

Summary

The direct action of triphenylchloromethane upon α -methyl-D-mannopyranoside in pyridine, yields 6-trityl- α -methyl-D-mannopyranoside, which is described. This substance forms a crystalline addition compound with calcium

chloride. The position of the trityl group was proved by conversion of the trityl methyl-mannopyranoside through a series of reactions to 6-monomethyl-glucosazone. The intermediate compounds are described.

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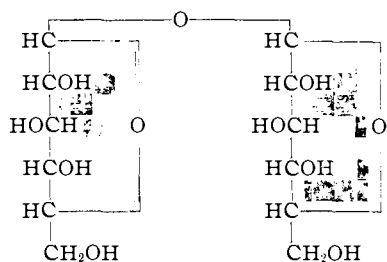
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Periodic Acid Oxidation of α,α -Trehalose¹

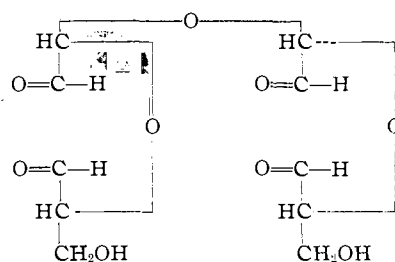
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The two glucose components of the molecule of naturally occurring trehalose ($[\alpha]^{20}_D + 197^\circ$ in water) are now generally recognized from methyl-

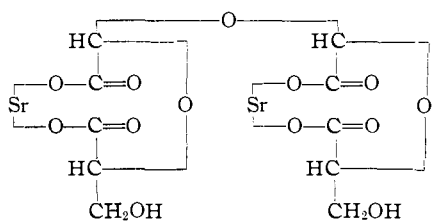
Trehalose (I) should be oxidized by periodic acid in the same manner as the methyl-D-aldohexopyranosides⁴ to produce the tetraaldehyde (II).



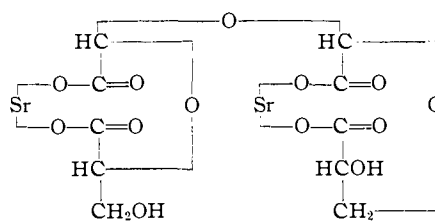
(I)
 α,α -Trehalose



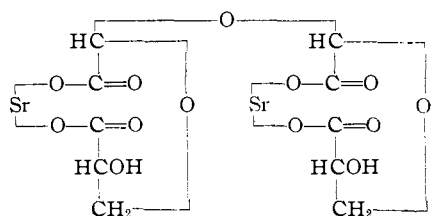
(II)
d',d'-Oxy-bis-(d-hydroxymethylidiglycolic aldehyde)⁵



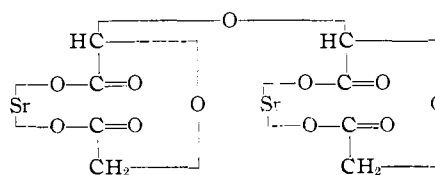
(III)
Di-strontium d',d'-oxy-bis-(d-hydroxymethylidiglycolate)



(IV)



(V)



(VI)

tion results to have the pyranoside structure² and from rotatory considerations the alpha, alpha configuration³ for carbon atoms 1 and 1'.

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Schlubach and Maurer, *Ber.*, **58**, 1178 (1925); cf. Bredereck, *ibid.*, **63**, 959 (1930).

(3) Hudson, *THIS JOURNAL*, **38**, 1566 (1916).

Oxidation of α,α -trehalose with periodic acid in aqueous solution has yielded a sirupy product, presumably the tetraaldehyde (II), which upon oxidation with bromine water kept neutral with

(4) Jackson and Hudson, *ibid.*, **59**, 994 (1937).

(5) The tetraaldehyde is named according to the plan previously adopted.⁴

strontium carbonate has produced in a yield of 55% a crystalline strontium salt ($C_{10}H_{10}O_{13}Sr_2$). The organic acid corresponding to the strontium salt yields, by hydrolysis and subsequent oxidation with bromine water, oxalic and D-glyceric acids, the latter isolated as calcium D-glycerate in a 65% yield. This limits the structure of the strontium salt to (III), (IV) or (V). Structures (IV) and (V), which require the septanoside (1,6) ring for one glucose component of the α,α -trehalose molecule in the case of (IV) and for both glucose components in the case of (V), are excluded by the known reactions of periodic acid.^{4,6} If the two glucose components have the septanoside ring structure the disaccharide, upon oxidation by periodic acid or sodium metaperiodate, would be expected to consume six moles of the oxidant and to produce four moles of formic acid. The disaccharide having the septanoside structure for one of the glucose units and the pyranoside structure for the other should consume five moles of the oxidant and produce three moles of formic acid. If both glucose units were of the pyranoside structure (I) the consumption of the oxidant should be four moles and the production of formic acid two moles. α,α -Trehalose actually consumes four moles of the oxidant when oxidized by either periodic acid or sodium metaperiodate; the acidity produced in the reaction with sodium metaperiodate corresponds to the formation of two moles of formic acid. These results are thus in agreement with the pyranoside structure for each of the glucose components of the α,α -trehalose molecule. The septanoside structure is also excluded by the presence of the D-glyceric acid moiety in the molecule of the strontium salt (III) derived from α,α -trehalose. A disaccharide having the septanoside structure for both glucose units would be expected to yield the strontium salt (VI) which has the glycolic acid moiety in its molecule. If one glucose unit possesses the septanoside structure and the other the pyranoside structure, the yield of calcium D-glycerate from the strontium salt could not attain the 65% actually isolated. This proof of the pyranoside structure for the two glucose components of the α,α -trehalose molecule furnishes another instance of the applicability of these oxidation reactions to structural studies among the carbohydrates.

