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MECHANISMS FOR HYDROPEROXIDE DEGRADATION OF DISACCHARIDES AND RELATED COMPOUNDS*

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ABSTRACT

The reactions of disaccharides with alkaline hydrogen peroxide were studied under diverse conditions. Treatment of cellobiose, lactose, and maltose with aqueous sodium peroxide afforded, in each instance, the corresponding aldobionic acid, the next lower aldobionic acid, 2-*O*-D-glucopyranosyl-D-erythronic acid, and formic acid. On the other hand, melibiose and gentiobiose afforded the corresponding aldobionic acid, the next lower aldobionic acid, and a 2-*O*-D-glycopyranosylglycolic acid.

The yields of products varied widely with the experimental conditions, especially with the proportions of alkali peroxide and hydrogen peroxide. The reactions with alkali peroxide were slow, but rapid in the presence of hydrogen peroxide with the gradual addition of alkali. The results indicate that degradation of carbohydrates by alkaline hydrogen peroxide takes place by five reaction paths. These are designated the alpha-hydroxy hydroperoxide cleavage-mechanism, the Baeyer–Villiger mechanism, the ester mechanism, the dihydroxy-epoxide mechanism, and a newly proposed peroxy-radical mechanism.

The last-named mechanism is more rapid than the others. With an excess of hydrogen peroxide and slow addition of alkali, it results in rapid, stepwise conversion of both reducing and nonreducing saccharides into formic acid. The process begins with formation of a hydroperoxide adduct of the carbohydrate. Reaction of the adduct with hydrogen peroxide affords a peroxy radical and a hydroxyl radical. The peroxy radical decomposes, affording formic acid, the next lower aldose and hydroxyl radical. Hydroxyl radical produced in a chain reaction oxidizes alditols and aldonic acids by reactions analogous to those of the Fenton reagent.

DISCUSSION OF REACTION MECHANISMS

The purpose of the investigation was to determine the reaction paths whereby disaccharides are degraded by alkaline hydrogen peroxide. The systems are

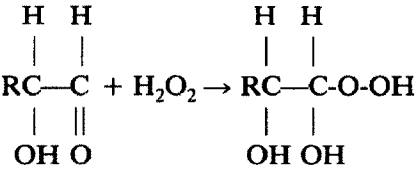
*Reactions of Carbohydrates with Hydroperoxides, Part XVII. For Part XVI, see ref. 1. For a preliminary report, see ref. 2.

complex, and the ensuing reactions depend upon several interrelated processes. By selecting conditions that favor one process over others, several reaction paths have been recognized, and used for rationalization of the products formed.

The course of the reactions under diverse conditions depends, in part, on the inherent properties of hydrogen peroxide as an oxidant. Under acid conditions, in the absence of a catalyst, carbohydrates are substantially inert to aqueous hydrogen peroxide; but, under alkaline conditions, carbohydrates having a free, or potentially free, carbonyl group react readily. The difference in the behavior of the oxidant under acid and alkaline conditions arises, in part, from the absence or presence of hydroperoxide anion (Eq. *1*). The anion reacts with hydrogen peroxide affording

$$H_2O_2 \rightarrow OOH^- + H^+ \qquad (1)$$

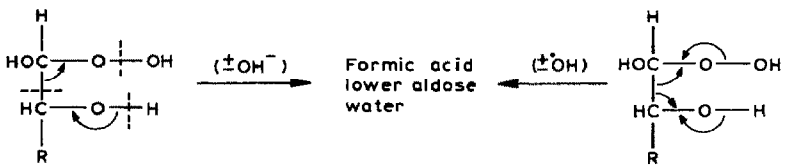
$$OOH^- + H_2O_2 \rightarrow {}^{\cdot}OOH + {}^{\cdot}OH + OH^- \qquad (2)$$



(3)

