ACETONATION OF CARBOHYDRATES UNDER KINETIC CONTROL BY USE OF 2-ALKOXYPROPENES

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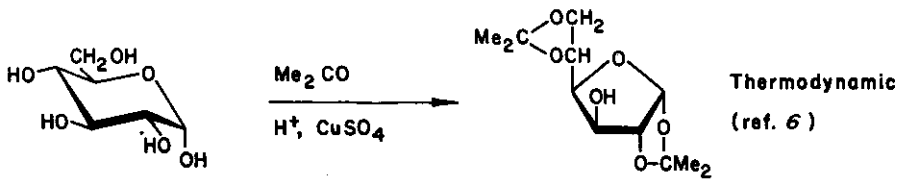
Abstract — Polyols, as exemplified by the sugars and their derivatives, undergo acetonation by 2-alkoxypropenes to give cyclic acetals under kinetic control. The products generally differ from those of conventional thermodynamic acetonation and constitute chirally substituted 1,3-dioxanes, 1,3-dioxolanes, and larger heterocycles, of wide potential utility in synthesis. Free sugars react without tautomerization, and the hemiacetal hydroxyl group does not generally take part in the reaction. The stoichiometry may be controlled to give either mono- or di-acetals, and strained-ring acetals.

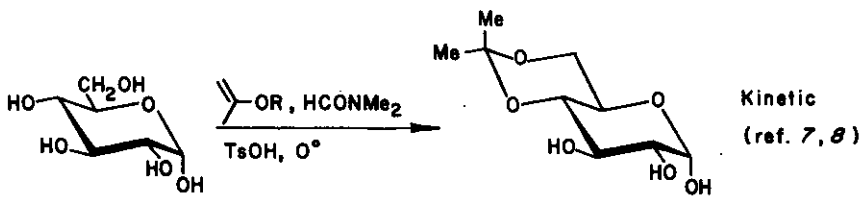
O-Isopropylidenation (acetonation) of selected diol groups in carbohydrates by use of acetone in the presence of an acid catalyst and a desiccant has long been established as a valuable method for selective temporary protection in synthetic carbohydrate and nucleic acid chemistry. The scope of this procedure has been extensively reviewed[1—4] and needs no further development here. The reaction normally proceeds under thermodynamic control, so that the composition of the product-mixture reflects the relative free energies of the components in the medium; frequently a single product is isolated in high yield because it is of low free-energy relative to other possible products.

Work in our laboratories has now developed a general method, based on the use of 2-alkoxypropenes (alkyl isopropenyl ethers), for effecting acetonation under exclusive kinetic control to furnish O-isopropylidene derivatives of carbohydrates of constitution entirely different, in most instances, from the products of thermodynamic control. The reaction offers broad general scope of application in synthetic transformations of sugars and their conjugates, both simple and complex.

The main features of the "classic" acetonation under thermodynamic control, as applied to free aldoses[1,2] or ketoses[3], involve the formation of polyacetalated products in a process wherein free interconversion of the tautomeric forms of the sugar takes place under the acid catalysis[4]. Isopropylidene acetals, both cyclic and acyclic, undergo constant formation and cleavage in the medium. Through operation of the principle of mass action, formation of polyacetalated products tends to be favored because of the excess of acetone used in the reaction, and cyclic 5-membered

(1,3-dioxolane) acetals constitute the common substitution-mode in the products isolated. Six-membered ring (1,3-dioxane) acetals are rarely encountered owing to their lower stability (a consequence of the Brown—Brewster—Shechter principle[5]), and acyclic acetal products generally do not survive the conditions of product isolation. When 5-membered cyclic acetals attached to cyclic systems are produced, they are almost always cis-fused. Cyclic acetals that engage the anomeric position of the sugar have particular stability, and consequently the anomeric hydroxyl group is almost invariably involved in acetal substitution, unless favored multiple substitution elsewhere in the molecule precludes this (as in the case of mannose). Even though aldoses and ketoses normally favor the pyranose tautomer in solution, the equilibrium driving-force of the acetal-forming reaction frequently transforms the ring skeleton into the furanoid form, as illustrated by the standard prototype-example[6], the conversion of D-glucopyranose into 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.





