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Alkali and Oxygen—Alkali Treatment of 4-Deoxy-2,3-hexodiulose and 3-Deoxy-*erythro*-pentose

LARS-ÅKE LINDSTRÖM and OLOF SAMUELSON

Department of Engineering Chemistry, Chalmers University of Technology, Fack, S-402 20 Göteborg, Sweden

In oxygen-free solutions ($NaHCO_3$ and NaOH), the decomposition of 4-deoxy-2,3-hexodiulose, *1*, to 3-deoxypentulose and formic acid is more important than rearrangement reactions. These give rise to 3-deoxy-2-*C*-(hydroxymethyl)pentonic and 1,4-anhydro-3-deoxypentitol-2-carboxylic acids. In NaOH a substantial amount of 3,4-dideoxypentonic acid is formed from 3-deoxypentulose. During treatment of *1* under oxygen pressure the cleavage to 3,4-dihydroxybutanoic and glycolic acids is the predominant reaction. Large amounts of less polar, UV-absorbing solutes were formed, particularly in the absence of oxygen.

3-Deoxy-2-*C*-(hydroxymethyl)pentonic (isosaccharinic) acids are formed by endwise degradation of cellulose and other 1,4-linked polysaccharides in alkaline media.[1] Investigations carried out in recent years by improved chromatographic methods show, however, that under the conditions employed in technical processes large amounts of several other hydroxy acids are produced.[2] The isosaccharinic acids are formed by a benzilic acid rearrangement [3] of 4-deoxy-2,3-hexodiulose (*1*). We now report a detailed study of the hydroxy acids formed from this dicarbonyl compound. Since 3-deoxypentulose was found to be an intermediate, results with 3-deoxy-*erythro*-pentose (which is rapidly isomerized) are included.

RESULTS AND DISCUSSION

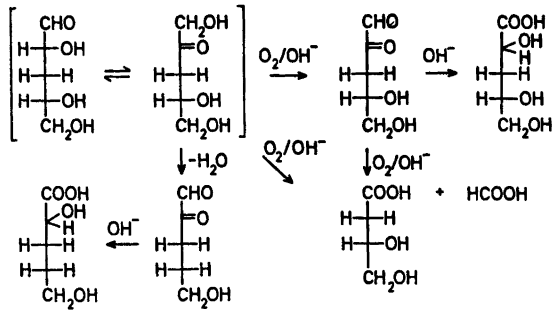
Degradation of 3-deoxy-erythro-*pentose.* The most abundant aliphatic carboxylic acid formed from 3-deoxy-*erythro*-pentose in aqueous NaOH at 75 °C in the absence of oxygen was 3,4-dideoxypentonic acid (yield 28 %). Except for 2,4-dihydroxybutanoic and 2-hydroxypropanoic acids (total yield 9 %) no appreciable amounts of other non-volatile carboxylic acids were produced.[4] Most of the sugar was converted to cyclic UV-absorbing compounds which were held firmly by the ion exchange resin (*cf.* Ref. 5).

Experiments in $NaHCO_3$ medium in the absence of oxygen showed that the yield of aliphatic hydroxy acids was even lower. Hence, the yield of 3,4-dideoxypentonic acid was only 10 % and the yields of 2,4-dihydroxybutanoic and 2-hydroxypropanoic acids less than 2 % under conditions which led to almost complete destruction of the sugar (5 h, 99 °C, 0.3 M $NaHCO_3$).

Table 1 shows that the formation of 3,4-dideoxypentonic acid was suppressed by the presence of oxygen and that 2,4-dihydroxy-

Table 1. Monocarboxylic acids obtained after degradation of 100 mg of 3-deoxy-D-*erythro*-pentose in 0.05 M sodium hydroxide at 90 °C under oxygen pressure (0.4 MPa) for 15 min.

Acid	Yield/mg
3-Deoxy-*threo*-pentonic	13.5
3-Deoxy-*erythro*-pentonic	2.3
3,4-Dideoxypentonic	6.6
3,4-Dihydroxybutanoic	25.6
2-Hydroxypropanoic	1.8
Glycolic	6.1
Formic	17.5
Total	73.4



Scheme 1.

butanoic acid was not formed. The formation of the two diastereomeric 3-deoxypentonic acids suggests that 3-deoxypentosulose is an important intermediate when oxygen is present. A benzilic acid rearrangement of this dicarbonyl compound explains the formation of these acids (Scheme 1). The observation that the *threo* form was the most abundant, is in agreement with the product composition observed after alkaline treatment of this dicarbonyl compound in the absence of oxygen.[6] The very large amounts of 3,4-dihydroxybutanoic and formic acids formed during O_2-NaOH-treatment of 3-deoxy-*erythro*-pentose suggest that the oxidative cleavage of its enediolate form and of 3-deoxypentosulose is important.