(6) Malaprade, *Bull. soc. chim.*, [5] 1, 833 (1934); [5] 4, 906 (1937); Hérissé, Fleury and Joly, *J. pharm. chim.*, [8] 20, 149 (1934); Fleury and Bon-Bernatets, *ibid.*, [8] 23, 85 (1936); Clutterbuck and Reuter, *J. Chem. Soc.*, 1467 (1935).

Experimental

Oxidation of α,α -Trehalose with Periodic Acid.—To 25 ml. of 0.532 *M* aqueous periodic acid solution (4.2 molecular equivalents) was added an aqueous solution of 1.978 g. of pure α,α -trehalose dihydrate. The solution, made up to 50 ml. with water and kept in a 21° room, showed the rotatory changes recorded in Table I. The final $[M]_D$ value of the reaction solution corresponds to a specific rotation of +160.0° for D',D'-oxy-bis-(D-hydroxymethylglycolic aldehyde). After twenty-four hours an analysis of 5 ml. of the solution showed an excess of 0.18 molecular equivalent of periodic acid; the consumption of the oxidant was thus 4.02 molecular equivalents.

The procedure for the isolation of D',D'-oxy-bis-(D-hydroxymethylglycolic aldehyde) was the same as that described in a previous paper⁴ for the methoxydiglycolic aldehydes from the methyl-pentopyranosides with the exception that, due to the low solubility of the tetraaldehyde from α,α -trehalose in cold absolute ethanol, the solvent for extraction of the aldehyde from strontium salts in the present case was absolute methanol. To the solution of the sirupy tetraaldehyde, obtained from 4.8 g. of α,α -trehalose dihydrate, in 1000 ml. of water were added 75 g. of strontium carbonate and 6 ml. of bromine. The mixture was shaken until the bromine had dissolved and then kept in the dark at room temperature for about seventeen hours with frequent shaking during the first hour. After removal of excess bromine by aeration, the strontium carbonate was filtered off and washed thoroughly with hot water. The solution, freed from bromine ions with silver carbonate and from excess silver with hydrogen sulfide, was concentrated *in vacuo* to about 100 ml. and filtered. Di-strontium D',D'-oxy-bis-(D-hydroxymethylglycolate) hexahydrate crystallized slowly as needles upon spontaneous evaporation of the aqueous solution; yield, 4.2 g. or 54%. Recrystallized thrice from water and dried to constant weight at 100° *in vacuo*, the pure anhydrous salt showed a specific rotation⁷ of -24.0° in water (*c*, 0.29; *l*, 4); the rotation was -52.8° in water at a concentration of 0.91 g. per 100 ml. of solution (*l*, 2).

Anal. Calcd. for $C_{10}H_{10}O_{13}Sr_2 \cdot 6H_2O$: H_2O , 17.40. Found (dried at 100° *in vacuo*): H_2O , 16.96, 16.81. Calcd. for $C_{10}H_{10}O_{13}Sr_2$: C, 23.38; H, 1.96; Sr, 34.14. Found: C, 23.26, 23.21; H, 2.12, 2.04; Sr, 33.94, 33.93.

The specific rotation of D',D'-oxy-bis-(D-hydroxymethylglycolic acid) in water, obtained by liberating it from the pure anhydrous strontium salt with an equivalent of hydrochloric acid, was +71.3° (*c*, 1.3; *l*, 2).

Proof of Structure.—D',D'-Oxy-bis-(D-hydroxymethylglycolic acid), prepared from 7.6 g. of the crystalline hydrated strontium salt as described for L'-methoxydiglycolic acid,⁴ was hydrolyzed by heating its solution in 100 ml. of water on the steam-bath for nine hours during which the rotation decreased to a small positive value. The hydrolyzed acid in aqueous solution was oxidized by bromine and from the products were prepared as previously described⁴ barium oxalate (2.5 g.) and calcium D-glycerate. Oxalic acid from the barium oxalate was characterized by

(7) Except where otherwise stated, all rotations in this article are specific rotations at 20° for sodium light.

