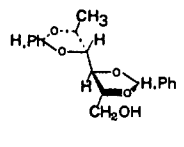
sharp melting point which indicates that they had isolated a single diastereomer. Compound **113** would be expected to exist as a mixture of diastereomers, and since the crystalline product was isolated in good yield, which suggests that a second isomer was not present or was present only in small amount, it indicates that the reaction had not reached equilibrium and that **113** was the product of kinetic control. Similarly benzylidenation of 1,6-di-*O*-benzoylgalactitol has yielded[121-123] two of the three possible stereoisomers of 1,6-di-*O*-benzoyl-2,3:4,5-di-*O*-benzylidene-(DL)-galactitol (**115, 116,** and **117**) rather than the 2,4:3,5-diacetal



115 DL-forms {R^1=H, R^2=Ph, R^3=H, R^4=Ph; R^1=Ph, R^2=Ph, R^3=Ph, R^4=H}
116 R^1=Ph, R^2=H, R^3=H, R^4=Ph
117 R^1=H, R^2=Ph, R^3=Ph, R^4=H

118

118 with two axial $-CH_2OBz$ groups. An examination[103] of these products by ^1H NMR spectroscopy showed that the lower melting isomer had two discrete benzylic proton signals and is clearly the DL form **115,** whereas the second isomer with the higher melting point showed only a single signal and is therefore one of the meso forms **116** or **117.** The higher melting point isomer (meso form) is formed under the more mild conditions, i.e., zinc chloride at room temperature,[122] and can be considered to be a kinetic product. From a consideration of the mechanism (see section III), one would predict the formation of a meso isomer during the kinetic phase of the reaction. Rearrangement about one of the acetal carbons would then give the thermodynamically more stable isomer, the lower melting point product (DL form), which is formed under more vigorous conditions,[121,122] i.e., zinc chloride at 60 °C. In agreement treatment of the meso isomer **116** or **117** in benzaldehyde with zinc chloride at 60 °C resulted[122] in isomerization to give the DL form **115.** The benzylidenation of 1-deoxy-D-galactitol has also been reported[124] and the product was shown to be a mixture of the 2,3:4,5- and 2,3:4,6-di-*O*-benzylidene derivatives, **119** and **120,** respectively, with no evidence for the presence of the 3,5:4,6-diacetal which would have an axial side chain in the preferred "O-inside" structure **121.**



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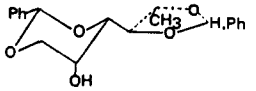

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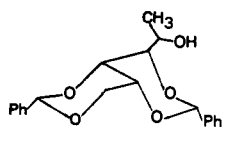
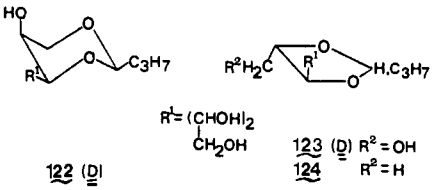


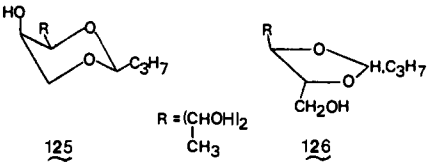
121

There are numerous examples of the formation of cyclic acetals, having a 1,3-dioxolane ring, during the early stages of the reaction but, since they are formed under kinetic control, no information on the thermodynamic stability of the diastereomers is possible. Thus Bonner et al.[99] have shown that both 1,3-*O*-butylidene-(DL)-galactitol (**122**) and 2,3-*O*-butylidene-(DL)-galactitol (**123**) are formed during the early stages of the reaction



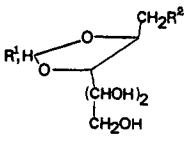
122 (DL) 123 (D) R^2=OH 124 R^2=H

of galactitol with butyraldehyde. Only one of the diastereomers of the 2,3-monoacetal was detected. In contrast acid-catalyzed monobutylidenation of 1-deoxy-D-galactitol gave[125] the diastereomeric 2,3-acetals **124** under kinetic control. At longer reaction times the main product is the 4,6 isomer **125** along with some of the 4,5 isomer **126.** The 4,5 acetal, which corresponds



125 126

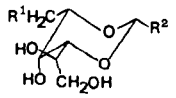
to the 2,3 acetal in galactitol itself, was isolated as a single diastereomer. A similar situation exists for the monoacetalation of D-glucitol and 1-deoxy-D-glucitol. Monobutylidenation of D-glucitol gave[126] what was probably a pure diastereomer of 2,3-*O*-butylidene-D-glucitol (**127**) during the kinetic phase of the reaction. Similarly the monoethylidenation of D-glucitol gave[127] crystalline 2,3-*O*-ethylidene-D-glucitol (**128**), and this crystalline product is again a single diastereomer. In contrast the reaction of D-glucitol with 1 mol of benzaldehyde gave[127] both diastereomers of 2,3-*O*-benzylidene-D-glucitol (**129**) in comparable



127 R^1=C_3H_7, R^2=OH
128 R^1=CH_3, R^2=OH
129 R^1=Ph, R^2=OH
130 R^1=C_3H_7, R^2=H

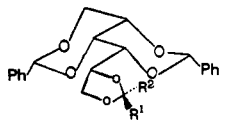
amounts. The difference in behavior between the aldehydes, butyraldehyde and acetaldehyde, on one hand, and benzaldehyde, on the other, may be in part due to the greater stability of the intermediate oxocarbonium ion, formed on ring fission, due to resonance stabilization by the phenyl group. Thus in the kinetic phase of the reaction one diastereomer will be formed preferentially (see mechanism, section III), and this will then rearrange to give an equilibrium mixture of both diastereomers. This pseudo-equilibrium state will be formed faster in the case of the benzylidene acetals, due to the greater stabilization of the intermediate oxocarbonium ion, and the formation of diastereomers in comparable amounts will result. It is likely that in the case of the other aldehydes that there was a small amount of the second diastereomer present which was not detected. This greater stability of the intermediate oxocarbonium ion also explains[127] the higher rate of hydrolysis of benzylidene acetals.

Monobutylidenation of 1-deoxy-D-glucitol gave[128] the 2,3-acetal **130** as the kinetically controlled product. Attempts to purify this product resulted in the isolation of only a small amount of a pure isomer, and it is therefore probable that the original product was a mixture of diastereomers, in agreement with the 1-deoxy-D-galactitol result.[125] Monoacetalation of D-glucitol and 1-deoxy-D-glucitol gave[126-128] the 2,4-monoacetals **131-134** as the main product under thermodynamic control. The rearrangement of **127-129,** in anhydrous *N,N*-dimethylformamide, in the presence of hydrogen chloride, to give **131-133** was also demonstrated.[126,127]

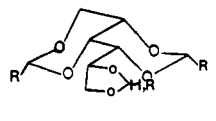


131 R^1=OH, R^2=C_3H_7
132 R^1=OH, R^2=CH_3
133 R^1=OH, R^2=Ph
134 R^1=H, R^2=C_3H_7

There are numerous examples of acyclic sugar derivatives forming cyclic acetals having α-rings, but there is still little information on the occurrence of diastereomers. As discussed earlier it is expected that there should be equal amounts of diastereomers at equilibrium. Both L-iditol[73] and D-talitol[75] react with benzaldehyde to give a triacetal with a 1,3:2,4:5,6 distribution, but no information on the presence or otherwise of stereoisomers about the acetal carbon atom of the 5,6 ring is available. The existence of diastereomers was suggested[13] as a possible explanation for the variable melting point quoted[76,129] for 1,3:2,4:5,6-tri-*O*-benzylidene-D-glucitol and this has recently been confirmed by Brecknell et al.[130] Thus benzylidenation of D-glucitol by three methods gave,[130] in each case, approximately equal amounts of two diastereomers. The isomers were separated by preparative TLC and the known tri-*O*-benzylidene derivative was shown to be **135** having the *S* configuration at the acetal carbon atom of the 5,6-dioxolane ring. The new diastereomer **136** had the *R* configuration at this position. D-Glucitol also gave a 1,3:2,4:5,6-tri-*O*-ethylidene derivative (**137**),[78,79,131]

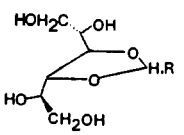


135 R^1=Ph, R^2=H
136 R^1=H, R^2=Ph



137 R=CH_3
138 R=C_3H_7
139 R=CH=$CHCH_3$

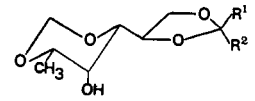
and the difficulty experienced in preparing a crystalline sample is again probably due to stereoisomerism in the five-membered ring. A crystalline tri-*O*-ethylidene compound has been reported,[78,131] but there was some doubt as to the structure since it could not be hydrolyzed to 1,3:2,4-di-*O*-ethylidene-D-glucitol. It has been observed,[132] however, that diastereomers may hydrolyze at very different rates, and therefore it is possible that the crystalline triacetal is a single diastereomer of **137** and that rate of hydrolysis of the five-membered ring is much slower than for the other diastereomer present in the syrupy product. The syrupy triacetal is presumably a mixture of both diastereomers. Furthermore, it is reported[78] that ethylidenation of crystalline 1,3:2,4-di-*O*-ethylidene-D-glucitol gave the crystalline triacetal. Syrupy tri-*O*-butylidene-D-glucitol (**138**) has been prepared[82] and it is undoubtedly a mixture of diastereomers since a crystalline 1,3:2,4:5,6-tri-*O*-butylidene-D-glucitol may be prepared[82] by hydrogenation of crystalline 1,3:2,4:5,6-tri-*O*-but-2′-enylidene-D-glucitol (**139**). The latter compound, which is presumably a pure diastereomer, was isolated[83] from the condensation of D-glucitol with crotonaldehyde. The major product from this reaction was a syrupy tri-*O*-but-2′-enylidene-D-glucitol which gave a 3,4-monoacetal (**140,** 7%) on partial hydrolysis indicating the presence of the isomeric 1,2:3,4:5,6-tri-*O*-but-2′-enylidene-D-glucitols. The formation of the analogous tri-*O*-butylidene acetal of D-glucitol is also possible since 3,4-*O*-butylidene-D-glucitol (**141**) was produced[82] on partial hydrolysis of the tri-



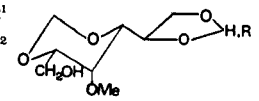
140 R = CH=$CHCH_3$
141 R = C_3H_7

acetals formed by the reaction of D-glucitol and butyraldehyde using a trace of *p*-toluenesulfonic acid as catalyst. In both cases the 3,4-monoacetal was isolated as a crystalline material and is probably a pure diastereomer. The 1,2:3,4:5,6-triacetals would undoubtedly be diastereomeric at the 3,4-acetal carbon, and the above results indicate that there is a considerable difference in the rate of hydrolysis of the diastereomeric 3,4-acetals.