The higher yield of hydroxy acids obtained in the presence of oxygen shows that the reactions which give rise to nonpolar compounds are less important than in oxygen-free medium.

Degradation of 4-deoxy-2,3-hexodiulose (1). In the experiments with sodium hydroxide, *1* was consumed completely while about 1 % remained after the treatments in $NaHCO_3$ solution. No sugars were present after the treatments in NaOH while in $NaHCO_3$ in the absence of oxygen 3-deoxypentulose was the main product (Table 2). It has been postulated [7] that the corresponding 1,2-enediol is formed as an intermediate, after the loss of C-1 in *1* as formic acid, during alkali degradation of hexoses substituted at C-4. In agreement with this reaction scheme, formic acid was the most abundant acid produced in oxygen-free solution.

The instability of reducing sugars in strongly alkaline solution explains the absence of 3-deoxypentulose in the solutions obtained after the treatments in sodium hydroxide. The fact that formic acid was by far the most abundant acid in the absence of oxygen, together with other results referred to below, strongly indicates that 3-deoxypentulose is an important intermediate in this medium as well.

As already mentioned this intermediate gives a very low yield of aliphatic hydroxy acids, rather it yields a complex mixture of cyclic UV-absorbing solutes. Compounds of this type were eluted from the anion exchanger with water. Partition chromatography of this solution (without previous evaporation) in 92.4 % ethanol on the sulfate form of an anion exchanger showed that at least ten UV-absorbing compounds were present. A larger proportion was obtained in the fraction eluted with 5 M acetic acid. In the experiment in NaOH this fraction corresponded to 40 % of the starting material, while in $NaHCO_3$ medium the corresponding figure was 16 % (Table 2).

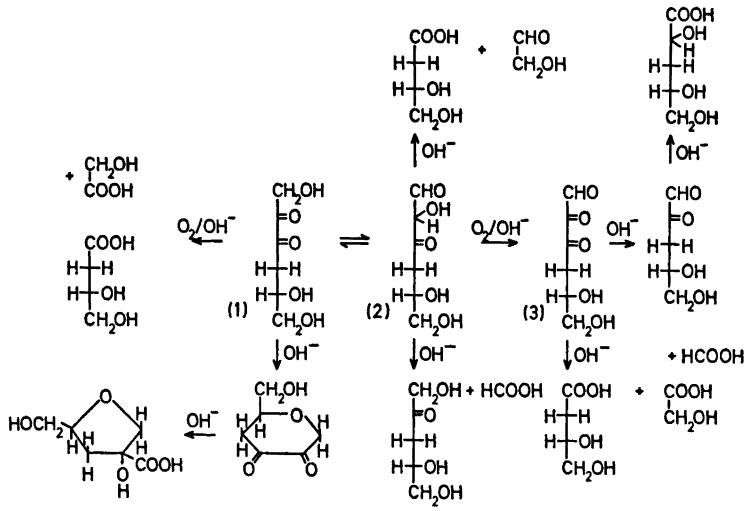
Only a minor amount of 3-deoxypentulose was present after the O_2-$NaHCO_3$-treatment. The low amount of formic acid produced in the experiments under oxygen pressure shows that reaction paths *via* 3-deoxypentulose are of little importance in the presence of oxygen.

Table 2 shows that the benzilic acid rearrangement of *1* to 3-deoxy-2-*C*-(hydroxymethyl) pentonic acids [8] is less important in bicarbonate than in sodium hydroxide solution. The same is true of the formation of 1,4-anhydro-3-deoxypentitol-2-carboxylic acid [8] which is an important reaction product in sodium hydroxide (Scheme 2). This acid has previously been isolated in appreciable amounts after alkali treatment of hydrocellulose and cellobiose.[4,9] Competing fragmentation reactions, of greater importance in the presence of oxygen, explain

Table 2. Products obtained after degradation at 90 °C of 100 mg of 4-deoxy-2,3-hexodiulose (*1*, purity 94 %).

