[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF POLAROID CORPORATION]

Studies on the Structure of Hydroxyethylcellulose[1]

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Introduction

The reaction of cellulose with an epoxide or chlorohydrin, leading to a hydroxyalkylcellulose, differs from ordinary etherifications and esterifications of cellulose in that as the hydroxyl groups of the anhydroglucose units enter into reaction new hydroxyl groups are formed, which, in the case of reaction with ethylene oxide, are primary. A large number of ethylene oxide molecules may add to each glucose unit via the three original hydroxyls and the hydroxyls of newly formed hydroxyethyl groups. Polyethylene oxide appendages may be built up, the molecular weight of the substituted glucose units rises and three hydroxyls remain on each unit. A recent publication[2] describes a careful study of the analysis by tosylation for the primary hydroxyl groups of a hydroxyethylcellulose of low ethylene oxide content. The article contains an excellent list of references pertinent to the chemistry of hydroxyethylcellulose.

The likely presence of polyethylene oxide side chains indicated to us that the ether and ester derivatives of such materials might be "internally plasticized" and show useful mechanical properties. Along with the preparation and characterization of a number of derivatives of one commercially available hydroxyethylcellulose, which will be reported separately, we have carried out studies on the structure of four samples of hydroxyethylcellulose containing combined ethylene oxide varying from 0.44 to 3.07 moles per anhydroglucose unit. Two samples were supplied by Mr. W. E. Gloor, Hercules Powder Company, Samples I and II. Hydroxyethylcellulose WPLH was obtained from Carbide and Carbon Chemicals Corporation, Sample III, and a sample of high ethylene oxide content was supplied by Mr. A. E. Broderick of that company, Sample IV. All samples had been prepared by treatment of alkali cellulose with ethylene oxide.

Ethylene Oxide Content.—Preliminary to examination of the position of the hydroxyethyl substituents, the samples were extracted with ethanol to remove possible polyethylene glycol contaminants, dried and analyzed for combined ethylene oxide. The extraction removed 6–10% of the material. The symbol M.S. is introduced for the average number of moles of combined ethylene oxide per anhydroglucose unit. This number may be greater than three. The symbol D.S. (degree of substitution) which is commonly used in discussion of cellulose derivatives will be used in our description of derivatives of hydroxyethylcellulose and will have its customary maximum value of three.

The first analyses were carried out by treatment of the samples with dilute (about 0.5 molar) acetic anhydride in pyridine and estimation of consumed acid, a method which has been used in the analyses of cellulose derivatives.[3] The results are summarized in Table I.

TABLE I

ANALYSIS OF HYDROXYETHYLCELLULOSE BY ACETYLATION

Sample	M. S. as a function of time of acetylation 24 hr.	66 hr.	144 hr.
I	0.92 ± 0.04	0.64 ± 0.02	0.60 ± 0.01
II	1.24 ± .01	1.09 ± .01	1.11 ± .01
III	1.76 ± .04		1.77 ± .01
IV	3.50 ± .01		3.59 ± .01

Sample I was apparently consuming acetic anhydride even after six days, and a plot of apparent combined ethylene oxide content *versus* reciprocal time of acetylation indicated a final content of 0.58 mole per anhydroglucose unit. Sample II apparently was completely acetylated after 66 hours, while samples III and IV seemed to have reacted completely within 24 hours.

Since several of these analyses of the *extracted* samples did not check the values indicated by the suppliers, the samples were analyzed by (a) apparent conversion to the triacetates by prolonged treatment with 1:1 acetic anhydride in pyridine followed by quantitative saponification[4] of the purified triacetates and (b) by the modified Zeisel alkoxyl analysis of Morgan.[5] The results of the three methods are summarized in Table II.