Butylidenation of both 1-deoxy-D-glucitol and 3-*O*-methyl-D-glucitol gave[133] the 2,4:5,6-diacetals **142** and **143,** respec-

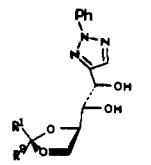


142a R^1=H, R^2=C_3H_7
142b R^1=C_3H_7, R^2=H



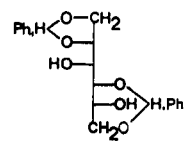
143 R=C_3H_7
144 R=Ph

tively, consisting of a mixture of isomers, differing in configuration at the acetal carbon of the five-membered ring, as the main thermodynamically controlled products. In the case of 1-deoxy-D-glucitol a small amount of one of the isomers was obtained pure and it was shown by ^{1}H NMR spectroscopy to be the isomer **142a** having the propyl group and C_4 trans with respect to the 5,6 ring. 2,4:5,6-Di-*O*-benzylidene-3-*O*-methyl-D-glucitol (**144**) has also been prepared[134] and both diastereomers, formed in equimolar amounts, as shown by the ^{1}H NMR spectrum of the crude product, were isolated crystalline. Treatment of D-glucose phenylosotriazole with benzaldehyde in dimethyl sulfoxide or tetrahydrofuran, solvents which favor the formation of kinetic products, using a little concentrated sulfuric acid as catalyst, gave[111] the diastereomeric 5,6-*O*-benzylidene derivatives **145** and **146,** in approximately equal amounts. A



145 R^1=H, R^2=Ph
146 R^1=Ph, R^2=H

crystalline dibenzylidene compound is formed[135] in high yield from the reaction of D-glucose phenylosotriazole with benzaldehyde and zinc chloride. D-Glucose phenylosotriazole has a four-carbon D-arabino side chain and thus resembles methyl D-arabinonate. The methylenation of this compound has been discussed (section IV.A) and the benzylidenation of D-glucose phenylosotriazole might be expected to conform to a similar pattern. The crystalline product was shown[111] to be the 3,4:5,6-diacetal **102** having the *R* configuration at both acetal carbon atoms. The product is undoubtedly the result of kinetic control since at equilibrium the three other possible isomers of the 3,4:5,6-diacetal as well as the diastereomeric 3,6:4,5-diacetals and the 2,4:3,5-diacetal should be present. Dimethyl sulfoxide has been used as the solvent, to promote the formation of the kinetically favored five-membered dioxolane ring product, in the benzylidenation of D-mannitol, and all the possible stereoisomers of 1,2:4,6- and 1,2:5,6-di-*O*-benzylidene-D-mannitol (**148** and



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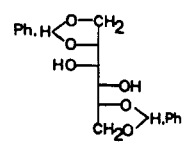
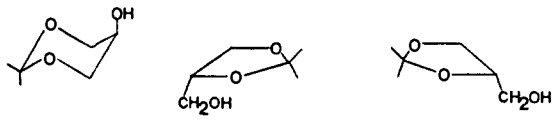


149

149, respectively) have been prepared.[136] The 1,3:2,5:4,6-triacetal and the 1,3:4,6-diacetal are the products of the reaction at equilibrium.[136]

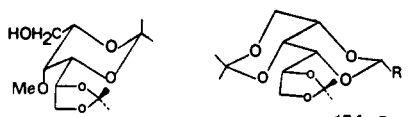
V. Cyclic Ketals Derived from Acyclic Sugar Derivatives

The condensation of alditols with ketones normally results in the formation of five-membered rings. Formation of six-membered *O*-isopropylidene ketals is inhibited because one of the methyl groups is necessarily axial in the chair conformation of the six-membered ring.[137] This preference is well illustrated by the reaction of glycerol with acetone to give the 1,3-dioxane derivative **150** and the 1,3-dioxolane enantiomers **151** and **152.** In practice it has been shown[138] that isopropylidenation of glycerol leads essentially entirely to the formation of 1,2-*O*-isopropylidene-(DL)-glycerol (**151** and **152**).



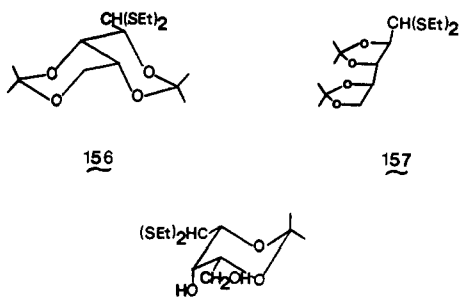
150 151 (D) 152 (L)

There are few examples of the formation of a six-membered cyclic ketal directly from the reaction of ketones with alditols. Isopropylidenation of 3-*O*-methyl-D-glucitol gave mainly the 1,2:5,6-di-*O*-isopropylidene derivative, but ca. 10% of a second isomer, identified[134] as the 2,4:5,6-diketal **153,** was also formed. A di-*O*-isopropylidene derivative of 2,4-*O*-benzylidene-D-glucitol has been reported[139,140] which presumably has the 1,3:2,4:5,6 structure **154.** Supporting this assignment is the report[141] that 2,4-*O*-methylene-D-glucitol affords a 1,3:5,6-di-*O*-isopropylidene derivative (**155**). A small amount of 2,4:3,5-di-*O*-isopropyli-



153 154 R = Ph 155 R = H

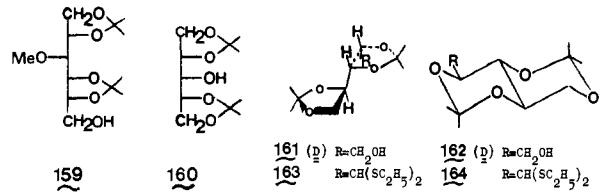
dene-D-xylose diethyl dithioacetal (**156**), having two axial methyl groups, was isolated by van Es[142] on isopropylidenation of D-xylose diethyl dithioacetal when zinc chloride was used as the catalyst; the main product was the expected 2,3:4,5-diketal **157.** The 2,4:3,5-diketal **156** has also been prepared by Lance and Jones[143] from the 2,4-monoketal **158.** The monoketal **158** was



156 157 158

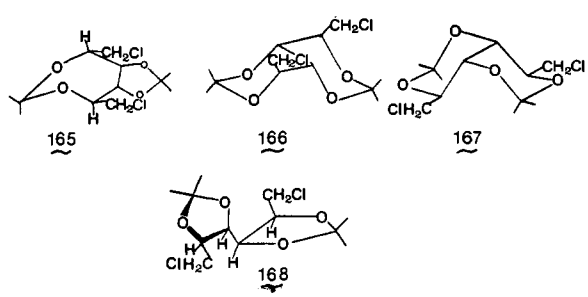
isolated in low yield during the early stages of the isopropylidenation using anhydrous copper sulfate as the catalyst.

As we have seen (section II.B) the formation of a 1,3-dioxolane ring from hydroxyl groups with the threo configuration is preferred to formation from hydroxyl groups with the erythro configuration since the latter will have substituent groups at the 4 and 5 positions with the unfavorable cis arrangement. An example of the lack of stability of the α-erythro ring may be seen from the isopropylidenation of 3-*O*-methyl-D-glucitol[134] just discussed. An alternative structure to the 2,4:5,6-di-*O*-isopropylidene derivative **153** would be the 1,2:4,5-diketal **159** with an α-erythro ring. That it is not formed indicates that, in this



159 160 161 (D) R=CH_2OH 163 R=$CH(SC_2H_5)_2$ 162 (D) R=CH_2OH 164 R=$CH(SC_2H_5)_2$

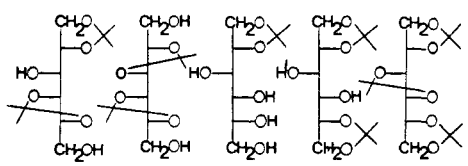
example at least, a 1,3-dioxane ring with an axial methyl group is preferred to a 1,3-dioxolane ring with cis substituents. Indeed there are very few references to the formation of compounds with this arrangement although if no other type of ring is possible, as in the case of *erythro*-1,2-diphenyl-1,2-ethanediol,[144] then the formation of an α-erythro ring may occur. It has been reported,[145] however, that the isopropylidenation of ribitol gave a mixture of di-*O*-isopropylidene ribitols. The minor product was shown to be 1,2:4,5-diisopropylideneribitol (**160**) and the major 2,3,4,5-di-*O*-isopropylidene-(DL)-ribitol. This result was surprising since the major isomer must contain either a 1,3-dioxolane ring with cis 4,5-substituents (**161**) or a ring system related to *trans*-decalin with the two axial methyl groups (**162**). Confirmation of this result was obtained when D-ribose diethyl dithioacetal readily gave[145] a 2,3,4,5-di-*O*-isopropylidene derivative corresponding to either **163** or **164.** Subsequent use of crystalline ribitol, however, gave[146] a mixture of isomers in which **160** was the major diketal. Partial hydrolysis studies showed[146] that, providing there was no rearrangement during the hydrolysis, the minor isomer had the 2,4:3,5 structure **162** and thus that the di-*O*-isopropylidene derivative of D-ribose diethyl dithioacetal was the 2,4:3,5-diketal **164.** Szarek and co-workers[77] observed the presence of two diketal derivatives in the isopropylidenation of D-ribose diethyl dithioacetal, using anhydrous copper sulfate as the catalyst. This result was confirmed by Blumberg et al.[173] who isolated the 2,3:4,5-diketal **163** and the 2,4:3,5-diketal **164** in good yield. Foster's group[145] used a mixture of anhydrous copper sulfate and concentrated sulfuric acid as catalyst in the above reaction and thus it is possible that the 2,4:3,5-diketal **164** is the thermodynamic product and that the 2,3:4,5-diketal **163** is formed only in the early part of the reaction. This would be in agreement with the observation (section VII) that the use of anhydrous copper sulfate alone, as catalyst, promotes the formation of kinetic products. The diketal **163** contains an isopropylidene ring, formed from hydroxyl groups with the erythro configuration, and might be expected to be less stable because of the nonbonded interactions between the cis substituents. Also of interest is the report[96] that 1,6-dichloro-1,6-dideoxy-D-mannitol gave two isomeric di-*O*-isopropylidene derivatives. Of the three possibilities, 2,5:3,4, 2,4:3,5, and 2,3:4,5, the 2,5:3,4 structure **165,** with a five-membered ring trans-fused to a seven-membered ring, may be considered to be the most likely since the major product from the reaction is the 3,4-monoketal. Further the two alternative structures are found to be conformationally very unfavorable. Thus the 2,4:3,5 structure in the "O-inside" conformation **166** has two axial methyl and two axial $-CH_2Cl$ groups and in the "H-inside" conformation **167** has two axial methyl groups "inside" while the 2,3:4,5 structure **168** has two α-erythro rings. No decision as to the structure of the second



165 166 167 168

isomer is therefore possible although the 2,3:4,5 distribution would appear to be the more likely. The reaction of 1,6-di-*O*-benzoyl-D-mannitol with acetone under similar conditions gave[147,148] only the 3,4-*O*-isopropylidene derivative.

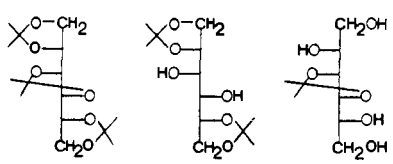
In general the maximum possible number of rings is formed from the condensation of either an aldehyde or a ketone with alditols, and also the more symmetrical substitution of a ring tends to increase stability. Thus glucitol (gulitol), mannitol, and iditol, which have hydroxyl groups on C_3 and C_4 with the threo configuration, would be expected to give the respective 1,2:3,4:5,6-tri-*O*-isopropylidene derivatives in good yield. In agreement the tri-*O*-isopropylidene derivatives of these alditols are readily prepared.[39,108,149] Galactitol, which has an erythro arrangement of hydroxyl groups at C_3 and C_4, does not form a triketal but forms a mixture of the 1,2:4,5- and the 2,3:4,5-di-*O*-isopropylidene derivatives **169** and **170,** respectively, the relative proportion depending on the conditions employed.[40,149-152] It was shown[40] that the 1,2:4,5-diketal readily rearranged to give the 2,3:4,5 isomer **170,** and so it may be said that the 1,2:4,5-diketal is the kinetic product and that the 2,3:4,5-diketal is the thermodynamic product. Mild conditions and short reaction times should thus favor the formation of the former. A kinetic phase in the isopropylidene reaction has been demonstrated[153] in the condensation of D-glucitol with acetone using zinc chloride as the catalyst. The reaction was followed by GLC and it was shown[153] that the 1,2-mono- and the 1,2:5,6-diketal, **171** and **172,** respectively, were present in ap-



169 170 171 172 173

proximately equal amounts in the early stage of the reaction. It was concluded that there was initial attack at the primary hydroxyl group on C_1 giving the 1,2-monoketal followed by rapid formation of the ring at HO_5 and HO_6. After 3 h the 1,2:3,4:5,6-triketal **173** is the major component of the reaction mixture.