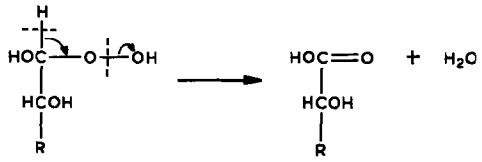
hydroxyl radical, hydroperoxide radical, and hydroxyl ion (Eq. *2*). The anion also forms an adduct with any carbonyl group in the substrate (Eq. *3*). In the course of time, the adduct decomposes, with cleavage of the O–O bond. The bond may be ruptured by any of the following mechanisms: the alpha-hydroxy hydroperoxide-cleavage mechanism (see Scheme 1); the Baeyer–Villiger mechanism (Scheme 2); the ester mechanism (Scheme 3); the dihydroxy-epoxide mechanism (Scheme 4); and the peroxy-radical mechanism (Scheme 5).

The process of Scheme 1, the alpha-hydroxy hydroperoxide cleavage-mechanism (hereinafter called the αHHP cleavage mechanism) is the most common process for the degradation of reducing carbohydrates by alkaline hydrogen peroxide. With a molecule of an aldose, it results in a molecule of formic acid and of the next lower aldose. Repetition of the process leads to stepwise degradation of the aldose to lower aldoses and formic acid[3–5]. The process may take place



Ionic mechanism Free-radical mechanism

Scheme 1. Alpha-hydroxy hydroperoxide cleavage mechanism.



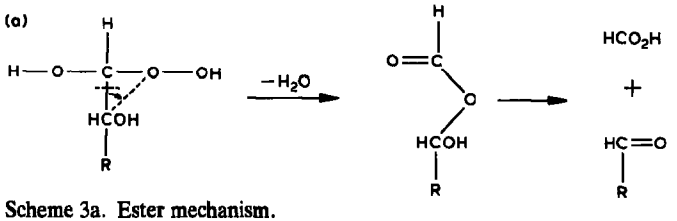
Scheme 2. Baeyer–Villiger mechanism.

heterolytically with elimination of hydroxyl ion, or homolytically, with elimination of hydroxyl radical.

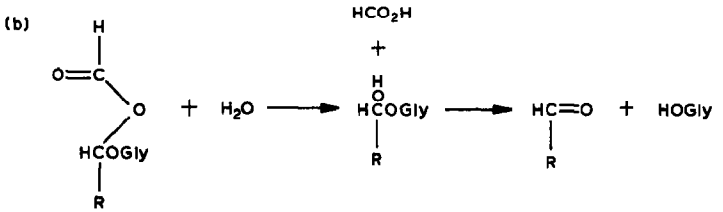
The process of Scheme 2, the Baeyer–Villiger mechanism, involves rupture of the O–O bond by electrons from the C-1–hydrogen bond, with production of a carbonyl group and water. The reaction leads to the corresponding aldobionic acid without loss of formic acid. The mechanism is considered to be ionic in character[6].

The process of Scheme 3a, the ester mechanism, involves formation of a hydroperoxide adduct, followed by rupture of the O–O bond by electrons from the C-1–C-2 bond. Hydrolysis of the resulting formic ester affords formic acid and the next lower aldose or aldose derivative. With a 2-*O*-glycosylaldose, this affords the easily hydrolyzable glycosyl hemiacetal of the next lower aldose. Hydrolysis of the hemiacetal affords two aldoses which, by further reaction with hydrogen peroxide, are degraded to formic acid (see Scheme 3b).

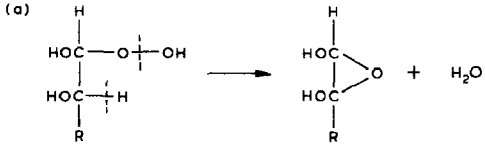
The process of Scheme 4, the dihydroxy-epoxide mechanism, begins with the rupture of the O–O bond (Scheme 4a) and formation of the epoxide, which may serve as an intermediate in numerous reactions. By reaction with hydrogen peroxide (see Scheme 4b), it affords two acids, RCO_2H and $R'CO_2H$, where R and R′ depend on the location of the epoxide within the molecule.