TABLE II

COMBINED ETHYLENE OXIDE CONTENTS OF HYDROXYETHYLCELLULOSE

Sample	M. S. (Moles of ethylene oxide per anhydroglucose unit) By acetylation	By saponification of triacetates	By Morgan's Zeisel	Suppliers' data
I	0.58	0.53	0.44 ± 0.02	0.48
II	1.09	1.01	0.97 ± .02	0.82
III	1.76	1.54	1.50 ± .04	..
IV	3.50	3.06	3.07 ± .08	..

The saponification of the triacetate led to values uniformly lower than those of the acetylation analysis probably because under the more vigorous conditions the preparation of the triacetate had proceeded more nearly to completion. The alkoxyl method and the saponification of the triacetates led to similar results except with sample I, which contained the lowest amount of combined

(1) This work was carried out under Quartermaster Corps Contract No. W-44-109-qm-2007.

(2) Tasker and Purves, THIS JOURNAL, **71**, 1023 (1949).

(3) Malm, Genung and Williams, *Ind. Eng. Chem., Anal. Ed.*, **14**, 935 (1942).

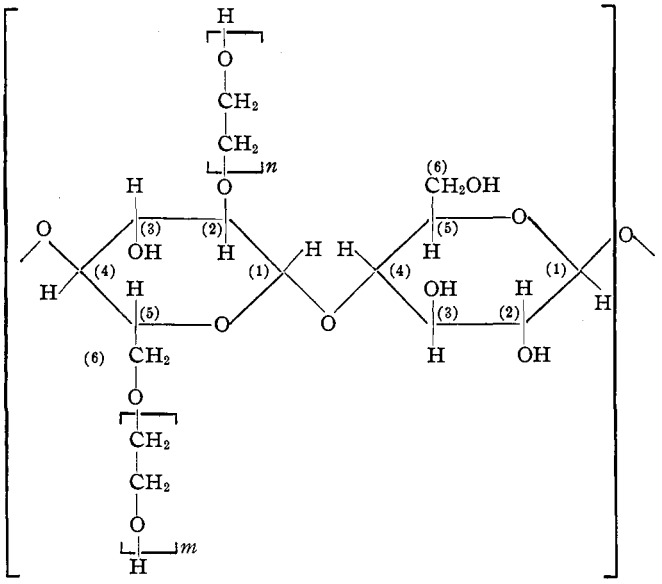
(4) Genung and Mallatt, *ibid.*, **13**, 369 (1941).

(5) Morgan, *ibid.*, **18**, 500 (1946).

ethylene oxide, was fibrous, and may have been most difficult to acetylate completely. The values obtained by the alkoxyl method are used in the following calculations and discussion.

Residual Glycol Content.—To obtain information about the course of the ethylene oxide-cellulose reactions, the samples of hydroxyethylcellulose were analyzed for the fractions of the anhydroglucose units which retained unsubstituted hydroxyl groups in both the 2 and 3 positions, *i. e.*, their residual glycol content (see Formula I).

In a preliminary experiment, sample III was treated with lead tetraacetate and the loss in oxidizing power was followed as a function of time.



Formula I, n and m integers

A slow continuing loss in oxidizing power was observed which did not lend itself well to extrapolation. In a blank run triethylene glycol, which may be comparable in structure to a part of the hydroxyethylcellulose molecule, led to appreciable loss in oxidizing power, and it appeared that the reaction with lead tetraacetate was not sufficiently specific under our conditions.

Sodium metaperiodate appeared to be a satisfactory reagent[6] for assay of the residual 2,3 glycol groups in the anhydroglucose unit. The reagent was stable alone and in the presence of triethylene glycol. Its stoichiometric reaction with *trans*-cyclohexanediol[7] was very rapid under our conditions and this was followed by a slower reaction which was linear with time, probably oxidation of the dialdehyde. Extrapolation of this part of the curve back to zero time led to 99 ± 1% of the theoretical 1,2 glycol content (Fig. 1).

(6) (a) Jackson and Hudson, THIS JOURNAL, **59**, 2049 (1937); (b) Davidson, *J. Text. Inst.*, **32**, T109 (1941); (c) Jayne and Sätre, *Ber.*, **75B**, 1840 (1942); **77B**, 242 (1944); (d) Jayne and Maris, *Ber.*, **77B**, 383 (1944).