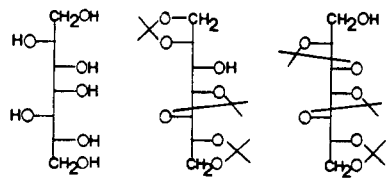
Isopropylidenation of D-glucitol in anhydrous *N,N*-dimethylformamide, containing hydrogen chloride, using an equimolar amount of acetone, under homogeneous conditions, gave[153] 1,2-*O*-isopropylidene-D-glucitol (**171**) as the major product. However, the difference in behavior of this reaction and the heterogeneous zinc chloride catalyzed reaction was thought possibly to be due, in the latter, to the relative insolubility of the D-glucitol and the preferential reaction of the soluble portion with excess acetone. With concentrated sulfuric acid as catalyst the reaction was extremely rapid and after 30 s the mixture was composed of virtually all triketal. A kinetic phase is also undoubtedly present during the isopropylidenation of D-mannitol and, as above, the use of concentrated sulfuric acid as the catalyst ensures the formation of the 1,2:3,4:5,6-triketal **174.**[39] Use of either concentrated hydrochloric acid[154] or zinc chloride[155-160] as catalyst gives an appreciable amount of the 1,2:5,6-diketal **175,**[157-159] which may be considered to be the kinetic product. That the 3,4-ketal is the most stable monoketal, in these examples, may be seen from partial acid hydrolysis



174 175 176

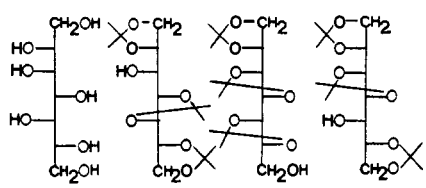
studies. Thus the partial acid hydrolysis of the 1,2:3,4:5,6-tri-*O*-isopropylidene derivatives of D-glucitol,[109] D-mannitol,[39,110] and D-iditol[108] gave the respective 3,4-*O*-isopropylidene ketals (e.g., 3,4-*O*-isopropylidene-D-mannitol, **176**).

More recently Okuda et al.[161] have reported the isopropylidenation of a number of heptitols. Isopropylidenation of D-*glycero*-L-*galacto*-heptitol (**177**) gave a mixture of the 1,2:4,5:6,7-triketal **178** and the 2,3:4,5:6,7-triketal **179.** The triketal **179,**



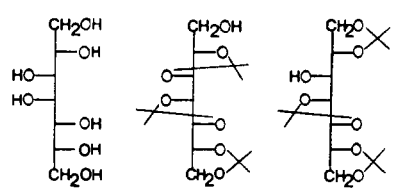
177 178 179

having a more symmetrical substitution, might be expected to be the thermodynamically more favored product and in agreement it was formed in higher yield. Further it was considered that **178,** with a terminal ketal group, should be the kinetic product which would rearrange to give **179.** Support for this assumption was provided by the observation that the yield of **179** increased, accompanied by a decrease in the yield of **178,** upon prolonged reaction. Isopropylidenation of D-*glycero*-L-*gulo*-heptitol (**180**) gave the 1,2:4,5:6,7-triketal **181** and 1,2:3,4:5,6-triketal **182.**



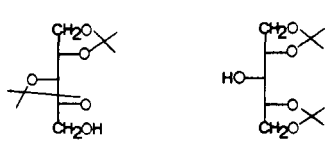
180 181 182 183

Again the latter with a free primary hydroxyl group would be expected to be the preferred product and this was found to be the case. The triketal **183** would presumably be the precursor of **182** but it was not isolated. Similarly isopropylidenation of perseitol (**184**) gave, as the major component, the 2,3:4,5:6,7-triketal **185,** with the 1,2:4,5:6,7-triketal **186** as a minor component.



184 185 186

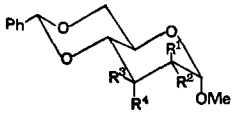
The preferential formation of cyclic acetal derivatives involving secondary hydroxyl groups rather than primary is also demonstrated by the isopropylidenation of xylitol. Thus Baggett et al.[141] have shown that, under various conditions of catalysis, 1,2:3,4-di-*O*-isopropylidene-(DL)-xylitol (**187**) is the major product and 1,2:4,5-di-*O*-isopropylidene-xylitol (**188**), involving both primary hydroxyl groups, is a minor product.



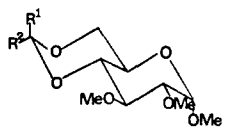
187 (DL) 188

VI. Cyclic Acetals Derived from Cyclic Sugar Derivatives

Condensation of an aldehyde with the aldohexoses, either as the free sugar or as the glycopyranoside, can lead to the formation of a cyclic acetal with two fused six-membered rings related to either *trans*- or *cis*-decalin. Unlike the situation occurring with the condensation of ketones (see section V), the bulky group at the acetal carbon may be equatorial, and so this pattern of condensation is expected to be favored. In agreement the methyl 4,6-*O*-benzylidene-α-D-aldohexopyranosides with the allo (**189**), altro (**190**), gluco (**191**), and manno (**192**) configurations and having the *trans*-decalin type fused ring system are all readily formed. These acetals are prepared by an acid-catalyzed condensation reaction and the nature of the product is thermodynamically controlled. Benzylidenation under basic conditions has been employed with the formation of the kinetically controlled product.[162,281] Thus benzylidenation of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside with α,α-dibromotoluene and potassium *tert*-butoxide gave[162] the diastereomeric forms of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (**193** and **194**) in approximately equal amounts. Addition



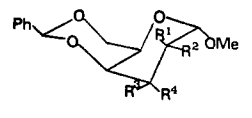
189 $R^1=R^3=H$; $R^2=R^4=OH$
190 $R^1=R^4=OH$; $R^2=R^3=H$
191 $R^1=R^4=H$; $R^2=R^3=OH$
192 $R^1=R^3=OH$; $R^2=R^4=OH$



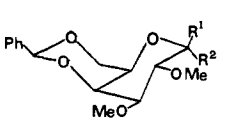
193 $R^1=H$, $R^2=Ph$
194 $R^1=Ph$, $R^2=H$

of hydrogen chloride to a solution of **194** in carbon tetrachloride resulted in smooth and complete isomerization into the more stable diastereomer **193.**

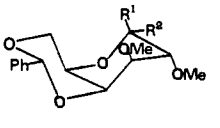
The methyl 4,6-*O*-benzylidene-α-D-aldohexopyranosides with the galacto (**195**), gulo (**196**), ido (**197**), and talo (**198**) configurations and having the *cis*-decalin type fused ring system are also readily prepared. The situation here is slightly more complicated since two diastereomers are possible both with an equatorial phenyl group. One diastereomer will have an equatorial phenyl group on the "O-inside" conformer, shown for structures **195-198,** and the other an equatorial phenyl group on the "H-inside" conformer, shown for methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-galactopyranoside (**200**). In general the "H-inside" conformation is not favored for bicyclic diacetals[13,93] (see also section IV.A) and only one diastereomer, undoubtedly corresponding to the "O-inside" structure, is formed. In agreement the base-catalyzed benzylidenation[162] of methyl 2,3-di-*O*-methyl-α- and -β-D-galactopyranoside resulted in the formation of two sets of diastereomers, **199** and **200,** and **201** and **202,** respectively. That diastereomers **200** and **202** are thermodynamically less stable was shown by the ready isomerization



195 $R^1=R^4=H$; $R^2=R^3=OH$
196 $R^1=R^3=H$; $R^2=R^4=OH$
197 $R^1=R^4=OH$; $R^2=R^3=H$
198 $R^1=R^3=OH$; $R^2=R^4=H$

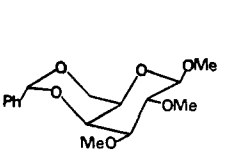


199 $R^1=H$, $R^2=OMe$
201 $R^1=OMe$, $R^2=H$



200 $R^1=H$, $R^2=OMe$
202 $R^1=OMe$, $R^2=H$

of **200** and **202** into **199** and **201,** respectively, in the presence of acid. The crystal structure of the thermodynamically less stable diastereomer of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-galactopyranoside has recently been determined[163] and the 2-phenyl-1,3-dioxane ring was shown to adopt a chair conformation having the phenyl group axial (**203**). A similar situation is expected in solution, and thus the "O-inside" conformer **203,** having an axial phenyl group, is preferred to the "H-inside" conformer **202** or a boat conformation **204.**[162]



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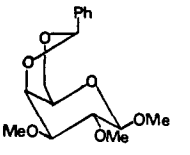

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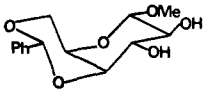
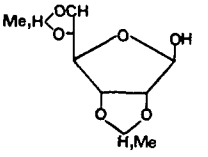
The formation of diastereomers is most likely for methyl 4,6-*O*-benzylidene-α- and -β-D-idopyranoside since the diastereomer, with an equatorial phenyl group on the "O-inside" conformer (**197,** α-anomer), has axial hydroxyl groups on C_2 and C_3 while the alternative diastereomer, with an equatorial phenyl group on the "H-inside" conformer (**205,** α-anomer), has



205

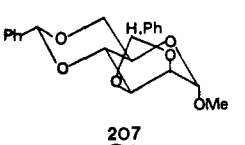
equatorial hydroxyl groups at these positions. Benzylidenation of a mixture of methyl L-idosides gave[164] methyl 4,6-*O*-benzylidene-α- and -β-L-idopyranoside with the same physical properties (opposite sign of rotation) as the corresponding derivatives prepared[165] from the galactosides (**195,** α-anomer). Since there was no inversion of configuration at the acetal carbon atom, in the preparation from the galactoside derivatives, the idosides must correspond to the diastereomer having the "O-inside" structure (**197,** α-D anomer). No diastereomer corresponding to the "H-inside" structure was observed.[164] A study[166] of the conformation of the idoside derivatives showed that the pyranoid ring of the α-D anomer existed in the $^4C_1$ conformation in $CHCl_3$ and a skew-boat conformation in Me_2SO/H_2O while the pyranoid ring of β-D anomer existed in a skew-boat conformation.

The 4,6-*O*-alkylidene derivatives of the free hexoses are likewise readily formed. One exception was D-allose which gave[167] the 2,3:5,6-furanose derivative **206** on ethylidenation.



206

Condensation of a second mole of the aldehyde readily occurs for sugars having vicinal *cis*-hydroxyl groups. Thus, for example, methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**207**)[168,93] and 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose



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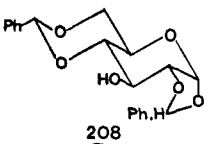
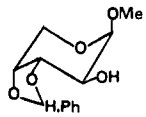


208

(**208**)[169] may be prepared. In these examples isomerism at the acetal carbon of the 1,3-dioxolane ring is possible and the formation of diastereomers is expected (see below).

The formation of a decalin-type system is not possible in the case of the pentoses and either six–five or five–five fused ring systems are found. Thus, on benzylidenation, methyl β-D-arabinopyranoside gave[170] methyl 3,4-*O*-benzylidene-β-D-arabinopyranoside (**209**), with a five-membered cyclic acetal fused to the pyranoid ring, and D-ribose gave[171] 2,3-*O*-benzylidene-β-D-ribofuranose (**210**) with two fused five-membered rings. In



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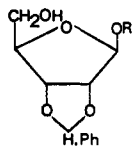
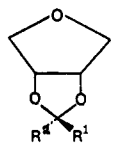


210 R=H
211 R=Me

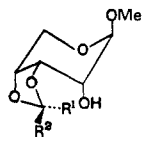
each case isomerism at the acetal carbon is possible, and it is found[132,172] that the diastereomers are formed in approximately equal amounts. The latter example has two fused five-membered rings, and Mills[13] predicted that because of the greater stability of exo isomers, only one isomer should be obtained. However, the acid-catalyzed benzylidenation of the model compound, 1,4-anhydroerythritol,[60,61] gave equal amounts of both diastereomers **212** and **213** at equilibrium. Furthermore, it was shown



212 R^1=H, R^2=Ph
213 R^1=Ph, R^2=H

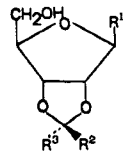
that the *endo*-phenyl isomer **212** was formed first, reflecting initial kinetic control, followed by the slow formation of the *exo*-phenyl isomer **213.** In agreement with this result, diastereomers are nearly always formed on the condensation of an aldehyde to give the system of two five-membered fused rings. Indeed, it will be seen that the methyl group of five-membered cyclic ethylidene acetals prefer the endo configuration.

