[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

2-Methylcellulose[1]

BY J. M. SUGIHARA[2] AND M. L. WOLFROM

The selective substitution of the hydroxyl group on carbon-2 of carbohydrates has been accomplished by the preparation of 2-methyl-starch by Gaver,[3] of 2-methyl-D-glucose diethyl mercaptal by Lieser,[4] and of 2-methyl-D-glucose and 3-methyl-D-glucose, as derivatives, from a partially methylated cellulose by Heddle and Percival.[5] Lieser[6] has described a methylated cellulose, containing approximately one methoxyl group per two anhydro-D-glucose units, that on hydrolysis yielded 2-methyl-D-glucose, isolated as its phenylhydrazone. Since certain cellulose derivatives of known structure were desired in this Laboratory, the general method described by Gaver[3] was applied to the preparation of a 2-methylcellulose.

It is a commonly accepted fact that hydroxyl groups on carbon atoms α to carbonyl groups are acidic. In the cellulose molecule the hydroxyl group on carbon-2 might be expected to be a stronger acid than the other hydroxyl groups. The reaction of cellulose in an activated form with sodium hydroxide in a near anhydrous medium appeared to justify this assumption. One to 1.2 equivalents of base could be introduced for each anhydro-D-glucose unit. The amount in excess of one was undoubtedly base, not removed by washing and still adsorbed on the cellulose. This appeared probable since the alkali content of those preparations containing more than one equivalent of base per anhydro-D-glucose unit could be reduced to one by suspending at room temperature, the alkali cellulose in anhydrous acetone containing acetyl chloride.

The reaction of the alkali cellulose with methyl iodide occurred with no difficulty. The color of the former, which varied from a light buff to a yellow brown, was in every case removed upon methylation to form colorless, fibrous 2-methylcellulose. The latter had considerable water solubility. This product followed the trend of other methylcelluloses in being less water-soluble at a higher temperature with solubility increasing as the solution was cooled.[7]

To determine the degree of degradation which occurred in the formation of 2-methylcellulose, the cotton linters, the activated cellulose and 2-methylcellulose were nitrated and viscosities were determined by the method of Berl.[8] The calculated degrees of polymerization for the cotton linters, activated cellulose and 2-methylcellulose were 1680, 570 and 88, respectively. The figures are primarily of comparative significance. The nitrate exhibited good film-forming properties.

The structure of 2-methylcellulose was clarified using a degradative procedure. The polymer was methanolyzed in the usual fashion. The methyl D-glucoside mixture obtained was hydrolyzed by acid, and the resultant sugar was converted into the diethyl thioacetal. Crystalline 2-methyl-D-glucose diethyl thioacetal was isolated by a chromatographic technique. No other crystalline compounds were isolable. Control experiments demonstrated that it was possible to detect and to separate small quantities of D-glucose diethyl thioacetal had such been present. Since the methoxyl content of the methylcellulose was 1.03 groups per anhydro-D-glucose unit and since no D-glucose diethyl thioacetal was obtained, the contribution of dimethyl derivatives would not be significant. Therefore, we believe that the cellulose was in all probability uniformly methylated with the methyl group located mainly on C-2 of each anhydro-D-glucose unit.

Experimental

Sodium 2-Cellulosate.—Twenty grams of cotton linters (defatted and bleached) was dissolved in 600 ml. of cuprammonium hydroxide[9] and was regenerated by pouring the viscous solution into 1.5 liters of 6 *N* sulfuric acid. The activated cellulose was filtered and was washed thoroughly with water; yield 192 g. (wet). The water in 96 g. of the wet fibers was replaced by butanol-1. This was accomplished by vigorously stirring the heated suspension while distilling the water–butanol-1 azeotrope, at atmospheric pressure, through a 30-cm. Vigreux column. A solution of 20 g. (8 equivs. per anhydro-D-glucose unit) of sodium hydroxide in 30 ml. of water was added and distillation was continued to remove the additional water. When the temperature at the top of the column reached 100°, distillation was continued for three hours at a rate sufficient to remove any additional water present or formed in the reaction. The alkali cellulose formed was filtered and washed thoroughly with absolute ethanol; yield 10.9 g. (dried in vacuum desiccator over anhydrous calcium chloride).

Anal. Na, 1.08 equivs. per anhydro-D-glucose unit (detd. by suspension in excess standard acid followed by titration with standard base to phenolphthalein endpoint).

2-Methylcellulose.—A suspension of 9.82 g. of the alkali cellulose and 20 ml. of methyl iodide was placed in a bomb tube and heated at 100° for two and one-half hours. The methylated product was treated with sodium hydroxide again as previously described; yield 7.30 g. (dried in vacuum desiccator over anhydrous calcium chloride).