(7) Price and Knell, THIS JOURNAL, **64**, 552 (1942).

The periodate oxidations of the hydroxyethylcelluloses were similar but slightly less clear cut. The initial oxidations were less rapid, possibly reflecting the lower reactivity of the substituted polymeric molecules; the subsequent reactions, linear with time, were also slower. It seemed reasonable to estimate the 1,2 glycol content by extrapolation of the slow reaction back to the extension of the curve defined by the slope of the initial reaction. The data are summarized in Figs. 1, 2, 3 and 4 and in Table III.

In Fig. 5 there are plotted curves of the fraction of the glucose units which have free 2,3 glycol groups as a function of the moles of substituent per glucose unit for samples I–IV of hydroxyethylcellulose and for a series of methylcelluloses recently studied by Timell.[8] The initial introduction of hydroxyethyl substituent leads to greater reduction in 2,3-glycol content than does equivalent introduction of methyl groups,[8] indicating that ethylene oxide attacks the secondary hydroxyls more readily than does methyl sulfate, and/or that the ethylene oxide reaction is the more homogeneous, each under its respective reaction conditions. At further extent of reaction at D.S. ≃ 2, introduction of methyl groups causes greater decrease in glycol content than does ethylene oxide, since the methyl groups must react with the remainder of the original hydroxyls, and when the degree of substitution becomes three (or somewhat less) no glycol can remain. An ethylcellulose of D.S. = 2.48 has been found by lead tetraacetate oxidation to contain only 0.01 mole of glycol per glucose unit.[9] However, at high extents of reaction ethylene oxide apparently reacts with primary hydroxyls introduced by the earlier reaction of ethylene oxide and the glycol content falls less rapidly. In sample IV, M.S. = 3.06, some 34% of the anhydroglucose units appear to retain unsubstituted hydroxyls at both carbon atoms 2 and 3. The shape of the curve of residual glycol *vs.* M.S. indicates that with still further addition of ethylene oxide the glycol content will decrease quite slowly.

TABLE III

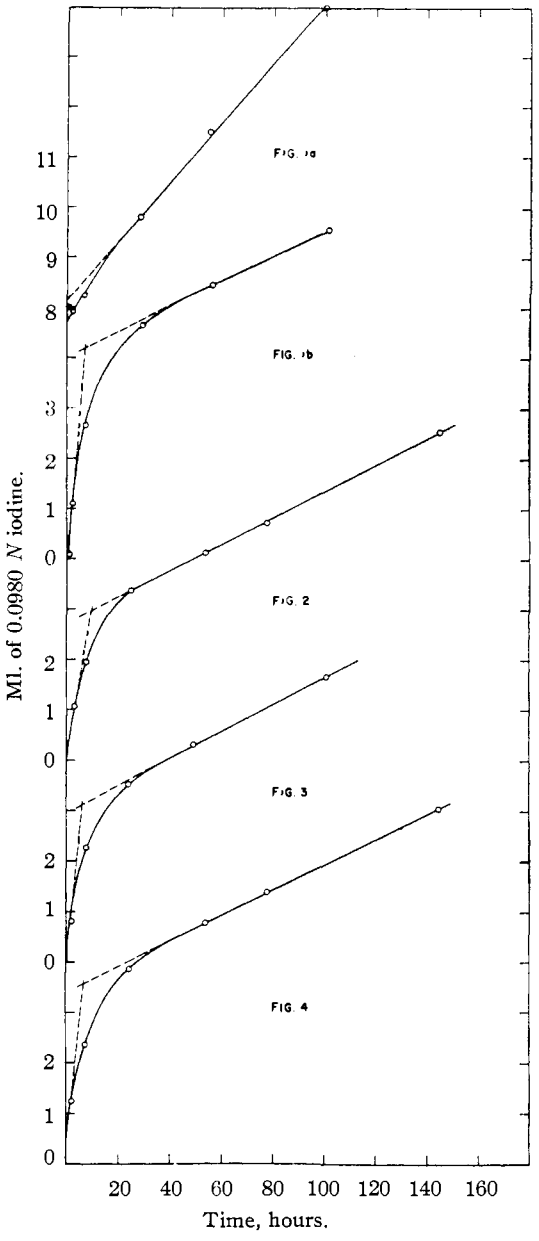
2,3-GLYCOL CONTENT OF HYDROXYETHYLCELLULOSE