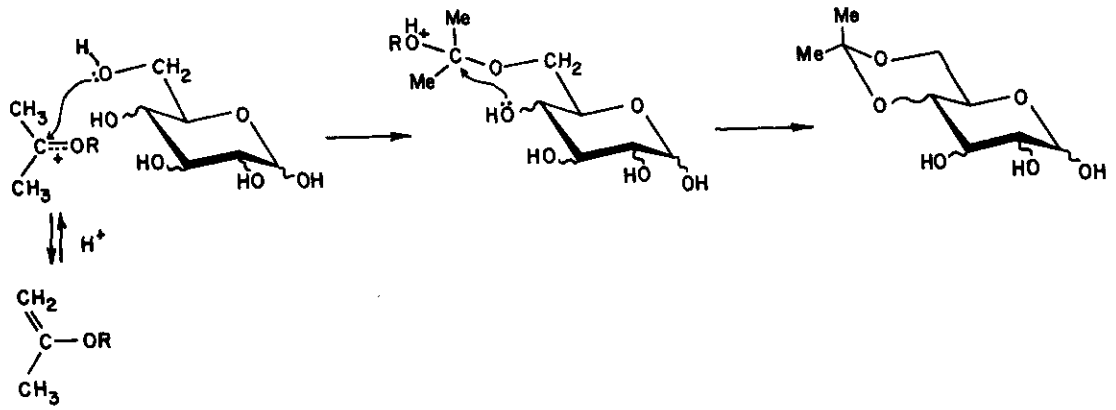
As the thermodynamic approach usually leads to polyacetalated products, recourse is commonly made to selective hydrolytic removal of one or more cyclic acetal groups for access to products having only partial acetal substitution.

The lability of the glycosidic bond under acid conditions precludes the general use of the classic acetonation procedure for protection of oligo- and polysaccharides, although examples exist of controlled acetonation of certain derivatives wherein the cleavage of glycosidic linkages is minimized.

The direct contrast between thermodynamic acetonation and kinetically controlled acetonation with a 2-alkoxypropene is clearly illustrated[7] with reference to D-glucose. Optimal conditions for

kinetic acetonation[8] involve use of ~2 mol of 2-methoxy(or 2-ethoxy)propene per mol of D-glucose at 0° in a nonhydroxylic solvent (N,N-dimethylformamide) compatible with the free sugar and the reagent, together with a trace of acid catalyst (p-toluenesulfonic acid). Reaction is rapid and the sugar is transformed in high (~95%) yield into a monoisopropylidene acetal in which the pyranoid ring-form is retained and the acetal is engaged in 4,6-substitution (1,3-dioxane type of acetal). It is essential that the amount of acid catalyst used be restricted to a trace and the established experimental conditions[7,8] must be followed carefully, otherwide irreversibility of the process is not assured and a mixed mode of reaction may ensue through partial equilibration, with consequent diminution of yield of the kinetic product and difficulties in its isolation because of its admixture with a proportion of thermodynamic products.

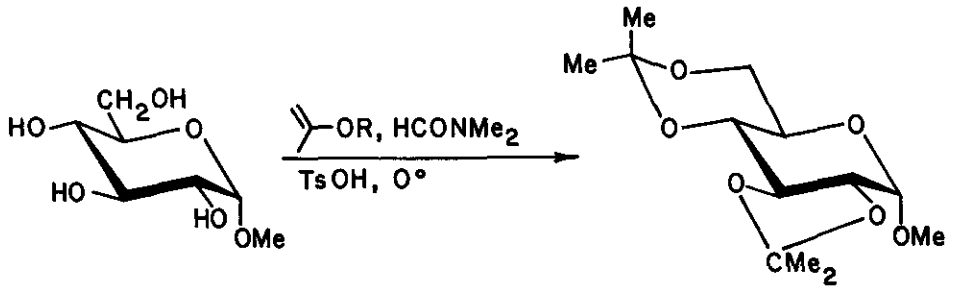
Formation of 4,6-O-isopropylidene-α-D-glucopyranose under kinetic conditions may be envisaged as proceeding by initial attack at the most accessible (primary) hydroxyl group, with subsequent ring-closure at the hydroxyl group then the most sterically available, namely O-4; the entire process takes place before any appreciable acid-catalyzed tautomerization of the sugar occurs.



Acetonation of sugars by use of 2,2-dimethoxypropane and a trace of acid catalyst leads to a mixed mode of acetonation; under careful control it is possible to obtain mainly the kinetic product in selected instances[9]. However, extensive comparative investigations in our laboratories have shown that the highest yields of acetonated products, formed under exclusively kinetic conditions, are achieved by use of the 2-alkoxypropene reagent; yields of kinetic product are invariably lower when 2,2-methoxypropane is used, and greater or lesser proportions of thermodynamic product are present

in the reaction product.

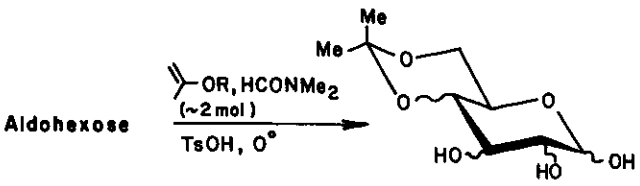
A significant illustration of the kinetic acetonation is afforded by the behavior of methyl α-D-glucopyranoside when treated with ~4 mol of 2-methoxypropene. The reaction produces[10] in 95% yield the crystalline 2,3:4,6-diacetal of the glycoside; the anomeric configuration and ring size of the glycoside remains unchanged, one acetal group spans the 4,6 positions as already observed with D-glucopyranose, and a second acetal group enters with the strained trans-fused 1,3-dioxolane ring at positions 2 and 3 of the glycoside. Such trans-fused acetal groups, previously obtainable[11] in only extremely low yield, are particularly susceptible to hydrolytic removal with retention of other cyclic acetal groups, and thus offer considerable potential scope in synthetic design through selective protection and deprotection.