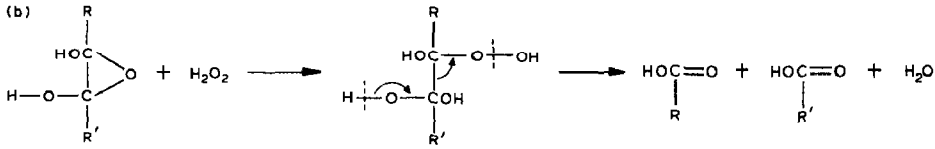
Scheme 3a. Ester mechanism.



scheme 3b. Ester cleavage of a 2-*O*-glycosyl derivative.

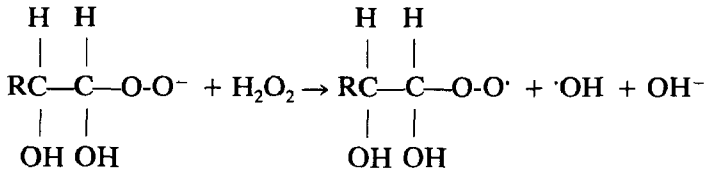


Scheme 4a. Formation of a dihydroxy-epoxide.



Scheme 4b. Hydroperoxide cleavage of a dihydroxy peroxide.

The process of Scheme 5a, the peroxy-radical mechanism, involves rupture of the O–O bond of the hydroperoxide adduct of an aldose by way of an intermediate peroxy radical. The peroxy radical may be formed by reaction of the hydro-



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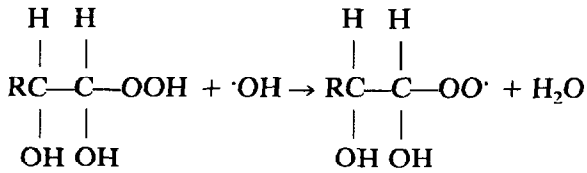
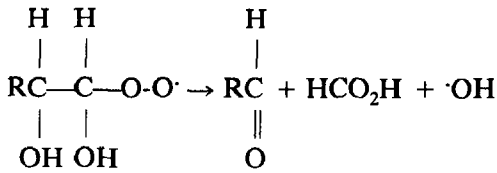


(4b)



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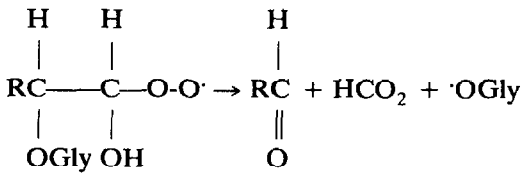
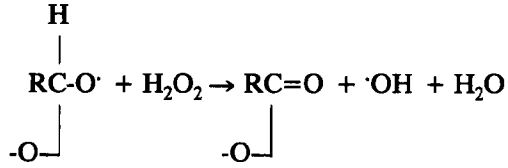


(6)

Gly = glycosyl group



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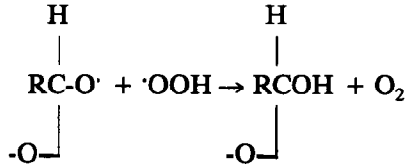
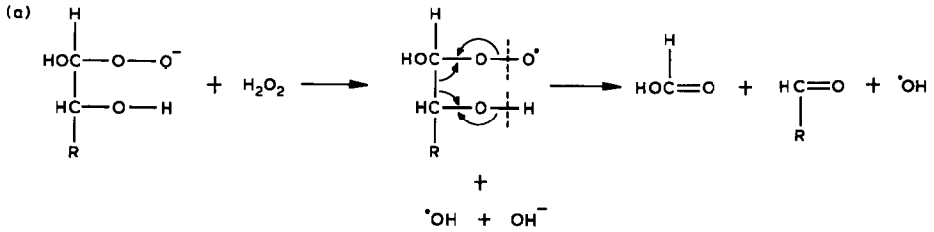
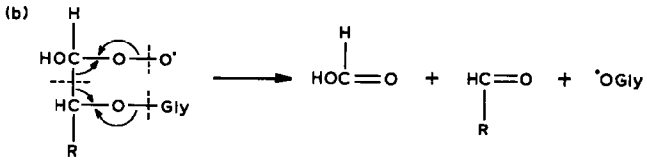