Sample	M. S.	Mol. wt. anhydro-glucose unit	Glycol mmole./g.	Glycol per anhydroglucose unit
I	0.44	181	3.94	0.71 ± 0.02
II	0.97	205	2.78	.57 ± .02
III	1.50	228	2.11	.48 ± .02
IV	3.07	297	1.15	.34 ± .02

Primary Hydroxyl Content.—Additional information as to the course of the ethylene oxide-cellulose reaction results from consideration of

(8) Timell, *Svensk Papperstidn*, **51**, 199 (1948).

(9) Mahoney and Purves, THIS JOURNAL, **64**, 9 (1942).



Figs. 1, 2, 3, and 4.—Periodate oxidations at 30°: 1a, *trans*-cyclohexanediol; 1b, hydroxyethylcellulose, sample III; 2, hydroxyethylcellulose, Sample I; 3, hydroxyethylcellulose, Sample II; 4, hydroxyethylcellulose, Sample IV.

the content of primary hydroxyl groups. Sample III was of particular interest to us as the starting material for the preparation of a number of derivatives. The primary hydroxyl content was estimated by the method of Tasker and Purves,[2] *i. e.*, treatment of the hydroxyethylcellulose with *p*-toluenesulfonyl chloride in pyridine, analysis of the tosylates for sulfur, ethylene oxide and chlorine as functions of time of tosylation, and conversion of these data to tosyl, chlorine and ethylene

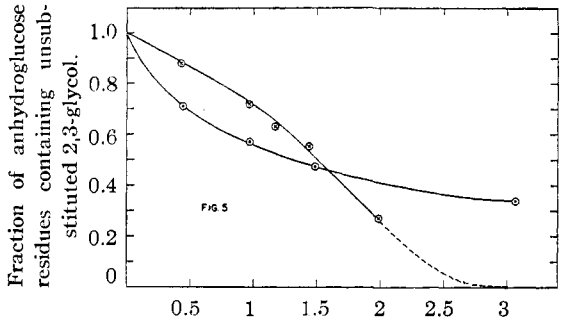


Fig. 5.—Residual glycol content of hydroxyethylcellulose and methylcellulose as function of content of substituent: ⊗, methylcellulose; ⊙, hydroxyethylcellulose.

oxide contents on a mole substituent basis. The data are summarized in Table IV. Sulfur content and tosyl content rose through a slight maximum and then decreased, a rapid initial tosylation of primary hydroxyl groups being followed, apparently, by a slower tosylation of secondary hydroxyls and a replacement of tosyl groups by chloride ion. The ethylene oxide content fell from 1.50 to 0.66 moles per glucose unit. The loss was rapid initially, but appeared to be levelling off at the final measurement. Extrapolation of a plot of the sum of tosyl and chlorine content *vs.* time back to zero time led to a value of 1.46 primary hydroxyl groups per glucose unit in Sample III (Fig. 6).

