The Substituent Group Distribution in a Michael Reaction. Carbamoethyl Cellulose[1]

GERALD F. TOUZINSKY[2]

The Institute of Paper Chemistry, Appleton, Wisconsin

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A carbamoethyl cellulose was prepared by the Michael addition reaction of acrylamide and cellulose. The distribution of the substituents was studied by hydrolyzing the derivative, chromatographically separating the hydrolysate into glucose and the mono-, di-, and trisubstituted glucoses, and measuring the amount of each. The Spurlin equations for the mole fractions of substituted glucoses in terms of the relative equilibrium constants were reduced to a single cubic equation in the equilibrium constant. This equation was evaluated from the experimental data and solved for the constants. The relative equilibrium constants found were $K_2:K_3:K_6 = 9:1:19$.

The substituent groups of any partially substituted cellulose ether are distributed among the three hydroxyl groups on each anhydroglucose unit of the cellulose chain in an arrangement which is determined primarily by the relative reactivity of the hydroxyl groups and the nature of the substituting reaction. Spurlin[3,4] presented a statistical treatment of these distributions and developed expressions for the mole fractions of variously substituted glucose units in terms of the relative reaction constants. Later work[5,6] confirmed the accuracy and usefulness of these expressions and led to their use in essentially all recent distribution studies.

The factor which exercises the most influence on the distribution of substituents in a cellulose derivative is the nature of the chemical reaction. This determines whether the distribution is rate controlled or equilibrium controlled and also the relative reactivity of the hydroxyl groups. There are several different types of reactions which form cellulose ethers; each has its distinctive mechanism and distribution pattern.

The most common type of reaction is the simple nucleophilic substitution. The reactions of this type generally consist of the condensation of a cellulosic hydroxyl group with an alkyl halide or an alkyl ester of an inorganic acid. The reactions are essentially irreversible and, hence, give rate-controlled distributions.

Generally, the 2-position hydroxyl group has been found to be the most reactive. For a heterogeneous reaction of methyl chloride with alkali cellulose, the relative reaction constants ($k_2:k_3:k_6$) for the 2-, 3-, and 6-position hydroxyl groups were 5, 1, and 2.[7] Similar rate constants were found for ethyl chloride ($k_2:k_3:k_6 = 4.5:1:2$),[8] for dimethyl sulfate ($k_2:k_3:k_6 = 3.5:1:2$),[9] and even for sodium chloroacetate $k_2:k_3:k_6 = 2:1:2.5$)[10] when compensation was made for interference between the 2- and 3-positions. The variation in the constants can be attributed to differences in the steric and electrical properties at the reagent molecule.

Another type of reaction forming a cellulose ether is that involving the breaking of a ring. These reactions are also irreversible and give rate-controlled distributions but in these the 6-position hydroxyl is the most reactive. Croon[11] found the relative rate constants to be 3, 1, and 10 for the 2-, 3-, and 6-position hydroxyls and 20 for the hydroxyl group formed in the reaction.

The one type of cellulose etherification which proceeds by a reversible reaction is the Michael addition reaction.[12,13] This is the alkali-catalyzed addition of a hydroxyl group to an activated vinyl group. The reaction takes place with a wide variety of reagents such as acrylamide and vinyl sulfones, but cyanoethylation, the addition of acrylonitrile, has been studied the most. Partial studies of a cyanoethylated amylose[14] and a cyanoethyl glucomannan[15] have indicated that, in cyanoethylation, substitution occurs primarily at the 6-position. Very recently, the relative rate constants for the hydroxyls of 2-tetrahydropyranyl-β-D-glucopyranoside toward cyanoethylation were studied and found to be $k_2:k_3:k_4:k_6 = 3:1:2:8$,[16] but as yet no study has been made of the distribution of this or of any Michael reaction derivative of cellulose.

In this work, the substituent group distribution in carbamoethyl cellulose, the Michael addition product of acrylamide and cellulose was studied under equilibrium-controlled conditions.

