Reactions of Saccharides Catalyzed by Molybdate Ions. I. Preparation of D-Talose by Hydroxylation of D-Galactal

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Conditions of the hydroxylation of D-galactal by hydrogen peroxide under the catalytic action of sodium molybdate were investigated in detail. A procedure has been elaborated for conversion of D-galactal into D-talose in 90% yield. The stereoselectivity of the hydroxylation is considered to be a consequence of the formation of an initial transitory complex between the hydroxyl group at C-3 and permolybdenic acid which is subsequently decomposed under the formation of aldose with *cis* relationship at carbons C-2 and C-3.

Hydroxylation of glycals leads to the formation of corresponding aldose epimers. Their ratio depends on the conditions of hydroxylation and on the starting glycal. As hydroxylating agents, perbenzoic acid or hydrogen peroxide in the presence of osmium tetraoxide have been used. Hydroxylation of glycals by perbenzoic acid affords preferentially *cis* 2,3-substituted products when OH-3 is unsubstituted. Substitution of OH-3 results in the formation of *trans* 2,3-substituted products. Thus, D-glucal gives preponderately D-mannose [1], and 3,4,6-tri-*O*-acetyl-D-glucal [2] and 3,4,6-tri-*O*-methyl-D-glucal [3] afford the corresponding derivatives of D-glucose. Similarly, D-talose is formed from D-galactal [4, 5], D- and L-ribose from D- and L-arabinal [6—8] and D-lyxose from D-xylal [9]. Epi-maltose [10], epi-cellobiose [11, 12], epi-lactose [13—16], and epi-gentiobiose [17] were also prepared by perbenzoic acid hydroxylation of unsubstituted glycals of disaccharides.

Treatment of glycals with hydrogen peroxide and osmium tetraoxide in *tert*-butanol gave predominantly the aldoses having *trans* substituents at positions 2 and 3, regardless of substitution of OH-3 [18, 19]. Tungsten trioxide and in smaller extent also molybdenum trioxide and selenium dioxide were reported to be suitable catalysts of the hydroxylation of unsaturated compounds by hydrogen peroxide in water solution [20]. Hydroxylation of glycals of monosaccharides by hydrogen peroxide in the presence of MoO_3 proceeded with high stereoselectivity yielding aldoses with *cis* relationship at carbons 2 and 3. The reaction carried out with WO_3 also gave *cis* 2,3-substituted products, but was less stereoselective. *Trans* 2,3-substituted products were predominantly obtained in the presence of SeO_2, in lower yields, however [21].

This paper presents the results of the study of optimum conditions of hydroxylation of D-galactal by hydrogen peroxide in the presence of molybdate ions carried out in water solution. The evaluation of the catalytic effect of Na_2MoO_4, MoO_3, Na_2WO_4, and WO_3 in the hydroxylation showed that the replacement of MoO_3 with Na_2MoO_4 enhanced the stereoselectivity of the reaction. Smaller amount of both epimeric aldose—galactose and 2-deoxy-D-lyxo-hexose was formed as a consequence of the reduced acidity

Table 1

Formation of by-products during hydroxylation of D-galactal in the presence of different catalysts

Catalyst	D-Galactose [%]	2-Deoxy-D-lyxo-hexose [%]	Reaction time* [hrs]
Na_2MoO_4	3	3	6
MoO_3	5	7	40
Na_2WO_4	8	3	6
WO_3	10	7	40

* Time of the conversion of all D-galactal.

Table 2

Formation of D-galactose during hydroxylation of D-galactal as the function of the amount of Na_2MoO_4

$Na_2MoO_4 \cdot 2H_2O$ [mg]	D-Galactose [%]	Reaction time [hrs]
0.8	8	48
8	5	24
40	4	6
80	4	3
160	3	3

Table 3

Effect of pH on stereoselectivity of hydroxylation of D-galactal

pH	D-Galactose [%]	pH	D-Galactose
2	8	6	6
3	7	7	7
4	6	8	10
-	5	9	13

Table 4

Effect of temperature on stereoselectivity of hydroxylation of D-galactal

Temperature [°C]	D-Galactose [%]	Reaction time [hrs]
0	10	60
20	7	10
40	5	4
60	5	2
80	6	1
100	7	0.5

Table 5

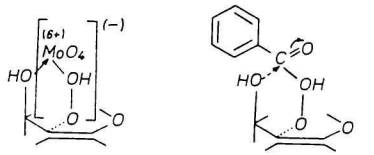
Effect of methanol concentration on stereoselectivity of hydroxylation of D-galactal

