CATALYSIS BY MERCURIC ION OF REACTIONS OF GLYCALS WITH WATER*

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ABSTRACT

In the presence of mercuric sulfate, 3,4,6-tri-*O*-acetyl-D-glucal (**4**), dissolved in 1,4-dioxane–dilute sulfuric acid at room temperature, is rapidly and quantitatively converted into 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo* D-*erythro*-*trans*-hex-2-enose (**8**). With acetone as the organic component of the solvent, this product is accompanied by the 5,6-di-*O*-acetyl isomer (**10**). The corresponding, α,β-unsaturated aldehydes (**12** and **13**; **15**) are formed in an analogous way from 3,4,6-tri-*O*-acetyl-D-galactal (**11**) and 3,4-di-*O*-acetyl-D-arabinal (**14**). Similarly, instead of hydration, D-glucal (**1**) and D-galactal undergo elimination catalyzed by mercuric ion and acid to yield 2-(D-*glycero*-1,2-dihydroxyethyl)furan (**3**) as the sole product. Possible mechanisms for these transformations are discussed.

INTRODUCTION

A variety of products are formed when glycals are treated with water under differing reaction-conditions[1–4]. The best known reaction involves acid-catalyzed hydration to yield 2-deoxyaldoses[5], and serves as a general route to this class of sugars[2,6]. Thus, D-glucal (1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol) (**1**) forms 2-deoxy-D-*arabino*-hexopyranose (**2**) in dilute sulfuric acid[5,7] at ~0°. However, little hydration occurs at 70° in aqueous acetic acid as the medium; instead, the main product is[8] 2-(D-*glycero*-1,2-dihydroxyethyl)furan (**3**). The latter was also undoubtedly the minor by-product isolated[7] in the low-temperature preparation of **2**, although it was regarded as the pyran analog (**3a**) of **3**.**

When briefly heated under reflux in water[9] or in aqueous 1,4-dioxane[10], D-glucal triacetate (**4**), yields mainly **5** (commonly referred to[1,11] as "di-*O*-acetyl-pseudoglucal"***). During more prolonged treatment, **5** undergoes ring opening and

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We have checked this possibility and, indeed, have found that the mother liquor from the crystallization of **2 contains a syrupy compound indistinguishable from **3** by chromatography and p.m.r. spectroscopy.
***Structure **3a** has also been suggested[3,12] as a possible representation of "protoglucal", one of the products formed[13] by *O*-deacetylation of **5**.

cis-trans isomerization—probably photochemically induced—to yield an α,β-unsaturated aldehyde [characterized[10] as its triacetate (**6**)].

Hence, elimination and rearrangement are the main features of the glycal–water reaction at elevated temperatures, whereas addition to the 1,2-enolic function predominates in the cold. For synthetic purposes, the latter route applies only to non-acetylated glycals, because it has been found (see the Experimental section) that tri-*O*-acetyl-D-glucal (**4**) yields little, if any, of the 2-deoxy compound **7** on treatment with aqueous acid: there is no reaction in four hours at 0°, and several (unidentified) products are slowly formed at room temperature. The present study originated in attempts to catalyze the hydration of **4** to **7** by means of metal ions. Among precedents for such experiments were (*a*) the well known practice of employing mercuric salts to promote the hydration of alkynes, and (*b*) their use in the exchange of ether functions of certain glycal analogs, namely, enolic ethers[14,15].