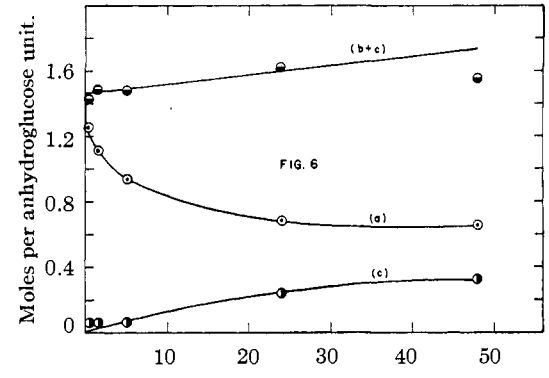


Fig. 6.—Analysis of tosylates of hydroxyethylcellulose, sample III, as function of time of tosylation: (a) combined ethylene oxide (moles per glucose unit); (c) chlorine (moles per glucose unit); (b + c) tosyl and chlorine (moles per glucose unit).

Residual glycol content of this sample is 0.48 glycol per glucose unit, indicating that at least 0.52 mole of secondary hydroxyl has been converted to primary by reaction with ethylene oxide. From this datum alone, as much as 1.04 moles of secondary hydroxyls might have reacted in the event that the 2- and 3-hydroxyls always reacted in pairs. However, the observed value of 1.46 primary hydroxyls rules out this possibility since

it indicates a reaction of only 0.46 secondary hydroxyls; the discrepancy between this figure and the minimum of 0.52 indicated by glycol analysis, is probably indicative of the error of these analyses. The similarity between the observed primary hydroxyl content and the minimum primary hydroxyl required by the glycol analysis indicates that each conversion of secondary hydroxyl to primary consumed a glycol unit, *i. e.*, in this material (Sample III), about 50% of the glucose units have hydroxyethyl or polyethylene oxide substituents on the secondary hydroxyls of either carbon atom 2 or carbon atom 3, about 50% have substituents on neither carbon atom 2 nor 3, and essentially no glucose units have substituents on both carbon atoms 2 and 3 (Formula I).

In this sample of M.S. = 1.5, 1.5 moles of ethylene oxide are distributed over 0.5 mole of secondary hydroxyl per glucose unit, and possibly on the original primary hydroxyl at C-6 also. However, if as has been proposed,[2] the loss of ethylene oxide (0.84 mole per anhydro-glucose unit) during tosylation results from the presence of polyethylene oxide chains and the formation of dioxane, then the ethylene oxide is not distributed equally but at least 0.84 mole per glucose unit is present as polyethylene oxide. From these considerations it can be shown that the fraction of original primary (C-6) hydroxyls remaining unsubstituted in this material may range from a minimum of 0.42 in the case that all polyethylene oxide chains are dimers to a maximum of about 0.80 per glucose unit if a maximum fraction of the polyethylene oxide chains are trimers.

Similar considerations may be applied to sample I, M.S. = 0.44, in which the glycol content is 0.71, indicating that at least 0.29 mole of secondary hydroxyl per glucose unit has been consumed and converted to primary hydroxyl. If one may ascribe to this material the primary hydroxyl content of 1.22 found by Tasker and Purves[2] in another sample of hydroxyethylcellulose of M.S. = 0.44, we note again a discrepancy of about 0.07 mole per glucose unit and, more important, the implication again that each conversion of secondary to primary hydroxyl effectively eliminates an unsubstituted glycol unit, *i. e.*, practically no anhydroglucose units have hydroxyethyl substituents on hydroxyls of both carbon atoms 2 and 3. The further conclusion of Tasker and Purves[2] that 0.30 mole of ethylene oxide may be present as diethylene glycol residues, if combined with the results of our residual glycol analysis and ascribed to sample I, indicates that only between zero and 0.07 mole of initial primary (C-6) hydroxyl can have reacted in this material.

Conclusion

It seems clear that the secondary hydroxyls in alkali-cellulose compete quite favorably with the primary hydroxyl for ethylene oxide. The preparation of 2-methylcellulose[10] may be relevant to this. We have no evidence as to whether the hydroxyl on carbon atom 2 or 3 is the more reactive in the reaction with ethylene oxide. The reaction apparently fails to occur at both carbon atoms 2 and 3 in a single glucose unit; this is opposite to what is observed in the preparation of methylcellulose[8] and may be related either to greater homogeneity in the reaction with ethylene oxide or to hindrance of an adjacent hydroxyl group by the rather large hydroxyethyl substituent. The presence of 34% residual glycol in hydroxyethylcellulose of M.S. = 3.07 indicates the presence of a considerable portion of polyethylene oxide appendages. With increasing extent of reaction beyond this value, ethylene oxide will in large part increase the length of such chains and only in small part will residual secondary hydroxyls of carbon atoms 2 and 3 enter into reaction.