Methanol [%]	D-Galactose [%]	Note
0	5	With increasing concentration of methanol larger quantities of 2-deoxy-D-lyxo-hexose and D-tagatose are formed
20	7	
40	7	
60	9	
80	10	

of the reaction medium (Table 1). The stereoselectivity of the reaction was not substantially reduced when Na_2MoO_4 and MoO_3 were substituted by Na_2WO_4 and WO_3, respectively. The use of Na_2MoO_4, readily soluble in water, instead of MoO_3 was advantageous because it enabled to find a suitable selection of concentration of molybdate ions which form permolybdate ions with hydrogen peroxide. Increase of permolybdate ions concentration in the reaction medium led to higher stereoselectivity of the reaction and to abridgement of the reaction time (Table 2). The stereoselectivity of hydroxylation of D-galactal was also dependent upon the pH of the solution. *Bayer* and *Voelter* [22] reported that aldoses form complexes with sodium molybdate in aqueous medium between pH 5 and 7.8. They observed that the optimum complex formation occurs at pH 5.7—6. The optimum pH range for hydroxylation of D-galactal was found between pH 4 and pH 6 (Table 3). Increased quantities of D-galactose and 2-deoxy-D-lyxo-hexose were formed at lower pH values. Higher pH values of the reaction mixture caused also an increase in the formation of D-galactose and destruction products. Furthermore, it was found that the optimum reaction temperature is at 40—50°C (Table 4). At lower temperatures the hydroxylation proceeded slower and less stereoselectively; higher temperatures caused an increment in destruction products. The addition of methanol to the reaction mixture lowered the reaction stereoselectivity resulting in increased quantities of 2-deoxy-D-lyxo-hexose and destruction products and in the formation of tagatose (Table 5). Selection of suitable values of individual factors affecting the stereoselectivity of hydroxylation of D-galactal enabled to elaborate a preparative procedure for the preparation of D-talose in 90% yield accompanied by the formation of 3% of D-galactose and 3% of 2-deoxy-D-lyxo-hexose.

The mechanism of stereoselective hydroxylation of glycals by hydrogen peroxide in the presence of molybdate ions may be suggested in the following way: The permolybdate ions $[HMoO_6]^-$ form an initial transitory complex with D-glycal (*I*). The hydroxyl group at C-3, under the effect of the $C_2=C_1$ double bond, is sufficiently electronegative to form a coordination bond with the central molybdenum atom. The hydroxylation at C-2 then occurs from the same side of the rigid system where the transitory complex with C-3 hydroxyl group has been formed what results in *cis* addition. Similar orientation of reacting components may be assumed in the hydroxylation of D-glycals by perbenzoic acid (*II*). The difference between the degrees of stereoselectivity of hydroxylation of glycals by permolybdate ions and perbenzoic acid probably consists in ability of formation and in stability of these transitory reaction stages (*I* and *II*) (Scheme 1).

The suggested mechanism of stereoselective hydroxylation of glycals by permolybdate is supported by the observation that the substitution of the hydroxyl group at C-3



I *II*

Scheme 1

results in the formation of epimeric aldoses in the ratio 1 1. Equal amounts of 3-*O*-methyl-D-glucose and 3-*O*-methyl-D-mannose were obtained from 3-*O*-methyl-D-glucal. The substitution of C_4-OH is not so significant since the hydroxylation of maltal gave epi-maltose in a high yield. These results will be the subject of the forthcoming paper.

Experimental

Specific rotations were measured with a ETL-NPL, type 143 A automatic polarimeter and melting points were determined with a Kofler microstage apparatus. Water solutions were deionized on columns (100 × 4 cm) of Amberlite IR-120 (H^+) and Dowex 3 (OH^-). Mother liquors obtained after crystallization of D-talose were fractionated by chromatography on a Whatman CF 12 Cellulose column (110 × 6 cm) with butanol—ethanol—water (5 1 : 4 v/v). Starting D-galactal, prepared according to [5], had m.p. 98—100°C and $[\alpha]_D^{24}$ −6.6° (*c* 2.0, water).