RESULTS AND DISCUSSION

Tri-*O*-acetyl-D-glucal (**4**) was treated with 0.02 molar equivalent of mercuric sulfate in a solvent consisting of 5mM sulfuric acid and sufficient 1,4-dioxane or acetone to bring the triacetate into solution. In 2–3 h at room temperature, the starting material was converted in >90% yield into a single product, a distillable oil that was found by analysis and spectroscopy to be an α,β-unsaturated aldehyde. Furthermore, the p.m.r. spectrum (see Table I) of the product obtained by using 1,4-dioxane as a solvent corresponded to that described[12] for 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose (**8**), which is one of the compounds formed on hydride reduction of the mercurial compound **9**. After peracetylation of the product, the p.m.r. spectrum of the peracetate (see Table I) corresponded to that reported[10] for **6**. The result was essentially the same when the reaction was performed at 0°, although, naturally, the rate of formation of **8** was much lower; again, however, it was clear that the simple hydration product **7** was not favored. With acetone as the solvent instead of 1,4-dioxane, the rate of reaction was higher, but the product consisted of a mixture of **8** and its 5,6-diacetate (**10**); whether the ester migration occurred during the reaction itself or during processing has not yet been determined.

Hence, in these reactions, mercuric ion promotes the elimination of acetic acid, rather than the direct hydration of the alkene, giving a result analogous to the overall, thermal reaction described by Fraser-Reid and Radatus[10]. Intermediate **5** found by these workers was not detected in the present study, and, although they showed that the subsequent formation of **8** is photosensitive, the rate of the Hg^{2+}-catalyzed reaction was not retarded in the dark nor in the presence of hydroquinone.

Under analogous conditions, 3,4,6-tri-*O*-acetyl-D-galactal (**11**) yielded the corresponding α,β-unsaturated aldehyde, also an oil, which proved to be a mixture of the 4,6- and 5,6-diacetates (**12** and **13**). 3,4-Di-*O*-acetyl-D-arabinal (**14**) afforded a crystalline product (**15**).

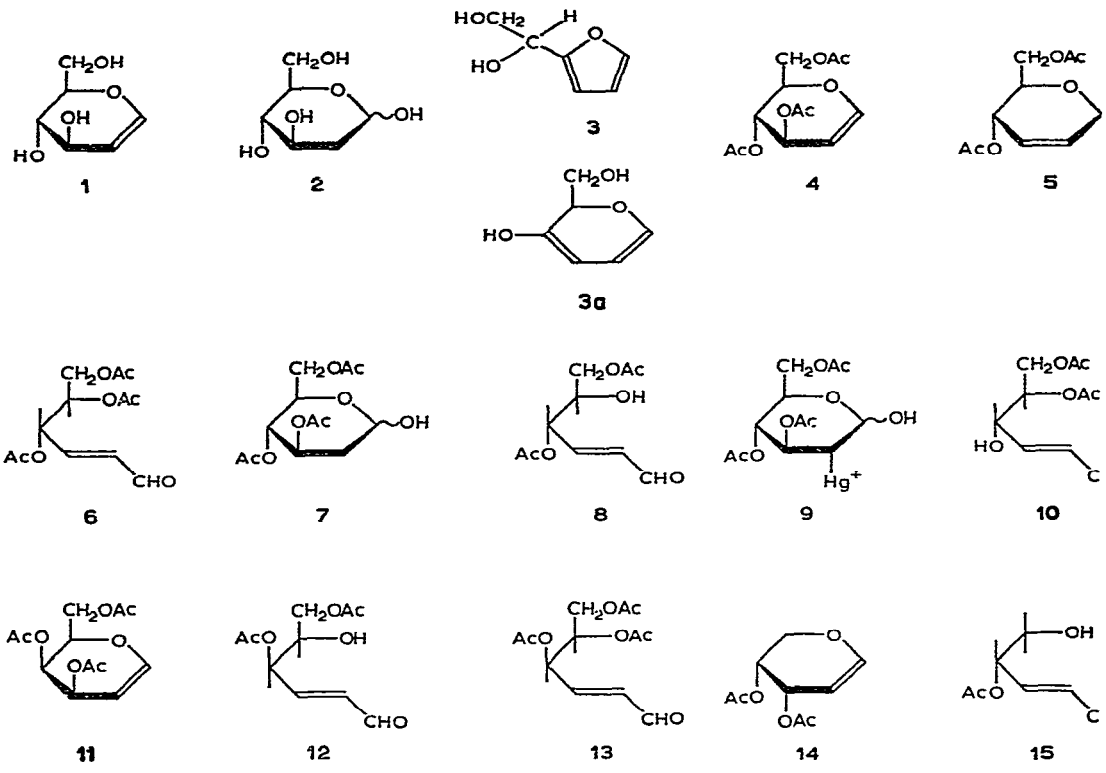
In view of the foregoing results, the effect of mercuric ion on the reaction of