Ref. *10* (compare ref.*11*)

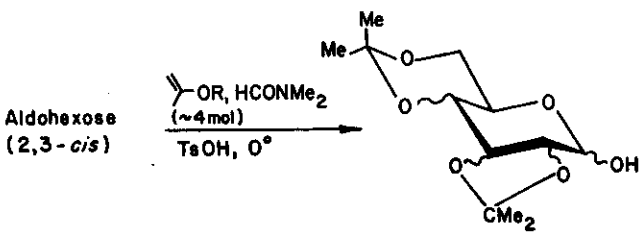
m. 84-86°
+97° ($CHCl_3$)

The behavior of D-glucopyranose when treated with ~2 mol of 2-alkoxypropene is evidently quite general for the aldohexoses; six of the eight D-aldohexoses have been studied in detail[7,8,12—14] and in every instance the reaction has afforded the corresponding 4,6-O-isopropylidenealdohexopyranose in 80—95% yield; analogous indications follow for the remaining examples (altrose and idose). Such significant acetamidohexoses as 2-acetamido-2-deoxy-D-glucose and -galactose similarly yield the 4,6-O-isopropylidene pyranose derivatives, and other aldohexose derivatives substituted at O-2 and/or at O-3 may be expected to react likewise.

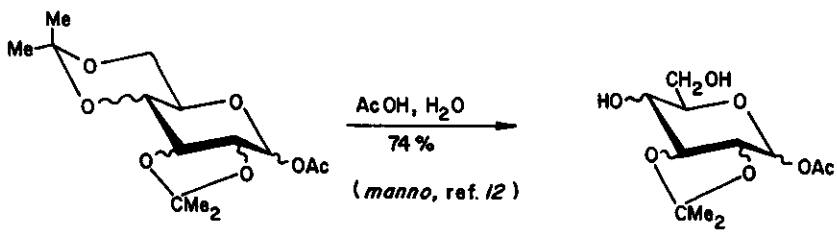


Isomer	*Yield (%)*	*Ref.*
D-*gluco*	95	*7, 8*
D-*manno*	90	*8, 12*
D-*galacto*	70	*13*
D-*talo*	90	*13*
D-*allo*	75	*13*
D-*gulo*	80	*14*

Those aldohexoses having the hydroxyl groups at C-2 and C-3 cis-disposed undergo further acetonation when ~4 mol of the reagent is used, and the corresponding 2,3:4,6-di-O-isopropylidene-aldopyranoses are obtained in high yield[12—14], as demonstrated with D-allose, D-gulose, D-mannose, and D-talose. This feature adds an extra element of synthetic versatility, such as products, after protection of the anomeric hydroxyl group as by acetylation, may be readily deacetonated by mild acid treatment with complete selectivity. The 4,6-acetal group (1,3-dioxane ring) is removed with retention of the 2,3-acetal group (1,3-dioxolane ring), as illustrated in the second of the following two charts.