Anal. Na, 0.31 equiv. per anhydro-D-glucose unit (by titer).

An amount of 7.00 g. of the above material was remethylated in a bomb tube with 20 ml. of methyl iodide at 100° for two and one-half hours. The product was

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[1] A preliminary communication on this work has appeared in *Abstracts Papers Am. Chem. Soc.*, **115**, 23Q (1949).

[2] Research Associate of The Ohio State University Research Foundation (Project 313).

[3] K. M. Gaver, U. S. Patent 2,397,732 (Apr. 2, 1946); Ph.D. Dissertation, The Ohio State University, 1945.

[4] T. Lieser and E. Leckzyck, *Ann.*, **511**, 137 (1934).

[5] W. J. Heddle and E. G. V. Percival, *J. Chem. Soc.*, 249 (1939).

[6] T. Lieser, *Ann.*, **470**, 104 (1929).

[7] J. F. Haskins, *Advances in Carbohydrate Chem.*, **2**, 291 (1946).

[8] E. Berl, *Ind. Eng. Chem., Anal. Ed.*, **13**, 322 (1941)

[9] R. A. Joyner, *J. Chem. Soc.*, **121**, 1912 (1922).

thoroughly washed with acetone and dried (over phosphoric anhydride at 78° *in vacuo*); yield 6.31 g. The fibrous substance showed a significant and reverse solubility in water; it was insoluble in methanol, acetone and chloroform but exhibited some solubility in pyridine.

Anal. Calcd. for $(C_6H_9O_4\text{-}OCH_3)_x$: OCH_3, 17.61. Found: OCH_3, 18.13; Na, 0.04 equiv. per anhydro-D-glucose unit (by titer).

Hydrolysis of 2-Methylcellulose to 2-Methyl-D-glucose Diethyl Thioacetal.—Following the general methanolysis procedure of Irvine and Hirst,[10] 2.3 g. of 2-methylcellulose was methanolyzed for sixty hours at 130° with 50 ml. of methanol containing 0.85% of dry hydrogen chloride. The resultant cooled solution was treated with silver carbonate and activated charcoal and concentrated to dryness under reduced pressure; yield 2.2 g. (85%).

Following the procedure of Haworth, Hirst and Teece,[11] the above glycoside (2.2 g.) was heated in 25 ml. of 2 *N* hydrochloric acid at 85–95° for fourteen hours. The cooled solution was neutralized with silver carbonate, residual silver was removed with hydrogen sulfide and the solution was concentrated to dryness under reduced pressure; yield 1.8 g. (88%).

The above product (1.8 g.) was dissolved at 0° in 2 ml. of concentrated hydrochloric acid (*ca.* 12 *N*) and treated with 2 ml. of ethanethiol. The resultant mixture was maintained at 0° for two hours with stirring. Cold, concentrated ammonium hydroxide (*ca.* 15 *N*) was added at 0° to neutrality and the precipitated solid was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was repeatedly extracted with chloroform. Solvent removal left a semisolid product which was combined with the initially precipitated material and treated with activated charcoal in methanol solution; yield 2.1 g. (76%). The ammonium chloride residue contained a negligible amount of organic material as determined by acetylation and extraction of the acetates formed.

An amount of 180 mg. of the above crude thioacetal was dissolved in 25 ml. of warm chloroform (containing 0.5% ethanol), and placed at the top of a column (200 mm. × 35 mm. diam.[12]) of acid-washed Magnesol–Celite.[13]

A mixture of 5 parts (by wt.) of Magnesol and 1 part of Celite was suspended with efficient stirring in a solution composed of 1 part (by vol.) of concentrated hydrochloric acid and 3 parts of water. The amount of Magnesol–Celite added to the diluted acid was regulated so that a very thin paste resulted. After stirring for sixty minutes, the slurry was filtered and washed free of chloride ion (to silver nitrate) with water and the water was displaced with acetone. The material was dried at room temperature overnight and then for two hours at 110°. The adsorbent was cooled, and only that portion which passed a 200-mesh (per linear inch) sieve was used in the chromatography as described. The chromatogram was developed with 350 ml. (5 column lengths) of 30:1 (by vol.) chloroform (containing 0.5% by vol. ethanol)-*t*-butyl alcohol and streaked with alkaline permanganate indicator.[14] The material in the main zone, located about one-third of a column length from the top, was eluted with 50 ml. of methanol; yield 93 mg. (52%), m. p. 115–125°, $[\alpha]^{25}\text{D}$ −18° (*c* 1.82, pyridine). This was recrystallized from methanol; yield 69 mg., m. p. 155–156° (unchanged on admixture with an authentic specimen of 2-methyl-D-glucose diethyl thioacetal of m. p. 154.5–155.5°), $[\alpha]^{23}\text{D}$ −25° (*c* 1.51, pyridine). The accepted constants[15] for this substance are: m. p. 156–157°, $[\alpha]^{20}\text{D}$ −25° (*c* 1.49, pyridine).