Experimental

Hydroxyethylcellulose samples I, II and III were extracted in a Soxhlet extractor with 95% ethanol for 18 hours and dried in vacuum. The extraction led to loss in weight of 8.2, 6.3 and 7.2%, respectively. Sample IV was extracted with ethanol at room temperature and dried, leading to 9.8% loss in weight. The samples were dried in vacuum at 75°.

Acetylation.—Pyridine was dried over potassium hydroxide and distilled. An acetylation reagent was prepared consisting of 50 ml. of acetic anhydride in 950 ml. of pyridine. One-gram portions of hydroxyethylcellulose were weighed into pressure bottles, 50-ml. portions of the acetylating reagent were added, and the bottles were stoppered and heated at 75–80° for stated periods of time. The bottles were cooled and opened and the contents were treated with 5 ml. of water, reheated to 80° for five minutes, transferred to a beaker containing 300 ml. of distilled water and titrated with standard 0.5 *N* sodium hydroxide to a phenolphthalein end-point. Blanks were carried along with the analyses; duplicate runs were made at each time. From the difference between the blank and sample titrations, the equivalent weights per hydroxyl group, and thus the combined ethylene oxide contents (M. S.) were calculated. The data are summarized in Table I. The indicated errors reflect only the agreement of duplicate runs.

Saponification of the Triacetates.[4]—Four-gram portions of each sample of hydroxyethylcellulose were treated with 100 ml. of 1:1 acetic anhydride–pyridine at 90°. The products were precipitated in water from half of each reaction after 24 hours and from the remainder after 48 hours. The products were reprecipitated several times from acetone and dried in vacuum at 55°. One-gram portions of each product were dispersed in 40 ml. of 75% ethanol and heated at 50° for 45 minutes with intermittent shaking; 40 ml. of standard half normal potassium hydroxide was added and the stoppered flasks were allowed to stand at room temperature for 48 hours or 72 hours. The excess alkali was titrated with standard acid and from the consumed alkali and the assumption that the materials were triacetates the molecular weights and thus the combined ethylene oxide contents of the anhydroglucose units were calculated. The samples which had been acetylated for 24 hours and 48 hours were saponified for 48 hours and 72 hours, respectively. There was no great difference between the two sets of results, but the longer acetylation and saponification times led to slightly lower values of combined ethylene oxide, and are listed in Table II.

Alkoxyl analyses of hydroxyethylcellulose were carried out according to the procedure of Morgan[5] in which the compound is decomposed by treatment with hydrogen iodide in phenol and the evolved ethyl iodide is absorbed by alcoholic silver nitrate and ethylene is absorbed by an

(10) Sugihara and Wolfrom, THIS JOURNAL, **71**, 3509 (1949).

acetic acid solution of bromine. In duplicate runs the relative amounts of ethylene and ethyl iodide varied widely but the total combined ethylene oxide checked well. The directions of Morgan should be followed carefully, since in early experiments in which less than the recommended volume of solution of bromine in acetic acid was used, low results were observed despite the presence of a large excess of bromine. The primary data are not included but the results are summarized in Table II.