Isomer	*Ref.*
D-*allo*	*13*
D-*gulo*	*14*
D-*manno*	*12*
D-*talo*	*13*

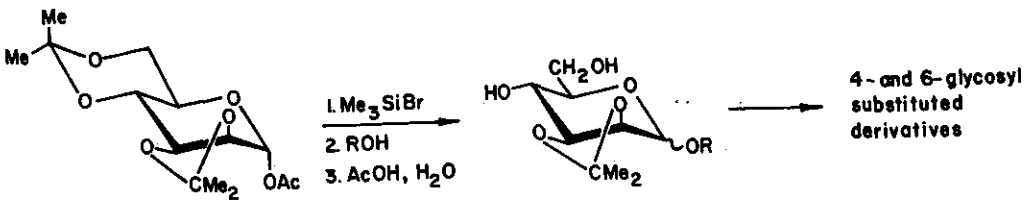


D-*allo* D-*gulo*

D-*manno* D-*talo*

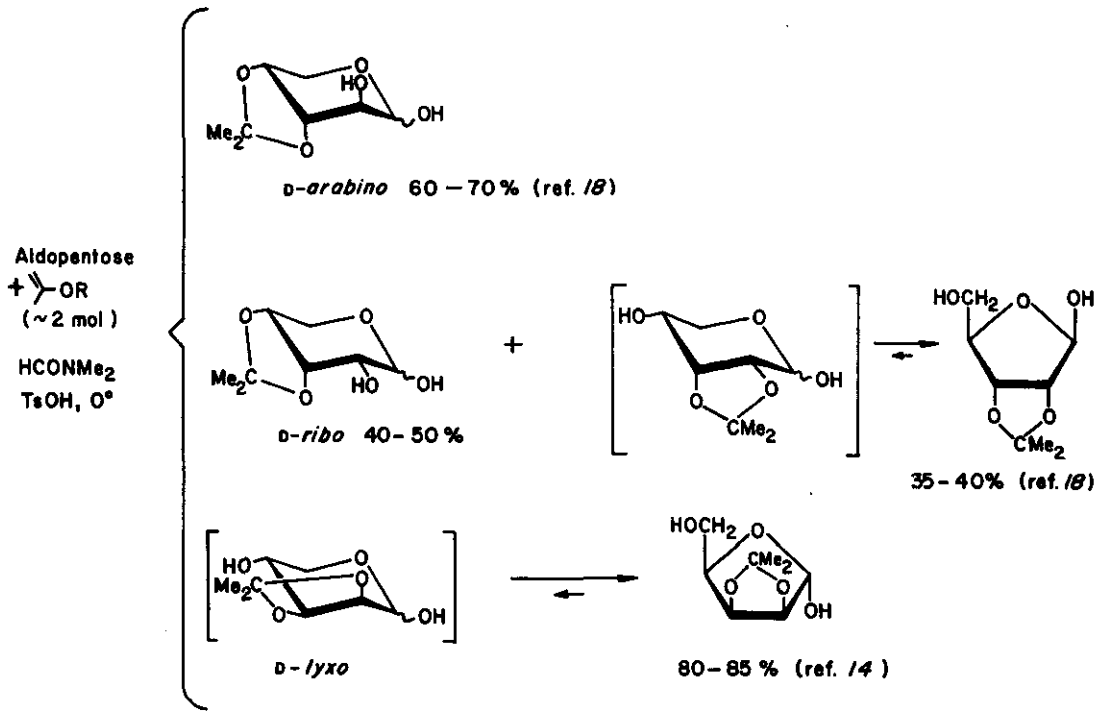
The foregoing, complete substitution of the 2,3-cis aldohexopyranoses by kinetic acetonation with an excess of reagent, followed by acylation at O-1, offers useful potential in synthesis of glycosides and complex saccharides[14,15]; replacement reactions at the anomeric center[16,17], either by direct displacement of a sulfonic or similar ester, or through conversion of a 1-O-acetyl derivative into an intermediate halide, affords glycosides (or nucleosides) having protecting groups removable by mild treatment with acid. Subsequent, selective removal of the 4,6-substituent

is an attractive feature for synthesis[14,15] of such important oligosaccharides as D-mannose derivatives having glycosyl substituents at positions 6 and 4.



It is noteworthy that these kinetic acetonation reactions give products in which the anomeric center remains unsubstituted; this feature of the reaction is consistently observed in practically all examples.

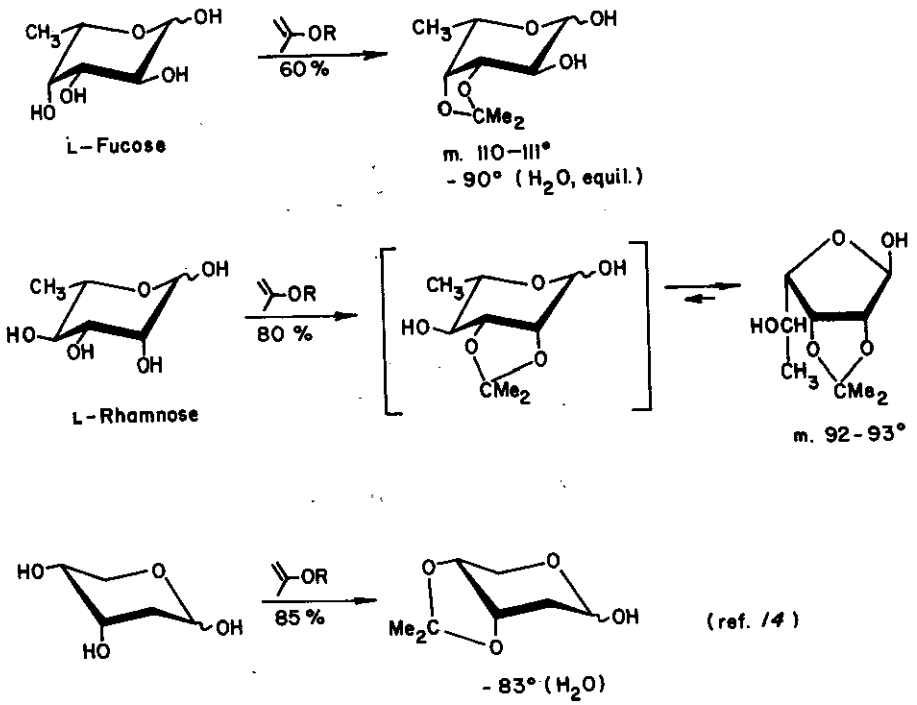
The behavior of the aldopentoses on acetonation with 2-alkoxypropenes[14,18] shows superficial differences that may nevertheless, be readily rationalized on the basis of considerations already advanced for the aldohexoses. The principal ring-form of each sugar is pyranoid (although ribose contains a significant proportion of the furanoid form), and thus a primary hydroxyl group is not accessible for initial attack. With D-arabinose, monoacetonation engaging the (cis-disposed) 3 and 4 positions takes place to give 60—70% of 3,4-O-isopropylidene-D-arabinopyranose; there is no tendency to produce the 2,3-acetal as the 2,3-hydroxyl groups are trans-related[18]. The same process is observed with D-ribose, but in this instance, the yield of 3,4-acetal is decreased (to 40—50%) because of competitive acetonation of the O-2,O-3 diol group, which is now cis-disposed. The 2,3-acetal, although presumably generated as the pyranose form, is actually isolated as the (more-stable) furanoid tautomer, to which it may readily rearrange after acetonation. The acetonation of D-ribose also leads to a small proportion of a furanoid diacetal having one acetal group at O-2,O-3 plus a second acetal group spanning O-5 and O-1; this is one of the exceptional examples where the anomeric position is involved, although the product still appears to arise[18] via an intermediate, acyclic acetal at O-5.