A zone appearing at the top of the column was eluted to yield a sirup; yield 24 mg. The effluent also gave a sirup; yield 4.9 mg. Both of the sirups failed to crystallize even when rechromatographed.

In a model experiment, 100 mg. of an equal mixture of D-glucose diethyl thioacetal and 2-methyl-D-glucose diethyl thioacetal was chromatographed as described above. Two zones formed, separated by a distinct though narrow interzone. The upper zone, located about one fourth of a column length from the top, contained the D-glucose diethyl thioacetal.

Action of Acidic Reagents on 2-Sodium Cellulosate.—An amount of 1.023 g. of alkali cellulose (Na, 1.24 equivs. per anhydro-D-glucose unit) was suspended in 4 ml. of acetyl chloride and 50 ml. of anhydrous acetone at 25° for three hours. The fibers were filtered and thoroughly washed with absolute ethanol; yield 1.013 g.

Anal. Na, 1.01 equivs. per anhydro-D-glucose unit (by titer).

An amount of 1.460 g. of alkali cellulose (Na, 1.25 equivs. per anhydro-D-glucose unit) was suspended in 7 ml. of acetic anhydride and 50 ml. of anhydrous acetone under reflux for five hours; yield 1.445 g.

Anal. Na, 1.09 equivs. per anhydro-D-glucose unit (by titer).

Viscosity Determinations.—Cotton linters, the cuprammonium activated cellulose and 2-methylcellulose were nitrated using the method described by Berl.[8] The nitrates were dissolved in *n*-butyl acetate, and the viscosities were measured in an Ostwald viscometer. The nitrate of the 2-methylcellulose could be cast into films. The times of flow in minutes at 25° were as follows: nitrated linters (12.9% N; *c*, 0.025; d^{25}_{4}, 0.871), 2.923; nitrated activated linters (12.4% N; *c*, 0.250; d^{25}_{4}, 0.873), 5.130; nitrated 2-methylcellulose (8.4% N; *c*, 0.224; d^{25}_{4}, 0.872), 2.432; solvent (d^{25}_{4}, 0.871), 2.001. Employing the formula of Staudinger and Mohr,[16] $K_m = 11 \times 10^{-4}$, the degrees of polymerization found were 1680, 570 and 88, respectively.

Acknowledgment.—This work was supported by the Ordnance Department under contract (W-33-019ord-6279; supervising agency, Ballistic Research Laboratories, Aberdeen Proving Ground, Maryland) with The Ohio State University Research Foundation. We wish to acknowledge the assistance of Mr. E. E. Dickey and Mr. H. C. Prosser.

Summary

Activated cotton linters reacted with sodium hydroxide in a nearly anhydrous medium to form an alkali cellulose, which reacted with methyl iodide to yield a methylcellulose (D. P. *ca.* 100 by nitrate viscosity) containing 1.03 methoxyl groups per anhydro-D-glucose unit. That the methylation was effected largely on C-2 results from the fact that methanolysis of the polymer followed by hydrolysis and mercaptalation yielded 2-methyl-D-glucose diethyl mercaptal as the only chromatographically isolable crystalline product.

COLUMBUS, OHIO RECEIVED MAY 12, 1949

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[10] J. C. Irvine and E. L. Hirst, *ibid.*, **121**, 1585 (1922).

[11] W. N. Haworth, E. L. Hirst and Ethel G. Teece, *ibid.*, 2858 (1931).

[12] Adsorbent dimensions.

[13] Magnesol, a product of Westvaco Chlorine Products Co., South Charleston, West Virginia. Celite 535, a product of Johns-Manville Co., New York, N. Y.

[14] W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

[15] P. E. Papadakis, *ibid.*, **52**, 2148, 3465 (1930); P. Brigl and R. Schinle, *Ber.*, **63**, 2884 (1930); Tollens-Elsner, "Kurzes Handbuch der Kohlenhydrate," J. A. Barth, Leipzig, 1935, p. 208, footnote 6.

[16] H. Staudinger and R. Mohr, *Ber.*, **70**, 2296 (1937).