(7a)

peroxide anion of the adduct with hydrogen peroxide (Eq. *4a*) or, alternatively, by reaction of the adduct with hydroxide radical (Eq. *4b*). The peroxy radical decomposes rapidly, giving the next lower aldose, formic acid, and hydroxyl radical (Eq. *5*). By the reactions of Eqs. *3, 4,* and *5*, the aldose is degraded to the carbon atom adjacent to the glycosidic group. The peroxy radical having the glycosidic group in the alpha position decomposes with production of the lower aldose, formic acid, and the glycosidic radical (Scheme 5b and Eq. *6*). The glycosidic radical, by reaction with hydrogen peroxide, gives the corresponding aldohexonic lactone (Eq. *7*). Alternatively, reaction with the hydroperoxide radical affords the corresponding hexose and oxygen (Eq. *7a*). It has been found experimentally that complete degradation of the disaccharide yields between 11 and 12 mol of formic acid per mol. Because degradation of the hexose would give 6 mol, and that of the lactone, 5 mol, the results indicate that both the lactone *and* the hexose are involved in the degradation.



Scheme 5a. Peroxy-radical mechanism.



Scheme 5b. Peroxy-radical cleavage of a glycosyloxy group (·OGly).

Carbohydrates lacking a carbonyl group are inert to aqueous hydrogen peroxide, but, as shown by Fenton[7], hydrogen peroxide in the presence of ferrous ion oxidizes alditols, aldonic acids, and other compounds with formation of carbonyl derivatives. The mechanism was unclear until Haber and Weiss[8] established that reaction of hydrogen peroxide with hydroperoxide anion affords hydroperoxide radical, hydroxyl radical, and hydroxyl ion (Eq. *2*), and that reaction of hydrogen peroxide with ferrous ion affords hydroxyl radical which oxidizes alcohol groups in the chain reactions of Eqs. *8*, *9*, and *10*.

$$H_2O_2 + Fe^{2+} \rightarrow {}^{\cdot}OH + OH^- + Fe^{3+} \qquad (8)$$

$$RCH_2OH + {}^{\cdot}OH \rightarrow R\dot{C}HOH + H_2O \qquad (9)$$

$$R\dot{C}HOH + Fe^{3+} \rightarrow \underset{\displaystyle H}{\overset{\displaystyle |}{RC{=}O}} + H^+ + Fe^{2+} \qquad (10)$$

A mixture of hydrogen peroxide and hydroperoxide anion oxidizes alditols and aldonic acids in much the same manner as does the Fenton reagent. Thus, hydroxyl radical formed in a chain reaction oxidizes an alcohol group, forming radical R$\dot{C}$HOH (Eq. *9*). This reacts with hydrogen peroxide instead of ferric ion affording a carbonyl group, hydroxyl radical, and water (Eq. *11*).

$$R\dot{C}HOH + H_2O_2 \rightarrow \underset{\displaystyle H}{\overset{\displaystyle |}{RC{=}O}} + {}^{\cdot}OH + H_2O \qquad (11)$$