In the case of lyxose, acetonation between positions 3 and 4 is disfavored as these hydroxyl groups are trans-related, but the cis-disposed 2,3-diol reacts readily. The 2,3-acetal is isolated in high (80—85%) yield[14]; again the isolation of the product as the furanose form may be considered to result from pyranose ⟶ furanose tautomerization after acetonation. The fourth aldopentose, xylose, has O-2, O-3, and O-4 mutually trans-disposed, and its treatment with 2-alkoxypropenes does not give any single, stable cyclic acetal in high yield[14]; the product-mixture contains significant proportions of rather unstable products containing acyclic acetal groups. Such acyclic acetals (compare[18,19]) are much less stable than the cyclic acetals. The absence of significant reaction at position 1 with the aldopentoses is again noteworthy.

The behavior of 6-deoxyaldohexoses on kinetic acetonation is readily explicable by reference to the reactions of similarly constituted aldopentoses. Thus, acetonation of L-fucose (6-deoxy-L-galactopyranose) with 2-methoxypropene affords in 60% yield the pyranoid 3,4-acetal[14], behaving therefore in a manner exactly analogous to that observed with D-arabinose. Similarly, the behavior of L-rhamnose (6-deoxy-L-mannopyranose) may be interpreted by reference to the reaction observed with D-lyxose; the final product obtained[14], in 80% yield, is 6-deoxy-2,3-O-isopropylidene-L-

mannofuranose, and the reaction may be supposed to involve initial acetonation of the 2,3-cis diol in L-rhamnopyranose, with subsequent tautomerization (compare[20]) to the more-stable furanose form.

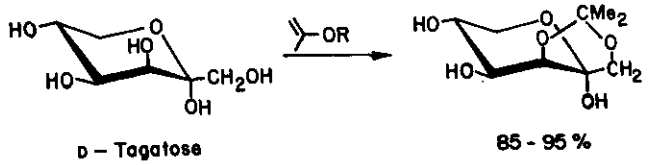


The behavior on acetonation of 2-deoxy-D-erythro-pentopyranose may be correlated directly with that of D-ribose; the product obtained[14], 2-deoxy-3,4-O-isopropylidene-α,β-D-erythro-pentopyranose (85% yield), results from straightforward acetonation of the 3,4-cis diol group.

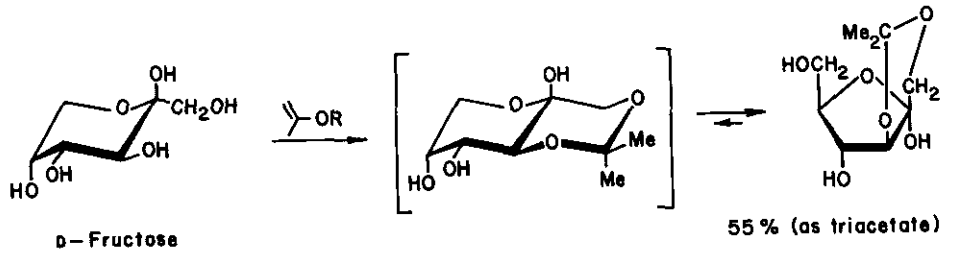
Such ribonucleosides as adenosine are converted by 2-alkoxypropenes into the corresponding 2',3'-isopropylidene acetals[14,21], but in this instance the kinetic acetonation procedure offers no obvious advantages over the standard thermodynamic route. Evidently, even if the alkoxypropene reagent tends to attack the primary hydroxyl group preferentially, the distance between O-5' and O-3' is too great for closure to an isopropylidene acetal, even a somewhat strained one, and so the cyclic acetal isolated is that resulting from classic bridging of the 2',3'-diol.