Investigation of the stereoselectivity of hydroxylation

The stereoselectivity of hydroxylation of D-galactal was followed by paper chromatography of reaction mixtures on Whatman No. 1 paper with butanol—ethanol—water (5 : 1 4 v/v). The chromatograms were detected by diphenylamine reagent [23] and directly scanned with an ERI-10 densitometer (Zeiss, Jena). The stereoselectivity of hydroxylation was expressed as percentage of the *trans* epimer (D-galactose) formed.

a) Comparison of the catalytic effect of Na_2MoO_4, MoO_3, Na_2WO_4, *and* WO_3

In a mixture of 25 mg of MoO_3 or WO_3 in water (10 ml), or in 2×10^{-4} M solution of $Na_2MoO_4 \cdot 2H_2O$ (48 mg) or $Na_2WO_4 \cdot 2H_2O$ (66 mg) in water (10 ml), 1 g of D-galactal was dissolved followed by addition of 1 ml of 15% aqueous hydrogen peroxide. After one and two hours additional 1-ml portions of 15% hydrogen peroxide were added and the reaction mixture was left to stand at room temperature (Table 1).

b) Effect of Na_2MoO_4 *concentration*

To solutions of D-galactal (1.0 g) in water (10 ml) various amounts of sodium molybdate were added followed by addition of 15% aqueous hydrogen peroxide (3.0 ml). Resulting mixtures were then allowed to stand at room temperature (Table 2).

c) Effect of pH

To solutions of $Na_2MoO_4 \cdot 2H_2O$ (48 mg) and D-galactal (1.0 g) in different buffers (10 ml) ($CH_3COOH-H_3PO_4$ buffer for the pH region 2—6 ± 0.2 and KH_2PO_4—NaOH buffer

for the pH region $7-9 \pm 0.2$) 3 ml of 15% hydrogen peroxide in water were hourly added by 1-ml portions. The solutions were then left to stand at room temperature (Table 3).

d) Effect of temperature

Solutions of D-galactal (1.0 g) and $Na_2MoO_4 \cdot 2H_2O$ (48 mg) in water (10 ml) were adjusted to the temperature of 0, 20, 40, 60, 80, and 100°C. After addition of 15% aqueous hydrogen peroxide (3 ml) they were kept at the above given temperatures for a desired time (Table 4).

e) Effect of methanol concentration

Solutions of sodium molybdate (48 mg) in 0.5, 2.5, 4.5, 6.5, and 8.5 ml of water were made up to 8.5 ml with methanol. After addition of D-galactal (1.0 g) and 30% aqueous hydrogen peroxide (1.5 ml) the mixtures were kept at room temperature for 8 hours (Table 5).

Preparation of D-*talose*

To a solution of sodium molybdate (5 g) and D-galactal (100 g) in water (650 ml) 15% aqueous hydrogen peroxide (350 ml) was added at a rate to maintain the temperature of the reaction mixture between 35—40°C. (The addition of hydrogen peroxide took approximately 2 hours and was accompanied by changes of the pH of the starting solution. One third of the total volume of hydrogen peroxide solution shifted the pH 8 to pH 6, two thirds to pH 5.5 and the whole volume to pH 5.) After standing for 4 hours at room temperature, 5% palladized charcoal (1—2 g) was added and the mixture was stored for next 24 hours. The filtered mixture was deionized on columns of cation and anion exchange resins and the eluate was evaporated under reduced pressure to syrupy consistence. Remnants of water were removed by evaporation with anhydrous ethanol. The syrupy product was dissolved in methanol (500 ml) and crystallized (5 days, room temperature) to give 84 g of D-talose. The mother liquor, evaporated to syrupy and crystallized from 50 ml of methanol, for 8 days at room temperature, gave additional 13 g of D-talose. The products were combined, dissolved in water (50 ml) under heating and crystallized after the addition of 400 ml of ethanol for 3 days (room temperature) to give 84 g of recrystallized D-talose. Crystallization of the concentrated mother liquors from the second crystallization and recrystallization from 50 ml of methanol with the aid of 0.1 g of crystalline D-talose for two weeks at room temperature and after that for two weeks at 5°C afforded 15 g of D-talose. Recrystallization of this product from the mixture of 7 ml of water and 60 ml of ethanol gave second crop of recrystallized D-talose, 11 g. Fractionation of the final mother liquor on a cellulose column yielded 16 g of D-talose, 3 g of D-galactose and 3 g of 2-deoxy-D-lyxo-hexose. The overall yield of D-talose was 111 g, 90%.

Next recrystallization of D-talose from 50% methanol gave material having m.p. 128—132°C, $[\alpha]_D^{26}$ $+20.0 \pm 0.5°$ (*c* 2, water). Ref. [5] m.p. 133—134°C, $[\alpha]_D^{20}$ $+20.8°$ and ref. [4] m.p. 130—135°C, $[\alpha]_D^{27}$ $+19.7°$.

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