TABLE I
ROTATORY CHANGES DURING THE OXIDATION OF α,α -
TREHALOSE TO THE TETRAALDEHYDE

1.1978 g. of α,α -trehalose dihydrate in 50 ml. of 0.266 <i>M</i> aqueous periodic acid solution. ^a		1.0254 g. of α,α -trehalose dihydrate in 50 ml. of 0.2277 <i>M</i> aqueous sodium metaperiodate solution ^a	
Time, min.	$[M]_D \times 10^{-2}$	Time, min.	$[M]_D \times 10^{-2}$
0	+674.4 ^b	0	+674.4 ^b
4.5	+601.2	5.1	+537.0
6.7	+575.3	10.0	+504.4
10.5	+538.9	16.0	+480.5
15.6	+509.7	25.2	+458.1
25.7	+483.7	42.2	+436.7
41.6	+472.8	78	+424.0
87	+461.9	125	+423.0
182	+455.0	200	+429.4
350	+448.2	335	+437.4
24 hrs.	+444.9	24 hrs.	+446.3

^a The solution was prepared at 20–21° and kept thereafter in a 20–21° room. ^b Calcd. from the specific rotation +197.1° in water for anhydrous α,α -trehalose.

usual methods. The yield of calcium D-glycerate rotating +14.6° in water was 2.26 g. or 65%. After recrystallization from water it melted at 141–142° (uncorr.) alone or mixed with authentic calcium D-glycerate and rotated +14.9° in water (*c*, 0.7; *l*, 2).

Anal. Calcd. for $C_6H_{10}O_8Ca \cdot 2H_2O$: Ca, 14.00. Found: Ca, 13.98, 13.95.

Oxidation of α,α -Trehalose with Sodium Metaperiodate.—An aqueous solution of 1.0254 g. of pure α,α -trehalose dihydrate was mixed with 25 ml. of 0.4555 *M* aqueous sodium metaperiodate solution (4.2 molecular equivalents). The solution, diluted with water to 50 ml. and kept in a 20° room, showed the rotatory changes recorded in Table I. The specific rotation of D',D'-oxy-bis-(D-hydroxymethyldiglycolic aldehyde), calculated from the final $[M]_D$ value of the oxidation solution, is +160.5° which is in excellent agreement with the value of +160.0° calculated from the final rotation of the periodic acid oxidation solution. After twenty-seven hours an analysis of

5 ml. of the solution showed an excess of 0.13 molecular equivalent of sodium metaperiodate, the consumption of the oxidant thus being 4.07 molecular equivalents. The acidity of the reaction solution at the end of twenty-seven hours corresponded to the production of 1.99 molecular equivalents of formic acid⁸ (10 ml., diluted with 300 ml. of water and neutralized to methyl red, required 10.77 ml. of 0.1 *N* sodium hydroxide; calcd. 10.84 ml.).

Summary

Oxidation of α,α -trehalose with periodic acid in aqueous solution, and subsequent oxidation of the product with bromine water kept neutral with strontium carbonate, produces in a yield of 55% the crystalline strontium salt, di-strontium D',D'-oxy-bis-(D-hydroxymethyldiglycolate). The structure of the strontium salt, particularly the presence of two D-glyceric acid moieties in its molecule, proves each of the two glucose components of the α,α -trehalose molecule to possess the pyranoside structure.

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(8) The formic acid can be determined accurately as shown by Malaprade⁶ for the formic acid produced in the oxidation of certain polyhydroxy alcohols by sodium metaperiodate. In an oxidation of α -methyl-D-glucopyranoside with sodium metaperiodate we have found the theoretical values both for the consumption of the oxidant and for the production of formic acid which was measured as the increase in the acidity of the reaction solution. A solution of 1.1238 g. of pure α -methyl-D-glucopyranoside in water was mixed with 25 ml. of 0.4875 *M* aqueous sodium metaperiodate solution at 20°. After being diluted with water to 50 ml. and kept in a 20° room for twenty-four hours, the solution showed $[M]_D \times 10^{-2} = +196.1^\circ$, which corresponds to a specific rotation of +121.0° for D'-methoxy-D-hydroxymethyldiglycolic aldehyde. The specific rotation obtained with periodic acid⁴ as the oxidant was +121.1°. The result of an analysis of 5 ml. of the solution for excess sodium metaperiodate showed the consumption of 2.00 molecular equivalents of the oxidant. The acidity of the reaction solution indicated the production of 1.00 molecular equivalent of formic acid (5 ml., diluted with 300 ml. of water and neutralized to methyl red, required 5.80 ml. of 0.1 *N* sodium hydroxide; calcd. 5.79 ml.).