A comparative investigation of three ketohexoses on kinetic acetonation has been conducted[22] and the results are presented in the following chart. As with the aldohexoses, the results may be interpreted in terms of initial attack on the ketohexopyranose at the primary hydroxymethyl group,

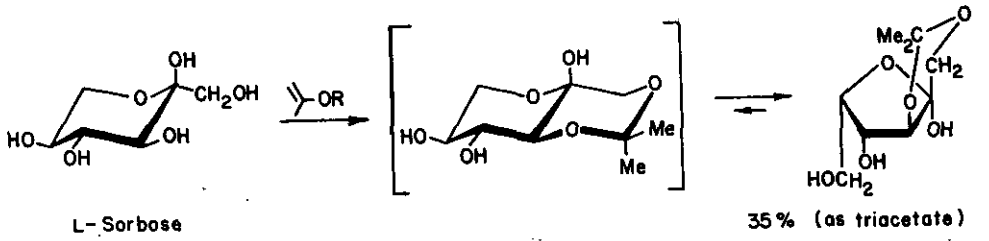
followed by ring-closure at the most accessible (non-anomeric) secondary hydroxyl group; subsequent pyranose ⟶ furanose tautomerization may take place if further stabilization is thereby achieved. Thus D-tagatose gives the 1,3-isopropylidene acetal in 85—90% yield and the isolated product retains the pyranoid ring-form, whereas D-fructose and L-sorbose, which likewise undergo acetal bridging between the primary (O-1) position and O-3, are isolated as the furanoid tautomers of their 1,3-isopropylidene acetals. The substitution-mode of the products from these three ketohexoses is entirely different from that in the products[3] of conventional thermodynamic acetonation.



D – Tagatose 85 - 95 %



D – Fructose 55 % (as triacetate)

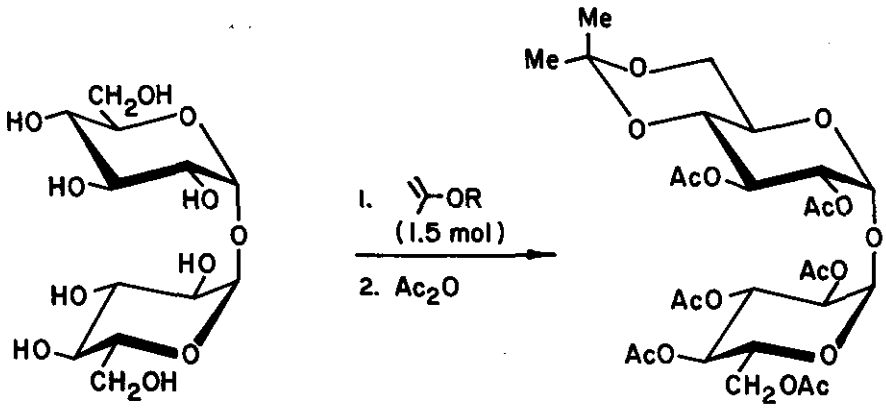


L-Sorbose 35 % (as triacetate)

(Ref. 22)

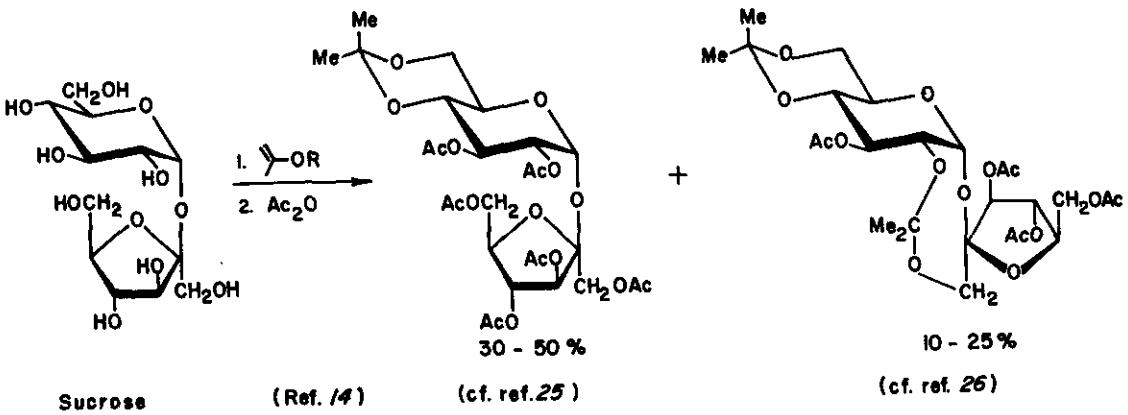
The branched-chain sugar D-apiose [3-(hydroxymethyl)-D-glycero-tetrose], which on classic acetonation[23] gives a mixture of two 1,2:3,3¹-diacetals isomeric at the spiro atom (C-3), reacts with 2-methoxypropene to give[14] a mixture of four monoacetal products, which are probably 3,3¹-spiro monoacetals in both 3-stereoisomeric forms, each existing as a pair of furanoid anomers.