Treatment of D-ribose with benzaldehyde, zinc chloride, and glacial acetic acid, for 24 h at 27 °C, gave[172] mainly a mixture of di-*O*-benzylidene-D-ribose derivatives but **210** was isolated in low yield as a 1:1 mixture of diastereomers. A similar reaction at 5 °C gave mainly the isomer of **210** having an *endo*-phenyl group. This is the product of kinetic control, the reaction not having been allowed to attain equilibrium. The corresponding glycoside **211** is also formed[174] as a 1:1 mixture of diastereomers. That the latter example is an equilibrium situation was confirmed by the rearrangement[175] of methyl 3,4-*O*-(*R*)- and 3,4-*O*-(*S*)-benzylidene-β-D-ribopyranoside (**214** and **215,** re-



214 R^1=Ph, R^2=H
215 R^1=H, R^2=Ph

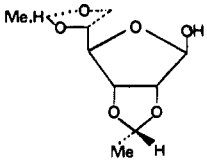
spectively), in acidified chloroform, to give **211.** Approximately equal amounts of both diastereomers were formed and the ratio was not altered over a long period. Similar results were obtained[60] on the benzylidenation of the nucleosides, adenosine, guanosine, cytidine, and uridine. Thus reaction at 0 °C gave the diastereomer with the phenyl group endo (**216**), and reaction at 100 °C gave an approximately equimolar mixture of the two diastereomers **216** and **217.** Again **216** is the product of kinetic control and at elevated temperatures equilibration occurs with formation of the thermodynamically most stable isomer. From the above results it is clear that the syn and anti isomers, for benzylidene acetals formed across C_2 and C_3 of a furanoid ring, are of comparable thermodynamic stability.



R^1=Base

216 R^2=H, R^3=Ph
217 R^2=Ph, R^3=H

The corresponding ethylidene derivatives have also been prepared, but in these examples it is found that there is a strong preference for the diastereomer with an *endo*-methyl group. This is in keeping with the work of Salomaa and Kankaanperä[42-45] and Eliel and his co-workers[46,47] on the configurational stability of 2,4-*cis*-5-trisubstituted 1,3-dioxolanes (see section II). Thus ethylidenation of D-allose gave[167] 2,3:4,6-di-*O*-ethylidene-β-D-allofuranose (**218**) as a mixture of diastereomers at the acetal carbon on the 5,6 ring. No compound diastereomeric at the acetal carbon on the 2,3 ring was observed and in agreement equilibration of 1,5,6-tri-*O*-acetyl-2,3-*O*-ethylidene-β-D-allofuranose (**219**), with an *endo*-methyl group, gave only 5% of **220**



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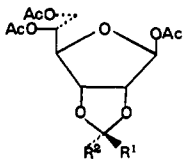
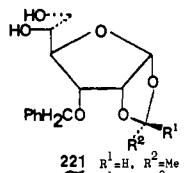
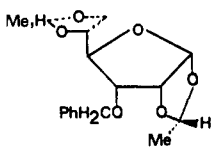


219 R^1=H, R^2=Me
220 R^1=Me, R^2=H

with an *exo*-methyl group. These authors[176] also studied the ethylidenation of 3-*O*-benzyl-D-allose and isolated 3-*O*-benzyl-1,2-*O*-ethylidene-α-D-allofuranose (**221**) and 3-*O*-benzyl-1,2:5,6-di-*O*-ethylidene-α-D-allofuranose (**223**), both with the

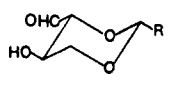


221 R^1=H, R^2=Me
222 R^1=Me, R^2=H

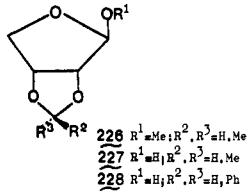


223

endo-methyl configuration at the 1,2-acetal carbon. Isomerization of a sample of **221** in chloroform-*d*, saturated with hydrogen chloride, resulted in the formation of **222,** with an *exo*-methyl group, to the extent of 18% as indicated by ^{1}H NMR spectroscopy. It has also been reported[177] that, on treatment with methanolic hydrogen chloride, 2,4-*O*-ethylidene-D-erythrose (**224**) rearranges to give mainly methyl 2,3-*O*-ethylidene-β-D-erythrofuranoside (**226**). Likewise with dilute aqueous acid 2,3-*O*-ethylidene-β-D-erythrofuranose (**227**) is formed. No evi-



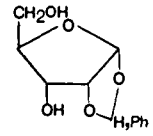
224 R=Me
225 R=Ph



226 R^1=Me; R^2, R^3=H, Me
227 R^1=H; R^2, R^3=H, Me
228 R^1=H; R^2, R^3=H, Ph

dence was obtained for the configuration at the ethylidene acetal carbon atom, but the related rearrangement[113] of 2,4-*O*-benzylidene-D-erythrose (**225**) gave **228** with the phenyl group endo. It is thus likely that both **226** and **227** also have an *endo*-methyl group, which is in agreement with the earlier discussion. Only the diastereomer with an *endo*-phenyl group was observed in the latter rearrangement. By analogy with previous examples[60,61] it is likely that this isomer is the product of a stereospecific rearrangement and that at equilibrium both diastereomers will be present.

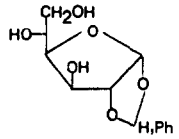
Acetal formation across C_2 and C_3 of the furanose ring is preferred to formation across C_1 and C_2 (see section VII), and in agreement benzylidenation of D-ribose gave[172] the 2,3-acetal **210** rather than the 1,2-acetal **229.** However, benzylidenation



229

at 27 °C for 24 h gave, in addition to di-*O*-benzylidene derivatives and the diastereomeric 2,3-acetals **210,** a crystalline product in very low yield which was considered to be **229.** This product showed a single benzylic proton signal in the ^1H NMR spectrum, and evidently only one diastereomer was present, contrary to the results discussed above, where equimolar amounts of benzylidene diastereomers are normally formed.

If the hydroxyl groups on C_2 and C_3 are trans, then acetal formation is not possible and the 1,2-acetal is produced. Thus 1,2-*O*-benzylidene-α-D-glucofuranose (**230**)[178,179] and 1,2:3,5-di-*O*-benzylidene-α-D-glucofuranose (**231**)[180] may be pre-



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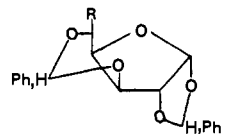
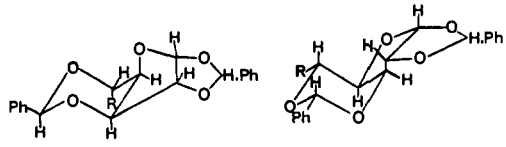


231 R = CH_2OH
232 R = H

pared. In each case only one diastereomer is present[181] but, since both compounds crystallized out in low yield, it is possible that a second diastereomer remained in the mother liquors. Supporting this possibility is the observation[182] that 1,2:3,5-di-*O*-benzylidene-α-D-xylofuranose (**232**) is formed as a mixture of diastereomers at the acetal carbon of the 1,3-dioxolane ring. It was also noted that, under kinetic control, a preponderant amount of the isomer with an *endo*-phenyl group was formed, whereas, at equilibrium the *endo*:*exo*-phenyl ratio was 1:2. It is also of interest to note that both **231** and **232** may exist as diastereomers about the acetal carbon of the 1,3-dioxane ring corresponding to the "O-inside" structure **233** and the "H-inside" structure **234** both having an equatorial phenyl group. The xylo

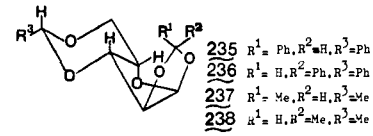


R = CH_2OH
R = H

233 234

derivative **232** (*endo*-phenyl and *exo*-phenyl isomer) have been shown[182] to be the diastereomers corresponding to the "O-inside" structure **233** (R = H), by a consideration of ^1H NMR coupling constant data. Likewise the *gluco* derivative **231** was shown[181] to have the configuration corresponding to the "O-inside" structure **233** (R = CH_2OH) with an axial hydroxymethyl group. However, in the latter case, it is not known if this is the more stable diastereomer since, as pointed out above, it is possible that a diastereomer corresponding to the "H-inside" structure **234** (R = CH_2OH), having an equatorial hydroxymethyl group, was present in the mother liquors.

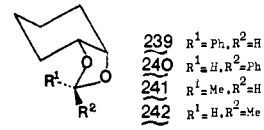
A six-membered cyclic acetal cis-fused to a furanoid ring is also formed on the acetalation of L-sorbose. Benzylidenation gave[183] 2,3:4,6-di-*O*-benzylidene-α-L-sorbofuranose (**235** and **236**), diastereomeric about the acetal carbon of the 2,3 ring, as



235 R^1 = Ph, R^2=H, R^3=Ph
236 R^1 = H, R^2=Ph, R^3=Ph
237 R^1 = Me, R^2=H, R^3=Me
238 R^1 = H, R^2=Me, R^3=Me

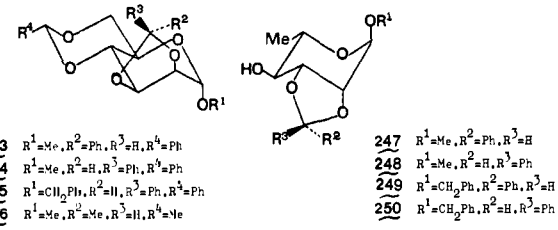
the final product. Similarly ethylidenation gave[184] the diastereomeric 2,3:4,6-diacetals **237** and **238.** Again diastereomer formation about the acetal carbon of the 4,6 ring is possible, but only a single isomer, undoubtedly corresponding to the structure with an equatorial phenyl or methyl group on the "O-inside" conformation (**235–238**), is formed. A study[183] of the benzylidenation reaction showed that there was a kinetic phase in the final stage of the reaction with the preferential formation of the *endo*-phenyl isomer **235.** At equilibrium approximately equal amounts of the diastereomers **235** and **236** were formed.