In the present reaction-system, degradation of the carbohydrate and formation of oxygen take place concurrently. Oxygen is formed by the chain reaction of Eqs. *2*, *12*, *13*, and *14*. In the first step, hydroperoxide radical is formed by reaction *2*. This radical is a weak acid; under alkaline conditions, it exists almost entirely

$$H_2O_2 + {}^{\cdot}OH \rightarrow {}^{\cdot}OOH + H_2O \qquad (12)$$

$${}^{\cdot}OOH \rightarrow {}^{\cdot}O_2^- + H^+ \qquad (13)$$

$$H_2O_2 + {}^{\cdot}O_2^- \rightarrow {}^{\cdot}OH + OH^- + O_2 \qquad (14)$$

in the form of superoxide radical O_2^- (Eq. *13*). Superoxide radical reacts with hydrogen peroxide affording hydroxyl radical and oxygen (Eq. *14*)[9]. The relative importance of the oxygen and carbohydrate reactions depends on the temperature, the concentration of constituents, and even the manner in which the reagents are mixed. This is not surprising, in view of the following quotation from Mellor's treatise on inorganic chemistry[10].

TABLE I

REACTIONS OF DISACCHARIDES WITH ALKALINE HYDROGEN PEROXIDE UNDER DIVERSE CONDITIONS

Experiment no.	*Reaction mixture per millimole of disaccharide*	*Temp. (degrees)*	*Time (days)*	*Millimoles of HCO_2H per millimole of disaccharide*				
				Cellobiose	*Lactose*	*Maltose*	*Melibiose*	*Gentiobiose*
1	50 mL of M Na_2O_2	4	1	0.9	0.8	1.0	2.3	1.5
			2	1.8	1.5	1.0	4.8	3.5
			3	1.9	1.8	1.3	6.2	4.2
			7	3.3	3.7	2.8	8.0	5.0
2	50 mL of saturated BaO_2	25	1	0	0.8	0.4	1.0	1.0
			3	1.0	1.4	0.6	1.9	2.2
			7	2.7	2.5	1.3	3.6	3.6
3	12.5 millimoles of Na_2O_2 in 50 mL of M KOH	4	1	0.4	0.4	0.3	1.3	1.0
			2	0.9	0.6	0.6	2.2	1.7
			5	1.5	1.6	1.3	4.1	3.3
			7	1.6	1.9	1.5	4.7	4.4
			15	3.4	3.7	2.6	6.7	6.4
4	12 mL of 2M KOH[a], 4 mL of 30% H_2O_2, 4 mL of H_2O	4	1	10.3	11.1	10.3	10.9	11.0
			2	11.1	11.5	11.0	11.2	11.1
			6	11.1	11.5	11.0	11.2	11.1

[a]KOH was added dropwise during 30 min to the H_2O_2–disaccharide solution.

"If sodium carbonate be added to hydrogen peroxide, the corresponding alkaline peroxide is formed and carbon dioxide is evolved; on the contrary, if hydrogen peroxide be added to a solution of the carbonate, oxygen is evolved.

$$2\,H_2O_2 + Na_2CO_3 = Na_2CO_3 + 2\,H_2O + O_2$$

The sodium carbonate acts as a catalytic agent in the latter case. It is not at all uncommon to find reactions progressing differently according to the way in which the substances were mixed together".

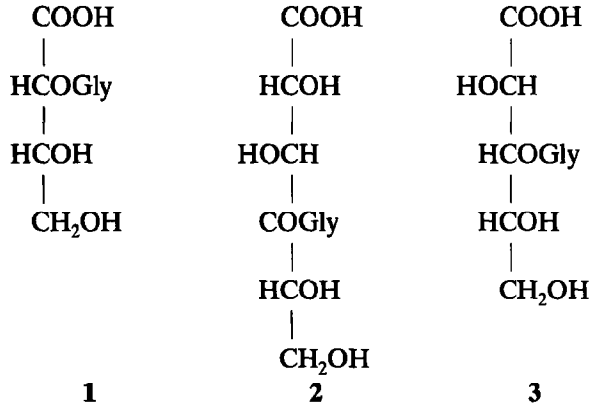
It is now known that sodium carbonate is not a catalyst for the process. Hydrogen peroxide decomposes sodium carbonate forming sodium peroxide, a normal acid–base reaction. As already noted, oxygen arises from the chain reaction of Eqs. *12, 13,* and *14*. The chain is terminated by Eq. *15*.