	Reaction time 30 min				Reaction time 15 min[a]			
	0.05 M $NaHCO_3$		0.05 M NaOH		0.05 M $NaHCO_3$		0.05 M NaOH	
	mg	mmol mol reacted *1*	mg	mmol mol reacted *1*	mg	mmol mol reacted *1*	mg	mmol mol reacted *1*
Hexoses (incl. uloses)	1.5	14	0		1.3	12	0	
Tetroses (incl. ulose)	0.5	6	0		<0.1		0	
3-Deoxypentulose	25.3	325	0		1.5	19	0	
3-Deoxy-2-*C*-hydroxymethyl-*threo*-pentonic acid[b]	2.9	28	9.3	89	1.6	15	6.4	61
3-Deoxy-2-*C*-hydroxymethyl-*erythro*-pentonic acid[b]	0.4	3.8	2.7	26	<0.1	1.0	1.4	13
1,4-Anhydro-3-deoxypentitol-2-carboxylic acid	0.5	5.3	2.5	27	0.1		2.0	21
3-Deoxy-*threo*-pentonic acid[b]	0.2	2.2	0.6	6.9	0.5	5.7	7.9	91
3-Deoxy-*erythro*-pentonic acid[b]	0.1	1.2	0.3	3.4	0.3	3.4	2.0	23
3,4-Dideoxypentonic acid	<0.1		9.6	120	—		0.3	3.8
3,4-Dihydroxybutanoic acid	4.8	70	4.3	62	32.9	472	26.6	382
2,4-Dihydroxybutanoic acid	—		1.9	27	—		0.2	2.9
Glyceric acid	<0.1		<0.1		0.1	1.6	<0.1	
2-Hydroxypropanoic acid	<0.1		1.0	19	<0.1		1.8	34
Glycolic acid[c]	2.6	60	2.1	48	24.1	547	16.3	370
Formic acid[c]	12.8	480	16.6	620	1.4	53	4.8	180
C-(2,3-Dihydroxypropyl)tartronic acid	—		—		0.4	3.6	1.0	8.9
Identified compounds (total)	51.6	996	50.9	1048	64.2	1133	72.1	1191
Nonidentified compounds								
Eluted with water	11.2		4.9		17.8		2.0	
Eluted with 5 M acetic acid	15.9		39.8		16.5		25.7	

[a] Partial pressure of oxygen 0.4 MPa. [b] Relative amounts of the diastereomers determined by ion exchange chromatography. [c] Determined by ion exchange chromatography.



Scheme 2.

the lower yield of these acids in the experiments with oxygen present.

In the absence of oxygen, 3,4-dideoxypentonic acid was the second most abundant acid formed in sodium hydroxide. This supports the conclusion that 3-deoxypentulose is an important intermediate. Only a trace amount was formed in bicarbonate solution, explained by the greater stability of 3-deoxypentulose in this medium and by its ability to be easily converted to cyclic compounds.

The fact that only a trace amount of 3,4-dideoxypentonic acid was formed in bicarbonate medium in the absence of oxygen may seem puzzling since this acid was a major reaction product after treatment of hydrocellulose with 0.2 M $NaHCO_3$ at 120 °C.[5] Separate experiments with 3-deoxy-*erythro*-pentose in bicarbonate medium show, however, that the yield of 3,4-dideoxypentonic acid increases markedly with increasing reaction temperature and bicarbonate concentration.

The observation that 3,4-dideoxypentonic acid was virtually absent after the O_2-NaOH-treatment supports the conclusion that reaction paths *via* 3-deoxypentulose are of little importance in the presence of oxygen. The low recovery of strongly polar solutes in these experiments (64 and 72 %) indicates that less polar compounds are also formed *via* other reaction routes.

The diastereomeric 3-deoxypentonic acids formed in large amounts during O_2-NaOH-treatment of *1* are among the more abundant acids produced during a similar treatment of hydrocellulose.[10] The results obtained in the present work show that the reaction path *via* *1* (see Scheme 2) is very important although these acids can also be formed from hexosulose end groups.[11] A possible route for their formation is *via* oxidation of *2* (Scheme 2) to a compound containing three carbonyl groups (*3*). Elimination of formic acid followed by benzilic acid rearrangement of the 3-deoxypentosulose intermediate, yields the expected 3-deoxy-pentonic acids.[12]

As shown by Machell and Richards, 3,4-dihydroxybutanoic and glycolic acids are the predominant products obtained by treatment of *1* in hydrogen peroxide solution.[3] Similarly, these acids are among the most abundant acids produced during O_2-NaOH-treatment of hydrocellulose.[10] Table 2 shows that the same holds true for the treatment of *1* with oxygen in both alkaline media. Evidently, the oxidative cleavage of the bond between C-2 and C-3 in *1* is a rapid reaction and of greater importance than the reactions which give rise to formic acid and 3-deoxy-pentulose. 3,4-Dihydroxybutanoic and glycolic acids can also be formed from *3* in an analogous way to the formation of formic and 3-deoxy-pentonic acids.

In agreement with the results obtained with hydrocellulose the yields of these acids were much less in the absence of oxygen.[9] Hydrolytic cleavage of *2* (see Scheme 2) will give rise to 3,4-dihydroxybutanoic acid and glycolaldehyde, which is unstable in the alkaline solutions. Among the remaining reaction products were tetroses and hexoses formed by aldol condensation. As expected these sugars were present in detectable amounts only after the treatments in bicarbonate solution.