Experimental

Preparation of Carbamoethyl Cellulose.—A solution of 100 g. of sodium hydroxide in 400 ml. of distilled water was kneaded into 50.0 g. of acetate-grade cotton linters. The mixture was cooled for 30 min. at 4°. A solution of 340 g. of acrylamide in 125 ml. of distilled water was kneaded into the alkali cellulose and the mixture was allowed to react at 4° for 73 hr. with occasional stirring. The mixture was then slurried in 1 l. of methanol and filtered, neutralized by soaking overnight in 1 l. of *N* sulfuric acid, reslurried in and washed with methanol, and dried in air. The analysis of the white fibrous product showed 3.10% nitrogen

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[2] Nalco Chemical Co., Chicago, Ill.

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and 6.21% carboxyl and therefore had a D.S.[17] as amide of 0.48, as acid of 0.30, and a total D.S. of 0.78.

A set of 1-g. reactions was run at the same concentrations and temperature for reaction times from 8 to 96 hr.

Preparation of 3-*O*-Substituted Glucoses.—Acrylamide, 4.40 g., and 4.0 g. of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose were dissolved in 7.72 ml. of 0.1 *N* sodium hydroxide and allowed to react at 44° for 10 hr. The mixture was then treated with Amberlite IR-120 resin in free-acid form, filtered, and concentrated to a thin, yellow sirup. The sirup was hyrolyzed with 25 ml. of 1 *N* sulfuric acid for 3 hr. at room temperature and then for 15 min. on a steam bath. The hydrolysate was neutralized with barium carbonate, filtered, and concentrated. A portion was separated chromatographically into glucose, 3-*O*-carbamoethyl-D-glucose, and 3-*O*-carboxyethyl-D-glucose. Both substituted glucoses were obtained only as sirups, but the 3-*O*-carbamoethyl-D-glucose gave a light yellow phenylosazone melting at 205.5–206.5°.

Preparation of Mixture of 2-*O*-, 3-*O*-, and 2,3-Di-*O*-carboxyethyl-D-glucose.—Acrylamide, 1.08 g., and 0.5 g. of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, prepared according to Evans and co-workers,[18] were dissolved in 1.5 ml. of tetrahydrofuran and 0.4 ml. of 1.0 *N* sodium hydroxide. The mixture was allowed to react for 48 hr. at 30°, then neutralized with Amberlite IR-120 resin, filtered, concentrated, and hydrolyzed by the procedure used to hydrolyze the cellulose derivatives and described below. Qualitative chromatography showed the hydrolysate to contain four materials considered to be D-glucose, 2-*O*-carboxyethyl-D-glucose, 3-*O*-carboxyethyl-D-glucose, and 2,3-di-*O*-carboxyethyl-D-glucose.

Cellulose Hydrolysis.—Essentially the method of Saeman and co-workers[19] was used. The samples were digested for 1 hr. in 72% sulfuric acid and then diluted to about 5% and heated on a steam bath for 4 hr. The hydrolysates were neutralized with barium carbonate, filtered, and concentrated to known volumes.

Chromatographic Separations.—All separations were made by descending paper chromatography using 9:2:2 ethyl actetate–acetic acid–water as the developer. Whatman No. 1 paper was used for the qualitative separations and washed Whatman No. 3 MM paper was used for the preparative and quantitative separations. The separated materials were detected with an aniline chloroacetate dip[20] which gave distinctive colors with each of the components of the hydrolysate.

Quantitative Measurements.—After development the quantitative chromatograms were steamed for 15 min. to remove residual acetic acid. The individual, separated samples were then cut out and eluted with water. The eluted samples were treated with Amberlite IR-120 resin, titrated conductimetrically with 0.02 *N* sodium hydroxide, neutralized, and oxidized quantitatively with alkaline hypoiodite according to Willstätter and Schudel.[21]

Results and Discussion

It has been well established that cyanoethylation of alcohols is a reversible reaction proceeding by the nucleophilic attack of the alkoxide ion on the vinyl group.[12,22] By analogy, the same mechanism is attributed to carbamoethylation of alcohols including cellulose. To show that the reaction as studied had actually proceeded to equilibrium-controlled conditions, a series of reactions was run in which the reaction time was varied from 8 to 96 hr. A plot of D.S. *vs.* reaction time showed the expected strong initial rise and subsequent leveling off (see Figure 1). The rates of reaction at 0 time and after 72 hr. were estimated from the graph. Using the standard rate expression, the reverse rate was calculated to be 98% of the forward rate at a 72-hr. reaction time. On the basis of this information, the reaction was considered to give an equilibrium-controlled distribution.