TABLE I

P.M.R. SPECTRAL PARAMETERS FOR PRODUCTS OF THE HYDROLYSIS OF GLYCALS CATALYZED BY MERCURIC ION

Compound[a]	*Chemical shift* (δ)							*Spacings* (*Hz*)					
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	CH_3	*1,2*	*2,3*	*3,4*	*4,5*	*5,6*	*2,4*
8[b]	9.58	6.40	6.98	5.61	4.1[c]		2.05 2.12	8.0	15.5	5.0	~5	[c]	1.0
10	9.58	6.28	7.02	4.64	5.12	4.1[c]	2.05(2)	8.0	15.5	5.0	4.5	~6(5,6) ~6(5,6')	1.0
6	9.56	6.27	6.75	5.78	5.30	4.29 4.23	2.05 2.13(2)	7.5	15.5	~5	4.5	4.5	1.5
12	9.57	6.25	6.87	5.64	4.4[c]	4.1[c]	2.07 2.18	7.5	15.5	~4	4.5	[c]	1.0
13	9.55	6.40	6.90	4.66	5.24	4.1[c]	2.03 2.07	7.5	15.5	4.5	4.0	4.0 7.0	1.0
15	9.53	6.17	6.97	4.70	4.18(2)	—	2.08	7.0	15.0	4.0	~6 ~6	—	2.0
	H-1'	*H-2'*	*H-3*	*H-4*	*H-5*	*OH-1'*	*OH-2'*	CH_3	*1',2'*	*3,4*	*3,5*	*4,5*	*OH-1',1'*	*OH-2',2'*
3[b]	4.67	3.58	6.20	6.31	7.48	5.07	4.71[d]	—	6.0	3.1	0.8	1.6	4.5	6.0 12.0
3 (diacetate)	6.11	4.43 4.44	6.4[c]		7.39	—	—	2.01 2.04	5.5 7.0	[c]	0.8	1.6	—	—

[a]In deuteriochloroform, except for **3** (in Me_2SO-d_6). [b]Analysis confirmed by spectral simulation using the NMRCAL program (Nicolet Instrument Corp., Madison, Wis.). [c]Unresolved. [d]Quartet.