In application of this acetonation procedure to di- and oligo-saccharides[22], the same selectivity as observed with monosaccharides is again evident, and the complete absence of glycosidic bond-cleavage makes the reaction attractive as a method for selective protection in synthesis. The symmetrical disaccharide α,α-trehalose is notoriously difficult to convert into derivatives substituted selectively at only one of the two α-D-glucopyranosyl residues, but nevertheless it is readily converted by the action of 1.5 mol of 2-methoxypropene into its 4,6-monoacetal, which can be isolated in 40% yield[8]; this reaction furnished the starting point for synthesis of a wide range of unsymmetrically substituted derivatives of trehalose of interest as potential inhibitors of trehalases[24].



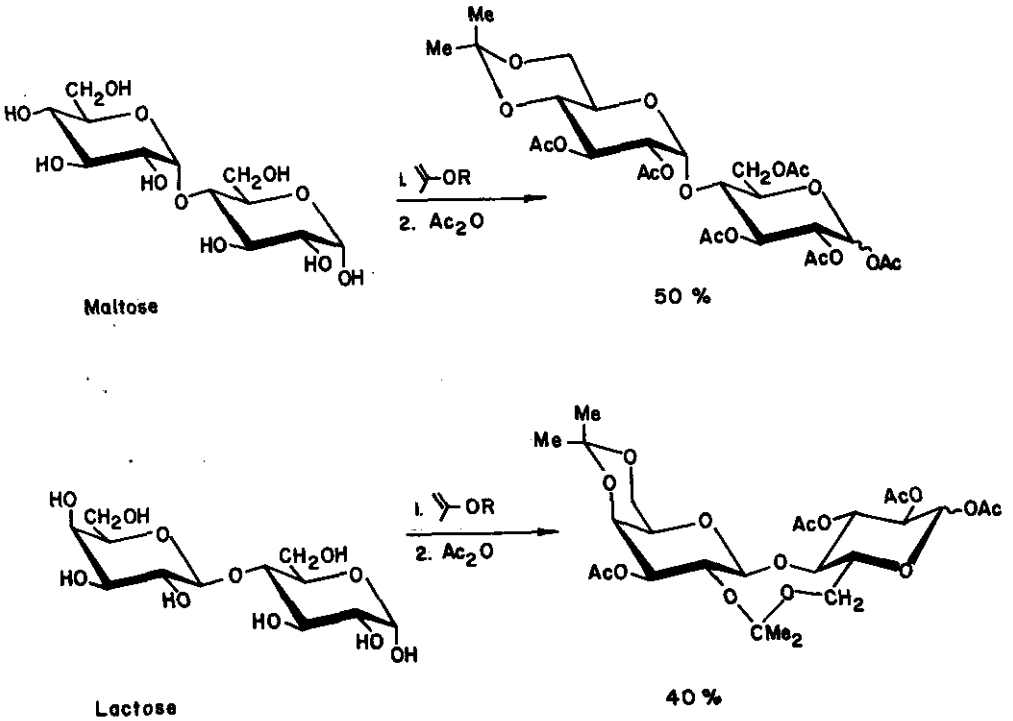
40 % (ref. 8, 24)

Another nonreducing disaccharide, sucrose, has a particularly labile glycosidic linkage, but acetonation with 2-alkoxypropenes under the standard conditions gave no evidence for glycosidic-bond cleavage. With ~2 mol or reagent, the main product was 4,6-O-isopropylidenesucrose, and use of a larger proportion of the reagent caused introduction of a second acetal group engaging the primary 1-hydroxymethyl group of the D-fructose moiety in linkage to O-2 of the D-glucose moiety. These products were isolated[14] as their peracetates and their structures established by direct comparison with products earlier obtained[25,26] from sucrose by the action of 2,2-dimethoxypropene under conditions where glycosidic hydrolysis is minimized.



Sucrose (Ref. *14*) (cf. ref. *25*) (cf. ref. *26*)

Among the reducing disaccharides examined, the behavior of maltose and lactose offers interesting contrasts[22]. The action of ~2 mol of 2-alkoxypropene on maltose led to 4,6-acetonation of the nonreducing residue; the product was isolated after acetylation in ~50% yield as a crystalline, peracetylated mixture of α and β anomers. It may be speculated that further reaction through attack of the reagent at O-6 of the reducing residue does not lead to ready stabilization through subsequent closure to a cyclic acetal because of stereoelectronic inaccessibility of a suitably disposed hydroxyl group for this process. This behavior is in contrast to the situation observed with sucrose, where an 8-membered ring is readily closed between O-1 of the fructose residue and O-2 of the glucose residue. Indeed, this reaction may develop into a useful probe to indicate inter-residue conformational proximity-effects in oligo- and poly-saccharide chains.