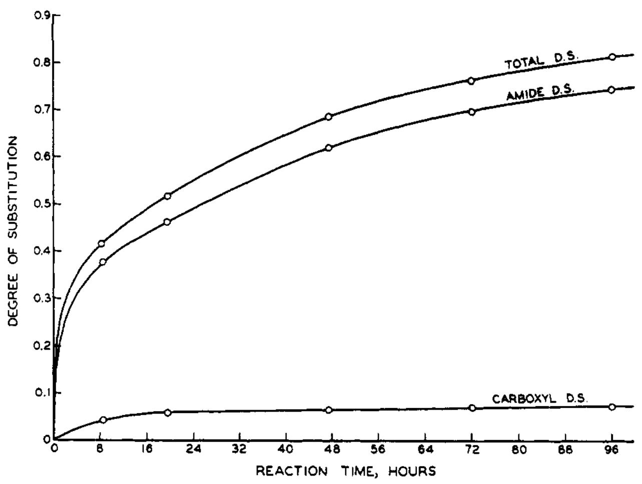

Figure 1.—Plot of D.S. *vs.* reaction time.

The substitution reaction was considered to proceed by reaction of acrylamide only and to give rise to carboxyethyl groups by hydrolysis of the carbamoethyl groups on the basis of two pieces of evidence. First, Frick and co-workers[13] found the extent of reaction of acrylamide more than seven times that of acrylic acid under similar conditions. Second, in the course of the present study, two preparations were made which were identical except that in one the acrylamide was partially hydrolyzed before the cellulose was added. The D.S. of the unhydrolyzed preparation was three times that of the hydrolyzed preparation but the ratio of carbamoethyl D.S. to carboxyethyl D.S. was the same for both. Thus, it was concluded that carboxyethyl substitution by acrylic acid was essentially negligible.

The hydrolysis was considered complete because no cellobiose or other oligosaccharide spot was found chromatographically and quantitative because the hydrolysate was obtained in 95% yield. The procedure gave complete hydrolysis of carbamoethyl groups to carboxyethyl groups because no nitrogen was detected in any of the separated materials from the hydrolysate, whereas 3-*O*-carbamoethyl-D-glucose gave a clearly positive test with the Nessler reagent.[23] Since the D.S. calculated from the mole fractions was the same as that calculated from carboxyl and nitrogen analyses, there was no apparent loss of substituent groups and the hydrolysate was considered representative of the substituent distribution in the cellulose derivative.

Chromatography separated the hydrolysate into seven materials in four groups: A material, B_1 and B_2 materials, C_1, C_2, and C_3 materials, and glucose. The molar ratio of their carboxyl content to their aldehyde content showed the C, B, and A groups to be mono-, di-, and trisubstituted, respectively. Chromatographic comparison of the hydrolysate with 3-*O*-carboxyethyl-D-glucose and the mixture of 2-*O*-, 3-*O*-, and 2,3-di-*O*-carboxyethyl-D-glucose by both adjacent and mixed chromatography indicated that the C_1, C_2, and C_3 materials were 2-*O*-, 3-*O*-, and 6-*O*-carboxyethyl-D-

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[17] D.S. is Degree of Substitution, the average number of substituent groups per glucose unit.