The formation of diastereomers about the acetal carbon of five-membered ring acetals cis-fused to the pyranose ring is to be expected. In agreement benzylidenation of the model compound cyclohexane-*cis*-1,2-diol gave[60,185] a nearly equimolar mixture of the diastereomers **239** and **240.** An initial kinetic



239 R^1=Ph, R^2=H
240 R^1=H, R^2=Ph
241 R^1=Me, R^2=H
242 R^1=H, R^2=Me

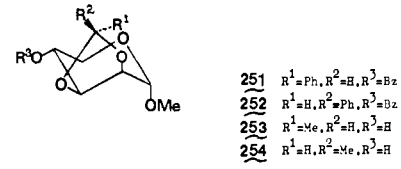
phase was observed in this reaction with the selective formation of the isomer with an *endo*-phenyl group (**239**). Other examples include the benzylidenation of methyl-α-D-mannopyranoside which gave[93,168] the diastereomeric forms of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**243** and **244**) in approximately equal amounts. Similarly benzylidenation of methyl α-L-, and benzyl-α-L-rhamnopyranoside gave[186,187] the diastereomers **247** and **248,** and **249** and **250,** respectively, in



243 R^1=Me, R^2=Ph, R^3=H, R^4=Ph
244 R^1=Me, R^2=H, R^3=Ph, R^4=Ph
245 R^1=CH_2Ph, R^2=H, R^3=Ph, R^4=Ph
246 R^1=Me, R^2=Me, R^3=H, R^4=Me

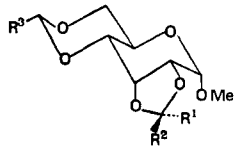
247 R^1=Me, R^2=Ph, R^3=H
248 R^1=Me, R^2=H, R^3=Ph
249 R^1=CH_2Ph, R^2=Ph, R^3=H
250 R^1=CH_2Ph, R^2=H, R^3=Ph

approximately equal amounts. The diastereomeric acetals **251** and **252** have been prepared[188] from methyl α-D-lyxopyranoside,



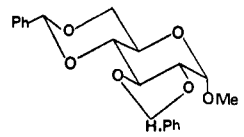
251 R^1=Ph, R^2=H, R^3=Bz
252 R^1=H, R^2=Ph, R^3=Bz
253 R^1=Me, R^2=H, R^3=H
254 R^1=H, R^2=Me, R^3=H

but no information concerning the ratio of the two isomers was given. The formation of a single isomer from the benzylidenation reaction has been reported; thus treatment of benzyl α-D-mannopyranoside gave[189,190] benzyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside with an *exo*-phenyl group (**245**) as the only diastereomer detected. This result is of interest since normally the *endo*-phenyl isomer is formed during the kinetic phase of the reaction, and so it appears that at equilibrium there is a strong preference for the isomer with an *exo*-phenyl group in this reaction. The formation of a single isomer has also been reported on treatment of methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**189**) with α,α-dichlorotoluene in pyridine, to give[191] the 2,3:4,6-diacetal. Only one isomer was isolated and, since the benzylic proton signal was at relatively low field (τ 3.68 in $CDCl_3$), it is probably the *exo*-phenyl isomer **255.** The reaction



255 R^1=H,R^2=Ph,R^3=Ph
256 R^1=Me,R^2=H,R^3=Me
257 R^1=H,R^2=Me,R^3=Me

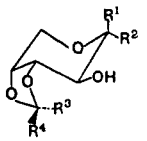
was, however, conducted under basic conditions[162,192,193] and so is probably irreversible with the formation of a kinetically controlled product. Benzylidenation of methyl 4,6-*O*-benzylidene-α-D-allopyranoside with benzaldehyde–zinc chloride did not give[191] any of the 2,3:4,6-diacetal. Benzylidenation of methyl α-D-glucopyranoside, under basic conditions,[193] resulted in acetal formation across vicinal *trans*-hydroxyl groups to give, in low yield, the diastereomeric forms of methyl 2,3:4,6-di-*O*-benzylidene-α-D-glucopyranoside (**258**) in equal amounts.



258

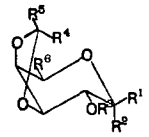
Ethylidenation, in contrast to benzylidenation, normally gives a preponderance of the isomer having an *endo*-methyl group, and thus acid-catalyzed ethylidenation of the model compound cyclohexane-*cis*-1,2-diol gave[194] the diastereomers **241** and **243** in the ratio 2:1. Similarly ethylidenation of methyl α-D-lyxopyranoside gave[194] the diastereomeric forms of methyl 2,3-*O*-ethylidene-α-D-lyxopyranoside (**253** and **254**) in the ratio ~2.5:1. Methyl 2,3:4,6-di-*O*-ethylidene-α-D-allopyranoside (**256** and **257**) has been prepared[195] in 67% yield by the reaction of methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**189**) with acetaldehyde–sulfuric acid. The major isomer, representing 90% of the mixture, was assigned the *endo*-methyl configuration **256.** By analogy with the above results the methyl 2,3:4,6-di-*O*-ethylidene-α-D-mannopyranoside, isolated by Honeyman and Morgan,[196] was probably the *endo*-methyl isomer **246.**

Benzylidenation of benzyl α- and β-D-arabinopyranoside and methyl β-D-arabinopyranoside gave equimolar amounts of the diastereomeric pairs **259** and **260,**[192] **261** and **262,**[197] and **263** and **264,**[132] respectively. In the last example it was observed[93,132] that benzylidenation using the Gerhardt method[198] resulted in the preponderant formation of the isomer with an *endo*-phenyl group (**263**). That a 1:1 mixture of isomers is an equilibrium mixture was shown[132] by the ready isomerization of **263** in chloroform-*d* containing *p*-toluenesulfonic acid to give equal amounts of both **263** and **264.** It is clear that the *endo*-phenyl isomer **263** is formed initially under kinetic control, and in agreement it was found that this isomer was also hydrolyzed at a faster rate. Thus the hydrolysis of a mixture of **263** and **264** could be followed by ^{1}H NMR spectroscopy and the *exo*-phenyl isomer **264** was isolated after the disappearance of the benzylic proton signal corresponding to **263.**



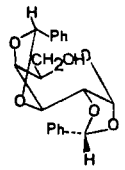
259 R^1=H,R^2=OCH_2Ph,R^3=Ph,R^4=H
260 R^1=H,R^2=OCH_2Ph,R^3=H,R^4=Ph
261 R^1=OCH_2Ph,R^2=H,R^3=Ph,R^4=H
262 R^1=OCH_2Ph,R^2=H,R^3=H,R^4=Ph
263 R^1=OMe,R^2=H,R^3=Ph,R^4=H
264 R^1=OMe,R^2=H,R^3=H,R^4=Ph

The 3,4-*O*-benzylidene derivatives of various substituted galactopyranosides and fucopyranosides have been prepared. Thus Baggett et al.[162] have prepared methyl 3,4-*O*-benzylidene-2,6-di-*O*-methyl-α-D-galactopyranoside (**265** and **266**) and,



265 R^1=H,R^2=OMe,R^3=Me,R^4=Ph,R^5=H,R^6=CH_2OMe
266 R^1=H,R^2=OMe,R^3=Me,R^4=H,R^5=Ph,R^6=CH_2OMe
267 R^1=OCH_2Ph,R^2=H,R^3=CH_2Ph,R^4=Ph,R^5=H,R^6=CH_2OCH_2Ph
268 R^1=OCH_2Ph,R^2=H,R^3=CH_2Ph,R^4=H,R^5=Ph,R^6=CH_2OCH_2Ph
269 R^1=OPh,R^2=H,R^3=CH_2Ph,R^4=Ph,R^5=H,R^6=CH_3
270 R^1=OPh,R^2=H,R^3=CH_2Ph,R^4=H,R^5=Ph,R^6=CH_3
271 R^1=H,R^2=OMe,R^3=H, R^4=Me,R^5=H,R^6=H
272 R^1=H,R^2=OMe,R^3=H, R^4=H,R^5=Me,R^6=H
273 R^1=H,R^2=OMe,R^3=Me,R^4=Me,R^5=H,R^6=H
274 R^1=OMe,R^2=H,R^3=CH_2Ph,R^4=Me,R^5=H,R^6=CH_2OCH_2Ph
275 R^1=OMe,R^2=H,R^3=CH_2Ph,R^4=H,R^5=Me,R^6=CH_2OCH_2Ph

under conditions of homogeneous acid catalysis, kinetic control was operative initially, with the preferential formation of the *endo*-phenyl isomer **265.** Equimolar amounts of **265** and **266** were formed at equilibrium. Liptak[199] has reported the diastereomeric forms of benzyl 2,6-di-*O*-benzyl-3,4-*O*-benzylidene-β-D-galactopyranoside (**267** and **268**) and phenyl 2-*O*-benzyl-3,4-*O*-benzylidene-β-D-fucopyranoside (**269** and **270**), but no information as to the composition (ratio of isomers) of the reaction mixtures was given. The benzylidenation of D-galactose itself gave a low yield of 1,2:3,4-di-*O*-benzylidene-α-D-galactopyranose which was shown[93] to be the isomer having both phenyl groups endo (**276**). Also of interest is the report by Boivin et al.[200] who isolated the *exo*-phenyl isomer **277** from the benzylidenation of methyl 2-deoxy-β-L-fucopyranoside and the



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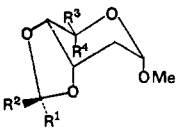
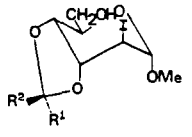
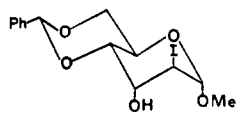


277 R^1=H,R^2=Ph,R^3=H,R^4=Me
278 R^1=Ph,R^2=H,R^3=Me,R^4=H

endo-phenyl isomer **278** from the benzylidenation of methyl α-D-digitoxopyranoside. A difference in the thermodynamic stability of benzylidene diastereomers has been demonstrated[201] for methyl 3,4-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside. Thus the *endo*-phenyl isomer **279** rearranged, when stored in benzene containing *p*-toluenesulfonic acid at room temperature, to give the *exo*-phenyl isomer **280** and methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**281**).

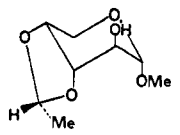


279 R^1 = Ph,R^2 = H
280 R^1 = H,R^2 = Ph



281

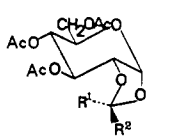
The above results may again be compared with the results of ethylidenation. Thus treatment of methyl β-L-arabinopyranoside with paraldehyde and *p*-toluenesulfonic acid gave[194] a mixture of acetals of which the isomer with an *endo*-methyl group **271** constituted 80–90%. That the acetal mixture had equilibrated under the reaction conditions was confirmed by treating each isomer separately with *p*-toluenesulfonic acid in chloroform. The *endo*-methyl isomer **271** was the major product in each case and was isolated in 70% yield after acid treatment of the *exo*-methyl isomer **272.** Similar ethylidenations of methyl 2-*O*-methyl-β-L-arabinopyranoside and methyl α-D-arabinopyranoside gave the *endo*-methyl isomers **273** and **282,** respectively, as the preponderant products. Ethylidenation of methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside, with excess 1,1-dimethoxyethane and a catalytic amount of sulfuric acid, gave[202]

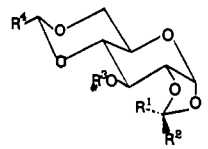


282

the diastereomers **274** and **275** with the *endo*-methyl isomer **274** predominating. The structure of **274** was confirmed by X-ray crystallography.

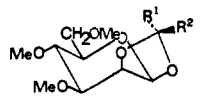
An extensive study[203] on the configuration in diastereomeric 1,2-*O*- and 1,2:4,6-di-*O*-alkylidene-α-D-glucopyranose derivatives, prepared by reduction of intermediate dioxolenium chloride ions with sodium borohydride, by ^{1}H NMR spectroscopy has shown that the 3,4,6-tri-*O*-acetyl-1,2-benzylidene-α-D-glucopyranose obtained by previous workers[169,204] has the *exo*-phenyl configuration **284** and not the *endo*-phenyl configuration **283** as reported by Lemieux and Detert.[205] It was further suggested that the 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose obtained by Wood et al.[169] and Coxon,[206] also had the *exo*-phenyl configuration **288.** That the crystalline diastereomer **284** was not the





283 R^1=Ph, R^2=H
284 R^1=H, R^2=Ph
285 R^1=CH_3, R^2=OC_2H_5
288 R^1=H, R^2=Ph, R^3=H, R^4=Ph
289 R^1=Me, R^2=H, R^3=Ac, R^4=Me
286 R^1=H, R^2=Me, R^3=Ac, R^4=Me
287 R^1=H, R^2=CH_3

thermodynamically more stable isomer was shown[206] by treatment of this compound with equilibrating reagents. The resulting mixture contained a major proportion (74%) of a second diastereomer which must correspond to the *endo*-phenyl isomer **283.** A similar mixture has recently been prepared[205] by reaction of tri-*O*-acetyl-1,2-*O*-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (**285**), in the presence of *p*-toluenesulfonic acid, with benzaldehyde. Dick et al.[203] also prepared the diastereomeric forms of 3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene-α-D-glucopyranose (**286** and **287**) and 3-*O*-acetyl-1,2:4,6-di-*O*-ethylidene-α-D-glucopyranose (**289** and **290**) by reduction of intermediate dioxolenium chloride ions with sodium borohydride. In the solvents 1,2-dimethoxyethane and pyridine the *endo*-methyl isomers **286** and **289** were clearly predominant, but in *N,N*-dimethylformamide each isomer was formed in nearly equal amounts. Since the above compounds were not prepared under equilibrating conditions, it is not possible to say which isomer is the more stable. However, in line with previous results it is expected that the *endo*-methyl isomer, in each case, should be the major isomer present at equilibrium. In agreement the hydrogenolysis of either 1,2-(1-*exo*-methoxyethylidene)-3,4,6-tri-*O*-methyl-β-D-mannopyranose (**292**) or a diastereomeric mixture (**291** and **292**) gave[207] 1,2-*O*-ethylidene-3,4,6-tri-*O*-

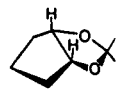


291 R^1=OMe, R^2=Me
292 R^1=Me, R^2=OMe
293 R^1=Me, R^2=H
294 R^1=H, R^2=Me

methyl-β-D-mannopyranose (**293**) with an *endo*-methyl group. Equilibration of **293** with $CDCl_3$–HCl gave a mixture of **293** and **294** in the ratio 4:1.