$$\cdot OOH + \cdot OH \rightarrow O_2 + H_2O \qquad (15)$$

RESULTS

In a preliminary study[2], it was found that, when certain disaccharides are treated with aqueous sodium peroxide, the optical rotations show a fairly rapid change, followed by a slow change whereby the optical rotations approach zero. To obtain a clearer understanding of the degradation under diverse conditions, the course of the reactions was monitored by determining formic acid and by separating and identifying other reaction products. In view of the optical rotations and the products formed, it seemed probable that concurrent heterolytic and homolytic reactions occurred, to some extent, in all experiments.

Table I reports the yields of formic acid obtained from several disaccharides by reaction with alkaline hydrogen peroxide under diverse conditions. Under the conditions of Experiment 1 (M sodium peroxide at 4°) little oxygen was evolved, indicating that homolytic reactions were of little importance. The disaccharides reacted slowly and gave the products expected for heterolytic cleavage of the hydroperoxide adducts. After three to seven days, each of the 4-*O*-glycosyl-D-glucoses afforded a 2-*O*-glycosylaldonic acid (**1**), small proportions of the aldobionic acid (**2**) corresponding to the original substrate, and the aldobionic acid (**3**) containing one carbon atom fewer than **2**. Formation of **1** may be explained by stepwise degradation of the disaccharide by the αHHP cleavage mechanism to the carbon atom adjacent to the glycosidic linkage (see Scheme 1), followed by the oxidation of the resulting 2-*O*-glycosyl-aldose by the Baeyer–Villiger reaction (Scheme 2). This reaction also accounts for the formation of aldobionic acid **2** by oxidation of the original disaccharide, whereas formation of aldobionic acid **3** may be ascribed to decomposition of the hydroperoxide adduct of the disaccharide by the dihydroxy-epoxide reaction (Scheme 4).



1 **2** **3**

Gly = glycosyl group.

Crystalline brucine salts of aldobionic acids of types **1, 2,** and **3** were prepared by the procedure developed by El Khadem[11] for preparation and separation of the brucine salts of 3-*O*-α-D-glycopyranosyl-D-arabinonic acid and 3-*O*-β-D-galactopyranosyl-D-arabinonic acid.

The reactions of disaccharides with barium peroxide in suspension (Experiment 2) were similar to those with sodium peroxide, but slower, because of the low solubility of barium peroxide. The concentration of hydroperoxide anion remained fairly constant during the reaction period, because barium peroxide dissolved as the reaction proceeded.

Experiment 3 was conducted to ascertain the effect of the addition of an alkali hydroxide to a reaction mixture containing sodium peroxide. The reaction was less rapid than that with sodium peroxide alone, presumably because the highly alkaline solution contains less of both hydroperoxide anion and hydrogen peroxide. The production of more formic acid per mol of melibiose and gentiobiose than per mol of cellobiose, maltose, and lactose shows that, in a disaccharide, sodium peroxide ruptures the 6-*O*-glycosyl more readily than the 4-*O*-glycosyl bond.

Experiment 4 was conducted in order to study the degradation of disaccharides by hydrogen peroxide, with *gradual* addition of an alkali. The results were entirely different from those obtained with hydrogen peroxide alone. The reactions were rapid, and accompanied by the evolution of much oxygen. In the course of a few hours, the optical rotations of the reaction mixtures decreased to zero, showing complete conversion of the substrates into optically inactive products. Surprisingly, after only one day, 11 of the 12 carbon atoms in the substrate had been converted into formic acid. In other experiments, it was found that, under the same conditions, aldonic acids, alditols, and other nonreducing saccharides are also nearly completely degraded to formic acid, although they are not oxidized by either hydrogen peroxide or alkali peroxide alone.