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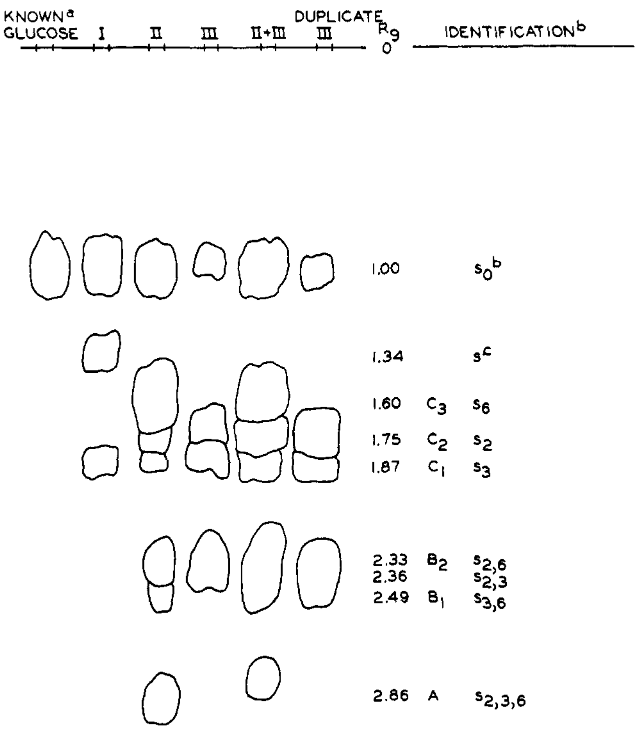

Figure 2.—Chromatographic comparison of separated materials: a, I = hydrolysate of carbamoethylated 1,2:5,6-di-*O*-isopropylidene-D-glucose, II = hydrolysate of carbamoethyl cellulose, III = hydrolysate of carbamoethylated methyl 4,6-*O*-benzylidene-α-D-glucopyranoside; b, s_i = carboxymethyl glucose substituted only in the *i*-position; c, 3-*O*-carbamoethyl glucose.

glucose, respectively (see Figure 2). These results are consistent with the order usually obtained with hydrolysates of cellulose derivatives. With developers that move the substituted materials faster than glucose, the regular order of glucose, 6-substituted, 2-substituted, 3-substituted, 2,6-disubstituted, 3,6-disubstituted, 2,3-disubstituted, and 2,3,6-trisubstituted glucose has been observed with hydrolysates of methyl,[9] ethyl,[8,24] hydroxyethyl,[10,11,25] and carboxymethyl[10] cellulose in a total of seven different developers. Chromatographic comparison with 2,3-di-*O*-carboxyethyl-D-glucose, the apparent dominance of 6-position substitution, and the usual order of chromatographic separation indicate B_1 and B_2 to be 2,6- and 3,6-di-*O*-carboxyethyl-D-glucose, respectively.

The mole fractions of glucose, mono-, di-, and trisubstituted glucoses were 0.36, 0.48, 0.16 and 0.006, respectively, as measured by quantitative chromatography and hypoiodite oxidation.[21]

Spurlin's equations[3] for the mole fractions of variously substituted glucoses in an equilibrium reaction were reduced to a cubic equation in AK, the relative equilibrium constant, with coefficients of c_i, the mole fraction of glucose units having *i*-substituents.

$$c_0(AK)^3 - c_1(AK)^2 + c_2AK - c_3 = 0$$

Because of the mathematical symmetry of the original equations, the three roots of the equation are the constants for the three different hydroxyl groups. When the equation was evaluated with the above data and solved, the resulting AK values were 0.045, 0.407, and 0.868 or, on a relative basis, 1.0, 9.0, and 19.2. The values were assigned to the three hydroxyl positions according to the relative amounts of the three monosubstituted glucoses. Thus, the values are $AK_2{:}AK_3{:}AK_6 = 9{:}1{:}19$.

These results are the first measured equilibrium constants for a Michael reaction of cellulose. The predominance of 6-position substitution would be anticipated from the greater extent of reaction of primary alcohols than secondary in cyanoethylation. The minimal reactivity of the 3-position is a general phenomenon in cellulose substitutions. Hence, the present results are consistent with what might be expected for a Michael addition reaction of cellulose.

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