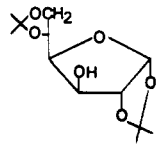
VII. Cyclic Ketals Derived from Cyclic Sugar Derivatives

Cyclopentane-*cis*-1,2-diol forms[208] an *O*-isopropylidene derivative (**295**) readily in contrast to the trans isomer which does



295

not form this ketal. The difference may be explained by the considerable strain that would be introduced on formation of an *O*-isopropylidene derivative from the trans Isomer. Examples of *O*-isopropylidene rings cis-fused to the furanoid ring occur in the 1,2:5,6-di-*O*-isopropylidene derivatives of D-glucose,[154,209] D-idose,[210] D-galactose,[211] and D-altrose,[212] and the 2,3:5,6-di-*O*-isopropylidene derivatives of D-mannose,[213-215] D-allose,[216,217] D-talose,[218] and D-gulose.[219] The first group of four sugars have a trans arrangement of the hydroxyl groups on C_2 and C_3 and thus only the 1,2:5,6-diketal is formed (e.g., 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, **296**). The second group of four sugars have a cis arrangement of these hydroxyl groups, and therefore a mixture of the 2,3:5,6- and 1,2:5,6-diketals might be expected. This is found to be the case in practice although, in all examples, the 2,3:5,6 isomer predominates (e.g., 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose, **297**). D-Ribose[220,221] and D-lyxose,[222] with a cis arrangement of the hydroxyl groups on C_2 and C_3, form a 2,3-*O*-isopropylidene furanoid derivative (e.g., 2,3-*O*-isopropylidene-D-ribofuranose, **298**) while



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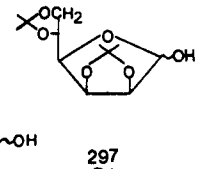

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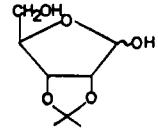
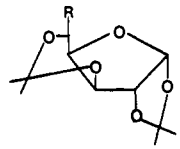


298

D-xylose and D-arabinose, with a trans arrangement of these hydroxyl groups, give 1,2-*O*-isopropylidene derivatives. The latter two sugars are able to accommodate a second isopropylidene group, and D-xylose gives the furanoid derivative, 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**299**),[223-225] while L-

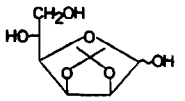


299 R = H
300 R = CH_2X

arabinose gives the pyranoid derivative, 1,2:3,4-di-*O*-isopropylidene-β-L-arabinopyranose (**304**).[228,227] In the former we have the formation of a six-membered *O*-isopropylidene ketal with an axial methyl group. The formation of such a ring is unfavorable, and thus, in contrast to acetalation (section VI), isopropylidenation of the free hexoses gives 5,6-*O*-isopropylidene furanoid derivatives rather than the alternative 4,6-pyranoid compounds. Six-membered *O*-isopropylidene rings are formed, however, if there is no alternative, and consequently 1,2:3,5-di-*O*-isopropylidene derivatives (**300**)[228,229] are obtained from D-glucose if position 6 is masked.

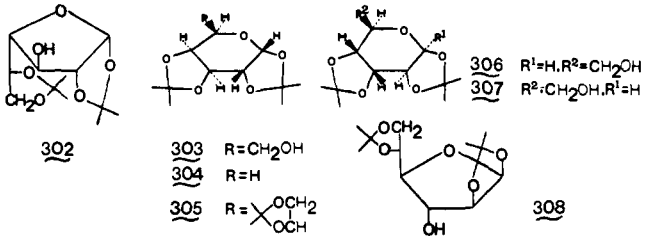
Partial hydrolysis of the diketal of D-glucose (**296**),[215] D-mannose (**297**),[215] and D-xylose (**299**)[223,225] results in formation of the monoketal having a bicyclic system of two five-membered

rings; e.g., 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**297**) gives 2,3-*O*-isopropylidene D-mannofuranose (**301**). This system



301

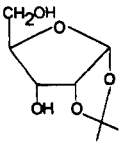
of two fused five-membered rings is evidently favored and further examples of this preference may be seen in section VIII. However, 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**302**) is only formed[211] in low yield, the major product being the 1,2:3,4-diketal **303**, and L-arabinose readily forms 1,2:3,4-di-*O*-isopropylidene-β-L-arabinopyranose (**304**).[226,227] The other hexose, with a cis arrangement of hydroxyl groups on C_3 and C_4 trans to the hydroxyl on C_2, D-altrose, gave[230] 1,2:3,4-di-*O*-isopropylidene-β-D-altropyranose (**306**), isolated in 17% yield, and the 1,2:5,6-diketal **308**, isolated in 23% yield. The pyranoid



302 **303** R=CH_2OH; **304** R=H; **305** R= **306** R^1=H,R^2=CH_2OH; **307** R^2=CH_2OH,R^1=H; **308**

ring of D-fructose also has this arrangement, and 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**307**) is formed at equilibrium.[231] Similarly isopropylidenation of D-*glycero*-D-*galacto*-heptose, under conditions of thermodynamic control, yielded[232] the 1,2:3,4:6,7-tri-*O*-isopropylidene pyranoid derivative **305.** The ketals **303–307** have a cis-anti-cis arrangement of rings, and it is clear that this is a particularly stable steric arrangement which may be formed in preference to the system of cis-fused five-membered rings. Coupling constant data from ^{1}H NMR spectroscopy indicate[232,233] that **303–305** exist as twist-boat conformers, and it is probable that **306** and **307** also have this conformation.

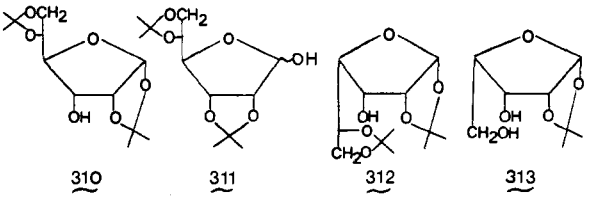
Isopropylidenation of D-ribose gave[234] 2,3-*O*-isopropylidene-D-ribofuranose (**298**) in 59% yield, and the alternative 1,2-*O*-isopropylidene-α-D-ribofuranose (**309**) in only 6% yield.



309

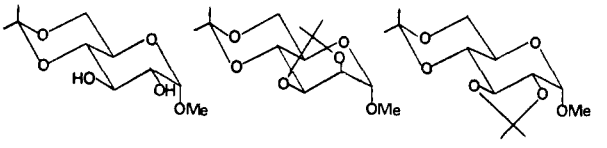
The preference for the 2,3-ketal may be due, in part, to the presence of two endo substituents (a methyl group and the hydroxyl group at C_3) in the 1,2-ketal. In the β form the 2,3-ketal has only one endo substituent, a methyl group.[235]

Similar arguments would explain the observed preference for the formation of the 2,3:5,6-diketals of D-mannose, D-allose, D-talose, and D-gulose, and the 2,3-ketal of D-lyxose. A number of branch chain sugars have also been found to give a 2,3-*O*-isopropylidene derivative in preference to the 1,2 isomer.[238,237] That the 2,3-ketal is more stable than the 1,2 form is clearly demonstrated by the facile rearrangement[216] of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**310**) in acidified acetone to give 2,3:5,6-di-*O*-isopropylidene-D-allofuranose (**311**). Also significant is the sensitivity to acid of the 1,2-*O*-isopropylidene groups of 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**312**) and 1,2-*O*-isopropylidene-β-L-lyxofuranose (**313**).[238] Cyclo-



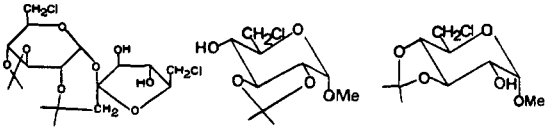
310 **311** **312** **313**

hexane-*cis*-1,2-diol is known[49] to form an *O*-isopropylidene derivative more readily than cyclohexane-*trans*-1,2-diol, which requires forcing conditions to bring about formation of its cyclic ketal. In agreement with this, the formation of cyclic ketals from cis-vicinal hydroxyl groups on a pyranose ring is found to be much easier than formation from *trans*-hydroxyl groups. Thus isopropylidenation of methyl α-D-glucopyranoside, using anhydrous zinc chloride as the catalyst and boiling the reaction overnight, gave[240] a low yield of the 4,6-*O*-isopropylidene derivative **314** and no diketal. In contrast isopropylidenation of methyl α-D-mannopyranoside readily gave[241] the 2,3:4,6-di-*O*-isopropylidene derivative **315.**



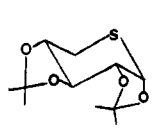
314 **315** **316**

More recently the use of either 2,2-dimethoxypropane[242] or ethyl isopropenyl ether[243] has allowed the production of cyclic ketals formed under kinetic control. Thus treatment of methyl α-D-glucopyranoside with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in *N,N*-dimethylformamide gave[242] **314** in 70% yield. Also isolated in 18% yield was methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranoside (**316**) with a 2,3-ketal bridging vicinal *trans*-hydroxyl groups on the pyranose ring. The rigid *trans*-decalin system is apparently responsible for the special difficulty experienced in forming **316** since isopropylidenation of 6,6′-dichloro-6,6′-dideoxysucrose, with the 2,2-dimethoxypropane reagent, gave[244] the 3,4:1′,2-diketal **317** in 39% yield. Similarly, isopropylidenation of 6-chloro-6-deoxy-α-D-glucopyranoside gave a mixture of the 2,3-ketal **318** (28%) and 3,4-ketal **319** (9%). Treatment of 5-thio-D-xylose with the above



317 **318** **319**

reagent, after treatment with acidified acetone had failed, gave[245] a good yield of 1,2:3,4-di-*O*-isopropylidene-5-thio-α-D-xylopyranose (**320**). The product contained a cyclic ketal derived from a trans diol and demonstrated the exceedingly strong preference for the forms with the sulfur in the sugar ring since a similar reaction with D-xylose gave the known 1,2:3,5-diketal **299.** Recently, a further example of the formation of a cyclic ketal from a trans diol and having sulfur in the pyranoid ring has been reported by this group.[246] Thus a brief treatment of 5-thio-α-D-glucose, with acetone containing 2,2-dimethoxypropane, gave 2,3:4,6-di-*O*-isopropylidene-5-thio-α-D-glucopyranose (**321**), with a trans-fused ring junction, and none of the cis-fused isomer **322.** The diketal **321** was evidently formed under kinetic control since isopropylidenation of 5-thio-D-glucose in the presence of acid or treatment of **321** with acidified acetone gave the thermodynamically controlled isomer, the 1,2:5,6-diketal **323.**



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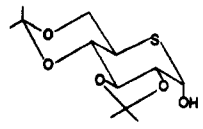

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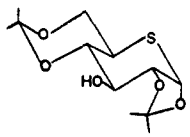