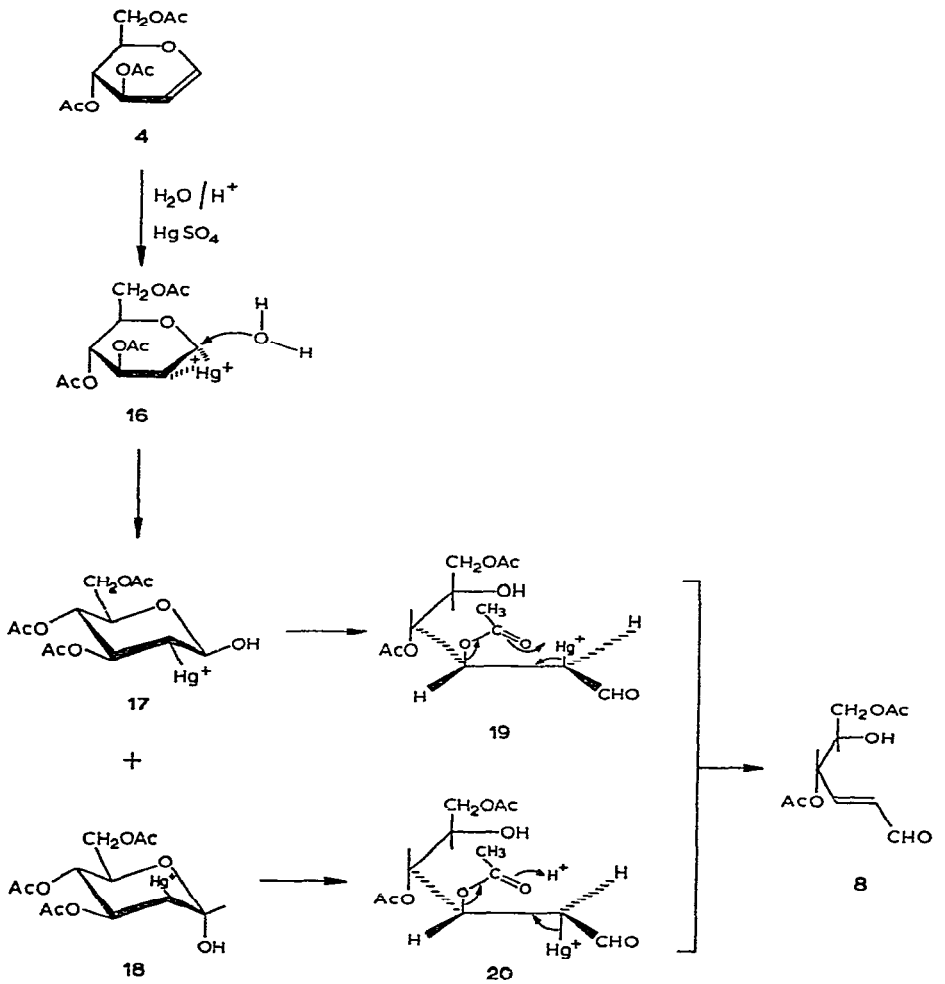


D-glucal (**1**) itself with water was examined. When treated for 3–4 h in 5mM sulfuric acid at room temperature with a trace of mercuric sulfate, **1** (and also **11**) gave a yield of over 80% of an oil, characterized as **3** by p.m.r. spectroscopy (see ref. 8 and Table I*). Introduction of the metal ions under conditions that normally promote the ready formation of the simple-addition product **2**, *i.e.*, in cold M sulfuric acid, again led mainly to the production of **3**. Therefore, the presence of mercuric ions also favors rapid elimination and rearrangement for unprotected glycals at room temperature (or lower), although the outcome is markedly different from that found with the *O*-acetylglycals.

Several features of these metal-assisted reactions are noteworthy. First of all, the catalysis observed takes place under acidic conditions, for product **3** or **9** is formed much more slowly at room temperature in water, or aqueous 1,4-dioxane, to which a trace of mercuric sulfate has been added. Hence, the rate-enhancement due to mercuric ions is superimposed on, or is accompanied by, an acid-catalyzed reaction. Although

*In methyl sulfoxide solution, **3** produced signals (see Table I) due to a primary (quartet) and a secondary (doublet) hydroxyl group. Spin decoupling showed that the proton of the latter group was coupled to H-1′, and that of the former to H-2′ (see Table I). This confirmed, therefore, that the hydroxyl groups of **3** are vicinal and that the compound is a furan derivative rather than, as might have been anticipated[7], a pyrandiol (**3a**).

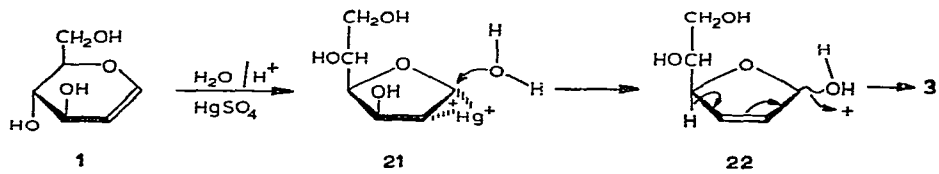
the latter would normally yield a 2-deoxy compound, it nevertheless does not, because 2-deoxy-D-*arabino*-hexose (**2**) is itself stable under the reaction conditions*. It appears more likely that the 1,2 π-bond is first attacked by mercuric ion (*e.g.*, as in **16**) and, as the formation of **3** or **9** requires a ring opening, subsequently by water at C-1. The hydration products (**17** plus **18**) then presumably undergo elimination at C-2 and C-3 to yield **8**. In order to account for formation of the *trans*-alkene (**8**) without an intervening thermal or photochemical *cis-trans* isomerization, the D-*gluco* isomer (**17**) must undergo *cis* elimination to **19**, whereas formation of the D-*manno* adduct (**18**) would involve *trans* elimination.