EXPERIMENTAL

General. — Evaporations were conducted under diminished pressure at a bath temperature of less than 40°. Optical rotations were measured with a Perkin–Elmer model 141 photoelectric polarimeter; i.r. spectra were recorded in either Nujol mulls or potassium bromide pellets, with a Perkin–Elmer Infracord model 137 spectrophotometer. Lactose, cellobiose, and maltose were of the highest commercial grade. Melibiose[12] and gentiobiose[13] were prepared by the methods cited. The 30% hydrogen peroxide was represented as containing <0.005% of Fe, and the potassium hydroxide (A.C.S. grade), <0.001% of Fe. Amberlite IR-120 (H^+) cation-exchange resin and Duolite A-4 (OH^-) anion-exchange resin were employed for deionizations. Formic acid was determined by the mercuric chloride method as previously described[5].

Experiment 1 of Table I. — Oxidation of disaccharides by sodium peroxide. Samples of cellobiose, lactose, maltose, melibiose, and gentiobiose (3 mmol each) were dissolved in ice-cold, aqueous sodium peroxide (150 mL, M). The solutions were held at 4° in lightly stoppered flasks. From time to time, 5-mL samples of the reaction mixture were withdrawn, and formic acid was determined by the mercuric chloride method. For isolation and identification of the non-volatile organic acids, a 50-mL sample of each reaction mixture was taken after five days. The excess of peroxide in each sample was decomposed by adding moist cation-exchange resin (75 mL) and activated carbon (2 g) and warming slightly. When evolution of oxygen had ceased, the resin and activated carbon were separated by filtration, washed with water, and discarded. Portions of the effluent were used for (*a*) preparation of the nonvolatile acids, (*b*) hydrolysis of the nonvolatile acids and identification of their components, and (*c*) preparation of the brucine salts of the nonvolatile acids.

(*a*) *Preparation of the nonvolatile acids.* — A portion of the decationized solution, containing the products from 1 mmol of the disaccharide, was passed through anion-exchange resin (10 mL). The acids retained on the resin were eluted with 10% ammonium hydroxide. After concentration to remove the excess of ammonia, the solution was passed through cation-exchange resin, and the effluent was freeze-dried. The yields of the nonvolatile acids are reported in Table II.

(*b*) *Hydrolysis of the nonvolatile acids, and identification of their constituents.* A portion of the nonvolatile acid fraction from the oxidation of each disaccharide was heated with 2.5% sulfuric acid (10 mL) for 4 h under reflux. Sufficient barium carbonate was added to neutralize the sulfuric acid and saponify any lactone present. After filtration, the filtrate was passed successively through cation- and anion-exchange resins (20 mL each). Evaporation of the neutral effluents afforded crystalline D-glucose ($[\alpha]_D^{25}$ +52 ±2°) from cellobiose, maltose, and gentiobiose, and crystalline D-galactose ($[\alpha]_D^{25}$ +80 ±2°) from lactose and melibiose. The sugars were identified by comparative i.r. spectra.

The acids retained on the anion-exchange resins in these experiments were eluted with aqueous ammonium hydroxide. Each eluate was concentrated to

TABLE II

PREPARATION AND HYDROLYSIS OF NONVOLATILE ACIDS FROM DISACCHARIDES[a]

Substrate	*Formic acid (millimoles per millimole)*	*Nonvolatile acids percent by weight*	*Major reaction-product*	*Major hydrolysis-products*	
				Sugar	*Acid*
Cellobiose	2.7	69.8	2-*O*-β-D-Glucopyranosyl-D-erythronic acid	D-Glucose	D-Erythronic acid
Lactose	2.8	60.1	2-*O*-β-D-Galactopyranosyl-D-erythronic acid	D-Galactose	D-Erythronic acid
Maltose	2.6	60.4	2-*O*-α-D-Glucopyranosyl-D-erythronic acid	D-Glucose	D-Erythronic acid
Melibiose	5.3	54.2	*O*-α-D-Galactopyranosylglycolic acid	D-Galactose	Glycolic acid
Gentiobiose	4.1	65.1	*O*-β-D-Glucopyranosylglycolic acid	D-Glucose	Glycolic acid