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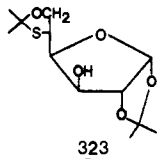

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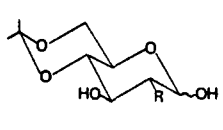
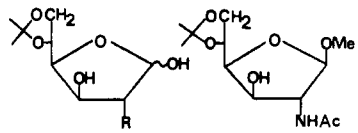
The isopropylidenation of D-glucose with the 2,2-dimethoxypropane reagent has been studied in detail by Kiso and Hasegawa.[247] At room temperature 4,6-*O*-isopropylidene-D-glucose (**324**) was formed in high yield while at 95 °C (30 min) 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**296**) and an acyclic di-*O*-isopropylidene derivative were formed. At shorter reaction time (10 min) the most prominent component was 5,6-*O*-isopropylidene-D-glucose (**326**). These results were explained[247]



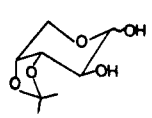
324 R = OH
325 R = NHAc



326 R = OH
327 R = NHAc

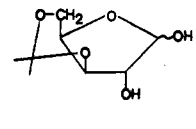
328

in terms of kinetic control with favored attack at the primary hydroxy group on C_6 to form either the 4,6- or 5,6-*O*-isopropylidene derivative as the initial step. The ratio of products was considered to reflect the pyranose–furanose equilibrium in which D-glucose exists in the pyranose forms at room temperature, but in the furanose and acyclic forms at 95 °C[248,249] and in the solvent *N,N*-dimethylformamide.[250,251] Similar results were obtained[252] on the isopropylidenation of 2-acetamido-2-deoxy-D-glucose except that the major product, after 15 min at 80–85 °C, was the 4,6-*O*-benzylidene derivative **325.** At longer reaction times (1 h) glycoside formation occurred and methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranoside (**328**) was the major product. It was suggested that, since large amounts of the 4,6-*O*-isopropylidene derivative **325** were present during the early stages of the reaction at 80–85 °C, isomerization of **325** to the 5,6-*O*-isopropylidene derivative **327** must also occur. Kiso and Hasegawa[253] have also studied the isopropylidenation of some pentoses with this reagent. Isopropylidenation of D-ribose at room temperature gave 2,3-*O*-isopropylidene-D-ribofuranose (**298**), the product of thermodynamic control, in 91% yield, and isopropylidenation of D-arabinose at 20 °C gave the 3,4-*O*-isopropylidene derivative **329** in 85%



329

yield. The latter is the product of kinetic control, and the thermodynamic product, the 1,2:3,4-diketal (**304,** L form), was obtained in 88% yield when the reaction temperature was raised to 80 °C. Initial attack at the primary hydroxyl group of D-xylose in its furanose form resulted in a disturbance of the pyranose–furanose equilibrium and the formation of 3,5-*O*-isopropylidene derivative **330** (32% yield), the product of kinetic control. This compound subsequently reacted to give the 1,2:3,5-diketal **299** isolated in 16% yield. 1,2-*O*-Isopropylidene-α-D-xylopyranose (**331,** 16%) was also isolated, and this was evidently formed by attack of the reagent on a secondary hydroxyl group of D-xylose in the pyranose form.



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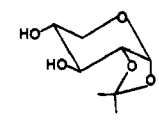
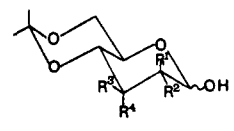
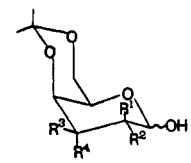


331

Treatment of D-glucose with ethyl isopropenyl ether in *N,N*-dimethylformamide, containing a trace of *p*-toluenesulfonic acid, gave[243] 4,6-*O*-isopropylidene-D-glucopyranose (**324**) in near-quantitative yield. Again **324** is the product of kinetic control and treatment of **324** with anhydrous acetone containing concentrated sulfuric acid gave a high yield of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**296**), the thermodynamic product of isopropylidenation with excess reagent. In the above reaction it is reasonable to assume that the 4,6-acetal rearranged directly to give the 5,6-acetal, although hydrolysis and re-formation is a possibility. The generality of this reaction was affirmed by a recent investigation[239] which showed that D-galactose, D-allose, and D-talose may be converted to their 4,6-*O*-isopropylidene derivatives **334, 332,** and **334a,** respectively, in high yield. Copeland and Stick[254] have also studied this reaction and have shown that treatment of D-mannose and D-gulose, with isopropenyl methyl ether, gave the respective 4,6-*O*-isopropylidene

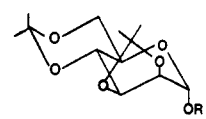


332 R^1=H, R^2=OH, R^3=H, R^4=OH
333 R^1=OH, R^2=H, R^3=OH, R^4=H

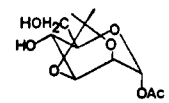


334 R^1=H, R^2=OH, R^3=OH, R^4=H
334a R^1=OH, R^2=H, R^3=OH, R^4=H
334b R^1=H, R^2=OH, R^3=H, R^4=OH

derivatives **333** and **334b.** In compounds **334–334b** the cyclic ketal is contained in a *cis*-decalin type of structure. Gelas and Horton[255] have examined the reaction of D-mannose with this reagent in some detail and with excess they prepared 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranose (**335**), via its 1-*O*-acetate **336.** Partial acid hydrolysis of **336** gave 1-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannopyranose (**337**). The results

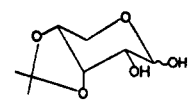


335 R = H
336 R = Ac



337

obtained for D-mannose above were in contrast to the results[256] of isopropylidenation of D-mannose with the 2,2-dimethoxypropane reagent which gave the thermodynamic product, the 2,3:5,6-diketal **297.** Gelas and Horton[257] have also extended this reaction to the pentoses, D-ribose and D-arabinose, and isolated the product of kinetic control, namely, the 3,4-*O*-isopropylidene

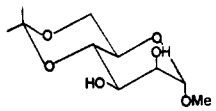


338

derivatives **338** and **329,** respectively, in yields of 40–50 and 60–70%. The result with D-ribose again contrasts with the observation of Kiso and Hasegawa[253] who obtained the product of thermodynamic control, 2,3-*O*-isopropylidene-D-ribofuranose (**298**), on reacting D-ribose with the 2,2-dimethoxypropane reagent.

Similar results were obtained on the isopropylidenation of

glycosides. Thus treatment of methyl α-D-glucopyranoside with the ethyl isopropenyl reagent[243] resulted in formation of the 4,6-*O*-isopropylidene derivative **314,** recovered in 82% yield, and the reaction of isopropenyl methyl ether with methyl α-D-mannopyranoside gave the corresponding derivative **339** in 91% yield.



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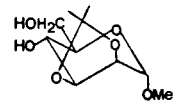
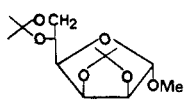


340

Monomolar isopropylidenation of methyl α-D-mannopyranoside with the 2,2-dimethoxypropane reagent also resulted[258] in kinetic control, and formation of the 4,6-monoketal **339.** If concentrated sulfuric acid was employed as the catalyst, in the above reaction, then thermodynamic control operated and the 2,3-monoketal **340** was the major product. A more satisfactory preparation of **340** involved partial acid hydrolysis of the 2,3:4,6-diketal **315,** the major product of the reaction using excess reagent.[241]

If methanol is added to the 2,2-dimethoxypropane reaction, then isopropylidene glycosides may be formed directly from the free sugar. Thus treatment of D-mannose with this reagent gave[259] methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (**341**). A similar treatment of D-allose gave[260] the corresponding 2,3:5,6-derivative **342.** Apparently glycoside formation occurs after ketal formation as these sugars give pyranosides on glycosidation.



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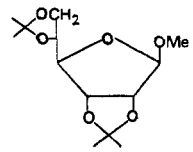
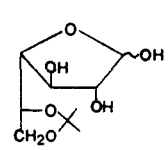


342

A measure of kinetic control has been achieved with other reagents, in particular, either anhydrous cupric sulfate or anhydrous zinc chloride. Thus 3,4-*O*-isopropylidene-D-ribose (**338**) was obtained[261] in 17% yield (compared to the 40–50% yield of Horton and Gelas[257] above) using anhydrous cupric sulfate in the absence of acid. Similarly 3,4-*O*-isopropylidene-L-arabinose (**329,** D form) may be prepared[262,263] using this reagent. Isopropylidenation of D-galactose under acidic conditions resulted[264] in the formation of the 1,2:3,4-diketal **303** and gas–liquid chromatography showed that less than 3% of the 1,2:5,6-diketal **302** was present in the product. If anhydrous cupric sulfate is used, however, and the reaction is heated on a steam bath, then **302** forms[211] 20% of the diketal mixture. Even better yields, approximately 54% of the mixture of diketals, were achieved when the D-galactose was dissolved in hot *N,N*-dimethylformamide prior to the reaction.[265] The increase in yield of the 1,2:5,6-diketal **302** was explained in terms of the higher proportion of furanose forms present when a reducing sugar is dissolved in *N,N*-dimethylformamide[250,251] at high temperature.[248,249] A further report by this author[266] described the formation of monoketals during the early part of this reaction and, as expected, reaction at the primary hydroxyl group of D-galactose, in either the pyranose or the furanose form, resulted in formation of either the 4,6-monoketal **334,** or the 5,6-monoketal **343.** 3,4-*O*-Isopropylidene-D-galactopyranose (**344**) was also formed and may arise either by attack at a secondary hydroxyl group, on either C_3 or C_4, or by rearrangement of the 4,6-monoketal **334.**

The use of anhydrous zinc chloride may also result in the formation of kinetic products. A classic example is the isopropylidenation of D-fructose where either 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**345**) or 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**307**) may be isolated depending on the conditions. Recently this reaction has been reinvestigated,[267] and it was shown that condensation of D-fructose with acetone, using sulfuric acid as the catalyst, resulted in initial formation of **345** and that **345** subsequently rearranged to give **307** at a rate dependent on the acid concentration. It was pointed out that **345** was the product of kinetic control and was formed as a result of the higher reactivity of the primary hydroxyl group on C_1. The diketal **307** was greatly preponderant at equilibrium and is thus the thermodynamically more stable isomer. In agreement it was found that a solution of **345** in acetone containing 5% sulfuric acid rearranged to give an equilibrium mixture consisting of 94% of **307** and 6% of **345.** Catalysis of the reaction by anhydrous zinc chloride resulted in the preponderant formation of **345** which did not appear to rearrange to **307** under the reaction conditions. Another example involves the isopropylidenation of L-dendroketose which gave[268] 1,2:3,4-di-*O*-isopropylidene-L-dendroketose (**346**) and 2,3:4,4′-di-*O*-isopropylidene-L-dendroketose (**347**) in the ratio of 14:9, whether concentrated sulfuric acid or H^+ resin was used as the catalyst. Apparently **346** with a ketal group cis-fused to the hydroxyl groups on C_2 and C_3 of the furanose ring is the thermodynamically more stable isomer. Catalysis of the reaction with anhydrous zinc chloride resulted in formation of **346** and **347** in the ratio 1:6 with the less stable isomer predominating greatly. Treatment of methyl α-D-altropyranoside with acetone and anhydrous zinc chloride gave[269] methyl 4,6-*O*-isopropylidene-α-D-altropyranoside (**348**) in 10% yield and methyl 3,4-*O*-isopropylidene-α-D-altropyranoside (**349,** 38%). That **348** was the product of kinetic control was confirmed by the observation that catalysis of the reaction with concentrated sulfuric acid gave only **349.** In agreement with these results **348** readily rearranged[270] to give an almost quantitative yield of the thermodynamically more stable ketal **349,** on treatment with acid. Similarly, isopropylidenation of methyl



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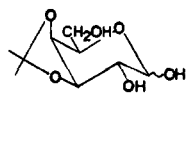

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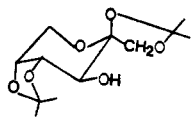

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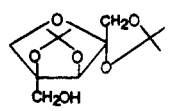

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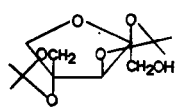

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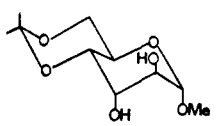

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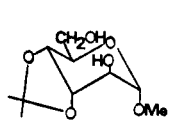

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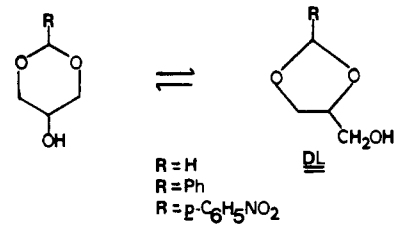
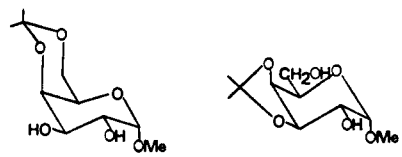


Figure 2. Interconversion of the cyclic acetals of glycerol in the presence of hydrogen chloride.