* Moreover, **8** was found to contain no deuterium when deuterated sulfuric acid was used as the solvent, implying that protonation at C-2 does not occur during the reaction.

Glycals, like other enols and alkenes in general, form stable adducts with mercuric ion, as represented[16] by **9**. As the proposed intermediate **17** closely resembles **9**, the latter was prepared, and treated under the conditions already described. The α,β-unsaturated aldehyde (**8**) was indeed formed from **9**, although much more slowly than from the glycal directly. However, in compound **17**, the carbon–mercury bond would undoubtedly be more ionic than that in **9**, and hence should allow for a more facile elimination-step. Protonation could also assist the ring-opening step (**17** → **19** and **18** → **20**), and departure of the acetoxyl group (as in **20**), making for an accelerated, overall rate.

In the reaction of D-glucal (or D-galactal), the presence of OH-4 and the absence of a 3-*O*-acetyl group permit consideration of a 1,2-chelated furanose species, such as **21**, which, upon elimination, leads successively to **22** and thence to the highly stable furan (**3**). Again, the presence of acid may facilitate elimination in steps **21** → **22** and **22** → **3**.



1 21 22

EXPERIMENTAL

General. — P.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer. I.r. spectra were recorded with a Unicam SP-200G spectrophotometer. Glass plates coated with silica gel G were used for thin-layer chromatography (t.l.c.); the solvent was 9:1 chloroform–acetone. Column chromatography was performed with silica gel (0.08 mm particle size). Evaporations were conducted at 40°, or lower, *in vacuo*. Melting points are uncorrected.

Attempted hydration of 3,4,6-tri-O-acetyl-D-glucal (**4**). — A solution of the triacetate (50 mg) in 1,4-dioxane (0.3 ml) was treated under the following conditions: (*a*) 1 ml of 5mM sulfuric acid was added at 25°: no reaction was detected (t.l.c.) in 8 h; (*b*) 1 ml of M sulfuric acid was added at 0°: no reaction was detected in 4 h; (*c*) 1 ml of M sulfuric acid was added at 25°, and the solution was then examined by t.l.c.: three slow-moving products were detected at 5 h and six at 72 h.

4,6-Di-O-acetyl-2,3-dideoxy-aldehydo-D-erythro-trans-*hex-2-enose* (**8**). — Mercuric sulfate (5 mg) was added to a stirred solution of **4** (100 mg) in 1,4-dioxane (0.5 ml) and 5mM sulfuric acid (2.0 ml), and stirring was continued for 3 h; t.l.c. then showed that, during this period, the glycal was completely converted into a single, faster-moving product. An excess of barium carbonate was added, the suspension was shaken and filtered, and the filtrate was evaporated, giving a clear oil (95 mg); $[\alpha]_D^{23}$ +8.9° (*c* 1.0 chloroform); ν_{max}^{film} 3450 (OH) and 1695 cm^{-1} (C=O of C=C–CHO); for p.m.r. data, see Table I.

Anal. Calc. for $C_{10}H_{14}O_6$: C, 52.2; H, 6.1. Found: C, 51.9; H, 6.3.