Periodate Oxidation.[6]—A buffered 0.1 *N* periodate solution was prepared from 15.4 g. of sodium paraperiodate, 22.2 ml. of acetic acid, and 27 g. of sodium acetate dissolved in water and diluted to one liter. The solution was standardized by treatment with standard arsenite and titration of excess arsenite against standard iodine. Samples of hydroxyethylcellulose were weighed out, I, 0.3677 g.; II, 0.5487 g.; III, 0.9654 g.; and IV, 1.5168 g., transferred to 250-ml. volumetric flasks, dissolved in 40 ml. of water, treated with 200 ml. of standard periodate solution, brought to 30° and diluted to 250 ml. Aliquots (25 ml.) were removed periodically and treated with potassium iodide and a constant volume of standard arsenite, and the excess arsenite was titrated against iodine. *trans*-Cyclohexanediol prepared by hydrolysis of cyclohexene oxide,[11] and triethylene glycol were treated with periodate similarly. The data are summarized in Figs. 1–4 in which the titers of excess iodine solution over that of blank titrations are plotted against time. These excesses reflect the quantity of periodate consumed by the samples. Sample I was not completely soluble in the reagent, but became soluble quite rapidly.

Tosylation of Sample III.—Portions of hydroxyethylcellulose, 0.140 g., were weighed into five test-tubes and treated with 15 ml. of dried pyridine at 50–60° to form a homogeneous dispersion. They were cooled and treated with *p*-toluenesulfonyl chloride, 2.75 g., with shaking at room temperature. The contents of each tube were precipitated in water after stated reaction times and the tosylates were dried, washed with ether and water, and dried in vacuum at 60°. Analyses were obtained on the products for sulfur[12] and chlorine,[12] and for combined ethylene oxide by the modified Zeisel analysis. From these values the substituent contents were calculated.[2] The results are summarized in Table IV.

TABLE IV

COMPOSITION OF TOLUENESULFONATES OF HYDROXYETHYLCELLULOSE SAMPLE III

Tosylation time, hr.	S, %	Cl, %	C_2H_4O, %	Substituent, moles/glucose unit		
				C_2H_4O	Tosyl	Cl
0.5	10.2	0.6	12.8	1.25	1.36	0.07
1.5	10.5	0.6	11.4	1.12	1.41	.07
5	10.7	0.6	9.8	0.94	1.41	.07
24	10.8	2.2	7.2	.68	1.38	.25
48	10.2	3.0	7.5	.66	1.23	.33

(11) Criegee and Stanger, *Ber.*, **69**, 2753 (1936).

(12) Elementary analyses were performed by Dr. C. K. Fitz.

Summary

Four samples of hydroxyethylcellulose have been obtained and analyzed. Their contents of combined ethylene oxide after purification are I, 0.5; II, 1.0; III, 1.5; and IV, 3.1 moles per anhydroglucose unit based on analyses made by saponification of the triacetates and by a modified Zeisel procedure.[5]

The residual glycol contents—glucose units unsubstituted on both carbon atoms 2 and 3—have been estimated by periodate oxidation and are I, 0.7; II, 0.6; III, 0.5; and IV, 0.3 mole per glucose unit. If a comparison of the glycol contents of the four samples is allowed, despite the likelihood that they were prepared under somewhat different conditions, the inference would be drawn that the initial decrease in residual glycol is rapid, indicating that the secondary hydroxyls of the anhydroglucose units react rapidly with ethylene oxide. This type of reaction becomes less important with increasing extent of reaction, the ethylene oxide then reacting in large part with primary hydroxyls and forming polyethylene oxide appendages, residual secondary hydroxyls reacting quite slowly.

Comparison of the primary hydroxyl and glycol contents of sample III indicates that each conversion of a secondary to a primary hydroxyl consumes a glycol unit, essentially no glucose units are substituted on both carbon atoms 2 and 3, half of the glucose units are substituted on either carbon atom 2 or carbon atom 3 and half are unsubstituted on both carbon atoms 2 and 3. Estimation of the polyethylene oxide content indicates that at least 40% of the original primary (C-6) hydroxyls remain unsubstituted, the initial reaction occurring quite readily at a secondary position. Similarly, sample I appears to have no glucose units substituted on both carbon atoms 2 and 3, and not more than 7% of the original primary (C-6) hydroxyls appear to have reacted.

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