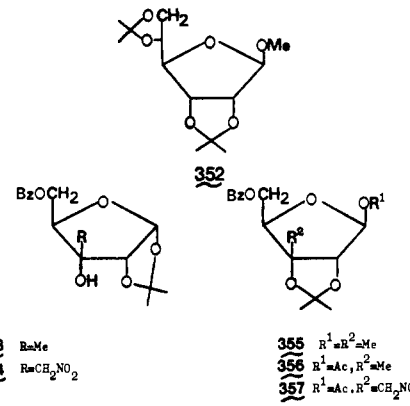
α-D-galactopyranoside with anhydrous zinc chloride as catalyst gave[269] the 4,6- and 3,4-ketals (**350** and **351,** respectively) in equal amounts whereas isopropylidenation with concentrated sulfuric acid as the catalyst gave **350** and **351** in the ratio 1:3.



350 351

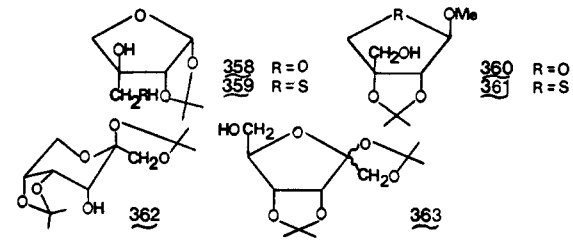
VIII. Acetal Migration

Acetal migration is a well-established phenomenon. One of the earliest examples was observed by Hibbert and co-workers[114-116] who found that the isomeric methylidene, benzylidene, and *p*-nitrobenzylidene cyclic acetals of glycerol were readily interconverted in the presence of hydrogen chloride (Figure 2). Acetal migration has more recently been studied[113,61] by following the change in the signal pattern in the benzylic proton region of the ^{1}H NMR spectrum. Other examples include the observation made by Williams[271] that methyl 2,3-*O*-isopropylidene-β-D-allofuranoside (**352**) and methyl 2,3:5,6-di-*O*-isopro-

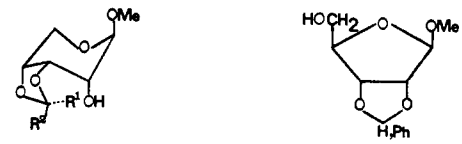


pylidene-β-D-allofuranoside (**342**) were two of the products obtained during the acid-catalyzed methanolysis of 1,2:5,6-di-*O*-isopropylidene-β-D-allofuranose (**310**). Similarly Ballard and Stacey,[216] and Haga et al.[217] showed that treatment of **310,** with acidic acetone, resulted in the formation, in good yield, of the 2,3:5,6-di-*O*-isopropylidene derivative **311.** Closely related to the above is the rearrangement of 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**353**) to the 2,3-*O*-isopropylidene derivative **355** in acidic methanol solution.[272] The rearrangement of **353** and **354** to give **356** and **357,** respectively, under acetolysis conditions has also been reported.[273]

Examples of the opening of the sugar ring accompanying acetal migration are known. Thus 1,2-*O*-isopropylidene-α-D-apio-L-furanose (**358**) and its 5-thio analogue **359** rearranged, in the presence of anhydrous methanolic hydrogen chloride, to give the respective methyl 2,3-*O*-isopropylidene-β-D-apio-D-furanoside derivatives **360** and **361.**[274,275] Treatment of 1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**362**) with



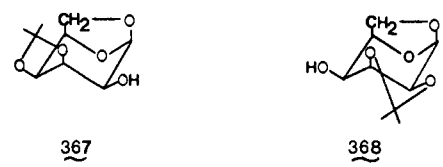
acidic acetone resulted in migration of the 4,5-ketal to the 3,4 position and ring opening to give 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose (**363**).[276] The acid-catalyzed isomerization of **362** to **363** has recently[277] been monitored by ^{1}H NMR spectroscopy, using acetone-d_6 as the medium, and it was found that the methyl signals, corresponding to the 1,2- and 4,5-ketal substituents, disappeared in time. This suggested that the rearrangement was not intramolecular but, rather, continuous exchange with acetone molecules in the medium. Similarly Clode[175] has shown that treatment of either methyl 3,4-*O*-(*R*)- or methyl 3,4-*O*-(*S*)-benzylidene-β-D-ribopyranoside (**364** and **365,** respectively), with acidified chloroform, resulted in mi-



364 R1=Ph, R2=H
365 R1=H, R2=Ph
366

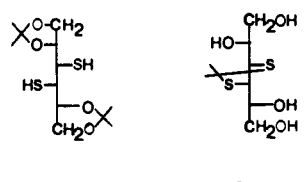
gration of the 3,4-*O*-benzylidene group to the 2,3 position, followed by ring contraction, to give diastereomeric forms of methyl 2,3-*O*-benzylidene-β-D-ribofuranoside (**366**). In this case, however, since the solvent was chloroform, the rearrangement was undoubtedly intramolecular. Benzylidenation of methyl β-D-ribopyranoside was reported[278] to give syrupy **366,** and the above results suggest that the ring contraction took place after condensation with benzaldehyde.

Acetal migration accompanying acid hydrolysis is also known. Thus 1,6-anhydro-2,3-*O*-isopropylidene-β-D-talopyranose (**368**) was formed as an intermediate in the hydrolysis, in aqueous acetic acid, of the 3,4-*O*-isopropylidene derivative **367.**[278]



367 368

Similarly, acid hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3,4-dithio-D-iditol (**369**), with trifluoroacetic acid and water, gave[280] 3,4-*S*-isopropylidene-3,4-dithio-D-iditol (**370**). However, in this

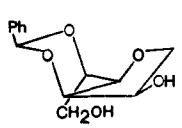


369 370

particular example, the authors showed that the O → S alkylidene migration is due primarily to external return of the hydrolytically liberated acetone.

The formation of a single diastereomer during the kinetic phase of the acetal migration reaction has also been observed.

Thus treatment[61] of 1,4-anhydro-3,5-*O*-benzylidene-D-mannitol, expected to have the "O-inside" structure **371**, with *N,N*-dimethylformamide containing *p*-toluenesulfonic acid, resulted in rearrangement to give the 2,3-acetal having an *endo*-phenyl group (**372**). Prolonged treatment with acid resulted in equili-



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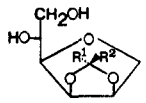
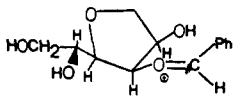


372 R^1 = Ph, R^2 = H
373 R^1 = H, R^2 = Ph

bration of 2,3-*O*-benzylidene group and the formation of the *exo*-phenyl isomer **373**. The formation of the *endo*-phenyl isomer **372** during the kinetic phase of the reaction may be explained by a consideration of the reaction mechanism. The acetal migration reaction will involve the same intermediates as the formation reaction, and thus the energetically favored transition state will resemble the oxocarbonium ion in the preferred anti-transoid conformation (see section III). For **371** protonation of O_5 and ring opening leads to the intermediate oxocarbonium ion **374**, having an anti-transoid conformation, and rapid ring closure by the hydroxyl group on C_2 will give the *endo*-phenyl isomer **372**. Either an anti-cisoid or a syn-transoid conformation, **375** and **376**, respectively, of the intermediate oxocarbonium ion is



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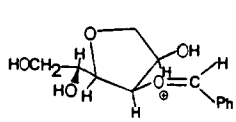

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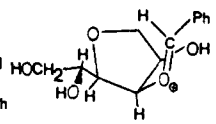
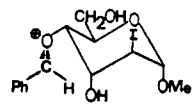


376

required for formation of the *exo*-phenyl isomer **373**. These ions will resemble energetically unfavored forms of the transition state, and thus reaction via these ions will be slower than reaction via the anti-transoid ion **374**.

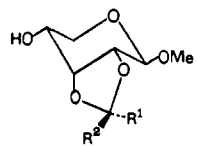
Another example is the facile, acid-catalyzed, migration of methyl 4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**281**) to give[201] methyl 3,4-*O*-(*R*)-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (**279**). That **279** was the kinetic product was demonstrated by the rearrangement of **279** into the thermodynamically more stable *S* isomer **280**. Again the anti-transoid conformer **377**, formed by protonation of O_6 and ring opening,



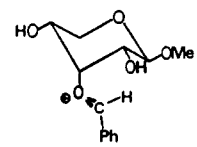
377

should be the most stable conformation of the intermediate oxocarbonium ion. Structure **377** may be assumed to resemble the rate-limiting transition state, and ring closure by the hydroxyl group on C_3 will give the *endo*-phenyl isomer **279**. Again the formation of the *exo*-phenyl isomer **280** may only occur via the less stable anti-cisoid or syn-transoid conformers of the oxocarbonium ion intermediate.

A kinetic phase was also observed on the acid-catalyzed (acidified chloroform) rearrangement of methyl 3,4-*O*-(*R*)-benzylidene-β-D-ribopyranoside (**364**) with the selective formation of methyl 2,3-*O*-(*R*)-benzylidene-β-D-ribopyranoside (**378**).[175] At longer reaction times equilibration took place with the formation of the 3,4-(*S*) and 2,3-(*S*) isomers, **365** and **379**, respectively, in addition to the *R* isomers **364** and **378**. With higher acid concentrations ring contraction occurred and the final product of the rearrangement was **366**. This result is in agreement with cyclization via the preferred anti-transoid conformer **380** of the intermediate oxocarbonium ion, formed by protonation



378 R^1 = Ph, R^2 = H
379 R^1 = H, R^2 = Ph



380

at C_4 and ring opening. Formation of either **365** or **379** requires the cyclization to proceed via the less stable anti-cisoid or syn-transoid conformers of the oxocarbonium ion intermediate. No kinetic phase was observed[175] on rearrangement of the *S* isomer **365** with simultaneous appearance of the isomers **364, 378,** and **379**. The formation of these isomers was also found to be slower than the formation of **378** from the corresponding reaction with the *R* isomer **364**. This result may be rationalized as follows. Ring opening, by protonation at either O_3 or at O_4, would lead to the slow formation of intermediate oxocarbonium ions with either the unfavored anti-cisoid or syn-transoid conformation. Once formed the oxocarbonium ions will rapidly rearrange to the more stable anti-transoid conformers which will lead to the simultaneous formation of **364** and **378**. The *S* isomer **379** may be formed by cyclization of the oxocarbonium ion, either anti-cisoid or syn-transoid conformer, formed by protonation at O_4 and ring opening.

Finally, as described earlier (section VI), treatment of 2,4-*O*-benzylidene-D-erythrose (**225**) with *p*-toluenesulfonic acid in *N,N*-dimethylformamide resulted in stereospecific rearrangement to give[113] 2,3-*O*-benzylidene-β-D-erythrofuranose with an *endo*-phenyl group (**228**). It is probable that this product was the result of kinetic control, and the formation of the *exo*-phenyl isomer might be expected on prolonged exposure to acid. Again the selective formation of **228** may be explained by the above mechanistical considerations.

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IX. References and Notes

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