Effect of solvent. Formation of **8** *and its 5,6-di-*O*-acetyl isomer* (**10**). — The time needed for completion of the formation of **8** was increased from 3 (see preceding section) to 24 h on increasing the ratio of 1,4-dioxane to sulfuric acid to 1:1. When the solvent for the reaction was 1:1 acetone–5mM sulfuric acid, the conversion of **4** into product was complete in 2 h. The oil formed in the latter reaction was found by p.m.r. spectroscopy to consist of **8** (70%) and its 5,6-di-*O*-acetyl isomer (**10**) (30%). P.m.r. data for **10** are given in Table I.

*4,5,6-Tri-*O*-acetyl-2,3-dideoxy*-aldehydo-D-erythro-trans-*hex-2-enose* (**6**). — A solution of the diacetate **8** (0.42 g) in acetic anhydride (7 ml) and pyridine (13 ml) was kept for 4 h, poured into a slurry of ice and dilute hydrochloric acid (50 ml), and extracted three times with chloroform; the extracts were combined, successively washed with aqueous sodium hydrogen carbonate solution and water, dried, and evaporated to an oil (yield, 0.46 g), $[\alpha]^{23}$ +11.7° (*c* 4.6, chloroform); for p.m.r. data, see Table I.

*4,6- and 5,6-Di-*O*-acetyl-2,3-dideoxy*-aldehydo-D-threo-trans-*hex-2-enose* (**12** *and* **13**). — The title compounds were obtained as a syrupy mixture (**12**:**13** = 3:2 by p.m.r. analysis) by treatment of 3,4,6-tri-*O*-acetyl-D-galactal[17] (107 mg) with mercuric sulfate (5 mg) in 1,4-dioxane (0.5 ml) and 5mM sulfuric acid (2.0 ml) for 3 h, as for the preparation of **8**; yield, 77 mg (82%), $[\alpha]_D^{23}$ +52.1° (*c* 8.7, chloroform); for p.m.r. data, see Table I.

Anal. Calc. for $C_{10}H_{14}O_6$: C, 52.2; H, 6.1. Found: C, 51.4; H, 6.2.

*4-*O*-Acetyl-2,3-dideoxy*-aldehydo-D-glycero-trans-*pent-2-enose* (**15**). — To a stirred solution of **14** (484 mg) in 1,4-dioxane (0.5 ml) and 5mM sulfuric acid (5.0 ml) was added mercuric sulfate (10 mg), and stirring was continued for 3 h; the acid was neutralized with barium carbonate, the suspension was filtered, and the filtrate was evaporated to a colorless oil (337 mg, 88%); $[\alpha]_D$ 0° (*c* 5, chloroform). P.m.r. data are given in Table I.

The product afforded a (2,4-dinitrophenyl)hydrazone having m.p. 215–217° after two recrystallizations from ethyl acetate.

Anal. Calc. for $C_{13}H_{14}N_4O_7$: C, 46.2; H, 4.1; N, 16.6. Found: C, 45.9; H, 4.5; N, 16.7.

2-(D-glycero-*1,2-Dihydroxyethyl)furan* (**3**). — A solution of **1** (127 mg) in 5mM sulfuric acid (3 ml) containing mercuric sulfate (5 mg) was stirred for 2 h; t.l.c. examination then showed that the glycal had been completely converted into a single, faster-moving material. The acid was neutralized with barium carbonate, the suspension filtered, and the filtrate evaporated, affording a colorless oil; 90 mg (81%), $[\alpha]_D$ +38.0° (*c* 3.3, chloroform). The p.m.r. spectrum of the product (Table I) was in close accord with that reported[8] for the title compound.

Under the same reaction-conditions, D-galactal[17] (107 mg) yielded 77 mg of an oil indistinguishable by chromatography and p.m.r. spectroscopy from compound **3** obtained from D-glucal; $[\alpha]_D$ +38.4° (*c* 11.0, chloroform).

When **3** was treated with acetic anhydride in pyridine, it afforded a syrupy

diacetate (for p.m.r. data, see Table I); and with *p*-nitrobenzoyl chloride in pyridine, it gave a crystalline di-*p*-nitrobenzoate, m.p. 95–97° (lit.[8] m.p. 95–97°).

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