In the experiments carried out in the absence of oxygen no dicarboxylic acids of the types produced during alkali treatment of cellulose [13] and cellobiose [4] were recorded. On the other hand appreciable amounts of *C*-(2,3-dihydroxypropyl) tartronic acid were formed in the presence of oxygen. This acid is the major dicarboxylic acid formed during O_2-NaOH treatment of cellulose [14] and cellobiose.[15] Evidently one reaction path for the formation of this acid is *via 1*. Only trace amounts of other dicarboxylic acids were recorded.

EXPERIMENTAL

Preparation and characterization of 1. Maltose (20 g) was heated [3] under paraffin oil in 1000 ml of 0.05 M NaOH for 5 h at 25 °C. A cation exchanger (H^+) was added under stirring to decrease the pH to 7. The solution was then passed through 35 ml of an anion exchanger in the acetate form. The effluent was evaporated to a syrup at 35 °C. The syrup was chromatographed in 85 % (w/w) ethanol at 40 °C on an anion exchange resin in the sulfate form (Dowex 1-X8, 14 × 720 mm, 24 – 32 μm). The first 400 ml of eluate were evaporated. Rechromatography on the same column gave a broad peak (refractive index detector) with an adjusted retention volume of 1.5 bed volumes. This fraction was evaporated and rechromatographed in 92.4 % ethanol on Dowex 1-X8 (6 × 615 mm, 13 – 18 μm) in the sulfate form. The yield of the syrup was 1 %.

Oxidation with hydrogen peroxide gave 3,4-dihydroxybutanoic and glycolic acids.[3] Gas chromatography of the oxime-Me_3Si derivatives showed that besides the major product (*1*), 3 % of 3-deoxypentulose and 3 % of unknown compounds were present. The mass spectrum (AEI Organic MS-20, EI, 70 eV) of the major component confirmed the identity. [*m/e* 552, M^+, (0.1 % of base peak at *m/e* 73) 537 (0.4), 462 (0.9), 449 (2.4), 373 (4.4), 359 (3.2), 345 (0.8), 317 (1.2), 293 (0.5), 283 (2.3), 253 (5.3), 230 (3.0), 218 (5.0), 215 (2.5), 205 (9.0), 191 (11.0), 188 (7.0), 147 (36.0), 117 (6.5), 103 (16.0)]. Reduction to 3-deoxyhexitols confirmed that the purity was 94 %.

Procedure. In the experiments in the absence of oxygen paraffin oil was layered onto a boiled solution (90 ml) of NaOH or $NaHCO_3$. The solution was kept at 90 °C and the sample (60 mg) dissolved in boiled water (5 ml) was injected with an all-glass syringe into the aqueous solution which was stirred magnetically. The experiments under oxygen pressure (0.4 MPa) were made in a Teflon-lined autoclave under efficient magnetic stirring. Oxygen (10 ml/min determined at 22 °C and atmospheric pressure) was passed through the preheated solution and the sample was introduced as described above. After the reaction times given in the tables the reaction vessels were cooled with ice water.

Analyses. Formic acid was determined in an aliquot of the reaction solution.[10] The other products were analyzed after a group separation on an anion exchange resin in the acetate form. Sugars and other strongly polar non-electrolytes were washed out with water (5 bed volumes). Monocarboxylic acids and "less polar solutes" were eluted with 5 M acetic acid (15 bed volumes). Dicarboxylic acids were eluted with 0.5 M magnesium acetate (4 bed volumes).

The sugars were determined by partition chromatography in 85 % (w/w) ethanol on the sulfate form of an anion exchanger or on a cation exchanger in the lithium form.[16,17] The peak positions and colour responses were compared with those of authentic samples. The results were confirmed by gas chromatography of the oxime – Me_3Si derivatives.[18] The mass spectrum of the major sugar was consistent with that of 3-deoxypentulose. Partition chromatography of the *erythro* and *threo* forms of 3-deoxypentitol obtained after borohydride reduction confirmed the indentity. This method was also employed for confirmation of the identity of the tetroses.

The fraction eluted with 5 M acetic acid was rechromatographed in 0.08 M sodium acetate (acetic acid added to pH 5.9) and in 0.5 M acetic acid on anion exchange columns coupled to a three-channel analyzer.[19] The quantitative determinations of the monocarboxylic acids were made either from these chromatograms or by temperature programmed (80 – 240 °C) gas chromatography of the Me_3Si derivatives on two parallel columns.[20] Perseitol was used as internal standard. Analysis of a solution containing known amounts of gluconic, arabinonic and glyceric acids showed that the response of the detector (FID) was approximately proportional to the weight of the derivatives. This relationship was employed for the determination of the acids obtained in the present work. Final identification was obtained by gas chromatography-mass spectrometry.[18,21]

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