(Ref. 22)

The acetonation of lactose[22] proceeds to give a diacetal as the major (40%) product in which the nonreducing residue has the anticipated 4,6-acetal substituent, and the second acetal group spans the primary position (O-6) of the reducing residue in a 9-membered ring that engages O-2 of the nonreducing residue. Again, the reaction is of interest as a chemical probe for assessing group-proximity relations in those conformations, generated by rotation about the ϕ,ψ angles of the interglycosidic bond, that are sterically allowed. Thus, in addition to the evident utility of these products in the chemical synthesis of such important carbohydrates as oligosaccharide haptenic determinants, the acetonation reaction has potential for affording fundamental information on the nature of saccharide chain conformations, as well as possibly useful methods for stabilization and modification of fiber properties (through inter-residue acetalation along a linear chain) and generation of three-dimensional structures (through inter-chain cross-linking). In this regard, the behavior of the cello-oligosaccharides on the one hand, and the cycloamyloses on the other, will be of interest.

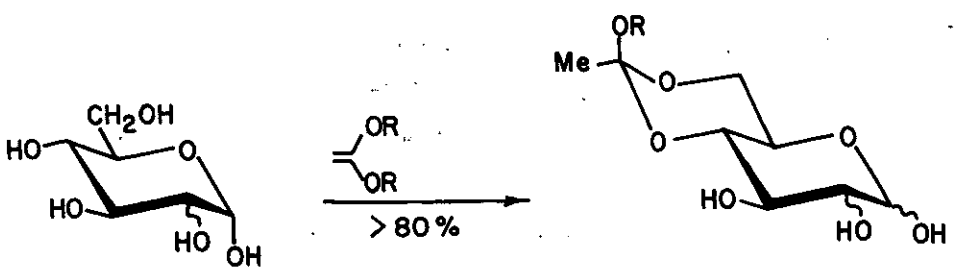
From a different viewpoint, such macrocyclic polyethers as the 9-membered ring formed from

lactose[22] are of interest as they constitute chirally substituted, cyclic polyethers susceptible to functional modification as by glycol-cleavage degradation of the sugar rings, with subsequent applications in chiral synthesis and for specific complexation of various cations.

Other potential applications of these kinetic acetonation reactions, at present only in a very preliminary stage, involve their use in structural modification of carbohydrate antibiotics, especially in the aminocyclitol field, in the quest for semisynthetic analogs of improved or modified response as compared with the parent, microbially synthesized agents. Here, the kinetic mode of reaction, leading to unusual bridged structures, together with the freedom from problems associated with hydrolytic degradation, offer a wide range of useful possibilities.

Final mention should also be made of the extensions feasible with minor structural variations in the reagent used. Thus, the use of 1-alkoxycyclohexenes instead of 1-alkoxypropenes opens up access, by an exactly comparable sequence, to cyclohexylidene acetals produced under kinetic control[27]. Although such cycloalkylidene acetals are rather less attractive than isopropylidene acetals in exploratory synthesis, notably because their n.m.r. spectra are less readily interpreted, they do on occasion afford stable, crystalline products in structures where the corresponding isopropylidene analogs may be liquids; the availability of crystalline intermediates offers procedural convenience.

Another variant of this type involves the use of vinylidene acetals for the formation of cyclic orthoesters under kinetic control. Thus, under conditions similar to those used for kinetic acetonation of D-glucose, the reaction of D-glucose or D-mannose with 1,1-dialkoxyethenes gives[28] in >80% yield the 4,6-cyclic orthoesters. The differences of chemical reactivity between orthoesters and acetals offer a wealth of opportunities for exploiting use of both groups, introduced under conditions of kinetic control, in chemical synthesis.



(Ref. 28)

In summary, the work presented here leads to the following generalizations:

1. 2-Alkoxypropenes permit acetonation of sugars and their derivatives under exclusive kinetic control.

2. The favored site for initial attack by the reagent is at a primary hydroxyl group.

3. Sugars not having a primary hydroxyl group in the favored tautomer in solution react without tautomerization to give dioxolanes.

4. The anomeric hydroxyl group does not generally take part in the reaction.

5. Stoichiometric control of the reaction may be exercised, to permit access to either monoacetals or diacetals.

6. Acetals of oligo- and poly-saccharides are readily accessible, as the conditions do not affect glycosidic linkages.

7. The method permits access to strained-ring acetals and to medium-sized rings.

8. Extension of the method by use of other alkoxyalkenes affords a wide variety of different cyclic acetals and orthoesters, formed under conditions of kinetic control.

The reactions described here provide a general base of novel protecting-group strategy of wide potential utility in the synthesis and modification of carbohydrate structures.

This work was first presented as part of the Symposium on Blocking Groups at the 179th National Meeting of the American Chemical Society, Houston, Texas, March 24—27, 1980, Division of Carbohydrate Chemistry.

Acknowledgments

This work was supported, in part, by Grant No. GM-11976 from the National Institute of General Medical Sciences, N.I.H., Bethesda, Md. 20014, and by RCP 529 of the Centre National de la Recherche Scientifique.

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Received, 24th March, 1981