[a]Prepared after 5 days under the conditions of Experiment 1 of Table I.

remove ammonia, and then passed through cation-exchange resin (20 mL). The resulting solutions containing the aldonic acids derived from the cellobiose, lactose, and maltose experiments were evaporated to dryness and dehydrated by adding and evaporating three successive portions of toluene (5 mL) with intermediate heating for 2 h at 100°. Extraction of the residue with hot ethyl acetate (100 mL), and evaporation of the extract afforded, in each instance, crystalline D-erythrono-1,4-lactone[14]. This was identified by its melting point (102 ±2°) and its optical rotation ($[\alpha]_D^{25}$ −73 ±2°). Its i.r. spectrum was identical to that of authentic D-erythrono-1,4-lactone.

The acid solutions obtained by hydrolysis of the products from gentiobiose and melibiose were neutralized with lithium hydroxide. The acid from gentiobiose (0.23 g) required, for neutralization, 55.0 mL of 0.5M lithium hydroxide (theory, 60.5 mL), whereas that from melibiose (0.25 g) required 58.0 mL (theory 65.8 mL). Concentration of the neutral solutions, followed by addition of methanol to incipient turbidity gave, in each instance, crystalline lithium glycolate. Its i.r. spectrum was identical to that of authentic lithium glycolate.

(*c*) *Preparation of the brucine salts of the nonvolatile acids.* A portion of the nonvolatile acids prepared from 1 mmol of each disaccharide was dissolved in water (10 mL), and sufficient brucine was added to neutralize the acid and leave a small excess. After a reaction period of 18 h, the excess of brucine was extracted with three 10-mL portions of 1,2-dichloroethane. The aqueous solutions containing the brucine salts were evaporated to thick syrups in a rotary evaporator. Each syrup was stored over calcium chloride in a desiccator until a nearly solid, crystalline mass formed.

Experiment 2 of Table I. — Oxidation of disaccharides by barium peroxide. Each disaccharide (2 mmol) was added, with stirring, to a suspension of barium peroxide (5 g) in water (100 mL). The mixture was stirred at ambient temperature (<25°). From time to time, samples were taken, and after removal of the excess of barium peroxide, formic acid was determined as recorded in Table I.

Experiment 3 of Table I. — Oxidation of disaccharides by sodium peroxide in a high concentration of potassium hydroxide. Each of the disaccharides (2 mmol) listed in Table I was dissolved in an ice-cold solution (100 mL) containing sodium peroxide (25 mmol) and potassium hydroxide (100 mmol). The mixture was kept at 4°. At suitable intervals, optical rotation measurements were made, and 5-mL aliquots of the solutions were used to determine formic acid. There was little evolution of oxygen, and considerable peroxide was present after 7 d, when the experiment was terminated. The formic acid from cellobiose, maltose, and lactose was <2 mmol per mmol of disaccharide. However, the formic acid from melibiose and gentiobiose was >4 mmol per mmol, indicating that the glycosidic linkage had been ruptured, and the resulting D-glucose or D-galactose partially degraded to formic acid.

Experiment 4 of Table I. — Oxidation of disaccharides in media containing substantial concentrations of both hydrogen peroxide and hydroperoxide anion.

During 30 min, ice-cold potassium hydroxide (12 mL, 2M) was added dropwise, with mechanical stirring, to ice-cold aqueous hydrogen peroxide (8 mL, 4.5M) containing 1 mmol of the disaccharide. The mixture was held at 4°. Evolution of oxygen began almost immediately, and continued for several hours. After 24 h, the volume of the solution was adjusted to 50 mL, the optical rotation was measured, and a sample (10 mL) was taken for determination of formic acid. In the course of one day, the optical rotation of the reaction mixture decreased to zero, and ~11 mmol of formic acid were derived from each 12-carbon sugar.

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